SYNTHETIC APPROACHES TO SOME SULPHUR-CONTAINING HETEROCYCLES

By

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A thesis in the Department of Chemistry

Submitted in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

of the

UNIVERSITY OF LAGOS

April 1990

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The synthetic chemist is more than a logician and a strategist; he is an explorer strongly influenced to speculate, to imagine and even to create. These added elements provide the touch of artistry which can hardly be included in cataloguing of the basic principles of synthesis, but they are very real and extremely important.

E.J. Corey.

To be a good synthetic organic chemist, you've got to have the smelling power of a dog, the standing capacity of a horse and the tenacity of an ass; no human quality at all !

K. Mahalanabis, 1987.

SCHOOL OF POSTGRADUATE STUDIES

UNIVERSITY OF LAGOS

C E R T I F I C A T I O N

THIS IS TO CERTIFY THAT THE THESIS -

SYNTHETIC APPROACHES TO SOME SULPHUR-CONTAINING HETEROCYCLES

SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES UNIVERSITY OF LAGOS FOR THE AWARD OF THE DEGREE OF **DOCTOR OF PHILOSOPHY** IS A RECORD OF ORIGINAL RESEARCH CARRIED OUT BY

OLUWOLE BABAFEMI FAMILONI
B.Sc Hons (Chem), M.Phil. (Lagos)

IN THE DEPARTMENT OF CHEMISTRY

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D E D I C A T I O N

This thesis is dedicated to my late father, Mr. Gabriel Ibitoye FAMILONI (1917-1966) and also to my benefactor, Chief Jonathan Mayomi AKINOLA (1928-1990).

ACKNOWLEDGEMENT

First of all, I will like to give thanks to God, for giving me good health to complete this programme successfully.

I will like also to thank my able Supervisor, Dr. Babajide Alo, Associate Professor, for his brotherly advice, encouragement and constructive criticism throughout the programme.

The encouragement, advice and support of my research group - comprising; Dr. R. Ewedemi, Mr. Luqman Adams, Dr. Ligali A. Mamoudou and others are highly appreciated.

I acknowledge the technical assistance of all members of staff of the Department in their various capacities.

Part of this work which was carried out at the Institut National des Science Appliquées (INSA), Rouen, France was made possible through the kind assistance of the C.I.E.S., France through the French Embassy in Nigeria, and especially Madam Marie-Helène Esteve (the Cultural Counsellor). Their contribution to this work is recognised with gratitude.

I am very grateful to Professor Guy Quequiner and Dr. Francis Marsais, for providing laboratory facilities and making their wealth of experience available to me.

I will like to appreciate with thanks the understanding, love, moral and financial support I enjoyed from my family as a whole especially my wife - Bosede, my children, Babajide, Olumuyiwa and Omolabake during the dull moments of the programme without which this work may not have been possible.

To all others like Miss M. Alagoa and Madam Barret who had contributed in various ways, I say thank you and God bless.

Abstract

This thesis is in two parts. The first part deals with metalation of aromatic compounds with organolithium reagents as a route to sulphur-containing heterocycles.

As the studies are directed towards synthesis of new aromatic sultones: benzooxathiins; compounds with an ortho-β-hydroxy group contiguous to an aromatic sulphonamides were required. Consequently N-t-butylbenzenesulphonamide was lithiated with n-BuLi to obtain the corresponding 2-lithio species which were quenched with a variety of expoxides as electrophiles.

The reactions gave the appropriate alcohols in low yields. The alcohols were converted to alkyl halides on which heterocyclisation were attempted with sodium hydride. Dehydrohalogenation products were obtained instead.

Metalation of the tertiary sulphonamide : N-(benzenesulphonyl) piperidine gave the corresponding anion but the desired corresponding compounds were not obtained. Benzylic metalation was considered as an alternative method of introduction of the β-hydroxy functionality. N-t-butyl-2-methylbenzene sulphonamide was lithiated and coupled with benzophenone to give a carbinol which on cyclisation did not give the desired sultone but gave a new benzothiazine.

Benzylic lithiation of ethyl 2-methylbenzenesulphonate gave anions which were coupled smoothly with a range of electrophiles giving a variety of new substituted benzene sulphonates.

Metalations of ethyl 2,4-dimenthylbenzenesulphonate gave the 2-lithiomethyl anion mainly, giving credence to a predominant coordination mechanism in benzylic lithiation.

In attempts to obtain new pyridine-fused sultones, 2 and 4(N,N-dialkylamino)sulphonylpyridines were lithiated with LDA to give a 3-lithio species in both cases. These were coupled with benzophenone to give pyridine carbinols. Thermal cyclisation of the six carbinols gave two new pyridine-fused sultones. N-t-butylpyridine-3-sulphonamide was also metalated with LDA to give 4-lithio compounds which were quenched with benzophenone and carbon dioxide furnishing a carbinol and an acid respectively in good yields. The latter acid was cyclised with PPA or phosphorous oxychloride to give isothiazolo (5,4-c) pyridines.

Part II of the thesis deals with the synthesis of pyrido (1,2-b) 1,2,4-benzothiadiazines and its substituted analogues via readily generated endocyclic iminium ions. Appropriate sulphonyl chlorides were condensed with piperidine-2-carboxylic acid. Five benzene analogues were obtained in good yields.

N-(Arylsulphonyl) tetrahydropyridinium salts were obtained regiospecifically and in high yield by smooth triflate-assisted decarbonylation of the corresponding N-(arylsulphonyl)piperidine-2-carboxylic acid chlorides at room temperature. These iminium salts were converted to the corresponding nitroamines. These compounds underwent a smooth reductive exo-tet cyclocondensation reaction to give corresponding new 9-substituted tricyclic azacycles: : 1,2,3,4,11,11a-hexahydropyrido (1,2-b)-1,2,4-benzothiadiazine-6,6-dioxides.

LIST OF ACRONYMS

DMG	-	Directed Metalation Group
THF	-	Tetrahydrofuran
n-BuLi	-	n-Butyl lithium
LDA	-	Lithium diisopropylamide
LiTMP	-	Lithium 2,2,6,6- tetramethyl piperidine
THP	-	Tetrahydropyran
$CDCl_3$	-	Deuterated chloroform
DMSO-d_6	-	Deuterated dimethyl sulphoxide
D_2O	-	Deuterated Water
d	-	doublet
q	-	quartet
t	-	tertiary
dd	-	doubletof a doublet
m	-	multiplet
ether	-	diethyl ether
TMEDA	-	N,N,N',N' - tetramethylethylene diamine
DABCO	-	diazabicyclooctane
OMOM	-	methoxymethoxy

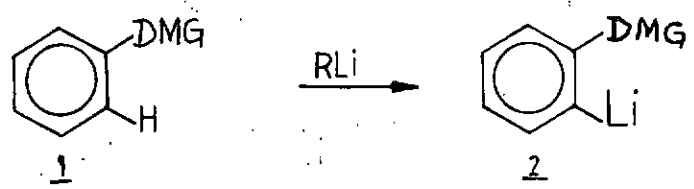
PART I

CHAPTER ONE

INTRODUCTION

AROMATIC METALATION - LITHIATION

Metalation in general denotes the direct replacement of hydrogen atom by a metal[1], while lithiation is the specific replacement of a hydrogen atom by lithium metal and usually lithiation refers to the removal of hydrogen attached to an sp^2 hybridized carbon atom[2]. This direct replacement of hydrogen can be effected by treatment of aromatic hydrogen with alkyl or aryllithium compounds. An aromatic lithio compound can also be synthesised by halogen-metal exchange reaction, but that will not be classified as metalation



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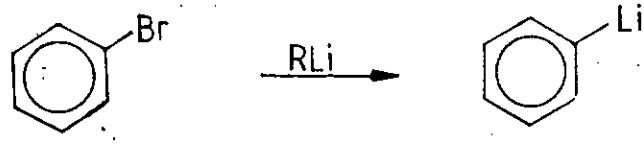


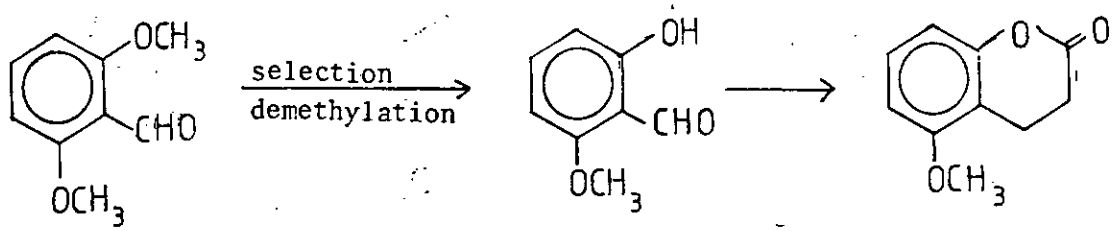
3 4

Uniqueness of Metalation

Metalation was discovered by Gilman[3] and Wittig[4] in 1938. Between then and now considerable work has been done on lithiations. This has been facilitated by the availability of a variety of

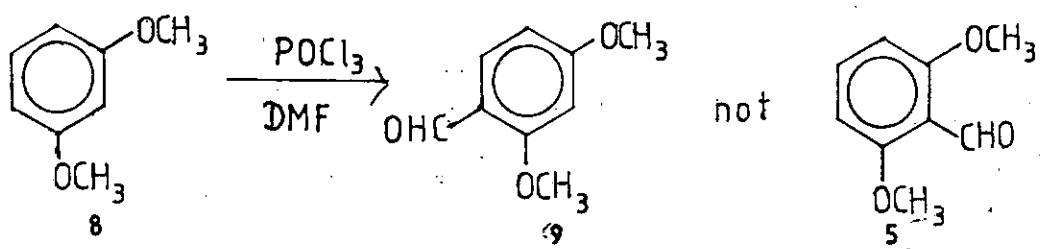
commercial organolithium compounds and also uses of catalysts, complexing agents which enable these reactions to be carried out with a lot of dexterity.

Several compounds that are not feasible by other methods or those that were obtained through winding routes are now possible and sometimes in one pot and in better yields. This can be illustrated[5] with the synthesis of 5-Methoxy Coumarin which could be synthesised via a resorcinol derivative 5 by the proposed scheme below



5 6 7

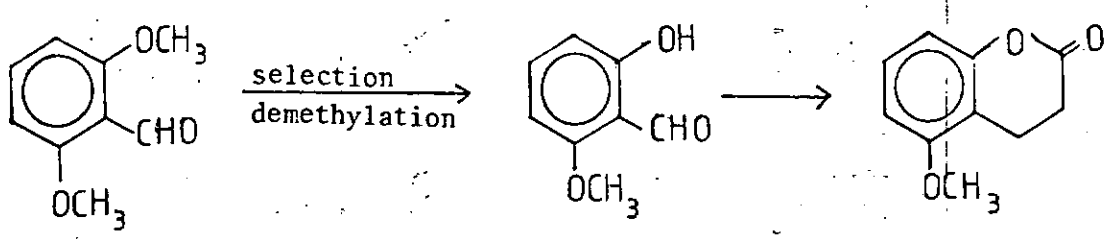
This appears a simple synthesis, but to obtain the resorcinol 5 under the classical methods is not feasible because it should be obtained by formylation of 1,3-dimethoxybenzene. Such reactions are generally effected by acid catalysed electrophilic substitutions or Vilsmeyer-Haack reactions[6,7]. The reaction would lead to another analogue 9, therefore the desired 5-methoxycoumarin is not obtainable through this route.



8 9 5

commercial organolithium compounds and also uses of catalysts, complexing agents which enable these reactions to be carried out with a lot of dexterity.

Several compounds that are not feasible by other methods or those that were obtained through winding routes are now possible via shorter and simple routes, and sometimes as one pot reaction and in better yields.[5] This can be illustrated with the synthesis of 5-methoxy coumarin which could be synthesised via a resorcinol derivative 5 by the proposed scheme below



5 6 7

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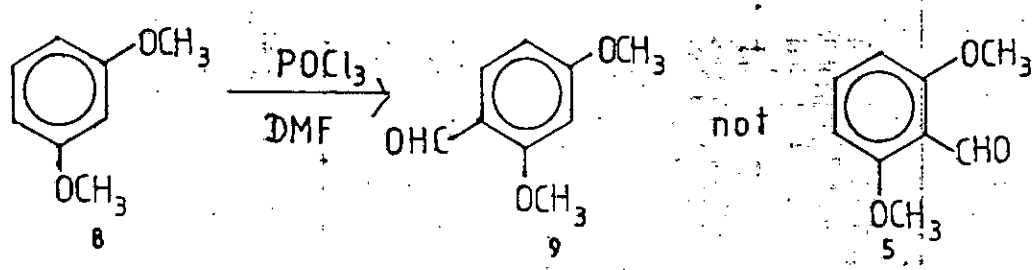

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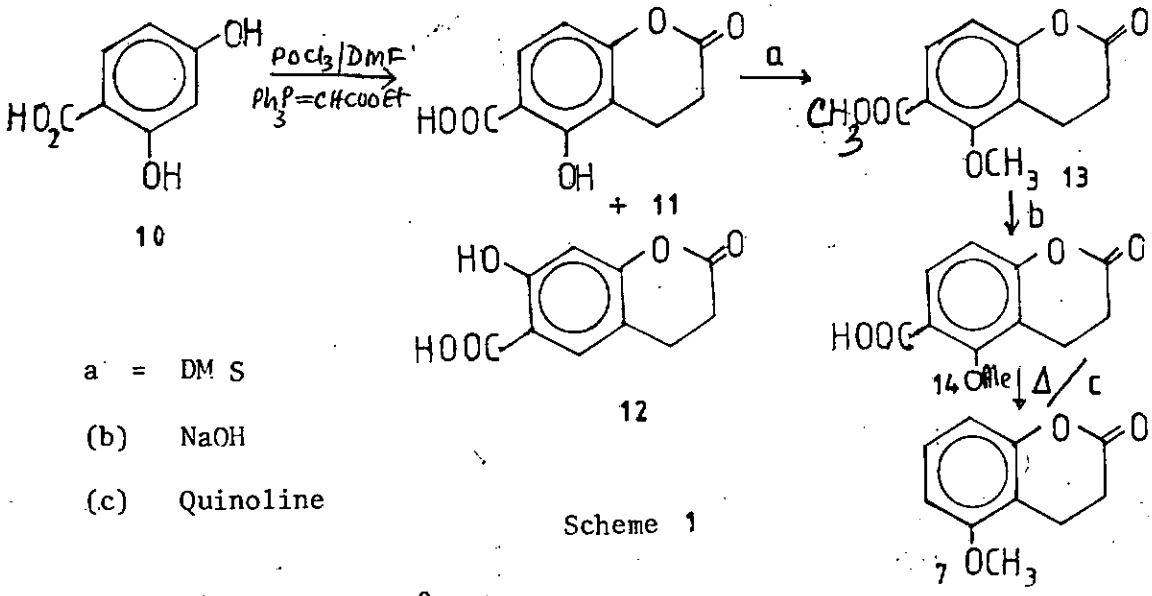
Therefore, aside from metalation techniques the synthesis of 5-Methoxycoumarin is only achieved through a winding route as outlined:



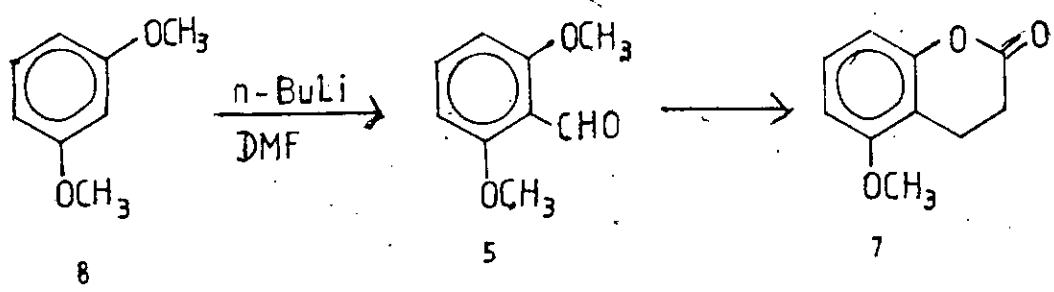
a = DM S

(b) NaOH

(c) Quinoline

Scheme 1

The lithiation[8] method, however, gives these previously unattainable resorcinol derivative and the 5-Methoxycoumarin easily in good yield.



These types of synthetic improvements make lithiation an ever growing method of synthetic heterocyclic chemistry.

Structure of Organolithiums

Organolithiums are usually designated as RLi like a free compound but in actual sense most organolithiums associate with themselves

forming oligomers.[9] For example most alkyllithiums are in hexamers, tetramers etc, Butyllithiums are usually dimers. They maintain this structure in dilute solutions and even in the gas phase[10]. Infrared and Raman spectra of n-butyllithium hexamers in benzene solution show features which suggests that the structure in this case involves carbon bridges.[11]

Despite these molecular associations, structural studies show that a considerable amount of ionic character is found in the C-Li bond which results from low -CH-Li bonding force. The ionic character of the alkyllithium shows in their electronegativity values e.g. Ethyllithium has 1.5, and n-Butyllithium 1.43.

The ionic character confers on the organolithium, Lewis acid Character. Therefore bases such as ether, amines coordinate with the organolithium with consequent depolymerisation to varying extent. This depolymerisation causes the reagent to increase in kinetic ability[8] and this makes them more basic as their polymer size reduces It has been shown that coordinated organolithiums are reactive. Table I shows that when electron donating solvents are used there is appreciable depolymerisation.

Table I

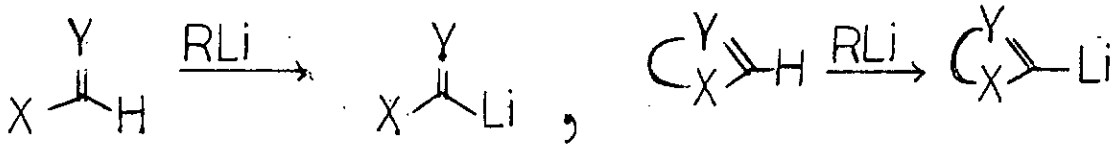
Lithiating agent	Solvent	State of Aggregation
n-BuLi	Hydrocarbon	Hexameric
	Ether	Tetrameric
	THF	Dimeric (solvated)
n-BuLi/TMEDA	Hydrocarbon	Monomeric
t-BuLi	Hydrocarbon	Tetrameric
	THF	dimeric

The effect of this coordination can be illustrated by the example of benzene which is almost inert to the uncomplexed n-BuLi whereas it is readily metalated by n-BuLi-DABCO Complex[12].

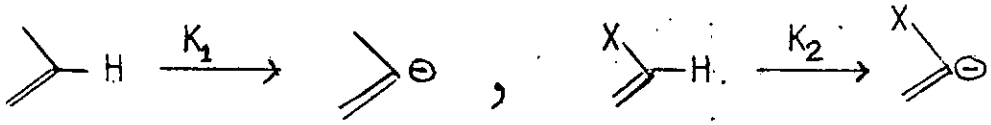
Mechanism of Lithiations

Two main types of Mechanisms of lithiations have been observed and they are (a) alpha lithiation (b) beta or ortho lithiation.

Alpha lithiations are obtained in π-excessive heterocycles e.g. thiophene. The metalating agent deprotonates the Sp^2-carbon atom alpha to form a carbon-Lithium bond.



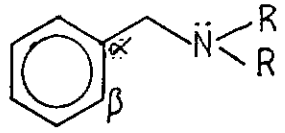
This may be part of an olefinic or heteroaromatic π system. In this case the heteroatom does not actually aid the depolymerisation of the lithiating agent. Therefore, a coordinating agent like THF still has to be added. The regiospecificity of such reaction therefore depends on the inherently higher acidity of the alpha hydrogen present so the mechanism[1] is therefore more of an acid- base mechanism. For example thiophene α-hydrogen has pKa $\approx$ 30[23], while trichloro ethylene has pKa $\approx$ 18. Therefore it is a base-catalysed hydrogen exchange aided by the heteroatom.



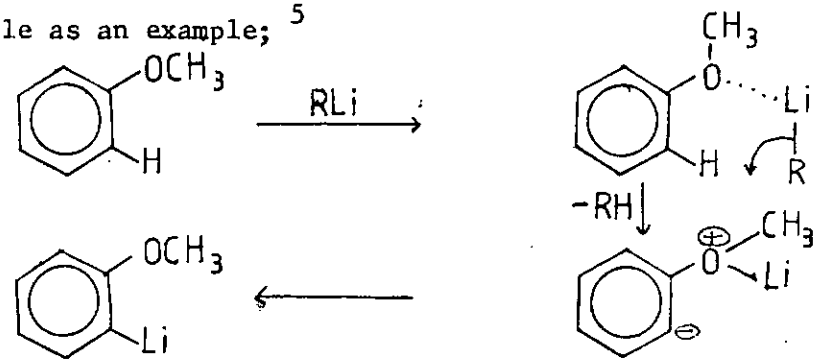
$$K_2 \gg K_1$$

Beta Lithiation (Ortho Lithiation)

This is an example of coordination-only mechanism with the heteroatom in the directing group. This is the commonest type of lithiation reactions employed in synthesis.

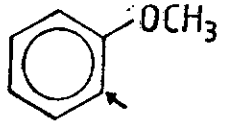


The organolithium abstracts the hydrogen ortho to the directing group in the aromatic ring. This occurs by forming a coordination with the directing group and the nearest available proton then suffers protolytic attack leading to initial disruption of the oligomer of the alkyllithium to yield a reactive complex with the substrate. In the intermediate species, the carbon-lithium bond of the metalating agent and the carbon-hydrogen bond are polarised to a great extent thus rendering the proton easily removable and replacement by a lithium atom follows[13]. This is illustrated below. Using anisole as an example; [5]



The primary requirement of a directing group is that it must have a heteroatom with an unshared electron pair for coordination. The ortho exclusive mechanism was first put forward by Robert and Curtin[14]. The substituents that direct ortho/para and those that direct meta in acid catalysed eletrophilic substitution all direct exclusively ortho in lithiations, whether they are electron-withdrawing

or electron-donating.



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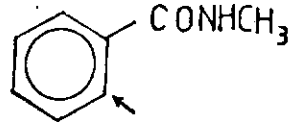

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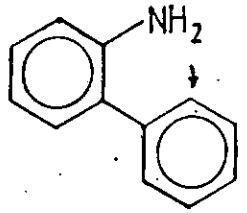
Determination of position of lithiation:

(a) Aromatic ortho lithiation occurs at sterically close positions [15,16] in which the most acidic hydrogen is resident.



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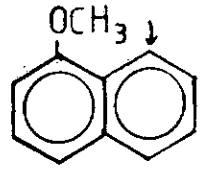

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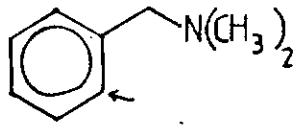
(b) Lithiation occurs at ortho or sterically close position even when the heteroatom is one or two carbon atoms away from the aromatic ring



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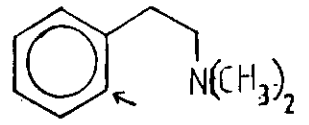

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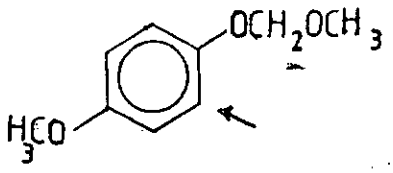
(c) When there are two groups that can complex the organolithium, as in the example 22 23 24 below the lithiation occurs ortho to the group which can complex better with the lithiating agent[17]. However when they both have equal or almost equal complexing ability, then a mixture of ortho lithiated species is formed.



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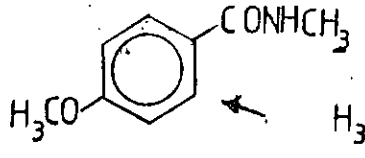

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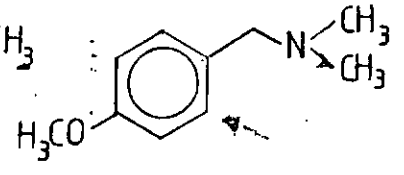

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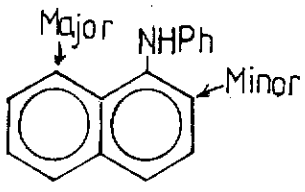
(d) When there is only one directing group but there are two acidic hydrogens lithiation occurs predominantly at that position which carries the most acidic hydrogen.



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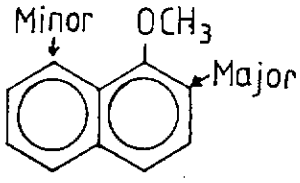

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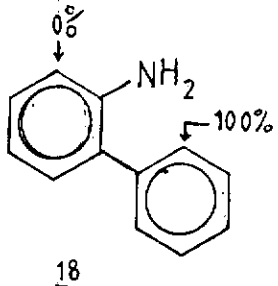

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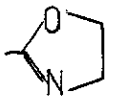
Classification of Directed Metalation Groups [18]

After an extensive study of lithiating abilities of groups by various workers, a classification of these groups has been put forward.

Strong Directing Group (carbon-based)

-CONHR, CSNHR, $CONR_2$,  , CH=NR, CH_2 NHR, $(CH_2)_n$ NR_2

n=1, or 2,

Strong Directing Group (Heteroatom-based)

NHCOR, $NHCO_2R$, $OCONR_2$, OCH_2OCH_3, OCH(Me)OEt

OTHP, SO_2NHR, SO_2NR_2, SO_3H.

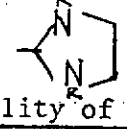
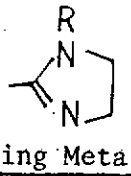
Moderate Directing Group (carbon-based)

CF_3, CN

Moderate Directing Group (Heteroatom based)

$-NR_2$, -O e, $-OPO(OR)_2$, -SMe, -F, -Cl, $-PO(NR)_2$.

Weak directing group (carbon based)

$-CH(OR)_2$, $-CH_2OH$,  , 

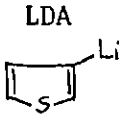
Relative Directing ability of Activating Metalation Groups [19]

SO_2NR_2, SO_2NHR, CONHR, $CONR_2$ > O e > CH_2 CH_2 NR_2, NR_2, CF_3, F.

Synthetic utility of Lithio Species

The synthetic utility of metalation is enhanced by the numerous lithiating agents available commercially. Similarly a variety of complexing agents are also available. The following are some of organolithiums that have been used along with their complexing agent.

TABLE 2

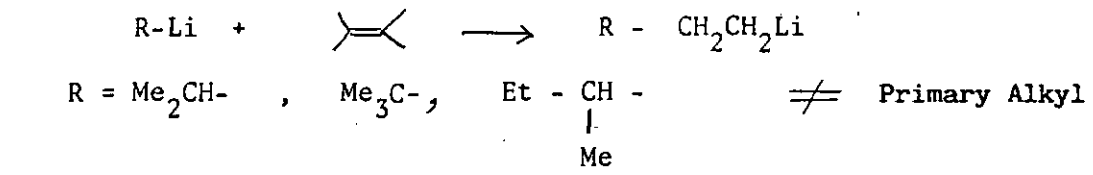
Organolithium	Complexing agent	Ratio of RLi to Complexing agent	Ref.
MeLi	Et_2O	1:1	20
EtLi	Et_2O	1;1	20
n-BuLi	Me_2S	1:1	20
n-BuLi	TMEDA	1:1	21
n-BuLi	DABCO		22
n-BuLi	Hexane		23
n-BuLi	THF		24
n-BuLi	Et_2O		25
n-BuLi	THF		26
Me-SO-CH_2Li	THF		27
$PhCH_2Li$	DABCO	2:3	28
PhLi	Dioxan	4:1	29
PhLi	DABCO	1:2	22
$C_{13}H_9Li$	Et_2O	4:1	20
LDA	THF/TMEDA		30
LDA	THF		31
	Et_2O		32
LTMP	THF		33

The numerous lithiating agents available make the use of lithiation as a synthetic methodology facile and a considerable number of electrophiles that can be applied on the lithio species formed further makes the method incredibly invaluable in organic synthesis. A short discussion on some of the electrophiles that have been in use follows:

Electrophiles used on lithio species

(1) Addition to Unconjugated -C=C- bond

Organolithiums react with unconjugated carbon-carbon multiple bonds to form an addition product with alkyllithium. Consider the reaction of ethylene



For n-BuLi the reaction takes place under vigorous condition while secondary and tertiary alkyl lithium in presence of ether reacts under mild conditions.[34]

The mechanism elucidated for the reaction indicates that some interaction between the electron deficient organolithium and the π-system preceed the addition.

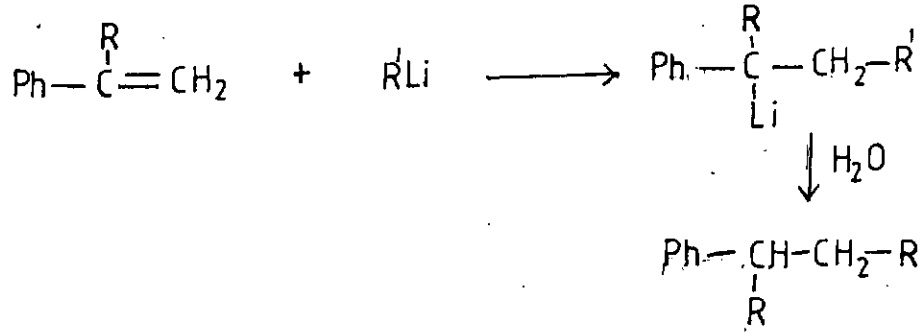
Alkenyl groups are more succeptible to α-lithiation than alkenes.

(2) Addition to conjugated C-C multiple bond.[8]

The addition of conjugated dienes and styrenes to organolithium compounds initiates polymerisation of such conjugated dienes. This reaction had infact been used to produce polymers

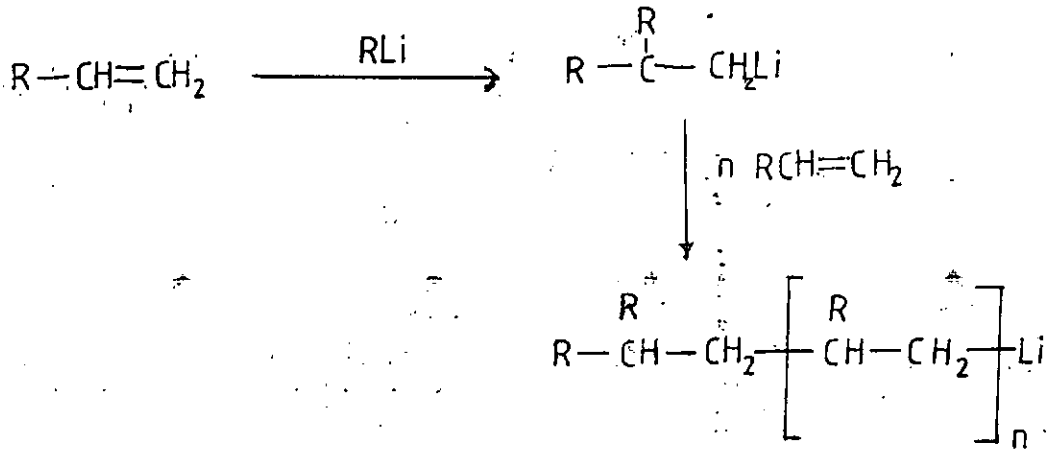
industrially.

To obtain the addition product, the reactions are carried out at very low temperatures e.g. addition was obtained in diethyl ether at -45° when isopropyl lithium reacts with an α-substituted styrene[35].



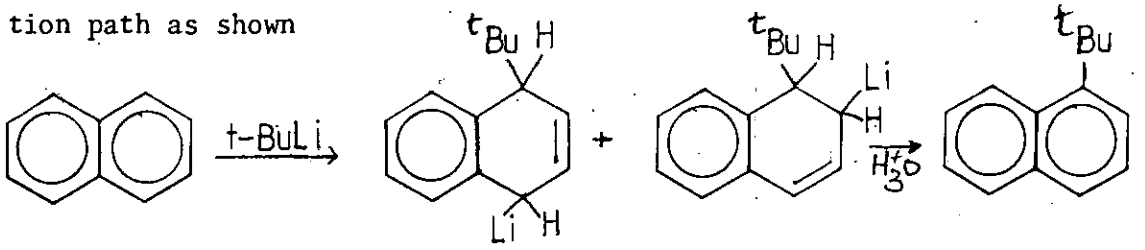
Reactions of butan-1, 3-diene with s or t-butyllithium at 35° in pentane gave addition products: 5-Methylhept-1-ene 11%, cis 5-Methyl-hept-2-ene, 25% and trans - 5-Methylhept-2-ene 64%.[36]

Isoprene could be polymerised with lithium metal or organolithiums to give the cis-polymers with properties that resemble those of natural rubber. This method has been applied on industrial scale. The mechanism is the addition of an organolithium to a molecule of the monomer leading to another alkyllithium compound and this in turn adds to another molecule of the monomer and so on, as postulated by Ziegler[37]



3. Addition to Aromatic Rings

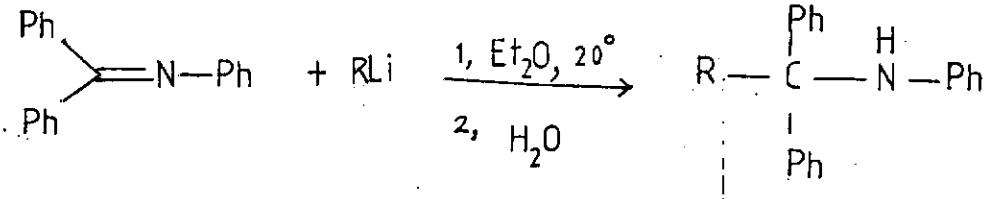
Aromatic compounds will only react with organolithium under vigorous conditions. t-butyllithium in decaline at 165° will alkylate naphthalene in position 2 to give 1-t-butylnaphthalene in 20% yield[38]. The reaction follows an addition and elimination path as shown



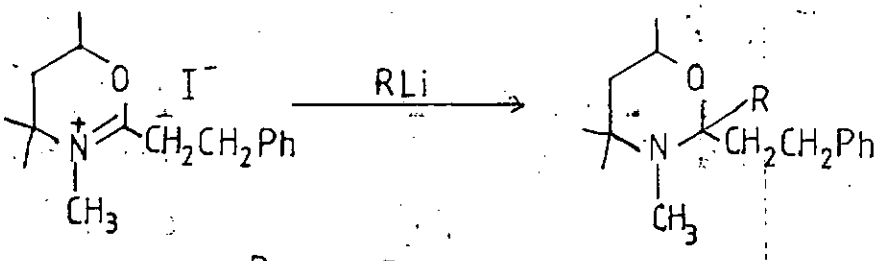
Other examples have been performed on benzene[38], biphenyl[8], anthracene[8] and phenanthracene[8]

4. Addition to Imine Carbon-Nitrogen bond

Addition product has been reported for the reaction between imine and organolithium compounds even though the α-proton of such groups are susceptible to lithiation e.g. the addition to the C=N bond on benzophenone-N-phenyl amine[39]

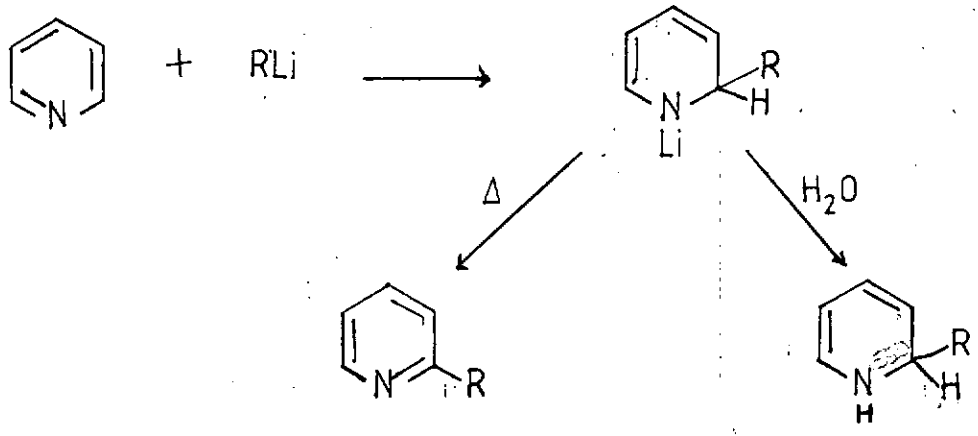


The same type of addition reaction has been achieved when an iminium salt was added to an organolithium salt[40].



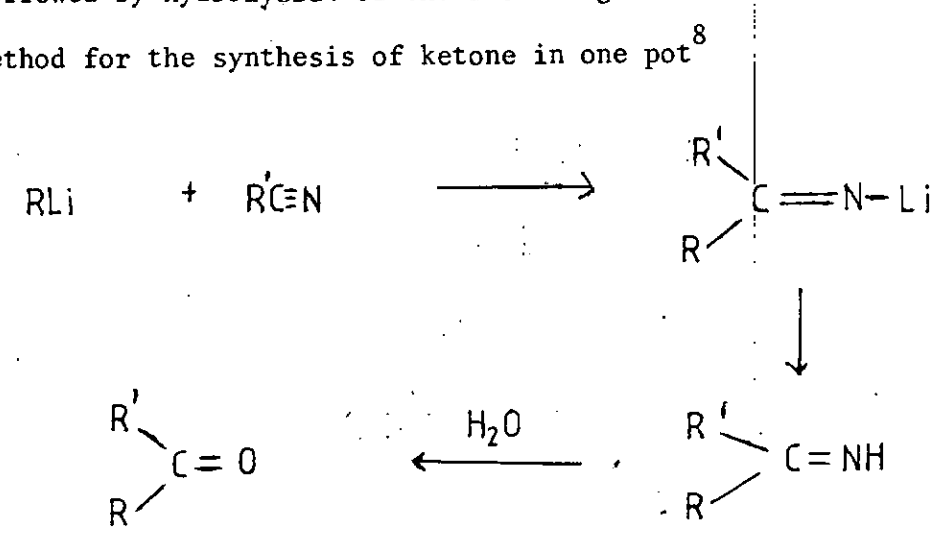
R = n-Bu , t-Bu.

In aromatic -C=N- bonds e.g. in pyridine, the same type of addition reaction commonly takes place, but there is an option for the aromatic ring remaining intact or becoming broken[41].

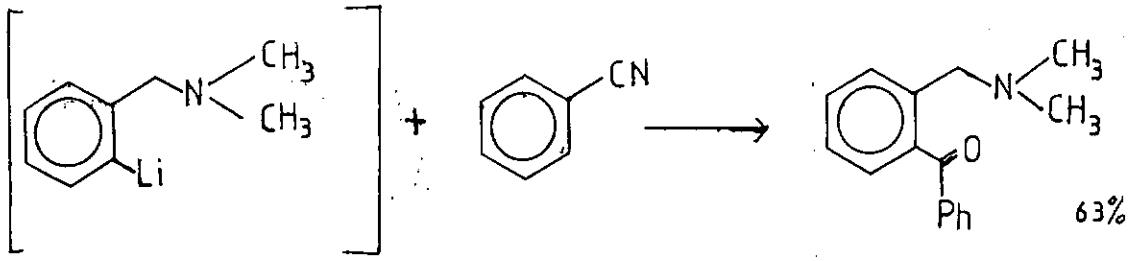


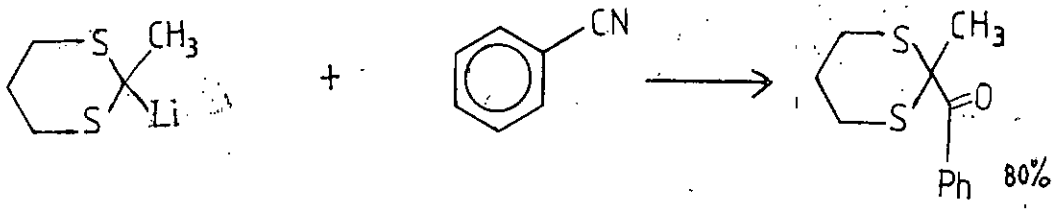
5. Addition to nitriles and isonitriles

The addition of nitriles to organolithium compounds followed by hydrolysis of the resulting imine is a versatile method for the synthesis of ketone in one pot[8]

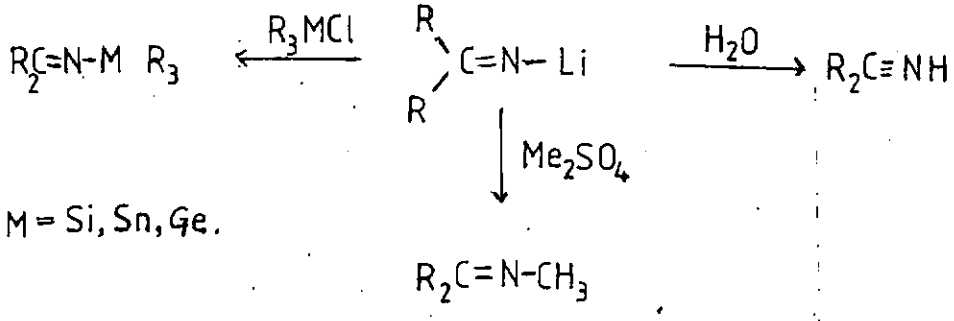


The subsistuent on the nitrile group does not impede the reaction [42, 43, 44]





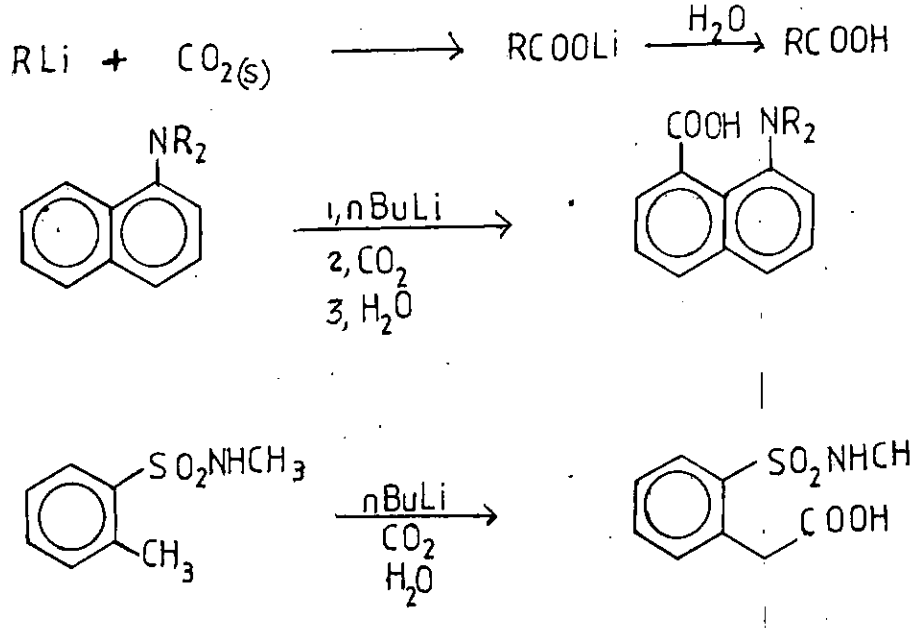
Despite the above reactions, other products can be obtained from nitriles when the reaction takes place at low temperature or the lithio species is trapped with other reagents[8]



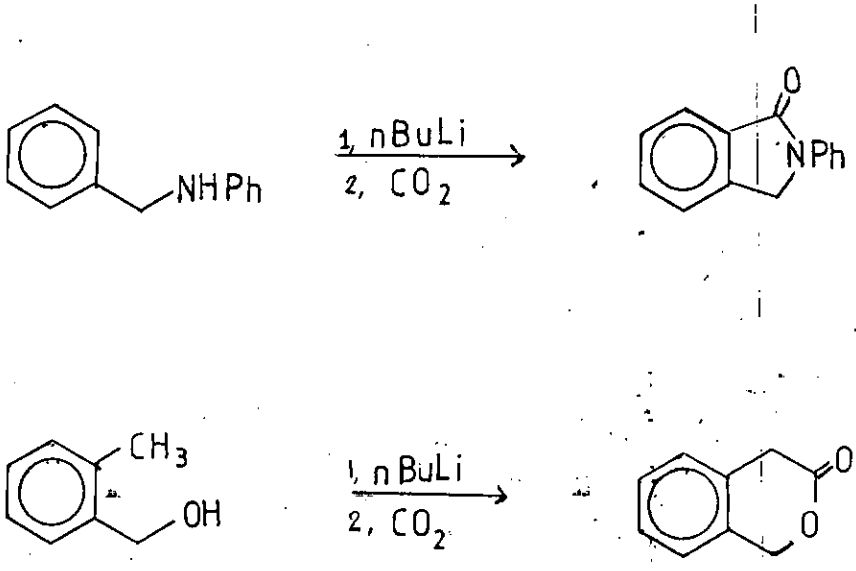
6. Addition of Carbon dioxide

The reaction of organolithium compounds with carbon dioxide is one of the commonest reaction in metalations,[45, 46] as it serves as an excellent route to the preparation of

of carboxylic acid. It has even been used as a simple way of characterising the formation of anion. The reaction is achieved usually by addition of crushed solid carbon dioxide to the organolithium salt or the addition of a solution of carbon dioxide gas in a suitable solvent.

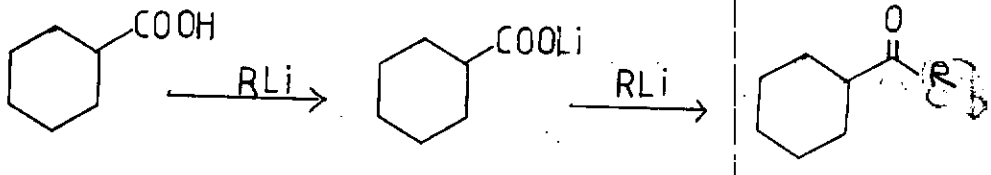


The reaction has been utilized to construct some fused rings in one step [47, 48]



Metal Carboxylates

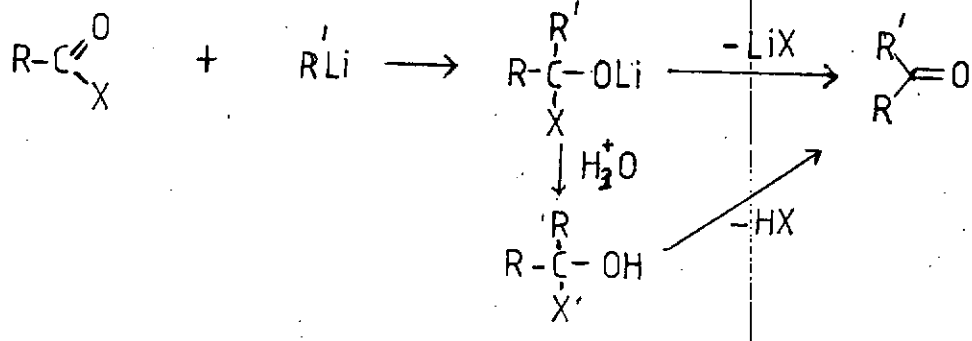
A lithiated acid or a metal carboxylate can react with a mole of organolithium to form ketone in good yield when other protons have been eliminated[49]



In this reaction, the stereochemistry of the α-carbon atom of the carboxylate is preserved[50]

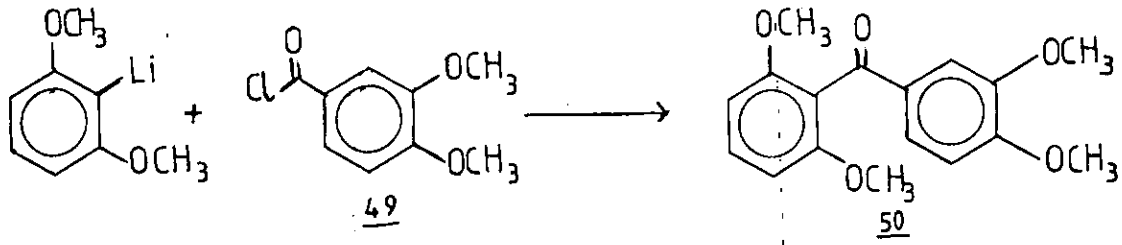
7. Addition of Acyl Derivatives

Acid chlorides react with organolithiums to give a ketone:



Sometimes hydrolysis of the lithio species terminates at carbinol but invariably this loses HX to give Ketone.

Aromatic acyl chlorides behave like their aliphatic counterpart giving ketones.

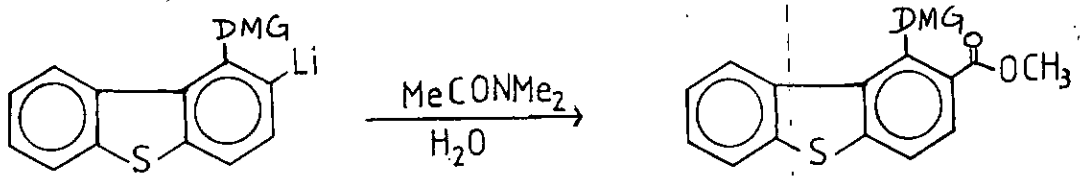


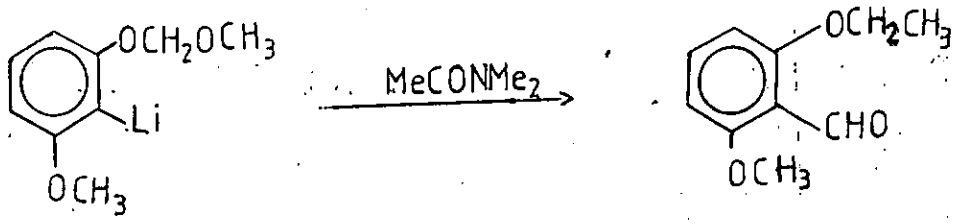
49 50

This gives a substituted benzophenone which is otherwise difficult to obtain,[51] since normal Friedel-Craft will not allow the attack at position 2 but at position 4. The presence of the lithio species at position 2 facilitates this coupling.

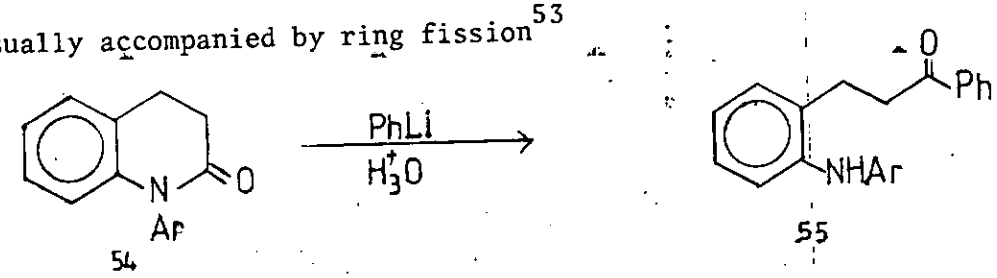
8. Addition of Amides

Primary aliphatic amides may add to organo-lithium compounds to form aldehydes [52] while secondary aliphatic amides give ketones. This is a well-known route for the introduction of the aldehyde functionality to aromatic rings[18]



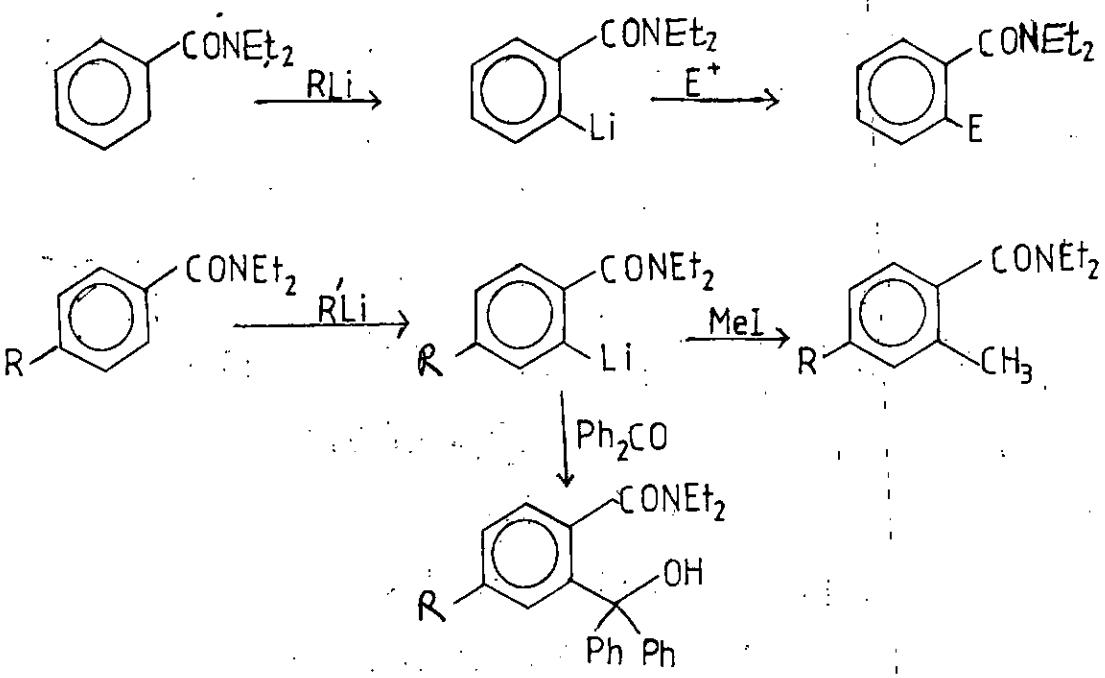


When the amide is a lactam the formation of a ketone is usually accompanied by ring fission[53]



54 55

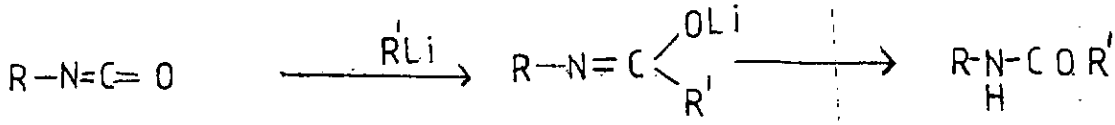
Aromatic amides however do not add to organolithiums. Beak and Brown[54] showed that the $CONR_2$ functionality did not suffer the expected nucleophilic attack by alkyllithium reagents. Instead, the amides cleanly underwent ortho metalation as evidenced by reaction with electrophiles[55]

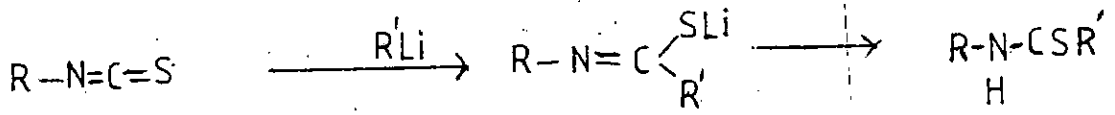


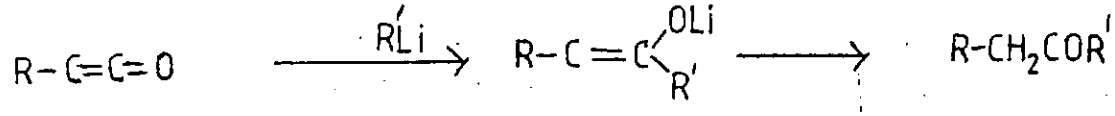
This property of aromatic amides has been exploited extensively in the development and utility of aromatic amides as excellent directing groups in aromatic metalation [56]

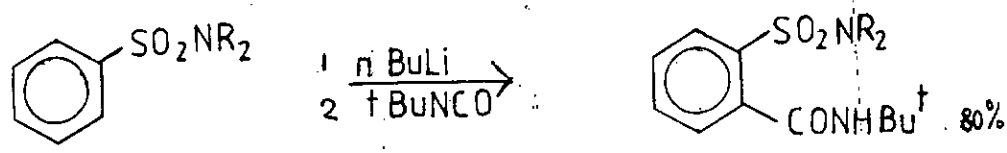
9. Addition of Isocyanates, Isothiocyanates and Ketenes

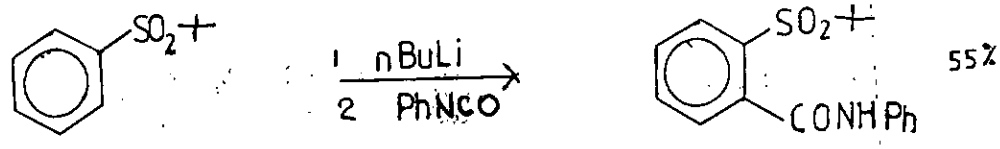
These compounds could be considered together as anion because attack on them do take place on the carbonyl moiety. The products in each case after appropriate hydrolysis are amides, thioamides or ketones respectively.[57, 58]



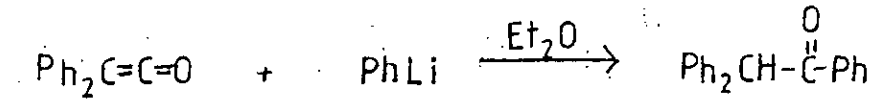








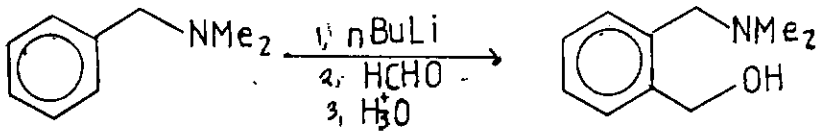
Diphenyl Ketene reacts with phenyl lithium[59]



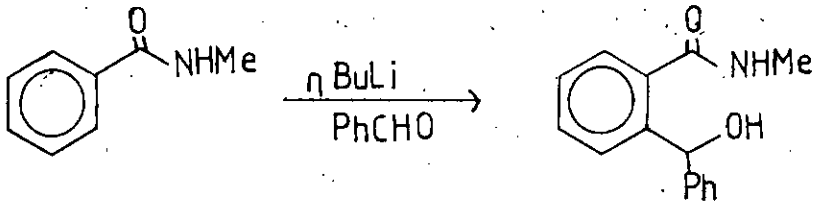
10. Addition of Aldehydes and Ketones

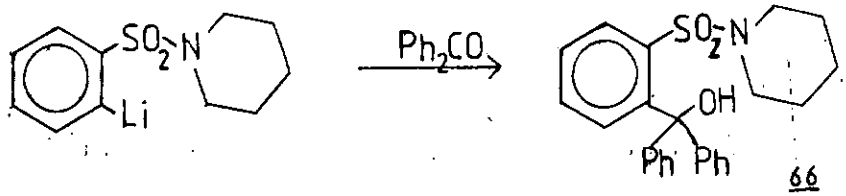
These are the commonest electrophile currently used in metalation reactions, they generally form alcohols in good to excellent yields

Unsubstituted alcohols are produced with formaldehyde [60]



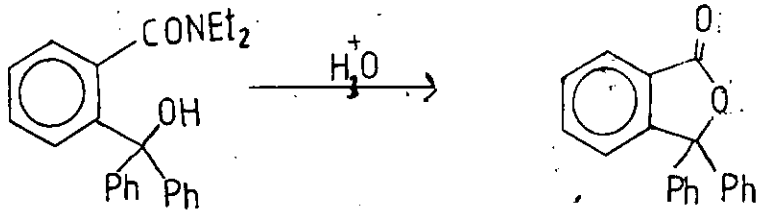
Higher alcohols are obtained by using benzaldehydes,[61] acetaldehydes[62], benzophenone[54, 63] etc.





66

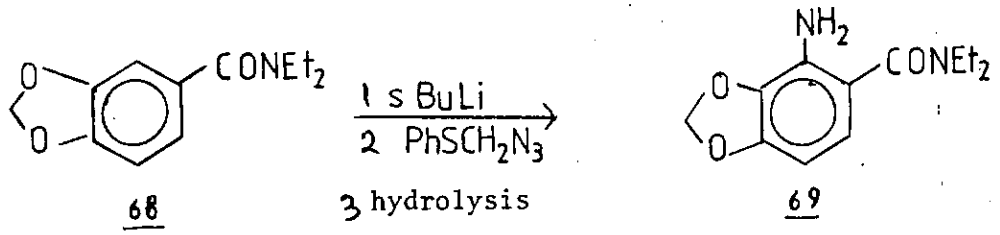
This reaction provides a general method of synthesis of coumarins or phthalides in one pot on treatment of the amide alcohols with acids.[54]



58b 67

11. Addition of Azides

Azides[64] add to organolithiums to give amines after appropiate hydrolysis or reduction. This has been the main route for the preparation of amines via lithiation reactions[65, 66, 67]



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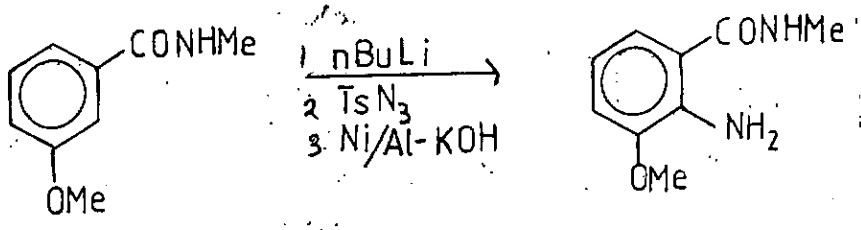
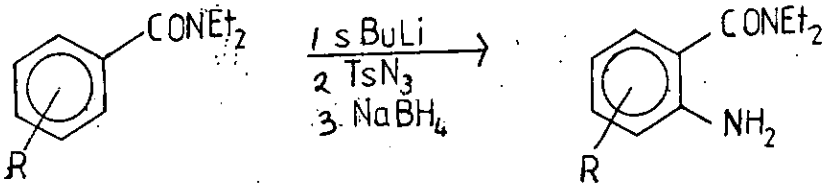
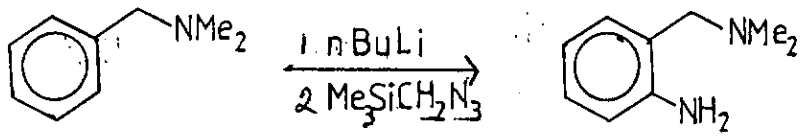
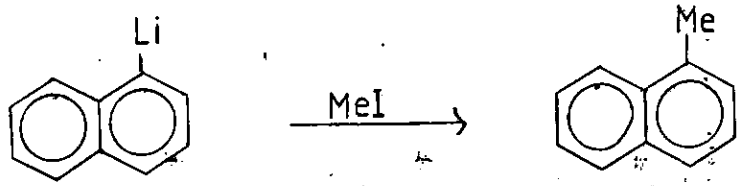


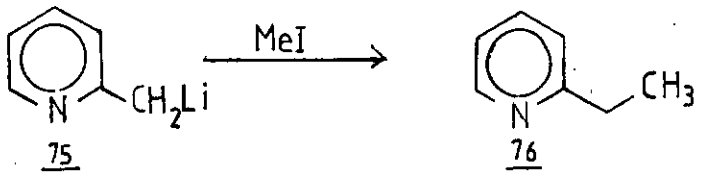




Alkylation and arylation using organic halides

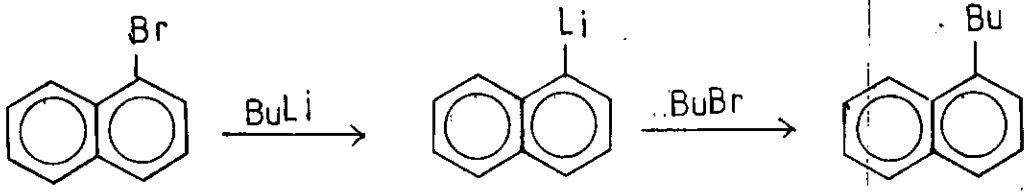
Organolithiums react readily with alkyl halides to form alkanes.[68] The reaction with simple alkyl halides e.g. Methyl iodide, gives very little side reaction. Therefore, the products are obtained in good yield.[69]



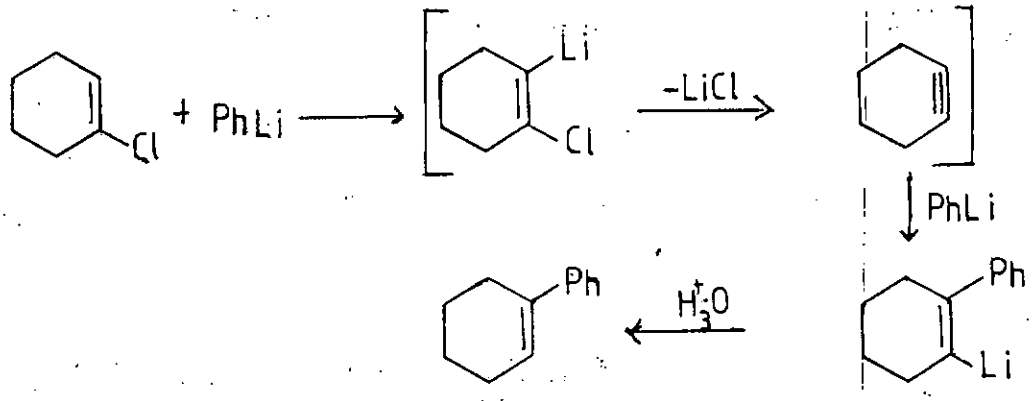


75 76

The predominant side reaction that often occurs is the metal halogen exchange reaction, i.e. the alkyl halide becomes lithiated. Wittig[70] showed that the reaction may still go to completion but in a two step process. It was shown that fluoro, chloro, and Bromo alkylate in two steps while iodo will undergo direct replacement.[71, 72.]

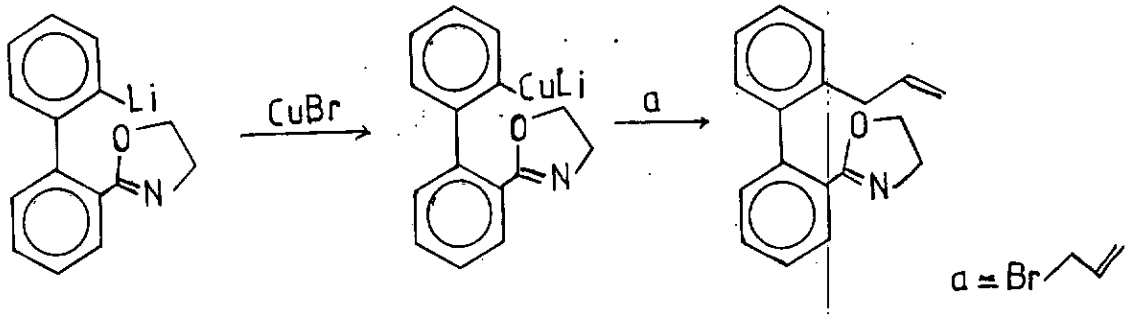


Halides also form alkyne or benzyne with elimination before alkylation.

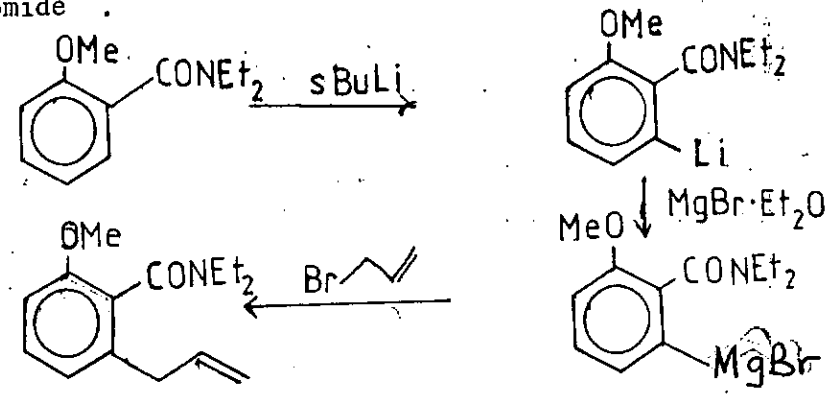


These side reaction that compete with the main reaction has led to the development of alternate routes via transmetalations i.e. an exchange of the lithium atom to a less reactive

metal atom. Good example in this case is the use of copper. This metal when present couples cleanly with a wide variety of organic bromides and iodates especially vinylic and aryl halides[24]

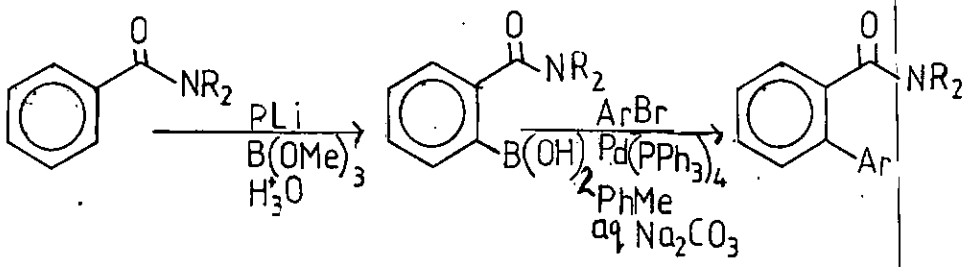


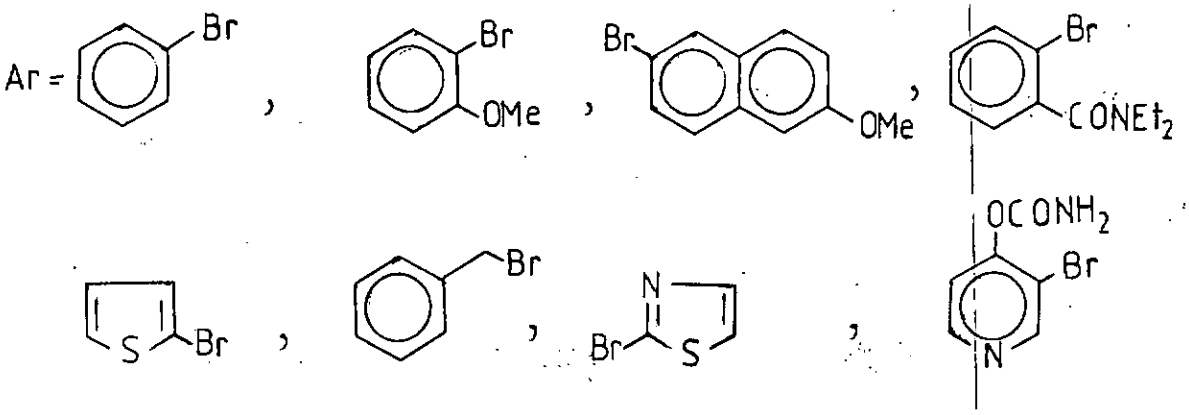
Recently, Snieckus and his group have shown that on transmetalation to Magnesium (using Magnesium bromide - etherate) the lithio species can cleanly couple with allyl bromide[73].



Cross-coupling reactions using the well-known easy reaction of the boron atom with halides in the presence of transition metal catalysts is the recent addition to arylation. Snieckus, Alo et al. have shown that arylboronic acids with trimethoxyborane[78] give efficient palladium-catalysed cross coupling reaction with a variety of arylhalides to yield

unsymmetrical biaryl compounds[18, 75-78]

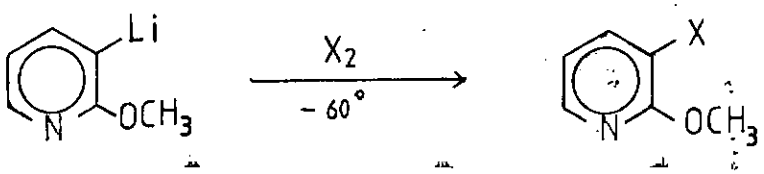




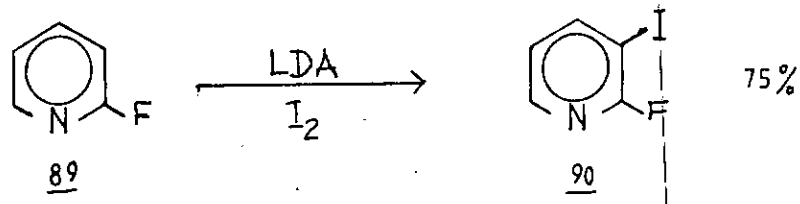
This method has been used in the synthesis of several natural products.

Halogenation of Organolithiums

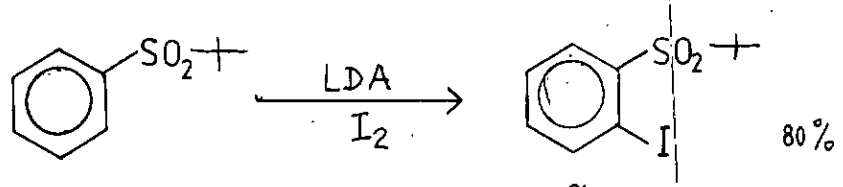
Halogens can be introduced to organometallic compounds by direct or indirect addition of the halogen to the lithio species,[50,79]. The halogen commonly used are iodine and bromine. Fluorine and chlorine are hardly employed either because they could act as directed metalation groups[80] and lead to further metalation of the ring or due to their extreme reactivities.



X = Br Yield 15%
I 30%

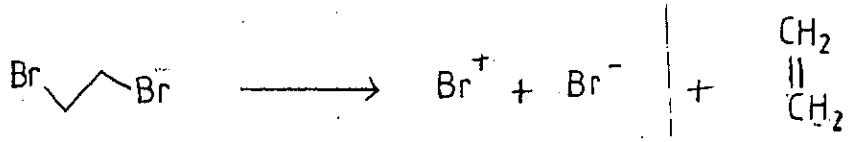


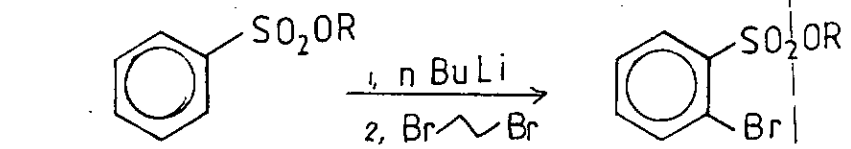
89 90



61 91

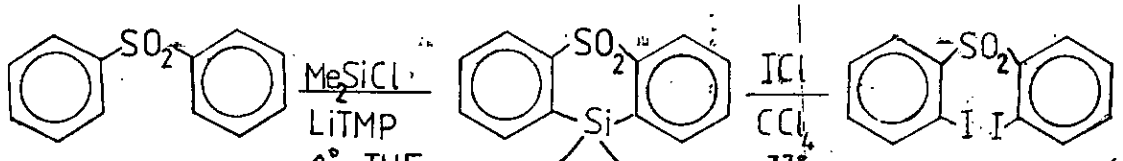
Halogenation could also be through an indirect means. For example the use of 1,2-dibromoethane furnishes the bromonium electrophile (Br^+) [80]





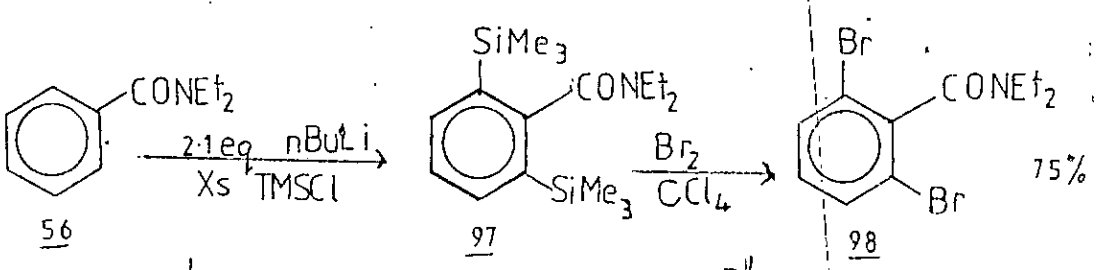
R = Et, iPr 92 93

Ipso-desilylation and halogenation seem to also provide a general method: [81]

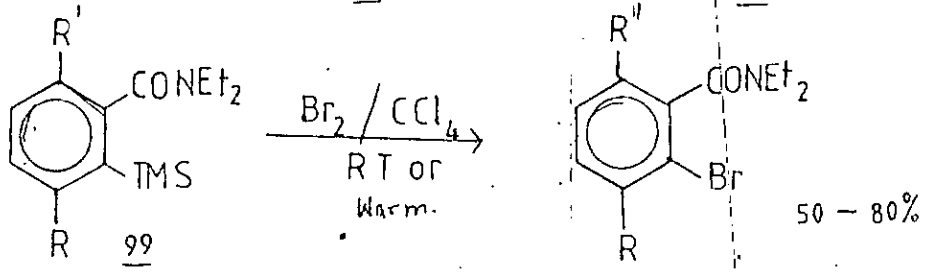


94 95 96

Dihalogenation can be obtained by replacement with excess halogen [82, 83]



56 97 98



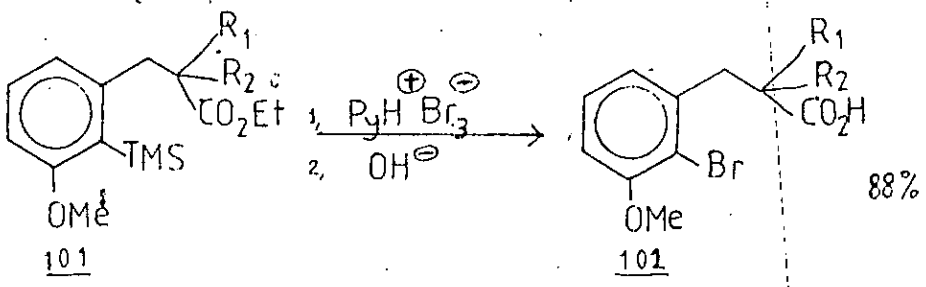
99 100

$R_1 = R_2 = H$

$R_1 = Me, R_2 = H$

$R_1 = Me, R_2 = Cl$

Similarly, Snieckus, Alo, et. al.[84] obtained bromoacids 102 through a successful ipsobromo desilylation.

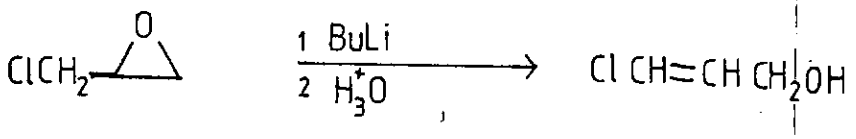


101 101

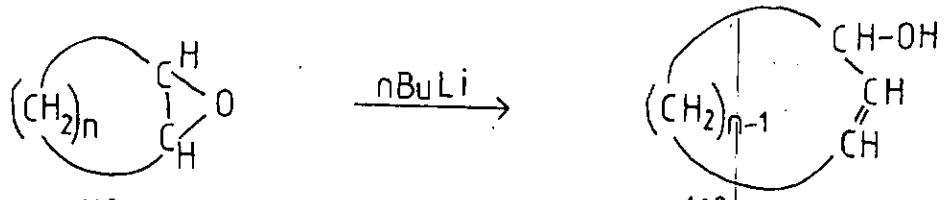
Cleavage of ethers by Organolithium Compounds

Ethersare attacked by organolithium compounds. Olefins result from such reaction with aliphatic ethers. This is usually prevented if the reaction takes place at low temperatur This is important as ethers serve as solvents used in metal

(b) The presence of electron withdrawing group incorporated in the epoxide. This promotes metalation e.g. in case of chloromethyl ethylene oxide [89]

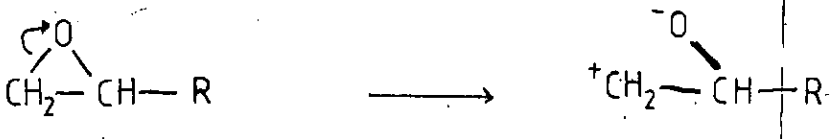


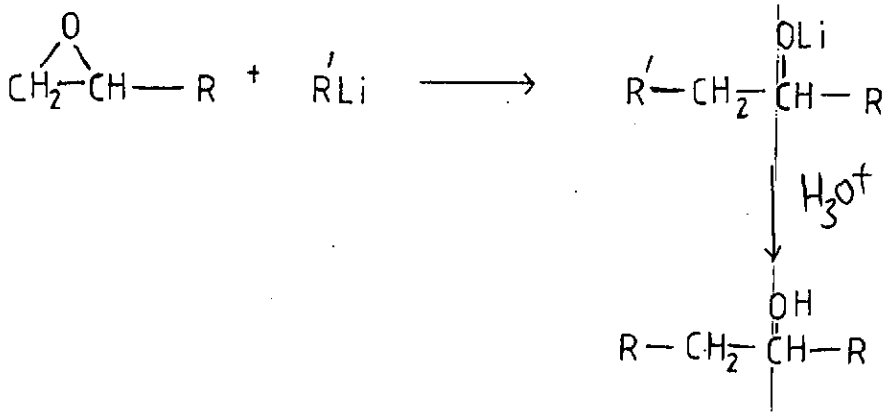
When the epoxide is fused to a large ring, allyl alcohols incorporated into the ring are obtained [9] even with cyclohexane oxide



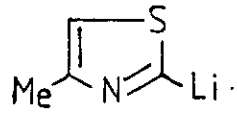
108 109

Normal reactions are however obtained when these factors are absent. The direction of addition of assymetrically substituted ethylene oxide is predictable because the organic group of the organolithium compound becomes attached to the least electron rich carbon of the epoxide ring.





Some illustrative examples includes, [61,(90,91,92,93)]



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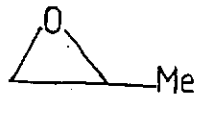
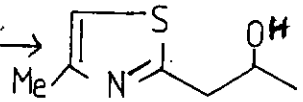
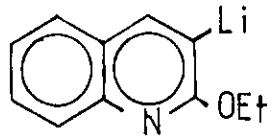




112

51%



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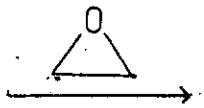

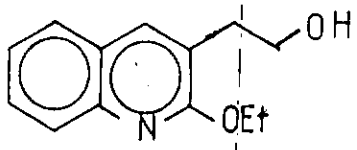

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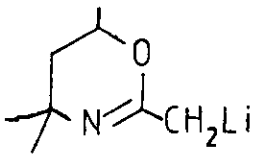

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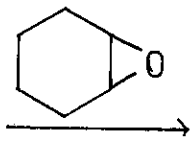
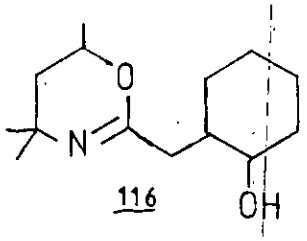
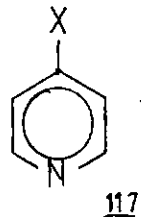




116



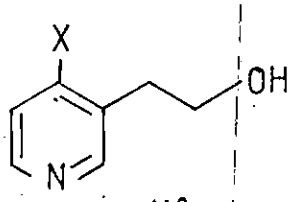
117

X=F, Cl

1, LDA

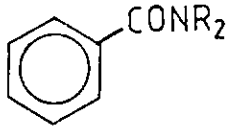
2, 

3, H_3O



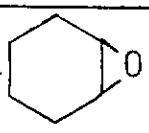
118

30%

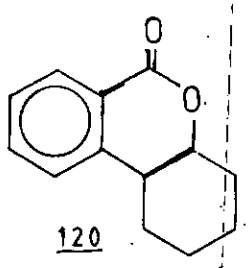


119

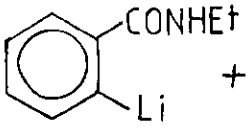
n BuLi

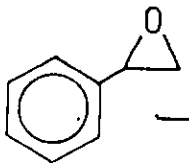


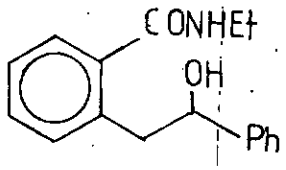
reflux



120



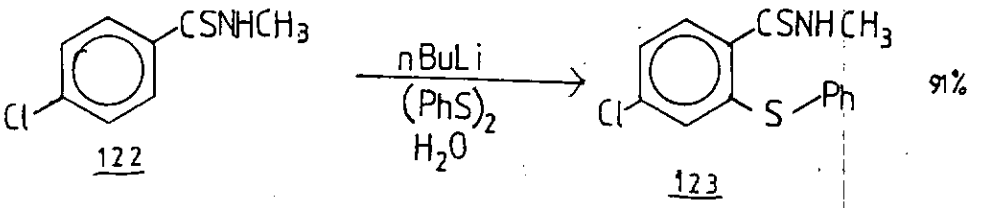




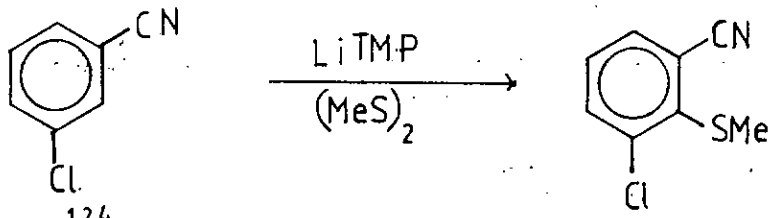
121

Disulphides as Electrophiles

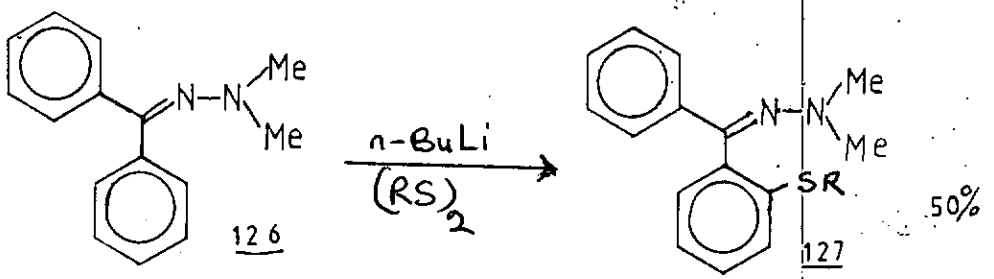
The reactions of disulphides (unlike most other sulphur functional groups) with organolithiums to form thio ethers are well known [1,62]. These reactions are accompanied by cleavage at the -S-S- bond.



122 123

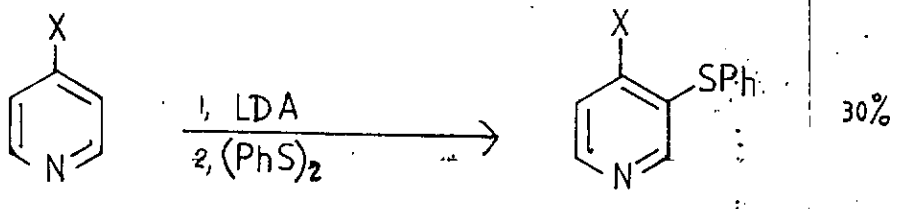


124 125



126 127

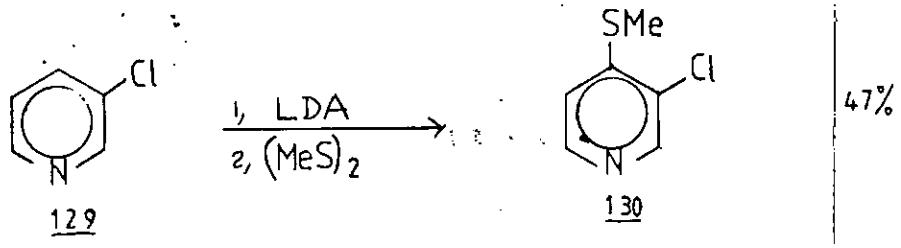
Marsais et al [92] used diphenyl disulphides on the lithio anion of 4-halogeno pyridines generated with LDA, to obtain the corresponding 3-phenylthioether.



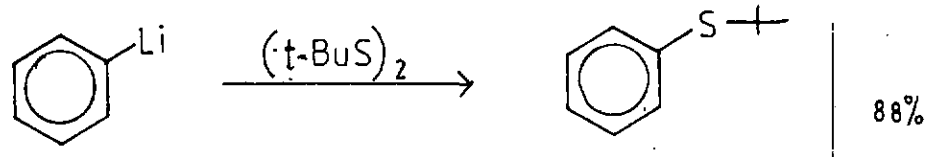
117 128

X = Cl , F.

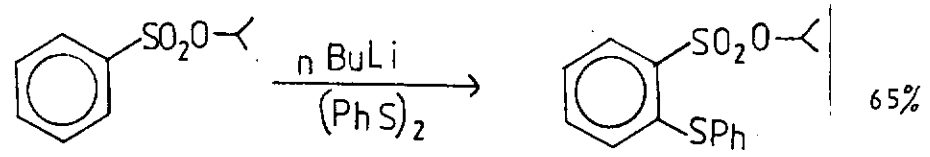
The same group also used dimethyldisulphide on 3-chloropyridines to obtain 3-chloro -4-methyl thiolpyridine in 47%.



129 130

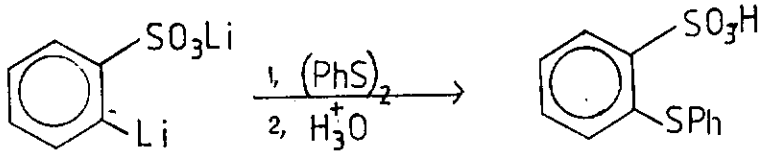


Disulphides was also used on lithiated phenyl sulphonates giving 2-phenylthioetherbenzenesulphonate [80]

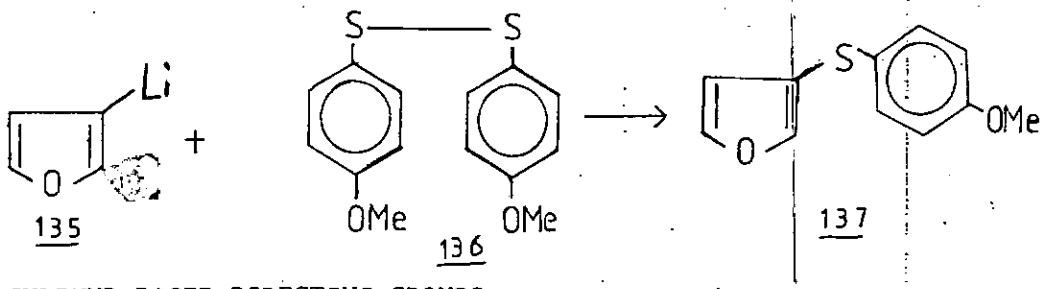


92b 133

Dilithio species of sulphonic acid also gave thioether with diphenyldisulphide [95]



134



135 136 137

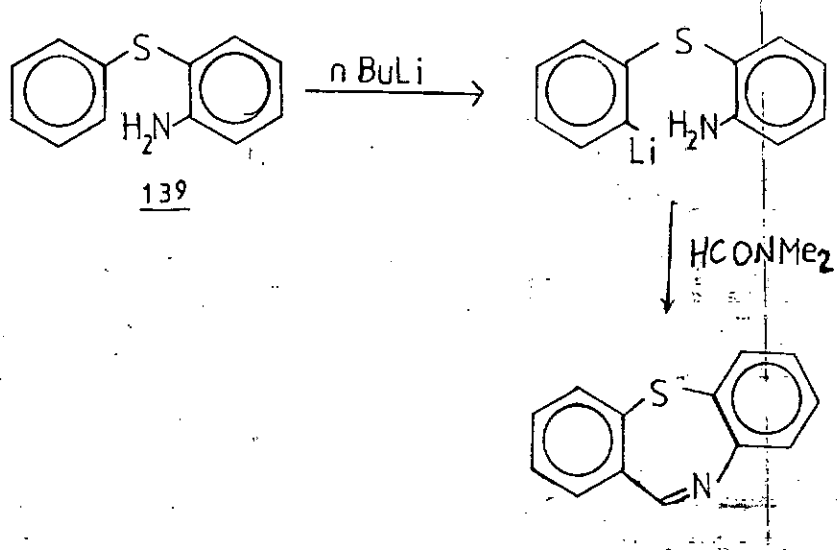
SULPHUR-BASED DIRECTING GROUPS

Sulphur-based directing groups are about the strongest directed metalation groups. Snieckus et. al,[58] have made a comparison between sulphones, Secondary carboxylamides, and tertiary carboxylamides.

The group[58] showed sulphones are a more powerful directed ortho metalation group than the tertiary carboxylamide. The sulphone was described as an excellent directed ortho-metalation group as a latent directiong group for the synthesis of meta disubstituted substituted aromatics.

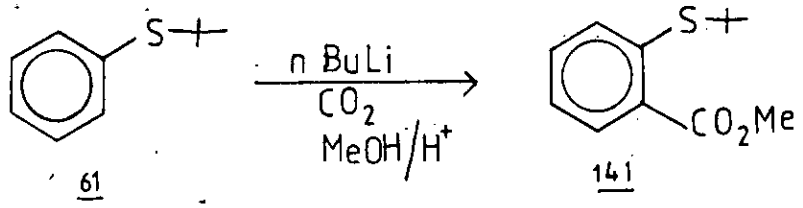
a. Sulphides as Directing Group

Narasimhan and Chandrachood[97] made use of lithiated sulphides to obtain dibenza(b,f)(1.4) oxazepine. In this case the sulphide group directs ortho:



139 140

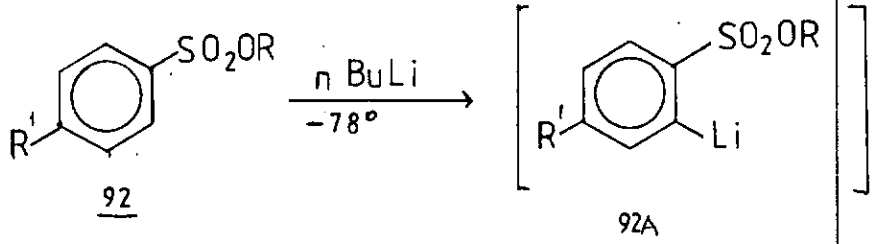
Sulphides were also lithiated by Babin et. al.[98] to obtain 95% ortho products in about 5 minutes.



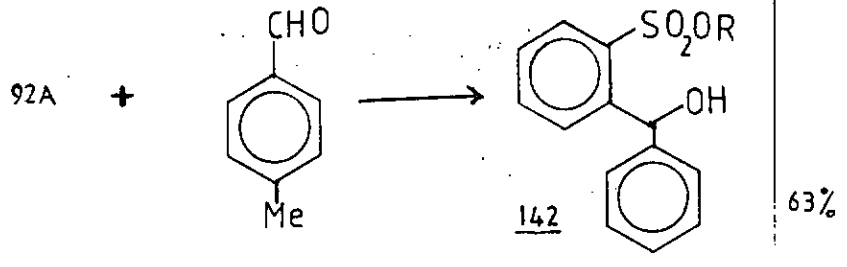
61 141

Sulphonic Esters as Directing Groups

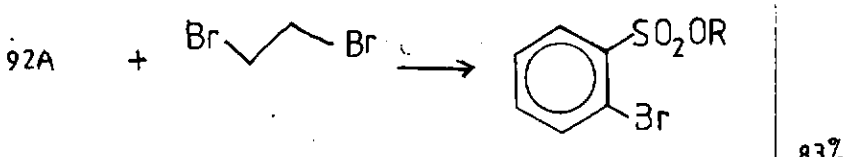
Metalation of alkylarene sulphonates have been known to be facile and the organolithium reagent can be trapped by a wide variety of electrophiles. Bonfiglio in 1986 [80] treated alkyl phenyl sulphonate with n-BuLi in THF without complexing agent followed by a range of electrophile giving various products.



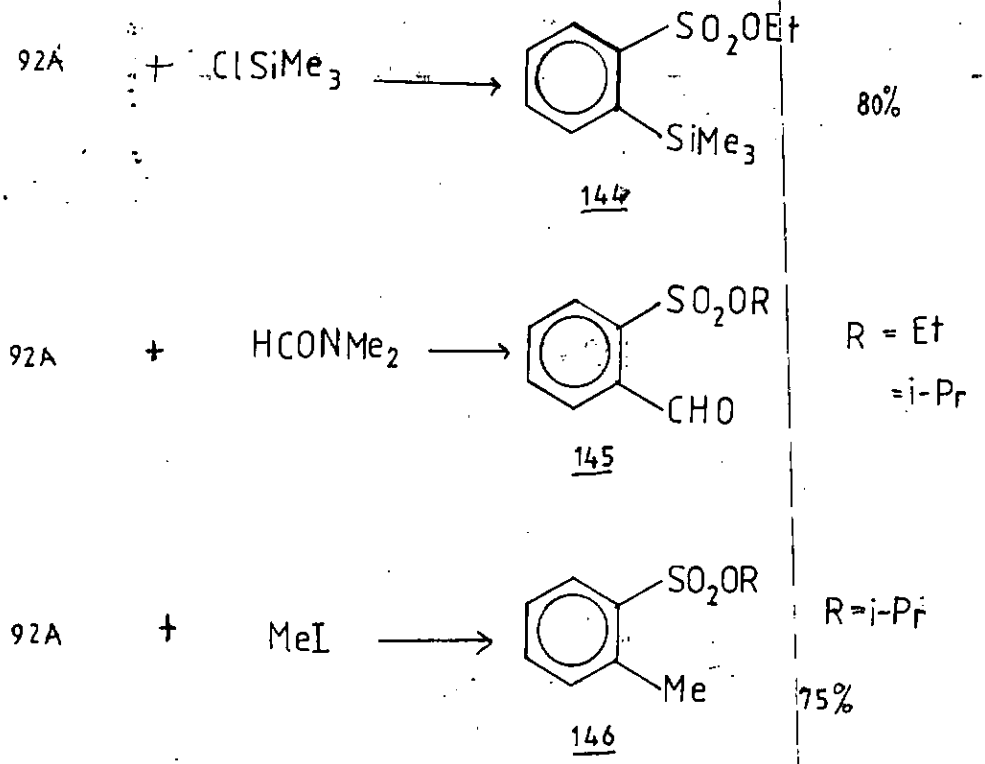
92 92A



142 63%



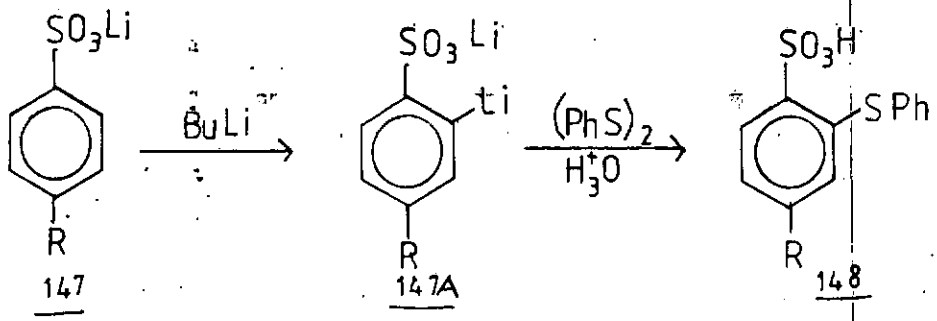
143 83%

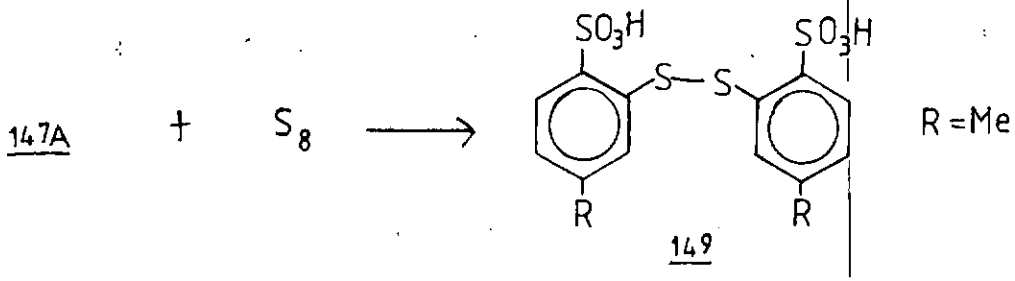


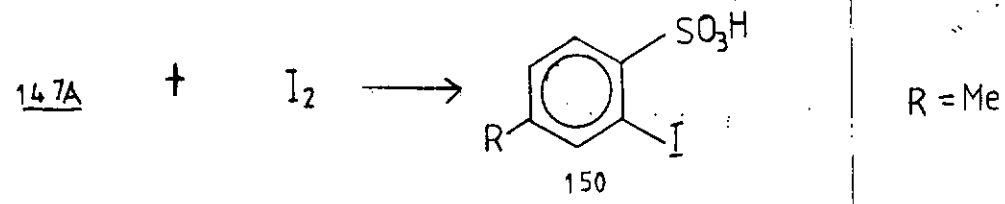
As indicated earlier disulphides gave 65% yield of the corresponding thioether.

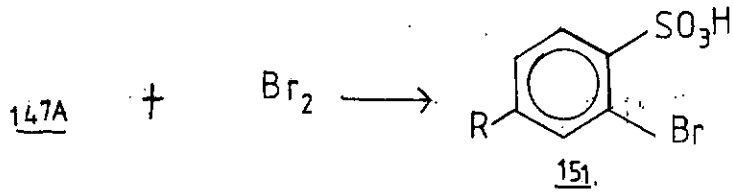
Arene Sulphonic Acid lithiation [95]

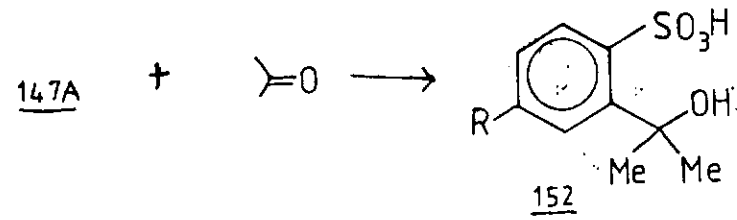
Lithium salts of arenesulphonic acids gave ortho lithiated products with n-BuLi in THF at 0° in high yields. This provides a method of ortho substitution of sulphonic acids, as normal electrophilic substitution leads to the meta-substituted products. Figuly and Martin obtained the dilithio species 147a which was coupled with various electrophiles namely: disulphides, elemental sulphur, Iodine, bromine, and acetone respectively.





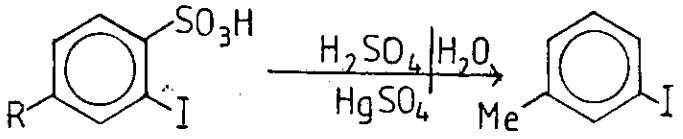




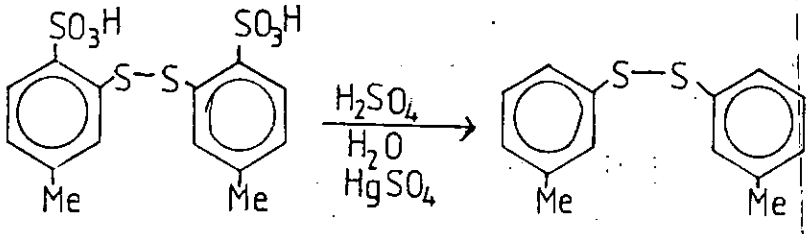


The advantage of this method is that the SO_3H group is easily removed and therefore affords unusual substituted benzene derivatives.

The problem with the method however is the purification of the product obtained without chemical modification of the product



65%

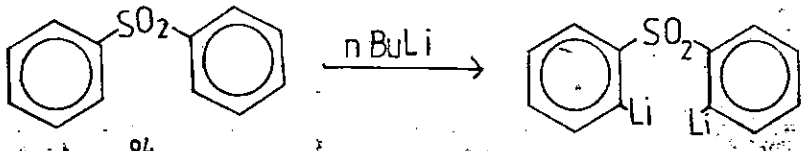


The special advantage of the sulphonic acid or sulphonic acid as directing group is the ready replacement of the group by hydrogen thus providing overall a directing group which can be removed after it performs it's directing function in a multi step synthesis of a substituted aromatic compound.

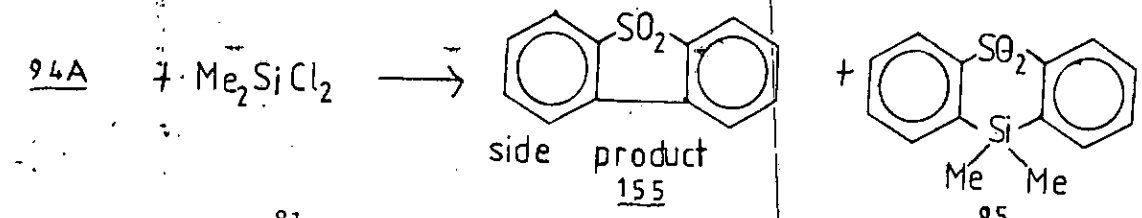
Arylsulphones as Directing Groups

Arene sulphones have been in use as powerful directed metalation group (DMG) for a long time. Several reactions involving them have been carried out in good yields.

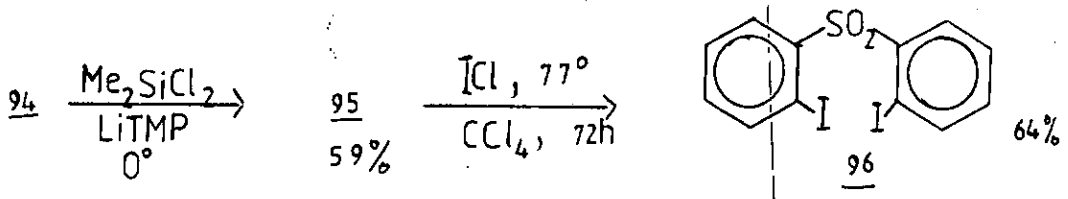
Oita and Gilman [99] used BuLi on diphenyl sulphones to obtain a dilithio species, which was reacted with dichloro methyl silane. A low yield of product was obtained as an intermediate intra molecular cyclisation side reaction occured.



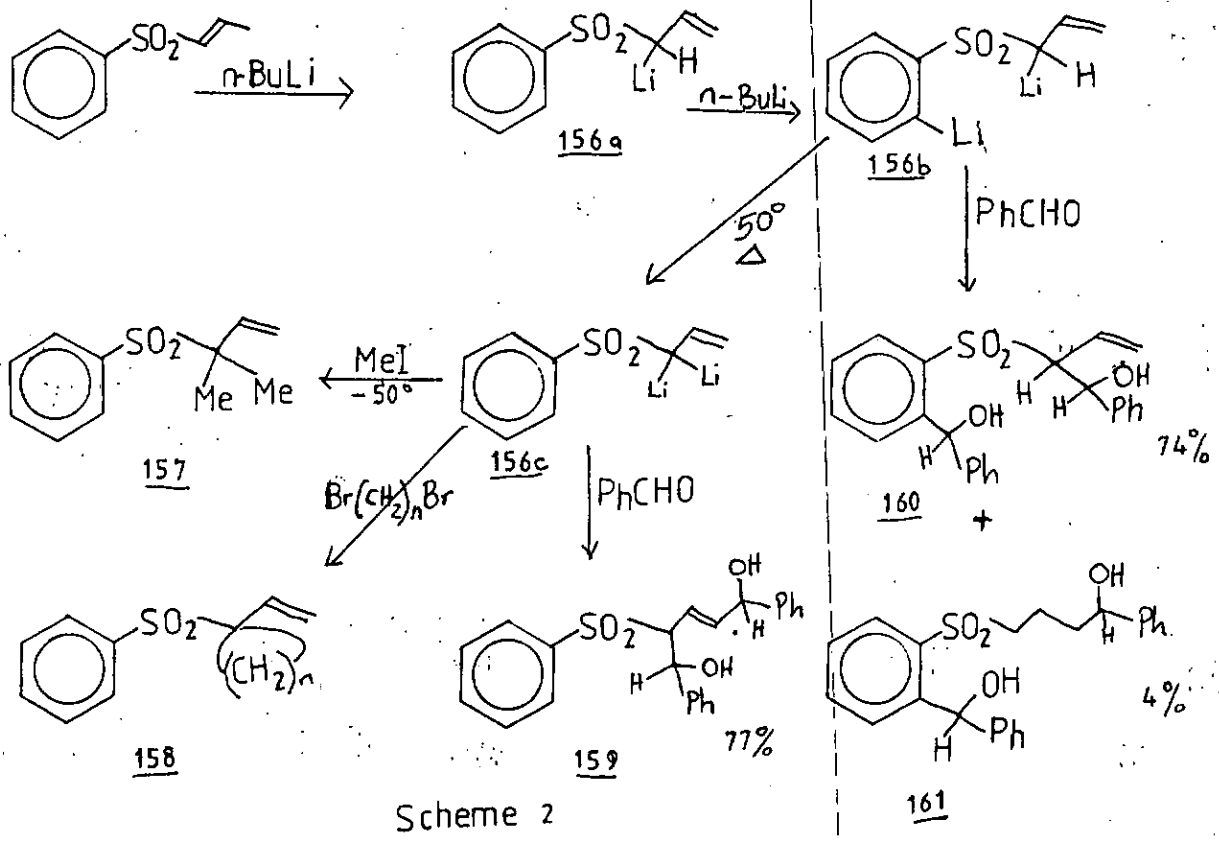
94 94A



Krizan and Martin[81] improved on this method by employing dichloro dimethyl silane as an internal trap that could react with the dilithio species as soon as formed.



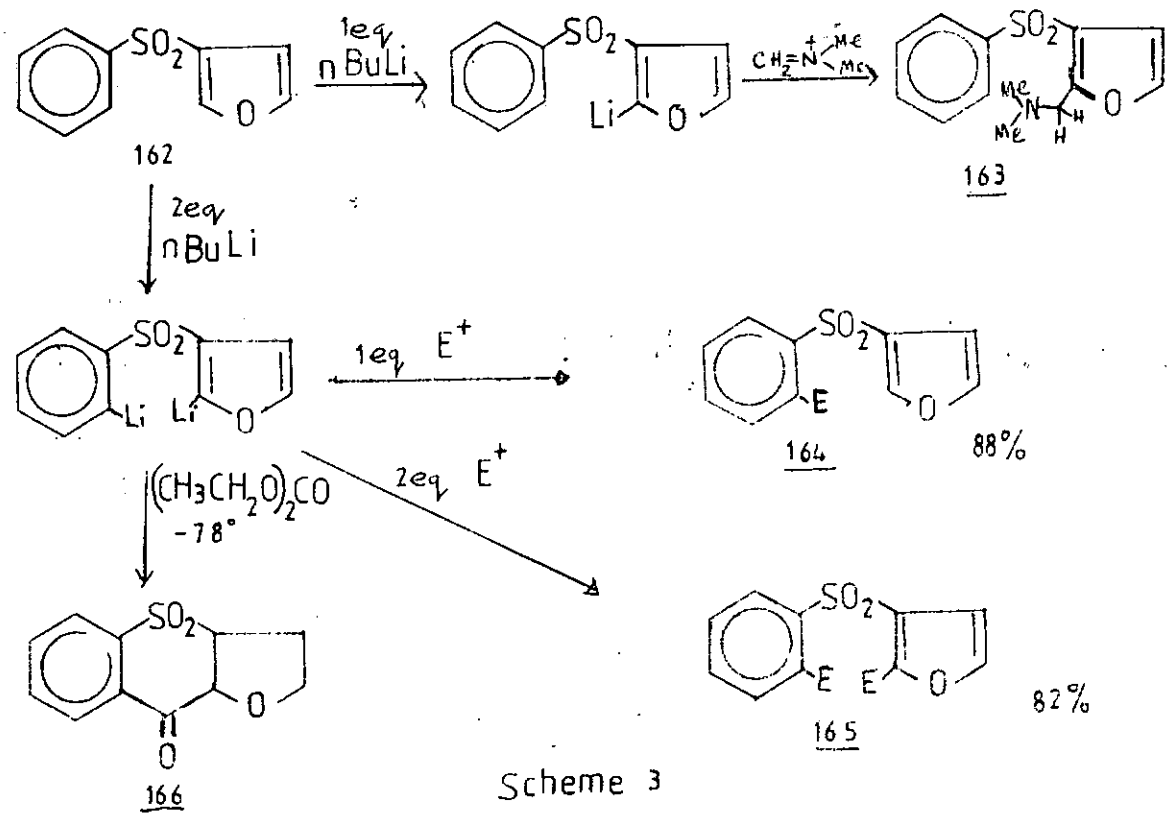
Using an arylalkyl sulphone instead, a dilithio species could also be formed. This type of dilithio species have been used in a variety of ways.[100]



Scheme 2

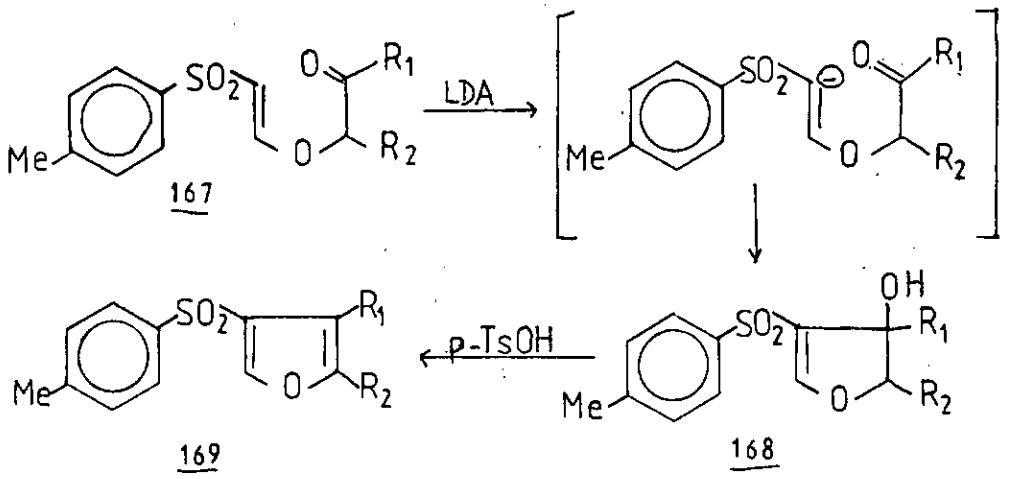
When one equivalent of n-Buli was used, the aliphatic position is lithiated and on addition of the second equivalent of n-BuLi there is a choice of dilithiating the alkyl portion or lithiation of the ortho position of the aryl ring. The authors found that there is an interconversion of 156b - 156c when the temperature of 156b is raised to about 50°. All the lithio species were converted to different coupled products.

Hartman and Halczenko [96] found that using one equivalent of n-BuLi on the phenylsulphone 162 gave metalation on the furan and when two equivalents of n-BuLi was used, dilithiation of both rings takes place. The dilithio species formed is stabilized by the two oxygen atoms of the sulphone. The lithio species could be coupled with one or two equivalents of electro philes



Scheme 3

On reaction of the lithio anion with one equivalent of electrophile, only the more reactive phenyl anion reacts. The sulphone 167 was lithiated with LDA. The anion formed underwent intra molecular trapping to form furans [101]

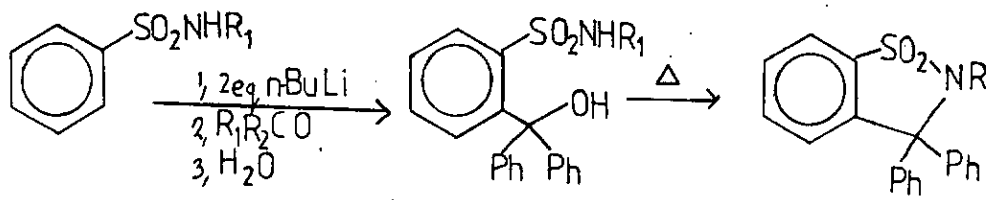


In intermolecular experiments; Snieckus et al [58] recently compared the ortho directing abilities of sulphones and other directed metalation groups like $CONiPr_2$, $OCONiPr_2$, OMOM, $NHCOBu^t$ and found that sulphones are the more powerful directors except in $NHCOBu^t$ group. Similar intra molecular competition trials, the sulphone group proved a better director than the $CONEt_2$, $OCONEt_2$, OMOM etc. Ortho metalation to the sulphone was obtained without the detection of the ortho lithiation to the amide group. However, full interpretation of the intramolecular experiments results was precluded by uncertainty of the other factors such as electronic and steric effects interplaying.

Aromatic sulphomamides as Directing Groups

Aromatic sulphonamides are one of the most powerful directing metalation group in aromatic systems [102]. They readily form the corresponding organolithiums without any complexing agent added to the lithiating agent which is usually n-BuLi at 0^{o}. Such lithio species are known to be stable between -10^{o} to 25^{o} [18] (the temperature range at which the lithio species are usually employed in synthesis).

Work on the lithiation of benzene sulphonamides was first encountered in 1968, when Watanabe et. al.[103] reported ortho lithiation of N-substituted benzene-sulphonamide (Primary sulphonamides do not undergo lithiation) with n-BuLi. These lithio species were coupled with electrophiles like benzophenone and acetophenone to obtain carbinol sulphonamides which were readily thermally cyclised to give sultams in good yields.



(1) $R_1 = CH_3$, $R_2 = R_3 = Ph$

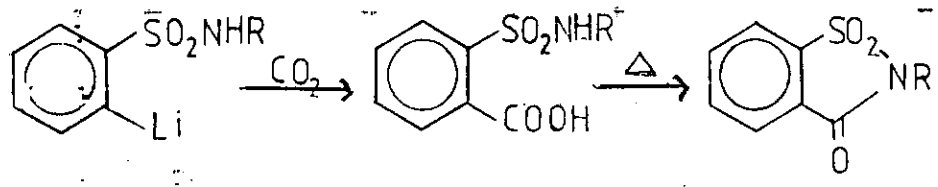
(2) $R_1 = R_2 = R_3 = Ph$

(3) $R_1 = R_2 - CH_3$, $R_3 = Ph$

(4) $R_1 = R_2 = Ph$ $R_3 = CH_3$

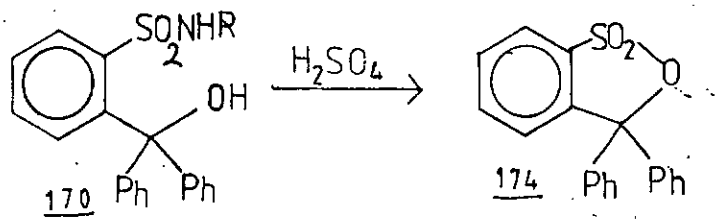
(5) $R_1 = CH_3$ $R_2 = H$, $R_3 = Ph$

When lithiated sulphonamides were reacted with carbon dioxide, the carboxylic acid derivative was obtained which gave benzo-thiazolone in 49% yield.



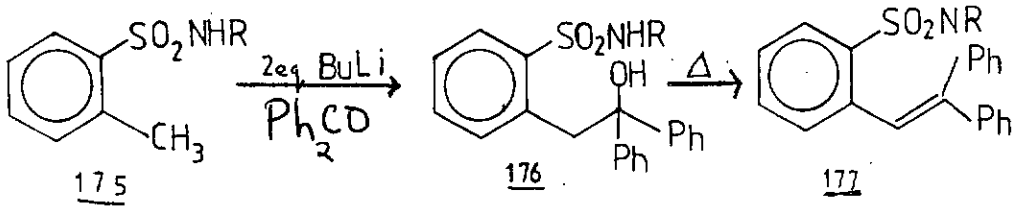
170 171

Attempted formation of sultones via the action of concentrated sulphuric acid on the carbinol gave the products in only 18% yield.



170 174

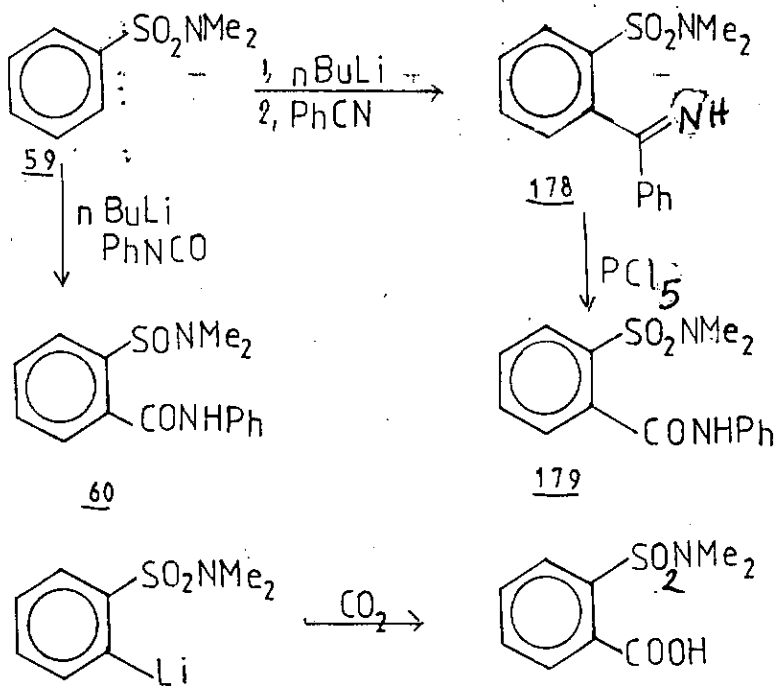
Watanabe and Hauser [104] in 1968 obtained benzylic anions of O-Methylbenzenes sulphonamides with n-BuLi which was coupled with benzophenone to give a carbinol 176



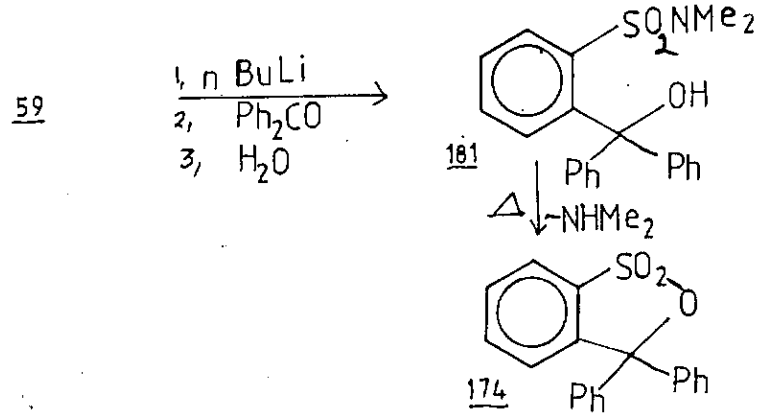
175 176 177

Attempts to cyclise the carbinol to a sultone with sulphuric acid as was previously done, led to a dehydration.

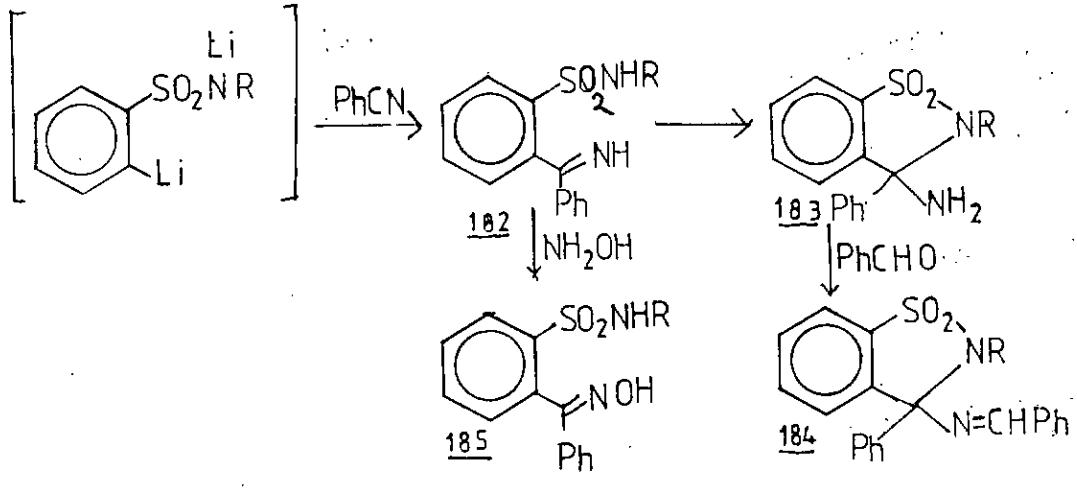
Tertiary sulphonamides were lithiated with n-Buli giving ortholithiated sulphonamides [105] which were coupled with benzophenone, benzonitrile, phenylisocyanate and carbon dioxide to give the varyingly substituted benzene sulphonamides.

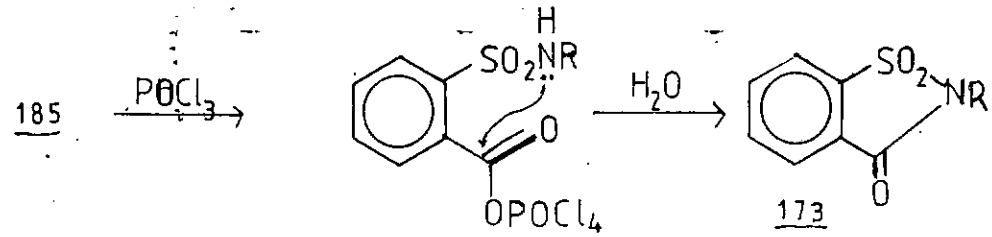


The benzophenone product was thermally cyclised to a sultone.

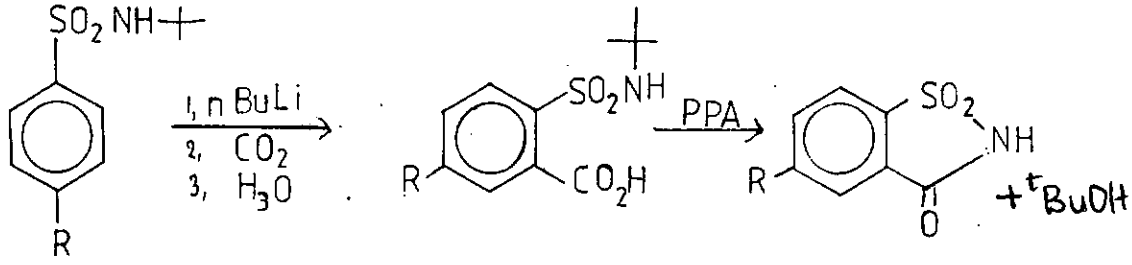


In 1969 Watanabe et. al [106] obtained sultams from coupling lithiated N-alkyl benzene sulphonamides with benzonitriles.

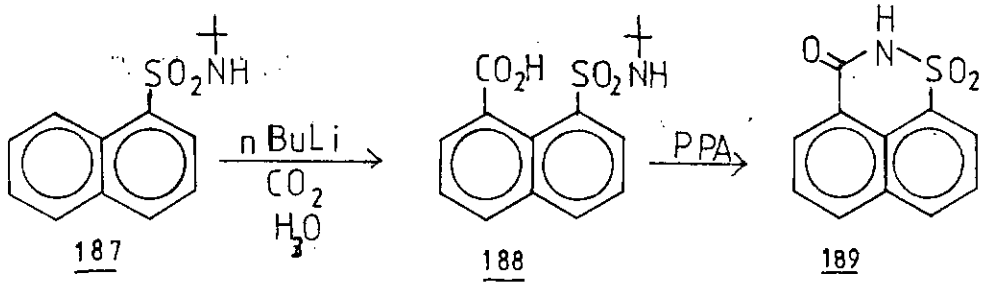




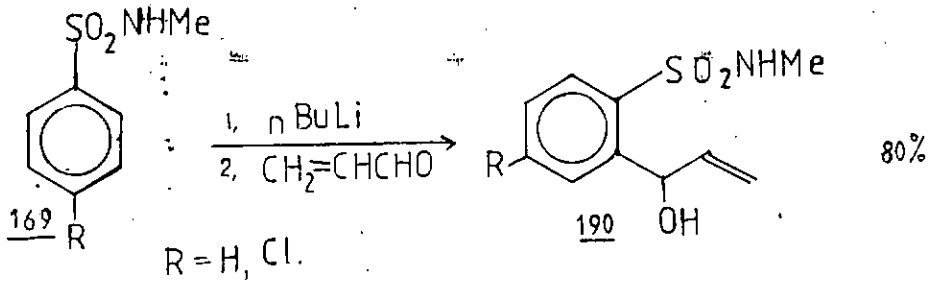
Lombardino in 1971 [107] used the lithiated benzene sulphonamide to obtain a 5-substituted - 2H -[1,2]benzoiso - thiazolin - 3 - one - 1,1 - dioxide by initially coupling the lithio species with carbon dioxide. The corresponding acid (obtained in good yield) was cyclised to the required compounds. Naphthalene sulphonamides have also been used as substrates.



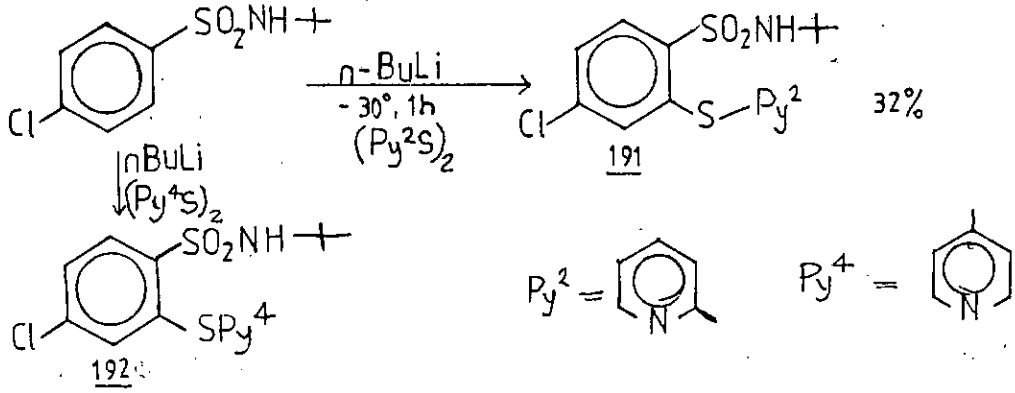
R = H, Me, Cl, OMe, F



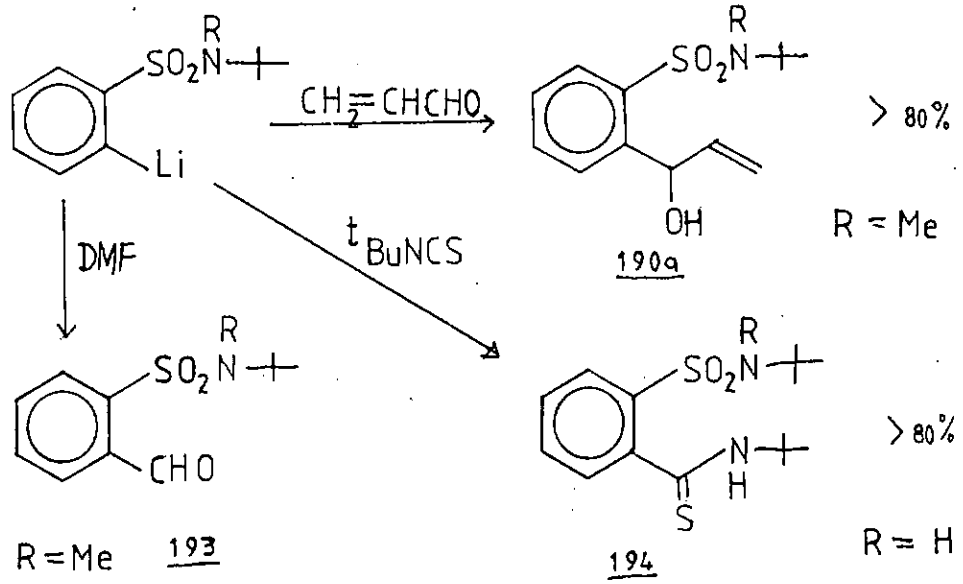
Successful metalation of p-Chloro-N-Methyl benzene sulphonamides with n-BuLi followed by coupling with propenal[1] as electrophile has been reported.



Using disulphides as electrophiles on the anion gave the corresponding thioethers albeit in poorer relative yields.

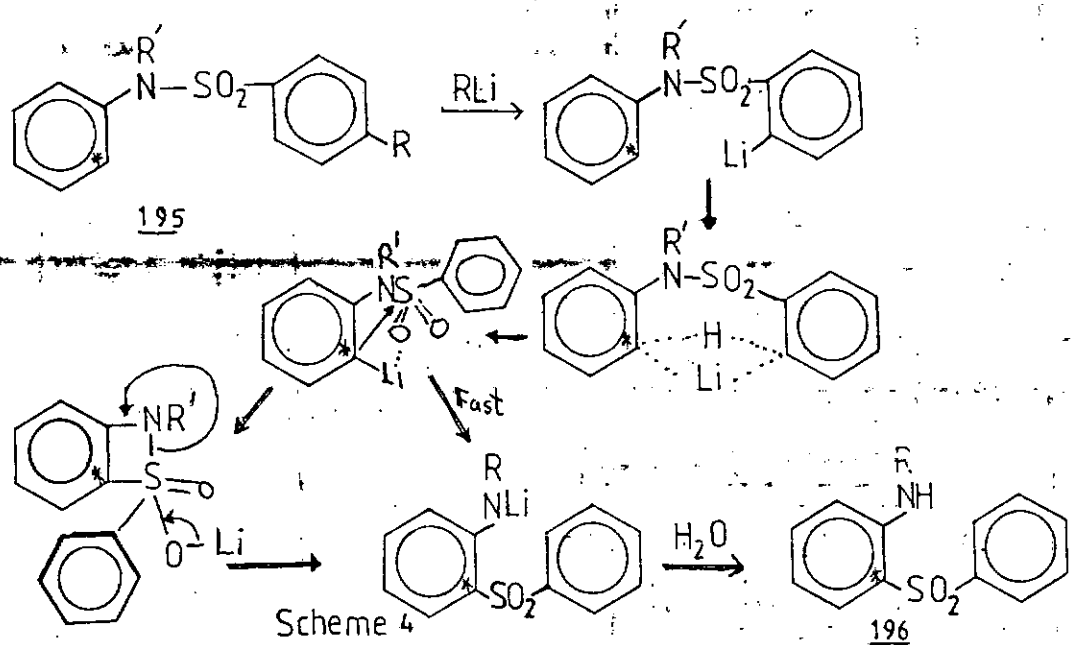


In another work of Rodriguez, Isothiocyanate and DMF were used as electrophiles.



The Sulphonamide group in N-aryl benzenesulphonamides will direct lithiations ortho to the sulphonamide[108], but there is a problem of migration of the lithio species in the ortho position. This type of migration reaction have been thoroughly reviewed by Hellwinket et. al.[108]. The use of this migration in synthesis was also explored.

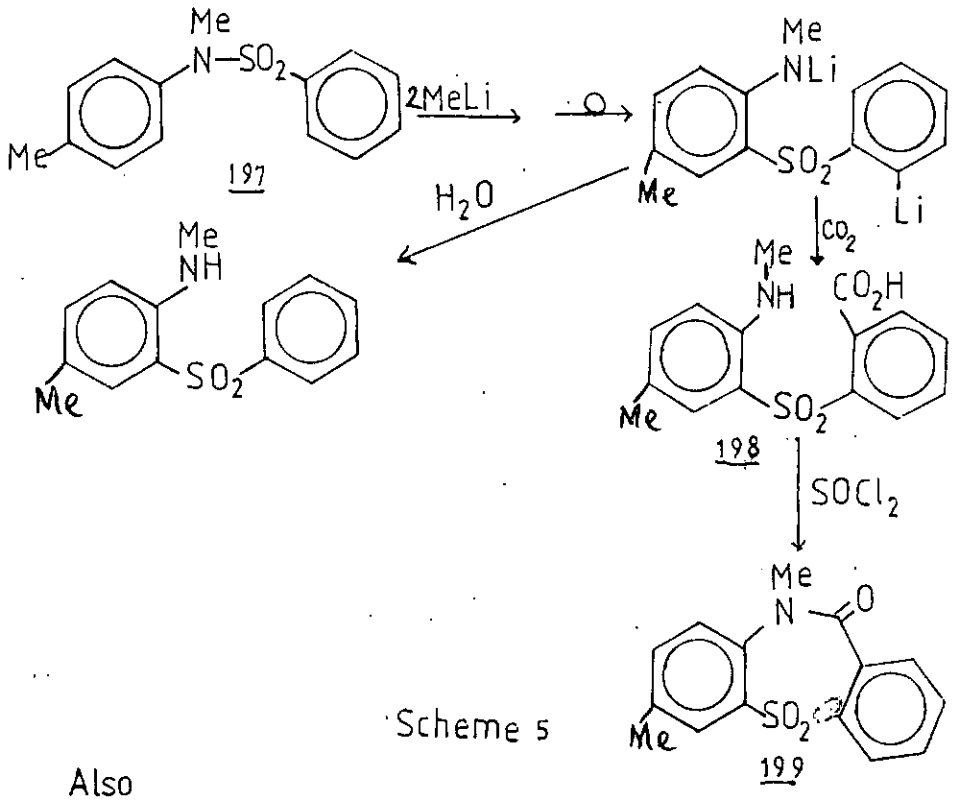
When N-aryl benzene sulphonamides e.g. 195 is lithiated with n-BuLi, the lithiation takes place first at the phenyl group attached to the sulphonyl function, followed by a trans-metalation or rearrangement sequence which leads to the O-amino diphenyl sulphone



Scheme 4

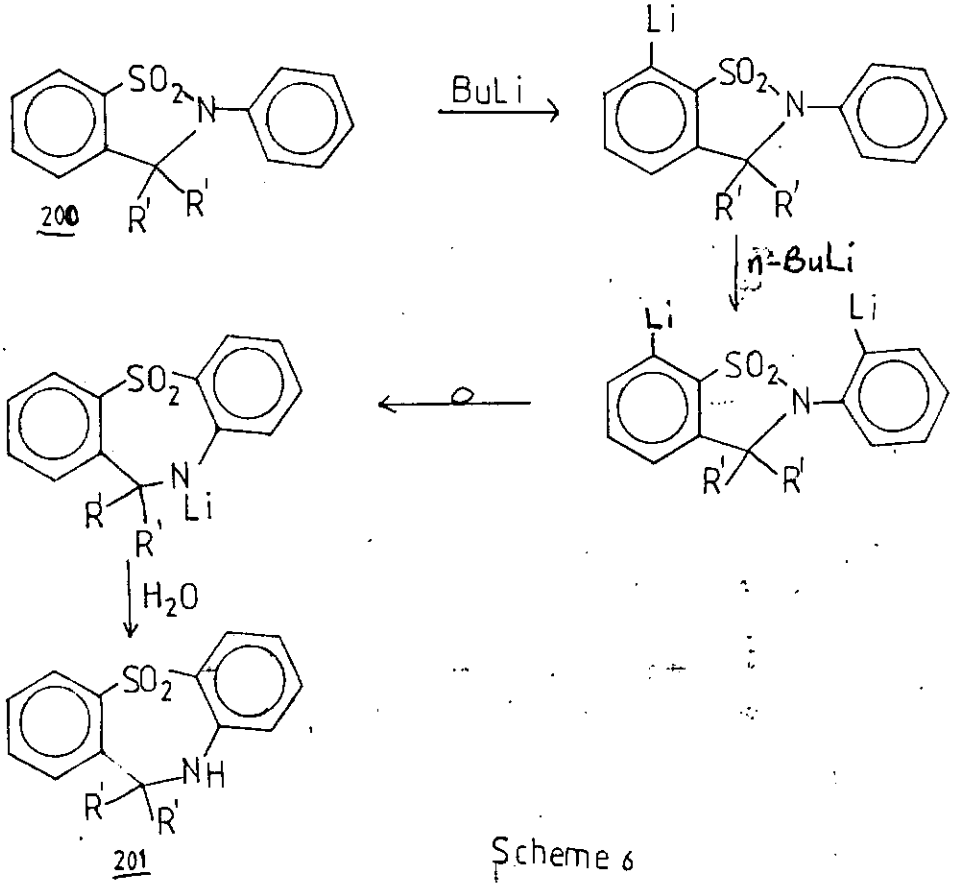
These reactions take place at -30° and 0° for N,N-diphenyl benzene sulphonamides and N,N-Methyl phenylbenzene sulphonamides respectively. This type of transmetalation and rearrangement has not been observed in the carboxyamide series. The rearrangement has been exploited in the synthesis of 7,10-

dimethyl dibenzo (b,f) (1,4) thiazepin-11-(10H) one-5,5-dioxide as shown below:



Scheme 5

Also

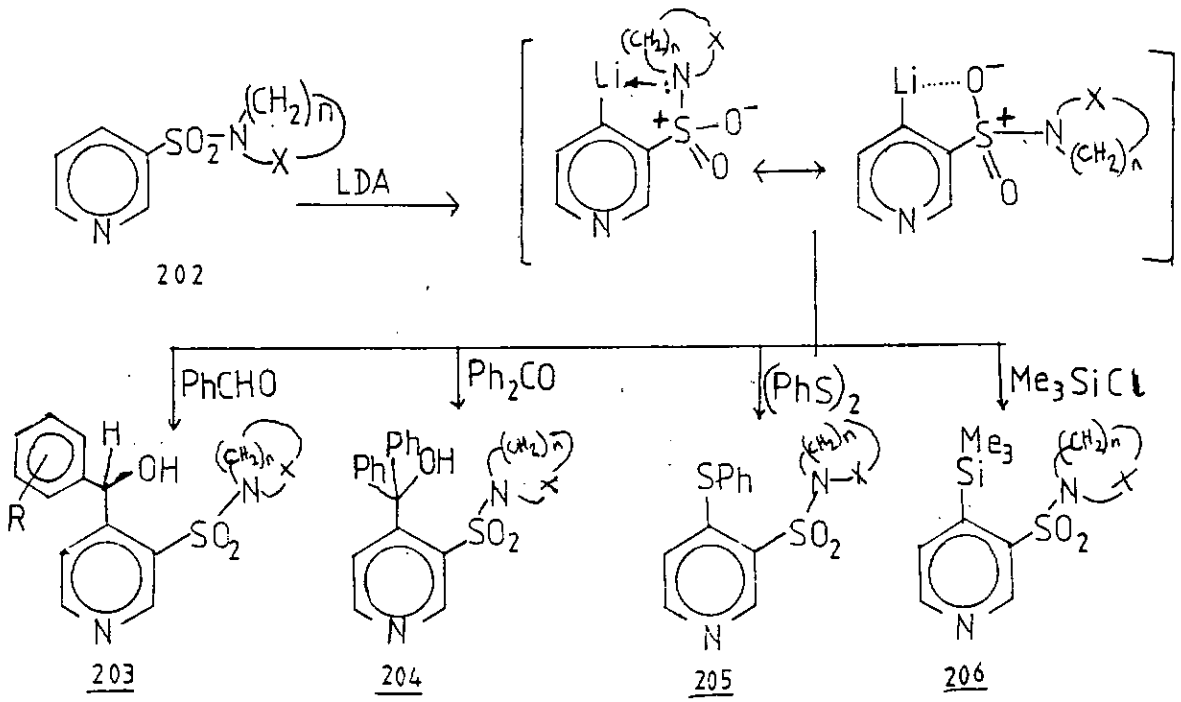


Scheme 6

Lithiation of Pyridine Sulphonamides

As far as we are aware, there are only two publications on the lithiation of pyridine sulphonamides to date.

In 1983, Quequiner et al [109] reported for the first time the use of sulphonamide group for directed lithiation in the pyridine series. Lithiated pyridine sulphonamides were obtained with LDA at -70°. The lithio species obtained were coupled with a series of electrophiles which included aldehydes chloro trimethylsilane disulphides, ketones etc, giving good yields of products. A variety of pyridine sulphonamides which included those of piperidine, pyrrolidine and morpholine were used.

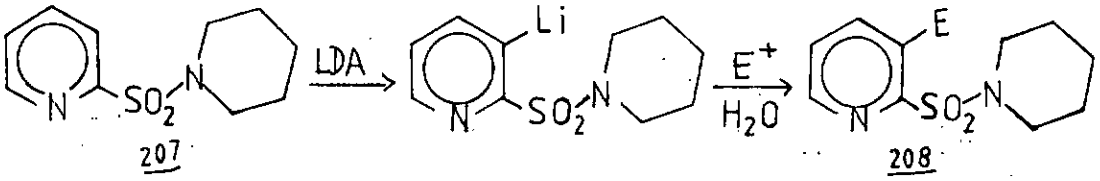


202 203 204 205 206

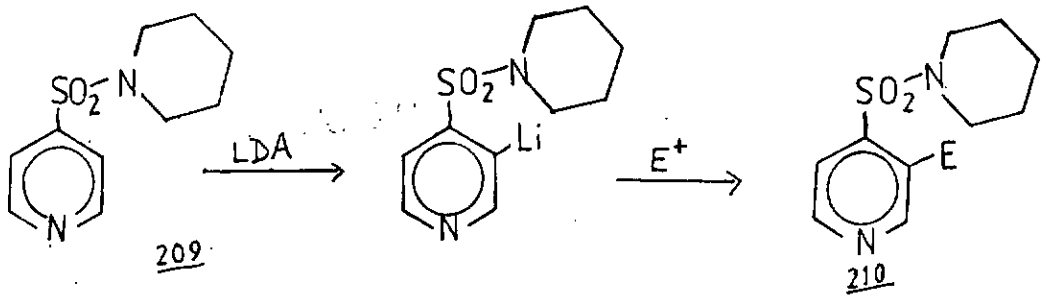
They observed exclusive lithiation at the 4-position contrary to the results earlier obtained for halogen as DMG [110] but consistent with results obtained for CONHR[111], NHCOBu^t, OMOM [128]

To prevent attack on the pyridine ring the lithiation was carried out at -70°, unlike in benzene series where successful lithiation was obtained at 0°.

The report was followed in 1987 [63] with the lithiation of pyridine-2- and 4-sulphonamides by the same group. Both isomers gave the 3-substituted products exclusively. The anion was smoothly coupled as earlier with various electrophiles.



207 208



209 210

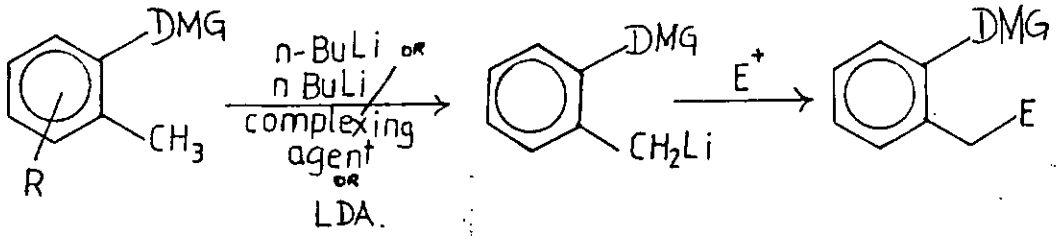
E = $-CHO$, $-CO_2H$, $-CH(OH)CH_3$.

Directed Metalation of Ortho Methylsubstituted arene

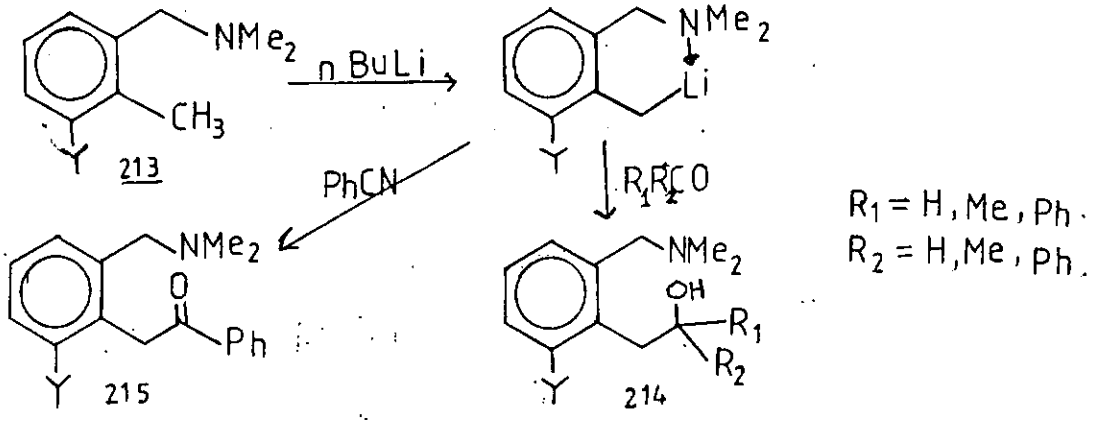
The use of Directed Metalation Groups (DMG) on aromatic rings in directing lithium ortho to their positions has been extensively discussed. DMGs have also been found to direct metalation to ortho methyl groups when present on the ring. n-Buthyl lithium or LDA are known to be appropriate bases to give the corresponding benzylic anions rather than ring metalated species [112] in substituted toluenes.

The methyl in the ortho position is preferencially metalated essentially because, the protons of the ortho methyl group are more acidic than the ring protons.[113] The strongly acidifying effect of certain DMGs are well known to promote facile deprotonation of ortho methyl groups. Furthermore, the protons are favourably disposed to based deprotonation because a stable five or six membered ring intermediate can be easily formed during coordination of the DMG with the metalating agent. However, the formation of the ring metalation anion always competes with benzylic anion formation. This competition may be eliminated by the use of a complexing agent[113] which ensures exclusive benzylic lithiation.

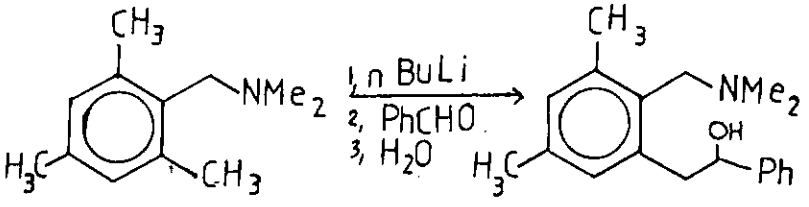
Several DMGs have been shown to have the ability to direct metalation to benzylic positions providing anions which can be trapped with various electrophiles. Usually this leads to an overall chain extension. Such directing groups include: $-CONR_2$, $-CONHR$, $-COOH$, CO_2R, -2-Oxazolinyl, $-SMe$, $-CH_2NR_2$, $-SO_2NR_2$, $-NR_2$, $-NHCOR$, NC, $-OMe$, $-OCONR_2$



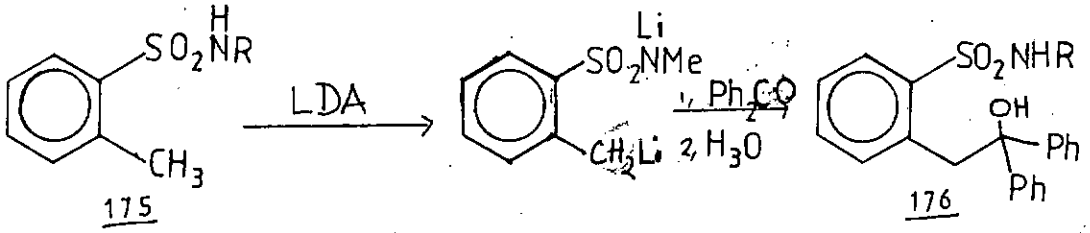
Example of each of the DMG is treated below. The first example of the generation of benzylic anions obtained by metalation was with tertiary benzylamine in 1964[114]. The anion was generated with n-butyllithium and coupled with a ketone, an aldehyde and a benzonitrile giving the respective corresponding products smoothly:



Metalation was also carried out on N,N-dimethyl -2,4,6-trimethylbenzyl amine in which only one of the methyl group was metalated.



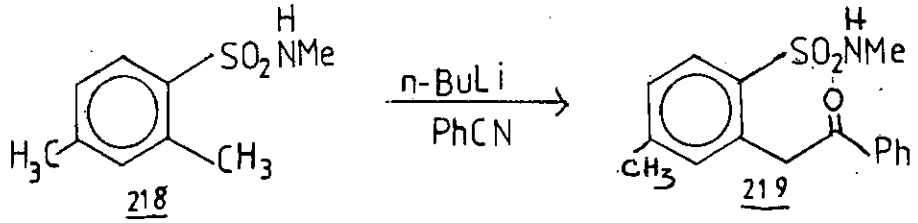
Watanabe et. al. (1968)[104] found that N-substituted -o-toluene sulphonamides undergo metalation with butyllithium at the methyl group (as well as N-metalation) giving benzylic anions. This is evidenced by coupling it with benzophenone to give a carbinol sulphonamide 176.



175 176

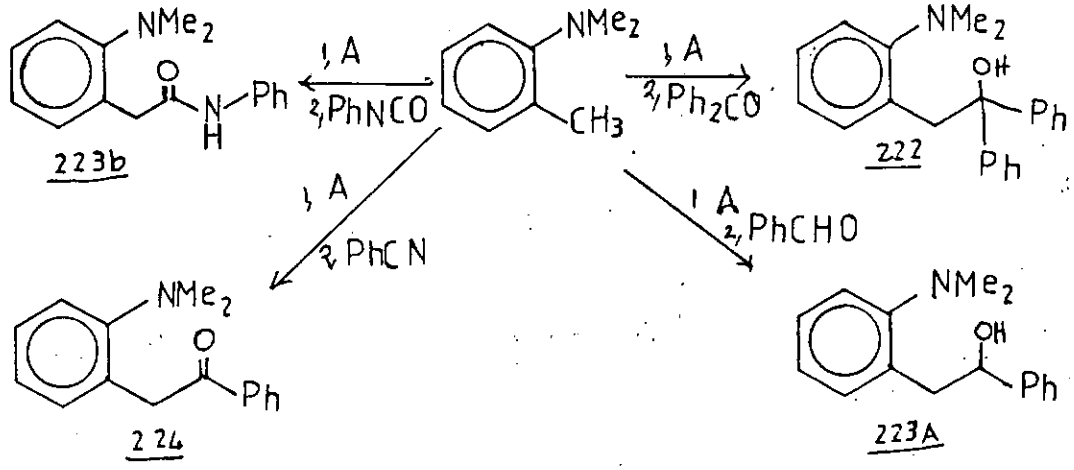
R = Me, Ph.

Watanabe et al [106] further coupled the dilithiospecies of the sulphonamide 218 with benzonitrile giving a ketone product.



218 219

Metalation of N,N-dimethyl-O-toluidine [113] with n-BuLi/ TMEDA selectively form benzylic anion from the ortho-methyl group. The anions obtained were coupled with benzophenone, benzaldehyde, phenylisocyanate and benzonitrile forming a carbinol 222, carbinol 223a, amine-amide 223b, keto-amine 224 after hydrolysis respectively.

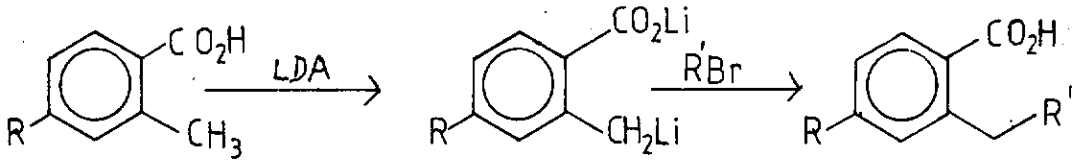


223b 222 224 223A

A = n-BuLi / TMEDA

The metalation of the N,N-dimethyltoluidine with n-BuLi alone gave a competition between ring metalation and ortho methyl lithiation. This was eliminated by using n-BuLi/TMEDA.

P.L Cregen[115] in 1970, metalated O-toluic acids and dimethylbenzoic acids without modification of the acid functionality with LDA, obtaining only ortho methyl group lithiation. The dilithio species obtained were successfully coupled with 1-bromobutane and 1-bromo-4-methylpentane with yields of 73% and 65% respectively.

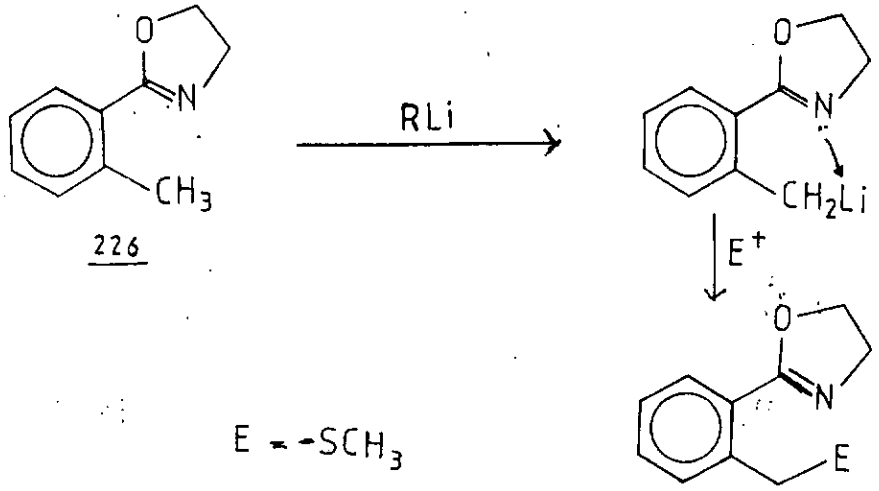


R = H, Me

R' = $-CH_2(CH_2)_2CH_3$

= $-CH_2(CH_2)_2CH(CH_3)CH_3$

In 1975, Gschwend and Hamdan[116] utilized the 2-Oxazolinyl group in directing lithiation to the ortho-methyl group leading to generation of benzylic anions. The anions were coupled with the appropriate electrophile to give the desired products.



226

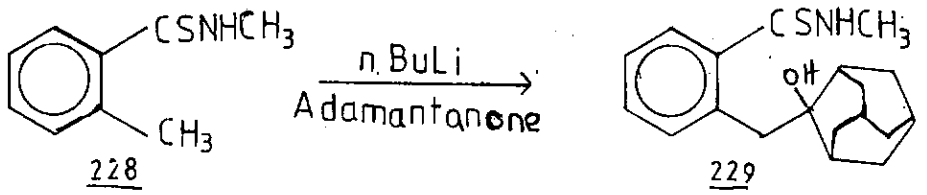
E = $-SCH_3$

= $-CH_2CH{=}CH_2$

227

The advantage of the oxazoline group is it's ready transformation into a ketone via alkylation and addition of organometallic reagent[117], or to aldehyde by reduction[118, 119] and into ether or carboxylic acid by solvolysis[120].

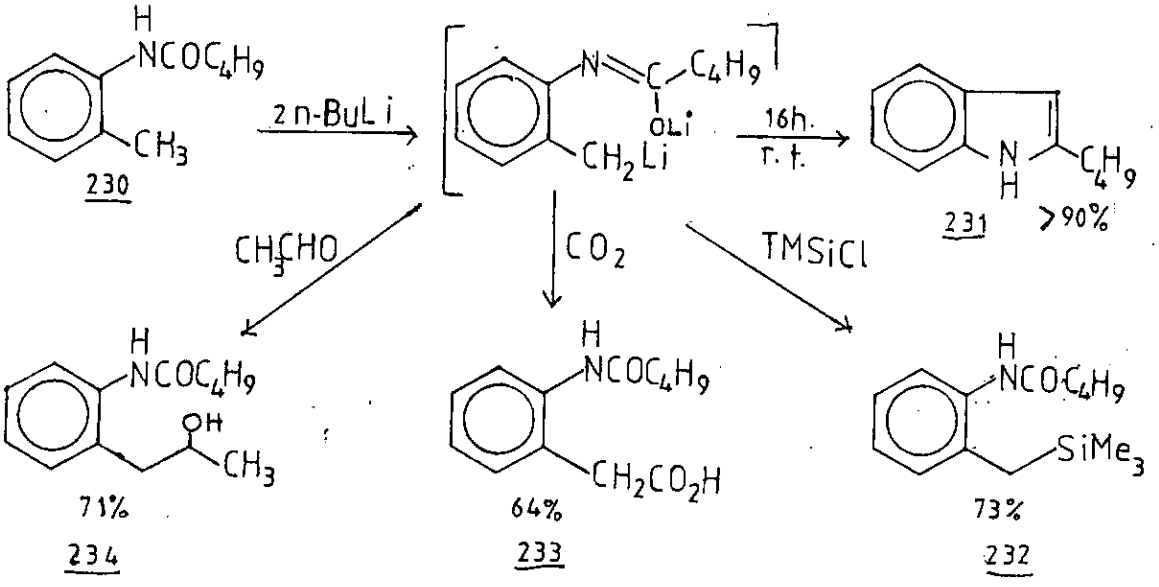
Secondary thioamide has been used as a directed Metalation Group (DMG) by Fitz and Gschwend[121] in 1976, for lithiation of the orthomethyl group in 2-methylbenzenethioamide. Adamantanone reacted with the anion to give 229 in 89%.



228 229

Acetylated amines[122] function as Directed Metalation Group in metalation of 2-methyl acetanilides 228. The benzylic anions (generated with two equivalent of n-BuLi) were coupled with chloromethylsilane, CO_2 and acetaldehyde giving the product in 73%, 64% and 71% respectively.

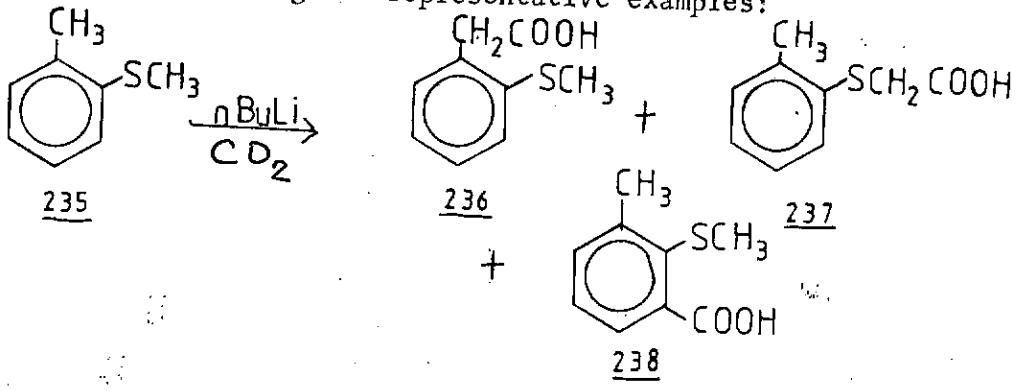
When the anion generated was left at room temperature for 16h the dilithiospecies cyclised to a 2-substituted indole.



230 231 234 233 232

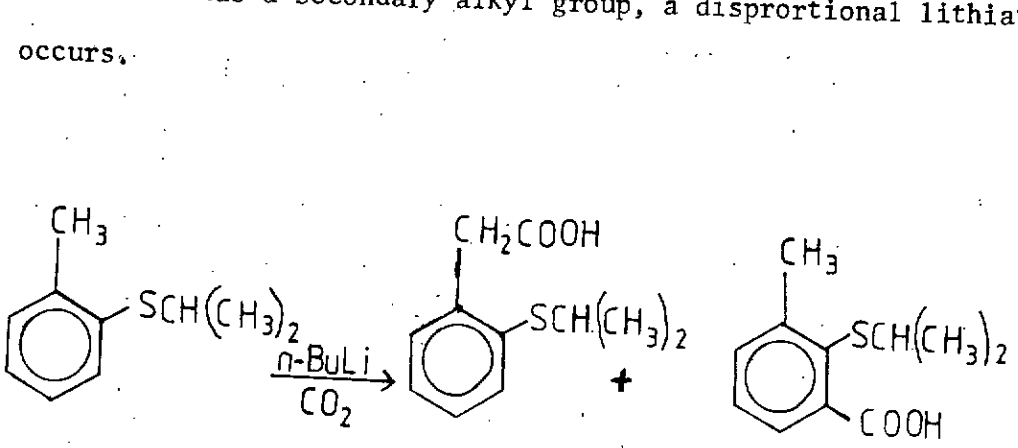
Thioethers have demonstrated ortho directing capability in lithiation of ortho-methyl groups using n-BuLi alone as lithiating agent, the ring ortho proton, the ortho-methyl proton and also the methyl protons of the ether were deprotonated. The use of n-BuLi-TMEDA however favoured ring metalation over the ortho methyl group.

The following are representative examples:



235 236 237 238

With n-BuLi/TMEDA 238 was obtained in > 95%. When the thio ether has a secondary alkyl group, a disprortional lithiation occurs.

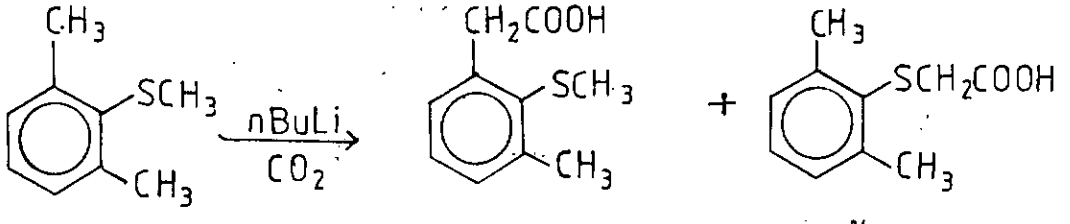


57% 43%

With nBuLi/TMEDA. 5% 95%

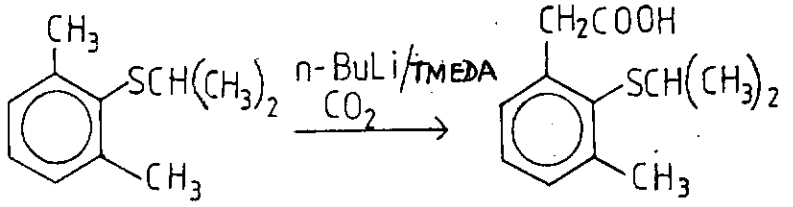
239 240 241

When there are ortho dimethyl groups to the thioether only one of the methyl groups is metalated as well as the methyl group on the thioether[123].



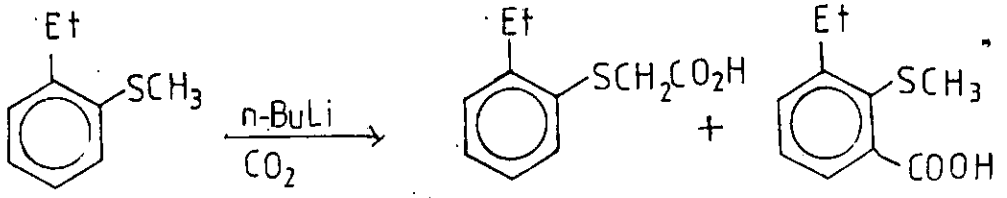
with n BuLi/TMEDA	70%	30%
	4%	96%
242	243	244

With the same ortho dimethyl substrate, but the ether having a secondary alkyl group, only one product was obtained on treatment with n-BuLi/TMEDA.



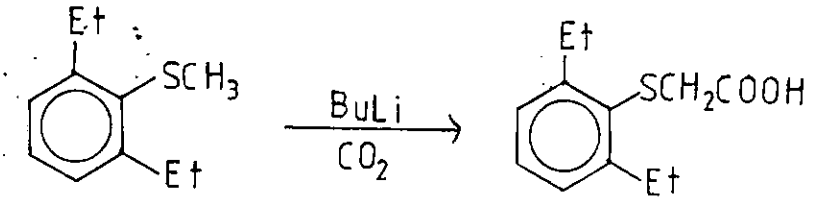
245 246 T = TMEDA

Ethyl groups ortho to the thioether functionality are not metalated as the example below shows: compound 248 is the main product even with n-BuLi/TMEDA, only traces of 249 was obtained.



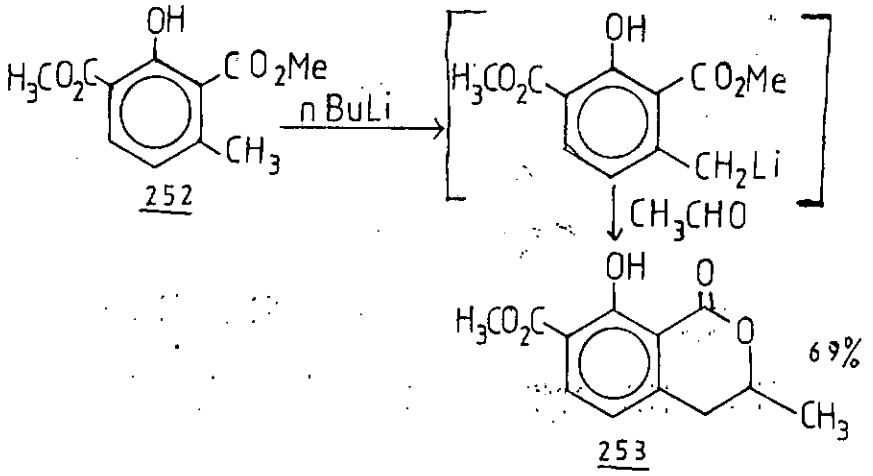
247 248 249

With two ortho diethyl groups, then exclusive metalation of the thioether's methyl group was observed.



250 251

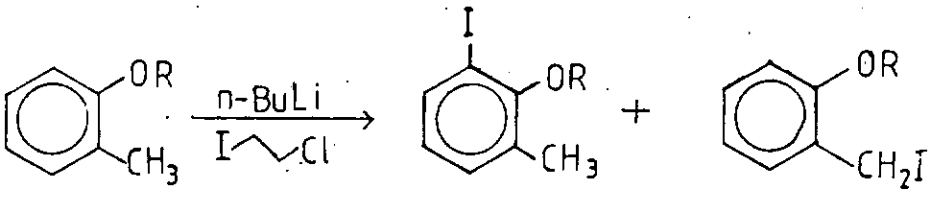
In 1981, Kraus[124] used carboxylic esters as directed metalation groups in the metalation of the ortho methyl groups of substituted toluic acid ester.



252 253

The heterocycle 253 was hitherto obtained in the literature in 20% yield.

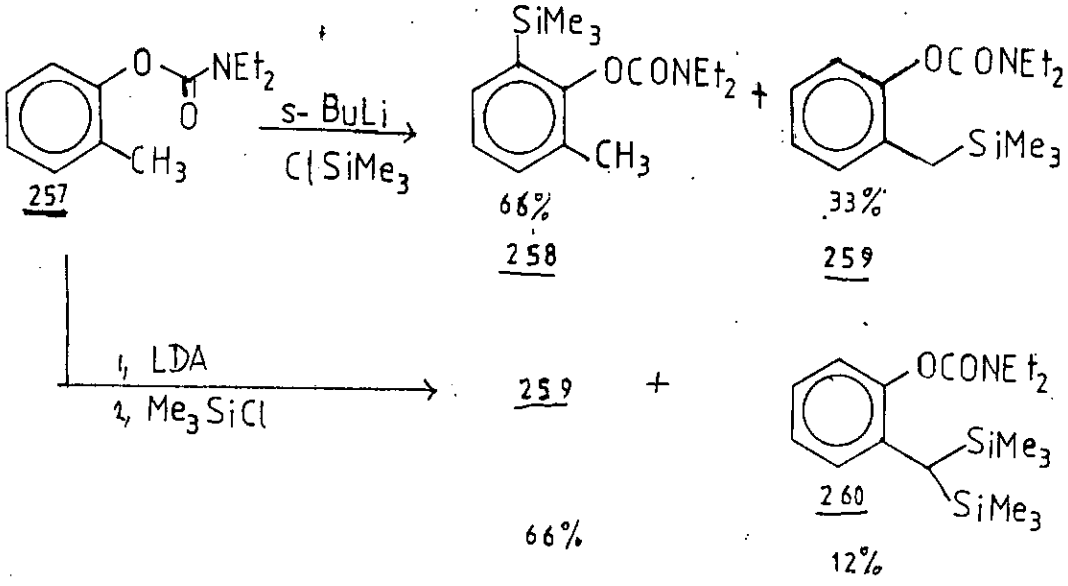
Ronald and Winkle[125] in 1982 explored the use of ethers as a DMG in benzylic anion generation. Using methoxyl and methoxymethoxyl substituents, it was observed that benzylic anions are not obtainable with the methoxymethoxyl groups but ring metalation occurs predominantly in >99%. The methoxyl group however gave 58% benzylic lithiation and 42% ring metalation.



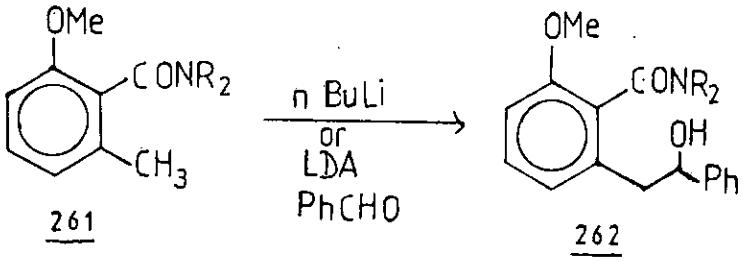
254 255 256

R = OMOM	99%	nil
= OME	42%	58%
	254	255	256.

Carbamates serves as excellent DMGs in metalation of ortho methyl groups. Sibi and Snieckus[126] in 1983, used s-BuLi in the metalation of carbamate. On quenching with chloromethyl silane, it gave a ring metalation: benzylic anion product ratio of 2:1. The use of LDA gave a better selectivity in favour of the formation of benzylic anion.

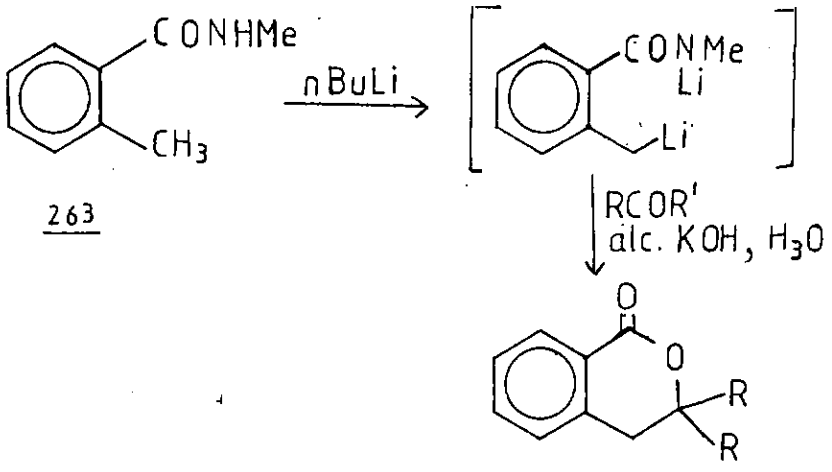


Snieckus et al[18] in 1984 illustrated the use of tertiary benzamide as DMG in lithiation of ortho methyl groups. The metalation was achieved with both LDA and n-BuLi.



R = Me; Et.

Secondary amides also serve just as the tertiary amide with the example of N-methyl-o-toluamide.

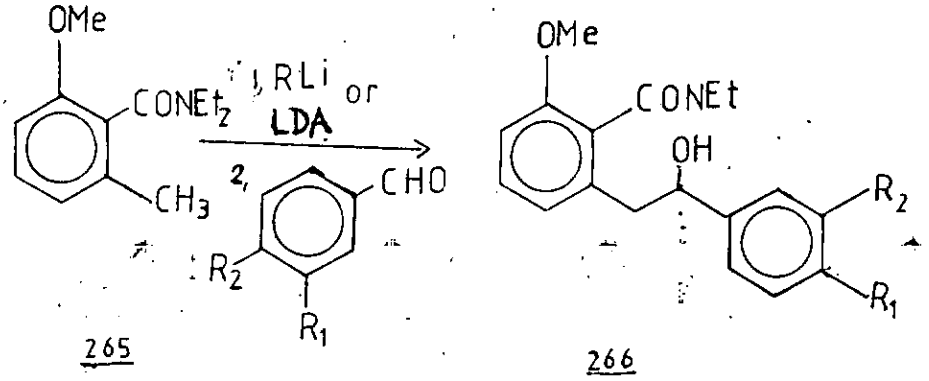


263 264

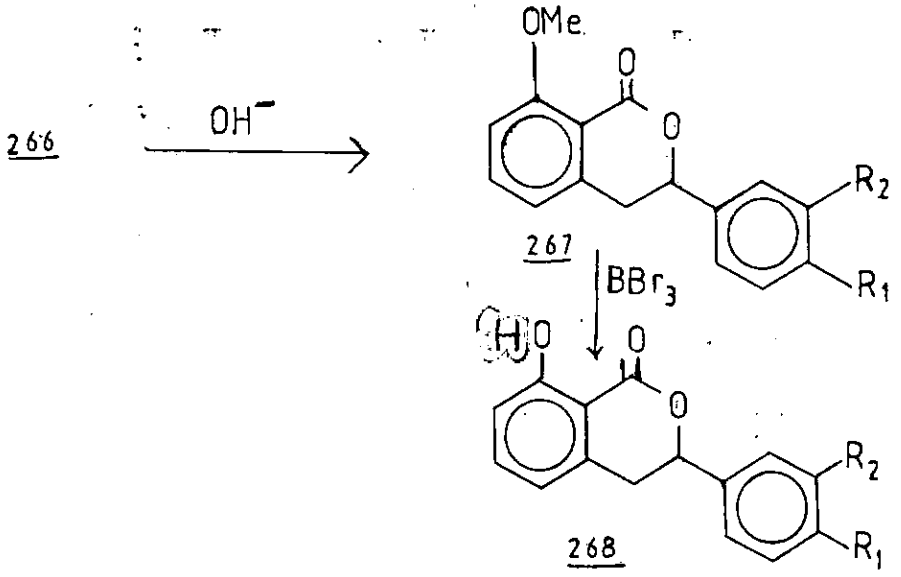
All these DMGs have directed metalation to ortho methyl group to provide synthetic strategy for the elongation of the side chain via substituted o-tolyl anions.

Such processes have been demonstrated for a number of directed metalation groups but their exploitation for heterocyclic synthesis has not been quite explored.

Snieckus et al[18] for example, utilized the strategy for construction of the isocoumarin and hydrangenol:



265 266



Hydrangenol

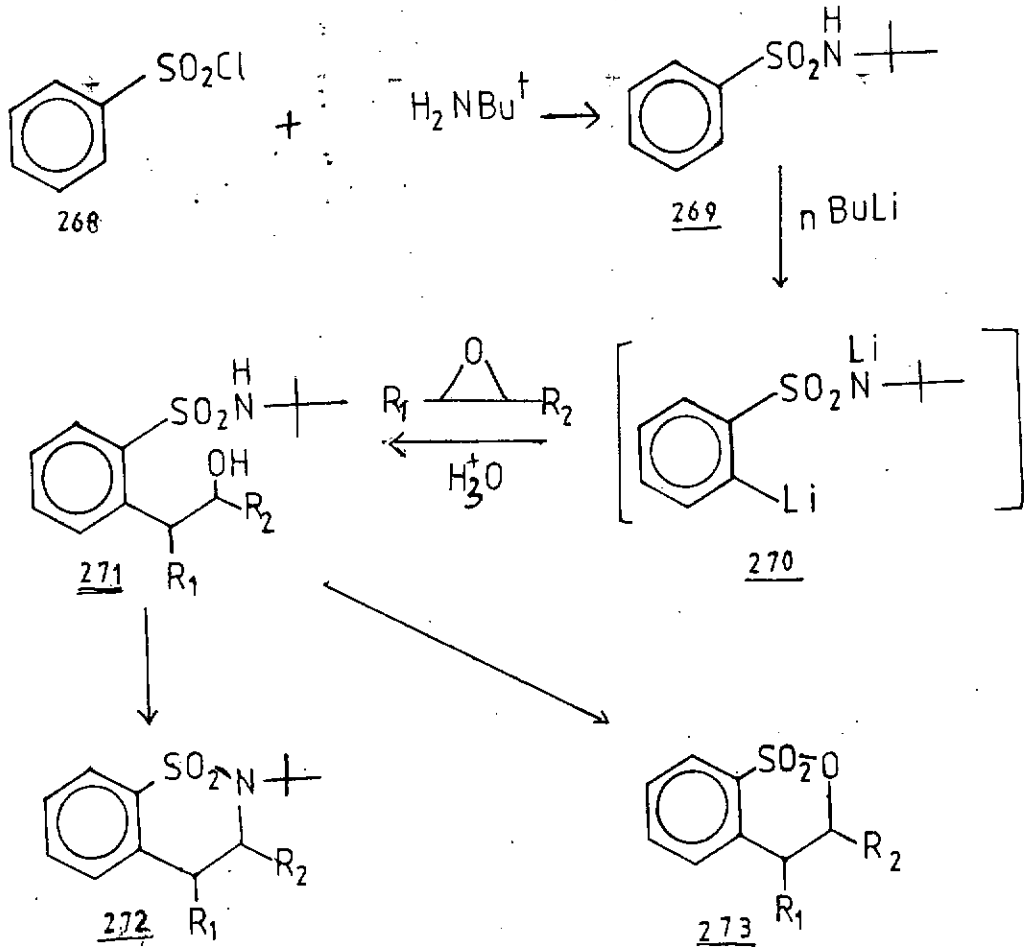
Benzylic lithiation of the o-toluamide followed by quenching with p-anisaldehyde gave the amide alcohol. Basic hydrolysis converted the amide alcohol to the isocoumarin. The natural product was then obtained by BBr_3-mediated demethylation.

PRESENT STUDY

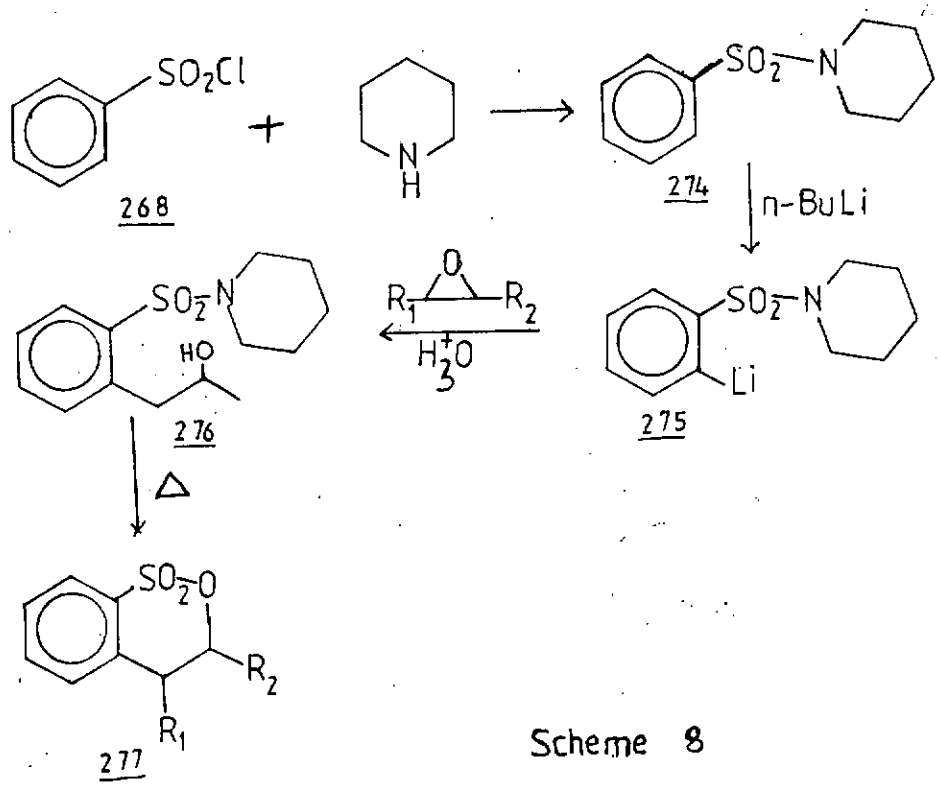
The ever growing use to which organolithiums are put in the synthesis of previously unattainable organic compounds of natural origin and other unnatural bioactive compounds made the further development and extension of this methodology to newer types of DMGs and electrophiles that have not been previously used, necessary. Such experimentation could be exploited for the synthesis of interesting heterocycles.

While the reaction of aromatic organolithium compounds with epoxides leading to the cleavage of such epoxides to give a β-substituted hydroxyl group on the aromatic ring had been in use in synthesis, there has been no systematic methodological study carried out. The commonly used epoxides like 1,2-epoxypropane had also been used. More substituted epoxides sometimes give elimination/dehydration product as side reactions, due to ensuing steric hindrance especially if such epoxides are fused to rings, e.g. cyclohexene oxide for example commonly gives vinyl alcohol as the product.

Experimentation will commence with secondary sulphonamides, e.g. t-butylbenzenesulphonamide (synthesised from a benzene sulphonyl chloride and tert-butylamine). These will be precursors for the exploratory metalations. The lithiated tert-butyl-benzenesulphonamides will then be coupled with different epoxides.

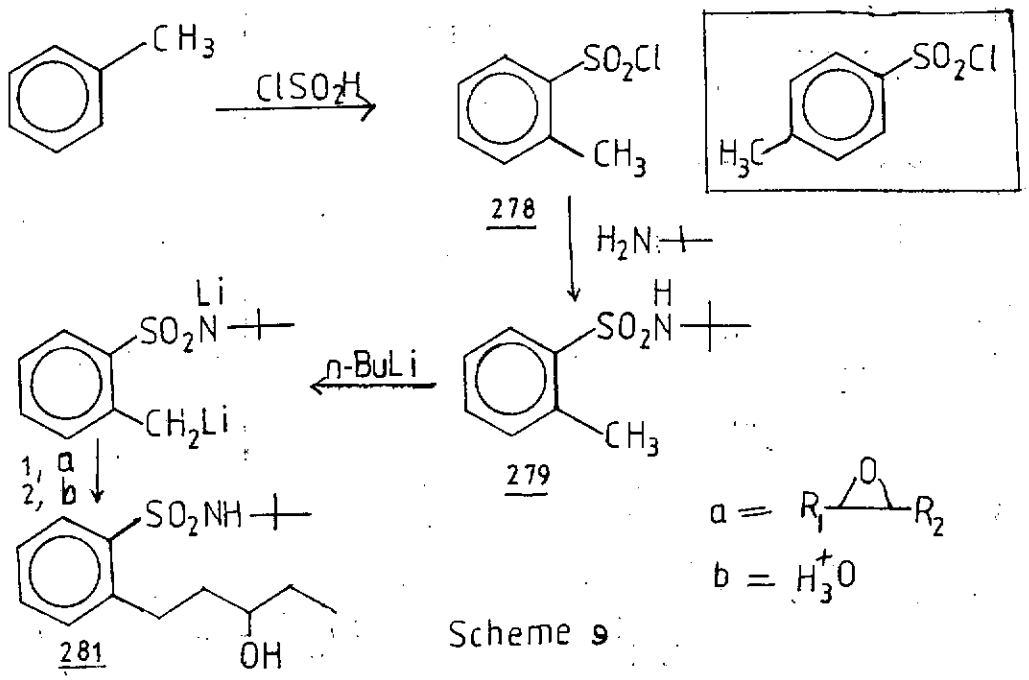


Scheme 7



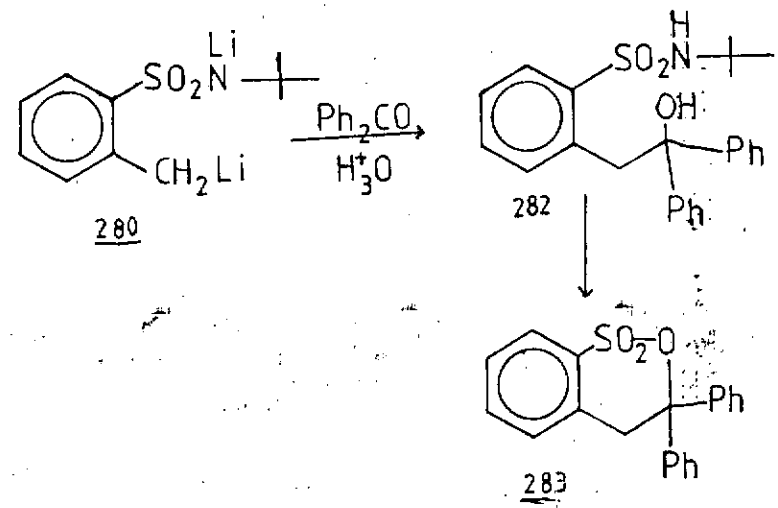
Scheme 8

Furtherstill, it was considered necessary to explore the reaction of epoxides or carbonyls with benzylic anions which could also provide the precursors to the desired heterocycles. There was no information in the literature on such reactions. The reaction of benzylic anions generated from secondary sulphonamides with primary epoxides will therefore be explored.

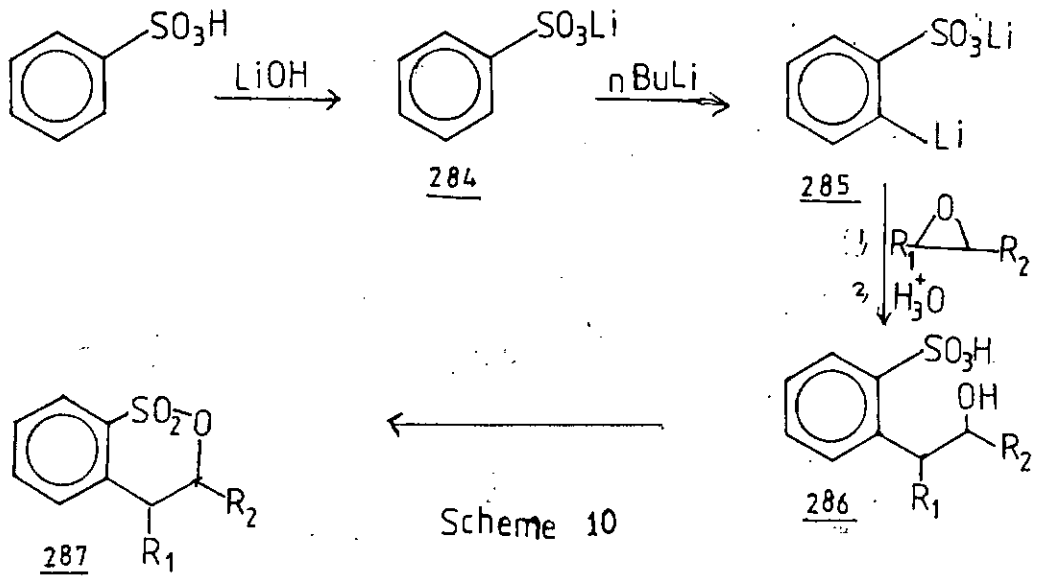


Scheme 9

Similarly, the reactions of ketones with the lithiomethyl benzenesulphonamides (benzylic anions) will also be examined towards possible utility in the construction of some appropriate sulphur-containing heterocycles: benzooxathiins.

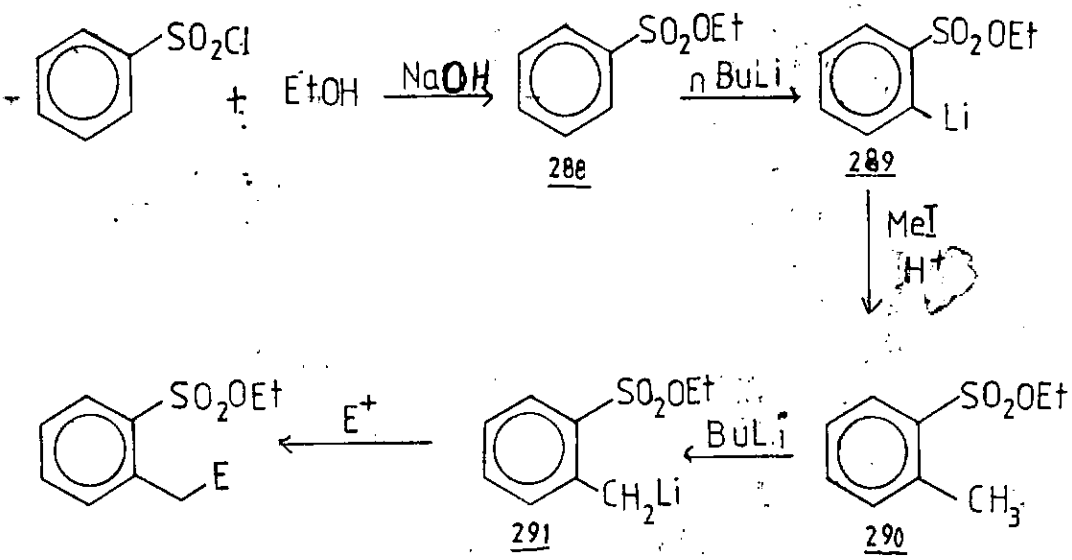


Also, the reaction of epoxides with dilithio species of benzene sulphonic acids was anticipated to provide an ortho β-hydroxyl group required for the synthesis of the benzooxathiins. Martin and Figuly had earlier reported on the reaction of electrophiles other than epoxides with such dianions. The utility of epoxides in this reaction was to be explored.



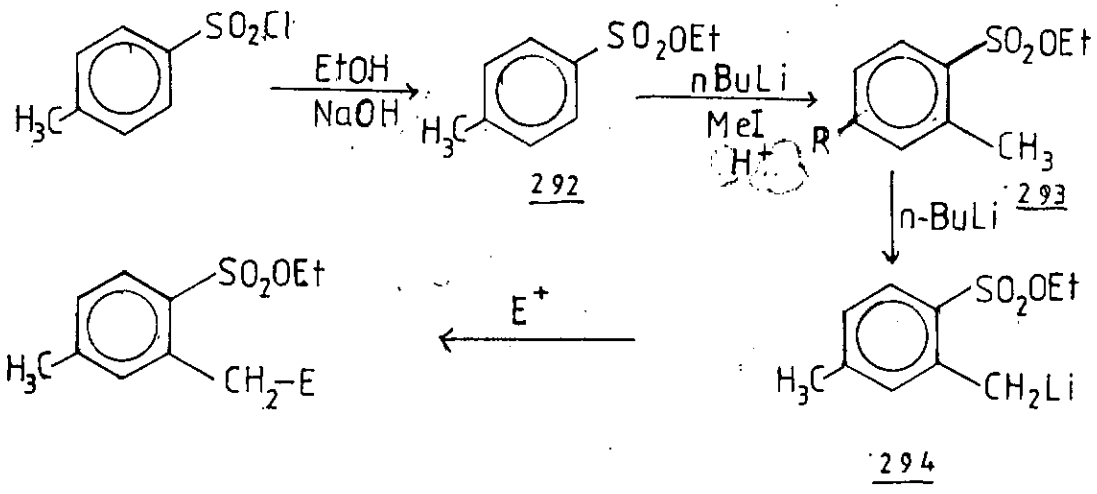
Scheme 10

Alkylarene sulphonate has been recently reported as an excellent ortho-directing metalation groups to provide ortho lithio species.[80] However, the use of this new DMG for the formation of benzylic anions has not been reported. This directed lithiation will therefore be studied. Alkyl-2-methyl benzenesulphonate will be lithiated and the reactions of the organolithium with various electrophiles will be attempted. The products from these attempts should be suitable starting materials for the preparation of new sulphur containing heterocycles.



E = CH_3CH_2CHO, $(CH_3)_2CO$, CO_2, $ClCO_2Et$, PhCHO, Ph_2CO. PhNCO, $PhSO_2Cl$.

Regioselectivity of this metalation will be explored. Lithiation of the 2,4-dimethylbenzenesulphonate isomer should provide evidence for this and also elucidation of the mechanism of the lithiation i.e. whether coordination mechanism is occuring predominantly or otherwise. It is expected that lithiation would probably give the 2-lithiomethyl compound exclusively.

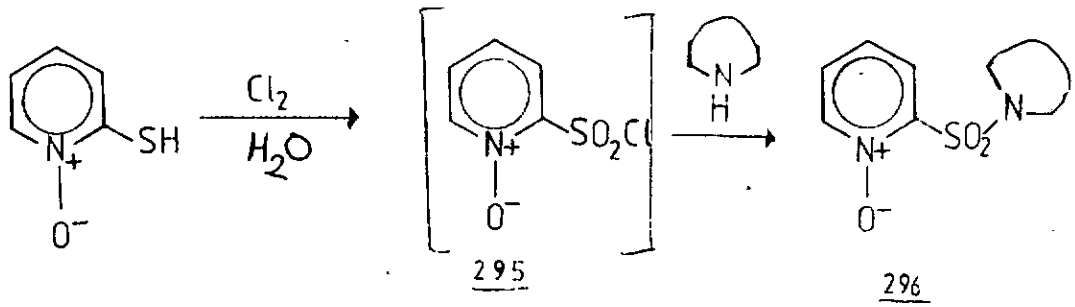


E = CO_2, PhCHO, Ph_2CO.

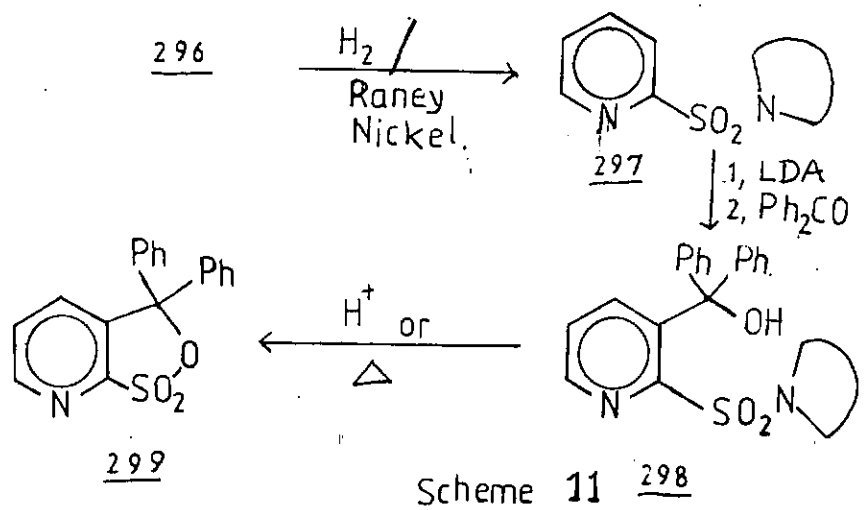
Studies with pyridine sulphonamides

Synthesis of fused pyridine heterocycles incorporating sulphur have precedence in literature[63], although very little is known on their methods of preparation. The products obtained from the metalation of pyridines in which a sulphonamide is the directing group should serve as useful synthons in the synthesis of such pyridine heterocycles. To this end, the relatively unexplored pyridine-2-sulphonamides and pyridine-4-sulphonamides will be lithiated and coupled with benzophenone as electrophile to give a product which will be used in the attempt to obtain fused pyridine sulphur-containing heterocycles.

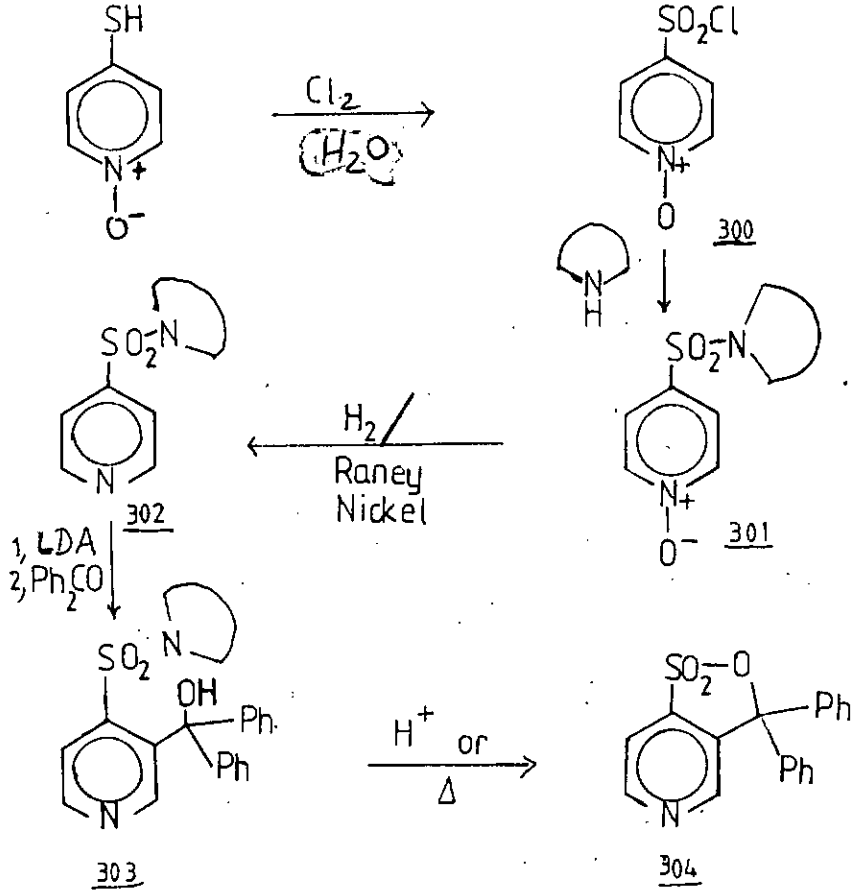
The alkyl aminopyridine sulphonamide would be prepared by condensing pyridine-2-sulphonyl chloride with the appropriate amine: piperidine, pyrrolidine and morpholine. Similarly these amines would be condensed with pyridine-4-sulphonyl chloride. The sulphonamides obtained would be lithiated with lithium diisopropylamide(LDA) and the organolithium thus obtained would be used in the attempt to obtain the heterocycles: oxathiino (1,2) (5,4-c) pyridine oxathiino (1,2)(4,5-c) pyridine respectively via the Scheme below:



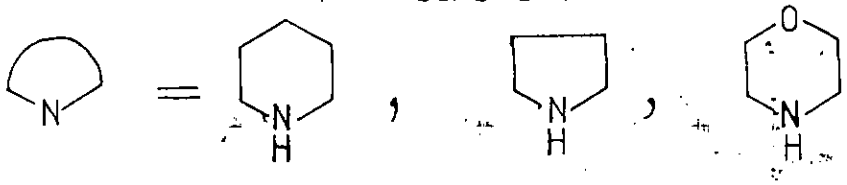
295 296



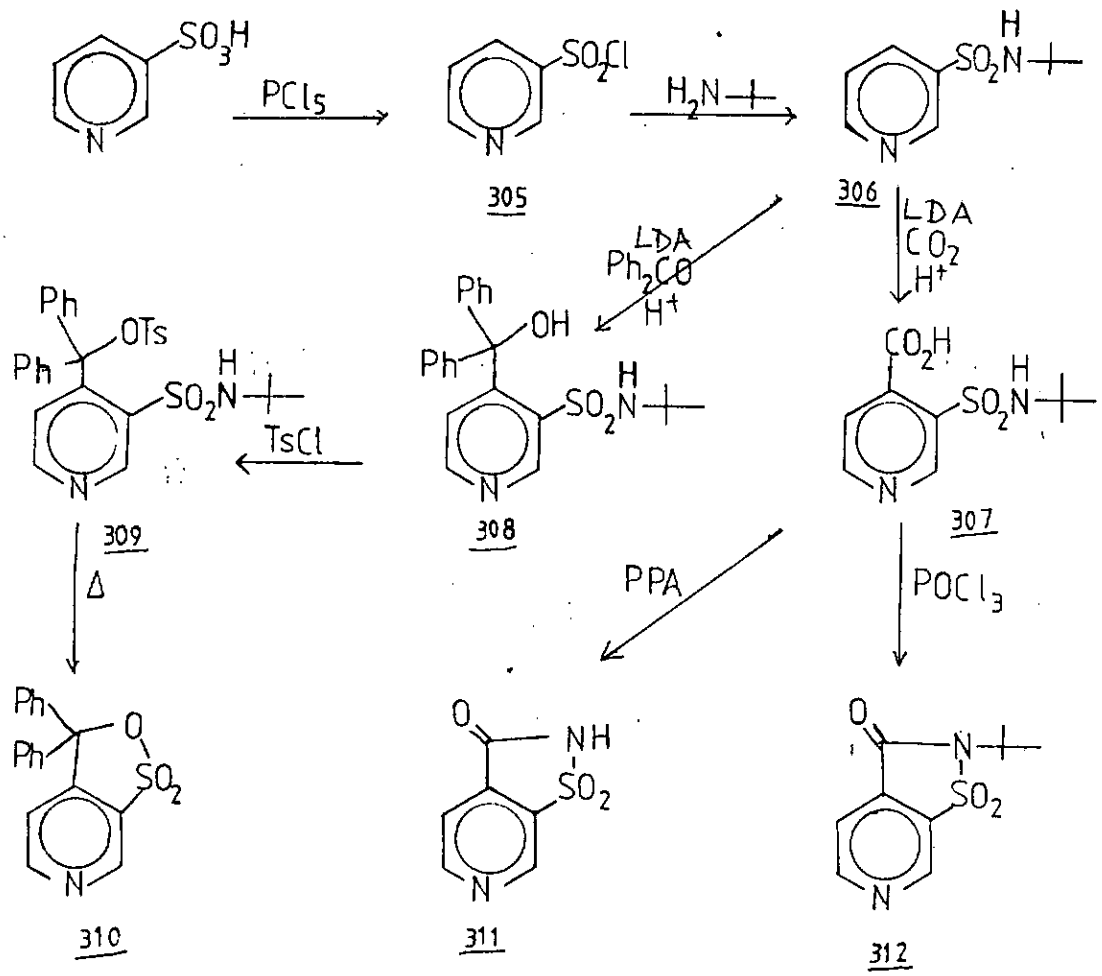
Scheme 11



Scheme 12



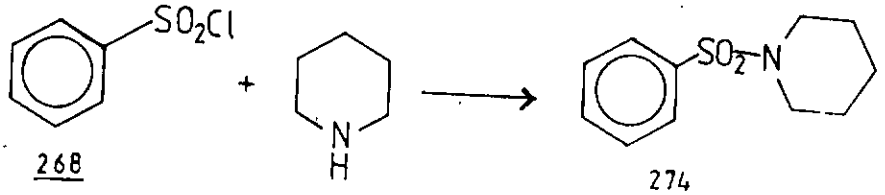
Tertiary pyridine -3-sulphonamide was metalated by Marsais et al in 1983[109] and subsequently no work has been done in this area. Secondary pyridine-3-sulphonamide obtained by condensation of pyridine-3-sulphonyl chloride with tert-butyl-amine will be metalated to obtain some precursor which will be used in the attempt to synthesise the heterocycles:
Isothiazolo (5,4-c) pyridine-3-one-1, 1-dioxide, 2-t-butyl isothiazolo (5,4-c) pyridine -3-one-1, 1-dioxide and 3,3-diphenyl isothiazolo (5,4-c) pyridine-1, 1-dioxide respectively.



Scheme 13

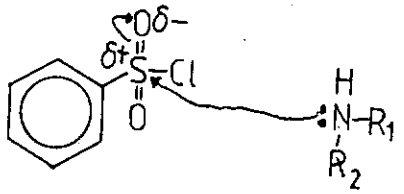
singlet at δ 5.0 exchangeable with D_2O represented the -NH absorption. A 3H multiplet at δ 7.5 and a double doublet at δ 7.9 represented the C-3,C-4,C-5 and C-2,C-6 aromatic protons respectively. Fig.1.

N-(benzenesulphonyl) piperidine was obtained similarly by reacting purified piperidine with benzenesulphonyl chloride. Recrystallisation from diethyl ether gave analytically pure product in 87% yield m.p. 91-92 (lit 91°)[92]. The ^{1}H-NMR spectrum showed absorptions at δ1.4, six proton multiplet of the piperidine hydrogens; a multiplet at δ 2.0 represented the protons next to the nitrogen of the piperidine. An unresolved multiplet at δ7.5 represented the aromatic ring protons. The aromatic proton could not be differentiated like the N-t-butyl-benzenesulphonamide.



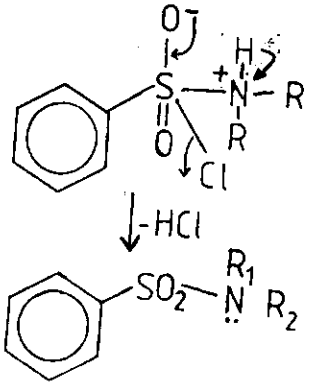
268 274

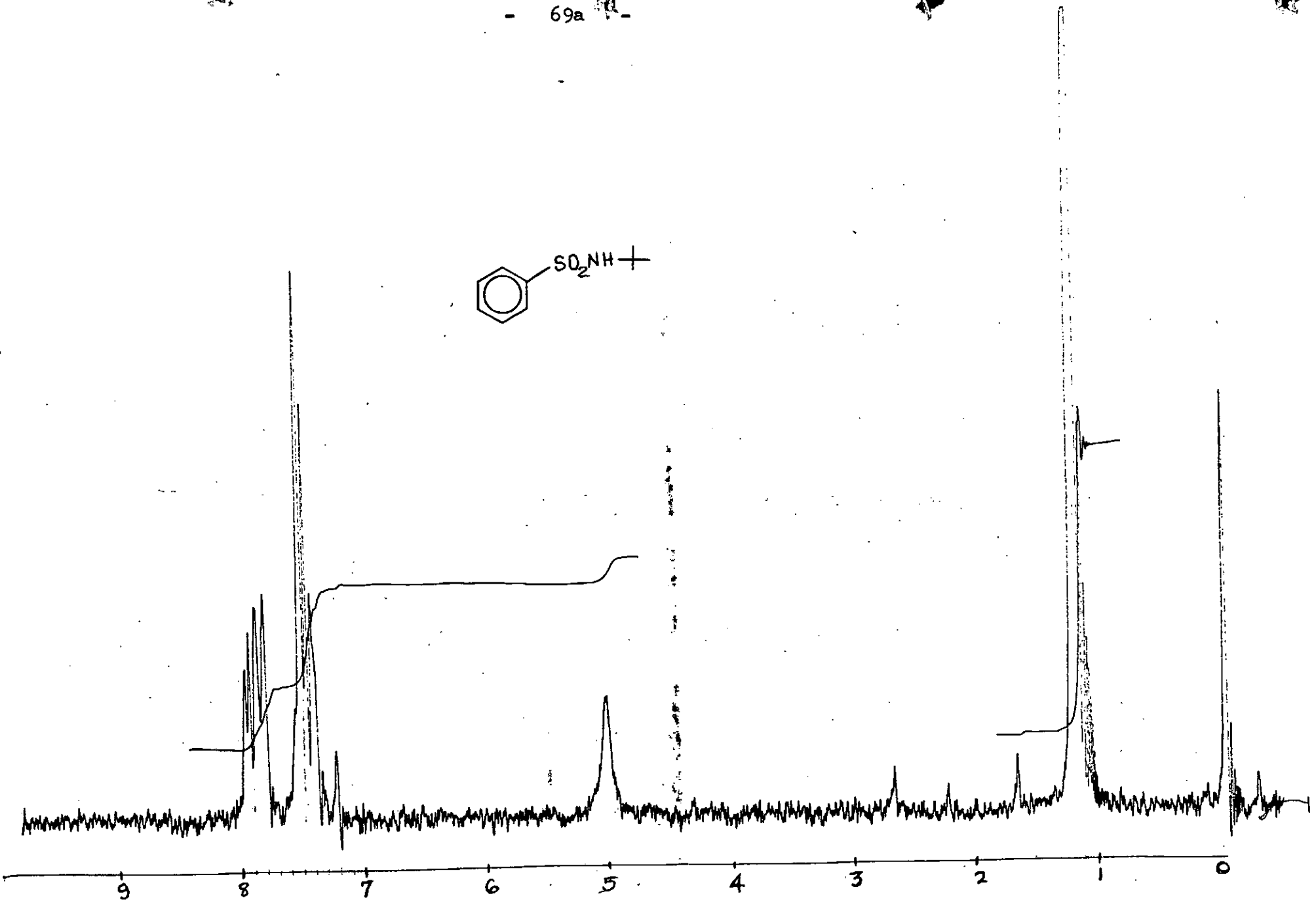
The mechanism of Schotten-Baumann reaction is well known to involve the attack of the sulphonyl group by the lone pair of electrons on the nitrogen of the nucleophile with subsequent elimination of hydrogen chloride:

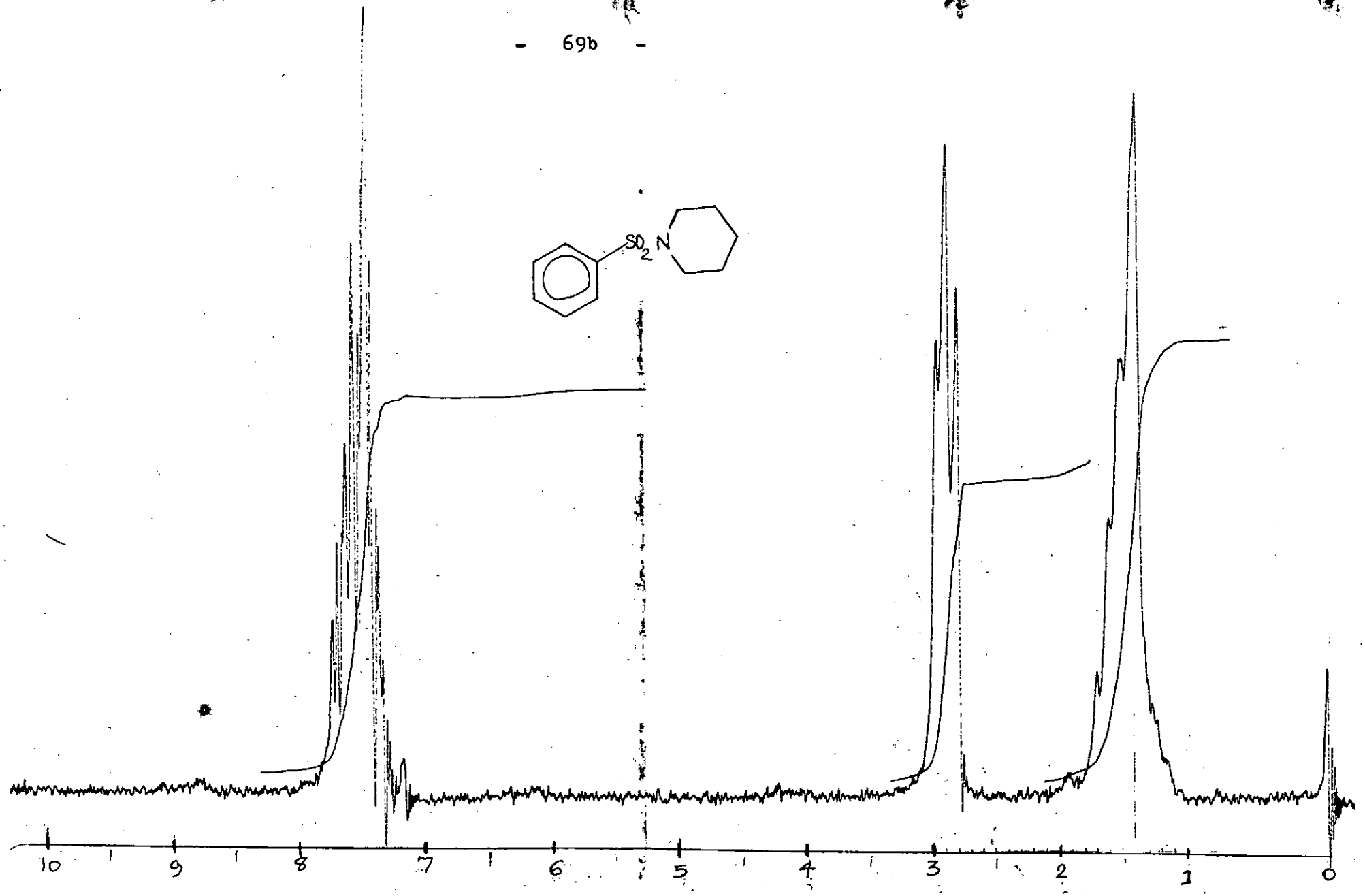


R_1 = t-butyl, R_2 = H

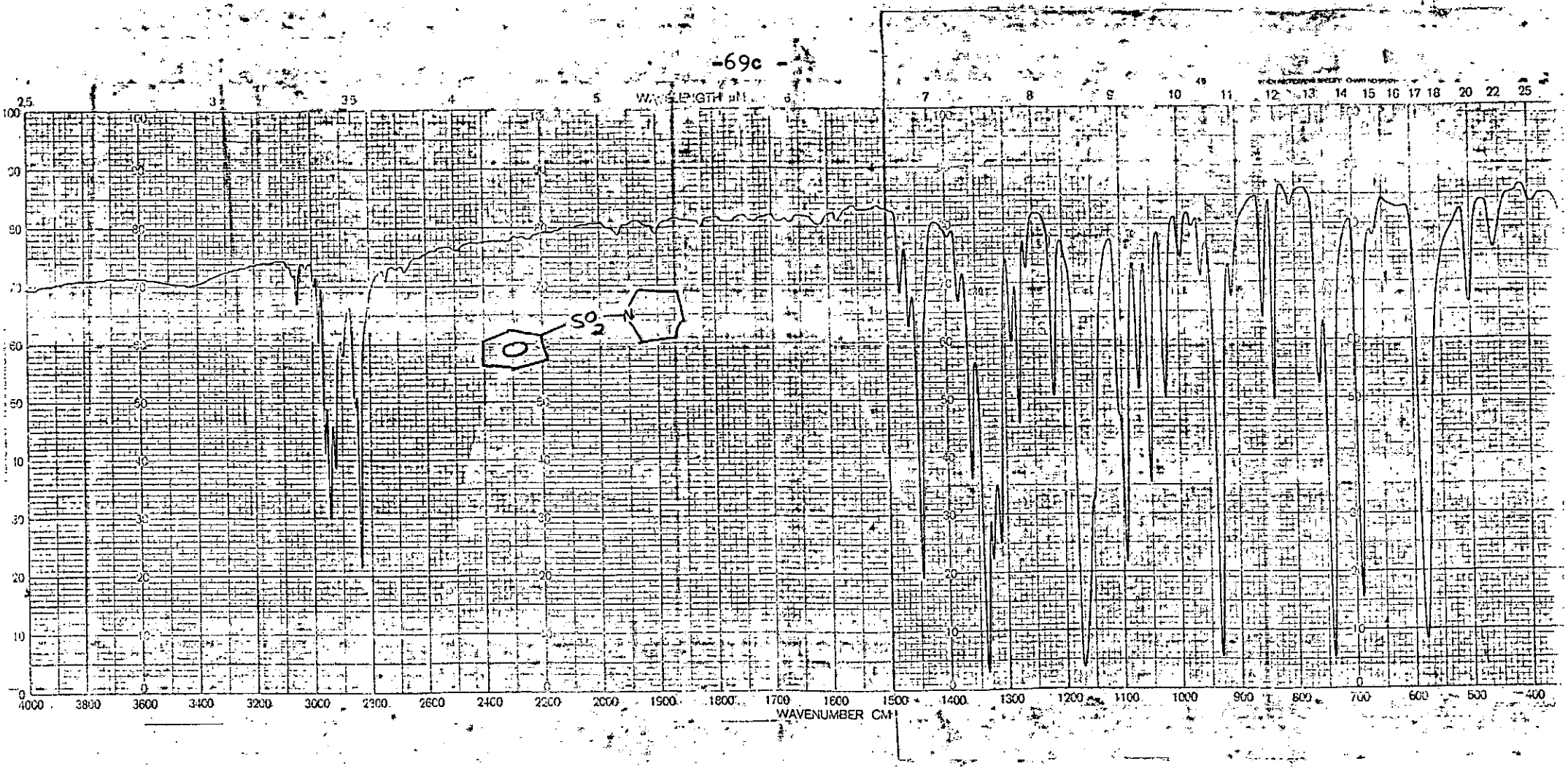
R_1R_2 = Piperidine




SO2NH
9
8
7
6
5
4
3
2
1
0
SOLVENT - CDCl3
27-12-88

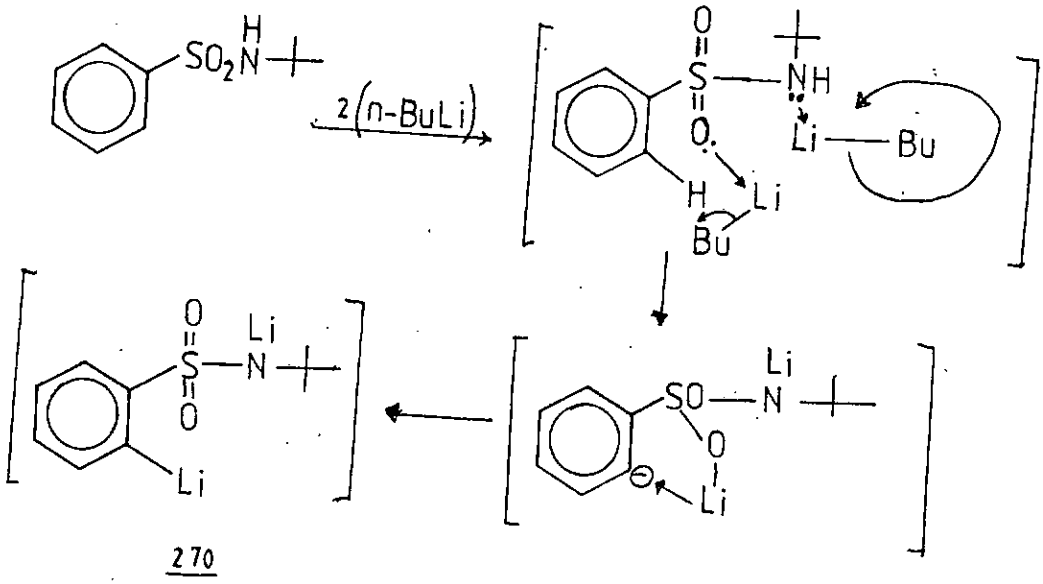


Solvent – $CDCl_3$
19/12/88


WAVELENGTH μm
WAVENUMBER CM
SO2
N
O

The sulphonamides thus obtained were vaccuum-dried after appropriate purification step and the subsequent metalation reaction with n-BuLi in hexane was carried out as customary for air sensitive reaction[127].

The N-t-butylbenzenesulphonamide metalation in dry THF could be typical of the reaction. For such secondary sulphonamides, 2 equivalents of n-BuLi was necessary as a dilithio species had to be formed (see Scheme).



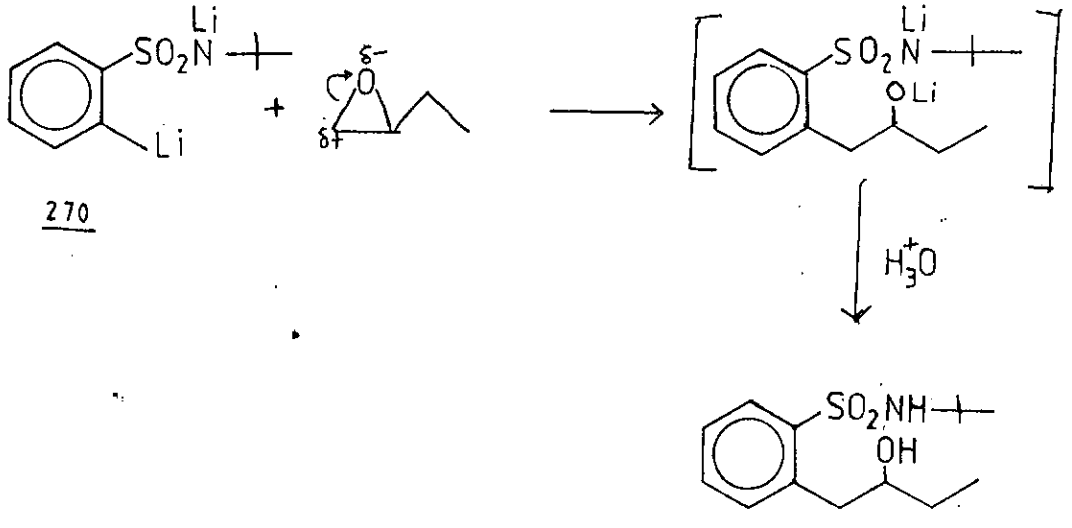
270

The lone pair of electron on the heteroatoms i.e. oxygen and nitrogen of the sulphonamides coordinated with the lithium of the butyllithium making the butyl to Li bond highly polarised with the cleavage of the butyl portion of the organolithium along with the abstraction of the proton ortho to the sulphonamido group to form an aromatic carbanion. Also the N-proton is similarly abstracted to give a dilithio species overall.

In obtaining the desired ortho β-hydroxy group contiguous to the aromatic sulphonamido functionality required for synthesis of the aromatic sultones-benzooxathiins, the electrophiles used were the available commercial epoxides with organilithiums. The carbanion attacks the least substituted position, in this case C-2. The N-Li is not attacked by the epoxides since such anions are not nucleophilic enough[128], therefore an exclusive aromatic ring attack was anticipated.

Reactions with 1,2-epoxybutane

On stirring the initial electrophile 1,2-epoxybutane with the lithio species for 3 hours at 0^{o}, it gave back essentially the starting material. It was initially suggested that the lithio species was decomposing at that temperature. Subsequently, the lithio species solution was cooled to -78^{o} before 1.2 equivalent of the electrophile was added. After stirring at -78^{o} for 4 hours, work-up similarly gave starting material only. Prompted by Ellefsons[24] earlier report with carboxylamides and epoxides, the reaction was then carried out at room temperature for 24h.



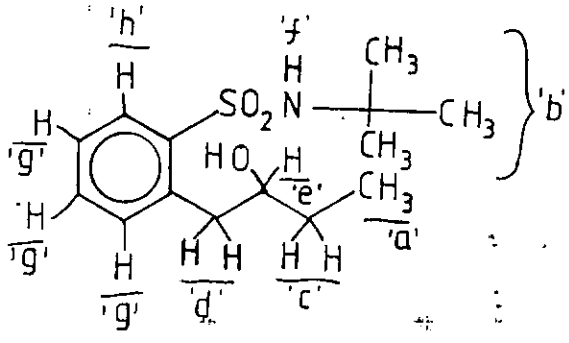
270

313

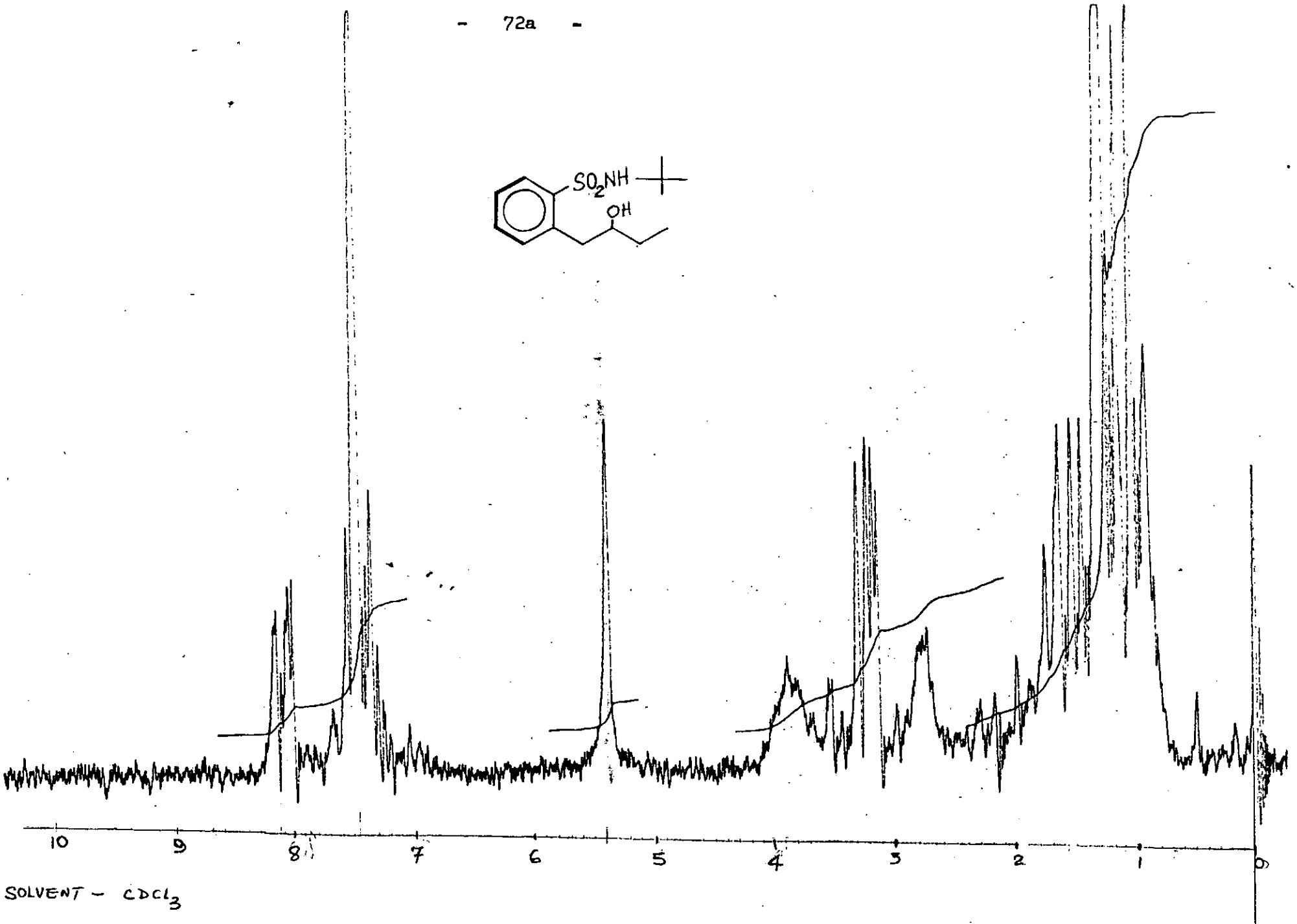
This time, the red colour of the organolithium species was discharged in about 5h and a pale yellow colour remained at the end of the reaction. Silica gel flash chromatography of the crude obtained gave three products: a yet unidentified compound, the starting material and a white solid m.p. 110-112° in 40% yield.

IR of the solid showed a band at 3490 cm^{-1} for an OH group and a band at 3280 for a secondary -NH stretching, 2970, 2930 cm^{-1} (CH stretching). 1600 cm^{-1} for aromatic -C=C-, 1320, 1150 cm^{-1} are for the SO_2-N= group, others include 980 and 870 cm^{-1}.

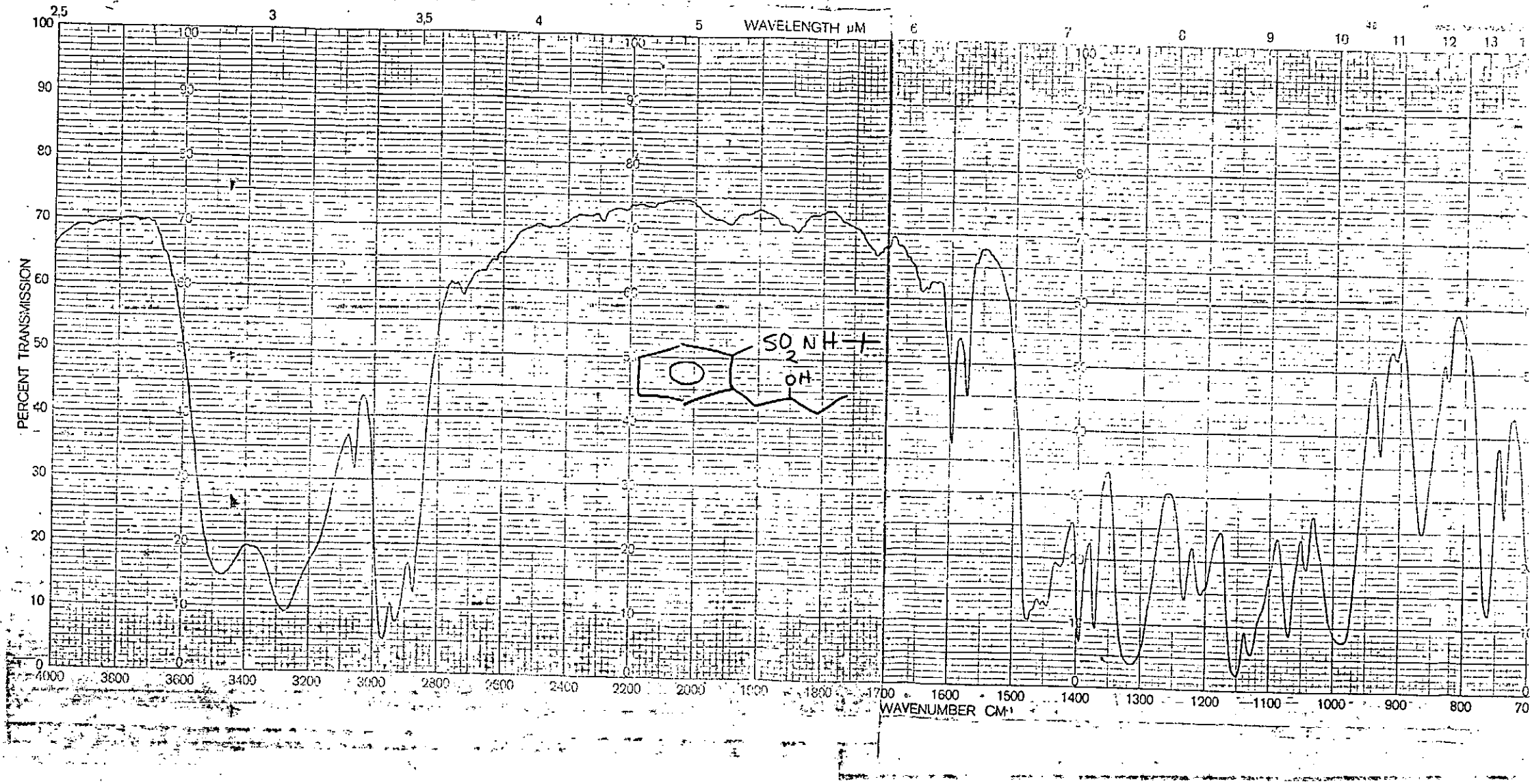
The ^{1}H-NMR of the solid showed a 3H triplet at δ1.1 for the $-CH_3$ type 'a', 9H singlet at δ1.3 for the nine protons of the t-butyl group, a multiplet at δ1.6 for the two protons of type 'c'; a broad absorption at δ 2.8 was for the one proton of the -OH, which was exhangeable with D_2O; a 2H, multiplet at δ 3.3 was assigned to the methylene next to the phenyl group type 'd'. The 1H multiplet at δ5.5 was for the -NH of the amide. A 3H multiplet at δ 7.5 represented the aromatic ring type 'g' while a 1H proton at δ 8.15 represented the signal of the proton ortho to the sulphonamide group. These data were used in assigning the ortho-β-hydroxybenzene-sulphonamide structure 313 to the solid.



313



SOLVENT – $CDCl_3$

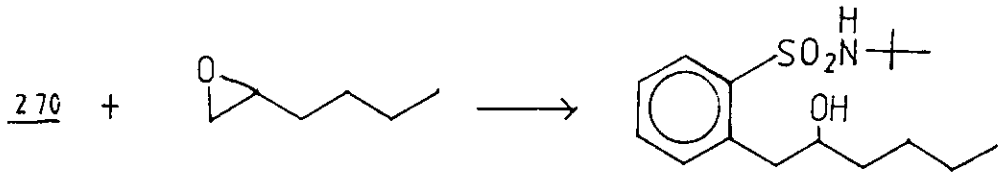

WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹
SO2NH
OH

The elemental analysis of the solid was satisfactory and consistent with a formula $C_{14}H_{23}NO_3S$ for the desired compund.

As there was recovery of a large quantity of unreacted material, the reaction time was extended to 48h at room temperature without any significant improvement in yield Therefore all subsequent reactions were carried out at 0^{o} and allowed to warm to room temperature with stirring for 24h.

Reaction with 1,2-epoxyhexane

The reaction of the lithio species with 1,2-epoxyhexane in THF was similar to that of 1,2-epoxybutane above.



270 314

Work-up as usual gave a mixture of three compounds on t.l.c. Flash chromatography and recrystallisation gave analytically pure reaction products.

I.R. analysis of the product showed 3480 cm^{-1} for the -OH stretching, 3280 cm^{-1} for the -NH stretching of the amide, 2960, 2930 cm^{-1} for -CH stretching of the alkyl group. 1600 cm^{-1} for -C=C- bond of benzene, 1480 cm^{-1}, with 1330 and 1160 cm^{-1} for the $SO_2N<$ bond, others include 990 and 760 cm^{-1}.

400-MHZ ^{1}H-NMR in DMSO of the product showed a 3H triplet at δ 0.85 for the methyl group and a 9H singlet at δ 1.2 represented the t-butyl group. A 2H multiplet at δ 1.35 was the methylene next to the CHOH, a broad absorption exchangeable with

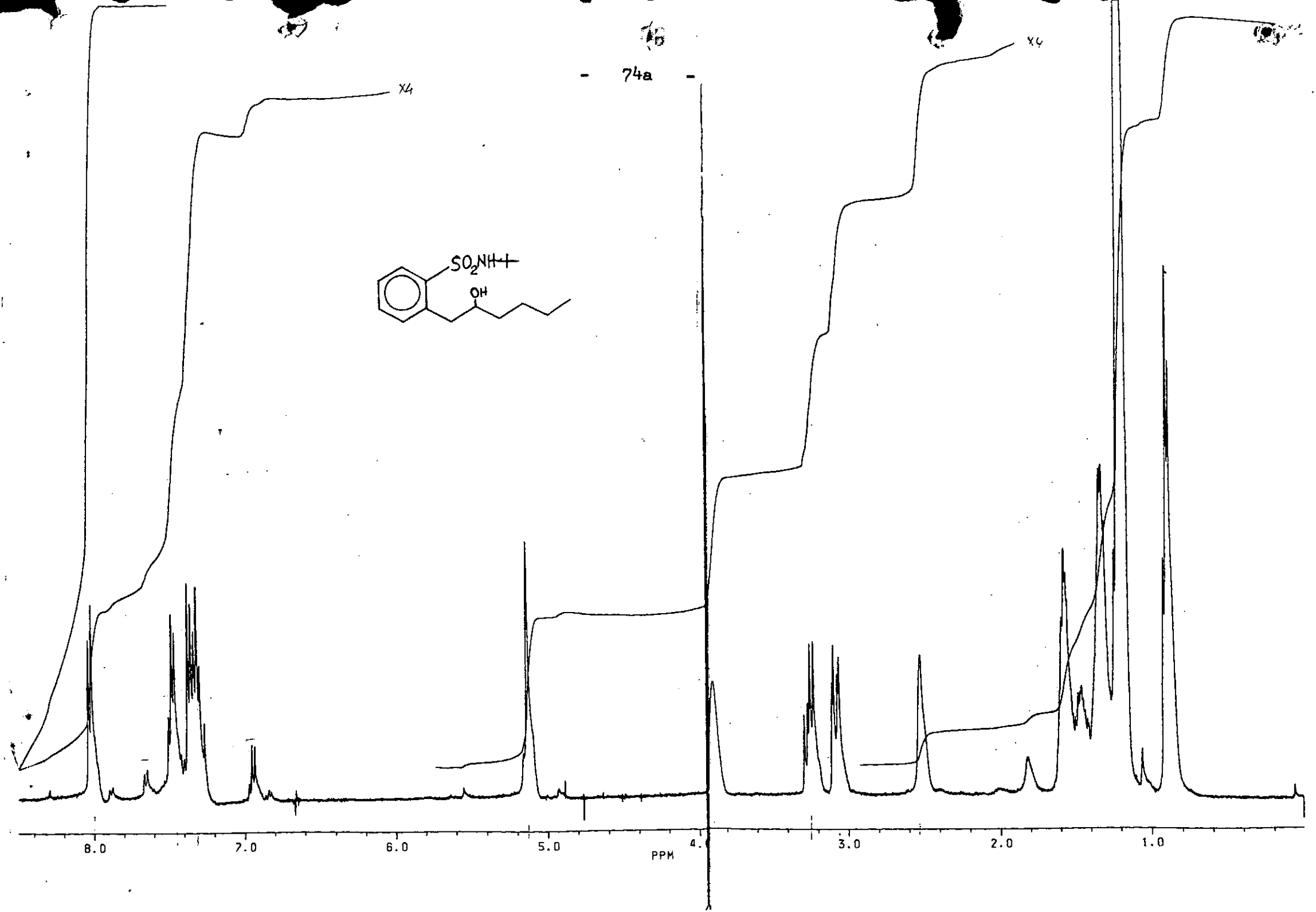
D_2O at δ2.5 was due to the OH. The signals at δ 3.1 and δ3.25 represented the methylene group next to the phenyl ring while a δ3.9 absorption was for the base proton of the hydroxyl group. The NH proton appeared at δ5.1 and the signal collapsed with D_2O. δ7.4 represented the three protons of the aromatic ring H-3, H-4, H-5 while the one proton ortho to the sulphonamide appeared at δ 8.0 as a 1H doublet. The satisfactory combustion analysis gave a molecular fomular $C_{16}H_{27}NO_3S$ which further confirmed the structure of the compound as 1-(2-N-butyl benzene-sulphonamido)hexan-2-ol.

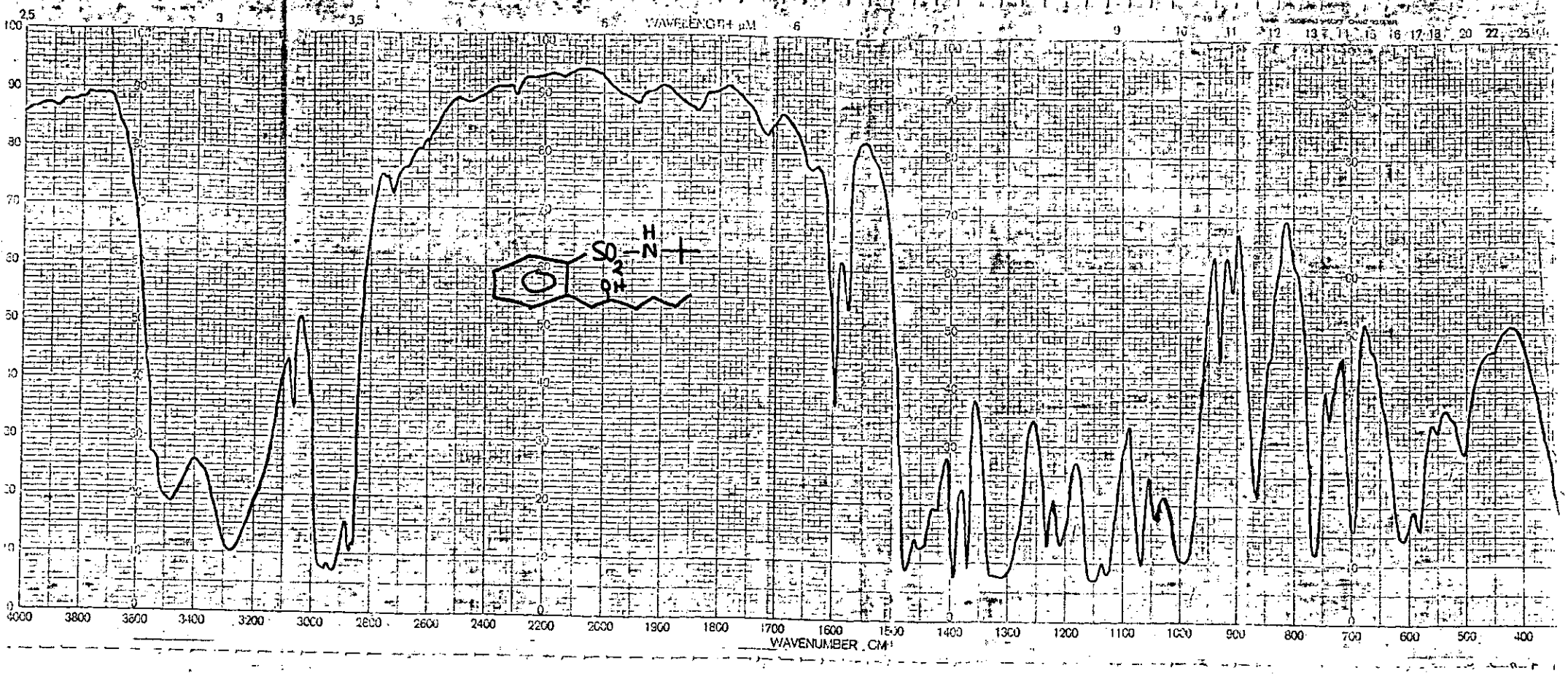
Reaction with 1,2-epoxy-3-phenoxypropane

(±) 1,2-Epoxy-3-phenoxypropane in THF was reacted with the lithiospecies at room temperature for 24h. Hydrolysis of the product with 5% HCl at 0° gave a crude oil which was purified by flash chromatography to give the desired compound as an oil which later crystallised as white prisms m.p. 104-106°, 35% yield.

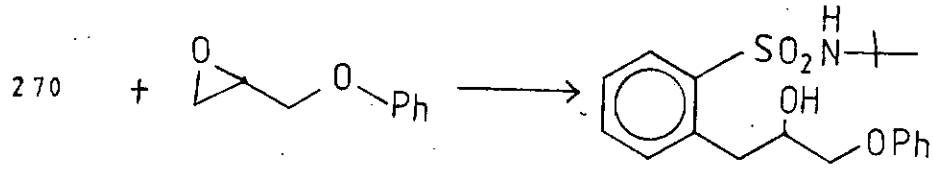
The I.R. spectrum showed bands at 3500 cm^{-1} for an OH group, 3280 cm^{-1} for a NH group of an amide, 2960 cm^{-1} for the -CH stretching of a butyl group. The -C=C- of an aromatic ring showed at 1600 cm^{-1}, 1330 and 1150 cm^{-1} for an SO_2-N group.

The ^{1}H-N.M.R. spectrum gave signals at δ1.3 for 9H singlet of a t-butyl group. A deuterium exchangeable hydroxyl group proton was observed at δ3.1. The double doublet at δ3.4 represented the methylene group with non-equivalent protons next to a phenoxyl group, while δ4.1 doublet was for methylene next to the phenyl ring,


X4
X4
SO2NH
OH
8.0
7.0
6.0
5.0
4.
PPM
3.0
2.0
1.0


WAVELENGTH μM
WAVENUMBER CM⁻¹
4000 3800 3600 3400 3200 3000 2800 2600 2400 2200 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400
2.5 3 3.5 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 20 22 25
100 90 80 70 60 50 40 30 20 10 0
H
N
SO2
OH

the 1H multiplet of the base proton of the hydroxy group was observed at δ 4.3. The 1H proton of the -NH exchangeable with deuterium was at δ 5.2, δ 7.0-7.6 multiplet of 8 protons was for the aromatic rings while 1H doublet was assigned for the proton ortho to the sulphonamido group. Finally, satisfactory combustion analysis confirmed the structure of the new compound as N-(2-t-butylbenzenesulphonamido)-3-phenoxy propan 2-ol.

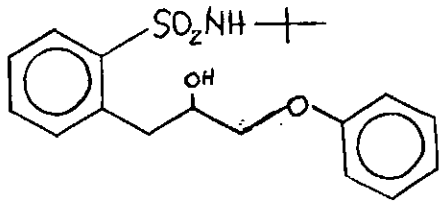


315

Reaction with styrene oxide

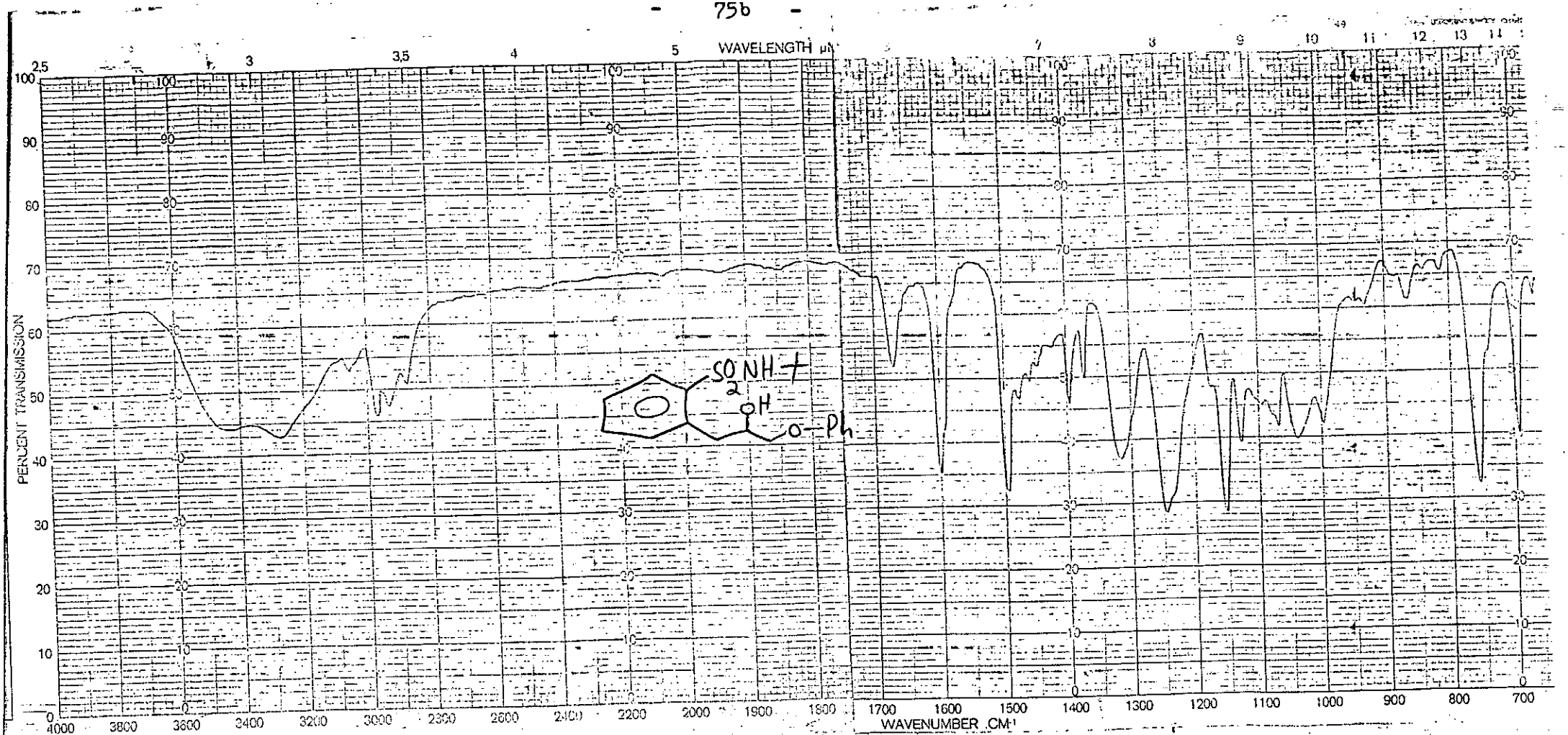
On reaction with styrene oxide in THF, the lithio species gave a crude product. The crude oil was as usual flash chromatographed to give a very viscous oil. The oil had to be subjected to a second flash chromatography, before analytically pure product could be obtained in 30%.

The I.R. spectrum showed absorption at 3480 cm^{-1} for the OH group, 3280 cm^{-1} for the NH of an amide, 2980, 2940 cm^{-1} for the -CH stretching of the alkyl group, 1605 cm^{-1} is for the -C=C- of the aromatic ring, 1320, 1150 cm^{-1} is for the SO_2N- group absorption. Others include 990, 860 and 760 cm^{-1} for the substitution pattern of the benzene rings.

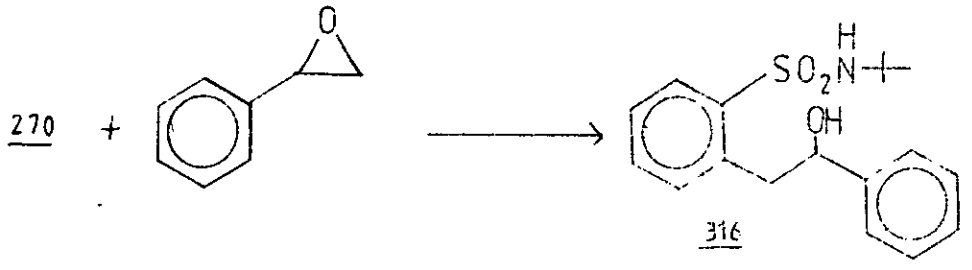


SOLVENT - $CDCl_3$

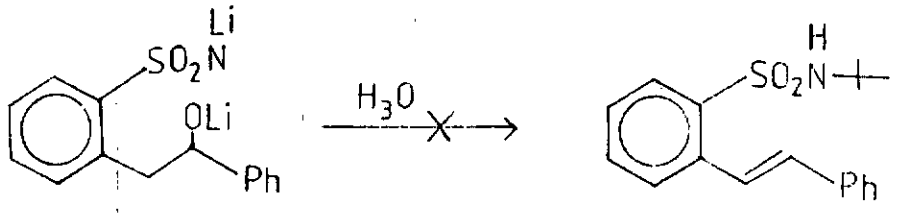
7/3/89

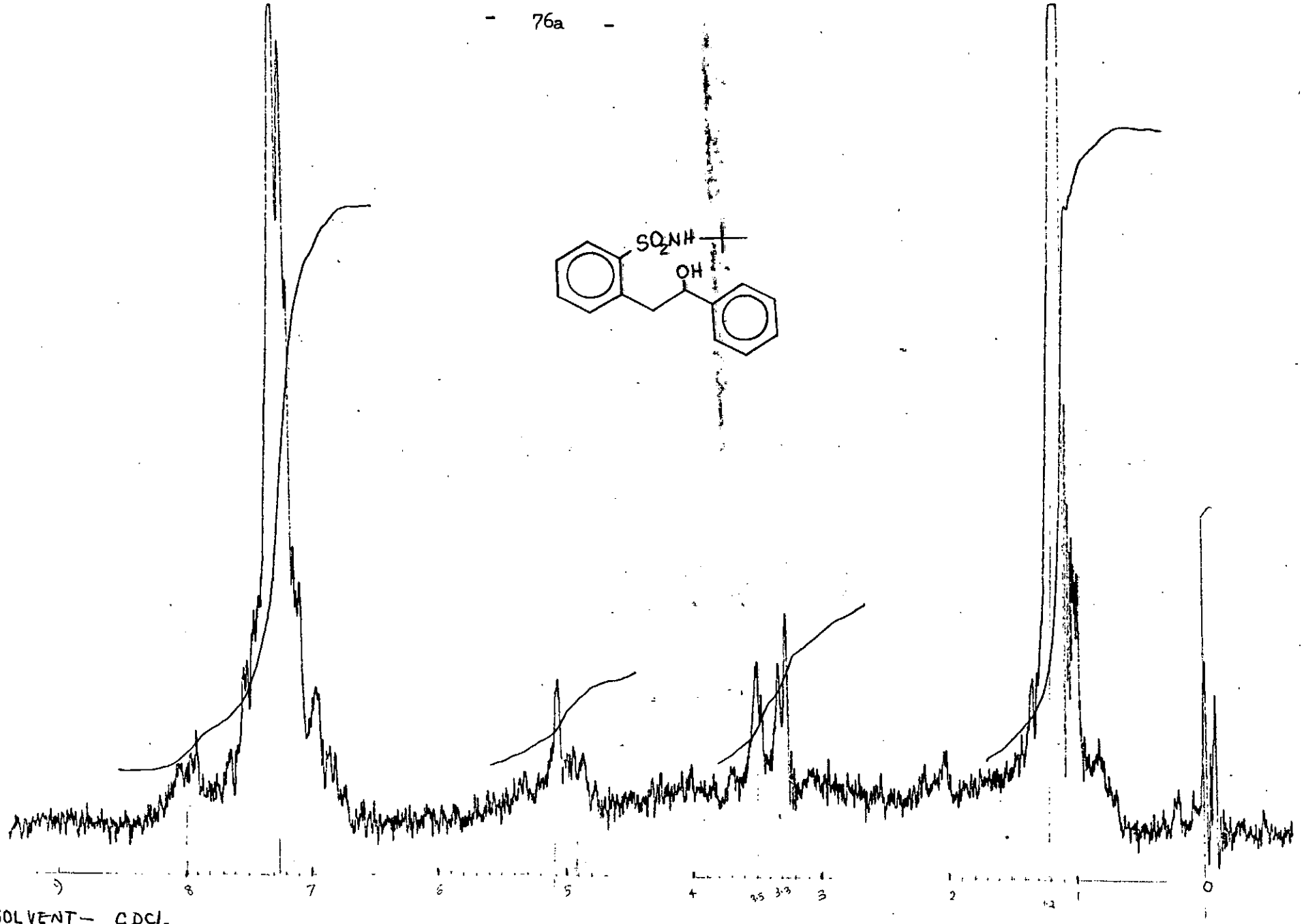

WAVELENGTH μ
PERCENT TRANSMISSION
WAVENUMBER CM-1
SO2NH+
OH
o-Ph

^{1}H-NMR spectrum gave a 9H singlet at δ2.1 representing the t-butyl group, a 2H multiplet of the methylene group absorbed at δ3.3 while 1H multiplet for the base proton of the carbon atom with hydroxyl group absorbed at δ3.5. The 1H broad absorption of the hydroxyl group which is exchangeable with D_2O absorbed at δ4.9. The NH proton showed as a broad peak at δ5.1 which is exchangeable with D_2O. A signal for 8H multiplet for eight protons of the aromatic ring was at δ7.3 while 1H double doublet is for H-6 ortho to the sulphonamido group.

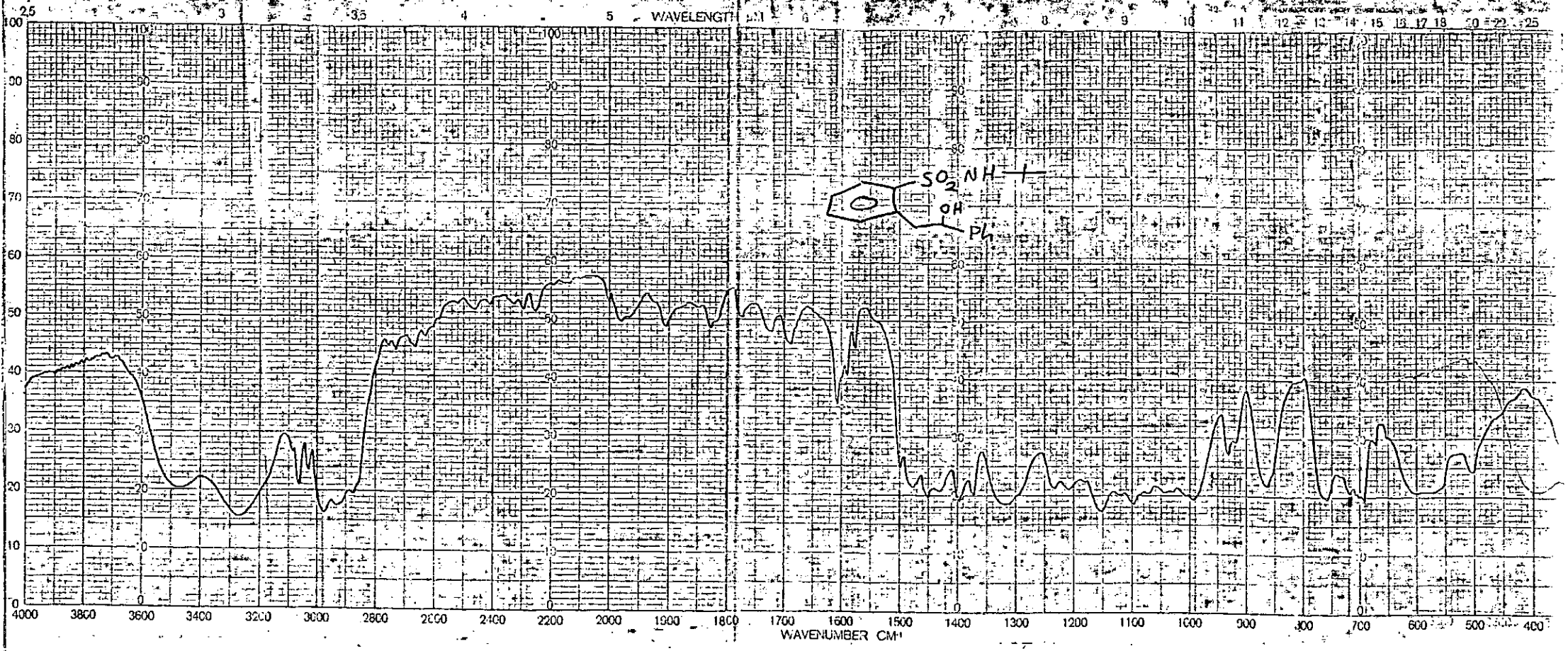


The acid treatment on hydrolysis could have lead to dehydration giving an olefin. However the distinct presence of the hydroxyl group in the I.R. spectrum and exact elemental analysis confirmed the structure proposed as 2-(2-H-t-butylbenzene-sulphonamido)-1-phenylethanol.





SOLVENT — $CDCl_3$
3/2/89

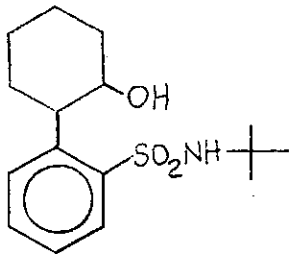

WAVELENGTH
WAVENUMBER CM⁻¹
SO2 NH
OH
Ph

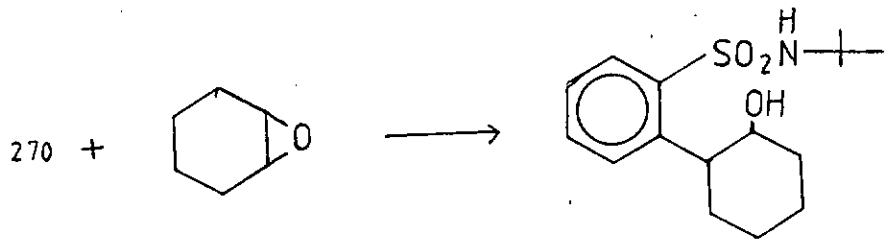
Reaction with Cyclohexene Oxide

Cyclohexene oxide in THF was reacted with the lithiated N-t-butylbenzenesulphonamide. After the usual change of colour, a pale yellow solution was obtained which on work-up gave a viscous oil. The oil was purified as usual by flash chromatography to give the pure product in 25% yield as viscous oil.

A report[129] of the successful use of cyclohexene oxide as an electrophile on metalated carboxamides indicated that the epoxide had to be refluxed with the lithio species, Whereas when cyclohexanone was used, a successful reaction was obtained at -78°, The aberrant behaviour of cyclohexene oxide may be due to it's being a secondary epoxide when compared to the primary epoxides which are devoid of steric hindrance and thus smoothly react even at low temperatures. In cyclohexene oxide as in other secondary epoxides, opening of the epoxide may not provide an electrophilic carbon that is as positive as those of primary epoxides where inductive effect of the methylene groups are absent thereby increasing the positivity of the electrophilic carbon,

The ^{1}H-NMR of the oil gave signals for 9H singlet of the t-butyl group at δ1.2, a 8H multiplet at δ1.4 and δ1.8 represented the cyclohexene methylene protons. The 1H singlet (exchangeable with D_2O) represented the hydroxyl proton absorbed at δ 3.2 while the 2 base protons absorbed as a multiplet at δ 3.7. The NH 1H singlet absorbed at δ5.4 (collapsed with D_2O), a 3H multiplet at δ7.5 represented the H-3, H-4 and H-5 protons, while the H-6 doublet of a doublet signal is at δ8.0. The elemental analysis was satisfactory and confirmed the structure of the product as 2-(2-N-t-butylbenzene-sulphonamido) cyclohexanol.

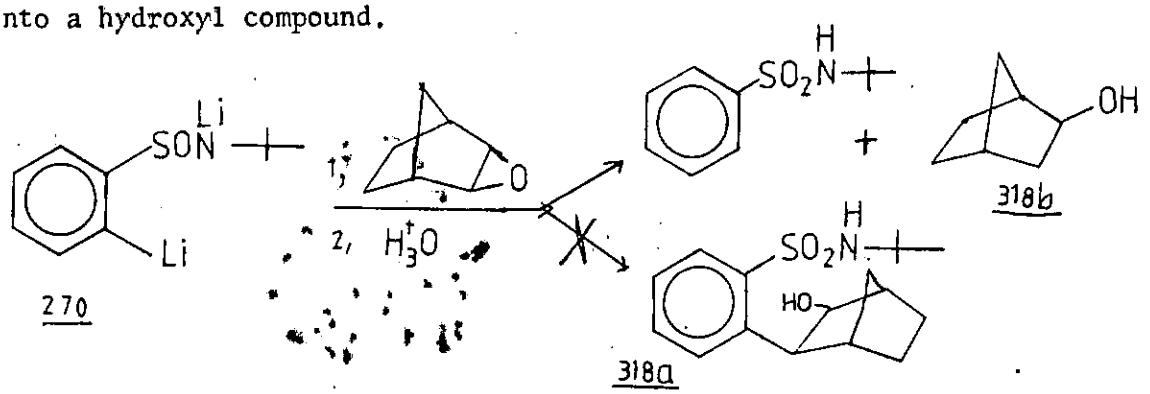

OH
SO2NH



317

Reaction with exo-2,3-epoxynorbonane as electrophile

Exo-2,3-epoxynorbonane dissolved in THF was added to the lithio species and stirred for 24h at room temperature. Hydrolysis of the reaction mixture with 5% HCl gave an oil. Low pressure fractional distillation of the crude oil gave a white solid product as a sublimate and a clear oil. The N.M.R. of the oil showed it was the starting sulphonamide, while the N.M.R. of the solid sublimate however showed it was the norbonane opened up into a hydroxyl compound.

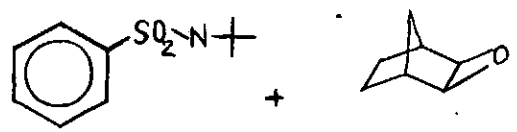


270 318b 318a

Microanalysis of the sublimate further confirmed that it was hydroxynorbonane 318b with a quarter mole water of crystallisation.

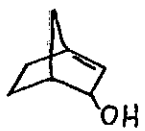
Reaction with N-(2,3-epoxypropyl)-phthalimide as electrophile

After the generation of the lithio species as usual, N-(2,3-epoxypropyl)-phthalimide dissolved in THF was added at 0° and stirred at room temperature for 24h. The usual colour change was not obtained; instead a precipitate was formed. Work-up of the

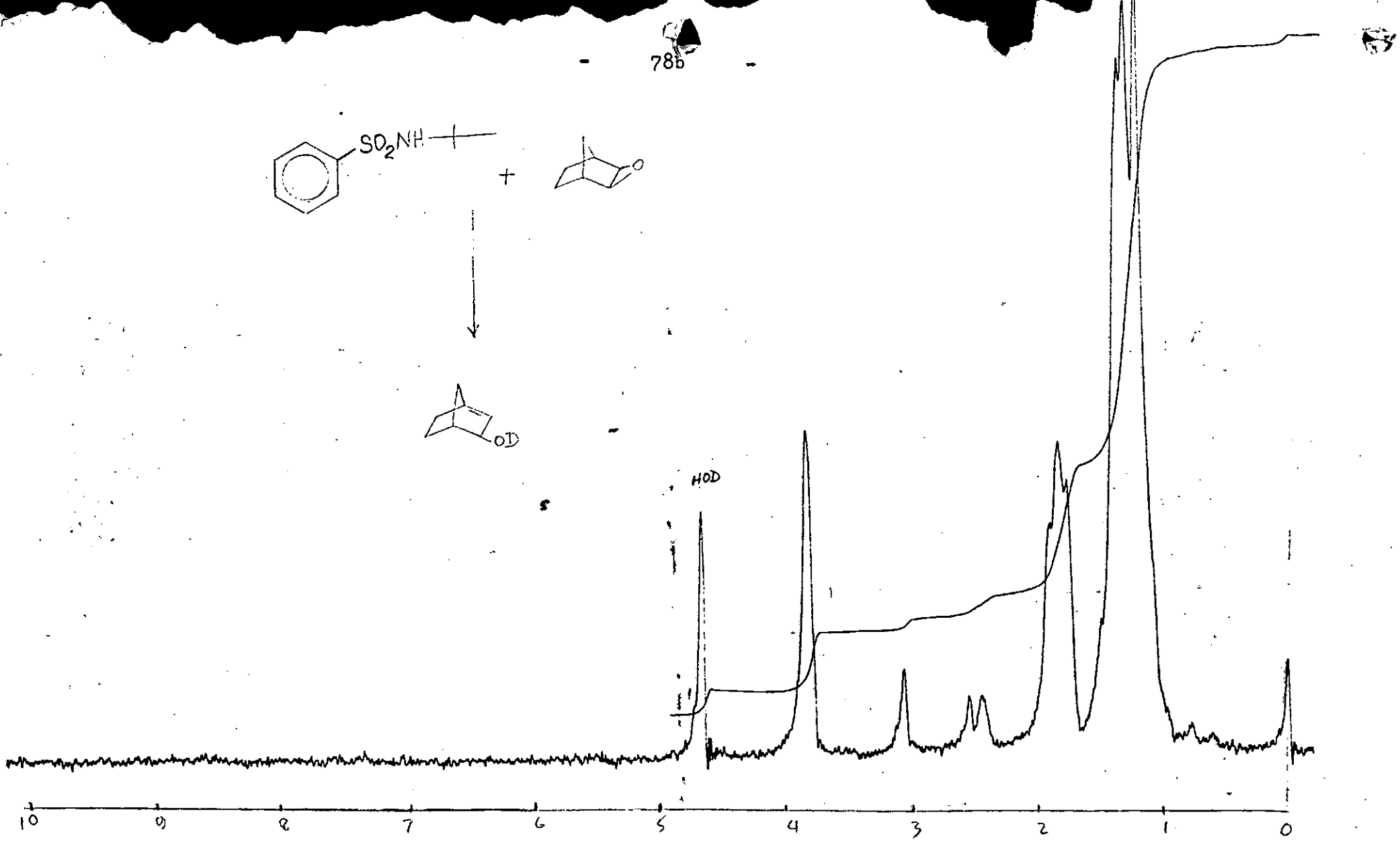

SO2N+

+

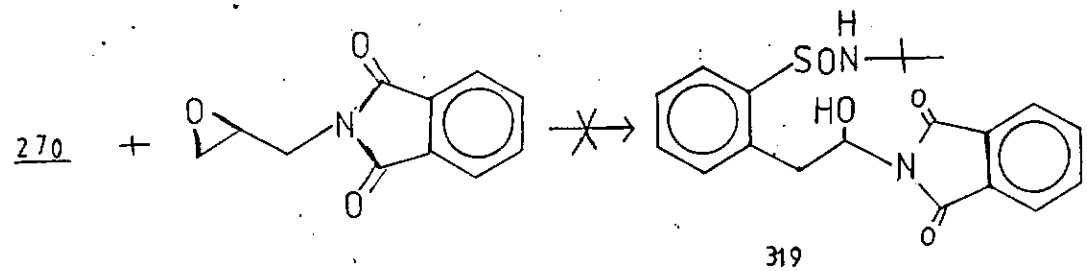
O


OH

10
9
8
7
6
5
4
3
2
1
0


SO2NH
+
O
OD
HOD
1
10
9
8
7
6
5
4
3
2
1
0

reaction mixture eventually gave a brown solid. Thin layer and column chromatography of the solid gave several compounds that were not the expected products.



270 319

The possible rationale for the unexpected reaction could be due to the presence of the lactam bonds which can react with the organolithium to form a ketone and secondary amine[1]. These may override the primary nature of the epoxide.

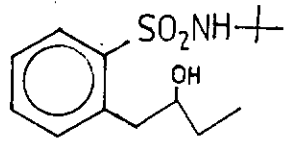
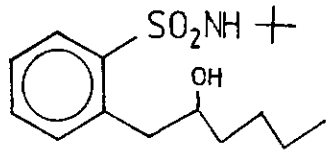
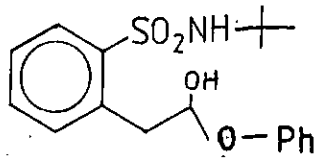
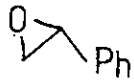
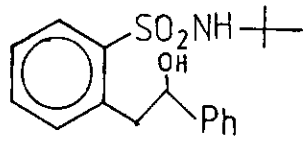
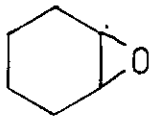
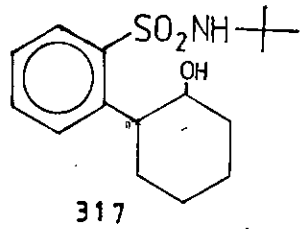
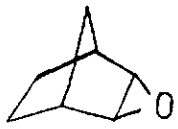
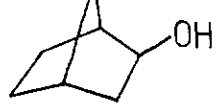
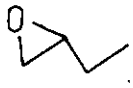
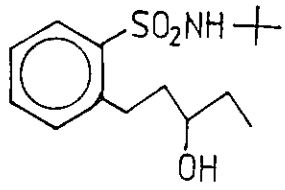
Reaction with trans-2,3-epoxybutane

As the use of secondary epoxides fused with other rings proved not suitable as electrophiles on lithiated benzenesulphonamides, a monocyclic secondary epoxide was then attempted. A geometric isomer such as trans-2,3-epoxybutane is anticipated to give only one isomer predominantly viz:

270 320

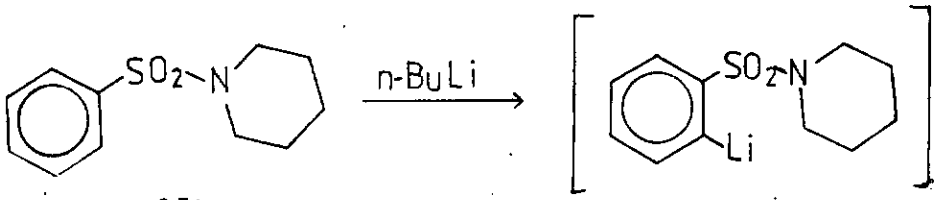
The above epoxide dissolved in dry THF was treated with the lithiated benzenesulphonamide as usual and stirred for 24h at room temperature. Work-up gave a brown oil. Thin layer chromatography of the crude oil showed four spots with a large quantity of starting material. Attempted chromatographic separation of this crude product into its components did not yield any useful results.

Reactions of lithio species with different epoxides:

Type	Substrate	Epoxides	Products	(%)	m.p. °C
1	270		 313	40	110-112
2	270		 314	41	oil
3	270		 315	35	104-106
4	270		 316	30	oil
5	270		 317	25	oil
6	270		270 +  318b		
7	280		 338	45	oil

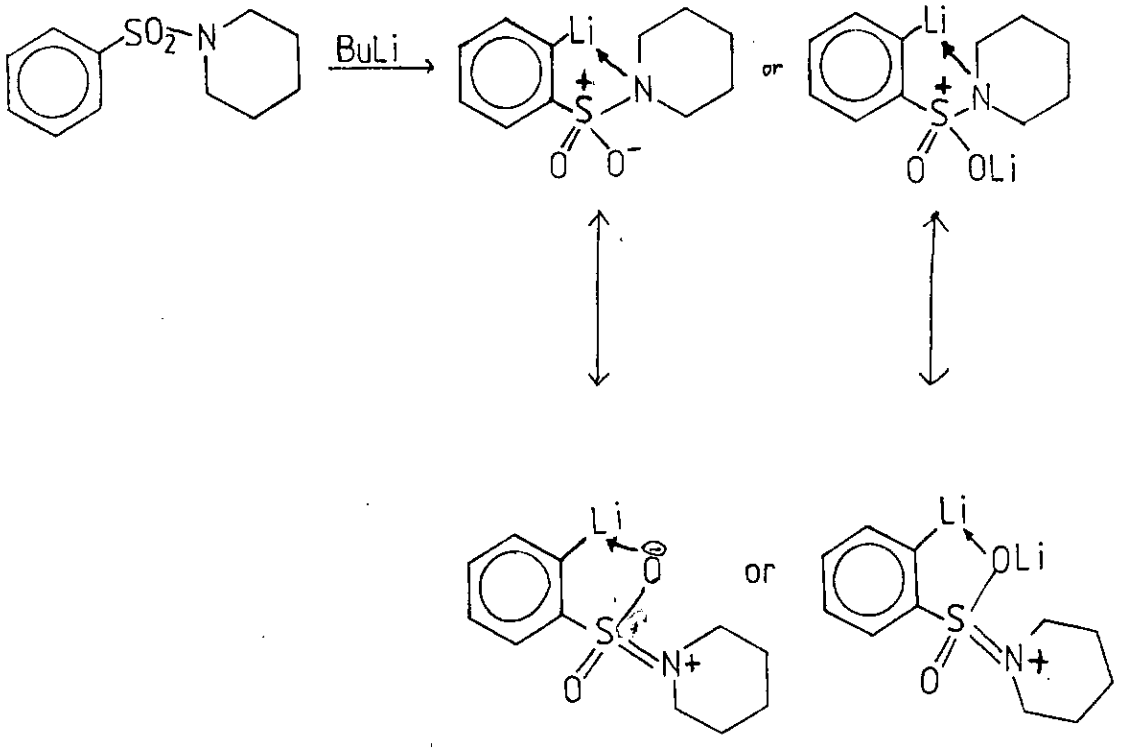
Reactions of Epoxides with Tertiary Benzenesulphonamide

Attention was then directed to the reaction of tertiary sulphonamides with both primary and secondary epoxides. N-(benzenesulphonyl) piperidine prepared by methods reported earlier was lithiated with 1.1 equivalent n-BuLi to generate the ortho lithio benzenesulphonamide.



274 274a

The deep red organolithium is proposed to be generated by the following mechanism below:



Reactions of Primary Epoxides with Lithiated Tertiary Benzenesulphonamides

The lithiated (piperidinosulphonyl) benzene was reacted with 1,2-epoxybutane, since this epoxide was earlier used on the lithiated secondary sulphonamide-N-t-butylbenzenesulphonamide and had given the expected alcohol product. On reaction of the electrophile with the lithio species at room temperature for 24h, the usual red colour of the lithio species was discharged. However, work-up and separation of the crude product obtained did not give the desired compound.

1,2-epoxyhexane, (±)-epoxy-3-phenoxypropane as well as styrene oxide which had previously reacted smoothly with secondary benzenesulphonamides all failed to react.

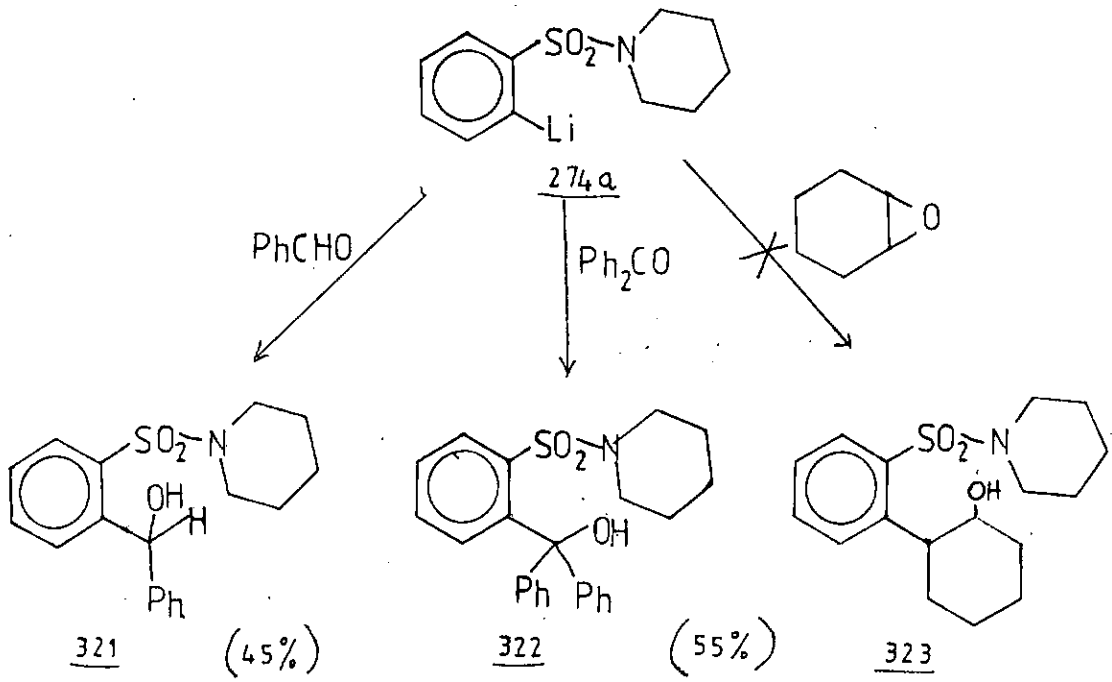
Reaction of Secondary Epoxides with the Lithiated Tertiary Benzenesulphonamides

Cyclohexene oxide in THF was added to lithiated (piperidinosulphonyl) benzene at 0^{o} and stirred at room temperature for 24h. Standard work-up gave products which were not the expected products just like with the primary epoxides reaction.

The phenomenon may not be totally unexpected as Snieckus[93] had observed this in lithiated carboxybenzamides before, in which styrene oxide reacted smoothly with a lithiated secondary carboxybenzamide but failed to react with tertiary benzamide.

The ability of the tertiary benzenesulphonamide to form lithio species and react with electrophiles is not in doubt, because Queguiner et al[63] had generated ortho lithio species of (piperidinosulphonyl)benzene and had coupled the species with benzophenone in 55% yield at 0^{o}.

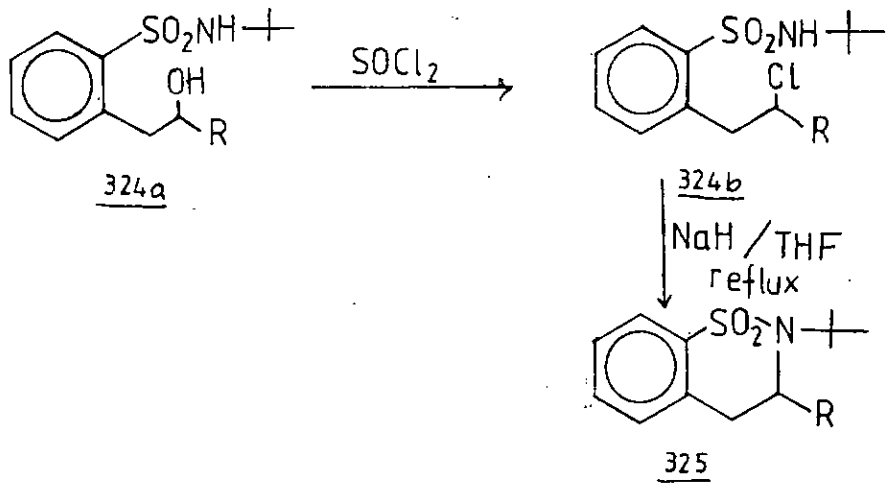
This was further confirmed by using an aldehyde-(benzaldehyde) on this lithio species which gave the expected product at 0°. These confirmed that the epoxides are simply weak electrophiles that failed to couple.



As attempts to obtain the ortho β-hydroxybenzenesulphonamides required for the synthesis of the S-containing heterocycles; benzooxathiins failed, attention was directed to possible use of the products of the reaction of secondary benzenesulphonamides in heterocycle synthesis.

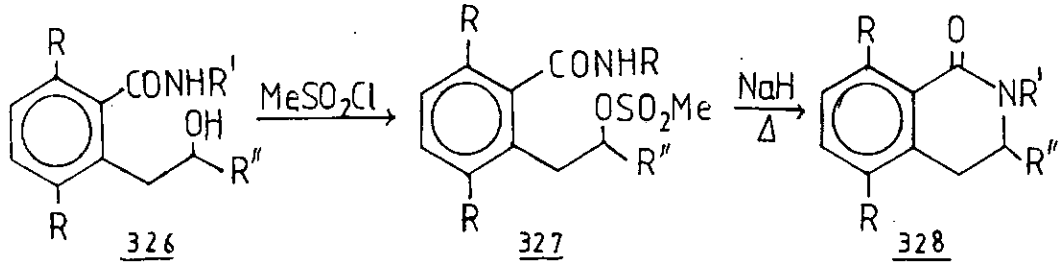
2.2 Attempted Utilization of the Metalation Products as Heterocyclic Synthetic Precursors

The product obtained from the successful reaction of primary epoxides and secondary sulphonamides were to serve as precursors in the formation of substituted heterocycles for example, benzothiazines through the route delineated below:



324a 324b 325

As a precedence Ellefson[24] had reported the use of the reaction of lithiated secondary carboxylamide with epoxides in the synthesis of coumarins by conversion of a β-hydroxy group to a good leaving group, e.g. sulphonate. The latter group was readily cleaved to give the desired compound on reflux. The use of an analogous method that utilizes a different leaving group in this case, a chloro was attempted:



326 327 328

The carbinol 324a was smoothly converted to a chloro compound by refluxing with thionylchloride for 2h, as evidenced by the total absence of the hydroxyl absorption in both the NMR and IR and the downfield shift of the base proton on the carbon bearing the chloro atom, due to the higher electronegativity of the chlorine atom.

CHAPTER 2

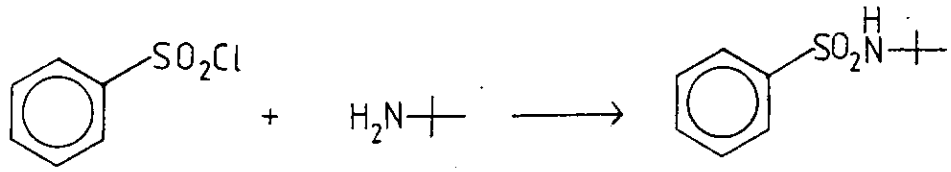
RESULTS AND DISCUSSION

2.1 HETEROCYCLES THROUGH 2-LITHIOBENZENESULPHONAMIDE

The heterocyclic synthesis intended in this study were essentially new aromatic sultones: benzoxathiins. The proposed route outlined requires ortho β-hydroxyl group contiguous to an aromatic sulphonamide functionality. Such ortho β-hydroxymethyl benzenesulphonamide precursors were designed to be obtained via metalation of benzenesulphonamides and subsequent coupling reactions of the lithio benzenesulphonamides with epoxides.

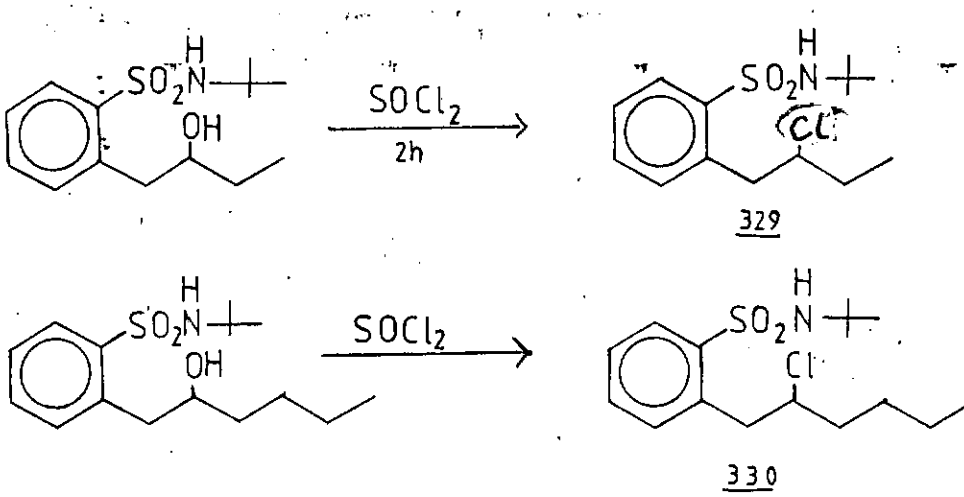
As reported in the introduction, the alkyl benzenesulphonamides which are the precursors in the metalation strategy to be adopted were synthesised by the usual Schotten-Baumann reactions. Coupling of the appropriate amine in an inert solvent with redistilled benzenesulphonyl chloride, gave the desired precursor compounds.

N-t-butylbenzenesulphonamide was obtained by using tertiary butylamine. Three equivalents of the amine was necessary to each mole of the benzenesulphonyl chloride.



268 269

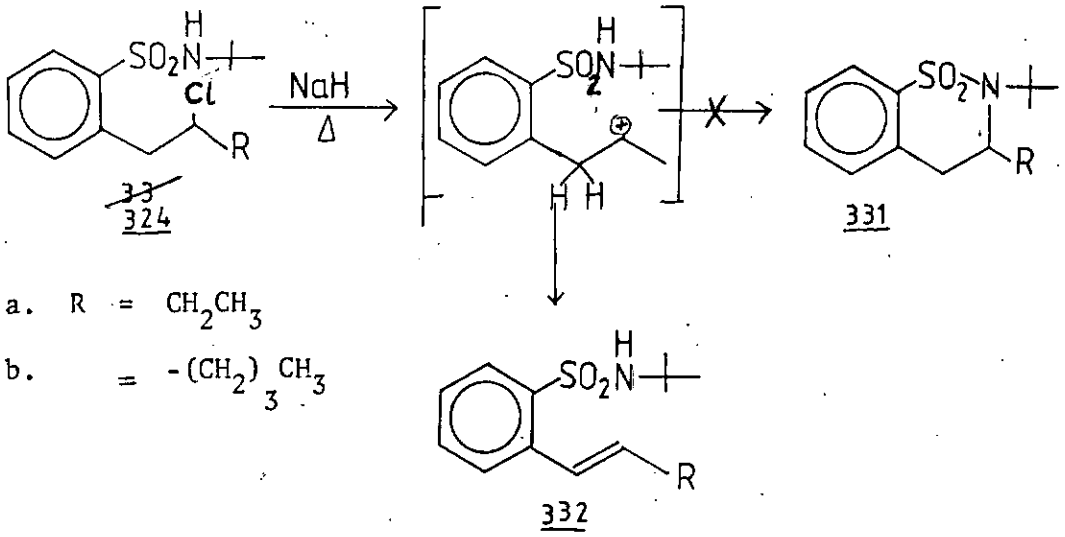
Work-up each time gave analytically pure product N-t-butylbenzenesulphonamide in 93% yield. (Lit[107] m.p. 77-80°) melting point obtained was 78-80°. The ^{1}H-N.M.R. spectrum showed nine proton singlet at δ 1.2 for the t-butyl group, while a broad



329

330

Each of the chloro compound was dissolved in dry THF and sodium hydride (which was to abstract the chlorine ion) was added. It was anticipated that on the departure of the chlorine ion, a carbonium ion will be generated, which the lone pair of electrons on the nitrogen can attack to form the expected benzothiazine.



~~33~~ 324

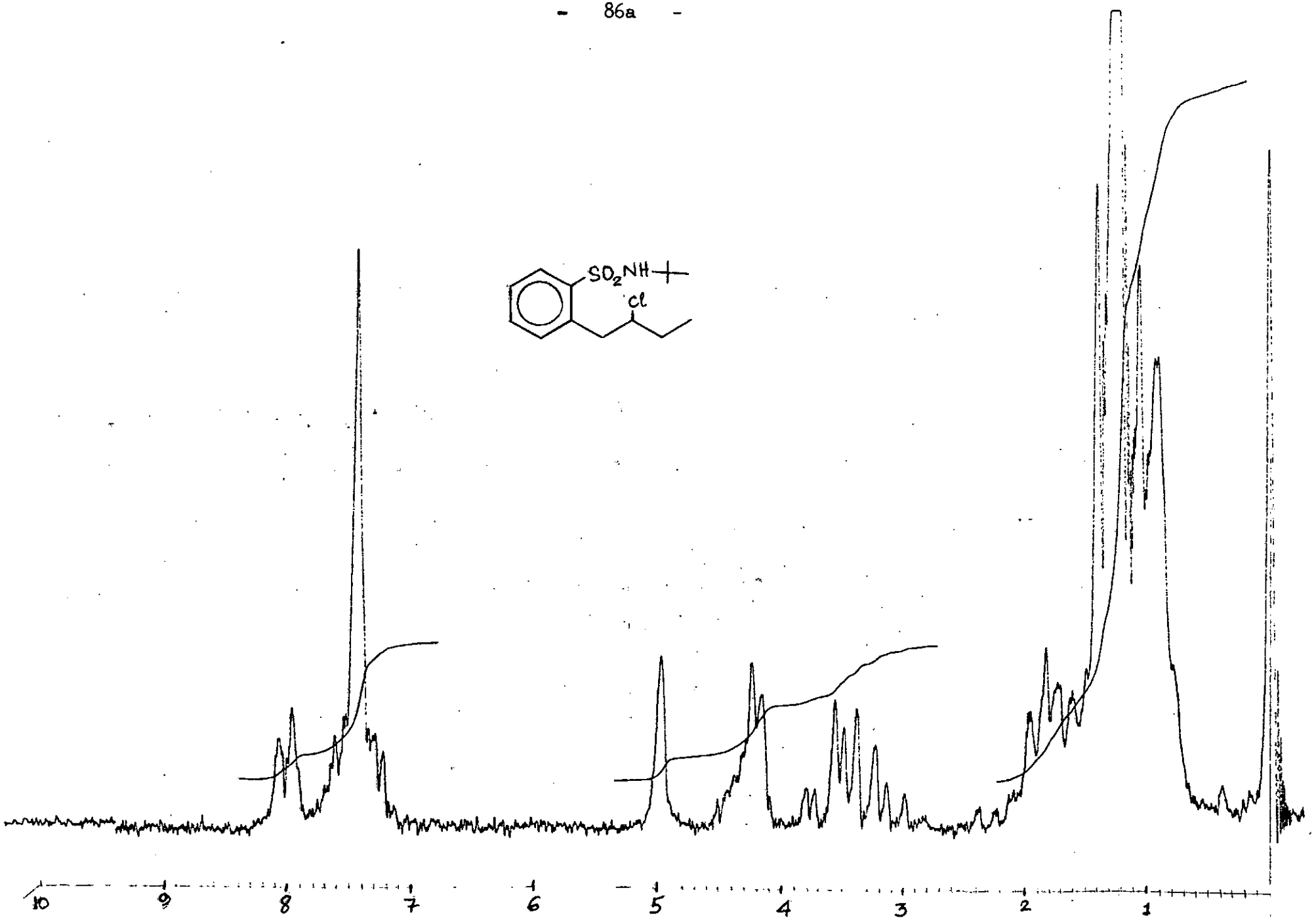
331

a. R = CH_2CH_3

b. = $-(CH_2)_3CH_3$

332

However, on work-up of the reaction mixture, the expected product was not obtained in each case. Rather a dehydrochlorination product was formed. The rate of dehydrochlorination of the compound seems to have been faster than the nucleophilic attack of the lone pair of the nitrogen on the carbonium ion.


SO2NH
Cl
10
9
8
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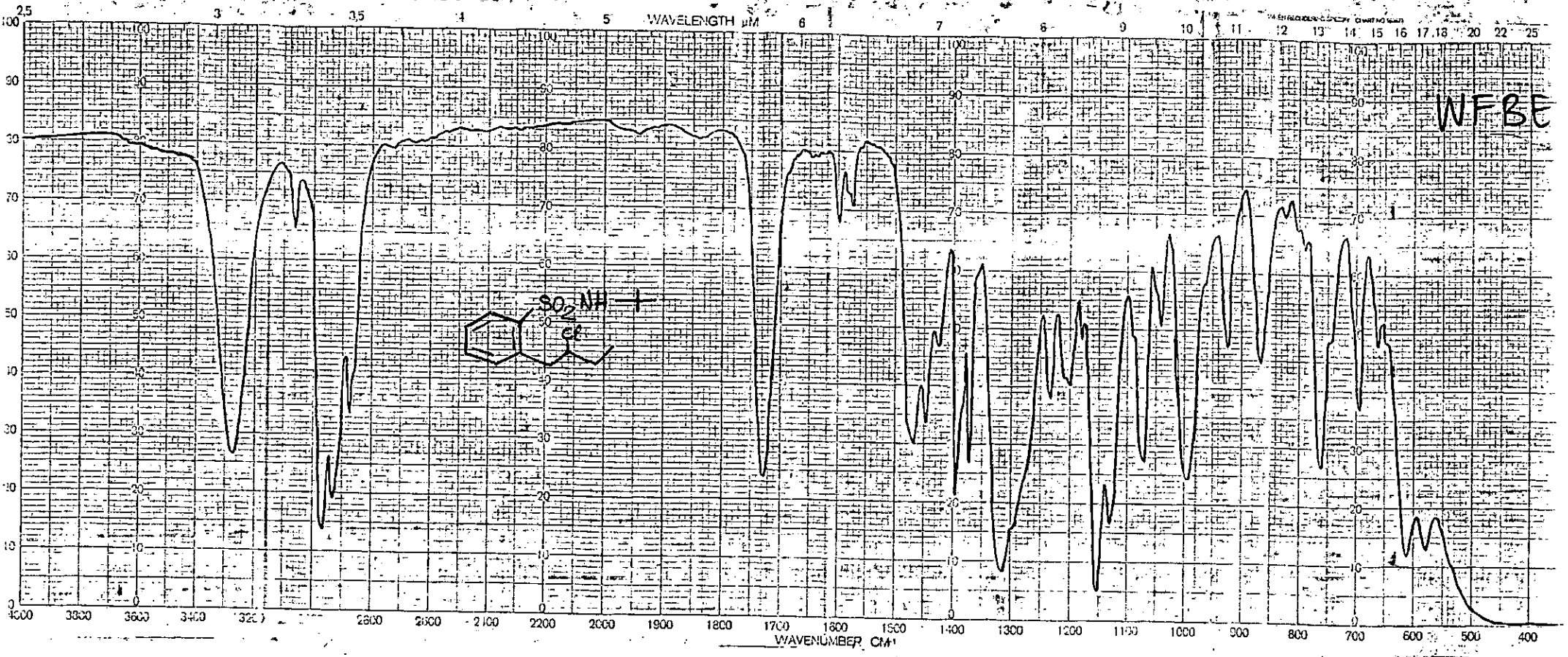
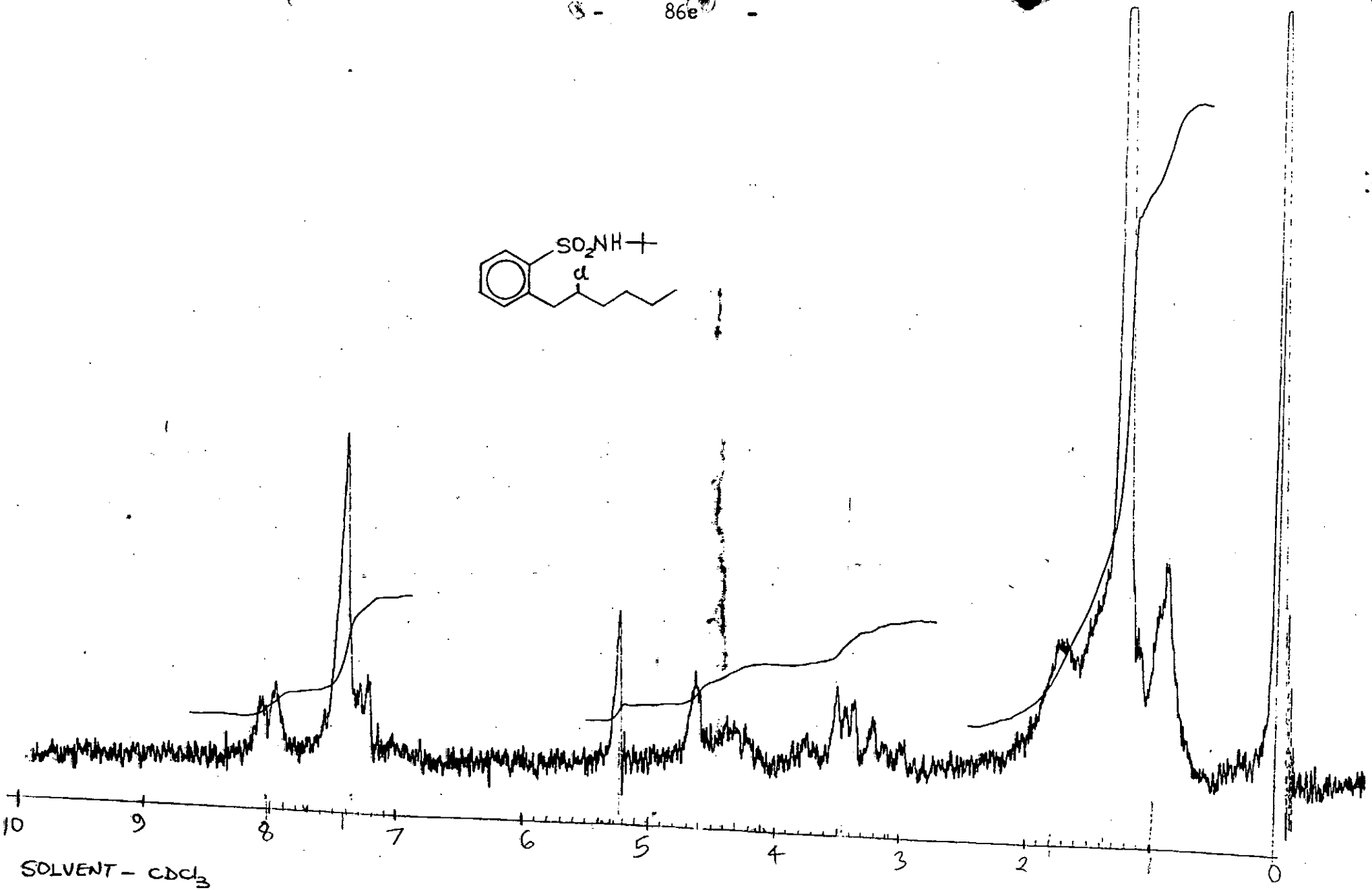
4
3
2
1



WF BE 16


SO2NH
a
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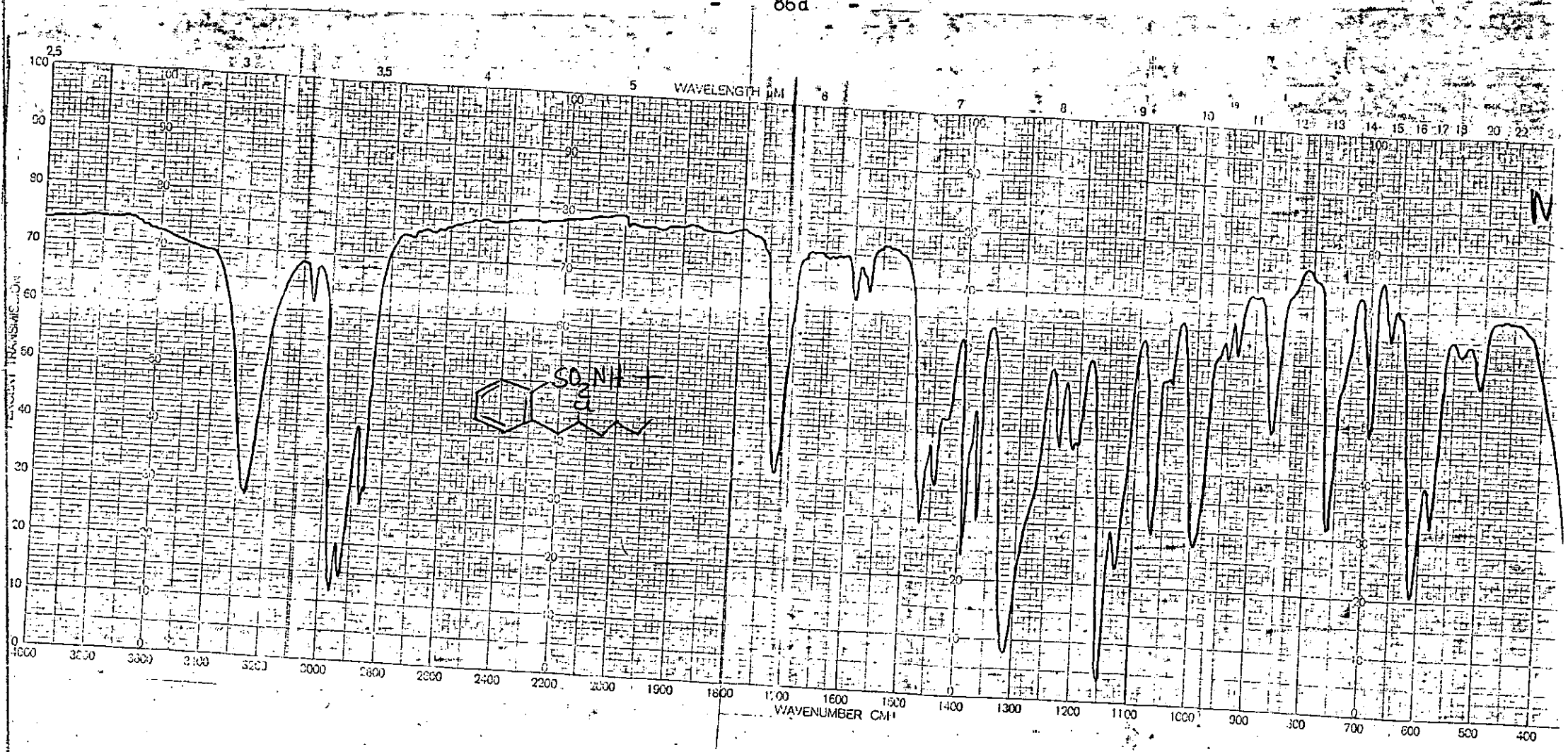
SOLVENT – CDCl3
15/4/89

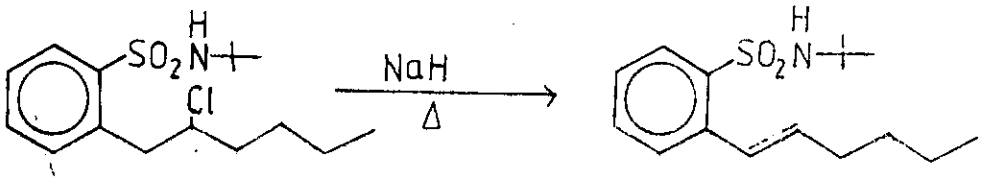

WAVELENGTH μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION
SO2NH
Cl

The N.M.R. of the dehydrohalogenated products confirmed the elimination reactions as the vinylic double bond protons were observable in the low field region.

The t-butyl 9H singlet was overlapping the 3H triplet of the side chain methyl group at δ1.2. A methylene 2H multiplet absorbed at δ2.4, while the NH broad absorbed at δ4.8. The vinylic 1H multiplet was observed at δ6.1 while the other vinylic 1H multiplet for the second vinylic proton was at δ6.3. The aromatic 3H multiplet at δ7.6 represented H-3,H-4, and H-5 while H-6 showed a 1H doublet of a doublet at δ8.1.

Micro analysis was satisfactory for the proposed product.

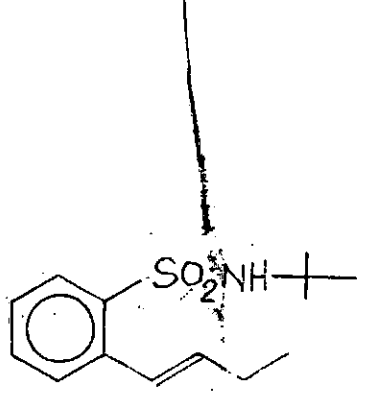
The collapse of the CH_2 bond adjacent to the phenyl ring was obvious. The presence of the -NH absorption at δ4.8 which was expected to disappear upon formation of the target compound was confirmatory evidence for the non-formation of the benzothiazine target.

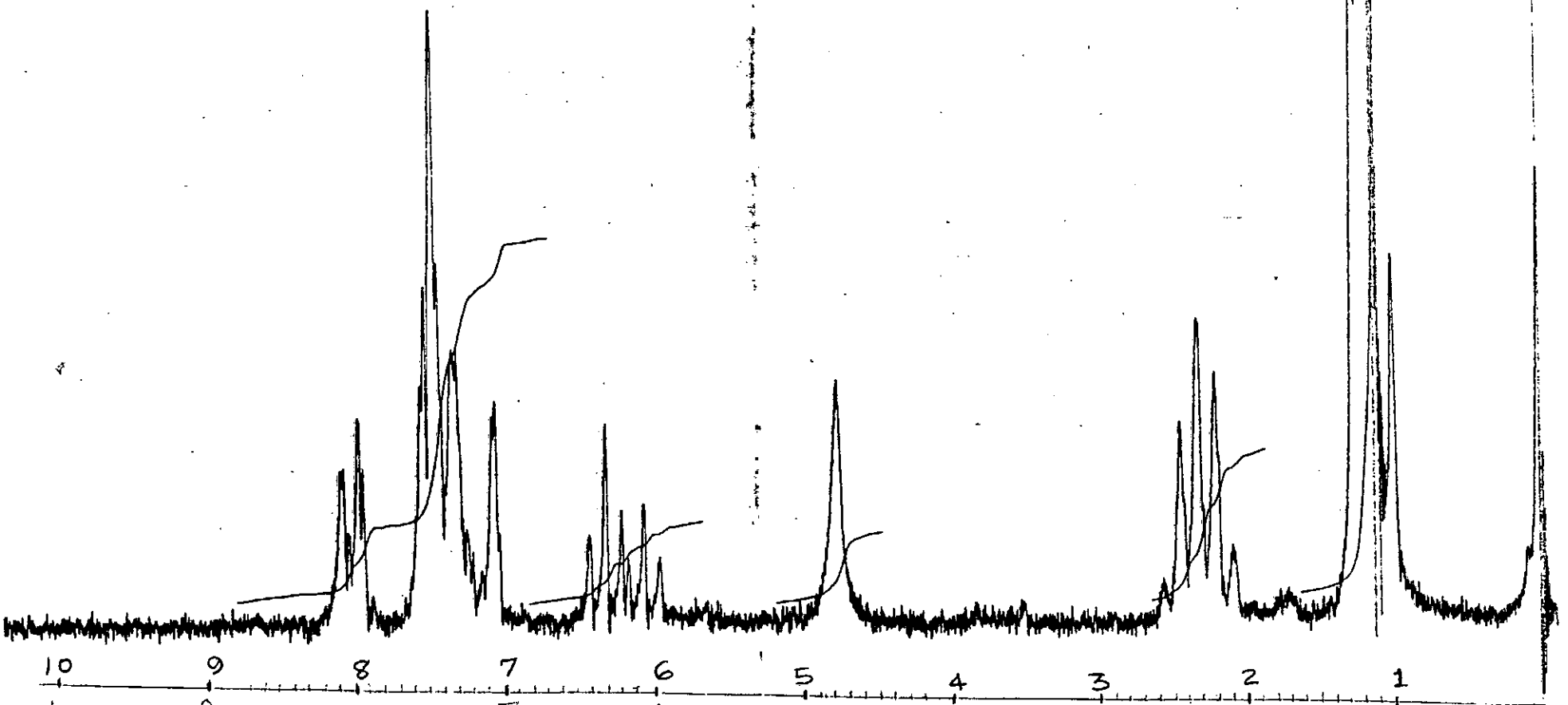


330 333

2.3 S-Containing Heterocycles through Lithiomethyl-Benzenesulphonamides

As earlier attempts through the use of epoxides directly on aromatic ring anion failed to produce the desired heterocycle precursors, efforts were then directed at using other metalation routes for obtaining the desired ortho β-hydroxybenzenesulphonamide functionality. Benzophenone reaction with benzylic anions was designed as outlined below:


SO2NH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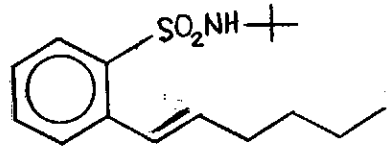
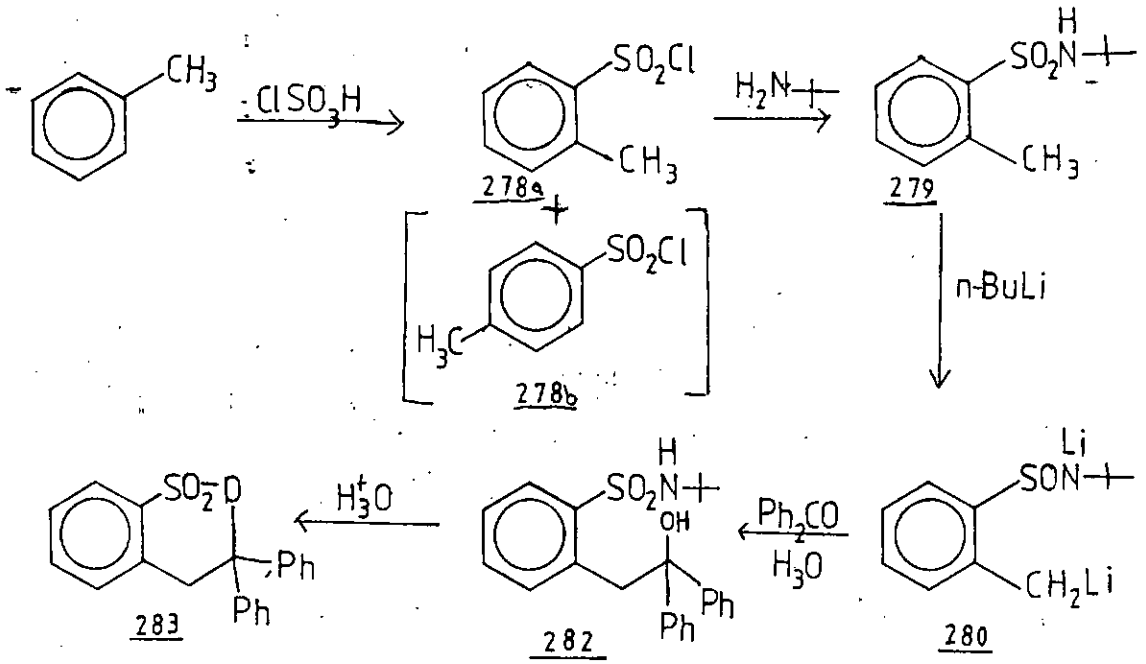
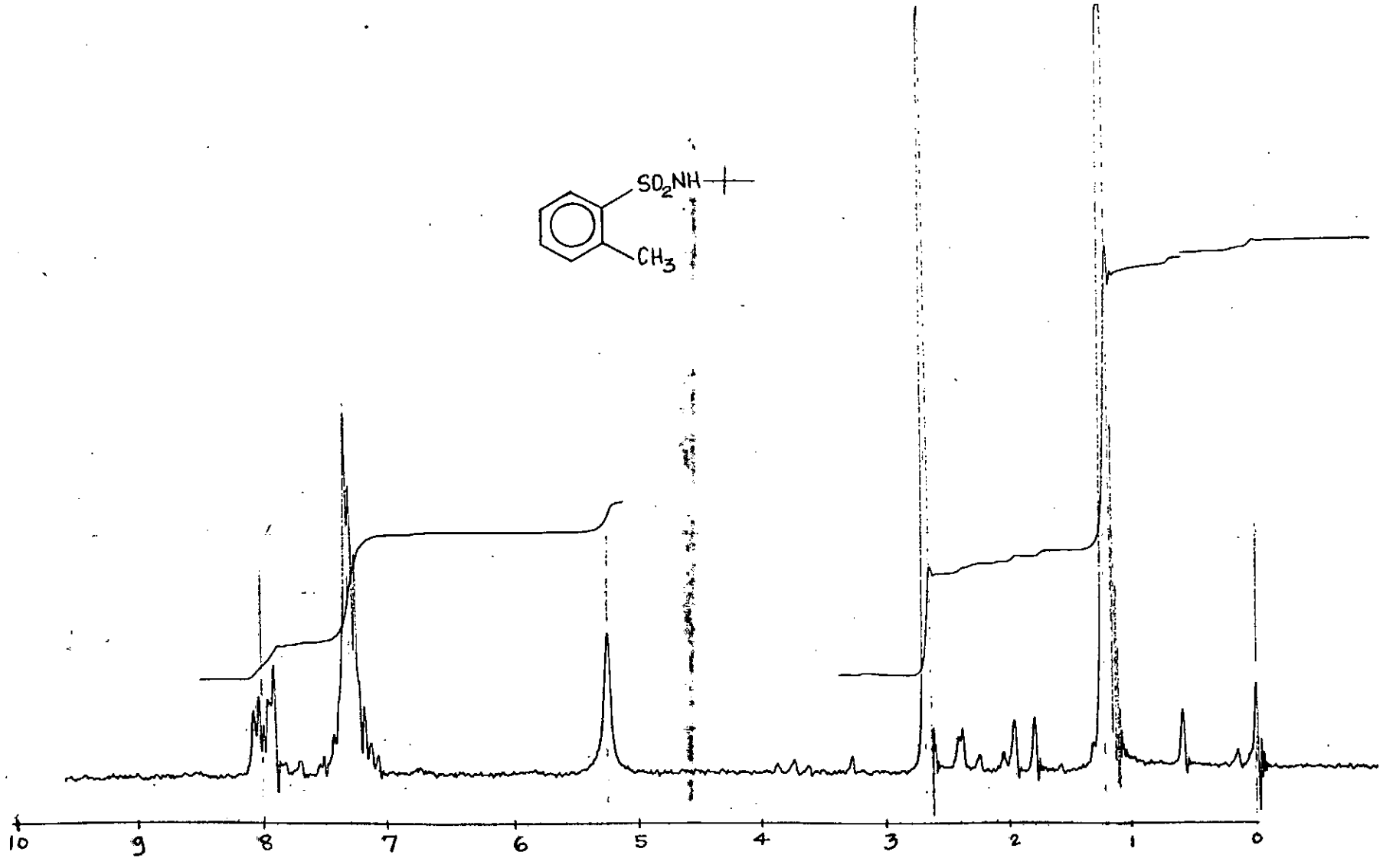


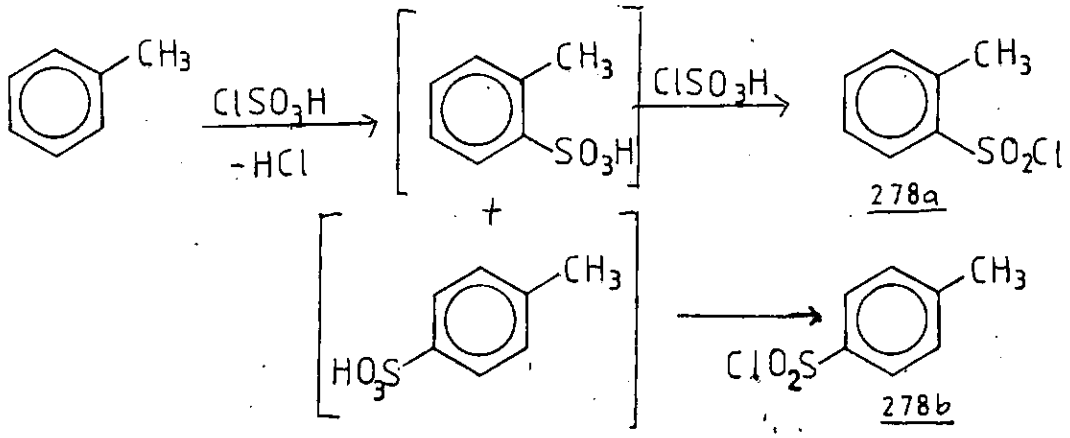
SOLVENT – $CDCl_3$
22/4/89



The synthesis was started with the chlorosulphonylation of toluene at low temperatures to give a mono sulphonyl chloride. At high temperatures, 2,4-disulphonyl chlorides predominated. Even the mono chlorosulphonylation reaction gave a mixture of ortho and para toluene sulphonyl chlorides, with the ortho predominating.

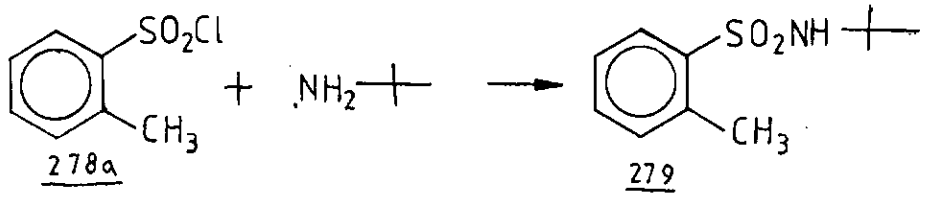
The separation of the two isomers exploits the difference in their physical property. The ortho isomer is a liquid at room temperature while the para isomer melts at 67°. The crude product was cooled to -20° for 6h, after which the solid para isomer was filtered, while the required liquid ortho compound was recovered and redistilled. Separation by column chromatography or fractional distillation was not possible as the two isomers show the same R_f in several solvent mixtures and form an azeotropic boiling point.


SO2NH
CH3
10
9
8
7
6
5
4
3
2
1
0



Mechanistically the sulphonyl chloride is known to be formed from the initial intermediate sulphonic acid that is formed by the excess chlorosulphonic acid present as shown above .

The sulphonyl chloride obtained was coupled with t-butylamine at 0^{o} via the typical Schotten-Baumann reactions.



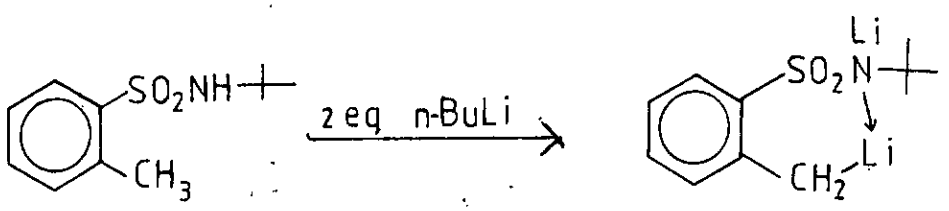
Recrystallisation of the sulphonamide gave analytically pure compound as white needles m.p 127-129°, ^{1}H-N.M.R. of the product showed a 9H singlet for the t-butyl group at δ1.2 while the 3H singlet of the methyl group three protons was at δ2.7. The NH 1H singlet absorbed at δ5.3 (exchangeable with D_2O). The 3H multiplet of aromatic protons H-3, H-4 and H-5 was at δ7.3, the H-6 doublet of a doublet absorbed at δ7.9.

Microanalytical data was also in agreement with the expected values.

The N-t-butyl-2-methylbenzenesulphonamide was further vacuum-dried before use in metalation reactions.

Lithiation of N-t-butyl-2-methylbenzenesulphonamides

N-Alkylbenzenesulphonamides are known to be good ortho directors in aromatic lithiation reactions[103]. However, when one of the ortho positions is substituted by a methyl group, the methyl group itself is deprotonated by n-BuLi in preference to ring metalation. This is due to the relatively more acidic nature of the methyl protons because of the acidifying effect of the sulphonamide group and the ready formation of a six-membered lithiation intermediate as compared with the five-membered lithiation intermediate in the ring metalation process.

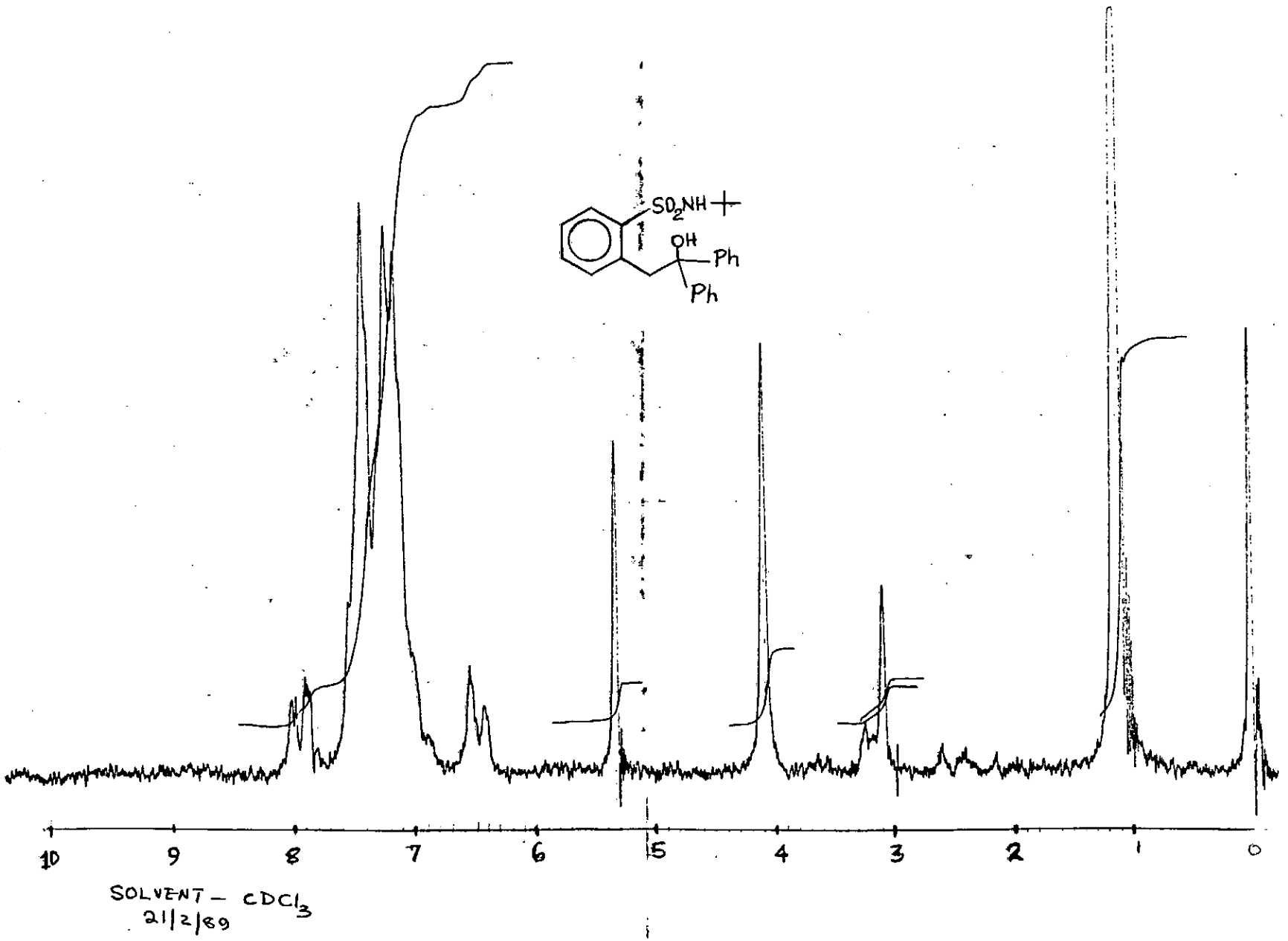


279 280

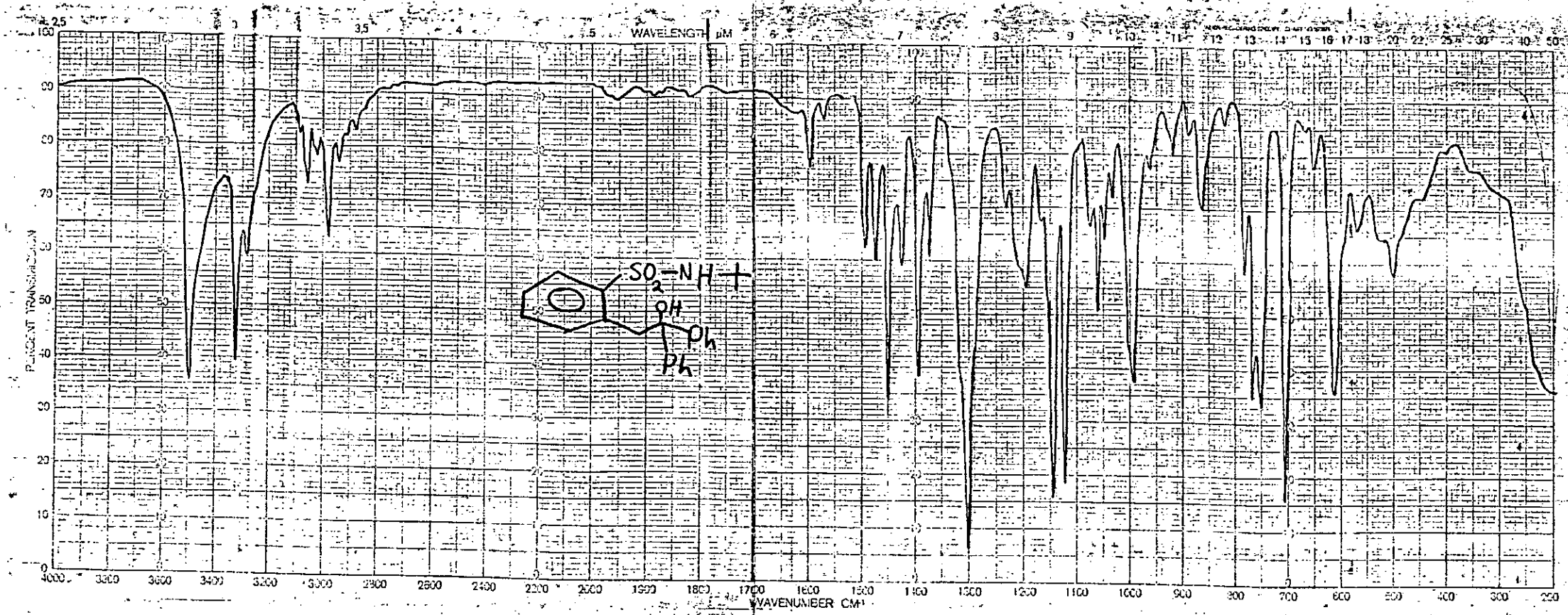
The benzylic anion formation therefore seems to be faster and more preferred than the ring metalation. Reaction times of half hour at 0^{o} for the side chain metalation and two hours at room temperature for the ring metalation seem to confirm this.

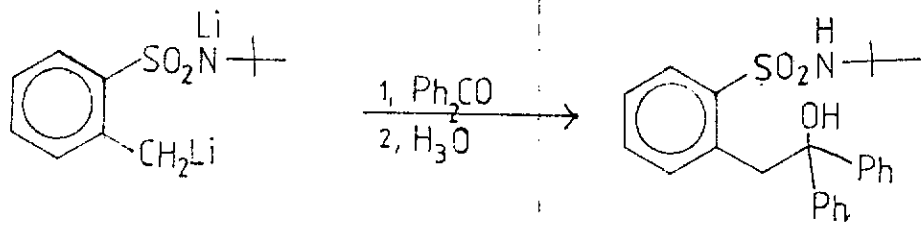
Addition of two equivalent of n-BuLi to a solution of N-t-butyl-2-methylbenzenesulphonamide gave a red solution of the 2-lithiomethylbenzenesulphonamide. The benzylic anion was immediately coupled with benzophenone in THF at 0^{o} and stirred for two hours.

Hydrolysis of the reaction mixture gave a viscous solid which was recrystallised from methanol to give white crystalline material which was further purified by silica gel flash chromatography with ether: cyclohexane mixture.


SO2NH
OH
Ph
Ph
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – CDCl3
21/2/89

90b


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹
SPECTROPHOTOMETER



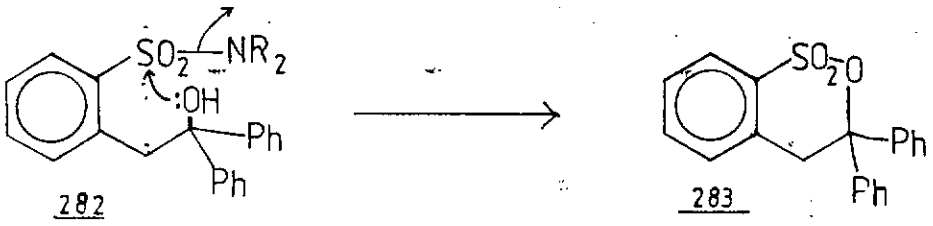
The NMR of the product showed a 9H singlet at δ1.1 for the t-butyl group while the exchangeable OH proton appeared at δ3.1. The methylene protons 2H singlet absorbed at δ4.1 while a signal at δ5.3 was due to -NH. The ten protons of the unsubstituted phenyl groups absorbed at δ7.1 - 7.4 along with the H-3,H-4,H-5 of the substituted phenyl ring while the 1H doublet of the H-6 absorbed at δ8.0.

Microanalytical data were in accord with expected values for the product being 2-(2-N-t-butylbenzenesulphonamido)-1,1-diphenyl-ethanol.

Heterocyclisation Attempts

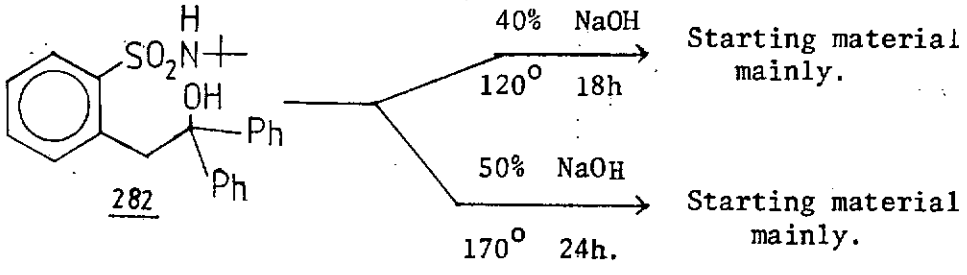
The carbinol 282 could be cyclised into the desired heterocycle by either refluxing the carbinol with 50% sodium hydroxide as reported by several authors on the carboxylamide analogues[24] or by refluxing with 6N HCl.[18] However, the possible dehydration of the hydroxyl group as obtained by Watanabe et al[104] when concentrated sulphuric acid (which could have been the best reagent) was used had to be avoided. Dilute hydrochloric acid that will prevent dehydration or better still basic hydrolysis was therefore planned for the cyclisation.

Basic hydrolysis was first tried. Normally sulphonamides do not undergo basic hydrolysis[129a] but it was thought that with very high temperatures and in the presence of nucleophilic hydroxyl group, the S-N bond cleavage might be possible.



282 283

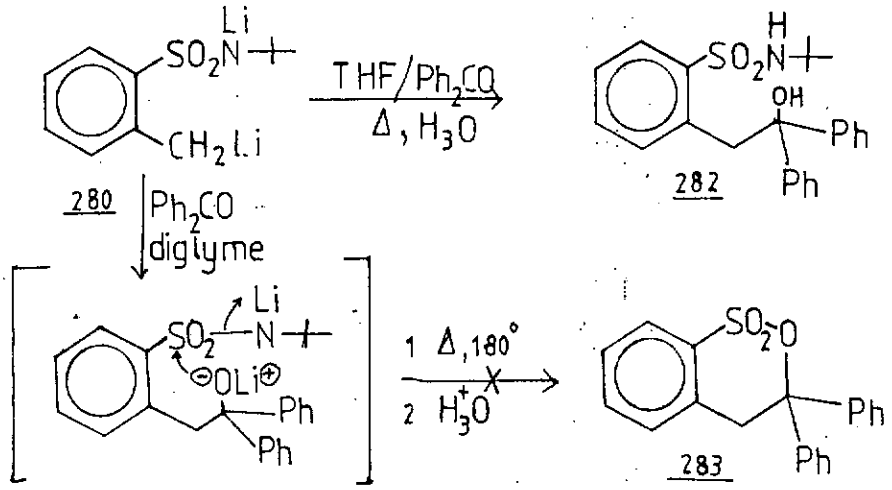
This was attempted by refluxing the carbinol with 40% sodium hydroxide at 120° for 18 hours. On work-up the starting material was recovered. The reaction was also tried by using 50% sodium hydroxide and a higher temperature of 170° for 24h; starting material was also obtained. Basic hydrolysis therefore did not give a successful cyclisation despite the harsh conditions and the presence of an internal nucleophile in the molecule.



282

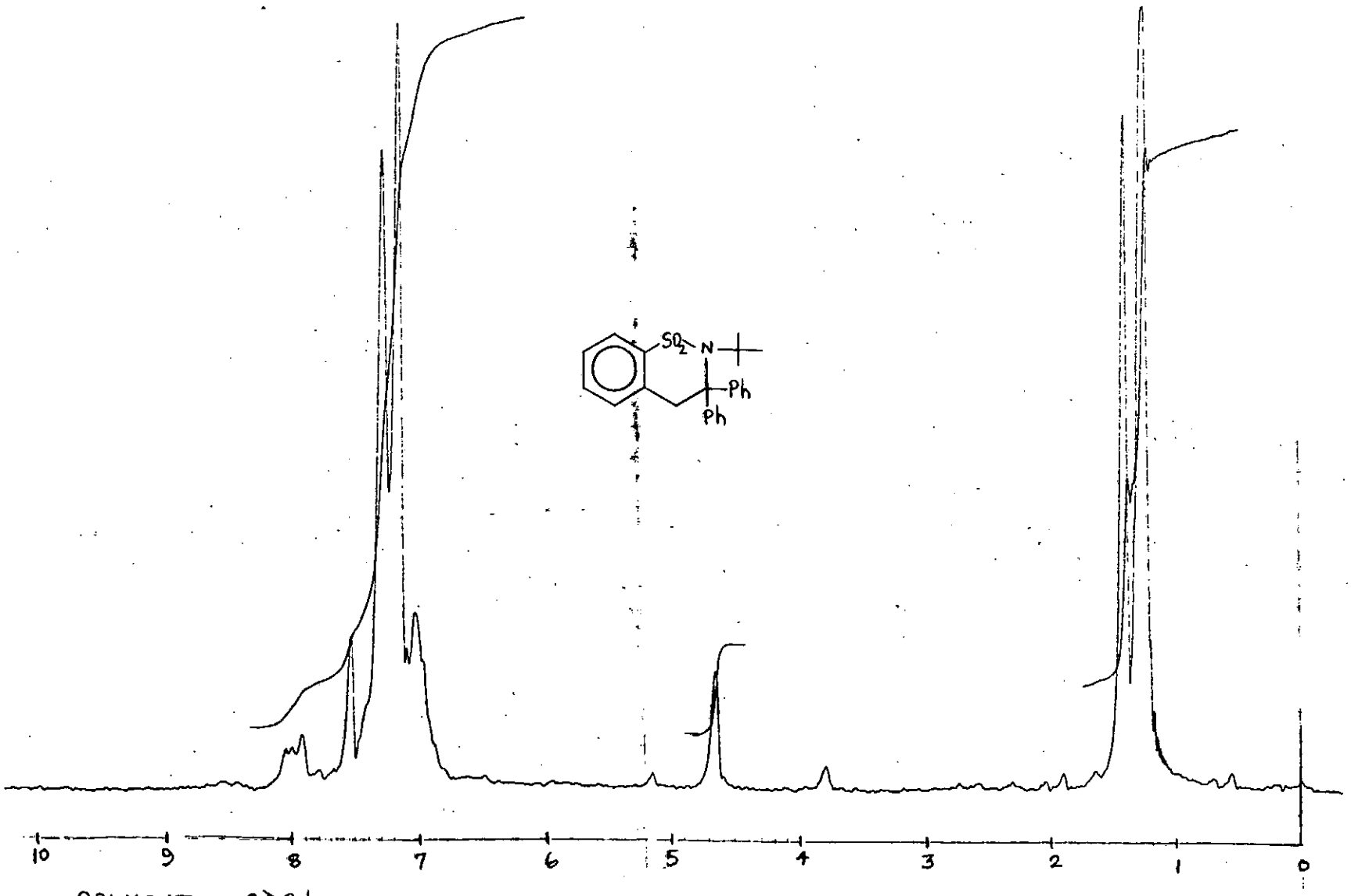
The cyclisation was attempted with the unhydrolysed lithiation product. It was thought that the oxygen atom in the -OLi form should be very nucleophilic and therefore appropriate treatment at that stage may make the cyclisation occur. Work-up of the reaction mixture after refluxing in THF for eight hours gave the carbinol 282 without any cyclisation.

Attention was then directed to a change of the lithiation solvent. Diglyme was then used as lithiation solvent, i.e. from low boiling THF to higher boiling diglyme to enable higher temperature reflux for the cyclisation reactions. The O-toluyl anion of N-t-butyl-2-methylbenzenesulphonamide generated in CaH-dried diglyme and benzophenone also in diglyme was coupled with the lithio species to give the intermediate. Refluxing the intermediate at 180° did not effect a cyclisation either.



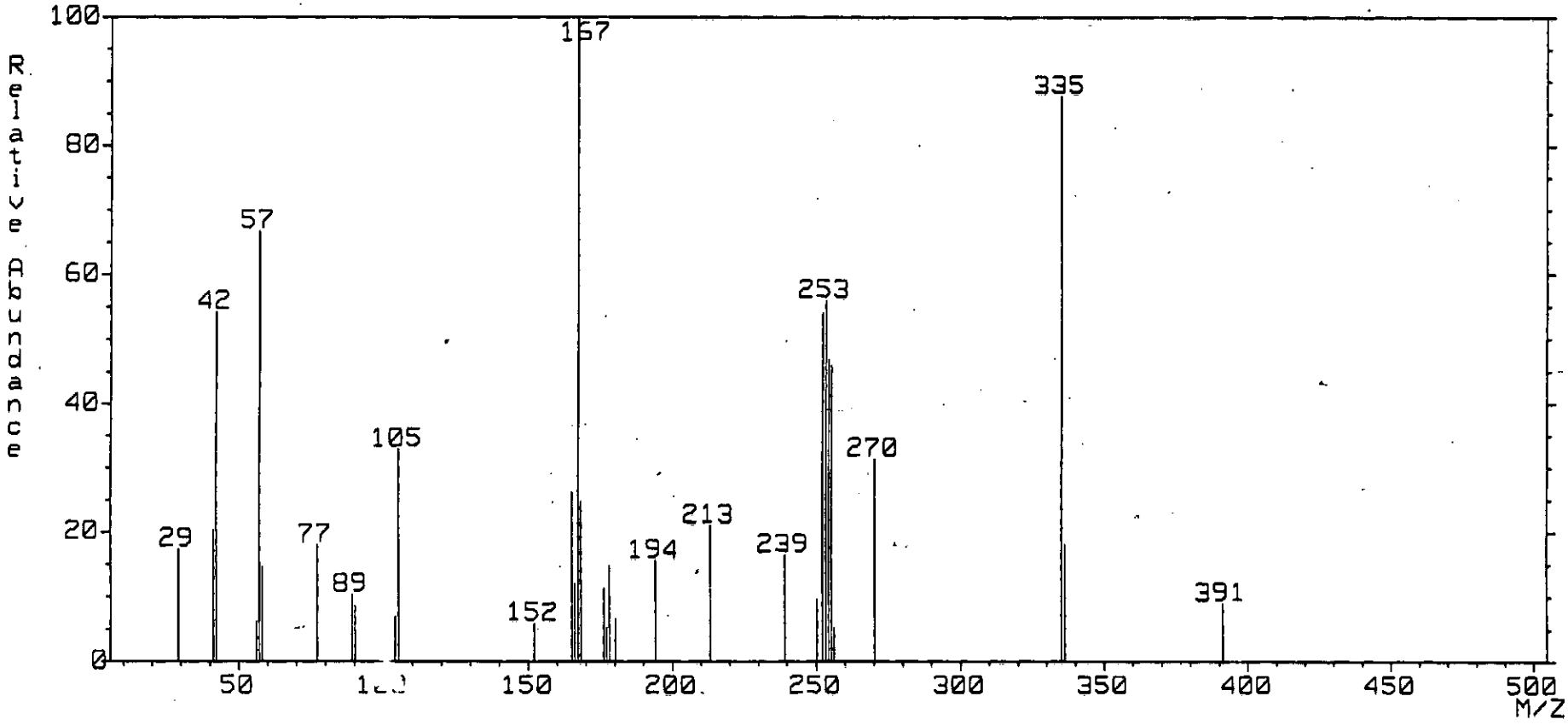
The reaction condition was changed to the use of dilute hydrochloric acid. Refluxing with 33% hydrochloric acid at 130° for 48h gave on work-up, an oil which later solidifed.

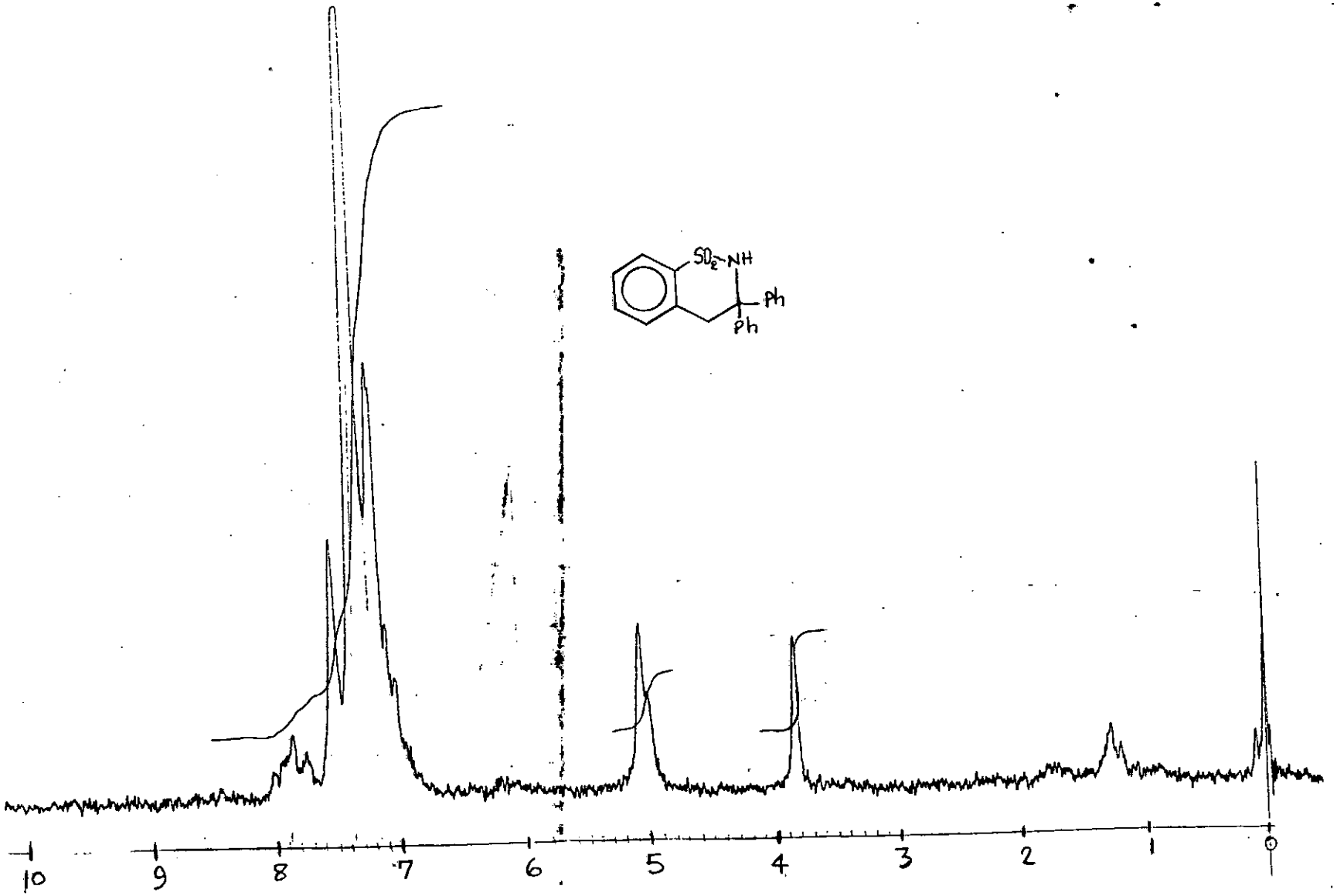
T.l.c. of the white product showed two spots in cyclohexane: ether 1:1. Flash chromatography of the product gave two compounds. The ^{1}H-NMR of the compound with the high R_f showed a 9H singlet of the t-butyl group at δ1.40 and other absorptions included a 2H singlet at δ4.7 for the two protons of the methylene group, while the aromatic protons showed an unresolved 10H multiplet of the two



SOLVENT – $CDCl_3$
17-3-89

MASS SPECTRUM Data File: JCRWFBM1 26-APR-89 11:26
Sample:
RT 1'38" EI (Pos.) GC 102.4c BP: m/z 167.0000 Int. 4.3609 Lv 5.00
Scan# (50)





SOLVENT - $CDCl_3$

MASS SPECTRUM Data File: JCRWFBM3 26-APR-89 11:57
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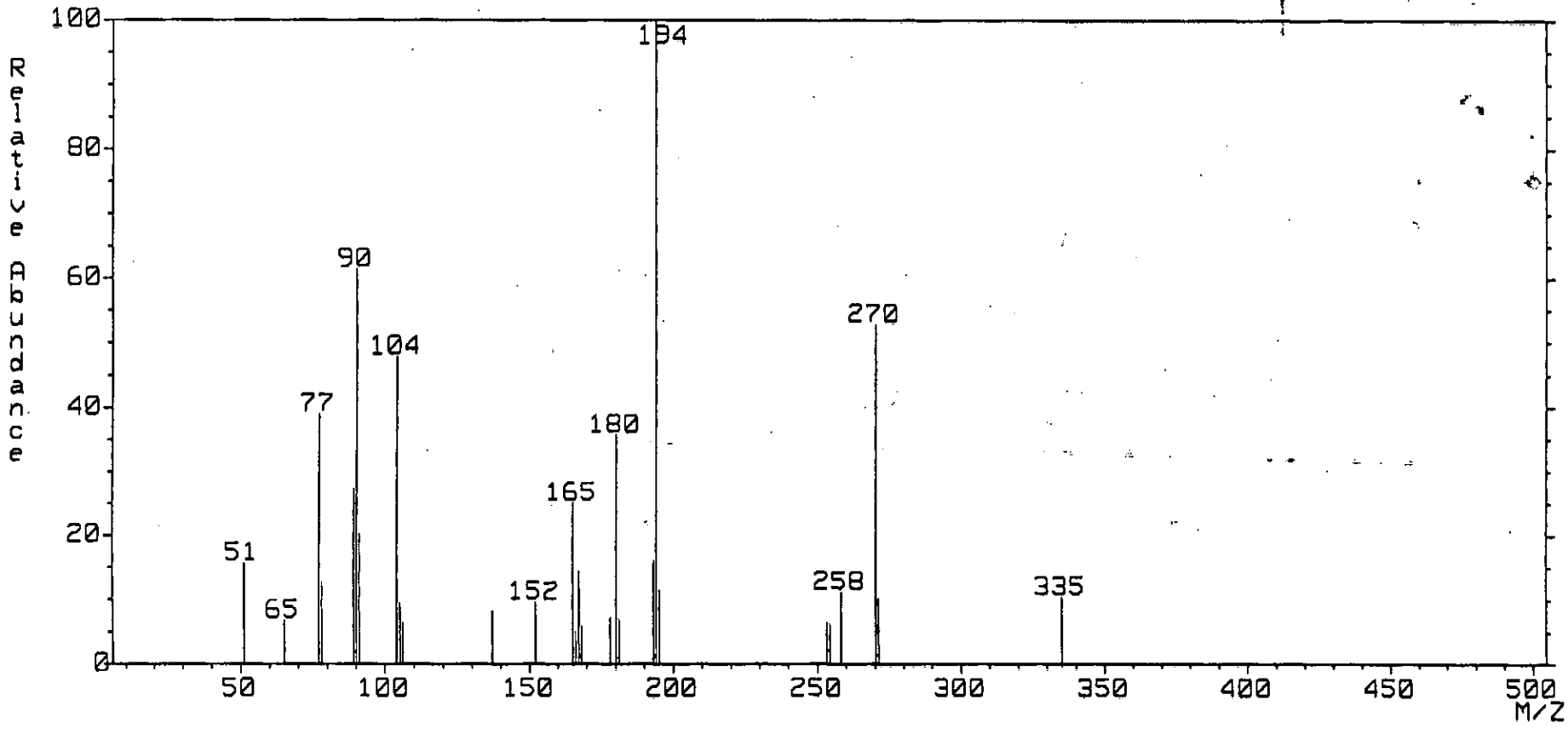
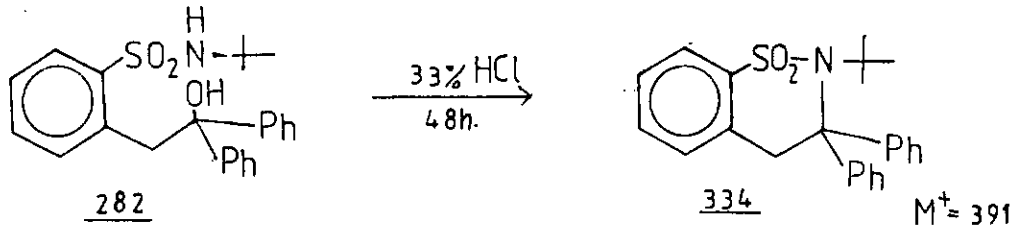
Scan# (28)

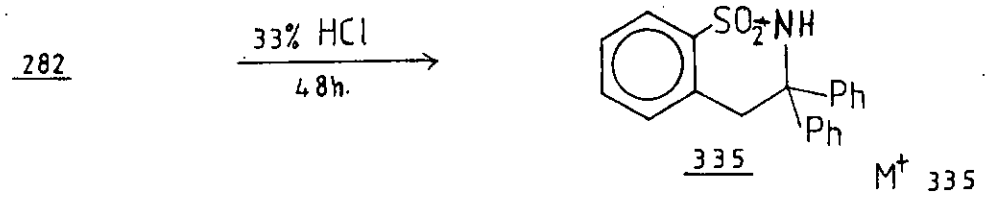


phenyl groups along with H-3,H-4,H-5 protons of the substituted ring at δ 7.0 - 7.5 and a 1H double doublet at δ 8.0. The mass spectrum gave abundant molecular ion at $^{m}/_{z}$ 391. These analytical data combined with the elemental analysis indicated the probable product obtained as a benzothiazide rather than a sultone.



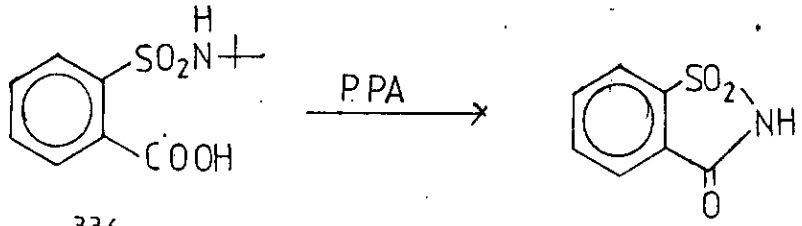
282 334

The lower R_f compound's ^{1}H-NMR spectrum did not show a t-butyl group, but gave an -NH group absorption at δ 5.1 and methylene 2H singlet at δ 3.9. The mass spectrum gave a molecular ion peak at $^{m}/_{z}$ 335. The probable product was a benzothiazide formed by cyclisation with loss of the t-butyl group. It was incorrectly expected that the loss of the t-butyl group could accompany the loss of the S-N bond.



Increase of the concentration of the hydrolysing acid from 33% to 50% hydrochloric acid and refluxing at 170° for 40h gave three products on t.l.c. The first was a low yield oil, while the second product was a solid obtained in only 10% yield.

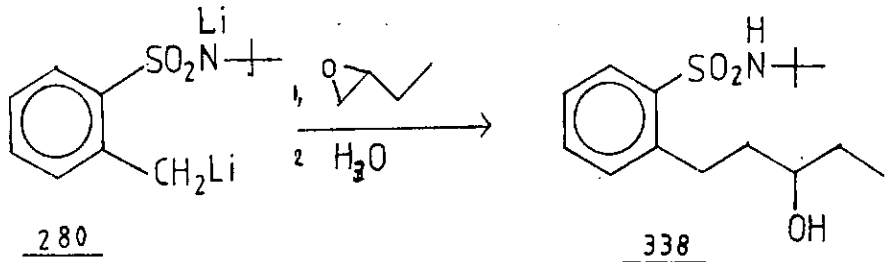
These two compounds were not further pursued. However, the main product did not show a t-butyl group in it's N.M.R. spectrum and had a M^+ of 335. It therefore showed similar characteristics to the low R_f product from the 33% hydrochloric acid earlier reaction. Thus higher acid concentration seems to lead to preferential cleavage of the t-butyl group. Such loss of t-butyl group of alkylsulphonamide was also observed in acid cyclisations by Lombardino[107].



336 337

Epoxides as Electrophiles on Benzylic Anions of Benzenesulphonamides

N-t-butyl-2-methylbenzenesulphonamide was lithiated with n-BuLi according to previously reported procedure in which the sulphonamide was treated with n-BuLi in n-hexane at 0^o for 30 min. The electrophile: 1,2-epoxybutane in THF was added and allowed to stir at room temperature for 24h as usual. Work-up gave an oil which was separated by flash chromatography to give a colourless oil in 45% yield.



280 338

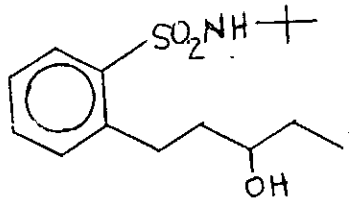
The I.R. spectrum of the product showed strong absorptions at 3500 cm^{-1} for an-OH, 3280 cm^{-1} for the -NH absorption, 2960 and 2940 (C-H stretch), 1600 cm^{-1} for the -C=C- of the aromatic ring, 1320 and 1150 cm^{-1} (SO_2-N<).

The ^{1}H-N.M.R. spectrum showed 5H multiplet at δ1.0 representing five protons for the $-CH_3$ and $-CH_2-$, a 9H singlet at δ1.3 represented the nine protons of the t-butyl group and a 2H multiplet for the methylene protons at δ1.8. The -OH proton came up at δ3.1 (exchangeable with D_2O). The methylene group next to the phenyl group 2H multiplet absorbed at δ3.3, while -NH singlet was at δ6.0 (exchangeable with D_2O). A 3H multiplet for three aromatic protons H-3,H-4,H-5 absorbed at δ7.35 and 1H double doublet for H-6 was at δ8.05.

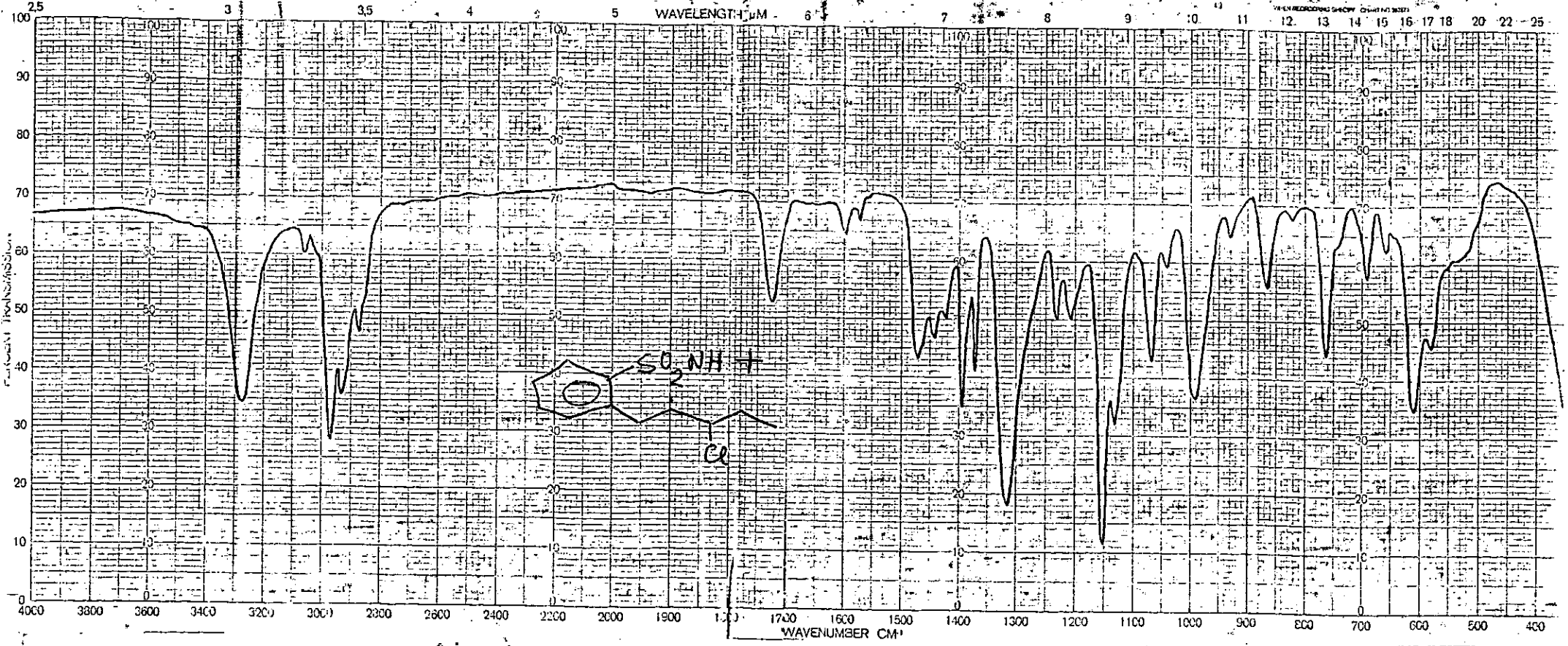
Elemental analysis data which were congruent with expected values were further corroborative evidence for the new compound being 1-(2-N-t-butylbenzenesulphonamido)pentan-3-ol.

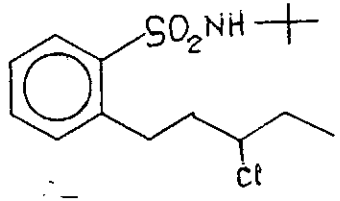
The reaction was faster than it was for ring metalation using the colour discharge as a criteria but it was still allowed to go for 24h. Probable reason for the faster reaction might be the less steric hindrance that may be encountered during the reaction which is less in the benzylic anion than in the ring metalation.

The use of the product obtained from the successful reaction in heterocyclic synthesis will be discussed later.


SO2NH
OH

10
9
8
7
6
5
4
3
2
1
0


WAVELENGTH μM
2.5
3
3.5
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
20
22
25
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
WAVENUMBER CM⁻¹
SO2NH
Cl

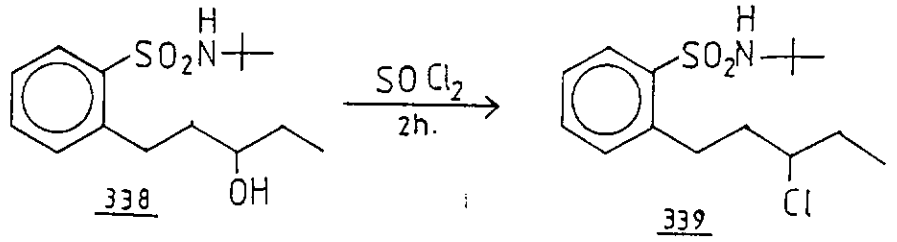


SOLVENT - $CDCl_3$

15/4/89

Attempted Utilization of the Metalation Products as Heterocyclic Synthetic Precursors

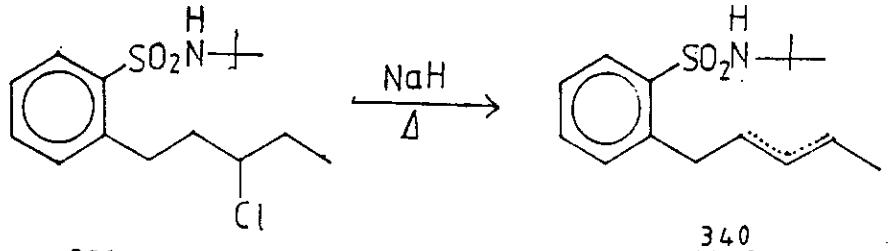
As reported earlier for the ring metalation procedure the carbinol 338 was smoothly converted to a chloro compound by refluxing with thionyl chloride for 2h. The hydroxyl absorption disappeared in N.M.R. and I.R. and the downfield shift of the proton carbon bearing the chloro atom.



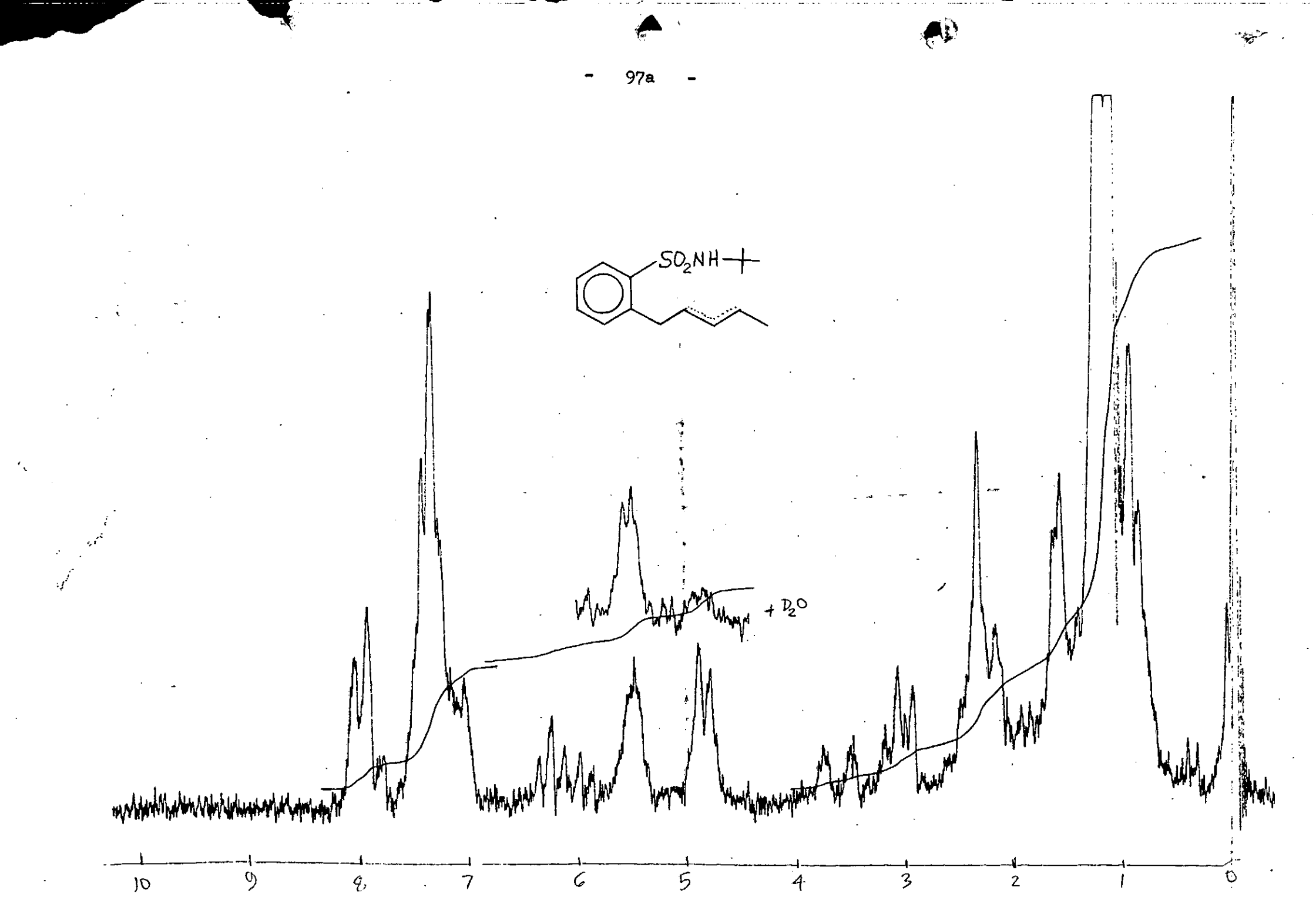
338 339

The sodium hydride was added to the THF solution of the 1-(2-N-t-butylbenzenesulphonamido)-3-chloropentane, and refluxed. Dehydrochlorination was observed on work-up as for 271, even though the bond formed was not conjugated to the aromatic ring.

'H-NMR of the product showed the collapse of the methylene protons next to the phenyl ring at δ3.1 to give vinylic protons at δ6.2 - 6.4. This shows that the target benzothiazepine was not obtained.

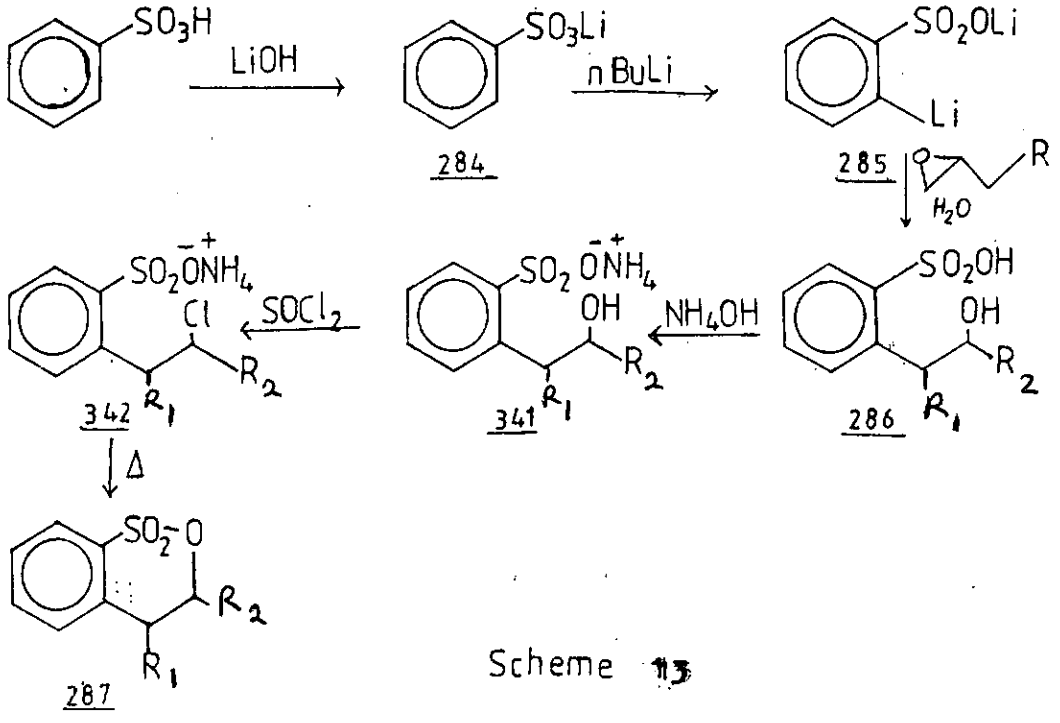


339 340


SO2NH
+ D2O
10
9
8
7
6
5
4
3
2
1
0

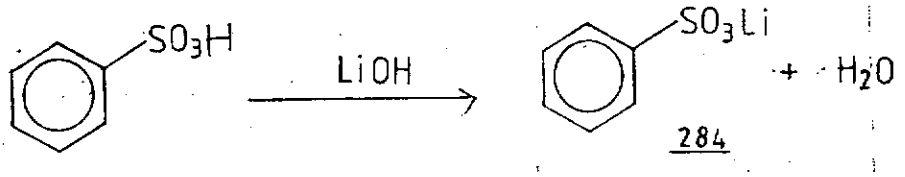
2.4. HETEROCYCLES VIA METALATION OF BEZENESULPHONIC ACIDS

After failures with N-alkylbenzenesulphonamides to give desired heterocycles, and in continuation of the attempted reactions of lithio anions from sulphur-based directed metalation groups (DMG) with epoxides, the sulphonic acid group was considered. Figuly and Martin[95] had used the sulphonic acid group as a DMG in the form of lithium sulphonates to generate lithio species which were coupled with some electrophiles that did not include oxiranes. The problem of isolation of products on work-up without chemical modification of the sulphonic acid group was reported by the authors. Our synthesis anticipated that the presence of a large organic side chain on our oxirane electrophile will make the hydroxy-sulphonic acid products extractable into organic solvents and therefore eliminate the work-up problem reported earlier. The hydroxyl sulphonic acids 286 obtained from this reaction will be used in attempts to synthesise sultones, as proposed in the scheme below.



Scheme 13

The directed metalation group ($-SO_3Li$ group) was generated by the reaction of benzenesulphonic acid with exactly equimolar amount of lithium hydroxide forming lithium benzenesulphonate as a white solid. The crude product was recrystallised in ethanol -toluene mixture and oven-dried before use.

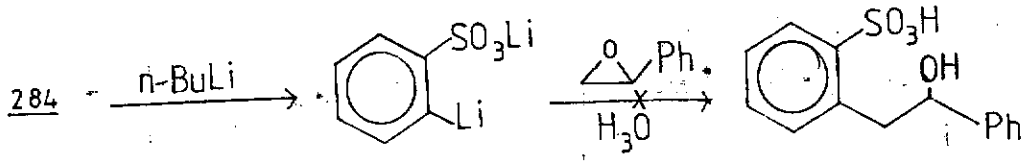


284

Lithiation of the sulphonate with n-BuLi was done according to literature[95] to give a dilithio species.

On coupling with styrene oxide in THF, there was the normal colour discharge (indicative of quenching of anion species). After 24h stirring and work-up with 15% HCl, both the aqueous and the organic phases were examined.

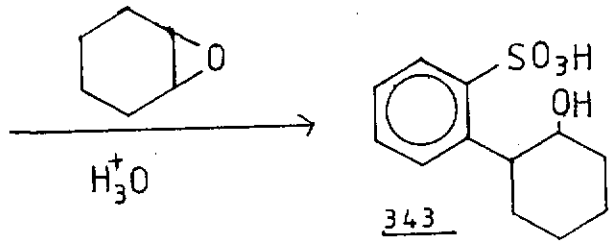
N.M.R. of the crude residue from evaporation of the organic phase showed some aliphatic proton and the t.l.c. showed three non-polar components. Column chromatography of the crude gave five products, N.M.R. analysis showed that none of the compounds was the desired product.



285 286

With cyclohexene oxide as electrophile on the same dilithio species 285, the desired product could also not be obtained either.

285



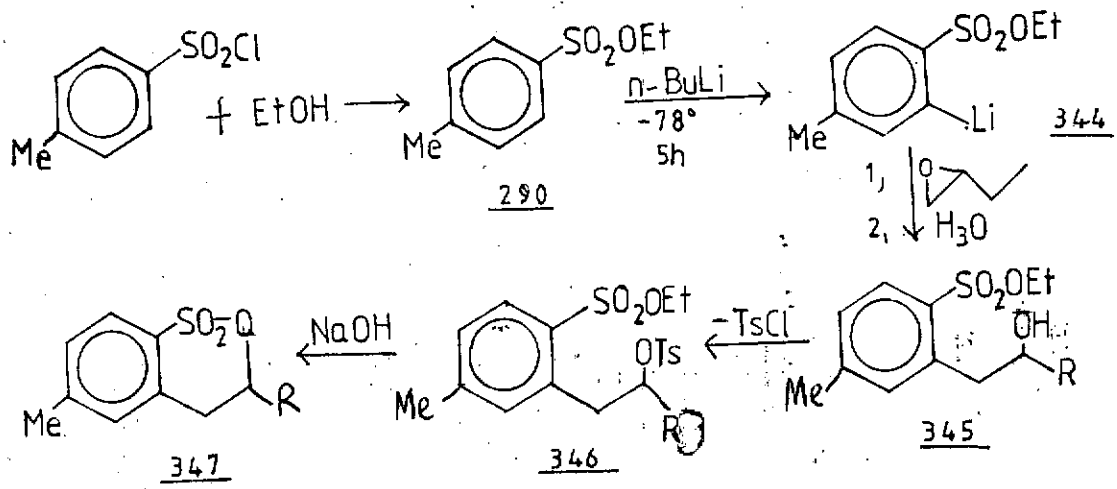
343

The inability to obtain the desired product in both cases may either be due to epoxides being poor electrophiles or due to the isolation problem of the sulphonic acid lithiation products.

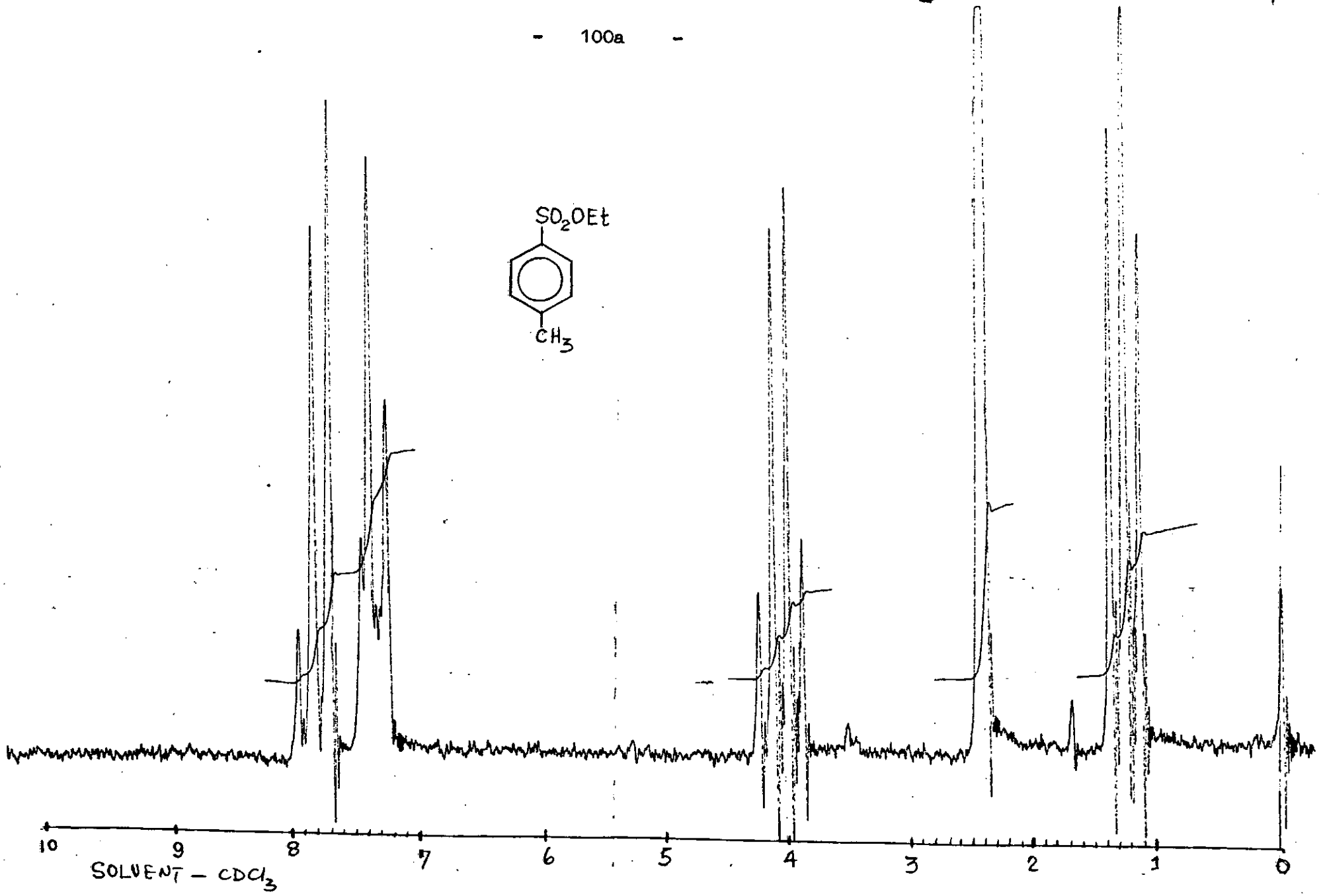
2.5. ETHYL BENZENESULPHONATE METALATIONS FOR SYNTHESIS OF HETEROCYCLE SYNTHONS

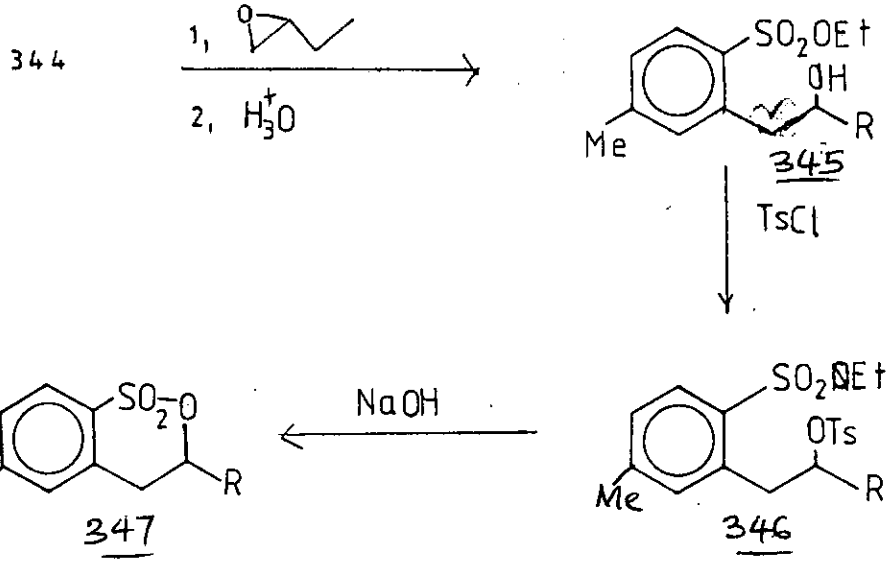
In an effort to use other sulphonic acid derivatives that may be able to couple with epoxides, attention was directed to the ethyl esters of the sulphonic acid. The esters should obviate the work-up problems earlier mentioned.

Bonfiglo[80] had recently reported the lithiation of alkyl arenesulphonate and the reaction of the resulting lithio species with a variety of electrophiles in good yields. The reactions of oxirane was not attempted. It was therefore auspicious to examine the reactions of the lithio ester with oxiranes as outlined below:



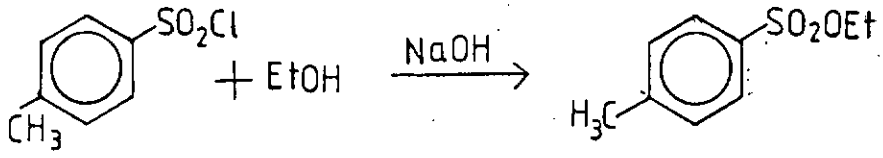
290 344 345 346 347


SO2OEt
CH3
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – CDCl3

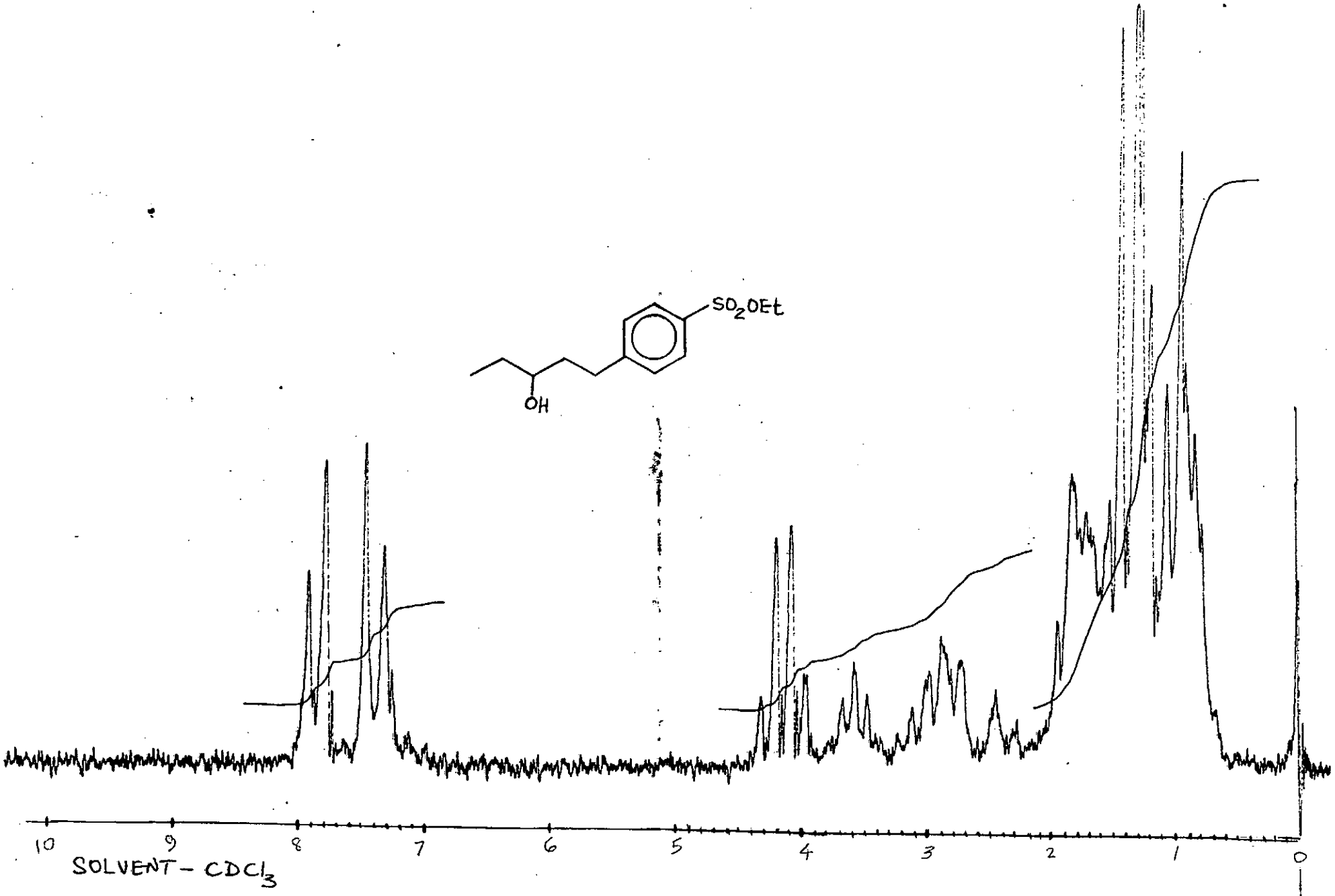


The ethyl 4-toluenesulphonate was prepared according to the method of Roosé et al[30]. The pure hydroscopic product was obtained after distillation.

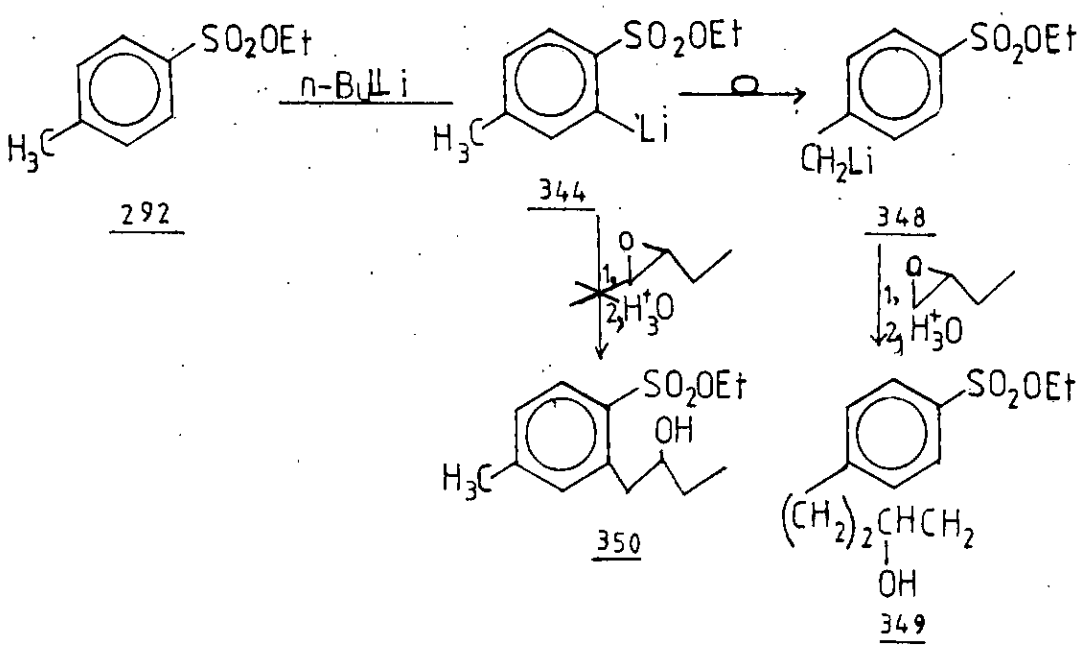
The N.M.R. spectrum showed the signal of the methyl of the ethyl as a 3H triplet at δ1.3, The methylene 2H quartet at δ4.1 and the 3H singlet of the 4-methyl group absorbed at δ2.4. The 2H aromatic doublet of H-3 and H-5 absorbed at δ7.3 while H-2 and H-6 2H doublet was at δ7.8., m.p. 32° with 96% yield.

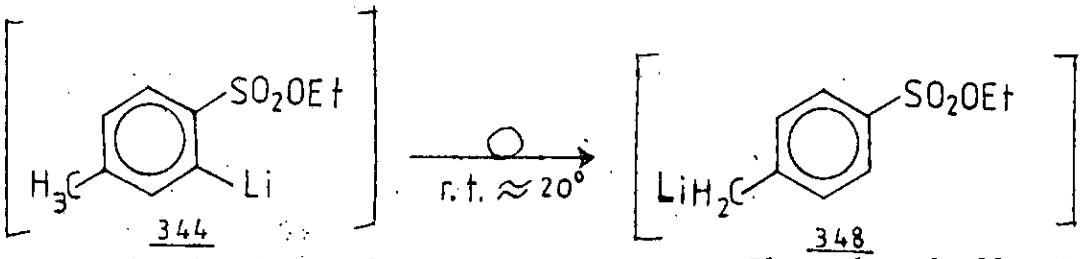


Lithiation of ethyl 4-toluenesulphonate with n-BuLi alone at -78° over five hours gave a red solution. Addition of 1,2-epoxybutane did not cause the colour discharge. The reaction was then allowed to continue at room temperature for 24 h. T.l.c. of the crude product after standard work-up showed two main components. Flash chromatography of the crude then gave the


SO2OEt
OH
10
9
8
7
6
5
4
3
2
1
0
SOLVENT - CDCl3

starting material and a new compound. The ^{1}H-N.M.R. of the viscous oily product showed AB,A'B' of four aromatic protons intact and the loss of the 4-methyl group signal. This side chain lithiation product is presumed to have been formed when the temperature of the kinetically stable 2-lithio species was raised to room temperature. This facilitated it's rearrangement to a thermodynamically stable 4-lithiomethyl benzenesulphonate species on which the epoxide reacted.

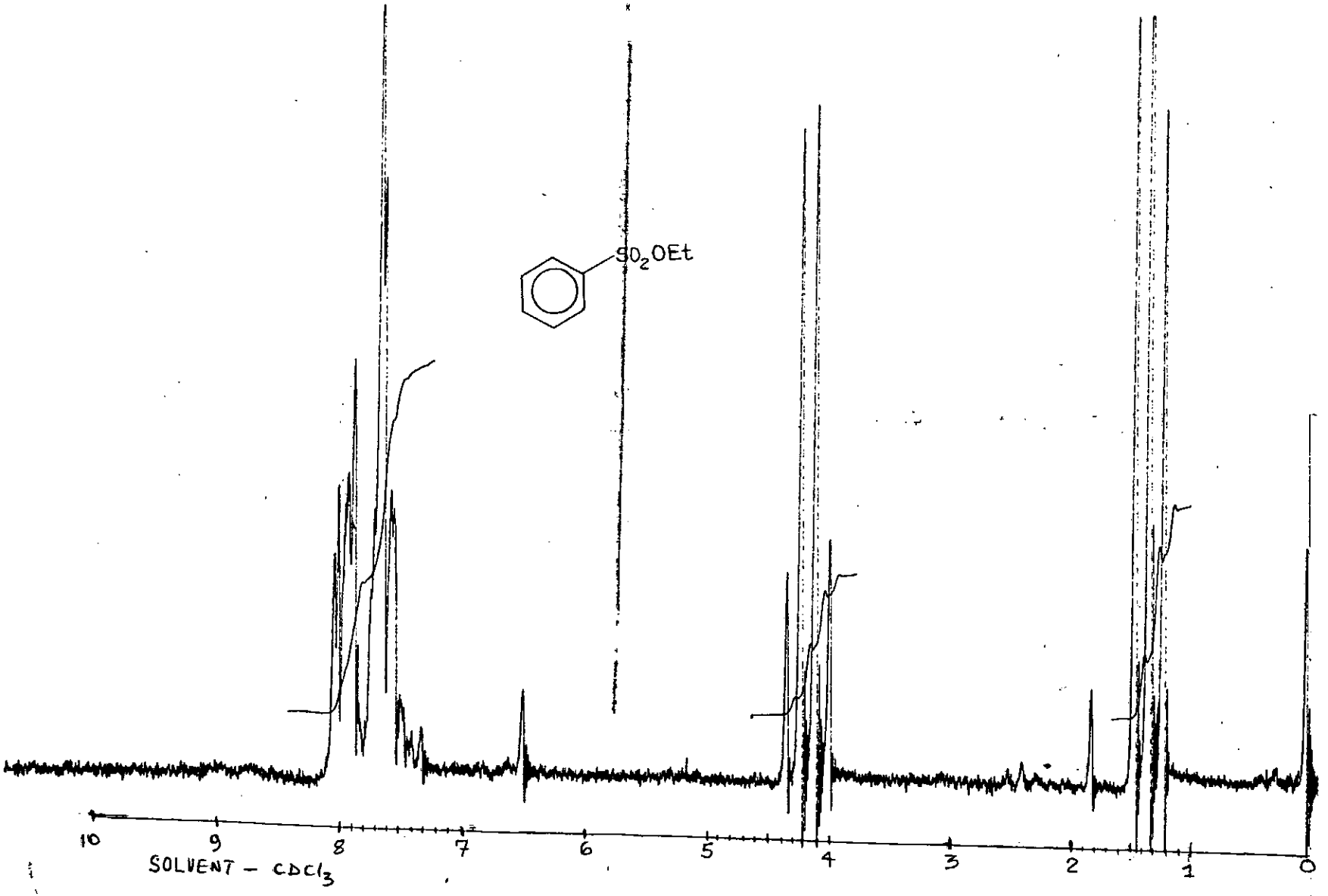




344 Kinetically stable

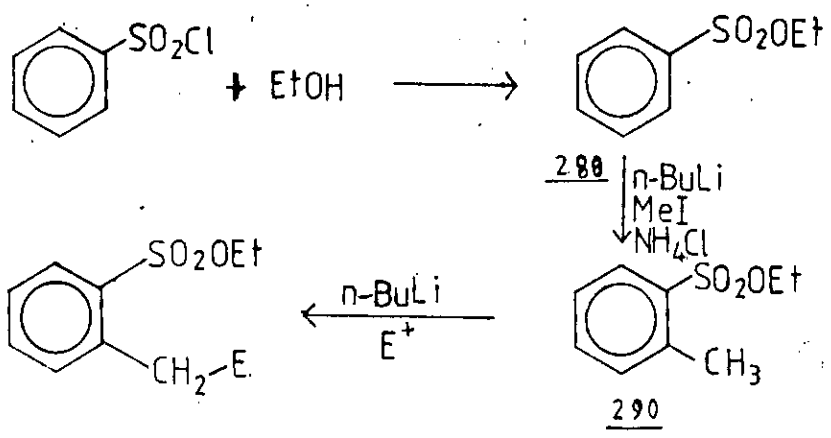
348 Thermodynamically stable

Apparently, the epoxide will not react with the lithio species at -78° or 0° but only at room temperature. The nuclear lithio species is unstable and rearranges. Bonfiglo[80] had reported


SO_2OEt
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – $CDCl_3$

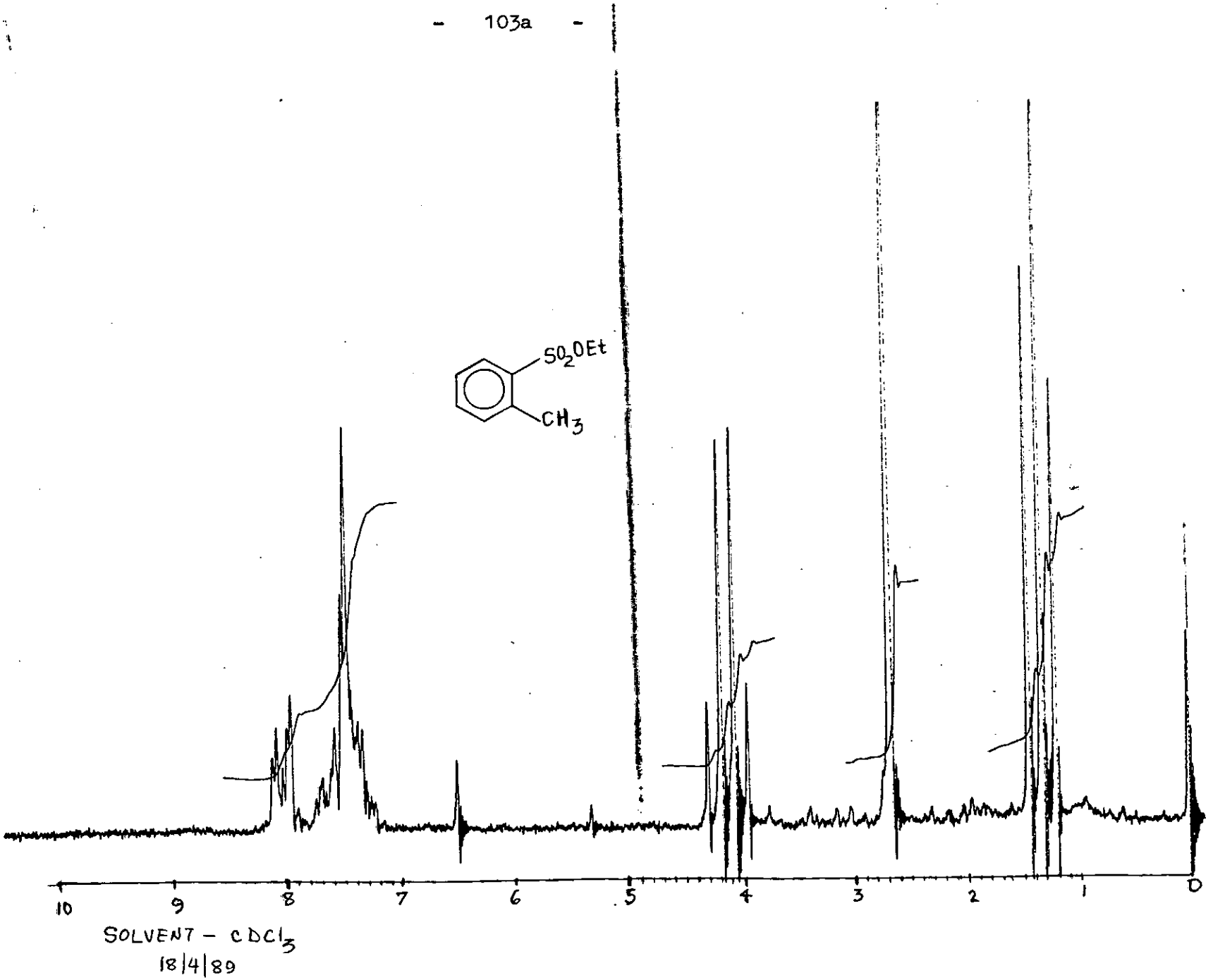
4-lithiomethylbenzenesulphonate species, although it was obtained only with the use of a complexing agent: TMEDA at low temperatures.

The substrate was therefore changed to ethyl 2-methylbenzenesulphonate in a bid to exploit ortho-benzylic lithiation for synthesis of heterocycle synthons. As far as we are aware, the formation of benzylic anion with alkylsulphonate esters as a DMG has not been reported before. Therefore, a range of electrophile will be used on the ortho-benzylic anion if obtained. The route to these reaction is outlined below:



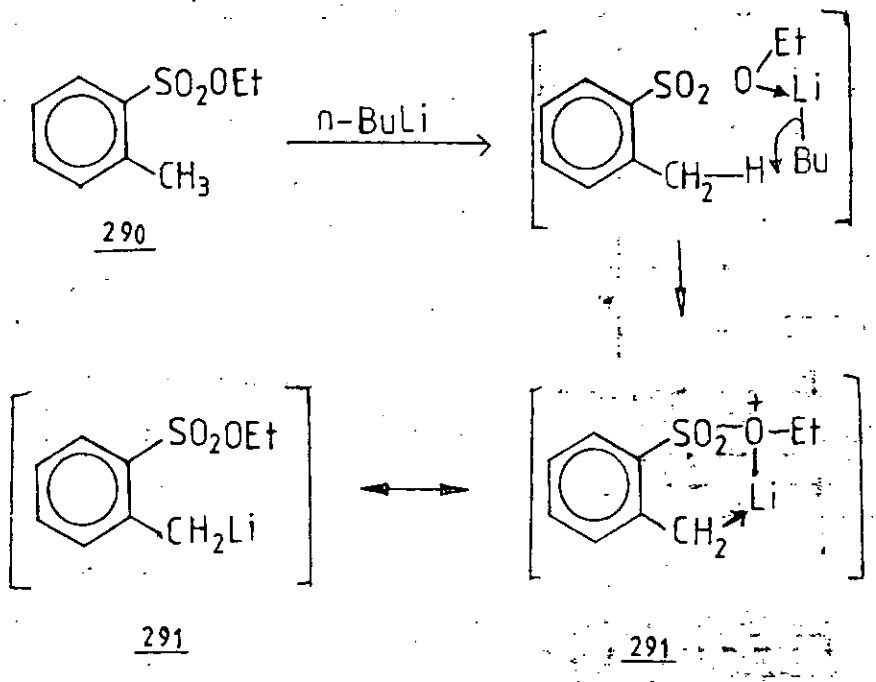
Pure redistilled ethyl benzenesulphonate was prepared as reported earlier for ethyl 4-toluenesulphonate.

Treatment of the ester with n-BuLi at -78° for five hours gave the ortho-lithiobenzenesulphonate which on reaction with methyl iodide gave the desired ethyl 2-methylbenzenesulphonate in 80% yield.


SO2OEt
CH3
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – CDCl3
18/4/89

'H-N.M.R. of the product gave a 3H triplet at δ1.3 for the methyl of the ethyl group, a 3H singlet for the newly added methyl group at δ2.7. The 2H quartet of the methylene of the ethyl absorbed at δ4.1, while the aromatic protons had changed from 2:3 pattern to 1:3 pattern showing that of the ortho hydrogen had been substituted. A 3H multiplet representing H-3, H-4,H-5 was at δ7.5 and 1H double doublet of H-6 absorbed at δ8.0.

Treatment of the ethyl 2-methylbenzenesulphonate with n-BuLi at -78°, gave a quantitative generation of the benzylic lithio species in 1½ h. unlike the case of ring metalation in which the lithio species was obtained only after five hours. This is not unexpected as the sulphonate group increases the acidity of the methyl group which leads to easier methyl proton deprotonation than nuclear deprotonation. Furthermore, the benzylic deprotonation is presumed to occur through a six-membered intermediate coordination complex facilitated by the oxygen atom; forming a monolithio species.



290

291 291

Six-membered intermediate complex.

The benzylic anions obtained were coupled with the following electrophiles in a bid to exploit the anions for heterocyclic synthesis.

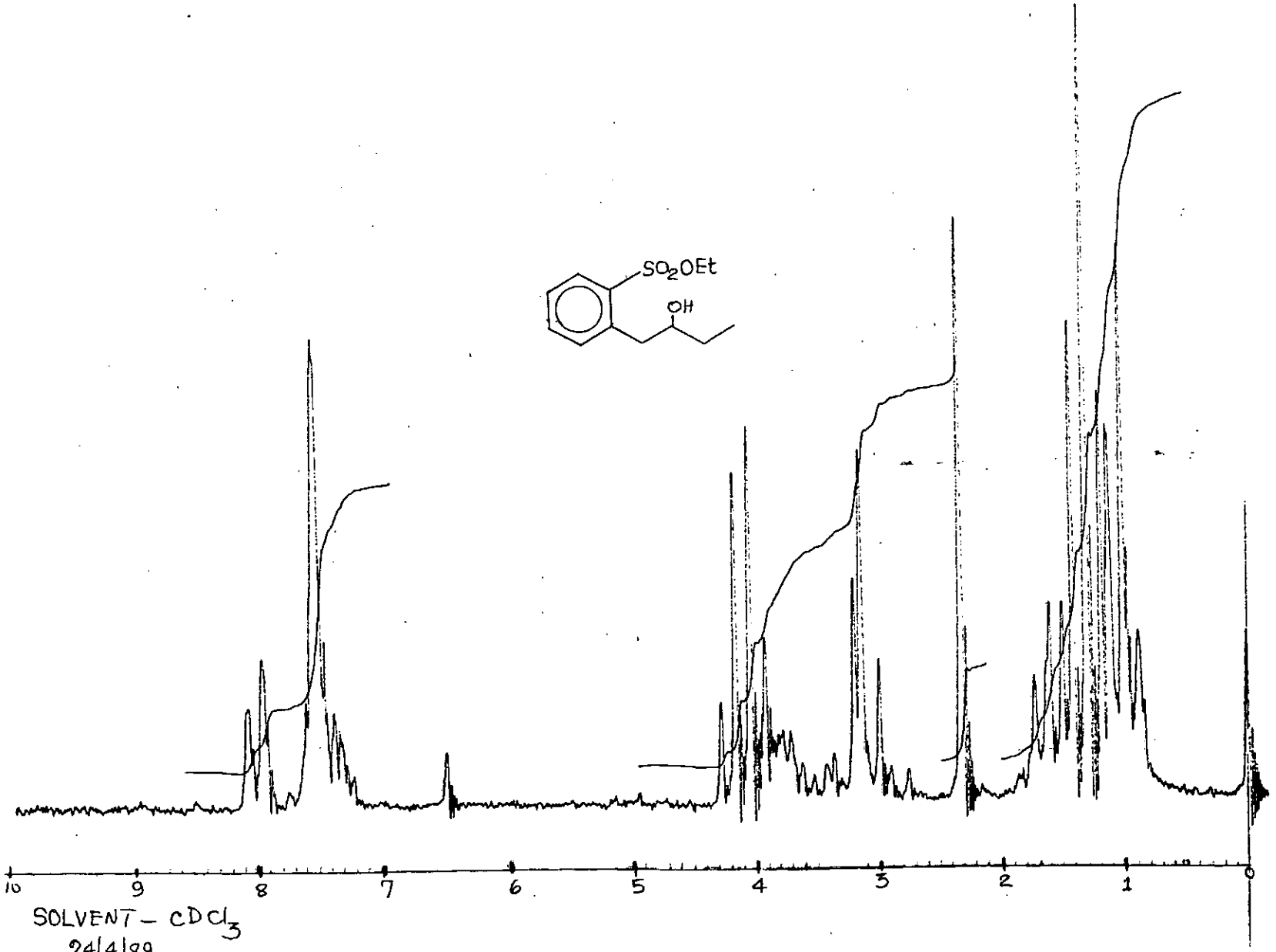
Propanal as electrophile:

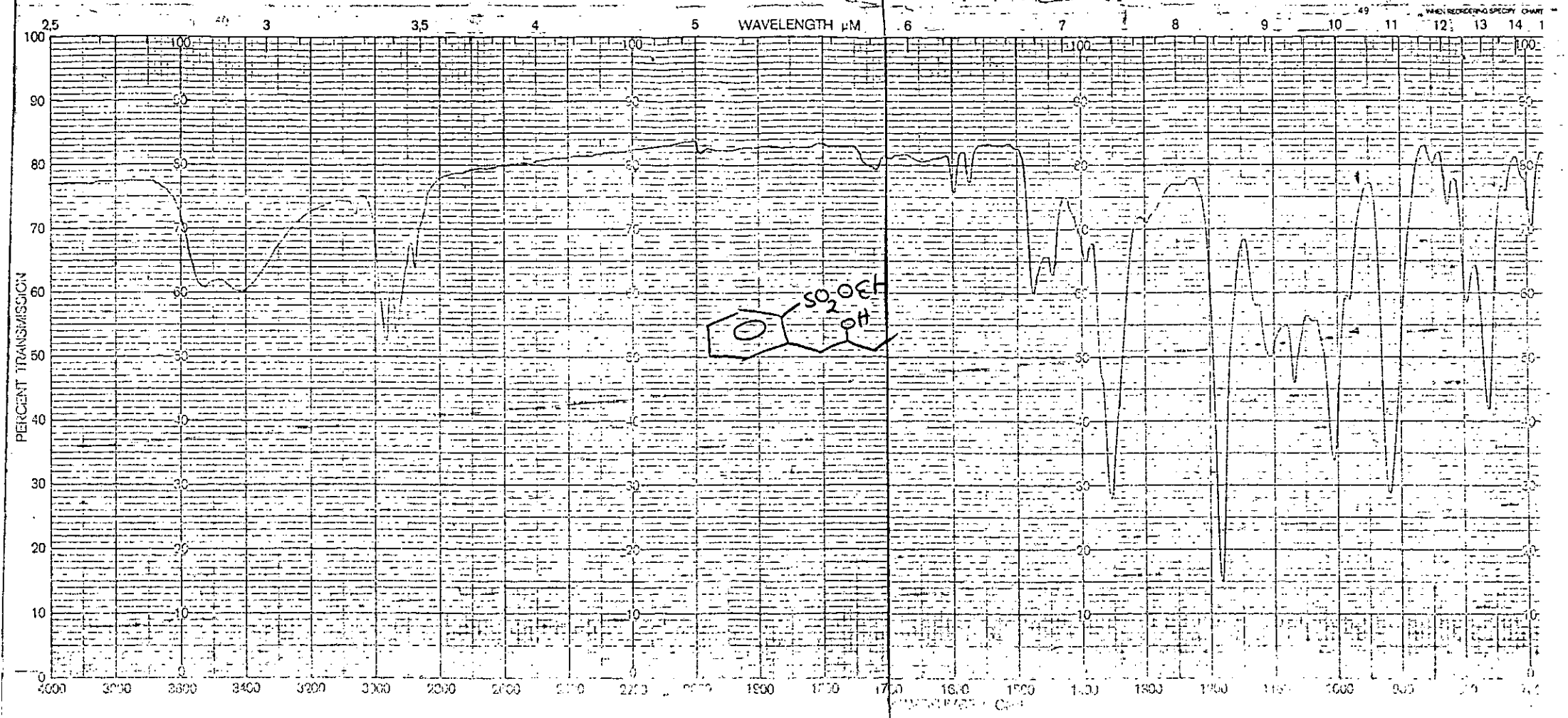
Reaction of the benzylic anion with electrophiles started with the reaction of 1.1 equivalent of propanal in THF to the generated anion solution at -78^{o} for one hour and at 0^{o} for further one hour before the standard work-up. Flash chromatography of the oil obtained gave some starting material with another compound in 75% yield.

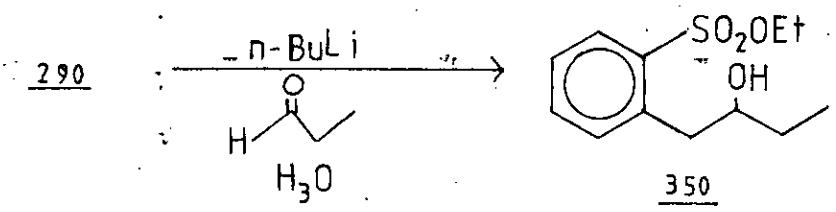
IR of the compound showed an OH broad at 3630 cm-1. There were also absorptions at 2980, 2940^{cm-1} for the-CH stretching, aromatic stretching was at 1660 cm^{-1} and bands appeared at 1350, 1180cm^{-1} for the SO_2O group.

The 'H-NMR spectrum showed an 8H multiplet absorption at δ 0.8 - 1.6 for the 2 methyl protons and the side chain methylene proton. A 1H broad signal at δ2.2 exchangeable with D_2O, represented the -OH of the carbinol 350. A 2H triplet at δ 3.1 represented the methylene next to the phenyl ring, while the base proton of the carbinol appeared at δ3.8. A 2H quartet absorption at δ4.1 was due to the methylene of the ethyl of the sulphonate. The three aromatic protons of H-3, H-4, H-5 gave a multiplet of δ7.5 while a double doublet at δ8.0 was due to H-6.

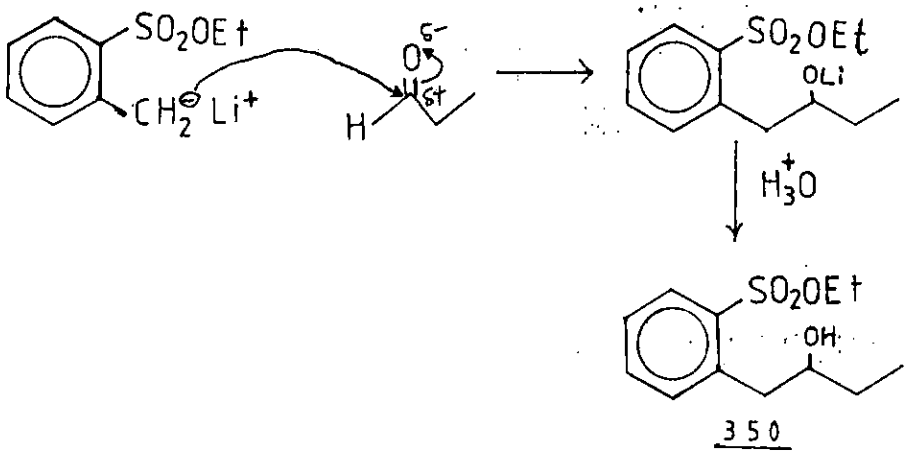
Microanalysis agreed with the expected values. These data confirmed the compound obtained as 1-(2-ethoxylsulphonylbenzene) butan-2-ol.


SO2OEt
OH
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – CDCl3
24/4/89


WAVELENGTH µM
PERCENT TRANSMISSION
2,5
3
3,5
4
5
6
7
8
9
10
11
12
13
14
100
90
80
70
60
50
40
30
20
10
0
4000
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
SO2OEt
OH



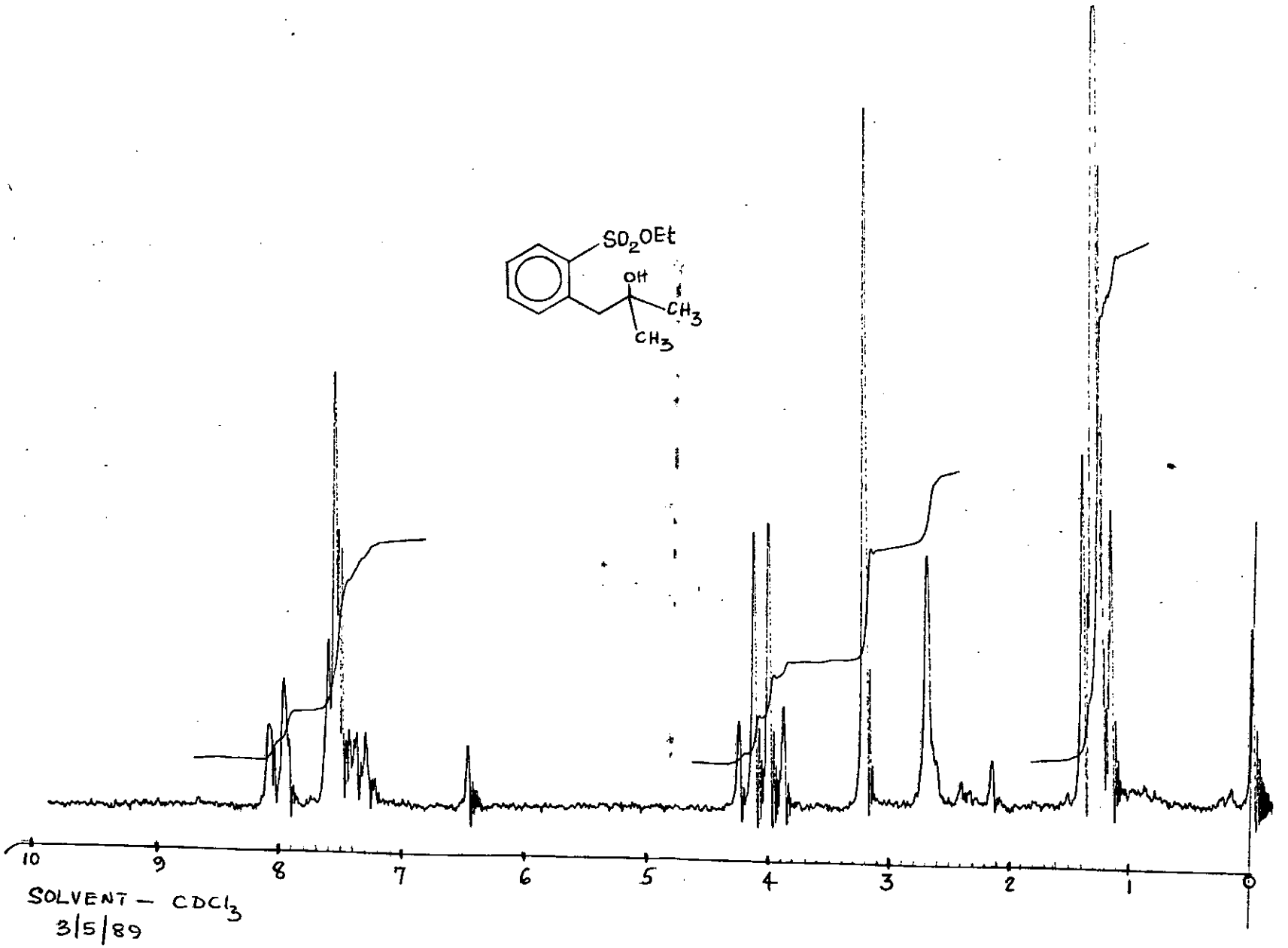
Mechanism.

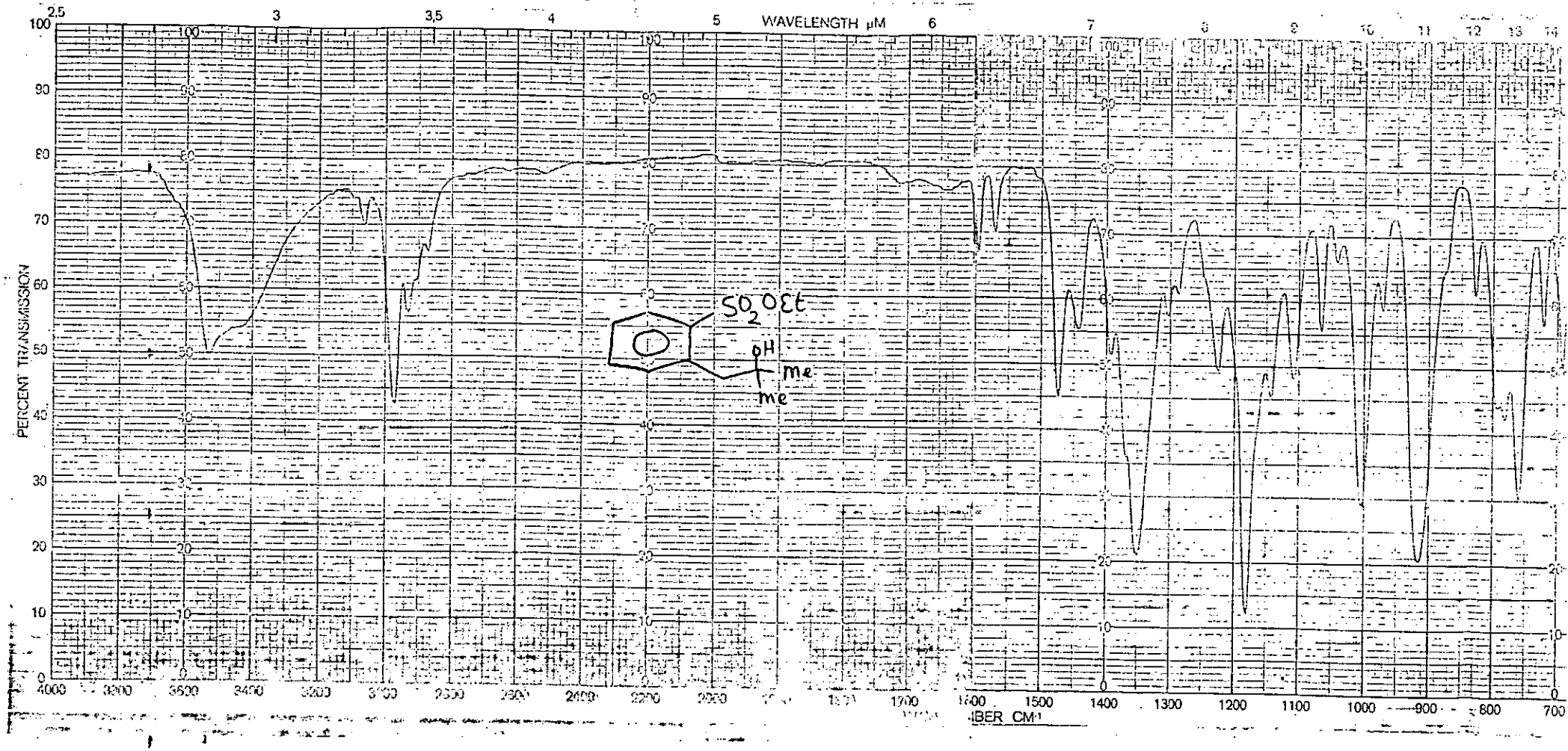


Acetone as Electrophile

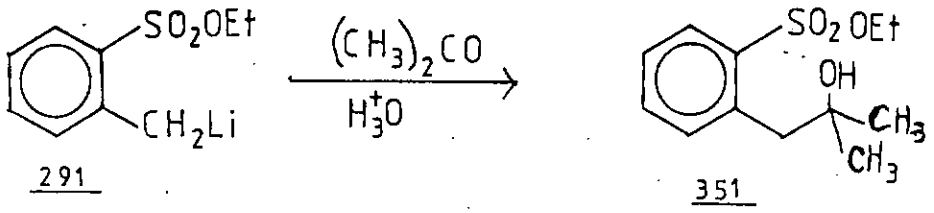
Acetone dissolved in THF was added to the benzylic anion and allowed to stir at -78° for one hour and at 0° for further one hour. Usual work-up gave an oil. Flash chromatography of the oil gave a colourless compound in 50% yield along with some starting material.

I.R. of the new compound showed a broad absorption at 3560 cm^{-1} for the hydroxyl, and other absorptions at 2980, 2950 cm^{-1} for -CH stretching, 1600 cm^{-1}, 1470 cm^{-1} (-CH deformation), 1350, and 1180 cm^{-1} for the SO_2O- bond.


SO2OEt
OH
CH3
CH3
10
9
8
7
6
5
4
3
2
1
SOLVENT – CDCl3
3/5/89


WAVELENGTH µM
PERCENT TRANSMISSION
SO2OEt
OH
Me
Me

The ^{1}H-NMR spectrum showed a 9H multiplet at δ 1.2 for three methyl groups, a IH broad absorption at δ2.8 was exchangeable with D_2O and it indicated the OH group. Another 2H singlet at δ3.2 was due to the methylene next to the phenyl group. The methylene protons of the ethyl showed up as a quartet at δ4.0 while the aromatic protons 3H multiplet H-3, H-4, H-5 absorbed at δ7.6 and H-6 doublet of a doublet was at δ8.0. These data indicated the product obtained as 1-(2-ethoxysulphonylbenzene)-2-methylpropan-2-ol and this was confirmed by microanalysis which was in agreement with the calculated values.

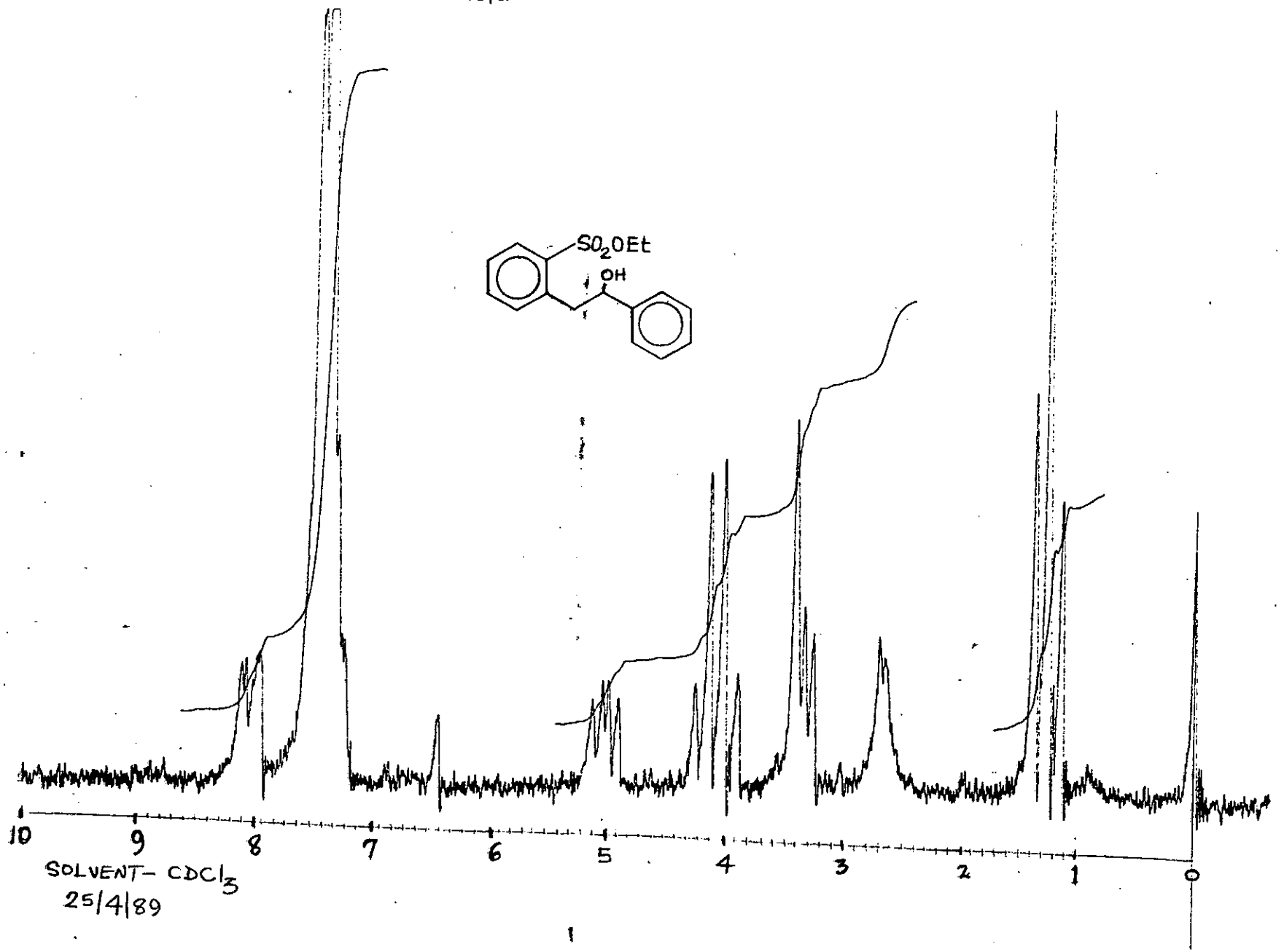


291 351

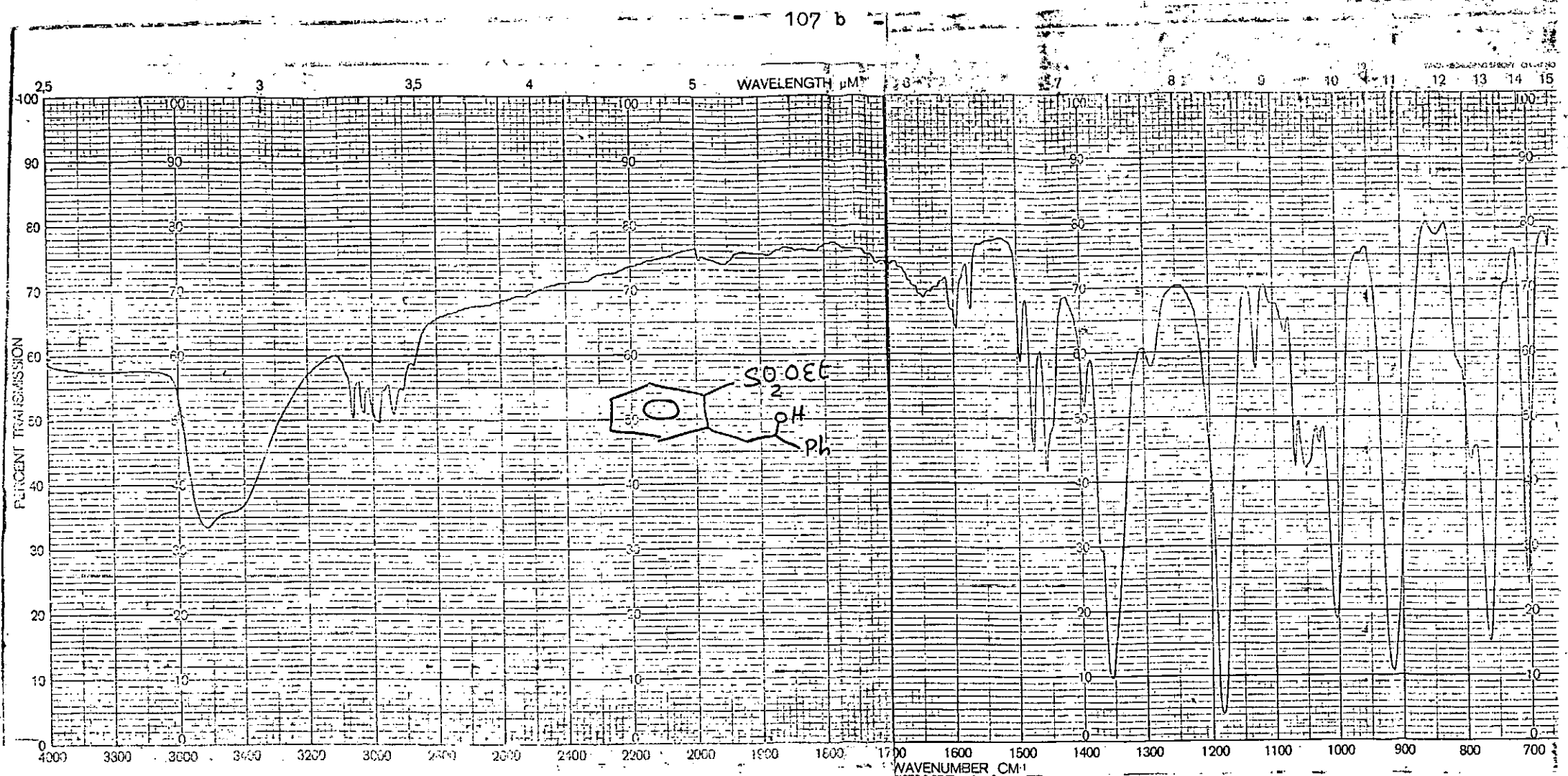
Benzaldehyde as Electrophile

Redistilled benzaldehyde in THF coupled smoothly with the lithio species and work-up gave an oil which solidified on standing by the next day. Recrystallisation in petroleum ether gave white needless, m.p. 56-58^o in 65% yield.

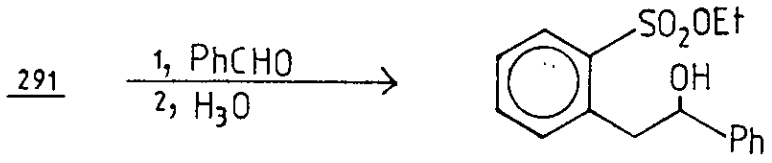
The I.R. spectrum of the needles showed an OH broad absorption at 3520 cm^{-1} and at 2990 cm^{-1} for the -CH stretching, 1600 cm^{-1} for the aromatic ring, 1455cm^{-1} for the -CH deformation. The SO_2O bonds were present at 1355 and 1185 cm^{-1}. The ^{1}H-NMR spectrum showed a 3H triplet at δ1.3 for the methylene of the sulphonate and a 1H absorption at δ 2.7 for the OH, (exchangeable with D_2O).


SO2OEt
OH
10
9
8
7
6
5
4
3
2
1
0
SOLVENT- CDCl3
25/4/89

107 b


WAVELENGTH μM
2,5
3
3,5
4
5
7
8
9
10
11
12
13
14
15
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3300
3000
2400
2200
2000
1600
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
WAVENUMBER CM-1
SO2OEt
OH
Ph

A 2H doublet at δ3.4 was indicative of the methylene adjacent to the phenyl ring, while a 2H quartet at δ4.1 indicated the methylene of the ethyl. A 1H absorption at δ 5.0 was ascribed to the base proton on the carbon bearing the OH group. An 8H multiplet at δ7.45 and a 1H doublet of a doublet were ascribed to the aromatic protons. The satisfactory elemental analysis data further confirmed the structure of the product as 2-(2-ethoxysulphonylbenzene)-1-phenyl ethanol.



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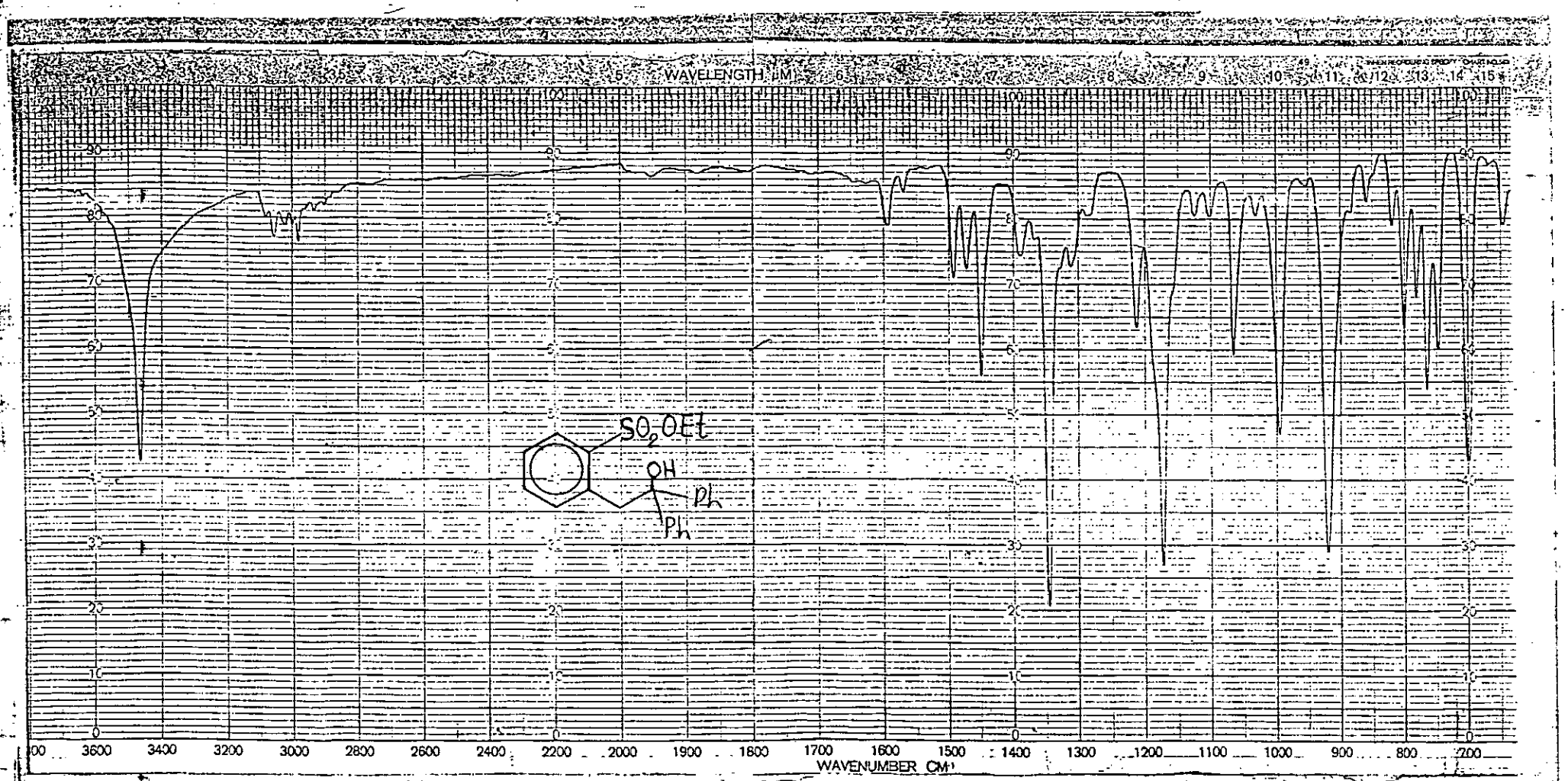
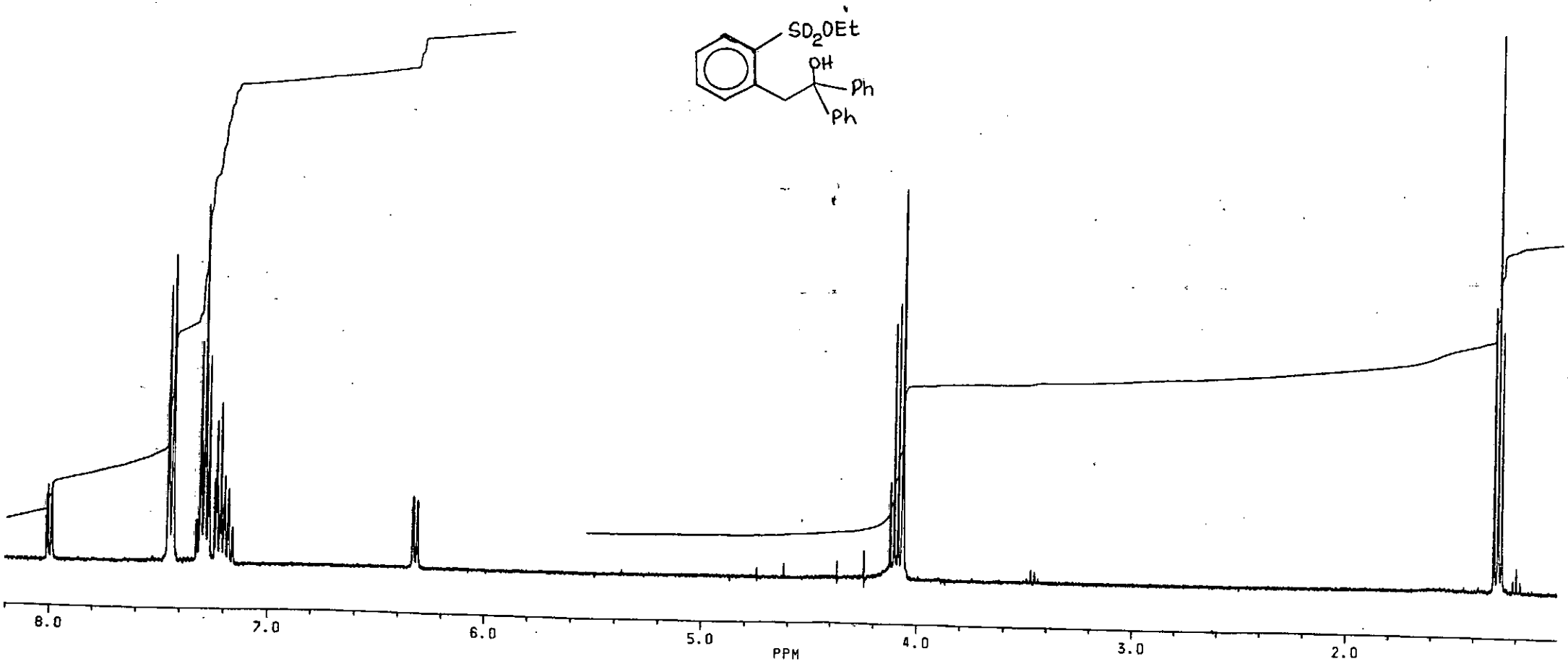
Benzophenone as Electrophile

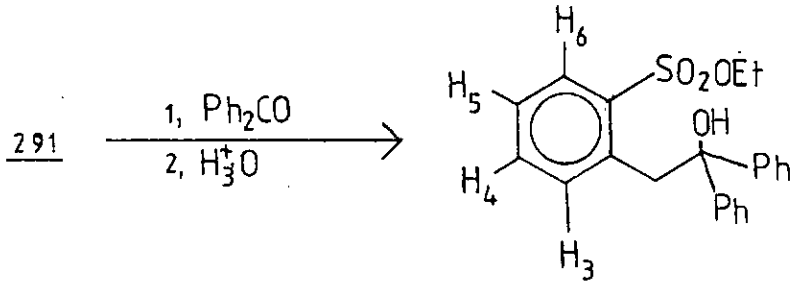
Benzophenone smoothly coupled with the benzylic anion at -78° after one hour at that temperature and one hour at 0°. Work-up gave a white solid. The solid was recrystallised to give white needles m.p. 130-132°C in 91% yield. The I.R. spectrum of the product showed strong absorptions at 3460cm^{-1} for the OH, 1600, 1450, and 1345, 1175 cm^{-1} (SO_2O). The ^{1}H-NMR spectrum as usual showed a 3H triplet at δ1.3 for the CH_3 of the ethyl group, a 1H broad absorption at δ3.1 for the -OH group (exchangeable with D_2O), a 2H singlet at δ4.05 was indicative of the methylene adjacent to the ring while a 2H quartet at δ4.10 represented the methylene of the ethyl group.


WAVELENGTH µM
5
6
7
8
9
10
11
12
13
14
15
100
90
80
70
60
50
40
30
20
10
0
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
WAVENUMBER CM⁻¹
SO2OEt
OH
Ph
Ph


SO2OEt
OH
Ph
Ph
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM

The assignment of the aromatic proton signals at δ6.3 and δ8.0 was done unambiguously using nuclear Overhauser effect (n.O.e.) experiments. When the doublet at δ6.3 (H-3) was irradiated, there was no change in the doublet at δ 8.0 (H-6) and vice versa. Since neither of the doublets collapsed on irradiation, they were therefore not coupled. The H-3 seems shielded by the two phenyl rings and therefore absorbs at δ6.3 and appears as a doublet due to H-4, while H-6 deshielded by the sulphonate group and therefore appears downfield at δ8.0 as a doublet having been split by H-5.

The elemental analysis which was in agreement with the theoretical values further confirmed the structure of the product as 1,1-diphenyl-2-(2-ethoxysulphonylbenzene) ethanol.

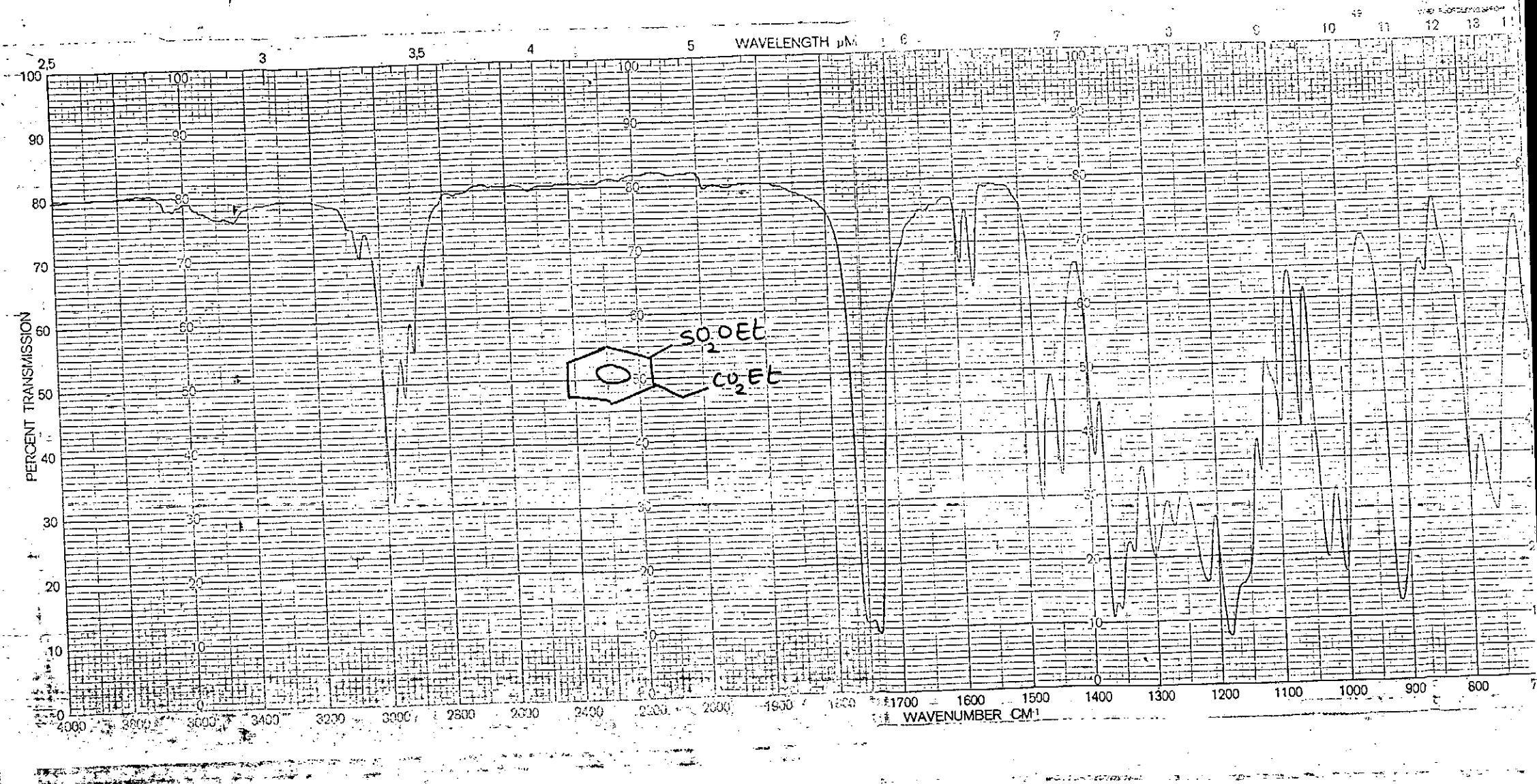


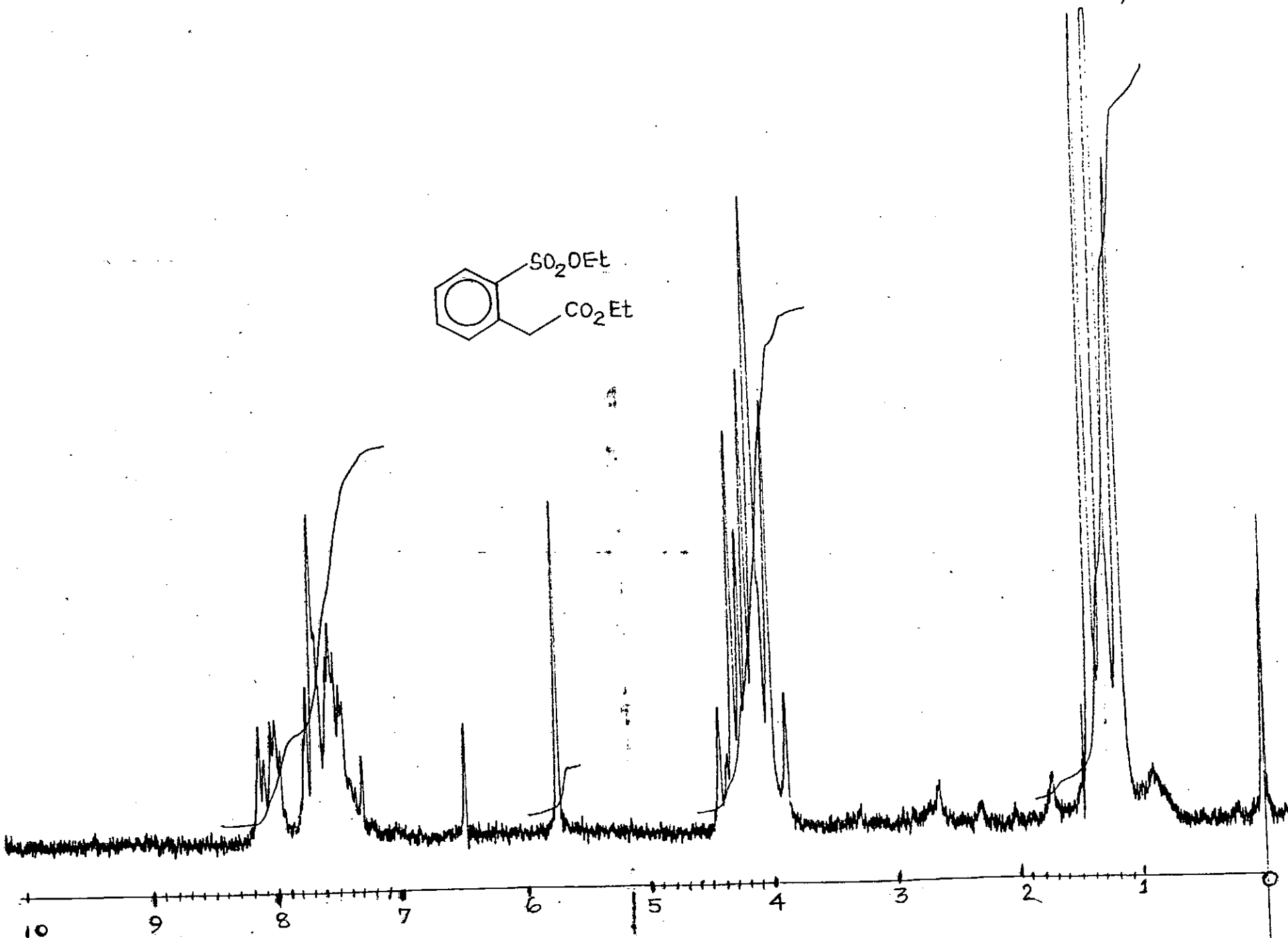
353

Ethylchloroformate as an Electrophile

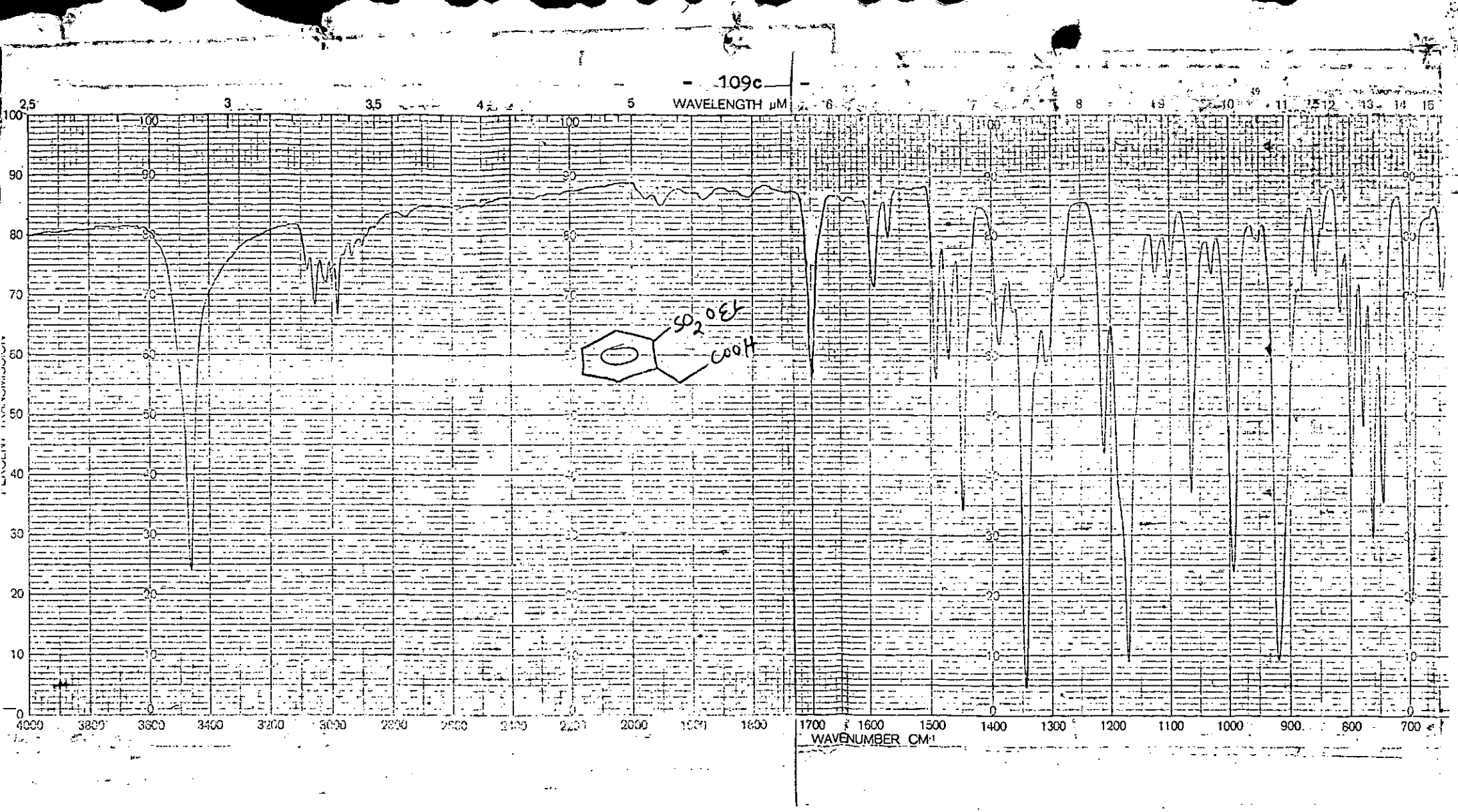
The use of ethylchloroformate to generate carboethoxy derivative from lithio species is well known[131, 132].

Ethylchloroformate dissolved in THF was added to the benzylic anion solution. On standard work-up, a crude oil was obtained. This was purified by flash chromatography using pet ether; diethyl ether 1.1 to give a colourless oil in 50% yield.


WAVELENGTH μM
PERCENT TRANSMISSION
WAVENUMBER CM-1
SO2OEt
CO2Et

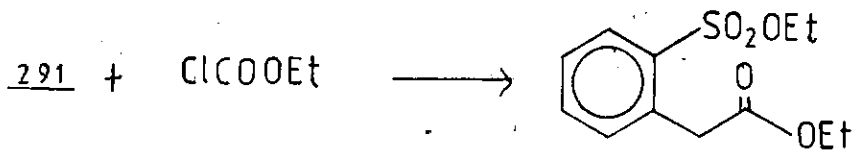

SO2OEt
CO2Et
10
9
8
7
6
5
4
3
2
1
0

- 109c -


WAVELENGTH µM
2,5
3
3,5
4
5
6
7
8
9
10
11
12
13
14
15
WAVENUMBER CM-1
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
100
90
80
70
60
50
40
30
20
10
0
SO2OEt
COOH

The infra-red spectrum of the oil showed strong bands at 1730 cm^{-1} (C=O), 1600 (aromatics) 1470, 1440, 1370, 1180 cm^{-1} (SO_2O).

The ^{1}H-NMR spectrum showed a six proton multiplet at δ1.3 which represented two methyls of the ethyl group. Another six protons multiplet was observable at δ4.1 assigned to the methylene adjacent to the phenyl ring which was therefore not differentiated on the 60MHz instrument from the other two methylene groups. However, an absorption at δ7.6 for the three aromatic protons of H-3, H-4, H-5 was different from the H-6 doublet of a doublet at δ8.1. Microanalysis data further confirmed the structure to be the expected ethyl 2-(ethoxysulphonyl)phenyl acetate.



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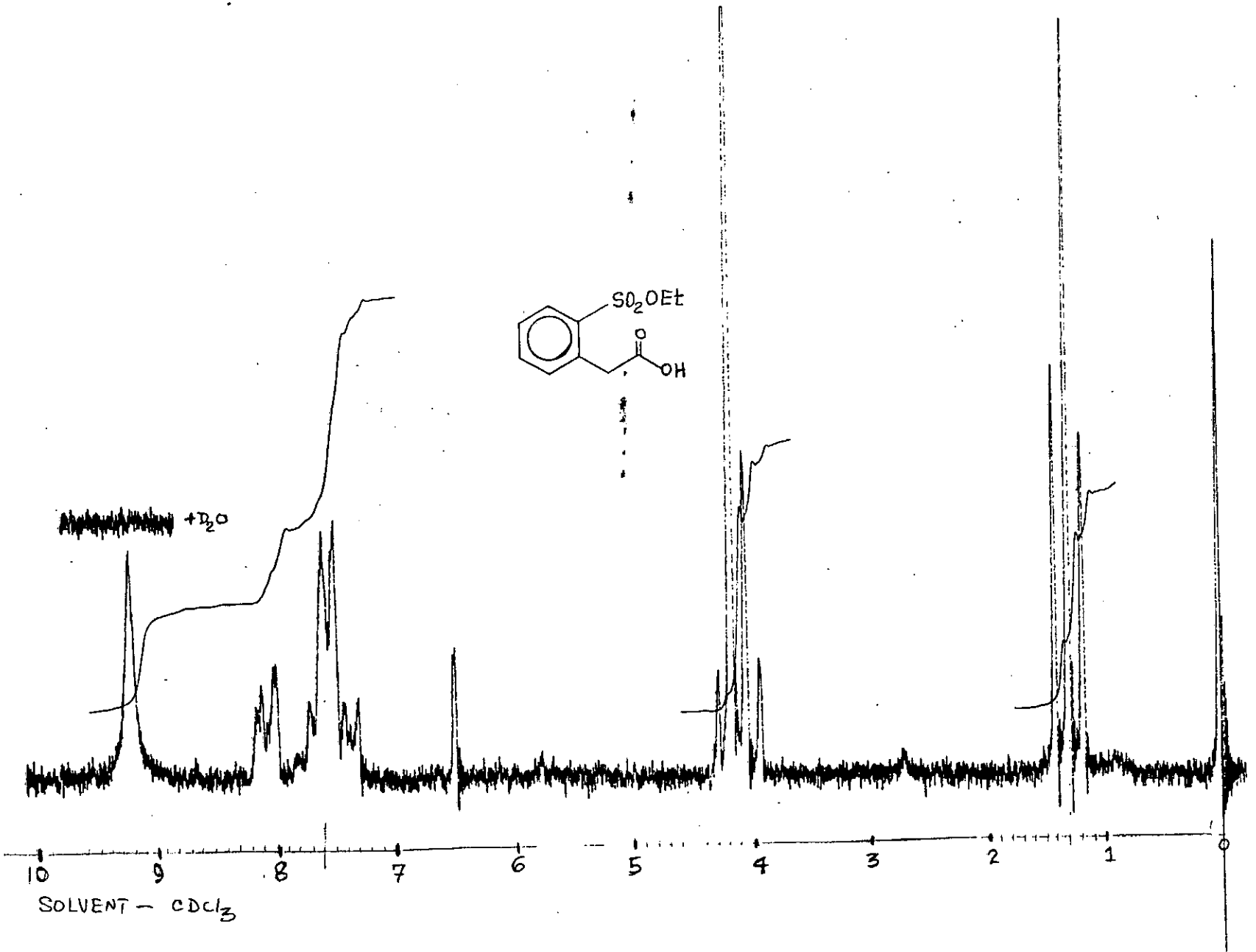
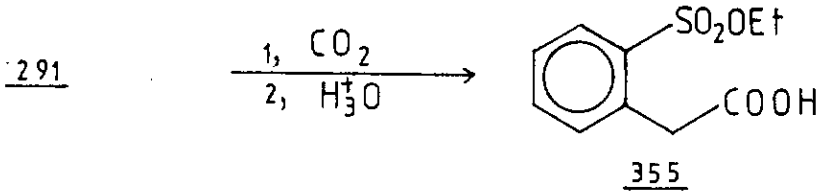
CO_2 as an Electrophile

Carbon dioxide reaction with organolithiums is a prefered way of introducing the carboxylic functionality into organic compounds.[9] Work-up of this reaction gave a crude white solid which was recrystallised to give white needles m.p. 106-108° in 70% yield.

The infra-red spectrum of the needles showed 3300 - 2500 (-COOH dimer), 1710 for the (-COOH) 1600, 1450, 1350, 1180 cm^{-1} (SO_2O). The ^{1}H-NMR spectrum showed a 3H triplet which represented the methyl group and a 2H quartet at δ4.1.


SO_2OEt
O
OH
+D_2O
10
9
8
7
6
5
4
3
2
1
SOLVENT — $CDCl_3$

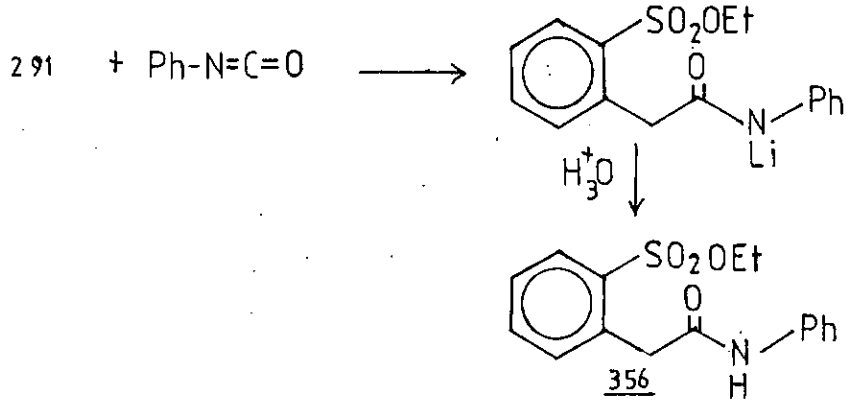
In this case the methylene adjacent to the phenyl ring showed up as a 2H singlet at δ4.2. Other absorptions were a multiplet at δ7.6 representingH-3,H-4,H-5 and a 1H singlet at δ8.1. The D_2O exchangeable proton of the acid was observed at δ9.3.



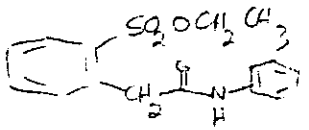
Phenylisocyanate as an Electrophile[57, 58]

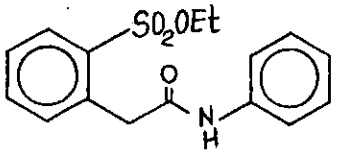
Phenylisocyanate in THF was added to the lithio species and on usual work-up, light-yellow solid was obtained which was recrystallised to give pale yellow needles m.p. 124-126° in 78% yield.

The attack of the carbanion was at carbonyl carbon leading to the formation of an amide on hydrolysis as outlined below:

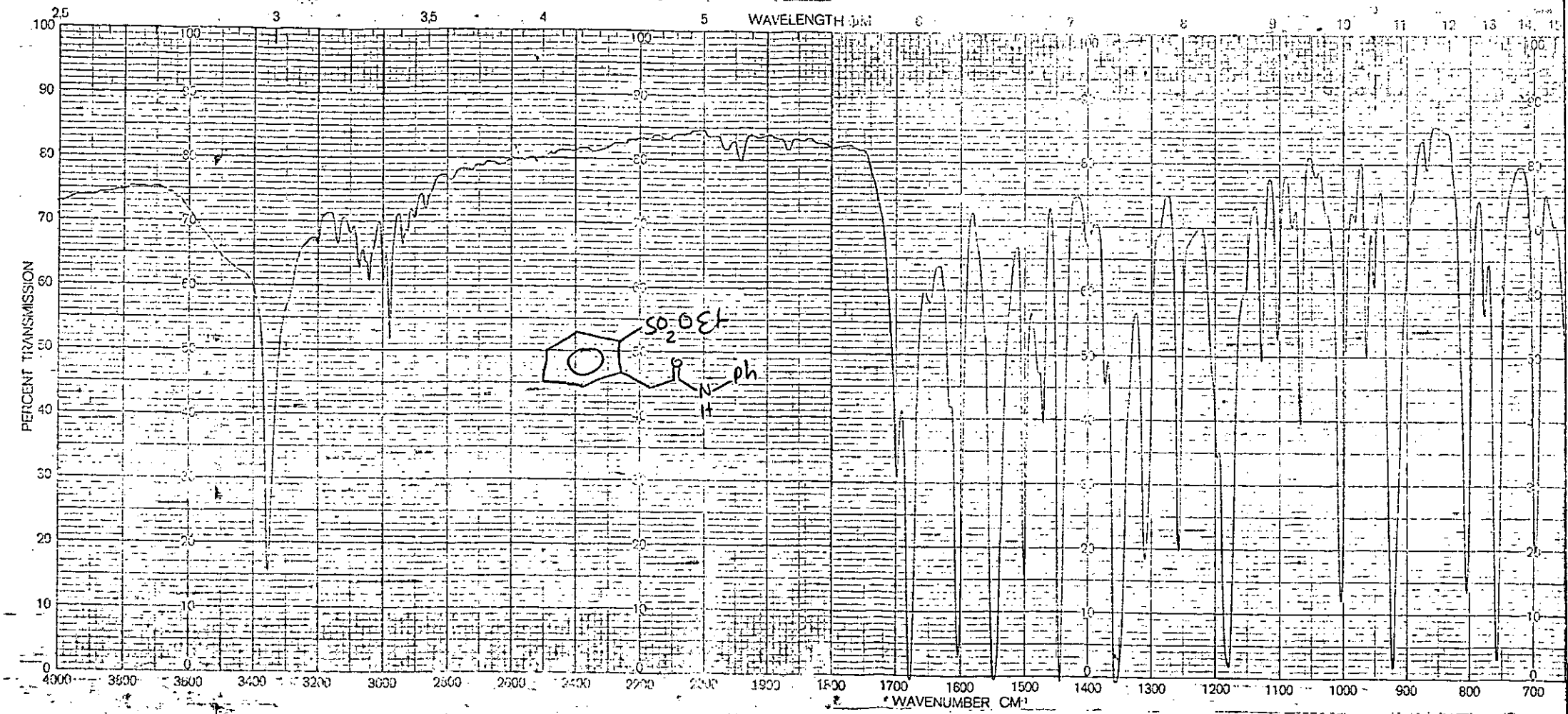


The KBr-dispersion i.r. spectrum of the amide showed strong absorption at 3360 (NH of the secondary amide), 2990, 1680 (CONHPh), 1550, 1450, 1350 and 1180 cm^{-1} (SO_2O).





Solvent
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – $CDCl_3$

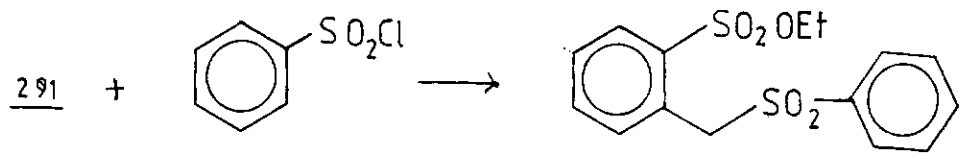

WAVELENGTH μM
2.5
3
3.5
4
5
6
7
8
9
10
11
12
13
14
15
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
WAVENUMBER CM⁻¹
SO2OEt
N
H
ph

The ^{1}H-NMR spectrum had a 3H triplet at δ1.2 for the methyl of the ester, a 4H quartet at δ4.1 gave absorptions of 2 groups, that of the methylene next to the phenyl group as a singlet and the ester methylene as a quartet. The amide phenyl group 5H protons showed at δ7.1-7.4 while the H-3,H-4,H-5 absorbed at δ7.6 as a multiplet. A doublet of a doublet of the H-6 was at δ8.0. The NH proton of the amide absorbed at δ8.35 (exchangeable with D_2O.)

Benzenesulphonyl chloride as an Electrophile

There is very little literature precedence on the use of sulphonyl chloride as electrophile on organolithiums despite their long use in electrophilic reactions with amines to form sulphonamides. Care however need be taken in the use of sulphonyl chlorides with acidic protons as these may be attacked by organolithium.

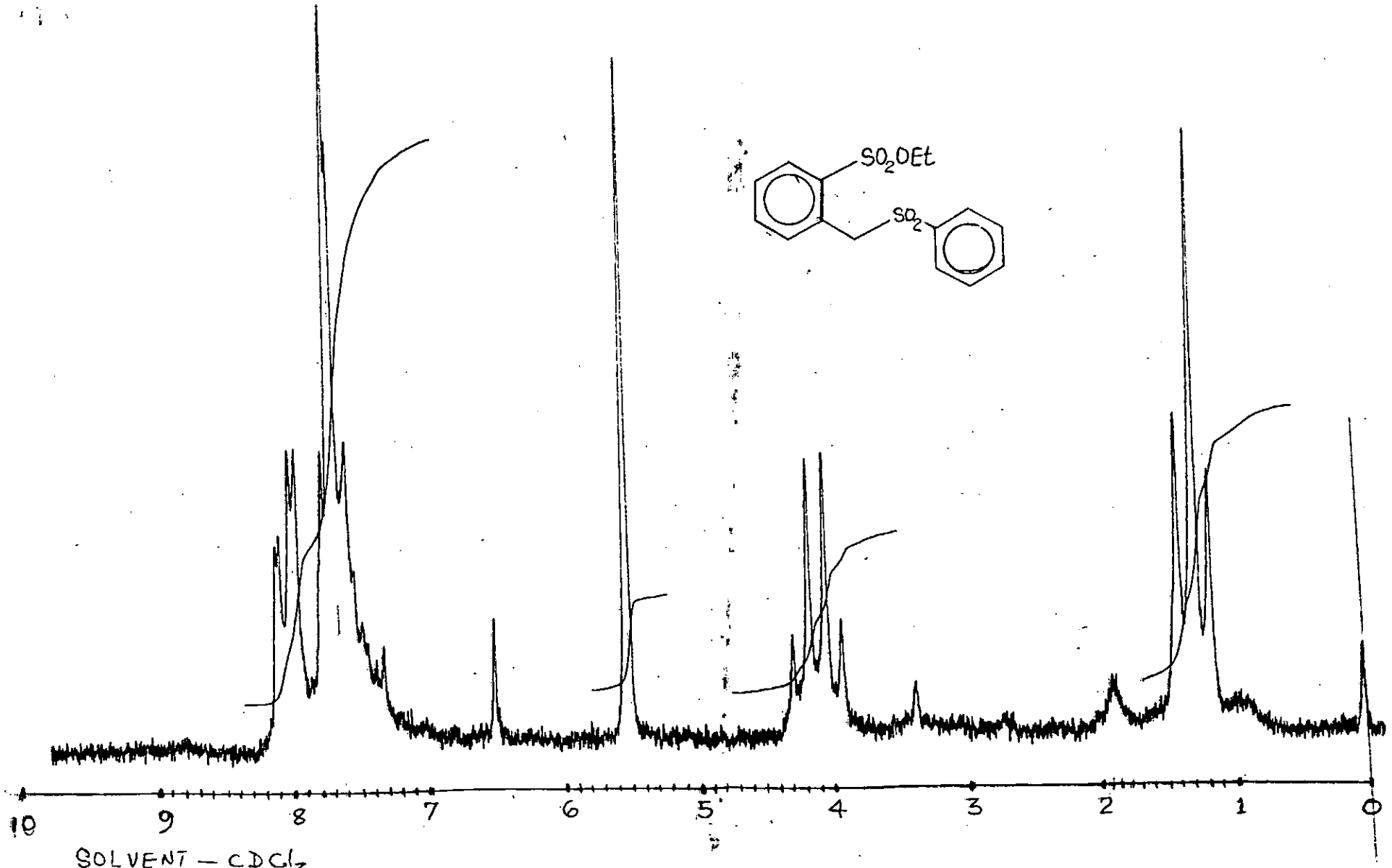
The lithio species was appropriately treated with benzenesulphonyl chloride dissolved in THF. Usual work-up gave an oil which on t.l.c. showed four compounds.



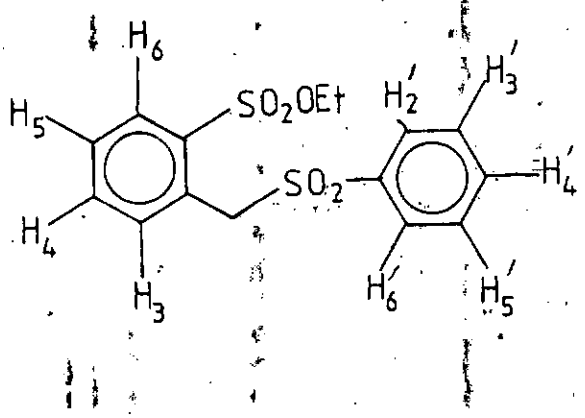
357

Flash chromatography of the oil gave mainly the starting material, and two other compounds.

A white solid whose nmr did not show the aromatic protons of the benzenesulphonyl group and also microanalytical data did not


SO2OEt
SO2
10
9
8
7
6
5
4
3
2
1
0
SOLVENT — CDCl3
13/5/89

conform with the expected value. However, the N.M.R. spectrum of the other compound an oil that separated in 50% yield, showed a 3H triplet at δ1.3 and a 2H quartet at δ4.1 for the ethyl group. A 2H singlet at δ5.5 was representative of the methylene next to the phenyl ring deshielded by the $-SO_2$ group. A 6H multiplet at δ7.6 was assigned to $H\text{-}3^1$, $H\text{-}4^1$, $H\text{-}5^1$ and H-3, H-4 and H-5 and H5 while 3H doublet of a doublet at δ8.1 was assigned to $H\text{-}2^1$, $H\text{-}6^1$ and H6.

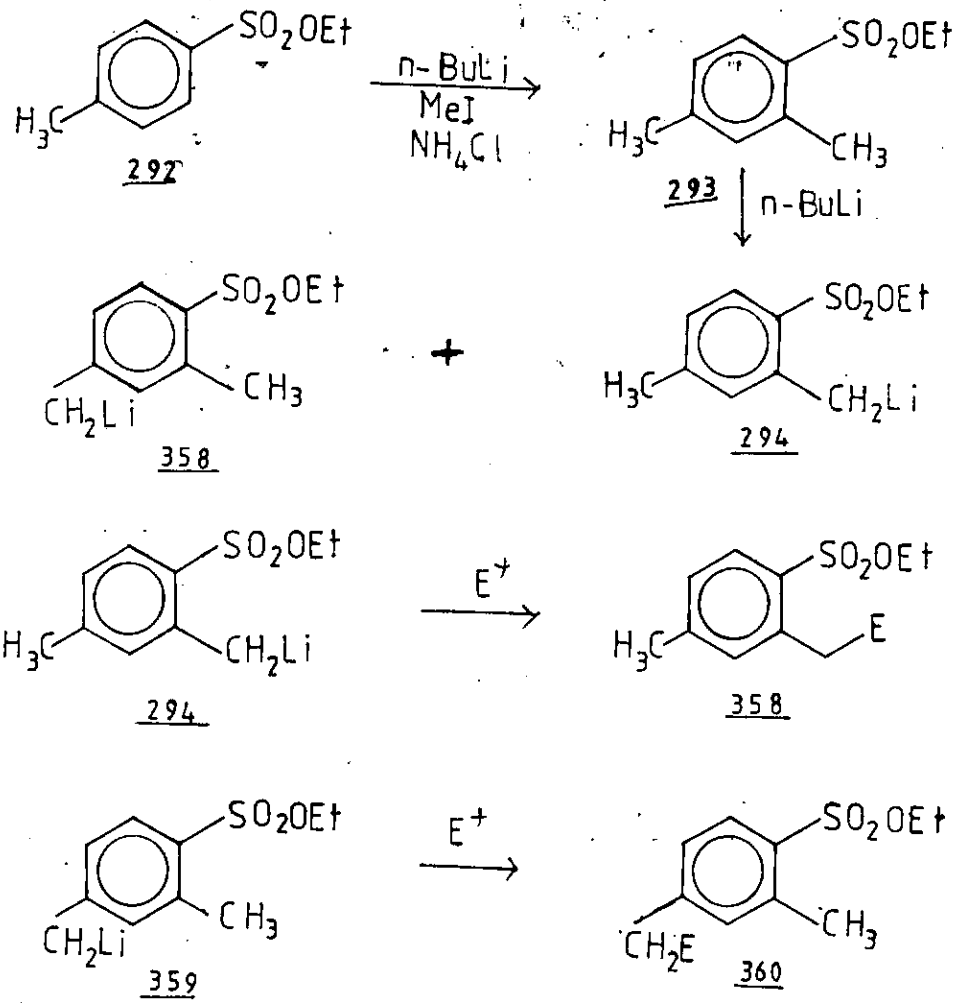


Microanalysis of the oil further confirmed the structure as the expected phenyl [(2-ethoxysulphonyl)benzyl] sulphone.

A summary of the reactions of the benzylic anions with various electrophiles is given in Table 2 (page 119).

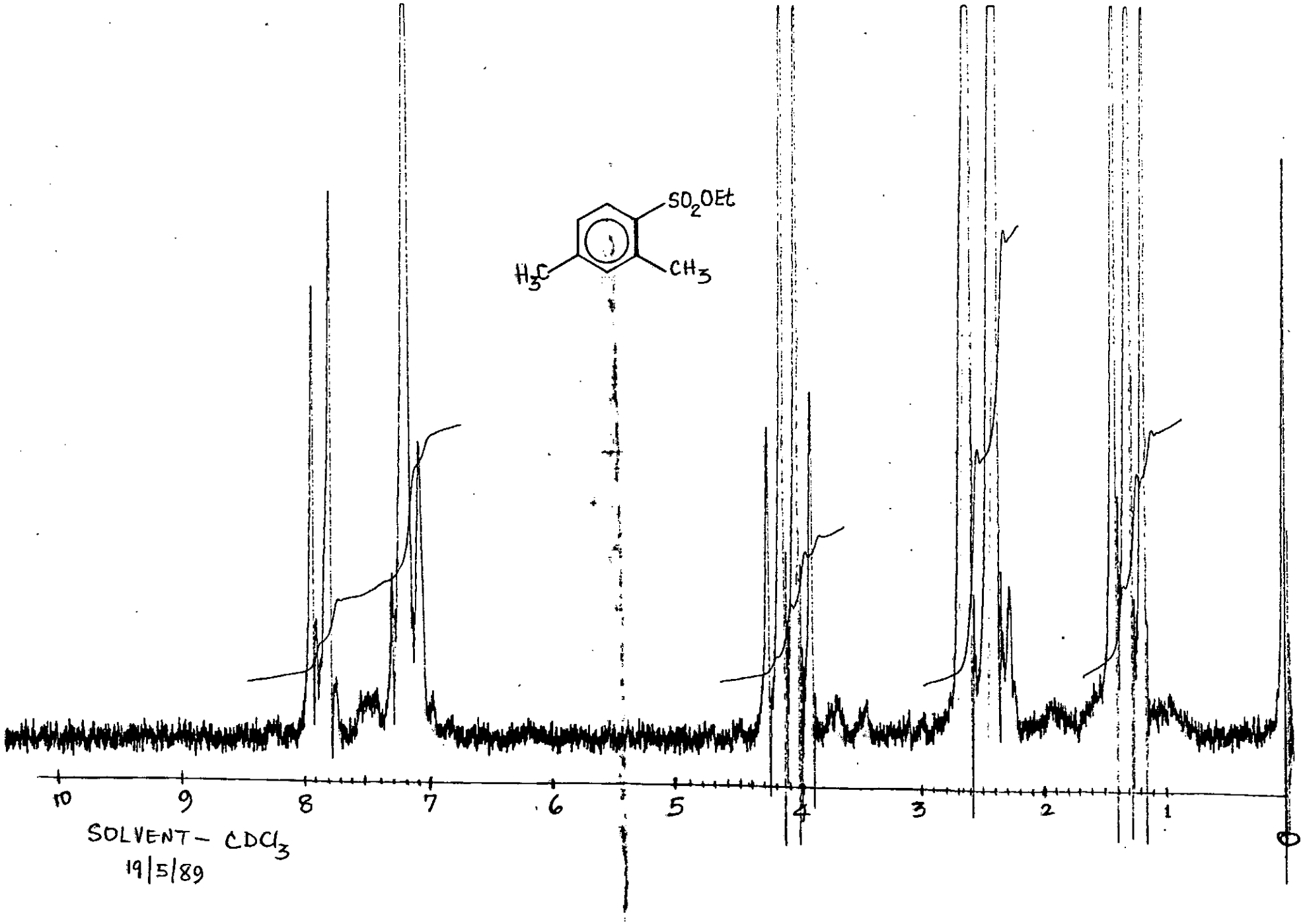
Mechanistic Study:

In a bid to obtain evidence to corroborate the coordination mechanism proposed for the reactions above, experiments were designed to explore the preferential site of lithiation amongst two benzylic positions. The experiment design was to explore the reaction of 2,4-dimethylbenzene sulphonate with organolithium metalating agents during which the ortho methyl group which can undergo coordination with the heteroatom directing group should be exclusively lithiated. In this regard, the following scheme for the experiment was delineated:



Preparation of the required ethyl 4-toluenesulphonate was carried out as described for ethylbenzene sulphonate earlier, using 4-toluenesulphonyl chloride and ethanol in the presence of alkali. Treatment of ethyl 4-toluenesulphonate in THF at -78° with n-BuLi gave a lithiospecies which was reacted with methyl iodide. With methyl iodide, work-up gave a white homogenous gum in 83% yield.

^{1}H-NMR of the oil showed a 3H triplet at δ1.3 for the methyl group of the ethyl, a 3H singlet at δ2.45 ortho methyl group and another 3H methylene singlet for the 4-methyl group. The methylene


SO2OEt
H3C
CH3
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – CDCl3
19/5/89

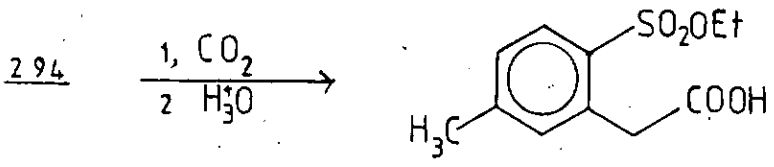
group of the ethyl showed at δ4.2 as a quartet. δ7.2 for 2H aromatic protons of H-3, and H-5 while H-6 was at δ7.9 as a doublet. This values conform to the ethyl 2,4-dimethyl-benzenesulphonate.

Benzylic anion was generated from ethyl 2,4-dimethylbenzene-sulphonate with n-BuLi at -78° and it was reacted with some electrophiles as appropriate.

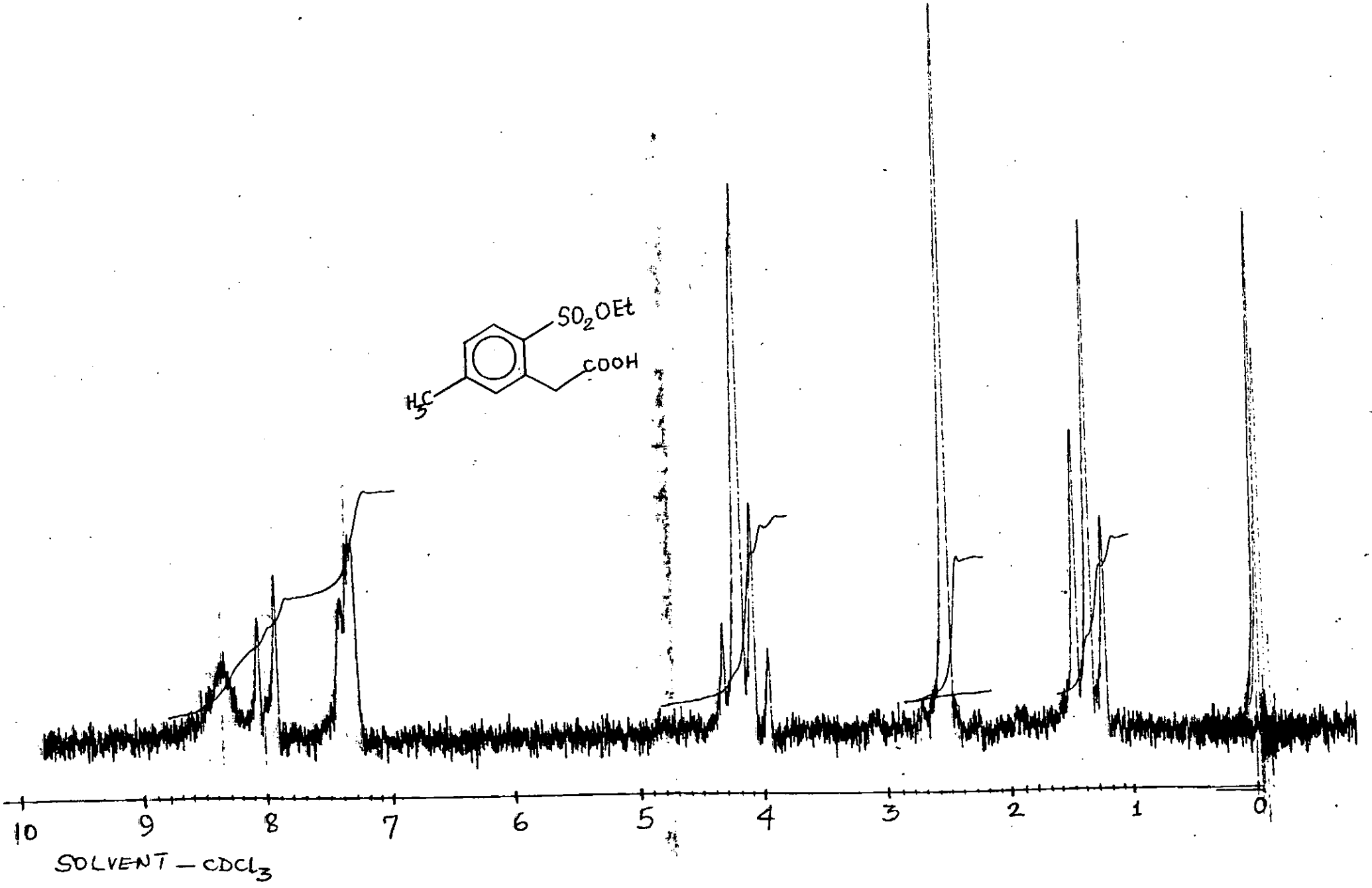
CO_2 as Electrophile

With solid carbon dioxide, work-up gave a crude solid which was recrystallised with Pet. ether: diethyl ether mixture to give colourless plates m.p. 108-110° in 85% yield.

The I.R. spectrum of the plates showed a broad absorption between 3300 and 2530 cm^{-1} for the hydroxyl group, 1710 (COOH), 1600, (-C=C- of the aromatic ring), 1360 and 1180 cm^{-1} (SO_2-O).



The ^{1}H-NMR spectrum of the compound showed the 3H triplet of the $-CH_3$ of the ethyl at δ1.4, a sharp 3H singlet at δ2.55 represented the p-methyl group while the ortho methyl singlet which usually appears at δ2.7 had completely collapsed and showed as a 2H singlet at δ4.2 which almost overlapped with a quartet at δ4.15 ($\underline{CH}_2$-CH_3) indicated a replacement of the ortho methyl


SO2OEt
COOH
H3C
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – CDCl3

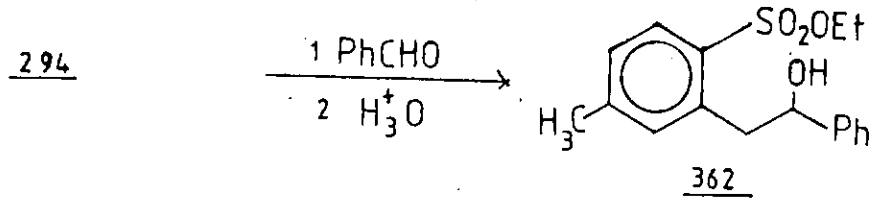
with a methylene next to a carboxylic acid. The two aromatic protons H-3 and H-5 appeared as a multiplet at δ7.4 along with a 1H doublet of H-6 at δ8.0. The proton of the carboxylic acid absorbed at δ 8.35 and was exchangeable with D_2O.

Benzaldehyde as an Electrophile

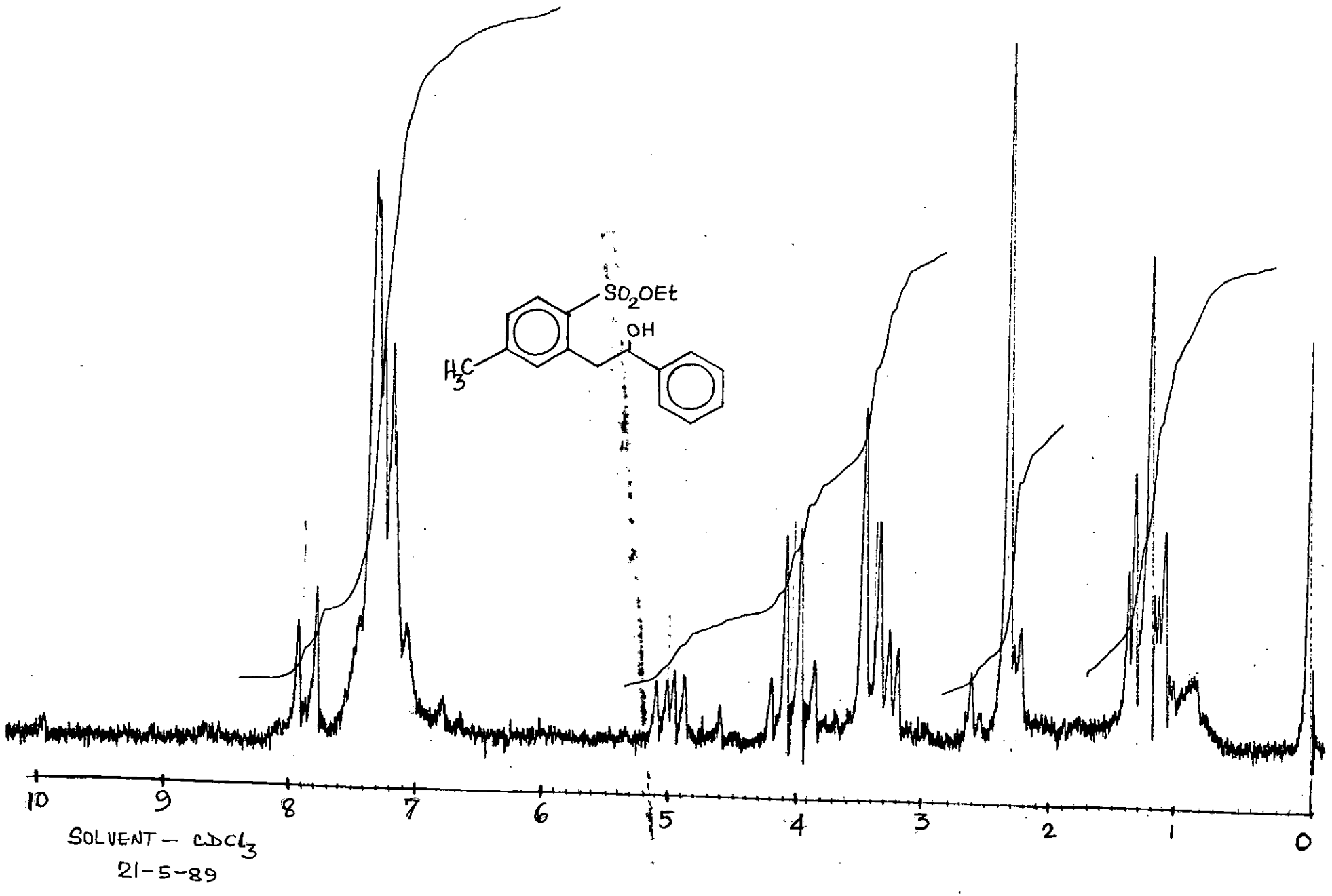
Benzaldehyde dissolved in THF was added to the lithio species and on work-up gave a crude oil which was purified by flash chromatography to give a white solid m.p. 49-51° in 65% yield.

The KBr-dispersion i.r. spectrum of the solid showed absorptions at 3460 cm^{-1} (-OH group), 1600 (aromatic 1340, 1170 cm^{-1} (SO_2-O).

The ^{1}H-NMR spectrum showed a 3H triplet of the $-CH_3$ of the ethyl at δ1.3, a sharp 3H singlet at δ2.3 represented the 4-methyl group, and a 2H singlet-doublet at δ3.4 represented the methylene next to the phenyl group. The methylene of the ethyl group showed a 2H quartet at δ4.1, while the absorption at δ 5.0 for one proton on the carbon bearing the O-H was a quartet. A 7H multiplet at δ7.3 was ascribed to the aromatic protons and a 1H doublet at δ7.0 was for H-6 proton.



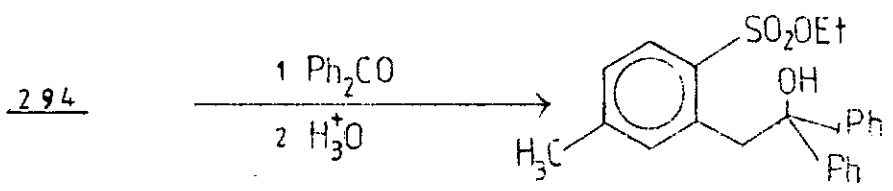
Microanalysis of the compound agreed with calculated values and further confirmed the structure as the expected [2-(2-ethoxysulphonyl)-5-methylbenzene]-1-phenylethanol.

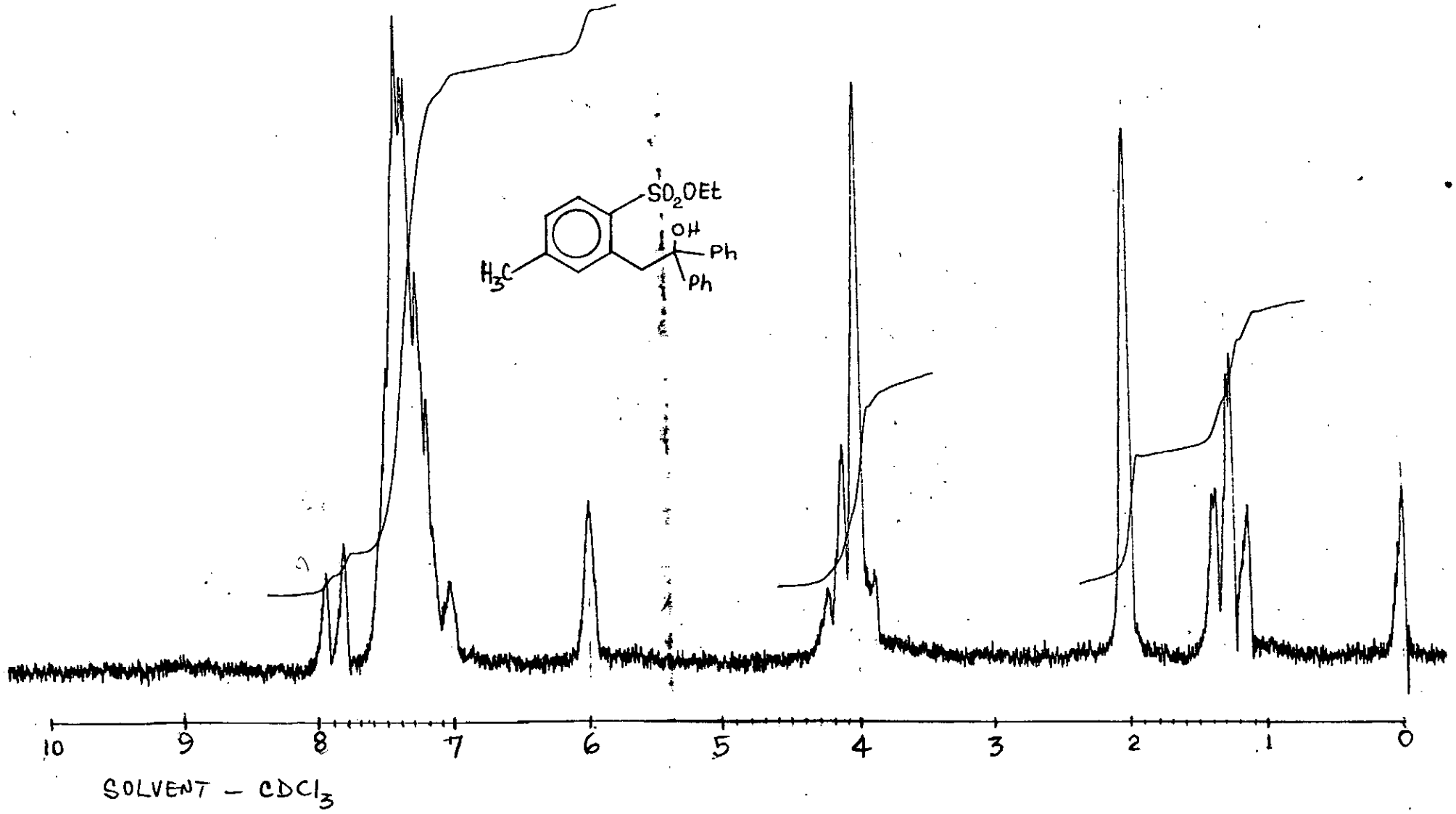

SO2OEt
OH
H3C
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – CDCl3
21-5-89

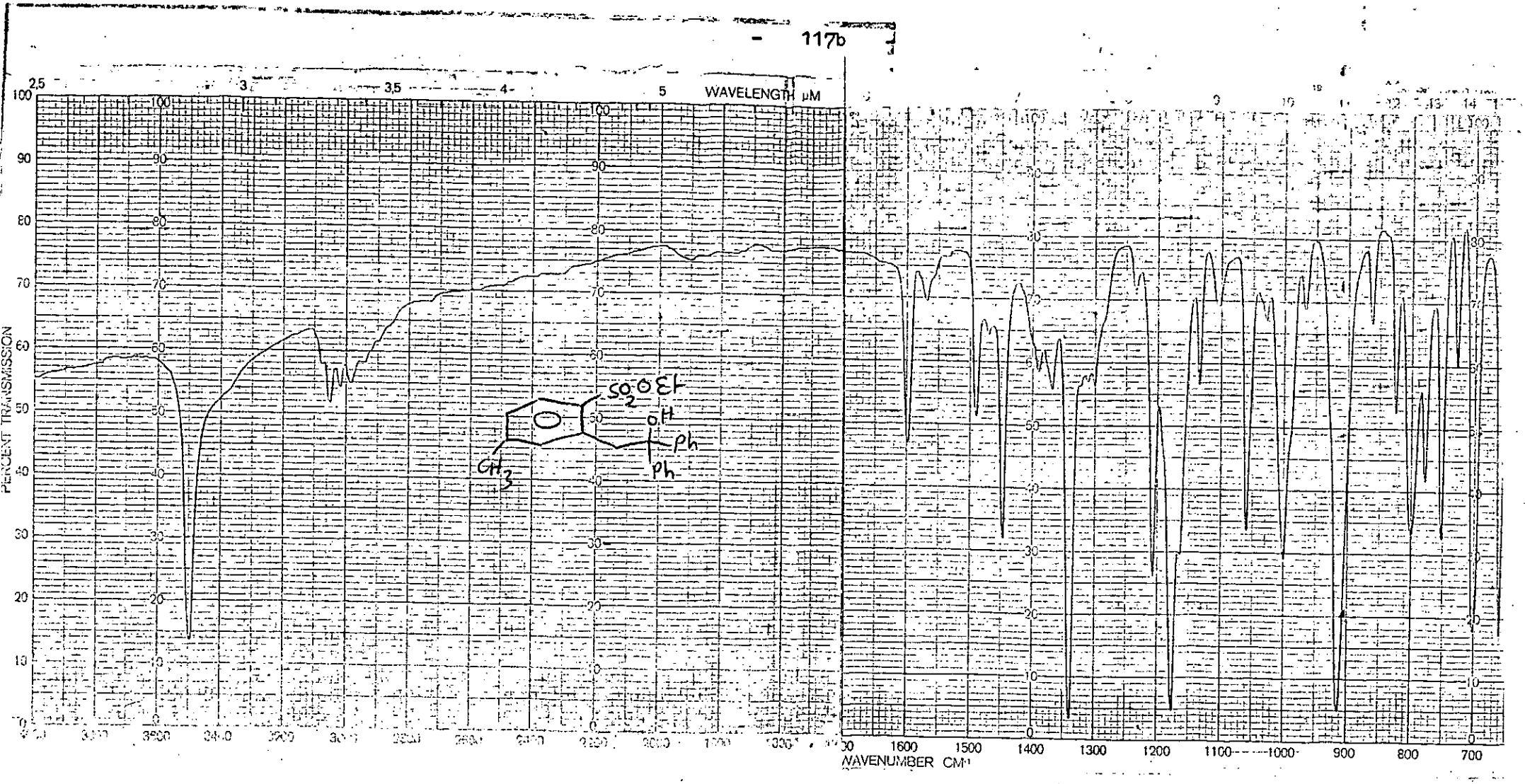
Benzophenone as Electrophile

With benzophenone as electrophile, work-up gave a white solid which was recrystallised to give white needles, m.p. 114-116° in 90% yield.

The infra-red spectrum of the solid showed strong absorptions at 3500 broad (-OH group), 3060, 1600 cm^{-1} (aromatic), 1490, 1450, 1340 and 1180 cm^{-1} (SO_2-O). The ^{1}H-NMR spectrum of the solid showed a 3H triplet for the methyl of the ethyl at δ1.3, a 3H singlet at δ2.0 is ascribed to the 4-methyl group, while signals of three groups of protons appeared together as a 5H-quartet at δ4.1. The groups are the 2H methylene adjacent to the phenyl ring, the methylene of the ethyl and the hydroxyl proton (exchangeable with D_2O). The singlet at δ6.0 is ascribed to the aromatic H-3, which is in contrast to 1,1-diphenyl-(2-ethoxysulphonylbenzene)ethanol's H-3 which was a doublet. This must be due to lack of an ortho proton at C-4. However, the H-3 is shielded by the two phenyl rings. The 11H multiplet at δ7.4 represented the two phenyl rings and H-5 protons. The 1H doublet at δ7.9 is ascribed to H-6. The elemental analysis which was in agreement with theoretical values further confirmed the structure of the product as 1,1-diphenyl-2-[(ethoxy sulphonyl)-4-methylbenzene] ethanol.

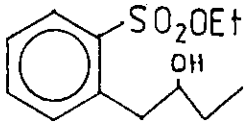
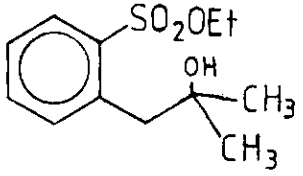
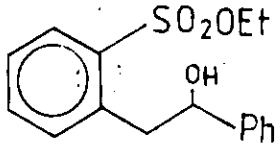
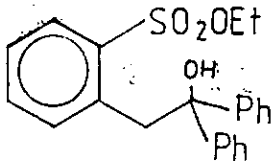
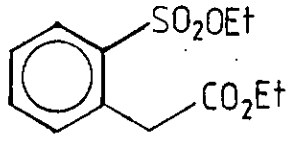
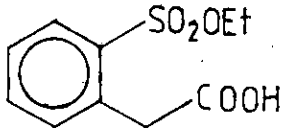


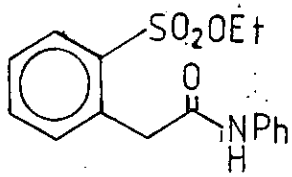
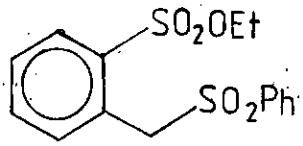
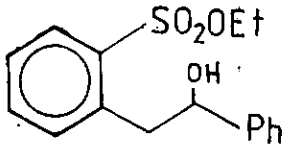
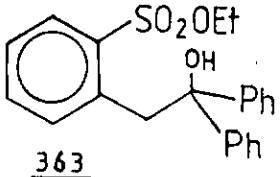
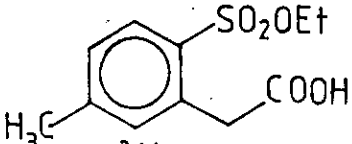
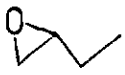
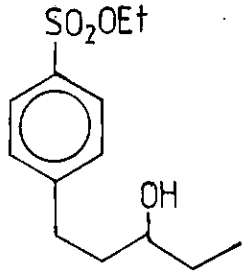

SO2OEt
OH
Ph
Ph
H3C
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – CDCl3


WAVELENGTH µM
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹
SO2OEt
OH
Ph
Ph
CH3

With the exclusive lithiation of the ortho methyl group of the dimethylbenzenesulphonate in these experiments, credence appears to have been given to a coordination mechanism involving the oxygen atom of the sulphonate with the ortho methyl leading to preferential lithiation at the 2-methyl position exclusively.

TABLE 2

Entry	Reactant	Electrophile	Product	Yield, %
1	291	CH_3CH_2CHO	 350	75
2	291	CH_3COCH_3	 351	50
3	291	PhCHO	 352	65
4	291	Ph_2CO	 353	91
5	291	$ClCO_2Et$	 354	50
6	291	CO_2	 355	70

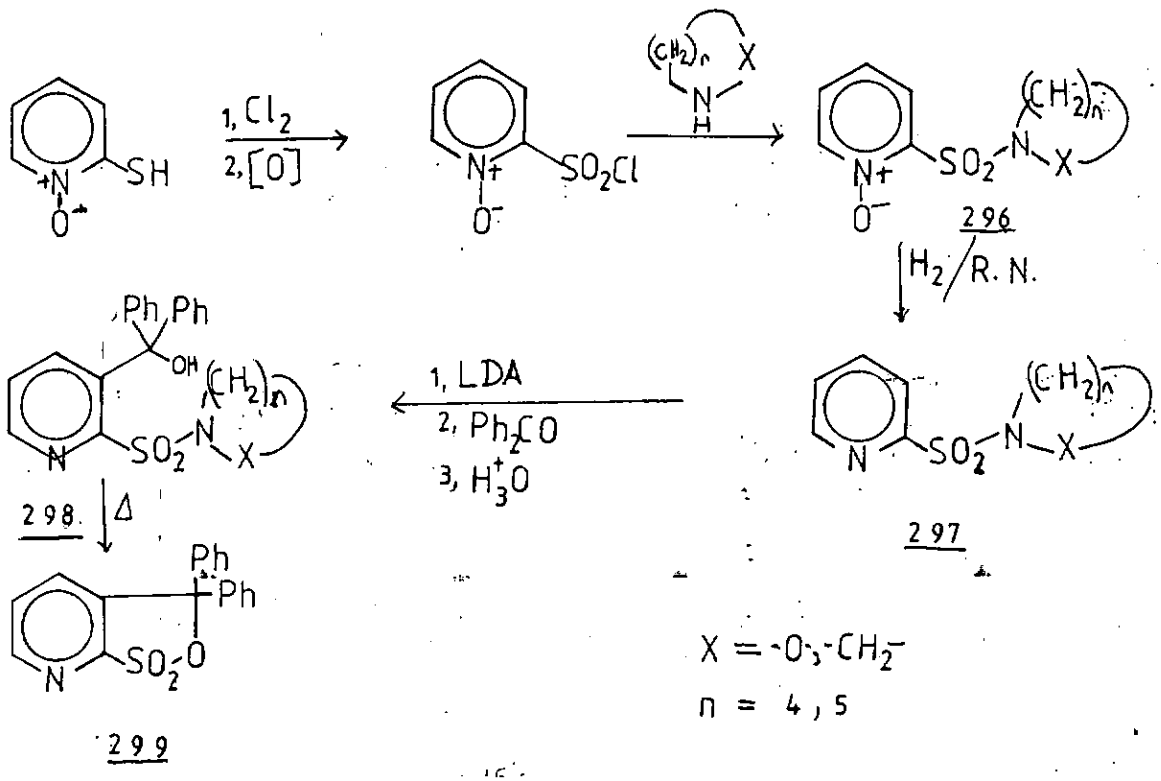
7	291	PhNCO	 356	78
8	291	$PhSO_2Cl$	 357	50
9	294	PhCHO	 362	60
10	294	Ph_2CO	 363	90
11	294	CO_2	 361	85
12	348		 349	40

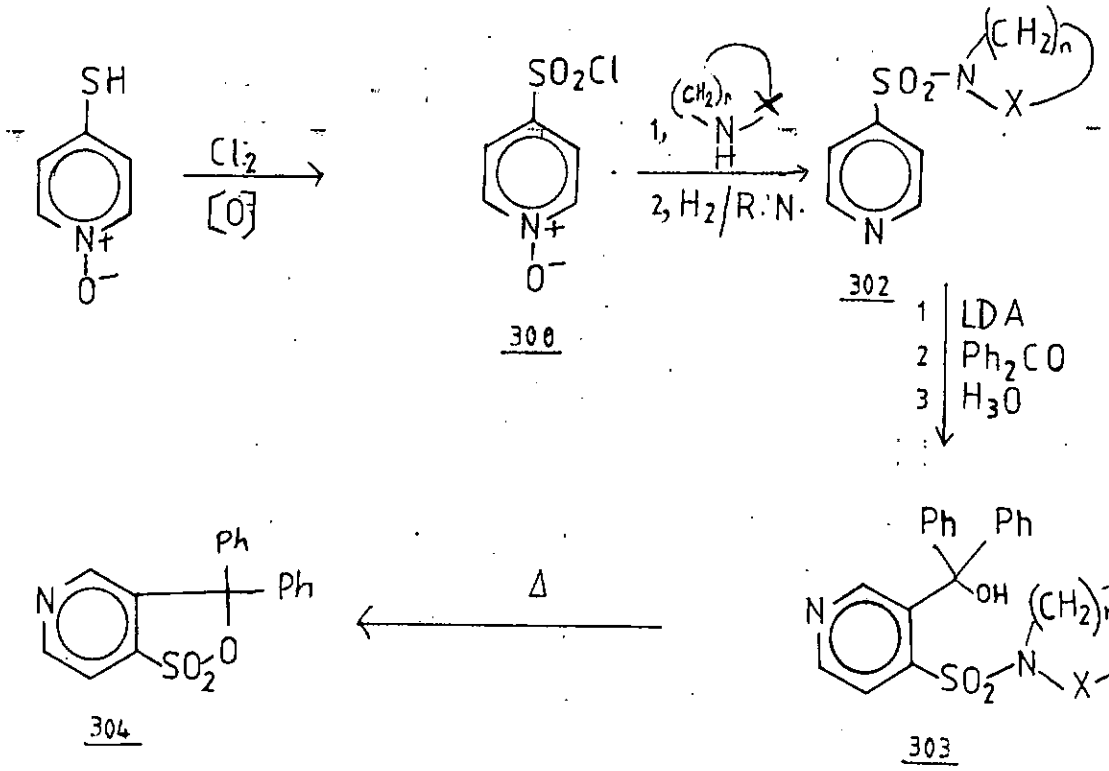
2.6. SULPHUR CONTAINING HETEROCYCLES THROUGH METALATION OF PYRIDINESULPHONAMIDES

The sulphonamido group is known to function as a DMG in pyridines[109] leading to regiospecific metalation of the pyridine system with organolithiums. The lithiospecies thus formed is also established to couple with electrophiles which when made to undergo further transformations may furnish novel heterocycles.

2-(piperidinosulphonyl)pyridine and 4-(piperidinosulphonyl) pyridine had been metalated[63] with both pyridine derivatives leading only to their 3-lithio species. When coupled with benzophenone, diphenyl(2-(piperidinosulphonyl)-3-pyridyl) methanol and the 4-pyridyl equivalent were obtained respectively. It was hoped that these products can be made to undergo cyclisation to produce fused heterocycles of interest, especially since sulphur-containing pyridine rings usually possess interesting pharmacological activity[133].

The proposed scheme for the metalation is outlined below:

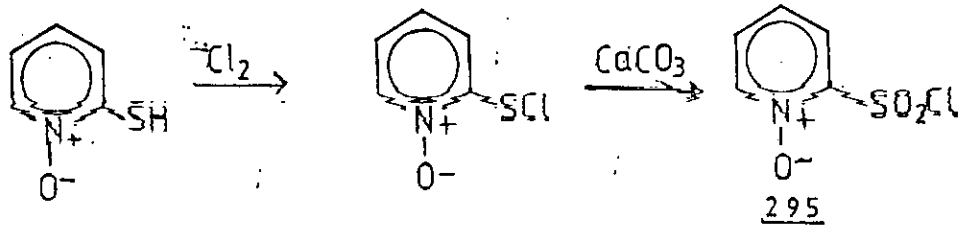


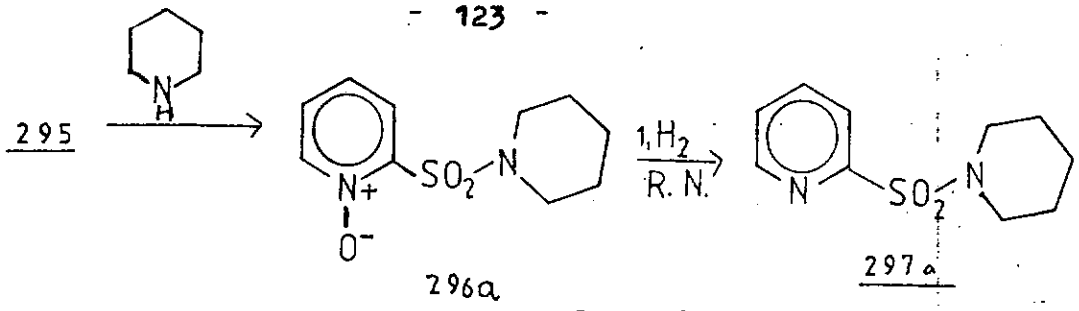


n = 4,5,4

x = 0, $-CH_2-$

Experimentation started with the <u>in-situ</u> preparation of the N-oxide of 2-pyridinesulphonyl chloride by chlorination of 2-mercaptopyridine-N-oxide. The 2-pyridinesulphonyl chloride, N-oxide obtained was condensed directly with the appropriate secondary amine: piperidine, pyrrolidine and morpholine to obtain respectively 2-(piperidinosulphonyl), 70%; 2-(pyrrolidinosulphonyl), 72%; 2-(morpholinosulphonyl) pyridine, 68%.





296a 297a

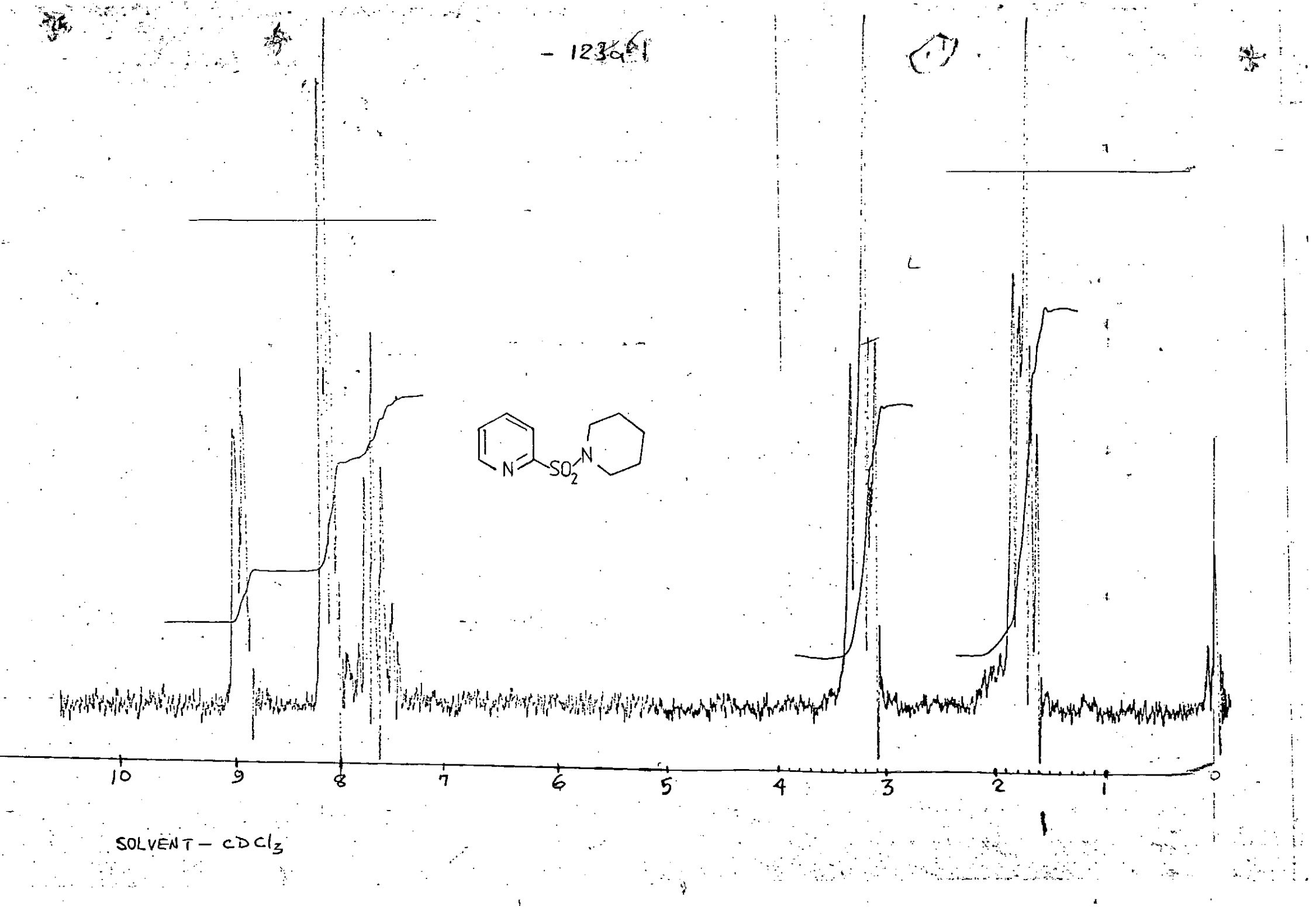
R.N. = Raney Nickel

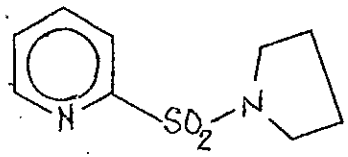
The presence of N-oxide makes the thiol at the 2-position more reactive towards chlorine oxidation. The sulphonyl chlorides were generally not isolated (because their high reactivity sometimes lead to decomposition). When the amine had been added, the amide formed was more stable and then the pyridine compound was more amenable to the removal of the N-oxide without decomposition of the molecule. The N-oxides were reduced under pressure in a bomb by hydrogenation in the presence of Raney nickel as a catalyst. The characteristics of the amides were as follows:

2-(Piperidinosulphonyl)pyridine 297a gave a m.p. of 58-59° (Lit.[63] 59°).

The ^{1}H-NMR spectrum showed a 6H multiplet at δ1.8 for the piperidine protons (type a). The 4H multiplet at δ3.3 is assigned to the piperidine protons next to the nitrogen atom. The pyridine H-5 appeared as a multiplet at δ7.5 while the doublet at δ8.0 represented the H-3 and H-4 protons. The doublet at δ8.75 is assigned to the H-6 proton which is the most deshielded due to the lone pair of electrons of the nitrogen.

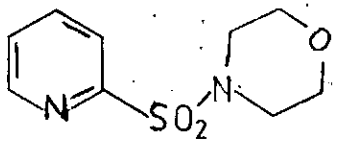
- 12396-1



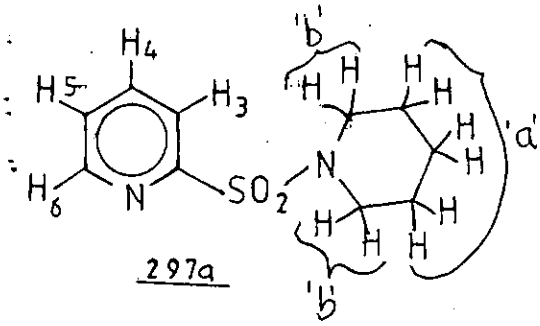

N
SO2
N

10
9
8
7
6
5
4
3
2
1
0
SOLVENT — CDCl3

123-C



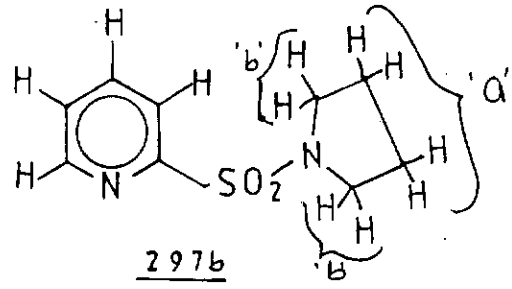
SOLVENT — $CDCl_3$



297a

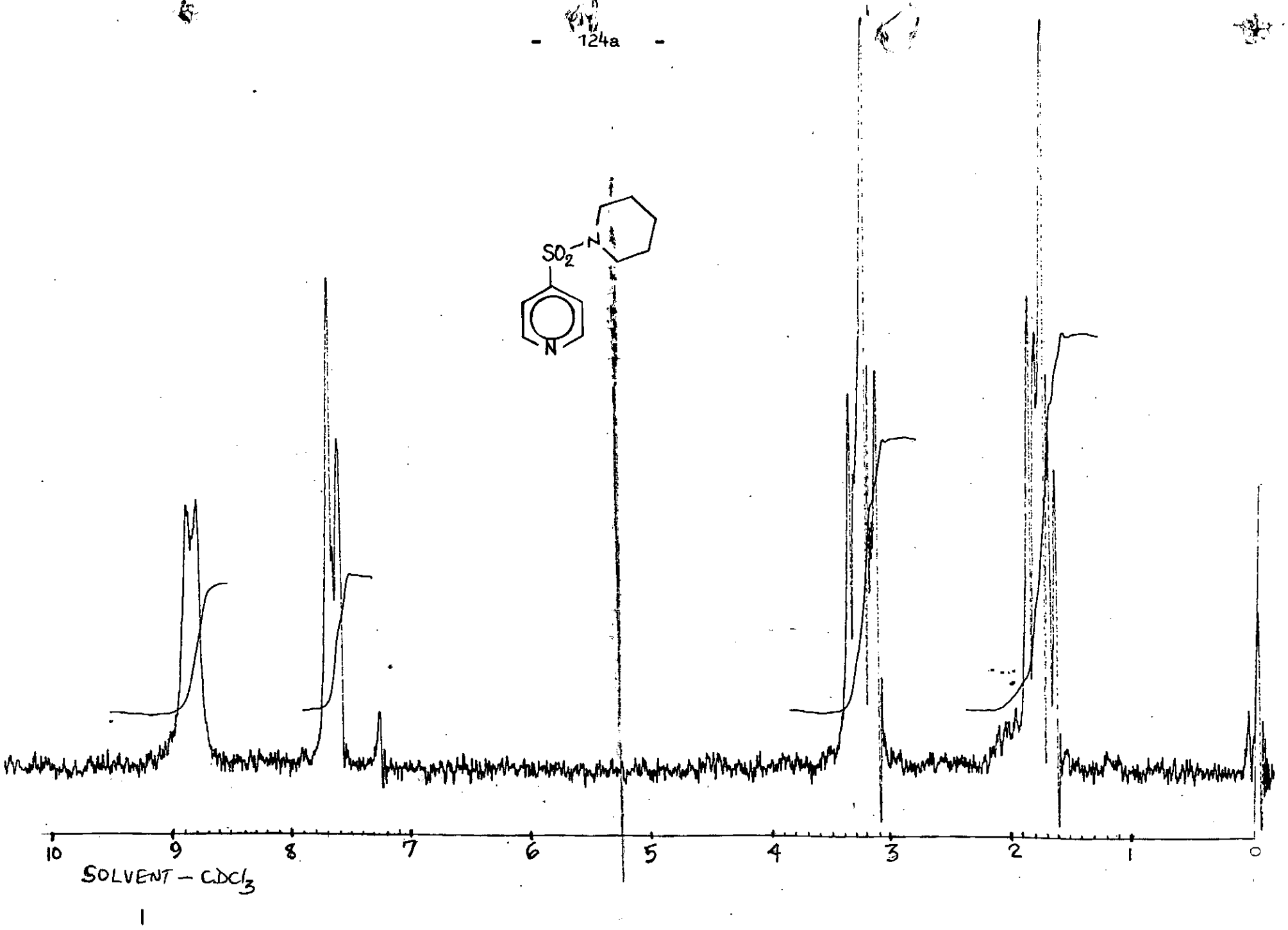
KBr-dispersion I.R. spectrum showed a strong absorption at 3090, 3000, (CH stretching), 1575 (aromatic -C=C-) 1340, 1180 cm^{-1} (SO_2-N).

2-(pyrrolidinosulphonyl)pyridine 297b gave a m.p. of 39-40°. ^{1}H-NMR spectrum showed a 4H multiplet absorption at δ 1.9 for the pyrrolidine ring (type a) while another 4H multiplet at δ 3.5 is for 4 protons adjacent to the nitrogen of the pyrrolidine ring. The aromatic region showed a 1H multiplet at δ 7.5 for the H-5 proton, the 2H doublet at δ 8.0 is assigned for H-3 and H-4 while the doublet for 1H at δ 8.75 is for H-6 proton.

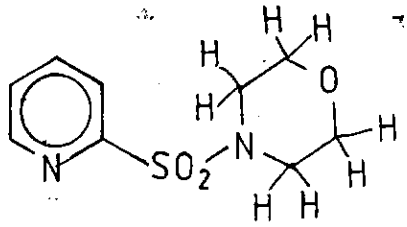


297b

The ^{1}H-N.M.R. spectrum of 2-(morpholinosulphonyl) pyridine showed a 4H multiplet at δ 3.0 for the 4 proton adjacent the oxygen atom. The signal at δ 3.8 (4H multiplet) is assigned to the 4 protons adjacent to the nitrogen atom of the morpholine. The aromatic region showed a 1H multiplet for the H-5 proton at δ 7.5, at 2H doublet at δ 8.0 is assigned to H-3 and H-4 of the


SO2
N
N
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – CDCl3

pyridine while the doublet at δ8.7 is for the H-6 proton.



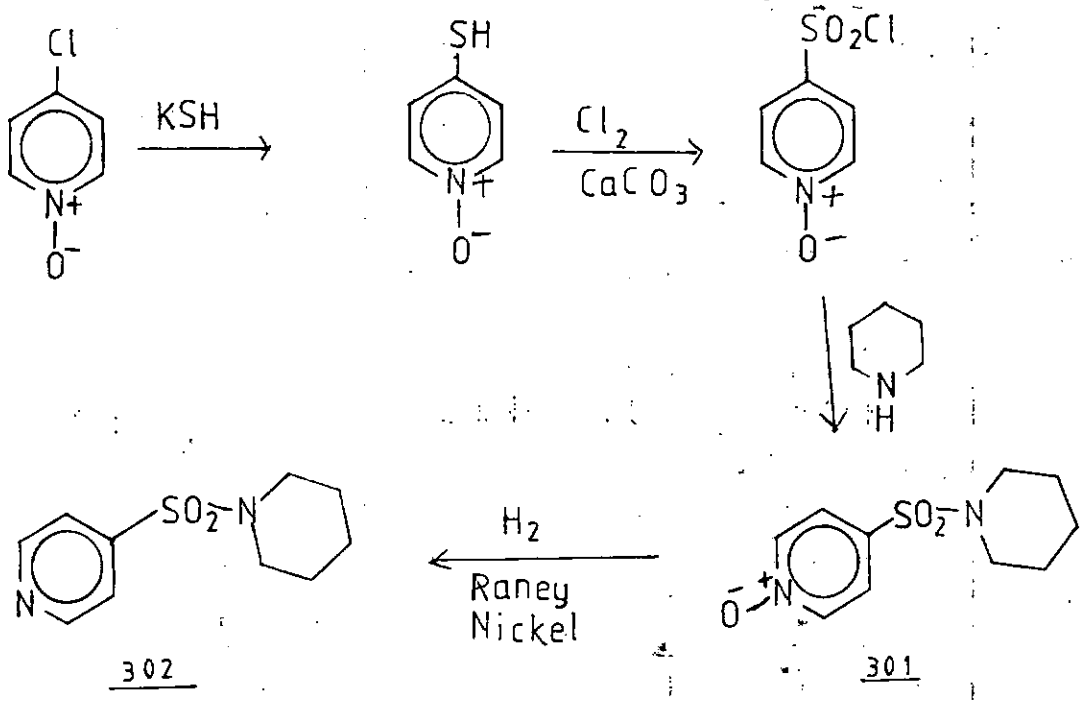
297c

The 4-substituted analogues were similarly prepared by starting with 4-mercapto-N-oxides which were obtained from 4-chloropyridine-N-oxides with potassium hydrogen sulphide, KSH. Chlorine oxidation of the mercapto smoothly gave the sulphonyl chloride in good yields. The sulphonyl chloride was not isolated but immediately condensed with the appropriate amine to form the corresponding sulphonamide-N-oxide.

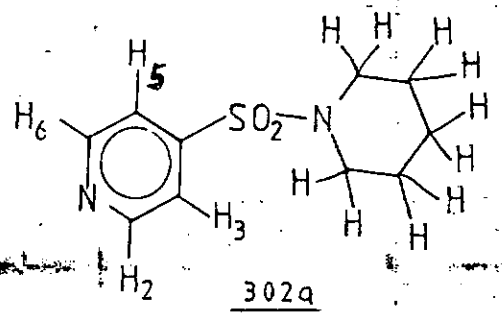
The N-oxide was eliminated reductively with hydrogen gas in the presence of Raney nickel in methanol giving 4-(piperidinosulphonyl)pyridine, 4-(pyrrolidinosulphonyl)pyridine and 4-(morpholinosulphonyl)pyridine respectively. Each of the sulphonamides was characterised spectroscopically.

The ^{1}H-NMR of the 4-(piperidinosulphonyl)pyridine showed a 6H multiplet at δ1.55 (type a), a 4H multiplet at δ3.00 is assigned to the methylene next to the pyrrolidine nitrogen. The aromatic region showed two types of absorptions: a 2H multiplet at δ 7.55 for the H-3 and H-5 protons and another 2H multiplet at δ 8.82 for the H-2 and H-6 protons.

The KBr-dispersion I.R. spectrum showed absorptions at 3100, 3040, 2960, (-CH), 1575 (aromatic -C=C-), 1340, 1180 cm^{-1} ($SO_2N<$).

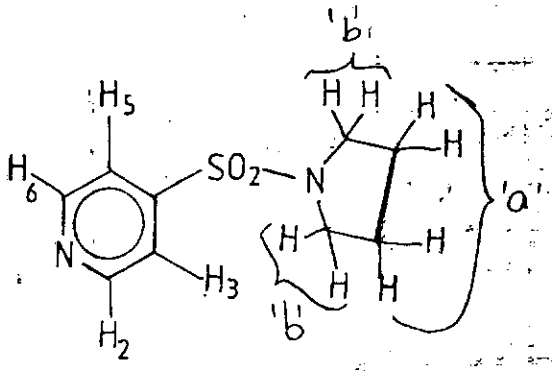


302 301

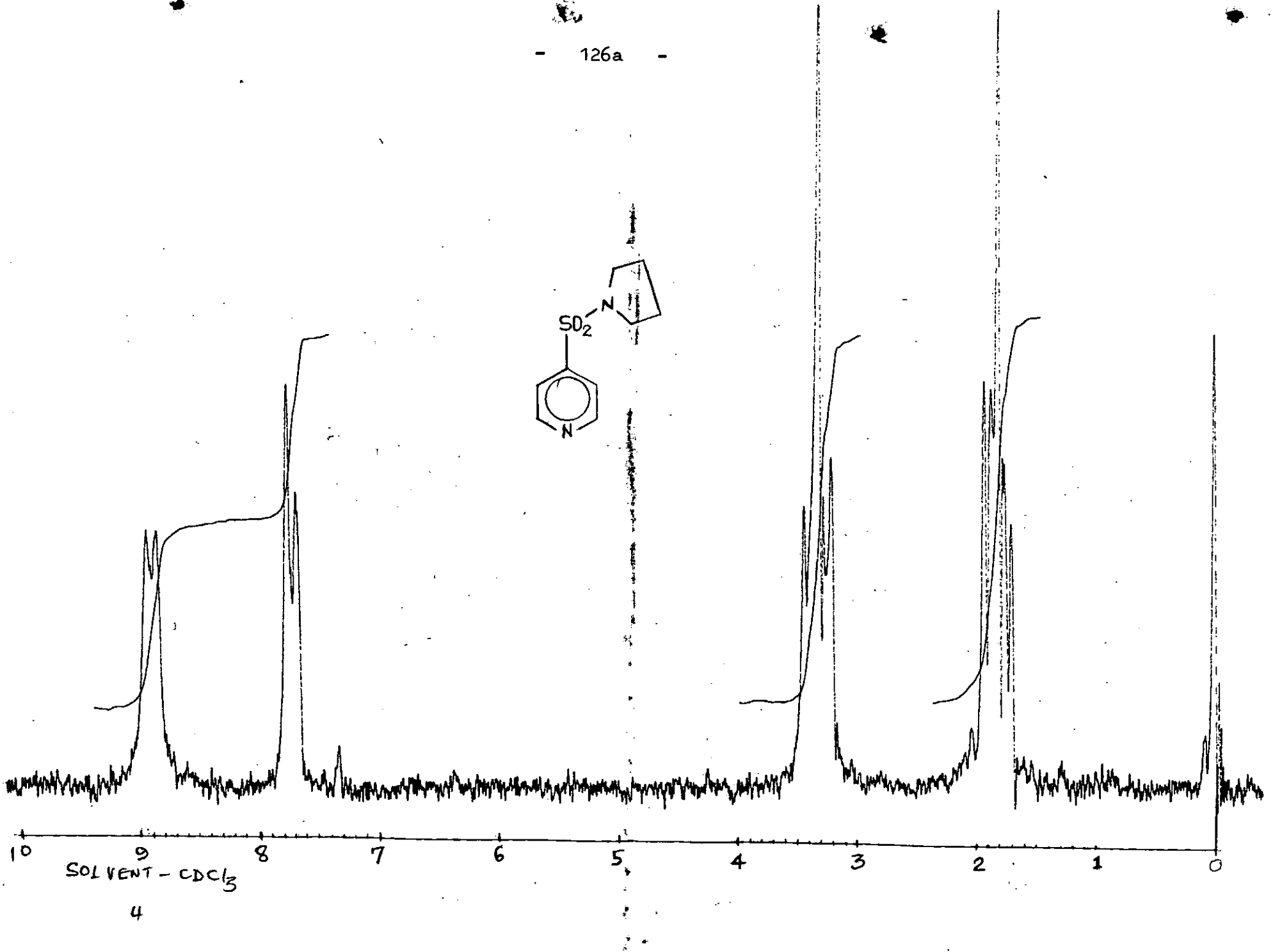


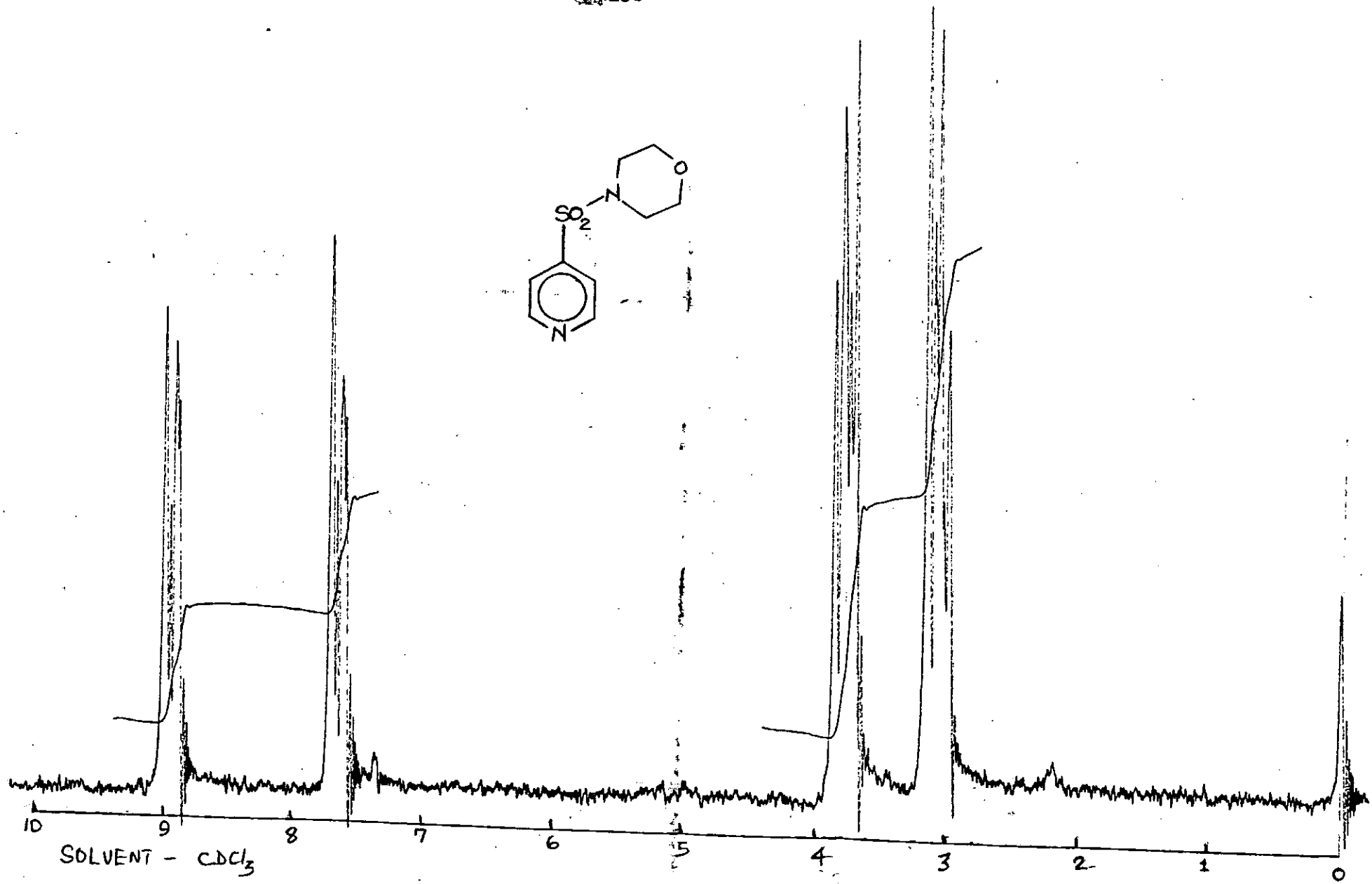
302a

4(pyrrolidinosulphonyl)pyridine gave a 111-112°. It's ^{1}H-NMR showed a 4H multiplet at δ 1.8 for the protons of the pyrrolidine ring. The equivalent H-3, and H-5 absorbed as a 2H multiplet at δ7.7 and the 2H multiplet at δ8.85 represented H-2 and H-6 protons.



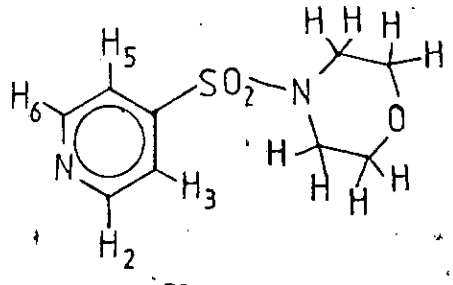
302b


SO2
N
N
10
9
8
7
6
5
4
3
2
1
0
SOLVENT - CDCl3
4



7

The ^{1}H-N.M.R. of 4-(morpholinosulphonyl)pyridine 302c showed a 4H multiplet absorption at δ3.0 for the two methylenes adjacent to the oxygen atom, while another 4H multiplet at δ3.8 is for the two methylenes next to the nitrogen. The 2H multiplet of H-5 and H-6 absorbed at δ7.7 and another 2H multiplet of H-2 and H-6 absorbed at δ8.95.



302c

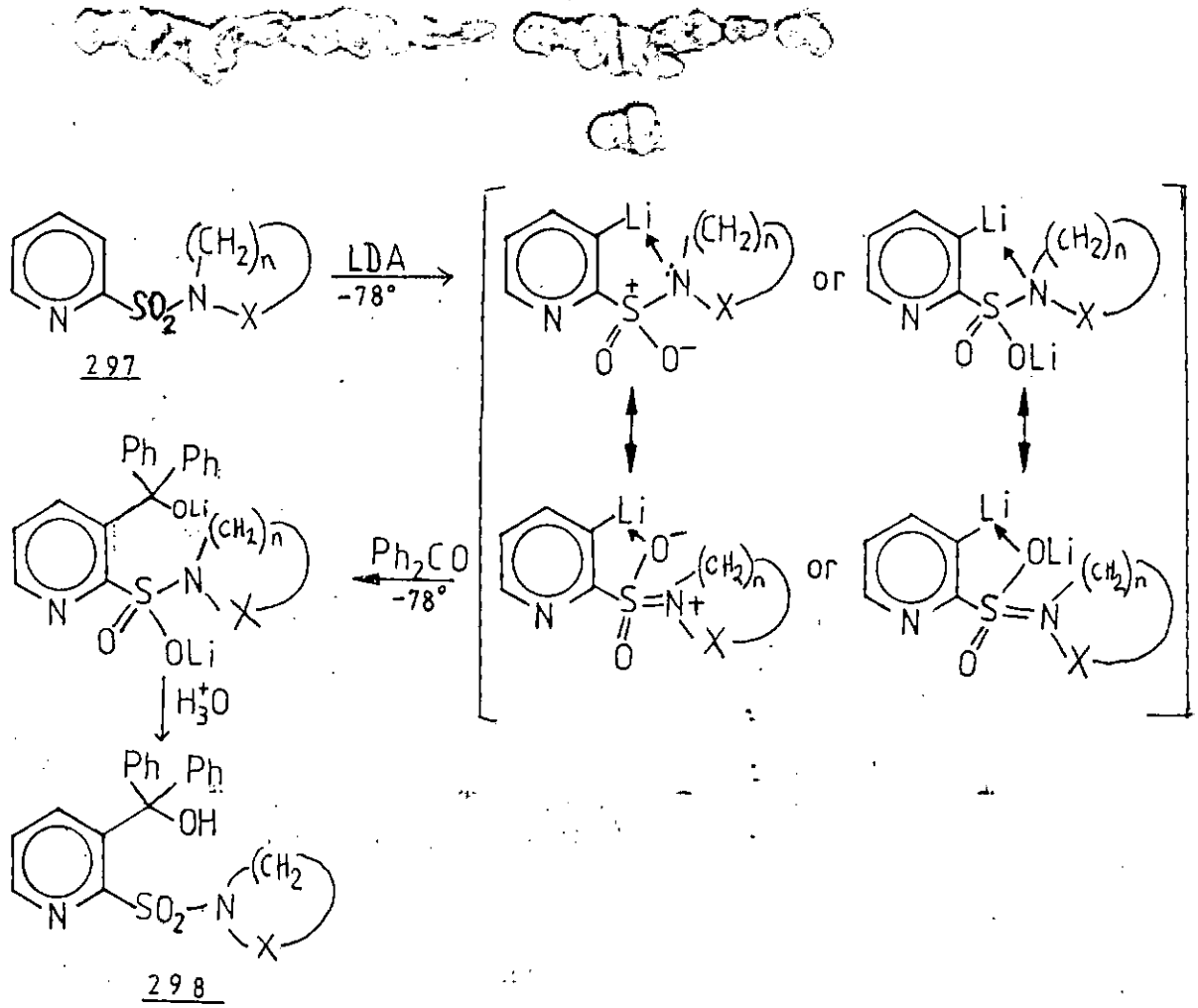
Lithiation Reactions of the Pyridinesulphonamides

Hauser and Watanabe had in 1968 published the lithiation of N-substituted benzenesulphonamides with n-BuLi and the reaction of the lithio species with benzophenone. The product was subsequently cyclised to give a sultone. No previous work had been done on pyridine sulphonamide metalation except those reported by Queguiner et al[63, 109] in 1983 and 1987 in which lithiated pyridine sulphonamide was coupled with benzophenone. Following the same method; the 2-(sulphonamido)pyridine and the 4-(sulphonamido)pyridine which were prepared earlier were sequentially lithiated with LDA. The LDA was used instead of n-BuLi or PhLi because the latter two reagents had previously been observed to undergo nucleophilic addition to pyridine[134]. Also the reactions were carried out at low temperature (-78^o) because the lithio pyridines are known to be unstable at higher temperatures unlike lithio-benzenes that are stable up to 25^o.

Two equivalent of LDA was necessary for these pyridine lithiations as the first equivalent normally formed a chelate with the nitrogen of the pyridine sulphonamide and the second equivalent achieved the lithiation. The LDA was generated in situ with the addition of n-BuLi in hexane to a solution of redistilled diisopropylamine in diethyl ether at -70° and stirring for 1h at -30°.

Benzophenone as electrophile on 3-lithiopyridine-2-sulphonamide

The pyridinesulphonamide in THF was added at -78°C to LDA solution and stirred for 3h at that temperature to generate the lithio species. Benzophenone dissolved in THF was added. Standard work-up precipitated a solid which was recrystallised as appropriate.



297

298

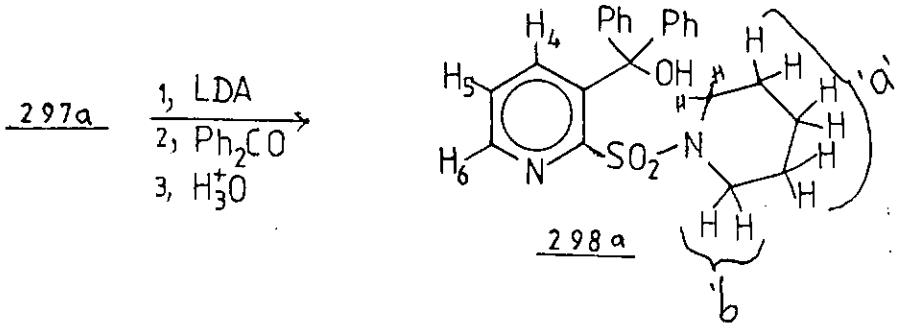
a n = 5, x = $-CH_2-$

b = 4, x = $-CH_2-$

c = 4, x = -O-

Scheme 14

For the piperidine analogues 298a. The solid obtained was recrystallised to give white needles m.p. 182-183° in 90% yield.

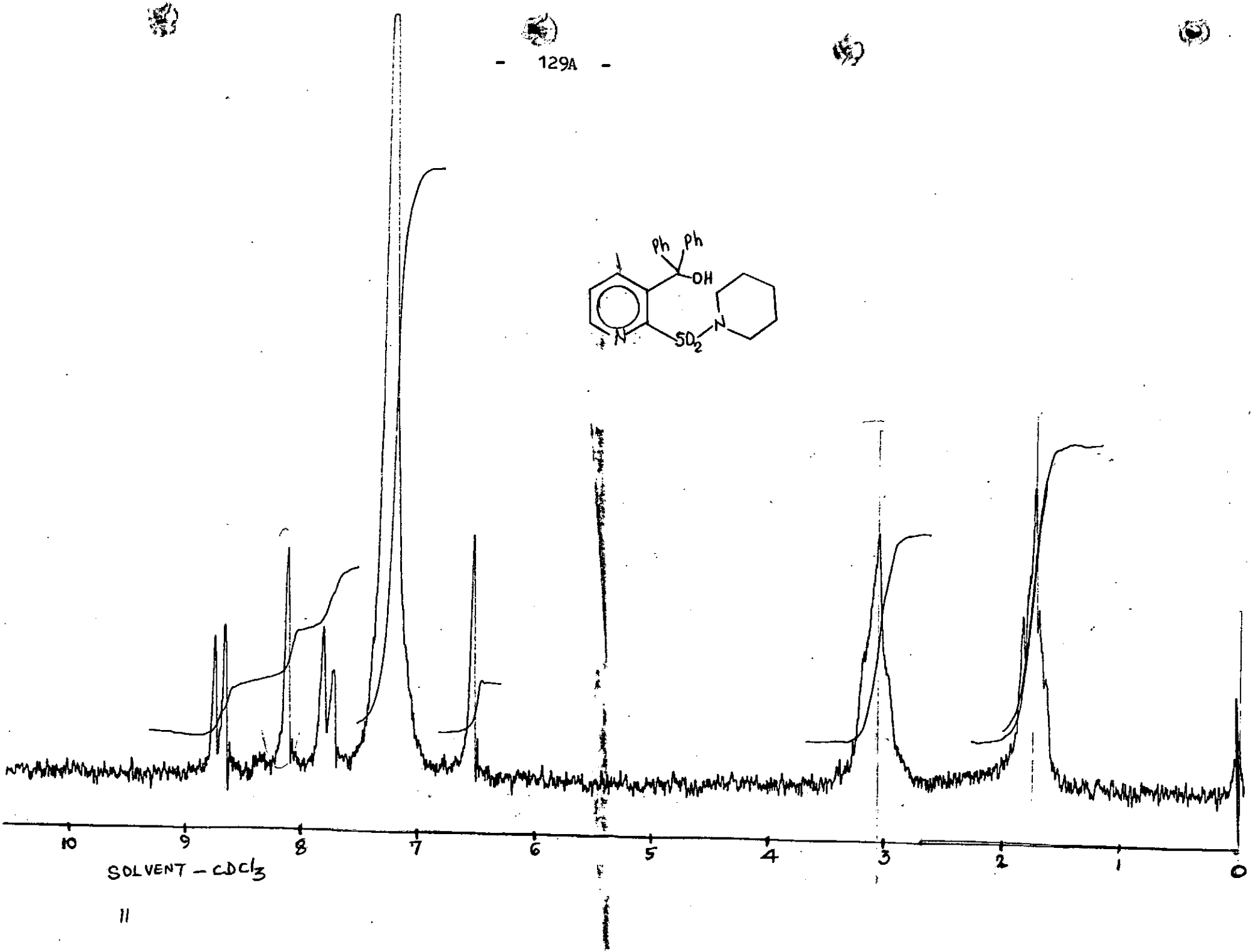


298a

The ^{1}H-NMR of the needles showed a 6H multiplet at δ 1.60 (type a), a 4H multiplet at δ 3.0, ($-CH_2-N<$). A sharp 1H singlet (collapsable on deuteration) at δ6.6 represented the -OH. The aromatic region was not quite resolved. A twelve proton multiplet at δ7.4 was indicative of the proton of the diphenyl system, H-4 and H-5 protons, while a 1H multiplet at δ8.5 represented H-6.

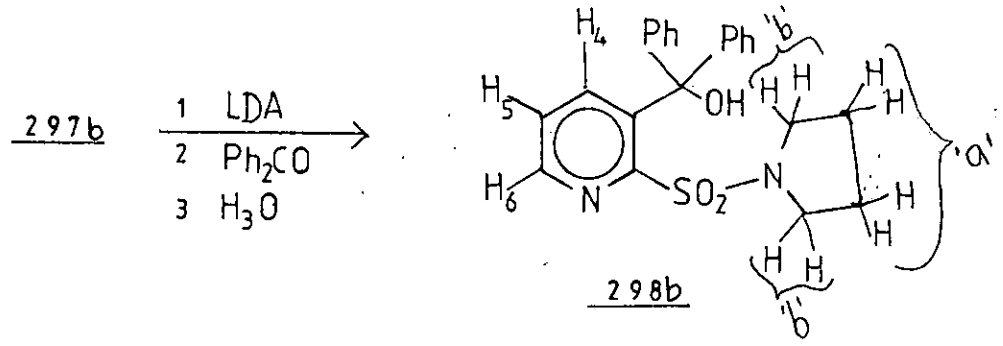
The KBr dispersion I.R. spectrum showed absorption at 3400, (OH broad) 1600, 1570 (pyridine ring -C=C-) 1375, 1160 cm^{-1} (SO_2N).

Satisfactory microanalysis data further confirmed the structure to be the expected diphenyl(2-(piperidinosulphonyl)-3-pyridyl)methanol.



11

For the pyrrolidine analogues, similar procedures as above gave an off white solid which was recrystallised to give white plates m.p. 163-164° in 70% yield.



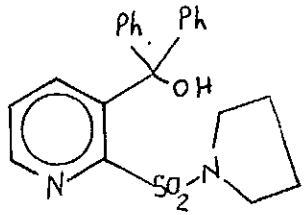
298b

'H-N.M.R. spectroscopic analysis of the plates gave 4H multiplet at δ1.90. A 4H multiplet at δ3.1 represented the $-CH_2N$ of the pyrrolidine while a 1H singlet (exchangeable with D_2O) for the -OH absorbed at δ6.8. The aromatic region also did not resolve but showed a 12H multiplet at δ 7.4 for the two phenyl rings and H-4, H-5. The proton at H-6 appeared as a 1H singlet at δ8.5.

The microanalysis of the plates was satisfactory and confirmed the structure as diphenyl[2-(pyrrolidinosulphonyl)-3-pyridyl]methanol.

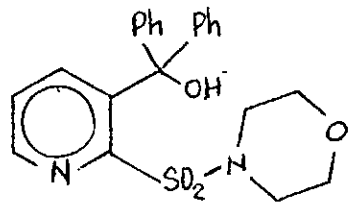
The morpholine analogues were obtained using similar procedures as above. The crude off-white solid was recrystallised to give off white needles m.p. 159-160°C in 69% yield.

The 'H-N.M.R. spectrum showed a 4H multiplet at δ3.40 (CH_2-O) and another 4H multiplet at δ3.65 for the methylene adjacent to the nitrogen. A 1H singlet (collapsable on deuteration) at δ6.5 represented the -OH. The aromatic region showed the two phenyl groups as a 12H multiplet along with H-4 and H-5. The 1H multiplet of H-6 absorbed at δ8.5.



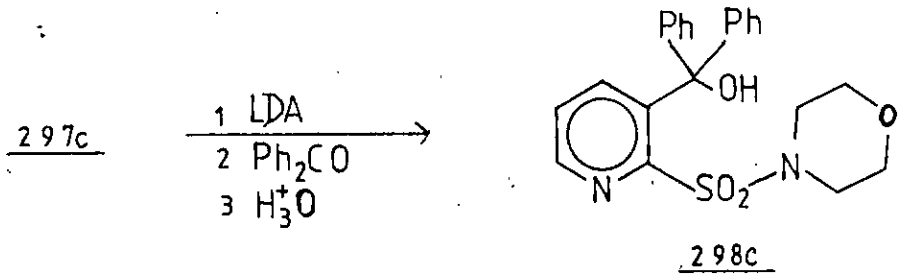
10 9 8 7 6 5 4 3 2 1

SOLVENT.- $CDCl_3$
29-1-89


Ph
Ph
OH
N
SO_2
N
O

9
8
7
6
5
4
3
2
1
0
SOLVENT – $CDCl_3$

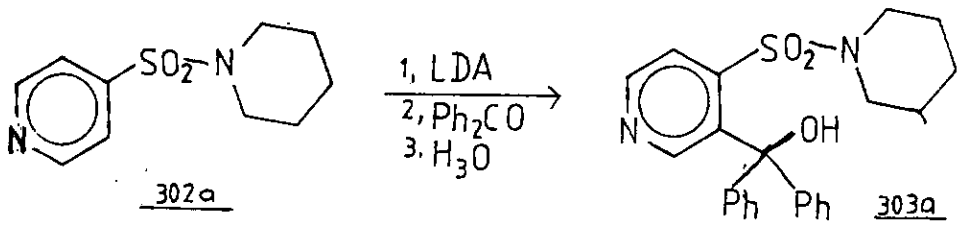
Elemental analysis further confirmed the expected product as diphenyl [4-(morpholinosulphonyl)-3-pyridyl] methanol.



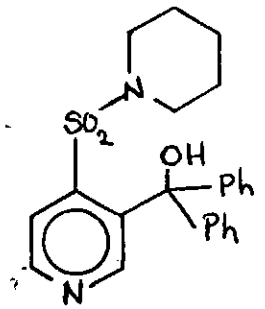
298c

Benzophenone as electrophile on 3-lithiopyridine-4-sulphonamides

All three diphenyl substituted products were obtained in a similar manner as above for the 2-pyridinesulphonamides.



With the piperidine analogues however, the crude products obtained from the metalation in this case were first purified by steam distillation to eliminate the excess benzophenone. The product left was then recrystallised in diethyl ether to give a white solid 80% m.p. 135-136°C. The ^{1}H-NMR showed a 6H multiplet for the methylene (type 'a') at δ 1.60 and a 4H multiplet at δ 3.1 (CH_2-N). A 1H singlet (collapsable on deuteration) at δ 6.6 represented the -OH. The aromatic region showed a 10H multiplet at δ 7.3 for the diphenyl system while a 1H doublet at δ 7.7 was assigned to H-5. A 1H singlet at δ 8.2 was assigned to H-2, while the 1H doublet for the H-6 absorbed at δ 8.7.



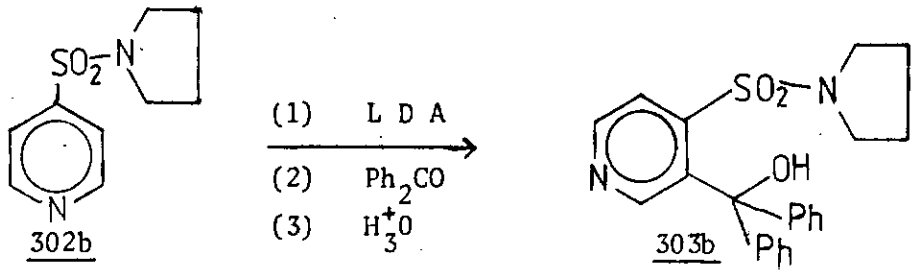
SOLVENT — $CDCl_3$

23-1-89

2

Microanalytical data were satisfactory. These confirmed the compound obtained as diphenyl(4-(piperidinosulphonyl)-3-pyridyl)-methanol.

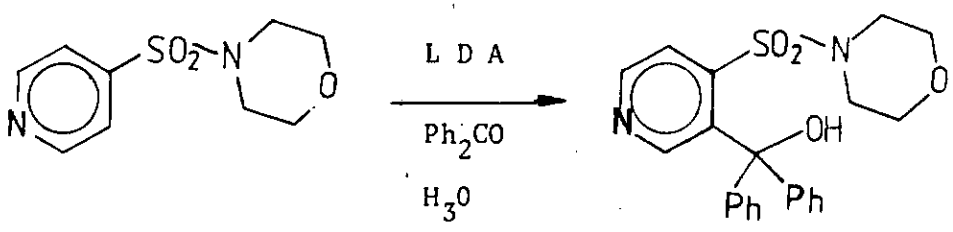
With the pyrrolidine analogues, the crude product obtained from the metalation was purified by flash chromatography giving beige needles in 65% yield m.p. 126-127°C.



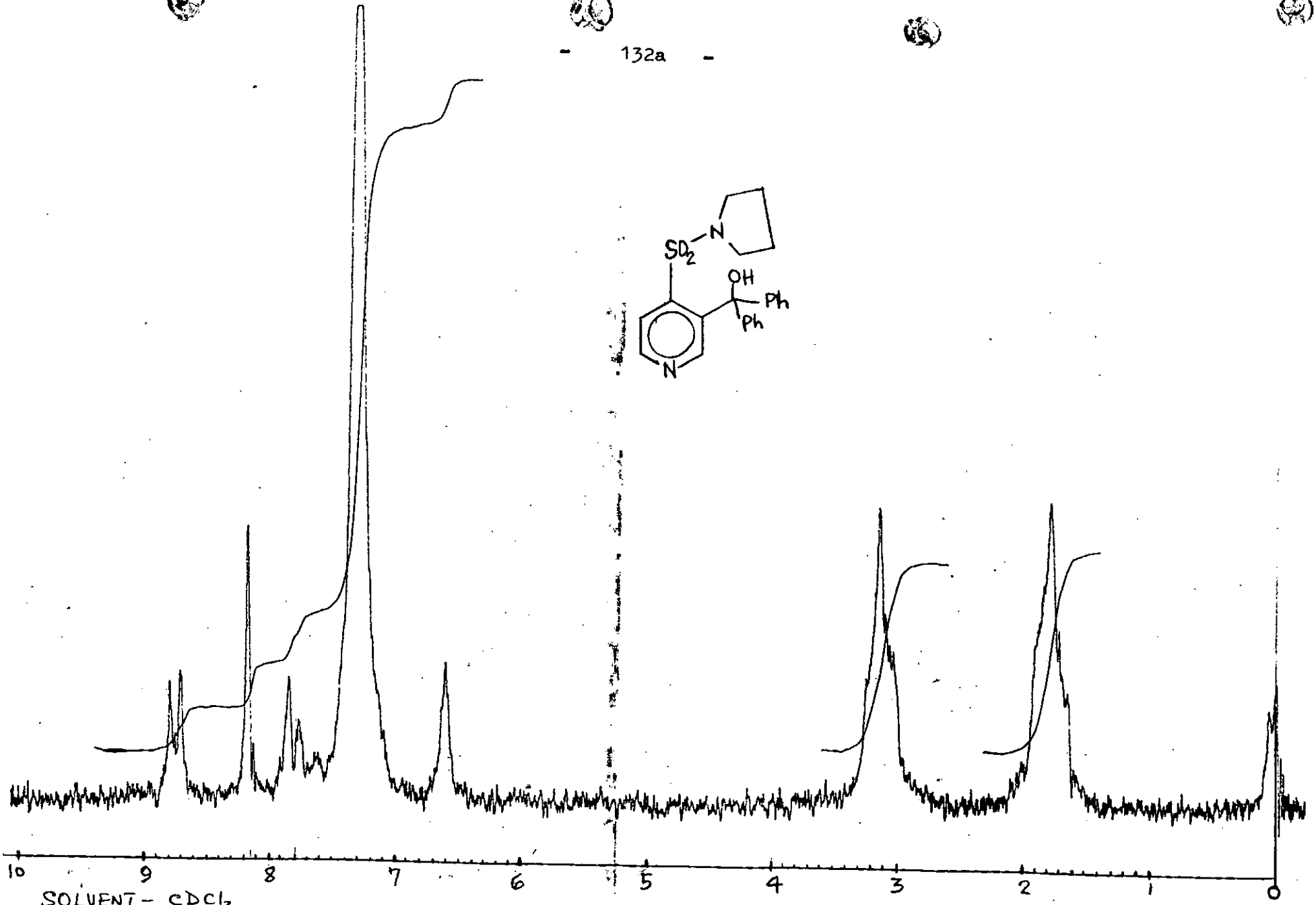
302b 303b

The ^{1}H-N.M.R. of the needles showed a 4H-multiplet for the methylene of the pyrrolidine (type a) at δ1.8 and another at δ3.1 for the methylene (-CH_2N). The hydroxy group 1H singlet absorbed at δ6.6, (exchangeable with D_2O). The 10H aromatic multiplet at δ7.3 is assigned to the two phenyl groups while the 1H doublet of H-5 absorbed at δ7.8. A singlet at δ8.15 is assigned to H-2 while the 1H doublet of H-6 absorbed at δ8.65. Elemental analysis corroborated the structure as diphenyl([4-(pyrrolidinosulphonyl)-3-pyridyl)methanol.

With the morpholino analogue, the crude product obtained was recrystallised to give white plates m.p. 158-159° in 78%.



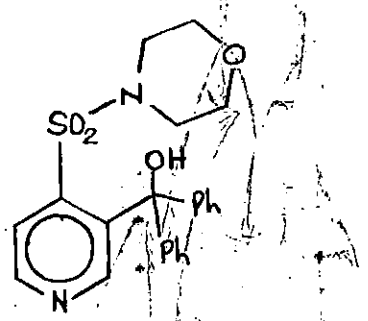
302C 303C



SOLVENT - $CDCl_3$

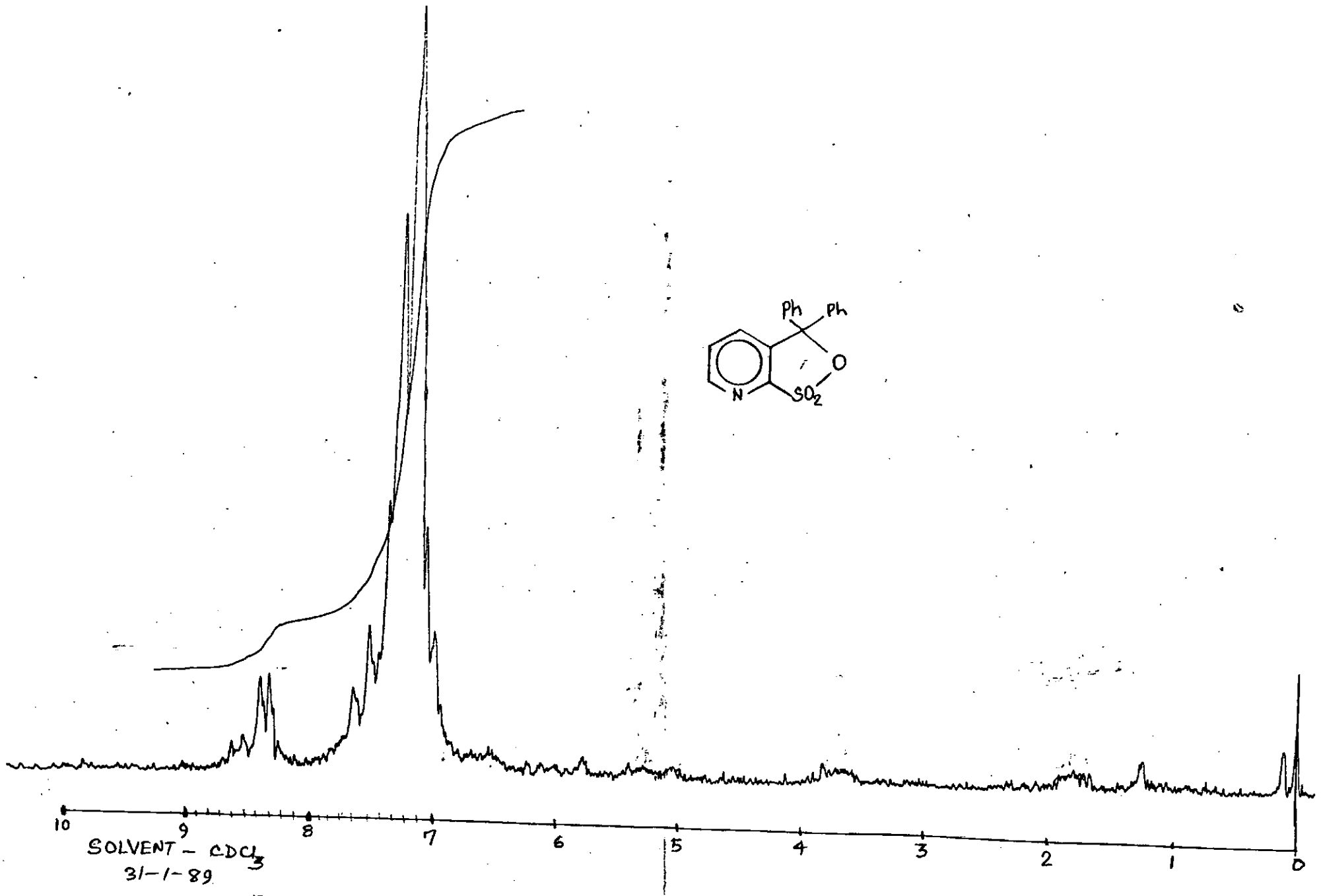
11-2-89

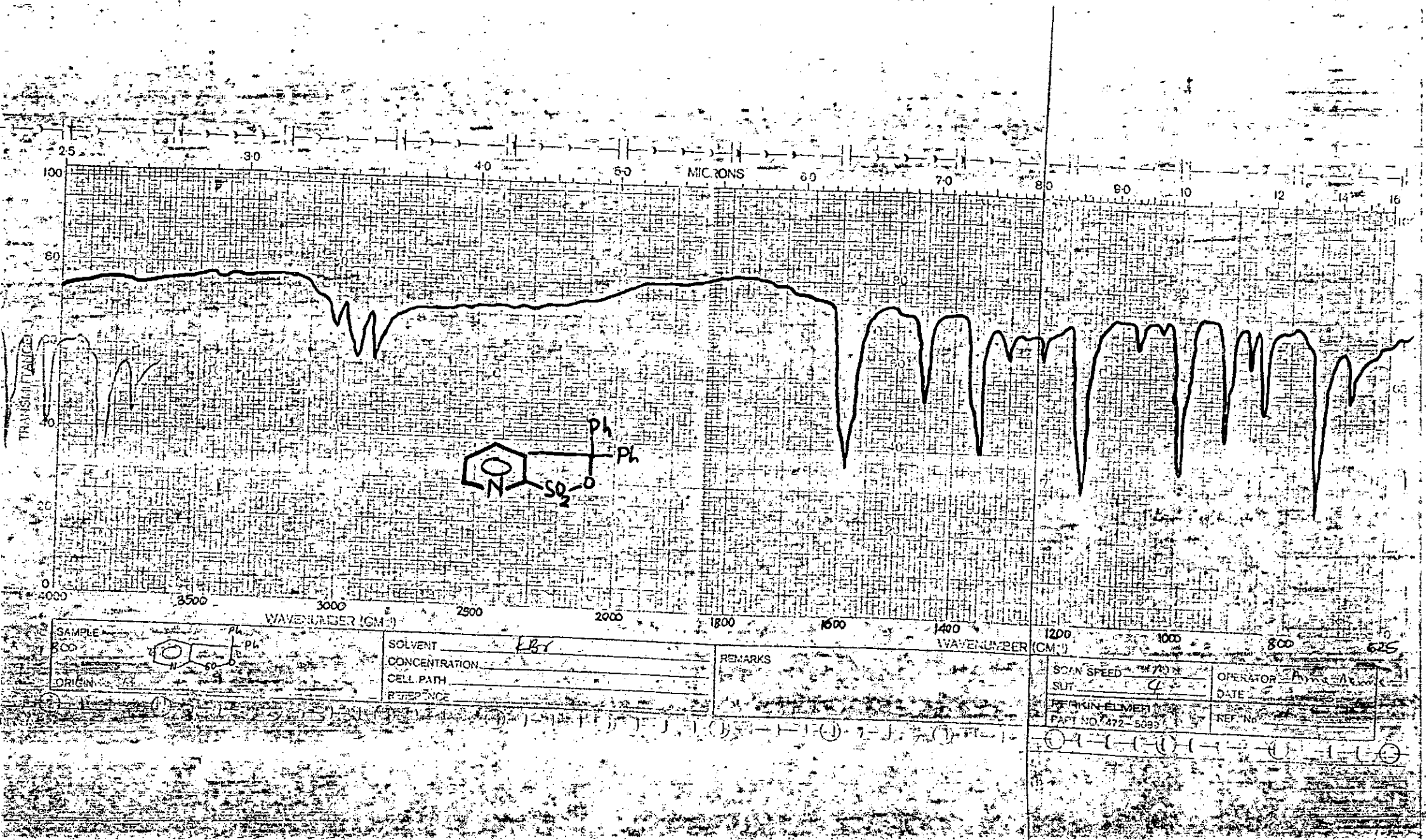
5



SOLUENT- $CDCl_3$

8

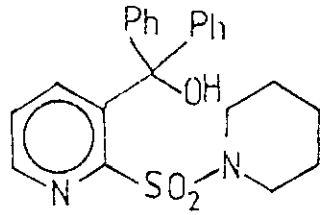
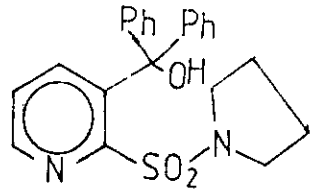
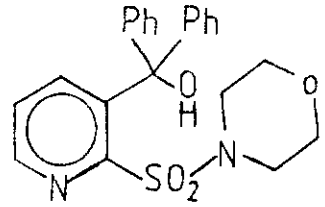
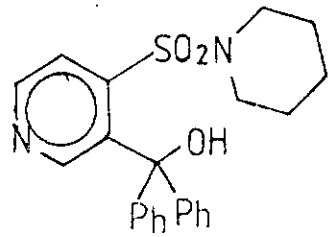
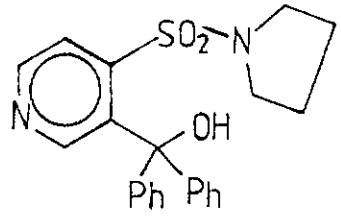
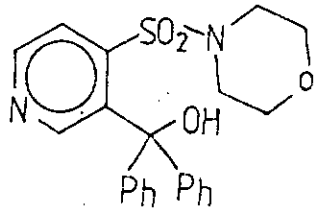

Ph
Ph
O
N
SO_2
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – $CDCl_3$
31-1-89


MICRONS
TRANSMITTANCE
WAVENUMBER (CM⁻¹)
Ph
Ph
N
SO2
O
SAMPLE
SOLVENT KBr
CONCENTRATION
CELL PATH
REMARKS
SCAN SPEED
SLIT
OPERATOR
DATE
PERKIN-ELMER
PART NO. 7472-5093
REF. No.

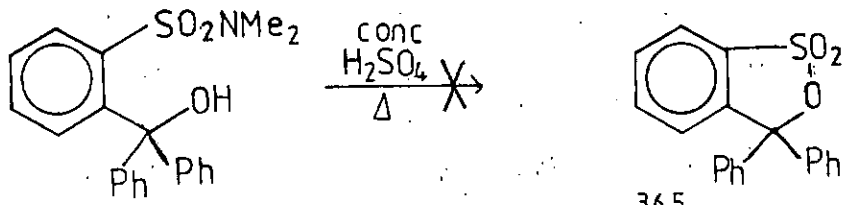
The ^{1}H-N.M.R. spectrum of the product showed a 4H multiplet of the methylene ($-CH_2-O$) at δ3.0 and another 4H multiplet for methylene (CH_2-N) showed up at δ3.6. A 1H singlet at δ6.35 is assigned to the -OH(exchangeable with D_2O). The diphenyl rings absorbed as a 10H multiplet at δ7.3, while the 1H doublet at δ7.65 is for H-5. A 1H singlet at δ8.20 represented H-2 while a doublet at δ8.70 is for H-6.

Table 3 shows a summary of the reactions of the lithiopyridines with various electrophiles.

Table 3:

Entry	Substrate	Product	%	m.p.
1	297a	 298a	90	182-183°
2	297b	 298b	70	163-164°
3	297c	 298c	69	159-160°
4	302a	 303a	80	135-136°
5	302b	 303b	65	126-127°
6	302c	 303c	78	158-159°

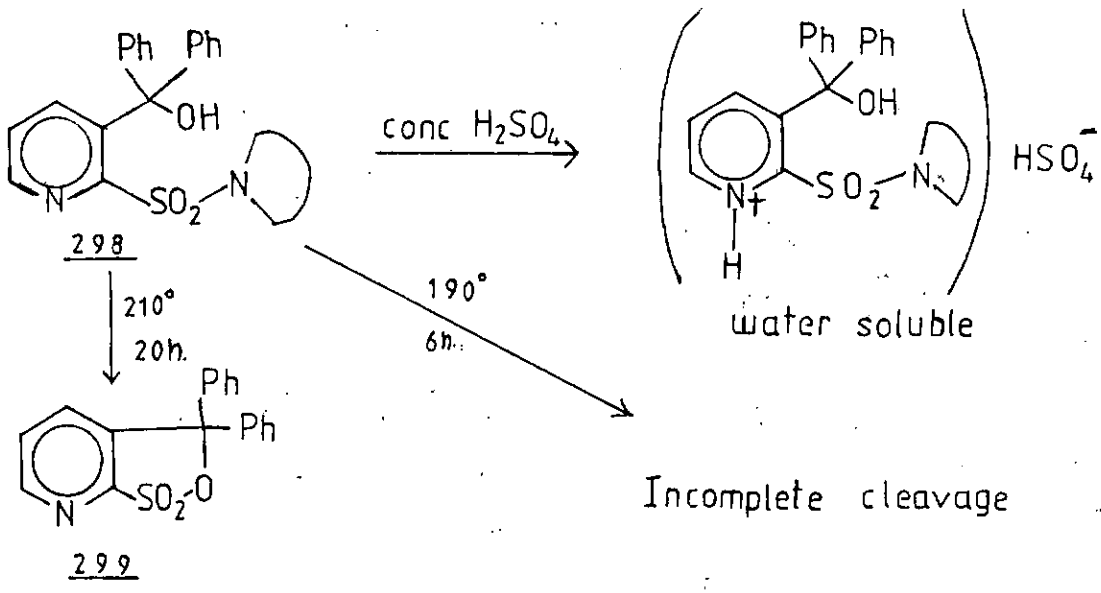
With all these precursors synthesised, efforts werethen directed to the cyclisation of the sulphonamide alcohols to obtain sultones. Several attempts failed. The attempts commenced with the use of sulphuric acid at room temperature to promote an initial cleavage of the SO_2N and then achieve heterocyclisation by heating, as reported for the benzene series[107].



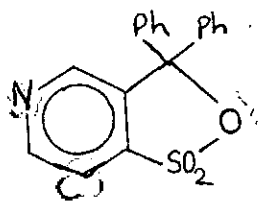
364 365

Work-up in this case however gave a watersoluble product which was not the desired sultone. The reaction was not pursued.

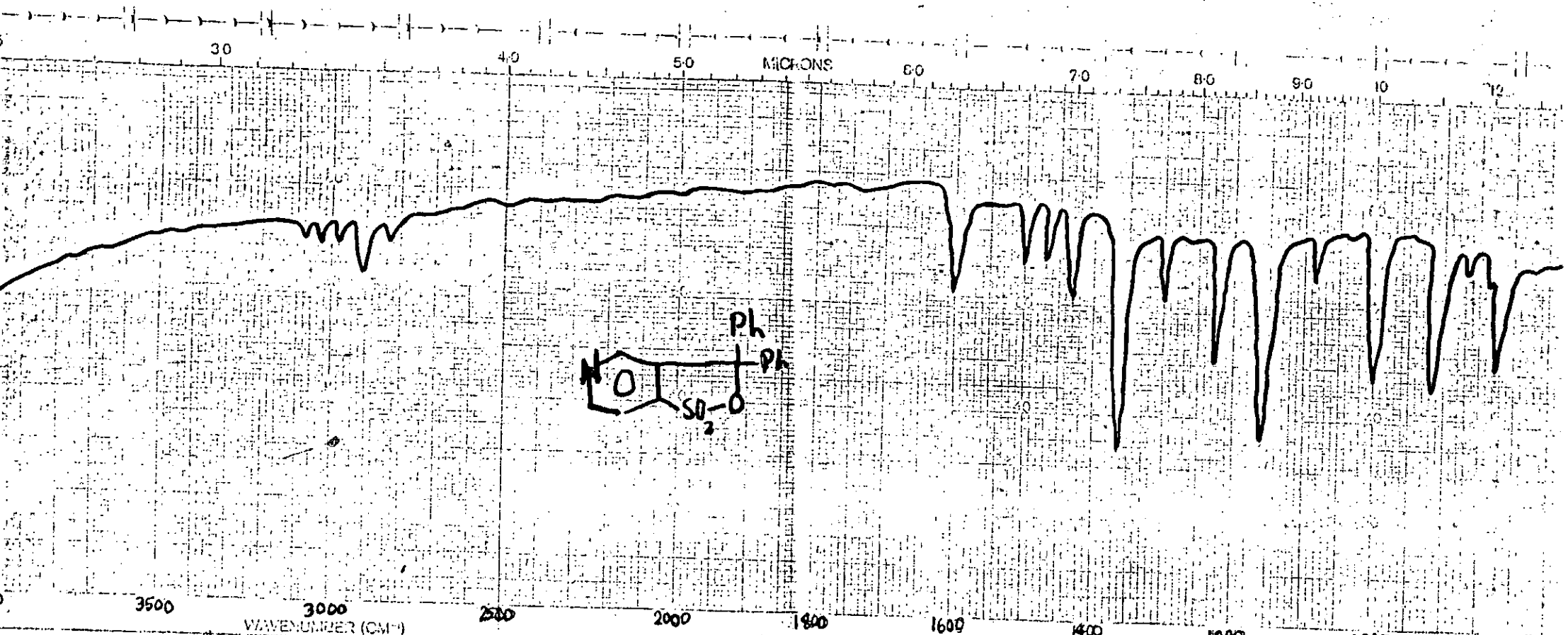
Oxygen-free thermal cyclisation on a woodmetal bath at 200° was then attempted. Initial effort at 190° for 6h gave an incomplete cleavage of the sulphonamide. The reaction was monitored by ^{1}H-NMR analysis of the product. The reaction time was changed to 20h at 210° to effect a complete cleavage.



135a

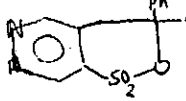


SOLVENT – $CDCl_3$
3-1-89



AMPLE

RIPTION



SOLVENT KBr

CONCENTRATION

CELL PATH

REFERENCE

REMARKS

SCAN SPEED M

SLIT U

OPERATOR Anne

DATE

PERKIN-ELMER

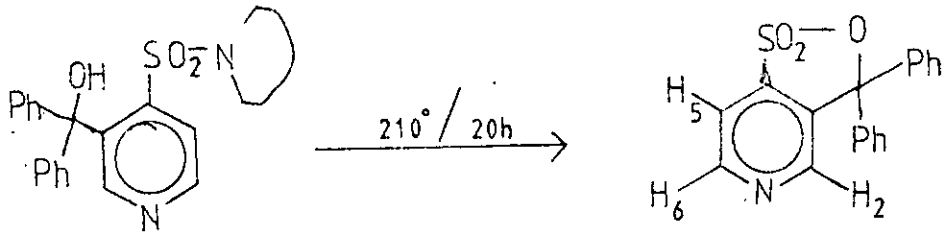
PART NO. 472-5080

REF. No.

All three diphenyl[2-(sulphonamido)-3-pyridyl) methanol precursors (208a, b, c) gave the same product from the thermal cyclisation attempt.

Evidence for the structure of the new compound can be obtained from a study of N.M.R. spectrum which showed loss of the aliphatic region of the sulphonamide. The N.M.R. also showed a 12H multiplet of the diphenyl system at δ7.3 along with H-4 and H-5. A 1H doublet at δ8.4 for the H-6, m.p. 141-143°. The KBr dispersion I.R. spectrum showed the loss of the -OH absorption and absorptions at 3000, 2940 and 2880 for CH absorptions, 1580 (-C=C-) aromatics, 1450, 1350 and 1170 cm^{-1} for (SO_2-O). These data confirm the structure of the compound as oxathiino (1,2)(5,4-b)pyridine.

The same thermal cyclisation was carried out on the 4-substituted carbinols (303a,b,c). They all gave similar products as above.



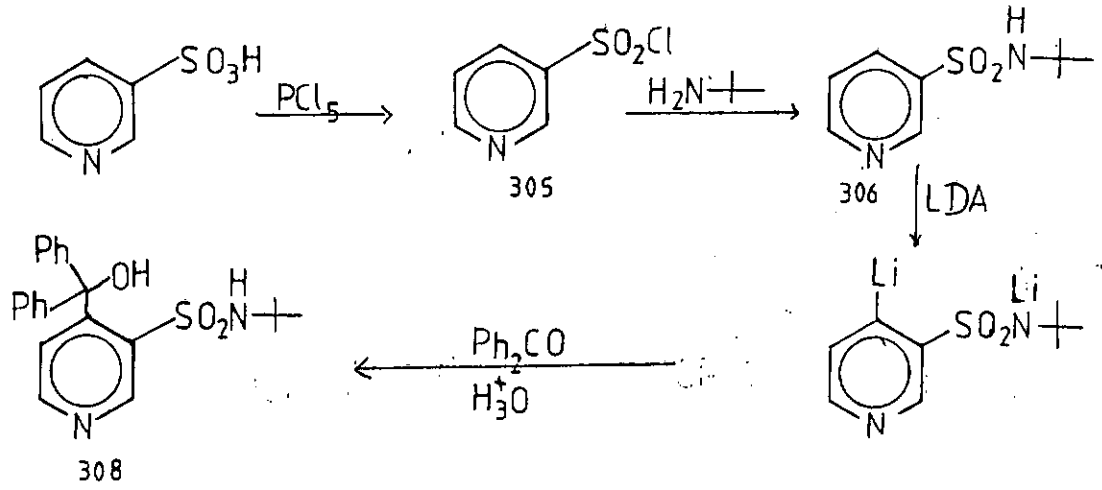
303 304

The ^{1}H-NMR spectrum of this oxathiino (1,2)(4,5-c)pyridine showed a 11H multiplet representing the diphenyl rings along with H-5 at δ7.0 while a 1H doublet of H-6 came up at δ 8.4. The 1H singlet of H-2 absorbed at δ8.65.

The KBr dispersion spectrum showed the loss of the hydroxyl group while the -CH absorption was at 2900, 1600 for -C=C- aromatic 1340 and 1160 cm^{-1} absorption is for SO_2-O, m.p. 80-81°.

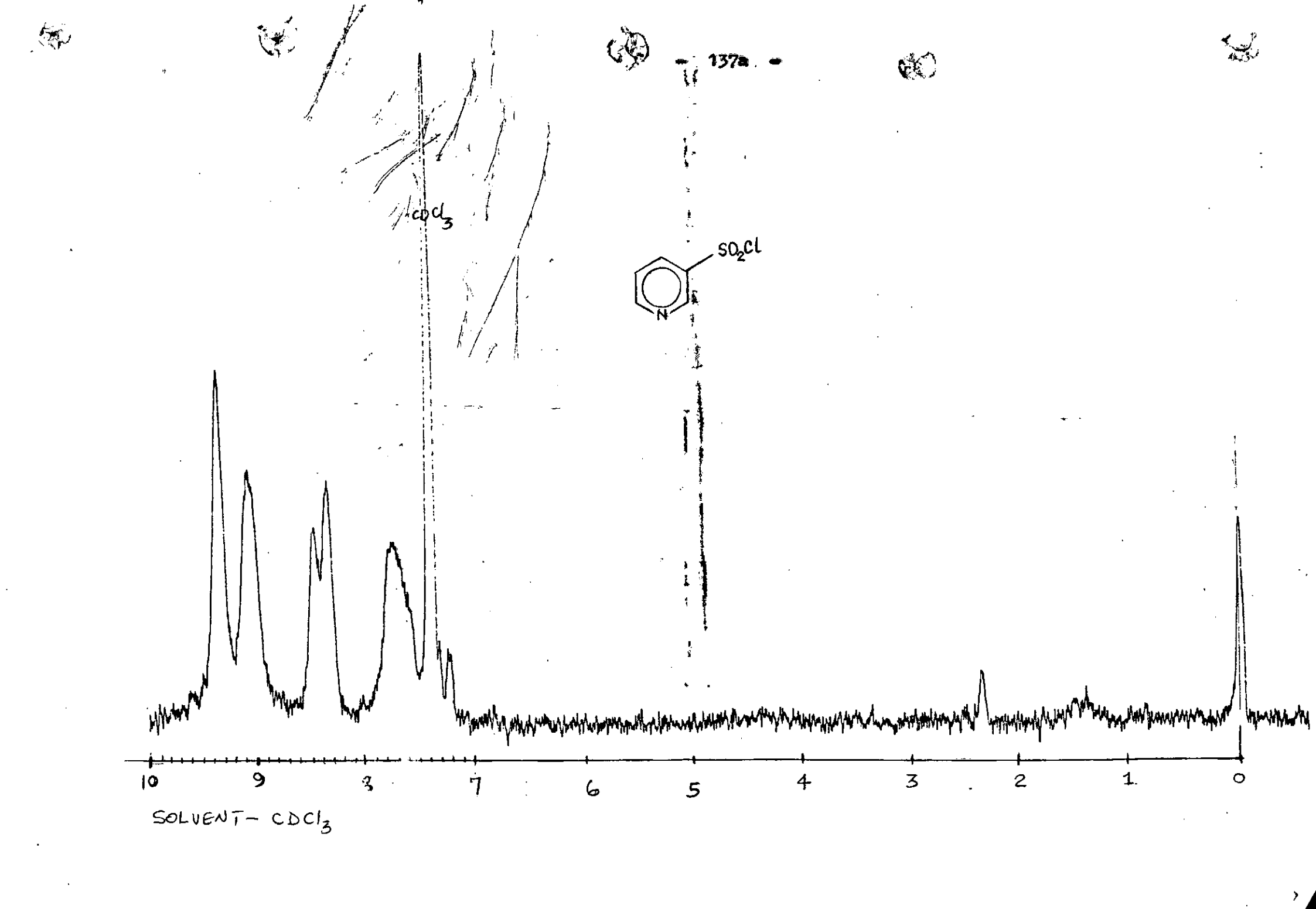
Metalation of Secondary Pyridinesulphonamides

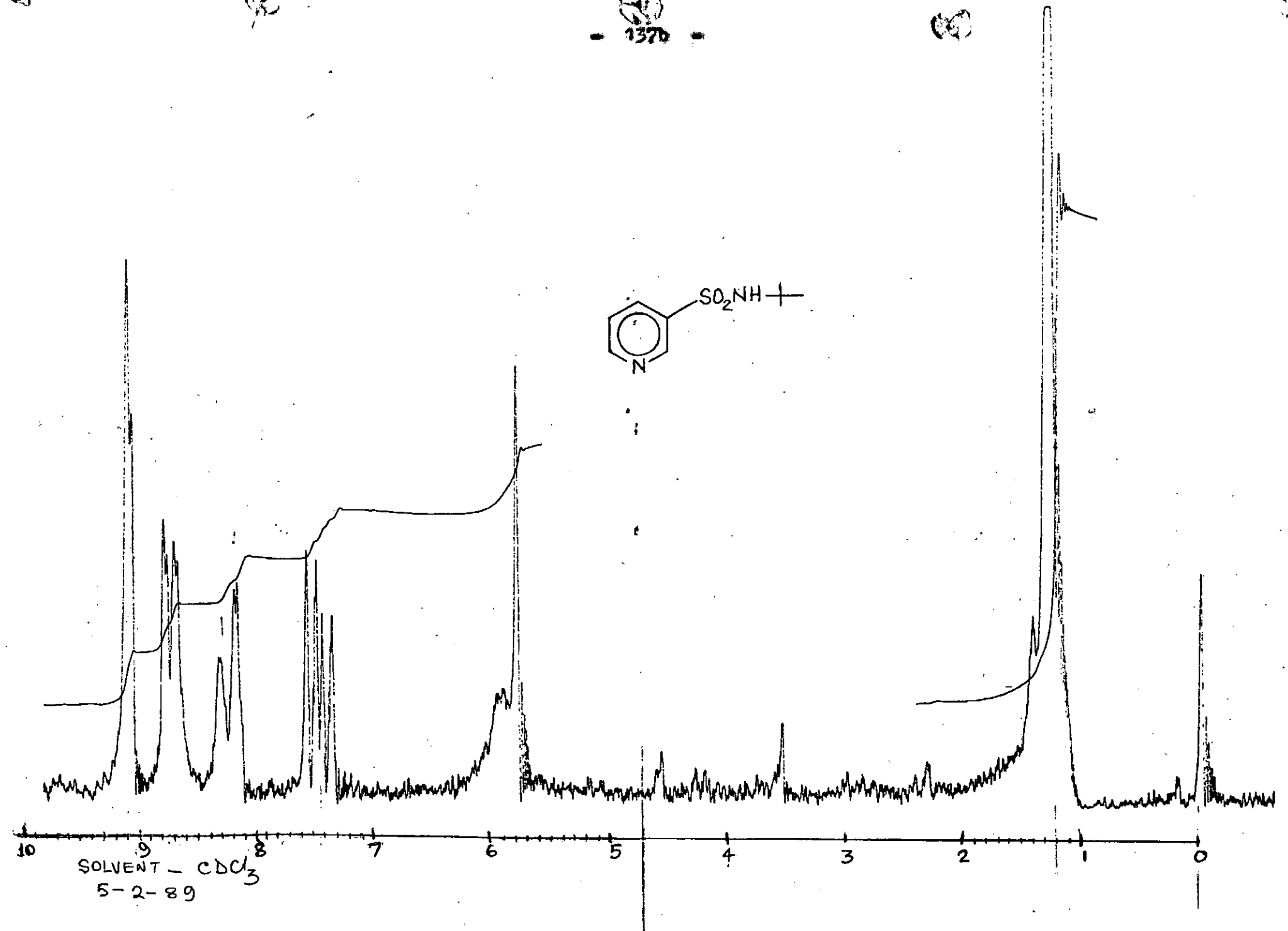
In earlier work in literature, Marsais et. al.[109] reported only on the use of tertiary sulphonamide as a directing group in metalation of pyridines. It was of interest therefore to investigate the utility of secondary sulphonamides as directing groups in the metalation of pyridines. The scheme below was therefore delineated starting from commercially available 3-pyridine sulphonic acid.

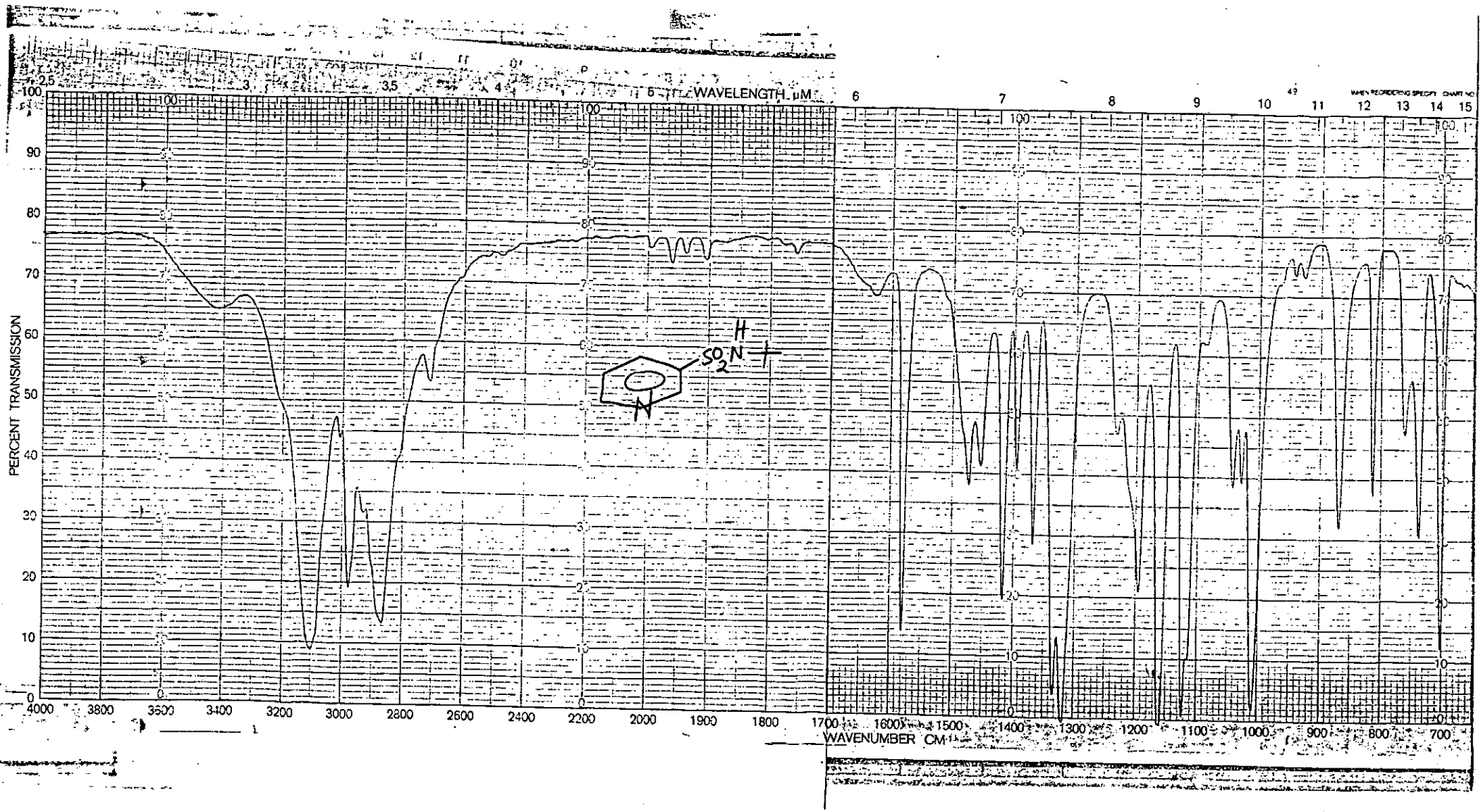


The solid 3-pyridinesulphonyl chloride obtained was either isolated under special conditions (as it was extremely sensitive to air) or it was immediately converted to the sulphonamide.

Three molar equivalents of the t-butylamine was smoothly reacted with pyridine-3-sulphonyl chloride at 0^{o} to give a yellow solid which showed in it's ^{1}H-NMR spectrum a 9H singlet at δ 1.2 assigned to the t-butyl group; a 1H broad absorption at δ 5.9 represented the NH. The 1H doublet of doublet at δ 7.4 represented H-5 while a 1H doublet at δ 8.2 was assigned to H-4. The 1H doublet of a doublet at δ 8.8 was for H-6 and the 1H singlet at δ 9.1 represented H-2.


$CDCl_3$
SO_2Cl
N
10
9
3
7
6
5
4
3
2
1
0
SOLVENT – $CDCl_3$

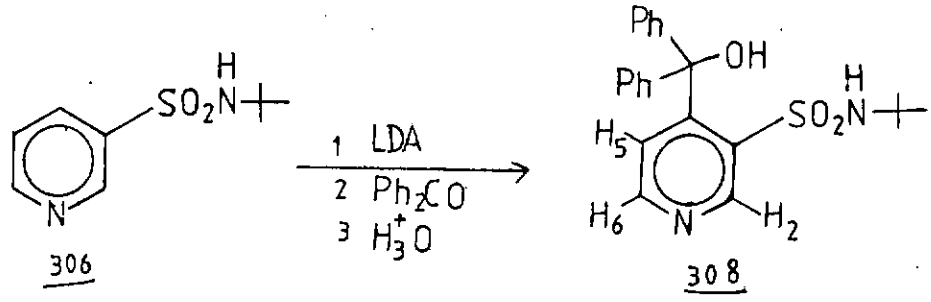

SO2NH
N
10
9
8
7
6
5
4
3
2
1
0
SOLVENT – CDCl3
5-2-89


WAVELENGTH, μM
WAVENUMBER CM⁻¹
PERCENT TRANSMISSION
H
SO2N

The elemental analysis of the N-t-butylpyridine--3-sulphonamide, obtained was satisfactory.

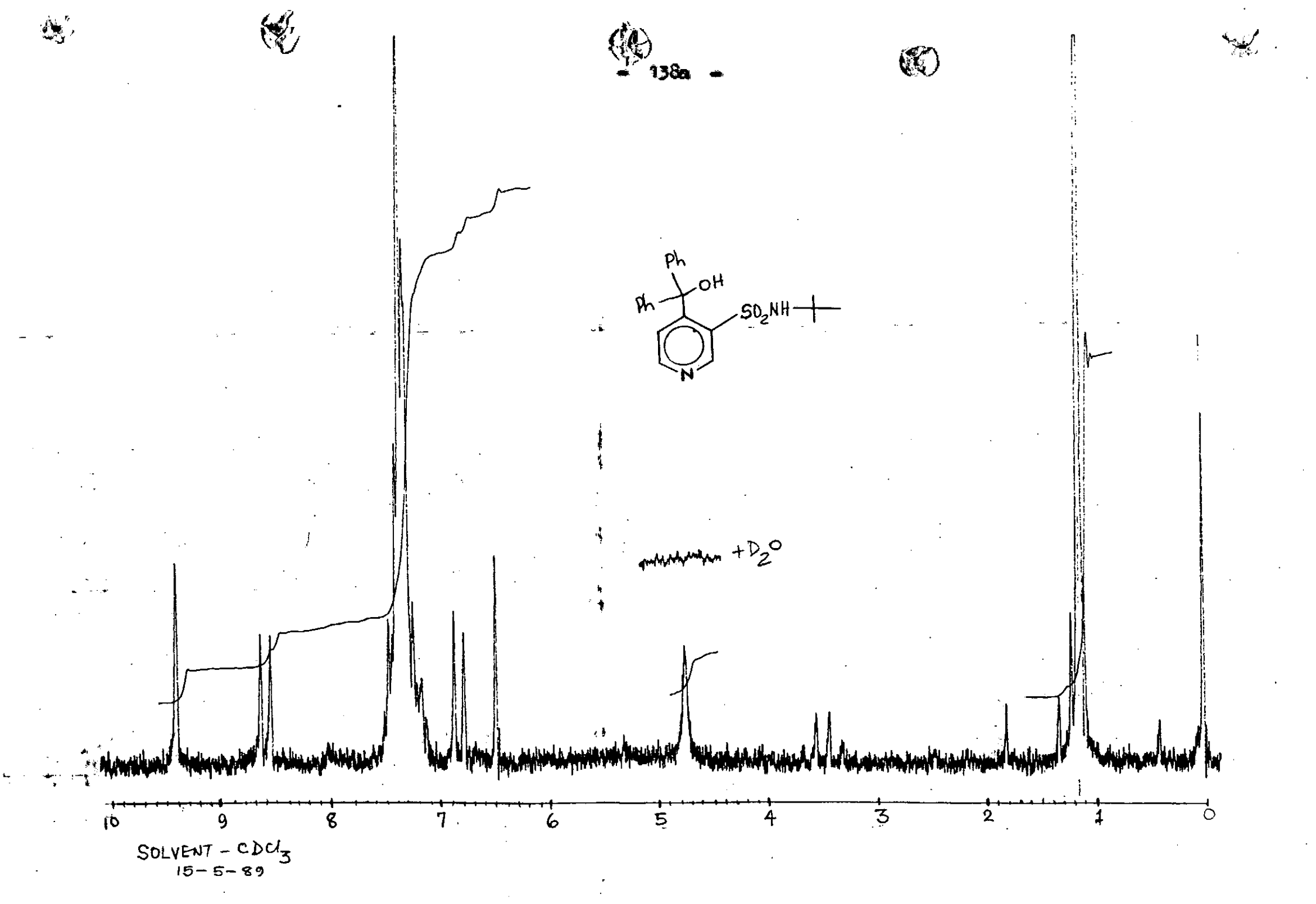
Treatment of the sulphonamide in THF with LDA (3 equivalents) at -78° followed by quenching with benzophenone as electrophile gave on work-up a crude product. This was purified by flash chromatography to give a white solid m.p. 180-182°C (85%). The ^{1}H-N.M.R. of the compound showed a 9H singlet at δ1.2 for the t-butyl group. A 1H signal (exchangeable with D_2O) represented the -NH absorption. The hydroxyl proton absorbed as a singlet at δ6.5. The aromatic 1H doublet of H-5 absorbed at δ6.80 while the 10H multiplet of the diphenyl rings absorbed at δ7.30. The 1H doublet of H-6 absorbed at δ8.6 while a singlet at δ9.4 was assigned to H-2

The KBr dispersion I.R. showed absorptions at 3360 (-OH), 3290 (-NH), 2980, 2870 (-CH), 1580 (aromatic -C=C-), 1340, 1160 cm^{-1} (SO_2N).



306 308

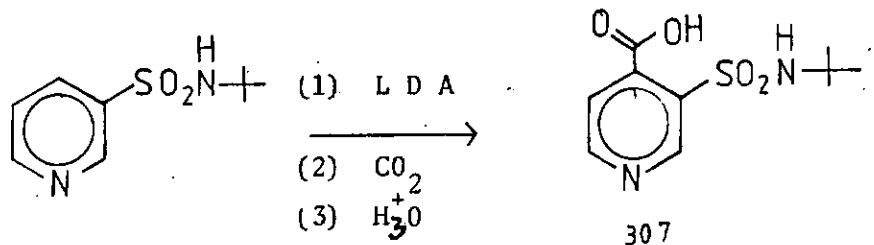
These data therefore seem to confirm the structure of the new compound as diphenyl[3-(N-t-butylsulphonyl)-4-pyridyl]methanol.


Ph
OH
Ph
SO2NH
N
+D2O
10
9
8
7
6
5
4
3
2
1
0
SOLVENT - CDCl3
15-5-89

When carbon dioxide was used as electrophile, a white solid was obtained, m.p. 207-208°C.(80%).

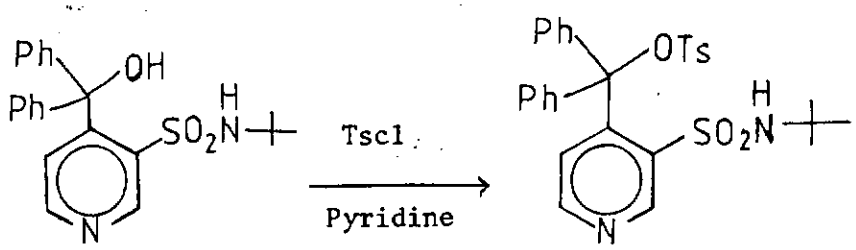
The ^{1}H-NMR (DMSO-d_6) of the solid showed a 9H singlet for t-butyl group at δ 1.1. The 1H signal of the NH absorbed at δ6.6, while the -OH of the acid was at δ7.4. The 1H doublet of the H-5 showed up at δ7.6, while 1H doublet of H-6 absorbed at δ8.8. The H-2 absorbed as a singlet at δ9.1.

The I.R. spectrum had strong absorptions at 3300 (-NH); 3190, (OH), 1750 (COOH), 1580 (aromatics) 1350, 1170 cm^{-1} (SO_2N).



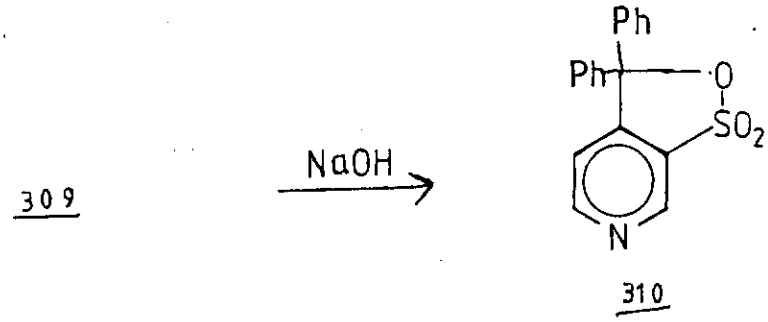
306 307

Attempts were made to put the products obtained from the metalations above into synthetic use. For example, tosylating the diphenyl [3-(N-t-butylsulphonyl)-4-pyridyl] methanol obtained should provide a good leaving group for heterocyclisation to be smooth (See Scheme).



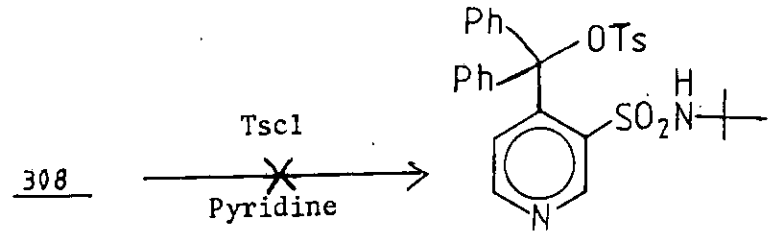
308 309

SOLVENT – DMSO-d_6



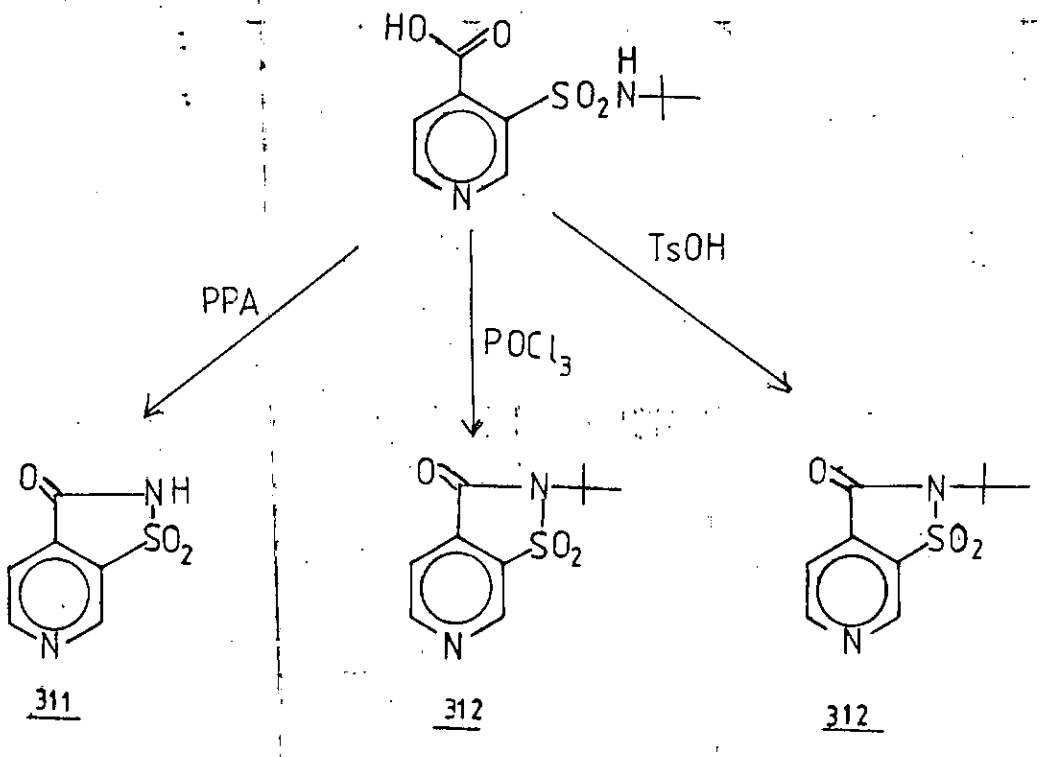
309 310

However, attempted tosylation reaction failed. This may be due to the fact that tertiary hydroxy compounds are not easily esterified[135], because of facile decomposition as soon as they are formed even at room temperature.



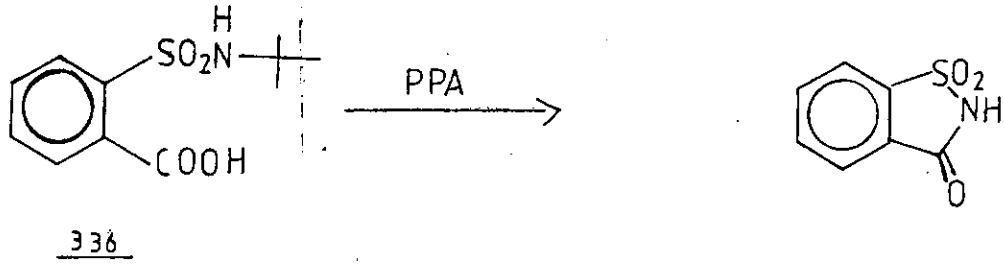
308 309

The pyridine-4-carboxylic acid product was also subjected to cyclisation attempts to obtain a sultam in accordance with Lombardino's earlier work[107]. (See Scheme).

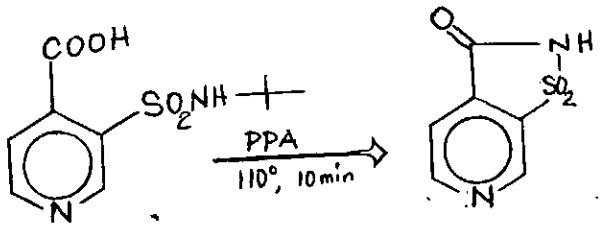


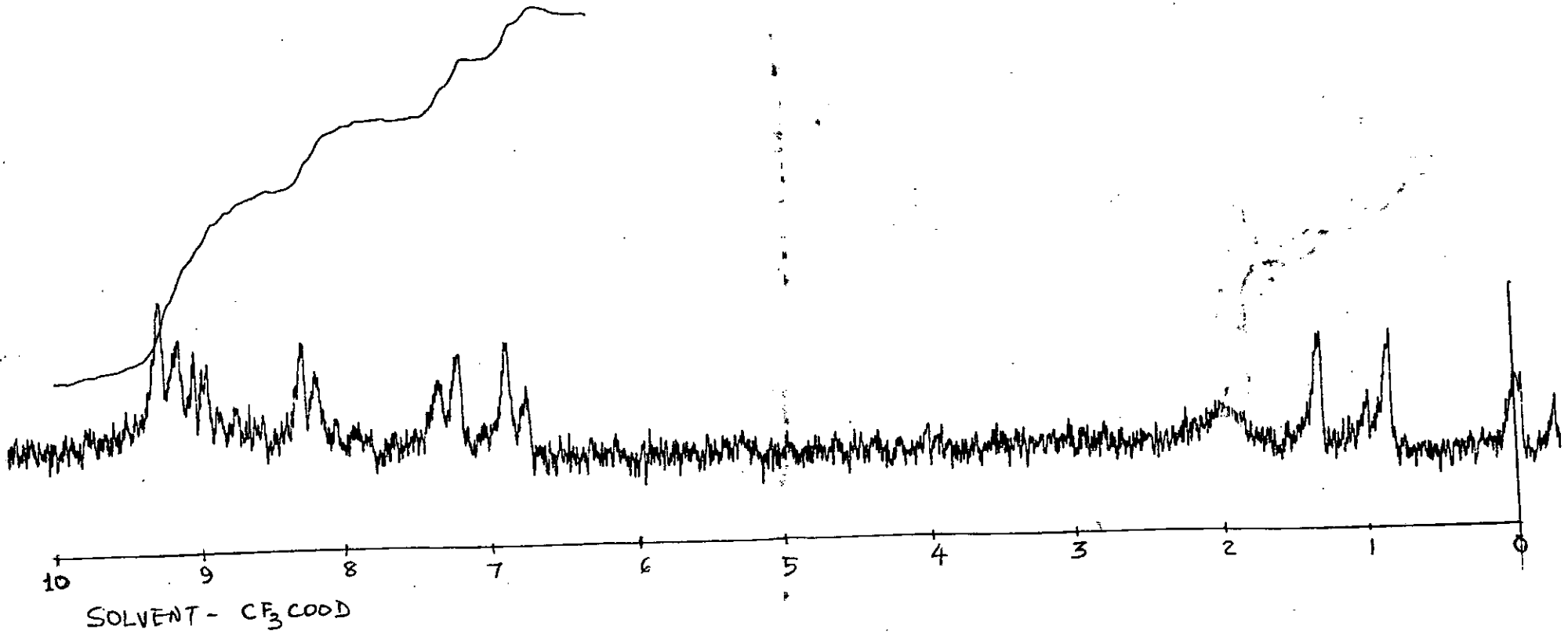
Scheme 15

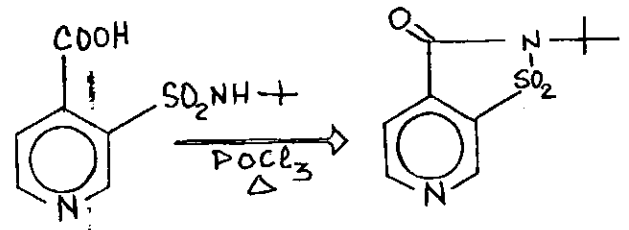
Lombardino[107] had reported the use of polyphosphoric acid (PPA) in obtaining cyclocondensation of substituted -2-(N-t-butylsulphonamido)benzoic acids to give sultams. The reaction is accompanied with the elimination of the t-butyl substituents of the sulphonamide.



336 337

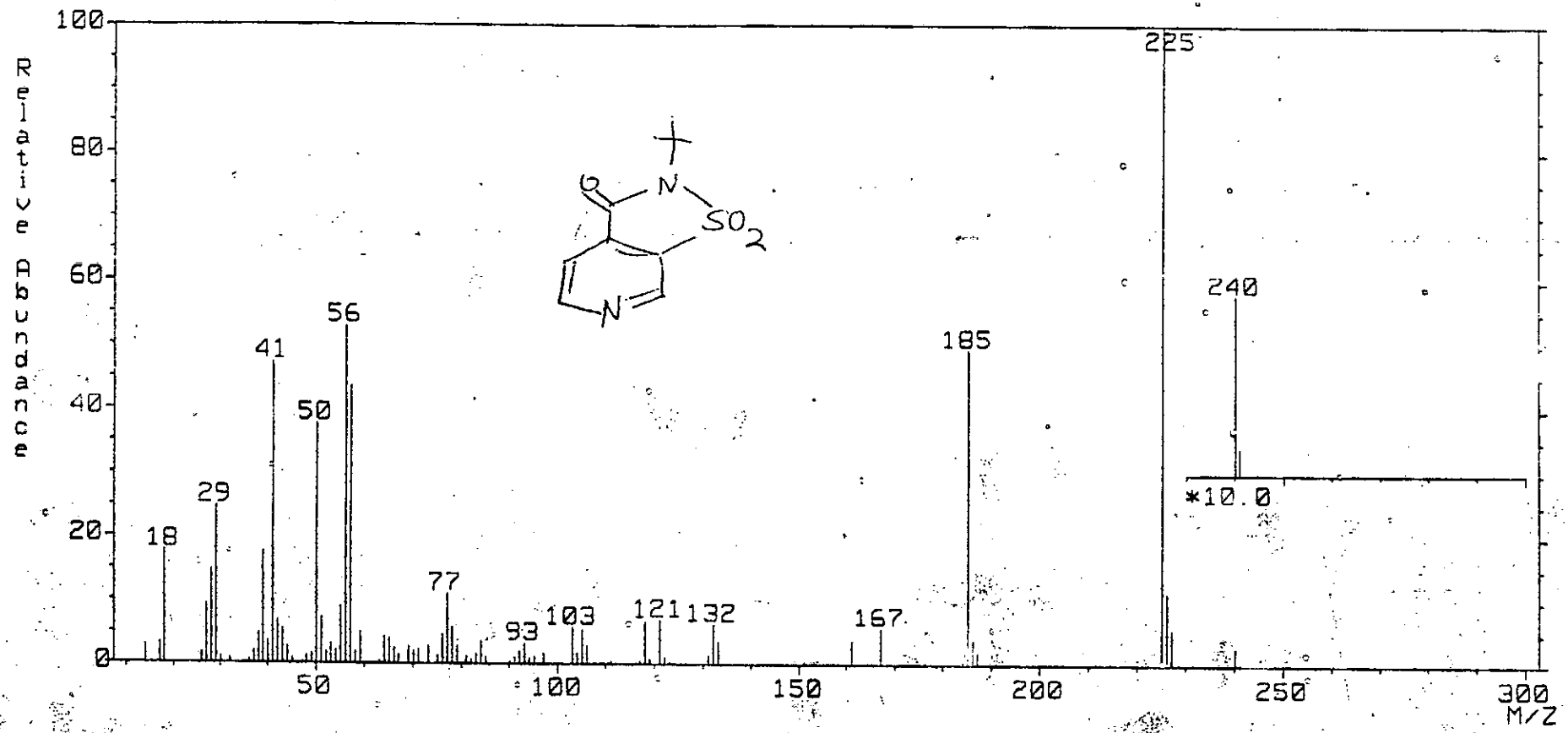

COOH
SO2NH
PPA
110°, 10 min
O
NH
SO2
N
N


10
9
8
7
6
5
4
3
2
1
0
SOLVENT - CF3COOD


COOH
SO_2NH +
$POCl_3$
Δ
O
N
SO_2
N

10
9
8
7
6
5
4
3
2
1
0
SOLVENT – $(CD_3)CO$

MASS SPECTRUM Data File: JCRWPY14 +2c 23-MAY-89 16:43
Sample:
RT 0'50 (Pos.) GC 194.9c BP: m/z 225.0000 Int. 41.6183 Lv 0.00
Scan# (26) - (15, 47) [coef. 1.00]



The mass spectrum of the product showed the molecular ion as expected at $^{m}/_{z}$ 240. But a good NMR spectrum could not be obtained due to insolubility problems.

The reactions were therefore not further pursued.

CHAPTER 3

EXPERIMENTAL

General Data:

The ^{1}H-N.M.R. spectra were determined using Varian EM360L or Bruker 400 MHz spectrometers and were recorded in ppm downfield of the internal standard of TMS in $CDCl_3$, or HMDS in DMSO-d_6. I.R. spectra were recorded on a Beckman IR 4250 spectrometer (film for liquids, KBr dispersion for solids). Elemental analysis were performed on a Carlo Erba 1106 instrument. Mass spectra were recorded at I.N.S.A. Rouen France. Melting points were obtained on a Kofler hot plate apparatus, and are uncorrected. THF was freshly distilled from sodium-benzophenone ketyl before use and the water content of the solvent was estimated by a modified Karl-Fisher method[136] to be $<$45 ppm. Metalations were performed under a dry deoxygenated argon atmosphere. The n-butyllithium (BuLi) content of the commercial hexane solution was estimated by the Gilman double titration method. *

* M.R. Winkle, J.M. Lansinger, R.C. Ronald

Chem. Comm 1980, 87

1. Preparation of N-t-butylbenzenesulphonamide (269)

A stirred solution of N-t-butylamine (0.45 mole, 32.9g) in dry chloroform, (75mL), at 0^{o} was slowly added to a solution of benzenesulphonyl chloride (0.015 mole, 26.5g) in chloroform (100mL). After the addition, the cooling bath was removed, the suspension was stirred at room temperature for 1h. The suspension cooled, washed successively with 3N HCl (200ml) and twice with water. The chloroform solution was dried with $MgSO_4$ and evaporated; giving 29.09g, (94%) of analytically pure product, m.p. 78-80^{o} (lit . m.p. 78-80^{o})
'H-NMR m($CDCl_3$) δ 1.2 (9H,s); 5.0, (1H,br,s); 7.5 (3H,m) 7.9 (2H,dd).

2. Preparation of (piperidinosulphonyl)benzene) (274)

Benzenesulphonyl chloride (0.057 mole, 10g) was slowly added at room temperature to a solution of piperidine (0.0114 mole, 9.7g) in dry toluene (50mL). The mixture was stirred for 3h and washed with water (3 x 50mL). Drying over $MgSO_4$, evaporation of the solvent and crystallisation of the residue from Et_2O afforded (piperidinosulphonyl)benzene in 80%, m.p. 90-91°C. (lit . 91°C).
'H-NMR ($CDCl_3$) δ 1.4(6H,m); 2.9(4H,m); 7.5(5H,m).

General Metalation Procedure

3. Metalation of Secondary Sulphonamides

To a stirred solution of the sulphonamide (0.0125 mole) in dry THF (30mL) under argon at 0°, was added n-BuLi (2.2 mole equivalent) and stirred at room temperature for 2h. At the end of 2h., the reaction was brought to 0° and the epoxide (1.1 equivalent) dissolved in THF (30mL) was added before allowing it to warm to room temperature for 24h.

At the end of the reaction time, water was added before acidification with 5% HCl. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extract was washed once with brine and dried over anhydrous $MgSO_4$. Solvents were then stripped off in vacuo to give the crude product.

4. Metalation of Tertiary Sulphonamides

To a stirred solution of the tertiary sulphonamide (0.0125 mole) in dry THF under argon (30mL) at 0°, was added n-BuLi (1.1 equivalent) and stirred for 10 minutes and after which it was stirred at room temperature for 2h. The reaction mixture's temperature was brought to 0°. The epoxide (1.1 mole) dissolved in THF (30mL), was added, stirred at room temperature for 24h and the work-up is same as for secondary sulphonamides.

5. 1-(2-N-t-butylbenzenesulphonamido)butan-2-ol (313)

Using 1,2-epoxybutane as an electrophile, the crude oil obtained was purified by flash chromatography with ether: hexane 1:1 giving a colourless oil that gave a white solid on standing, m.p. 110-112° in 40% yield.

^{1}H-NMR: δ 1.1 (3H,t); 1.3(9H,s); 1.6(2H,q); 2.8 (1H,br OH, exchangeable with D_2O); 3.2(2H,m); 3.9(1H, m - CHOH); 7.5(3H,m ArH); 8.15 (1H,d,ArH). I.R. (film) V_{max} 3490 (br,OH), 3280 (NH) 2970, 2930, 1600, 1480, 1320, 1150, 980, 870 cm^{-1}.

Anal. Calcd. for $C_{14}H_{23}NO_3S$, M^+, 285, C, 58.94; H, 8.07, N, 4.91; Found: C, 58.64; H, 8.42; N, 4.84.%

6. 1-(2-N-t-butylbenzenesulphonamido)hexan-2-ol (314)

Using 1,2-epoxyhexane as electrophile, the crude oil obtained was purified by flash chromatography with ether: hexane, 1:1, giving a colurless viscous oil (41%).

^{1}H-NMR (DMSO-d_6) δ 0.85(3H,t); 1.2(9H,s); 1.35(2H,m); 1.6 (2H,m); 2.5(1H,br,OH, exchangeable with D_2O); 3.1(1H,dd); 3.25 (1H,m); 3.9(1H,m); 5.1(1H,br, exchangeable with D_2O); 7.4 (3H,m); 8.0 (1H,d).

I.R. (film) V_{max} 3480, 3280, 2960, 2930, 1600, 1480, 1330, 1160, 990, 760. cm^{-1}

Anal. Calcd. for $C_{16}H_{27}NO_3S$, M^+, 313, C, 61.34; H, 8.62; N, 4.47; Found C, 61.08; H, 8.91; N, 4.77.%

7. 1-(2-N-t-butylbenzenesulphonamido)-3-phenoxypropan-2-ol (315)

Using (±)1,2-epoxy-3-phenoxypropane as electrophile, the crude oil obtained was purified by flash chromatography in diethyl ether: cyclohexane 1:1 gave white needles, m.p. 104-106°, (35%). ^{1}H-NMR: δ 1.3 (9H,s); 3.1(1H,br, OH,exchangeable with D_2O); 3.4 (2H,dd); 4.1(2H,d); 4.3(1H,m), 5.2(1H, br, for NH,exchangeable with D_2O); 7.0 - 7.6 (8H, m); 8.0 (1H, dd).

I.R. (KBr), 3500(br, OH); 3280, 2960, 1600, 1470, 1330, 1150, 990, 860 cm^{-1}.

Anal. Calcd. for $C_{19}H_{24}NO_4S$:, C, 62.98; H, 6.62; N, 386; Found C, 62.78; H, 6.36; N, 3.68.%

8. 2-(2-N-t-butylbenzenesulphonamido)-1-phenyl ethanol (316)

Using styrene oxide as electrophile, the crude yellow oil obtained was purified by flash chromatography with diethyl ether: cyclohexane 1:1 giving a colourless oil in 30% yield.

^{1}H-N.M.R. ($CDCl_3$): δ 1.2 (9H, s); 2.0 (1H, OH, exchangeable with D_2O); 3.3 (1H, d); 3.5 (1H, d); 4.9 (1H, m, base proton); 5.1 (1H, br, NH,exchangeable with D_2O); 7.3 (8H,m) 8.0 (1H, dd).

I.R. (film) V_{max} 3480, (br,OH); 3280 (NH); 2980, 1605, 1450 1320, 1150, 990, 860, 760 cm^{-1}.

Anal. Calcd. for $C_{18}H_{23}NO_3S$: M^+, 333; C, 64.86; H, 4.20; N, 6.90; Found; C, 64.87; H, 4.47; N, 7.10;%

9. 2-(2-N-t-butylbenzenesulphonamido)Cyclohexanol (317)

Using cyclohexane oxide as an electrophile, the crude yellow oil obtained was purified by flash chromatography with diethyl ether: cyclohexane, 2:1 gave a colourless oil in 25% yield.

^{1}H-N.M.R. ($CDCl_3$): δ1.25 (9H,s), 1.4-1.8(8H, m); 3.2(1H,S, exchangeable with D_2O); 3.6 (2H, m two base protons) 5.2(1H, NH, exchangeable with D_2O), 7.5 (3H,m,ArH), 8.0 (1H,dd). I.R. (film): V_{max} 3480, (br, OH); 3280, 3000, 2980, 2960, 1600, 1470, 1340, 1170, 990, 860 cm^{-1}.

10. Attempted Synthesis of 2-(2-N-t-butylbenzenesulphonamido) norbonanol (318A)

Using 2,3-epoxylnorbonane as an electrophile. The crude oil obtained on subject to reduced pressure, gave the starting sulphonamide and norbonanol 318, m.p. 115-117°C. characterised as follows:

^{1}H-NMR ($CDCl_3$): δ1.2 (7H, M); 1.8(2H, m); 2.4(1H,s,OH, exchangeable with D_2O); 3.9(1H,S).

Anal. Calcd. for $C_{17}H_{10}O.1/4H_2O$; C, 73.04; H, 9.6; Found C, 72.91, H, 9.5.%

11. Attempted Synthesis of 1-(2-N-t-butylbenzenesulphonamido) -3-phthalimide propan-2-ol (319)

Using N-(2,3-epoxypropyl)phthalimide as an electrophile, the crude brown solid obtained was separated with ethyl acetate/ ether but the above named compound was not obtained.

12. Attempted Synthesis of 3-(2-N-t-butylbenzenesulphonamido) butan-2-ol (320)

Using trans 2,3-epoxybutane as an electrophile the crude oil was separated by flash chromatography with ether: hexane 1.1, the column product was the starting material and the expected product was not obtained.

13. 1-(2-N-t-butylbenzenesulphonamido)-2-chlorobutane (329)

Redistilled thionyl chloride (5ml) was added to (1-2-N-t-butylbenzenesulphonamido)butan-2-ol (0.7g) in a round bottom flask, equipped with a condenser and a $CaCl_2$ guard tube and refluxed for 3h, after which the excess thionyl chloride was distilled off. The residue was dissolved in chloroform and washed several times with water, dried and evaporated to give an oil. Yield 0.7g, 91%.

^{1}H-NMR ($CDCl_3$); δ 0.8 (3H,m); 1.2(9H, s); 1.8(2H,m) 3.6(2H, t); 4.2(1H,m); 4.9(1H, NH); 7.4(3H,m), 8.0(1H, d)

I.R. (Film). V_{max} 3280 (NH), 2960, 2940, 2880, 1600, 1470, 1320, 1150, 1000, 920, 760.

14. 1-(2-N-t-butylbenzenesulphonamido)-2-chlorohexane (330)

Using 1-(2-N-t-butylbenzenesulphonamido)hexane-2-ol as the substrate, the above compound was obtained as oil in 83%.

^{1}H-NMR: $CDCl_3$ δ 1.0 (3H, m); 1.4(9H, s); 1.8(2H, m); 3.5(2H, t); 4.6 (1H, base proton); 5.25 (1H, NH) 7.4 (3H, m, ArH), 8.0 (1H, d).

15. 1-(2-N-t-butylbenzenesulphonamido)but-2-ene (332a)

Sodium hydride (80% in mineral oil) (0.5g) was washed in n-hexane (to remove the oil) and suspended in dry THF. 1-(2-N-t-butylbenzenesulphonamido)2-chlorobutane (0.5g) was dissolved in THF, then added to the sodium hydride suspension and refluxed gently overnight. After cooling, water was added dropwise to decompose excess hydride. The solvent was removed and the residue taken up in methylene chloride, washed with water, dried and the solvent stripped off in vacuo leaving a brown solid which was recrystallised in cyclohexane to give yellow flakes, m.p. 121-122°(62%).

^{1}H-N.M.R. ($CDCl_3$): δ 1.2 (s, t, 12H); 2.4(2H, m); 4.8 (1H, NH); 6.3 (1H, m, vinylic proton; 7.2(1H, m vinylic proton) 7.6(3H, m); 8.1(1H, dd).

Anal. Calcd. for $C_{14}H_{21}NO_2S$; C, 62.92; H, 7.86; N, 5.86; Found: C, 62.75; H, 7.92, N, 5.15.%

16. 1(2-N-t-butylbenzenesulphonamido)hex-2-ene (333)

Using 1-(2-N-t-butylbenzenesulphonamido)-2-chlorohexane (0.5g), on work-up as above, gave on recrystallisation a pale yellow solid m.p. 100-1° (56%).

^{1}H-N.M.R. ($CDCl_3$): δ 0.8 (3H, m); 1.3 (13H, m); 2.3 (2H, m); 4.7(1H, NH); 6.2 (1H, m, vinylic proton); 7.1 (1H, m vinylic proton); 7.4(3H, m); 8.0(1H.d).

17. Ortho-Toluenesulphonyl chloride (278a)

Chlorosulphonic acid (100g) in a 3-necked round bottom flask, equipped with pressure equalising dropping funnel, a thermometer and magnetic stirrer was cooled to -10° with ice-salt mixture. Dry toluene (25g, 28.75mL) was added through the dropping funnel dropwise at such a rate that the temperature of the well stirred mixture does not rise above 5°, when all the toluene had been added, the reaction mixture was stirred for 4h and allowed to stand in the freezing mixture overnight.

The mixture was poured into ice (250g) and the ortho and para-toluenesulphonyl chloride separated as oilly layer and it was washed with cold water. The ortho and the paratoluenesulphonyl chloride was separated from each other by cooling the oil at -10° to -20°C for several hours. The paratoluenesulphonyl chloride was removed by filteration at the pump. The filterate was dissolved in carbon tetrachloride, removing the solvent and fractionating the oil at reduced pressure, b.p. 126°/10nm yield 23.5g.

18. N-t-butyl-2-methylbenzenesulphonamide (279)

Solution of N-t-butylamine (0.37 mole, 27.0g) in dry chloroform (100mL) at 0° was slowly added to a stirred solution of o-toluenesulphonyl chloride (0.123 mole, 23.5g) in chloroform (60mL). After the addition, the cooling was removed, the suspension was stirred at room temperature for 1h. The suspension was cooled, washed successively with 3N HCl

(100mL) and twice with water. The chloroform solution was dried with $MgSO_4$ and evaporated, yielding 23.6g, 95%. Recrystallisation was done in ethanol giving white needles m.p. 127-129°.

^{1}H-N.M.R.: $CDCl_3$, δ 1.2 (9H, s); 2.7 (3H, s); 5.3 (1H, NH, exchangeable with D_2O); 7.3 (3H, m); 7.9 (1H, d).

19. Metalation of N-t-butyl-2-methylbenzenesulphonamide

A solution of N-t-butyl-2-methylbenzenesulphonamide (0.020 mole) in THF (70mL), under argon was cooled to 0° and n-BuLi (1.6M in n-hexane) (30mL, 0.046 mole) was added in 4-5 minutes. After stirring for 30 minutes at 0°, the clear deep red solution contain 0.020 mole of the dilithio specie was used at 0°.

20. 2-(2-N-t-butylbenzenesulphonamido)-1, 1-diphenyl-ethanol (282)

Benzophenone (0.013 m, 2.37g) in 15mL of THF was added with stirring during 3 minutes to the lithio specie (0.01 mole) obtained above and stirred for 1h at 0°, yielding on standard work-up an oilly compound. Recrystallisation of the oil in methanol and flash chromatography in ether: cyclohexane 2:3 gave 3.0g; (75%), m.p. 160-162°C.

^{1}H-NMR ($CDCl_3$) δ 1.2 (9H, s); 3.1(1H, OH, exchangeable with D_2O); 4.1(2H s); 5.3(1H, NH, exchangeable with D_2O); 6.5 (1H, ArH, H-3); 7.3(12H, m) 7.9(1H, dd).

Anal. Calcd. for $C_{24}H_{27}NO_3S$: C, 70.4; H, 6.6; N, 3.4; Found: C, 70.1; H, 6.72; N, 3.38.%

21. Reaction of 2-(2-N-t-butylbenzenesulphonamido)-1,1-diphenylethenal with 33% HCl

Hydrochloric acid (33%) (40mL) was added to the carbinol (282) and heated under reflux to 130° for 48h. The reaction mixture was cooled in ice, the acid solution was decounted, and the solid obtained was washed several times with water.

The solid was dissolved in dichloromethane and washed with 5% hydrochloric acid and water several times, dried over $MgSO_4$, the solvent was removed in vacuo to give white solid. The product gave two spots in t.l.c. and was separated in ether: cyclohexane 1:1. It gave the two products described below.

Product A (334) (2-Butyl^t-3, 3-diphenyl (1,2)benzothiadiazine)

m.p. 68-70°, (48%), ^{1}H-N.M.R., ($CDCl_3$); δ 1.4 (9H, s); 4.7 (2H, s); 7.3(13H, m); 8.0(1H, m).

Anal. Calcd. for $C_{24}H_{25}NO_2S$: C, 73.60, H, 6.39; N, 3.50;
Found: C, 73.79; H, 6.18; N, 3.42.%

Mass spectrum $^m/_z$ 391, (10%), 335(90%), 270 (32%) 253, 167 (100%), 105 (32%), 57 (67%).

Product B (335) 3, 3-Diphenyl (1,2)benzothiadiazine

m.p. 80-81°, (52%)

^{1}H-N.M.R.: ($CDCl_3$): δ 3.9 (2H, s); 5.1(1H, NH); 7.2 (13H, m); 7.9 (1H, m).

Anal. Calcd. for $C_{20}H_{17}NO_2S$: C, 71.64; H, 5.07; N, 4.12;
Found: C, 71.72; H, 5.54; N, 3.86.%

Mass spectrum: $^m/_z$ 335 (85%); 270(52%) 194(100%), 165(25%) 77, (40%).

22. Using 50% hydrochloric acid (40mL) on the carbinol (282) above instead of 33% HCl and refluxed at 180° for 48h gave mainly product B on work-up, m.p. 80-81°(75%).

23. Attempted synthesis of sultone through cyclisation of intermediate product. THF method

A solution of N-t-butyl-2-methylbenzenesulphonamide (0.020 mole) in THF (70mL) under argon was cooled to 0° and n-BuLi (30mL, 0.046 mole) was added in 4-5 minutes. After stirring for 30 minutes at 0°, benzophenone (0.022 mole) in THF (20mL) was added during 3 minutes and stirred for 1h at 0°.

At the end of 1h, the set-up was changed to refluxing under argon for 13h before quenching with water. Standard work-up gave on purification with ether: hexane 1:1, a white solid. The spectroscopic analysis of this compound was essentially that of the product of experiment 20.

24. Attempted synthesis of a sultone through cyclisation of intermediate product - diglyme method

The above reaction was repeated but using diglyme instead of THF (so that the reflux temperature was up to 180°). Standard work-up gave the same product as above.

25. 1-(2-N-t-butylbenzenesulphonamido)pentan-3-ol (338)

Using 1,2-epoxybutane on the dilithiospecie obtained in experiment 19 above and on standard work-up gave a pale yellow oil which was purified by flash chromatography with ether: cyclohexane 2:1 gave a colourless oil in 45% yield.

^{1}H-N.M.R.: ($CDCl_3$) δ1.0 (5H, m); 1.3(9H, s); 1.8 (2H, m); 3.1 (1H, OH, exchangeable with D_2O); 3.3(2H, m); 3.6(1H, m) 6.0(1H, s, NH, exchangeable with D_2O); 7.35(3H, m, ArH); 8.05 (1H, dd, ArH).

I.R.: ν_{max} 3500, (br,OH); 3280, 2970, 2930, 1600, 1570, 1465, 1320, 1150, 980, 870, 760 cm^{-1}.

Anal. Calcd. for $C_{15}H_{25}NO_3S$: C, 60.2; H, 8.36; N, 4.68;

Found: C, 60.0; H, 8.26; N, 4.51.%

26. 1-(2-N-t-butylbenzenesulphonamido)-3-chloropentane (339)

Using 1-(2-N-t-butylsulphonamido)pentan-3-ol 338 as a substrate in experiment 13, gave the above named compound as an oil in 79% yield.

^{1}H-N.M.R.: ($CDCl_3$)δ1.0(3H, t); 1.2(9H, s); 1.6(2H, m) 2.0(2H, m); 3.1(2H, m); 4.7(1H, NH); 6.5(1H, base proton); 7.3 (3H, m); 8.0(1H, d).

27. 1-(2-N-t-Butylbenzenesulphonamido)pentene (340)

Using 1-(2-N-t-butylbenzenesulphonamido)-3-chloropentane as substrate in experiment 15, on work-up and recrystallisation gave a pale yellow solid m.p. 111-112^o in 50% yield.

28. Lithium benzenesulphonate (284)

Benzenesulphonic acid (15.8g, 0.10 mole) was dissolved in water (15mL). Lithium hydroxide (4.2g, 0.10 mole) in water (20mL) was added to the acid solution and the water was stripped off in vacuo.

The crude lithium benzenesulphonate was recrystallised by dissolving it in minimum volume of ethanol and toluene was added to precipitate it. The white solid obtained was filtered off and dried in an oven for 3h yielding 13.8g, 97 %.

29. Attempted metalation of lithium benzenesulphonate and coupling with styrene oxide:

Lithium benzenesulphonate (5.0g, 0.03 mol) was added to n-BuLi in n-hexane (21.5mL, 1.60 M, 0.033 mol), cooled to 0^{o} and the mixture stirred for 30 minutes.

Styrene oxide (0.033 mol, 3.96g) in THF (40 mL) was added at 0^{o} and stirred for 24h at room temperature. The reaction was quenched with 15% HCl and the organic phase was separated. The aqueous phase washed with dichloromethane twice and the aqueous phase was evaporated in vacuo. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent stripped off in vacuo. Crude yield of organic phase was 4.0g.

Purification by flash chromatography with ether: cyclohexane 1:4, gave 4 spots out of which none gave the desired product.

30. Attempted Metalation of Lithium benzenesulphonate and coupling with cyclohexane oxide

THF (20 mL) was added to lithium benzenesulphonate (5.0g, 0.03 mol) in a R.B.F. Under argon; n-BuLi (21.5 mL) was then added to 0^{o} and stirred for 30 minutes.

Cyclohexene oxide (3.3g, 3.2mL, 0.033mol) in THF (40 mL) was added at 0^{o} and stirred for 24h at room temperature. The reaction was quenched with 15% HCl and work-up as above gave a crude product that underwent flash chromatography with ether: cyclohexane 2:1, but did not give the desired product.

31. Ethyl p-Toluene Sulphonate (292)

To absolute ethanol (50mL) in a 3 necked flask was added pure p-toluenesulphonyl chloride (50g), 25% sodium hydroxide solution (50mL) was added to the mixture dropwise with stirring while keeping the temperature $< 20^{o}C$ when all the sodium hydroxide solution was added. The alkaline solution was left stirring for 3h. Solid ethyl-toluene sulphonate seperated and washed several times successively with water, 5% HCl, 5% Na_2CO_3 and water. The resulting white solid was filtered at the pump and dried in vacuo. The solid was stored in a desicator. Yield 96%, m.p. $32^{o}C$.

^{1}H-NMR ($CDCl_3$) δ 1.2(3H, t); 2.4(3H, s); 4.1(4H, q) 7.3(2H, d J = 10Hz) 7.8 (2H, d, J = 10Hz).

32. Metalation of Ethyl p-toluenesulphonate and Coupling with 1,2-epoxybutane (Synthesis of 1-(4-(ethoxy-sulphonylbenzene))Pentan-3-ol (349))

Ethyl p-toluenesulphonate (2.5g, 0.0125 mole) in THF (50 mL) cooled to -78^{o} under argon was added to n-BuLi (10ml, 0.0137 mole) and stirred for 5h at that temperature.

1,2-Epoxybutane(1.0 ml, 0.014 mole) in THF (30 mL) was added and stirred for 24h at room temperature. Hydrolysis with saturated ammonium chloride. The organic portion was separated and the aqueous portion was extracted twice with dichloromethane. The combined organic phase was washed with brine, dried over $MgSO_4$ and the solvent stripped off in vacuo to give a crude oil.

The crude oil obtained was purified by flash chromatography with ether: cyclohexane 1:1 giving a colourless oil, (40%).

I.R. (film) V_{max} 3540(S), 3050, 1600, 1490, 1450, 1340, 1180, 1000, 920 cm^{-1}

^1H-N.M.R. ($CDCl_3$): δ 0.8-1.2 (6H, m); 1.4(4H, m); 2.3(1H, OH, exchangeable with D_2O); 3.2(2H, m); 3.8 (1H, m) 4.1 (2H, q); 7.3(2H, d, J = 10 Hz); 7.8 (2H d, J = 10 Hz)

Anal. Calcd. for $C_{13}H_{20}O_4S$: C, 57.35; H, 7.35; Found: C, 57.60, H, 7.49.

33. Ethyl benzenesulphonate (288)

Absolute Ethanol (50 mL) in a 3-necked flask was added pure benzenesulphonyl chloride (50g), 25% sodium hydroxide solution (50mL) was added dropwise with stirring while the temperature $< 20^{\circ}$. When all the sodium hydroxide solution was added, the alkaline solution was stirred for 3h. The crude ethyl benzenesulphonate was washed several times with water and successively with 5% HCl, 5% $NaHCO_3$ solution and

and then with water. The resulting oil was vacuum distilled at 151°C and stored under argon. Yield 46.5g, 95%.

^{1}H-N.M.R. ($CDCl_3$): δ 1.3(3H, t); 4.2(2H, q); 7.6(3H, m); 8.0(2H, m).

34. Ethyl 2-methylbenzenesulphonate (290)

Ethyl benzenesulphonate (9.3g, 0.05 mol) was dissolved in dry THF (120 mL) and n-BuLi (0.055 mole, 1.1 eq, 37 mL) was added at -78° and stirred at that temperature for 5h. A red solution developed.

Methyl iodide (0.55 mol, 7.81g, 3.43 mL) in dry THF (30 mL) was injected into the reaction mixture and was allowed to warm to 0° with stirring continuing for 1h at that temperature. The reaction was quenched with cold saturated NH_4Cl solution. The organic portion was separated and the aqueous portion extracted with dichloromethane twice. The organic portions were washed with 5% K_2CO_3 solution, then brine and dried over $MgSO_4$. The solvent was stripped off in vacuo to give a slightly yellow oil.

T.l.c. gave one spot in ether: hexane 1:1 R_f 0.75

Yield 8.0g, 80%.

^{1}H-NMR ($CDCl_3$): δ 1.3(3H, t); 2.7(3H, s); 4.1(2H, q) 7.5(3H, m, ArH); 8.0(1H, dd, ArH).

35. General Metalation Procedure for 2-Methylbenzenesulphonates

n-BuLi (10 mL), 0.013 mol, 1.1eq) was added slowly to ethyl 2-methylbenzenesulphonate (2.5g, 0.0125 mol) in dry THF (50mL) at -78° and stirred at that temperature for 1.5h. The

lithiomethyl species gave a deep red solution.

The appropriate electrophile (0.0137 mol) in THF (30 mL) was added into the reaction mixture at -78°, stirred at that temperature for a further 1h before allowing it to warm to 0° and stirred at 0° for 1h. Water was added to the reaction mixture at 0°, and immediately acidified with 5% Hcl. The organic portion was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic portions were washed with brine, dried over $MgSO_4$ before solvents were stripped off in vacuo.

36. 1-(2-Ethoxysulphonylbenzene)butan-2-ol (350)

The crude oil obtained with the use of propionaldehyde was purified by flash chromatography on silica gel with ether: hexane 1:1 to give an analytically pure colurless oil, (75%).

I.R. (film) V_{max} 3530 (br); 2980, 2940, 1600, 1480, 1450, 1350, 1180, 1010, 920 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ 0.8-1.6 (8H, m); 2.2(1H, OH, exchangeable with D_2O); 3.1(2H, t); 3.8(1H m); 4.1(2H, q); 7.5 (3H, ArH, m); 8.0(1H, dd, J = 9Hz).

Anal. Calcd for $C_{12}H_{18}O_4S$: C, 55.81; H, 6.97; Found: C, 56.18; H, 7.34.

37. 1-(2-Ethoxysulphonylbenzene)-2-methyl-propan-2-ol (351)

The crude oil obtained with the use of acetone was purified by flash chromatography on silica gel with pet. ether: diethyl ether 1:1 to give a colourless oil (50%).

I.R. (film); V_{max} 3560 (br), 2980, 2950, 1600, 1470, 1350, 1180, 1010, 930 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ 1.2(9H, m); 2.8(1H, s, OH, exchangeable with D_2O); 3.2(2H, s); 4.0(2H, q); 7.6(3H, m, ArH ; 8.0(1H, dd).

Anal. Calcd. for $C_{12}H_{18}O_4S$: C, 55.81; H, 6.97; Found: C, 56.10; H, 7.26.

38. 2-(2-Ethoxysulphonylbenzene)-1-phenylethanol (352)

Using benzaldehyde as electrophile, the crude oil obtained solidified completely (on standing) the next day. Recrystallisation with pet. ether: ether gave white needles, m.p. 56-58°C, (65%).

I.R. (KBr): V_{max} 3520 (br), 3080, 3020, 2990, 1600, 1455, 1355, 1185, 1000, 915 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ 1.3(3H, t); 2.7(1H, br, OH, exchangeable with D_2O); 3.4(2H, m); 4.1(2H, q); 5.0(1H, q) 7.4(8H, m); 8.1(1H, dd).

Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.74; H, 5.88; Found: C, 62.63; H, 5.92.

39. 1,1-Diphenyl-2(2-ethoxysulphonylbenzene) ethanol (353)

The crude solid obtained by the use of benzophenone was recrystallised in ether: pet. ether to give white needles, m.p. 130-132°, (91%).

I.R. (KBr); V_{max} 3460, (br), 1600, 1450, 1345, 1175, 1000, 920 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ 1.3(3H, t); 3.1(1H, br, OH, exchangeable with D_2O); 4.05(2H, s); 4.1(2H, q); 6.3 (1H, d); 7.2 - 7.3(8H, m); 7.5(4H, m); 8.0(1H, d).

Anal. Calcd. for $C_{22}H_{22}O_4S$: C, 69.10, H, 5.76; Found: C, 69.20; H, 5.34.

40. Ethyl 2-(ethoxysulphonyl)phenyl acetate (354)

The crude oil obtained by the use of ethyl chloroformate was purified by flash chromatography using pet. ether: ether, 1:1, yielding a colourless oil, 50%.

I.R. (film): V_{max} 2980, 1730, 1600, 1570, 1470, 1440, 1370, 1220, 1180, 1030, 1000, 910 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ 1.3(6H, m); 4.1(6H, m); 7.6(3H, m, ArH); 8.1(1H, dd).

Anal. Calcd. for $C_{12}H_{16}O_5S$: C, 52.94; H, 5.88, Found: C, 53.02; H, 6.08.

41. Phenyl[(2-ethoxysulphonyl)benzyl]sulphone (357)

The crude oil obtained with benzenesulphonyl chloride as electrophile was purified by flash chromatography with ether: cyclohexane, 1:1 to give a slightly pale yellow oil, (50%).

I.R. (film): V_{max} 3000, 1600, 1450, 1350, 1180, 1000, 920 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ1.3(3H, t); 4.1(2H, q) 5.5(2H, s); 7.6 (6H, m); 8.1(3H, dd).

Anal. Calcd. for $C_{15}H_{16}O_5S_2$: C, 52.94; H, 4.70; Found: C, 52.54; H, 4.95.

42. 2-(Ethoxysulphonyl)benzene acetic acid (355)

The crude solid obtained by using solid CO_2 was recrystallised in ether: Pet. ether furnishing white plates, m.p. 106-108°, (70%).

I.R. (KBr) V_{max} 3300-2500, 1710, 1600, 1450, 1350, 1180, 1000, 920 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.3(3H, t); 4.1(2H, q); 4.2(2H,s); 7.6(3H, m); 8.1(1H, dd); 9.3(1H, br).

Anal. Calcd. for $C_{10}H_{12}O_5S$: C, 49.18, H, 4.92; Found: C, 49.17; H, 4.75.

43. N-Phenyl(2-ethoxysulphonyl)Phenyl acetamide (356)

The crude solid obtained using phenyl isocyanite was recrystallised in dichloromethane: pet ether to give a pale yellow solid, m.p. 124-126°, (78%).

I.R. (KBr): V_{max} 3360 (s), 2990, 1680, 1600, 1550, 1450, 1350, 1180, 1000, 920 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ 1.2(3H, t); 4.1(4H, q and s); 7.1-7.6 (8H, m); 8.0(1H, dd); 8.35(1H, NH).

Anal. Calcd. for $C_{16}H_{17}NO_4S$: C, 56.95; H, 5.76; N, 4.74; Found: C, 57.15; H, 5.38; N, 4.45

44. Ethyl 2,4-dimethylbenzenesulphonate (293)

Metalation of ethyl 4-methylbenzenesulphonate just as metalation of ethylbenzene sulphonate yielded a crude oil which was purified by flash chromatography in hexane: ether 1:1, giving a white gum, (83%).

^{1}H-N.M.R. ($CDCl_3$): δ 1.3(3H, t); 2.45(3H, s); 2.7(3H, s); 4.2(2H, q); 7.2(2H, m, ArH); 7.9(1H, d, ArH).

45. 2-[(2-Ethoxysulphonyl)4-Methylbenzene]-1-Phenyl ethanol (362)

Metalation of ethyl 2,4-dimethylbenzenesulphonate using general metalation procedure and coupling witn benzaldehyde as electrophile gave an oil which was purified by flash chromatography yielding white solid, m.p. 49-51°, 65%.

I.R. (KBr): V_{max} 3650, (s), 2990, 1600, 1480, 1450, 1350, 1180, 1000, 920 cm^{-1}.

'H-N.M.R. ($CDCl_3$): δ1.3(3H, t); 2.3(3H, s); 3.4(2H, m); 4.1,(2H, q); 5.0(1H, q); 7.3(7H, m); 7.9(1H, d)

Anal. Calcd. for $C_{17}H_{20}O_4S$: C, 63.75; H, 6.25; Found: C, 63.65, H, 6.15.

46. 1,1-Diphenyl-2-[(2-ethoxysulphonyl)-4-methylbenzene] ethanol (363)

The crude solid obtained with benzophenone as electrophile on lithiated 2,4-dimethylbenzenesulphonate was purified with flash chromatography in ether: pet ether, 1:1 to give white needles, m.p. 114-116°, (90%).

I.R. (KBr) V_{max} 3500 (s), 3060, 1600, 1490, 1450, 1340, 1180, 1000, 910 cm^{-1}.

'H-NMR ($CDCl_3$): δ 1.3(3H, t); 2.0(3H, s); 4.1(5H, including OH, exchangeable with D_2O), 6.0(1H, s, Ar, H) 7.4(11H, m); 7.9(1H, d).

Anal. Calcd. for $C_{23}H_{23}O_4S$: C, 69.87, H, 5.82; Found: C, 69.90, H, 6.21.

47. 2-(Ethoxysulphonyl)-5-Methylbenzene acetic acid)361)

The crude solid obtained with solid CO_2 on lithiated 2,4-dimethylbenzene sulphonate was recrystallised with Pet. ether: ether to give a colourless plates m.p. 108-110, (85%).

I.R. (KBr): V_{max} 3300-2530, 1710, 1600, 1460, 1360, 1180, 1110, 920 cm^{-1}.

'H-NMR ($CDCl_3$): δ 1.4(3H, t); 2.55(3H, s); 4.2(4H, q, s); 7.4(2H, m); 8.0(1H, d); 8.35(1H, br, OH).

Anal. Calcd. for $C_{11}H_{14}O_5S$: C, 51.16; H, 5.42; Found: 51.42; H, 5.60.

48. General Procedure for Synthesis of 2-[(Dialkylamino)Sulphonyl]Pyridine-N-Oxides

Chlorine gas was bubbled into a solution of 2-mercaptopyridine-N-oxide (10g, 0.08 mole) at -5° in 9N HCl (130 mL) for 1h. The solution was neutralized by the addition of calcium carbonate (10g) at -5°, then chloroform (200mL), and finally calcium carbonate (10g) at -10°. The supernatant liquid was separated and the remaining paste was washed twice in cold chloroform (50mL). The combined extracts were dried over $MgSO_4$ at 0° and filtered. The cold solution of the 2-chlorosulphonylpyridine-N-Oxide at 0° was added to the appropriate amine (2 equivalent, 0.16 mol) in chloroform (100 mL). Stirring was continued for 1h at 0° and for 2h at room temperature, before washing with water (2 x 50mL). Drying over $MgSO_4$ and removal of solvent gave a solid which was purified by crystalisation from Et_2O giving 2-[(dialkylamino)sulphonyl]pyridine-N-oxides.

49. Removal of the N-Oxide

2-[(dialkylamino)Sulphonyl]Pyridine-N-oxide (0.08 mol) dissolved in methanol (150mL), and Raney Nickel catalyst (40g) were added together in a bomb in presence of hydrogen for 5h at 1.3 atm. At the end of the reaction, the reaction mixture was filtered over celite, the solvent evaporated and pure white solid was obtained.

50. 2-(Piperidinosulphonyl)pyridine (297a)

Using piperidine as the amine in the above reaction, a white solid was obtained, m.p. 58-59° lit. 59°, (70%).

I.R. (KBr): Vmax 3100, 3040, 2960, 2880, 1570, 1340, 1180, cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.80(6H, m); 3.30(4H, m); 7.55(1H, m); 8.0(2H, d); 8.75(1H, d).

51. 2-(Pyrrolidinosulphonyl)pyridine (297b)

This product was obtained by using pyrrolidine as the amine in the above procedure, a light brown solid was obtained, m.p. 39-40°, (72%).

^{1}H-NMR ($CDCl_3$): δ 1.9(4H, m); 3.5(4H, m); 7.5(1H, ArH) 8.0(2H, d); 8.75(1H, d).

52. 2-(Morpholinosulphonyl)pyridine (297c)

Using a morpholine as the amine in the general procedure a light yellow solid was obtained, m.p. 43-45°C, (68%).

^{1}H-NMR ($CDCl_3$): δ 3.4(4H, m); 3.65(4H, m); 7.5(1H, m, ArH) 8.0(2H, d); 8.70(1H, d).

53. General Procedure for the Synthesis of 4-[(Dialkylamino)Sulphonyl)Pyridines

Chlorine gas was bubbled into a cold solution of 4-mercaptopyridine N-oxide (10g, 0.08 mol) at -5° in 9N HCl (130 mL) for 1h. The rest of the reaction follow the procedure of 2-[(dialkylamino)sulphonyl)pyridine experiment 48, 49.

54. 4(Piperidinosulphonyl)pyridine (302a)

Using piperidine as the amine in the general procedure above, a white solid was obtained, m.p. 121-122°(lit. m.p. 122°) (70%).

^{1}H-NMR ($CDCl_3$): δ 1.55(6H, m); 3.00(4H, m); 7.55(2H, m); 8.82(2H, m).

I.R. (KBr): V_{max} 3100, 3040, 2960, 2880, 1570, 1340, 1180.

55. 4(Pyrridinosulphonyl)pyridine (302b)

Using pyrrolidine as the amine in the general procedure above, on work-up a light brown solid was obtained, m.p. 111-112°C, (65%).

^{1}H-NMR ($CDCl_3$): δ 1.8(4H, m); 3.4(4H, m); 7.7(2H, m); 8.85(2H, m).

56. 4(Morpholinosulphonyl)Pyridine (302c)

Using morpholine as the amine in the general procedure above, on work-up a light yellow was obtained, m.p. 137-138°, (62%).

^{1}H-NMR ($CDCl_3$): δ 3.0(4H, m); 3.8(4H, m); 7.7(2H, m); 8.95(2H, m).

57 Lithiation of 2- and 4- [(dialkylamino)sulphonyl) pyridines and reaction the benzophenone

n-Butyllithium (1.6M in hexane, 15.5mL, 0.025) was slowly added to a solution of diisopropylamine (2.53g, 0.025 mol) in diethyl ether (50 mL) at -30° under argon. Stirring was continued for 1h at 0°. The resulting mixture was cooled to -70° and the 2-[(dialkylamino)sulphonyl]-pyridine or 4-[(dialkylamino)sulphonyl]pyridine (whichever is appropriate)(0.0125 mol) in THF (30 mL) was added dropwise. After the mixture was allowed to stand at -70° for 1.5h, a solution of benzophenone (0.025 mol) in THF (30mL) was added. The mixture was allowed to stand for 3h at -70° before hydrolysis at -70° and addition of water at room temperature. After the extraction of the aqueous layer with dichloromethane (2 x 100 mL), the combined organic extract were dried over $MgSO_4$ and the solvent removed in vacuo before purification.

58. Diphenyl[2-(piperidinosulphonyl)-3-pyridyl)methanol (298a)

Using 2-(piperidinosulphonyl)pyridine 297a as substrate, a white solid was obtained on purification with diethyl ether: m.p. 182-183° (lit. m.p. 182°), (90%).

^{1}H-N.M.R. ($CDCl_3$): δ 1.6(6H, m), 3.0(4H, m); 6.6(1H, s); 7.4(12H, m); 8.5(1H, d).

I.R. (KBr): ν_{max} 3400 (OH), 1600, 1570, 1375, 1160.

Anal. Calcd. for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86; Found: C, 67.60; H, 6.04, N, 6.93.

59. Diphenyl[2-(pyrrolidinesulphonyl)-3-pyridyl]methanol (298b)

Using 2-(pyrrolidinosulphonyl)pyridine 297b as substrate, a white solid was obtained on recrystallisation with diethyl ether: m.p. 163°-164°, (70%).

'H-N.M.R. ($CDCl_3$): δ 1.9(4H, m); 3.1(4H, m); 6.8 (1H, s); 7.4(12H, m) 8.5(1H, d).

Anal. Calcd. for $C_{22}H_{22}N_2O_3S$: C, 67.00; H, 5.58; N, 7.11, Found: C, 66.92, H, 5.50; N, 7.08.

60. Dipnenyl[2-(Morpholinosulphonyl)-3-pyridyl]methanol (298c)

Using 2-(morpholinosulphonyl)pyridine 297c as a substrate, a white solid was obtained on recrystallisation with diethyl ether: m.p. 159-160°, (69%).

'H-N.M.R. ($CDCl_3$): δ 3.4(4H, m); 3.65(4H, m); 6.5(1H, s) 7.25(12H, m); 8.5(1H, d).

Anal. Calcd. for $C_{22}H_{22}N_2O_4S$: C, 64.39; H, 5.36; N, 6.83, Found: C, 64.46; H, 5.26; N,6.56.

61. Diphenyl[4-(piperidinosulphonyl)-3-pyridyl] methanol (303a)

Using 4-(piperidinosulphonyl)pyridine as a substrate, a white solid was obtained on recrystallisation with diethyl ether: m.p. 135-6°, (80%).

'H-NMR ($CDCl_3$): δ 1.6(6H, m); 3.1(4, m); 6.6(1H, s ; 7.3 (10H, m); 7.7(1H, d); 8.2(1H, s); 8.7(1H, d)

Anal. Calcd. for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86; Found: C, 67.4; H, 5.90; N, 6.78.

62. Diphenyl[4-(pyrrolidinosulphonyl)-3-pyridyl] Methanol (303b)

Using 4-(pyrrolidinosulphonyl)pyridine as a substrate, a white solid was obtained, m.p. 126-7°, (65%).

^{1}H-N.M.R. ($CDCl_3$) δ 1.8(4H, m); 3.1(4H, m); 6.6(1H, OH) 7.3(10H, m); 7.8(1H, d); 8.15(1H, s); 8.65(1H,d).

Anal. Calcd. for $C_{22}H_{22}N_2O_3S$: C, 67.00; H, 5.58; N, 7.11; Found: C, 66.93; H, 5.32; N, 7.07.

63. Diphenyl[4-(Morpholinosulphonyl)-3-pyridyl] Methanol (303c)

Using 4-(Morpholinosulphonyl)pyridine as substrate, a white was obtained on recrystallisation with diethyl ether, m.p. 158-9, (78%).

^{1}H-NMR ($CDCl_3$): δ 3.0(4H, m); 3.6(4H, m); 6.35 (1H, s); 7.3(10H, m); 7.65(1H, d); 8.2(1H, s); 8.70 (1H, d).

Anal. Calcd. for $C_{22}H_{22}N_2O_4S$: C, 64.39; H, 5.36; N, 6.83; Found: C, 64.33, H, 5.11; N, 6.85.

64. Oxathiazolo[1,2][5,4-b]pyridine (299)

Diphenyl[2-(dialkylamino sulphonyl)-3-pyridyl] methanol (1.3g) was heated at 210° for 20h under argon. It was allowed to cool and the residue was extracted into methanol. The methanol was distilled off and the recidue dissolved in dichloromethane (50mL), washed with water (3 x 40 mL), dried over Na_2SO_4 and the solvent stripped off in vacuo giving a brown solid which was purified by flash chromatograpny with diethyl ether:, hexane 2:1 giving a solid, m.p. 141-143°.

I.R. (KBr) 3000, 2940, 2880, 1580, 1450, 1350, 1170 cm^{-1}.

^{1}H-NMR ($CDCl_3$)δ7.3(12H, m); 8.4(1H, d).

65. Oxathiazolo[1,2][4,5-c]Pyridine (304)

Diphenyl[4-(dialkylaminosulphonyl)-3-pyridy] methanol (1.0g) was heated at 210° for 2h under a slow stream of argon. It was allowed to cool and the residue was extracted into methanol. The methanol was distilled off and the residue dissolved in dichloromethane (50 mL), washed with water (3 x 40mL), dried over Na_2SO_4 and the solvent stripped off in vacuo giving a brown solid which was purified with diethyl ether to give a pale yellow solid, m.p. 80-81°.

I.R. (KBr) 2900, (CH), 1600 (-C=C-), 1340, 1160, (SO_2O) cm^{-1}.

N.M.R. ($CDCl_3$)δ7.0(11H, m); 8.40(1H, d); 8.65(1H, s).

66. Pyridine-3-sulphonyl chloride (305)

In a 3-necked flask with agitator, and reflux condenser with guard tube was added pyridine-3-sulphonic acid (14.5g, 0.09m) and phosphorus pentachloride (20.g, 0.1 mole). The mixture was stirred in an oil bath under reflux at about 110° for 3h. The phosphorus oxychloride was eliminated by distillation and toluene (50mL) was added to the residue and stirred. The whole solvent was eliminated in vacuo, the residue diluted in 50mL of benzene and filtered. The solution of the sulphonyl chloride was conserved in a deccicator.

^{1}H-N.M.R. ($CDCl_3$): δ 7.7(1H, m); 8.4(1H, d); 9.0(1H, dd) 9.3(1H, s).

67. N-t-Butyl pyridine-3-sulphonamide (306)

Pyridine-3-sulphonyl chloride (32.31g, 0.18 mol) in dry chloroform (100 mL) was added to t-butyl amine (39.9g; 0.54 mol) in chloroform (100mL) at 0^{o} and stirred for 1/2h. After stirring the solid hydrochloride was removed by filtration and the filtrate washed with water, dried over $MgSO_4$, stripped off solvent in vacuo to give a dark solid. The solid was recrystallised in ethyl acetate: hexane to give a yellow solid, m.p. 76 - 78^{o}C, (76%).

I.R. (KBr): ν_{max} 3100, 2980, 2870, 1580, 1470, 1320, 1160, 1010, 700 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ 1.2(9H, s); 5.9(1H, NH); 7.4 7.4(1H, dd); 8.2(1H, d); 8.8(1H, dd); 9.1(1H, s).

Anal. Calcd. for $C_9H_{14}N_2O_2S$: C, 50.46; H, 6.54; N, 13.08; Found: C, 50.04; H, 6.88; N, 12.89.%

68. 1,1-Diphenyl[3(N-t-butylsulphonyl)4-pyridyl]methanol (308)

n-Butyl lithium 1.6M, (0.0375 mol, 23.25 mL) was added to diisopropyl amine (3.7g, 5.12mL , 0.0375 mol) in diethyl ether (20 mL) at -30^{o} and stirred for 1h at 0^{o}. The resulting solution was cooled to -70^{o}. N-t-butylpyridine-3-sulphonamide (2.67g, 0.0125m) in THF (30mL) was added to the cooled solution and stirred for 1.5h.

Benzophenone (4.6g, 0.025 mol) in THF (30mL) was added to the lithio specie at -70° and stirred at that temperature for 3h. Hydrolysis at -70° was by addition of water (50mL) at room temperature. After extraction of the aqueous layer with dichoromethane (2 x 50mL), the combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum before purificiation from diethyl ether: Yield 85%, m.p. 180-182°.

I.R. (KBr): 3360, (OH), 3290(NH), 2980, 2870, 1580, 1340, 1160.

^{1}H-NMR ($CDCl_3$): δ 1.2(9H, s); 4.8(1H, NH, exchangeable with D_2O); 6.5(1H, s, OH); 6.8(1H, d); 7.30(10H, m); 8.6(1H, d); 9.4(1H, s).

Anal. Calcd. for $C_{22}H_{24}N_2O_3S$: C, 66.66; H, 6.06; N, 7.07; Found: C, 66.13, H, 6.30; H, 6.92.%

69 3-(N-t-butylsulphonyl)pyridine-4-carboxylic acid (30%)

Metalation of N-t-butylpyridine-3-sulphonamide as above and using solid carbon dioxide as an electrophile, the solution hydrolysed with water at 0°. The aqueous layer was extracted with dichloromethane (2 x 50mL), and the aqueous layer was acidified to pH 2, extracted with dichloromethane. The organic extract was dried over $MgSO_4$, evaporated and the residue was purified with diethyl ether giving white needles, m.p. 207-208° (80%).

I.R. (KBr) V_{max} 3300, 3190 (OH of acid) 1750, 1580, 1350, 1170 cm^{-1}.

^1H-NMR ($DMSOd_6$): δ 1.1(9H, s); 6.6(1H, NH); 7.4(1H, OH) 7.6(1H, d); 8.8(1H, d); 9.1(1H, s).

Anal. Calcd. for $C_{10}H_{14}N_2O_4S$ C, 46.51; H, 5.42, N, 10.85; Found: C, 46.47; H, 5.23; N, 10.47.

70. Isothiazolo[5,4-c]pyridine-3-one-1,1-dioxide (311)

3-(N-t-butylsulphonyl)pyridine-4-carboxylic acid (0.3g) and polyphosphoric acid (15g) were heated together at 110° for 20 minutes with manual stirring using spatula. At the end of the reaction, the thick syrup was poured into ice which was vigorously stirred. Filtration of the solid and a thorough wash with water gave 70% of pure product, m.p. 134-136°.

71. N-t-butyl Isothiazolo[5,4-c]pyridine-3-one-1,1-dioxides (312)

3(N-t-butylsulphonyl) pyridine-4-carboxylic acid (0.3g) was added to phosphorous oxychloride (6mL) and was refluxed at 110° for 3h. At the end of reaction, the reaction mixture was poured into crushed ice yielding a brown solid which was thoroughly washed with water, m.p. 124-126°C m/z 240.

REFERENCES

1. H. W. Gschwend, H. R. Rodriguez. Org. React. (NY) 1979, 26, 1.
2. H. Gilman and Y. Young., J. Amer. Chem. Soc. 1934, 56, 1415.
3. H. Gilman and A. L. Jacoby., J. Org. Chem. 1938, 3, 108.
4. G. Wittig, R. Pockets, H. Droge, Ber. 1938, 71, 1903.
5. N.S. Narasimhan and R. S. Mali. Tetrahedron 1987, 22, 65.
6. W.E. Truce: Org. React., 1957, 9, 37.
7. R.S. Mali, V.J. Yadav, K.N. Zawara; Indian J. Chem. 1982, 21B, 759.
8. N.S. Narasimhan, A.K. Ranade., Tetrahedron Letters, 1968, 4159.
9. J. Wakefield, "The Chemistry of organolithium Compounds", Pergamon Press Oxford, 1974, p.4.
10. G.E. Hartwell and T.L. Brown, Inorganic Chem. 1966, 5, 1257.
11. I. Craubner. Phys. Chem. (Frankfurt) 1966, 51, 15.
12. G.G. Eberhardt and W.A. Butte: J. Org. Chem. 1964, 29, 2928.
13. R.A. Ellifson and F.N. Kotsonis. Tetrahedron 1975, 29, 85.
14. J.D. Roberts and D.Y. Curtin: J. Amer. Chem. Soc. 1946, 68, 1658.
15. N.S. Narasimhan, P.S. Chandrachood, N.R. Shete. Tetrahedron 1981, 37, 825.

16. R.A. Barnes, L.J. Nehmsmann. J. Org. Chem. 1962, 27, 1939.

17. N.S. Narasimhan, R.S. Mali, R. Barve, Synthesis 1979, 906.

18. V. Snieckus 'Lectures in Heterocyclic Chemistry' Castle. R.N. Ed. 1984 p.95 - 106.

19. D.W. Slocum and C.A. Jennings: J. Org. Chem. 1976, 41, 3653.

20. H.W. Gschwend, H.R. Rodriguez, Org. React. N.Y 1979, 26, 201.

21. E. Campaigne and J. Ashby: J. Heterocyclic Chem. 1969, 6, 517.

22. E.J. Corey, H.A. Krist, J.A. Katzenllenbogen; J. Amer. Chem.Soc. 1970, 92, 6314.

23. A. G. Givmanini and G. Lercker: J. Org. Chem. 1970, 35, 3756.

24. C.F. Ellefson,: J. Org. Chem. 1979, 44, 1533.

25. D.A. Shirley and R. Roussel: J. Amer. Chem. Soc. 1953, 75, 3697.

26. E.J. Corey, D. Seebach, J. Org. Chem. 1966, 31, 4097.

27. H.M. Cohen, J. Organomet. Chem. 1967, 9, 375.

28. J.D. Cook and B.J. Wakefield., J. Chem. Soc. (C) 1969, 1973.

29. H. M. Cohen, and M. Wade, Organometalic compounds Methven Nondon 1967, Vol. 1, p.60.

30. L. Estel, F. Marsais, G. Quequiner, J. Org. Chem. 1988, 53, 2740.

31. J.E. Burks and J.K. Crandall, J. Org. Chem. 1984, 49, 4663.

32. S. Gronowitz, B. Erikson; Arkiv, Chem. 1963, 21, 335.

33. A. Turck, L. Mojovic and G. Quequiner, Synthesis, 1988, 881.

34. P.D. Bartlett, S.J. Tauber, W.P. Weber, J. Amer. Chem. Soc. 1969, 91, 6362.

35. J.A. Lansgrebe, J.D., Shoemaker, J. Amer. Chem. Soc. 1967, 89, 4465.

36. W.H. Glaze, P.C. Jones, Chem. Comm. 1969, 1435.

37. K. Ziegler, Angew. Chem. 1936, 49, 499.

38. J.A. Dixon, D.H. Fishmann; J. Amer. Chem. Soc. 1963, 85, 1356.

39. H. Gilman, R.H. Kirby, J. Amer. Chem. Soc. 1935, 57, 1267.

40. A.I. Mayer, E.M. Smith, J. Amer. Chem. Soc. 1970, 92, 1084.

41. R.A. Abramovitch, K.S. Ahmed, C.S. Giam; Can. J. Chem. 1963, 41, 1752.

42. T. Holm, Acta Chem. Scand. 1971, 25, 833.

43. F.N. Jones, R.L. VaulX, C.R. Hauser, J. Org. Chem. 1963, 28, 3461.

44. E.J. Corey, D. Seebach, J. Org. Chem. 1966, 31, 4097.

45. C. Eaborn, P. Golborn, R. Taylor, J. Organomet. Chem. 1967, 10, 171.

46. J. G. Lombardino, U.S. Pat., C. A. 1970, 73, 112092f

47. R.E. Ludt, and C.R. Hauser: J. Org. Chem. 1971, 36, 1607.

48. M. Braun, E. Ringer, Tetrahedron Letters: 1983, 24, 1233.

49. T.M. Bare, H.O. House: Org. Synth. 1969, 49, 81.

50. M.J. Jorgensen: Org. Synth. 1970, 18, 1.

51. H. D. Locksley, I. G. Murrey: J. Chem. Soc. (C) 1970, 392.

52. E. Compaigne and J. Ashby, J. Heterocycl. Chem. 1969, 6, 517.

53. M.R. Bell, A.M. Zalay, S.P. Oester Kin, G.O. Potts., J. Med. Chem. 1970, 13, 664.

54. P. Beak and R.A. Brown, J. Org. Chem. 1977, 42, 1823.

55. R.J. Mills and V. Sniekcus Tetrahedron Letters, 1984, 479, and 483.

56. M.P. Sibi, M.A.J. Miah, V. Snieckus, J. Org. Chem. 1984, 49, 737-42.

57. D.A. Shirley, M.D. Carmeron, J. Amer. Chem. Soc. 1952, 74, 664.

58. M. Iwao, T. Iihama, K. Mahalanabis, H. Perrier and V. Snieckus, J. Org. Chem. 1989, 54, 24.

59. J.A. Beel, V. Vejvoda: J. Amer. Chem. Soc. 1954, 76, 905.

60. N.S. Narasimhan, A.C. Ranade, Tetrahedron 1966, 603.

61. W.H. Peterbaugh, C.R. Hauser: J. Org. Chem. 1964, 29, 853.

62. J.J. Fitt, H.W. Gschwend: J. Org. Chem. 1976, 41, 4029.

63. F. Marsais, A. Cronnier, F. Trecourt and G. Quequiner J. Org. Chem. 1987, 52, 1133.

64. B. M. Trost and W.H. Peerson, J. Amer. Chem. Soc. 1981, 103, 2483.

65. N.S. Narasimhan and A. Radhakrishman: Tetrahedron Letters, 1983, 24, 4733.

66. J.N. Reeds and V. Snieckus: Tetrahedron Letters. 1983, 24, 3795.

67. K. Nishiyama and N.J. Tanaka, J. Chem. Soc. (Chem. Comm.) 1983, 1322.

68. G. M. Whitesides, W.F. Fiscker, S. Je SanFillippo, R.W. Bastie, H.O. House, J. Amer. Chem. Soc. 1969, 91, 4871.

69. C. Osuch and R. Levine, J. Amer. Chem. Soc. 1956, 78, 1723.

70. G. Wittig, G. Pierper and G. Fuhrmann; Ber. 1940. 73, 1193.

71. L. Fredman and D. Chlebowski, J. Amer. Chem. Soc. 1959, 81, 5512.

72. H. Gilman and F. Breyer: J. Amer. Chem. Soc. 1933, 55, 1262.

73. M.P. Sibi, M.A.J. Miah and V. Snieckus,: J. Org. Chem. 1984, 49, 737.

74. N.J. Thompson and J. Gaudino: J. Org. Chem. 1984, 49, 5237.

75. M.J. Sharp and V. Snieckus: Tetrahedron Letters. 1985, 26, 5997.

76. J.M. Fu, M.J. Sharp and V. Snieckus, Tetrahedron Letters. 1988, 29, 5459.

77. M.A. Siddique and V. Snieckus: Tetrahedron Letters. 1988, 29, 5463.

78. B. I. Alo, A. Siddiqui, V. Snieckus, 1987, Unpublished Results.

79. F. Trécourt, M. Mallet, F. Marsais and G. Quequiner J. Org. Chem. 1988, 53, 1367.

80. J.N. Bonfiglo, J. Org. Chem. 1986, 51, 2833.

81. T.D. Krizan, J.C. Martin. J. Amer. Chem. Soc. 1983, 105, 6155.

82. R.J. Mills, R. Horvath, M. Coquoz and V. Snieckus. in Lectures in Heterocyclic Chem. 1984, 22, 99.

83. R.J. Mills and V.Snieckus: Tetrahedron Letters. 1984, 479.

84. M.P. Sibi, K. Shankaran, B.I. Alo, W.R. Hahn and V. Snieckus: Tetrahedron Letters. 1987, 28, 2933.

85. R.D. Bates; L.M. Kroposki, D.E. Potter: J. Org. Chem. 1972, 37, 560.

86. M.J.S. Dewar, J.M. Harris: J. Amer. Chem. Soc. 1970, 92, 6557.

87. L. A. Walter, Org. Synth. Coll. Vol. III, 757.

88. J. K. Crandall, L.H.C. Lin, J. Amer. Chem. Soc. 1967, 89, 4527.

89. H.J. Fabris.: J. Org. Chem. 1967, 32, 2031.

90. N. S. Narasimhan and R.S. Mali, Tetrahedron, 1971, 27, 1351.

91. H. N. Adicks, I.R. Politzer, A.I. Meyers, J. Amer. Chem. Soc. 1969, 91, 2155.

92. F. Marsais, F. Trecourt, P. Breant and G. Quequiner J. Heterocycl. Chem. 1988, 25, 81.

93. J. N. Reed; V. Snieckus, Unpublished Results in J. Org. Chem. 1984, 49, 745.

94. V. N. Ipatieff, H. Pines, B.S. Fredman, J. Amer. Chem. Soc. 1938, 60, 2731.

95. G.D. Figuly and J.C. Martin; J. Org. Chem. 1980, 45, 3729,

96. G.D. Hartman and W. Halezenko, Tetrahedron Letters. 1987, 28, 3241.

97. N.S. Narasimhan and P.S. Chandrachood, Synthesis 1979, 589.

98. D. Babin, J.D. Fourneron, L.M. Harwood, and M. Julia Tetrahedron Letters. 1981, 37, 325.

99. K. Oita, H. Gilman: J. Org. Chem. 1957, 22, 336.

100. J. Volhardt, H. Gais, K.L. Lukas, Angrew Chem. Intern. Ed. 1985, 24, 610.

101. S.W. McCombe, B.B. Shanker, and A.K. Ganguly: Tetrahedron Letters. 1987, 28, 4123.

102. A..I. Meyer and K. Lutomski, J. Org. Chem. 1979, 44, 4464.

103. H. Watanabe , R.L. Gay and C.R. Hauser: J. Org. Chem. 1968, 33, 900.

104. H. Watanabe and C.R. Hauser, J. Org. Chem. 1968, 33, 4278.

105. H. Watanable, R.A. Schwarz and C.R. Hauser, J. Lewis, D.W. Slocum. Can. J. Chem. 1969, 47, 1543.

106. H. Watanabe, C. Mao, I.T. Barnish, C.R. Hauser, J. Org. Chem. 1969, 34, 919.

107. J. G. Lombardino, J. Org. Chem. 1971, 36, 1843.

108. D. Hellwinket, R. Lenz, F. Lammeranz, Tetrahedron 1983, 39, 2073.

109. P. Breant, F. Marsais and G. Quequiner: Synthesis 1983, 822.

110. F. Marsais, G. Quequiner, Tetrahedron 1983, 39, 2009.

111. F. Marsais, G. LeNard, G. Quequiner, Synthesis 1982, 235.

112. M. Watanabe, M. Sahara, M. Kubo, S. Furukawa, R.J. Billedeau; and V. Snieckus, J. Org. Chem. 1984, 49, 742.

113. R.E. Ludt, G.P. Crowder, C.R. Hauser: J. Org. Chem. 1970, 35, 1288.

114. R. L. Vaulx, F.N. Jones, and C. R. Hauser: J. Org. Chem. 1964, 29, 1387.

115. P.L. Creger, J. Amer. Chem. Soc. 1970, 92, 1396.

116. H.W. Gschwend and A. Hamdan, J. Org. Chem. 1975, 40, 2008.

117. A. I. Meyers, A. Nebeya, H.W. Adickes, I.R. Polizer, G.R. Malone, A. Kovelesky, R.L. Nolen and R.C. Portvoy. J. Org. Chem. 1973, 38, 36.

118. A. I. Meyer and E.M. Smith, J. Org. Chem. 1972, 37, 4289.

119. I.C. Nordin, J. Heterocycl. Chem. 1966, 3, 531.

120. A. I. Meyer, D. L. Temple, D. Haideikwych and E.D. Mihelich: J. Org. Chem. 1974, 39, 2787.

121. J.I. Fitz and H.W. Gschwend, J. Org. Chem. 1976, 41, 4029.

122. W. Fuhrer, and H. W. Gschwend, J. Org. Chem. 1979, 44, 1133.

123. S. Cabiddu, S. Melis, P.P. Piras, F. Sotgiu. J. Organomet. Chem. 1979, 178, 291.

124. G. A. Kraus, J. Org. Chem. 1981, 46, 201.

125. W. R. Winkle and R.C. Ronald: J. Org. Chem. 1982, 47, 2101.

126. M.P. Sibi, V. Snieckus: J. Org. Chem. 1983, 48, 1935.

127. C.F. Lane, G.W. Kramer, Selections from Aldrichimica Acta, 1984, 110.

128. M. E. Thompson, J. Org. Chem. 1984, 49, 1700.

129. W. H. Puterbaugh and C.R. Hauser; J. Org. Chem. 1964, 29, 853.

129a. Rodd's Chemistry of Compounds Ed. S. Coffey Vol. III Part p. 452.

130. A. T. Roose, H. Gilman, N.J. Beaber: Org. Synthesis Wiley.(New York)Coll. Vol. 1, p. 145 - 7.(1941)

131. M. Cushman, T.C. Choong, J.T. Valco, M.P. Koleck: J. Org. Chem. 1980, 45, 5067.

132. N.S. Narasimhan, R.S. Mali, B.K. Kulkarni, P.K. Gupta, Indian J. Chem. 1983, 22B, 1257.

133. (a) E.F. Rogers, R.L. Clark, U.S. Patent 3202576, 1965.

(b) B.G. Boggiano, V. Petrow: J. Pharm. Pharma Col. 1961, 13, 567.

134. (a) R.A. Abramovitch, K.S. Ahmed, Choo-Seng-Giam Can. J. Chem. 1963, 41, 1752.

(b) R. Huisgen, and J. Saner, Angew Chem. 1960, 72, 91.

135. (a) W. J. Hickinbottom and N.W. Rodgers. J. Chem. Soc. 1957, 4131.

(b) H.M.R. Hoffmann: J. Chem. Soc. 1965, 6748, 6753.

136. J. Bizot, Bull. Soc. Chim. France 1967, 151.

PART II

CHAPTER 4

INTRODUCTION

4.0. SYNTHESIS OF TRICYCLIC S-CONTAINING HETEROCYCLES: PYRIDOBENZOTHIADIAZINES VIA NEW ENDOCYCLIC IMINIUM IONS

Organic compounds have been in use as chemotherapeutics for a long time. Systmatic use however started with Paul Ehrlich as far back as 1907.[1] These organic compounds inhibit pathogenic microorganisms without affecting to any material extent the tissues of the host.

The history of chemotherapy is one of a series of empirical trials guided only to a limited extent by rational principles of structure-activity relationsips. Fleming's discovery of Penicillin in 1929 was quite accidental.[2] Since then there have been three approaches to the problem of finding the most suitable drug to combat a disease and which would also have little toxic side effects:

(a) The method of trial and error which involves the trial of all kinds of compounds-natural and synthetic.

(b) Having a knowledge of the cell system and then synthesising compounds which will interfere with it. This is based on the concept that chemical groups on a drug, match certain vital receptor groups in a lock-and-key fashion.

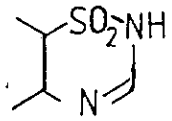
(c) Understanding the chemical structure of a new compound known to have some of required activity and then varying the structure of the molecule systematically until optimum activity is obtained.

This had resulted in compounds of high activity with little or no side effects.

Benzothiazides as Diuretic Compounds:

Fluid retention problems in the human body and the associated diseases had been treated with different organic chemicals of varying potency and side effects. These include organomercurials, aldosterone antagonists like spironolactone, aryloxyacetic acids and sulphonamides.

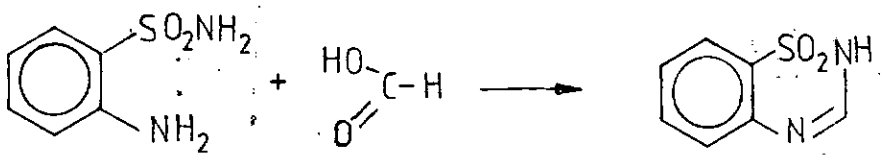
The low potency of the sulphonamides and their little side effects prompted further investigation into their activity. This led to the discovery that the sulphonamide functionality in cyclic system gave higher activity as a diuretic. These group of compounds are generally called thiazides.



1,2,4-Thiazides are well tolerated and potent when administered orally. The above therefore makes the synthesis of a variety of thiazides worthwhile.

Synthesis of Bicyclic Benzothiadiazines:

A review of the synthesis of bicyclic benzothiadiazines shows that their chemical synthesis started as far back as 1902[3] when benzo-1,2,4-thiadiazine-1,1-dioxide and the dihydro derivative were prepared by ring closure of o-aminobenzenesulphonamides with formic acid or formaldehyde respectively.



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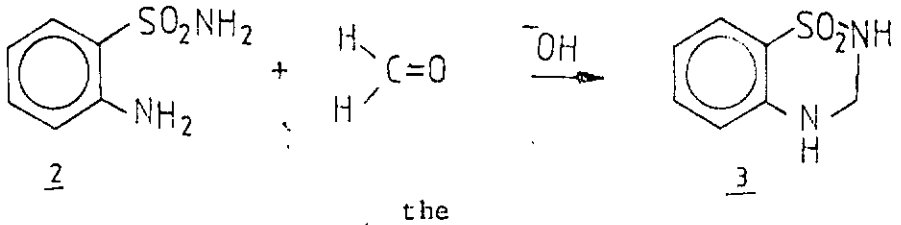

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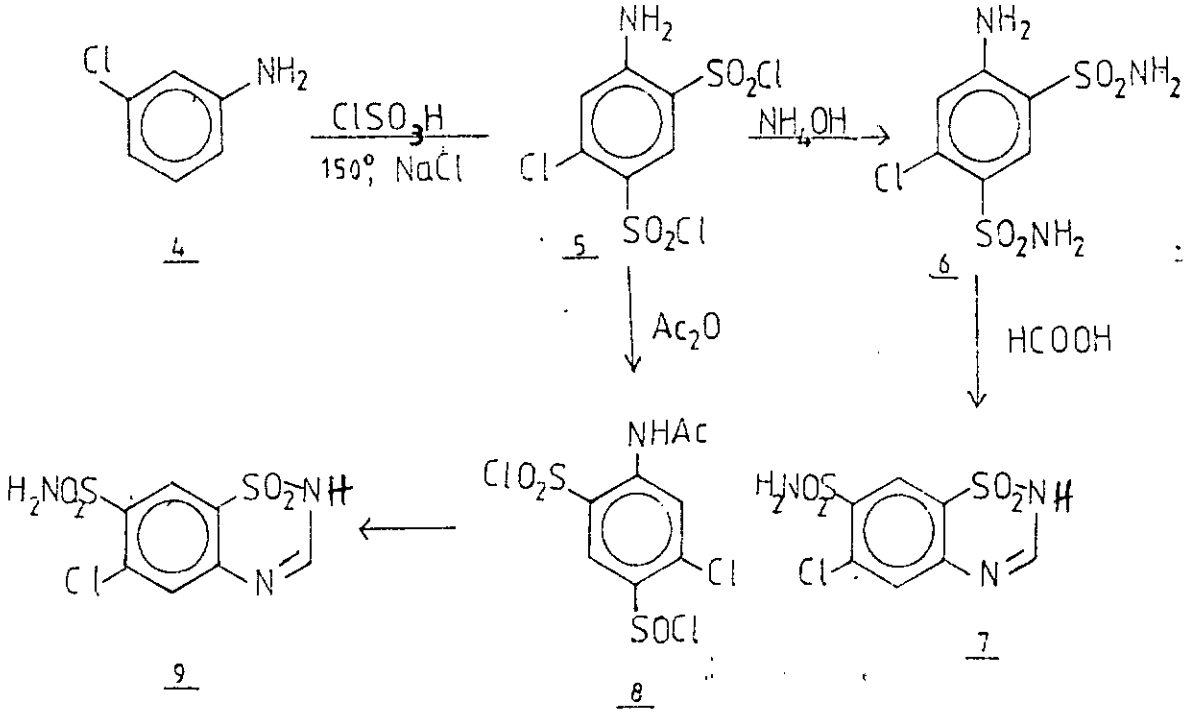
The synthesis of one of the most interesting compounds in the series, i.e. chlorothiazide 7 and 9 were reported by J.M. Sprague's group[4] at Merck, Sharp and Dohme Laboratories in USA.

The synthesis commenced with chlorosulphonation of 3 – chloroaniline furnishing the disulphonyl chloride. The sulphonyl chloride was converted to the sulphonamide with ammonia. The cyclocondensation of the sulphonamide was effected with formic acid.



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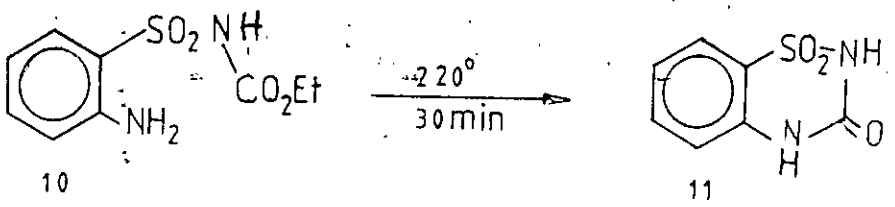
Thermal cyclisation of aminobenzene sulphonamide carboethoxy compounds was achieved giving also the corresponding 1,2,4-benzothiazinones [5]



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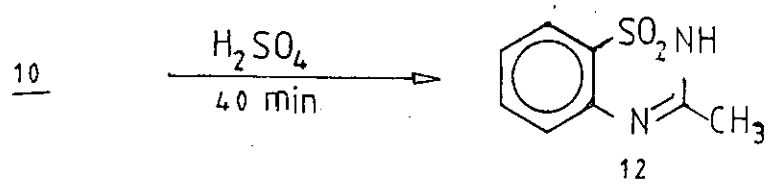
On heating such acetylated benzenesulphonamides in concentrated sulphuric acid for 40 minutes, gave the corresponding thiazides heterocycle [5].



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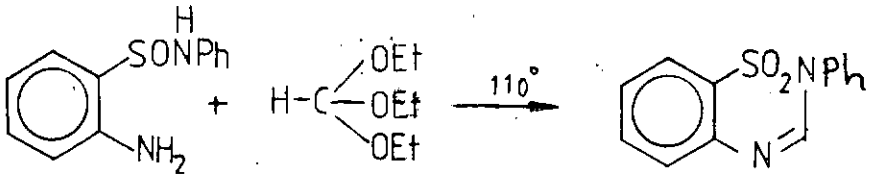
When N-phenyl-o-aminobenzenesulphonamide and an orthoester were heated together at 110°C, a phenyl substituted thiazide[6] was obtained. This represented the first 2-substituted thiazide.



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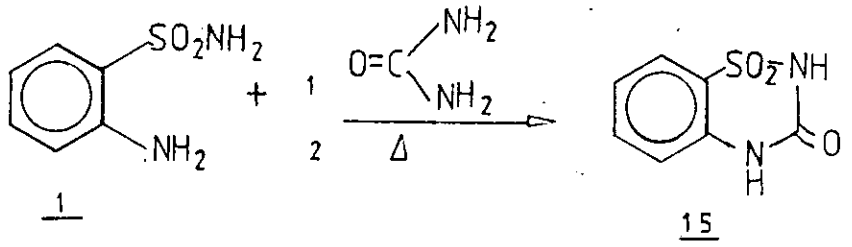
In 1950, Park and Williams[7] obtained 3-keto analogues of 1,2,4-benzothiadiazines in 94% yields by heating orthanilamides with urea at 180° for 30 minutes:



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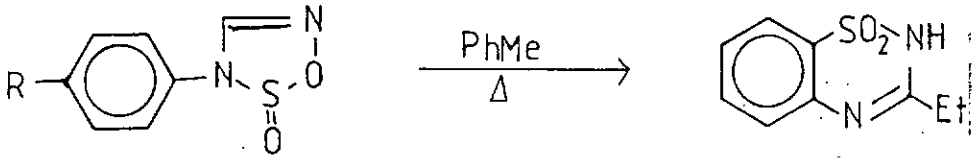
The thermal rearrangement of 4-alkyl-4-oxo-1,2,3,5-oxothiadiazoles 16 on heating in toluene leads to 3-ethyl-1,2,4-benzothiadiazines -1,1-dioxide. This rearrangement takes place in refluxing toluene.



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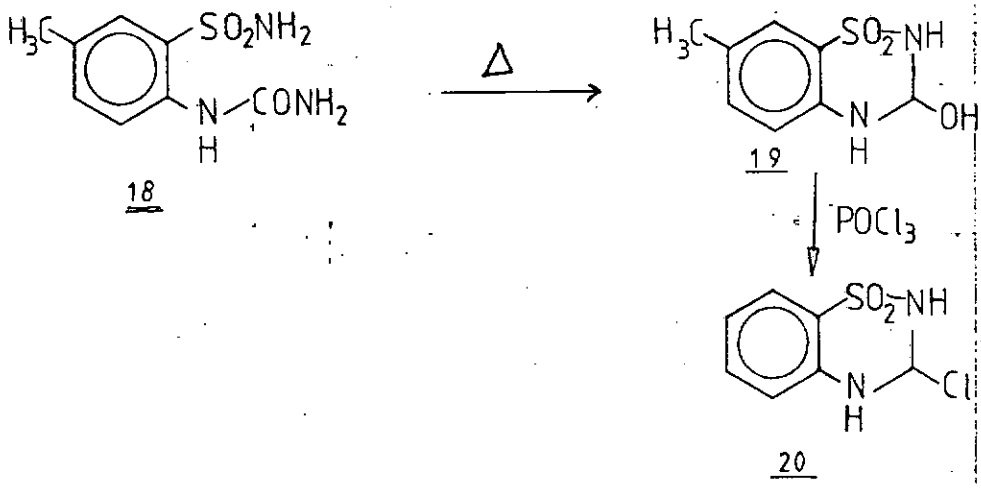
The 3-chlorosubstituted analogues were obtained from 4-ureiodotoluene-3-sulphonamides.

This reaction goes through a first stage of heterocyclisation and subsequent conversion of the hydroxy group to chloro.



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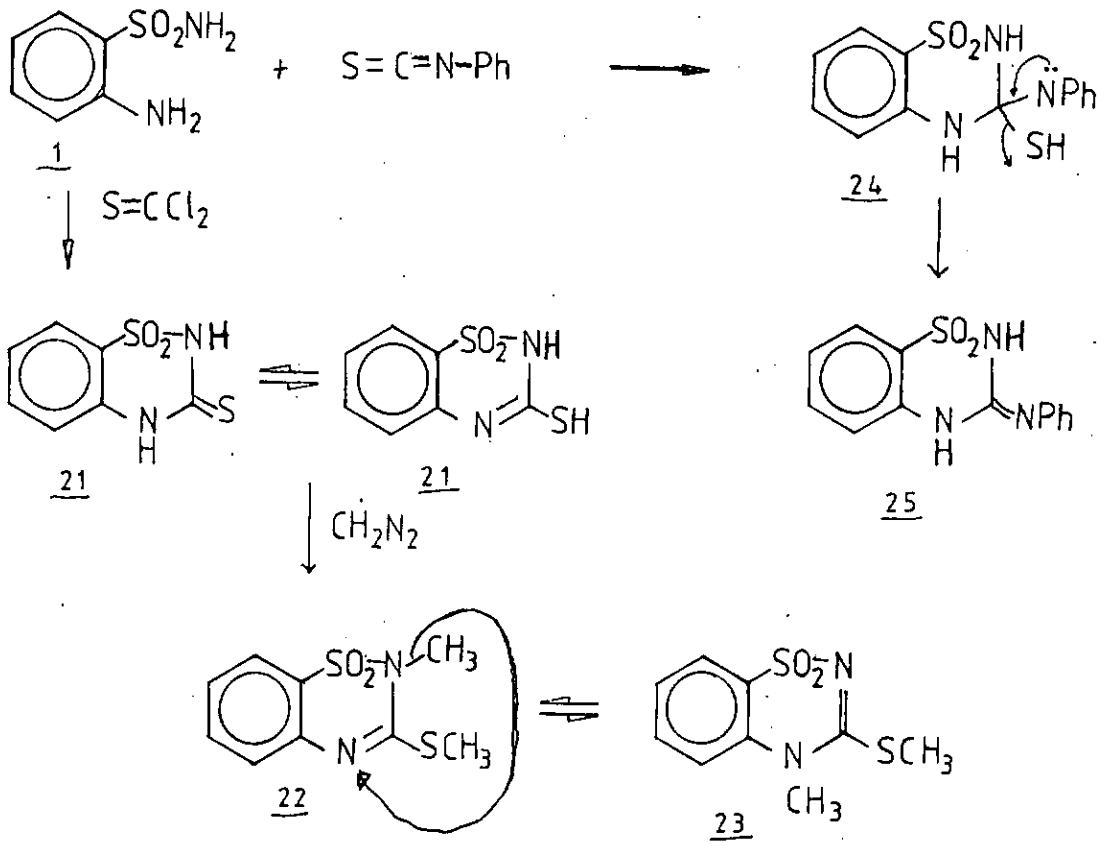
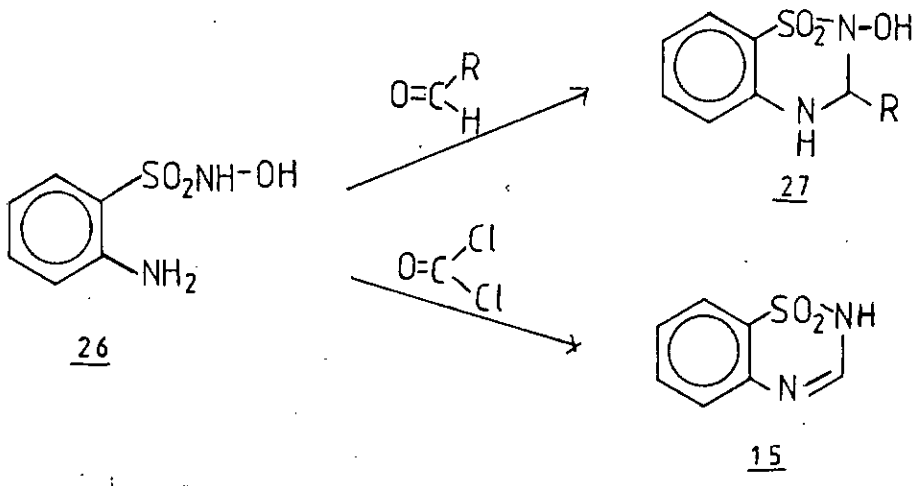
Phenylisocyanate reacts with o-aminobenzenesulphonamide to give 3-phenylimino-3,4-dihydro 1,2,4-benzothiadiazine--1,1-dioxide[3].



Similarly, thiophosgene reactions with o-aminobenzene-sulphonamide give 3,4-dihydro-1,2,4-benzothiazine-3-thione-1,1-dioxide[3] which tautomerises readily to give the preferred 3-mercapto analogue . Methylation of both analogues gave 2-methyl-3-thiomethyl derivative and a little quantity of the 4-methyl-3-thiomethyl compound.

Mann and Keilin showed that treatment of o-aminobenzene-sulphonylhydroxyl amine with aldehydes or with phosgene gives 2-hydroxyl-3-alkyl or 3-oxo-3,4-dihydro-1,2,4-benzothiazine-1,1-dioxide[8].



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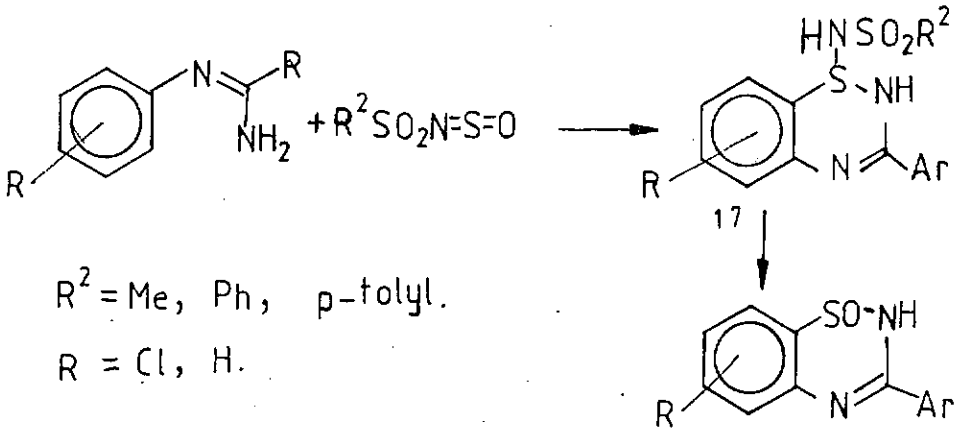
N-arylamidines react with N-sulphinylsulphonamides yielding 1-sulphonylimide-2H -1,2,4-benzothiadiazines which undergo acid hydrolysis to give substituted 3-arylbenzothiadiazine-1-oxide[9].

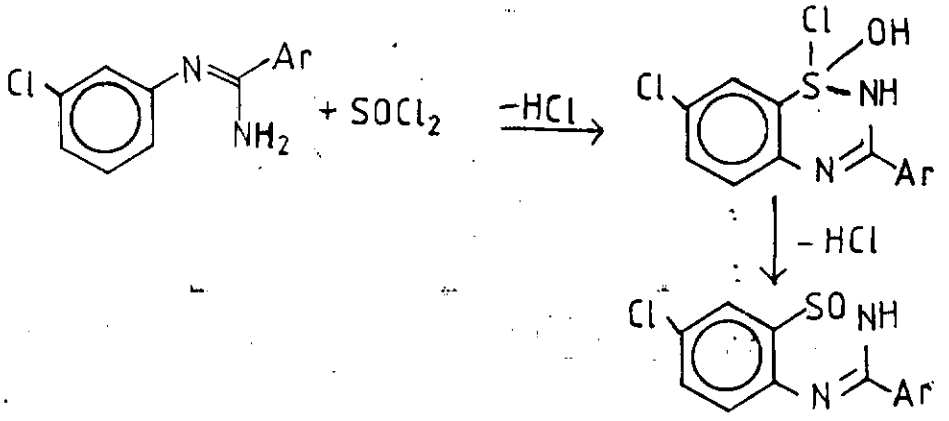


17

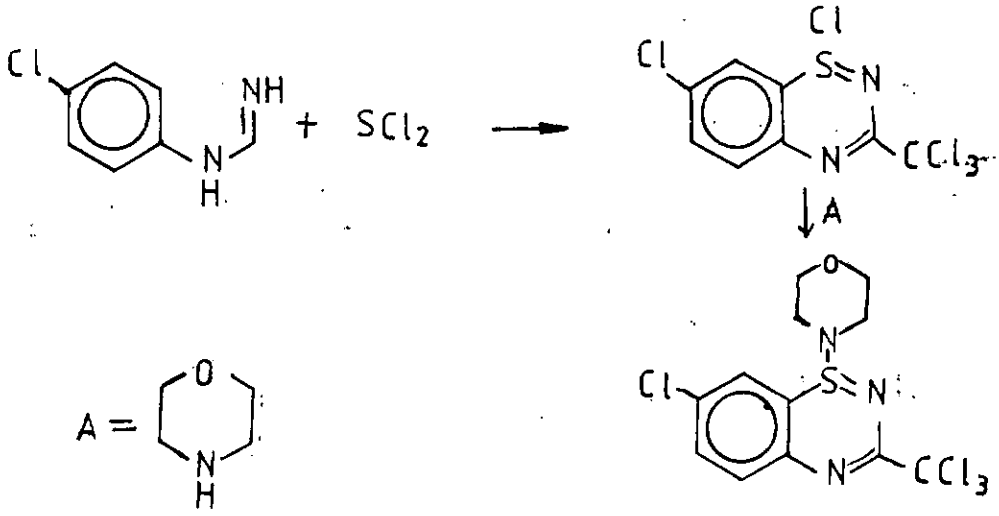
R^2 = Me, Ph, p-tolyl.

R = Cl, H.

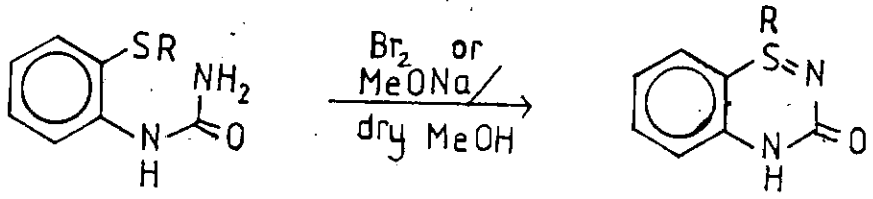
N-phenylbenzamidine react with thionyl chloride giving 7-chloro-3-phenyl-2H-1,2,4-benzothiadiazine-1-oxide.



Analogues lacking the hydroxy group were obtained by the treatment of N-phenylamidines with sulphurdichloride giving 1,7-dichloro-1H-1,2,4-benzothiadiazines. The latter can condense with morpholine to yield a 1-morpholine derivative.

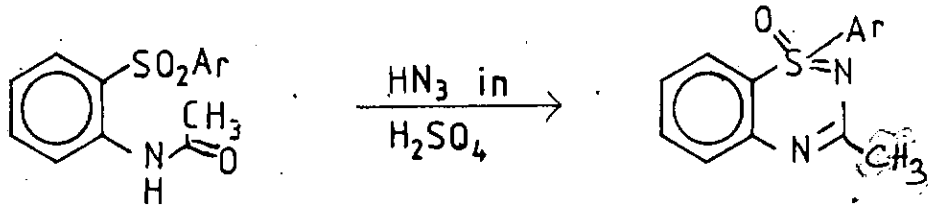


1-Alkyl or 1-aryl-3,4-dihydro-3-oxo-1H-1,2,4-benzothiadiazine was obtained by Wagner and Reinolhl[10] from o-alkylthiophenyl urea and arylthiophenyl urea when treated with bromine or sodium methoxide in anhydrous methanol.



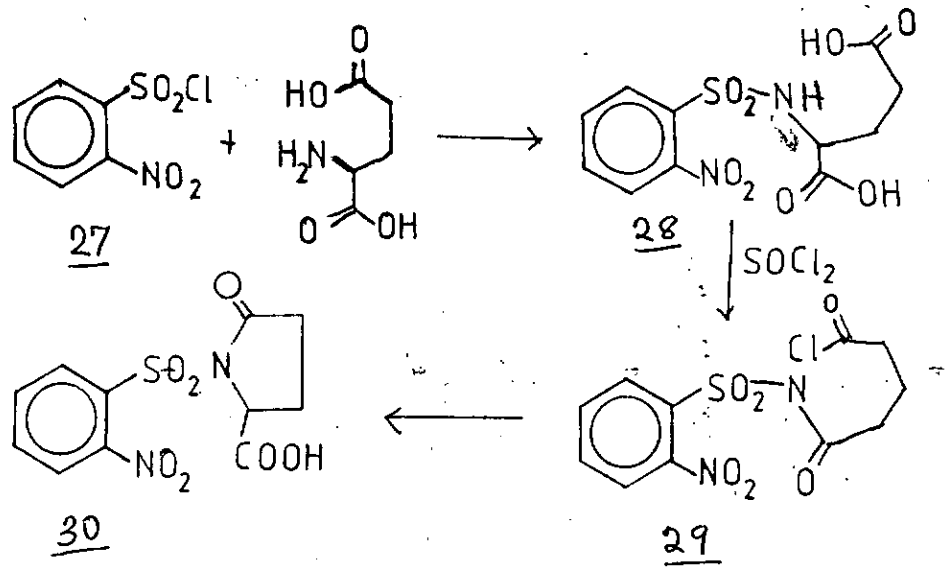
R = alkyl or aryl

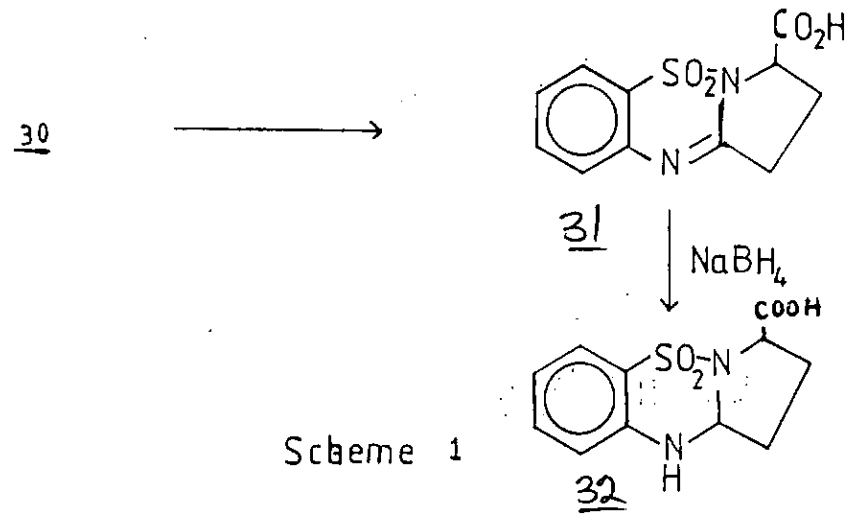
Diaryl sulphoxides are known to react with hydrazoic acid in concentrated sulphuric acid to give 1-arylsubstituted thiazides after going through a deacylation step:



4.2. TRICYCLIC BENZOTHIADIAZINES WITH A FIVE MEMBERED RING 'C'

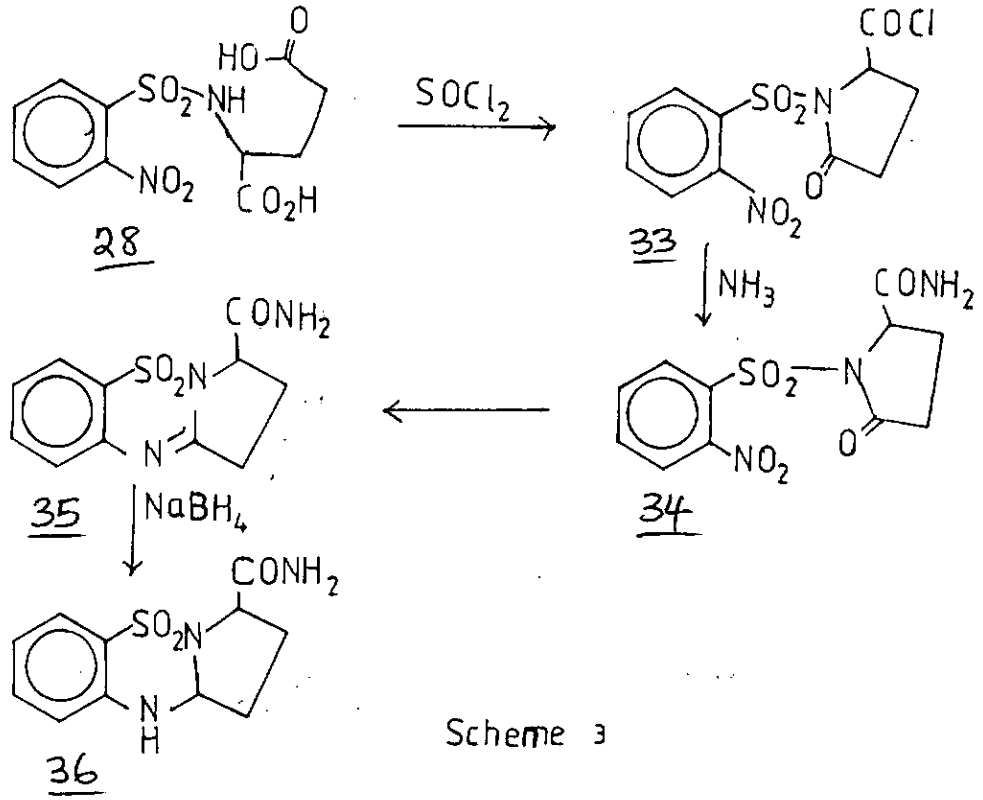
Tricyclic thiazides with five membered ring C was first encountered in 1963[11], when a number of pyrrolo (1,2,4)benzothiadiazines were synthesised. The synthesis started with the condensation of 2-nitrobenzenesulphonyl chloride with glutamic acid yielding N-(2-nitrobenzenesulphonyl)-l-glutamic acid by Takamatsu et. al.[11] The acid adduct was refluxed with thionyl chloride to give N-(2-nitrobenzenesulphonyl)-5-oxopyrrolidine-2-carboxylic acid. Reduction of the acid adduct with 10% palladium/charcoal in ethanol gave 2,3-dihydro-1H-pyrrolo (1,2-b)(1,2,4)-benzothiadiazine-3-carboxylic acid-1,1-dioxide. Reduction to the tetrahydro compound: 2,3,10,10a-tetrahydro-1H pyrrolo(1,2-b)(1,2,4)benzothiadiazine-3-carboxylic acid-1,1-dioxide was obtained by treatment of the dihydro analogue with an alkaline solution of sodium borohydride at room temperature.





Scheme 1

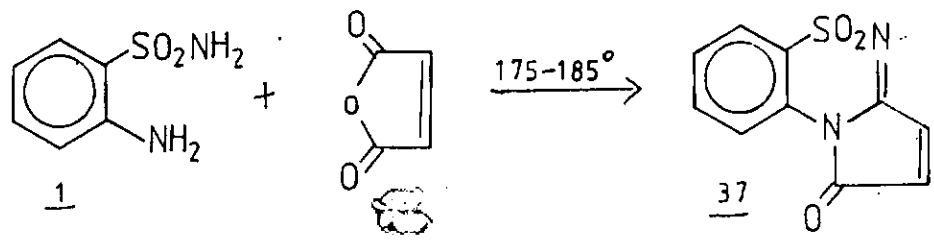
The amide analogue of the tricycle 32 was prepared from the pre-formed ketoamide as shown below:



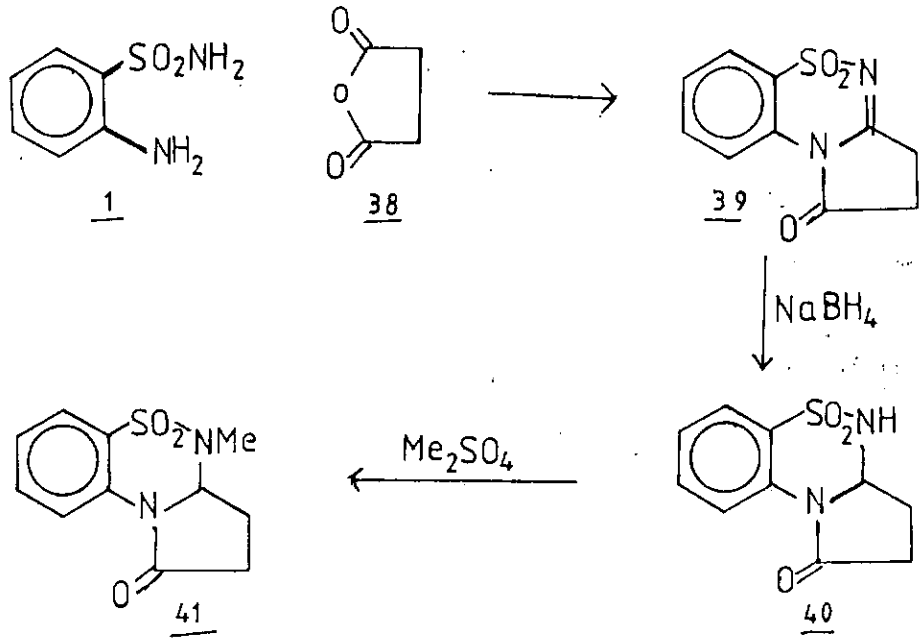
Scheme 3

Kratzl et. al.[12] in 1965, was able to obtain a series of tricyclic benzo(2,1-c)(1,2,4)thiazide-1,1-dioxide by heating o-aminobenzenesulphonamide with maleic anhydride for 20 minutes

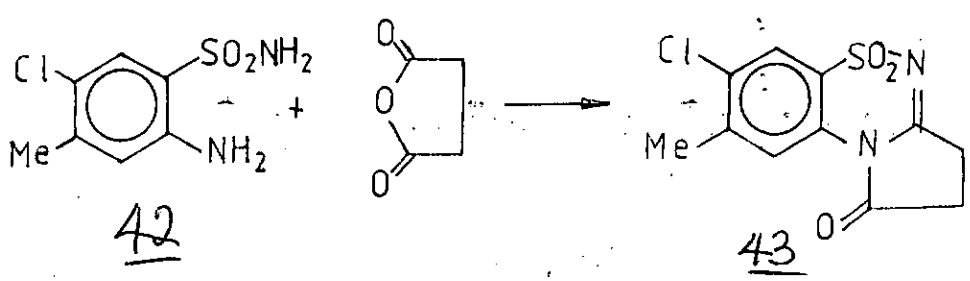
at 175-185°C furnishing 1-oxo-1H-pyrrolo(1,2-c)(1,2,4)benzothiadiazine-5,5-dioxide[12]. (37)



The 2,3-dihydro derivative of 37 was prepared by using succinic anhydride instead of maleic anhydride.

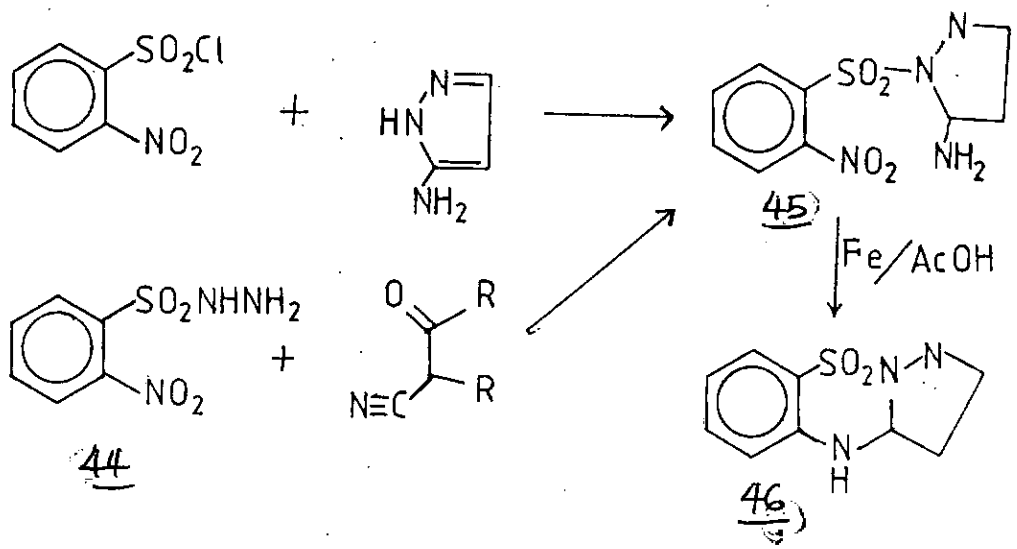


The saturated derivative was obtained by treatment with alkaline sodium borohydride and N-methylation was effected with dimethyl sulphate. Condensation of 2-amino-5-chloro-4-methylbenzenesulphonamide with succinic anhydride gave other analogues:



Plescia et al reported the synthesis of 4H-pyrazolo (1,5-b)(1,2,4)benzothiadiazine-5,5-dioxides from 2-nitrobenzenesulphonyl chloride[13]. The sulphonyl chloride was condensed with 3-aminopyrazole to give a nitroamine adduct. The latter on reduction gave a diamine which intramolecularly cyclised with iron in acetic acid to give the tricycle.

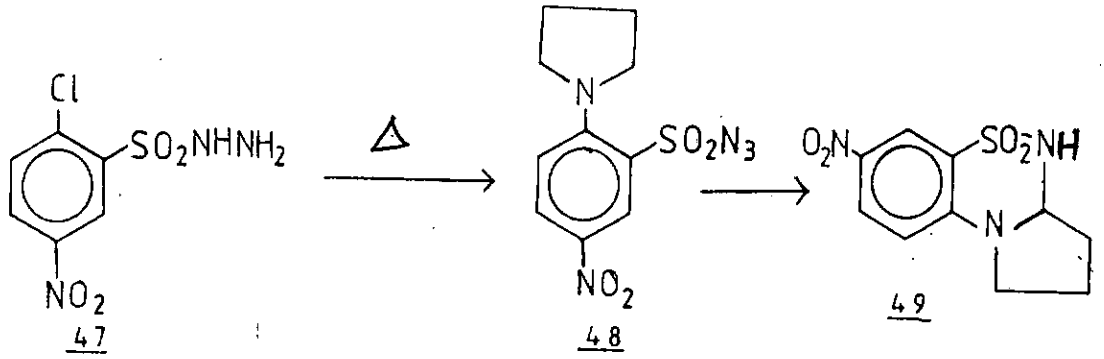
An alternate method developed by the same group involved the condensation of 2-nitrobenzenesulphonylhydrazine with β-ketonitrile giving the nitroamine adduct intermediate as above. Treatment of the nitroamine adduct as usual gave the desired heterocycle.



In 1974, Martin, Meth-Cohn and Suschitsky at Salford University, prepared other tricyclic benzothiadiazines, i.e. pyrrolo(2,1-c)(1,2,4)benzothiadiazine from sulphonyl azides[14].

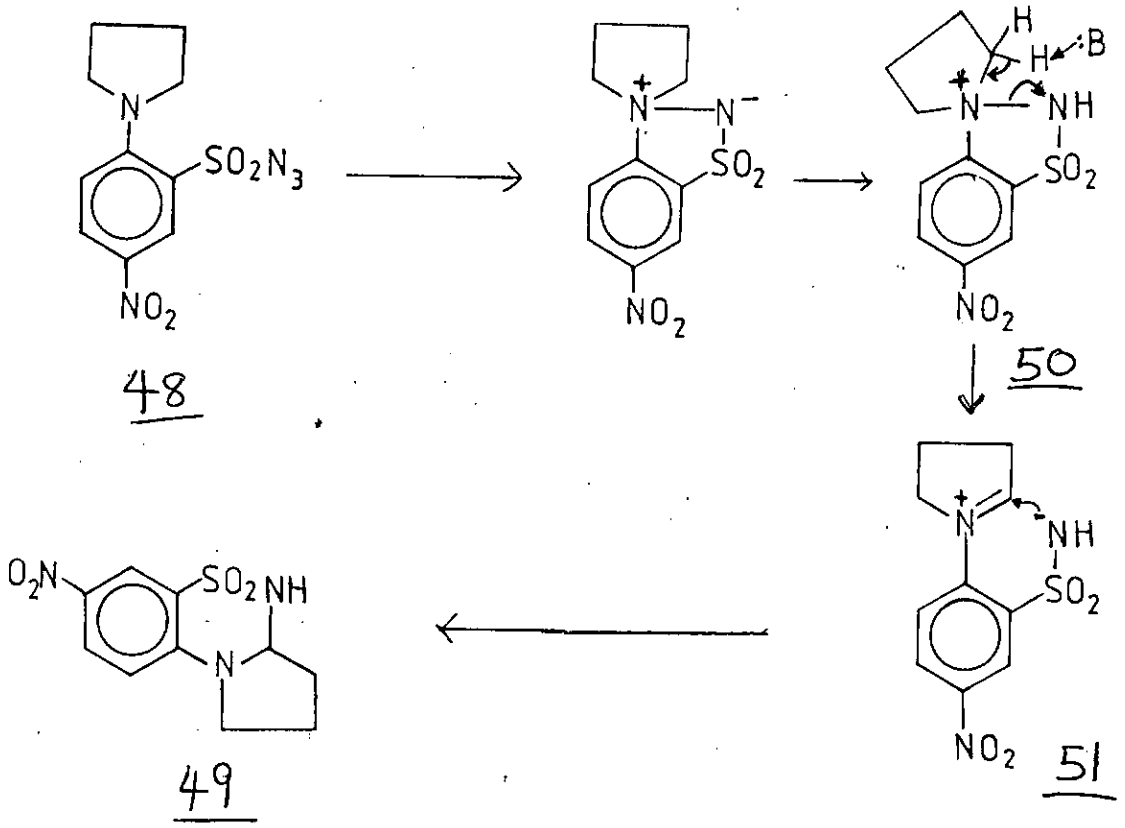
Pyrrolidinosulphonylazide was conveniently prepared by treatment of 2-chloro-5-nitrobenzenesulphonylazide with two mole equivalent of pyrrolidine in dry benzene. Thermal decomposition

of the compound in presence of a trace of secondary amine hydrochloride or large excess of secondary amine gave pyrrolo(2,1-c)(1,2,4) benzothiadiazine.



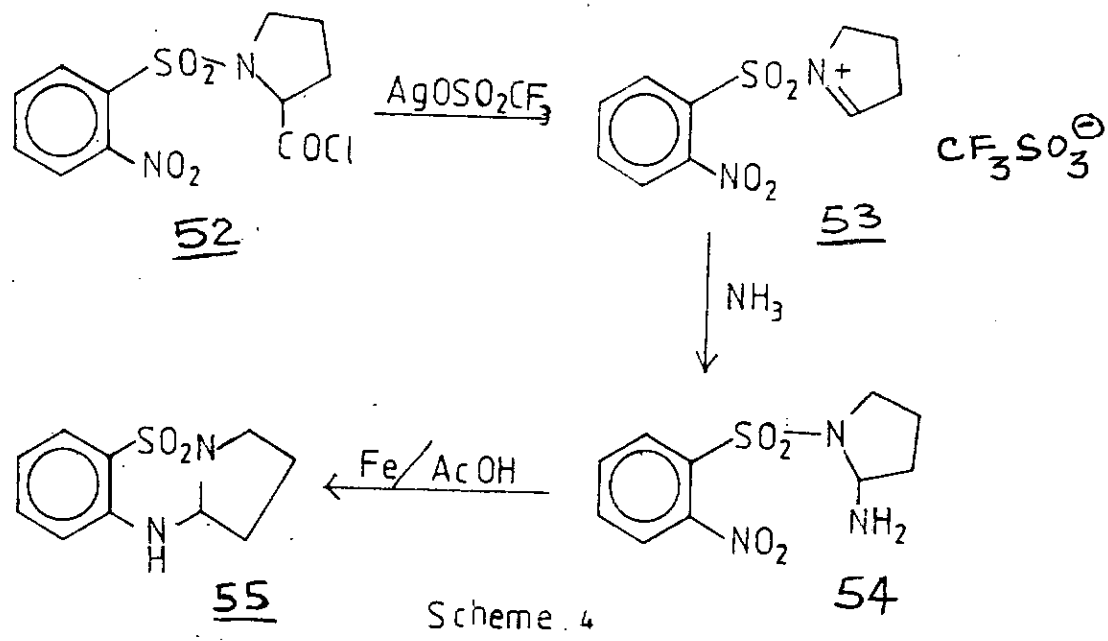
47 48 49

The probable course of reaction is outlined below:



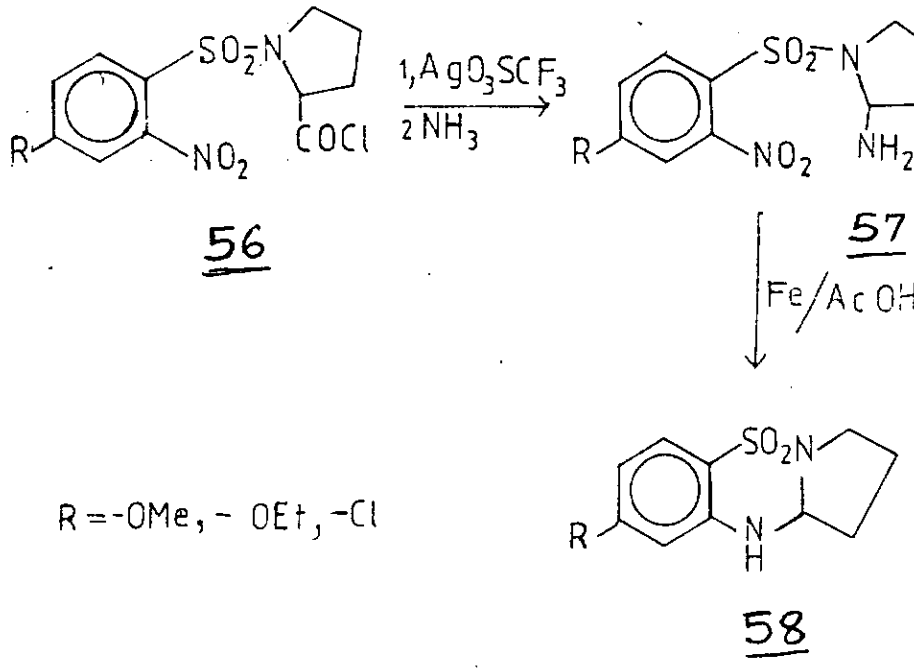
48 50 51 49

In 1979, Adesogan and Alo[15] reported a novel approach to the synthesis of tricyclic thiazides utilizing readily generated iminium salts to prepare the tricycles as outlined in the following scheme:



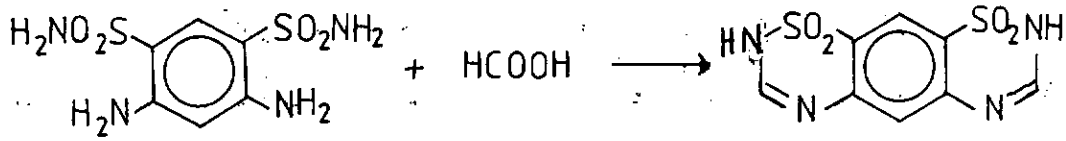
Scheme 4

Substituted derivatives of the tricycles were synthesised in 1986[16] from appropriate 4-substituted nitrobenzenesulphonamides. By this method, the methoxy, ethoxy, and chlorosubstituted products were obtained.



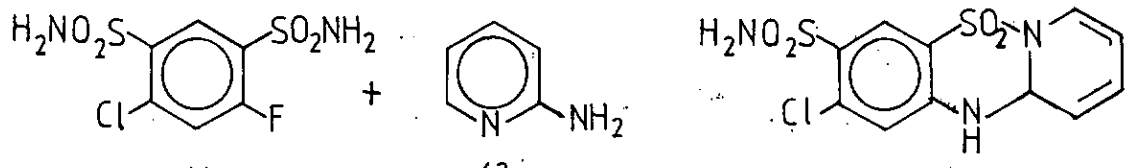
4.3. TRICYCLIC BENZOTHIADIAZINE WITH A SIX-MEMBERED RING 'C'

Synthetic approaches to tricyclic benzothiadiazine with a six-membered ring 'C' are very scanty in the literature. The first such tricyclic thiazide was prepared by Novello et al[17]. The heterocycle obtained was a bisthiazide and was constructed by ring closure of 5-amino-2,4-sulphonamidoaniline with formic acid. The benzo (1,2-e)(5,4-e)bis-1,2,4-thiadiazine-1,1-dioxide 60 obtained had a melting point above 500°.



59 60

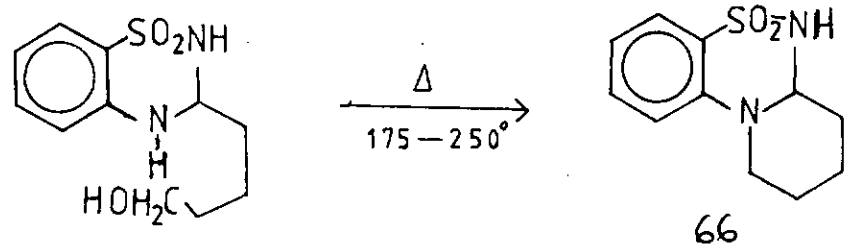
Jackman et al[18] were the first to report the preparation of pyrido(1,2-b)(1,2,4)benzothiadiazines. These were prepared by condensing some halogene-2,4-disulphonamidobenzene with amines e.g. 5-chloro-2,4-disulphonamido fluorobenzene was condensed with 2-amino pyridine by heating at temperatures between 140°-160° for 4 hours to give the tricycles.



61 62 63

Kratzl et al[12] also synthesized 1-oxo-1H-pyrido(2,1-c) -9-chloro-8-sulphonamido-1,2,4-benzothiadiazine-1,1-dioxide from 5-chloro-2,4-disulphonamidoaniline and glutaric anhydride.

Pyrido(2,1-c)(1,2,4)benzothiadiazine-6,6-dioxide was prepared by some Italian workers[19] in 83-93% yield by thermal cyclisation of 3(4-hydroxybutyl)-(1,2,4)benzothiadiazine-1,1-dioxide at 175-250°.

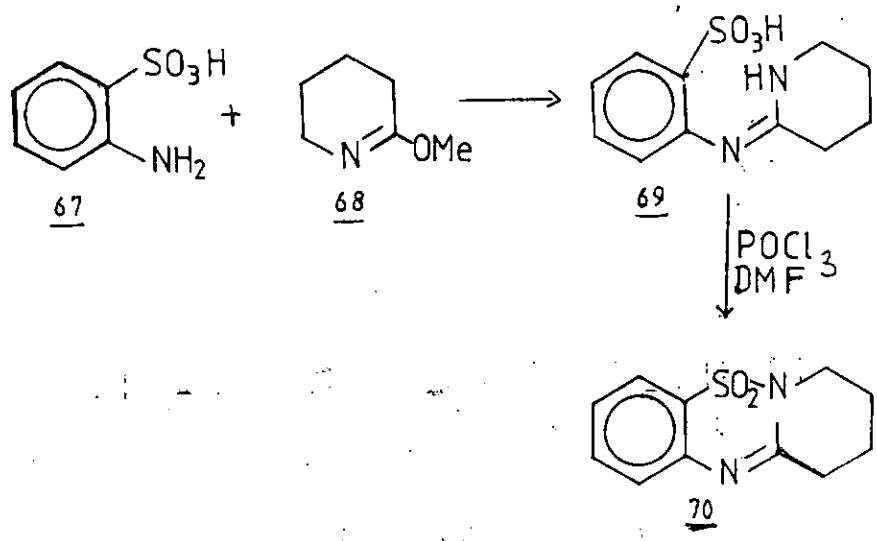


64 R_1 = -H, -Cl, $-NO_2$

65 R_2 = H -Me, -Cl

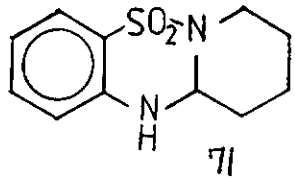
66

After a computer search (CAS-on-line), the only tetrahydro-pyrido(2,1-b)(1,2,4)benzothiadiazine found in the literature was reported in a U.S. patent[20]. It was obtained by initial condensation of 2-amino-benzenesulphonic acid with 2-methoxy-2-dehydropiperidine. The sulphonic acid adduct obtained was cyclised with phosphorous oxychloride in dimethylformamide. The 11,11a-dihydro product obtained here was shown to be less effective as a diuretic than the corresponding fully reduced analogues.[20]



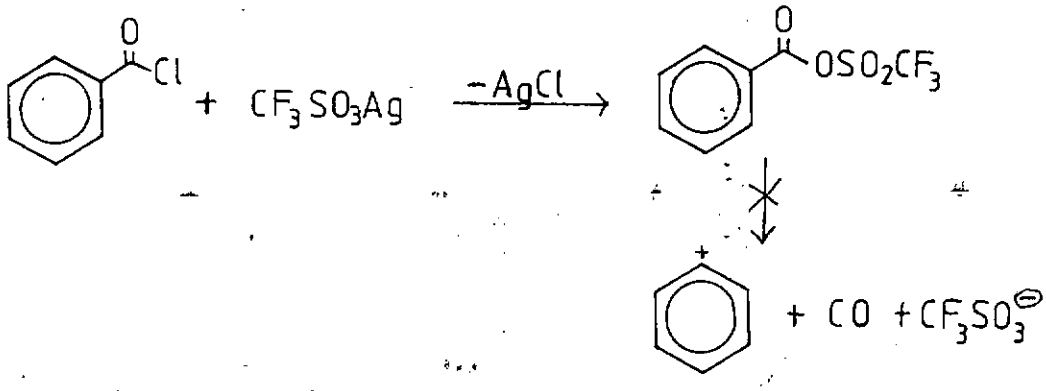
67 68 69 70

This compound was, however, found to be an effective sedative, mild tranquilizer, and an anticonvulsant. It was therefore thought that synthesis of hexahydroanalogues of pyridobenzothiadiazine dioxides should be worthwhile as the compounds are potential physiologically active compounds, especially as the derivatives are obtained directly without the need for reduction after cyclisation. These derivatives should be obtainable in good yields via the endocyclic iminium salt route developed earlier by Adesogan and Alo[15].

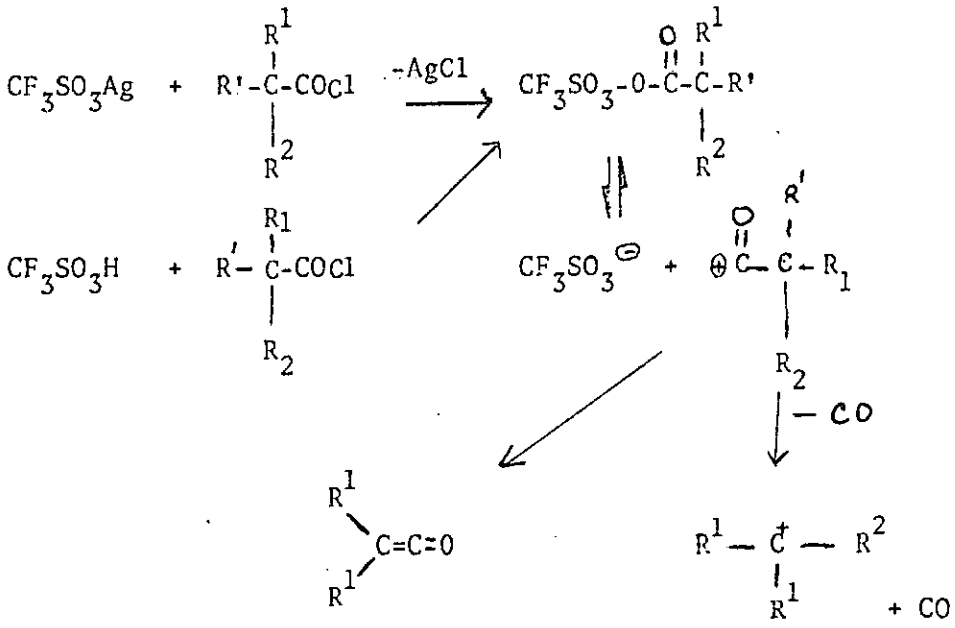


71

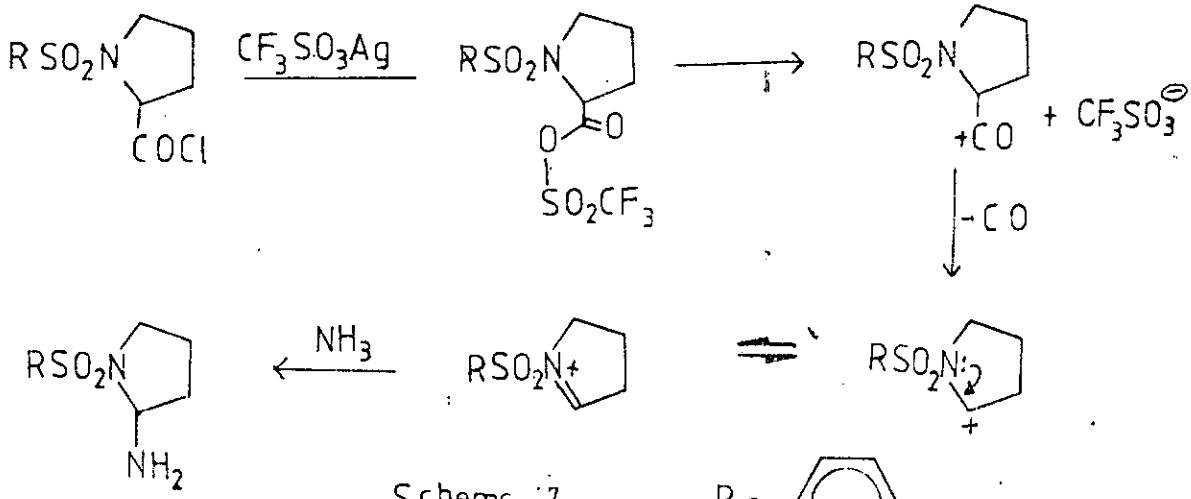
This synthetic route utilizes silver trifluoromethane-sulphonate as a Lewis acid in a triflate-assisted decarbonylation reaction of the N-(benzenesulphonyl)piperidine-2-carboxylic acid chlorides. Silver triflate has been previously used as acylating agent of aliphatic carboxylic acid chlorides by Effenberger and Epple[21]. A mixed anhydride is initially formed. This anhydride is only thermally stable in aromatic derivatives (can even be distilled) whereas the aliphatic mixed anhydrides are thermally unstable. They readily decarbonylate and decompose, losing carbon monoxide forming a carbonium ion:



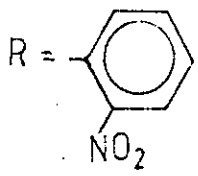
The aromatic derivative is stable because the above carbonium ion is not easily formed whereas the aliphatic mixed anhydride forms the carbonium ion easily as shown below:



Adesogan and Alo[15] exploited Effenberger and Epple's triflate-assisted decarbonylation reactions to generate endocyclic iminium salts from N-(benzenesulphonyl)α-amino acid chlorides. This reaction is based on the proximity of lone pair of electrons of the nitrogen adjacent to an ensuing carbonium ion. The resulting rearrangement leads to a loss of carbon monoxide and the generation of an iminium salt. See Scheme:



Scheme 7

R = 

The carbonium ion formation leading to a decarbonylation here is faster than in ordinary aliphatic mixed anhydrides. This is because the decomposition of the aliphatic mixed anhydride takes place with heat (40-80°C) while the decomposition of the mixed anhydride here takes place at room temperature without heat. This synthetic route had been utilized in preparing pyrrolobenzothiadiazines[15] and also for constructing substituted tricyclic benzothiadiazines[16] in high yields.

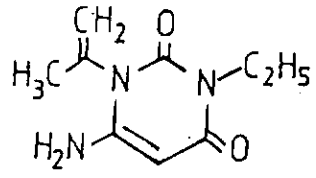
4.4. MEDICAL ACTIVITIES OF BENZOTHIADIAZINES

Excessive body fluid retention has been a physiological problem in humans and even more problematic in pregnant women. This problem is usually referred to as oedema. The oedemantous condition can be a causative agent for other medical problems like hypertension, heart failure; and diabetis.

The medical problem associated with fluid or electrolyte retention in the body has been known to be primarily due to retention of sodium ion in the body[22]. Therefore one of the most effective ways of reducing excess body water is to increase sodium ion excretion by the kidney thereby inducing a negative sodium balance, i.e. a state in which the sodium excreted is in excess of that which was taken in. It can also be treated by increasing the glumerular filtration or by potentiating a central thirst reducing factor.

A number of organic compounds have been utilized in the effort to to treat this unpleasant medical condition. These include the use of organomercurials[23], e.g. mersalyl which are very active in the removal of sodium and chloride ions from the body through an increase of urine quantity. However, these compounds have the disadvantages of being administered by intramuscular injection only and also the unsavoury deposition of mercury in the body. This usually leads to stomatitis, gastric disturbances and renal damage[24]. Thus, the use of organomercurials was discarded.

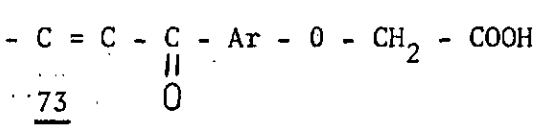
Pyrimidinediones were then found active against oedema. An example is 'mictine' - 1-allyl-3-ethyl-6-aminotetrahydropyrimidine-dione[22] 72.



72

The problem of intramuscular injection due to their insolubility still remained.

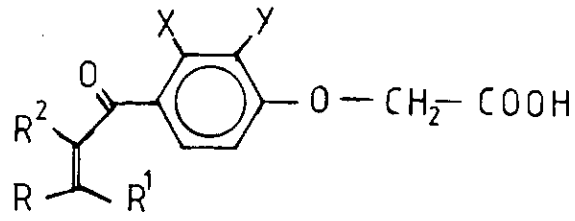
Another class of diureticsnamely $\alpha\beta$-unsaturated ketone derivatives of aryloxyacetic acids[25] having a general structure below evolved.



73

Ar = Phenyl, substituted phenyl or naphthyl.

The most active member of this class was ethacrynic acid 74a



74

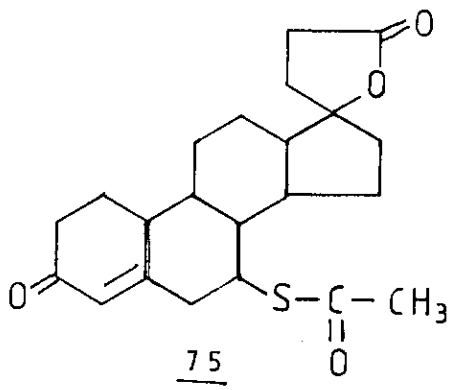
74a, $R = R^1 = H$, $R^2 = C_2H_5$; $X = Y = Cl$

b, $R = R_1 = H$, $R^2 = C_2H_5$; $X = Y = CH_3$

c, $R = R^1 = Y = H$; $R^2 = C_2H_5$, $X = Cl$

This class of diuretics were found to be overactive and caused undesirable side effects like hypokalemia and severe blood volume depletion or even hypotension.

Aldosterone antagonists like spironaloctone 75 were then developed.[26]

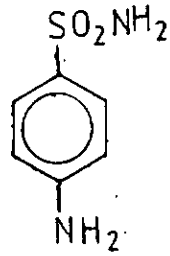


75

The steroid aldosterone initiates sodium reabsorption in the proximal part of the renal tubule. These compounds block the action of the steroid thereby causing diuresis. This group of diuretics were later found to have disturbing side effects particularly in men.

About 1940, it was observed that sulphonamides having an unsubstituted nitrogen were active as diuretics[8]. Their activity is derived from their acting as inhibitors of carbonic anhydrase. This enzyme system catalyses the conversion of carbon monoxide to carbonic acid in the body. Such metabolic process involved the utilization of hydrogen ions. However, conservation of hydrogen ions in the body allows the excretion of sodium causing a reduced retention of body fluids. Therefore the inhibition of this enzyme will result in an increase in the excretion of sodium, which will lead to diuresis or increase in urine flow.

These compounds however had the limitation of not being very potent even though their side effect were low. Some of the sulphonamides found active included sulphanilamide 76, and 2-acetamide-1,3,4-thiadiazole 77.



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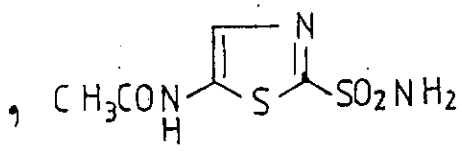
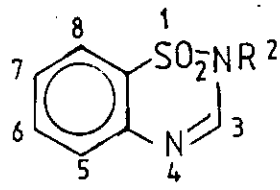


77

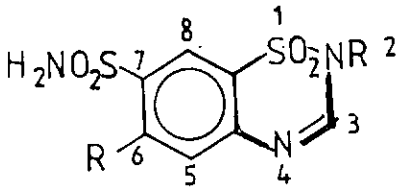
Efforts were then directed at improving the activity of the sulphonamides, since they did not show high toxicity. Heterocycles having the sulphonamide linkage were then suggested. This resulted in more potent compounds such as 1,2,4-benzothiadiazines (Thiazides) [28].



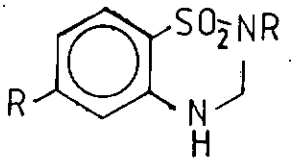
Thiazide

78

Evaluation of the biological activity of these bicyclic benzothiadiazines in dogs after oral or intravenous administration show that the sodium chloride or potassium excretion were increased. Structure activity relationship of the bicyclic benzothiadiazines show that a sulphonamido group is essential for any degree of diuretic activity. An additional sulphonamido group in the 7-position increases high activity. Other bioactivity increasing substituent includes the following: chlorine, bromine, trifluoromethyl and nitro groups, especially when present at position C-6 of the bicycle. Methyl, fluorine, methoxy and amino groups also potentiates the compounds but they are not as active as the earlier mentioned groups.



79

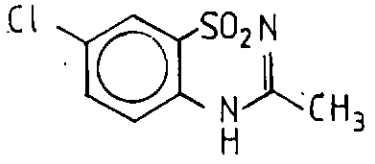


80

The conversion of unsaturated thiazides to the 3,4-dihydro-derivatives results in a ten-fold increase in potency[28]. An oxygen atom at position 3 depresses the activity of both the dihydro and 3-oxodihydro series of benzothiadiazines. Alkyl groups in the 3-position retain a high order of activity but 3-phenyl derivatives are less effective while any substitution on the nitrogen at position 4 results in lower activity.

When the 7-sulphonamido group was replaced with a methylsulphonyl group, there was little change in chemical and physical properties. However, the carbonic anhydrase inhibition and electrolyte excretion properties of the methylsulphonyl analogues are exc eedingly weak.

Effective antihypertensive agent in the bicyclic benzothiadiazines is found in the 7-chloro-3-methyl —1,2,4-benzothiadiazine -1,1-dioxide[4] 81.



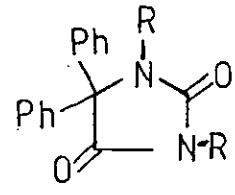
81

This compound is devoid of diuretic activity. Other biological activities of thiazides like antihypertensive action are achieved by reducing the blood pressure even in the presence of high body sodium levels[29]. This is possible because thiazides have been found

to potentiate ganglion blocking agents like reserpine and this action is independent of the effect of body electrolytes. This effect coupled with plasma volume reduction.

The anticonvulsant activity[30] of thiazides is related to their ability to inhibit the carbonic anhydrase in the brain. Although the drug had to be administered intraventricularly, it was effective.

Thiazides when used along with diphenylhydantoins potentiate the anti-eplileptic activity of the latter anti-epileptic drug[31].



diphenylhydantoin

82

The use of thiazides in the treatment of diabetis insipidus[32] is due to the decrease they cause in urine volume within six hours of administration. This is achieved by acting on a central thirst-reducing factor causing an increased glomerular filtration rate.

4.5. (BENZENESULPHONYL)TETRAHYDROPYRIDINIUM SALTS IN SYNTHESIS OF S-CONTAINING HETEROCYCLES

N-substituted tetrahydropiperidinium salts represented by structure 83 and 84 below, are made up of a six-membered azacycle with the nitrogen atom involved in double bond leading to a positive charge on the nitrogen.

83 84

R = Substituted benzene ring
= Substituted heteroaromatic ring
= Aliphatic chain.

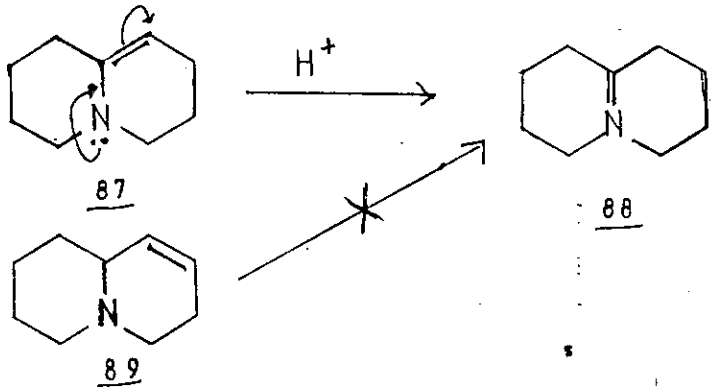
They belong to the general class of compounds called iminium salts which are well-known versatile synthetic intermediates. Iminium salts have a resonance structure represented by 85 and 86.

85 86

N.M.R. studies of iminium salts has shown that the positive charge is more resident on the nitrogen than on the carbon atom, therefore the equilibrum lies more to the left giving more of structure 85. The presence of a double bond in the α-position to the nitrogen atom leads to a very reactive grouping that is quite different from an ordinary aliphatic unsaturated amine in which the double bond is isolated from the nitrogen atom by at least one saturated carbon atom. The latter amine will be an olefinic

amine and will show only properties of amines and/or olefins. Their reactions will be devoid of the reactivity of the iminium salts.

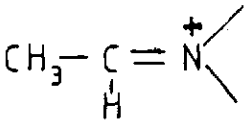
Unsaturated amines can be transformed into an iminium salt if the double bond is located $\alpha\beta$ to the nitrogen. Such transformations are not possible where the unsaturation is further away from the nitrogen:



87 88 89

Iminium salts possesses an extremely electrophilic carbon which is susceptible to attack at the α-carbon atom. These α-carbons are similar in reactivity to those of carbonyl carbon atoms. This reactivity of iminium salts make them versatile synthetic tools, because they readily undergo nucleophilic addition for example with amines[15], organometallic compounds[33], intermolecular trappings of aromatic or heteroaromatic compounds resulting in cyclisation[34], cycloaddition[35] and other miscellaneous reactions which will be discussed later.

There are saturated and aromatic iminium salts[36]. The saturated salts may be a straight chain or cyclic iminium salts in which there are no aromatic rings.



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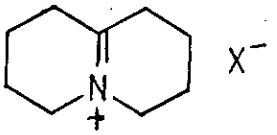
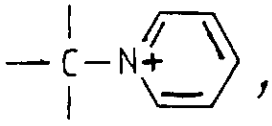
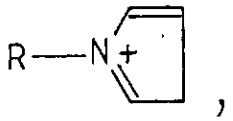
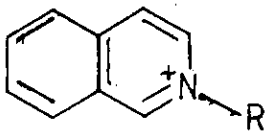


91

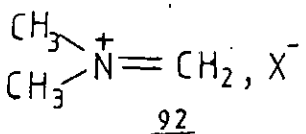
The aromatic iminium salts involve aromatic rings that contain nitrogen. They behave a little different from the saturated salts. These are not dealt with in this review.





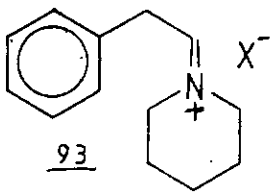


Different types of saturated iminium salts had been synthesised. They fall into the following categories: straight-chain and cyclic iminium. The cyclic examples can further be subdivided into exocyclic and endocyclic iminium salts. The former class have their double bond outside the ring while the latter have their double bond within the ring.



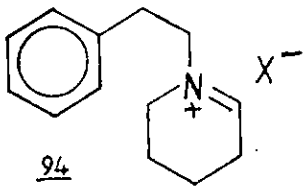
92

Straight-Chain



93

exocyclic



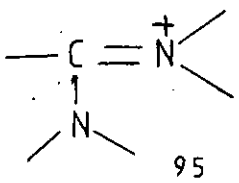
94

Endocyclic salt

Iminium salts are stabilized by different types of anions: These include inorganic ions like the halides (F^-, Cl^-, Br^-, I^-), perchlorate ClO_4^-, Nitrate, NO_3^-, $SnCl_6^-$, hexachloro antimony, $SbCl_6^-$, PF_6^-, BF_4^-, etc. or organic anions like picrates, acetates, or trifluoroacetates, CF_3COO^-, and trifluoromethane-sulphonates[37].

Heteroiminium Salts

These are iminium salts in which the α-carbon is attached to other heteroatom instead of carbon[38] which include N, O, S.



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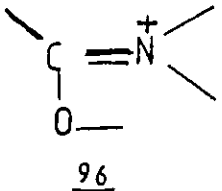

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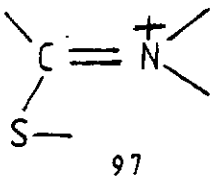
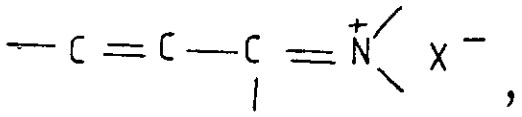


97

There can also be vinyl iminium salts or halogen substituted:



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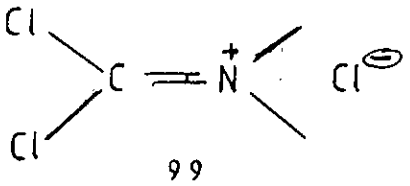
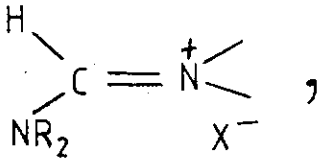


99

Examples of heteroiminium salts are:



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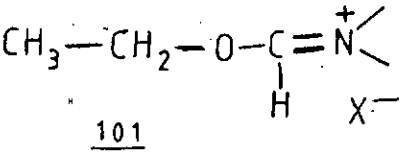

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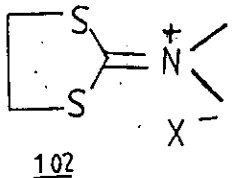

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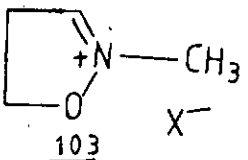
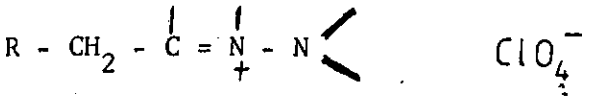


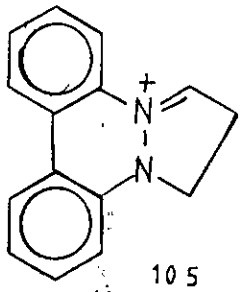
103

The nitrogen atom of the salt can also be attached to the heteroatom, examples include:

Nitrogen



hydrazonium salt



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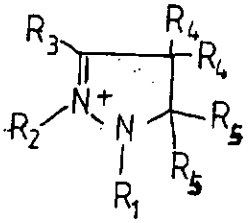
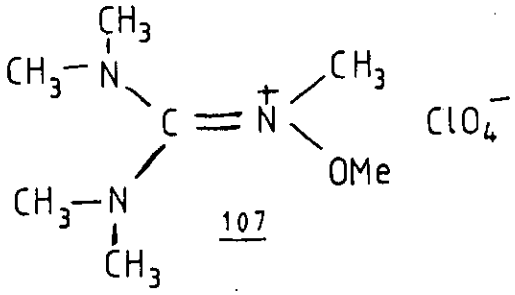


106

Oximinium Salt



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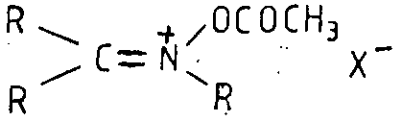
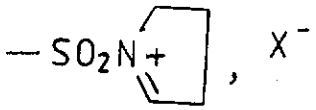


108

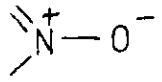
Sulphur-Containing iminium Salts

No name was found for this class and no examples were found in the literature except the compound reported by Adesogan and Alo[15] below.

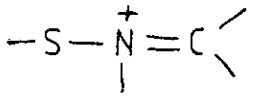


This may be classed as a thioamidonium salt.

In all these cases the other heteroatom should be neutral, because if it is charged, then the salt becomes a ylide e.g. azomethine ylide and nitrones.

e.g. 

Incidentally, sulphur atom in the sulphur analogues must necessarily be a neutral sulphur.

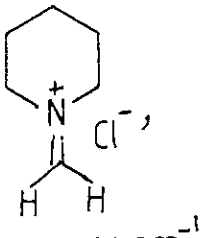


N-Substituted tetrahydropyridinium salts

Electronic Properties

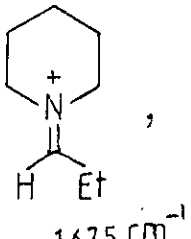
Electronic properties of N-substituted tetrahydro piperidinium salts have been studied with the aid of infra-red and NMR spectroscopy.

The infra-red spectrum of a typical tetrahydropiperidinium salt shows that the functionality absorbs strongly at Vmax 1666 - 1675 cm^{-1} depending on the stabilizing anion and the medium of analysis.



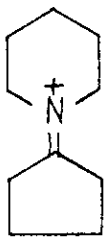
1666 cm^{-1} Mull[36]

109



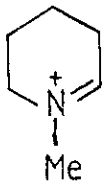
1675 cm^{-1} KBr[36]

110



111

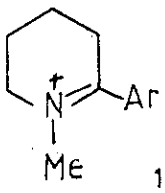
	V_{max} in cm^{-1}
ClO_4^-	- 1698 mull[39]
$SnCl_6^-$	- 1644 KBr[40]
NO_3^-	- 1691 KBr[40]
$SbCl_6^-$	- 1670 KBr[40]



ClO_4

1686 cm^{-1} (Nujol)[37]

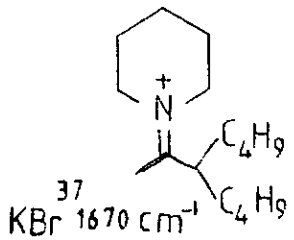
112



Picrate$^{\ominus}$

1630 cm^{-1} (Nujol)[37]

113



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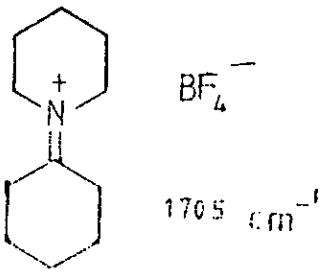
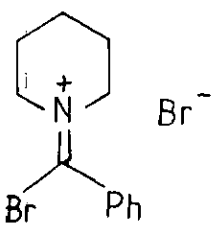


115

From the above examples, it is clear that the characteristic absorptions of N-substituted tetrahydropiperidinium salts in the infra-red spectrum lie between 1615 - 1705 cm^{-1}, and it is dependent mainly on the particular anion stabilizing the cation. This absorption is due to the $\rangle C{=}\overset{+}{N}\langle$ stretching which is typically at 1680 cm^{-1}. This is lower than the aliphatic amine stretching which normally appears in this region.

The stabilizing anion is also important in interpreting the IR spectra. It has been found that BF_4^- shifted the position of absorption of the iminium salts higher to over 1700 cm^{-1}. Other anions are not known to affect the wave number so drastically. Some exocyclic piperidinium salts have varying wave numbers as the anion changes.

Halogens are known to depress the λ_{max} of iminium salts to about 1590 - 1650 cm^{-1}, whenever they are present as anions or when they are substituents on the α- carbon[37,42], e.g.

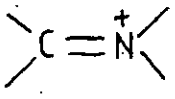


116

The frequency lowering here is due partially to the mass effect and the weakening of the double bond by the electron donating effect of the halogen. When double bonds are conjugated to the iminium salt there is virtually no change in the absorption frequency.

N.M.R. spectroscopy has become an important tool for studying iminium salts. Various N.M.R. experiments including those from ^{1}H-NMR, ^{13}C-NMR and ^{15}N-NMR assist to present different aspects of iminium salts that give complementary information to other physical methods.

<u>^{1}H-NMR</u> - Iminium salts present two types of functions: the carbonium ion and the $\rangle\!=\!\overset{+}{\mathrm{N}}\!\langle$ When the NMR of the two components were compared, the NMR signals of compounds containing these functions, i.e. $\rangle\!=\!\overset{+}{\mathrm{N}}\!\langle$ and tertiary carbonium ion represented by the proton next to the isopropyl cation, it was found that the isopropyl cation's hydrogen signals appears at δ13.0; whereas iminium ion's α-carbon hydrogen appeared between δ 7.5 - 10.0. Thus, the $\rangle\!=\!\overset{+}{\mathrm{N}}\!\langle$ ion has less positive charge compared with the positive charge on the carbonium ion. This indicates that the positive charge is more resident on the nitrogen than on the carbon atom.



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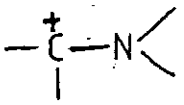
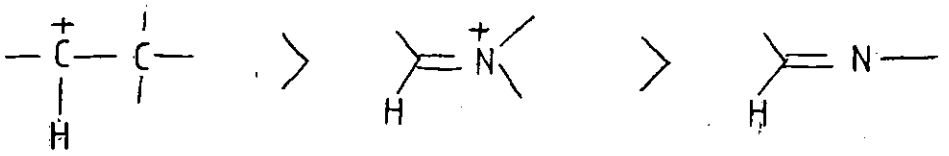


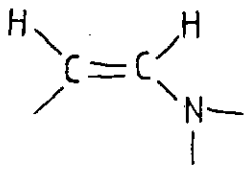
118

The proton on the α- carbon of an iminium salt behaves like an aldehydic proton in NMR as such protons absorb at δ 7.5-10.0, while aldehydic protons normally absorb at δ 10.0. On comparing the α- carbon protons of imines and iminium salts, it has been found that the protonation of the imine's nitrogen to form

iminium salt provides a deshielding effect of the ∝- carbon proton here and consequently a shift to lower frequencies[34].

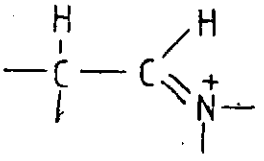


'H-NMR has also been used to compare enamine protons with that of iminium salts.



enamine

122



iminium ions

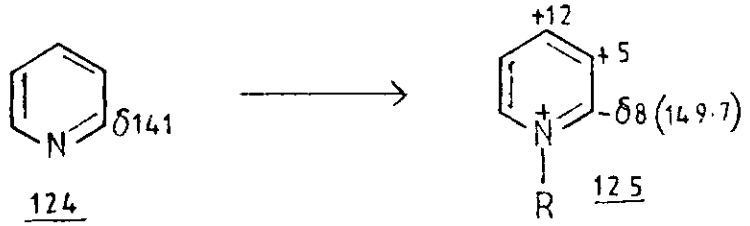
123

The hydrogens of iminium salts absorb at a higher frequency than that of enamines because the electron cloud shielding the latter protons are reduced as soon as a positively charged nitrogen atom is formed. This makes the electron on the nitrogen unavailable for any shielding effect.

^{13}C-NMR - spectroscopy can be used in studying N-substituted iminium salts. On comparing the ^{13}C-N.M.R. of carbonium ions[43] and the positive α - carbon of iminium salts, it is clear that the α - carbon of iminium salts is less positive compared to that of carbonium ions. The absorption of a typical carbonium ion is at δ317.5 while that of the α - carbon of an iminium salt is between δ130 - 180. These data complement those of the 'H-NMR which indicate that the positive ion on the α - carbon of an iminium salt is not very pronounced.

In ^{13}C-NMR of pyridinium salts, the protonation creates reduction in the electrons available and therefore the pyridinium salt carbons shifts upfield due to a reduction in the paramagnetic contribution. Such paramagnetic contribution are important in ^{13}C-NMR.

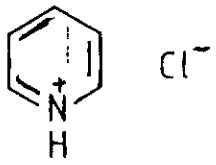
In pyridine, the protonated α- carbon signal moves upfield by about - δ8.0, while the β and γ - carbon signals move downfield by δ5.0 and δ12 respectively. Thus, the latter carbons are not affected.



124 125

Therefore, when iminium salts are formed, there should be a shift upfield in ^{13}C NMR signals of the carbons of the compound.

^{15}N-NMR[36]. The change in the ^{15}N-NMR spectrum on the formation of pyridinium salts from unprotonated pyridines is very pronounced. For example, the ^{15}N absorption for unprotonated pyridine will move by about 113 ppm on protonation using concentrated hydrochloric acid as solvent.



125

Neutral*	Protonated**	Solvent
292	169	TFA
297	178	cc HCl
286	179	cc HCl
297	184	MeOH

* - neat

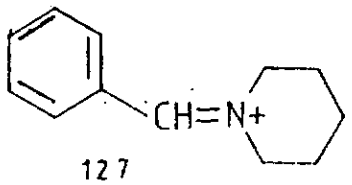
* - ppm relative to NH_4^+ (CH_3NO_2) = 354 ppm.

This shows that ^{15}N-NMR analysis is an excellent indicator of iminium salt formation. The use of this analytical tool is even more powerful when it is considered that most other nitrogen compounds like nitroso, nitrate and azide which do not absorb in this region.

Ultraviolet spectroscopy[40]

The use of ultraviolet spectroscopy in iminium salt characterisation analysis is not very important except in situations in which iminium salt is formed by compounds having conjugated double bonds. Simple iminium salts absorb at 219 nm in n-hexane ϵ = 5 - 5,000. However, if the iminium salt is within a highly conjugated system, then the λ_{max} will show a bathochromic shift to ~242.5 or 336.5 nm[44, 45].

e.g.



127

λ_{max} = 275nm
ϵ = 6 – 10,000

When iminium salt are derived from enamines, there is no significant change in it's λ max.

Mass Spectrum

Mass spectroscopy has not been a useful method of analysis of iminium salts as

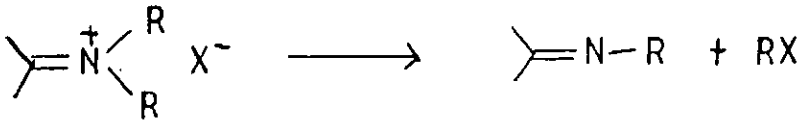
(i) the analysis is usually obtained by heating the specimen to vapour state before electron impact ionisation, field ionisation or field desorption techniques are applied.

(ii) It is also known that iminium salts usually make up a proportion of fragment ions obtained in the mass spectrum of nitrogen containing compounds.

As these samples are heated up before ionisation takes place, the mass spectra of the ions obtained are not usually those of the iminium salts alone. Other species formed by the salt via any of three different mechanisms[46] do occur. The mechanisms are:

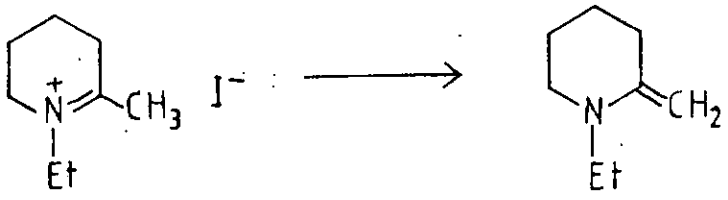
(a) Thermal elimination:

When iminium salts are heated and the anion or one of the components on the nitrogen is eliminated to leave an imine.



(b) β-Elimination

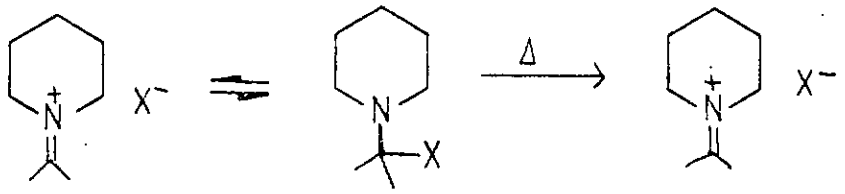
Where imines cannot be formed, a α-elimination process may take place[47].



The expected iminium salt m/e is not observed.

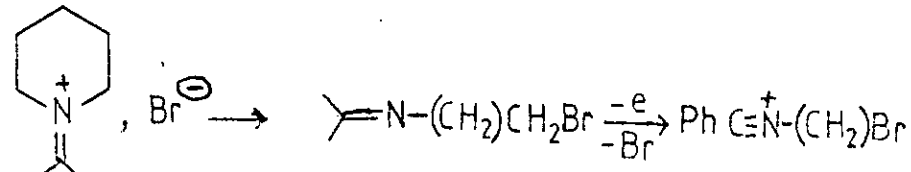
(c) Anion rearrangement

(i) If the anion is a good nucleophile, it could attack the iminium salt. On heating the adduct the parent iminium salt is regenerated:



132 133 132

(ii) The nucleophile anion may attack the sp^3 carbon in the α- position of the nitrogen leading to ring opening or other rearrangements as shown below[43].



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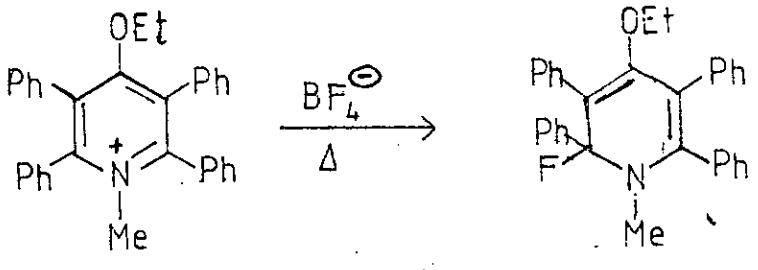
(iii) If BF_4^- is the anion, the thermal degradation of this provides an F^- which may attack the iminium salt and cause rearrangements.

$$BF_4^- \longrightarrow BF_3 + F^-$$



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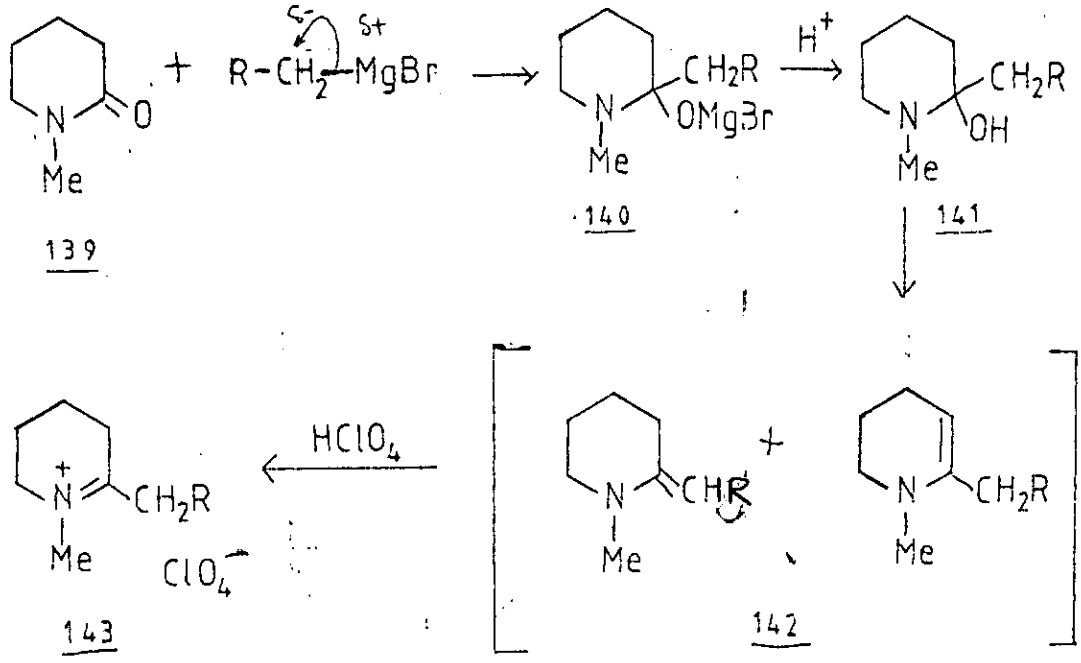
Of all the spectroscopic methods available, therefore, it seems that infra-red and NMR techniques are the most amenable and suitable for the detection, characterisation and or analysis of iminium salts.

4.6. Generation of N-Substituted Tetrahydropyridinium Salts:

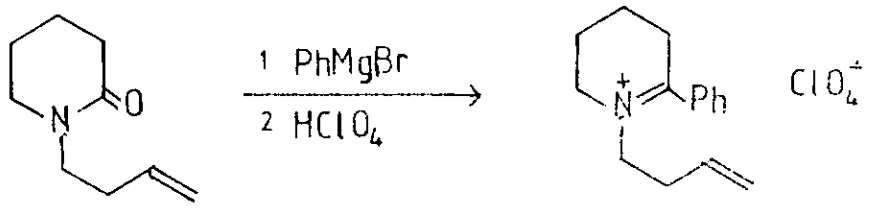
N-substituted tetrahydropyridinium salts have been known to be formed by various methods. Some of these are unique in their procedures, while many others are general methods. These, inter alia, include:

(1) Addition to Amides:

Leonard and Hay[49] in 1955, extended a method for generating aliphatic iminium salt to cyclic analogues Addition of Grignard reagent (alkylmagnessium halides) to N-methyl-2-piperidone followed by acid hydrolysis, gave two enamines which eventually gave an endocyclic iminium salt.



Martin et. al. has recently[50] further exemplified this method with the reaction of phenyl magnesium bromide with an N-alkylpiperidone followed by perchloric acid work-up to obtain excellent yields of an iminium salt:

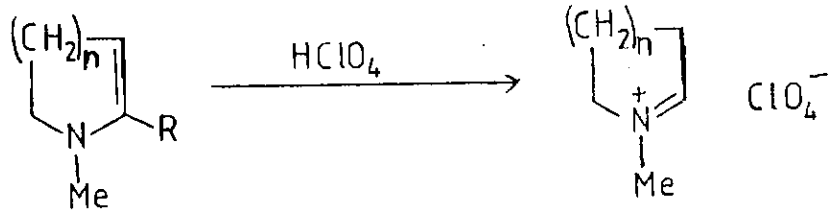


(2) From Enamines

The commonest method of obtaining iminium salt is by enamine transformations. This is achieved by a variety of ways. The reactions, however, generally occur by an addition reaction in which a H^+ adds to the β-carbon of the enamine to form an iminium salt. Some example follow:

(a) Treatment of the enamines with acids[51].

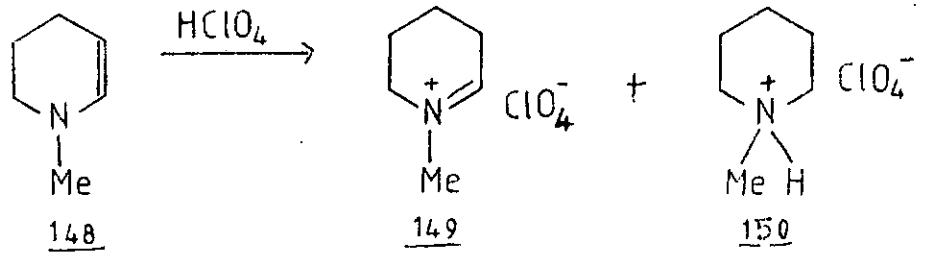
Five or six membered ring iminium salt could be formed by treatment of the appropriate enamine with perchloric acid. The perchlorate ion serves as a good stabilizing anion for the salt generated:



146 147

R = Alkyl.
n = 1, or 2

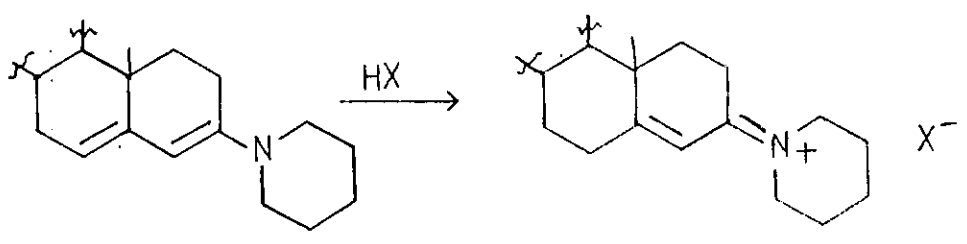
When the enamines are not substituted in position 2, there is a possibility of quartenary ammonium perchlorate[37] being formed in addition to the iminium salt:



148 149 150

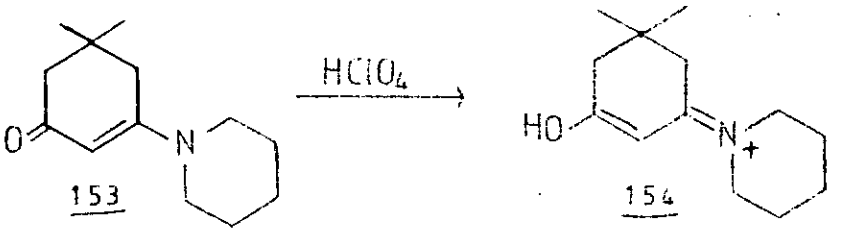
This arises because the mechanism of the reaction suggests that the ammonium salts is first formed before the iminium salt is eventually generated from the former.[37] Some enamines form the iminium salt directly without going through an ammonium salt especially if the acid used is an organic acid, although action of mineral acids also leads to iminium salt[52].

When other groups are conjugated to the enamine double bond, then the group could be involved in the ensuing reaction. For example, when a double bond is conjugated to the enamine, then the salt is formed with a shift of the double bond such that the olefin is conjugated with the iminium salt functionality[53].



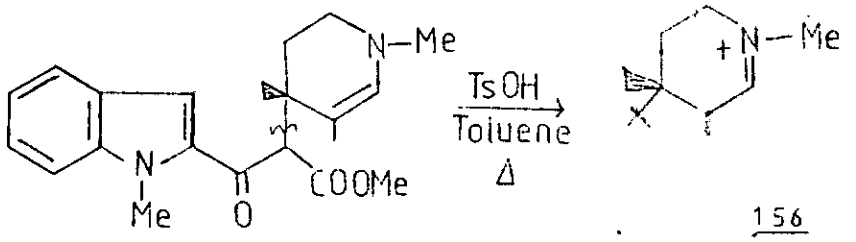
151 152

If the conjugated group is a carbonyl group, it enolises and remains in conjugation with the iminium ion formed. For example, 5,5-dimethyl-3-piperidino-2-cyclo hexenone on protonation gave 154.



153 154

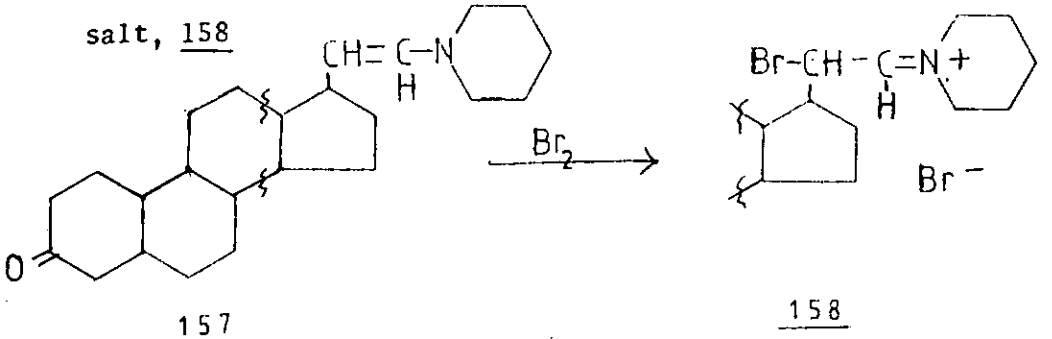
Dehydrating agents[54] like toluenesulphonic acid thermally reacts with enamines to give iminium salts.



155 156

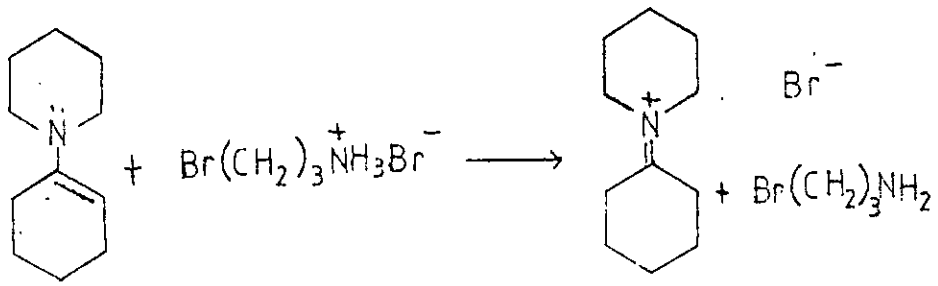
If the enamine's double bond in 155 were exocyclic to the cyclic tertiary amine, an iminium salt would be obtained[55].

(b) By reaction of enamine with other reagents[56], Bromine adds to the double bond of the enamine: 2,2-(piperidyl) bis nor - 4,20(22)choladien-3-one 157 to form an iminium salt, 158

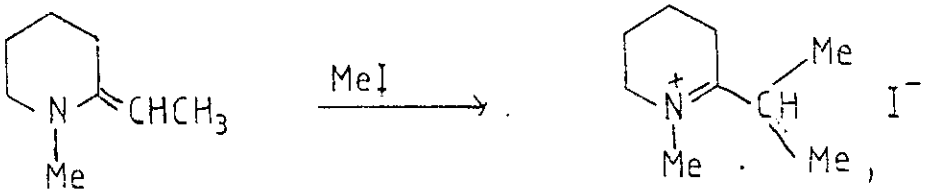


157 158

Percel[57] reacted N-piperidino-1-cyclohexene with 3-bromoaminopropyl bromide to form an exocyclic salt. The salt must be isolated or amine by-product will react to give an iminium salt.

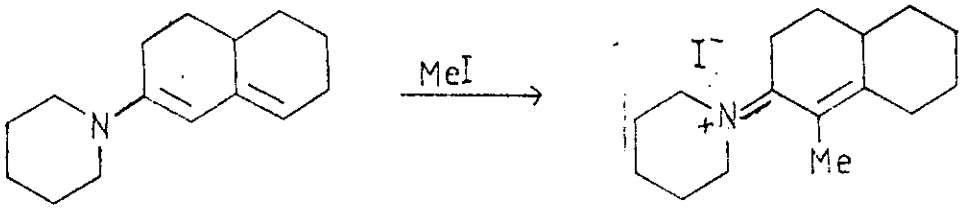


Methyl iodide addition to 1-methyl-2-ethylidenepiperidine[58] gave an iminium salt.



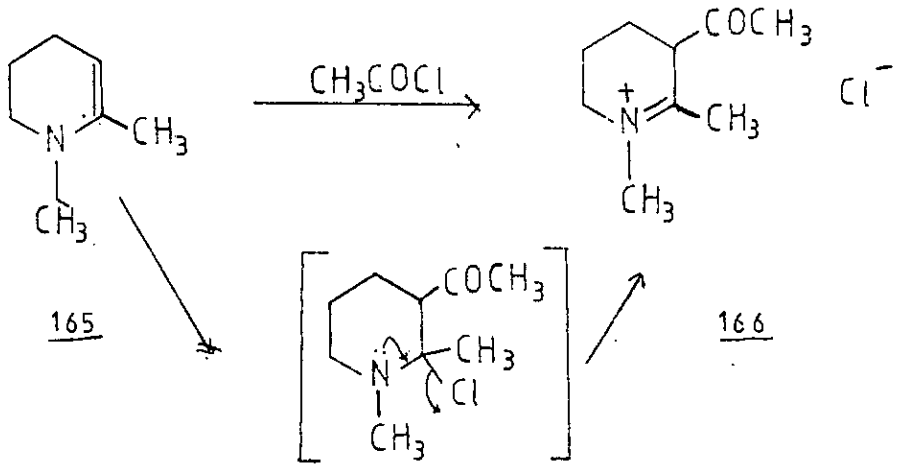
161 162

The unsaturated enamine below can be alkylated at C-2 position with methyl iodide to give a substituted iminium salt[59].



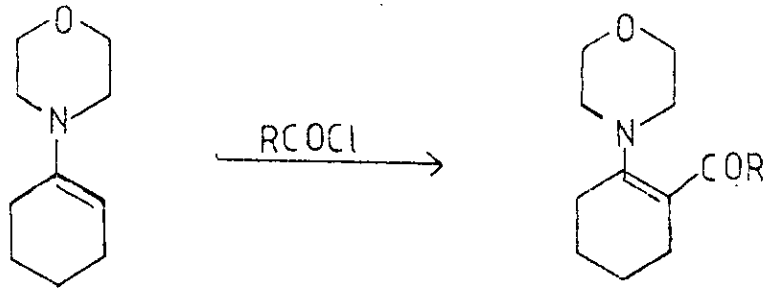
163 164

1,2-dimethyl- Δ^2-piperidine reacts with acetyl chloride to form an iminium salt[60].



165 166

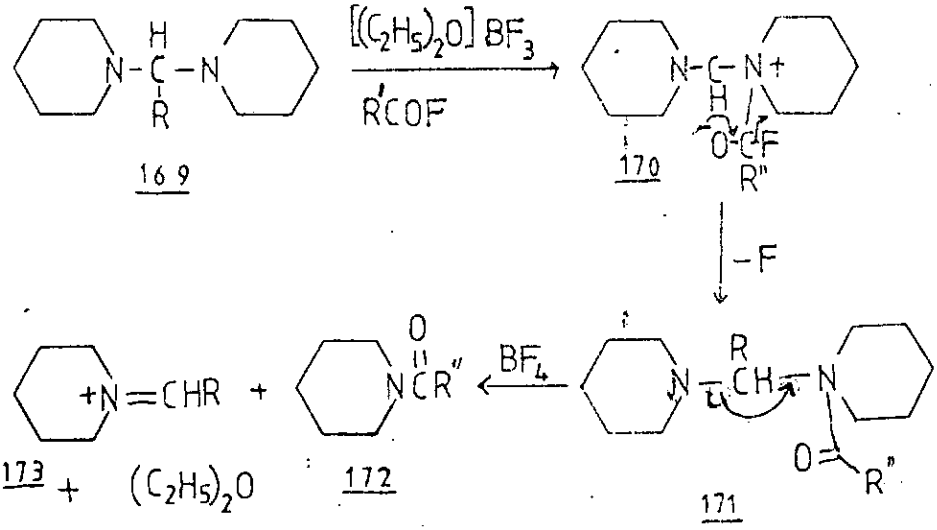
With morpholine enamine, however, the corresponding iminium salt is not formed.



167 168

3. Iminium salts through Aminals[61]

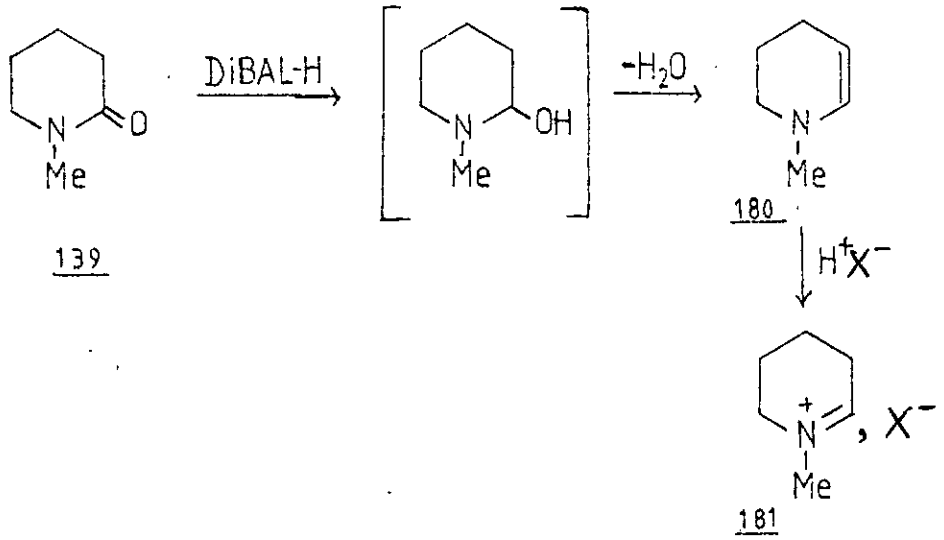
When aminals are treated with chlorine, they yield iminium salts. Same result is also obtained with carboxylic acid chloride.



169 170 171 172 173

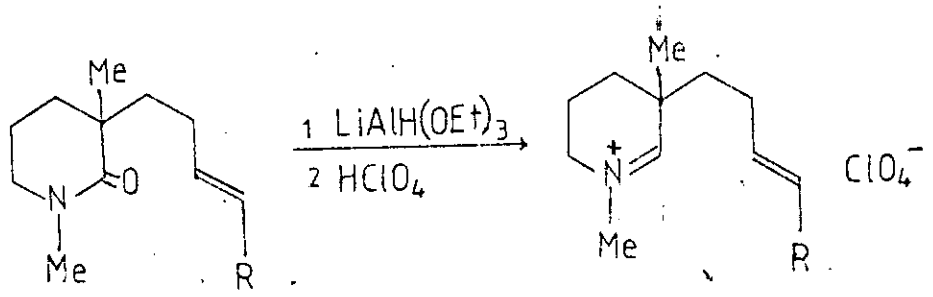
4. Reduction of Lactams:

Bohmann et. al.[62] used the reduction of lactams with disobutyl aluminium hydride (DIBAL-H) as a method for the formation of iminium salt and enamines:



139 180 181

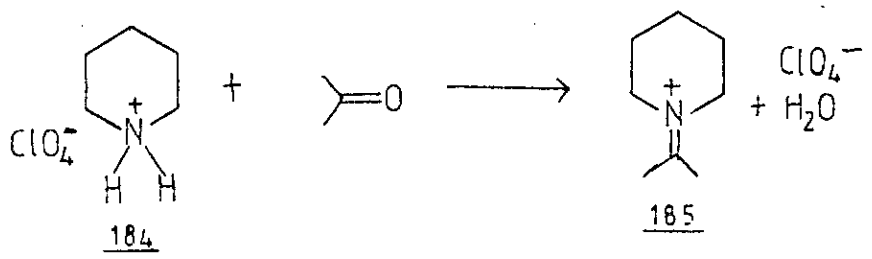
Similarly, lactams were also reduced by Martin et al[50] with lithium aluminium hydride trietherate as reducing agent, in the presence of perchloric acid to give endocyclic iminium perchlorates.



182 183

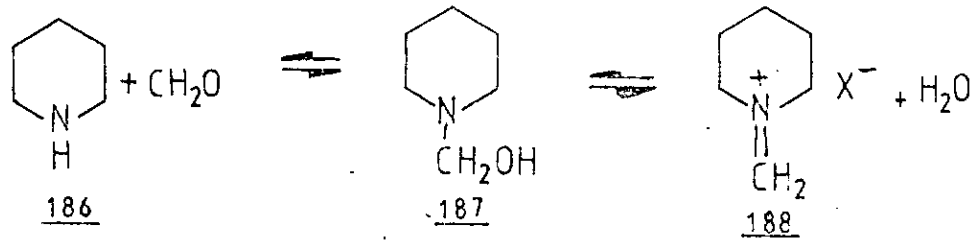
5. Condensation of amines with carbonyl compounds:

Leonard et. al.[63] condensed acetone with piperidine perchlorate in ethanol to give crystalline N-isopropyllidine piperidinium perchlorate in a few seconds and in good yields.



184 185

Iminium salt can also be generated by condensation of formaldehyde with piperidine followed by protonation:

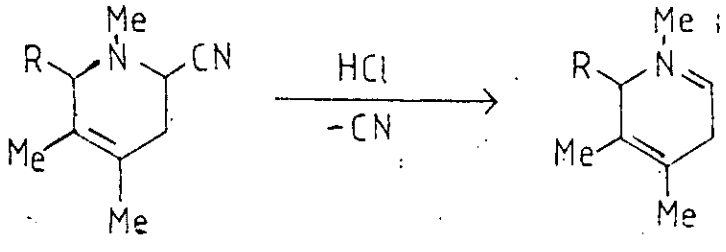


186 187 188

This iminium salt 188 is an intermediate in the Escheweiler-Clerk reaction used in alkylation of amines.

6. Elimination of Cyano groups:

Fry[64] used elimination of cyano groups from N-methylsubstituted piperidine rings to form iminium salts.

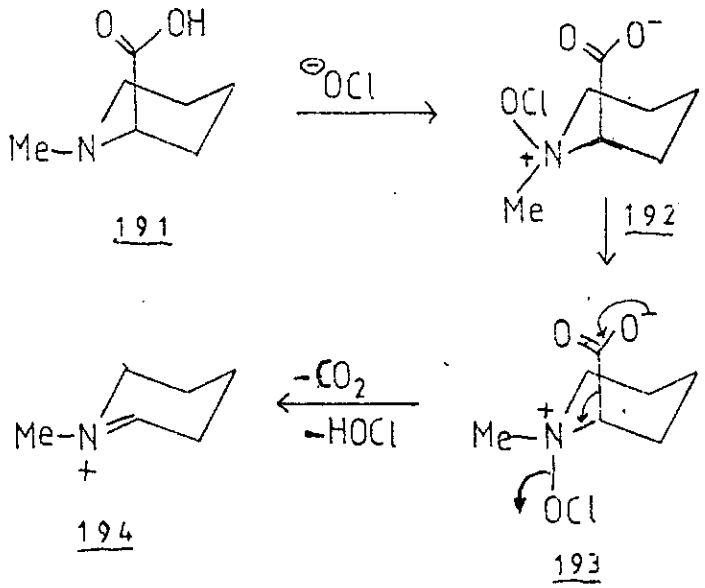


189 190

When the tetrahydropyridine nitrile 189 was treated with hot hydrochloric acid, the cyano group was eliminated and a dihydropyridinium salt 190 was obtained.

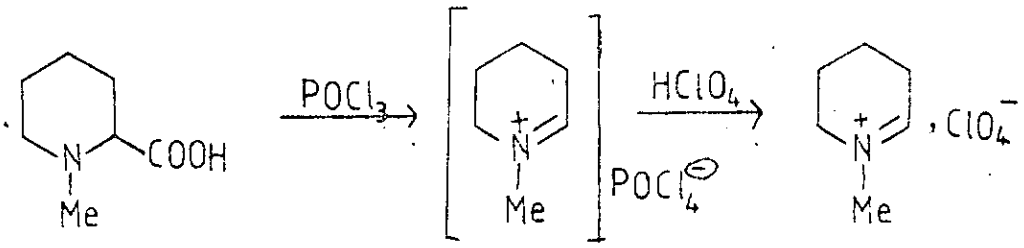
7. Hypohalite-induced decarbonylation of α-amino acids:

Hypohalite-induced decarbonylation of α-amino acids is also a source of tetrahydropyrolidinium salts as reported by Van-Tamelen, et al.[65]. The salt was obtained by reacting two equivalents of the hypohalite with N-methyl-2-pipecolinic acid and effective decarbonylation was obtained.

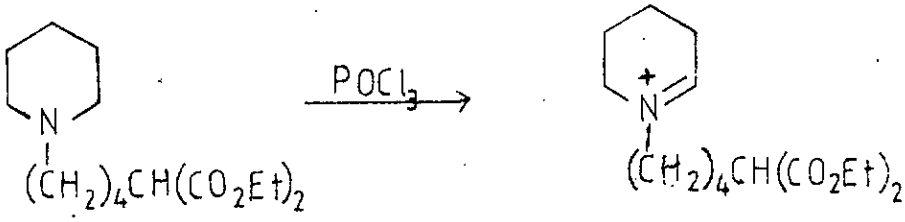


8. Phosphorous oxychloride-induced decarboxylations

Rapoport et. al.[66] in 1976 reported the exploitation of the well known thermal instability of α-tertiary amino acid chlorides for the formation of iminium salts. This was done by thermally decarbonylating α-tertiary amino acids with $POCl_3$, $POCl_2$ or $POPhCl_2$ to give tetrahydropyridinium salt regiospecifically and in high yields.

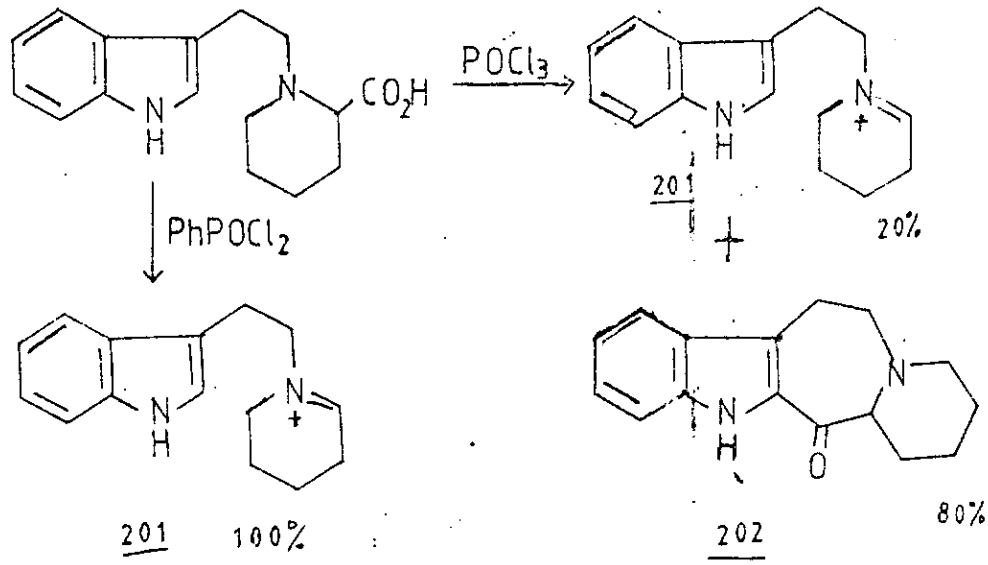


195 196 197



198 199

In some cases, the ∝-amino acid might give a mixture of products with $POCl_3$ due to the low boiling point of $POCl_3$. In such cases, phenyl phosphoric dichloride $POPhCl_2$[67] was used instead. Also the dichloride is used to prevent the formation of amino acylation side reactions.

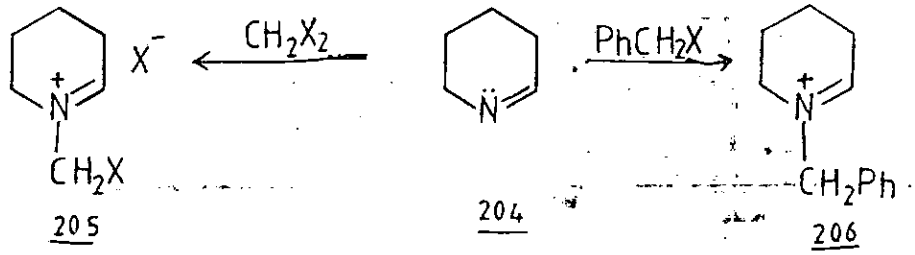


201 100% 201 + 20% 202 80%

The regiospecificity of the iminium salt formation in these cases is made possible because the position of the carboxylic acid group determines the location of the double bond in the iminium salts unambiguously.

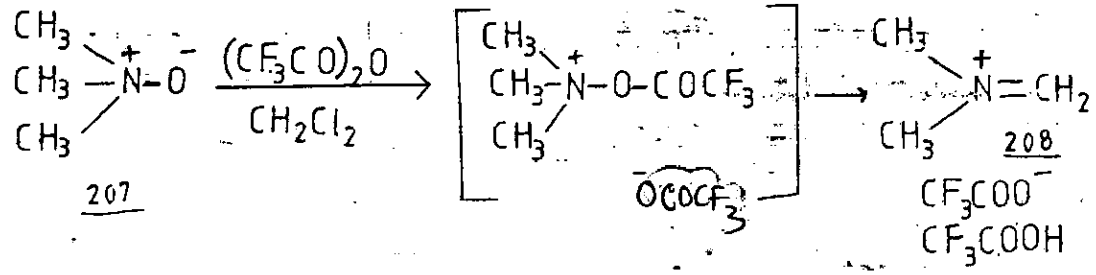
9. Alkylation of imine:

Shono et. al.[68] obtained tetrahydropyridinium salts by treatment of dihalogeno alkyl or benzylhalides with imines before electroreductions leading to the iminium salts:



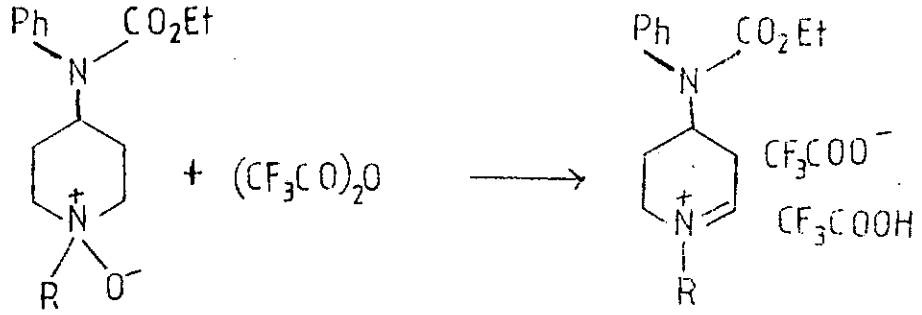
205 204 206

10. Ahond et. al.[69] using a modified Polonovski reaction converted trimethylamine oxide to N,N-dimethylformaldinium trifluoroacetate in dichloromethane, to obtain iminium salt.



207 208

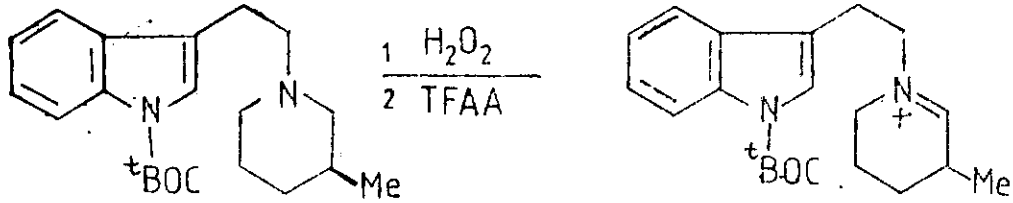
Essawi and Portoghese[70] in 1983 extended this method to piperidines when they obtained substituted tetrahydropiperidinium salts from the corresponding N-oxides:



209 200

R = Me, $PhCH_2$-, $PhCH_2CH_2$-

Jokela and Lounasmaa[71] extended this method to substituted indoles which on hydrogen peroxide treatment gave iminium salts:



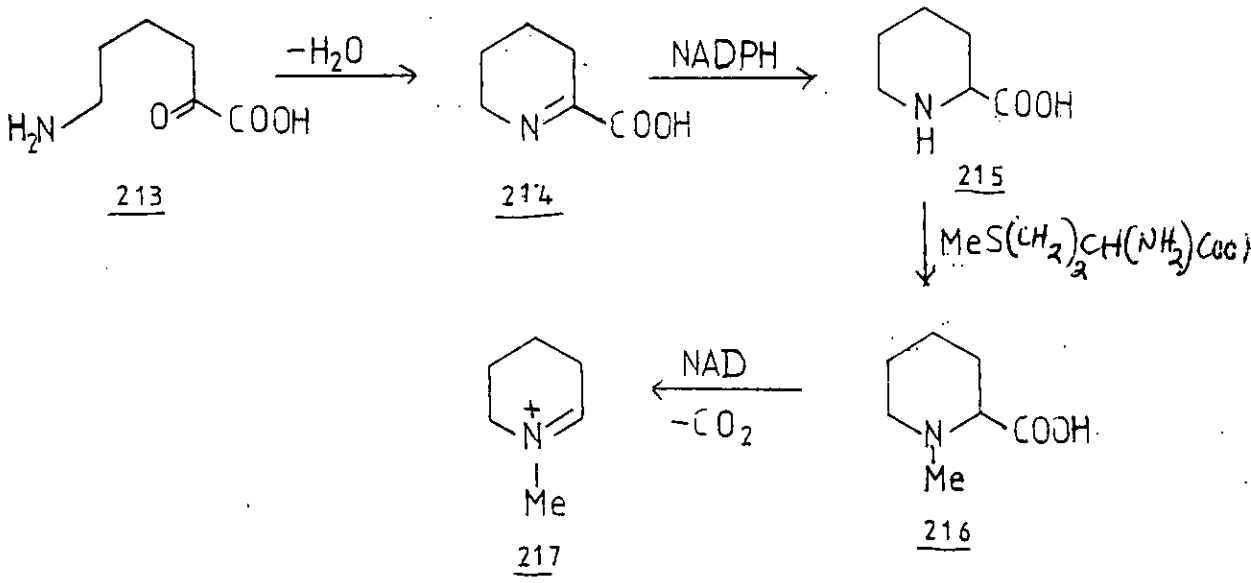
211 212

It is observed that in general, if the amine oxide is cyclic, the iminium salt obtained is always endocyclic. No exocyclic iminium salts are isolated. When the amine is aliphatic as with Ahond et. al.[69] more than one iminium salts are formed.

Biosynthesis of naturally-occurring N-tetrahydro pyridinium salts

When N-substituted tetrahydropyridinium salts occur in nature[72], the possible biosynthesis is presumed to commence from dehydration of the lysine derived compound 213. Protonation of 214 by NADPH gives L-Piperidine-2-carbboxylic acid.

in biosynthesis) followed by NAD-mediated decarboxylation gives the piperidinium salt:



213 214 215 216 217

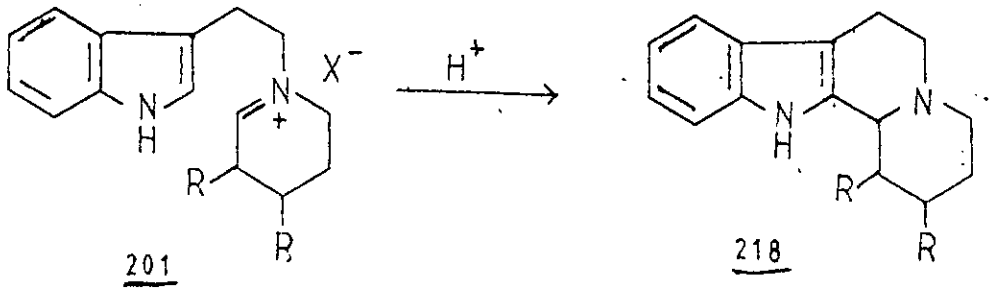
4.7. Synthetic applications of N-substituted tetrahydro pyridinium salts

The synthetic applications of iminium salts depend largely on their ability to undergo electrophilic additions. Some of the synthetically useful transformations these salts undergo are the followings:

(a) Heterocyclisation reactions

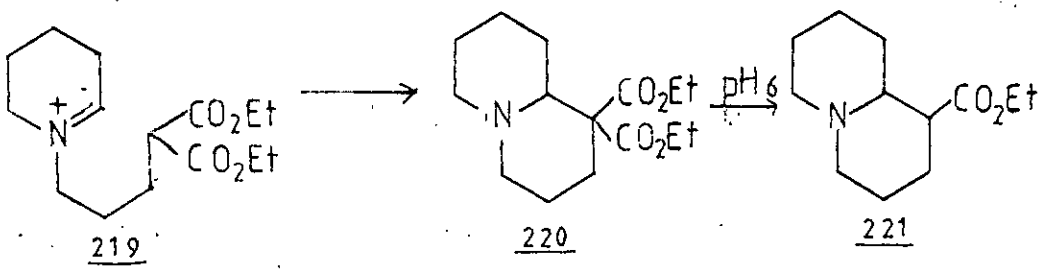
Iminium salts have been applied in cyclocondensation reactions of organic compounds leading to important natural and synthetic products. In many cases the cyclisation occur with an intermolecular trapping of an aromatic or hetero-aromatic ring which usually leads to the formation of six membered rings.

Chevolot et. al. in 1976[73] used iminium salts obtained by the action of trifluoromethylacetic anhydride on N-oxide compound, e.g. 201 to obtain the corresponding substituted indole alkaloid skeleton.



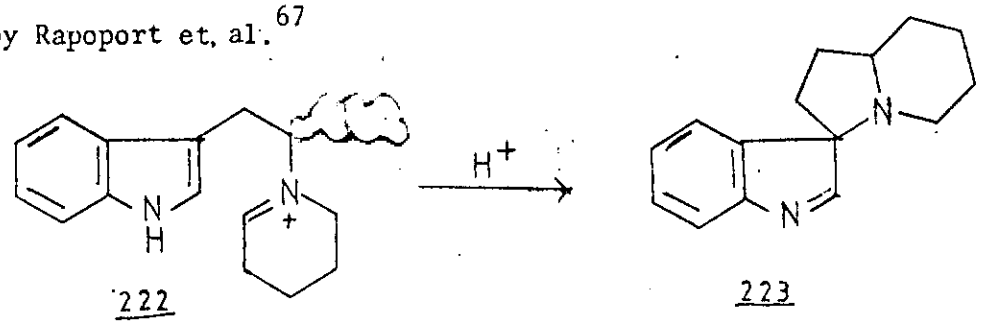
201 218

1-Azabicyclo-4.4.0-quinolizidine was synthesised by Rapoport et. al. [66,74] using N-substituted piperidinium salts:



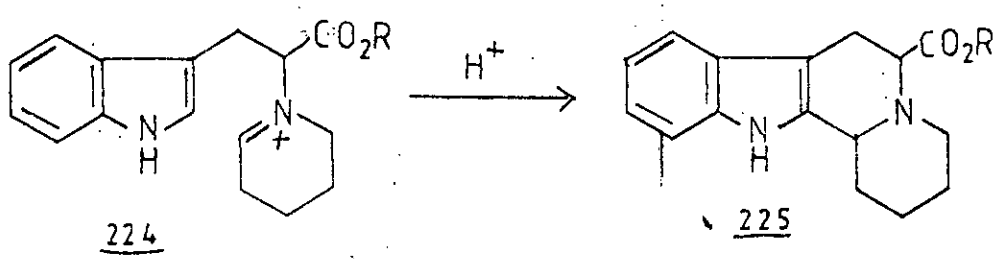
219 220 221

Similarly, iminium Salts were used in the construction of some indoles by Van-Tamalen and Poitier[65] in 1968. The defects of their synthetic procedures was improved upon by Rapoport et. al.[67]



222 223

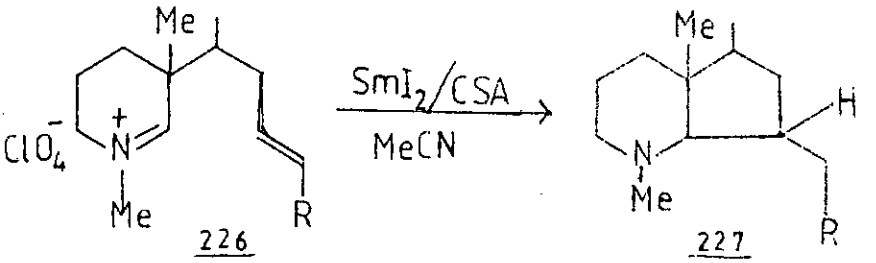
When the other α-carbon is substituted the course of the cyclisation is altered.



224 225

Substituted indoloquinolizine

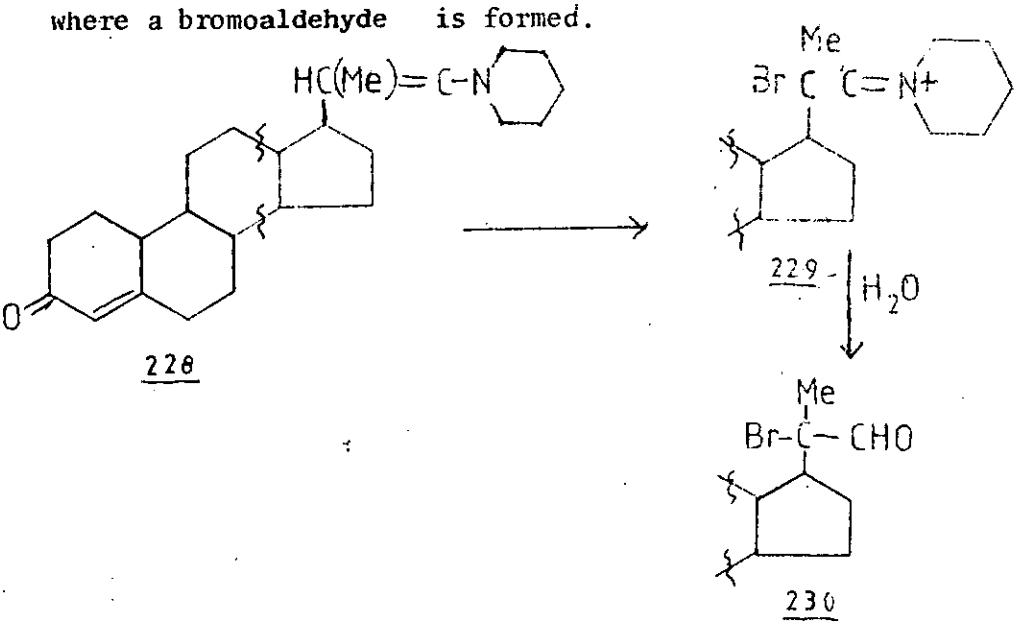
Lanthanide metals may mediate in the heterocyclisation of some iminium salts for example: samarium diiodide in anhydrous acetonitrile in presence of camphor sulphonic acid (CSA) gave the heterocycle 227 in 78%[50].



226 227

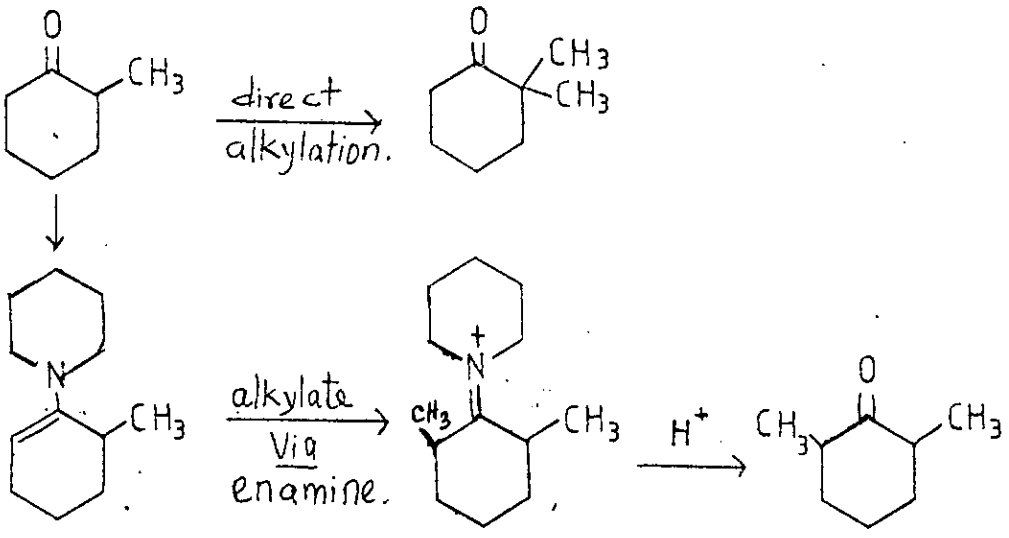
(b) Preparation of Substituted Ketone and aldehydes

Hydrolysis of iminium salts leads to the formation of carbonyl compounds: e.g. 3-oxo-20-bromobis nor-4-chlor-2-al[56] where a bromoaldehyde is formed.



228 230

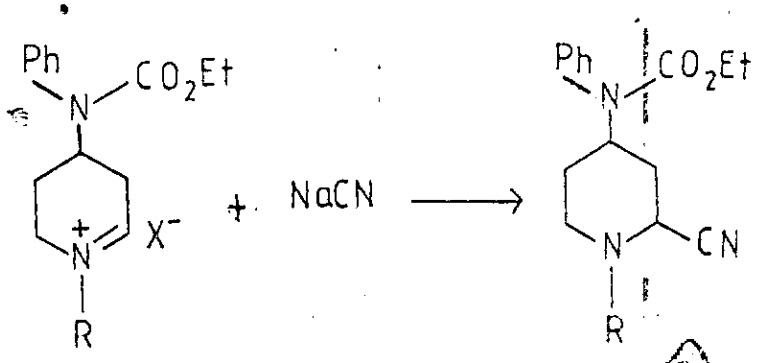
The use of iminium salts in the formation of α,α-disubstituted aldehydes and ketones enjoys some advantage over direct alkylation procedures[75]. Successful synthesis of 2,6-dimethylcyclohexanone is achieved through iminium salts only. Direct alkylation gives 2,2-dimethyl cyclohexanone preferentially as in the scheme below:



In direct alkylation, the most substituted carbon is always preferentially obtained, while in alkylation via iminium salts, the least substituted position is alkylated.

(c) Cyanation leading to organic nitriles

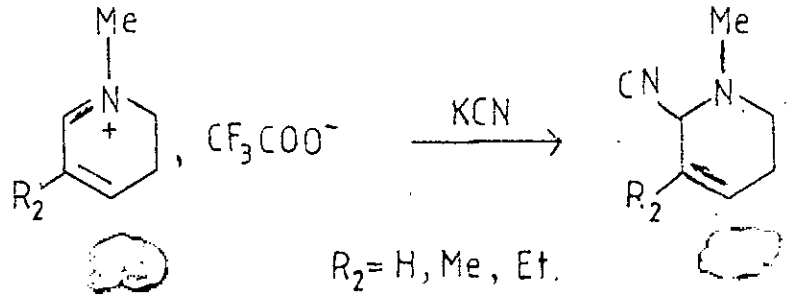
Cyano groups can be added to α-carbon of iminium salts by the use of sodium or potassium cyanide to produce organic nitriles. Nucleophilic addition of a cyano group to the 3,4,5,6-tetrahydropyridinium salt with sodium cyanide gave the 2-cyanopiperidine



210

R = Me, $PhCH_2$-, $PhCH_2CH_2$-

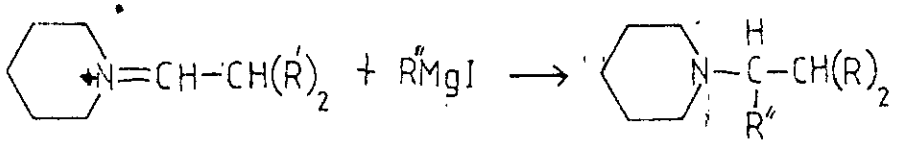
Cyano group also add only to the α-position in 5,6-dihydropyridinium salt despite the 3,4-unsaturation in 50-70% yield[76].



The easy transformation of the cyano functional group to other useful functional groups imparts versatility to this synthetic application of iminium salts.

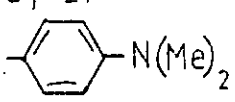
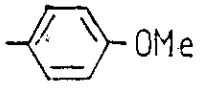
(d) Reaction with organometalic compounds

N-substituted tetrahydropyridinium salts react with organometallics, e.g. Grignards reagents to form α-aryl, α-alkyl substituted amines. Bohme and Plappert[77] in 1975, reported the reaction of iminium salts with aryl magnesium iodide to form arylsubstituted tertiary amines in good yield.

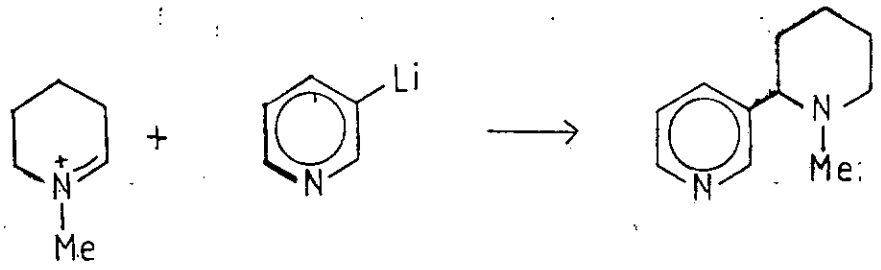


231 232

R' = Me, Et

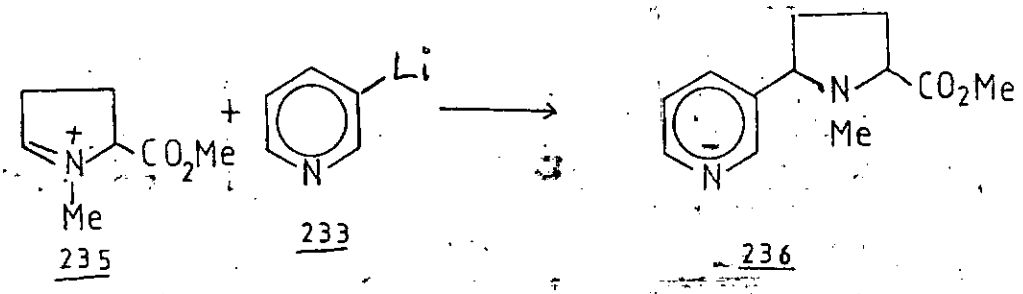
R'' =  , 

Similarly, Rapoport[67] reported the reaction of N-substituted piperidinium salts with lithiopyridines to form 3-(2-piperidinyl) pyridine.



232 233 234

When two competing reaction sites were present, i.e. an iminium salt and a carboxylic functionality, the reaction took place preferentially at the more reactive iminium salt site.



235 233 236

(e) Reaction with mercaptan and thiophenols

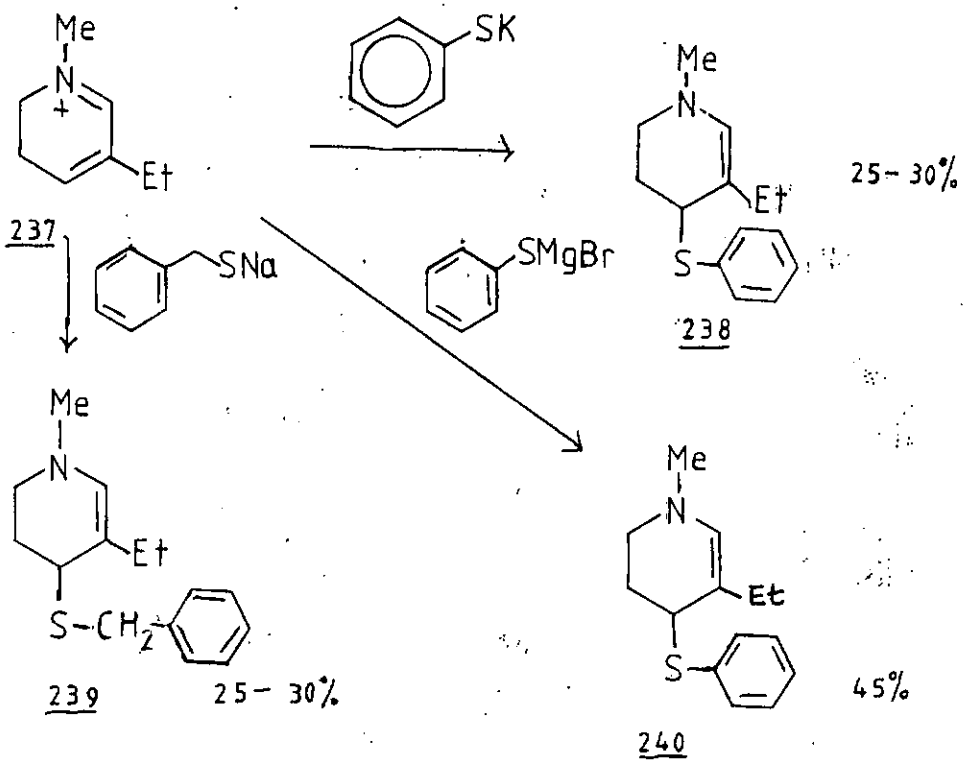
When potassium salts of aliphatic mercaptans react with iminium salts, addition products that readily decompose are obtained. With higher mercaptan, however, e.g. p-thiocresol and α-Naphthylmethyl mercaptan stable addition products are obtained[78].

Grierson et al.[76] reacted sodium thiophenoxide with 5,6-dihydropyridinium salts giving a C-4 addition product: 1-methyl-3-ethyl-4-thiophenyl-3,4,5,6-tetrahydropyridine in 25-30% yield.

The yield is improved on the use of thiobenzyl magnesium bromide to 45%, sodium benzylmercaptide also gave only 25-30% yield.

These product are sufficiently stable for recrystallisation when stored at low temperatures.

1,4-addition products sometimes obtained may be rationalised to have been formed through an initial formation of the C-2 addition product before rearrangement to the more stable C-4 product.

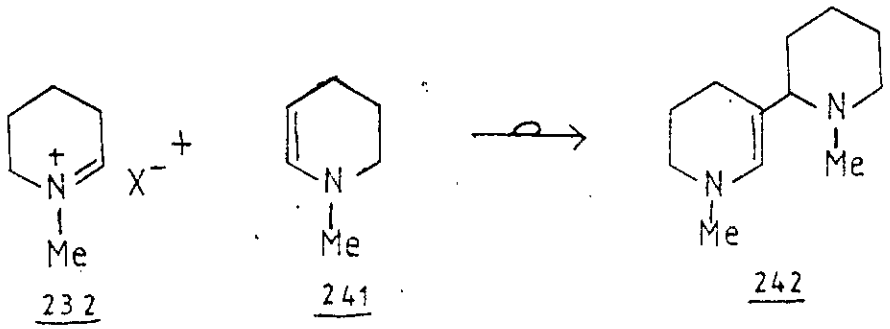


(f) Reaction with enamines

Enamines can couple with iminium salts leading to the formation of further substituted enamines. While the enamine remains unchanged, the iminium salt is transformed into a tertiary amine.

- 243 -

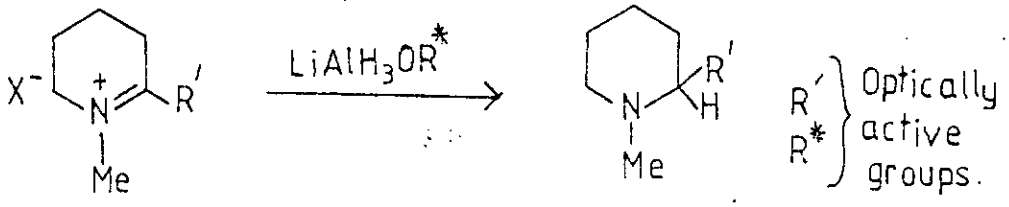
The yield is improved on the use of thiobenzyl magnesium bromide to 45%, sodium benzylmercaptide also gave only 25-30%



232 241 242

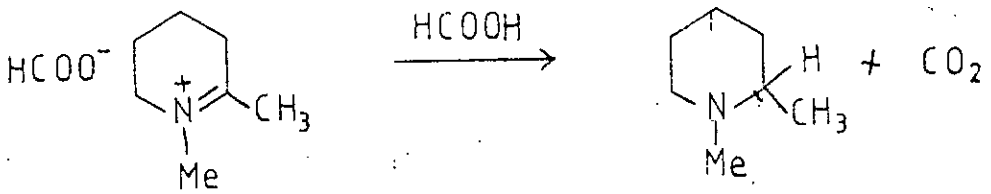
(g) Reduction of iminium salts

Iminium salts are reduced by lithium aluminium hydride or sodium hydride to saturated amines[79]. Optically active iminium salts can be reduced stereoselectively without the loss of chirality to a great extent by using an optically active reducing agent[80] like lithium aluminium hydride incorporating an optically active alcohol like (-) menthol.



243 244

Reduction of 1-methyl -2-alkyl Δ^{1} piperidinium salt or it's five membered analogues with formic acid was reported by Lukes et. al.[81]. The reduction is rationalised to go through an initial addition of a hydride ion from the formic acid to the α-carbon of the iminium salt followed by the loss of carbon dioxide.



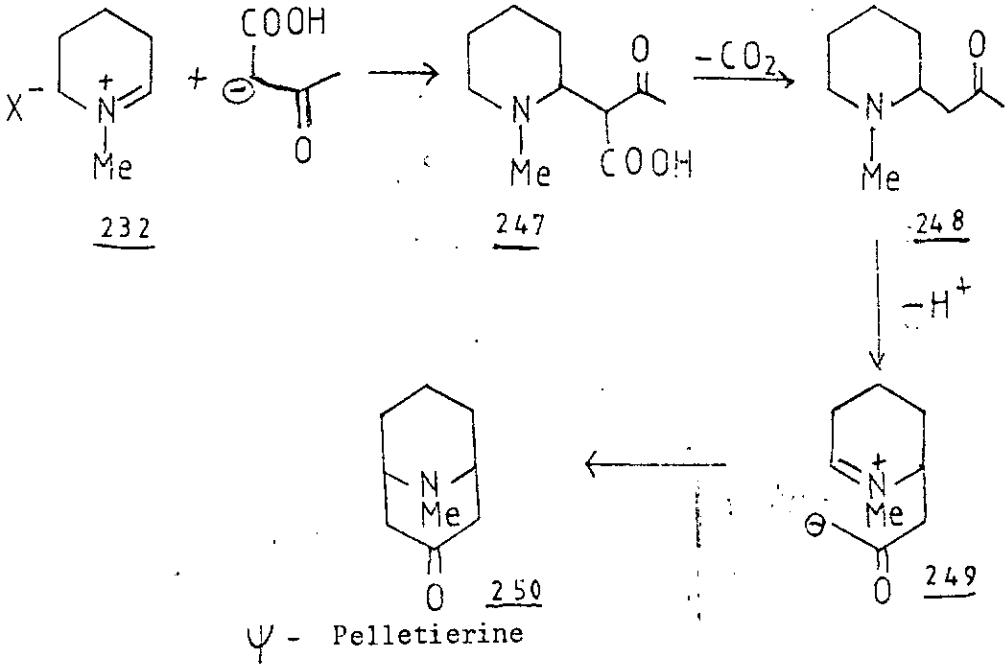
245 246

(h) Some uses of N-substituted tetrahydropyridinium salt in alkaloid synthesis

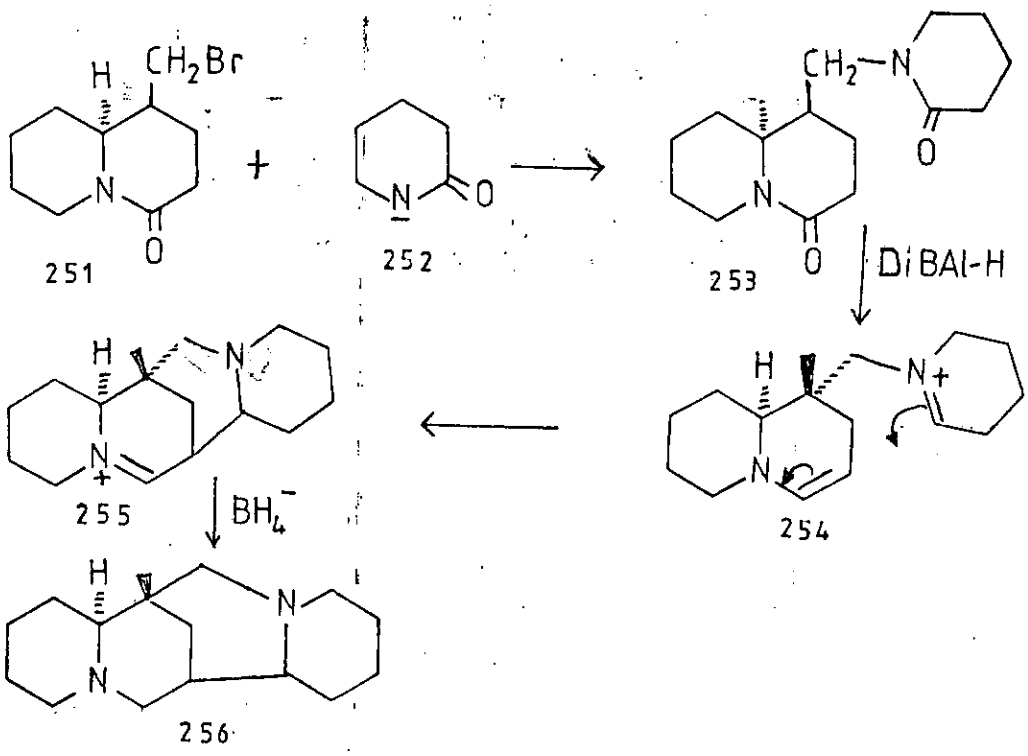
N-substituted tetrahydropyridium salts are sometimes utilized in alkaloid syntnesis. The use commonly involves intramolecular cyclisation of appropriately substituted iminium salts to obtain the desired alkaloid. An example discussed earlier is the construction of 1-azabicyclo[4.4.0] δ-quinolizidine, the yohimbane alkaloids and substituted indoles.

Piperidine alkaloids[72]

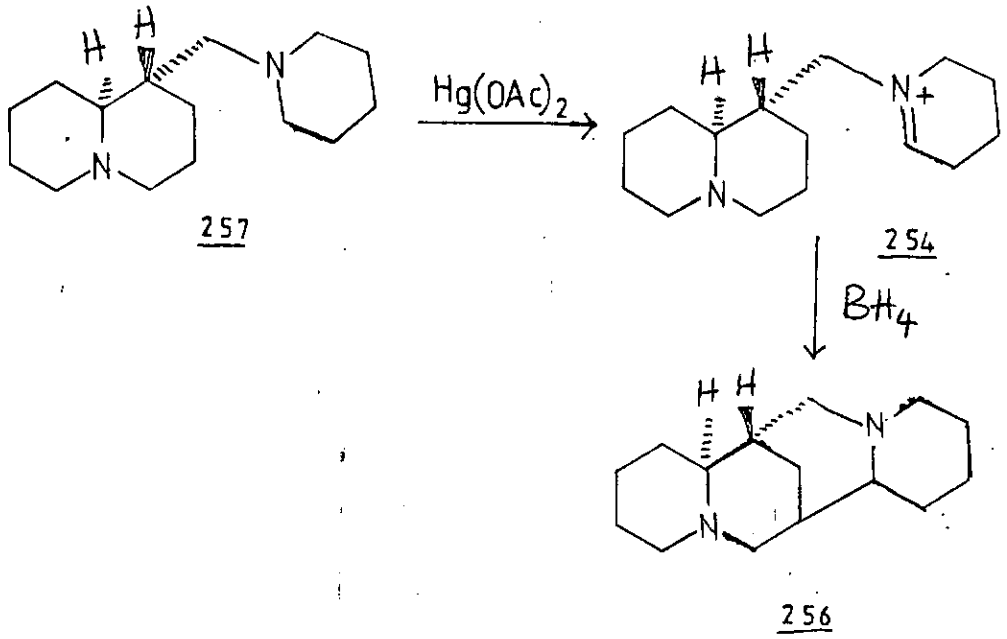
N-substituted piperidinium salts react with deprotonated acetoacetate to form N-methylisopelletierine and on further deprotonation gave ψ-pelletierine.



Spartein alkaloid was synthesised by Bohnmann et. al.[62] using iminium salt as one of the key step.



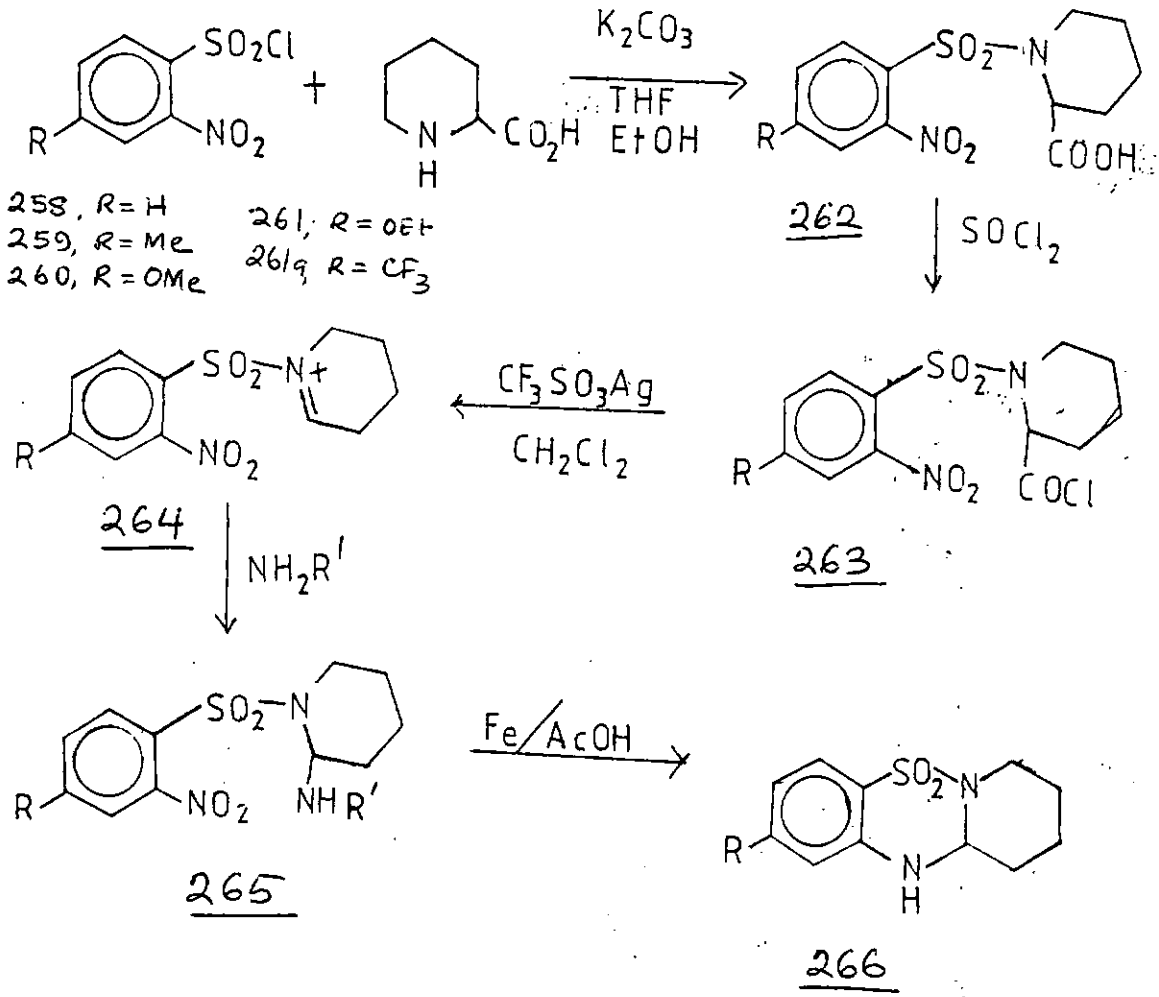
Another method that utilized iminium salt as a key step was done by Bohnmann et. al.[62] in spartein synthesis using oxidation of tertiary amines.



4.8. PRESENT STUDY

The success achieved in the formation and utilization of iminium salts from the five membered ring systems of pyrrolidine acid chlorides and the utilization of these iminium salts in the synthesis of diverse sulphur containing heterocycles: benzothiadiazines and their substituted analogues[16] prompted an extension of this methodology to the six membered analogues: piperidine-2-carboxylic acid chlorides. It was anticipated that the corresponding iminium salts could be reacted with ammonia or amine to give 2-aminopiperidines. These latter compounds should serve as excellent precursors for the synthesis of the new sulphur-containing heterocycles: pyrido[1,2-a][1,2,4] benzothiadiazines and derivatives.

The synthesis of these new heterocycles: pyrido [1,2-a] [1,2,4]benzothiadiazine-6,6-dioxide was proposed to be achieved by starting with substituted nitrobenzenesulphonyl chlorides which would be condensed with DL-piperidine-2-carboxylic acid forming N-(substituted-2-nitrobenzene sulphonyl)piperidine -2-carboxylic acids. These acid adducts will be converted to acid chlorides before appropriate triflate-assisted decarbonylation with silver trifluoromethanesulphonate to give the desired N-tetrahydropyridinium salt synthons. It was anticipated that reaction of the salts with ammonia or ethylamine will give nitroamines which could undergo an exo-tet reductive cyclisation appropriately to give sulphur-containing heterocycles in good yield.



258, R = H
259, R = Me
260, R = OMe
261, R = OEt
261q, R = CF_3

262

263

264

265

266

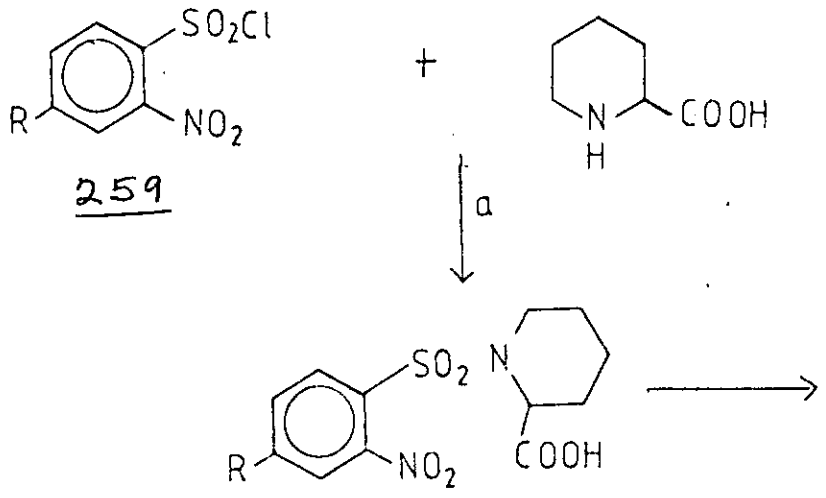
R' = H, Et.

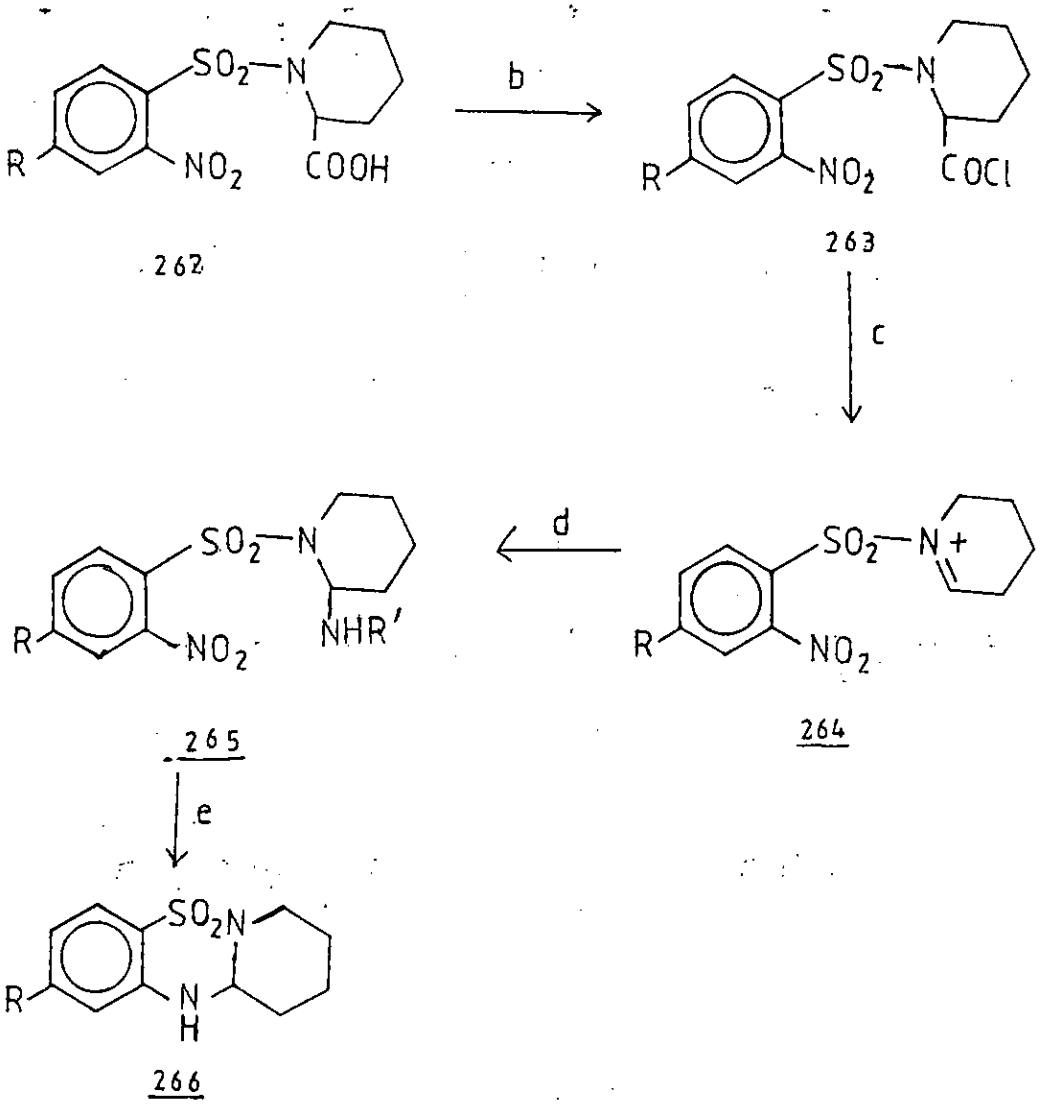
CHAPTER 5

RESULTS AND DISCUSSION

Triflate-assisted decarbonylation of five - membered cyclic tertiary α-amino acids[15.16] giving good yields of iminium salts and eventually excellent yields of nitroamine synthons successfully, provided a route for the synthesis of pyrrolo (1,2,4) (1,2-b) benzothiadiazines. This prompted studies into the extention of the methodology to the analogous six-membered cyclic α-amino acids with a presumption that these may similarly give the corresponding nitroamines which may also furnish the pyrido (1,2,4)(1,2-b) benzothiadiazines analogues and their substituted derivatives.

A scheme of reaction was delineated as shown below.





Scheme 11.

R = -H, -Me, - OMe', -OEt, $-CF_3$

(a) = K_2CO_3 | EtOH, | H_2O, THF, Δ

(b) = $SOCl_2$

(c) = CF_3SO_3Ag, CH_2Cl_2, RT

(d) = NH_4OH, NH_2R'

(e) = Iron dust | AcOH.

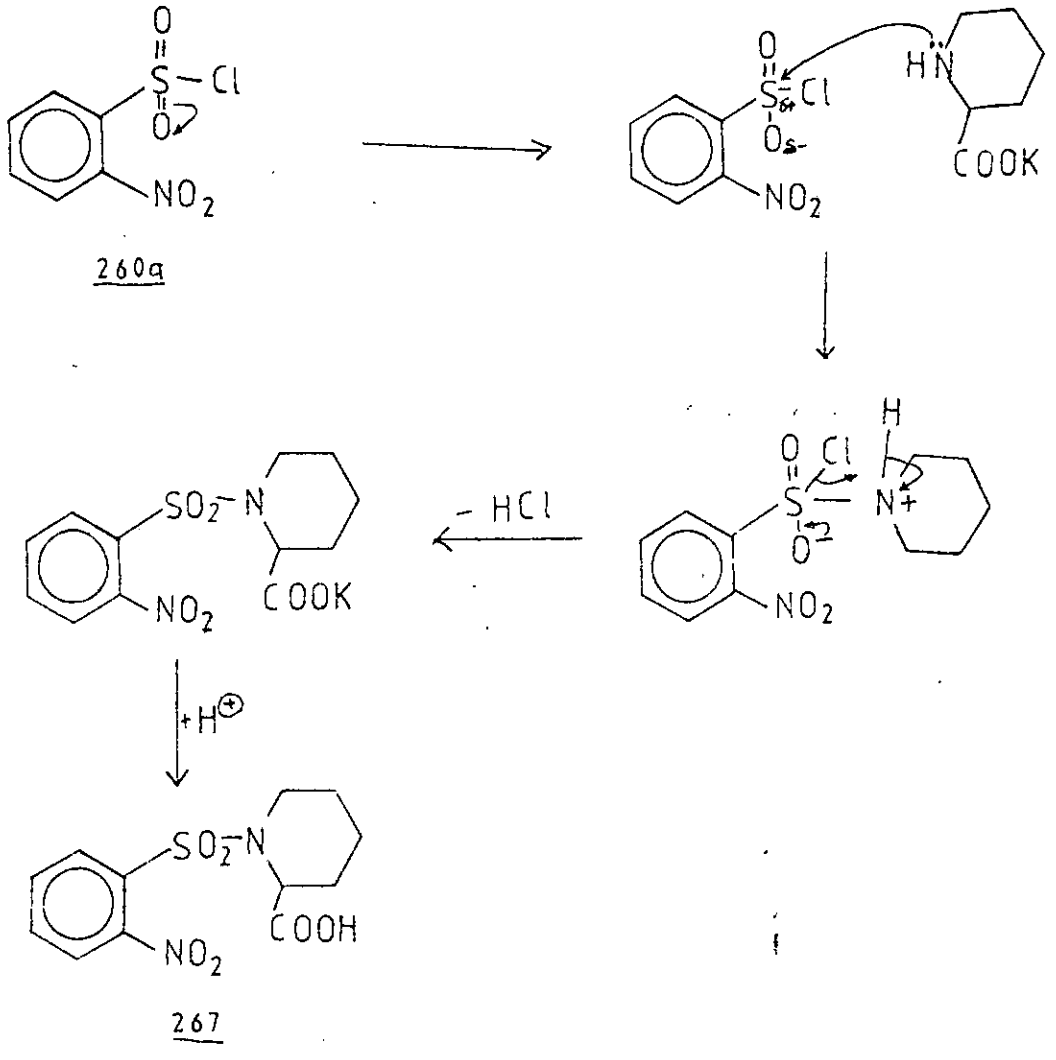
increasing the time of reaction to two hours or three hours did not cause any significant improvement in yield.

The synthesis commenced with the condensation of commercially available 2-nitrobenzenesulphonyl chloride with piperidine-2-carboxylic acid. Addition of the solid sulphonylchloride to aqueous hydroxide[82] solution of piperidine-2-carboxylic acid did not give a reasonable yield, despite the fact that the method worked very well for the condensation of L-pyrrolidine-2-carboxylic acid. Increasing the reaction time to 4h did not cause a significant change in yield, neither did reflux of the reaction mixture for one hour. A heterogeneous mixture constantly ensued.

In order to obtain a homogenous solution, the sulphonyl chloride was dissolved in diethyl ether and added to a solution of piperidine-2-carboxylic acid in triethylamine and water. This solution was stirred at room temperature for 2h. The yield obtained was just 10%. Refluxing the reaction mixture for 1hr. did not cause any significant change.

Another method [83] was therefore attempted. Using tetrahydrofuran (THF) as the sulphonyl chloride solvent, while the amino acid was dissolved in potassium carbonate, water and ethanol, a homogenous mixture was obtained. This was refluxed for one hour. On evaporation of all solvents and work - up, a significant yield (60%) of product was obtained. Efforts to improve the yield by increasing the time of reaction to two hours or three hours did not cause any significant improvement in yield.

The condensation reaction between an acid halide and an amine above is a typical Schotten-Bauman reaction. It involves the nucleophilic attack by the lone pair of electrons on the nitrogen of the piperidine-2-carboxylic acid on the sulphonyl group as shown below (Scheme 12).



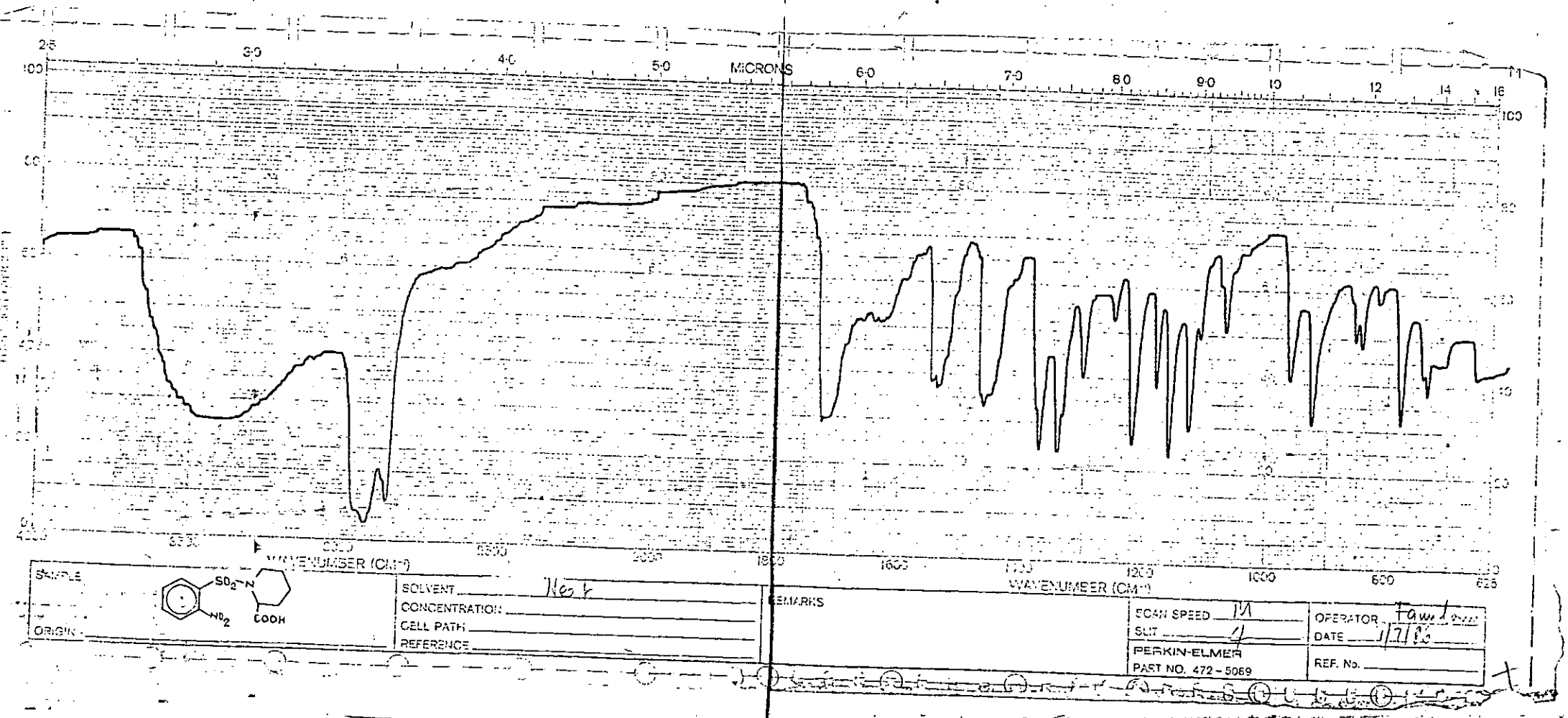
260a

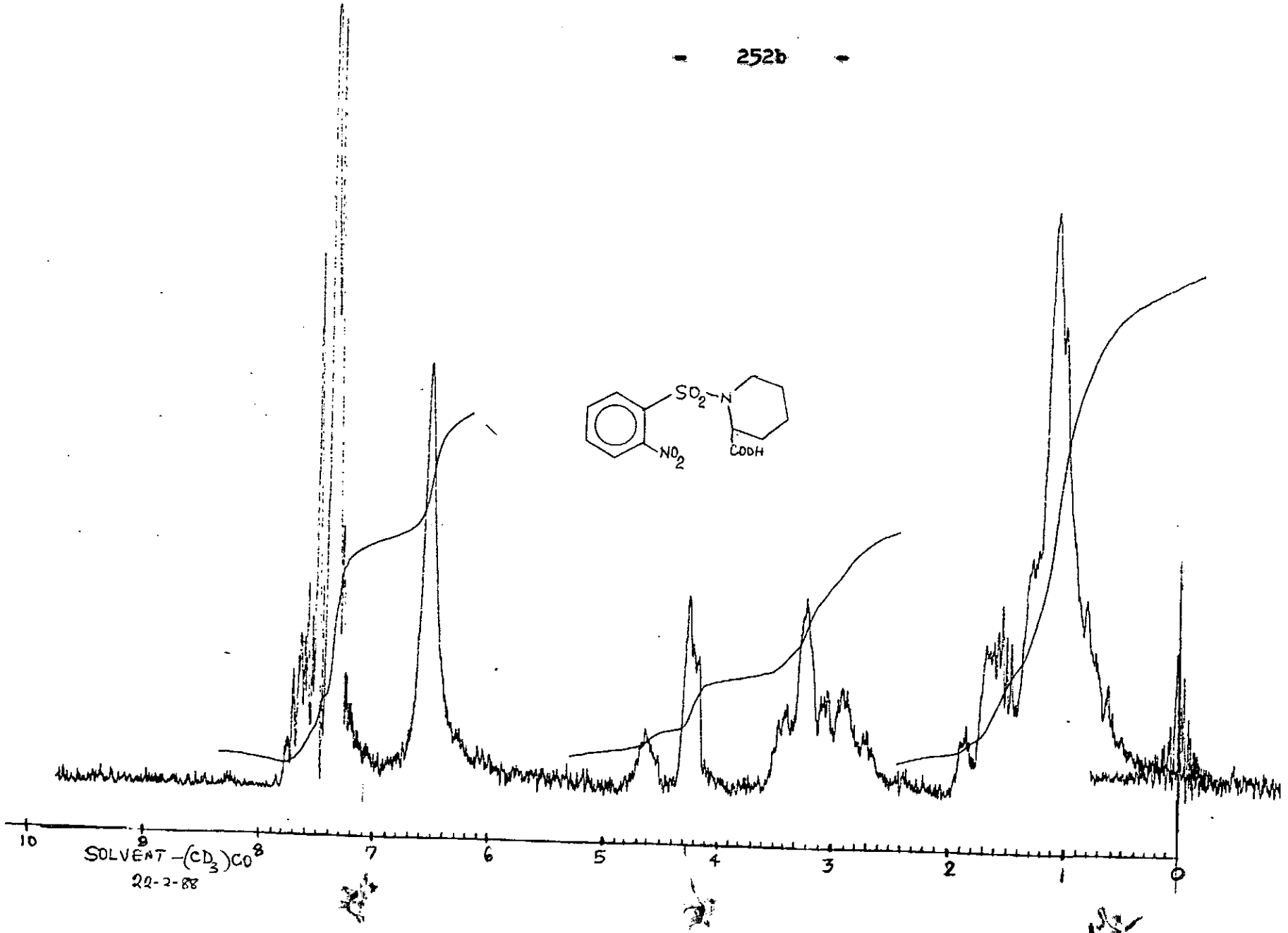
267

Scheme 12

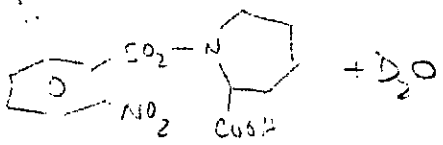
Elimination of HCl results in the sulphonamido acid.

2516

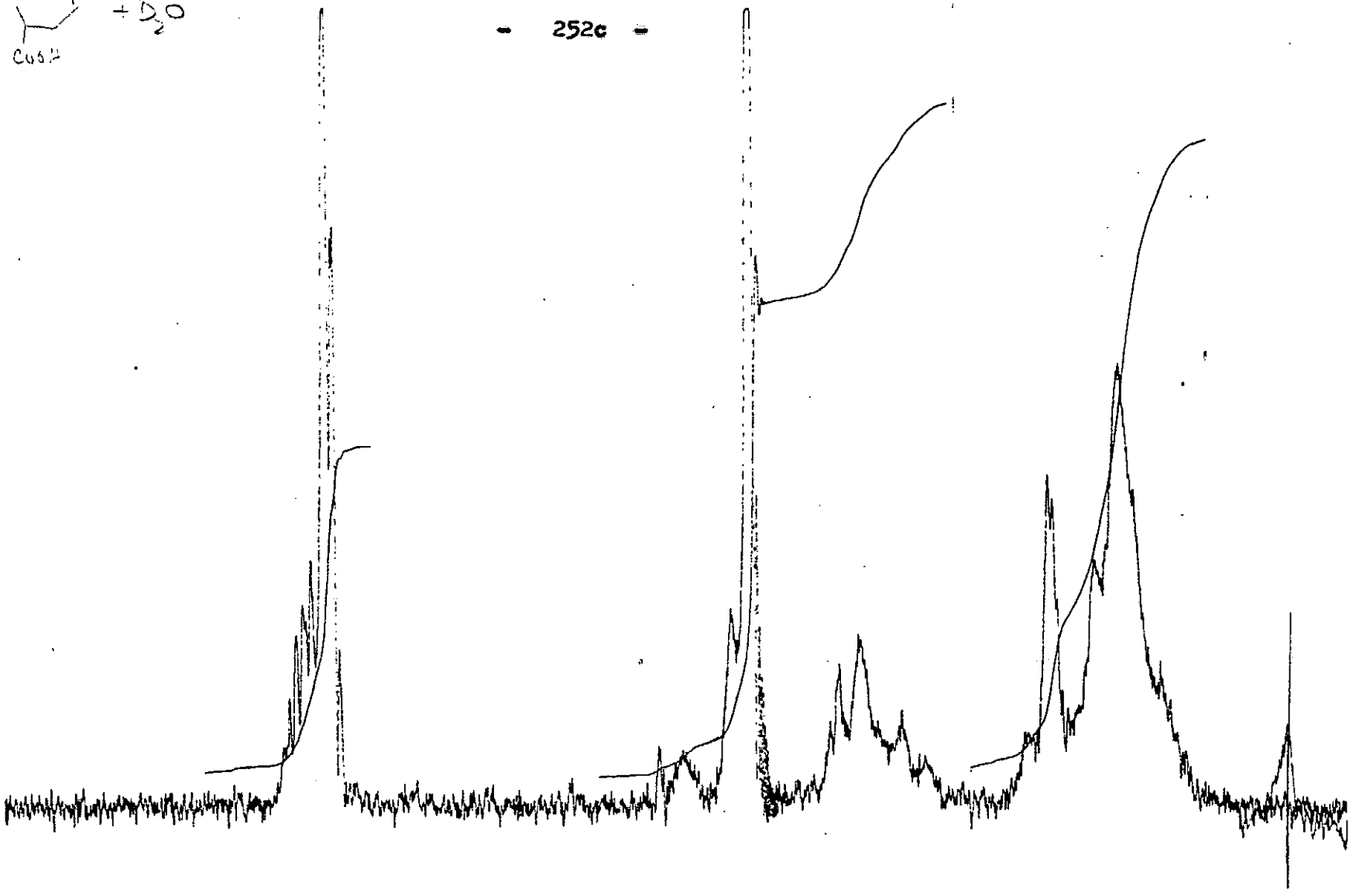

MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)
SAMPLE
ORIGIN
SOLVENT Neat
CONCENTRATION
CELL PATH
REFERENCE
REMARKS
SCAN SPEED
SLIT
PERKIN-ELMER
PART NO. 472 - 5069
OPERATOR
DATE
REF. No.


SO2-N
NO2
COOH
10
9
8
7
6
5
4
3
2
1
0
SOLVENT -(CD3)CO
22-2-88

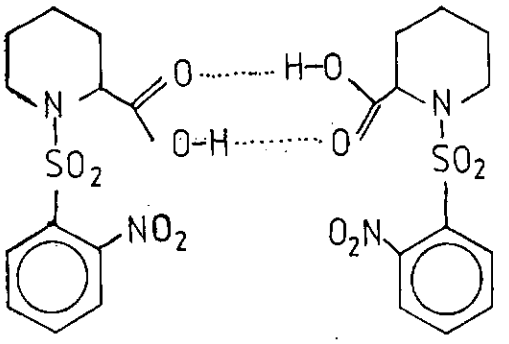
2/2/85

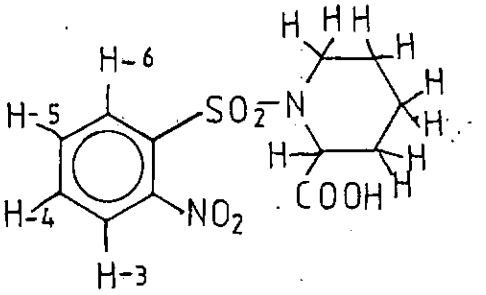


$+ D_2O$



The infrared spectrum of the product formed showed a band at 3400 - 2400 cm^{-1} due to the dimer formed by the acid adduct. Other bands included 1710 cm^{-1} for the acid carbonyl, 1520, 1340 cm^{-1} for the nitro group's stretching vibrations. 1370 and 1160 cm^{-1} for the sulphonamide (SO_2-N$\langle$) absorption. The ^{1}H-NMR in acetone-d_6 showed the four protons of type 'a' at δ1.1, the two protons of type 'b' at δ1.6, while the two protons next to the amine nitrogen are deshielded and appear at δ3.2. The base proton of the carboxylic acid group absorbed at δ4.2; while the broad absorption at δ6.6 represented the -OH of the acid which is exchangeable with D_2O. The three aromatic protons of H-3, H-4, H-5 appeared as a multiplet at δ7.2, while the proton H-6 appeared at δ7.6 slightly deshielded by the sulphonamide group.



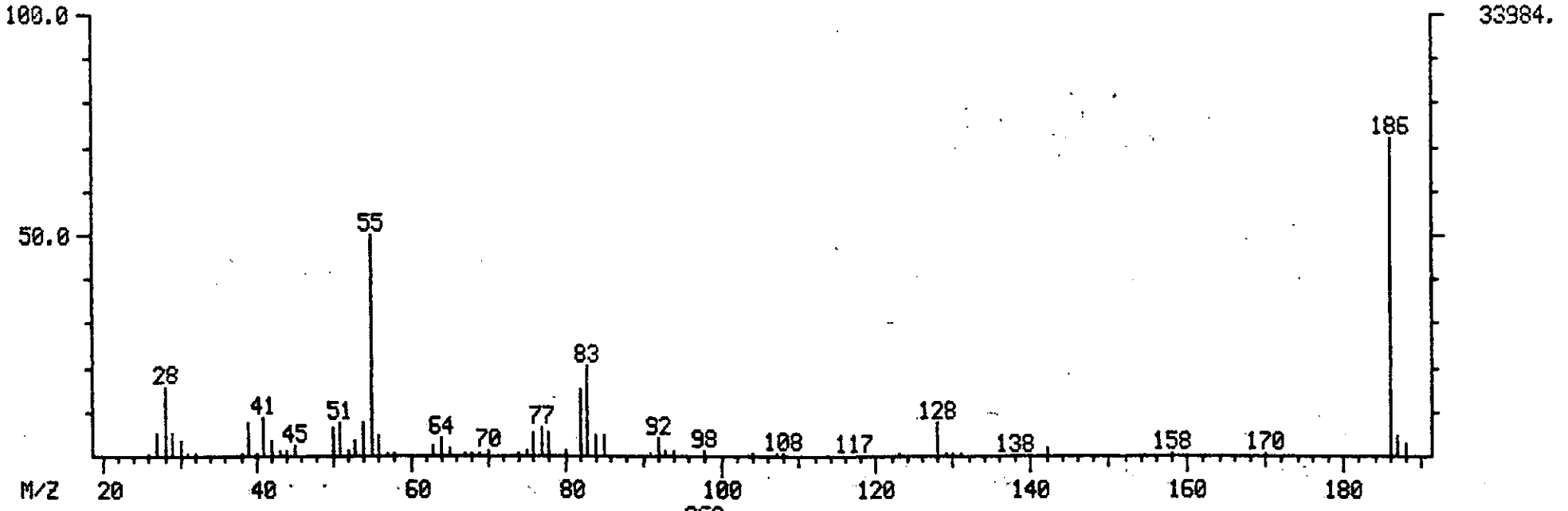


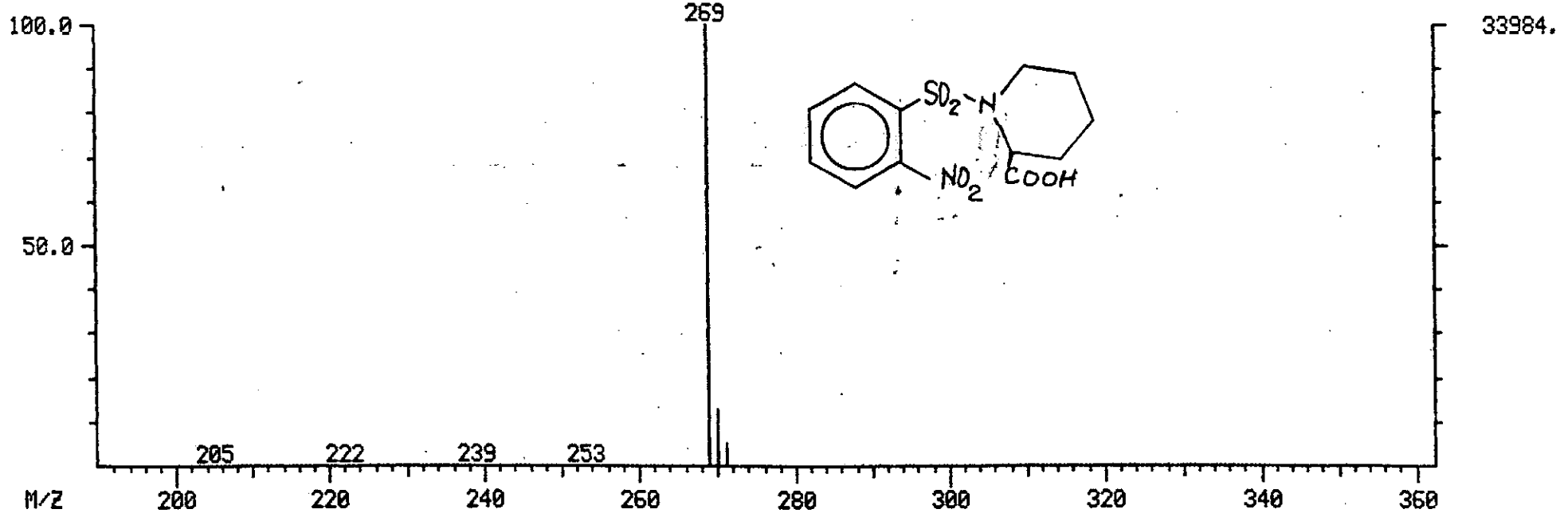
MASS SPECTRUM
09/12/86 11:02:00 + 1:15
SAMPLE: OBF 3
CONDS.: DISC 4
#14 TO #16 SUMMED

- 253a -

DATA: OBF3 #15
CALI: CAL12SEP86 #3

BASE M/Z: 269
RIC: 148932.

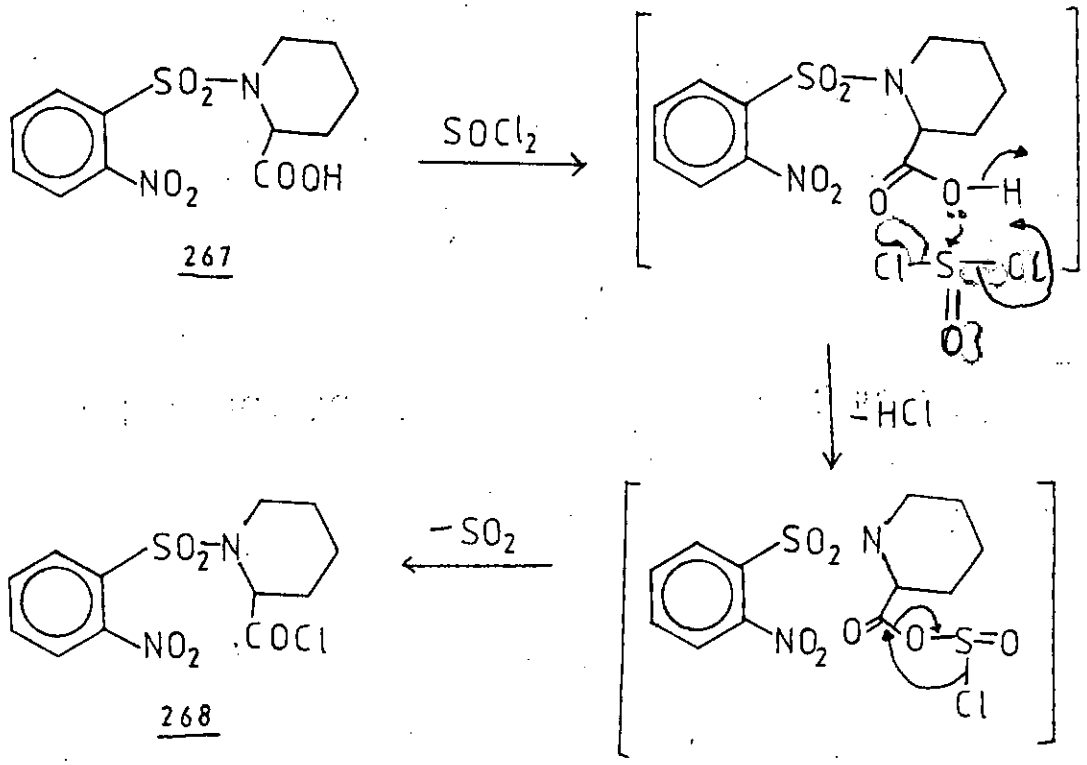




The microanalytical data obtained for the new compound were consistent with theoretical values. The mass spectrum of the compound showed an M^+ -45 peak at 269 as the base peak. This peak was obtained by loss of -COOH group and other notable absorptions included m/z 186 which represented NO_2-Ph-SO_2-; 128 and 83.

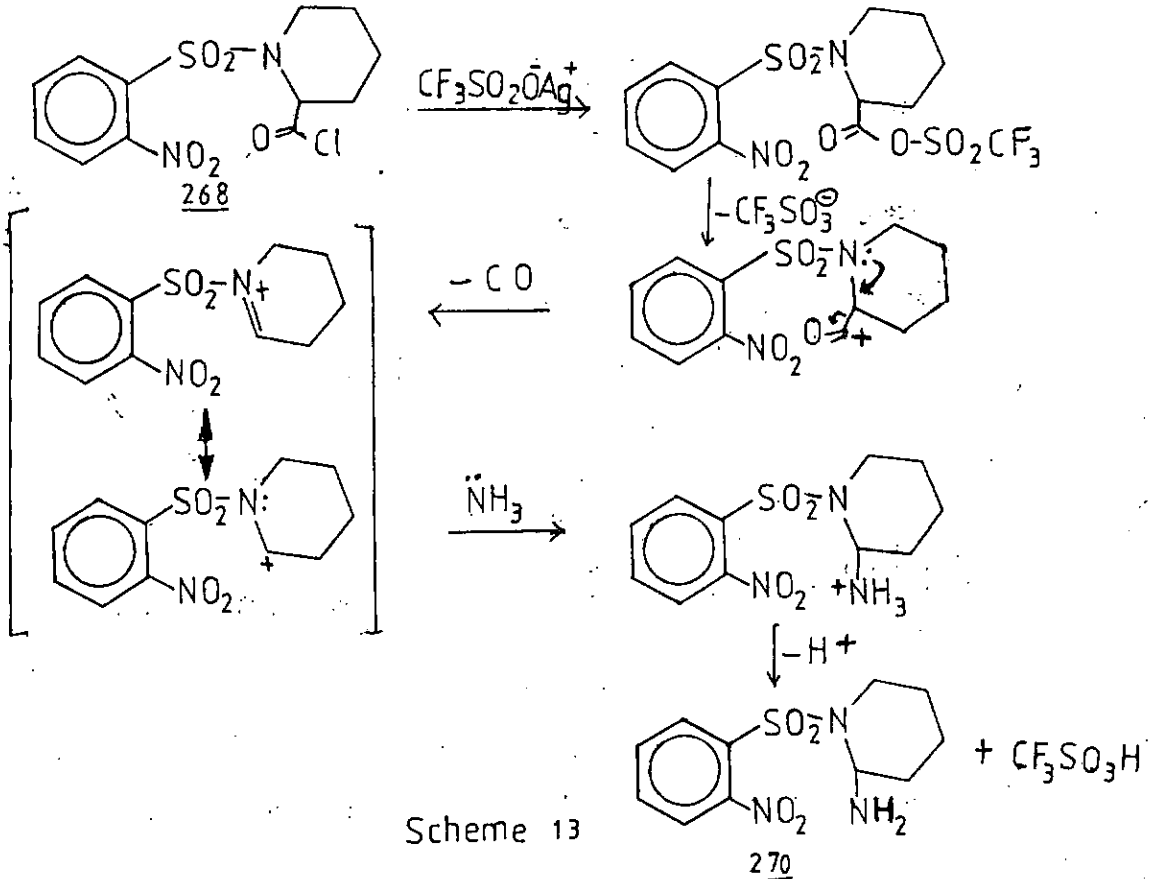
The acid adduct 267 was smoothly converted to the acid chloride by gentle reflux with thionyl chloride.

The mechanism [84] of the reaction of thionyl chloride on the acid group is identical with the reaction of thionyl chloride with alcohols. The reaction proceeds through a concerted process i.e. an initial formation of a chlorosulphite ester followed by loss of sulphur dioxide:



The infra-red spectrum of the viscous oil showed a strong acid chloride absorption at 1795 cm^{-1}. The carbonyl group of the nitro acid earlier absorbed at 1710 cm^{-1}.

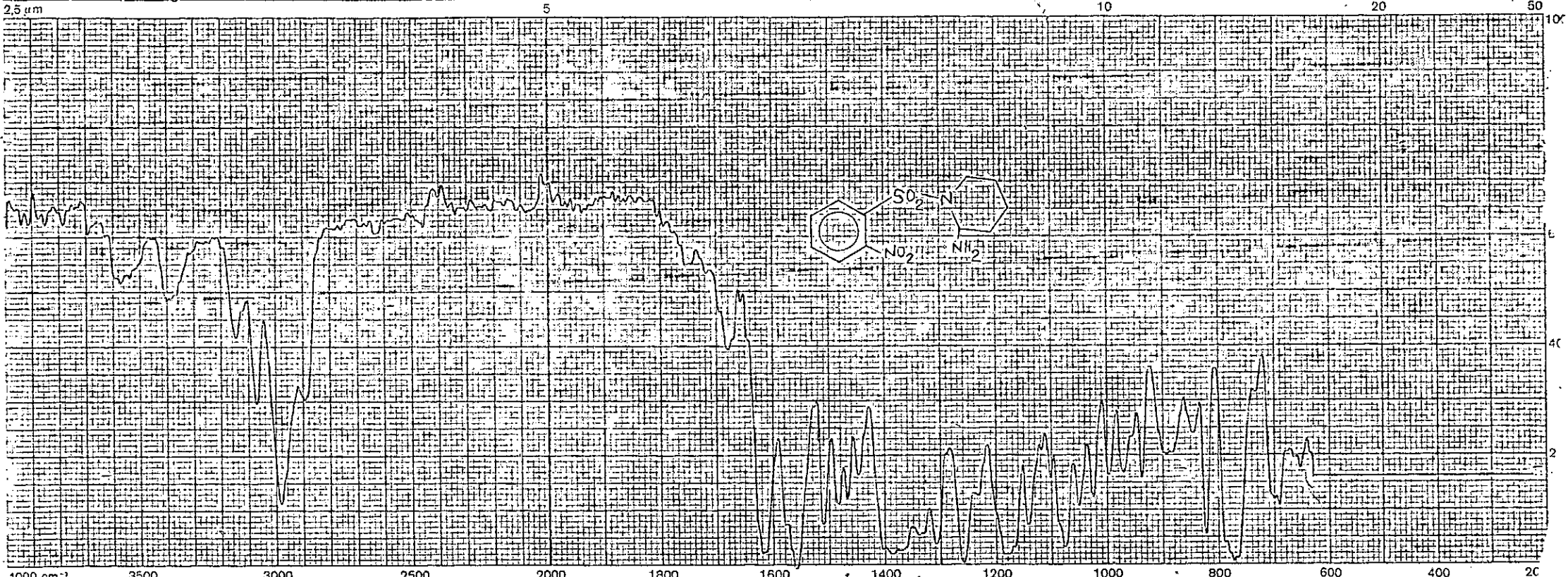
To the dichloromethane solution of the acid chloride was added silver trifluoromethanesulphonate under inert conditions. There was an instantaneous effervescence with evolution of carbon monoxide accompanied by the immediate generation of N-(2-nitrobenzenesulphonyl) tetrahydropyridinium trifluoromethanesulphonate salt. When the effervescence in the iminium ion generation reaction subsided, concentrated ammonia (S.G. 0.90) was added with stirring to the reaction mixture at room temperature. On work-up a brown solid was obtained. T.l.c. of the solid gave two main spots in chloroform: methanol, 10: 1



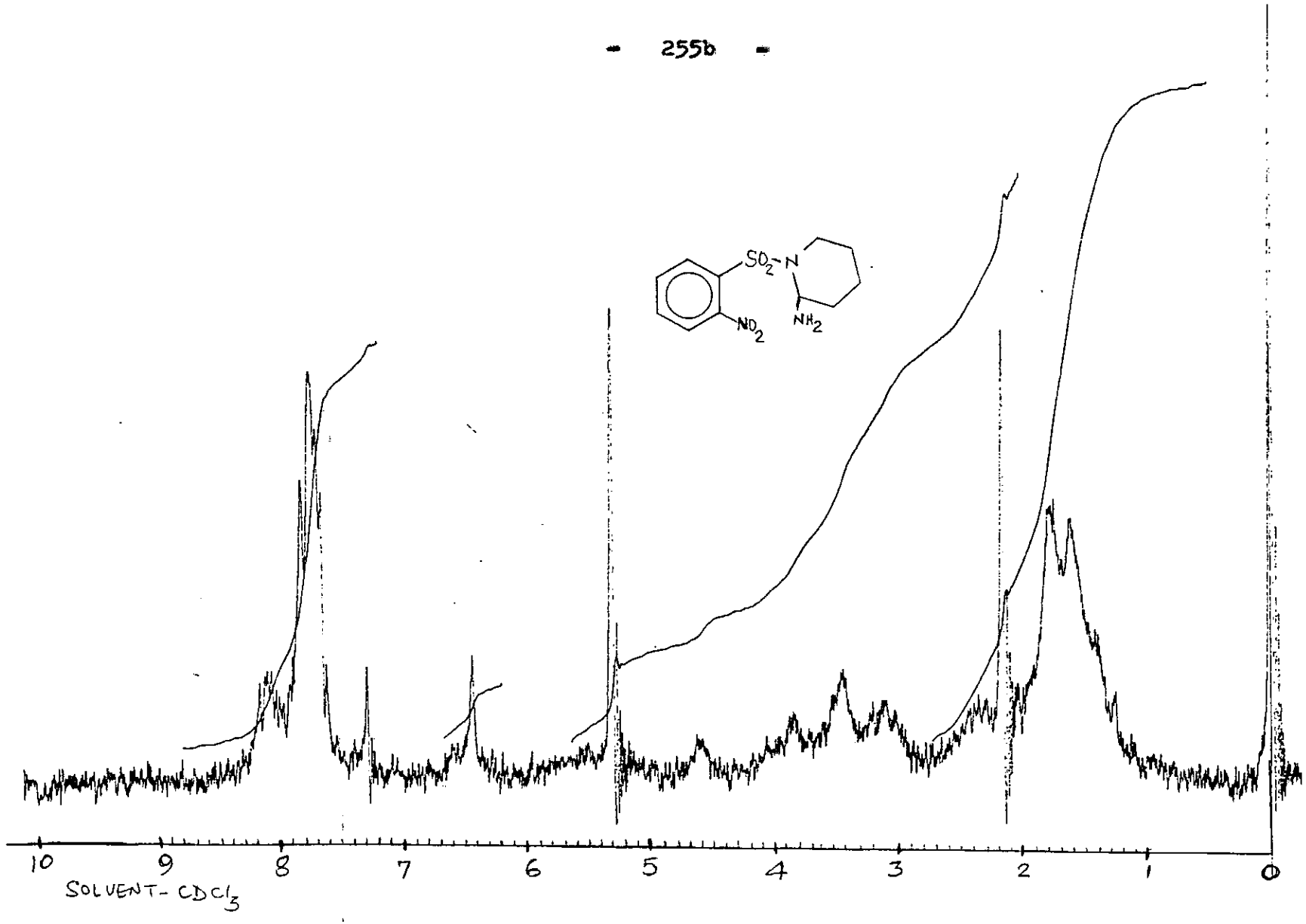
268 270

Scheme 13

SPECTRASET MODE	SINGLE BEAM / FIXED RESPONSE / AUTO SMOOTH	SCAN TIME	RESPONSE 1 2 3 4	cm⁻¹ EXP / SLITWIDTH	% T EXP / BACK OFF	REMARKS
	○ / ✓ / ○	8 MINS	○ ○ ○ ○			

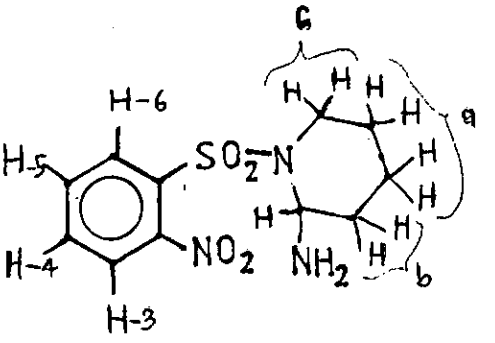


SAMPLE	TECHNIQUE Nujol	PATHLENGTH	OPERATOR Jamilm	PYE UNICAM LTD CAMBRIDGE ENGLAND
A	REFERENCE	CONCENTRATION	DATE / REF No	PART No 841749


SO2-N
NH2
NO2
10
9
8
7
6
5
4
3
2
1
0
SOLVENT- CDCl3

Flash chromatography of the compound on a silica gel column gave the desired compound as the lower Rf product. This was further purified by preparative t.l.c., The i.r. spectrum of the compound showed strong absorptions at 3400 (-NH-stretch) 3060, 2980 for the C-H stretch of aliphatics, 1680 cm^{-1} (NH-bending), 1600 for the -C=C- of aromatic ring. An intense absorption at 1540 cm^{-1} represented the nitro group's stretching vibration while absorption at 1380, 1180 cm^{-1} were due to the SO_2-N bond.

The ^{1}H-NMR of the product showed signals at δ1.7 for the 4 protons of the piperidine ring. The two protons of type 'b' appeared at δ2.3 while the signals at δ3.4 was for the proton adjacent to the nitrogen atom. A triplet at δ4.6 was due to the base of the amino group, while δ6.4 doublet was due to the amino $-NH_2$ absorption. The aromatic protons H-3, H-4, H-5 absorbed as a multiplet at δ7.7 while the deshielded H-6 proton appeared at δ8.1.

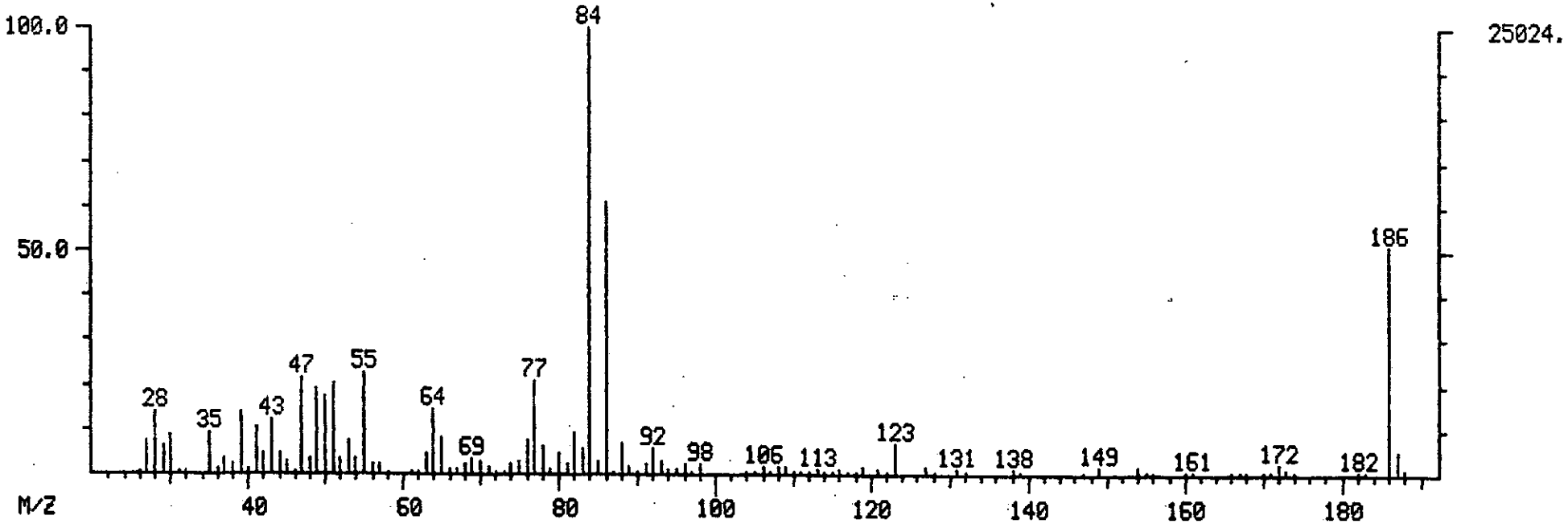


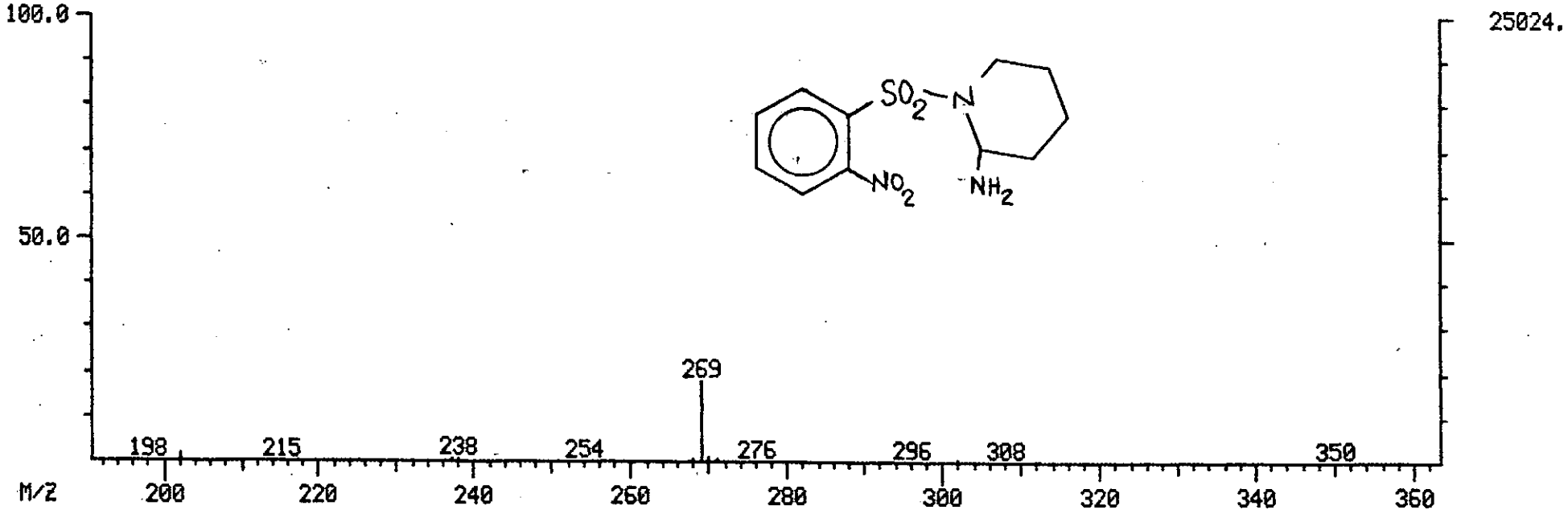
270

MASS SPECTRUM
09/12/86 11:16:00 + 1:20
SAMPLE: OBF 6
CONDS.: DISC 4
#15 TO #18 SUMMED

DATA: OBF6 #16
CALI: CAL12SEP86 #3

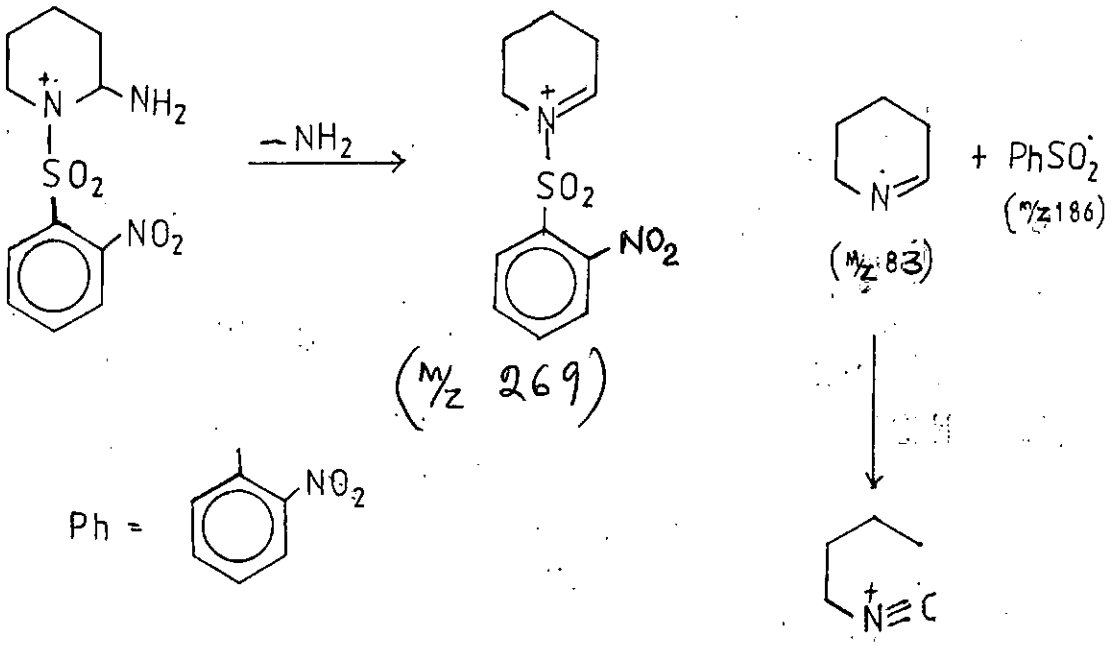
BASE M/Z: 84
RIC: 162048.





monoxide with assistance from the lone pair of electrons on the nitrogen, thereby forming an iminium salt.

The mass spectrum of the product showed the most abundant ion at m/z 269 ($M^+ - 16$) which represented a loss of $-NH_2$ grouping from the molecular ion. Other notable fragment ions include m/z 186, 123, 84. A plausible fragmentation pathway is outlined below:

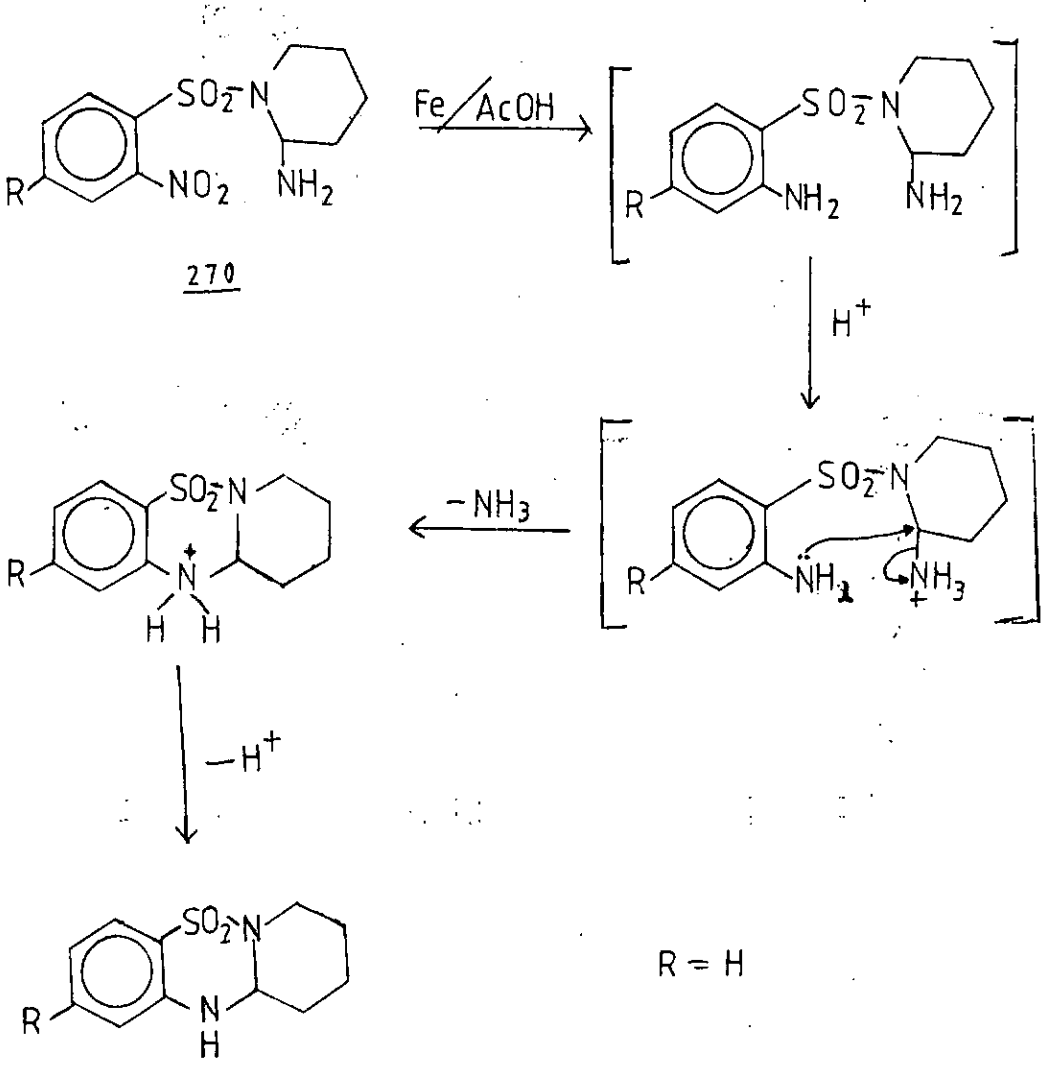


The lower R_f product was therefore characterised as N-(2-nitrobenzenesulphonyl)-2-aminopiperidine.

The formation of iminium ions from the acid chlorides is based on the observed instability of mixed anhydrides formed from aliphatic acid chlorides. The mixed anhydride formed is thermally unstable and is therefore decomposed leaving a carbonium ion which was cleaved off as carbon monoxide with assistance from the lone pair of electrons on the nitrogen, thereby forming an iminium salt.

The iminium ion here is stabilized by trifluoromethane-sulphonate anion as counter ion[82] (See scheme 13).

The reductive cyclisation of the nitroamine which should lead to the heterocyclic compound: 1, 2, 3, 4, 11, 11a-hexahydropyrido (1, 2, 4) (1, 2-b) benzothiadiazine -6, 6- dioxide was achieved with a mixture of iron dust and iron filing in glacial acetic acid[85].

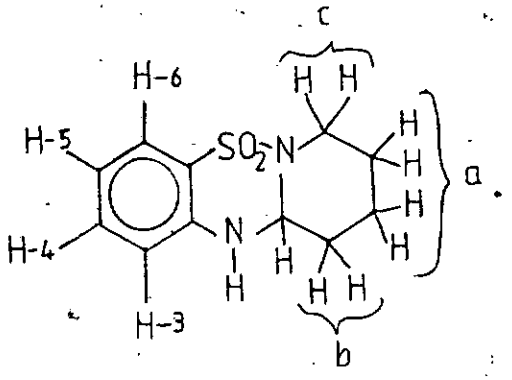


270

271 Scheme 14

The i.r. spectrum of the compound showed the following absorptions: 3500, 3400 cm^{-1} (NH stretch for the monomer and associated forms), 3080, 3000 cm^{-1} (C-H stretch of the piperidine ring) 1690 cm^{-1} (NH - deformation) 1610 cm^{-1} (aromatic -C=C-) 1350, 1170 cm^{-1} (SO_2-N<).

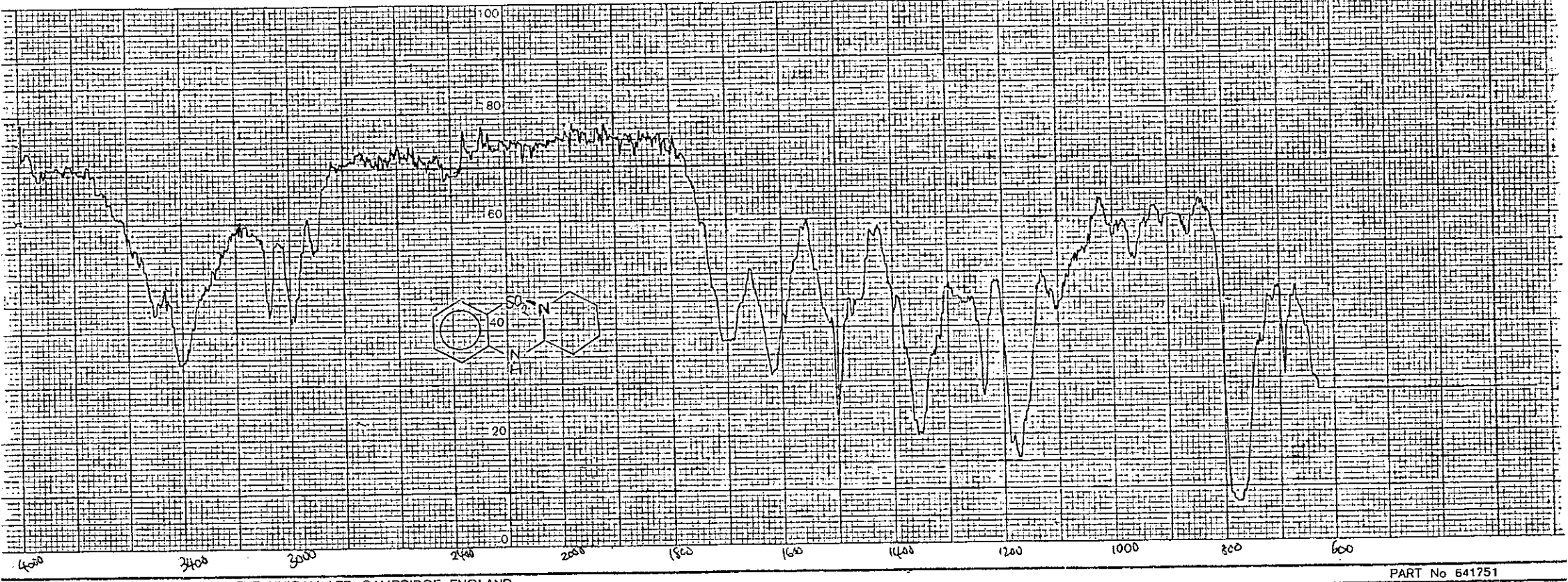
The 'H-NMR spectrum of compound 271 showed a 4H multiplet at δ1.2 (piperidine ring protons type 'a'), 2H multiplet at δ2.1 (piperidine ring protons type 'b'). The two protons adjacent to the nitrogen atom absorbed at δ3.3. The acetalidine N-C<u>H</u>-N proton appeared at δ5.1. The three aromatic protons H-3, H-4, H-5 appeared at δ7.1 while the deshielded H-6 proton absorbed at δ8.2. A broad signal at δ9.1 represented the NH.



271

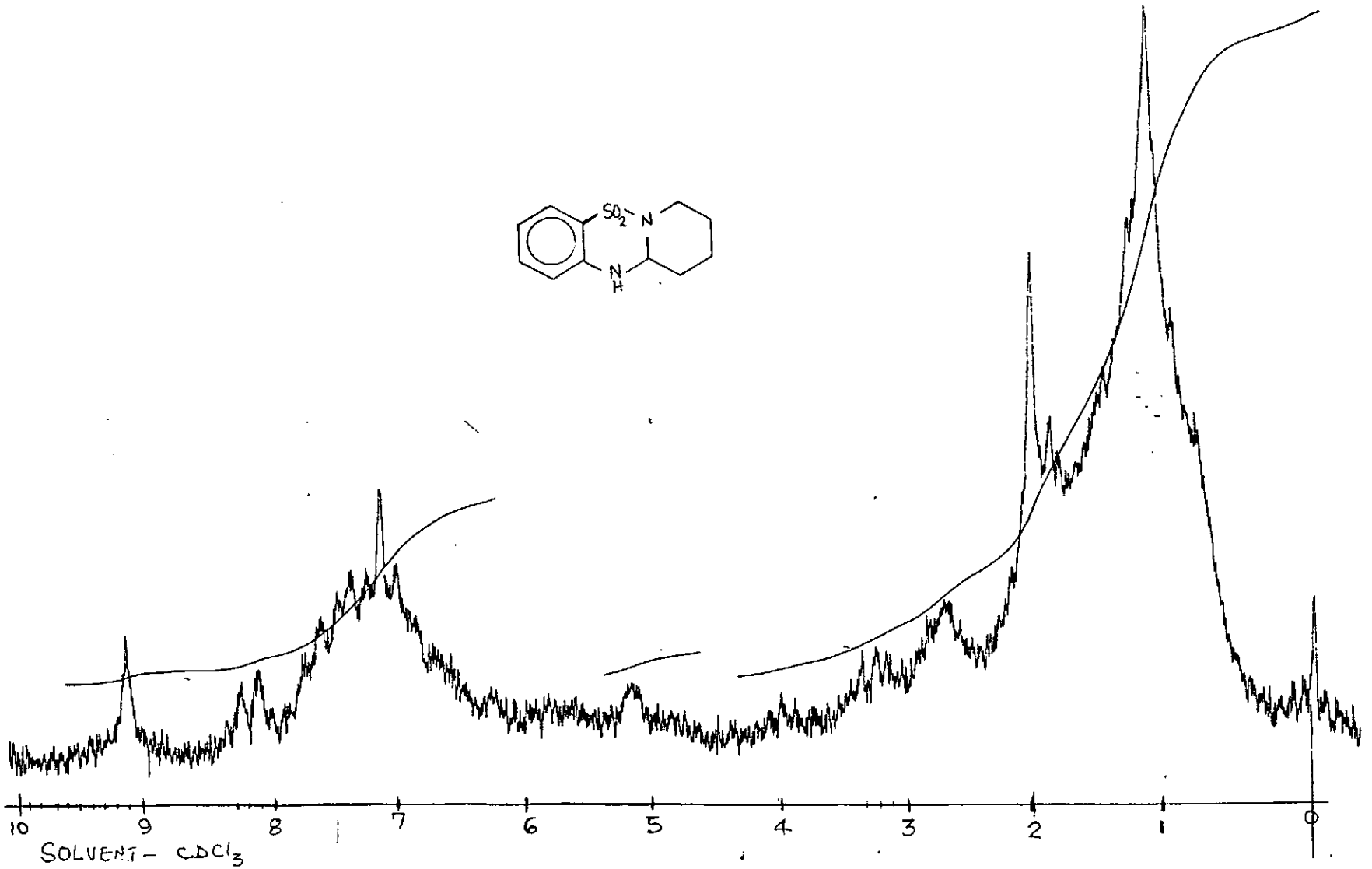
The mass spectrum of the heterocycle showed an abundant molecular ion m/z 238. Other notable peaks were at m/z 182 (64%), 173 (M^+ - SO_3H), 146 (M^+ - SO_2-N, HCN), 93.

scan time 8mins, solvent chloroform



PYE UNICAM LTD CAMBRIDGE ENGLAND

PART No 641751

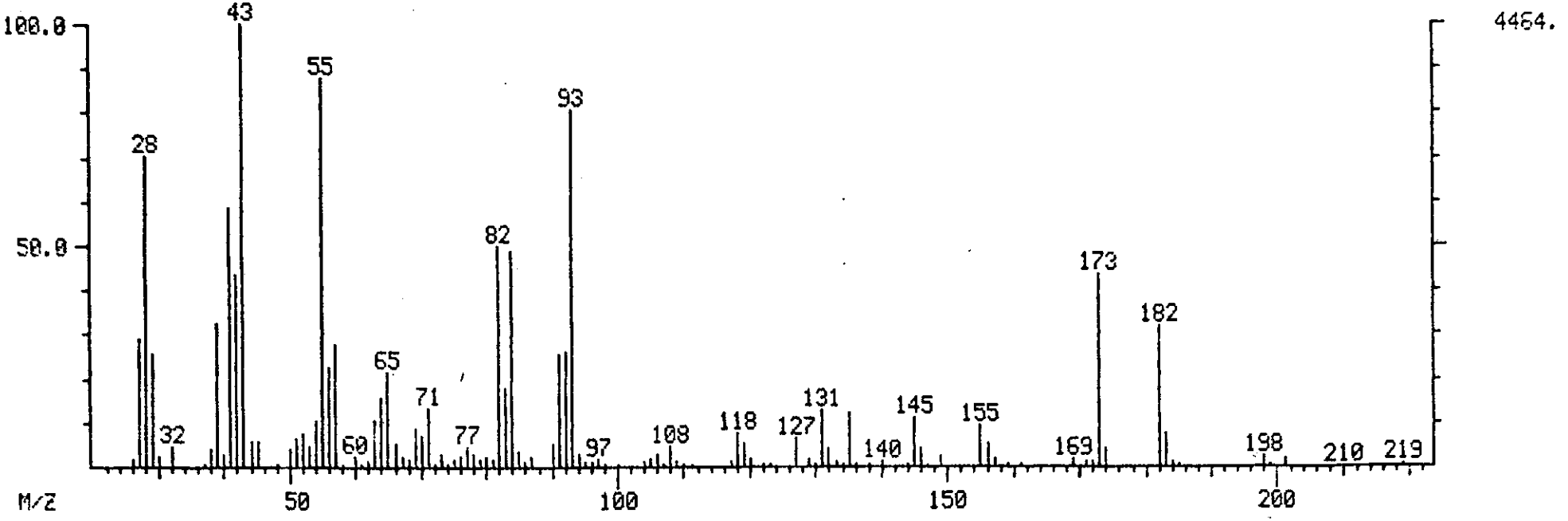

SO2
N
N
H
10
9
8
7
6
5
4
3
2
1
0
SOLVENT - CDCl3

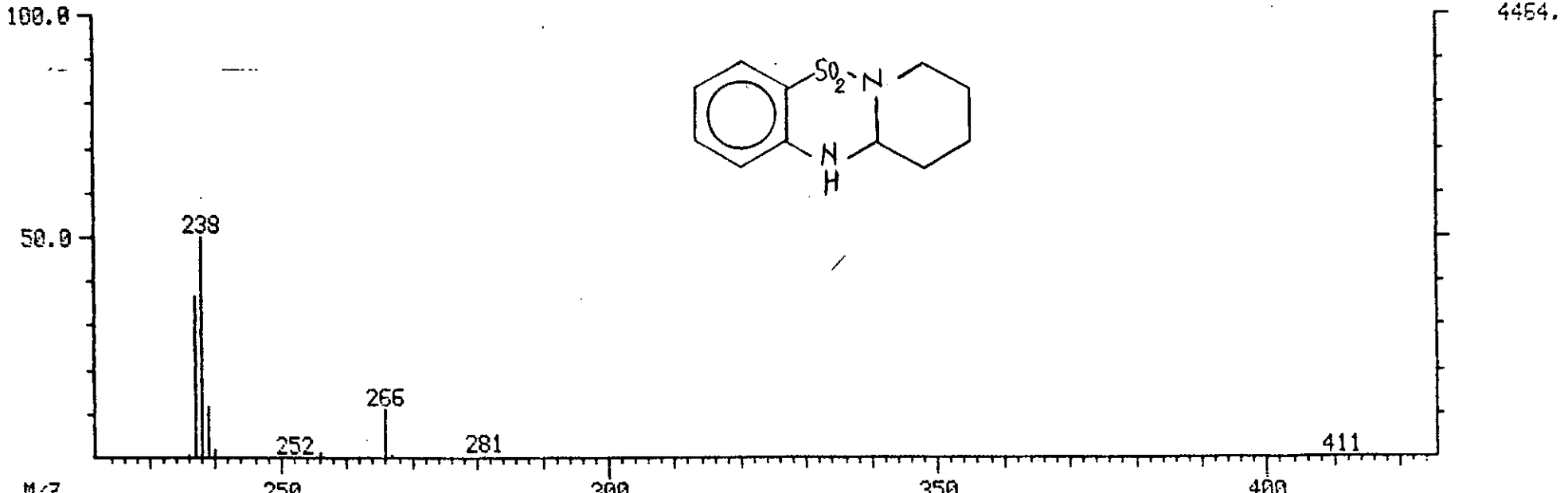
MASS SPECTRUM
09/12/86 10:56:00 + 1:05
SAMPLE: OBF 2
CONDS.: DISC 4
#12 TO #15 SUMMED

- 259c -

DATA: OBF2 #13
CALI: CAL12SEP86 #3

BASE M/Z: 43
RIC: 56384.

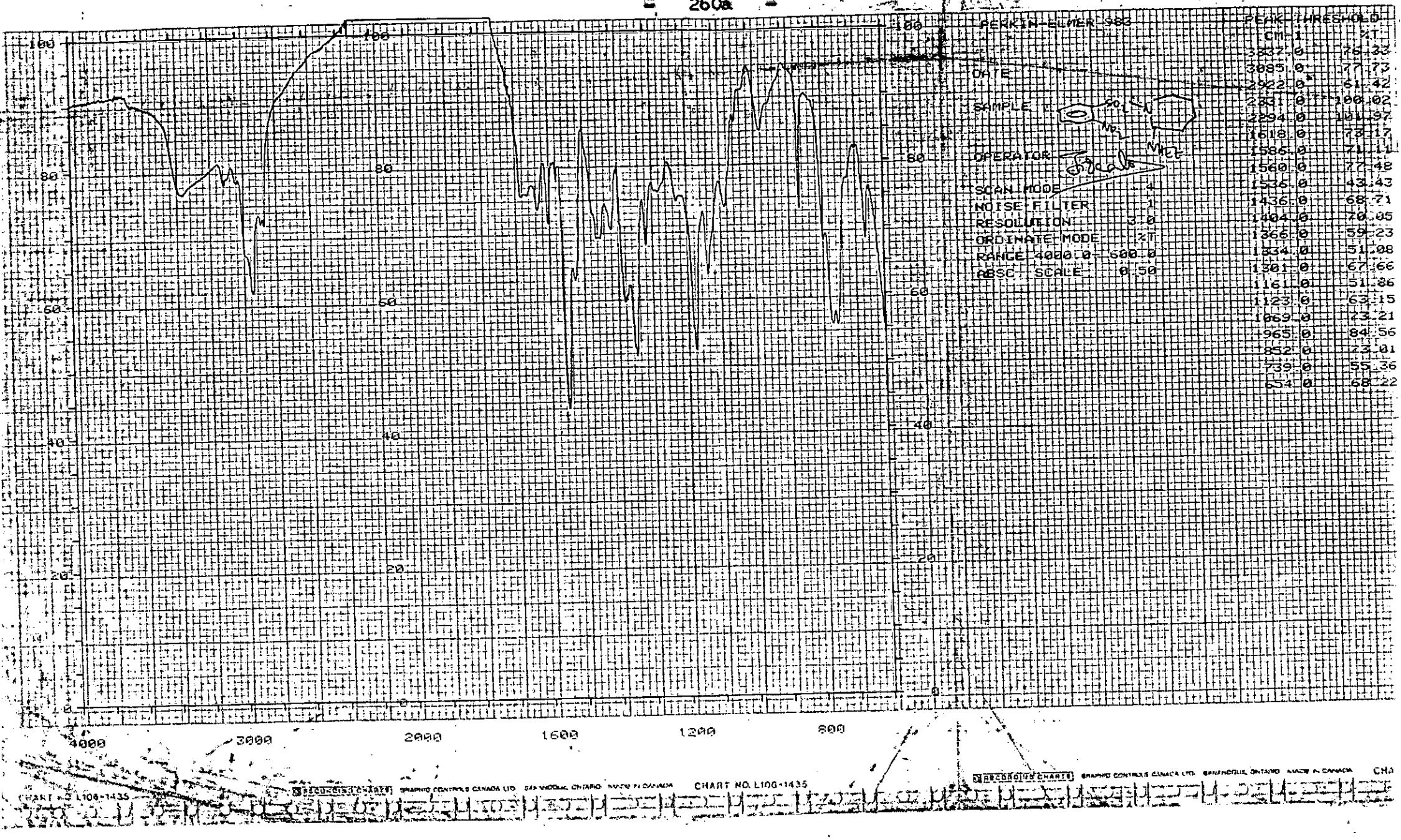


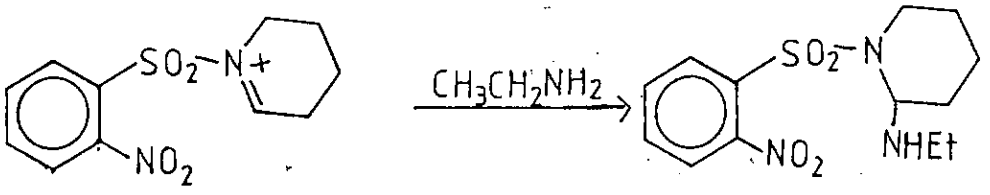


The reaction proceeds through an initial reduction of the nitro group to an amino function thereby forming a diamine intermediate. This is not isolated, but reacts immediately by loss of one amino function. The amine loss is achieved by preferential protonation of the more basic amino function followed by the nucleophilic displacement by the other amino group's nitrogen lone pair of electron. The cleavage of the protonated amine leads to a hetero ring closure. (See scheme 14).

In exploration of the utility of other amines (apart from ammonia) for possible preparation of N-substituted thiadiazines, the N-tetrahydropyridinium salt 269 was reacted with ethylamine to give a secondary amine, N-(2-nitrobenzenesulphonyl) -2-ethylaminopiperidine. Chilled liquid ethylamine was added to the iminium salt under dry and inert conditions at room temperature as described earlier for ammonia. The reaction gave a solid mixture which was separated by flash chromatography to give a brown solid m.p. 140-141°.

Infra-red analysis of the solid showed absorption at 3337 cm^{-1} (NH stretch), 3085, 2922 (-CH stretch of piperidine) 1618 cm^{-1} (NH deformation). Absorptions at 1536 and 1334 cm^{-1} represented the Nitro group's symmetric and asymmetric stretching vibrations. The $-SO_2N$ absorptions appeared at 1366 and 1160 cm^{-1}.


PERKIN-ELMER 580
DATE
SAMPLE
OPERATOR
SCAN MODE
NOISE FILTER 1
RESOLUTION 3.0
ORDINATE MODE %T
RANGE 4000.0- 600.0
ABSC. SCALE 0.50
PEAK THRESHOLD
CM-1 %T
3837.0 76.33
3085.0 77.73
2922.0 61.42
2851.0 100.02
2294.0 101.37
1618.0 73.17
1586.0 71.11
1560.0 77.48
1536.0 43.43
1436.0 68.71
1404.0 70.05
1366.0 59.23
1334.0 51.08
1301.0 67.66
1161.0 51.86
1123.0 63.15
1069.0 73.21
965.0 84.56
852.0 73.01
739.0 55.36
654.0 68.22
4000
3000
2000
1600
1200
800
CHART NO. L106-1435



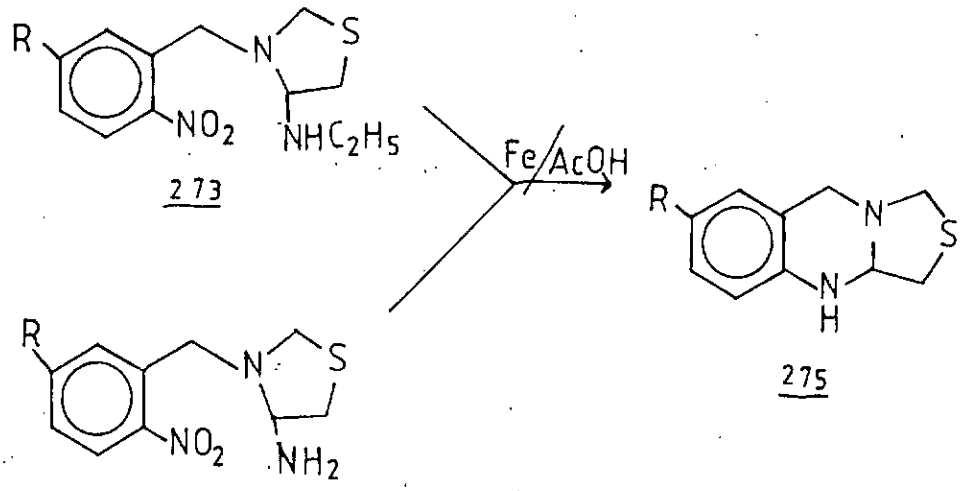
269 272

The nitroamine obtained was reductively cyclised with iron in acetic acid (as carried out earlier on the 2-amino compound). The resulting heterocyclic compound obtained showed the same melting point as the product from the cyclisation of N-(2-nitrobenzenesulphonyl)-2-amino piperidine.

All spectra obtained were identical to those obtained earlier. Thus the same 1, 2, 3, 4, 11, 11a-hexahydro-pyrido (1, 2-b)(1,2,4) benzothiadiazine-6,6-dioxides was obtained on cyclisation. This indicated that the ethyl amino grouping was preferentially protonated, relative to the amino function and therefore preferentially cleaved.

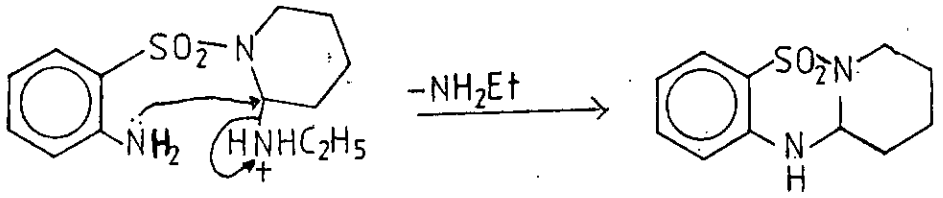
This appears consistent with earlier work by our group on quinazolines [83], in which 3-(2-nitrobenzyl) -4-ethylamino thiazolidine was cyclised with iron in glacial acetic acid giving 4-H,-3, 3a - dihydrothiazolo

(4,3-b) quinazoline 275. This was the product obtained when 3-(2-nitrobenzyl)-4-aminothiazolidine 274 was similarly cyclised.



273 275 274

The preferential cleavage may be due to the inductive effect of the ethyl group making the attached nitrogen atom more basic and therefore preferentially protonated.



271

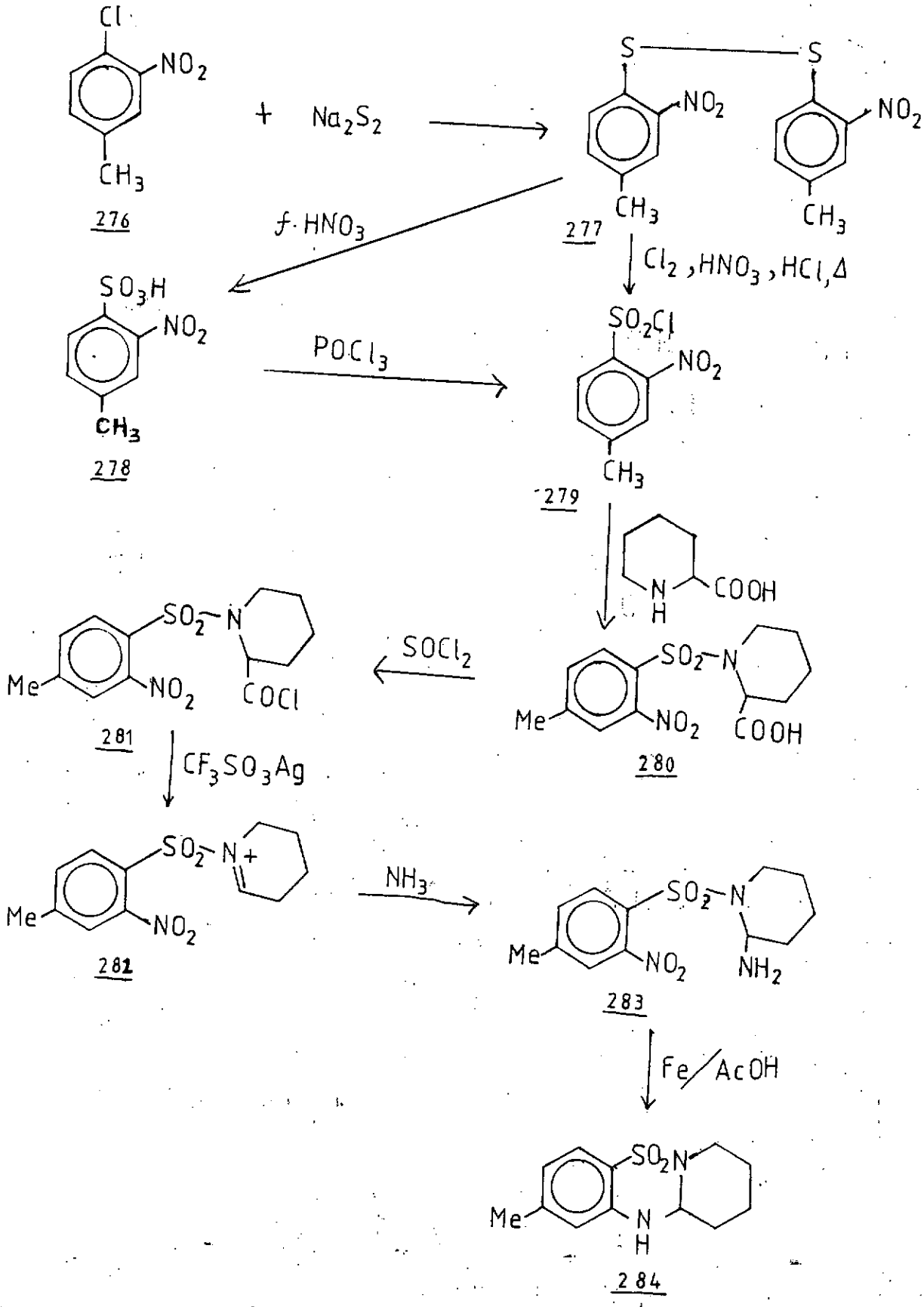
SYNTHESIS OF SUBSTITUTED PYRIDO(1,2-a)(1,2,4)BENZOTHIADIAZINE-6, 6-DIOXIDES:

1, 2, 3, 4, 11, 11a-Hexahydro-9-Methyl-pyrido (1, 2-b) (1,2,4) benzothiadiazine-6, 6-dioxide:

After successful completion of the synthesis of the parent skeleton attempts at the construction of the substituted analogues was embarked upon. The first attempt was to achieve the 9-methyl substituted pyridobenzothiadiazine-6, 6-dioxide. The synthetic design to obtain this analogue is delineated in scheme 15 below:

The synthesis started from the commercially available 4-chloro-3-nitrotoluene which was refluxed with sodium disdisulphide (formed *in situ* from sodium sulphide and elemental sulphur), to give 4,4'-dimethyl-2,2'-dinitrodiphenyl disulphide *via* a nucleophilic substitution reaction.

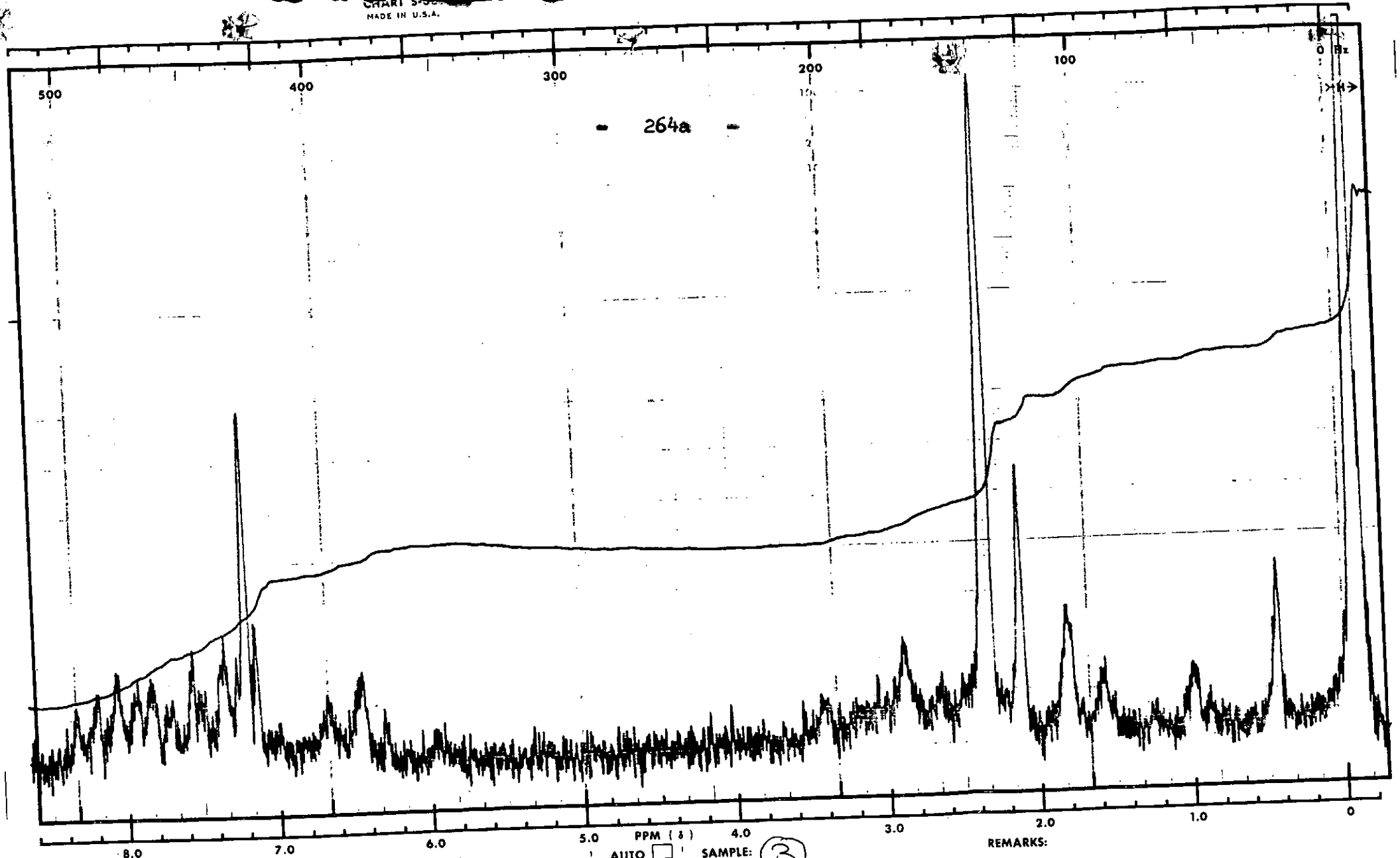
The replacement of the chlorine atom was possible because of the presence of the *ortho* nitro group even though the counteracting effect of the methyl group was apparent from the moderate yields obtained from the nucleophilic substitution reaction. The yield was relatively low (30 %). The use of the strong nucleophile: disulphide ion did not make much difference. Melting point of the disulphide corresponded with the literature value m.p. 164^{o} [86].


Cl
NO2
CH3
276
+ Na2S2
S
S
NO2
NO2
CH3
CH3
277
f·HNO3
Cl2, HNO3, HCl, Δ
SO3H
NO2
CH3
278
POCl3
SO2Cl
NO2
CH3
279
N
H
COOH
SO2
N
Me
NO2
COOH
280
SOCl2
SO2
N
Me
NO2
COCl
281
CF3SO3Ag
SO2
N+
Me
NO2
282
NH3
SO2
N
Me
NO2
NH2
283
Fe/AcOH
SO2N
Me
N
H
284

Scheme 15

MADE IN U.S.A.

- 264a -



SWEEP OFFSET (Hz): 0220

SPECTRUM AMPLITUDE: 63

INTEGRAL AMPLITUDE: 2

SPINNING RATE (RPS): 33

MANUAL

SWEEP TIME (SEC): 50 250

SWEEP WIDTH (Hz): 25 50 100 250 500

FILTER: W 2 3 4 5 6 7 8

RF POWER LEVEL: 0.05

AUTO ☐

(250)

(500)

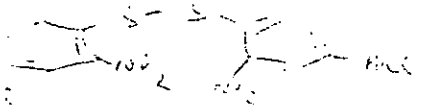
(2)

(.05)

SAMPLE: (3)

SOLVENT: $CDCl_3$

REMARKS:



varian
analytical instrument division

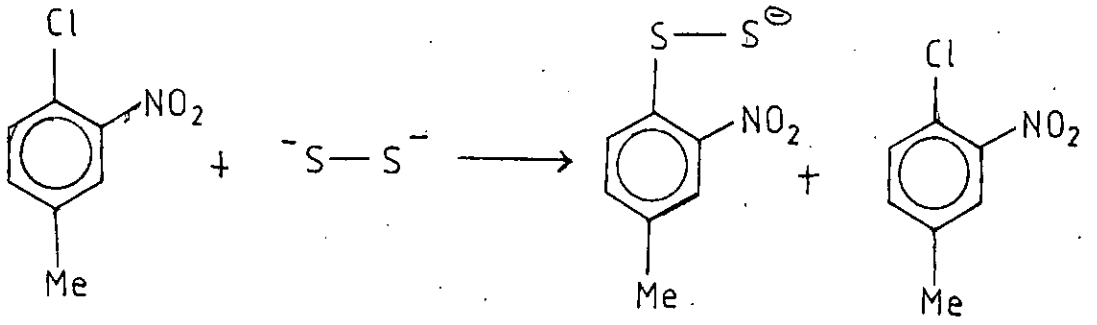
DATE: 22/10/87

OPERATOR: J.O. Olafinlikan

60 MHz NMR
SPECTRUM NO.

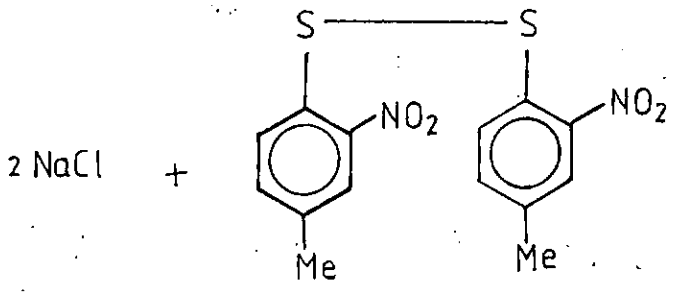
The substitution reaction is presumed to occur through a step wise reaction thus:

$$Na_2S + S \longrightarrow Na\text{-}S\text{-}S\text{-}Na \longleftrightarrow 2Na^{+} + {}^{(-)}S\text{-}S^{(-)}$$



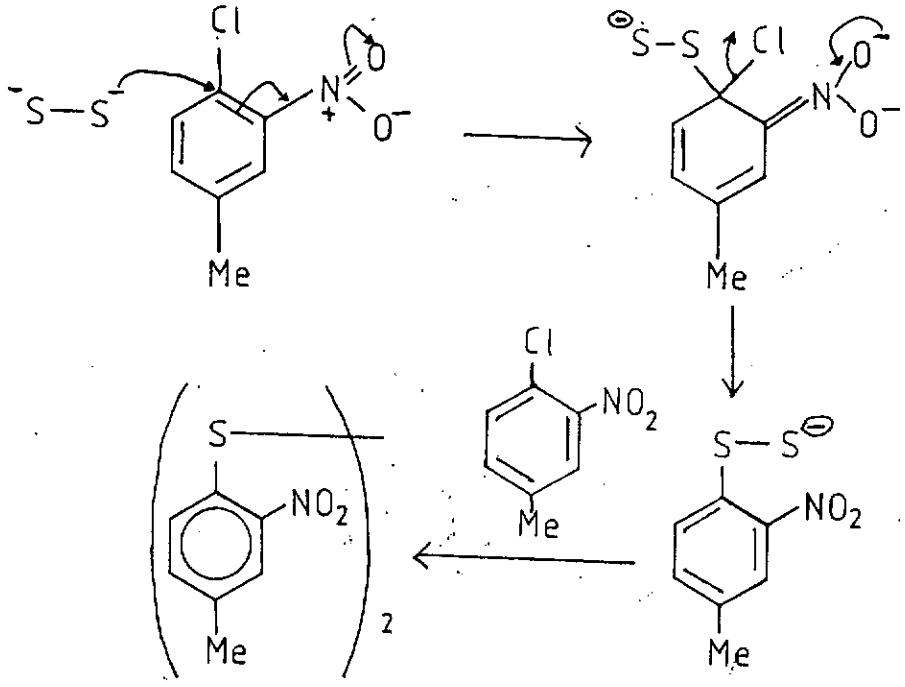
276

276a



277

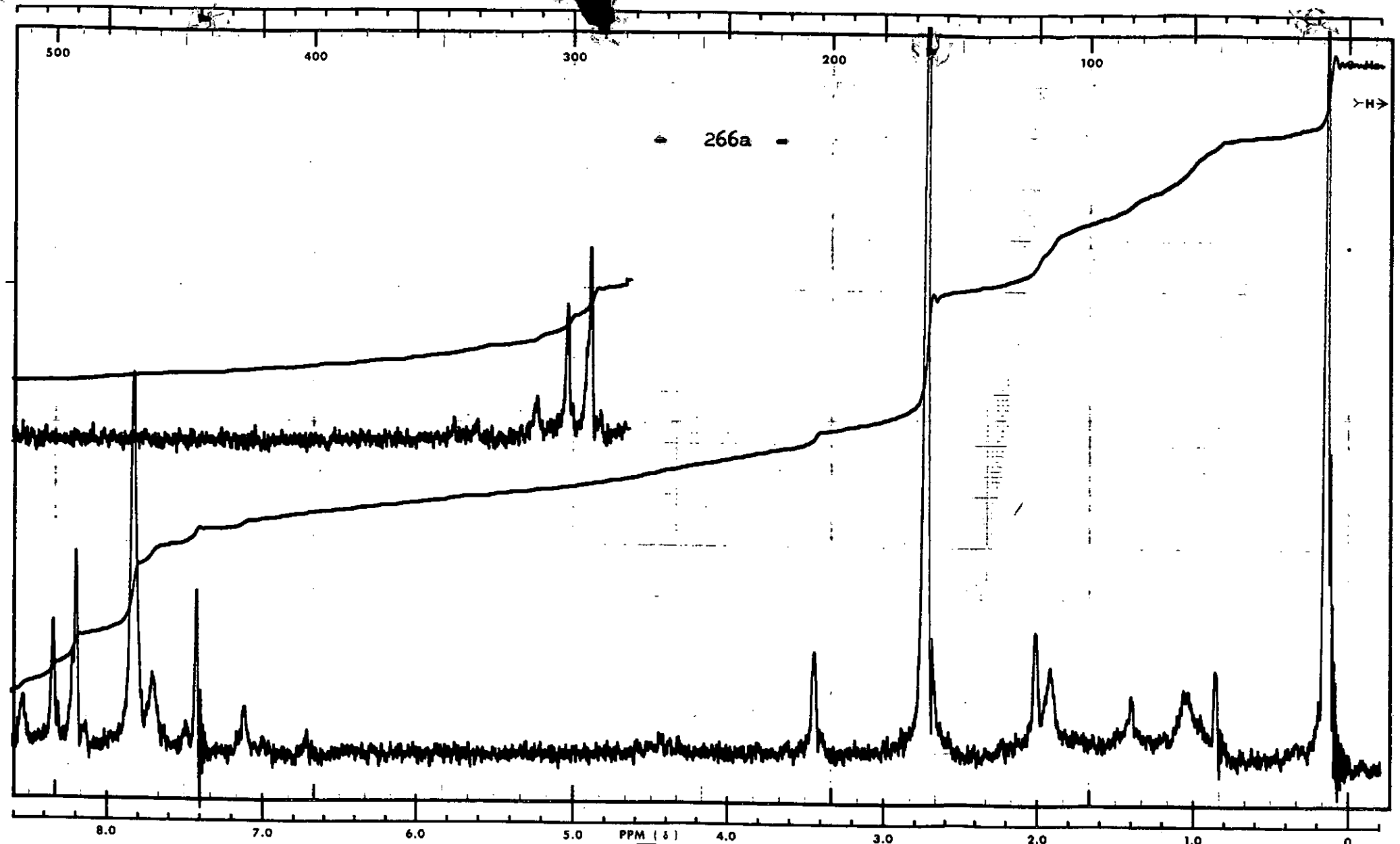
The anion 276a formed then attacks another molecule of 4-chloro-3-nitrotoluene to form the disulphide.



The conversion of 4,4'-dimethyl-2, 2'-dinitrodiphenyl disulphide to 4-methyl-2-nitrobenzenesulphonyl chloride was achieved *via* chlorine oxidation in nitric acid [84].

Recrystallisation of the product obtained from Pet-ether gave crystalline plates, m.p. 97 - 98°(lit 97 - 98°)[87].

The nitric acid was responsible for the breaking of the disulphide bond and converting the sulphide to the sulphonic acid. The sulphonic acid formed was converted *in situ* to the sulphonyl chloride by the chlorine gas.



SWEEP OFFSET (Hz): 000/200
SPECTRUM AMPLITUDE: 12.5
INTEGRAL AMPLITUDE: 4
SPINNING RATE (RPS): 43

MANUAL

SWEEP TIME (SEC): 50 250
SWEEP WIDTH (Hz): 25 50 100 250 500
FILTER: 1 2 3 4 5 6 7 8
RF POWER LEVEL: 0.05

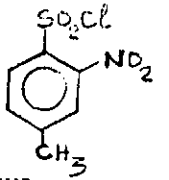
AUTO ☐

(250)
(500)
(2)
(.05)

SAMPLE: 2o

SOLVENT: $CDCl_3$

REMARKS:

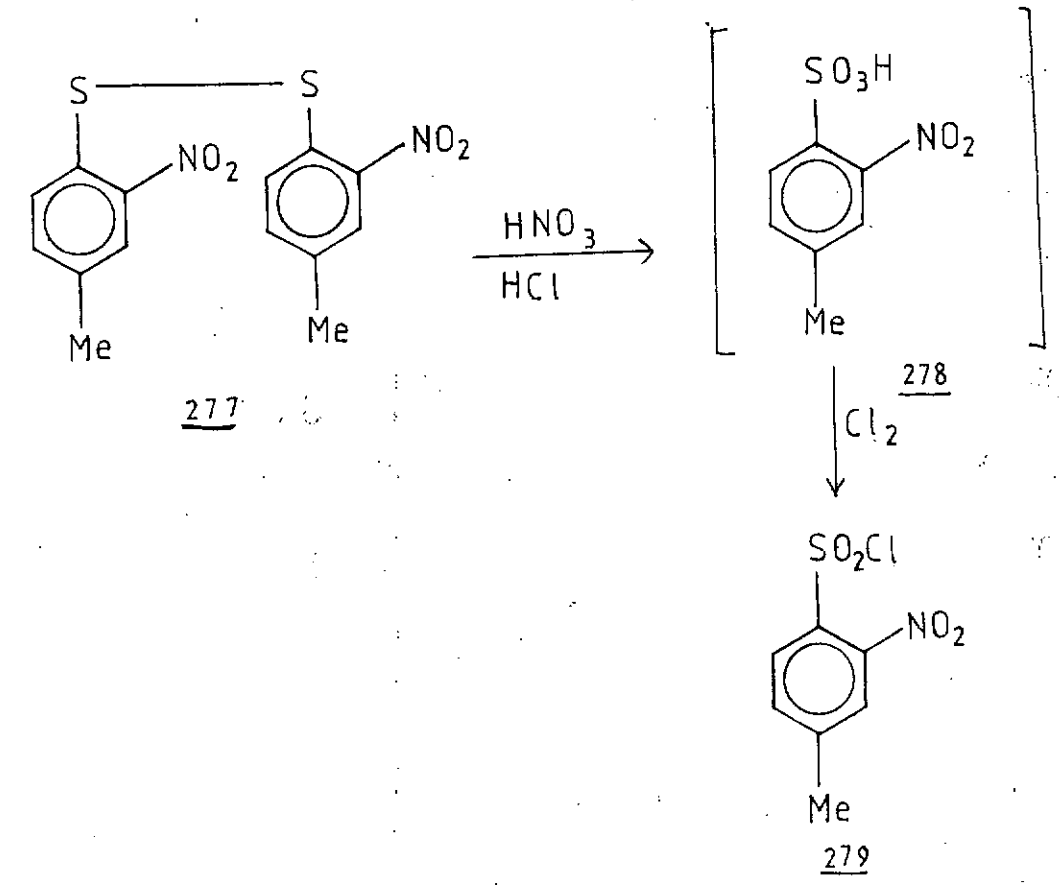


varian
analytical instrument division

DATE: 26/11/82

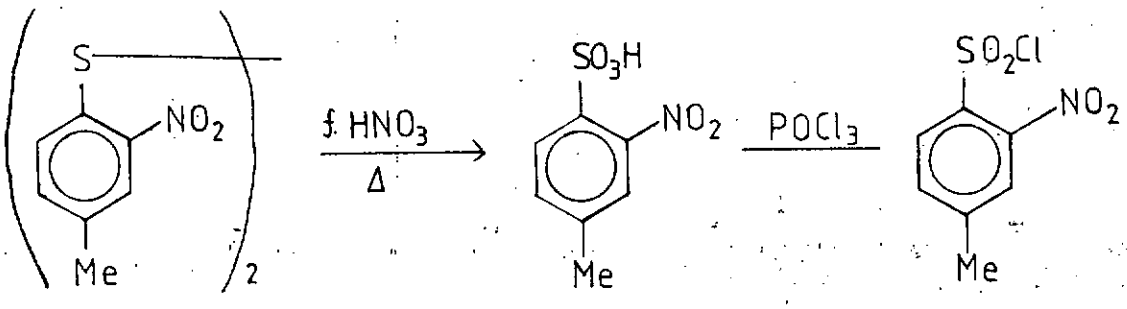
OPERATOR: Ben Beaya

60 MHz NMR
SPECTRUM NO.



277 279

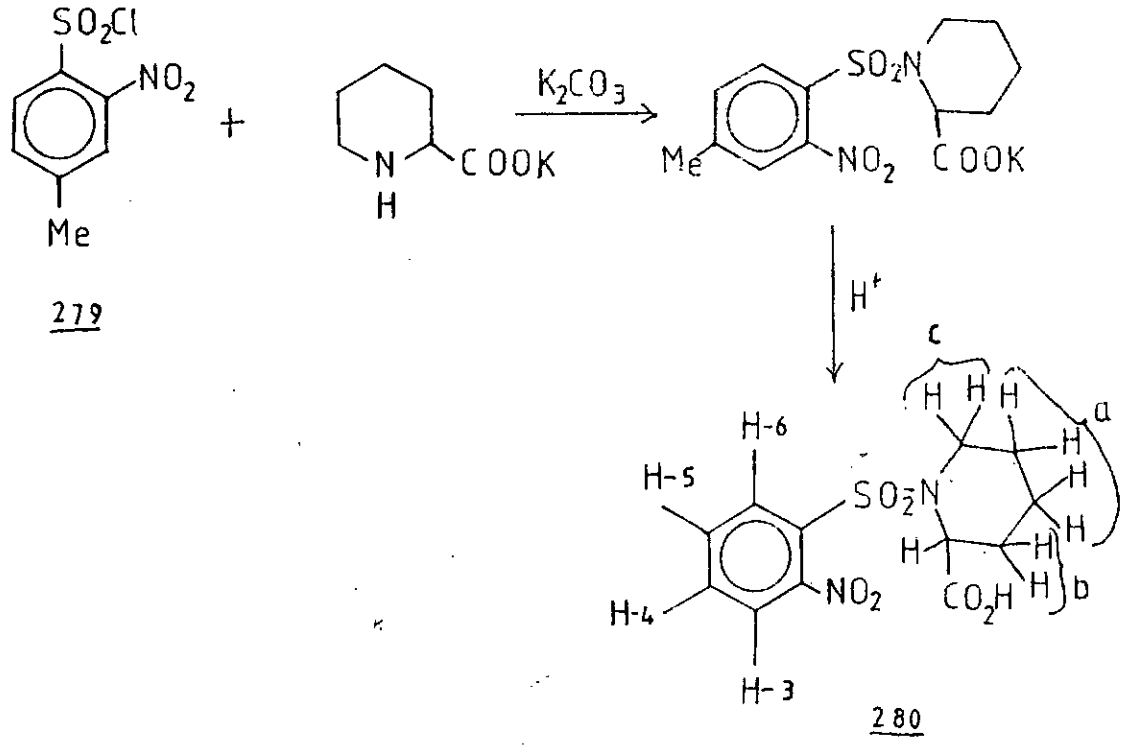
The preparation of the sulphonyl chloride was also carried out by adapting Pfieffer and Jager's method[88]. Fuming nitric acid (S. G. 1.52) was added cautiously to the disulphide and heated for 30 minutes to give the sulphonic acid. The sulphonic acid obtained was converted to the sulphonyl chloride with phosphorus oxychloride.



277 278 279

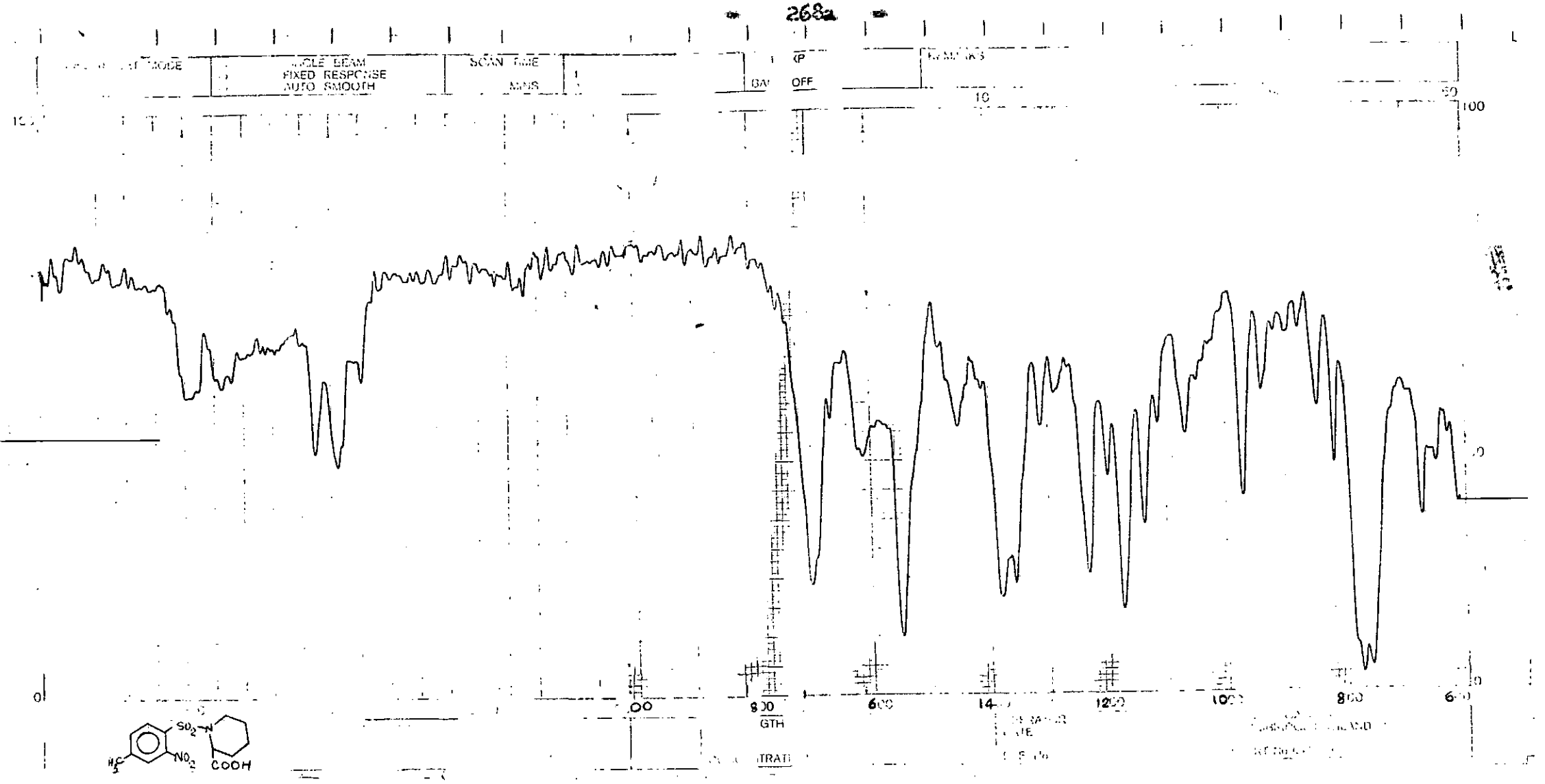
The product obtained here was comparable to the one obtained by the chlorine oxidation method used earlier.

The condensation of the 4-methyl-2-nitrobenzenesulphonyl chloride obtained with DL-piperidine-2-carboxylic acid was mediated by potassium carbonate in THF. The condensation reaction is basically a Schotten-Baumann reaction identical with the reaction of the unsubstituted analogue discussed earlier.

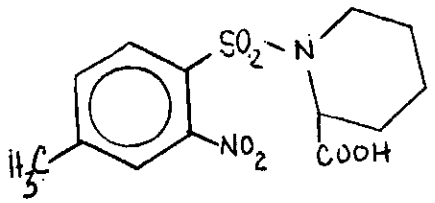


On work-up of the carbonate reaction mixture, a yellow oil which later solidified was clean on t.l.c. and did not require further purification. m.p. 169-170°C.

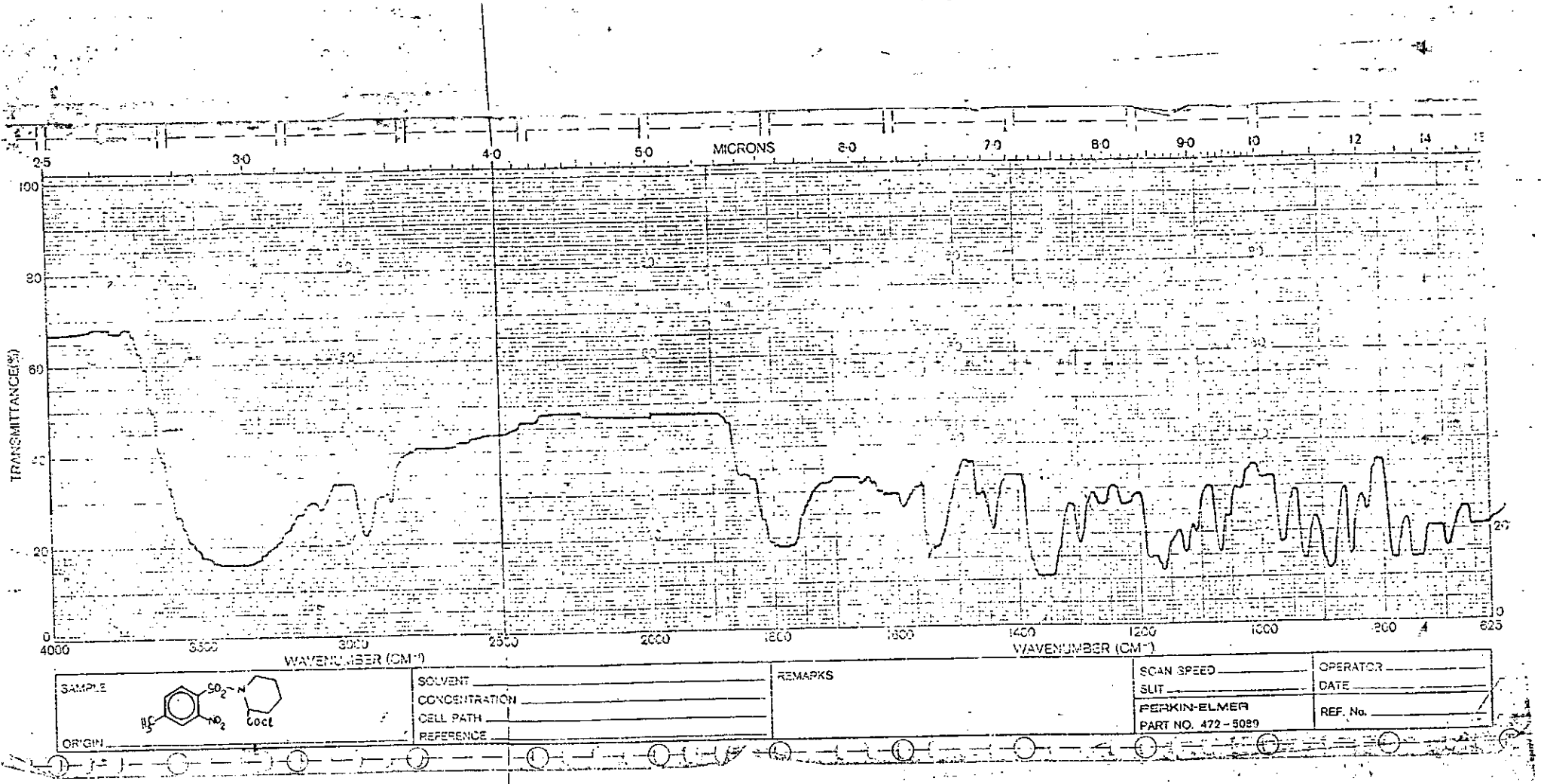
268a


SINGLE BEAM
FIXED RESPONSE
AUTO SMOOTH
SCAN TIME
MINS
OFF
10
50
100
800
600
1200
1000
800
GTH

SO2
N
NO2
H3C
COOH



. A10

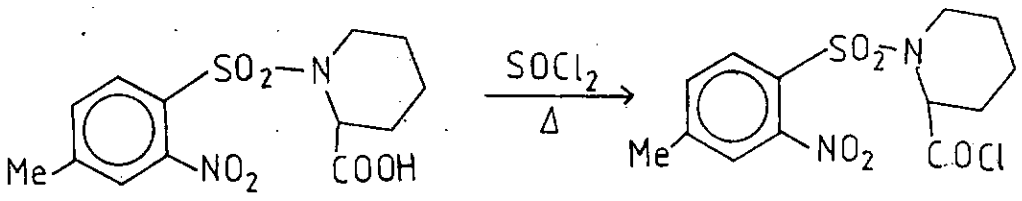

MICRONS
2·5
3·0
4·0
5·0
6·0
7·0
8·0
9·0
10
12
14
TRANSMITTANCE(%)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)
SAMPLE
ORIGIN
SOLVENT
CONCENTRATION
CELL PATH
REFERENCE
REMARKS
SCAN SPEED
SLIT
PERKIN-ELMER
PART NO. 472-5029
OPERATOR
DATE
REF. No.

The infra-red spectrum of the N-(4-methyl-2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid product showed absorptions at 3500 (-OH of the acid), 3060, 2980 cm^{-1} (C-H absorption of the piperidine ring), 1700 cm^{-1} (-C=O of the acid) 1550, 1360 cm^{-1} (nitro group), while the SO_2-N< grouping had strong absorption at 1380, 1180 cm^{-1}. ^{1}H-NMR in $CDCl_3$ gave a 4-H multiplet at δ 1.39 (a piperidine protons type 'a'), a 2H multiplet at δ 1.48 represented piperidine proton type 'b'. The methyl group proton absorbed as a 3H singlet at δ2.49, the piperidine proton type 'c' absorbed as a 2H doublet of a doublet at δ 3.60 while the 1H broad exchangeable with D_2O. represented the -OH of the acid. The base proton absorbed as a doublet at δ 4.70. The aromatic 2H proton for H-3, H-5 absorbed as multiplet at δ 7.50 while the 1H doublet of H-6 absorbed at δ 7.95.

The microanalysis of the compound gave satisfactory data as the values obtained were consistent with theoretical (expected) values.

The acid adducts obtained was converted to N-(4-methyl-2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid chloride on gentle reflux with thionyl chloride for 2h. This is a departure from Alo et.al's earlier method[22] of stirring at room temperature for 24h as it seems refluxing the acid with a chlorinating agent will not cleave any bond in the molecule.

The mechanism of the conversion to acid chloride is the same as discussed earlier for the unsubstituted analogue.



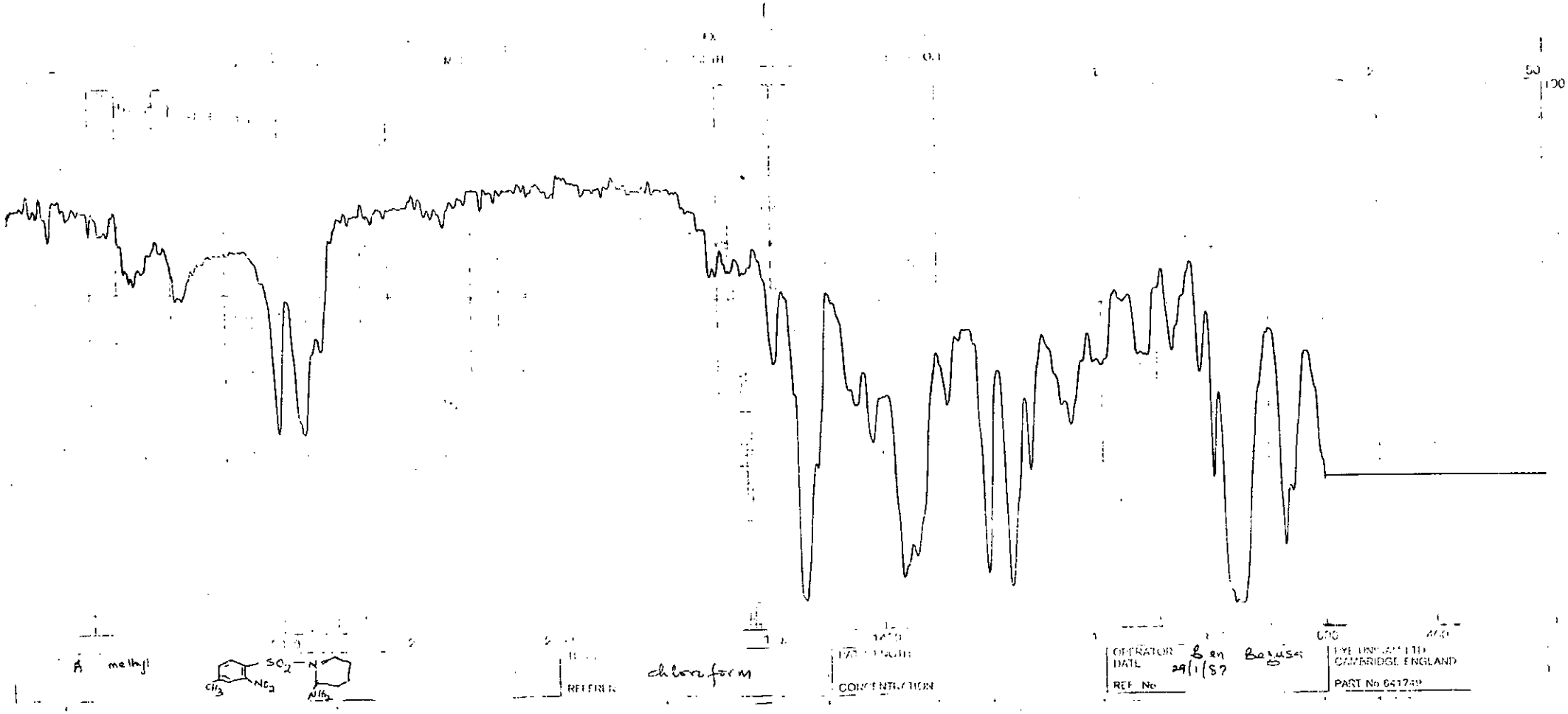
280 281

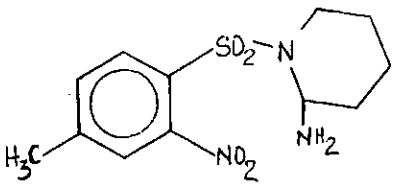
The i.r. spectrum of the acid chloride showed a strong band at 1780 cm^{-1} for the carbonyl bond. This is a shift from the 1700 cm^{-1} of the acid carbonyl which is due to the inductive effect of the chlorine atom attached to the carbonyl group.

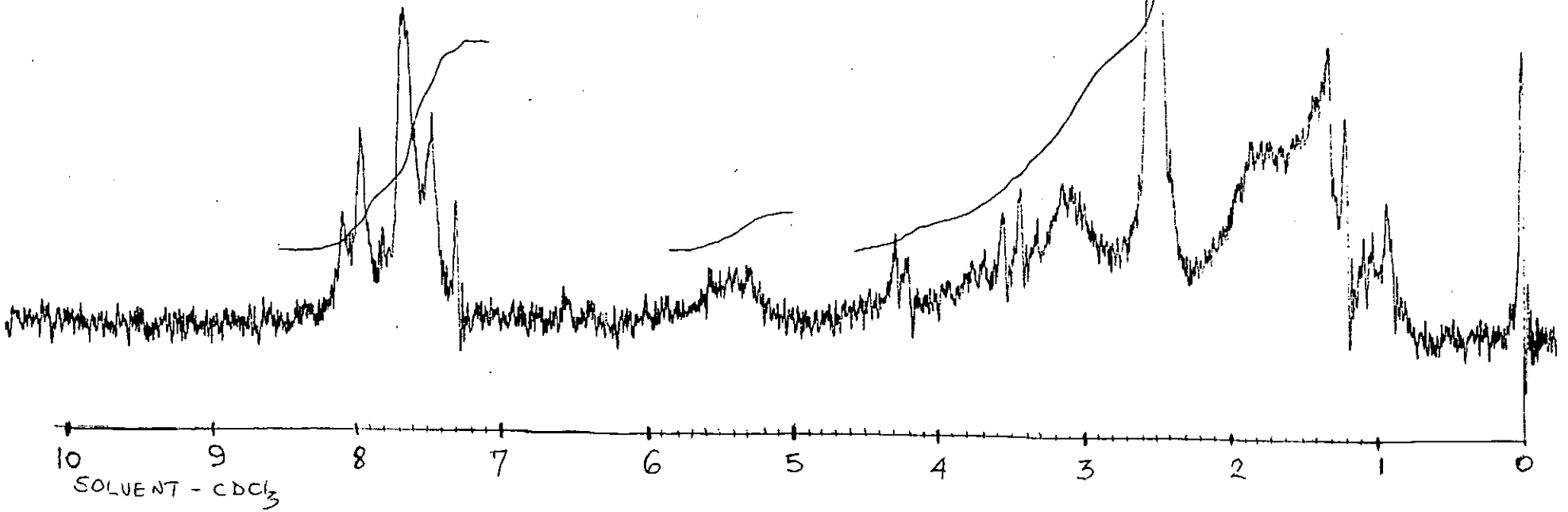
On treatment of the acid chloride with silver trifluoromethanesulphonate in dichloromethane solution gave an immediate effervescence which subsided only after about 1hr. After injection of concentrated ammonia and work-up, the product showed two major spots on t.l.c. The components were separated by column chromatography.

- 270 -

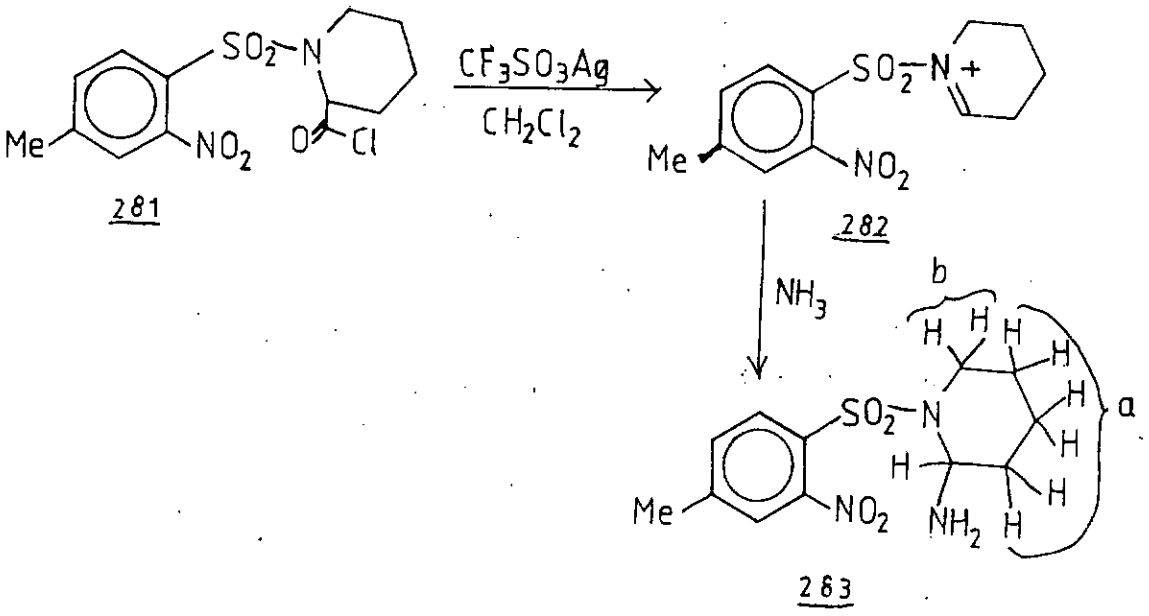
The mechanism of the conversion to acid chloride is


A methyl
chloroform
OPERATOR
DATE 29/1/87
REF No
PART No 661749


SO2
N
NH2
H3C
NO2


10
9
8
7
6
5
4
3
2
1
0
SOLVENT - CDCl3

appeared as a triplet at δ 4.2 while the NH proton of the amino function absorbed at δ 5.4. The two ortho protons to the methyl group i.e. H-3, and H-5 absorbed at δ 7.6

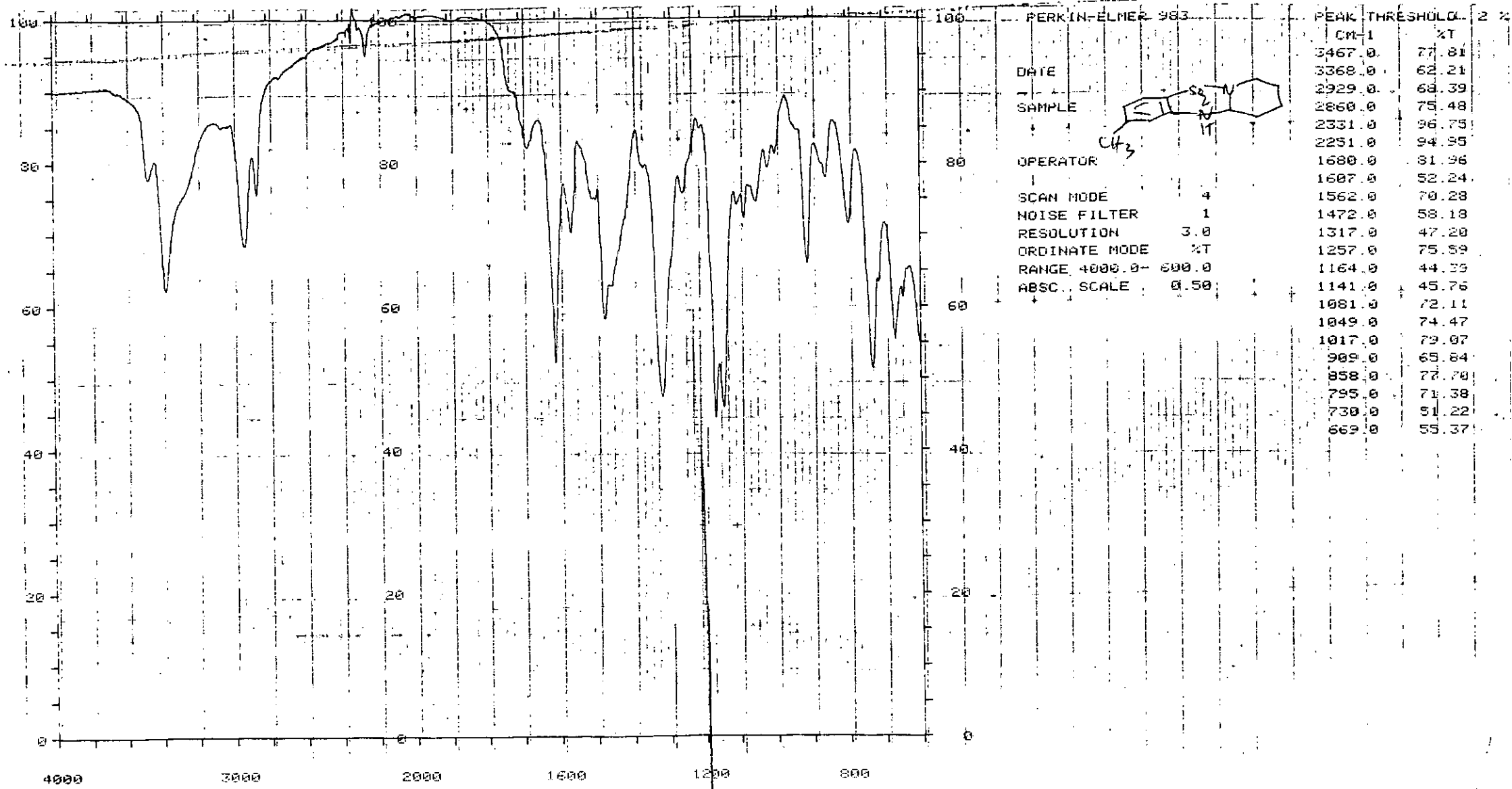


281 282 283

The infra-red spectrum of the nitroamine had absorptions at 3380 cm^{-1} (NH Stretching), 3000 and 2900 cm^{-1} (-CH stretching of the piperidine ring), 1600 (-C=C- of the aromatic ring), 1540 and 1340 cm^{-1} (NO_2 group) and the strong bands at 1365 and 1170 cm^{-1} represented the SO_2-N group.

The 'H-NMR spectrum in deuterated acetone showed a 6H multiplet at δ 1.2 - 1.8 (piperidine ring proton) type 'a', a 3-H- singlet at δ 2.6 represented the methyl group while the two protons adjacent to the nitrogen atom appeared at δ 3.2. The base proton of the amino group appeared as a triplet at δ 4.2 while the NH proton of the amino function absorbed at δ 5.4. The two ortho protons to the methyl group i.e. H-3, and H-5 absorbed at δ 7.6

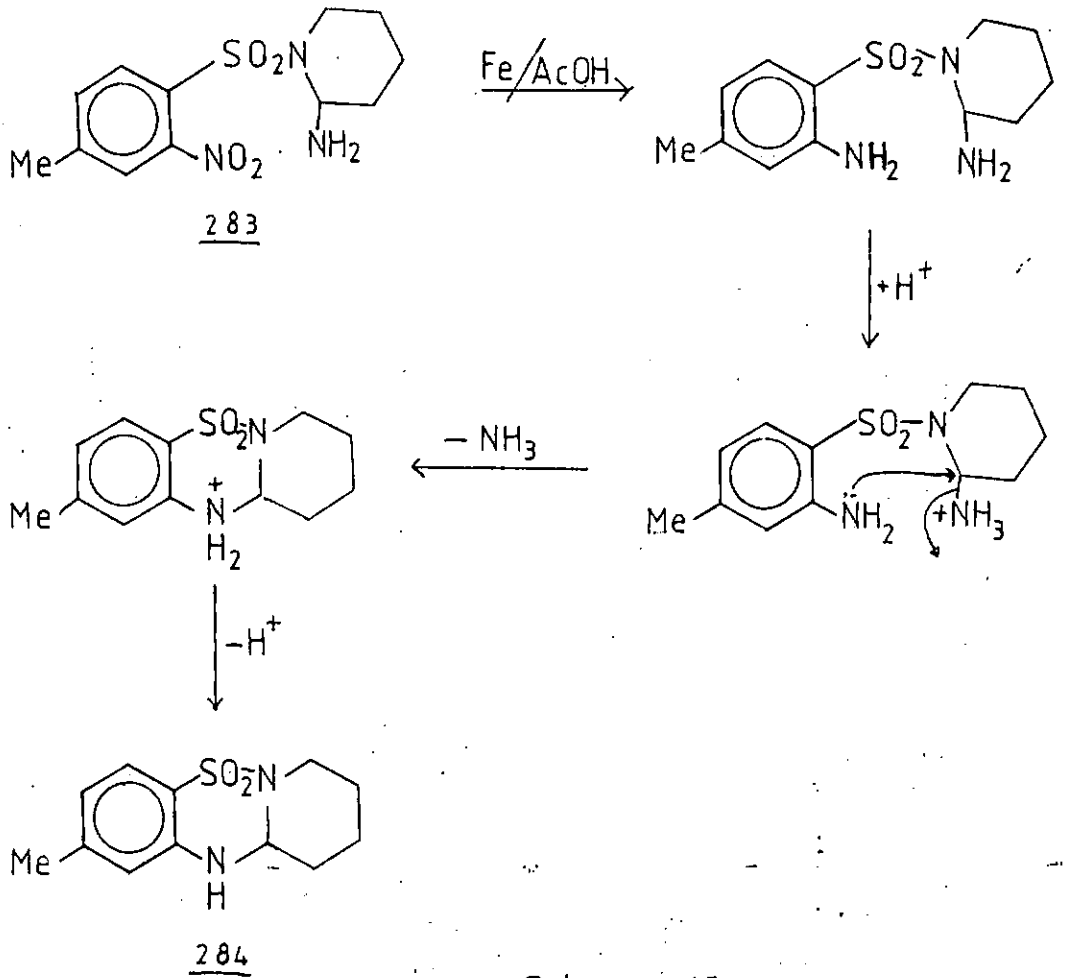
271a


PERKIN-ELMER 983
DATE
SAMPLE
OPERATOR
SCAN MODE 4
NOISE FILTER 1
RESOLUTION 3.0
ORDINATE MODE %T
RANGE 4000.0- 600.0
ABSC. SCALE 0.50
PEAK THRESHOLD 2 %
CM-1 %T
3467.0 77.81
3368.0 62.21
2929.0 68.39
2860.0 75.48
2331.0 96.75
2251.0 94.95
1680.0 81.96
1607.0 52.24
1562.0 70.28
1472.0 58.18
1317.0 47.20
1257.0 75.59
1164.0 44.23
1141.0 45.76
1081.0 72.11
1049.0 74.47
1017.0 79.07
909.0 65.84
858.0 77.70
795.0 71.38
730.0 51.22
669.0 55.37
100
80
60
40
20
0
4000
3000
2000
1600
1200
800

while the H-6 proton ortho to the sulphonyl group absorbed at δ8.0.

The mechanism is the same as reported for the formation of iminium salts for the unsubstituted analogues.

Reductive cyclisation of the N-(4-methyl-2-nitrobenzenesulphonyl)-2-aminopiperidine was achieved with a mixture of iron filings and iron dust in acetic acid and refluxing at 128-130° for 12h . On work-up, beige micro-crystals of 1,2,3,4,11, 11a-hexahydro-9- methyl-pyrido (1,2-b)(1,2,4) benzothiadiazines -6, 6-dioxide was obtained, m.p. 171 - 172°.

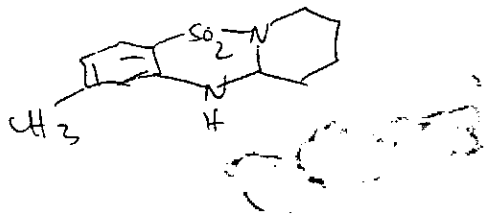


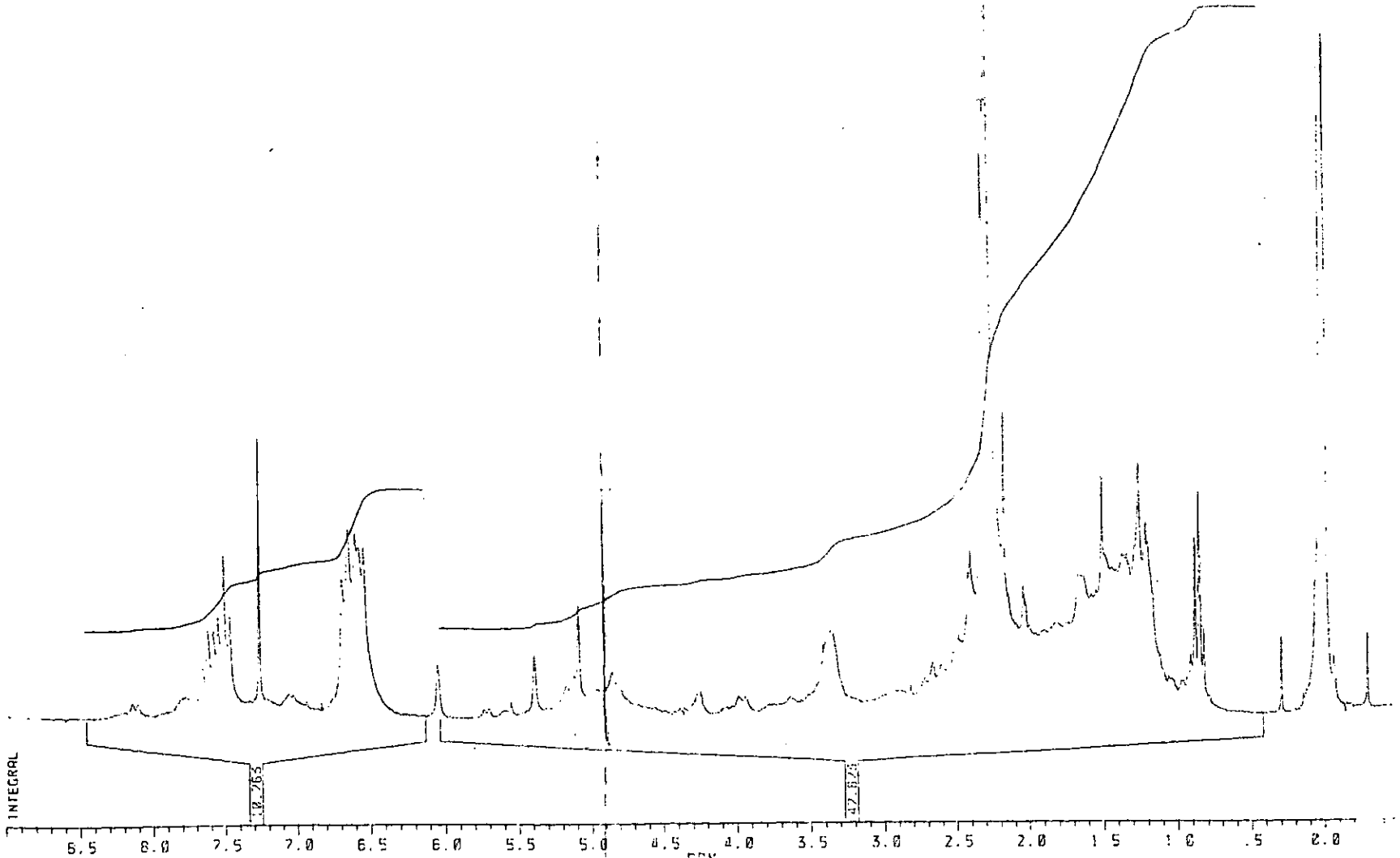
283

284

Scheme 15a

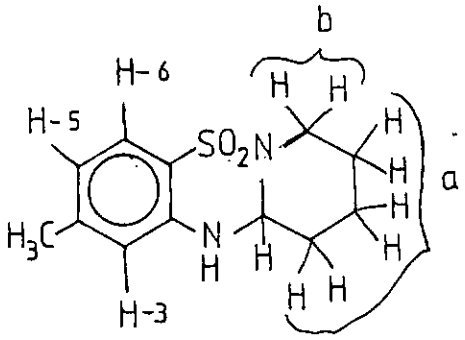
272a





The I.R. spectrum of the microcrystals showed the NH absorption at 3368 cm^{-1} and the -CH absorption of the piperidine ring at 2929 and 2860 cm^{-1}. The -C=C- of the aromatic ring appeared at 1608 cm^{-1}. While the sulphonamide function absorbed at 1317 and 1164 cm^{-1}.

The ^{1}H-NMR spectrum showed a 6H multiplet at δ1.1 - 1.7 for the piperidine ring. The methyl group signal appeared as a 3H singlet at δ2.3. Adjoining this signal is the 2H multiplet of the methylene group adjacent to the nitrogen of the piperidine ring. The N-C<u>H</u>-N proton absorbed as a 1H triplet at δ3.4 while the NH absorption of the secondary amine appeared as a broad signal at δ4.8. The two aromatic protons adjacent to the methyl group absorb as a 2H multiplet at δ6.7 while a 1H multiplet at δ7.55 represented one proton ortho to the sulphonyl group: H-6.



284

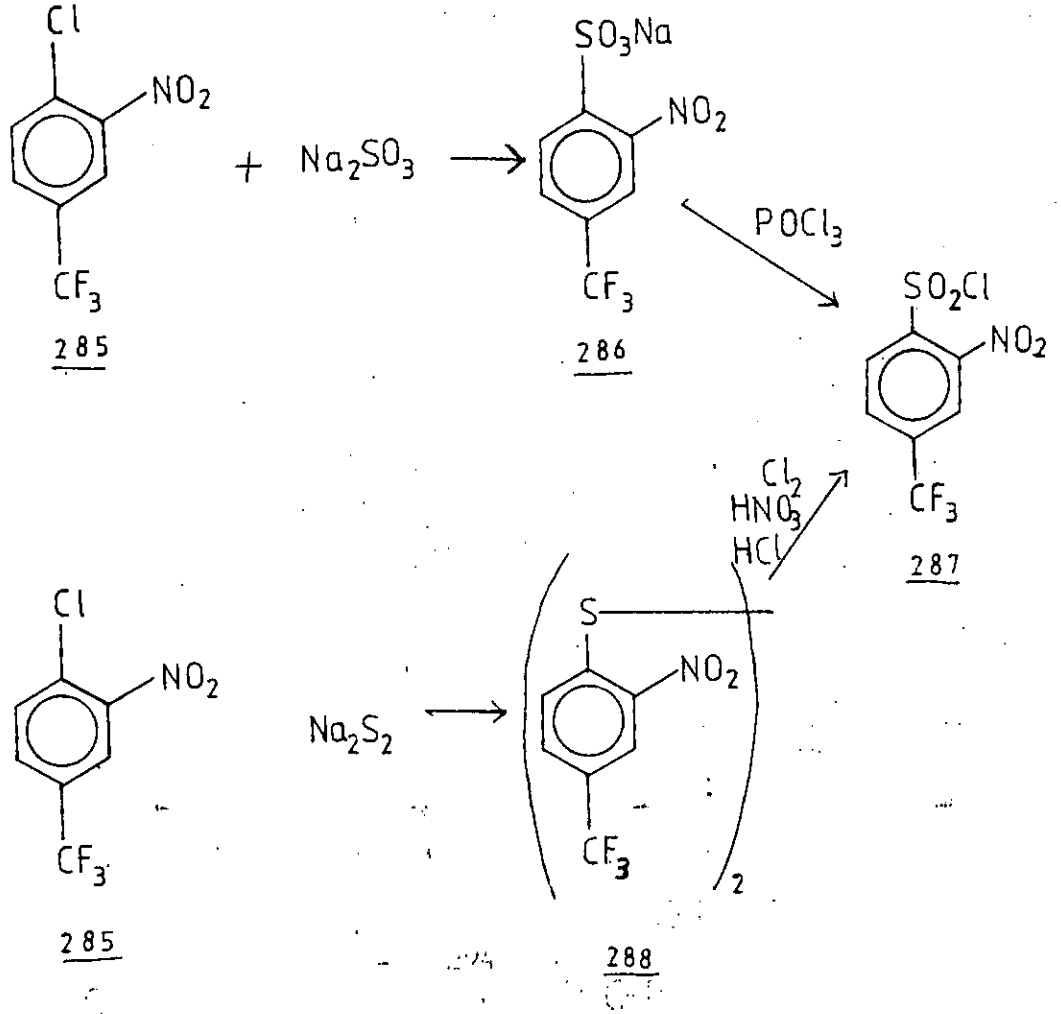
The reaction is presumed to occur <u>via</u> an initial reduction of the nitro group to give a diamine. Protonation of the amino group attached to the Sp^3 carbon leads to it's

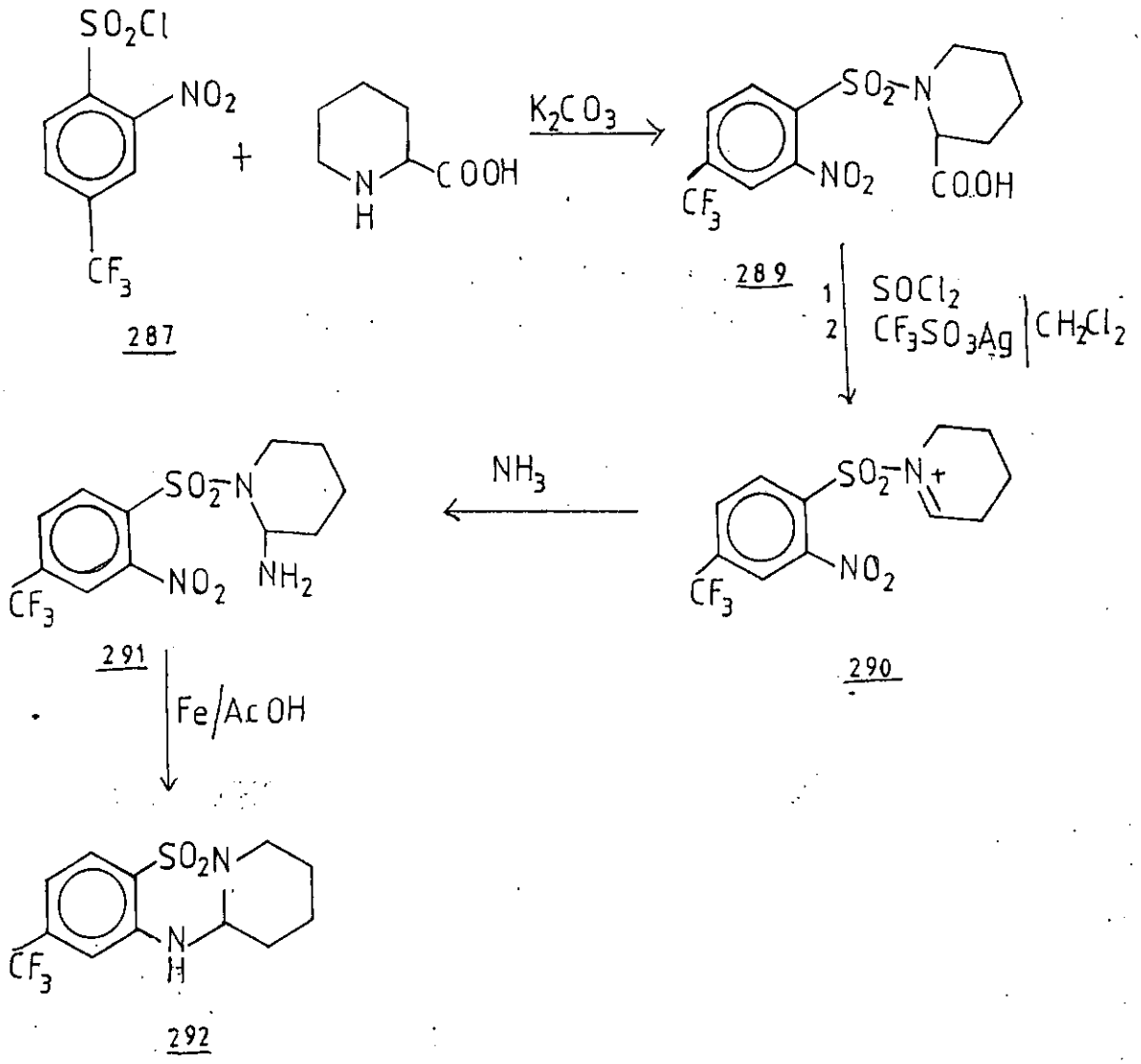
The I.R. spectrum of the microcrystals showed the NH

preferential cleavage to allow the intramolecular nucleophilic attack effecting the exo - tet ring closure. (See Scheme 15a).

9ααα-Trifluoromethyl - 1,2,3,4,11, 11a-hexahydropyrido (1, 2 - b)(1, 2, 4) benzothiadiazine - 6, 6 - dioxide:

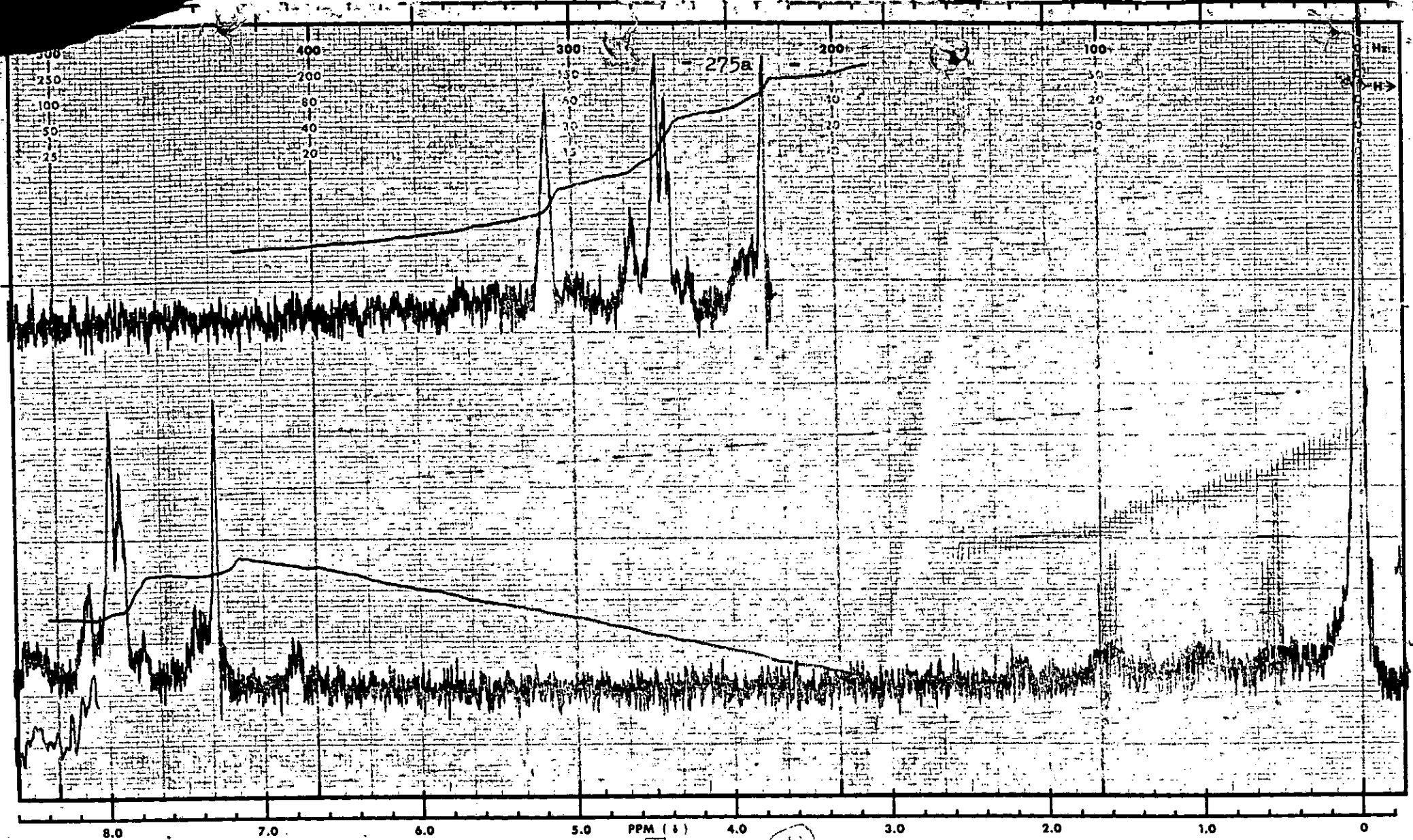
Trifluoromethyl substituted heterocycles are known to exhibit potent bioactivities. It was therefore of interest to attempt the construction of a trifluoromethyl analogue. The synthetic design for the preparation of the above compound is outlined in the scheme.





Scheme 16

Commercial 4-chloro-3-nitrobenzotrifluoride was converted to sodium 4-ααα-trifluoromethyl-2-nitro benzenesulphonate by an adaptation of Lint's method[89]. This was done by reacting sodium sulphite with 4-chloro-3-nitrobenzotrifluoride with vigorous stirring for 4h. The reaction is a nucleophilic attack on the ring by the



SWEEP OFFSET (Hz): 550

SPECTRUM AMPLITUDE: 65

INTEGRAL AMPLITUDE: 2

SPINNING RATE (RPS): 33

MANUAL

SWEEP TIME (SEC): 50 250 / AUTO ☐ (250)

SWEEP WIDTH (Hz): 25 50 100 250 500 (500)

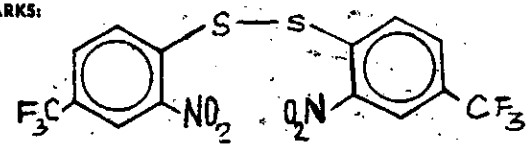
FILTER: 1 2 3 4 5 6 7 8 (2)

RF POWER LEVEL: 0.05 (.05)

SAMPLE: (4)

SOLVENT: $CDCl_3$

REMARKS:



varian analytical instrument division

DATE: 22/10/87

OPERATOR: J. C. McKinlay

60 MHz NMR

SPECTRUM NO.

sodium sulphite's lone pair of electron to form the sulphonate. This attack is possible because of the electron withdrawing effect of the trifluoromethyl group coupled with that of the ortho nitro group which make the chlorine atom susceptible to nucleophilic attack by the sodium sulphite.

The conversion of the sodium sulphonate to the 4-ααα-trifluoromethyl-2-nitrobenzenesulphonyl chloride was achieved with phosphorous oxychloride

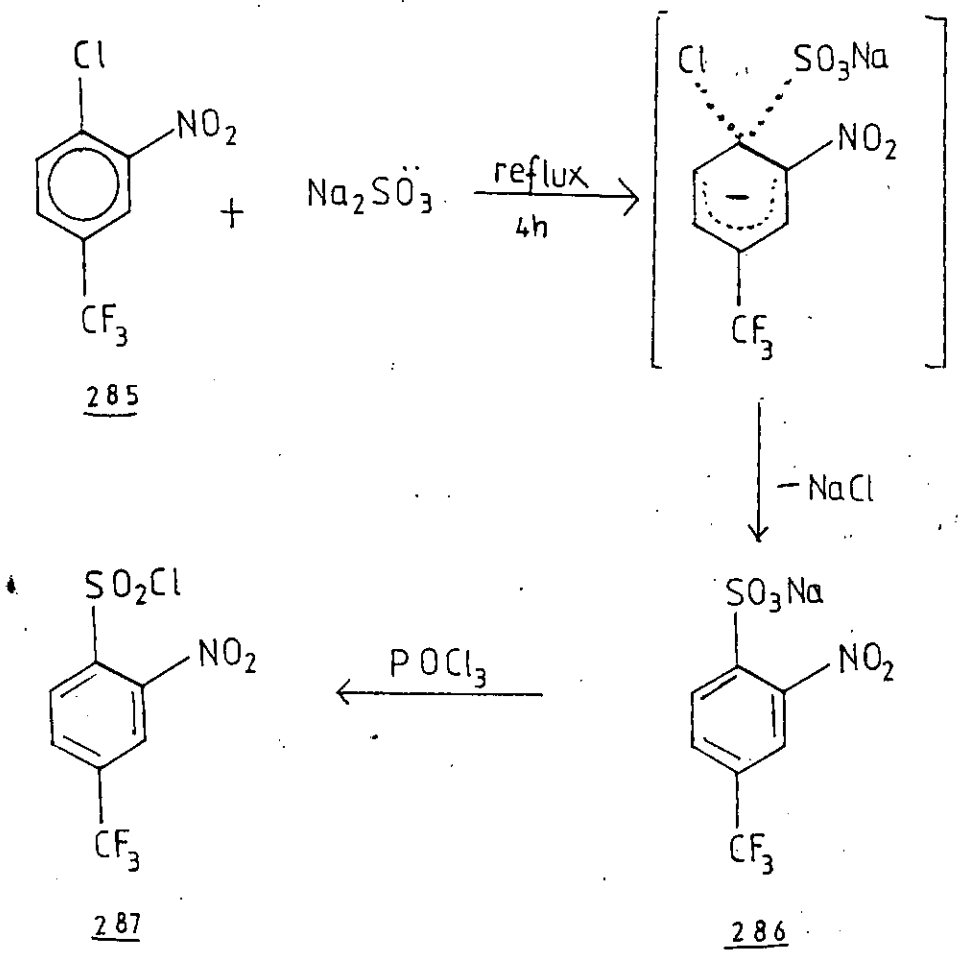
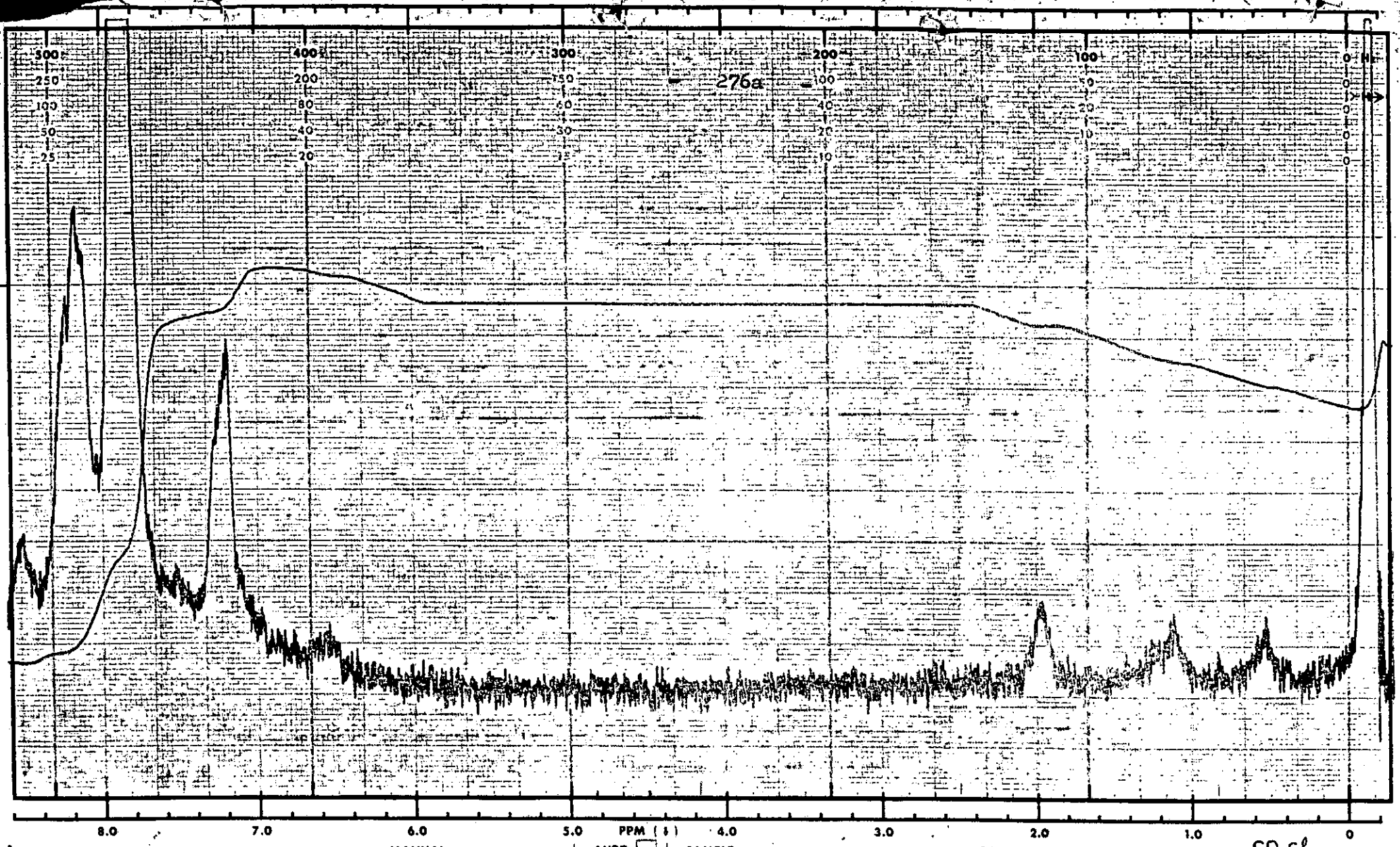


CHART 5-60T
MADE IN U.S.A.

276a



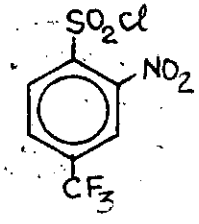
MANUAL | AUTO ☐

SWEEP OFFSET (Hz):	1000	SWEEP TIME (SEC): 50 250	(250)
SPECTRUM AMPLITUDE:	50	SWEEP WIDTH (Hz): 25 50 100 250 500	(500)
INTEGRAL AMPLITUDE:	1	FILTER: 1 2 3 4 5 6 7 8	(2)
SPINNING RATE (RPS):	42	RF POWER LEVEL: 0.05	(.05)

SAMPLE: 17

SOLVENT: $CDCl_3$

REMARKS:



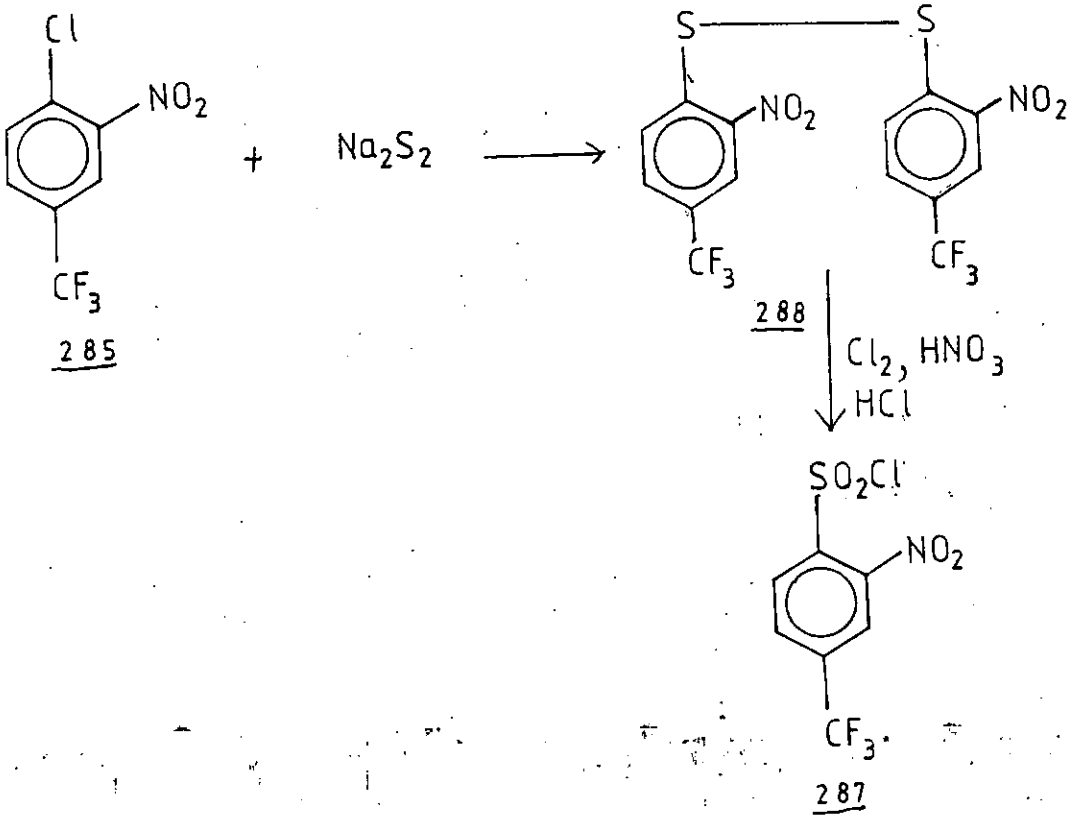
varian

60 MHz NMR

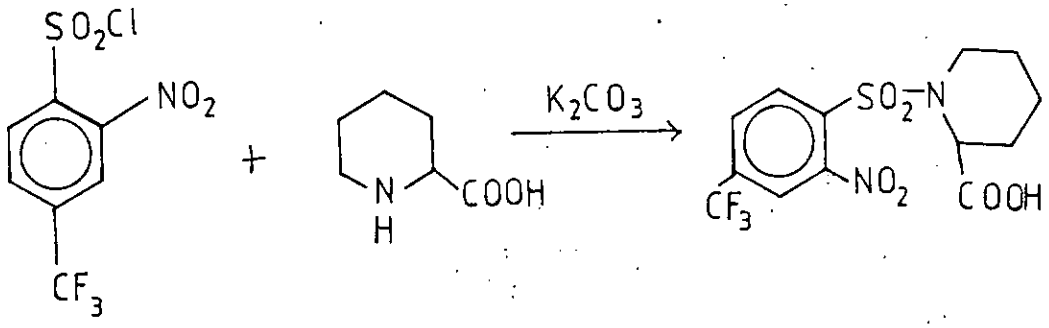
The sulphonyl chloride was also prepared from 4, 4'-ditrifluoromethyl-2, 2'-dinitrodiphenyl disulphide. The disulphide was obtained from the reaction of sodium disulphide and 4-chloro-3-nitrobenzo-trifluoride in the usual manner described earlier.

The disulphide underwent smooth chlorine oxidation in nitric acid like the methyl analogue. The sulphonyl chloride in this case however is an oil.

The ^{1}H-NMR spectrum of the red sulphonyl chloride oil showed a 2H-multiplet at δ7.9 representing protons ortho to the trifluoromethyl group (H-3 and H-5) while the H-6 proton ortho to the sulphonyl group absorbed at δ 8.2.



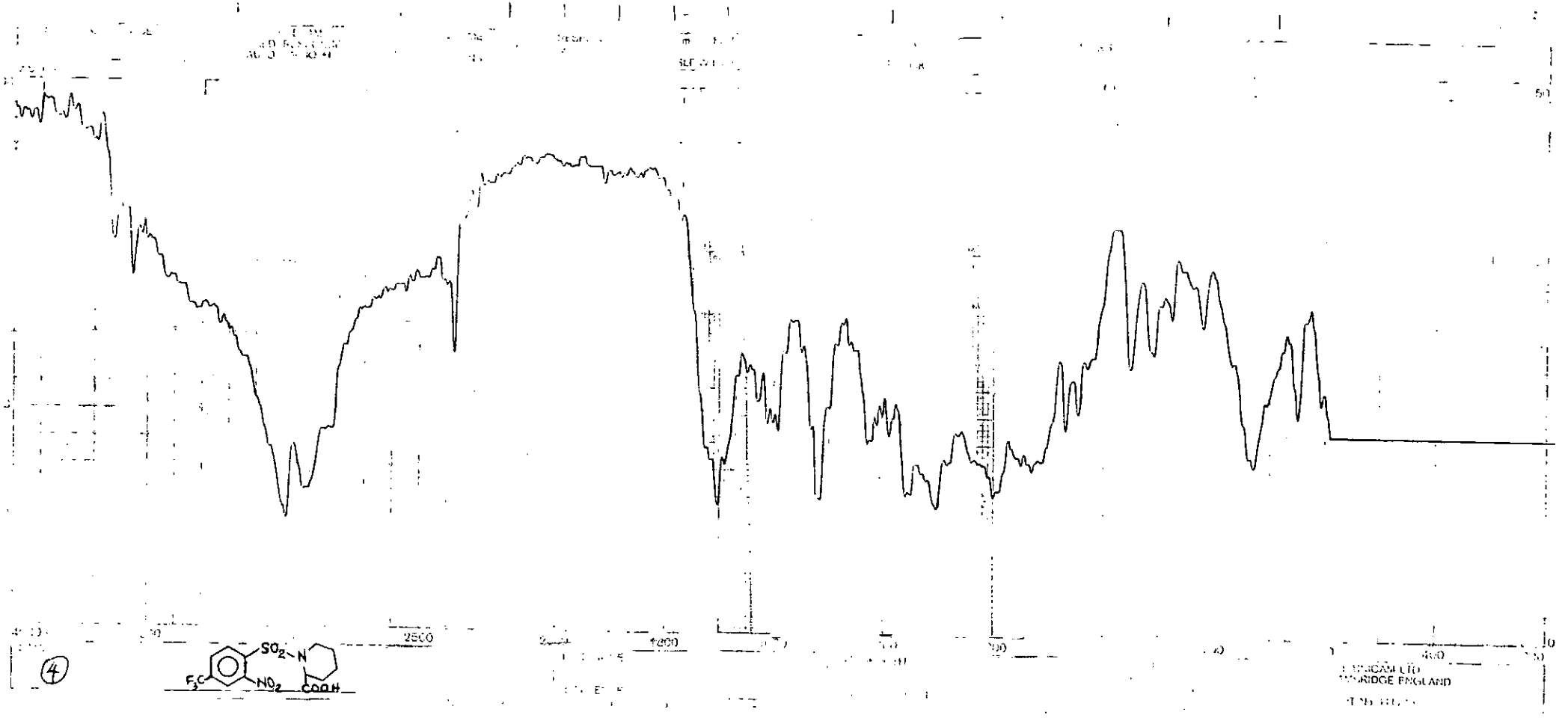
The sulphonyl chlorides obtained from the two methods were identical. These were condensed with piperidine-2-carboxylic acid in the same manner as with the unsubstituted analogues to give on work-up N-(4-ααα trifluoromethyl-2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid in low yields as an oil, which only solidied on standing for one month.



287 289

The infrared spectrum of the acid adduct showed broad absorptions at 3,000 cm^{-1} (COOH) 1700 cm^{-1} (carbonyl stretch) 1600, 1520, 1310 cm^{-1} (nitro group), 1360 and 1,200 cm^{-1} SO_2N

The ^{1}H-NMR spectrum in deuterated trifluoroacetic acid showed a 4H multiplet of the piperidine ring type 'a', protons at δ 1.3. A 2H multiplet at δ1.9 represented the piperidine proton type 'b'. The protons adjacent to the nitrogen absorbs as a 2H quartet at δ 3.2 type 'c'. The base proton of the carboxylic acid appeared at δ 4.5 while the protons ortho to the trifluoromethyl group



(4)

CHART 5-60T
MADE IN U.S.A.

278b

500 250 100 50 25 R

400 200 60 40 20

300 150 60 30 15

200 100 40 20 10

100 50 20 10 5

0 Hz

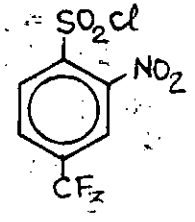
8.0 7.0 6.0 5.0 PPM (δ) 4.0 3.0 2.0 1.0 0

	MANUAL	AUTO ☐
SWEEP OFFSET (Hz): 1027	SWEEP TIME (SEC): 50 250	(250)
SPECTRUM AMPLITUDE: 50	SWEEP WIDTH (Hz): 25 50 100 250 500	(500)
INTEGRAL AMPLITUDE: 1	FILTER: 1 2 3 4 5 6 7 8	(2)
SPINNING RATE (RPS): 42	RF POWER LEVEL: 0.05	(.05)

SAMPLE: 17

SOLVENT: $CDCl_3$

REMARKS:



varian

60 MHz NMR

MASS SPECTRUM
03/12/86 10:48:00 + 2:40
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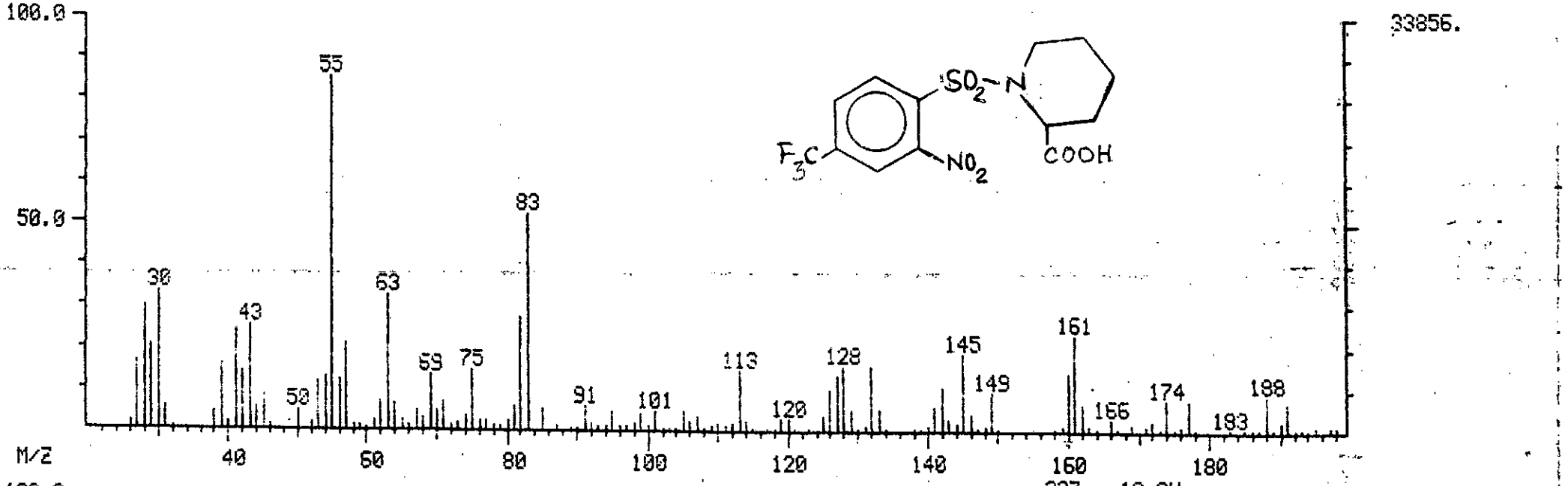
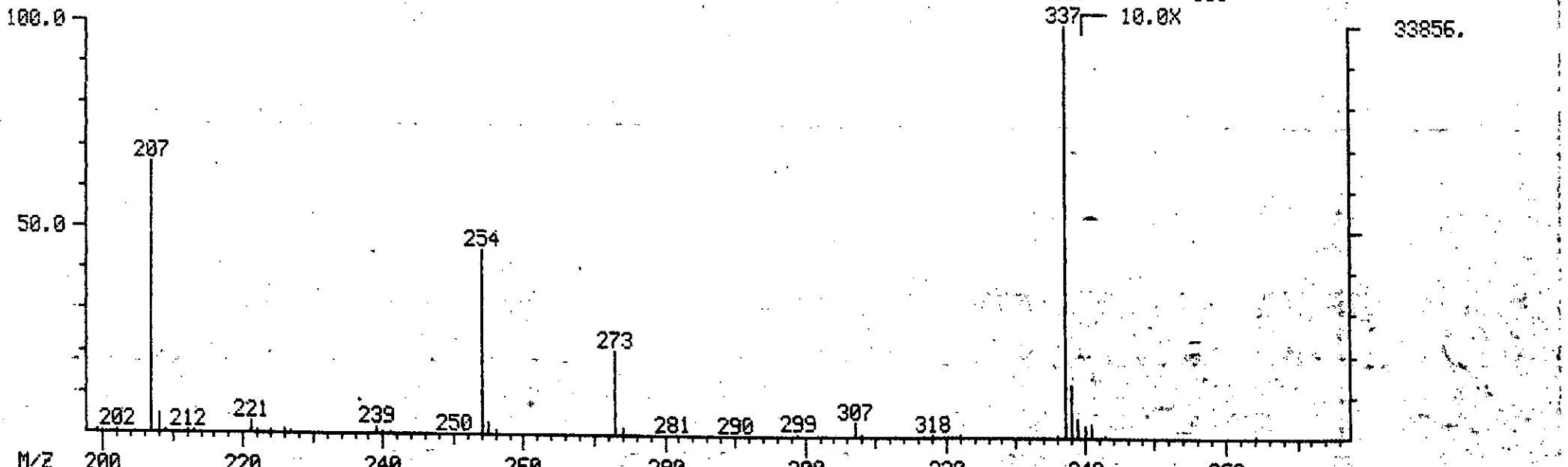
CONDS.: DISC 4
#31 TO #34 SUMMED - #13 TO #16 X1.00

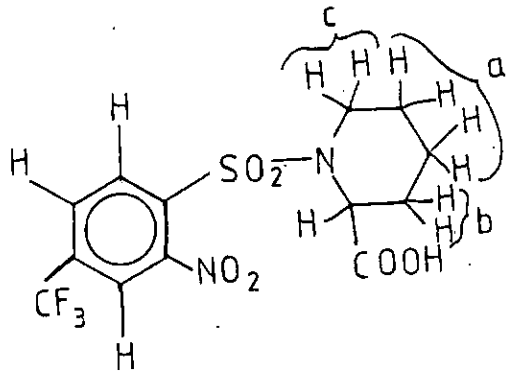
DATA: OBF1 #32
CALI: CAL12SEP86 #3

BASE M/Z: 337
RIC: 382976.





absorbed at δ7.3. The proton ortho to the sulphonyl group was slightly deshielded and appeared at δ7.7 as a 1H multiplet.



289

The mass spectrum of the compound showed the base peak at m/$\mathcal{Z}$ 337 (M^+ - 45) M^+ - COOH. Other significant peaks were at m/$\mathcal{Z}$ 318,254 (M^+ - piperidine-2-carboxylic acid) 207, 188, 161.

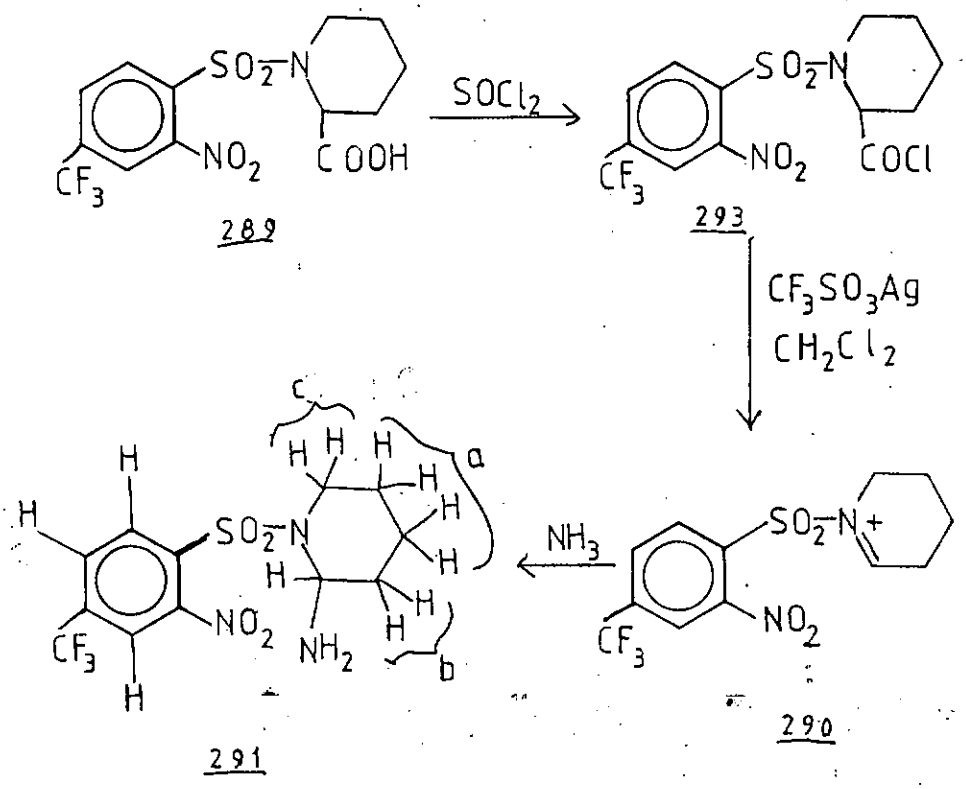
The nitroacid was treated with thionyl chloride as usual to give N-(4-ααα-trifluoromethyl-2-nitrobenzene-sulphonyl) piperidine-2-carboxylic acid chloride.

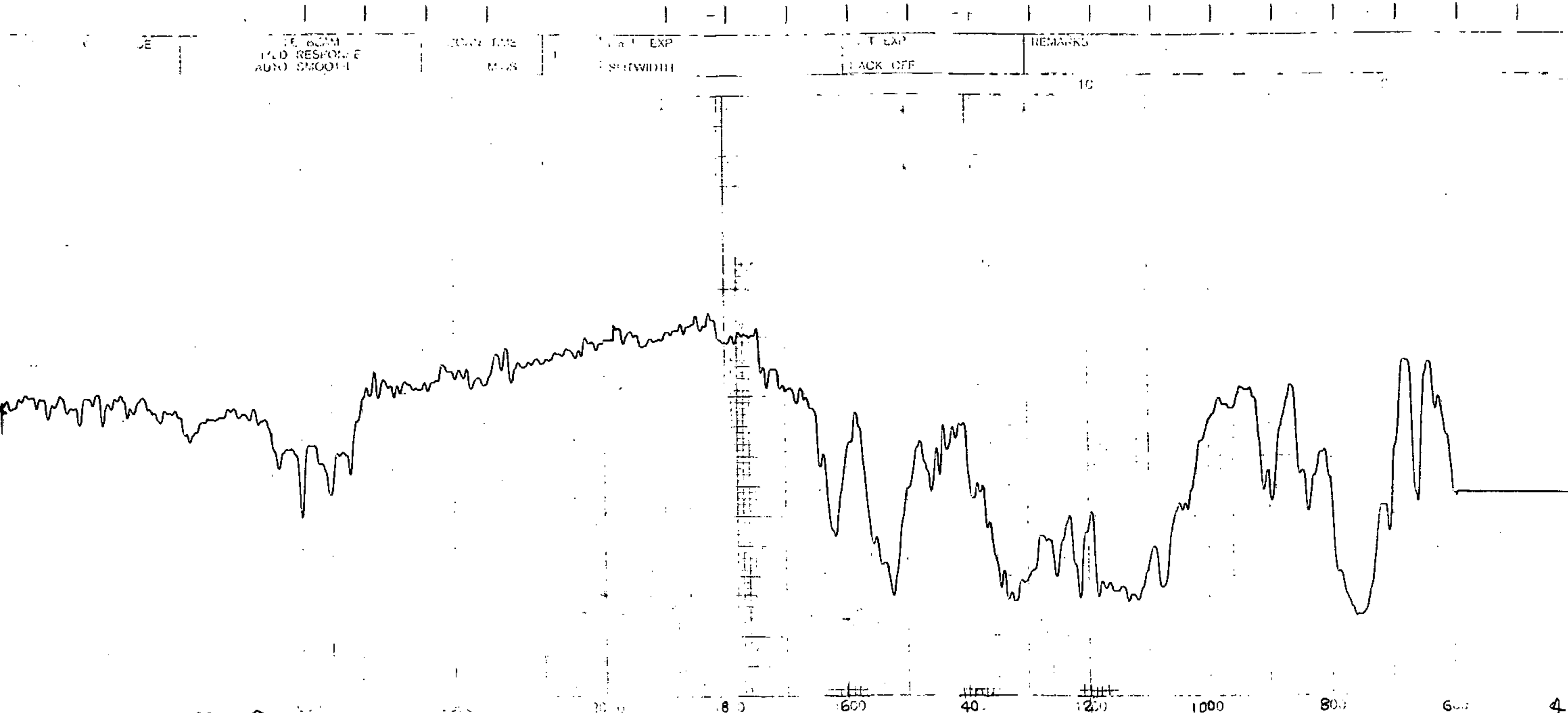
The infra red spectrum show a shift in the acid carbonyl from 1710 to 1780 cm^{-1} due to the introduction of the chlorine atom.

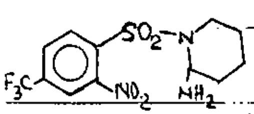
The acid chloride obtained above was dissolved in dry dichloromethane and silver trifluoromethanesulphonate was added. After a copious effervescence, the reacting mixture was treated with conc. ammonia. Standard work-up gave a solid product. T.l.c. of the product showed one main spot. Recrystallisation of the product gave a brown solid m.p. 144 - 5°.

The I.R. spectrum of the product showed absorptions at 3380 cm^{-1} for the NH stretch of the amine, 1610 cm^{-1} for -C=C- of the aromatic ring, 1520 and 1320 cm^{-1} (Nitro group). 1345 and 1135 cm^{-1} is for $SO_2N<$ group stretching.

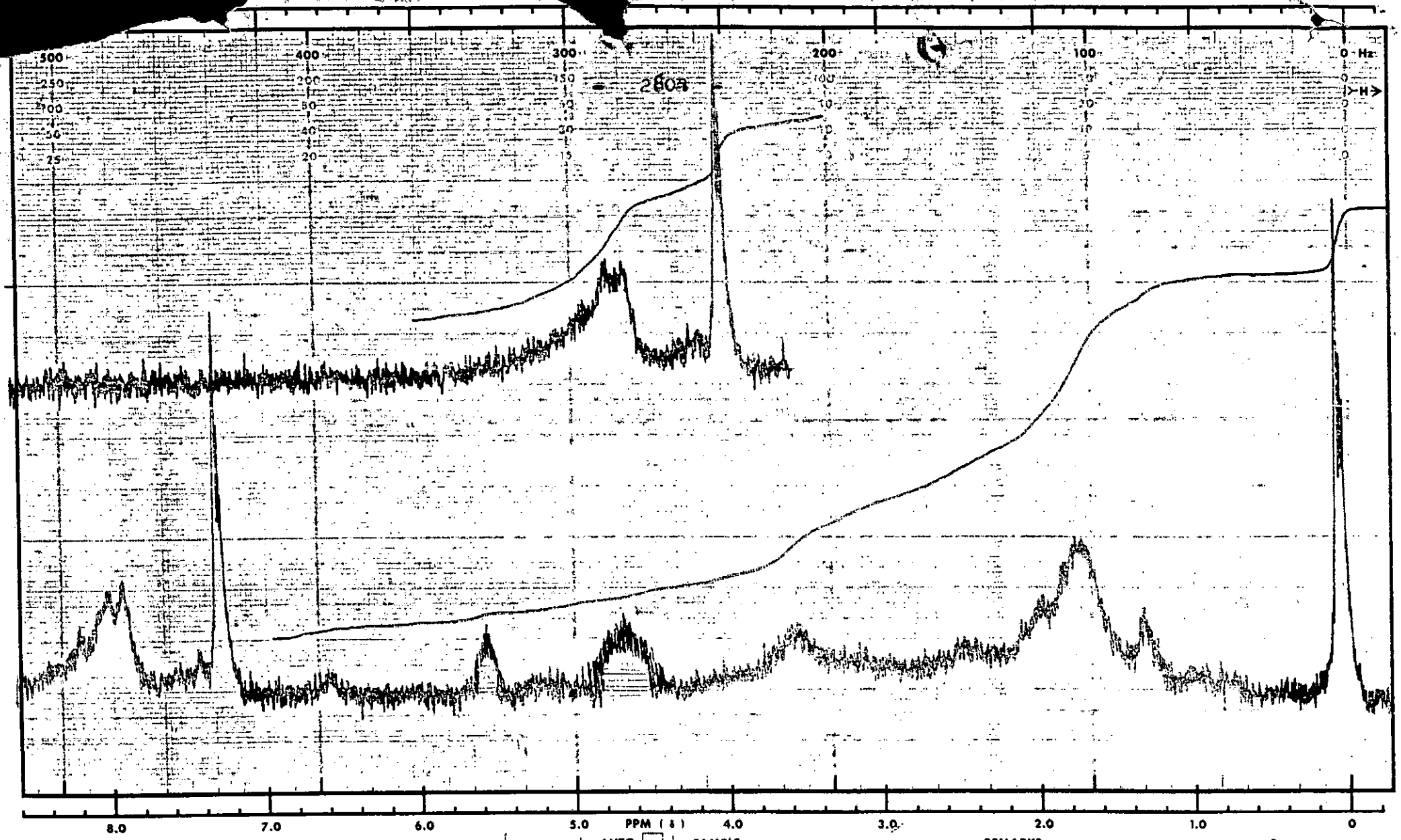
'H-NMR spectrum in deuterated acetone gave a signal for 4H multiplet of the piperidine ring (type a) at δ 1.0, a 2H multiplet also for the piperidine ring (type b) absorbed at δ 1.5 while the 2H multiplet for the protons adjacent to the nitrogen atom absorbed at δ 2.6. The N-CH-N 1H, multiplet showed at δ 4.2 and the NH proton absorbed at δ 5.6 (exchangeable with D_2O). The aromatic 3H proton did not quite reoslve and it absorbed at δ 7.1 - 7.7.







chloroform



SWEEP OFFSET (Hz): 2058 Hz
SPECTRUM AMPLITUDE: 40
INTEGRAL AMPLITUDE: 3
SPINNING RATE (RPS): 50

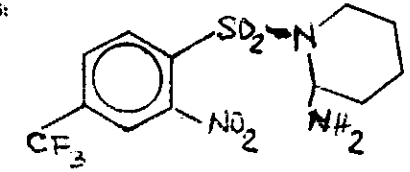
MANUAL / AUTO ☐

SWEEP TIME (SEC): 50 | 250 — (250)
SWEEP WIDTH (Hz): 25 | 50 | 100 | 250 | 500 — (500)
FILTER: 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 — (2)
RF POWER LEVEL: 0.05 — (.05)

SAMPLE:

SOLVENT: $CDCl_3$

REMARKS:



60 MHz NMR

varian
analytical instrument division

DATE: 4/20

OPERATOR: A/C

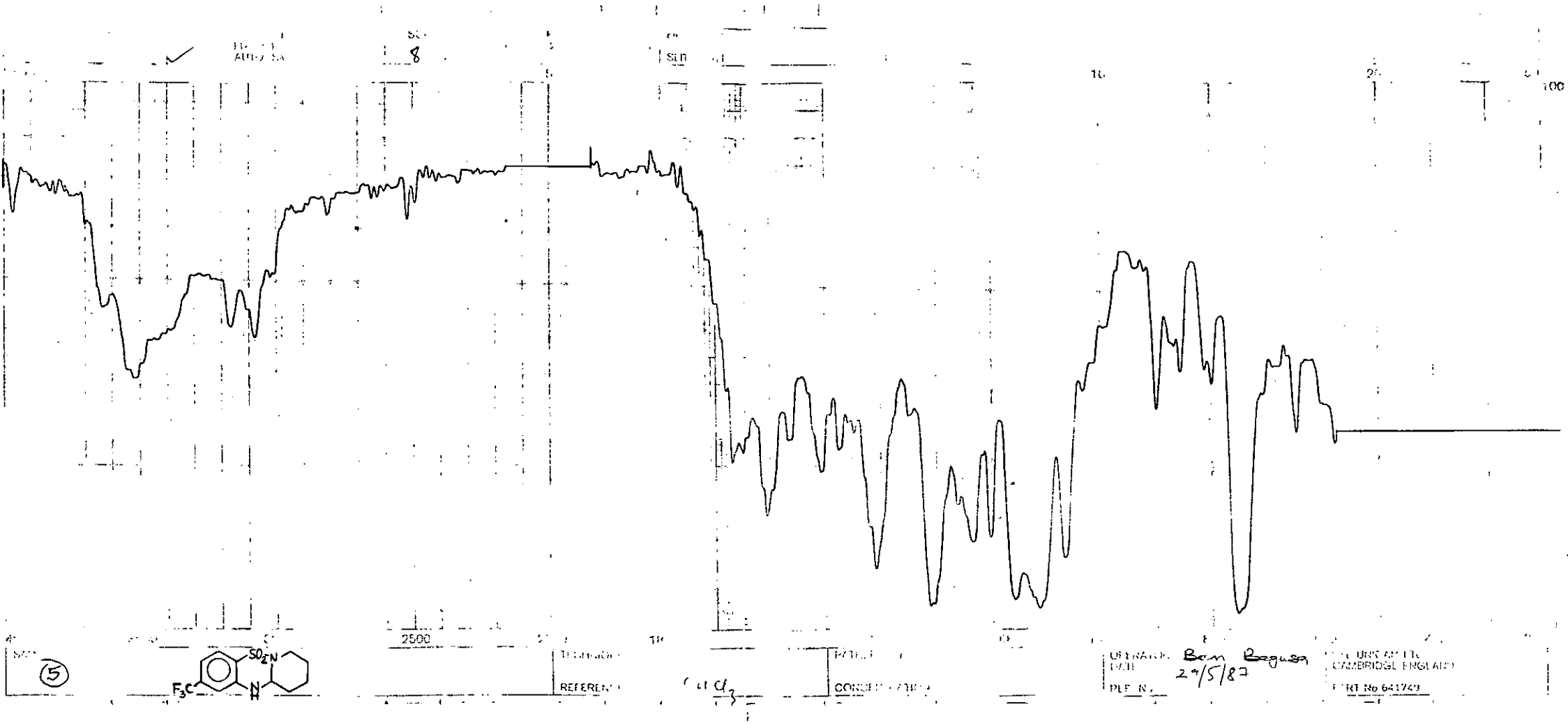
SPECTRUM NO.

The nitroamine 291 obtained was reductively cyclised with iron in acetic acid as usual for 12h.
Work-up gave a brown microcrystalline solid which was recrystallised twice from chloroform: Pet ether mixture

The I.R. spectrum of the product showed absorption at 3350 cm^{-1} (-NH stretch), 2990 (CH stretch) 1680 cm^{-1} (-NH deformation), 1610 cm^{-1} (-C=C- aromatic ring), 1340 and 1180 cm^{-1} ($SO_2N<$).
The ^{1}H-NMR spectrum in DMSO $-d_6$ showed a 6H multiplet for the piperidine ring (type 'a'), a 2H multiplet for the protons adjacent to the nitrogen atom (type 'b') absorbed at δ 2.6. A 1H multiplet representing the base proton (type 'c') absorbed at δ 4.8 while the 1H of the NH (exchangeable with D_2O) absorbed at δ 5.6. The aromatic protons was not resolved and showed as 3H multiplet at δ 8.0.

The mass spectrum gave the molecular ion at m/z 306. Other significant peaks were at 241, 223, 161, 82 and 55.

The mechanism is same as the initial reduction of the nitro group to amine and the preferential protonation of amine attached to the Sp^3 carbon and it's eventual cleavage facilitating intramolecular nucleophilic attack effecting the cyclisation to give 292.


8
2500
(5)
SO_2N
F_3C
N
H
CH_2Cl_2
Ben Begley
24/5/82

MASS SPECTRUM
09/12/86 11:57:00 + 0:50
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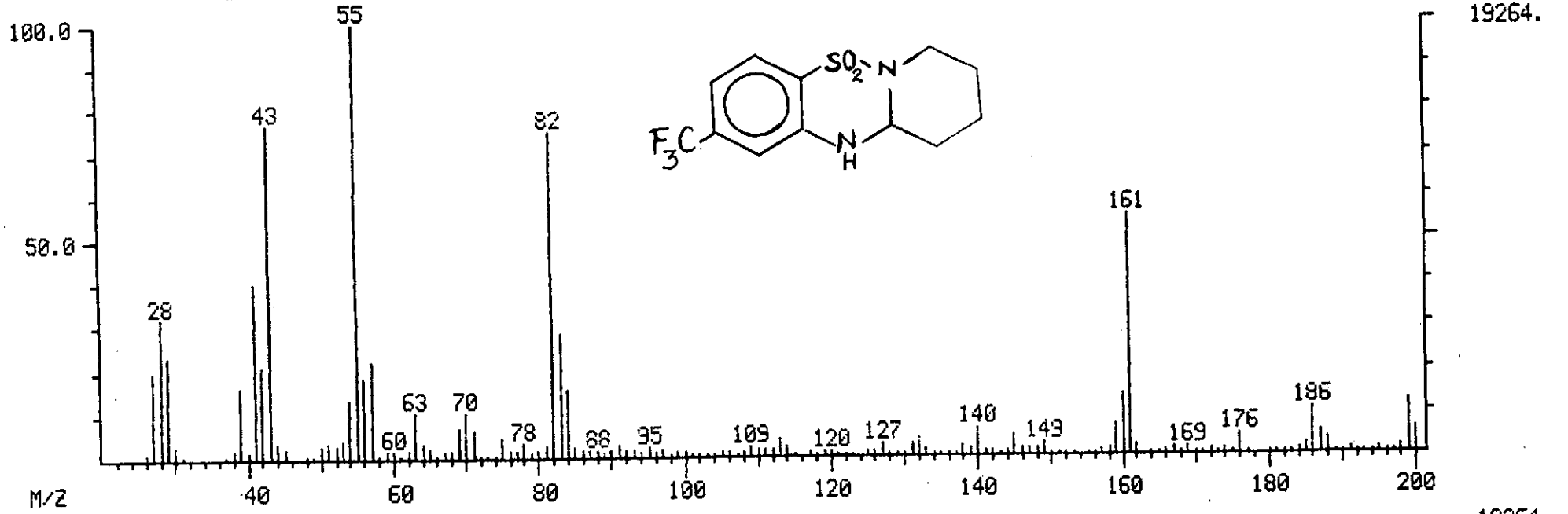
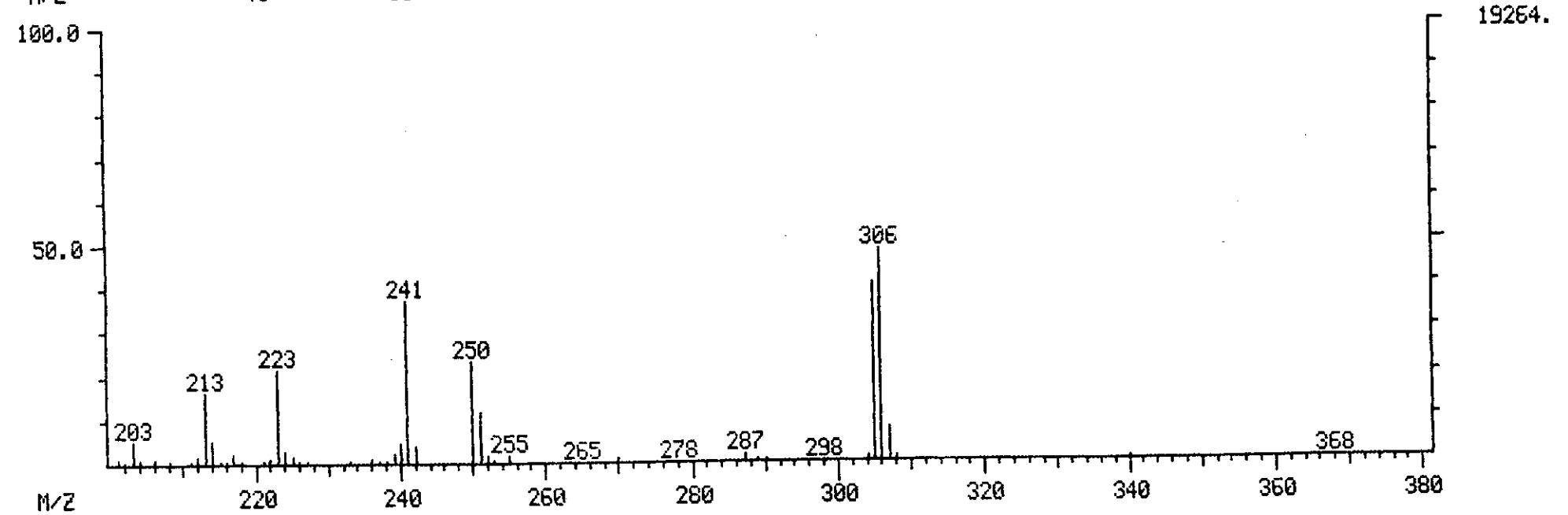
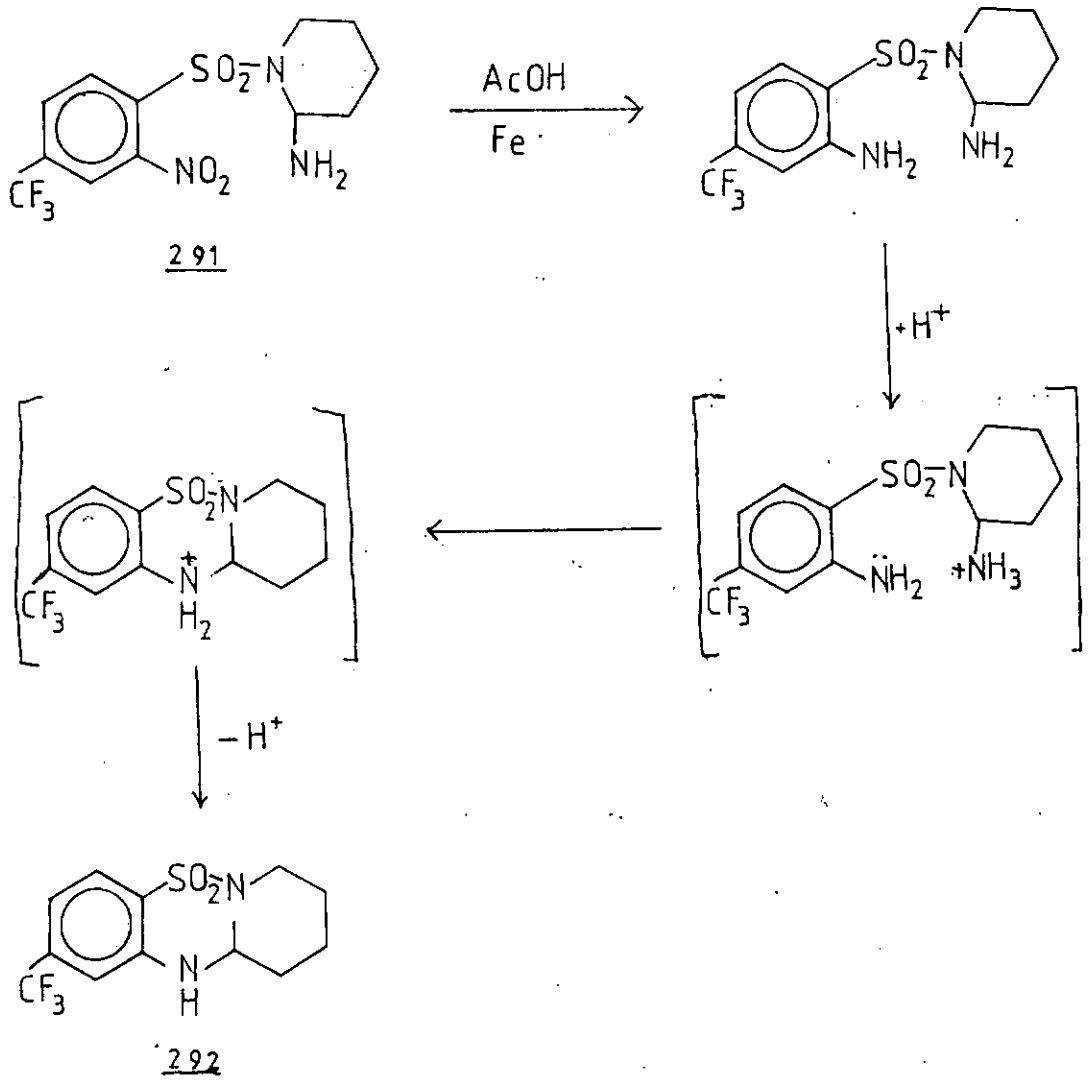
CONDS.: DISC 4
#9 TO #12 SUMMED

DATA: OBF12 #10
CALI: CAL12SEP86 #3

BASE M/Z: 55
RIC: 212480.





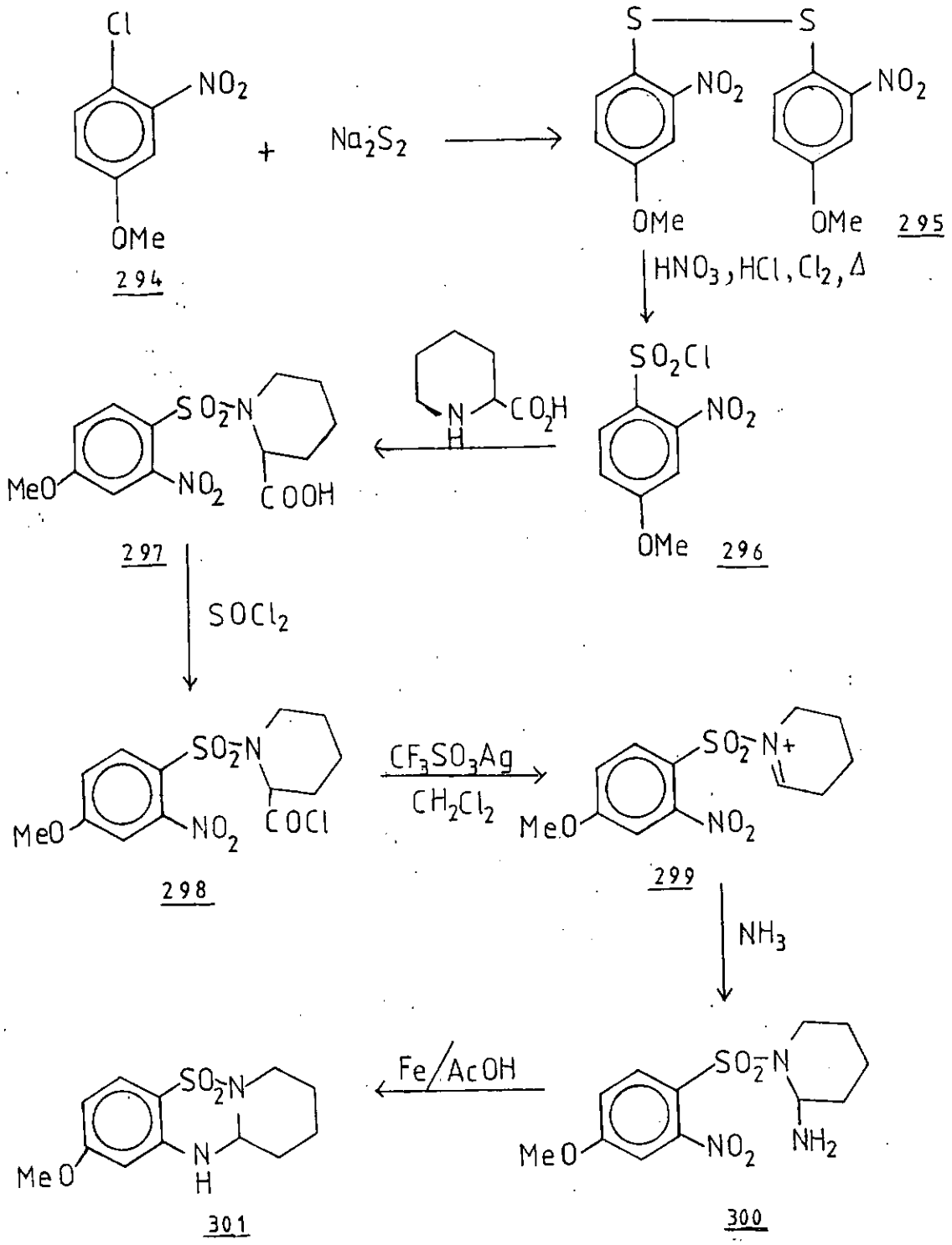


291

292

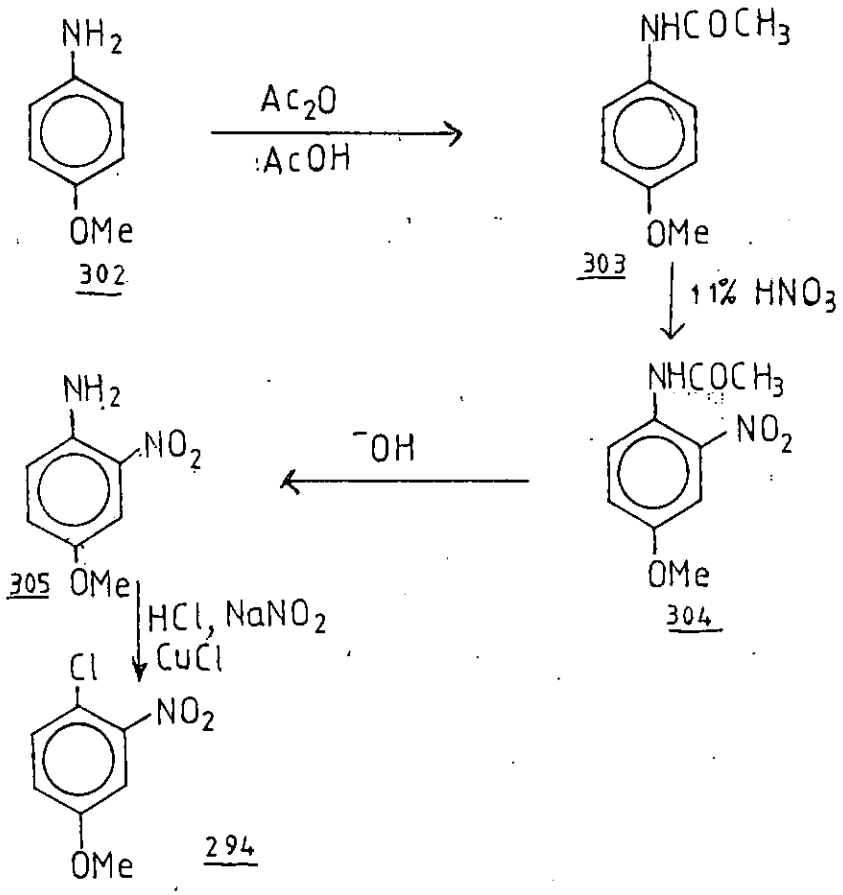
9-Methoxy-1, 2, 3, 4, 11-11a-hydrohydropyrido (1, 2-b)(1, 2, 4) benzothiadiazine-6, 6-dioxide:

Efforts were then directed towards obtaining a methoxy substituted derivative. The 9-methoxy substituted analogue was designed to be obtained via the scheme below:


Cl
NO2
OMe
294
+
Na2S2
S
S
NO2
NO2
OMe
OMe
295
HNO3, HCl, Cl2, Δ
SO2Cl
NO2
OMe
296
N
H
CO2H
SO2N
MeO
NO2
COOH
297
SOCl2
SO2N
MeO
NO2
COCl
298
CF3SO3Ag
CH2Cl2
SO2N+
MeO
NO2
299
NH3
SO2N
MeO
NO2
NH2
300
Fe/AcOH
SO2N
N
H
MeO
301

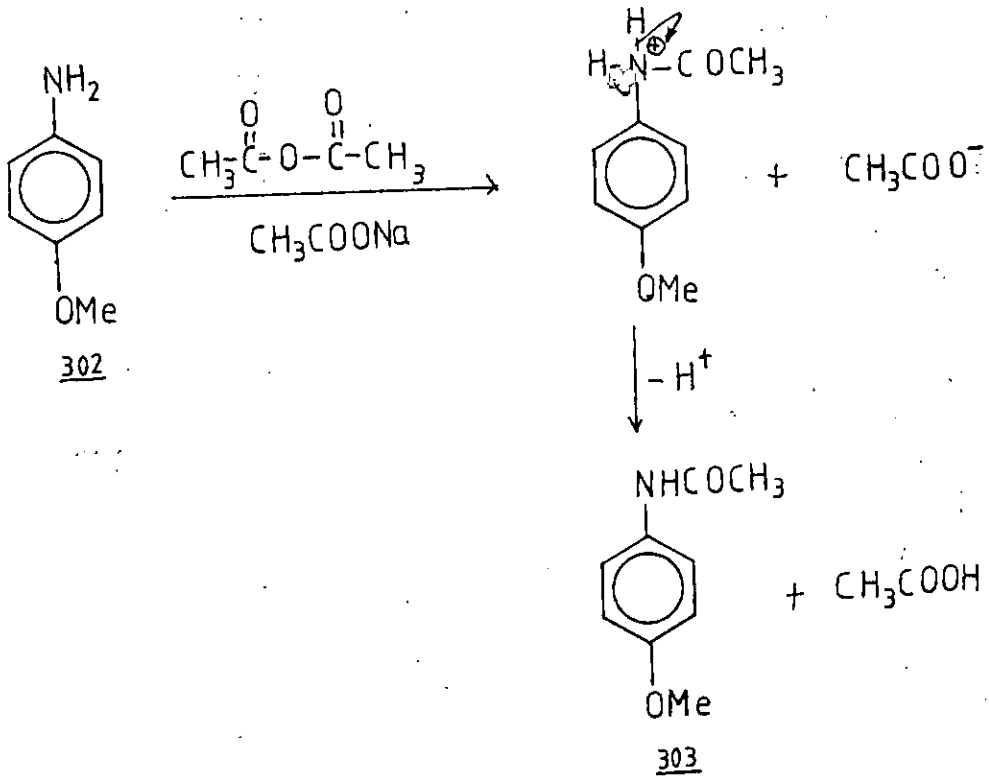
Scheme 17

Commercial 4-chloro-3-nitroanisole was to be the precursor to the desired disulphide on reaction with sodium disulphide. However, several attempts at obtaining the 4, 4'-dimethoxy-2, 2'-dinitrodiphenyl disulphide with this product failed. Therefore, 4-chloro-3-nitroanisole had to be prepared by the method outlined:



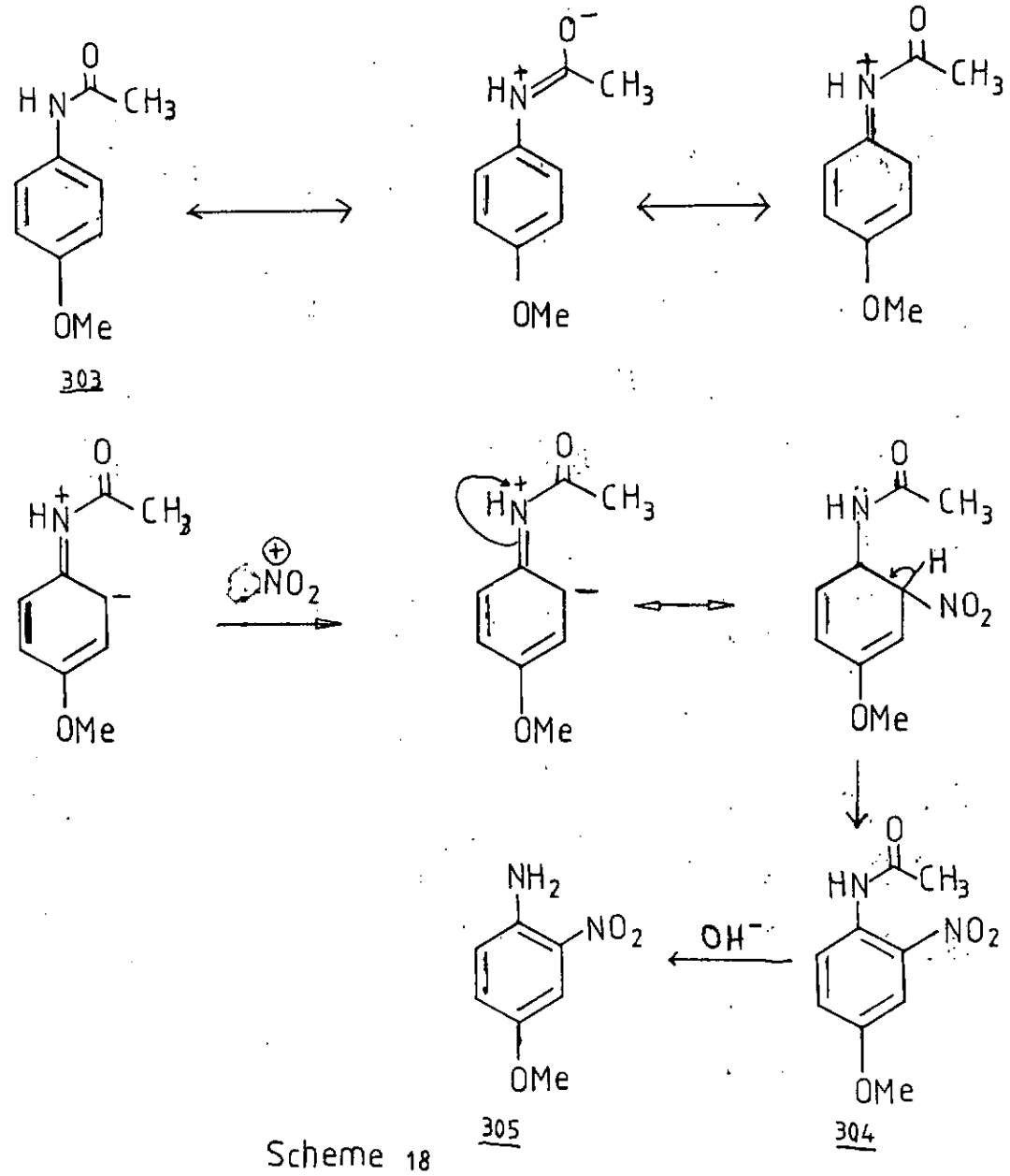
P-Anisidine was converted to it's hydrochloride and acetylated with acetic anhydride and sodium acetate. The p-acetaniside 303 was recrystallised several times in dilute ethanol to remove any trace of the contaminating diacetylated products.

The anisole was acetylated before nitrating it because the anisole ring is highly activated towards electrophilic substitution. The acetylation of the amino function modifies the interaction of the nitrogen lone pair of electron with the Π electron of the aromatic ring so that the ring is less powerfully activated towards electrophilic attack. This protection therefore permits mono ortho substitution of the ring by electrophilic reagents.



The m.p. of the p-acetaniside obtained was 131 - 132° (lit 131 - 132)[84].

The p - acetaniside was immediately nitrated to give 2-nitro-p-acetaniside with 11 % HNO_3 in acetic acid.



303

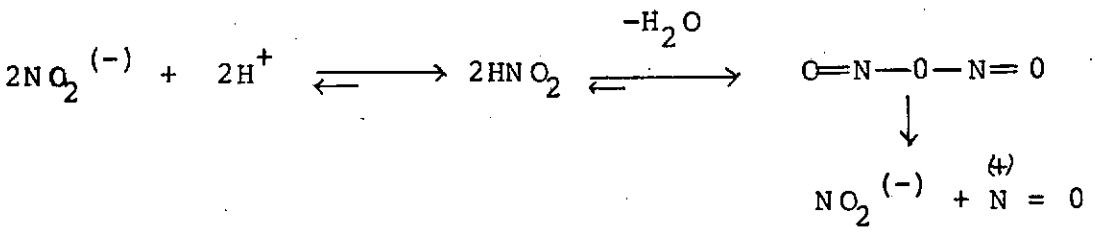
Scheme 18

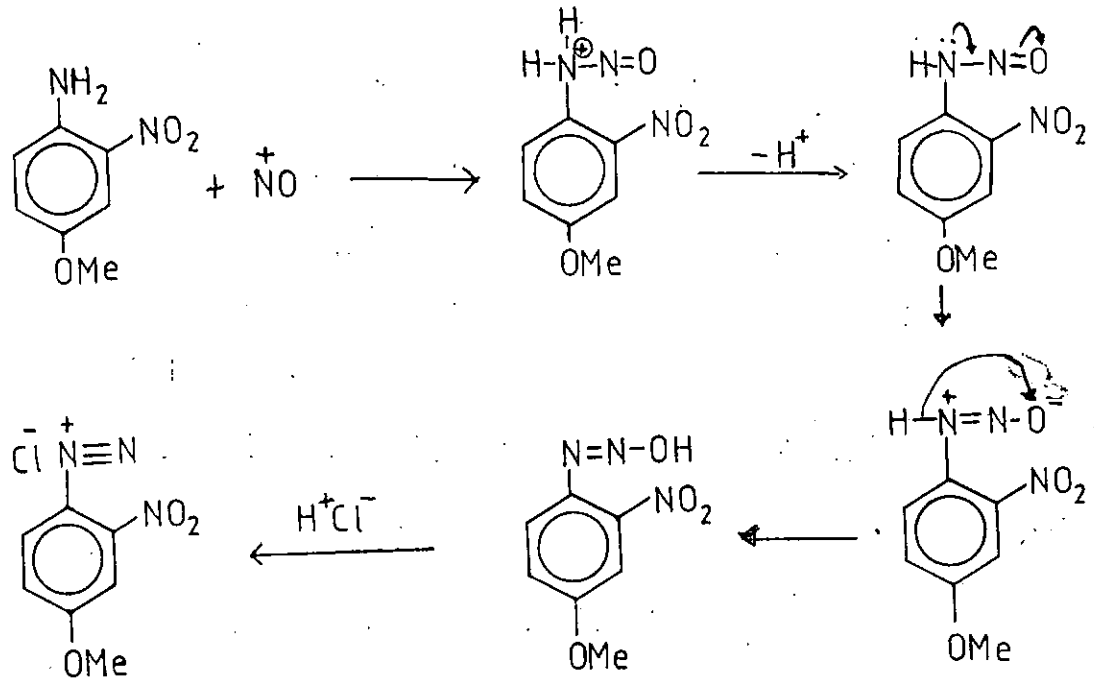
The infra red spectrum of the product showed the NH absorption at 3360 cm^{-1}, the carbonyl of the amide band was at 1700 cm^{-1} while the nitro group's absorption were at 1500 and 1380 cm^{-1}.

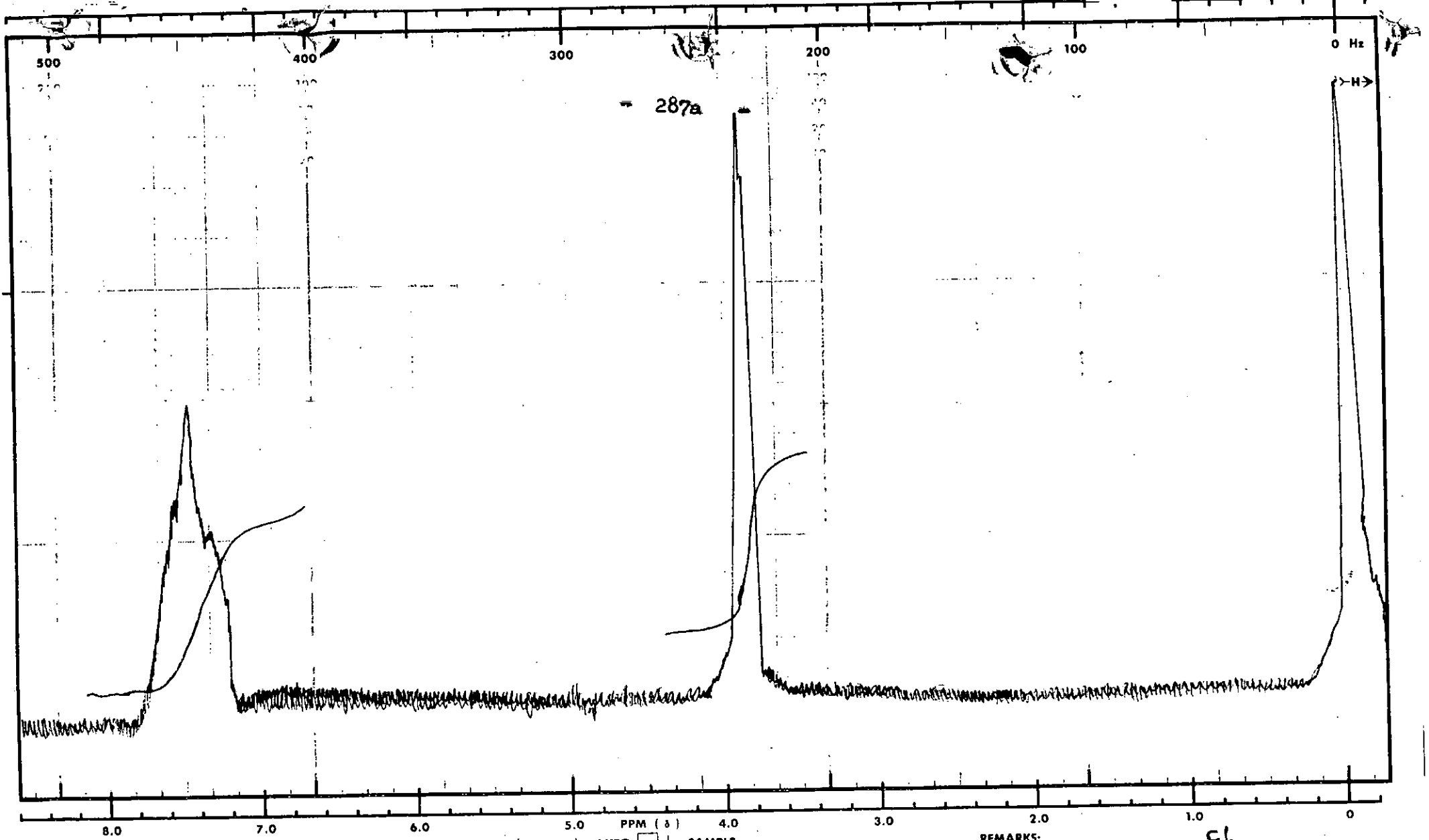
Deacetylation of the anilide was achieved with

Claisen's mixture. Claisen's mixture is a mixture of methanol, water and potassium hydroxide and effects a basic hydrolysis. On refluxing the anilide in the Claisen's mixture for only fifteen minutes and work-up gave the amine in 95% yield m.p. 115 - 116° (lit.[90] m.p. 117°).

Preparation of 4-chloro-3-nitroanisole from the amine above was achieved *via* a Sandmeyer reaction. The amine was converted to the corresponding diazonium salt with cold nitrite solution. This salt was then coupled with freshly prepared copper (I) chloride to give the chloroanisole compound.







MANUAL

SWEEP OFFSET (Hz): 000

SPECTRUM AMPLITUDE: 63

INTEGRAL AMPLITUDE: 1

SPINNING RATE (RPS): 45

SWEEP TIME (SEC): 50 250

SWEEP WIDTH (Hz): 25 50 100 250 500

FILTER: ✓ 2 3 4 5 6 7 8

RF POWER LEVEL: 0.05

AUTO ☐

(250)

(500)

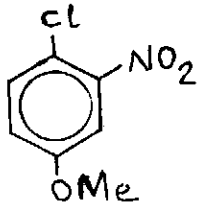
(2)

(.05)

SAMPLE:

SOLVENT: CD Cl_3

REMARKS:

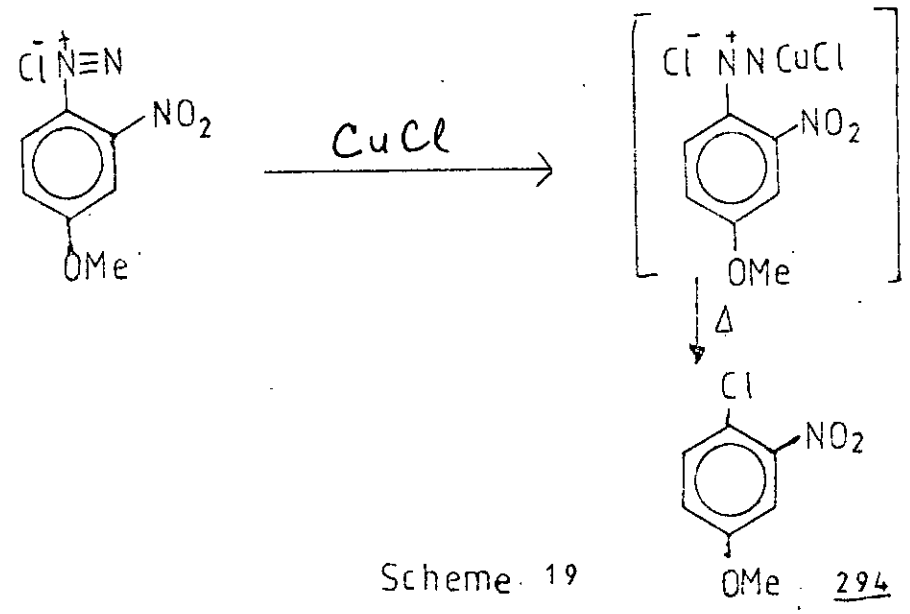


varian
analytical instrument division

DATE: 20/10/87

OPERATOR: J. O Olafimihan

60 MHz NMR
SPECTRUM NO.



Scheme 19 294

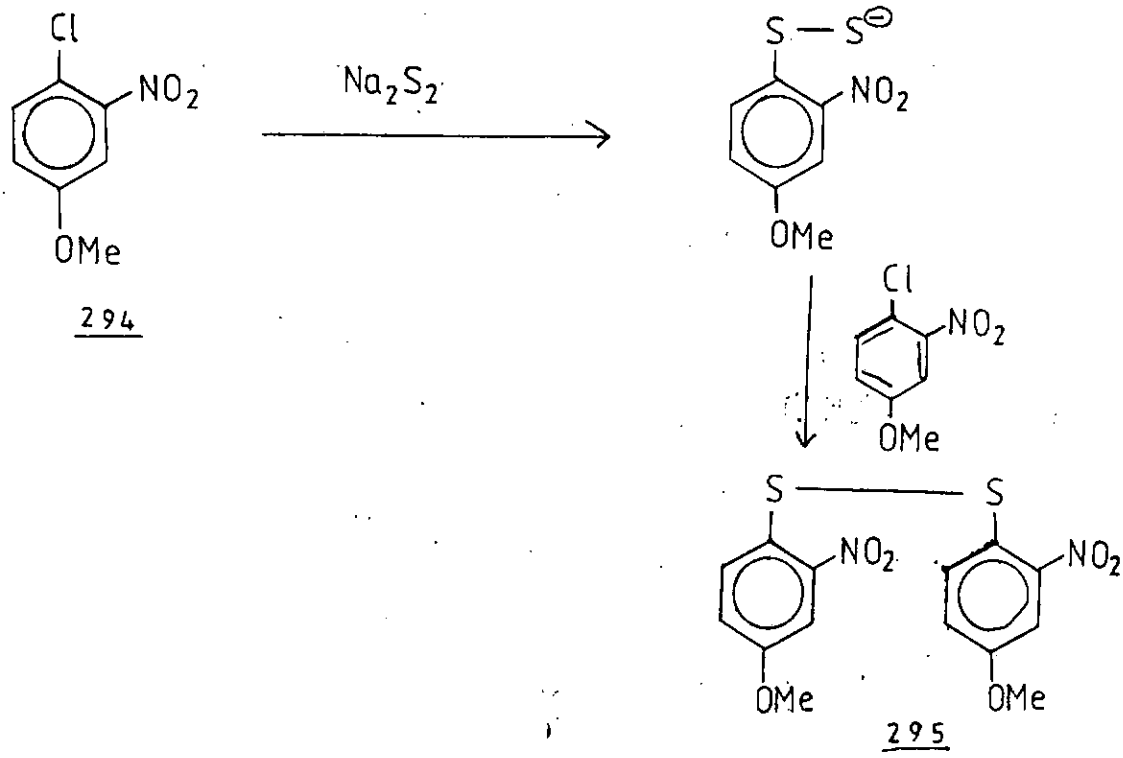
The infra red spectrum of the product obtained had absorptions at 1600 cm^{-1} for the -C=C- bond of the aromatic ring, 1550 and 1370 cm^{-1} ($-NO_2$), 1240 cm^{-1} (OMe).

The 'H-NMR spectrum showed two groups of absorptions a 3H-singlet at δ3.9 for the OMe, a 3H-Multiplet at δ7.2 - 7.7 for the three aromatic protons.

The mechanism of Sandmeyer Reaction is well-known[84] and it is given in the scheme 19 above.

4, 4'-dimethoxy-2,2'-dinitrodiphenyldisulphide was prepared from the 4-chloro-3-nitroanisole obtained above and sodium disulphide formed in situ. The prepared anisole gave the desired disulphide unlike the commercial sample. The counteracting effect of the methoxy substituent reduced the activation and lability of the halogen on the ring towards nucleophilic substitution by the nitro group. Consequently, even with an increase of the reaction time from two hours to four hours to ensure complete reaction,

the yield of the disulphides was still only about 31 % on the average.

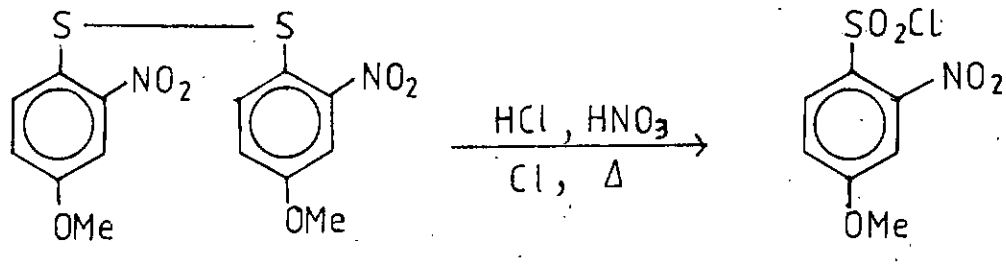


294

295

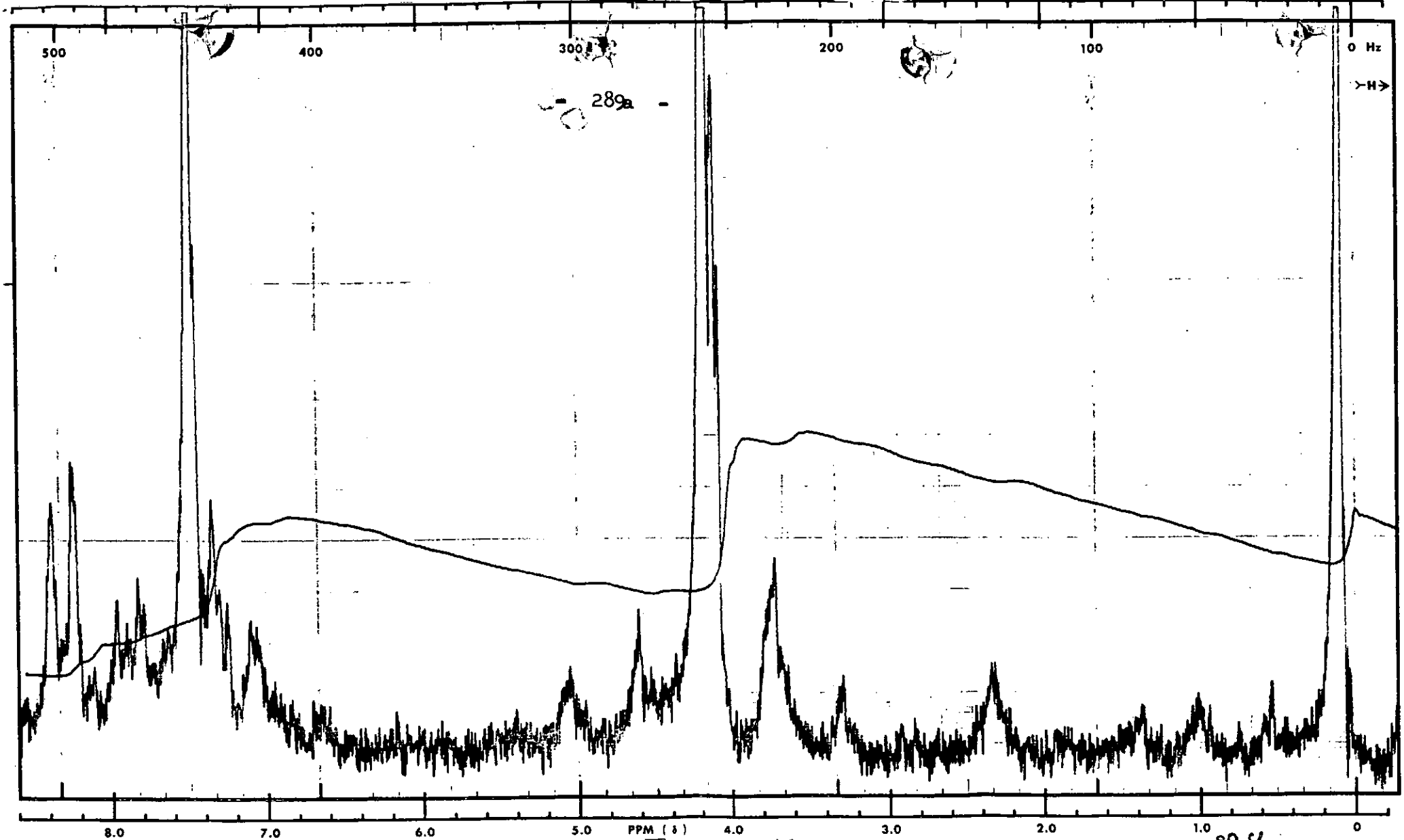
The m.p. of the product obtained was 163 - 164° (literature m.p. 164.7)[91].

Chlorine oxidation of the above disulphide in nitric acid/hydrochloric acid as usual furnished the 4-methoxy-2-nitrobenzenesulphonyl chloride.



295

296



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SPECTRUM AMPLITUDE: 63

INTEGRAL AMPLITUDE: 1

SPINNING RATE (RPS): 2-1

MANUAL

SWEEP TIME (SEC): 50 | 250

SWEEP WIDTH (Hz): 25 | 50 | 100 | 250 | 500

FILTER: 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8

RF POWER LEVEL: 0.05

AUTO ☐

(250)

(500)

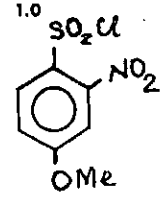
(2)

(.05)

SAMPLE: 12

SOLVENT: $CDCl_3$

REMARKS:



varian
analytical instrument division

DATE: 23/12/87

OPERATOR: S. O. Olalinichan

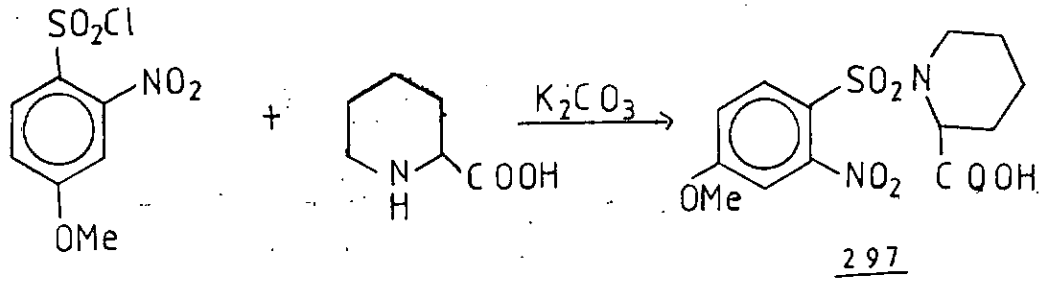
60 MHz NMR

SPECTRUM NO.

The I.R. spectrum of the compound showed the absorptions at 1600, 1540, 1370 (NO_2) 1170 cm^{-1} for the SO_2Cl bond.

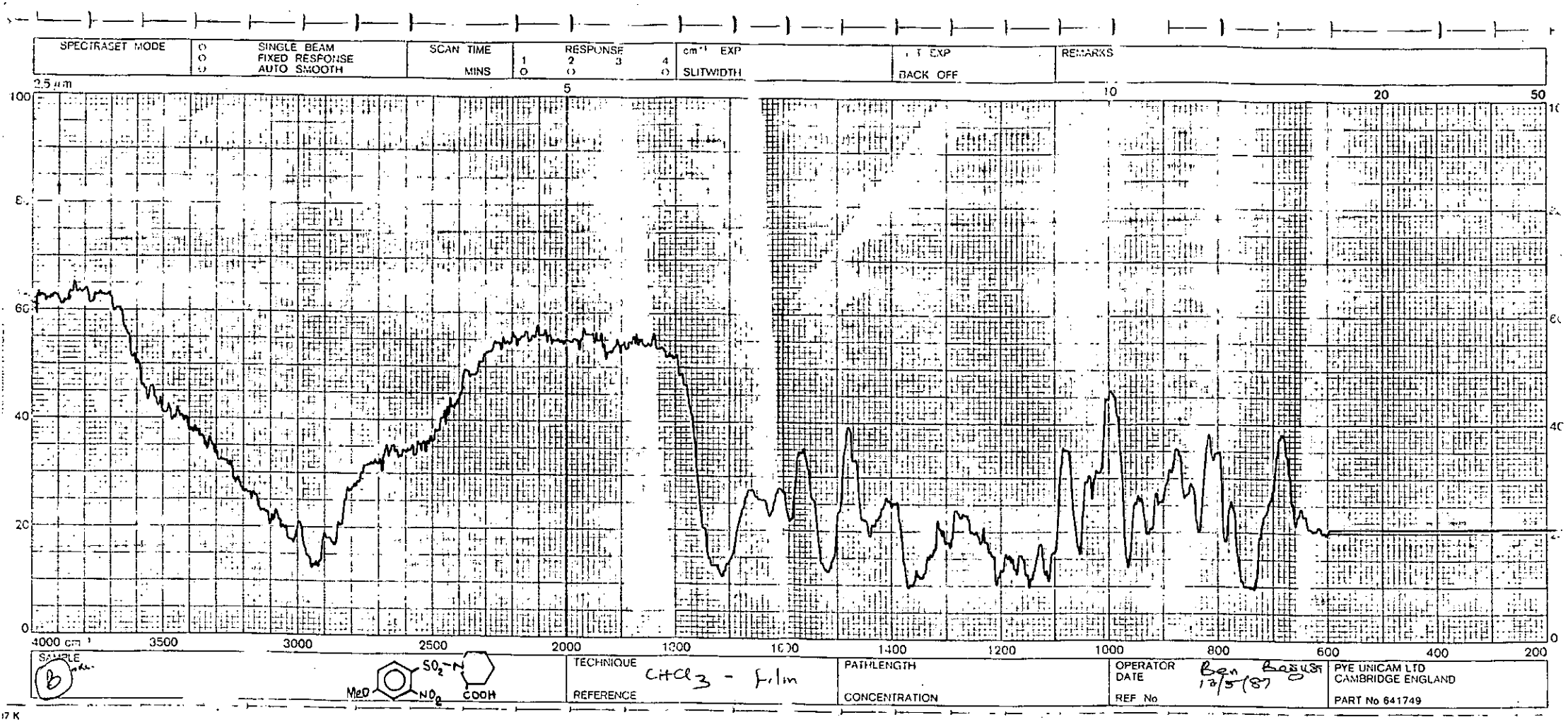
The ^{1}H-NMR spectrum showed a 3H singlet for the methoxy group at δ4.2. The aromatic proton absorption at δ7.5 is assigned to the two H-3 and H-5 which are less shielded while the deshielded H-6 proton appeared as a doublet at δ8.4. The aromatic protons in this case showed deshielding effect relative to those of 4-chloro-3-nitroanisole due to the presence of the sulphonyl chloride grouping.

4-Methoxy-2-nitrobenzenesulphonyl chloride was made to couple with DL-piperidine-2-carboxylic acid in potassium carbonate solution, to give N-(4-methoxy-2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid 297.



296 297

The infra red spectrum of the acid adduct had carbonyl absorption at 1715 cm^{-1}, while the nitro group absorbed at 1520 and 1350 cm^{-1}. The $SO_2N<$ of the tertiary


SPECTRASET MODE
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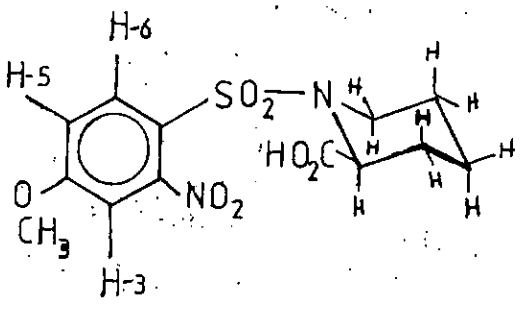
FIXED RESPONSE
AUTO SMOOTH
SCAN TIME
MINS
RESPONSE
1 2 3 4
SLITWIDTH
BACK OFF
REMARKS
2.5 μm
5
10
20
50
100
80
60
40
20
0
4000 cm⁻¹
3500
3000
2500
2000
1500
1000
1400
1200
1000
800
600
400
200
SAMPLE
B
MeO
NO2
SO2-N
COOH
TECHNIQUE
CHCl3 - Film
REFERENCE
PATHLENGTH
CONCENTRATION
OPERATOR
Ben Bass
DATE
12/5/87
REF No
PYE UNICAM LTD
CAMBRIDGE ENGLAND
PART No 641749

sulphonamide absorbed at 1370 and 1150 cm^{-1}. The C-O-C ether linkage of the methoxy group was distinct at 1210 cm^{-1}.

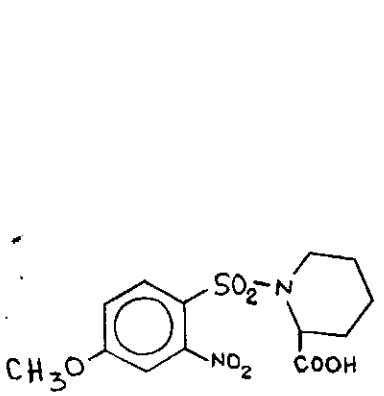
The 'H-NMR spectrum of the adduct showed the piperidine ring protons showed four signals which included the following, a 2H - multiplet at δ1.4 (type 'a'), a 3H - multiplet at δ1.7 and a 1H doublet at δ2.3 while a 1H doublet and another 1H doublet at δ3.65 absorption are for the protons adjacent to the nitrogen atom. The methoxy group 3H singlet absorbed at δ3.9 while the 1H broad exchangeable with D_2O represented the -OH of the acid at δ4.6. The N-CH-N 1H-doublet was at δ4.7. The 2H-multiplet of the H-3 and H-5 absorbed at δ7.2 while the deshielded 1H-doublet of H-6 absorbed at δ8.0.



297

The acid adduct was converted to the N-(4-methoxyl-2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid chloride on gentle reflux with thionyl chloride.

SOLVENT – CD_3OD

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DATE 16-7-87
TIME 15.01

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TD    16384
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SW2   3205.128
HZ/PT     .391

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AQ        2.556
RG         32
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TE        297

FW     4100
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CY       17.00
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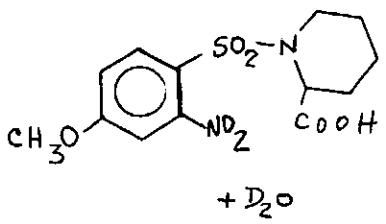

+ D_2O

BRUKER

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TIME 15:07

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HZ/PT     .391

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AQ       2.556
RG        20
NS        24
TE       297

FW     4100
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DP   63L PD

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MI          .01
OC        1.000
HZ/CM   78.177
PPM/CM    .391
IS          4
SR     2308.34
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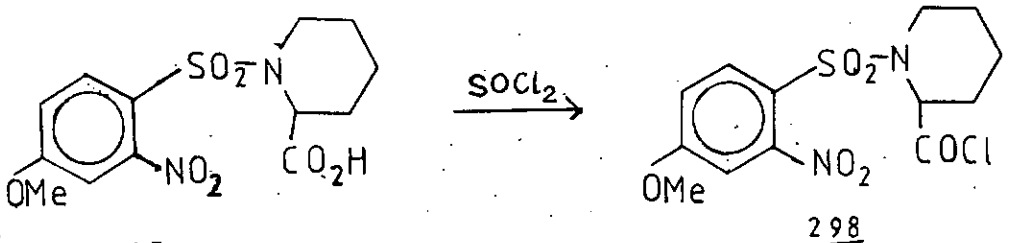
The infra red spectrum of the compound showed the acid, carbonyl shifting from 1710 cm^{-1} to 1790 cm^{-1} due to the replacement of -OH group by a chlorine atom.

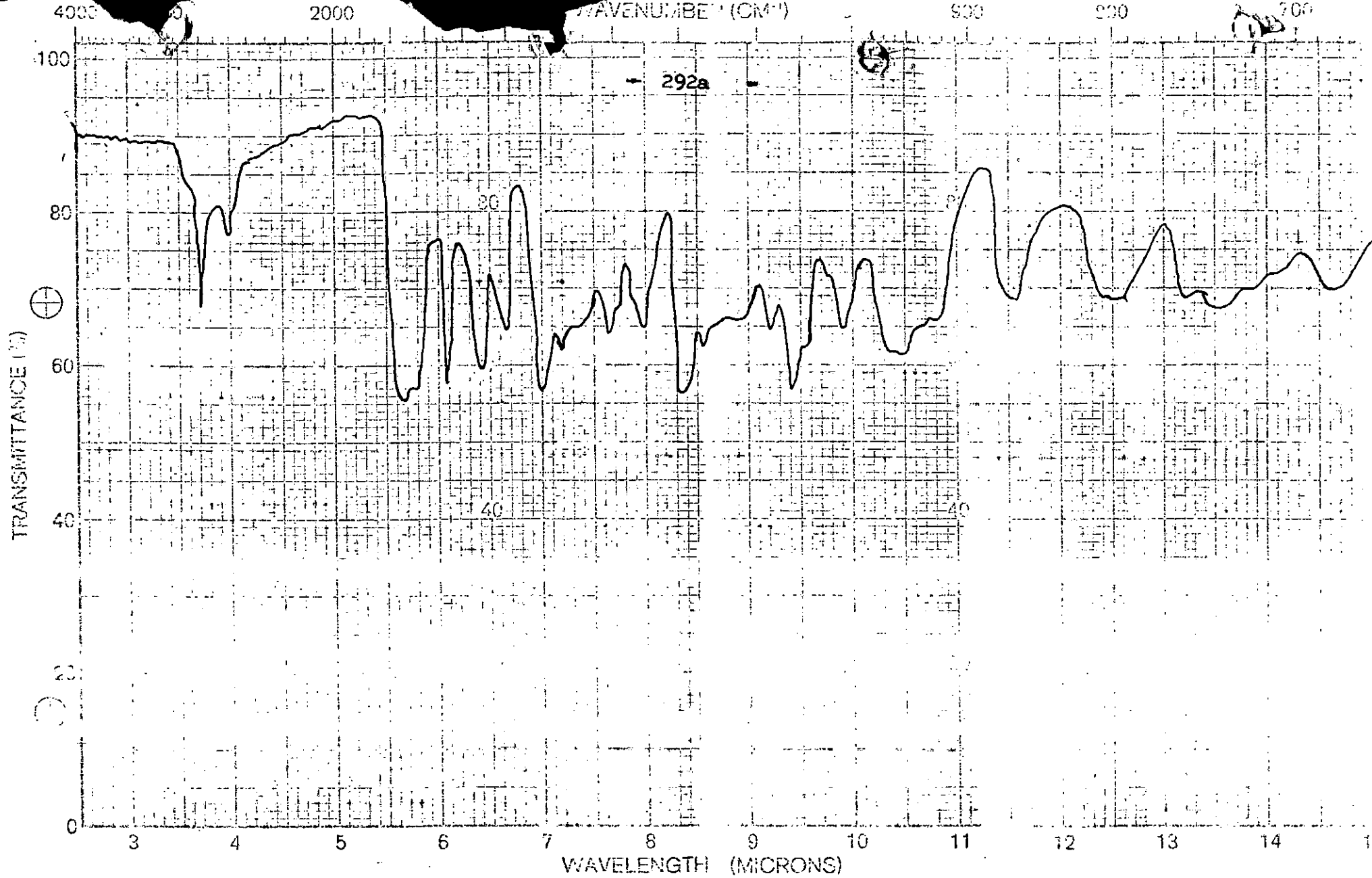


297 298

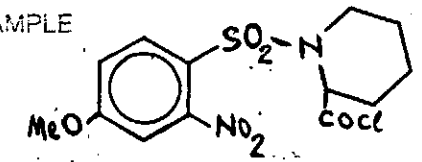
The preparation of N-(4-methoxy-2-nitrobenzenesulphonyl)-2-aminopiperidine was achieved by dissolving the above acid chloride in dry dichloromethane and reacting and addition of silver trifluoromethanesulphonate. There was copious effervescence as usual, which only subsided after one hour. Addition of ammonia and work-up as usual gave the crude amine which was purified by flash chromatography to give a brown solid.

The I.R. spectrum of the solid had - NH absorption at 3360 cm^{-1}, methylene absorptions at 3,000 and 2940 cm^{-1}, aromatic -C=C- bond absorptions at 1600 cm^{-1}, the nitro group absorption appeared at 1540 and 1325 cm^{-1} while the SO_2-N of the sulphonamide absorbed at 1350 and 1170 cm^{-1}.

The ^{1}H-NMR spectrum of the nitroamine showed a 6H multiplet at δ 1.6 for the piperidine ring type 'a'.



SAMPLE



ORIGIN

SOLVENT neat
CONC.
CELL PATH
REFERENCE

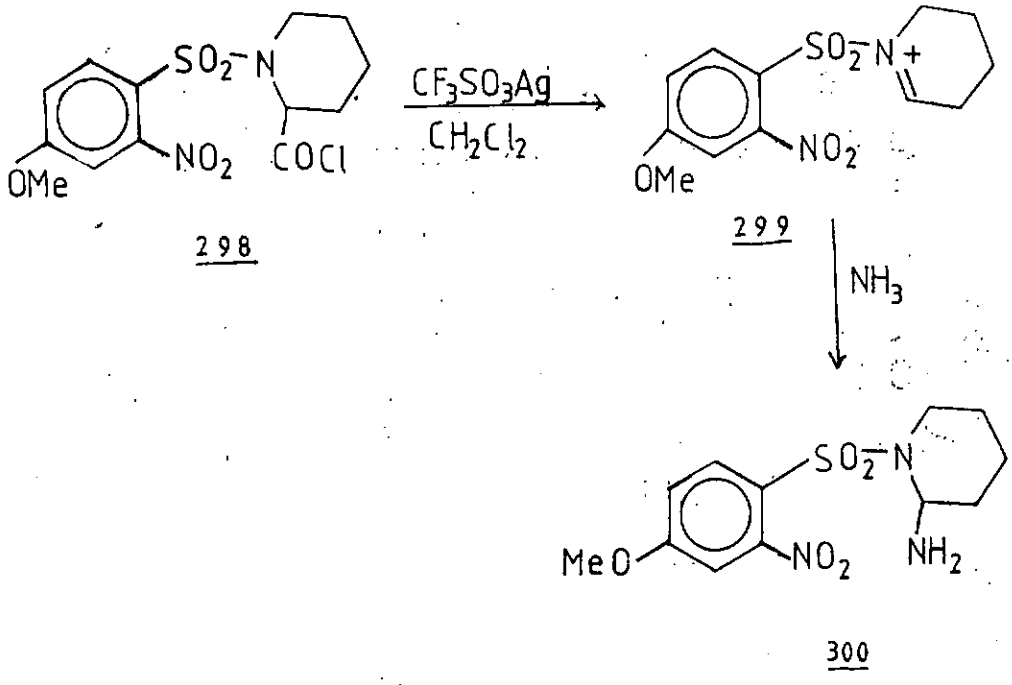
SCAN F
SLIT N
OPERATOR
DATE 20/7/87

PERKIN-ELMER PART NO. 471-5232

REMARKS

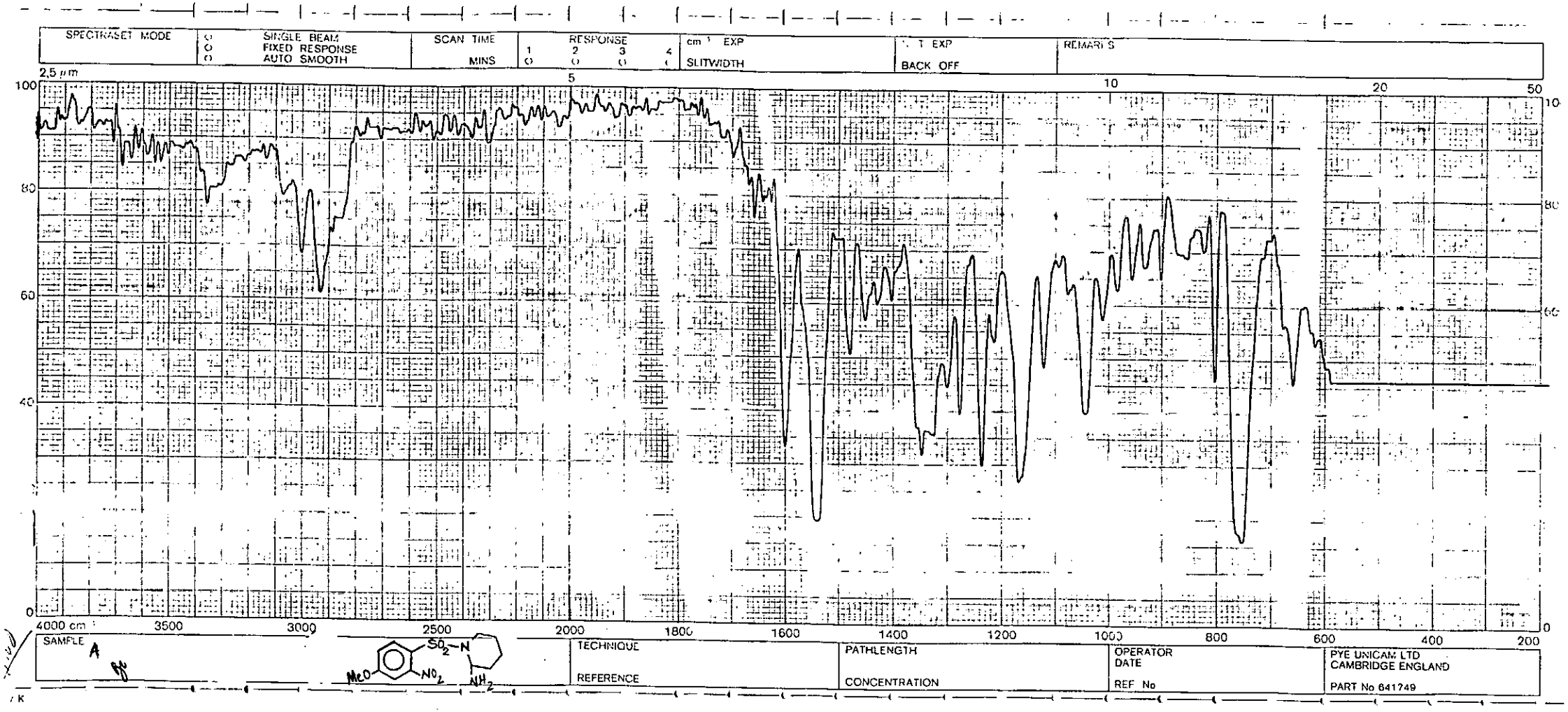
REF. No.

Two 1H-multiplets for the piperidine proton adjacent to the nitrogen atom absorb at δ3.2 and δ3.6. The methoxy 3H-singlet showed at δ3.95 while the 2H-broad of the -NH absorption was at δ5.6. A 2H multiplet of the aromatic H-3 and H-5 was at δ7.1 while the deshielded 1H-doublet was at δ7.9.



298 299 300

The nitroamine obtained above was made to undergo a reductive exo-tet cyclisation, using the usual reducing mixture of refluxing iron in acetic acid, to give 9-methoxy-1,2,3,4,11, 11a-hexahydropyrido (1,2-b)(1,2,4) benzothiadiazine-6, 6-dioxide as brown solid.


SPECTRASET MODE
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AUTO SMOOTH
SCAN TIME
MINS
RESPONSE
1 2 3 4
cm⁻¹ EXP
SLITWIDTH
% T EXP
BACK OFF
REMARKS
2,5 μm
5
10
20
50
100
80
60
40
0
4000 cm⁻¹
3500
3000
2500
2000
1800
1600
1400
1200
1000
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600
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200
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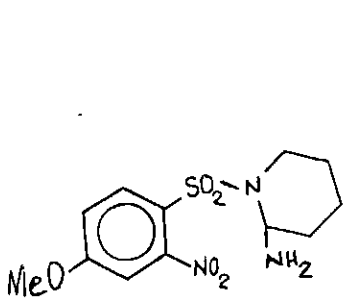
CAMBRIDGE ENGLAND
PART No 641749



BRUKER

JUL 84.075
DATE 23-7-87
TIME 16.36

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TD	16384
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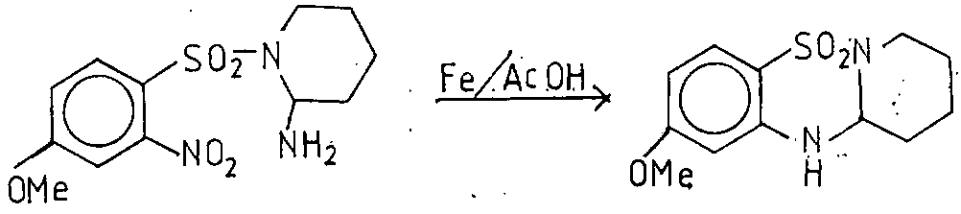
SW2	3205.128
HZ/PT	.391
PW	7.2
RD	2.000
AQ	2.556
RG	20
NS	296
TE	297
FW	4100
O2	2882.815
DP	12L PD
LB	.160
GB	0.0
CX	32.00
CY	17.00
F1	8.934P
F2	-.565P
MI	.01
DC	1.000
HZ/CM	59.409
PPM/CM	.297
IS	5
SR	2339.76

The infra red spectrum of the solid showed a - NH deformation band 1650 cm^{-1}, the aromatic -C=C- bond stretching was at 1600 cm^{-1}, the sulphonamide SO_2-N< band appeared at 1360 cm^{-1} and 1375 cm^{-1}.

The ^{1}H-NMR spectrum in DMSO-d_6 gave a 4H-multiplet at δ2.0 for the piperidine ring (type 'a'), a 2H-multiplet at δ2.6 while a 2H-multiplet at δ3.6 represented the protons adjacent to the nitrogen atom. The methoxy 3H - singlet absorbed at δ3.9 and the N-CH-N 1H multiplet showed at δ4.5. The low field absorptions consists of a 2H multiplet representing H-8 and H-10, a 1H doublet at δ7.8 for the H-7 signal. The 1H signal of NH proton absorbed at δ10.0 and it is exchangeable with D_2O.



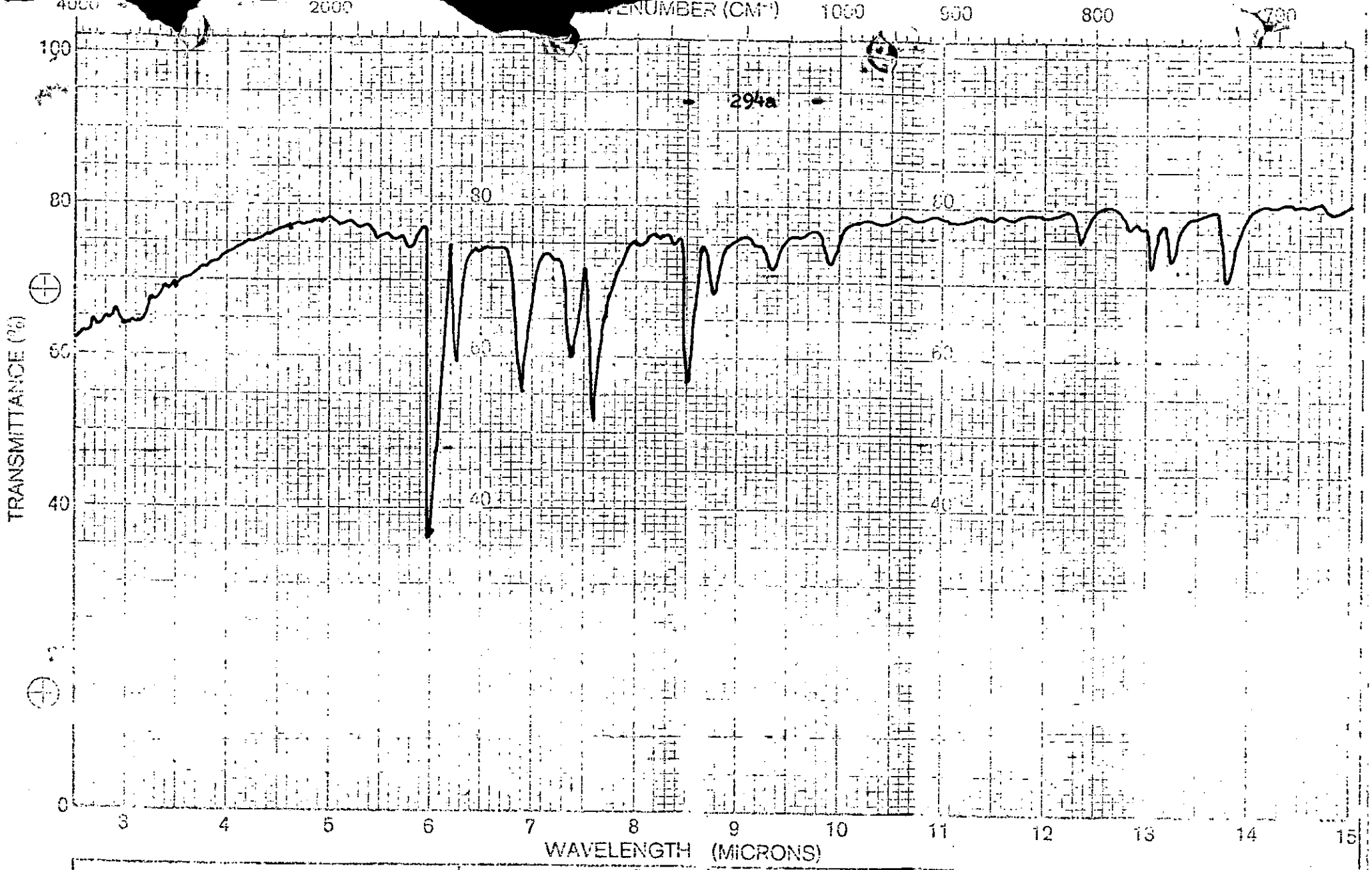
300 301

9-Ethoxy-1,2,3,4,11, 11a-hexahydropyrido (1,2-b) (1,2,4) benzothiadiazine - 6, 6 - dioxide:

In continuation of efforts to obtain alkoxy derivatives, attention was directed towards the 9-ethoxy analogues. This heterocycle was designed to be constructed through scheme 20 delineated below:

- 294 -

The infra red spectrum of the solid showed a - NH



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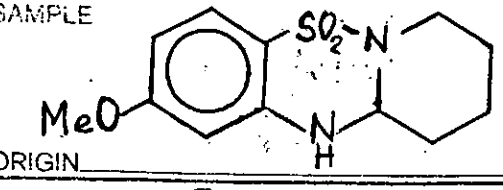


ORIGIN

SOLVENT Nujol

CONC.

CELL PATH

REFERENCE

SCAN F

SLIT M

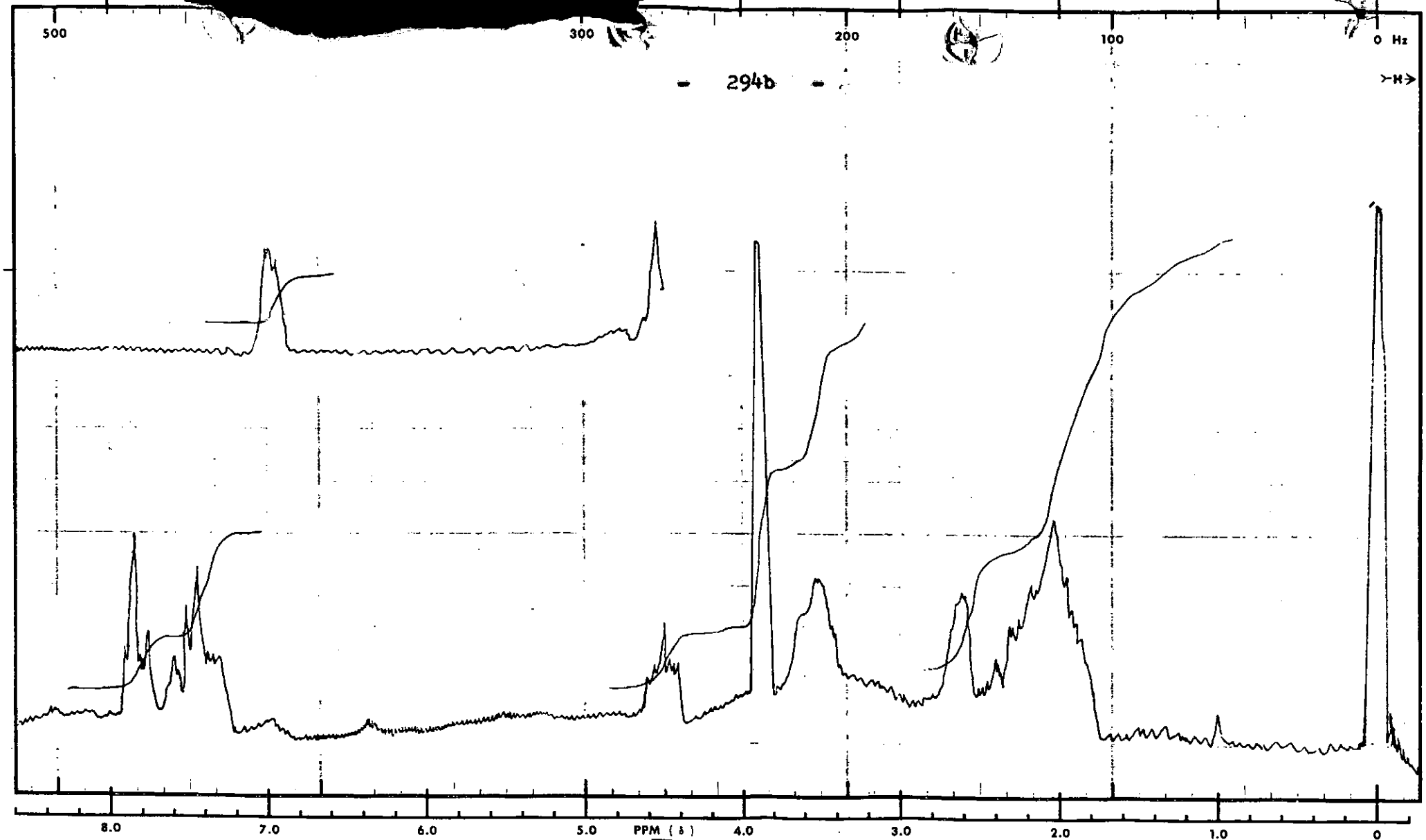
OPERATOR Famulari

DATE

REMARKS

PERKIN-ELMER PART NO. 471-5032

REF. No.



SWEEP OFFSET (Hz): 200
SPECTRUM AMPLITUDE: 32
INTEGRAL AMPLITUDE: 2
SPINNING RATE (RPS): 38

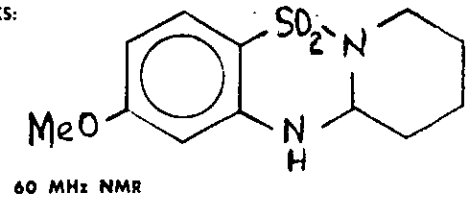
MANUAL | AUTO ☐

SWEEP TIME (SEC): 50 | 250 — (250)
SWEEP WIDTH (Hz): 25 | 50 | 100 | 250 | 500 — (500)
FILTER: 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 — (2)
RF POWER LEVEL: ——— (.05)

SAMPLE:

SOLVENT: DMSO-d_6

REMARKS:

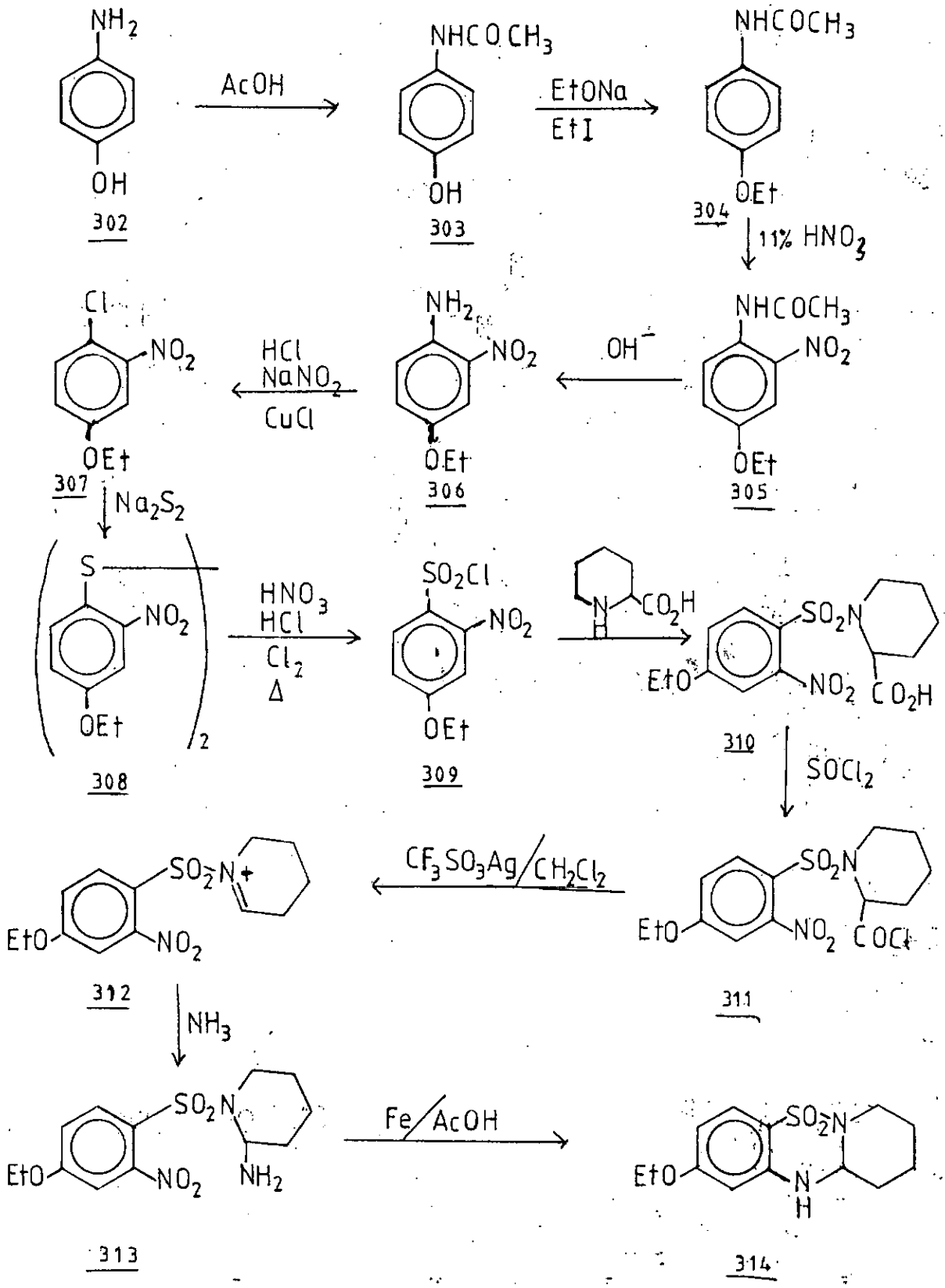


varian
analytical instrument division

DATE: 2/10/87

OPERATOR:

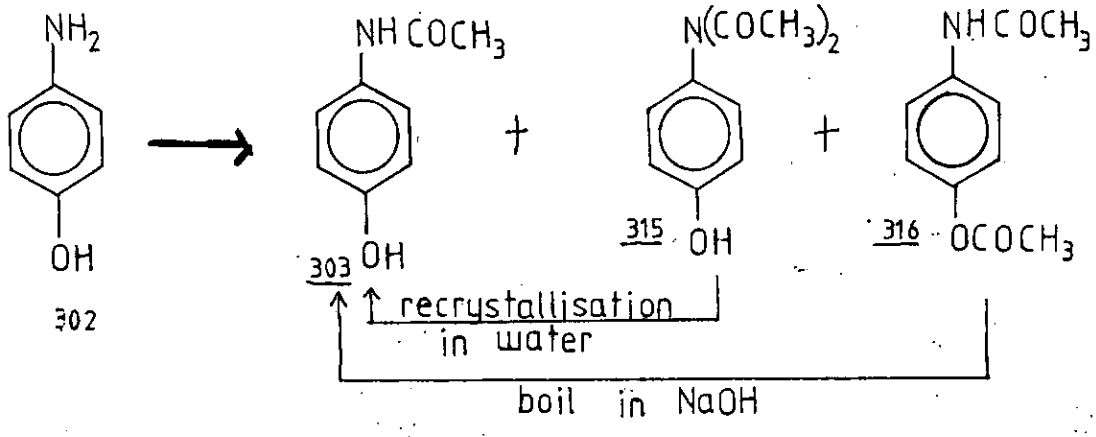
60 MHz NMR
SPECTRUM NO.


AcOH
EtONa
EtI
11% HNO3
OH⁻
HCl
NaNO2
CuCl
Na2S2
HNO3
HCl
Cl2
Δ
SOCl2
CF3SO3Ag/CH2Cl2
NH3
Fe/AcOH
302
303
304
305
306
307
308
309
310
311
312
313
314

Scheme 20

Commercial p-aminophenol was acetylated with acetic anhydride affording good yields of p-hydroxyacetanilide m.p. 168° (lit m.p. 169°)[84].

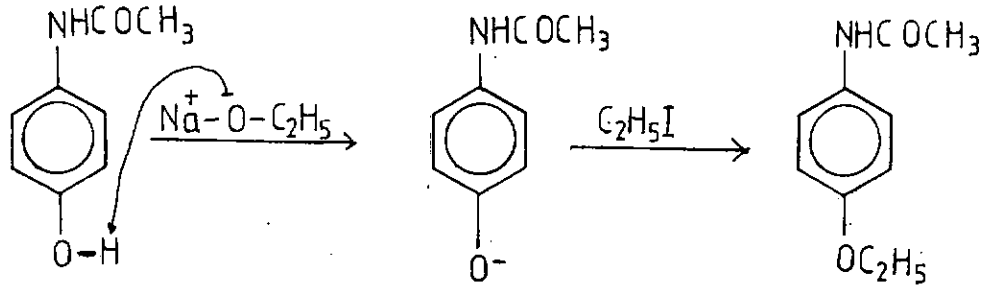
The N, N-diacetylate side product was removed by recrystallisation of the product from water while any O-acetylated derivatives are converted to the p-hydroxy-acetanilide by boiling in dilute alkali precipitated with acid, and recrystallisation from ethanol.



The ethoxyacetanilide was obtained in good yields from p-hydroxyacetanilide by reactions of the latter with sodium ethoxide and ethyl iodide. The sodium ethoxide abstracts the hydrogen of the phenol thereby making it highly nucleophilic and available for alkylation by the ethyl iodide.

- 296 -

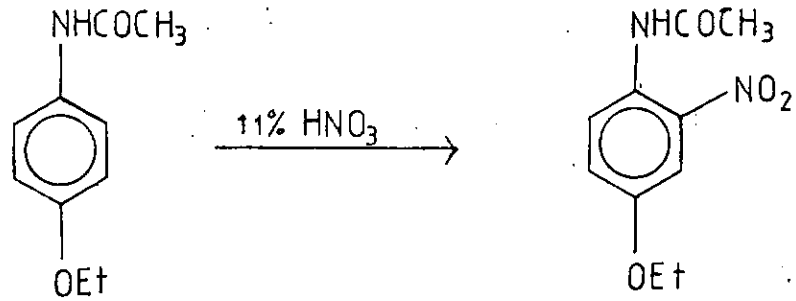
p-aminophenol was acetylated with acetic



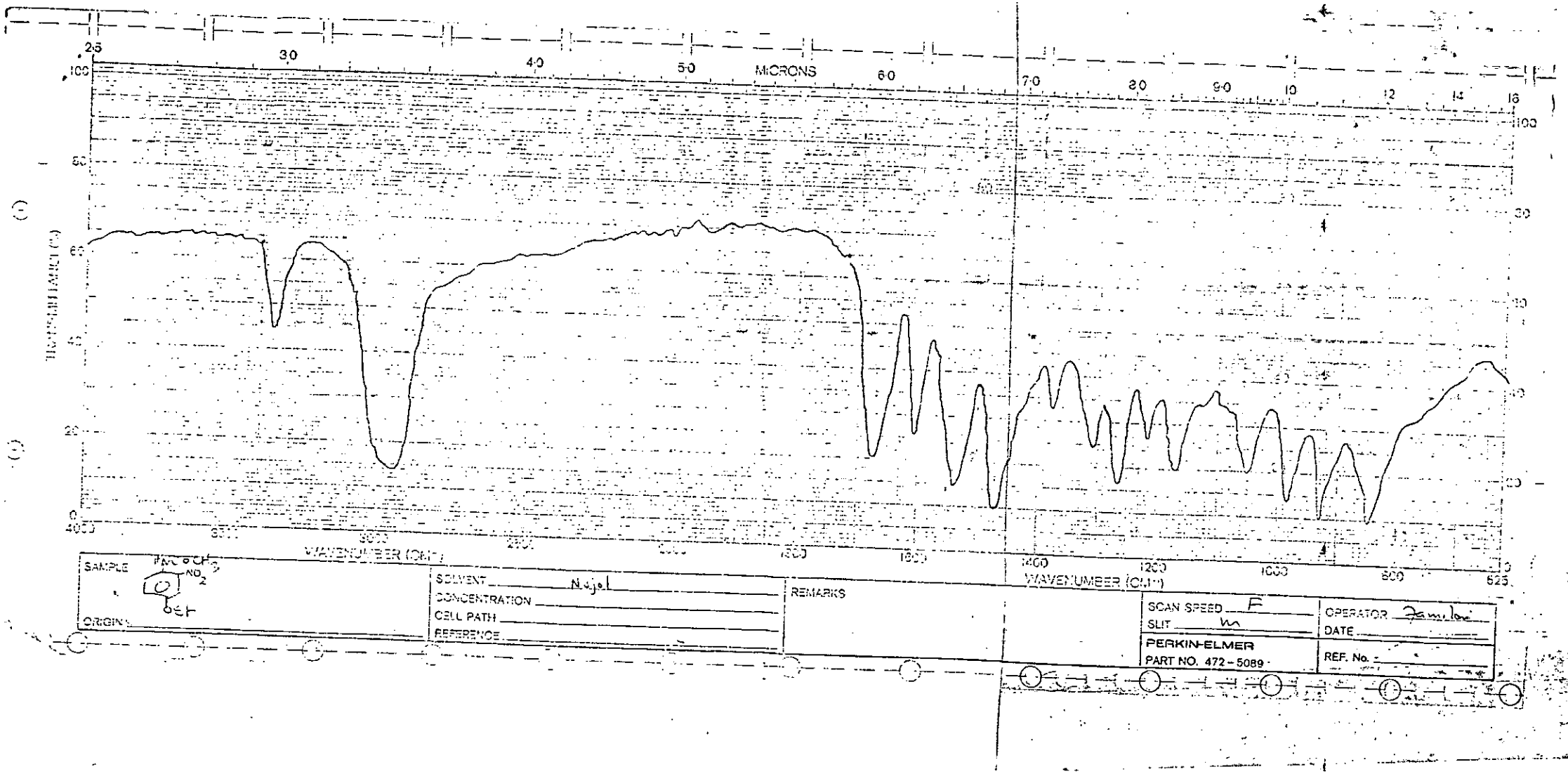
303 304

The melting point of the ethoxyacetanilide of 136° - 137° agreed with the literature m.p. 137° - 138°[84].

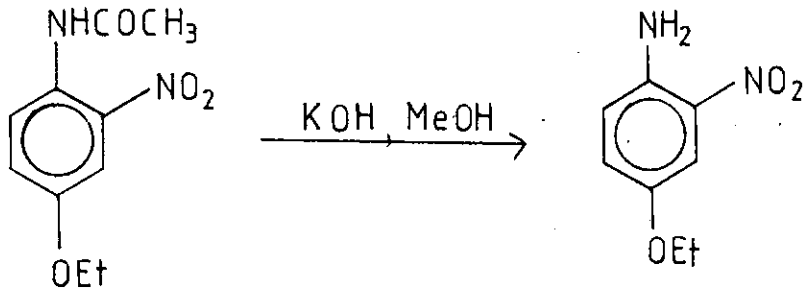
The nitration of the p-ethoxyacetanilide was carried out like that of methoxyacetanilide using 11% nitric acid solution. The nitro product had a melting point of 102 - 103° which was identical with the literature melting point of 103°[90].



304 305

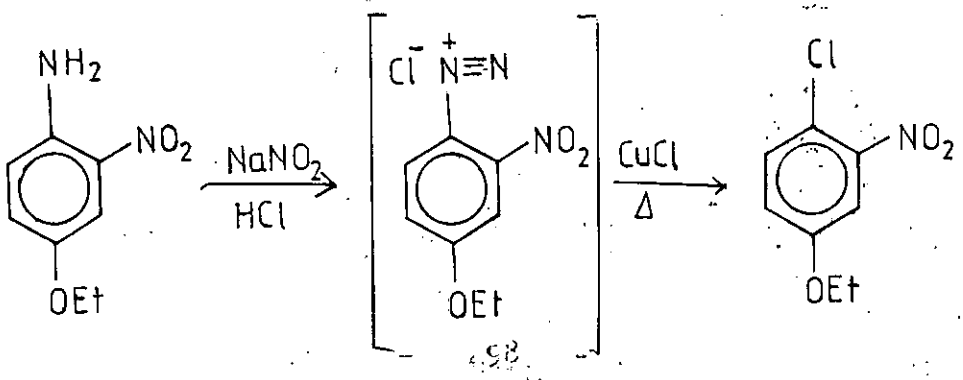

2.5
3.0
4.0
5.0
MICRONS
6.0
7.0
8.0
9.0
10
12
14
16
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
WAVENUMBER (CM⁻¹)
SAMPLE
ORIGIN
SOLVENT Nujol
CONCENTRATION
CELL PATH
REFERENCE
REMARKS
SCAN SPEED F
SLIT m
PERKIN-ELMER
PART NO. 472-5089
OPERATOR
DATE
REF. No.

Hydrolysis of 4-ethoxy-2-nitroacetanilide to 4-ethoxy-2-nitroaniline was also carried out with Claisen's mixture as earlier described for the methoxy case. A good yield (90%) of the red needles was obtained m.p. 113°, literature m.p. 113° [91].

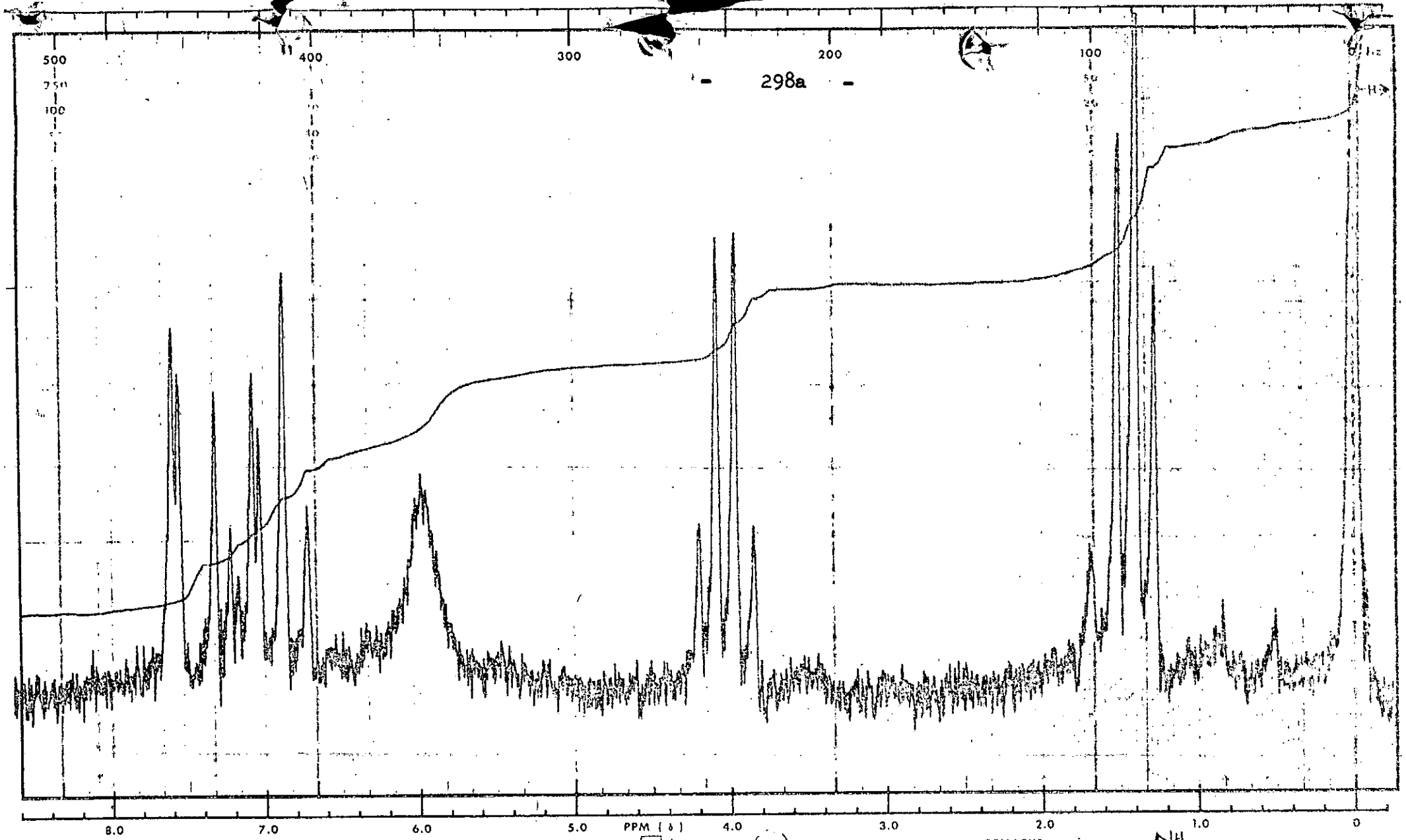


305 306

4-Ethoxy-2-nitroaniline was also converted to 4-ethoxy-2-nitrochlorobenzene through a Sandmeyer reaction similar to that earlier described for 4-methoxy-2-nitroaniline. Diazotisation was achieved with cold acidic sodium nitrite followed by coupling with freshly prepared copper (1) chloride. Steam distillation of the crude product gave pure needles; melting point 48 - 49° literature m.p. 49° [91].



98



SWEEP OFFSET (Hz): -6262
SPECTRUM AMPLITUDE: 62
INTEGRAL AMPLITUDE: 1
SPINNING RATE (RPS): 33

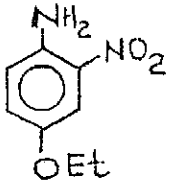
MANUAL
SWEEP TIME (SEC): 50 | 250
SWEEP WIDTH (Hz): 25 | 50 | 100 | 250 | 500
FILTER: 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8
RF POWER LEVEL: 0.05

AUTO ☐
(250)
(500)
(2)
(.05)

SAMPLE: (10)

SOLVENT: $CDCl_3$

REMARKS:



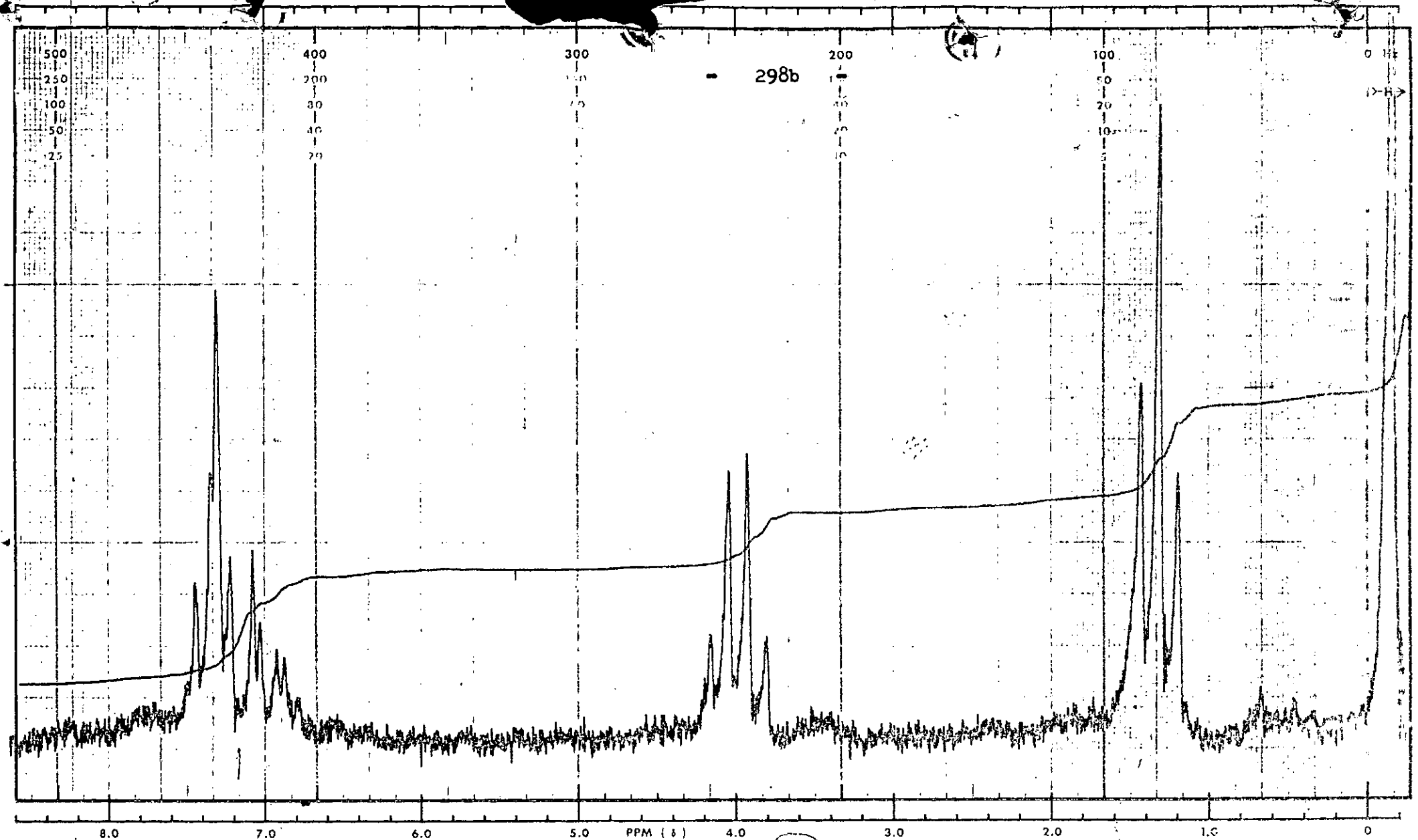
varian
analytical instrument division

DATE: 2/3/87

OPERATOR: [illegible]

60 MHz NMR
SPECTRUM NO.

298b



SWEEP OFFSET (Hz): 6250
SPECTRUM AMPLITUDE: 40
INTEGRAL AMPLITUDE: 1
SPINNING RATE (RPS): 49

MANUAL

SWEEP TIME (SEC): 50 | 250
SWEEP WIDTH (Hz): 25 | 50 | 100 | 250 | 500
FILTER: 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8
RF POWER LEVEL: 0.05

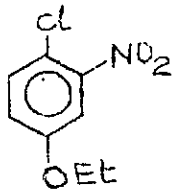
AUTO ☐

(250)
(500)
(2)
(.05)

SAMPLE: 13

SOLVENT: CDCl3

REMARKS:



varian
analytical instrument division

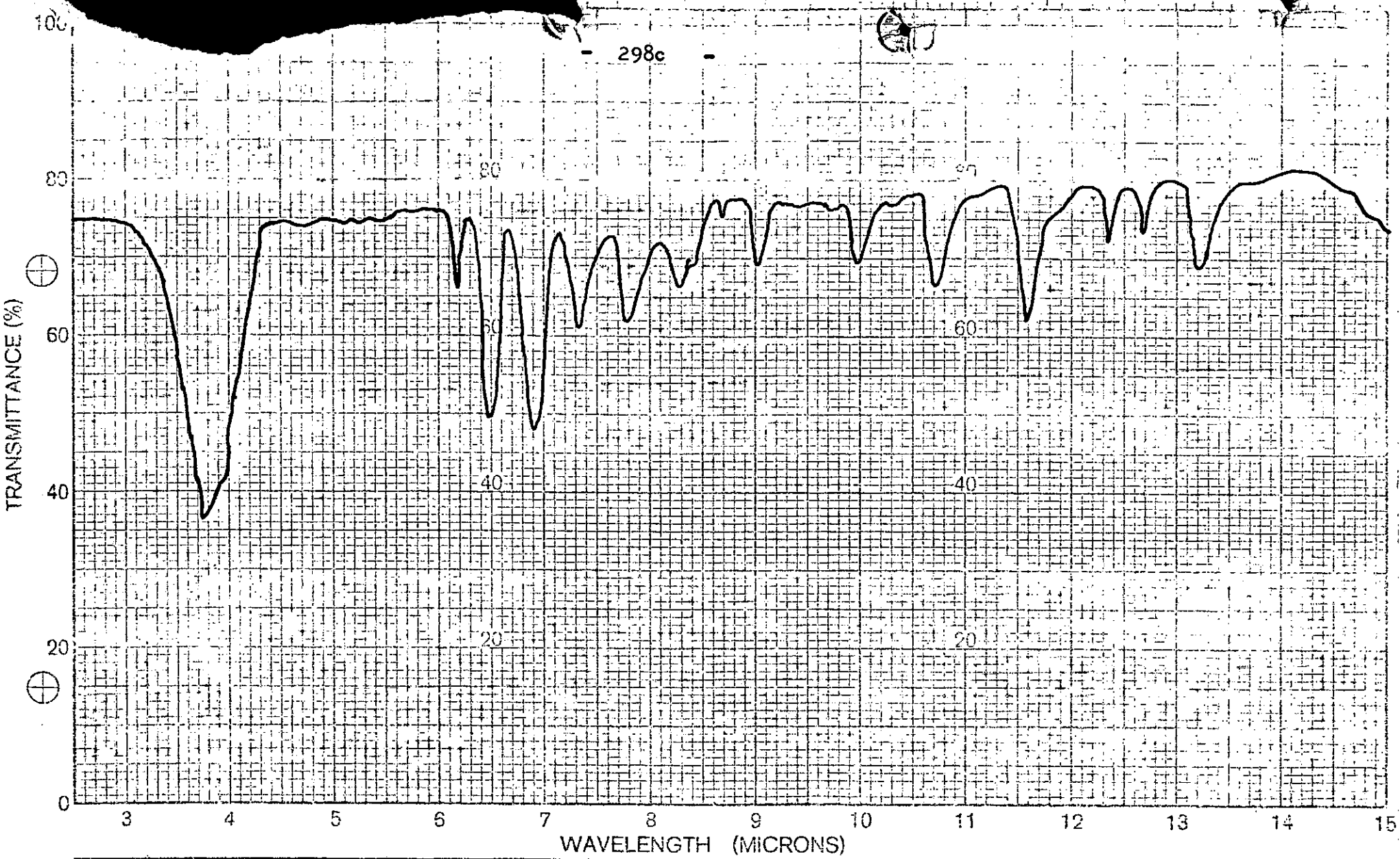
DATE: 23/10/87

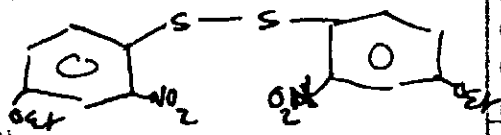
OPERATOR: D. O. Cabral

60 MHz NMR
SPECTRUM NO.

[redacted]

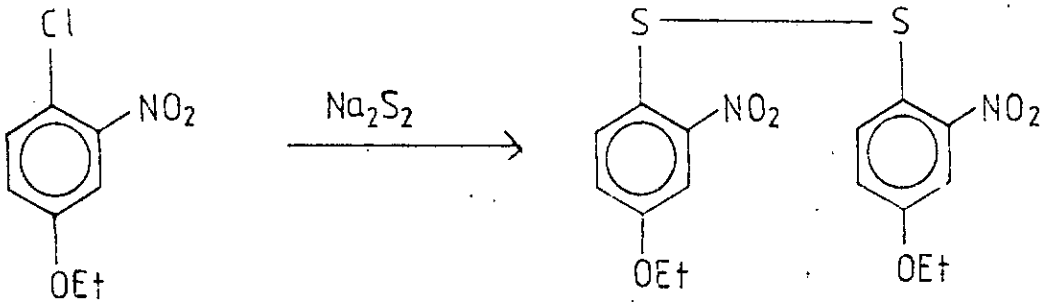
- 298c -



SAMPLE  ORIGIN	SOLVENT Nujol	SCAN F	REMARKS
	CONC.	SLIT m	
	CELL PATH	OPERATOR	
	REFERENCE	DATE	
	PERKIN-ELMER PART NO. 471-5032		REF. No.

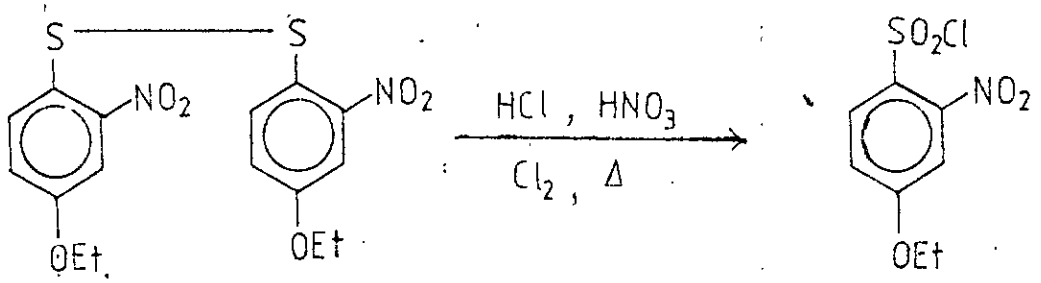
4, 4'- diethoxy-2,2'-dinitrodiphenyldisulphide was prepared from 4-ethoxy-2-nitro chlorobenzene with sodium disulphide produced in situ from sodium sulphide and sulphur. The yield of product was low (30%). This again may be due to the effect of the ethoxy group counteracting the activating effect of the ortho nitro group on the chlorine atom.

The infra red spectrum of the disulphide showed the -C=C- stretching of the aromatic ring at 1600 cm^{-1}. Bands at 1510 and 1340 cm^{-1} represented the nitro group while the C-O-C ether bond stretching absorbed at 1230 cm^{-1}.



307 308

4-Ethoxy-2-nitrobenzenesulphonyl chloride was obtained from the disulphide by chlorine oxidation of the disulphide, as discussed earlier for 4-methyl-2-nitrobenzenesulphonyl chloride.



308 309

The melting point of the sulphonyl chloride 73 - 74° was consistent with the literature melting point 74.7° [91].

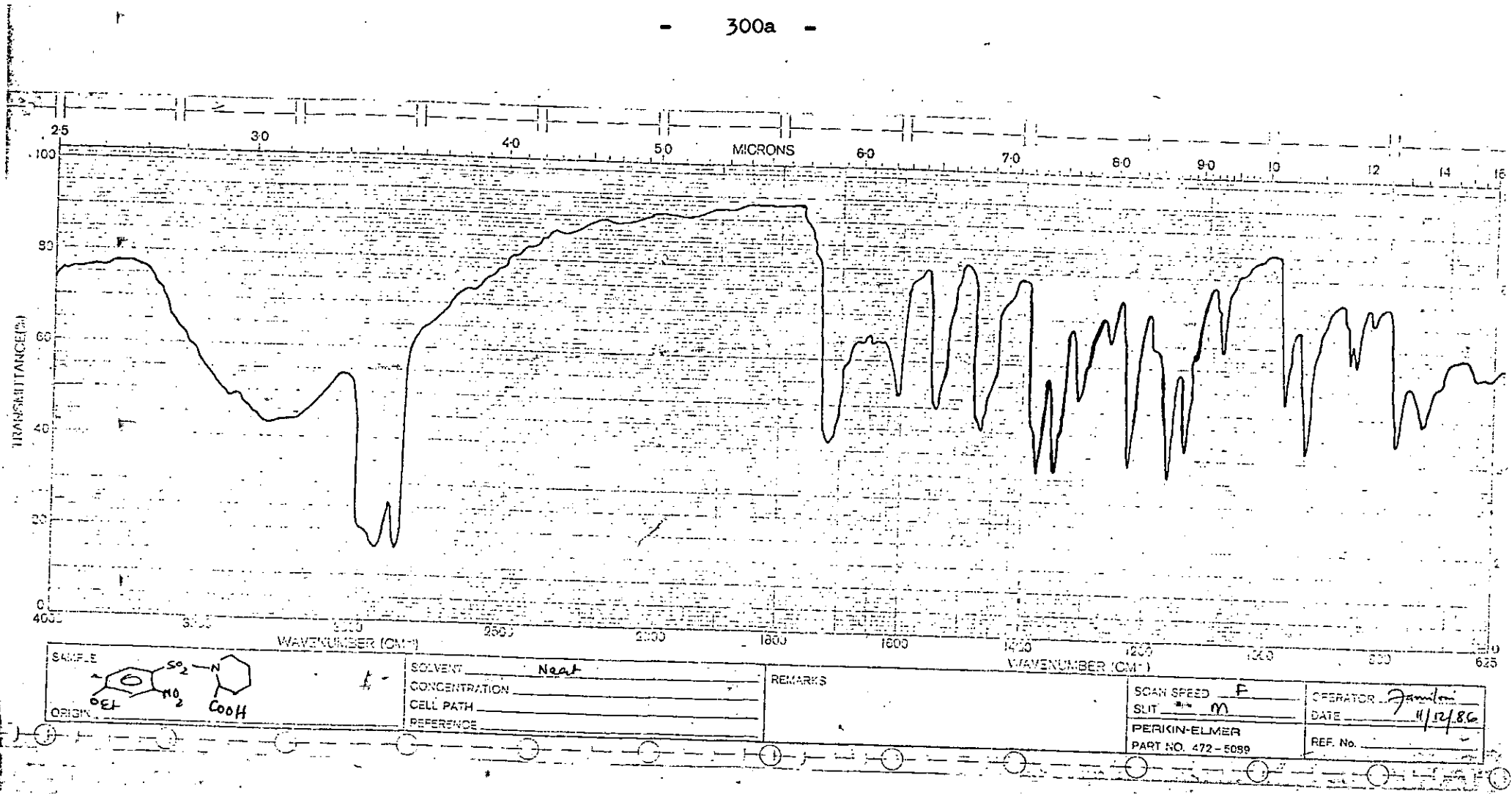
4-Ethoxy-2-nitrobenzenesulphonyl chloride was condensed with DL piperidine-2-carboxylic acid in the presence of potassium carbonate under reflux for 1h. Work-up, as reported earlier gave N-(4-ethoxy-2-nitrobenzene sulphonyl) piperidine-2-carboxylic acid. The mechanism of the reaction is the same as that of any Schotten - Baumann reaction.

The infra red spectrum of the product showed a band at 1720 cm^{-1} for the acid carbonyl stretching, the -C=C- of the aromatic was at 1600 cm^{-1}. Other bands included 1540 and 1340cm^{-1} (NO_2 group), 1380 and 1170 cm^{-1} ($SO_2N<$) and the -C-O-C ether linkage of the ethoxy absorbed at 1230 cm^{-1}.

The ^{1}H-NMR spectrum showed a 3H-triplet of the methyl of the ethyl group at δ1.40 along with a 2H multiplet of the piperidine ring type 'a' protons. A 3H - multiplet at δ1.7, a 1H multiplet at δ2.2 are for piperidine ring proton type 'b' and 'c' respectively, while two protons adjacent to the nitrogen absorbed as a 1H multiplet at δ3.3 and another 1H doublet at δ3.6. A 2H multiplet at δ4.2 represented the $-CH_2-$ of the ethoxy group. The broad of signal, the -OH of the acid absorbed at δ4.5 (exchangeable with D_2O). The N-C<u>H</u>-N- proton appeared as

- 300 -

The melting point of the sulphonyl chloride 73 - 74°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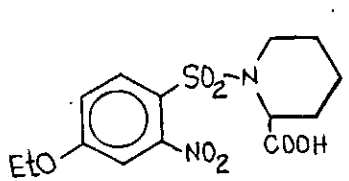
3.0
4.0
5.0
MICRONS
6.0
7.0
8.0
9.0
10
12
14
16
100
80
60
40
20
0
TRANSMITTANCE(%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)
SAMPLE
ORIGIN
SOLVENT Neat
CONCENTRATION
CELL PATH
REFERENCE
REMARKS
SCAN SPEED F
SLIT M
PERKIN-ELMER
PART NO. 472-5099
OPERATOR Jamilmi
DATE 11/12/86
REF. No.

- 300b -

SOLVENT CD_3OD

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JULY03.000
DATE 16-7-97
TIME 15.14

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SFØ    200.130
SF2    200.132
SY   80.0
Ø1    3200.000
SI   16384
TD   16384
SW    3205.128
SW2   3205.128
HZ/PT     .391

PW        7.5
RD        2.000
AQ        2.556
RG       16
NS       32
TE      297

FW     4100
Ø2        0.Ø
DP   63L PO

LB         .140
GB         0.0
CX        32.00
CY        12.00
F1        12.000P
F2         -.500P
MI          .02
DC         1.000
HZ/CM    78.177
PPM/CM     .391
IS         5
SR     2286.43
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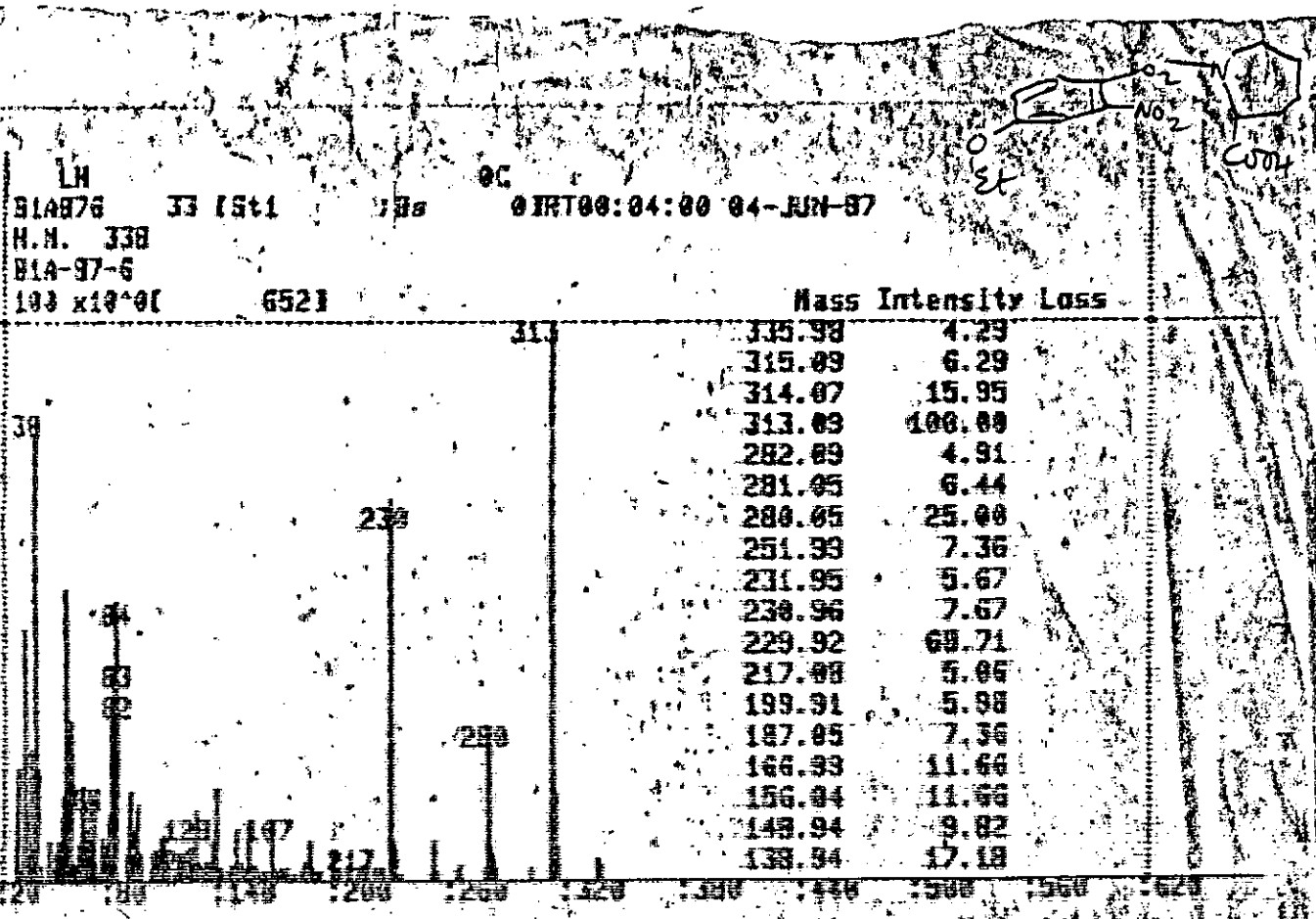
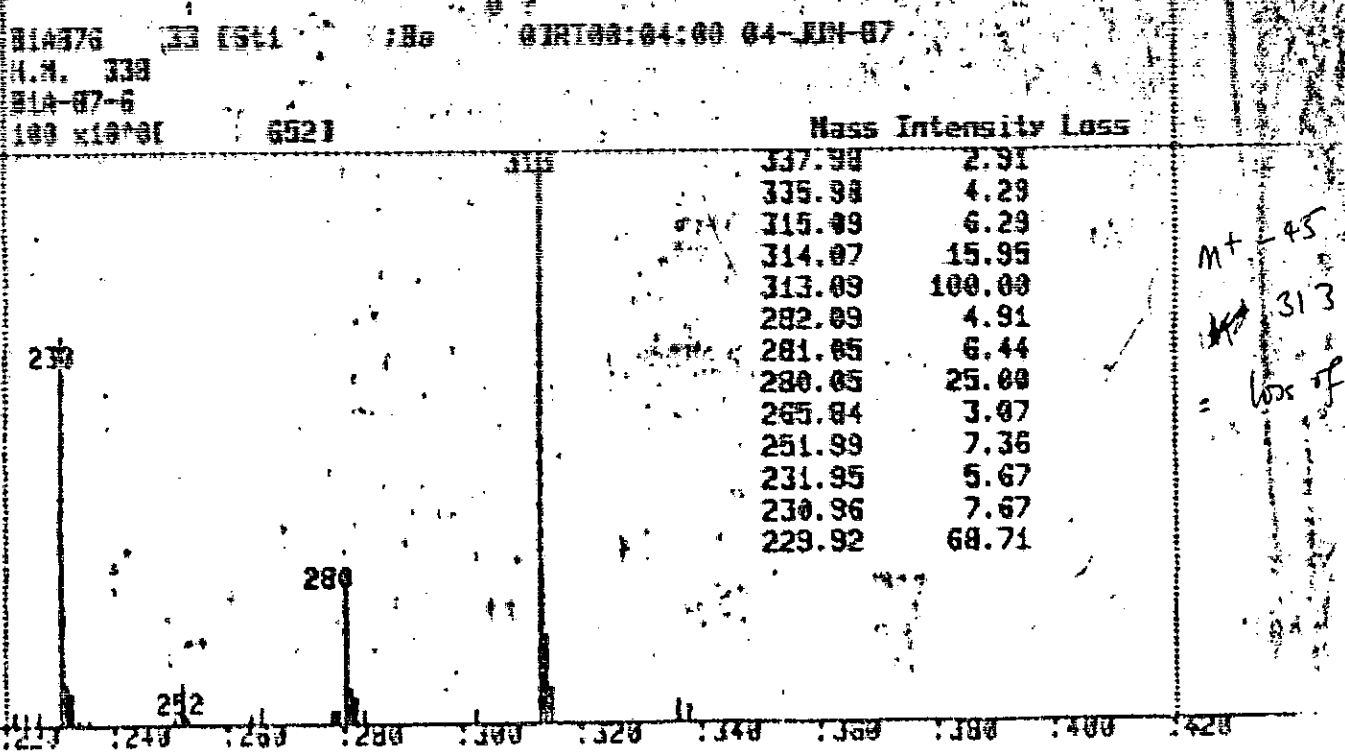
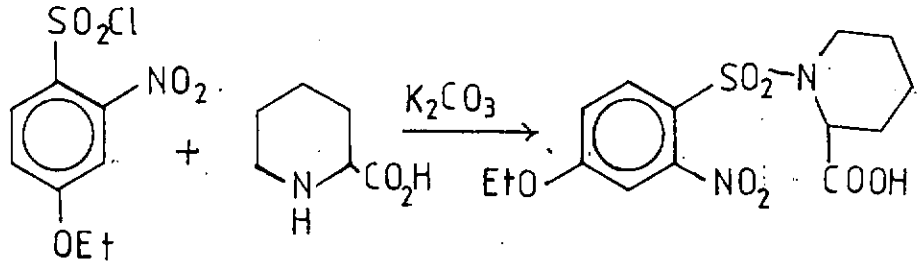




M+ - 45 = 313
= loss of CO_2Et

a 1H - doublet at δ4.7. The doublet observed may be due to the orientation in space in which only one of the two adjacent protons interacts with the base proton. A 2H multiplet representing H-3 and H-5 appeared at δ7.15 while the 1H - doublet at δ7.9 was assigned to the H-6.



309 310

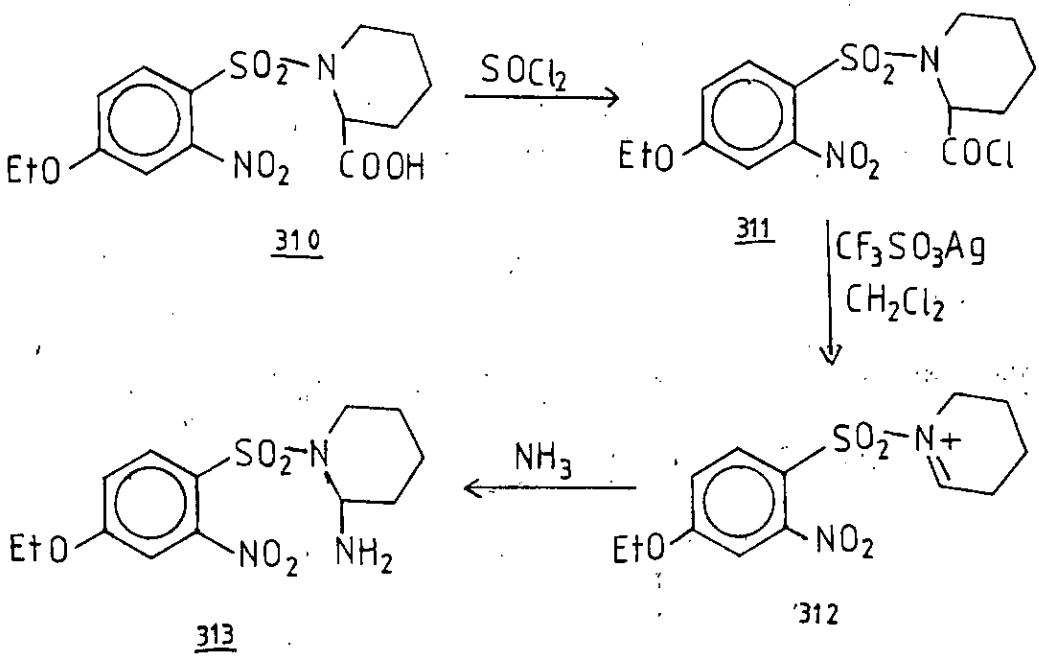
The acid adduct was converted to N-(4-ethoxy-2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid chloride with gentle reflux with thionyl chloride, which on work-up left a light brown oil.

The preparation of N-(4-ethoxy-2-nitrobenzenesulphonyl)2-amino piperidine was achieved by the addition of silver trifluoromethanesulphonate to the dichloromethane solution of the acid chloride under inert conditions. There was an instantaneous effervescence with evolution of carbon monoxide accompanied by the immediate generation of N-(4-ethoxy-2-nitrobenzenesulphonyl)tetrahydropyridinium/ trifluoromethanesulphonate salt. After injection of concentrated ammonia and work-up, a brown solid was obtained.

- 301 -

1H - doublet at δ4.7. The doublet observed may be due

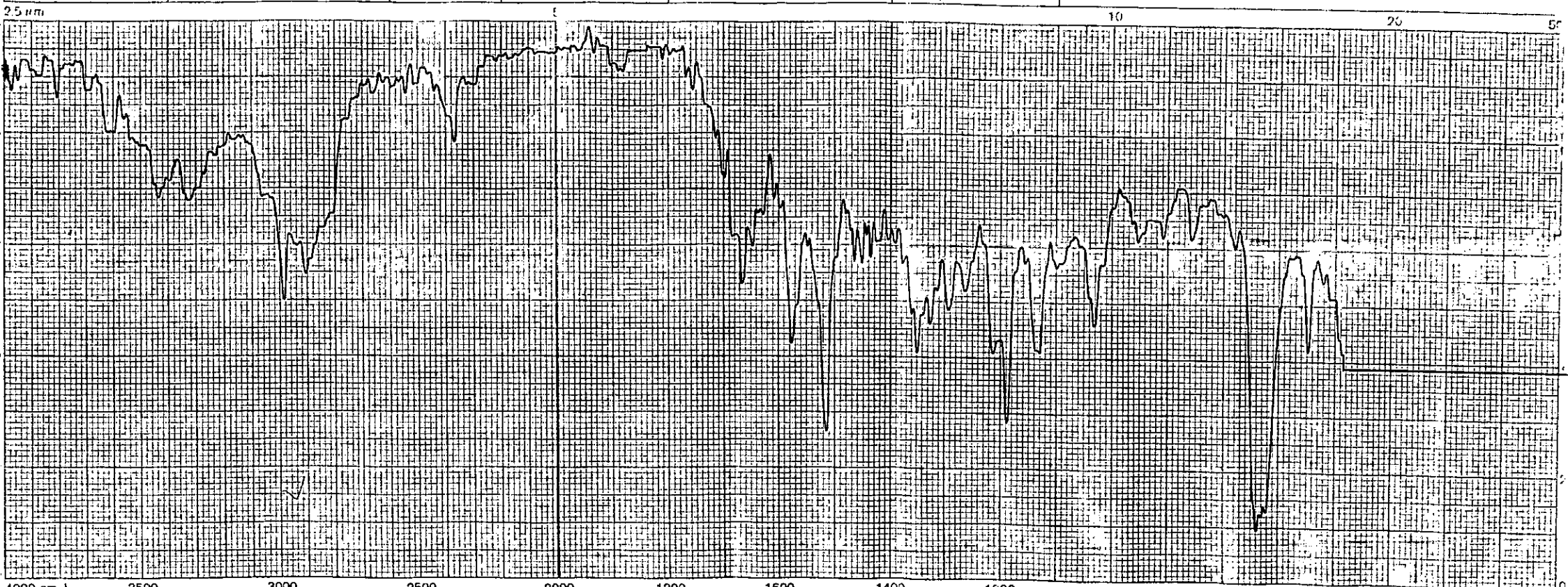
Flash chromatography of the product gave the pure amine as a brown microcrystalline solid m.p. 120 - 121°.

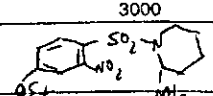


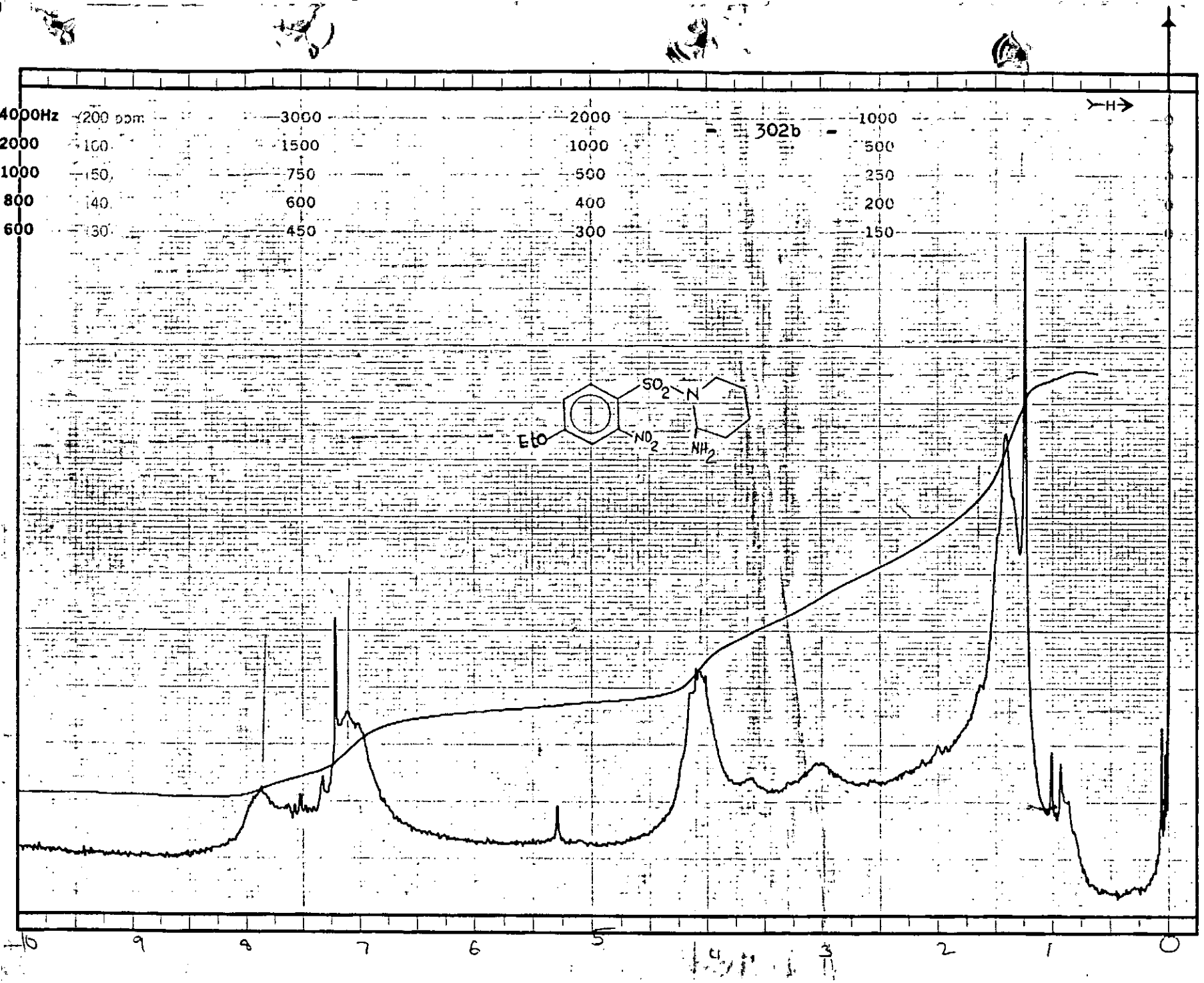
The infra red spectrum of the nitroamine had absorptions at 3440 and 3320 cm^{-1} for primary amine, 2980, 2900 (-CH stretching of the piperidine ring), 1660 (-NH deformation), 1580 cm^{-1} (-C=C- stretching aromatic). The absorption at 1520 and 1320 cm^{-1} were assigned to the nitro group while 1350 and 1190 cm^{-1} represented the SO_2-N band. The ether linkage was at 1190 cm^{-1}.

The ^{1}H-NMR spectrum showed a 3H-triplet representing the methyl group of the ethoxy at δ1.3, a 6H-multiplet at δ1.6 for the piperidine ring protons and a 2H-multiplet at δ3.0 was assigned to the methylene adjacent to the

SPECTRASET MODE		SCAN TIME	RESPONSE				cm⁻¹ EXP	T EXP	REMARKS
✓	○ SINGLE BEAM ○ FIXED RESPONSE ○ AUTO SMOOTH	MINS	1 ○	2 ○	3 ○	4 ○	SLITWIDTH	BACK OFF	



SAMPLE	TECHNIQUE	PATHLENGTH	OPERATOR	PYE UNICAM LTD CAMBRIDGE ENGLAND
	REFERENCE	CONCENTRATION	DATE % REF No	PART No 641749



FT-80A SPECTRUM NO. _____

OPERATOR _____ DATE 1/9/87

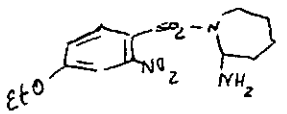
NUCLEUS ^{1}H FREQUENCY 80MHz

SYNTHESIZER SETTING _____

EXPERIMENT NAME _____

FILE NAME _____

SAMPLE OBF1



LOCK ☐ INTERNAL ☐ EXTERNAL

LOCK SIGNAL $CDCl_3$

SPIN RATE ____ rps. TEMP ____ °C

INSERT 5 mm

ACQUISITION

SPECTRAL WIDTH (SW) 1000 Hz

NO. OF TRANSIENTS (NT) 200

ACQUISITION TIME (AT) 1.023 sec.

PULSE WIDTH (PW) 30 μsec.

PULSE DELAY (PD) 0 sec.

DATA POINTS (DP) _____

TRANSMITTER OFFSET (TO) 43

HIGH FIELD _____ LOW FIELD _____

RECEIVER GAIN (RG) 3

DECOUPLER MODE (DM) _____

DECOUPLER OFFSET (DO) _____

NOISE BANDWIDTH (NB) _____ kHz

ACQUISITION MODE (AM) _____

DISPLAY

SENS. ENHANCEMENT (SE) 0 sec.

WIDTH OF PLOT (WP) 8250 Hz

END OF PLOT (EP) 0 Hz

WIDTH OF CHART (WC) 8250 Hz

END OF CHART (EC) 0 Hz

VERTICAL SCALE (VS) 350

REFERENCE LINE (RL) 1143

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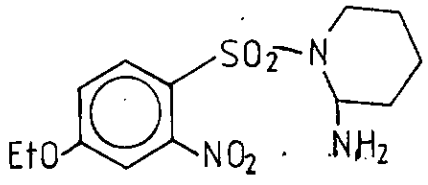
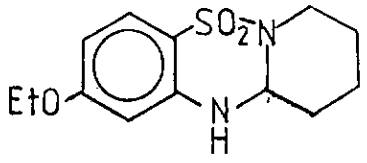
nitrogen atom while the 3H multiplet at δ 4.1 represented the signals of the methylene of the ethoxy group and the base proton of the amino group. The aromatic 2H-multiplet at δ7.1 is assigned to H-3 and H-5, while the 1H multiplet at δ7.9 represented H-6.

Reductive cyclisation of the nitroamine was achieved as usual with a mixture of iron filing and iron dust in acetic acid and refluxing at 128 - 130^{o} for 12h. Work-up of the reaction mixture gave a brown solid which on flash chromatography furnished 9-ethoxy-1,2,3,4,11, 11a-hexahydro-pyrido (1,2,b) (1,2,4) benzothiadiazine - 6, 6 - dioxide as light brown microcrystals.

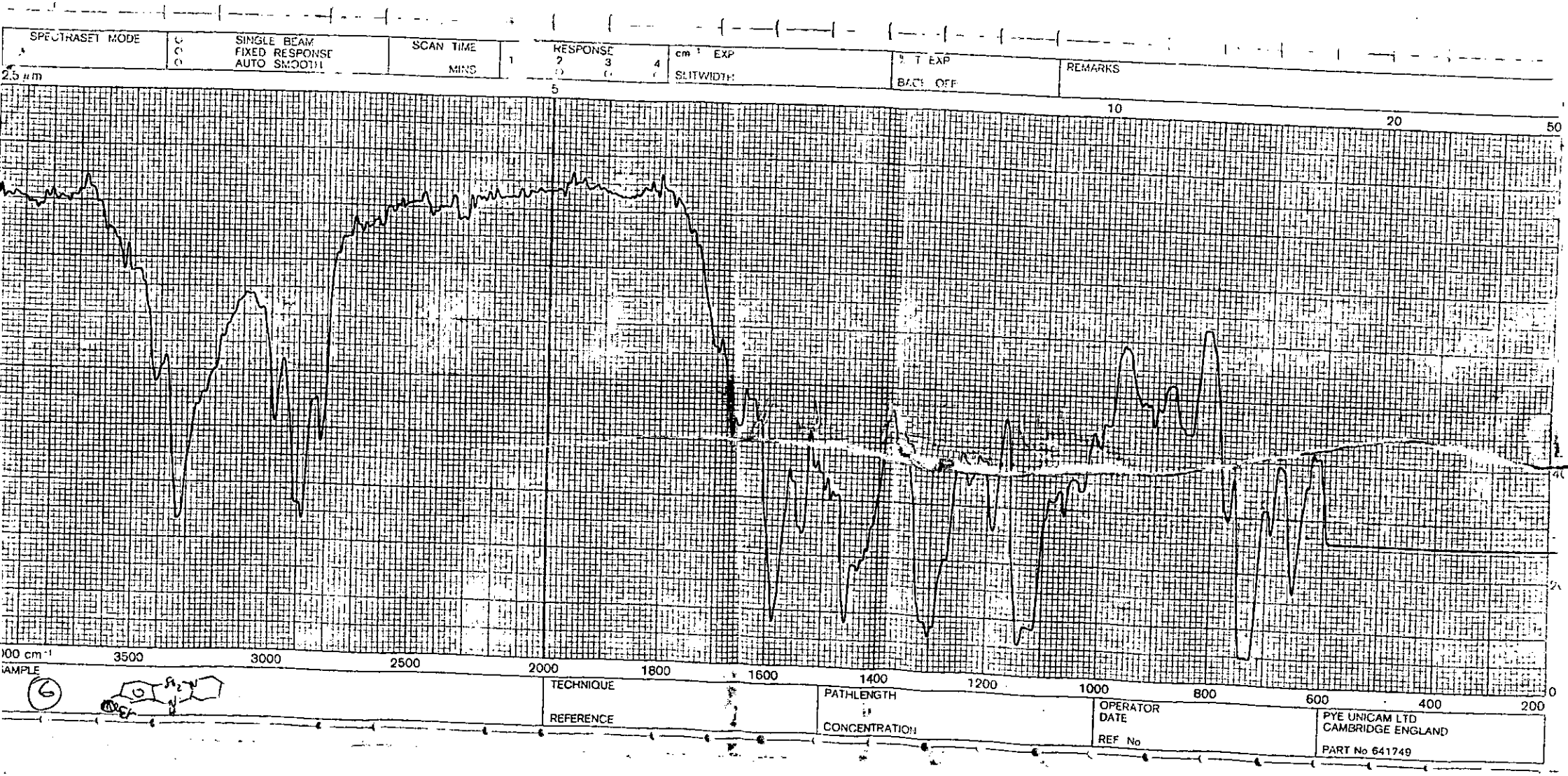


313



314

The infra red spectrum of the microcrystalline product showed an -NH absorption band at 3340 cm^{-1} other significant absorptions include 2995, 2900, 2820 cm^{-1} (-CH stretching of the piperidine), 1660 cm^{-1} (-NH deformation), 1600 cm^{-1} (-C=C- aromatic). The absorptions at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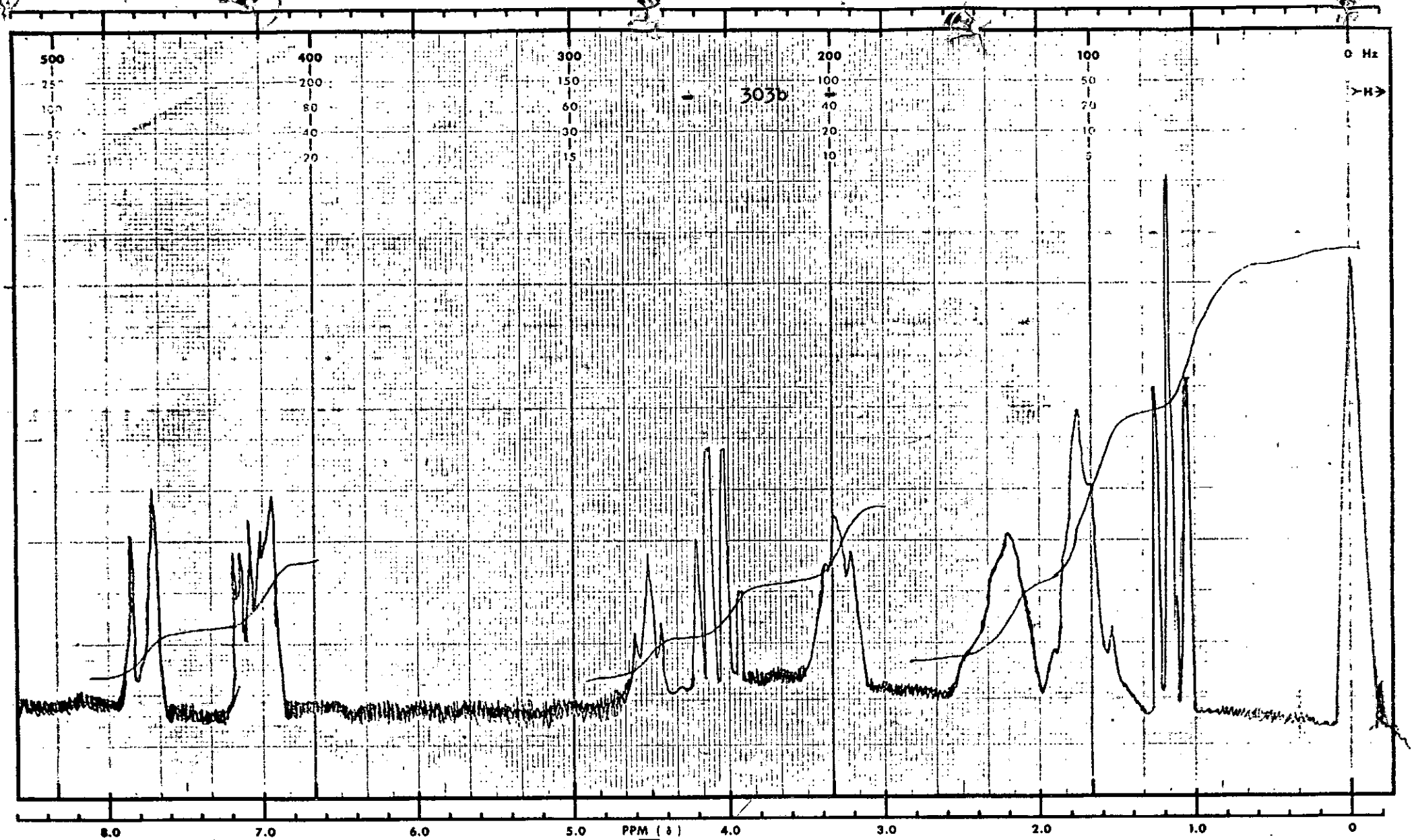
AUTO SMOOTH
SCAN TIME
MINS
RESPONSE
2
3
4
cm⁻¹ EXP
SLITWIDTH
% T EXP
BACK OFF
REMARKS
2.5 μm
5
10
20
50
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
TECHNIQUE
REFERENCE
PATHLENGTH
CONCENTRATION
OPERATOR
DATE
REF No
PYE UNICAM LTD
CAMBRIDGE ENGLAND
PART No 641749

CHART S-601
MADE IN U.S.A.



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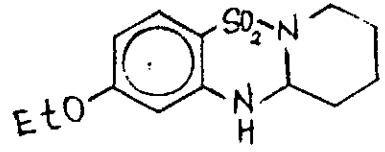
SPECTRUM AMPLITUDE:	48	SWEEP WIDTH (Hz):	25 50 100 250 500	(500)	
INTEGRAL AMPLITUDE:	1	FILTER:	1 2 3 4 5 6 7 8	(2)	
SPINNING RATE (RPS):	33	RF POWER LEVEL:	0.95	(.05)	SOLVENT: $(CD_3)_2CO$

MANUAL ✓ AUTO ☐

REMARKS:



varian
analytical instrument division

DATE: 2/14/87

OPERATOR: D.O. Olafimihan

60 MHz NMR

SPECTRUM NO.

1300 and 1140 cm^{-1} are assigned to the $-SO_2N<$ group and the ether linkage of the ethoxy absorbed at 1190 cm^{-1}. The ^{1}H-NMR spectrum of compound 314 showed a 3H-triplet representing the methyl of the ethoxy at δ1.2. A 6H - multiplet at δ1.7 and a 2H multiplet at δ 3.3 represented the protons adjacent to the nitrogen atom of the piperidine ring, respectively. A 2H-quartet at δ 4.2 is assigned to the methylene of the ethoxy group. The N-CH-N- proton absorbed as a 1H - multiplet at δ 4.5. The aromatic proton signals appeared as a 2H multiplet at δ 7.1 for H-3 and H-5 while H-6 absorbed as a 1H - multiplet at δ7.8.

CONCLUSION

The use of N-(arylsulphonyl) piperidinium salts as intermediates for multiring heterocycles is herewith demonstrated. The desired intermediates for heterocyclisation: N-(4-substituted-2-nitrobenzenesulphonyl)-2-aminopiperidines which serve as excellent precursors for the synthesis of the tricycles - 9 - substituted hexahydro (1,2-b)(1,2,4) benzothiadiazine - 6, 6-dioxide derivatives have been obtained smoothly and in excellent yields. These heterocycles are potential chemotherapeutics. The thiadiazines that result from this scheme are saturated at 11, 11a position directly. Such compounds are more active than 11, 11a - unsaturated analogues. The more active analogues have been obtained without having to resort to difficult reductions of unsaturated compounds.

The different substituents that were accomodated in the iminium salt generation reaction show it's versatility and it's potentials for synthesis of more substituted heterocycles.

CHAPTER 6

EXPERIMENTAL

General Data: The ^{1}H-N.M.R. spectra were determined using Varian T60, EM 360L, Bruker 400 MHz, AM 250 and Varian FT 80A and were recorded in ppm downfield of the internal standard of TMS in either $CDCl_3$, CD_3OD, DMSO-d_6 or $(CD_3)_2$ CO. I.R. spectra were recorded on Perkin Elmer 257, Perkin Elmer 983, PYE Unicam SP3-100 in either Nujol, KBr discs, or as neat films. Elemental analysis was carried out on a Carlo Erba 1106 instrument at the I.N.S.A. Rouen, France. Mass spectra were carried out both at the University College, London and at the Guelph - Waterloo Centre for Graduate Work in Chemistry $(GWC)^2$ Guelph, Ontario, Canada, Melting points were obtained on a Kofler hot plate apparatus and were uncorrected.

1. Preparation of N-(2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid

2-Nitrobenzenesulphonyl chloride (5.0g 23m mole) was dissolved in tetrahydrofuran 25mL. Piperidine-2-carboxylic acid (4.3g 33m mole) was dissolved in a solution of potassium carbonate 5.0g in water 50mL and ethanol 50mL.

The tetrahydrofuran solution was added to the piperidine 2-carboxylic acid solution and was heated under reflux for 1h. Ethanol and THF were distilled off, the solution was allowed to cool, washed with chloroform (to remove the unreacted materials) and acidified with 6M hydrochloric acid. The resulting adduct was extracted with dichloromethane, the extract dried with magnessium sulphate and evaporated to leave a brown solid. The solid was air dried and recrystallised in chloroform/petroleum ether. Yield 80% m.p. 158-9°C

Anal. Calcd for $C_{12}H_{14}O_6S$: C, 46.27; H, 4.87, N, 8.53,

Found: C, 47.01; H, 4.62; N, 8.53.%

I.R. (Film) Vmax 1710, 1520, 1350, 1340, 1160, 930 cm^{-1}

^{1}H-N.M.R. $(CD_3)CO$: δ 1.1(4H, m); 1.6(2H, m); 3.2(2H, m) 4.2 (1H, t); 6.6(1H, br, exchangeable with D_2O); 7.2(3H, m) 7.6 (1H, m).

m/s: m/z 269 (100%) (m^+ - 45) 186, 128, 83.

2. Preparation of N-(2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid chloride

The acid adduct (0.5g) was treated with purified thionyl chloride 2.5cm^3 and refluxed for 2h. before excess thionyl chloride was removed leaving the acid chloride as a brown fuming oil.

3. Preparation of N-(2-nitrobenzenesulphonyl)-2-amino piperidine

N-(2-nitrobenzenesulphonyl)piperidine-2-carboxylic acid chloride (0.5g 1.59m mole) was dissolved in dry redistilled dichloromethane (10 cm^3). Recrystallised silver trifluoromethane (0.5g, 1.95 mole) was added. There was an immediate and copious effervescence which ceased only after about 1h, and stirring was continued for a further 1h.

Ammonia 5cm^3 was injected through a septum stopper into the reaction mixture which turn deep brown while pale fumes were observed. Stirring continued for 1 1/2 before water was poured into the mixture, and was washed three times with water to remove silver chloride and trifluoromethane sulphonic acid. The organic solution was further washed with sodium hydrogen chloride, water and dried with sodium sulphate. The solvent was stripped off giving an oil, which turned to solid.

Flash chloromatography with chloroform: methanol 10:1 gave 2 main products on silica gel. The lower fraction was purified on p.t.l.c. m.p. 108-110°C , (78%).

I.R. (Nujol): Vmax 3400, 3060, 2980, 1680, 1600, 1540, 1380, 1180, 1080 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ 1.7(4H, m); δ2.3(2H, m); δ3.4(2H, m) δ4.6(1H, t), δ6.4(1H, exchangeable with D_2O); δ 7.7 (3H, m), δ8.1 (1H, m).

M.S: m/z 269 (100%, m^+ - 16); 216(72%); 152 (38.9%); 83.

4. Preparation of 1,2,3,4,11,11a hexahydro pyrido(1,2-b) (1,2,4)benzothiadiazine-6,6-dioxide

N-(2,nitrobenzene sulphonyl) -2-amino piperidine (0.3g, 1.05m mole) was dissolved in glacial acetic acid (15ml). Iron filing (0.2g) and iron dust 0.2g (washed free of greese with diethyl ether) was added over 2h to the above solution, before it was refluxed for 8h at 125-30°C. After cooling,the mixture was pured on crushed ice and the aqueous mixture was then extracted thrice with chloroform. The organic extract was successively washed with 5% sodium hydrogen carbonate solution and water; after which it was dried over $MgSO_4$ and the solvent stripped off in vacuo affording a brown crystalline solid.

Recrystalisation from chloroform/pet. ether gave 70% m.p. 140-141°.

I.R. (Nujol): γ_{max} 3500, 3400, 3080, 3000, 1690, 1610, 1350, 1170 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ 1.2(4H, m);δ2.1(2H, m);δ3.3(2H, m); δ5.1(1H, m);δ7.1(3H, ArH, m);δ8.2 (1H, ArH, m);δ9.1(1H, NH).

m.s.: m/z 238, m^+, 182 (64%), 173, 146, 93.

5. Preparation of N-(2-nitrobenzenesulphonyl)-2-ethyl amino piperidine

N-(2-nitrobenzenesulphonyl)piperidinium salt was generated as in experiment 3. Anhydrous ethyl amine (previously chilled to -5°) 10cm^3 was added to the iminium salt and the work up was also like that of experiment 3.

Flash chromatography of the solid product obtained gave brown solid. Yield 63%, m.p. 145-7°C.

I.R. Nujol: Vmax 3337, 3085, 2922, 1618, 1586, 1536, 1366, 1334, 1161 cm^{-1}.

6. Preparation of 4,4'-dimethyl-2,2'-dinitrodiphenyl disulphide

Sodium sulphide (6.0g) was dissolved in methanol ($25cm^3$) in a round bottom flask with a reflux condenser. The flask was heated until the sulphide dissolved. Sulphur (0.8g) was then added and heated until the sulphur dissolved forming the disulphide.

A solution of 4-chloro-3-nitrotoluene (5.0g) in methanol (10mL) was prepared in a round bottom flask with a reflux condenser. The sodium disulphide prepared was added to the toluene solution through the reflux condenser at such a rate to control the reaction.

After the addition, the reaction mixture was heated vigourously for 2h. The reaction flask was allowed to cool and filtered at the pump. The solid obtained was washed with water (10mL), and methanol (2mL) to remove unreacted toluene. Yield 40% m.p. 129-130° (Lit m.p. 129-130)[87].

^{1}H-N.M.R. ($CDCl_3$): δ 2.4 (6H, s); δ7.2(4H, m); δ8.0(2H, m).

7. Preparation of 4-methyl-2-nitrobenzenesulphonyl chloride

A 500mL 2-necked round bottom flask was equipped with magnetic follower, an inlet for introducing chlorine gas well below the surface of the liquid and a reflux condenser. The top of the condenser was connected to a funnel which is dipped into a stirred

solution of sodium hydroxide 4,4^1-dimethyl-2,2^1-dinitrophenyl disulphide 5.0g was placed in the flask containing concentrated hydrochloric acid (30cm^3) and concentrated nitric acid (10cm^3). A stream of chlorine passing through 2 empty bottles into the mixture at the rate of 2 bubbles a second. The solution was warmed on a water bath at 70^{o}C, after 30 minutes, the disulphide dissolved and the passage of chlorine and heating were continued for one more hour. The supernatant liquid was then separated by decantation, the remaining syrup was washed with 2 portions of water (15mL) at 70^{o}C and then allowed to solidify. The water was completely drained from the solid mass and was dissolved in glacial acetic acid (10mL). The acid solution was rapidly filtered at the pump. The filterate was cooled in an ice bath with vigourous stirring so that the sulphonyl chloride separated in small crystals. The mixture was titurated with cold water (15mL) and filtered twice before a solution of cold water (20mL) and ammonia 1mL was added stirred and filtered immediately. The solid obtained was then washed with water (10mL) and drained well. The resulting 4-methyl-2-nitrobenzenesulphonyl chloride 7.0g, m.p. 97^{o}C (Lit. 98^{o}C)[93], was obtained after recrystallisation with pet. ether.

^{1}H-N.M.R. $CDCl_3$: δ 2.75(3H, s);δ7.8(2H, ArH, m);δ8.3(1H, d, ArH).

8. Preparation of 4-methyl-2-nitrobenzenesulphonic acid

4,4'- dimethyl-2,2'-dinitrodiphenyl disulphide (3.4g, 0.01m) was added to fuming nitric acid (15 mL) d. 1.52 in a conical flask with care. There was violent reaction, when it had subsided, it was heated over a water bath for 20 minutes, water 40 mL was added and the little undissolved solid (which is unchanged disulphide) was filtered off.

The filterate was evaporated to dryness and the near solid left was the sulphonic acid. The sulphonic acid was with little water amount of water was salted out. The sodium sulphonate was filtered and dried at 140° for 2h, yield 4.0g.

9. Preparation of 4-methyl-2-nitrobenzenesulphonyl chloride via sulphonic acid[88]

Previously dried sodium sulphonate above (6.4g) was placed in a round bottomed flask with $CaCl_2$ guard tube on the condenser.

Phosphorous oxychloride ($POCl_3$) (6.0mL) was added and heated for 2h at 140°. After the reaction, the content was poured into crushed ice in a beaker, stirred and solid sulphonyl chloride separates. The sulphonyl chloride was filtered and recrystallised from pet. ether 40-60°. Yield 4.0g, 63% m.p. 96-97°C.

10. N-(4-methyl-2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid

4-methyl-2-nitrobenzenesulphonyl chloride (1.0g; 4.2mmol) in tetrahydrofuran (THF) (10mL) and piperidine-2-carboxylic acid in solution of potassium carbonate (1.0g) in water (10mL) and ethanol (10mL) were prepared.

The THF solution was added to the piperidine-2-carboxylic acid solution and refluxed for 1h on water bath. Ethanol and tetrahydrofuran were distilled off and the reaction mixture was allowed to cooled, washed with chloroform (10mL), acidified with 6M hydrochloric acid. The resulting adduct was extracted with dichloromethane, dried over magnessium sulphate, and the solvent stripped off in vacuo leaving a brown solid which was recrystallised in chloroform/pet. ether. m.p. 169-170°C, (69%).

Anal. Calcd for $C_{13}H_{16}N_2O_6S$: C, 45.85; H, 4.45; N, 8.91, Found: C, 46.27; H, 4.68; N, 8.81.

I.R. (film) 3500, 3060, 2980, 1700, 1550, 1380, 1360, 1180 cm^{-1}.

^{1}H-NMR ($CDCl_3$): 1.4(2H, m); 1.75(3H, m); 2.3 (1H, d); 2.5(3H, s); 3.4(1H, t); 3.7(1H, d); 5.5(1H, OH, br exchangeable with D_2O); 4.7(1H, d); 7.5(2H, ArH, d); 7.95(1H, d, ArH).

11. N-(4-methyl-2-nitrobenzenesulphonyl)piperidino -2-carboxylic acid chloride

N-(4-methyl-2-nitrobenzenesulphonyl)piperidine-2-carboxylic acid (0.5g 1.52m mole), dissolved in purified thionyl chloride (2.5mL) was refluxed for 2h after which excess thionyl chloride was removed leaving the acid chloride as a brown fuming oil.

I.R., (film), 1780, 1590, 1540 cm^{-1}.

12. N-(4-metnyl-2-nitrobenzenesulphonyl)-2-amino piperidine

The acid chloride (0.5g; 1.44m.mole) was dissolved in dry dichloromethane (10mL) in 50mL two necked round bottom flask equipped with calcium chloride guard tube at one inlet and a rubber seal at the other. Silver trifluoromethanesulphonate

(0.55g, 1.5m eq.) was added to the solution and immediate effervescence developed. The rest of the work up was carried out as experiment 3.

On work-up, the crude product obtained was decolourised with norit. Flash chromatograpny of the compound gave a light brown solid m.p. 70-71°C, yield 70%.

I.R. 3380, 3000, 2900, 1600, 1540, 1365, 1340, 1170cm^{-1}.

^{1}H-NMR $(CD_3)_2CO$: 1.2-1.8 (6H, m) 2.6 (3H, s); 3.2 (2H, m); 4.2(1H, d); 5.4(1H, NH, exchangeable with D_2O) 7.6 (2H, ArH, m); 8.0(7H, d, ArH).

13. 9-methyl-1,2,3,4,11,11a-hexahydropyrido[1,2-b][1,2,4]benzo thiadiazine-6,6-dioxide

N-(4-methyl-2-nitrobenzenesulphonyl)-2-amino piperidine (0.6g, 1.8 m mole) was dissolved in glacial acetic acid (20mL). Iron filing (1.0g) and iron dust 1.0g (washed free of grease with dry diethyl ether) was added over 2h to the solution above and refluxed for 10h at 125-130°.

On cooling the reaction mixture, it was poured into crushed ice and the usual work-up gave crystalline beige solid (78%) m.p. 171-172°C.

I.R. (film) 3368, 2929, 2860, 1680, 1608, 1317, 1164 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ1.1 (6H, m); 2.3(5H, m); 3.4(1H, m); 4.8(1H, NH); 6.7(2H, m); 7.55(1H, m).

14. 4,4^1-ditrifluoromethyl-2,2^1-dinitrodiphenyl disulphide

Sodium sulphide (18.0g, 0.075 mole) in ethanol (75mL) was heated until the sodium sulphide dissolved. Sulphur (2.4g, 0.075) was added and heated until all dissolved.

A solution of 4-chloro-3-nitrobenzotrifluoride (22.2g, 0.099 mole) in ethanol 30mL was placed in a round bottom flask and the sodium disulphide prepared above was added through the condenser and heated for 3h, the work up was done as reported in experiment 6.

Yellow needles were obtained 9.7g, m.p. 156°C (litt. 158°C)[92].

^{1}H-N.M.R. ($CDCl_3$): δ8.0 (4H, m); δ8.7(2H).

15. 4-α,α,α-trifluoromethyl-2-nitrobenzenesulphonyl chloride[92]

The set up was like that of experiment 7. 4,4'-ditrifluoromethyl-2,2'-dinitrodiphenyl disulphide (8.0g, 18.0m mole) was suspended in concentrated hydrochloric acid (40mL) and concentrated nitric acid (16mL). A stream of chlorine passing through 2-empty bottles was passed into the mixture. The solution was warmed on water bath at 70°, after 1h, the disulphide dissolved and the passage of chlorine continued for another 1h. The supernatant liquid was then decaunted off, and the syrup left was washed with water (25mL x 2) at 70°C. The gum obtained was dissolved in toluene washed with water and dried over magnessium sulphate, the solvent removed leaving a red oil as the sulphonyl chloride 4.0g, 36.3%.

^{1}H-NMR ($CDCl_3$): δ 7.9(2H, m); δ8.2(1H, m).

16. Sodium 4-trifluoromethyl-2-nitrobenzene sulphonate[89]

To the solution of 4-chloro-3-nitrobenzotrifluoride (10g) in ethanol (20mL) heated almost to boiling on a steam bath was added with vigourous stirring, a solution of crystalline sodium sulphite (13g) in water (70mL).

The yellow reaction mixture was refluxed with stirring for 4h. The volume of the reaction mixture was reduced to half and it was cooled to between 0-5°. Yellow crystalline sodium salt was filtered and washed with cold 50% aqueous ethanol. Yield 8.35g.

17. 4-Trifluoromethyl-2-nitrobenzenesulphonyl chloride

Phosphorous oxychloride (5mL) was added to finely powdered sodium 4-trifluoromethyl-2-nitrobenzenesulphonate 5.0g (dried at 90°C for 4h) and the mixture heated in a r.b.f. with $CaCl_2$ guard tube on the condenser at 140°C for 3h.

The reaction mixture was allowed to cool and cautiously poured onto crushed ice with vigorous stirring, the water was decaunted from the oil and the oil was extracted into toluene and dried over magnessium sulphate to give a red oil. Yield 4g, 67%.

18. N-(4-trifluoromethyl-2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid

A solution of 4-trifluoromethyl-2-nitrobenzenesulphonyl chloride (2.0g, 6.5m mole) in tetrahydrofuran (THF) (15mL) and piperidine-2-carboxylic acid (0.7g) in a solution of potassium carbonate (2.0g) in water (20mL) and ethanol (20mL) were prepared.

The THF solution was added to the piperidine-2-carboxylic acid and were refluxed for 1h on water bath.

Ethanol and THF were distilled off and the solution was allowed to cool, washed with dichloromethane before acidifing with

- 316 -

6M HCl. The resulting acid adduct was extracted with dichloromethane dried over magnessium sulphate giving a red oil after removal of solvent. The oil solidified on standing for about 2 months. m.p. 80-1°C yield 67%.

I.R. (film): 1700, 1600, 1520, 1360, 1310, 1200 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): 1.3 (4H, m); 1.9(2H, m), 3.2(2H, m); 4.5(1H, m); 7.3(2H, d); 7.7(1H, m).

m.s.: m/z 337 (m^+ - 45) 318, 254 (m^+ - piperidine-2-carboxylic acid) 207, 188, 161.82, 55.

19. Preparation of N-(4-trifluoromethyl-2-nitrobenzene sulphonyl)piperidine-2-carboxylic acid chloride

The acid adduct obtained above (1.0g) was treated with purified thionyl chloride 5cm^3 and refluxed for 2h before excess thionyl chloride was removed leaving the acid chloride as a brown fuming oil.

I.R. (film) 1780 cm^{-1} (C = O).

20. N-(4-trifluoromethyl-2-nitrobenzenesulphonyl) -2-amino piperidine

N-(4-trifluoromethyl-2-nitrobenzenesulphonyl) piperidine -2-carboxylic acid chloride (1g, 2.6m mole) was dissolved in dry dichloromethane (20mL) in a 50mL two necked round bottomed flask equipped with a calcium chloride guard tube at one inlet and rubber seal at the other end.

Recrystallised silver trifluoromethanesulphonate (1.06g, 4.1m mole) there was effervescence, the reaction grew dark and the mixture was stirred for 3h.

- 317 -

6M HCl. The resulting acid adduct was extracted with dichloromethane dried over magnessium sulphate giving a red

A solution of concentrated ammonia 12mL was injected and stirred for further 3h. After the usual work-up, the crude solid obtained was recrystallised from chloroform and pet. ether 8 yield 80% m.p. 144-5°C.

I.R. (film) 3380, 1610, 1520, 1345, 1320, 1135 cm^{-1}.

^{1}H-NMR $(CD_3)_2CO$: 1.0(4H, m); 1.5(2H, m); 2.7(2H, m); 3.5(1H, m); 5.45 (1H, NH); 7.1(2H, m); 7.6(1H, m).

21. Preparation of 9ααα trifluoromethyl-1,2,3,4,11,11a-hexahydropyrido [1,2-b][1,2,4]benzothiadiazine-6,6-dioxide

The nitro amine obtained above 1.0g, 2.8m mole was dissolved in glacial acetic acid (40mL). Iron filing (2.0g) and iron dust (2.0g) were washed twice with diethyl ether and added to the acetic acid solution in portions during 2h, after the addition the mixture was refluxed for another 8h. in oil bath maintained at a temperature of 125-130°C.

The mixture was allowed to cool and poured into crushed ice 20g and worked up as usual to give a light brown needles after recrystallisation. 78%, m.p. 120-121°C.

I.R. (film) 3350, 1680,, 1610, 1500, 1340, 1180 cm^{-1}.

^{1}H-NMR ($DMSOd_6$), 0.6-1.1 (6H, m); 2.6(2H, m) 4.2(1H, m) 5.6(1H, NH exchangeable with D_2O), 8.0(3H, ArH).

m.s.: m/z 306, m^+ (50%), 241, 223, 161, 82, 55(100%).

22. P.Acetaniside[84]

P-Anisidine (5.42g, 0.044m mole) in a mixture of water (100mL) and concentrated hydrochloric acid (3.66mL, 0.043mole) was stirred until the p-anisidine passed completely into solution.

A solution of concentrated ammonia 12mL was injected and stirred for further 3h. After the usual work-up, the

The mixture was warmed to about 50°C with stirring for 5 minutes and filtered. To the resulting solution redistilled acetic anhydride (5.51g, 5.12 mL, 0.054 mole) was added.

The mixture was stirred until it dissolved, it was then poured into a solution of crystallised sodium acetate (6.6g; 0.08 mole) in water (20mL). The resulding mixture was stirred vigourously and cooled in ice. The p.-acetaniside was filtered with suction washed with little water and filtered. Recrystallisation from a mixture of boiling water (80 mL) and ethanol (20mL) gave the product 4.9g, 69% m.p. 131°C (litt. [84], 131-132°C).

23. 2-Nitro-p-Acetaniside

P-Acetaniside (5.0g, 0.03 mole) was added to glacial acetic acid (20.0mL) to form a solution. 11% HNO_3 solution (20mL, 0.038 mole) was added to the mixture. The reaction mixture was transferred to a water bath that was just switched on, this heated the mixture to boiling (35 minutes) at which time it was removed from the water bath and the boiling was substained by the heat of the reaction for about 15 minutes. The reaction mixture was allowed to cool and the red solution was poured into crushed ice (32g) with stirring. The solid obtained was filtered thrice with water and air dried.

Recrystalisation with water, the crystal obtained gave m.p. 115-116°C (lit. 117°C), [90], 4.0g, 65%.

I.R. (film): 3360, 1700, 1580, 1500, 1380 cm^{-1}.

24. Claisen's Mixture:

Claisen's mixture was prepared by dissolving potassium hydroxide (88g) in water (64 mL). The resulting solution was allowed to cool and was diluted to 250mL methanol. This solution was stirred with a glass rod.

25. 4-Methoxy-2-nitroaniline

Claisen's mixture 10mL was added to 4-methoxyl-2-nitro acetanilide (5.0g) in a round bottomed flask with a reflux condenser. The resulting solution was stirred magnetically while refluxing on water bath for 15 minutes. Water (10mL) was added while stirring for another 15 minutes on water bath. The solution obtained was poured over crushed ice (30g) to give a red solid which was filtered and washed with water and filtered again.

Recrystallisation from ethanol gave pure red 4-methoxy-2-nitroaniline 3.8g, 95%, m.p. 123°C (lit. m.p. 123°C).

I.R. (film) 3480, 3360, 1640, 1595, 1575, 1380, 1250 cm^{-1}.

26 4-chloro-3-nitroanisole

Sodium nitrite (4.1g) was added with stirring to concentrated sulphuric acid (45 mL) over a period of 2 minutes, when the addition was completed, the temperature was raised to 70°C to dissolve the sodim nitrite. The solution was cooled in an ice bath to 25-30°C.

A solution of 4-methoxy-2-nitroaniline 10g in glacial acetic acid (110mL) was added at such a rate that the temperature did not exceed 40°C. The solution was stirred at 40° for additional 30 minutes, this was slowly added to a cold solution

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4. Claisen's Mixture:

Claisen's mixture was prepared by dissolving potassium

of 11.8g of copper (1) chloride in 110mL of concentrated hydrochloric acid over a period of 5 minutes. The mixture was heated on a steam bath with occasional stirring until the evolution of nitrogen ceased. Water (300mL) was added to the reaction mixture. The product was isolated by steam distillation and the solid obtained was filtered. Yield 8.0g, 75% m.p. 44°C (lit. 45°C)[95].

^{1}H-NMR ($CDCl_3$): 3.9(3H, s); 7.2-7.7(3H, m).

27. Preparation of Copper (1) Chloride

To obtain 11.8g of copper (1) Chloride:
Copper (11) sulphate pentahydrate (17.5g) and pure sodium chloride was dissolved in water (65mL) with heating. Sodium metabisulphite (4.4g) dissolved in water (45mL) was added to the hot solution with stirring. The mixture obtained was cooled to room temperature with ice bath and the supernatant liquor was decaunted from the colourless copper (1) chloride. The white solid was washed with dilute solution of sulphurous acid twice to prevent oxidation and hydrochloric acid (110 mL) was added to dissolve and preserve the copper (1) chloride.

28. Preparation of 4,4'-dimethoxyl-2,2'-dinitrodiphenyl disulphide

Sodium sulphide (4.8g, 0.02 mole) in ethanol and heated until the sodium sulphide dissolved. Sulphur (0.64g, 0.02 mole) was added and heated until it dissolved.

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of 11.8g of copper (1) chloride in 110mL of concentrated hydrochloric acid over a period of 5 minutes. The mixture

A solution of 4-chloro-2-nitroanisole (5.0g, 0.026 mole) in dry methanol (32mL) was placed in a round bottomed flask, the sodium disulphide prepared above was added through the condenser and heated for 3h. The work-up was done like that of experiment 6. Yield 1.8g, 36.0%, m.p. 163-4°C (litt - 164.9°)[96].

29. 4-methoxy-2-nitrobenzene sulphonyl chloride

The set up was similar to that reported for experiment 7. 4,4'-dimethoxyl-2,2'-dinitrodiphenyl disulphide (3.0g) was placed in the flask containing concentrated hydrochloric acid (15mL) and concentrated nitric acid (3.0 mL).

A stream of chlorine was passed into the mixture at the rate of 2-bubbles a second and then heated to 70°C on the water bath. The disulphide dissolved after 30 minutes and the heating continued for another hour.

The work-up was same as for 4-methyl-2-nitrobenzene sulphonyl chloride (experiment 7). Yield 3.0g, 76%, m.p. 72-73°C (litt. 73.8°)[97].

^{1}H-NMR ($CDCl_3$): δ 4.2(3H, s); 7.5(2H, m); 8.4(1H, d.)

30. N-(4-methoxy-2-nitrobenzenesulphonyl) pyrrolidine-2-carboxylic acid

A solution of 4-methoxy-2-nitrobenzenesulphonyl chloride (3.0g, 0.012 mole) in THF (25mL) and that of piperidine-2-carboxylic acid (2.10g, 0.016 mole) in a solution of potassium carbonate (3.0g) in ethanol (30mL) and water (30mL) were prepared.

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A solution of 4-chloro-2-nitroanisole (5.0g, 0.026 mole) in dry methanol (32mL) was placed in a round bottomed

The THF solution of the sulphonyl chloride was added to the piperidine-2-carboxylic acid and was refluxed for 1h on the water bath.

Ethanol and THF were distilled off and the solution was allowed to cool, washed with dichloromethane before acidifying with 6M hydrochloric acid. The resulting acid adduct was extracted with dichloromethane dried over magnessium sulphate and the solvent stripped off leaving a light brown solid, 62%, m.p. 138-9°C.

I.R. (film): 1715, 1590, 1520, 1370, 1350, 1150, 1210cm^{-1}.

^{1}H-NMR (CD_3OD): δ 1.4(2H, m); 1.7(3H, m); 2.3(1H, d); 3.3(1H, m); 3.65(1H, d); 3.9(3H, s); 4.6(1H, OH); 4.7(1H, d); 7.2(2H, m); 8.0(1H, d).

31. N-(4-methoxy-2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid chloride

Purified thionyl chloride (5mL) was added to N-(4-methoxy-2-nitrobenzenesulphonyl)piperidine-2-carboxylic acid (1.0g) and refluxed for 2h, after which excess thionyl chloride was removed leaving the acid chloride as a light brown oil.

I.R. (film): 1790, 1600, 1540, 1350, 1310, 1250, 1180 cm^{-1}.

32. N-(4-methoxy-2-nitrobenzenesulphonyl)-2-amino piperidine

The acid chloride obtained above (0.5g, 1.57m mole) was dissolved in dry dichloromethane (10mL) in 50cm^3 round bottomed flask equipped with calcium chloride guard tube at one inlet and a rubber septum at the other.

Recrystallised silver trifluoromethanesulphonate (0.52g. 2.04m mole) was added to the solution, there was effervescence and the reaction mixture grew dark and allowed to stirr for 3h.

Concentrated ammonia (10mL) was added and stirred for 3h, after the usual work-up the crude solid obtained was recrystallised from dichloromethane and pet. ether 40-60°C, yield 76% m.p. 140-141°C.

I.R. (film): 3360, 3000, 2940, 1600, 1540, 1350, 1325, 1170 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ 1.6(6H, m); 3.2(1H, m); 3.6(1H, m); 3.95(3H, s); 5.6(NH); 7.1(2H, ArH, m); 7.9(1H, ArH, d).

33. 9-methoxy-1,2,3,4,11,11a-hexahydro pyrido [1,2-b] [1,2,4]benzothiadiazine-6,6-dioxide

N-(4-methoxy-2-nitrobenzenesulphonyl)-2-amino piperidine (0.5g, 1.67m mole) was dissolved in glacial acetic acid (25mL) Iron fillings (1.0g) and iron dust (1.0g) (washed free of greese with diethyl ether) was added over 2h to the above solution, before the mixture was refluxed for a further 8h at 125-130°C.

After cooling the mixture, it was poured onto crushed ice and the usual work-up gave a crystalline solid yield 69%, m.p. 146-147°C.

I.R. (film) 1650, 1600, 1360, 1325 cm^{-1}.

^{1}H-NMR ($DMSOd_6$): 2.0(4H, m); 2.6(2H, m); 3.6(2H, m); 3.9(3H, s); 4.5(1H, m); 7.4(2H, m); 7.8(1H, m); 10.0(1H, NH, exchangeable with D_2O).

34. 4-hydroxy acetanilide

4-aminophenol (22g, 0.2 mole) was suspended in water (60mL) in a 500mL beaker and acetic anhydride (24mL, 0.254 mole) was added, the mixture was vigourously stirred and warmed on a

water bath. The solid dissolved after 10 minutes and the mixture was cooled. The solid acetyl derivative was filtered at the pump, washed with a little cold water and on recrystallisation from hot water (about 150mL) and drying upon filter paper in air gave 4-hydroxyacetanilide 27.0g, 90% m.p. 169°C (lit. 169°C)[84].

35. 4-Ethoxyacetanilide (p-phenacetin)

Clean sodium (3.1g, 0.135 mole) was placed in a 500mL round bottomed flask equipped with reflux condenser. Absolute ethanol (80mL) was added, after the vigourous reaction had subsided, the flask was warmed on water bath until solution is complete. The mixture was cooled and 4-hydroxyacetanilide (20.g, 0.132) was added. Ethyl iodide (30.0g, 16mL, 0.2 mole) was introduced slowly through the condenser and the mixture refluxed slowly for 1h. Water (200mL) was poured through the condenser at such a rate that the crystalline product did not separate. (If crystals do separate, the mixture must be refluxed until they dissolved). The flask was then cooled in ice bath, the crude product was collected with suction and washed with a little cold water. The crude product was dissolved in ethanol (160mL) boiled with norit and filtered. The resulting clear solution was allowed to cool and the pure 4-ethoxyacetanilide was collected at the pump and dried in air yielding 16.5g, 71%, m.p. 135-6°. (Lit. m.p. 137°C).

36. 4-Ethoxy -2-nitroacetanilide

11%, HNO_3 solution (31.0mL) was added to a solution of 4-ethoxyacetanilide (10g, 0.056 mole) in glacial acetic acid (75mL). The mixture was stirred without heat for 20 minutes by means of mechanical stirrer, it was then transferred to a water bath. The water was put on and the heating was continued gently for 30 minutes while stirring the reaction mixture. The red solution obtained was poured onto crushed ice (75g) with stirring. The solid obtained was filtered at the pump, washed with cold water (40mL x 3) and on recrystallisation from water gave yellow crystals. Yield 8.5g; 70% m.p. 102°C (lit. m.p. 104°C)[90].

37. 4-Ethoxy-2-nitroaniline

Claisen's mixture ($20cm^3$) was added to 4-ethoxy-2-nitroacetanilide (10g, 0.044 mole) in 2 neck round bottomed flask. The resulting mixture was stirred by means of mechanical stirrer for 15 minutes while refluxing on a water bath. Water (20mL) was added to the paste formed through the second neck while stirring and heating continued on the water bath for additional 15 minutes.

The resulting solution was poured onto a crushed ice (60g) and the product filtered at the pump, washed with water and refiltered.

Recrystallisation from ethanol gave red needle like crystals 7.5g, 95% m.p. 112°C. (Lit. m.p. 113°C)[91].

^{1}H-NMR in $CDCl_3$: 1.4(3H, t); 4.1(2H, q); 6.0(2H, NH, br); 6.8-7.2(2H, m); 7.6(1H, d).

38. 4-Ethoxy-2-nitro chlorobenzene or 4-chloro-3-nitrophentole

Sodium nitrile 4.1g was added with stirring to concentrated sulphuric acid (45mL) over a period of 2 minutes, when all the addition was completed, the temperature was raised to 70° to dissolve the sodium nitrite. The solution was cooled in an ice bath to 25-30° and a solution of 4-ethoxyl-2-nitroaniline (10.92g, 0.06 mole) in hot glacial acetic acid (110mL) was added at such a rate that the temperature does not exceeds 40°. The solution was stirred at 40° for additional 30 minutes; this was slowly added to a solution of copper chloride 11.8g in 110mL concentrated hydrochloric acid over a period of 5 minutes. The mixture was heated on a steam bath with occational stirring until evolution of nitrogen ceased.

Water (300mL) was added and the product steam distilled, the solid obtained was filtered, yielding pure product 70%, m.p. 47°C (lit. 47.8°C)[91].

^{1}H-NMR $CDCl_3$: δ 1.4(3H, t); 4.0(2H, q); 7.2(3H, m).

39. 4,4'-Diethoxy-2,2'-dinitrodiphenyl disulphide

Sodium sulphide (5.7g; 0.024 mole) in methanol (24mL) and heated until the sodium sulphide dissolved. Sulphur (0.77g, 0.024 mole) was added and heated until it dissolved.

A solution of 4-chloro-2-nitrophenetole (6.3g, 0.031 mole) in dry methanol (40mL) was placed in a round bottomed flask and the sodium disulphide prepared above was added through the condenser and heated for 3h. The work up was done as reported for 4'4-dimethyl-2,2'-dinitrodiphenyl disulphide (expt. 6.)

Yield 2.0g, 32%, m.p. 164°C (lit. 164°C)[96].

40. 4-Ethoxy-2-nitrobenzenesulphonyl chloride

The set up is similar to that of experiment 7. 4,4'-diethoxyl-2,2'-dinitrodiphenyl disulphide (3.0g, 7.6 mole) was placed in the flask and concentrated hydrochloric acid (15mL) and concentrated hydrochloric acid (3.0mL).

A stream of chlorine passing into the mixture at the rate of 2 bubbles a second and then heated to 70°C on the water bath. The disulphide dissolved after 30 minutes and heating continued for 1h. The work up is similar to 4-methyl-2-nitrobenzene sulphonyl chloride (experiment 7).

Yield 2.8 70% m.p. 73°C (lit. 74.7°C)[91].

41. N-(4-Ethoxy-2-nitrobenzenesulphonyl) piperidine-2-carboxylic acid

4-Ethoxy-2-nitrobenzenesulphonyl chloride (1.3g, 5.1m mole) was dissolved in THF (13mL) and piperidine-2-carboxylic acid (1.0g, 7.7m mole) in solution of potassium carbonate (1.3g) in water (13mL) and ethanol (13mL) were prepared. The THF solution added to the piperidine-2-carboxylic acid solution and was refluxed for 1h on water bath.

Excess ethanol and THF were distilled off and the solution was allowed to cool, washed with chloroform before acidifying with 6M hydrochloric acid. The resulting acid adduct was extracted with dichloromethane dried over magnessium sulphate, the solvent evaporated, leaving a brown solid which was recrystallised in chloroform/petroleum ether 40-60°C, m.p. 140-141°C yield 73%.

I.R. (film): 1720, 1600, 1540, 1380, 1340, 1230, 1170cm^{-1}.

^{1}H-NMR (CD_3OD); δ 1.40(5H, m); 1.7(3H, m); 2.2(1H, d); 3.3(1H, m); 3.6(1H, d); 4.2(2H, q); 4.5(1H, s, OH, exchangeable

with D_2O); 4.7(1H, d); 7.15 (2H, m); 7.9(1H, d).

m.s: m/z 313 (100% m^+ - 45); 280, 229.92, 166.99, 138.

42. N-(4-Ethoxy-2-nitrobenzenesulphonyl) piperidine -2-carboxylic acid chloride

N-(4-Ethoxy-2-nitrobenzenesulphonyl)piperidine-2-carboxylic acid (1.0g), was treated with purified thionyl chloride (5mL) and it was refluxed for 2h before excess thionyl chloride was removed leaving the acid chloride as a brown viscous oil.

43. N-(Ethoxy-2-nitrobenzenesulphonyl)-2-aminopiperidine

N-(4-Ethoxy-2-nitrobenzenesulphonyl) piperidine -2-carboxylic acid chloride (0.5g, 1.33m mole) was dissolved in dry dichloromethane (15mL) in 50mL two necked round bottomed flask equipped with a calcium chloride tube in one inlet and rubber septum at the other.

Recrystallised silver trifluoromethane sulphonate (0.34g, 1.73 mole) was added to the dichloromethane solution. There was effervescence and the this subsided in 1h. The solution grew dark and stirring continued for 3h.

A solution of concentrated ammonia (10mL) was added and stirred for 3h, after which the usual work-up was carried out giving a crude solid. Flash chromatography of the crude gave a light brown microcystaline solid m.p. 120-121°C yield 73%.

I.R. (film): 3440, 3320, 2980, 2900, 1660, 1580, 1520, 1350, 1320, 1190 cm^{-1}

^{1}H-NMR ($CDCl_3$): δ 1.3(3H, m); 1.6(6H, m); 3.0(2H, m); 4.1(3H, m); 7.1(2H, m); 7.9(1H, m).

44. 9-Ethoxy-1,2,3,4,11,11a-hexahydropyrido[1,2-b][1,2,4] benzothiadiazine-6,6-dioxide

The nitroamine obtained above (1.0g, 3.03m mole) was dissolved in glacial acetic acid (40mL). This was warmed with shaking to dissolve the compound.

Iron filling (2.0g) and iron dust (2.0g) were combined and washed twice with sodium dried diethyl ether. This was added to the glacial acetic acid solution in portions for 2h, after which the mixture was refluxed for another 8h in oil bath maintained at a temperature at 125-130°C.

The mixture was allowed to cool to room temperature and poured onto crushed ice (20g) and worked up as usual to give a crystaline solid m.p. 150-1°, 68%.

I.R. (film): 3340, 2995, 2900, 2820, 1660, 1590, 1300, 1190, 1140.

^{1}H-NMR ($(CD_3)_2CO$): 1.2(3H, t); 1.7(4H, m); 3.3(2H, m); 4.2(2H, q); 4.5(1H, m); 7.1(2H, m); 7.8(1H, d).

REFERENCES

1. P. Ehrlich, Lancet 1913, 2, 445-451.
2. E. P. Abraham, E. Chain, C. M. Fletcher, H. W. Florey Lancet 1941, 241 177-189.
3. G. W. Stacy in Heterocyclic compounds Vol. 7 p.797 Ed. R. Elderfield Willey N.Y. 1961.
4. F. C. Novello, S. C. Bell, L. A. Adams, C. Ziegler and J. M. Sprague J. Amer. Chem. Soc. 1957, 79, 2028-9.
5. L. Raffia, Famaco Ed. Sci 1957, 12, 41-8. C.A. 1959, 53, 20081h.
6. J. H. Freeman, E. C. Wagner J. Org. Chem. 1951, 16, 815.
7. D. V. Parke, and R. T. Williams J. Org. Chem. 1951, 16, 815.
8. T. Mann, D. Keilin, Nature, 1940, 146, 164-5.
9. G. Kresze, C. Seyfried and B. Trede, Ann. 1968, 715, 223.
10. W. Wagner and R. Reinolhl Ann. 1964, 675, 189.
11. H. Takematsu, H. Nishimura, O. Yamauchi; Yakugaku Zasshi. 1963, 83, 1061, C.A. 1963, 60, 8034b.
12. K. Kratzl and H. Ruis, Monatsh Fur. Chimie. 1965, 96, 1603.
13. S. Plescia, E. Aiello, G. Daidone, J. Heterocycl. Chem. 1976, 13, 395.
14. J. Martin, O. Meth-Cohn and H. Suschitsky, J. Chem. Soc. Perkin Trans I; 1974, 2451-8.
15. E. K. Adesogan and B. I. Alo: J. Chem. Soc, Chem. Comm. 1979, 673-4.

16. B. I. Alo, E. A. Adegoke, M. Ligali-Ali and E.K. Adesogan: J. Chem. Soc. Perkin Trans I; 1986, 806.

17. F. C. Novello, S. C. Bell, J. M. Sprague; J. Org. Chem. 1960, 25, 970.

18. L. P. Jackman, V. Petrow, O. Stephenson, A.M. Wild. J. Pharmacol, 1960, 12, 648-55.

19. R. Cameroni, V. Feroli, Famaco Ed. Sci. 1972, 27, 1104-12.

20. R.G. Griot, U. S. Patent, 3, 257, 398: C. A., 1966, 65, 7201b.

21. F. Effenberger and G. Epple, Angew, Chem. Int. Ed. 1972, 11, 299-300.

22. B.I. Alo. Ph.D Thesis, University of Ibadan 1979.

23. E. Frey. Arch. Ges. Physio. 1907, 115, 223-48.

24. J. F. Schamberg. J. Amer. Med. Assoc. 1915, 66, 62. C. A. 1915, 10, 784.

25. E. M. Schultz, E. J. Grague, J. M. Sprague; J. Med. Pharm. 1962, 5, 660.

26. J.G., Topliss, Diuretics in Medicinal Chemistry Ed. A. Burger Willey interscience N.Y. p.976-1012.

27. W. H. Miller, A. M. Dessert, and R. C. Robin J. Amer. Chem. Soc. 1950, 72, 4893.

28. G.H. Mudge in the Pharmacological Basis of Therapeutics 6th Ed. by A.G. Gilman, L.S. Goodman. A. Gilman Macmillian Inc. N.Y. 1980 p. 899 - 902.

29. (a) W. Hollander, A. V. Chobarian and R. Wilkins Circulation 1959, 19, 827; C.A. 1959, 54, 7897f

(b) B. Winer Circulation 1961, 23, 211.

30. H. Tanimukai, M. Inni, H. Hariguichi; Biochem. Pharmacol. 1965, 14, 961 - 70.

31. P.G. Dashputra and M.D. Kharpe. Indian J. Med. Research, 1971, 58, 1459-66.

32. J. D. Crawford, and G. C. Kennedy; Nature. 1959, 183, 891-2.

33. G. D. Hartmann and W. Halezenko. Tetrahedron Letters 1987, 28, 3241-4.

34. C.J. Flann, L.E. Overman. J. Amer. Chem. Soc. 1987, 109, 6115.

35. K.M. Ryan, R.A. Reamer, R.P. Volante and I. Shinkai Tetrahedron Letters. 1987, 28, 2103-6.

36. H. Bohme and H.G. Viche in 'Iminium Salt in Organic Chemistry' Part I J. Wiley and Sons N.Y. 1976.

37. K. Blaha, O. Cervinka Adv. Heterocycl. Chem. 1966, 6, 147.

38. J. Elguero and C. Marzin in 'Iminium Salts in organic Chemistry' Part I: J. Wiley and Sons N.Y. 1976 p.534.

39. W. Dorscheln, H. Hiefenthaler, H. Goth, P. Ceruhi and H. Schmid. Helv. Chem. Acta. 1967. 50, 1759.

40. G. Opitz; H, Hellmann and H. W. Schubert; Ann. Chim. 1959, 623, 117.

41. G. A. Olah, Angew. Chem. Int. Ed. 1973, 12, 173.

42. B.A. Phillips, G. Fodor, J. Gal, F. Letourneau J.J. Ryan Tetrahedron Letters. 1973, 29, 3309.

43. E. Lippmaa, M. Magi, S.S. Novikov, L.I. Khimelnitski A.S. Prihodko, O.V. Lebedov and L.V. Epishina.

Org. Magn. Resonance. 1972, 4, 197.

44. C. Jutz Chem. Ber. 1964, 97, 2050.

45. H. Bohme and G. Anterhoff; Chem. Ber. 1971, 104, 2013.

46. H. J. Veith, M. Hesse Helv. Chim. Acta. 1971, 27, 123.

47. P.R. Briggs, T.W. Shannon; P. Vouros, Org. Mass. Spectrom. 1971, 5, 545.

48. J. Gal, B.A. Phillips and R. Smith, Can. J. Chem. 1973, 51, 132.

49. N.J. Leonard, A.S. Hay, R.W. Fulmer, V.W. Gash. J. Amer. Chem. Soc. 1955, 77, 439.

50. S.F. Martin, C.Y, William, L. Laswell and H. Rveger Tetrahedron Letters. 1988, 29, 6685-88.

51. H. Hellmann and G. Opitz., Angew. Chem. 1956, 68, 265.

52. C.F. Hammer and R.A. Hines. J. Amer. Chem. Soc. 1955, 77, 3649.

53. J.L. Johnson, M.E. Herr, J.C. Babcock, A.E. Fonken, J.E. Stanfford, and F.W. Heyl. J. Amer. Chem. Soc. 1956, 78, 430.

54. M. Harris, D. Grierson, C. Richie, H.P. Hasson Tetrahedron Letters. 1980, 21, 1957.

55. A. G. Cook, J. Amer. Chem. Soc. 1963, 85, 648.

56. R. L. Pederson, J. L. Johnson, R. P. Holysz and A. C. Ott. J. Amer. Chem. Soc. 1959, 79, 1115.

57. R.F. Percell. J. Amer. Chem. Soc. 1959, 79, 2596.

58. L. Lukes and R. Dedek. Chem. Listy. 1957, 51, 2059.

59. G. Stock and G. Birnbaun. Tetrahedron Letters. 1961, 10, 313.

60. S. Hunig, E. Benzing and E. Lucke. Chem. Ber. 1957, 90, 2833.

61. H. Borhme and H. Hertke: Chem. Ber. 1960, 93, 1305.

62. F. Bohmann, H. Muller, D. Schman. Chem. Ber. 1973, 106 3026-34.

63. N.J. Leonard and J.V. Pankstelis. J. Org. Chem. 1963, 28, 3021.

64. E. M. Fry, J. Org. Chem. 1963, 28, 1869.

65. E. E. Van - Tamelen, V.B. Haarsted, R.L. Oruis. Tetrahedron. 1968, 24, 687.

66. R. T. Dean, H. C. Padgett and H. Rapport. J. Amer. Chem. Soc. 1976, 98, 7448.

67. H. Rapoport. Lectures in Heterocyclic Chem. 1978, 4, 57.

68. T. Shono, K. Yoshida, K. Arido, Y. Ushi, H. Hamaguchi. Tetrahedron Letters. 1978, 4819-22.

69. A. Ahond, A. Cave, C. Kan-fan, H. Phillipe, J. Rostalan P. Poitier. J. Amer. Chem. Soc. 1958, 90, 5622.

70. M.Y.H. Essawi, P.S. Portoghese. J. Org. Chem. 1983, 48, 2138-40.

71. R. Jokela, and M. Lounasmaa, Tetrahedron 1987, 43, 6001-6.

72. I. L. Finar, Organic Chemistry Vol. II, Longman 5th Ed. 1975, p. 763.

73. I. Chevolot, H.P. Husson and P. Portier Bull. Soc. Chim. Fr. 1970, 2707.

74. I.G. Csendes, Y.Y. Lec, H.C. Padgett and H. Rapoport J. Org. Chem. 1979, 44, 4173.

75. G. Stock, R. Terrell and Szmszkowicz. J. Amer. Chem. Soc. 1954, 76, 2029.

76. D.S. Grierson, M. Harris and H. Hussion. J. Amer. Chem. Soc. 1980, 102, 1064-82.

77. H. Bohme and V. Plappert. Chem. Ber. 1975, 108, 2827-33.

78. N.J. Leonard and A.S. Hay. : J. Amer. Chem. Soc. 1956, 78, 1984.

79. J.A. Marshall and W.S. Johnson, J. Org. Chem. 1963, 28, 421.

80. O. Cervinka, Collection of Czech. Chem. Comm. 1961, 26, 673.

81. R. Lukes and D. Dedek : Collection of Czech Chem. 1958, 23, 2053 and References therein.

82. O. B. Familoni, M.Phil. Dissertation. University of Lagos, 1986.

83. E. A. Adegoke, B. I. Alo, O. B. Familoni. J. Heterocycl. Chem. 1987, 24, 107.

84. A Vogel in"Textbook of Practical Organic Chemistry" 4. Ed. Longman 1980 p. 382, 684.

85. E. Aiello, G. Dattolo, and G. Cirrincione: J. Chem. Soc. Perkin Trans. I. 1981, 1.

86. E. E. Reid in "Organic Chemistry of Bivalent Sulphur" Vol. I p.21, Chemical Publishing Company, New York 1958.

87. W. H. Denus. Synthesis 1974, 4, 295.

88. P. Pfeiffer and H. Jager. Ber. 1942, 75, 1885.

89. E. Lint, J. Appl. Chem. 1957, 7, 466.

90. K. Hata, K. Takematsu and B. Kubota, Bull. Chem. Soc. Japan. 1935, 10, 425.

91. M. Ligali-Ali: M.Sc. Dissertaion, University of Lagos, 1984.

92. C. T. Holdrege. J. Amer. Chem. Soc. 1959, 81, 4807.

93. C. Holdstead. J. Chem. Soc. 1952, 1886.

94. F. Reverdin. Ber. 1896, 29, 2595.

95. E. A. Nodiff, E. Oda, T. Hayazaki, S. Ina, T. Ito, S. Nashibe, T. Ueda, K. Suzuki, M. Hausman, A. A. Manian: J. Heterocycl. Chem. 1968, 5, 165.

96. K. Blanksma. Rec. Trav. Chim. 1900, 19, 111.

97. R. Gnehm and E. Knecht. J. Prakt. Chem. 1906, 74, 92.

Sulphur-based Directed Benzylic Metallations: Lithiations of Alkylarenesulphonates

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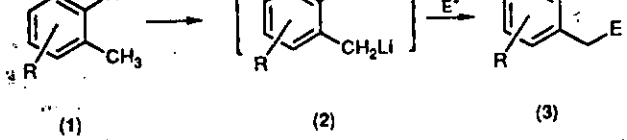
Benzylic anions (**6**) are obtained by regio-specific lithiations of ethyl 2-methylbenzenesulphonates. Evidence for the presence of the ethyl 2-lithiomethylbenzenesulphonates was obtained by efficient quenching studies with a range of electrophiles. Lithiations of the 2,4-dimethyl compound (**9**) gave the 2-lithiomethyl anion only, indicative of a predominant co-ordination mechanism in the lithiations.

Organolithium intermediates continue to occupy a prime position in synthetic chemistry [1] since they may facilitate a large variety of transformations. In the elaboration of homo- and hetero-aromatic [2] systems, their use is increasing owing to the continuing development of substituents capable of directing the introduction of the metal in a predictable manner.[3-6] Sulphur-based directed metallation groups have attracted particular attention. Substituents on homo- and hetero-aromatic systems including a sulphur atom such as sulphides,[7] sulphones,[8] sulphonamides,[9] and especially sulphonates [10] have proved to be excellent *ortho*-directing groups for metallation. Recently,[10b] alkyl sulphonates have been used as sulphur-based directed aromatic metallation groups. Their relatively facile reactions gave product yields ranging from good to excellent on trapping of the organolithium reagent with a variety of eletrophiles. Snieckus *et al.*[11] have demonstrated the use of sulphur groups for regioselective construction of polysubstituted aromatic compounds, providing novel and varied methodological possibilities.

Benzylic anions from the *ortho*-methyl substituent of aromatic systems containing various directed metallation groups have been used in synthesis. Deprotonation of the methyl group has been achieved in a variety of ways: Bu^{n}Li has been used either alone [12] (1 or 2 equiv.) or with an appropriate complexing agent as promoter,[12e,13] and lithium dialkylamides (e.g. Pr$^i_2$NLi) [14] or other bases [15] have also been used (Scheme 1).



(1) (2) (3)

Scheme 1. Directed metallation group X = $CONR_2$,[12a] SO_2NHR,[12b] CONHR,[12c] CSNHR,[12d] NR_2,[12e] CH_2NR_2,[12f] dihydro-oxazolyl,[12g] OMe,[6] NHCOR,[12h] SR,[12i] CO_2H,[14d] CO_2R,[14b] $OCONR_2$,[14c] or CN.[15] *Conditions:* Bu^{n}Li, Bu^{n}Li–complexing agent, Pr$^i_2$NLi, or other base.

Products of the reactions of such anions with electrophiles are not usually obtainable by classical methods.

In some cases, competing ring lithiation has been observed during benzylic anion generation, but the use of a complexing agent or a suitable change in metallation conditions seems to eliminate this competition.[12e,13] We have now explored the use of alkyl sulphonates as directed metallation groups in benzylic anion-forming processes as an extension of their synthetic utility. Sulphur-based directed metallation groups in general have the advantage that they are easily removed.

Table. Reaction of the lithio compounds (**6**), (**9**), and (**12**) with electrophiles.

Entry	Reactant	Electrophile	Product	R	% Yield
1	(6)	EtCHO	(7a)	EtCH(OH)	75
2	(6)	Me_2CO	(7b)	$Me_2C(OH)$	50
3	(6)	PhCHO	(7c)	PhCH(OH)	65
4	(6)	Ph_2CO	(7d)	$Ph_2C(OH)$	91
5	(6)	$ClCO_2Et$	(7e)	EtO_2C	50
6	(6)	CO_2	(7f)	HO_2C	70
7	(6)	PhNCO	(7g)	PhNHC(:O)	78
8	(6)	$PhSO_2Cl$	(7h)	$PhSO_2$	50
9	(9)	PhCHO	(10a)	PhCH(OH)	60
10	(9)	Ph_2CO	(10b)	$Ph_2C(OH)$	90
11	(9)	CO_2	(10c)	HO_2C	85
12	(12)	$\overline{OCH_2CHCH_2Me}$	(13)	—	40

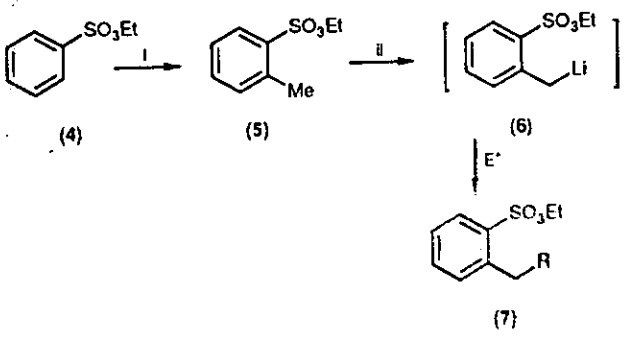
Results and Discussions

Ethyl 2-methylbenzenesulphonate (**5**)* was obtained *via* treatment of ethyl 2-lithiobenzenesulphonate with methyl iodide according to Bonfiglio's reported procedure [10b] and unambiguously characterized. The lithiation of the 2-methyl compound (**5**) with Bu^{n}Li (1.1 equiv.) at −78 °C proceeded rapidly to give a deep red benzylic anion species rather than the ring metallation product, as expected since the more acidic methyl proton should be removed more readily than the nuclear protons. The anion generated reacted smoothly (with the loss of the red colour) with a range of electrophiles leading to benzyl substituted products in good to excellent yields (see Table). No competing ring metallation giving the 2-lithio-6-methyl-benzenesulphonate was observed. As reported previously,[12e,13] a complexing agent may be necessary to enhance the ratio of side chain to ring metallation.

Exposure of the anion to aliphatic aldehydes gave the expected phenyl alcohols without any accompanying lactonization even on flash chromatography.

Since the use of sulphonyl chlorides as electrophiles has received relatively little attention, and new benzyl sulphones are required, we attempted to trap the anion with benzenesulphonyl chloride. Such anion trapping with sulphonyl chlorides should provide a better method for preparation of sulphones than the cumbersome classical protocol of formation of a sulphide

* Ethyl benzenesulphonate was used as earlier reported [10b] rather than the methyl ester to avoid the possibility of competition from the easy methyl group displacement reaction initially observed.

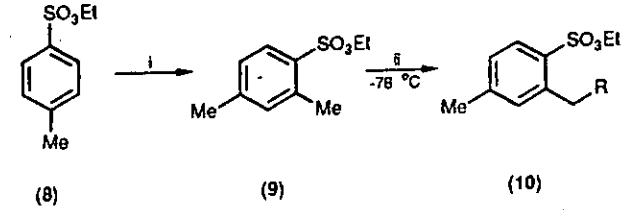


Scheme 2. *Reagents:* i, Bu^{n}Li, MeI, NH_4Cl; ii, Bu^{n}Li, −78 °C.

followed by oxidation.[8] A good yield of the sulphone was obtained in the representative example (entry 8).

The benzylic anions are presumably generated by the initial co-ordination of the Bu^{n}Li with the heteroatom of the directing group to form a monolithio complex from which the methyl proton is then abstracted. Similarly the success of the present *ortho*-metallation presumably depends on the possible co-ordination of the lithio anion with the sulphonate group at low temperatures.

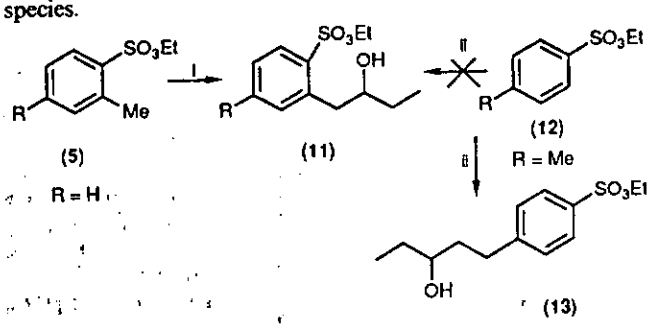
Corroborative evidence for a predominant co-ordination mechanism for these alkyl benzenesulphonate-directed metallations was obtained from lithiation experiments with ethyl 2,4-dimethylbenzenesulphonate (**9**) in which regiospecific 2-methyl lithiation was obtained. [The sulphonate (**9**) was obtained by



Scheme 3. *Reagents:* i, Bu^{n}Li, MeI, NH_4Cl; ii, Bu^{n}Li, E^+; H_3O^+.

ortho-metallation from ethyl 4-methylbenzenesulphonate (**8**)]. Lithiation of (**9**) was performed with 1.1 equiv. of Bu^{n}Li during 1.5 h to give quantitatively the benzylic anion which was trapped with various electrophiles. Product analysis by NMR spectroscopy indicated exclusive formation of the 2-substituted methyl compounds with no trace of any 4-substituted methyl compounds.

Of special interest is the use of oxiranes as electrophiles in reactions of products derived from *ortho*-lithiation of ethyl 4-methylbenzenesulphonate. The 4-methyl substituted compound (**13**) was isolated rather than the product (**11**) from the 2-lithio species.



Scheme 4. *Reagents:* i, Bu^{n}Li, EtCHO, H^+; ii, Bu^{n}Li, $EtCHCH_2O$, H_3O^+.

As quenching of the oxirane was slow at low temperatures, the reaction required warming to room temperature during 24 h for completion. This observation was therefore rationalized on the basis of a migration of the initially formed kinetic product (the 2-lithio species as previously shown) to the thermodynamic product (4-lithio-methyl species) at higher temperatures. The thermodynamically stable 4-benzyl anion predominates at room temperature wherein the epoxide formed the 4-(3-hydroxypentyl)sulphonate (**13**). Such 4-tolyl anions were previously formed only by addition of the Bu^{n}Li complexing agent tetramethylethylenediamine.[16]

The present strategem furnishes a convenient means not only for homologations of 2-alkylbenzenesulphonates but also for the construction of sulphur-containing heterocycles (thiazines or sultones) on cyclisation of the appropriate products from quenching with electrophiles. The benzylic lithiations should also provide access to aromatic compounds bearing unusual methyl substituents.

Experimental

General.—^{1}H NMR spectra were obtained using Varian EM360L or Bruker 400 MHz spectrometers and are reported in ppm downfield of the internal standards Me_4Si in $CDCl_3$ or hexamethyldisilazane (HMDS) in $(CD_3)_2SO$. IR spectra were recorded on a Beckman IR 4250 spectrometer (films for liquids; KBr dispersions for solids). Elemental analyses were performed on a Carlo Erba 1106 instrument. M.p.s were obtained on a Kofler hot-stage apparatus and are uncorrected. Tetrahydrofuran (THF) was freshly distilled from sodium diphenylketyl before use and the water content of the solvent was estimated by a modified Karl–Fisher method[16] to be <45 ppm. Metallations were performed under dry deoxygenated argon. The n-butyllithium content of the commercial hexane solution was estimated by the Gilman double titration method.

Ethyl Benzenesulphonate (**4**).—Aqueous sodium hydroxide (50 g; 25% solution) was added dropwise to a stirred solution of benzenesulphonyl chloride (50 g) in ethanol (50 ml) with the temperature below 20 °C. The alkaline mixture was then stirred for 3 h. The crude product was washed several times with 5% hydrochloric acid, 5% aqueous $NaHCO_3$, and then with water. The resulting oil was vacuum distilled at 151 °C/10 mmHg (lit.,[10b] 156 °C/15 mmHg) and the sulphonate (**4**) stored under argon, yield 46.5 g (95%); ^{1}H NMR, ($CDCl_3$) δ 1.3 (3 H, t), 4.2 (2 H, q), 7.6 (3 H, m), and 8.0 (2 H, m).

Ethyl 2-Methylbenzenesulphonate (**5**).—To a solution of ethyl benzenesulphonate (**4**) (0.05 mol, 9.3 g) in dry THF (120 ml), Bu^{n}Li (0.055 mol, 1.1 equiv.) in hexane (37 ml) was added at −78 °C, and the solution stirred at −78 °C for 5 h. The solution became red. Methyl iodide (0.055 mol, 7.81 g) in dry THF (30 ml) was then slowly injected at −78 °C. After 1 h at −78 °C, the mixture was allowed to warm to 0 °C, and stirred for 1 h at 0 °C, when the reaction was quenched with cold saturated aqueous NH_4Cl. The organic portion was separated and the aqueous portion extracted (×2) with dichloromethane. The combined organic portions were washed with 5% aqueous K_2CO_3 solution and brine, and dried over $MgSO_4$. Evaporation *in vacuo* gave a pale yellow oil. TLC gave one spot in ether–hexane (1:1), R_f 0.75; yield 8.0 g (80%); ^{1}H NMR ($CDCl_3$) δ 1.3 (3 H, t), 2.7 (3 H, s), 4.1 (2 H, q), 7.5 (3 H, m, ArH), and 8.0 (1 H, dd, ArH).

General Metallation Procedure.—n-Butyl-lithium (0.0137 mol, 1.12 equiv.) in hexane (10 ml) was added slowly to ethyl 2-methylbenzenesulphonate (**5**) (0.0125 mol, 2.5 g) in dry THF (50 ml) at −78 °C and the mixture stirred at −78 °C for 1.5 h. The ester lithio species gave a deep red solution.

The appropriate electrophile (0.0137 mol) in THF (30 ml) was then added at −78 °C. The mixture was stirred at −78 °C

for a further 1 h, allowed to warm to 0 °C, and stirred at 0 °C for 1 h. Water was then added at 0 °C followed by 5% HCl. The organic portion was separated and the aqueous layer extracted (×2) with dichloromethane. The combined organic portions were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*.

Ethyl 2-(2-Hydroxybutyl)benzenesulphonate (**7a**). The crude oil obtained from the use of propionaldehyde as electrophile was purified by flash chromatography on silica gel with diethyl ether–hexane (1:1) as eluant to give the *alcohol* (**7a**) as an analytically pure colourless oil (75%) (Found: C, 56.2; H, 7.3. $C_{12}H_{18}O_4S$ requires C, 55.8; H, 7.0%); IR (film) ν_{max} 3 530br, 2 980, 2 940, 1 600, 1 480, 1 450, 1 350, 1 180, 1 010, and 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–1.6 (8 H, m), 2.2 (1 H, OH, exchangeable with D_2O), 3.1 (2 H, t), 3.8 (1 H, m), 4.1 (2 H, q), 7.5 (3 H, ArH, m), and 8.0 (1 H, dd, *J* 9 Hz, ArH).

Ethyl 2-(2-Hydroxy-2-methylpropyl)benzenesulphonate (**7b**). The crude oil obtained from the use of acetone as electrophile was purified by flash chromatography on silica gel with light petroleum–diethyl ether (1:1) as eluant to give *compound* (**7b**) as a colourless oil (50%) (Found: C, 56.1; H, 7.3%); IR (film) ν_{max} 3 560br, 2 980, 2 950, 1 600, 1 470, 1 350, 1 180, 1 010, and 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (9 H, m), 2.8 (1 H, s, OH, exchangeable with D_2O), 3.2 (2 H, s), 4.0 (2 H, q), 7.6 (3 H, m, ArH), and 8.0 (1 H, dd, ArH).

Ethyl 2-(2-Hydroxy-2-phenylethyl)benzenesulphonate (**7c**). The crude oil obtained solidified after 24 h. Recrystallization from light petroleum gave *compound* (**7c**) as white needles, m.p. 56–58 °C (Found: 62.6; H, 5.9. $C_{16}H_{18}O_4S$ requires C, 62.7; H, 5.9%); IR (KBr) ν_{max} 3 520br, 3 080, 3 020, 2 990, 1 600, 1 475, 1 455, 1 355, 1 185, 1 100, and 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (3 H, t), 2.7 (1 H, br, OH), 3.4 (2 H, m), 4.1 (2 H, q), 5.0 (1 H, q), 7.4 (8 H, m), and 8.1 (1 H, dd).

Ethyl 2-(2-Hydroxy-2,2-diphenylethyl)benzenesulphonate (**7d**). The crude solid obtained from the use of benzophenone as electrophile was crystallized from ether–light petroleum to give the *tertiary alcohol* (**7d**) as white needles, m.p. 130–132 °C (91%) (Found: 69.2; H, 5.3. $C_{22}H_{22}O_4S$ requires C, 69.1; H, 5.7%); IR (KBr) ν_{max} 3 460br, 1 600, 1 450, 1 345, 1 175, 1 100, and 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (3 H, t), 3.1 (1 H, br, OH, exchangeable with D_2O), 4.05 (2 H, s), 4.1 (2 H, q), 6.3 (1 H, d), 7.2–7.3 (8 H, m), 7.5 (4 H, m), and 8.0 (1 H, d).

Ethyl 2-(Ethoxycarbonylmethyl)benzenesulphonate (**7e**). The crude oil obtained from the use of ethyl chloroformate as electrophile was purified by flash chromatography using light petroleum–diethyl ether (1:1) as eluant to give the *acetate* (**7e**) as a colourless oil (50%) (Found: C, 53.0; H, 6.1. $C_{12}H_{16}O_5S$ requires C, 52.9; H, 5.9%); IR (film) ν_{max} 2 980, 1 730, 1 600, 1 570, 1 470, 1 440, 1 370, 1 220, 1 180, 1 030, 1 000, and 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (6 H, m), 4.1 (6 H, m), 7.6 (3 H, m, ArH), and 8.1 (1 H, dd).

Ethyl 2-(Carboxymethyl)benzenesulphonate (**7f**). The crude solid obtained from using solid CO_2 as electrophile was recrystallized from diethyl ether–light petroleum furnishing the *acid* (**7f**) as white plates, m.p. 106–108 °C (70%) (Found: C, 49.2; H, 4.75. $C_{10}H_{12}O_5S$ requires C, 49.2, H, 4.9%); IR (KBr) ν_{max} 3 300–2 500, 1 710, 1 600, 1 450, 1 350, 1 180, 1 000, and 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (3 H, t), 4.1 (2 H, q), 4.2 (2 H, s), 7.6 (3 H, m), 8.1 (1 H, dd), and 9.3 (1 H, br).

Ethyl 2-(N-Phenylcarbamoylmethyl)benzenesulphonate (**7g**). The crude solid obtained from using phenyl isocyanate as electrophile was recrystallized from dichloromethane–light petroleum to give the *amide* (**7g**) as pale yellow needles, m.p. 124–126 °C (78%) (Found: C, 57.15; H, 5.4; N, 4.45; $C_{16}H_{17}NO_4S$ requires C, 56.95; H, 5.8; N, 47%); IR (KBr) ν_{max} 3 360s, 2 990, 1 680, 1 600, 1 550, 1 450, 1 350, 1 180, 1 000, and 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (3 H, t), 4.1 (4 H, q and s), 7.1–7.6 (8 H, m), 8.0 (1 H, dd), and 8.35 (1 H, NH).

Ethyl 2-(Phenylsulphonylmethyl)benzenesulphonate (**7h**). The crude oil obtained with benzenesulphonyl chloride as electrophile was purified by flash chromatography with diethyl ether–cyclohexane (1:1) as eluant to give the *sulphone* (**7h**) as a pale yellow oil (50%) (Found: C, 52.5; H, 4.95. $C_{15}H_{16}O_5S_2$ requires C, 52.9; H, 4.7%); IR (film) ν_{max} 3 000, 1 600, 1 450, 1 350, 1 180, 1 000, and 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (3 H, t), 4.1 (2 H, q), 5.5 (2 H, s), 7.6 (6 H, m), and 8.1 (3 H, dd).

Ethyl 2,4-Dimethylbenzenesulphonate (**9**).—Lithiation of ethyl 4-methylbenzenesulphonate (**8**) with Bu^nLi at −78 °C followed by reaction with methyl iodide and quenching with aqueous NH_4Cl gave an oil which was purified by flash chromatography with hexane–diethyl ether (1:1) as eluant to give the sulphinate (**9**) as a clear white gum (83%); ^1H NMR ($CDCl_3$) δ 1.3 (3 H, t), 2.45 (3 H, s), 2.7 (3 H, s), 4.2 (2 H, q), 7.2 (2 H, m, ArH), and 7.9 (1 H, d, ArH). The sulphonate (**9**) was lithiated and treated with electrophiles as for the sulphonate (**5**).

Ethyl 2-(2-Hydroxy-2-phenylethyl)-4-methylbenzenesulphonate (**10a**).—The oil obtained from the reaction with benzaldehyde as electrophile was purified by flash chromatography with diethyl ether–cyclohexane (1:1) as eluant giving the *4-methyl compound* (**10a**) as a white solid, m.p. 49–51 °C (65%) (Found: C, 63.65; H, 6.2. $C_{17}H_{20}O_4S$ requires C, 63.75; H, 6.25%); IR (KBr) ν_{max} 3 650s, 2 990, 1 600, 1 480, 1 450, 1 350, 1 180, 1 000, and 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (3 H, t), 2.3 (3 H, s), 3.4 (2 H, m), 4.1 (2 H, q), 5.0 (1 H, q), 7.3 (7 H, m), and 7.9 (1 H, d).

Ethyl 2-(2-Hydroxy-2,2-diphenylethyl)-4-methylbenzenesulphonate (**10b**). The crude solid obtained from the reaction with benzophenone as electrophile was recrystallised from diethyl ether–light petroleum to give the *alcohol* (**10b**) as white needles, m.p. 114–116 °C (90%) (Found: C, 69.9; H, 6.2. $C_{23}H_{23}O_4S$ requires C, 69.9, H, 5.0%); IR (KBr) ν_{max} 3 500s, 3 060, 1 600, 1 490, 1 450, 1 340, 1 180, 1 000, and 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (3 H, t), 2.0 (3 H, s), 4.1 (5 H, including OH), 6.0 (1 H, s), 7.4 (1 H, m), and 7.9 (1 H, d).

Ethyl 2-(Carboxymethyl)-4-methylbenzenesulphonate (**10c**). The crude product obtained from the reaction with solid CO_2 was recrystallized from light petroleum–diethyl ether to give the *acid* (**10c**) as colourless plates, m.p. 108–110 °C (85%) (Found: C, 51.4; H, 5.6. $C_{11}H_{14}O_5S$ requires C, 51.2; H, 5.4%); IR (KBr) ν_{max} 3 300–2 500, 1 710, 1 600, 1 460, 1 350, 1 180, 1 110, and 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (3 H, t), 2.55 (3 H, s), 4.2 (4 H, q with s), 7.4 (2 H, m), 8.0 (1 H, d), and 8.35 (1 H, br, OH).

Ethyl 4-(3-Hydroxypentyl)benzenesulphonate (**13**).—Metallation was carried out as for ethyl benzenesulphonate. 1,2-Epoxybutane in THF was then added at 0 °C and the mixture was allowed to warm to room temperature during 24 h. Standard work-up gave a crude oil which was purified by flash chromatography with diethyl ether–cyclohexane (1:1) as eluant giving the *sulphonate* (**13**) as a colourless oil (40%) (Found: C, 57.6; H, 7.5. $C_{13}H_{20}O_4S$ requires C, 57.35; H, 7.35%); IR (film) ν_{max} 3 540s, 3 050, 1 600, 1 490, 1 450, 1 340, 1 180, 1 000, and 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–1.2 (6 H, m), 1.4 (4 H, m), 2.3 (1 H, OH, exchangeable with D_2O), 3.2 (2 H, m), 3.8 (1 H, m), 4.1 (2 H, q), 7.3 (2 H, d, *J* 10 Hz), and 7.8 (2 H, d, *J* 10 Hz).

Acknowledgements

We thank the C.I.E.S. French Ministry of Foreign Affairs, for the award of a Scholarship to O. B. F.

References

1 H. W. Gschwend and H. R. Rodriguez, *Org. React.*, 1979, **26**, 1; V. Snieckus and P. Beak, *Acc. Chem. Res.*, 1982, **15**, 305.
2 F. Marsais and G. Queguiner, *Tetrahedron*, 1983, **39**, 2009; V. Snieckus, *Bull. Soc. Chim. Fr.*, 1988, 67; A. Turck, L. Mojovic, and G. Queguiner, *Synthesis*, 1988, 881.
3 S. O. deSilva, J. N. Reed, and V. Snieckus, *Tetrahedron Lett.*, 1978, 5099.
4 J. M. Muchowski and M. C. Venuti, *J. Org. Chem.*, 1980, **45**, 4798.
5 C. A. Townsend and L. M. Bloom, *Tetrahedron Lett.*, 1981, 3923.
6 M. R. Winkle and R. C. Ronald, *J. Org. Chem.*, 1982, **47**, 2101.
7 N. S. Narasimhan and P. S. Chanrachood, *Synthesis*, 1979, 589; D. Babin, D. J. Fourneron, L. M. Harwood, and M. Julia, *Tetrahedron*, 1981, **37**, 325; L. Horner, A. J. Lawson, and G. Simons, *Phosphorus Sulphur*, 1983, **12**, 729.
8 F. M. Stoyanovich and B. P. Fedorov, *Angew. Chem.*, 1966, **78**, 116; F. M. Stoyanovich, R. G. Karpenko, and Y. Goldfab, *Tetrahedron*, 1971, **27**, 433; F. M. Stoyanovich, R. G. Karpenko, G. I. Gorushkina, and Y. Goldfarb, *ibid.*, 1972, **28**, 5017.
9 H. Watanabe, R. A. Schwarz, C. R. Hauser, J. Lewis, and D. W. Slocum, *Can. J. Chem.*, 1969, **47**, 1543; J. G. Lombardino, *J. Org. Chem.*, 1971, **36**, 1843; P. Breant, F. Marsais, and G. Queguiner, *Synthesis*, 1983, 822; F. Marsais, A. Cronnier, F. Trecourt, and G. Queguiner, *J. Org. Chem.*, 1987, **52**, 1133.
10 (*a*) G. D. Figuly and J. C. Martin, *J. Org. Chem.*, 1980, **45**, 3729; (*b*) J. N. Bonfiglio, *ibid.*, 1986, **51**, 2833.
11 M. Iwao, T. Iihama, K. K. Mahalanabis, H. Perrier, and V. Snieckus, *J. Org. Chem.*, 1989, **54**, 24.
12 (*a*) M. Watanabe, M. Sahara, M. Kubo, S. Fukuwara, R. J. Billedeau, and V. Snieckus, *J. Org. Chem.*, 1984, **49**, 743; (*b*) H. Watanabe, C. Mao, I. T. Barnish, and C. R. Hauser, *ibid.*, 1968, **33**, 4278; (*c*) V. Snieckus, *J. Heterocycl. Chem.*, 1984, **22**, 95; (*d*) J. I. Fitz and H. W. Gschwend, *J. Org. Chem.*, 1976, **41**, 4029; (*e*) R. E. Ludt, G. P. Crowther, and C. R. Hauser, *ibid.*, 1970, **35**, 1288; (*f*) R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, 1964, **29**, 1387; (*g*) H. W. Gschwend and A. Hamdan, *ibid.*, 1975, **40**, 2008; (*h*) W. Fuhrer and H. W. Gschwend, *ibid.*, 1979, **44**, 1133, (*i*) S. Cabiddu, S. Melis, P. P. Piras, and F. Sotgiu, *J. Organomet. Chem.*, 1979, **178**, 291.
13 R. E. Ludt, J. S. Griffith, K. N. McGrath, and C. R. Hauser, *J. Org. Chem.*, 1973, **38**, 1668.
14 (*a*) P. L. Greger, *J. Am. Chem. Soc.*, 1970, **92**, 1396; (*b*) G. A. Kraus, *J. Org. Chem.*, 1981, **46**, 201; (*c*) M. P. Sibi and V. Snieckus, *ibid.*, 1983, **48**, 1935.
15 C. K. Bradsher and T. G. Wallis, *J. Org. Chem.*, 1978, **43**, 38.
16 J. Bizot, *Bull. Soc. Chim. Fr.*, 1967, 151.

Paper 9/04980K
Received 23rd *November* 1989
Accepted 9th *January* 1990

N-(Arylsulphonyl)tetrahydropyridinium Salts: Intermediates for Multi-ring Heterocycles. Part 1. Synthesis of Hexahydropyrido[1,2-*b*][1,2,4]-benzothiadiazine Dioxides[1]

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N-(Arylsulphonyl)tetrahydropyridinium salts were obtained regiospecifically and in high yield by smooth triflate-assisted decarbonylation of the corresponding *N*-(arylsulphonyl)piperidine-2-carboxylic acid chlorides at room temperature. These synthons were converted into the nitroamines, which reductively cyclocondensed to give the new 9-substituted tricyclic azacycles, hexahydropyrido[1,2-*b*][1,2,4]benzothiadiazine 6,6-dioxides.

The use of iminium ions as intermediates in the synthesis of polycyclic heterocycles either *via* nucleophilic additions,[2] [3 + 2],[3,4] [4 + 2],[5] or 1,3-dipolar cycloadditions,[6] or *via* intramolecular trapping of the iminium ions by electron-rich aromatic nuclei[7] continue to attract conspicuous attention. Earlier we reported[8] the use of silver trifluoromethanesulphonate (silver triflate)[9] as a reagent for the generation of *N*-(arylsulphonyl)pyrrolinium salts at room temperature. We also demonstrated the usefulness of the iminium salts in the synthesis of a variety of novel tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxides.[10] In connection with our continuing interest in the triflate-assisted decarbonylation reactions of cyclic amino acid chlorides, it seemed appropriate, therefore, to explore the generation of the six-membered analogues: *N*-(arylsulphonyl)tetrahydropyridinium salts. These compounds should be powerful synthons for the preparation of several well known functionalised piperidine alkaloids. We now record their utility in the construction of multi-ring heterocycles such as the new hexahydropyrido[1,2-*b*][1,2,4]benzothiadiazines (21)–(25).

The therapeutic utility of the 1,2,4-benzothiadiazine dioxides as potent diuretics,[11] hypotensives,[11] anticonvulsants,[12] and tranquilising agents has been widely recognised. In fact, 1,2,4-benzothiadiazines with the 3,4-double bond saturated are well known to be considerably more active than their unsaturated analogues.[13] This therefore gives promise for the new compounds reported here. Despite their potential clinical success, there has been no report on the synthesis of the hexahydropyrido[1,2,4]benzothiadiazines. Apart from a patent by Griot[12] on the synthesis and biological activities of some related seven-membered analogues, azepino[1,2,-*b*][1,2,4]-benzothiadiazine dioxides, no report of the title compounds has appeared in the literature.

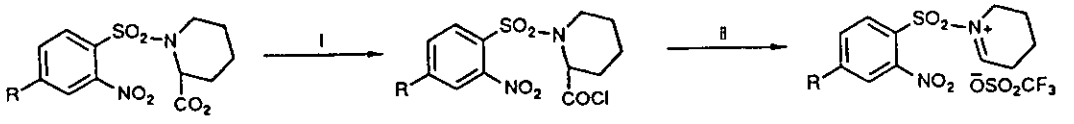
In continuation of our studies in developing the use of the readily generated endocyclic iminium ions as synthons in the regiospecific synthesis of *N*-heterocycles, we decided to extend the reaction to the preparation of the unknown hexahydropyrido[1,2,4]benzothiadiazine dioxides using our readily occurring nucleophilic amino addition to the corresponding readily generated *N*-(arylsulphonyl)tetrahydropyridinium ion, followed by a nucleophilic-electrophic *exo-tet* cyclocondensation process.

The starting acid chlorides were prepared by condensation of the appropriately substituted 2-nitrobenzenesulphonyl chloride with piperidine-2-carboxylic acid and cold treatment of the resulting new acid adducts (1)–(5) with thionyl chloride or oxalyl dichloride (Scheme 1).

The decarbonylation reaction of the resulting *N*-(arylsulphonyl)piperidine-2-carboxylic acid chlorides (6)–(10) on reaction with silver trifluoromethanesulphonate (1.1 mol equiv.) in dichloromethane solution proceeded at room temperature with copious evolution of carbon monoxide. It provided the desired iminium salts (11)–(15) in excellent yield. As previously suggested[8–10] for the reactions of the *N*-(substituted)pyrrolidine acid chlorides, we also suggest that the decarbonylation of these six-membered analogues proceeds in a parallel manner to the route proposed by Effenberger and Epple[14] for non-aromatic acyl chlorides and therefore proceeds *via* a mixed anhydride[15] intermediate as in Scheme 2.

On quenching with either anhydrous ethylamine or ammonia, the iminium salts were then smoothly converted into the nitroamines (16)–(20). Interestingly, relatively high and even quantitative yields of the nitroamines were obtained in this instance. No nucleophilic attack at the SO_2 moiety as previously reported by us[8] for the *N*-(arylsulphonyl)pyrrolidinium salts was observed.

The mass spectra of the nitroamines consistently gave weak molecular ions but abundant $M - 16$ or $M - 44$ peaks due to loss of NH_2 or NHEt. Thus cleavage at the α-carbon was the major fragmentation process. After this cleavage, it then became difficult to discern clear trends in the fragmentation pattern of the compounds, except for abundant 2-nitrobenzenesulphonyl ions.



(1) – (5) (6) – (10) (11) – (15)

(1) R = H (4) R = Me
(2) R = OMe (5) R = CF_3
(3) R = OEt

(6) R = H (9) R = Me
(7) R = OMe (10) R = CF_3
(8) R = OEt

(11) R = H (14) R = Me
(12) R = OMe (15) R = CF_3
(13) R = OEt

Scheme 1. *Reagents and conditions:* i, $SOCl_2$ or $(COCl)_2$; ii, CF_3SO_3Ag–CH_2Cl_2, room temperature.

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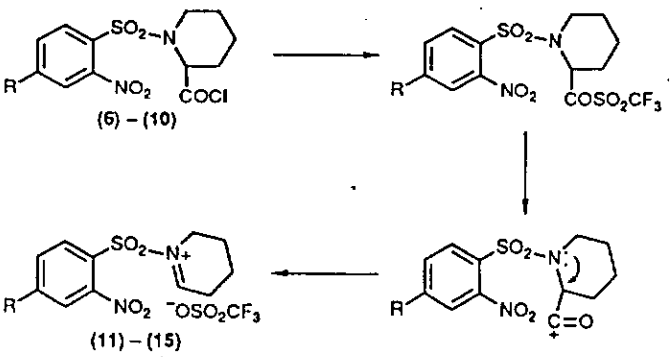


Scheme 2. Mechanism of reaction, of the acid chlorides (6)–(10) to give the salts (11)–(15).

The appropriately substituted nitroamines were then subjected to catalytic hydrogen-transfer reductive conditions[16] to give the correspondong diamines quantitatively as oils. These diamines on reflux in acetic or trifluoroacetic acid (TFA) gave the respective 9-substituted hexahydropyrido[1,2-*b*][1,2,4]-benzothiadiazines 6,6-dioxide in >80% yield (Scheme 3). Alternatively, the nitroamines were heated with iron dust in acetic acid as reported earlier by us,[8] to obtain the aforementioned cyclocondensation products. No *N*-ethyl compounds were isolated from the cyclocondensation of compound (19).[17]

The use of the *N*-(arylsulphonyl)tetrahydropyridinium salts in the construction of other multi-ring *N*-azacycles, for example as heterodienophile synthons for the synthesis of indolizidine or quinolizidine skeletons, is under active investigation.

Experimental

For general experimental details, see ref. 10. The nitrobenzenesulphonyl chlorides were either obtained commercially or were prepared by chlorine oxidation of the corresponding disulphides.

N-(4-Substituted-2-nitrophenylsulphonyl)piperidine-2-carboxylic Acids (1)–(5).—The appropriate arenesulphonyl chloride (5 mmol) was dissolved in tetrahydrofuran (10 cm^3). A solution of piperidine-2-carboxylic acid (5.1 mmol) in ethanolic potassium carbonate (?? cm^3) was added dropwise and then the mixture was refluxed for 1 h. The mixture was brought to pH 4 with dil. HCl. Solvents were evaporated off and the residue was taken up in dichloromethane. The organic layer was dried and evaporated. The following acids were thus prepared:

N-(2-Nitrophenylsulphonyl)piperidine-2-carboxylic acid (1) was obtained as off-white needles after recrystallisation (80%) m.p. 158–159 °C (Found: C, 47.0; H, 4.6; N, 8.25. $C_{12}H_{14}N_2O_6S$ requires C, 46.27; H, 4.87; N, 8.53%); ν_{max} 1 710 (CO_2H), 1 520 (NO_2), 1 350, and 1 100 cm^{-1} (SO_2N); δ($CDCl_3$) 1.6 (4 H, m), 2.2 (2 H, m), 3.7 (2 H, t), 4.8 (1 H, m, base proton), 7.5 (1 H, br, collapses with D_2O), 7.7 (2 H), and 8.1 (2 H, ArH); *m/z* 269 (100%, $M^+ - 45$), 186, 128, and 83.

N-(4-Methoxy-2-nitrophenylsulphonyl)piperidine-2-carboxylic acid (2) was obtained as prisms from ethanol (82%), m.p. 138–139 °C (Found: C, 45.1; H, 4.55, N, 8.0. $C_{13}H_{16}N_2O_7S$ requires C, 45.34; H, 4.65; N, 8.13%); ν_{max} 1 725 (CO_2H), 1 540, 1 350, 1 250, and 1 120 cm^{-1}; δ($CDCl_3$) 1.64 (4 H, m), 3.41 (2 H, m), 3.94 (3 H, s), 4.7 (1 H), 7.18 (2 H, d), and 8.0 (1 H, d, ArH); *m/z* 299 (100%, $M^+ - 45$).

N-(4-Ethoxy-2-nitrophenylsulphonyl)piperidine-2-carboxylic acid (3) was recrystallised from ethanol to give light-brown prisms (73%), m.p. 140–141 °C (Found: C, 46.8; H, 5.0; N, 7.7. $C_{14}H_{18}O_7S$ requires C, 46.92; H, 5.02; N, 7.82%); ν_{max} 1 720, 1 600, 1 535 (NO_2), 1 360, 1 170 (SO_2N), 1 235, and 1 045 cm^{-1}; δ($CDCl_3$) 1.42 (4 H, m), 1.78 (2 H, m), 3.5 (2 H, dd), 4.2 (2 H, q), 4.6 (2 H, m), 4.7 (1 H, base proton, NCHN), 7.17 (2 H, m), and 8.0 (1 H, d, *J* 9.53 Hz); *m/z* 358 (M^+), 313 (100%, $M^+ - 45$), 280, and 230 (68.7%).

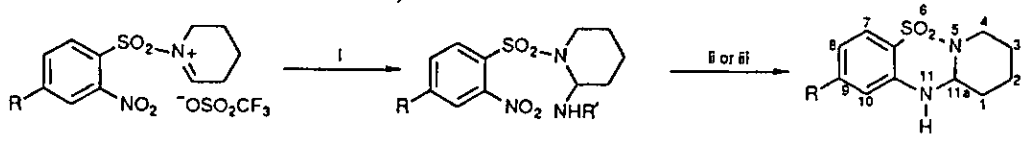
N-(4-Methyl-2-nitrophenylsulphonyl)piperidine-2-carboxylic acid (4) was obtained as beige microcrystals (69%), m.p. 169–170 °C (Found: C, 46.3; H, 4.7; N, 8.81. $C_{13}H_{16}N_2O_6S$ requires C, 45.85; H, 4.45; N, 8.91%); ν_{max} 1 700, 1 610, 1 550, 1 360, and 1 180 cm^{-1}; δ($CDCl_3$) 1.39 (4 H, m), 1.48 (2 H, m), 2.49 (3 H, s), 3.60 (2 H, dd), 4.54 (1 H, br, exchangeable with D_2O), 4.71 (1 H, d, *J* 4.9 Hz), 7.47 (2 H, d, *J* 10.36 Hz), and 7.95 (1 H, d, *J* 7.96 Hz); *m/z* 328 (M^+), 283 (100%, $M^+ - 45$), and 200 (44.9%).

N-(2-Nitro-4-trifluoromethylphenylsulphonyl)piperidine-2-carboxylic acid (5) was obtained as red needles from light petroleum (97%), m.p. 80–81 °C (Found: C, 40.5; H, 3.3; N, 7.1. $C_{13}H_{13}F_3N_2O_6S$ requires C, 40.83; H, 3.40; N, 7.33%); ν_{max} 1 710, 1 590, 1 520, 1 350, and 1 110 cm^{-1}; δ($CDCl_3$) 4.4 (4 H, m), 2.1 (2 H, m), 3.6 (2 H, t), 4.7 (1 H, q), 7.8 (2 H), and 8.4 (1 H, ArH); *m/z* 337 (100%, $M^+ - 45$), 254, 207, 188, 161, and 83.

N-(4-Substituted-2-nitrophenylsulphonyl)piperidine-2-acid Chlorides (6)–(10).—The acid adducts (1)–(5) (10 mmol) were each treated with an excess of purified thionyl chloride or oxalyl dichloride in refluxing benzene to give the corresponding acid chlorides as off-white, fuming oils or waxy solids, ν_{max} 1 795 (COCl), 1 350, and 1 150 cm^{-1}.

2-Amino-N-(4-substituted-2-nitrophenylsulphonyl)piperidines (16)–(20).—Recrystallised silver triflate (10 mmol) was added to dry dichloromethane (50 cm^3) solutions of each of the acid chlorides (6)–(10). An immediate and vigorous effervescence ensued. The mixture was further stirred at room temperature for 1.5 h. Cooled, anhydrous ethylamine or conc. ammonia (as appropriate) was slowly injected into the mixture, which was then set aside for 2 h. Filtration of the mixture was followed by appropriate work-up as described for each compound below:

2-Amino-N-(2-Nitrophenylsulphonyl)piperidine (16) was obtained as yellow plates after flash chromatography of the filtrate (78%), m.p. 108–111 °C (Found: C, 46.7; H, 5.0; N, 14.3. $C_{11}H_{15}N_3O_4S$ requires C, 46.31; H, 5.26; N, 14.74%); ν_{max} 3 400, 3 300 (NH str), 1 600, 1 540, 1 370, and 1 150 cm^{-1}



(11) R = H
(12) R = OMe
(13) R = OEt
(14) R = Me
(15) R = CF_3

(16) R = H, R' = H
(17) R = OMe, R' = H
(18) R = OEt, R' = H
(19) R = Me, R' = Et
(20) R = CF_3, R' = H

(21) R = H
(22) R = OMe
(23) R = OEt
(24) R = Me
(25) R = CF_3

Scheme 3. *Reagents:* i, anhydrous $EtNH_2$ or conc. NH_3; ii, cyclohexene, Pd/C, EtOH; iii, TFA or CH_3CO_2H/Fe.

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(SO_2N); δ($CDCl_3$) 1.5 (4 H, m), 1.8 (2 H, m), 3.4 (2 H, m), 4.6 (1 H, NCHN), 5.6 (2 H, br, collapsed with D_2O), 7.8 (3 H, m, ArH), and 8.1 (1 H); *m/z* 269 (100%, $M^+ - 16$), 186, 123, and 84.

2-Amino-*N*-(4-methoxy-2-nitrophenylsulphonyl)piperidine (**17**) was obtained as a brown solid after MPLC of the filtrate (light petroleum–chloroform) in 76% yield, m.p. 140–141 °C; ν_{max} 3 410, 3 320 (NH), 1 600, 1 540, 1 370, 1 170 (SO_2), and 1 050 cm^{-1}; δ($CDCl_3$) 1.45 (4 H, m), 1.80 (2 H, m), 3.3 (2 H, m), 3.7 (1 H, q, base proton), 3.9 (3 H, s, OMe), 4.3 (2 H, NH, collapsed with D_2O), 7.18 (2 H, m, ArH), and 7.9 (1 H, ArH); *m/z* 299 (100%, $M^+ - 16$), 216 (70.2), 152 (38.9), and 83.

2-Amino-*N*-(4-ethoxy-2-nitrophenylsulphonyl)piperidine (**18**) was obtained as light-brown microcrystals after chromatography of the filtrate in 73% yield, m.p. 120–121 °C; ν_{max} 3 450, 3 310 (NH), 1 650, 1 535, 1 368, 1 170, and 1 170, and 1 060 cm^{-1} (OCHR); δ($CDCl_3$) 1.2 (3 H, t), 1.5–2.0 (6 H, m), 3.0 (4 H, m, NH_2 and NCH_2), 4.1 (2 H, q), 5.6 (1 H, t, NCHN), 7.2 (2 H, m, ArH), and 7.9 (1 H, ArH); *m/z* 313 (100%, $M^+ - 16$), 230 (78), 166 (42), and 83.

2-Ethylamino-*N*-(4-methyl-2-nitrophenylsulphonyl)piperidine (**19**) was obtained in 80% yield as light-yellow prisms after MPLC (light petroleum–chloroform), m.p. 144–145 °C; ν_{max} 3 380 (NH), 1 600, 1 540, 1 360, 1 340, and 1 165 cm^{-1}; δ[$(CD_3)_2CO$] 0.8–1.4 (6 H, m), 1.7 (3 H, t), 2.2 (3 H, s), 2.6 (2 H, m), 3.2 (2 H, m), 4.8 (1 H, m), 5.2 (1 H, NH), 7.3–7.6 (2 H, ArH), and 7.8 (1 H, ArH); *m/z* 327, 5.02% M^+), 283 (100, $M^+ - NHCH_2CH_3$), 200 (81), 136 (46), and 83.

2-*Amino*-N-(2-*nitro*-4-*trifluoromethiylphenylsulphonyl*)*piperidine* (**20**) was obtained as brown microcrystals after chromatography (80%), m.p. 88–89 °C (Found: C, 40.5; H, 3.8; N, 11.6. $C_{12}H_{14}F_3N_3O_4S$ requires C, 40.79, H, 3.96; N, 11.89%); ν_{max} 3 343br (NH), 1 613, 1 568, 1 524, 1 323, 1 125, and 1 084 cm^{-1}; δ[$(CD_3)_2CO$] 0.6–1.1 (6 H, m), 2.6 (2 H, m), 4.2 (1 H, m), 4.8 (1 H, NH, collapsed with D_2O), 5.3 (1 H, NH, exchangeable with D_2O), 6.8 (1 H, ArH), and 7.2 and 7.7 (2 H, ArH); *m/z* 337 (100%, $M^+ - 16$), 254, 240, 185, and 83.

Reductive Cyclisation of the Nitroamines.—To each of the nitroamines (**16**)–(**20**) (5 mmol) was added glacial acetic acid (40 cm^3). Diethyl ether-washed finely divided iron filings (2.0 g) were slowly added. The mixture was refluxed for 8–12 h before being poured on ice. The mixture was filtered and the filtrate was extracted several times with hot dichloromethane. The combined organic extract was successively washed with aq. 5% $NaHCO_3$ and brine, then dried. Evaporation of solvents gave the desired products. Alternatively, the nitroamines underwent selective hydrogen-transfer reductions as reported earlier.[19] The following compounds were thus prepared:

1,2,3,4,11,11a-*Hexahydropyrido*[1,2-b][1,2,4]*benzothiadiazine* 6,6-*dioxide* (**21**) was obtained as an off-white solid after recrystallisation (70%), m.p. 140 °C (decomp.) (Found: C, 55.2; H, 5.7; N, 12.0; S, 13.1. $C_{11}H_{14}N_2O_2S$ requires C, 55.46; H, 5.88; N, 11.76; S, 13.44%); *m/z* 238 (100%, M^+), 211 (45), 182 (64), 173 (86, $M^+ - SO_2H$), 146 (8.28, $M^+ - SO_2H - HCN$), and 93 (81); ν_{max} 3 337, 1 650, 1 570, 1 360, and 1 160 cm^{-1} (SO_2N); δ($CDCl_3$) 1.2 (4 H, m), 2.1 (2 H, m), 3.3 (2 H, m, CH_2N), 5.1 (1 H, t, NCHN), 7.1 (3 H, m, ArH), 8.2 (1 H, dd, *J* 9.3 Hz, ArH), and 9.1 (1 H, br s, NH).

1,2,3,4,11,11a-*Hexahydro*-9-*methoxypyrido*[1,2-b][1,2,4]-*benzothiadiazine* 6,6-*dioxide* (**22**) was obtained as white plates after recrystallisation ($CHCl_3$–MeOH) (69%), m.p. 146–147 °C; *m/z* M^+, 267.988 (Found: C, 53.7; H, 5.7; N, 10.45; S, 11.7. $C_{12}H_{16}N_2O_3S$ requires C, 53.73; H, 5.97; N, 10.45; S, 11.94%); ν_{max}(KBr) 3 400 (NH), 1 620, 1 330, 1 160, 1 025, and 750 cm^{-1}; δ[$(CD_3)_2SO$] 1.0–1.9 (6 H, m), 3.2 (3 H, s), 3.8–4.0 (3 H, m), 6.6 (2 H, m, ArH), 7.5 (1 H, dd, ArH), and 9.2 (1 H, br, NH).

9-*Ethoxy*-1,2,3,4,11,11a-*hexahydropyrido*[1,2-b][1,2,4]*benzothiadiazine* 6,6-*dioxide* (**23**) was obtained as light-brown microcrystals (68%) after MPLC with light petroleum–chloroform, m.p. 150–151 °C (Found: C, 55.2; H, 6.4; N, 9.9; S, 11.2. $C_{13}H_{18}N_2O_3S$ requires C, 55.31; H, 6.38; N, 9.92; S, 11.35%); *m/z* 282 (100%, M^+), 255 (47, $M^+ - HCN$), 217 (86, $M^+ - SO_2H$), and 190 (8.2, $M - SO_2H - HCN$); δ[$(CD_3)_2CO$] 1.42 (4 H, m), 1.78 (3 H, m), 3.5 (2 H, dd), 4.2 (2 H, q), 4.6 (2 H, m), 4.7 (1 H, t, NCHN), 7.12 (2 H, m, ArH), 8.0 (1 H, d, *J* 9.53 Hz, ArH), and 9.1 (1 H, NH).

1,2,3,4,11,11a-*Hexahydro*-9-*methylpyrido*[1,2-b][1,2,4]-*benzothiadiazine* 6,6-*dioxide* (**24**) was obtained as beige crystals after recrystallisation of the residue obtained on evaporation (78%), m.p. 171–172 °C (Found: C, 57.0; H, 6.4; N, 11.2; S, 12.9. $C_{12}H_{16}N_2O_2S$ requires C, 57.14; H, 6.35; N, 11.11; S, 12.69%); *m/z* 252 (100%, M^+), 225 (41, $M^+ - HCN$), 199 (16.8), 187 (81, $M^+ - SO_2H$), 169 (4.2), and 160 (9.6, $M^+ - SO_2H - HCN$); ν_{max} 3 368, 1 680, 1 607, 1 317, and 1 151 cm^{-1}; δ($CDCl_3$) 1.1–1.8 (6 H, m), 2.7 (3 H, s, Me), 3.27 (1 H, br), 4.6 (1 H, t), 6.6 (2 H, m, ArH), 7.6 (1 H, dd, ArH), and 9.5 (1 H, NH).

1,2,3,4,11,11a-*Hexahydro*-9-*trifluoromethylpyrido*[1,2-b]-[1,2,4]*benzothiadiazine* 6,6-*dioxide* (**25**) was obtained as light-brown needles after recrystallisation (78%), m.p. 120–121 °C (Found: C, 47.3; H, 4.55; N, 9.5; S, 10.6. $C_{12}H_{13}F_3N_2O_2S$ requires C, 47.06; H, 4.25; N, 9.15; S, 10.46%). *m/z* 306 (100%, M^+), 279 (33), 250 (23), 241 (37), 223 (22), 214 (16, $M^+ - SO_2H - HCN$); ν_{max}(KBr) 3 350, 1 600, 1 350, and 1 145 cm^{-1}; δ[$(CD_3)_2SO$] 0.6–1.1 (6 H, m), 2.6 (2 H, m), 4.8 (1 H, t), 6.8 (1 H, ArH), 7.1 (1 H, ArH), 7.4 (1 H, ArH), and 9.3 (1 H, NH).

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for supply of materials through a CIDA-NSERC Research Fellowship to B. I. A. We are grateful to Professors V. Snieckus and G. Queguiner for the mass spectra and the microanalysis respectively. Financial support of the University of Lagos Central Research Grants Committee is acknowledged.

References

1 A preliminary account of this work was presented at the 11th International Congress of Heterocyclic Chemistry, Heidelberg, W. Germany, August 1987. Abstract P7. 14.
2 T. R. Govindachari, P. Chinnasamy, S. Rajeswari, S. Chandrasekran, M. S. Premila, S. Natarajan, K. Nagarajan, and B. R. Pai, *Heterocycles*, 1984, **22**, 585 and references therein.
3 M. Westling, R. Smith, and T. Livinghouse, *J. Org. Chem.*, 1986, **51**, 1159.
4 N. Ataines, E. Guitian, C. Saa, L. Castedo, and J. M. Saa, *Tetrahedron Lett.*, 1987, **28**, 817.
5 S. M. Weinreb and J. I. Levin, *Heterocycles*, 1987, **12**, 949 and references therein.
6 A. Mkairi and J. Hamelin, *Tetrahedron Lett.*, 1987, **28**, 1397.
7 G. D. Hartman, W. Halczenko, and B. T. Phillips, *J. Org. Chem.*, 1986, **51**, 142.
8 E. K. Adesogan and B. I. Alo, *J. Chem. Soc., Chem. Commun.*, 1979, 673.
9 P. J. Stang, M. Hanack, and L. R. Subramanian, *Synthesis*, 1982, 85.
10 B. I. Alo, E. A. Adegoke, M. Ligali-Ali, and E. K. Adesogan, *J. Chem. Soc., Perkin Trans. 1*, 1986, 806.
11 P. C. Ferriola, M. A. Acara, and M. E. Duffey, *J. Pharmacol. Exp. Ther.*, 1986, **238**, 912.
12 R. G. Griot, U.S.P. 3 257 398/1962 (*Chem. Abstr.*, 1966, **65**, 7201b).
13 G. H. Mudge, in 'The Pharmacological Basis of Therapeutics,' 6th edn, eds. A. G. Gilman, L. S. Goodman, and A. Gilman, Macmillan, New York, 1980, pp. 899–902.
14 F. Effenberger and G. Epple, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 299.
15 B. Hulin and M. Koreeda, *J. Org. Chem.*, 1984, **49**, 207.

A. Adegoke, B. I. Alo, and F. O. Ogunsulire, *J. Heterocycl. Chem.*, 982, 19, 1169.
. A. Adegoke, B. I. Alo, and O. B. Familoni, *J. Heterocycl. Chem.*, 987, 24, 107.

Paper 9/03403J
Received 10*th August* 1989
Accepted 24*th January* 1990