STUDIES IN THE CHEMISTRY

AND

PROPERTIES OF

7,8,9,10-TETRAHYDROPYRIDO [1,2-a] QUINOXALIN-6-ONES

BY

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SCHOOL OF POSTGRADUATE STUDIES
UNIVERSITY OF LAGOS

CERTIFICATION

THIS IS TO CERTIFY THAT THE THESIS -

"STUDIES IN THE CHEMISTRY AND PROPERTIES OF 7,8,9,10-TETRAHYDRO PYRIDO[1,2-A]QUINOXALIN-6-ONES"

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IS A RECORD OF ORIGINAL RESEARCH CARRIED OUT BY

Mrs A. E. Graham-Ode

IN THE DEPARTMENT OF

Chemistry

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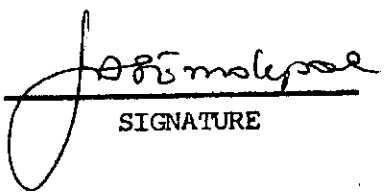
Prof T. A Emokpae INTERNAL EXAMINER'S NAME	 SIGNATURE	23/11/89 DATE
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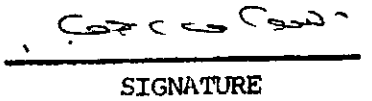
PROF. C. O. OKAFOR EXTERNAL EXAMINER'S NAME	 SIGNATURE	23-11-89 DATE

ABSTRACT

This thesis reports the results of investigations into the chemistry and properties of the new heterotricycle: 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one.

The chemistry and properties of quinoxalines, pyrrolo[1,2-a]quinoxalines and pyrido[1,2-a]quinoxalines are reviewed

A re-investigation of the methods of synthesis of the title compound and some of its derivatives was undertaken. Condensation of pipecolinic acid with the appropriately substituted 1-fluoro-2-nitrobenzene in ethanol basified with 10% sodium hydrogen carbonate solution followed by cyclization of the resulting N-[2'-nitrophenyl]piperidine-2-carboxylic acid with alkaline sodium dithionite was developed as the optimum method. The 2-fluoro- and 3-methyl- derivatives of the heterotricycle were prepared in this manner. The sodium dithionite reductive cyclization method however proved ineffective when there was another reducible group in the acid adduct. In this case selective hydrogen transfer reductive cyclization of the methyl ester of the carboxylic acid, via palladium on carbon, was the preferred method. The 3-nitro derivative of the heterotricycle was available only by this method.

The reactions of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one with electrophilic reagents have been studied. The tetrahydropyridoquinoxalinone was found to be completely unreactive to some reagents and in several other instances, intractable mixtures of compounds were obtained.

Nitration of the heterocycle was however achieved with a

mixture of potassium nitrate and sulphuric acid, giving the 2-nitro compound. Attempted nitration with concentrated nitric acid alone, or in other solvents, gave ring opened products, as the tricyclic skeleton is readily cleaved under these conditions.

Bromination of the heterocycle was examined under four different conditions in order to delineate the role played by the amine and amide nitrogen atoms in directing electrophilic substitution into the aromatic ring. With one mole equivalent bromine in acetic acid and with bromine in boiling hydrobromic acid, two different monobromo derivatives were obtained. Mixtures of products were obtained, on the other hand, from the reactions of the heterocycle with N-bromosuccinimide in 50% sulphuric acid and also with excess bromine in acetic acid.

^{1}H-NMR nuclear Overhauser enhancement studies involving the amide N-H of the 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-ones have been used to fully assign for the first time, the aromatic proton signals of the pyrido[1,2-a]quinoxalin-6-ones as well as to unambiguously characterize the products of nitration with potassium nitrate/sulphuric acid and bromination with one mole equivalent bromine in glacial acetic acid as the 2-nitro-; and 3-bromo compounds respectively.

Attempted N-alkylations of 7,8,9,10-tetrahydropyrido[1,2-a] quinoxalin-6-one by the conventional methods of reaction with an alkyl halide in the presence of a strong base such as sodium hydride or sodium methoxide were unsuccessful. A convenient and mild method of N-alkylation of the heterocyclic compounds via a

phase transfer process was however developed. N-Alkylation of the tetrahydropyridoquinoxalinones were accomplished in a solid-liquid two-phase system consisting of powdered sodium hydroxide/potassium carbonate suspended in benzene, in the presence of a catalytic amount of tetra-n-butylammonium hydrogen sulphate. Good yields of the relatively more soluble N-alkyl products were obtained.

Several attempts at selective replacement of the 6-oxo group in the title compound with chlorine by reaction with phosphoryl chloride were unsuccessful and gave rise to a suspected polychlorinated compound.

Products of attempted oxidation with manganese dioxide and alkaline potassium ferricyanide are described.

Full assignments of the ^{1}H and ^{13}C-NMR resonance of the new heterocycle 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one and some of its derivatives are reported for the first time. Unambiguous assignments were made by extensive NOE experiments in conjunction with the use of 2D one-bond and long range ^{13}C: ^{1}H chemical shift correlations.

The replacement of hydrogen with deuterium has been known to produce shifts in the position of the neighbouring carbon-13 NMR signals. The magnitude of these effects has recently been shown to possess a stereochemical dependance. Exchange of the amide N-H of the 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-ones with deuterium induces shifts in the carbon-13 resonances of the heterocycle. Evidence is presented in this work to show that the

magnitude of the deuterium isotope effect on these carbon-13 NMR sonance bears a geometrical relationship to the N-H.

Fungicide activity of the tetrahydropyridoquinoxalinones, their precursors and N-alkyl derivatives are also reported for the first time.

ACKNOWLEDGEMENTS

Thanks are due to innumerable people who have contributed in one way or the other to the successful completion of this work.

My profound gratitude goes to my supervisor Dr.B.I.Alo who initiated this study. I am happy to acknowledge his guidance, criticisms and in particular,the many "argument sessions" which were invaluable to me.

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Part of the work reported in this thesis was carried out in Dr.J.R.Hanson's laboratory at the School of Molecular Sciences, University of Sussex,Brighton, U.K. This was made possible by the British Caledonian Airways that awarded me a "Sir Adam Thomson" scholarship and the Lagos State University that granted me study leave to enable me utilize the opportunity. Their contribution to this work is recognized with gratitude.

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Thanks also to Dr. Tony Avent for the NOE experiments and Carbon-13 NMR spectra.

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I must also acknowledge Mrs Funke Kuyoro of R&D Holdings

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These acknowledgements would be incomplete without mentioning the encouragement and support given to me throughout the period of this work by my sister, Mrs Anne Augie, her husband, Alhaji Adamu Augie, my brothers Kenny, Roy and Nicky and many friends and colleagues.

Finally, I wish to express my heartfelt gratitude to my loving husband Gabriel and my children Ema, Jackie and Elameyi who in their own ways contributed to making this project a cumbersome and trying exercise although the end result has been very rewarding.

Dedicated to my father Mr Patrick Graham M.F.R, who sadly is not here today but who would have been proud to share this page with his wife, my mother Mrs. Eva Graham.

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ILLUSTRATIONS

COMPENDIUM OF ABBREVIATIONS AND ACRONYMS

We live in an acronymous age, but these shorthand collection of letters (Greek-akros, tip, and onyma, name) have a correct usefulness only if they are defined in context. The following short listing includes only those acronyms and abbreviations used in this thesis.

Ac ----------acetyl

Ac_2O ----------Acetic anhydride

AcOH or HOAc ----------Acetic acid

Bu ----------butyl

COSY ----------Correlation spectroscopy

DMAD ----------Dimethyl accetylenedicarboxylate

DMF ----------N,N-Dimethylformamide

DMSO ----------Dimethylsulphoxide

Et ----------ethyl

Et_2O ----------Diethylether

EtOH ----------Ethanol

FT ----------Fourier Transform

IR/i.r.----------Infrared

LAH ----------Lithium aluminium hydride

Me ----------methyl

MeOH ----------Methanol

NBS ----------N-Bromosuccinimide

NCS ----------N-Chlorosuccinimide

NMR/n.m.r ----------Nuclear magnetic resonance

^{13}C-NMR ----------Carbon-13 NMR

^{1}H-NMR/p.m.r -----Proton NMR

2D-NMR ----------Two dimensional NMR

Ph ----------phenyl

PPA ----------Polyphosporic acid

PTC ----------Phase Transfer Catalysis

Pyr ----------Pyridine

R.T. ----------Room Temperature

$TBAHSO_4$ ----------Tetrabutylammonium hydrogen sulphate

TEA ----------Triethylamine

THF ----------Tetrahydrofuran

NOTE : All NMR DATA ARE GIVEN IN ppm OR δ UNITS

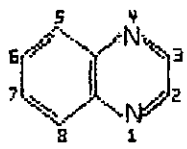
1.0 INTRODUCTION

The impressive biological activity of numerous nitrogen heterocycles has fostered continuing interest in the chemistry of this structural class. Notable among this class of compounds are the quinoxalines. Interest in the chemistry of quinoxalines has resulted in the appearance of a large number of publications both in the journal and patent literature as numerous derivatives have been prepared in work designed to produce biologically active materials. Polycondensed nitrogen heterocycles in particular have attracted considerable interest because of their importance in chemotherapeutics[1,2] and their marked activity in many biological systems[3].

1.1 GENERAL INTRODUCTION TO QUINOXALINE CHEMISTRY[4-9]

1.1.1 Nomenclature

The approved numbering for the quinoxaline ring system is shown in structure (1); positions 2 and 3 are sometimes designated β-positions. An alternative name for quinoxaline occasionally to be found in the literature is 1,4-diazanaphthalene.



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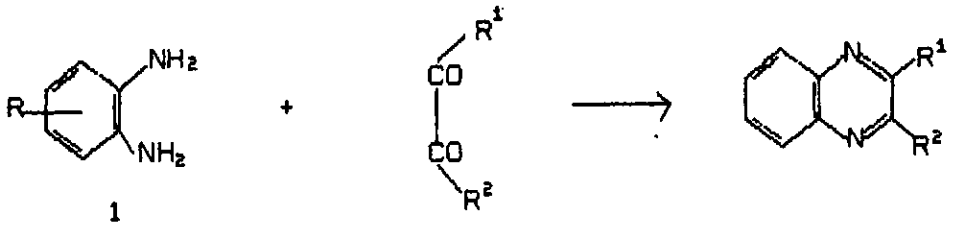
1.1.2 Syntheses of the ring system:

The vast majority of quinoxalines are of synthetic origin. The synthetic method generally used is to condense an o-disubstituted benzene with a two carbon synthon. Thus condensation of

o-phenylenediamines with α - dicarbonyl compounds results in quinoxaline formation as shown in scheme 1.



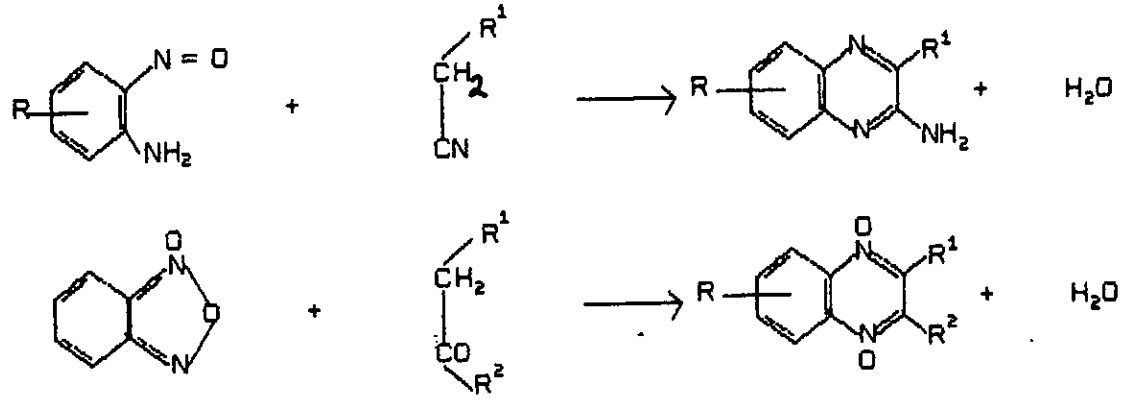
1

SCHEME 1

By suitable choice of the α-dicarbonyl component, alkyl and arylquinoxalines, quinoxalinones and quinoxaline carboxylic acids have been prepared.

Other two carbon synthons that have been reacted with o-phenylenediamine to form quinoxalines include α-halogenocarbonyl compounds, α,β-dihalides, and acetylene-1,2-dicarboxylic acid esters.

Major variants on this method are the use of o-nitrosoaminobenzenes and benzofuroxans as substrates for reaction with a two carbon component as illustrated in scheme 2. The o-nitrosoaminobenzene based synthesis has the advantage of leading to products of unambiguous structure. This is not the case when unsymmetrical o-phenylenediamines or benzofuroxans are used.



SCHEME 2

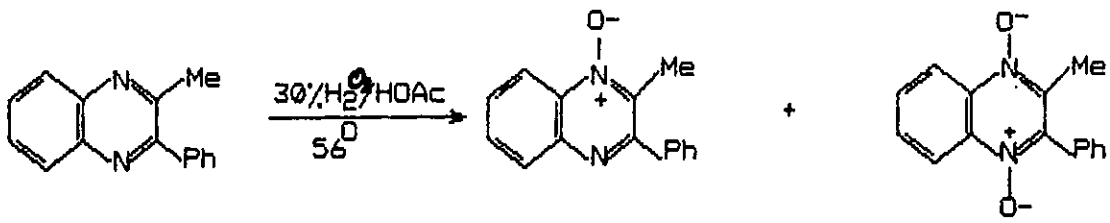
This construction of quinoxaline-di-N-oxides from benzofuroxans is known as the Beirut reaction and has been exploited extensively in recent years.

1.1.3 Reaction of Quinoxalines with Electrophilic Reagents

a) On Ring Nitrogen:

Quinoxaline (1,4-diazanaphthalene) has a pKa value of 0.6 and it is therefore less basic than either cinnoline (1,2-diazanaphthalene), quinazoline (1,3-diazanaphthalene) or phthalazine (2,3-diazanaphthalene). Quinoxaline is reported to have a second pKa of -5.52 and it is therefore only significantly diprotonated in a strongly acidic medium.

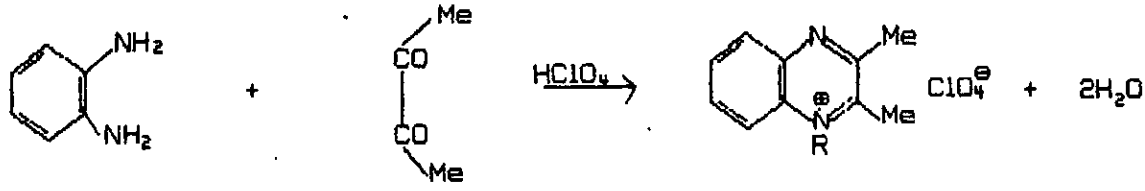
Quinoxaline and its simple derivatives are readily converted into both mono and di-N-oxides by oxidation with peracids (scheme 3). As mentioned above, di-N-oxides are also available from primary synthesis.



SCHEME 3

Quinoxalines form monoquaternary salts when treated with common quarternizing agents such as methyl sulphate and methyl p-toluenesulphonate. The quarternary salts of 2-alkyl quinoxalines are unstable and on oxidation are converted into complex coloured products. Quinoxaline quarternary salts have also been prepared by primary

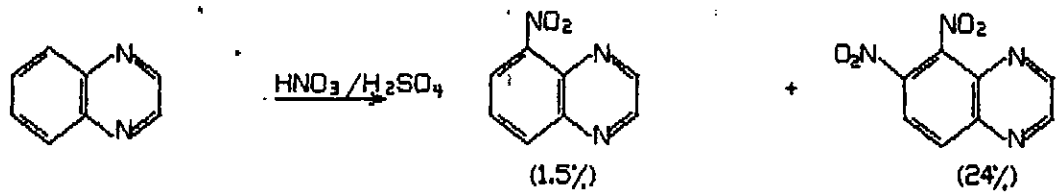
synthesis from N-substituted o-phenylenediamines and α-dicarbonyl compounds (scheme 4)



SCHEME 4

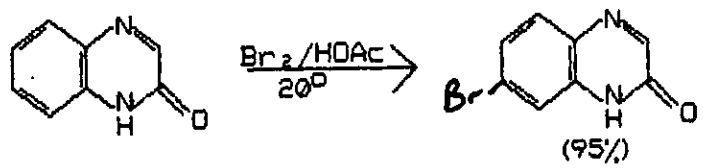
b) On carbon:

Quinoxaline itself and many of its simple derivatives do not readily undergo substitution on carbon when treated with electrophilic reagents. However, under forcing conditions, the parent base is nitrated with nitric acid and oleum to give 5,6-dinitroquinoxaline as the major product.



1 2 (1.5%) 3 (24%)

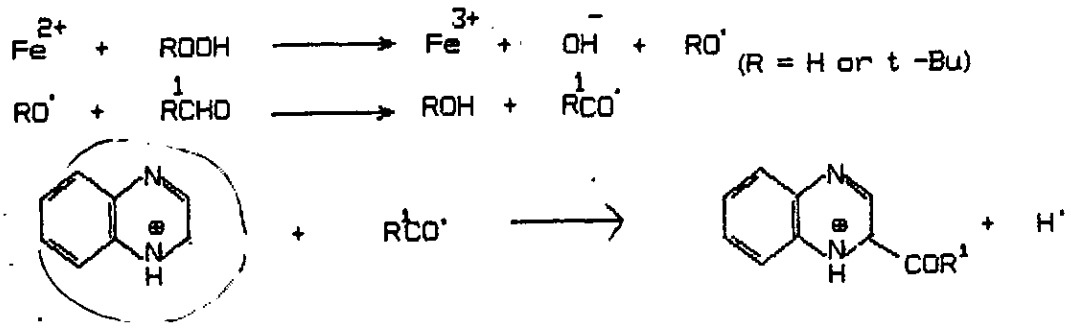
In contrast to quinoxaline, 2,hydroxyquinoxalines and related 1,2-dihydro-2-oxoquinoxalines are activated to electrophilic substitution. Nitration and halogenation occur smoothly in the 7-position when the reactions are carried out in acetic acid solution.



4 5 (95%)

Activation here is due to the NR.CO grouping (R = H or Me)

The quinoxalinium cation is susceptible to substitution at C-2 by a whole range of radical reagents. For example, acyl radicals (RCO) generated under oxidizing conditions from aldehydes react with quinoxaline to give 2-quinoxalinyl ketones. 2-alkyl carboxamido - and ethoxycarbonyl quinoxalines have also been prepared (Scheme 5).



SCHEME 5

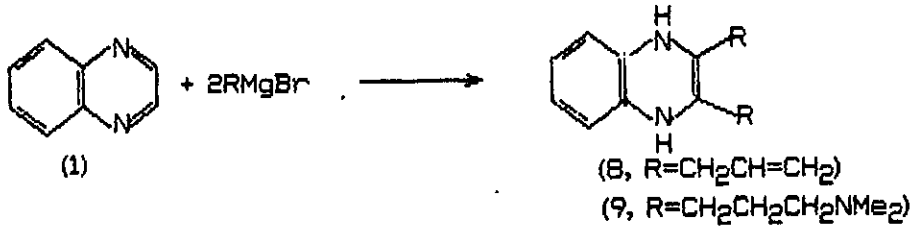
Homolytic γ-aminoalkylation of quinoxalinium cation also occurs at the 2-position. However, at high acidity, when a significant amount of diprotonated base is present, both 2- and 6- substitution occurs.

1.1.4 Addition Reactions of Quinoxalines:

Following hydride ion addition to quinoxalines, 1,2-dihydro,1,4-dihydro,1,2,3,4-tetrahydro and decahydroquinoxalines are known. Reduction of quinoxaline with sodium in tetrahydrofuran (THF) at 20° yields 1,4-dihydroquinoxaline (6) whereas aluminium hydride in ether yields 1,2,3,4-tetrahydroquinoxaline (7).

(1) (6)

The tetrahydroquinoxaline (7) is also obtained, albeit in lower yield, by reduction with sodium in refluxing alcohol. Quinoxaline also adds two molecular proportions of Grignard reagent to give a 2,3-disubstituted 1,2,3,4-tetrahydroquinoxaline (8 and 9).



Quinoxaline undergoes cycloaddition reactions with reagents such as diphenylcyclopropenone to form 1:1 molecular adducts.

1.1.5 Reactions of substituted Quinoxalines:

2-Alkylquinoxalines show enhanced reactivity in terms of their ability to undergo condensation reactions with aldehydes and their ability to undergo Michael additions. Similarly 2-halogenoquinoxalines have been found to participate in a wide range of nucleophilic substitution reactions with oxygen, sulphur, nitrogen and carbon nucleophiles. Chlorine in the 2-position is also readily removed by catalytic hydrogenation.

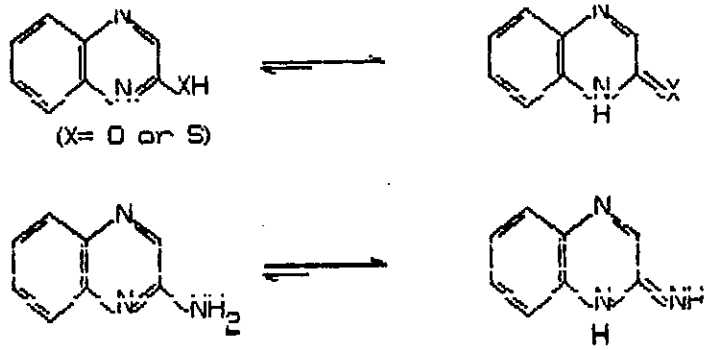
Quinoxaline-2-carboxylic acids are very readily decarboxylated which renders their purification difficult but in some

cases increases their utility as intermediates in other quinoxaline preparations. For example, 2-chloroquinoxaline (11) can be readily prepared from 3-chloroquinoxaline-2-carboxylic acid (10).

(10) (11)

1.1.6 Tautomerism of Quinoxaline Derivatives:

2-hydroxy- and 2-mercaptoquinoxalines exist in the quinoxalin-2-one and quinoxalin-2-thione forms whereas 2-aminoquinoxaline exists as such rather than as an imine (scheme 6).

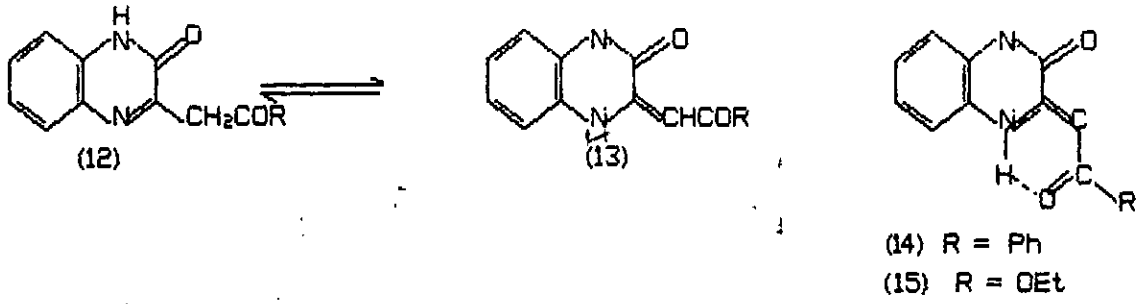


(X= O or S)

SCHEME 6

2,3-Dihydroxy- and 2,3-dimercaptoquinoxaline similarly exist in 2,3-dione and 2,3-dithione forms respectively. 3-substituted-2-quinoxalinones carrying an acyl-methyl function in the 3-position exhibit side chain-ring tautomerism, with the two tautomeric forms (12) and (13) contributing. Intramolecular hydrogen bonding is

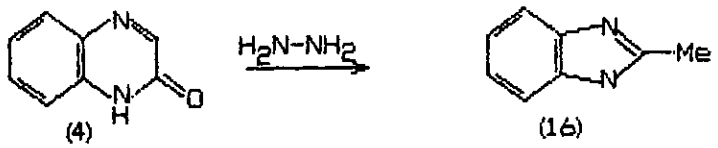
thought to contribute to the stability of the enamine tautomer.



(12) (13) (14) R = Ph (15) R = OEt

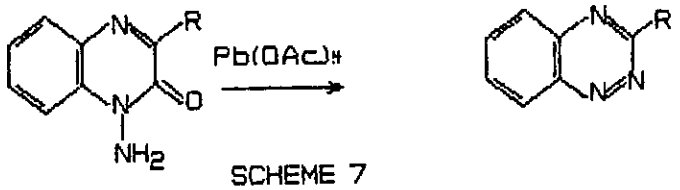
1.1.7 Reactions of Quinoxalines involving Ring Change:

Relatively few reactions of quinoxaline derivatives occur with change of ring size. The isolated examples known are described here. For example ring contraction to benzimidazole derivatives occur when 2,3-diphenylquinoxaline or 2-halogenoquinoxalines are treated with potassium amide in liquid ammonia and when quinoxalin-2-one is treated with hydrazine.



(4) (16)

It was also found that oxidation of 1-amino quinoxalin-2-ones with lead tetraacetate gives benzo-1,2,4-triazines (scheme 7).

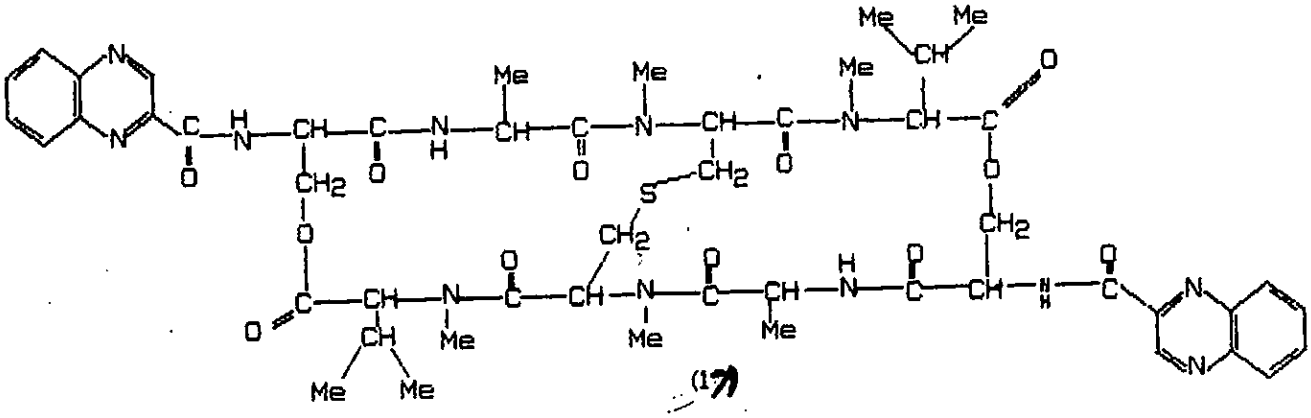


SCHEME 7

1.1.8 Biological properties of Quinoxaline Derivatives:

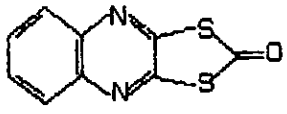
The main search for biologically active quinoxalines has

centred around the preparation of quinoxaline-N-oxides. 3-substituted-2-methylquinoxaline 1,4-dioxides with high antibacterial activity have been prepared. Quinoxaline-2-sulphonamide has had sustained use as a coccidiostat for poultry. Antibiotics of the triostin and quinomycin series, isolated from cultures of streptomyces aureus, have been shown by degradation study to contain a quinoxaline-2-carboxylic acid residue. The structure of quinomycin A (echinomycin) (17) is given below.



(17)

5,6,7,8-Tetrachloroquinoxaline (chlorquinox) is the active compound in various fungicidal formulations and Morestan (18) is used as an insecticide.

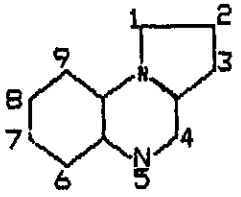


(18)

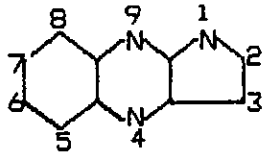
1.2.0 PYRROLOQUINOXALINES

In pyrroloquinoxalines, a pyrrole ring is fused to a

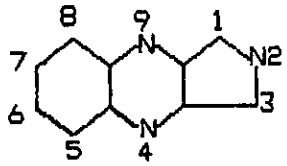
quinoxaline skeleton. There are four types of pyrroloquinoxalines, as illustrated below, which differ in the position of fusion of the rings. Thus we have pyrrolo[1,2-a]quinoxaline pyrrolo[2,3-b] quinoxaline , pyrrolo{3,4-b}quinoxaline and pyrrolo[1,2,3-de] quinoxaline.



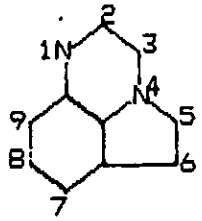
Pyrrolo[1,2-a]quinoxaline



Pyrrolo[2,3-b]quinoxaline



Pyrrolo[3,4-b]quinoxaline



Pyrrolo[1,2,3-de]quinoxaline

For the purpose of this study, the chemistry and properties of only the pyrrolo[1,2-a] quinoxalines which closely resembles the pyrido[1,2-a]quinoxaline ring system is reviewed.

PYRROLO[1,2-A]QUINOXALINES

1.2.1 PHYSICAL PROPERTIES:

The parent aromatic heterocycle has been subjected to extensive theoretical calculations in order to compare the predicted and found sites of electrophilic substitution [10]. HMO calculations suggest that the most susceptible position is the 2-position, whereas a consideration of localization energies indicates that the susceptibility to electrophilic substitution decreases in the

order 1>3>6>2. The latter prediction is regarded as more valid and agrees with the experimental results described. (Section 1.2.3)

The acidity constant (pKa) of the unsubstituted heterocycle is 3.94 in 50% aqueous ethanol[11] indicating the relatively weak basic nature of the ring system. Nevertheless, pyrrolo[1,2-a] quinoxalines are appreciably stronger bases than quinoxalines. Substitution of the ring system by methyl groups results in a base strengthening effect, as expected. This base strengthening effect is dependent on the site of substitution. The 4-methyl compound has a pKa of 4.58 in 50% alcohol[12] which is consistent with protonation at the 5-position as the increase in pKa (0.64) is characteristic of the effect of methyl substitution in six-membered rings α- to the site of protonation[13]. The much smaller increase in pKa between the 4-methyl compound (4.58) and the 2,4-dimethyl compound (4.89) is also consistent with protonation at the 5-position.

1.2.2 METHODS OF PREPARATION:

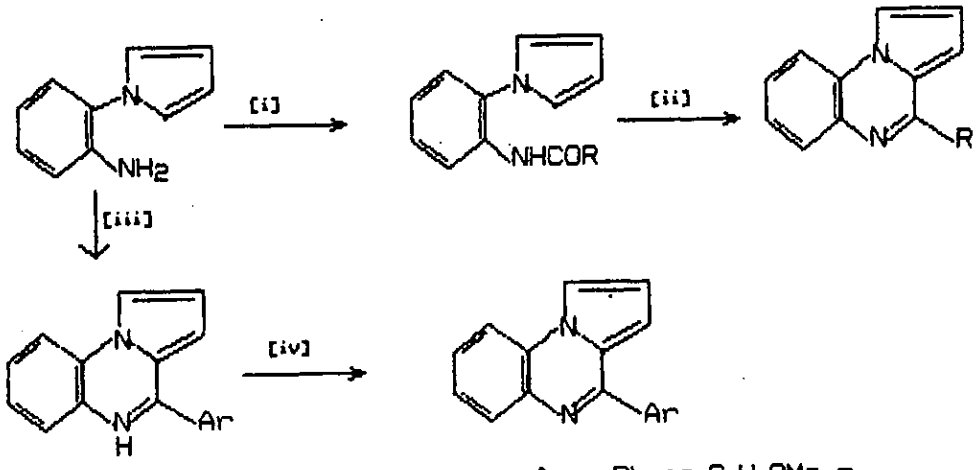
Several different approaches have been adopted for the synthesis of pyrrolo[1,2-a]quinoxalines. Particularly useful are approaches involving cyclization reactions of o-aminophenylpyrroles. Alternative syntheses have involved the use of o-phenylenediamine, the cyclization of β-quinoxalinylpropionic acids, quaternization of quinoxaline derivatives, as well as several other routes less amenable to classification.

A. Syntheses from o-Aminophenylpyrroles and Related Compounds:

Routes via o-aminophenlypyrroles present the most convenient

syntheses of pyrrolo[1,2-a]quinoxalines (scheme 8) [11,12,14,15,16,17]

A wide variety of reagents have been used for the cyclization step and variously substituted pyrroloquinoxalines have been prepared by using appropriately substituted o-aminophenylpyrroles and related compounds [11,12,14,19]

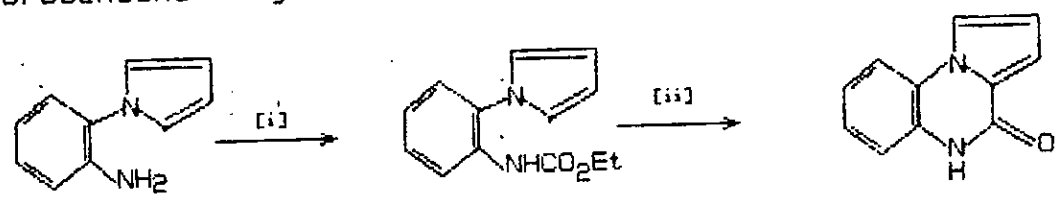


Reagents: i) $R(CO)_2O$
ii) $POCl_3$
iii) ArCHO
iv) MnO_2

Ar = Ph or C_6H_4OMe-p

SCHEME 8

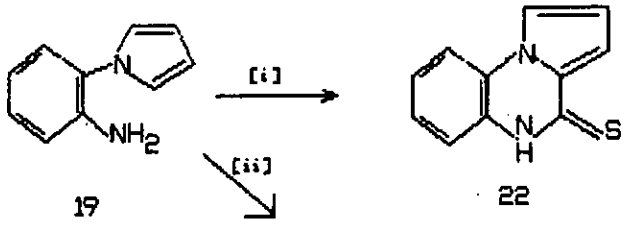
4,5-Dihydro-4-oxopyrrolo[1,2-a]quinoxaline (21) is obtained on reaction of the amino compound (19) with phosgene [19]. Cheeseman and Tuck [18] obtained the carbamate (20) on reaction of (19) with ethyl chloroformate. Compound (21) could not be cyclized with phosphoryl chloride but reacted with zinc chloride in refluxing o-dichlorobenzene to give the 4-oxo compound (21).



19 20 21

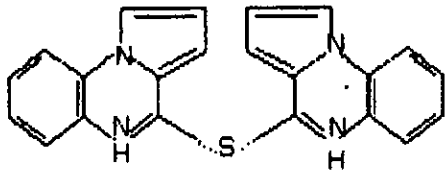
Reagents: (i) $ClCO_2ET$
(ii) $ZnCl_2$, o-$Cl_2C_6H_4$, Δ

Nagarajan et al[19], obtained the 4-thioxo compound (22) on treatment of compound (19) with carbon disulphide. Thiophosgene, on the other hand did not give the expected thioxo derivative (22) but the sulphide (23)[19].



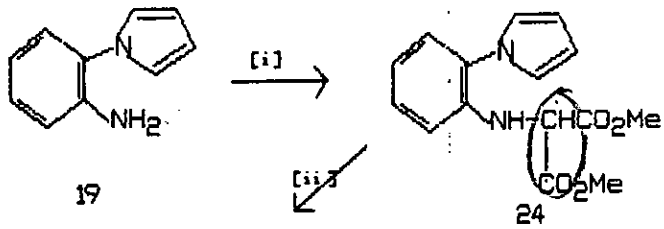
19 22

Reagents: (i) CS_2
(ii) $CSCl_2$

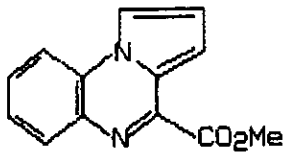


23

The adduct (24), from the reaction of the amino compound (19) with dimethylacetylenedicarboxylate was cyclized to the pyrrolo[1,2 -a]quinoxaline (25) using polyphosphoric acid. The anilino compound (27) was obtained by treatment of the urea (26) with phosphoryl chloride[19].



19 24



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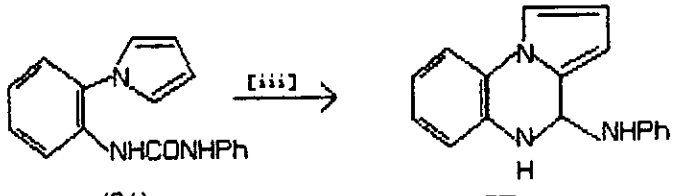
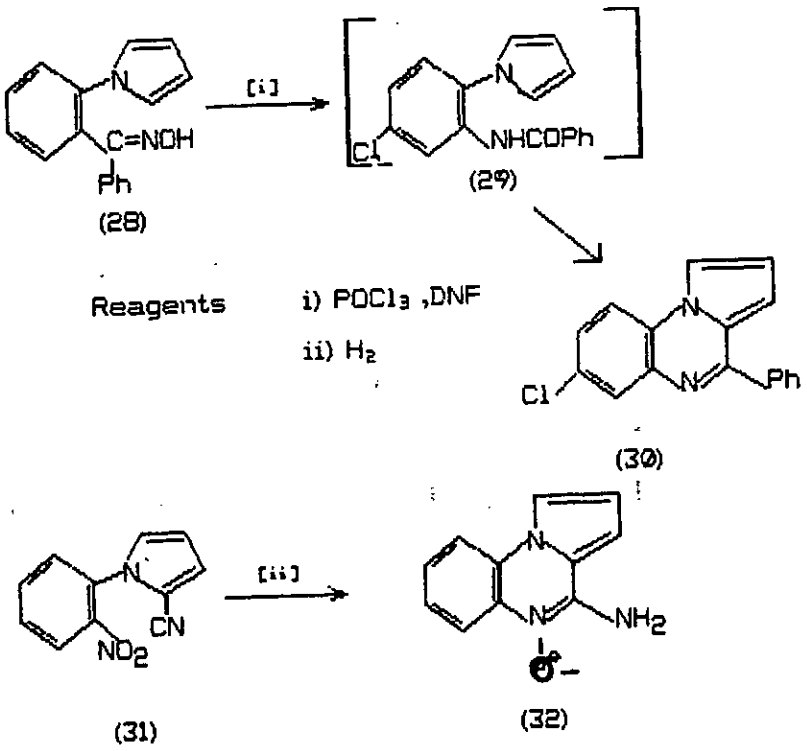


(26) 27

Reagents i) $MeO_2CC{\equiv}CCO_2Me$
ii) Polyphosphoric acid
iii) $POCl_3$

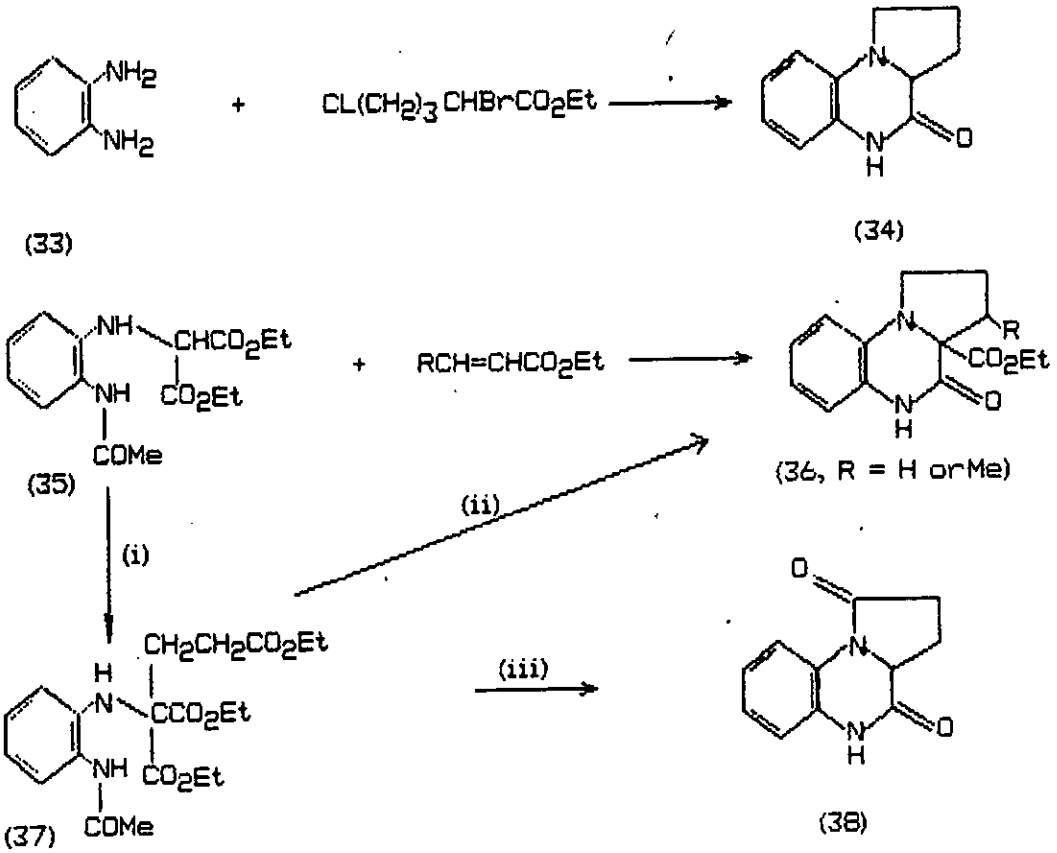
An attempt by Garcia et al[17], to formylate the pyrrole (28) with phosphoryl chloride in DMF gave the 4-phenyl compound (30) presumably by way of Beckmann rearrangement of the oxime followed by cyclization of the resultant amide.

Catalytic reduction of the nitrocyanide (31) gave the 4-amino-5-oxide (32)[14].



B. Syntheses from o-Phenylenediamines:

Pyrrolo[1,2-a]quinoxalines have also been prepared by reaction of o-phenylenediamine and disubstituted derivatives with appropriate esters. Thus the pyrroloquinoxalinone (34) is obtained from o-phenylenediamine (33) and the dihaloester.

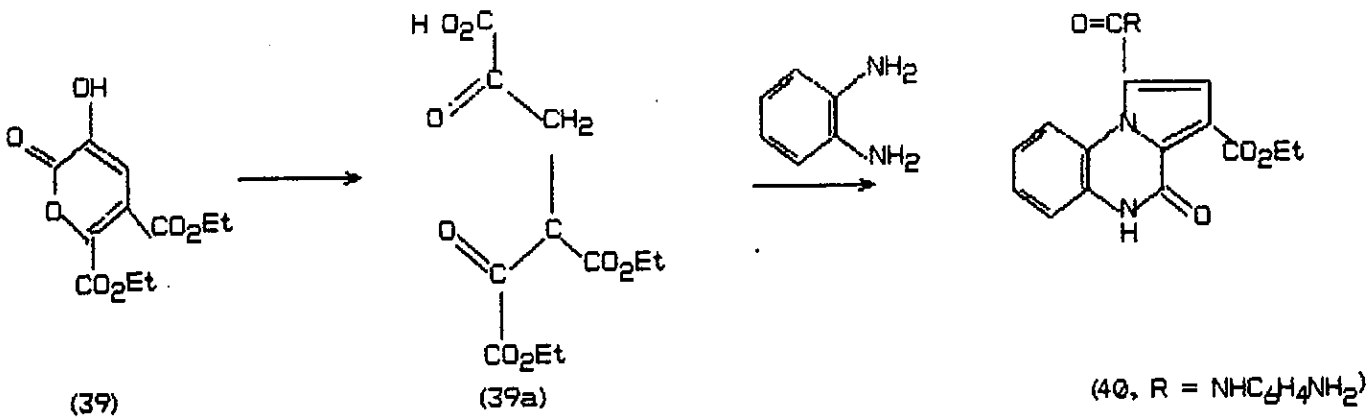


Reagents : (i) $BrCH_2CH_2CO_2Et$
(ii) NaOEt
(iii) H^+

The disubstituted phenylenediamine (35) has been condensed with methyl acrylate[20] and methyl crotonate[21] to give the cyclized Michael adducts (36). The product (36; R = H) was also prepared by reaction of the phenylenediamine (35) with ethyl 3-bromopropionate to give the triester (37) followed by cyclization

with sodium ethoxide. Acid cyclization of the intermediate (37) on the other hand, gave compound (38) by hydrolysis and decarboxylation of the 3 -ester group.

Two moles of o-phenylenediamine condense with the pyrone derivative (39) to give the anilide (40) in 75% yield[22].

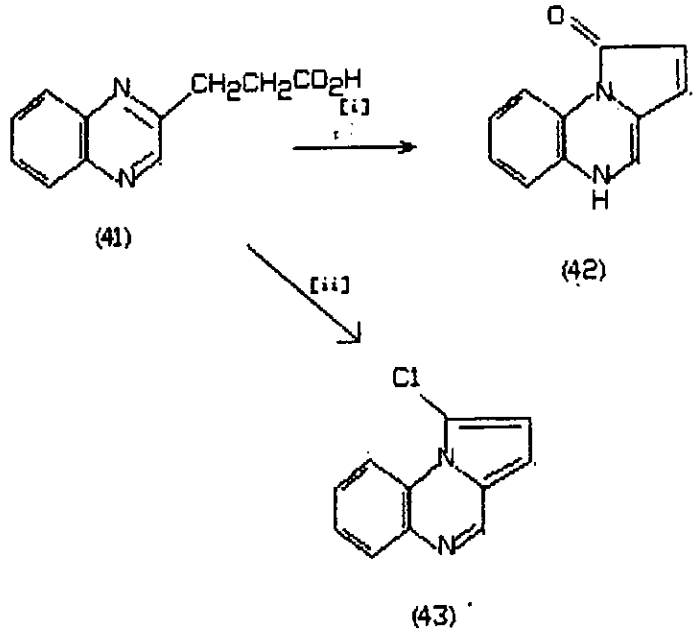


(39) (39a) (40, R = $NHC_2H_4NH_2$)

This reaction is most easily understood by regarding the pyrone (39) as an internal ester of the dicarbonyl compound (39a).

C. <u>The Cyclization of β-Quinoxalinylpropionic-Acids.</u>

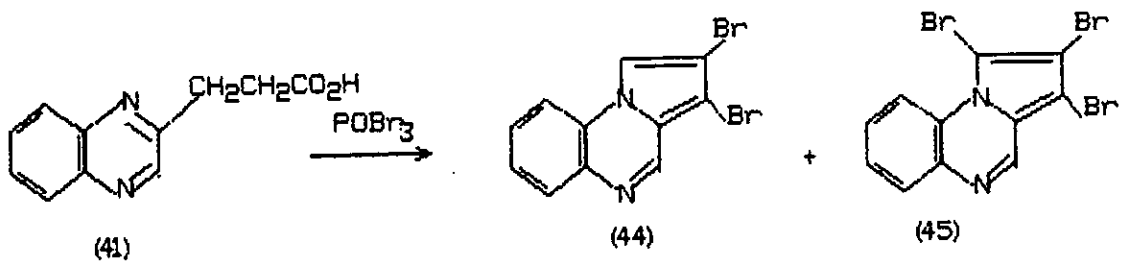
Cyclization of β-quinoxalinylpropionic acids presents another facile route to pyrrolo[1,2-a]quinoxalines. Cheeseman and Roy[23] obtained 1,5-dihydro-1-oxopyrrolo[1,2-a]quinoxaline (42) in 85% yield on heating the quinoxalinylpropionic acid (41) with polyphosphoric acid. Reaction of the propionic acid (41) with phosphoryl chloride, on the other hand, gives the 1-chloro compound[16] (43).



Reagents:
i) Polyphosphoric acid
ii) $POCl_3$

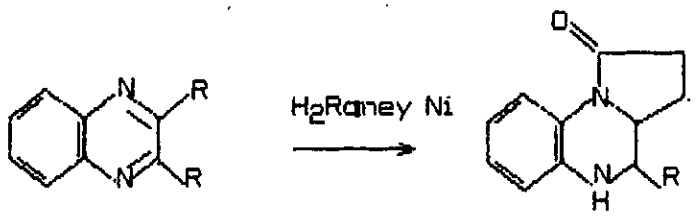
Various 2- and 4- substituted analogues of (42) have been prepared by cyclization of appropriately substituted quinoxalinyl-propionic acids using either acetic anhydride in sulphuric acid[24-26] or polyphosphoric acid[16] as cyclization reagent.

In contrast to the reaction with phosphoryl chloride, phosphoryl bromide reacts with the acid (41) to give, not the 1-bromo analogue of (43) but a mixture of the 2,3-dibromo compound (44) and the 1,2,3-tribromopyrrolo[1,2-a] quinoxaline (45)[27].



This mixture of polybromo compounds is also obtained on treatment of the parent heterocycle with bromine in refluxing hydrobromic acid.

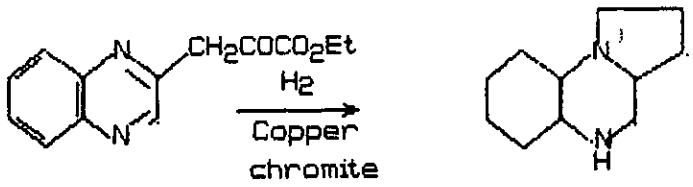
Reductive cyclization of quinoxalinyl propionic acids yields hexahydro-1-oxo compounds. Thus reduction with hydrogen and Raney nickel of the acids (46), yields the hexahydro compounds (47).[26,28]



(46) R'= $CH_2CH_2CO_2H$ Or $CH{=}CHCO_2H$
R = H, Me or Ph

(47)
R = H, Me or Ph

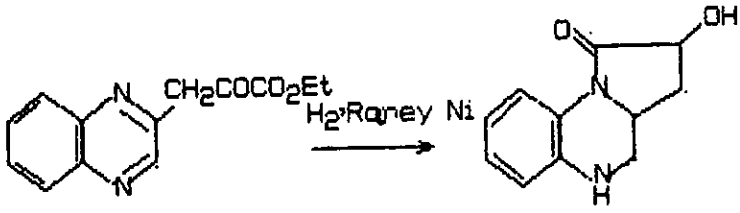
The earliest preparation of the ring system reported by Leonard and Boyer in 1950, involved hydrogenation of the keto ester (48) at high temperature and pressure over copper chromite. The perhydro compound (49) was obtained by this approach.



(48)

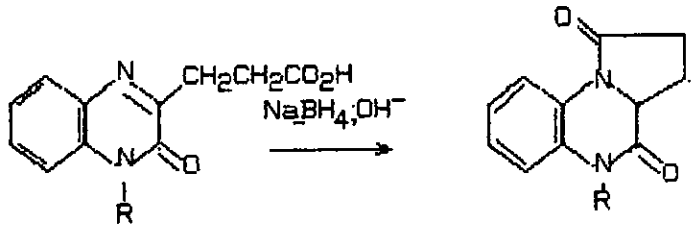
(49)

The use of hydrogen and Raney Nickel on compound (48) however, resulted in the synthesis of (50)[30].



(48) (50)

The most carefully studied approach concerned the preparation of dioxo compounds (38) and(52) from the propionic acids (51). The best reducing agent for this synthesis was found to be alkaline sodium borohydride.[31]



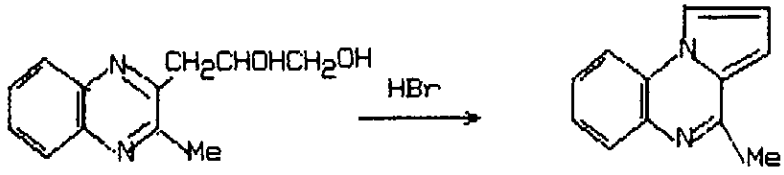
(51), R=H or Me (38) R = H (52) R = Me

D. Syntheses involving Quarternization of Quinoxalines.

In general, the quinoxaline ring system is quarternized only with difficulty, so that approaches to pyrrolo[1,2-a]quinoxalines that involve a quarternization step are unlikely to be very convenient. Nevertheless several different types of syntheses have been performed using quinoxaline quarternary salts.

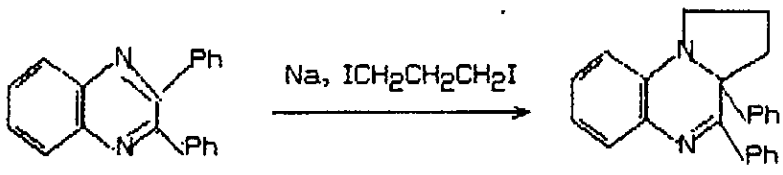
Cheeseman and Tuck[12] obtained the pyrrolo [1,2-a]quinoxaline (54) in low yield on treatment of the hydroxypropylquinoxaline (53) with hydrobromic acid.

This contrasts with the high yields obtained from this approach in the more readily quarternized quinoline series



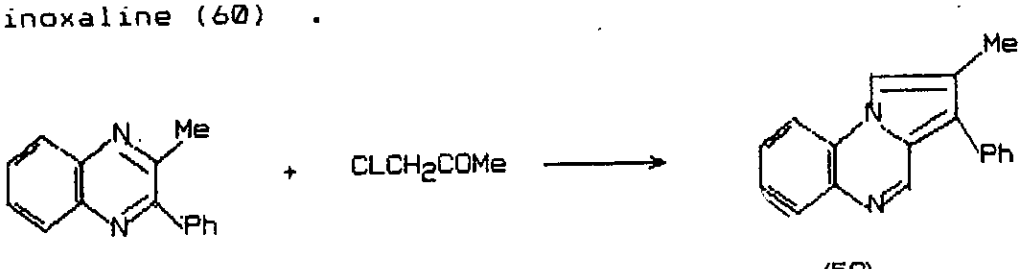
(53) (54)

2,3-diphenylquinoxaline (55) forms a dianion on treatment with sodium, and this has been alkylated with 1,3- diiodopropane to give the tetrahydro compound (56)[32].

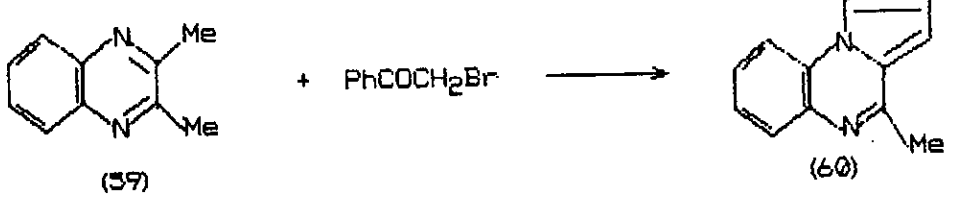


(55) (56)

Taylor and Cheeseman[26] obtained an unspecified yield of the pyrrolo compound (58) on reaction of 2-methyl-3-phenylquinoxaline (57) with chloroacetone. Apparently the intermediate quarternary salt cyclized spontaneously to give the tricyclic product. Similarly, quarternization of 2,3 - dimethylquinoxaline (59) with phenacyl bromide gave a low yield of the pyrrolo [1,2] quinoxaline (60)[12].



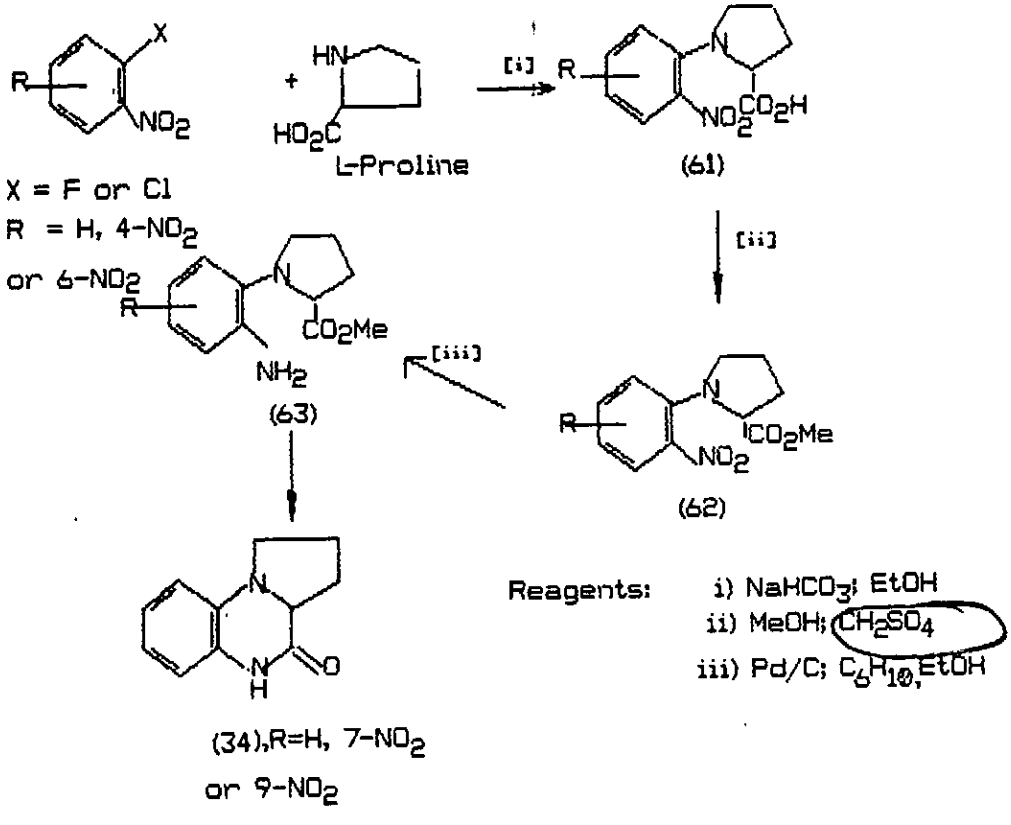
(57) (58)



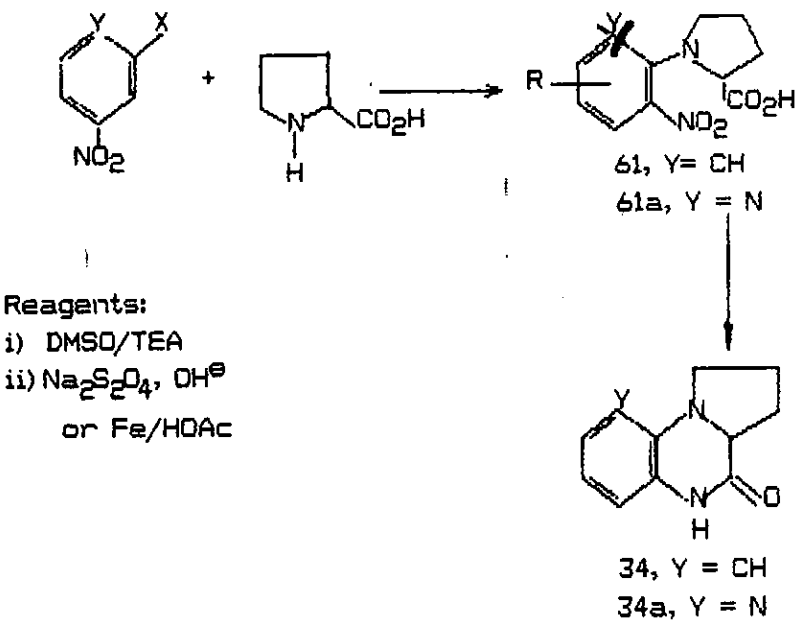
(59) (60)

E. Cyclization of N-[2-Nitrophenyl] Pyrrolidine-2-Carboxylic Acids:

Adegoke et al[33,34] first reported the synthesis of pyrrolo [1,2-a] quinoxalines via a hydrogen transfer reductive cyclization of the methyl esters of N-[2-nitrophenyl]pyrrolidine-2-carboxylic acids (62). These esters were prepared by condensation of L-proline (pyrrolidine-2-carboxylic acid) with the appropriate 1-halogeno-2-nitrobenzene in dilute bicarbonate solutions to give the N-[2-nitrophenyl] pyrrolidine-2-carboxylic acid (61) followed by esterification with acidified anhydrous methanol. Catalytic hydrogen transfer reduction of the nitroesters over 10% palladium on charcoal in ethanol and cyclohexene gave initially the N-[2-aminophenyl] derivatives (63) which were cyclized in situ intramolecularly to give the desired 1,2,3,3,a- tetrahydropyrrolo [1,2-a]quinoxalin-4-one (34).



In a modification of this route, Abou-Gharbia et al[35] synthesized a series of tetrahydropyrroloquinoxalines by direct reductive cyclization of N-[2-nitrophenyl] pyrrolidine-2-carboxylic acids. The key starting intermediates (61) and (61a) were prepared by reacting 1-fluoro-2-nitrobenzene or 2-chloro-3-nitropyridine with L-(-) - proline in dimethylsulphoxide in the presence of triethylamine at 60°c. Reductive cyclization of the resulting nitroacids via alkaline sodium dithionite or iron in glacial acetic acid afforded the 1,2,3,3-a tetrahydropyrrolo[1,2-a]quinoxalin-4 -ones (34) and (34a) in good yields.

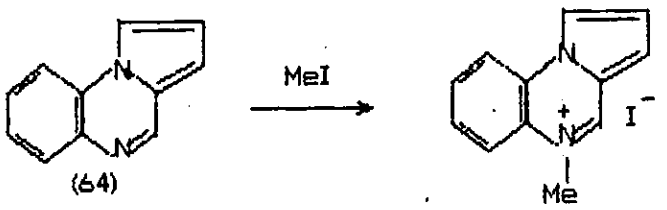


1.2.3. CHEMICAL PROPERTIES

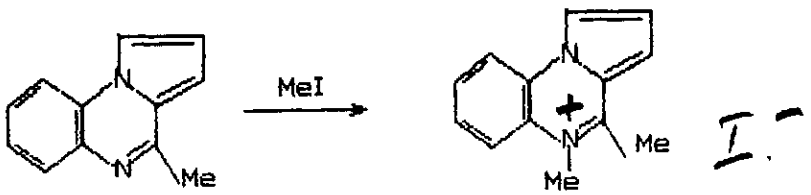
Considerable work has been done on the reactions of pyrrolo [1,2-a] quinoxalines. Alkylation , electrophilic and nucleophilic substitutions as well as oxidation and reduction reactions have all been studied in a bid to understand fully, the chemistry of the tricyclic ring structure.

A. ALKYLATION

Pyrrolo [1,2-a] quinoxaline reacts readily with methyl iodide to give the 5-methyl quarternary salt (65). Quarternization of the 4-methyl compound (54) to give the 4,5-dimethyl derivative (66) proceeds more slowly presumably because of steric hindrance to the reaction [18].

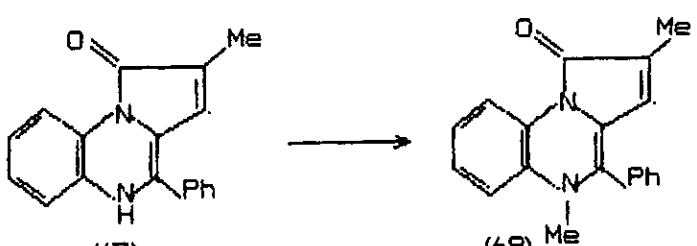


(64) (65)

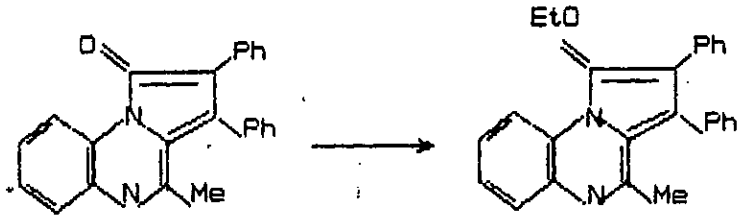


(54) (66)

The 1,5-dihydro-1-oxo derivative (67) reacts with methyl iodide in methanolic sodium methoxide to give a monomethyl derivative formulated as the 5-methyl derivative (68) on the basis of UV spectral data [26]. In contrast, J.W. Lown et al obtained the 1-ethoxy derivative (70) on treatment of the 1-hydroxy compound (69) with triethyloxonium fluoroborate



(67) (68)



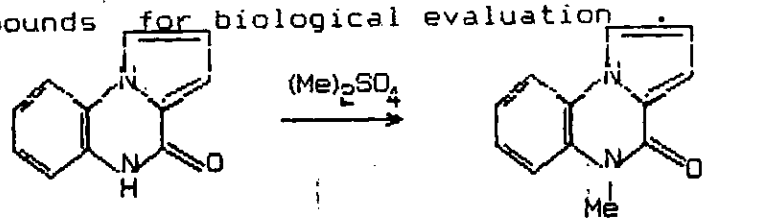
(69) (70)

Reagents:

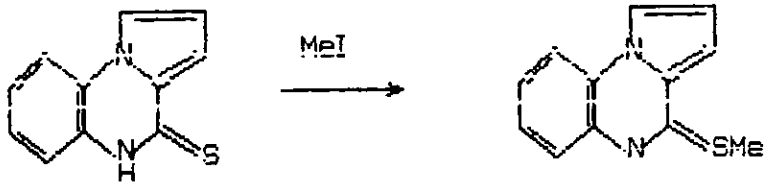
i) MeI, NaOMe, MeOH

ii) $(Et)_3OBF_4$

The 5-methyl compound (71) is obtained on methylation of the 4-oxo derivative (21) with methyl sulphate. The corresponding 4-thioxo compound (22), on methylation with methyl iodide gave the 4-methylthio derivative (72) as expected [18]. Both these reactions have been extended by Nagarajan et al, using more complex alkylating agents to give a series of dialkylaminoalkyl compounds for biological evaluation [19].



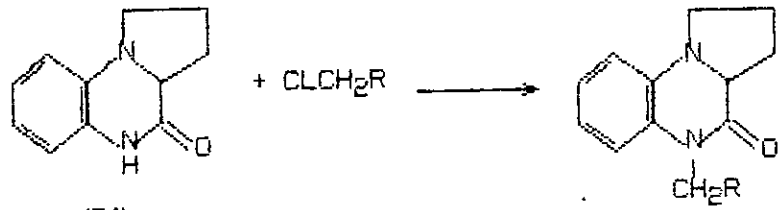
(21) (71)



(22) (72)

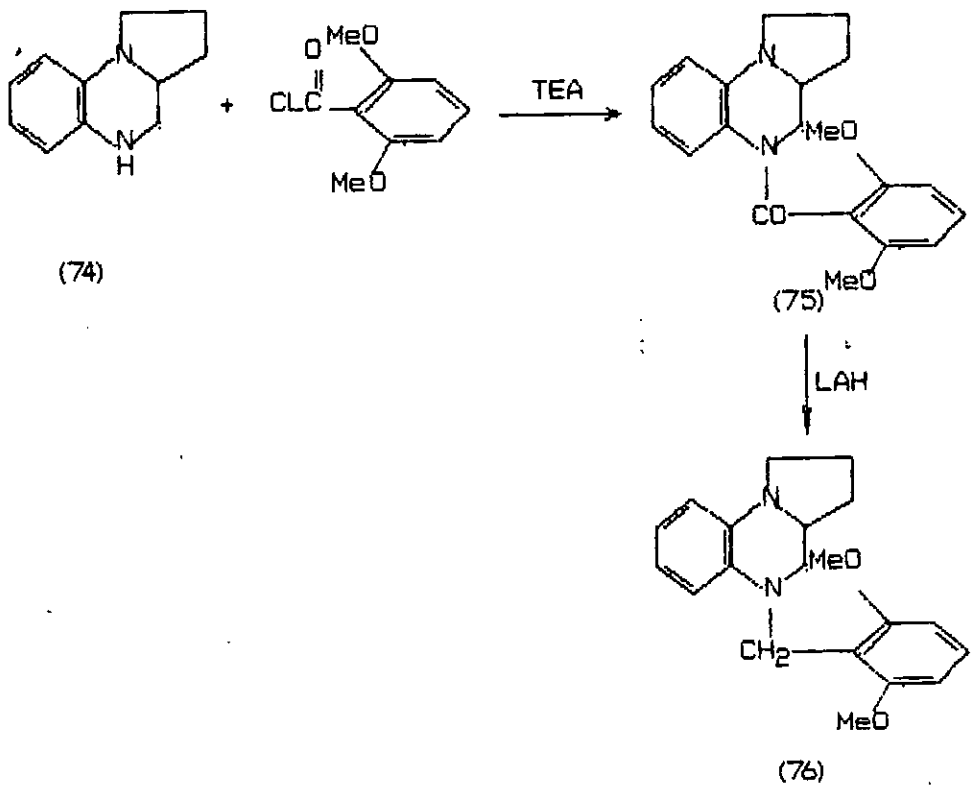
Abou - Gharbia et al [35] recently synthesized a series of N-alkyl and N - aroyl derivates of 1,2,3,3a,4,5,- hexa-hydropyrrolo [1,2-a] quinoxalines. Alkylations with appropriately substituted alkyl or aralkyl halides were carried out in

dimethylformamide in the presence of sodium hydride.



(34) R = C_6H_5; 4-C_6H_4N; 2,6-$(OMe)_2C_6H_3$; $CH_2N(Me)_2$ (73)

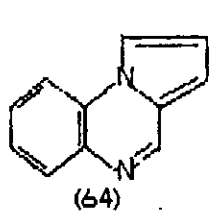
The 4 - oxo group was removed by reduction of compound (73, R = 2,6 - $(OMe)_2C_6H_3$) with Lithium aluminium hydride (LAH) a mixture of anhydrous ether-tetrahydrofuran to give (76). Compound (76) was prepared in higher yields by an alternate synthesis in which 2,6-dimethoxybenzoylchloride was reacted with the reduced quinoxaline (76) in acetone in the presence of triethylamine (TEA) to afford the corresponding N-aroyl derivative (77). Lithium aluminium hydride reduction of (78) in tetrahydrofuran afforded compound (76) in good yield[35].



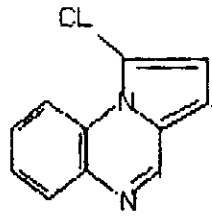
(74) (75) (76)

B. Electrophilic Substitution Reactions.

Pyrrolo[1,2-a] quinoxaline undergoes smooth electrophilic substitution in the pyrrole ring. Theoretical calculations predict that the most favoured positions for electrophilic substitution in decreasing order of susceptibility are 1>3>6>2. There have been reports describing electrophilic substitution at the 1,3 - and 2 - positions but no reaction at the 6 - position has yet been observed. The distribution of products obtained depends on the size of the incoming electrophile. With bulky reagents, steric interactions tend to inhibit reaction at the most electron rich carbon - 1 atom. For example, halogenation of pyrrolo [1,2-a]quinoxaline provides mixtures of products which increasingly disfavour substitution at the 1 - position, as the electrophiles increase in size in the order $Cl^+ < Br^+ < I^+$. All three halogenations with one equivalent halogenating agent provide mixtures of the 1-halo, 3-halo and 1,3 - dihalo compounds. Reaction at room temperature with N-chlorosuccinimide in 50% sulphuric acid[16] gives 75% 1-chloro, 2.5%, 3 - chloro and 0.5% 1, 3 - dichloro compounds. Cheeseman and Roy[27] obtained 42% 1-bromo, 2.7% 3-bromo and 0.7% 1,3-dibromo compounds with N-bromosuccinimide under the same conditions. Bispyridineiodonium nitrate[27] at room temperature yields 18% 1-iodo, 26% 3-iodo, and 0.11% 1,3 - diiodo compounds. 2,4-Dimethyl pyrrolo[1,2-a] quinoxaline gives similar mixtures on bromination and chlorination. All the monohalo compounds can be dihalogenated by use of excess of the halogenating agent.


(64)

[i]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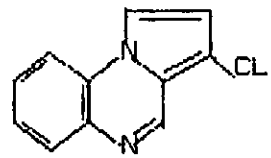
(77) 2.5%

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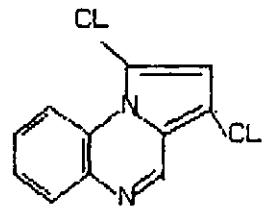
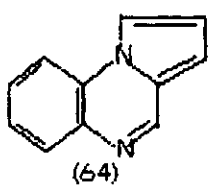
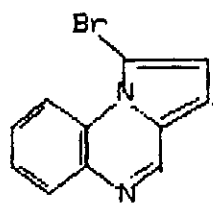

(78) 0.5%


(64)

[ii]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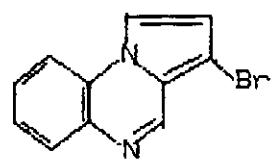
(80) 2.7%

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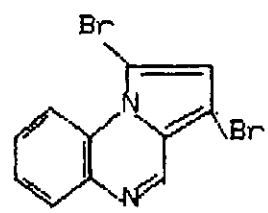
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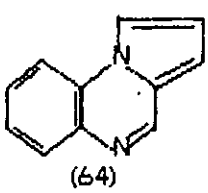
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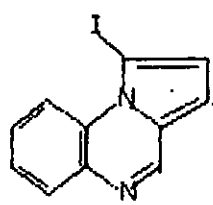
[iii]


(82), 18%

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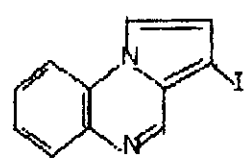
(83), 26%

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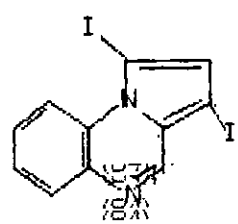
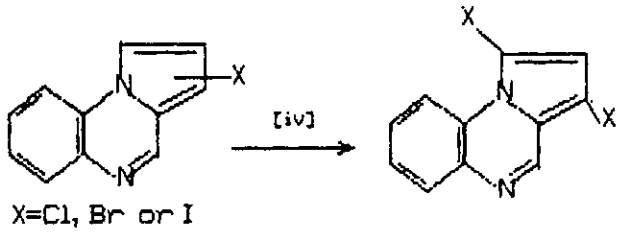




X=Cl, Br or I

Reagents:

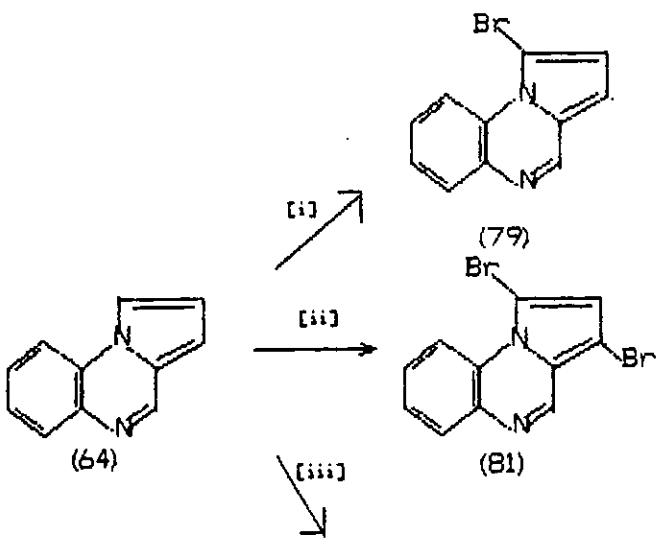
i) NCS, 50% H_2SO_4

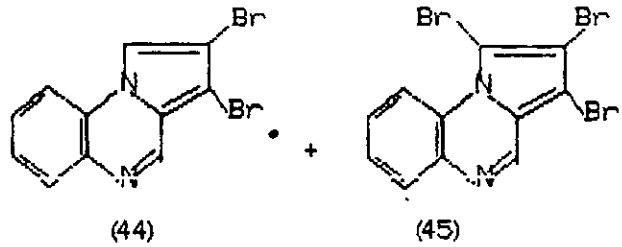
ii) NBS, 50% H_2SO_4

iii) Bispyridineiodine nitrate

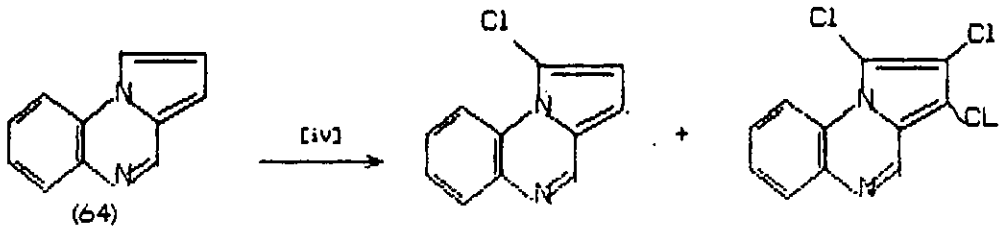
iv) Excess reagent

Nagarajan et al[19] obtained 1-bromopyrrolo[1,2-a] quinoxaline (79) on bromination of the parent heterocycle with one equivalent bromine in cold acetic acid whereas the 1,3-dibromo compound (81) was the product of reaction with two equivalents of bromine at room temperature. Three equivalents of bromine in boiling hydrobromic give a mixture of the 2,3-dibromo and the 1,2,3-tribromo compounds. High temperature chlorination with a mixture of phosphoryl chloride and phosphorus pentachloride gives a mixture of the 1-chloro and 1,2,3-trichloro derivatives[27].





(44) (45)



(64) (43) (85)

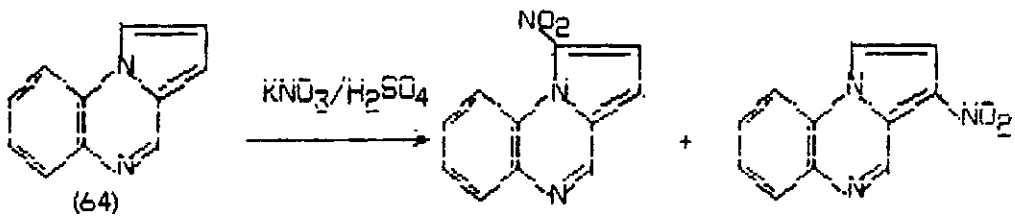
Reagents i) Br_2, HOAC , $\emptyset^{o}C$

ii) $2Br_2$, HOAC, RT

iii) $3Br_2$, HBr, $\triangle$

iv) $POCl_3$, PCl_5, $\triangle$

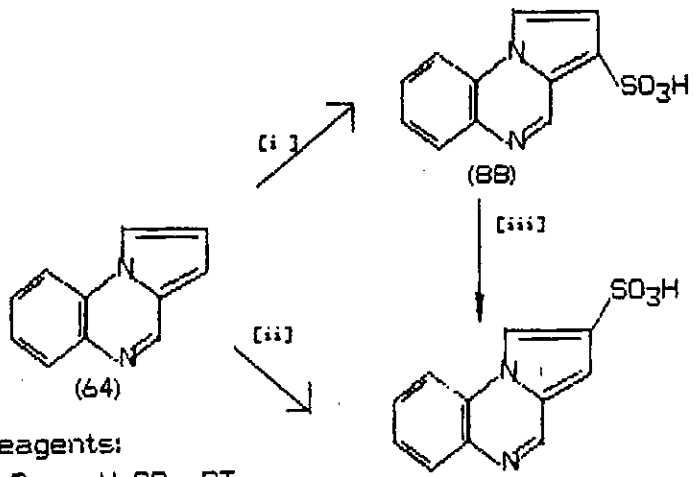
Nitration of pyrrolo [1,2-a] quinoxaline is achieved with a mixture of potassium nitrate and concentrated sulphuric acid and yields a mixture of 25% 1-nitro and 48% 3-nitro derivatives. No significant reaction was observed with potassium nitrate in trifluoroacetic acid, or in fuming nitric acid alone or fuming nitric acid and acetic anhydride [16].



(64) (86), 25% (87) 48%

The attempts to avoid the use of sulphuric acid were made because of the ease with which the heterocycle undergoes sulphonation. Thus treatment of pyrrolo[1,2,-a] quinoxaline with concentrated sulphuric acid at room temperature readily gives the 3-sulponic acid [16]. Apparently the electrophile is too large to allow formation of detectable amounts of the isomeric 1-suphonic acid and so sulphonation occurs exclusively at position 3 when carried out at room temperature.

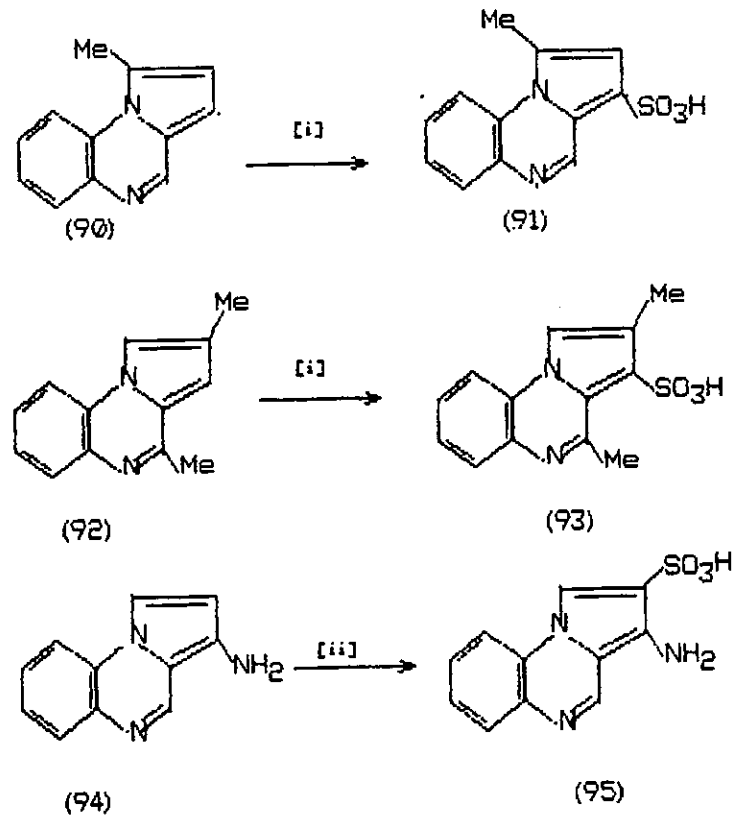
Sulphuric acid at 130 °C on the other hand, gives the 2 - sulphonic acid in about 49% yield. When the 3-sulphonic acid is heated in concentrated sulphuric acid rearrangement to the 2-acid occurs [23].



Reagents:
i) Conc. H_2SO_4, RT
ii) Conc. H_2SO_4, 130 °C
iii) Conc. H_2SO_4, Δ

These observations parallel the well-known α-sulponation of naphthalene at moderate temperatures and the rearrangement of the α-sulphonic acid to the thermodynamically more stable β-sulphonic acid on heating.

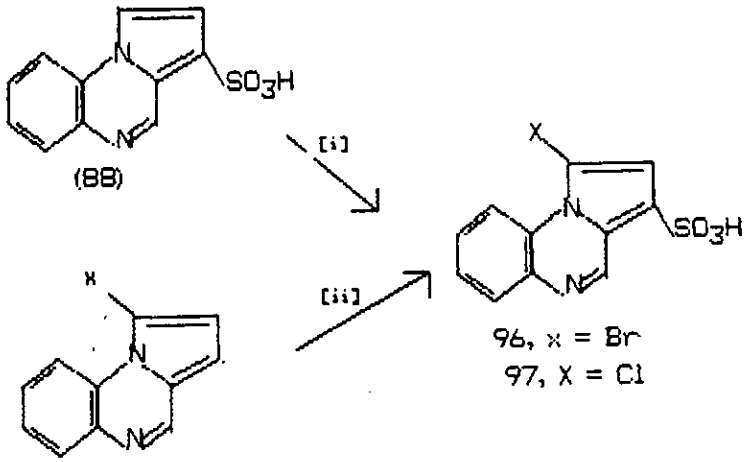
The 1-methyl and 2,4-dimethyl derivatives of pyrrolo [1,2-a] quinoxalines (94) are also readily sulphonated at room temperature [16]. Although 3-aminopyrrole[1,2-a] quinoxaline(94) gives the 3-amino-2-sulphonic acid (95), the 3-nitro compound (87) does not react [23].



Reagents; (i) Conc. H_2SO_4 : RT
(ii) Conc H_2SO_4 : 130°C

The 3-sulphonic acid nitrates readily in the 1-position, and 1-chloro [16] and 1-bromo-3-sulphonic acids [27] may be obtained by halogenation of the 3-sulpho-compound. Sulphonation of 1-chloro and 1-bromopyrrolo [1,2-a]quinoxaline takes place in the 3-position to give the 1-halo-3- sulphonic acids, identical

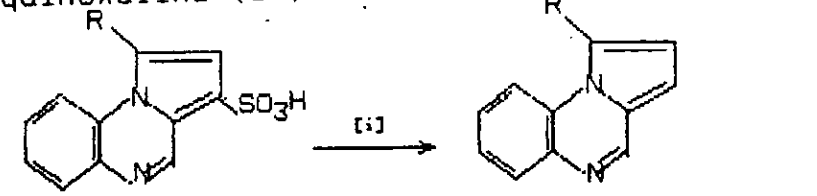
with those obtained by halogenation of the 3 - sulpho derivative.

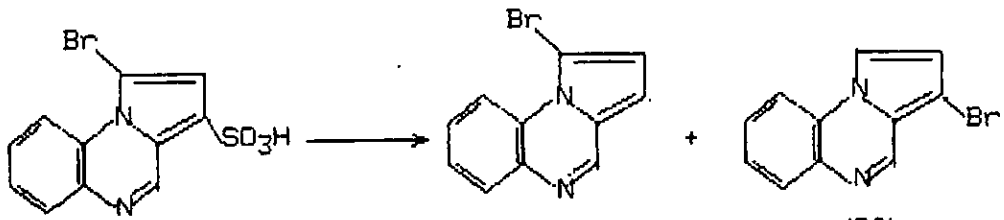


(i)
(ii)

The 3-sulpho-compounds (R = H, NH_2 NO_2 or Cl) desulphonate to the corresponding 3-unsubstituted derivatives on refluxing in aqueous sulphuric acid [23,27].

An anomalous reaction however occured in the case of the 1-bromo-3-sulphonic acid (96), which was converted into 3-bromo pyrrolo[1,2-a]quinoxaline (83) under similar conditions [24] (scheme 10)





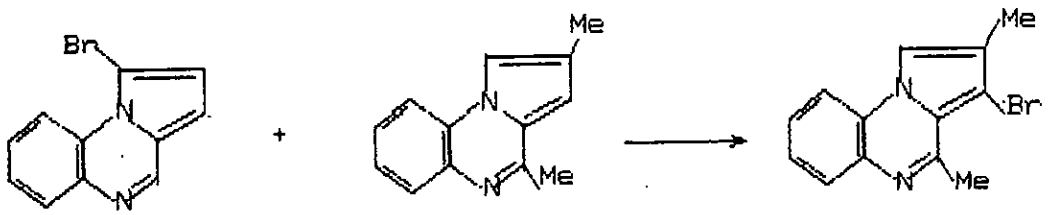
Reagents: (i) Aqueous H_2SO_4

SCHEME 10

The most probable intermediate in this reaction is the 1-bromo compound (79) and it was later shown by the same workers[27] that although 1-chloropyrrolo [1,2-a]quinoxaline is stable under the reaction conditions, the 1-bromo compound (79) rearranges to give the 3-substituted product (80). Similarly 1-bromo-2,4-dimethylpyrrolo [1,2-a] quinoxaline rearranges to the 3-bromo compound.

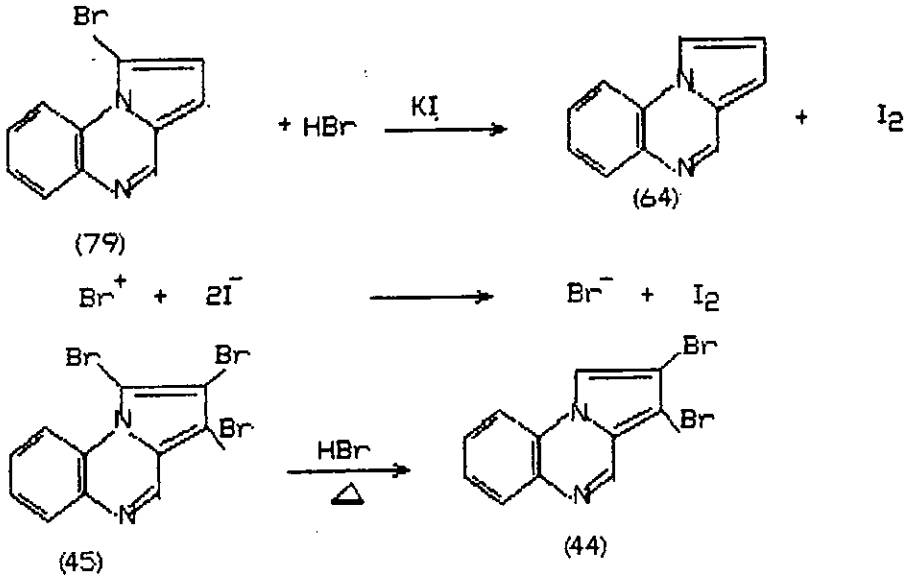
The difference in behaviour between the 1-chloro and the 1-bromo-3-sulphonic acids is attributed to steric interaction between the 1-halo substituent and the hydrogen. Such steric interaction is known to play a determining role in the electrophilic substitution reactions of pyrrolo [1,2 -a] quinoxalines. As noted earlier, with increasing size of electrophile substitution is favoured at position 3 rather than at position 1.

The above transformation may also be carried out in boiling hydrobromic acid[27] and seem to occur by an intramolecular rearrangement. Thus refluxing in hydrobromic acid a mixture of 1-bromo-pyrrolo [1,2-a] quinoxaline (79) and an excess of the 2,4-dimethyl compound (92) gives the cross over compound (98).

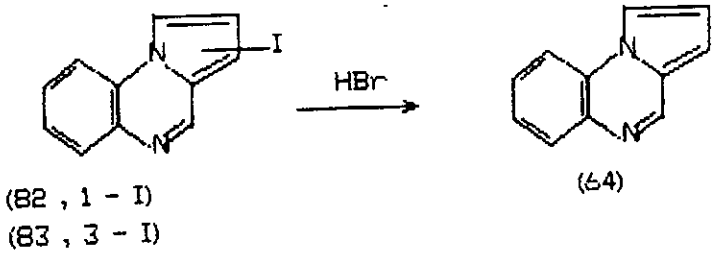


(79) (92) (98)

Also if potassium iodide is added to a solution of the 1-bromo compound in boiling hydrobromic acid, the parent heterocycle is obtained together with a sublimate of iodine, presumably formed by reaction of iodide ions with the released bromonium ions. Direct evidence for the release of Br^+ is provided by the conversion in acid solution of the 1,2,3 - tribromo compound into 2,3 - dibromopyrrolo [1,2-a] quinoxaline.



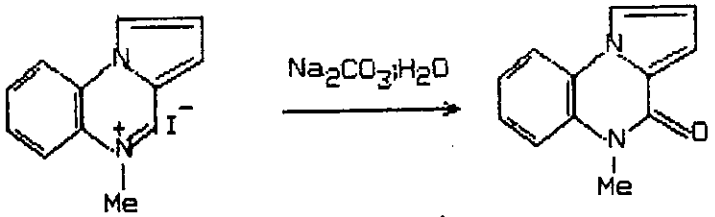
The 1- and 3-iodo derivatives of the ring system are also converted into the parent heterocycle by refluxing hydrobromic acid [27].



(82 , 1 - I)
(83 , 3 - I)

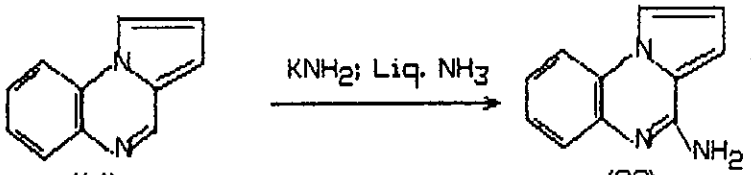
C. Reactions with Nucleophilic Reagents.

Pyrrolo [1,2-a] quinoxaline is quarternized at the 5-nitrogen with methyl iodide. Confirmation that quarternization had taken place at the 5-position was obtained by conversion of the methiodide (65) into the 5-methyl-4-oxo compound (72) on treatment with aqueous sodium carbonate[18].



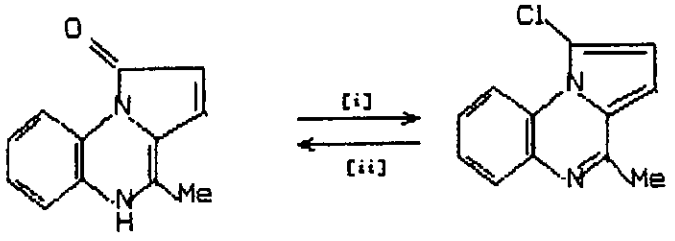
(65) (71)

Attempted Tschitschibabin Reaction i.e treatment with potassium amide in liquid ammonia, on the parent heterocycle afforded the 4-amino derivative in 56% yield[18].



(64) (99)

Phosphoryl chloride reacts with 1,5-dihydro-1-oxo compounds to give the 1- chloro derivatives which are apparently very stable. 1-chloro compounds are however hydrolyzed to 1,5-dihydro-1-oxo derivatives by refluxing with potassium hydroxide in ethylene glycol[26] or dimethyl sulphoxide[23].



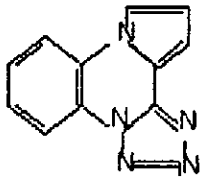
(100) Reagents: (101)

i) $POCl_3$

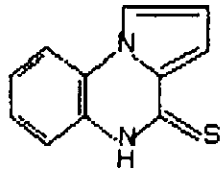
ii) KOH , DMSO

The 4,5-dihydro -4-oxo compounds are readily converted into 4-chloropyrrolo[1,2-a] quinoxalines by treatment with phosphoryl chloride. In contrast to the 1-chloro compounds, the 4-chloro derivatives are readily converted into other 4 - substituted pyrrolo [1,2-a]quinoxalines by nucleophilic substitution. A wide variety of nucleophiles have been used including MeO^- , HS^- , N_3^- , NH_3 [18] , NH_2NH_2 [37] , EtO [-22,37] as well as more complex reagents .

Displacement of the 4-chlorine with sodium azide gave the tetrazolo compound (102) whereas treatment with thiourea gave the 4-thioxo compound (22).



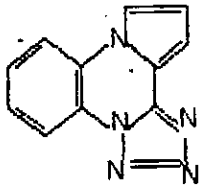
(102)



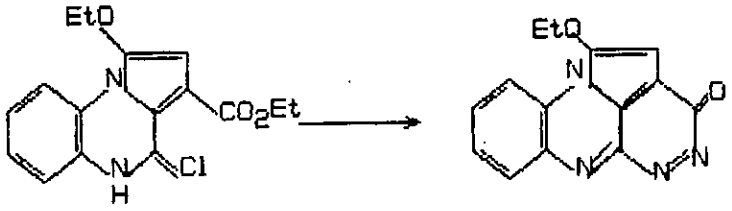
(22)

Kumashiro [37] obtained the triazolo compound (103) on reaction of the corresponding 4-hydrazinopyrrolo[1,2-a]quinoxaline with

formic acid. Reaction of the chloro compound (104) with hydrazine gave the fused pyridazine (105)[22].

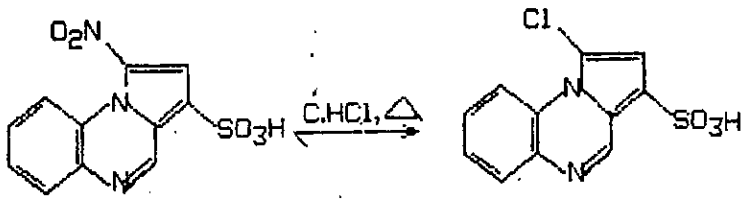


(103)



(104) (105)

Although, 1-nitropyrrolo[1,2-a]quinoxalin-3-sulphonic acid (106) is desulphonated on refluxing in aqueous sulphuric acid, in concentrated hydrochloric acid the sulphonic group is stable, but the nitro group undergoes nucleophilic displacement by chloride. The product of this reaction, 1-chloropyrrolo [1,2-a]quinoxalin-3-sulphonic acid (97) is formed in excellent yield[23].

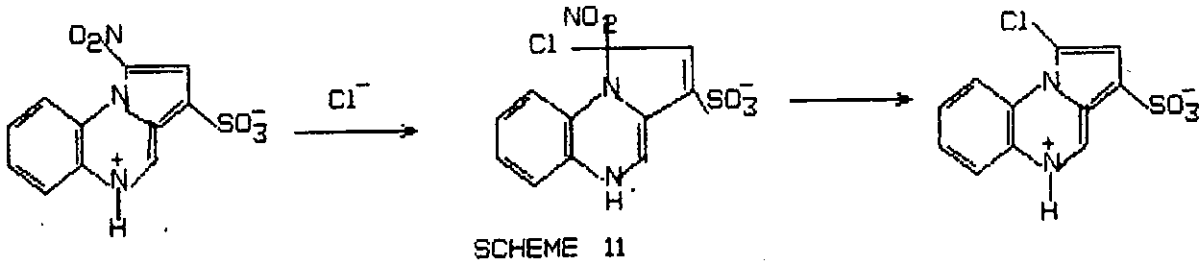


(106) (97)

Lithium chloride in boiling DMF also effects this transformation in good yield. The enhancement of reactivity towards nucleophilic substitution by the 3 - sulphonic acid function is important for this reaction, as 1-nitropyrrolo [1,2 -a] quinoxaline is only slowly converted into the 1-chloro

compound in refluxing hydrochloric acid, and with lithium chloride there is no reaction[23].

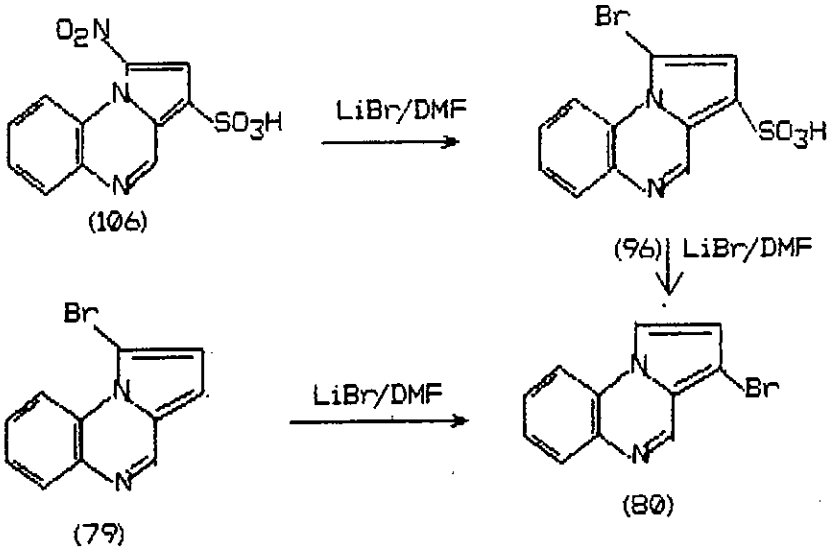
In these reactions the nitrosulphonic acid is presumably reacting as the zwitterion (scheme 11) and it is significant to note that the sodium salt of the acid did not react in a similar manner with lithium chloride.



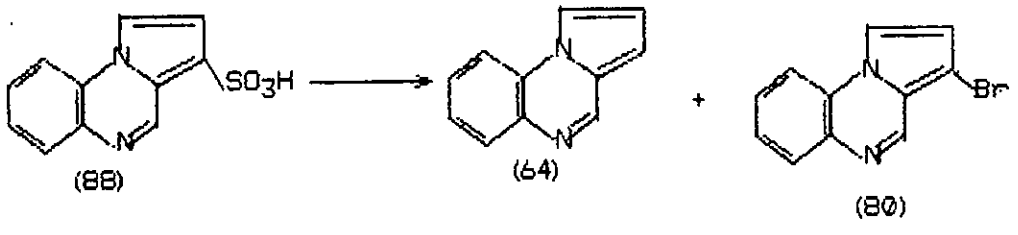
SCHEME 11

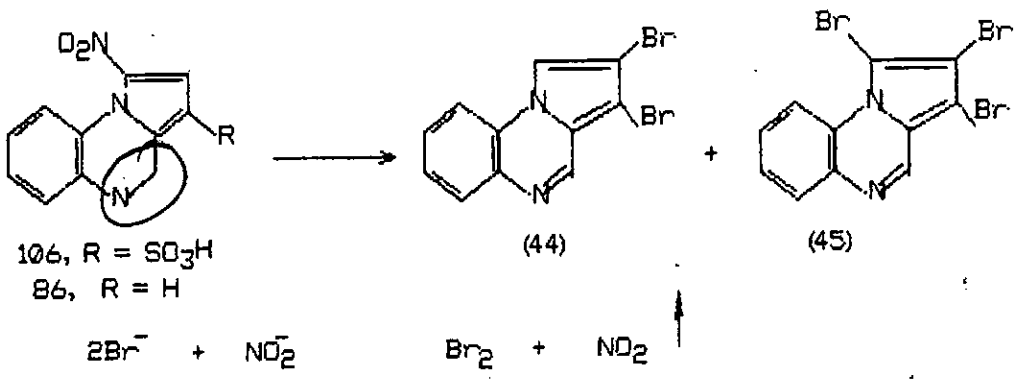
In this case therefore, it is plausible that activation to nucleophilic substitution is attributable to protonation at N-5.

The lability of the bromine in 1 - bromo pyrrolo [1,2-a] quinoxaline (79) makes the reaction of the nitrosulphonic acid (106) in either concentrated hydrobromic acid or in DMF containing lithium bromide, more complex. In the reaction of (106) with lithium bromide, the 1-bromo-3-sulphonic acid(96) may be isolated after 10 mins. However after 1 hr, only the 3-bromo compound (80) is obtained. In independent experiments by the same authors (Cheeseman and Roy), it was found that the intermediate (96) as well as the 1-bromo compound (79) and 1,3 -dibromopyrrolo[1,2-a]quinoxaline form the 3-bromo compound (80) on reaction with lithium bromide in DMF[23].

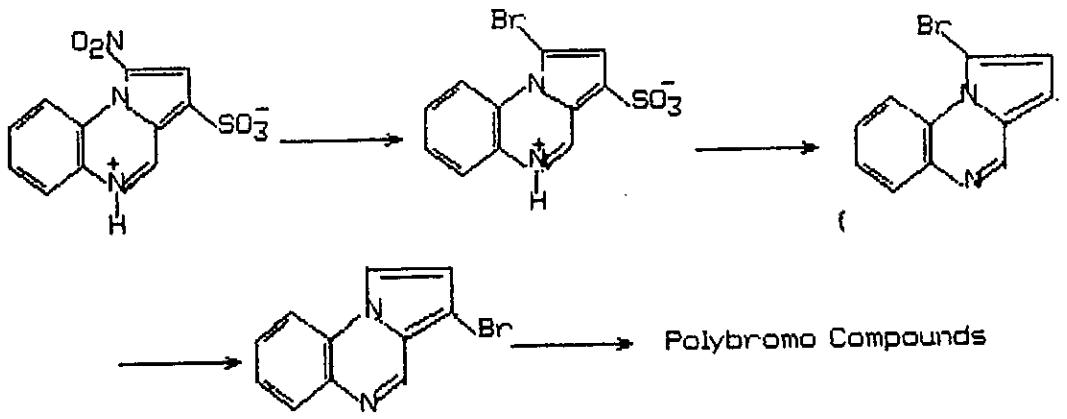


Concentrated hydrobromic acid may be used as well as sulphuric acid to convert the 3-sulphonic acid (88) into the parent heterocycle (64). However, with the former reagent a small amount of the 3-bromo derivative (80) is also obtained. When the reaction is repeated with the 1-nitro-3-sulphonic acid (106), a mixture of the di_and tri brominated products' (44) and (45) is obtained. The same two products are obtained, though in different proportions, by refluxing 1-nitro pyrrolo [1,2-a] quinoxaline in concentrated hydrobromic acid. It seems that a brominating species such as bromine is formed in situ by reaction between hydrobromic acid and the displaced nitrite ions.



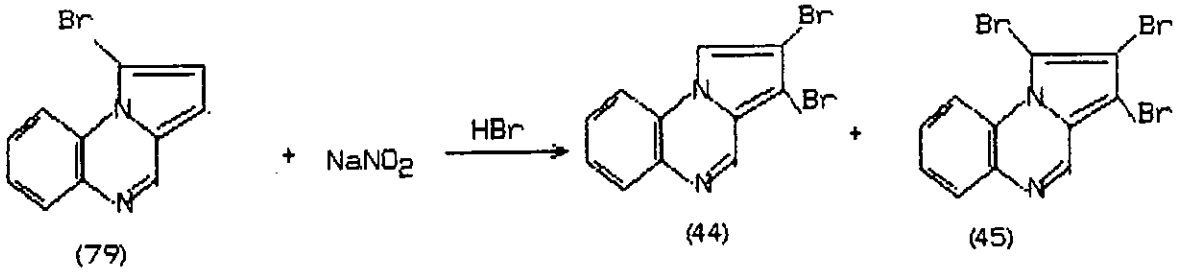


The displacement of the nitro group apparently requires protonation of the attacked species as in scheme 12 as no reaction occurs when 1-nitropyrrolo[1,2-a] quinoxaline is refluxed with lithium bromide in DMF [23].



SCHEME 12

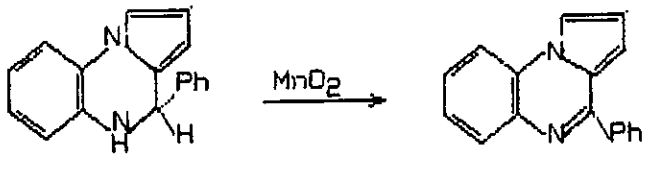
In an attempt to simulate the formation of polybrominated products, an equimolar mixture of 1-bromopyrrolo[1,2-a]quinoxaline and sodium nitrite in concentrated hydrobromic acid was heated under reflux and the expected mixture of 2,3-dibromo and 1,2,3-tribromo quinoxalines was obtained [23].



(79) (44) (45)

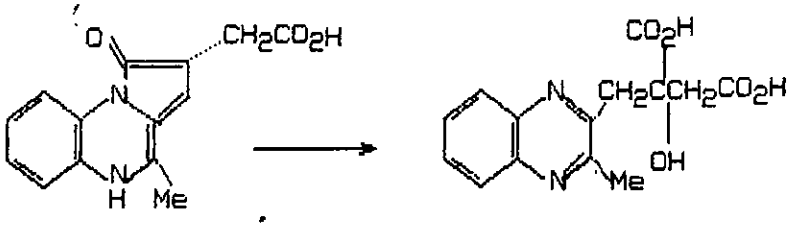
D Oxidation

Little work has been done on the oxidation of pyrrolo [1,2-a]quinoxalines. There are no reports of attempts at N-oxidation; the only N-oxide known was prepared by direct synthesis[14]. 4,5-Dihydro-4-phenylpyrrolo [1,2-a]quinoxaline (107) is readily oxidized to the 4 - phenyl derivative of the aromatic ring system by manganese dioxide[14]. Nickel in refluxing xylene has been used to aromatize a 6,7,8,9-tetrahydro compound[38]. Similarly, palladium on charcoal at 270 °C dehydrogenates 1,2,3,3-a,4,5-hexahydro compounds to give the aromatic ring system[20,21].



(107) (108)

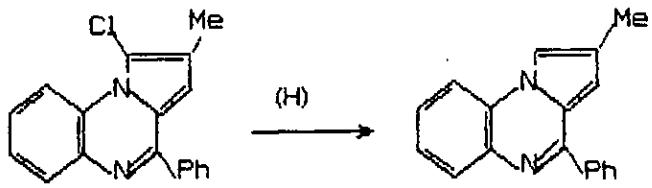
Taylor and Hand[24] obtained the ring opened compound (110) on treatment of the 1-oxo-1,5-dihydro compound (109) with alkaline potassium ferricyanide.



(109) (110)

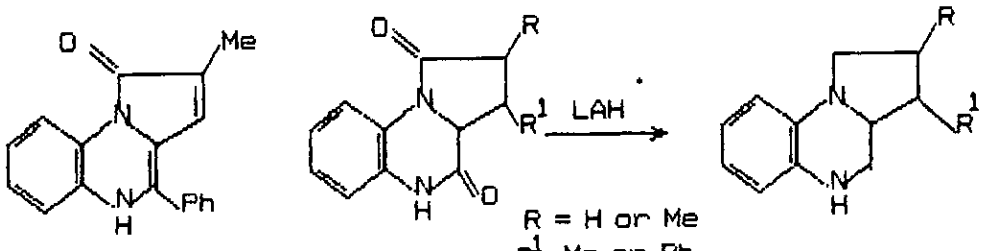
E Reduction

Catalytic hydrogenation of 1-chloropyrrolo [1,2-a] quinoxalines results in removal of the halogen atom. Apparently, the dechlorinated products are themselves reducible, and care must be taken in dechlorinations to allow the absorption of only one mole of hydrogen [12,26].



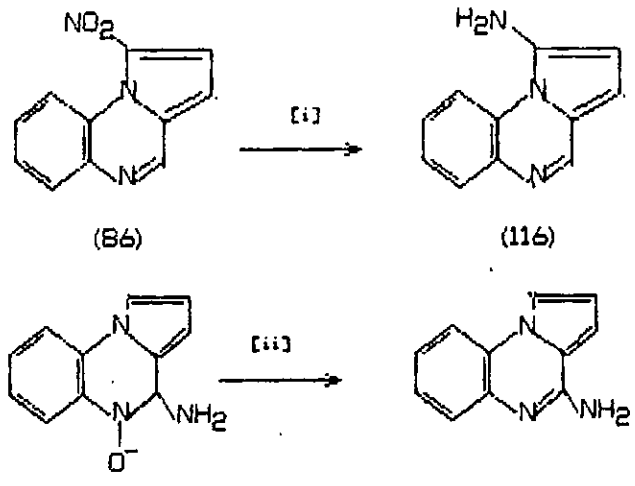
(111) (112)

1,5-Dihydro-1-oxo compounds are resistant to hydrogenation at atmospheric pressure. Reduction of the 1-oxo compound (113) was however achieved over palladium on charcoal at 2000 psi giving an unidentified tetrahydro derivative [26]. The dioxo compounds (114) have been reduced with lithium aluminium hydride to give the hexahydro products (115) [20,21].



(113) (114) (115)

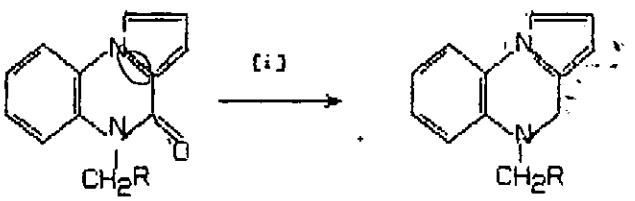
Stannous chloride has been used to reduce 1- nitro and 3-nitropyrrolo[1,2-a]quinoxalines to the corresponding amino compounds [16] and 4-amino pyrrolo [1,2-a] quinoxaline was obtained by Cheeseman and Rafiq on reduction of the 5-oxide (32) with sodium dithionite [14].



Reagents :
(i) $SnCl_2$
(ii) $Na_2S_2O_4$

De Martino et al[39] have described the reduction of the 4,5-bond in pyrrolo[1,2-a] quinoxalines. Heating 4,5-dihydro-4-thioxo derivatives with Raney nickel results in formation of the aromatic, desulphurized compound[37].

Lithium aluminium hydride has more recently been used to remove the 4-oxo group in some hexahydropyrrolo quinoxalines[35].



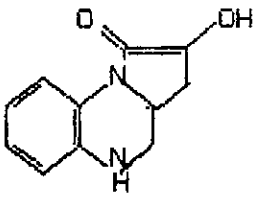
R = 2,6-$(OMe)_2C_6H_3$

Reagent : $LiALH_4$; Dry Et_2O/ THF

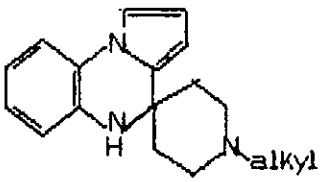
1.2.3 Uses

Although a large number of derivatives of this ring system are known, surprisingly few uses of pyrrolo [1,2-a]

quinoxalines have been described. An extended series of derivatives of the heterocycle have been described as uninteresting as antileukemia agents[39]. The 1- oxo compound (117) has however been patented as having analgesic and hypnotic activity.



(117)



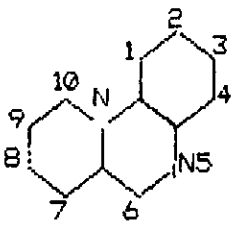
(118)

The spiro derivatives (118) are described in a patent as useful relaxants and tranquilizers[40].

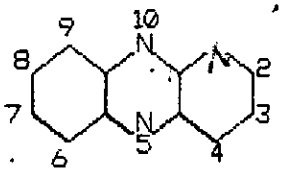
A series of tetrahydropyrrolo [1,2-a]quinoxalines e.g (76), were more recently synthesized and tested for their ability to relax K^+ - depolarized aortic smooth muscle and antihypertensive activity.

1.3.0 PYRIDOQUINOXALINES

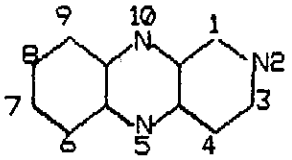
The group of heterocycles known as pyridoquinoxalines consist of a pyridine ring fused to a quinoxaline skeleton. There are four structural types differing in the position of fusion of the two rings. Thus we have pyrido[1,2-a]quinoxalines, pyrido[2,3-b]quinoxalines, pyrido[3,4-b]quinoxalines, and pyrido[1,2,3-de]quinoxalines.



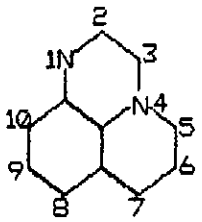
Pyrido (1,2-a) quinoxaline



Pyrido (2,3-b) quinoxaline



Pyrido (3,4-b)quinoxaline



Pyrido (1,2,3-de) quinoxaline

The chemistry and properties of only the pyrido[1,2-a] quinoxalines involved in this study, is reviewed here.

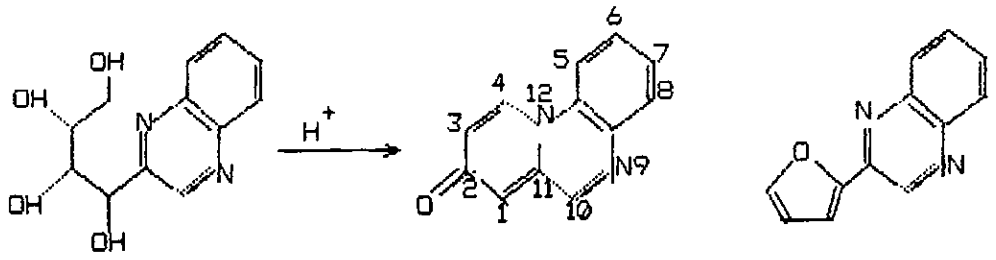
PYRIDO[1,2-A]QUINOXALINES:

1.3.1 Physical properties

There are no reports of physical properties such as acidity constants, HMO calculations etc of pyrido[1,2-a] quinoxalines. The little that is known about the spectroscopic properties is discussed in section 1.4.3

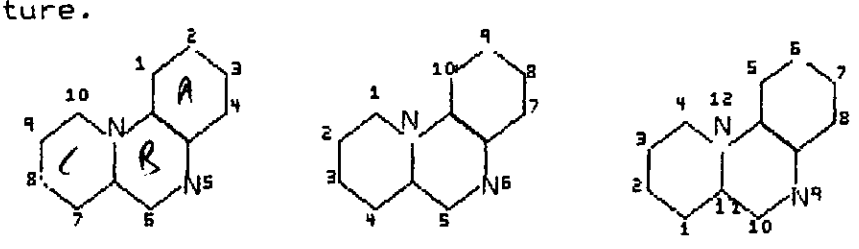
1.3.2 Syntheses of the Ring System:

The earliest claims to the synthesis of this ring system was by Maurer and his co-workers in 1934[41]. It had been found that many hexose sugars condense with o-phenylenediamine to yield quinoxalines such as (119). This reaction was extended by Maurer and his co-workers who found out that under acidic conditions (119) is converted into a new product, to which they assigned the structure (120) (with the numbering shown) and the trivial name glucazidone. later work by Gomez-Sanchez et al[42] showed that Maurer's glucazidones were actually furylquinoxalines (121).



(119) (120) (121)

More recently several authentic representatives of this heterocycle have been synthesized. The approved numbering system (Chem. Abstracts Ring Index) is shown in (122). The nucleus has also been referred to as pyridino[1,2-a]quinoxaline (123). A third numbering system (124) has also been used in early literature.

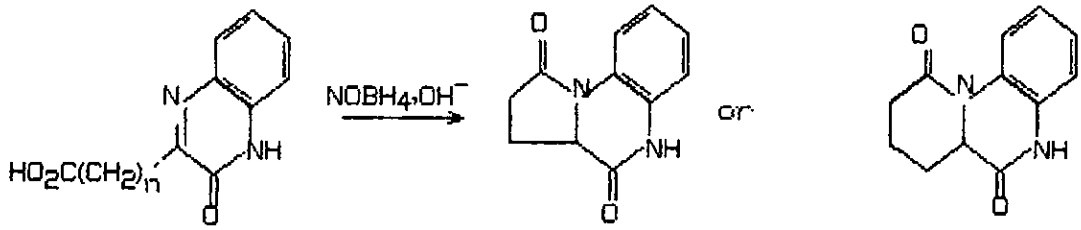


(122) (123) (124)

1.3.2.

A.From Quinoxaline and its Derivatives:

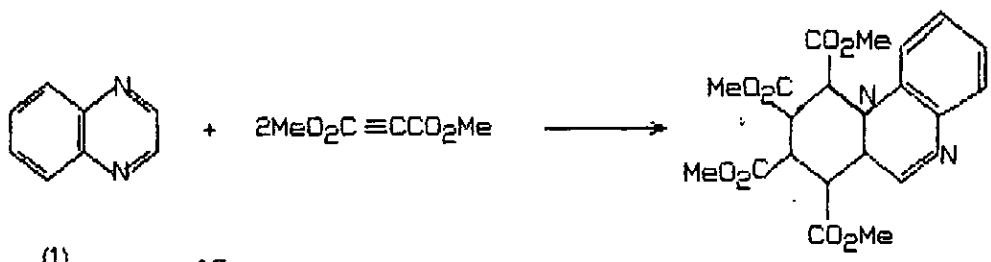
Pyrido[1,2-a] quinoxaline like the analogous pyrrolo [1,2-a] quinoxalines can be prepared from quinoxaline and its derivatives. Thus, the pyrrolo and pyrido ring systems (126) and (127) are obtained by cyclization of the quinoxalinyl alkanoic acids (125) with alkaline sodium borohydride. Both products are obtained in good yields [43].



(125) (126) (127)

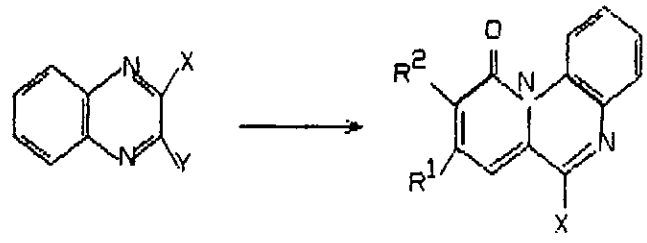
n = 2 or 3

Reactions of quinoxaline itself with two molecular equivalents of dimethyl acetylenedicarboxylate (DMAD) gives the tetrahydrotetramethoxycarbonyl derivatives (128) [44].



(1) (129)

Ames and Brohi [45] synthesized a series of pyrido[1,2-a] quinoxalin-10-one derivatives by condensation of 2-alkynyl quinoxalines (129) with carbanions of diethylmalonate. For example, reaction of 2-phenylethynyl quinoxaline with diethyl malonate in sodium ethoxide gave 9-ethoxycarbonyl-8-phenyl pyrido[1,2-a]quinoxalin-10-one (130, R^1 = Ph, R^2 = CO_2Et, X = H).



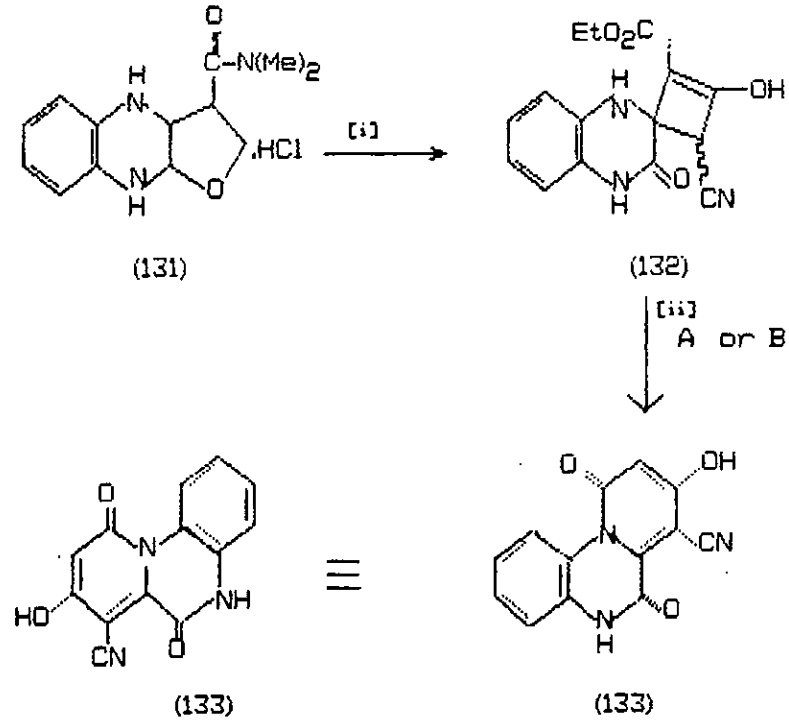
(129) (130)

Y = C ≡CPh R^1 = Ph

X = H, Me, NHMe, NHEt R^2 = CO_2Et, CN, H

Reagents: $CH_2(CO_2Et)_2$ or $AcCH_2Et$ or $NCCH_2CO_2Et$

Kurasawa et al[46] have described the synthesis of the pyridoquinoxaline (133) from the furoquinoxaline (131). Thus, reaction of the furoquinoxaline (131) with ethyl cyanoacetate and sodium ethoxide in ethanol gave the spiroquinoxaline derivative (132) which on treatment with dimethyl formamide followed by acetic acid afforded the pyridoquinoxaline (133). Compound (133) was also obtained by treatment of (132) with guanidine hydrochloride in acetic acid.



(131) (132) (133) (133)

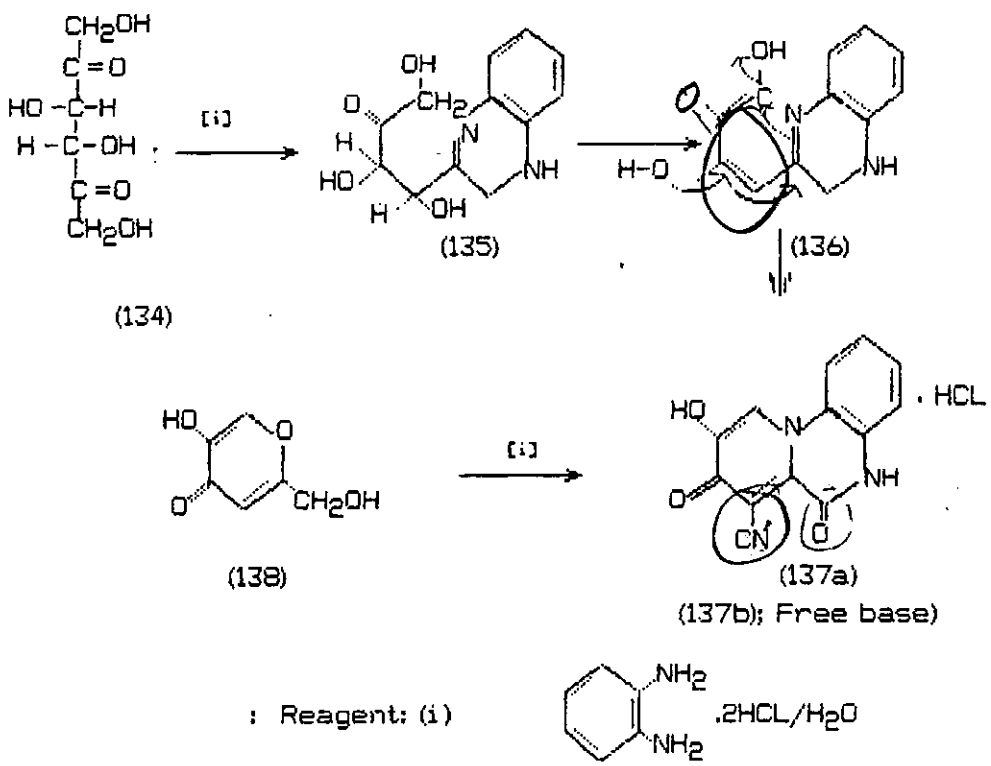
Reagents:

i) $NC\text{-}CH_2Et/EtO^- Na^+$ / EtOH
ii) Method A: 1. DMF, reflux
2. ACOH, reflux
Method B : HN = $C(NH_2)_2$.HCL/ACOH; reflux

B. From o-Phenylenediamines

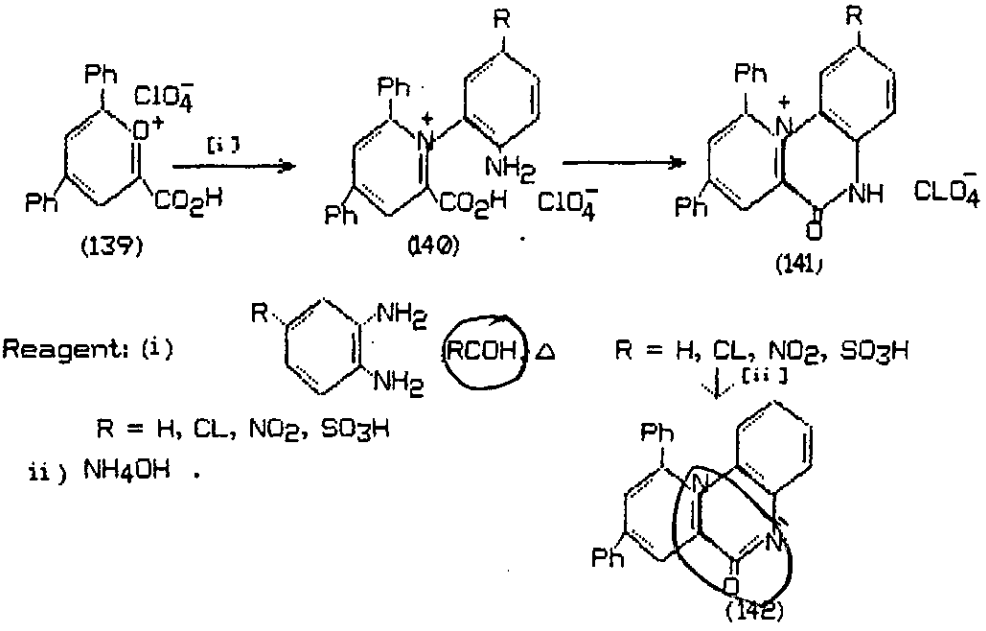
Another route to pyridoquinoxalines is by condensation of o-phenylenediamines with various substrates.

Imada[47] obtained the pyridoquinoxaline derivative (137a) as the reaction product of D-threo-2,5-hexodiulose (134) with o-phenylenediamine dihydrochloride. Compound (134) was also synthesized by condensation of Kojic acid (138) with o-phenylenediamine dihydrochloride in water. The free base (137b) was obtained by neutralization with potassium carbonate. The pathway via (135) and (136) explains the formation of the tricyclic compound from the hexodiulose.

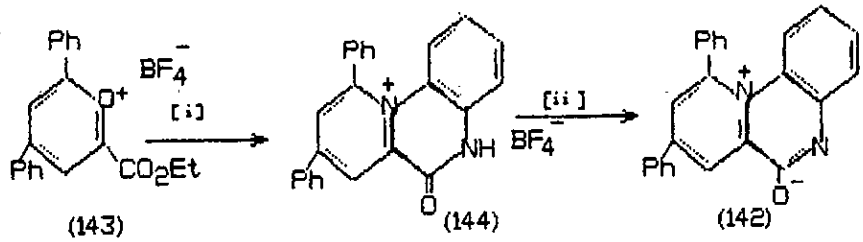


: Reagent: (i)

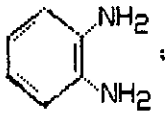
Cyclocondensation of pyrylium perchlorate (139) with derivatives of o-phenylenediamine gives a series of pyridoquinoxalinium salts (141) by way of the N-phenylpyridinium salts (140) [48,49]. Treatment of (141) with ammonium hydroxide gave the zwitterionic compound (142) in quantitative yield.



Similarly, the pyrylium tetrafluoroborate salt (143) reacts with o-phenylenediamine in methanolic solution to give the pyridoquinoxalinium salt (144) whereas in the presence of triethylamine leads to the zwitterionic compound (142) [50].



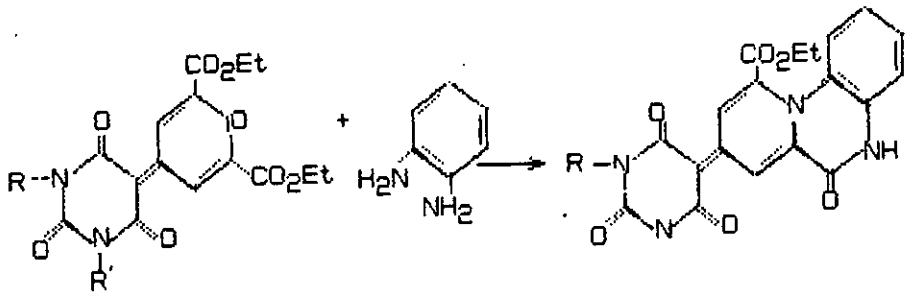
Reagents : i)



; MeOH

ii) TEA

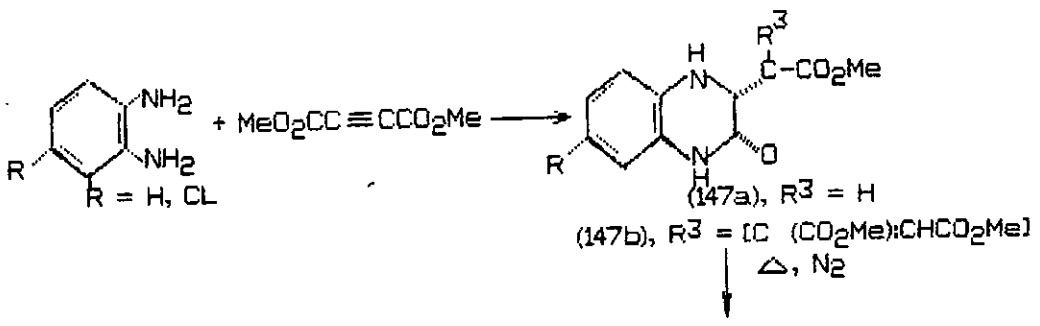
A series of complex derivatives of the ring system (146) have been prepared by reaction of the pyranylidene compounds (145) with o-phenylenediamine[51].



(145)
R, R' = H, Me or Ph

(146)

The pyrido[1,2-a]quinoxaline (148) was obtained by reaction of o-phenylenediamine with dimethyl acetylenedicarboxylate (DMAD). This gave the quinoxaline derivative (147a) which on further treatment with DMAD gave the aconitate ester (147b). Heating of (147b) under nitrogen afforded (148)[52].

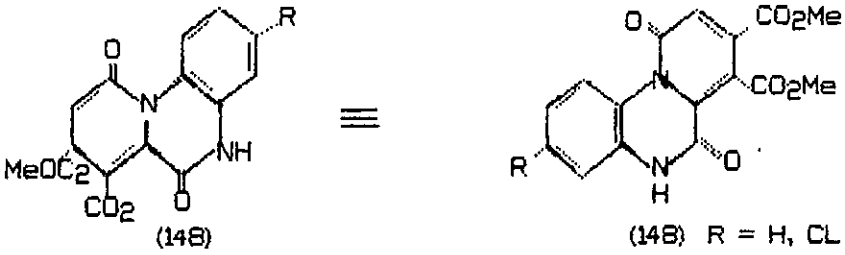


R = H, CL

(147a), R^3 = H

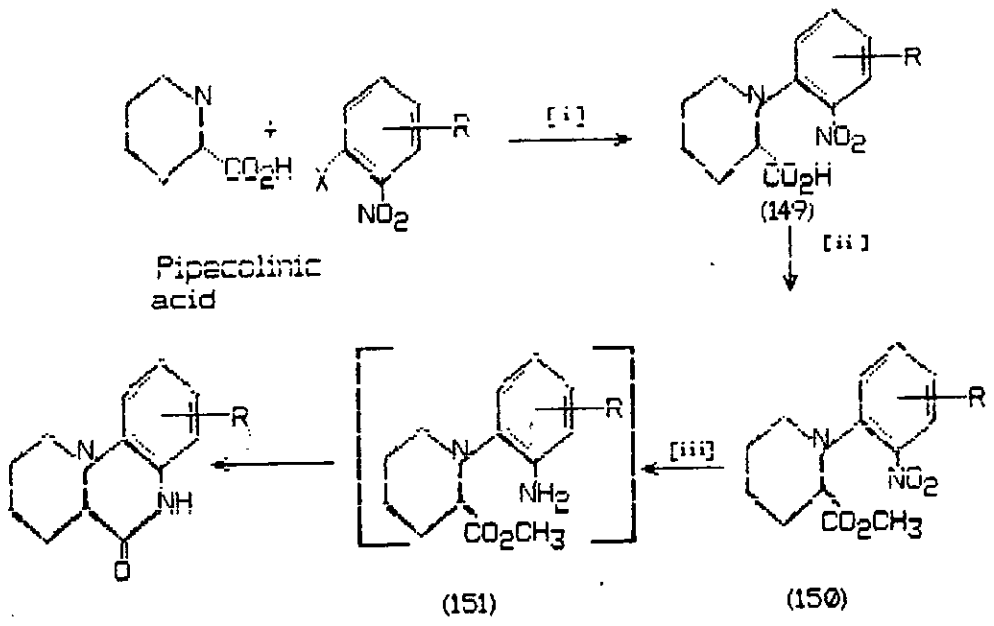
(147b), R^3 = [C (CO$_2$Me):CHCO$_2$Me]

△, N$_2$



C. From Pipecolinic Acid and 1-Halogeno -2-nitrobenzenes or pyridines.

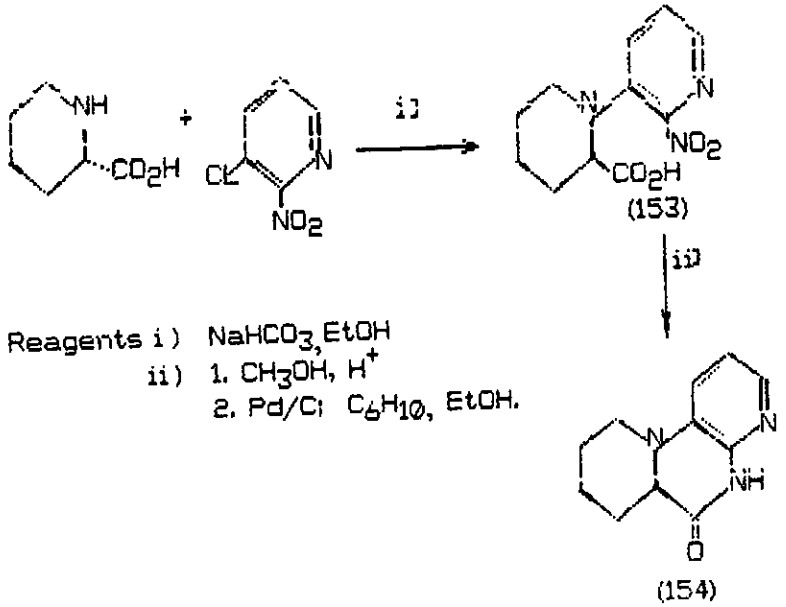
More recently, tricyclic pyrido[1,2-a]quinoxalin-6-one skeletons with a fully reduced ring "C" were obtained by Adegoke and co-workers by selective hydrogen transfer reductive cyclization of N-[2-nitrophenyl]piperidine-2-carboxylic acid methyl esters (150). These esters were prepared by condensation of pipecolinic acid with the appropriate 1-halogeno-2-nitrobenzene in dilute bicarbonate solutions to give the N-[2-nitrophenyl]piperidine -2- carboxylic acid (149), followed by esterification with acidified anhydrous methanol. Catalytic hydrogen transfer reduction of the nitro esters over10% palladium on charcoal in ethanol and cyclohexene gave in each case, the corresponding N-[2-aminophenyl]compounds (151) in situ. Continued reflux in added ethanol caused the latter to cyclize to the heterocyclic quinoxalin-6-ones (152) [33,34].



(152a), R = H
(152b) R = 3-NO_2
(152c) R = 1 - NO_2

Reagents i) $NaHCO_3$/ EtOH.
ii) CH_3OH; $C.H_2SO_4$
iii) Pd/C ; C_6H_{10}, EtOH.

The 4-aza analogue of the ring system was similarly obtained by reaction of 3-chloro -2- nitropyridine with pipecolinic acid followed by esterification and cyclization in the usual manner to give the 4-aza 7,8,9,10-tetrahydropyrido [1,2-a]quinoxalin-6-one (154) [34].

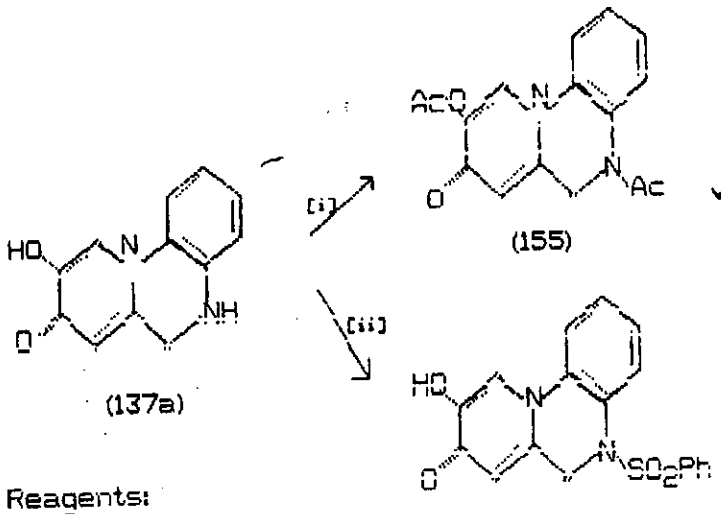


Reagents i) $NaHCO_3$, EtOH
ii) 1. CH_3OH, H^+
2. Pd/C; C_6H_{10}, EtOH.

This reaction demonstrates the utility of this method for the preparation of tricyclic quinoxalines with a fully reduced ring "C". The analogous pyrroloquinoxalines- 1,2,3,3-a-tetrahydropyrrolo[1,2-a]quinoxaline-4-ones were prepared in a similar manner starting with the appropriate cycloamine carboxylic acid (pyrrolidine-2-carboxylic acid). The method has the advantage of avoiding the use of refractory dicarbonyl compounds and is therefore the method of choice in this study.

1.3.3 Chemical Properties

Very little is known about the chemistry of this ring system. The few reactions that have been reported are described here. The structure of the pyridoquinoxaline (137b), prepared by Imada[47], was confirmed by its chemical behaviour. Thus, treatment of (137b) with acetic anhydride and pyridine afforded the corresponding diacetate (155) whereas the monobenzene sulphonate (156) was obtained on reaction of the pyridoquinoxaline with N-benzenesulphonyl chloride[47].

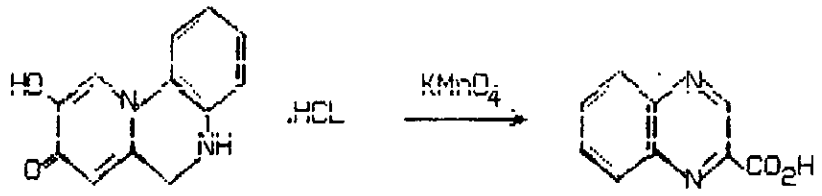


Reagents:

(i) Ac_2O/Pyr

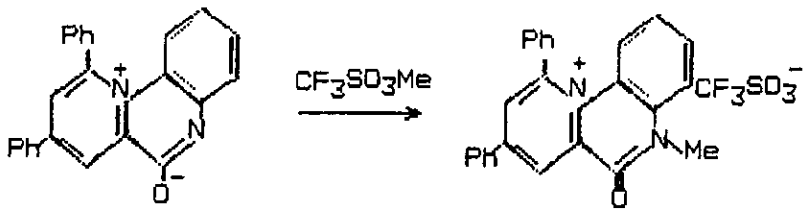
(ii) $PhSO_2Cl/C_6H_6$

Oxidation of the hydrochloride salt of the heterocycle (137a) with potassium permanganate afforded the quinoxaline-2-carboxylic acid (157), identical with an authentic sample[47].



(137a) (157)

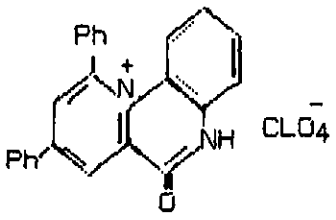
The only other reported reaction of the heterotricycle is the N-methylation of the zwitterion(142) with the powerful methylating agent, methyl trifluoromethane sulphonate[50].



(142) (158)

1.3.4 Uses

Surprisingly, little effort has been made at evaluating the biological properties of pyrido[1,2-a]quinoxalines. However, 8,10-diphenyl-6-oxopyrido [1,2-a] quinoxalinium perchlorate (141) was recently reported, by Chernavaskaya et al[49] to have a minimum bactericidal concentration of 2g per ml against Bacillus Substilis QB.



(141)

1.4.0 SPECTROSCOPIC PROPERTIES OF QUINOXALINES, PYRROLO[1,2-a]QUINOXALINES AND PYRIDO [1,2-a]QUINOXALINES.

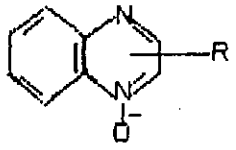
1.4.1 Quinoxalines

A. Ultraviolet, Infrared and Mass Spectra

The electronic spectra of quinoxaline and its 1-chloro, 2-methoxy, and 2-amino derivatives have been calculated by the Pariser-Parr-Pople method. The calculated and the observed spectra agree well [53].

Analysis of the UV spectra of the monoprotonated 2-substituted quinoxalines by Kaganskii and co-workers [54] shows a change in the position of protonation. Thus, 2-methoxyquinoxaline was found to protonate at N-4, and 2-aminoquinoxaline at N-1. However, the site of protonation of 2-chloroquinoxaline was ambiguous.

The UV spectra of substituted quinoxaline N-oxides (159) have been calculated and also observed experimentally [55] and the effect of solvent on the spectra of 2-amino-, 3-amino-, 2-methoxycarbonyl- and 3-ethoxycarbonyl-quinoxaline 1-oxide has been studied. As with pyrazine 1-oxides, the site of protonation was found to be the unoxidized N-4 atom [56].



R = 2- or 3- CL
2- or 3- OMe

(159)

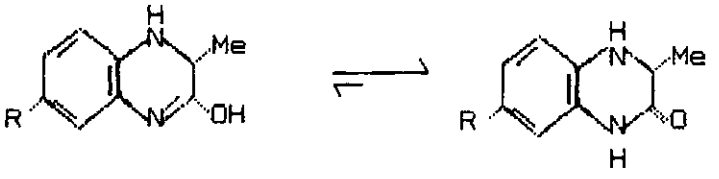
The UV spectrum of 1-methylquinoxalinium iodide in dilute aqueous alkali at pH 10.5 shows absorption maxima at 301 and 340nm, and in methanolic sodium methoxide, maxima at 304 and 344nm [57].

The fluorescence spectra of quinoxalin-2-one and 3-substituted quinoxalin-2-ones have been recorded by Kumashiro and a correlation with the absorption spectra was reported [58,59].

The $\pi - \pi^*$ triplet of quinoxaline has been observed in a single crystal in durene and the fine structure was found to be practically identical to that of the triplet state of naphthalene [60].

The infrared spectra of quinoxaline mono- and di-N-oxides; 3-quinoxalinone-1-oxides, and 1-hydroxyquinoxaline 2,3-diones have been reported by Khan and co-workers; the ring stretching vibrations and C=O and N-O stretching frequencies were assigned [61].

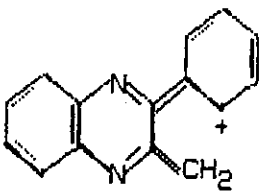
2-Methyl-6-amino and 2-methyl -6-nitro- 1,2,3,4 - tetrahydro-3-quinoxalinones(160) have been examined in the infrared, both in KBr disks and in solution in carbon tetrachloride and carbon disulphide. The predominant tautomer was found to be the lactam form (160b) [62].



(160a) (160b)

R = NH_2, NO_2 .

The mass spectra of a number of quinoxalines have been reported [63-65]. The parent heterocycle shows fragment ions resulting from the loss of one or two molecules of HCN. Similarly in the case of 2-alkyl and 2-arylquinoxalines, M-HCN, and M-RCN ions are observed. A notable feature of the spectrum of 2-methyl-3-phenylquinoxaline is the formation of an intense $(M-1)^+$ ion. This was shown by deuterium labeling to be the result of hydrogen migration from the methyl group to the phenyl ring, followed by expulsion of a hydrogen atom to give the cation (161) [64,65].



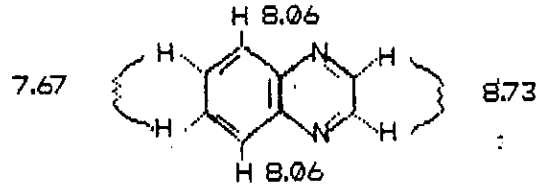
(161)

The M-17 peak with the expected metastable ion was found to be a significant feature of the mass spectra of all substituted mono-N-oxides examined and is assigned to a one - step elimination of the hydroxyl radical . For quinoxaline dioxides the M-16 peak is more important and is due to the preferential loss of an oxygen atom from the molecular ion [63].

B. Nuclear Magnetic Resonance Spectra.

NMR spectroscopy has become an indispensable tool for synthetic chemists, and an additional and very useful technique for examining tautomeric and conformational equilibria. Over recent years, there has been a great deal of work done on the detailed analysis of proton magnetic resonance spectra , and with increasing sophistication of Fourier Transform NMR spectrometers, ^{13}C-NMR spectra are now obtained routinely. In combination with proton NMR, ^{13}C-NMR provides the carbon- hydrogen framework of the molecule.

The ^{1}H-NMR spectrum of quinoxaline has been measured in acetone[66], carbon tetrachloride[66], dimethylsulphoxide[67], dichloromethane[68] and trifluoroacetic acid[68]. The signal for H-2 and H-3 in carbon tetrachloride appears as a low field singlet at 8.73 and the aromatic ring protons appear as an AA'BB' system. The low field half of the AA'BB' multiplet is assigned to the 5- and 8-protons and the high field half to protons 6 and 7. Some broadening of the signals from protons 6 and 7 is attributed to long range coupling with protons 2 and 3. The computed chemical shifts for protons 5 and 8 and 6 and 7 are 8.06 and 7.67 respectively. (Fig 1)



^{1}H- NMR CHEMICAL SHIFTS OF QUINOXALINE IN CCL4.

FIGURE 1

In the more polar solvent, acetone, there is a general small low-field shift. Coupling constant values are, $J_{5,6}$ 8.4Hz; $J_{5,7}$, 1.4Hz; $J_{5,8}$ 0.6Hz and $J_{6,7}$ 6.9Hz. Analysis of the ^{1}H-NMR spectra of a number of 2-,5- and 6-monosubstituted quinoxalines show the following coupling constant variations: $J_{2,3}$ 1.7-1.9Hz, $J_{6,7}$ 5.0-8.3Hz, $J_{7,8}$ 8.4-10.3Hz, $J_{5,7}$ 1.4-2.7Hz, $J_{6,8}$ 0.7-2.9Hz and $J_{5,8}$ 0.3-0.8Hz.

The very small value for $J_{2,3}$ is noteworthy. The chemical shifts of the ring hydrogens in 6-substituted quinoxalines have been correlated with σ- electron charge density, after correlation for N-anisotropic and ring current effects[69].

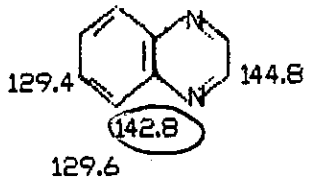
A study of the ^{1}H chemical shifts of 2,3,6-trimethylquinoxaline in carbon tetrachloride, trifluoroacetic acid and fluorosulphonic acid indicated that the carbocyclic ring participates in the positive charge distribution to the extent of about 25-30% in the mono protonated species and 15-20% in the di-protonated quinoxaline[70]. 2,3-Diphenylquinoxaline forms a stable monocation in trifluoroacetic acid, as indicated by the downfield hydrogen signals in this solvent, compared to those in dichloromethane[68]. The NMR spectra of quinoxaline 1-oxide, 1,4-dioxide[71] and the N-oxides of 2- and 3-substituted quinoxalines have been reported[72]. Analysis of the chemical shift values of quinoxaline -2,3-dicaroxylic acids in dimethyl formamide and carbon tetrachloride indicated the presence of an equilibrium between monomeric and dimeric species. In quinoxaline -2,3-dicarboxylic acid 1,4-dioxide no such equilibrium was observed,

owing to the presence of intramolecular hydrogen bonding[73].

Chemical shifts and coupling constants of substituted 1,2,3,4-tetrahydroquinoxalines, computed by Aguilera and co-workers, indicate that the heterocyclic ring in these derivatives is in the half-chair form[74]. The variation of the cis vicinal and geminal couplings resulting from acylation on nitrogen indicates that the acylated derivatives have a slightly flattened half-chair conformation[74].

The H-F spin-spin coupling of 2-substituted-3-trifluoromethylquinoxaline and their mono-and di -N- oxides was examined by Abushanab[75]. The study indicated that J_{H-F} alters as the H-F internuclear distance varies. The effect is best explained by a "through-space" interaction[75].

The ^{13}C chemical shifts for quinoxalines have been explained in terms of inductive and resonance effects of the substituents[76]. Resonances at 144.8 and 142.8 in the spectrum of quinoxaline in deuteriochlorofform are assigned to carbon atoms 2 and 3, and 9 and 10, respectively. Carbons 5 and 8 resonate at 129.6 and carbons 6 and 7 at 129.48 (Fig 2)[76,77].



^{13}C CHEMICAL SHIFTS OF QUINOXALINE

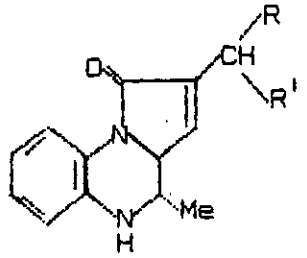
FIGURE 2

1.4.2 Pyrrolo[1,2-a]quinoxalines.

A. Ultraviolet, Infrared and Mass Spectra

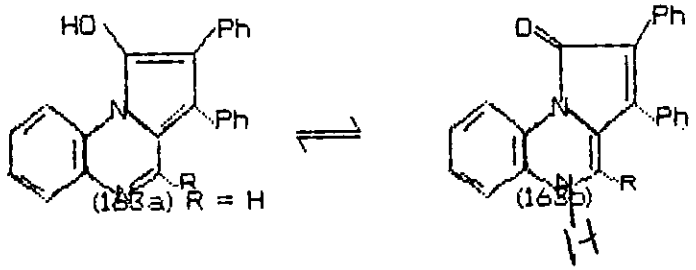
The ultraviolet spectrum of pyrrolo[1,2,-a]quinoxaline in aqueous buffer at pH 6.9 shows three maxima at 224, 247 and 334nm. A well defined change in spectrum occurs on protonation (pH 1.0) [11,12], the long wavelength band moving to 352nm. The ultraviolet spectra of various substituted derivatives were also examined by Cheeseman and Tuck. In all cases, the intensity of the long wavelength absorption increases and a bathochromic shift in the position of maximum from about 10 to 30 m is observed. This is most pronounced in the case of the 1-chloro compounds [12]. The infrared spectra of several salts of pyrrolo[1,2-a]quinoxalines suggest that protonation occurs at the 5-position [12].

Several 1-oxo-1,5 dihydro compounds (162) have had their ultraviolet spectra determined in 96% ethanol by Cheeseman and Tuck [12]. They show three characteristic bands, at ca. 235, 300 and 420-430nm. Apparently certain 2,3 -diphenyl derivatives exist in tautomeric hydroxy form (163a) as evidenced by a prominent OH stretching frequency (no details given) in their infrared spectra [36].



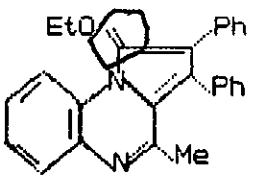
(162)

R = H, CO_2H or CO_2Me; R' = Me or Ph



(163a) R = H (163b)

It has been suggested that the compounds undergo a keto-enol type of tautomerism 163a ⇌ 163b which is influenced by changes in pH. In acetonitrile however, there appears to be marked differences between the ultraviolet spectra of compounds (163) and the 1-ethoxy derivative (70)



(70)

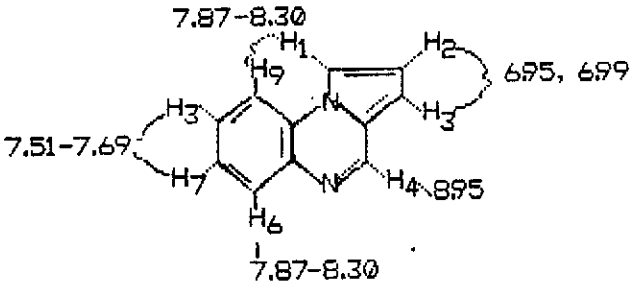
Kumashiro[58] has recorded the fluorescence spectra of certain pyrrolo[1,2-a]quinoxalines and compared them with those of various quinoxaline derivatives.

The mass spectra of the 1,2,3,3-a tetrahydropyrrolo[1,2-a] quinoxalin-4-ones prepared by Adegoke and co-workers shows abundant molecular ions consistent with their polycondensed character. A simple fission in each of the molecules results in the next abundant M-28 peak due to loss of CO. This is followed by the loss of HCN[33] .

B. Nuclear Magnetic Resonance Spectra

The proton-NMR spectra of several pyrrolo[1,2-a]quinoxalines, variously substituted in positions 1-4 have been recorded at 60

MHz, [12,16,27,78] (generally in CCL_4 solution). The PMR spectrum (CCL_4) of the parent heterocycle at 60 MHz shows signals at 6.95 and 6.99 (H-2, and H-3) multiplets in the ranges 7.51-7.69 (H-7, H-8) and 7.87-8.30 (H-1, H-6, H-9) and a singlet at 8.95 (H-4) (Figure 3).



^{1}H-NMR CHEMICAL SHIFTS OF PYRROLO[1,2-a]QUINOXALINE IN CCL_4 AT 60MHZ

FIGURE 3

Substitution at position 1 by halogen (CL,Br or I) resulted in a marked deshielding (0.8-1.0 ppm) of the proton in position 9 [12,27,78]. In 4-methylpyrrolo[1,2-a]quinoxalines unsubstituted at position 1, the shifts of H-6 and H-9 were found to differ by less than 0.25 ppm [12]. In 4-methylpyrrolo [1,2-a]quinoxaline itself, the signals from H-1, H-6 and H-9 were reported by Cheeseman and Tuck [12] as an unresolvable multiplet within the range 7.73-8.10 while those of H-2 and H-3 appeared as a doublet from 6.80-6.87, one of the peaks being slightly split. Protons H-7 and H-8 gave rise to a complex multiplet at 7.30-7.67. With further (alkyl) substitution in position 2, and where H-6 and H-9 could be distinguished from H-7 and H-8, the former two protons were assigned (X- portions of ABX systems) with H-9 to high field of H-6 but without given reason. The

signals for H-7 and H-8 were never distinguished in any of these studies.

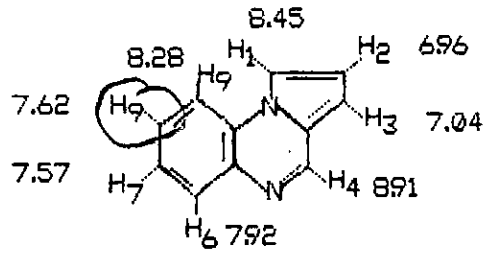
Feeney[79] found that $J_{1,2}$, $J_{1,3}$ and $J_{2,3}$ lie within the ranges 2.7-2.8, 1.1-1.4 and 4.0-4.1 respectively, in selected 4-substituted pyrrolo[,2-a]quinoxalines.

Artico et al[20] have briefly reported the spectrum at 60 MHz of the parent pyrrolo[1,2-a]quinoxaline in CCL_4, H-4 appearing as a singlet at about 8.58, H-2 and H-3 as an intense pair of lines at ca 6.67 and the remaining five protons forming a complex multiplet between 7.00 and 8.00.

However, a detailed analysis of the complex eight-proton p.m.r spectrum of pyrrolo[1,2-a]quinoxaline in $(CD_3)_2SO$ and $CDCL_3$ at 100 MHz has been reported by Heffernan and Irvine[80]. The spectrum of a vacuum degassed solution of pyrrolo[1,2-a] quinoxaline in $(CD_3)_2SO$ at 100 MHz shows proton H-4 appearing at 8.91 as a just resolved doublet of width 1.7Hz. The magnitude of the principal coupling constant (presumably $J_{1,4}$) could not be reliably obtained from this signal, but is evidently greater than 0.6 Hz.

Proton H-1 appears as a multiplet at about 8.45 with splittings of approximately 2.7, 1.3 and 0.8Hz. Irradiation of H-4 removed the 0.8Hz splitting and so the three splittings were identified with $J_{1,2}$, $J_{1,3}$ and $J_{1,4}$. Protons H-7 and H-8 appear as a pair of just overlapping "triplets" centred at about 7.63 and 7.50. the lines of the lower field proton are broader by almost 0.3Hz. Two "doublets" appear centred at about 7.92 and 8.28. The lines of the latter are broad (0.55 Hz) but

without resolution of a small long-range splitting while the former exhibits a small expected coupling between H-4 and H-6. The 7.92 signal is thus assigned to H-6 and the 8.28 signal is due to H-9. Figure 4 shows the full assignment of the signals.



^{1}H - NMR CHEMICAL SHIFTS FOR PYRROLO[1,2-A]QUINOXALINE IN $(CD_3)_2$ SO AT 100 MHz

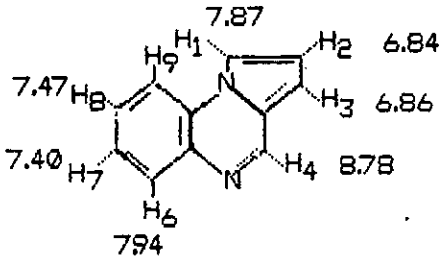
FIGURE 4.

In the spectrum of a vacuum-degassed 5% v/v solution of pyrrolo[1,2-a]quinoxaline in $CDCl_3$ proton H-4 appears at 8.80 as a signal 1.8Hz broad just split by approximately 0.6 Hz. Protons H-2 and H-3 occur again as the AB portion of an ABX system. The shifts of the two protons are however considerably closer than in $(CD_3)_2SO$ solution.

The signals from H-7 and H-8 lie between 7.30 and 7.60. The lines at the low-field and of this portion of the spectrum are roughly twice as broad (ca 0.6 Hz) as those of their high-field counterparts. This suggests that H-8, coupling to the greater extent with H-4 and presumably with the protons of the five membered ring, is again low-field of H-7.

The signals from H-1, H-6 and H-9 appear as a complex multiplet in the range 7.70-8.00. Confirmation that H-1 is situated very close to half way between the other two nuclei was obtained by irradiation of H-2 and H-3, resulting in an

intensity increase at the centre of the three - proton multiplet i.e a nuclear Overhauser enhancement was observed. H-6, appearing at 7.94 is now to low field of H-9 (7.80) (cf, the opposite case in $(CD_3)_2SO$ solution. The full assignment of signals is shown in figure 5.

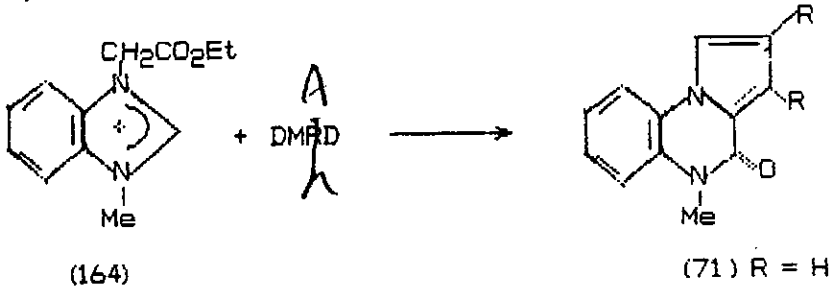


^1H - NMR CHEMICAL SHIFTS OF PYRROLO[1,2-a]QUINOXALINE IN $CDCl_3$ AT 100 MHz

FIGURE 5

Spectra of pyrrolo[1,2-a]quinoxaline in carbon tetrachloride, acetone, acetic acid, trifluoroacetic acid and benzene were also recorded by the same authors [80] although detailed analyses were not attempted.

^{13}C-NMR of pyrrolo[1,2-a]quinoxalines has received less attention; there are no attempts at detailed analysis. However, an application of ^{13}C-NMR in this field is in the establishment of the product of reaction of the benzimidazolium salt (164) with DMAD. Comparison of the ^{13}C-NMR spectrum with that of the authentic pyrrolo[1,2-a]quinoxaline (71) confirmed the product to be 2,3-dimethoxycarbonyl-5-methylpyrrolo[1,2-a]quinoxalin-4-one (165).

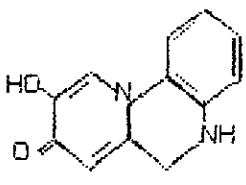


(164)

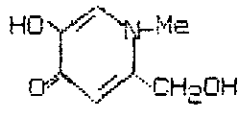
(71) R = H
(165) R = CO_2Me .

1.4.3 Pyrido[1,2-a]quinoxalines

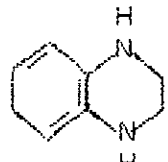
Unlike the quinoxalines and pyrrolo[1,2-a]quinoxalines, no definite attempts have been made at detailed spectroscopic analysis of pyrido[1,2-a]quinoxalines. The structures of pyrido [1,2-a]quinoxalines prepared by several authors, have however been deduced from spectroscopic evidence. Thus, the structure of the pyrido[1,2-a]quinoxaline (137) prepared by Imada[47], was deduced from the following spectroscopic evidence. The U.V spectrum of 137b is closely similar to spectra of authentic 1-methyl-2-(hydroxymethyl)-5-hydroxy-4-pyridone (166) [λ max nm ($\log \varepsilon$): 281 (4.09) and authentic 1,2,3,4 tetrahydroquinoxaline (7)[λ max nm ($\log \varepsilon$); 219(4.45), 254(3.63) and 310(3.54). The i.r.spectrum of (137b) shows a carbonyl vibration at 1640 cm attributable to the C=O group of a γ -pyridone.



(137a) Hydrochloride
(137b) Free base.



(166)

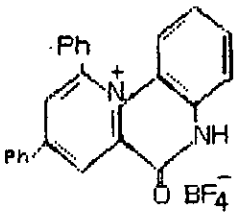


(7)

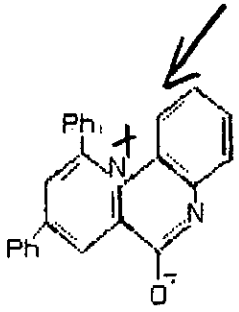
All of these data are consistent with the structure assigned to (137b).

Molina et al obtained the zwitterionic compound (142) on

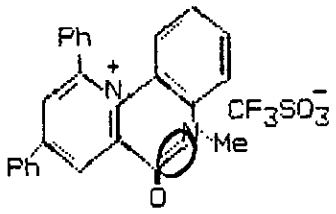
reaction of 2-ethoxycarbonyl-4,6-diphenylpyrylium tetrafluoroborate with o-phenylenediamine in the presence of triethylamine. In the absence of TEA, the tetrafluoroborate salt (144) is obtained. Reaction of (144) with methyl trifluoromethanesulphonate gave the N-methyl salt (158).



(144)



(142)

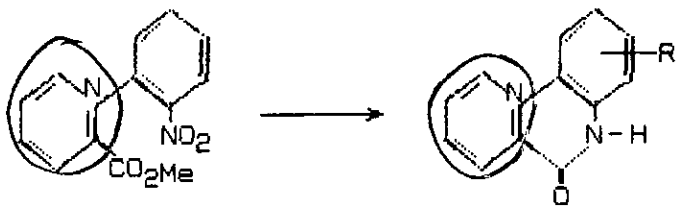


(158)

These structures were deduced from the following spectoscopic evidence. The IR spectra of compounds(144) and (158) show an absorption at 1710 cm^{-1} attributed to the C=O stretching vibration which is absent in(142).

The proton NMR spectrum of (158) shows amongst others, a signal as singlet at 3.30 due to the $N-CH_3$ group. Mass spectra of compounds (144) and (158) show the fragment ($M^+ - HX$) whereas compound (144) shows the expected molecular ion peak.

The structures of the pyrido[1,2-a]quinoxalin-6-ones obtained by Adegoke et al[33,34] were assigned on the basis of elemental analysis and spectroscopic data. The tricyclic quinoxalinones were obtained by reductive cyclization of the methyl esters of N-[2'-nitrophenyl]piperidine-2-carboxylic acids(150).



(150) (152)

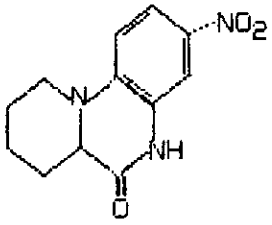
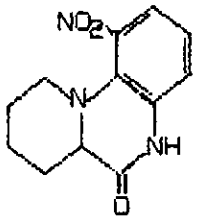
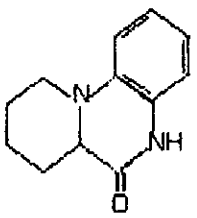
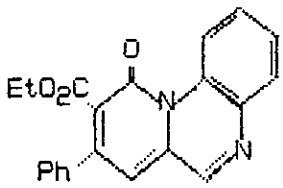
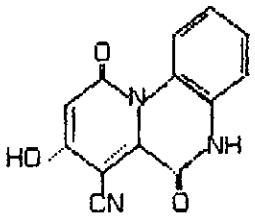
R = H,3-NO_2, 1- NO_2

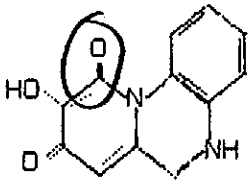
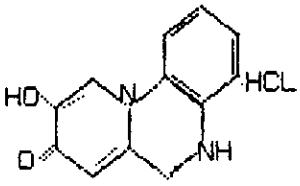
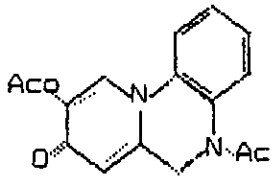
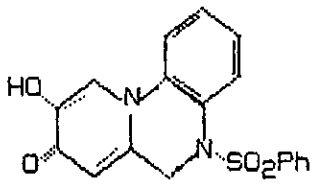
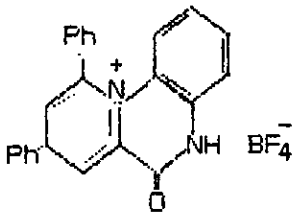
A shift of the carbonyl absorption from 1740 cm^{-1} in (150) to 1680 cm^{-1} in (152) was attributed to the formation of the lactam after cyclization. The NMR spectra substantiated this by a corresponding collapse of the -OMe singlet at ca 3.2 and a change in the positions of the aromatic H mutiplets from between 7.4 and 8.0 to between 6.0 and 7.0, The mass spectra of each of the quinoxalines showed abundant molecular ions consistent with their polycondensed character. A simple fission in each of the molecules resulted in the next abundant M-28 peak, due to loss of CO. This is followed by loss of HCN.

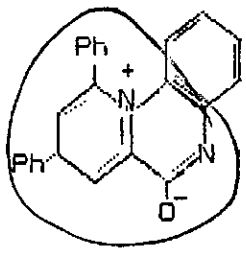
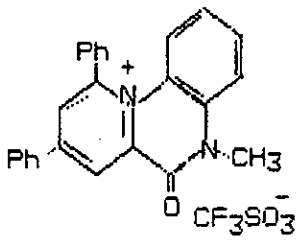
The IR and NMR spectroscopic data available on pyrido[1,2-a]quinoxalines prepared by several authors are given in Table 1.

TABLE 1

SPECTROSCOPIC PROPERTIES OF PYRIDO[1,2-a]QUINOXALINES

STRUCTURE NO	COMPOUND	Vmax cm^{-1}	^1H - NMR,	REF.
152a		3450 (N-H) 1680 (Lactam C=O) 1530 (- NO_2)	1.6 (m,4H, piperidine) 2.4 (m,2H) 3.6 (m,2H) 4.2 (m,1 H) 6.9 - 7.4 (aromatic 3H)	33
152b		3450 (N-H) 1670 (Lactam C=O) 1530 (-NO_2)	1.6 (m,4H, piperidine) 2.4 (m,2H) 4.2 (m, 1H) 6.0 - 7.0 (aromatic 3H)	33
152c		3400 (N-H) 1675 (Lactam C=O).	19 (6H, m, piperidine) 39 (2H, m) 4.0 (1H, m) 7.0 (4H, aromatic, s, broad at base) 9.08 (1H, broad, exchangeable with D_2O).	34
130		1720 (CO_2Et) 1655 (pyridone C = O)	1.10 (3H,t, J, 7Hz, $\underline{CH_2}$ CH_3) 6.82 (1H,S, H-7) 7.28 - 8.05 (9H, m aromatic H) 8.60 (1H,S, H-6)	45
133		2255, 1695, 1665.	6.90 - 7.37 (m, aromatic 3H + H-9) 9.18 (ddd, 1H, J; 1.2Hz, 1.2H_2 & 7.8 Hz, H-1) 9.77 (1H, br,S,-OH). 11.90 (1H, S, N-H)	46

STRUCTURE NO	COMPOUND	Vmax cm^{-1}	^1H - NMR,	REF.
137b		3060, 1640, 1600.	4.90, (2H, S, H-6) 6.38 (1H,S,H-7) 7.20-8.32 (Aromatic 4H,m). 8.67 (1H,S, H-10) 5.60 (1H,S, exchangeable with D_2O, N-H) 3.42 (1H,S, exchangeable with D_2O, O-H)	47
137a		3330 (OH or N-H), 1640 (C = O).	5.08 (2H, S, H-6) 6.70 (1H,S,H-7) 7.40 - 8.30 (Aromatic 4H, m) 9.02(1H, S, H-10)	47
155		1765 & 1735 (C = O)	5.62 (2H,S,H-6) 6.97 (1H,S,H-7) 7.40 - 8.20 (Aromatic 4H,m) 8.79 (1H,S,H-10) 2.10 (3H,S, $OCOCH_3$) 2.39 (3H,S, = $NCOCH_3$)	47
156		1618 (C=O) 1320, 1150 (SO_2).	——	47.
144		1710, 1620, 1590	9.40 (1H,S) 8.90 (1H, d, J = 2Hz) 8.70 (1H, d, J = 2Hz) 7.2 - 8.3 (14H, m)	50

STRUCTURE NO	COMPOUND	Vmax cm^{-1}	^1H - NMR,δ	REF.
142		1675, 1620, 1590	9.10 (1H,d,J=2Hz) 8.60 (1H, d, J = 2Hz) 7.2-8.3 (14 H, m)	50
158		1710, 1620, 1540	8.80 (1H, d, J=2Hz) 8.60 (1H, d,J=2Hz) 7.3 - 8.4 (14H, m) 3.30 (3H, S)	50

1.5.0 SCOPE OF PRESENT STUDY:

The synthetic route to 7,8,9,10-tetrahydropyrido[1,2-a] quinoxalin-6-one was reported by Adegoke and Alo[34] in 1983 but its properties had not been investigated at the onset of this work. The object of this research was therefore threefold:

1. A study of the electrophilic aromatic substitution reactions of the hexahydropyridoquinoxaline. The result was expected to provide an insight into the chemistry of this class of heterocycles.
2. A detailed study of the ^{1}H- and ^{13}C-NMR spectra of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one and variously substituted derivatives. This would provide the much needed information on spectroscopic identification of this group of heterocycles.
3. Synthesis of diverse derivatives for biological screening e.g by N-alkylation reactions, nucleophilic substitution of the carbonyl oxygen etc.

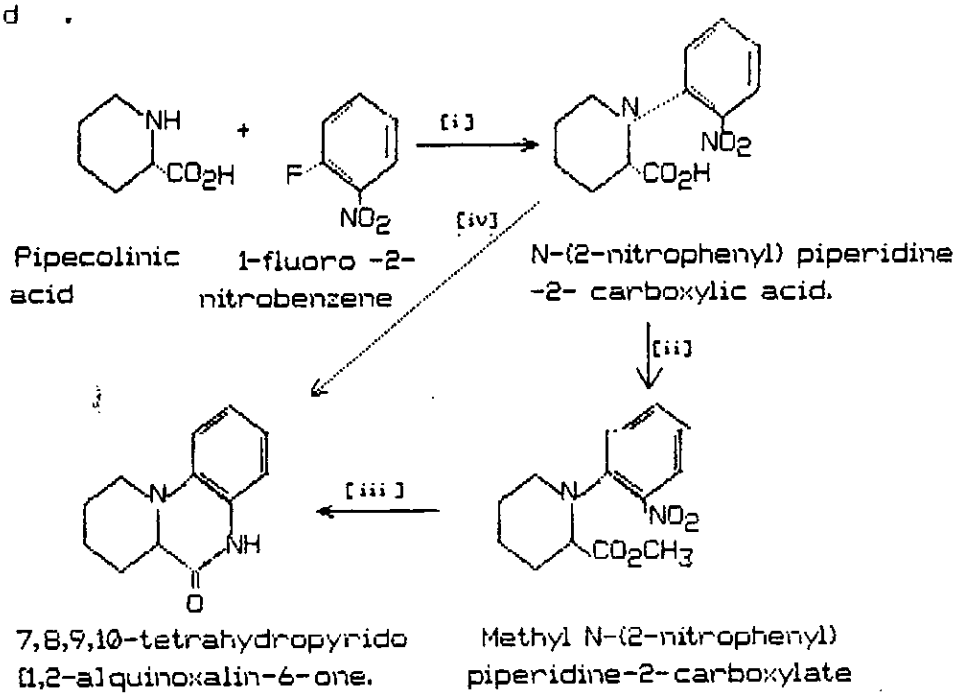
The overall result of the investigation was expected not only to provide more soluble derivatives,thus overcoming the insolubility problems associated with these tricyclic quinoxalinones in the biological testing regimen, but also to obtain novel derivatives with possible increased activity, either in the pharmaceutical or agrochemical industry.

The first step in this study was the preparation of the title compound: 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one. The synthetic route is outlined in scheme 13. Condensation

of 1-fluoro-2-nitrobenzene with pipecolinic acid in dilute bicarbonate solutions followed by methylation of the adduct and finally treatment of the resulting nitroester with 10% palladium on carbon in refluxing ethanol and cyclohexene gave the parent tricyclic quinoxalinone in good yields[34].

In the course of this study however, Abou-Gharbia et al[35] published the preparation of analogous pyrrolo[1,2-a]quinoxalin-4-ones by a similar route but their condensation reactions were carried out in dimethylsulphoxide with triethylamine as base. The resulting nitro acids were reductively cyclized via sodium dithionite or iron in glacial acetic acid. It was therefore worthwhile attempting to prepare the title compound by this modified route, as outlined in scheme 13 below, which has the advantage of precluding the formation of the nitroester precursor. It also avoids the use of the expensive palladium reagent.

Another reagent which has been used successfully for such reductive cyclizations is tin in concentrated hydrochloric acid[53].



Reagents. i)- $NaHCO_3$, EtOH or TEA, DMSO
ii) CH_3OH; H_2SO_4
iii) Pd/C; C_6H_{10}, EtOH
iv) $Na_2S_2O_4$, OH^-
or
Fe, CH_3COOH
or
Sn, HCL

SCHEME 13

The two methods of condensation and four methods of cyclization were to be examined with a view to developing the best method of synthesis of the compound with particular reference to

a) yields and purity of product

b) relative ease of reaction and work-up procedure

c) reaction economy vis-a-vis cost of chemicals.

In the second stage of the study, the reactions of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one with electrophilic reagents were to be examined. Bromination, nitration and sulphonation reactions were to be carried out under various conditions. The rationale for the selection of reaction conditions was based on the premise that the chemistry of the aromatic ring would be dominated by the interaction between the amine and amide nitrogen atoms. If electrophilic aromatic substitution is considered under mildly acidic or neutral conditions, the amine nitrogen will not be fully protonated and hence electrophilic substitution should take place predominantly at the 3-position. Thus, bromination for example was to be examined under various acidity conditions ranging from strong acid conditions such as with bromine in boiling hydrobromic

acid to weak acid conditions such as with bromine in acetic acid. The bromination reaction was also to be carried out with N-bromosuccinimide in dilute sulphuric acid. Similarly, nitration and sulphonation reactions were to be attempted under various acidity conditions.

The products of these reactions were to be analysed by new NMR techniques to determine the position of substitution in each case.

Nuclear Overhauser enhancement studies were to be carried out to determine the sites of electrophilic aromatic substitution and further corroborate earlier NMR assignments in the spectra of products. As classical methods for the orientation of groups which have been introduced by substitution on to an aromatic or heteroaromatic ring have often involved lengthy unambiguous synthesis, emphasis is shifting to more recent NMR spectroscopic methods which involve chemical shift and coupling constant arguments. The Nuclear Overhauser Effect provides a valuable method for interrelating contiguous protons. It has considerable potential in heteroaromatic chemistry where a cyclic N-H can be identified especially as such an -N-H will often exchange relatively slowly on an NMR time scale in solvents such as dimethylsulphoxide. The -N-H signal could therefore be utilized as an n.O.e. marker or reference probe in the molecule in order to determine the sites of electrophilic substitution in the heterocycle. It was necessary therefore, to synthesize variously substituted derivatives of the title

compound using interalia, 2,4-dinitrofluorobenzene (Sanger's reagent), 2,4-difluoronitrobenzene and 4-fluoro-3-nitrotoluene. Their ^{1}H-NMR spectra were to be examined and using the -N-H signal as a Nuclear Overhauser Enhancement probe, the value of this method for the determination of the substitution pattern in heterocycles in general and this series of compounds in particular could be determined.

One of the problems encountered in the study of electrophilic aromatic substitution of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one, was the insolubility of the compound itself and the new derivatives, in most organic solvents, which prevents purification of reaction products by the usual methods of column chromatography or preparative t.l.c This insolubility problem may be attributed partly to intermolecular hydrogen bonding and could therefore be solved by obtaining the N-alkyl derivatives.

N-alkylation of the heterotricycle was initially attempted by the conventional methods of reaction with methyl iodide or dimethylsulphate in the presence of a strong base (NaH or NaOMe). The pyridoquinoxaline proved difficult to alkylate under these conditions and so our attention was directed towards phase transfer catalysis (P.T.C) as an alternative method.

P.T.C is one of the most important recent methodological developments in organic synthesis. It is rapidly gaining popularity and a wide range of synthetic applications have

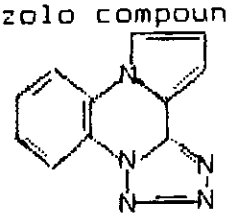
been reported[82]. In general, the term P.T.C describes the methodology for reactions of anionic species (inorganic, organic and complex organometallic anions) based on the continuous formation of lipophilic ion pairs with lipophilic cations. Such ion pairs are soluble in nonpolar solvents. This approach becomes particularly advantageous when reactions are carried out in systems containing two immiscible phases: the organic phase where all reations take place, and the inorganic phase (aqueous or solid anhydrous), which is the source of the anions or the base for their generation. The general principles of this technique and the concept behind it have been fully described[82,93]

A general problem in alkylation of nitrogen heterocycles is the regiochemistry of the corresponding anions. The ratio of N- versus C-alkylation usually depends on reaction conditions. In the review by Gallo et al[82], it was shown, from results published so far, that P.T.C strongly favours N-alkylation. For example during N-alkylation of pyrrole under conventional alkaline conditions, C-alkylation also occurs at position 2 and 3. An increase in the ratio of N- versus C- alkylation of pyrrole and of other heterocyclic compounds bearing an acidic atom has however been observed by several workers[82].

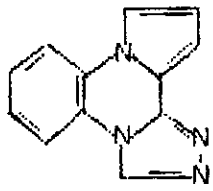
N-alkylation was therefore to be attempted under P.T.C conditions in order to determine the possible synthetic application of this method for the N-alkylation of this novel heterocycle and also to obtain more soluble N-alkyl derivatives

for biological screening.

The 4-chloro derivatives of the analogous pyrrolo[1,2-a]quinoxaline, obtained by reaction of 4,5-dihydro-4-oxo compounds with phosphoryl chloride are readily converted into other 4-subsituted derivatives by nucleophilic substitution with a wide range of nitrogen, oxygen and sulphur containing nucleophiles [18,19,22,37]. Tetracyclic systems such as the tetrazolo and triazolo compounds (102 and 103) have been prepared.



(102)



(103)

Successful synthesis of the 6-chloro derivative from the title compound would therefore be the first step in the synthesis of such interesting derivatives.

The increasing importance of NMR spectroscopy to synthetic chemistry and the paucity of information on spectroscopic analysis of pyrido[1,2-a]quinoxalines prompted a study of the ^{1}H and ^{13}C-NMR of the title compound and variously substituted derivatives. Such spectral studies are important as they provide information on the stereochemistry of these novel compounds and also aid in the characterization of these heterotricycles.

Prior to this work, there had been no previous report on ^{13}C-NMR of such compounds.

As mentioned earlier, very little effort has been made at

biological evaluation of pyrido[1,2-a]quinoxalines. In an attempt to rectify this, several derivatives of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one were sent for biological screening at Shell Research Centre, Sittingbourne, Kent, U.K. They were screened for antibacterial and anti fungal activity in plants and also for possible use as plant growth regulators.

2.0 RESULTS AND DISCUSSION

2.1.0 PREPARATION OF COMPOUNDS

The first step in this study was an investigation carried out to determine the optimum method of preparation of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one starting from 1-fluoro-2-nitrobenzene and piperidine-2-carboxylic acid.

As indicated in the introduction, the unsubstituted heterocycle and its 1- and 3- nitro derivatives were originally prepared [33,34] by selective hydrogen transfer reductive cyclization of the methyl esters of the appropriately substituted N-[2'-nitrophenyl]piperidine-2-carboxylic acid using palladium catalyst and cyclohexene. This method of synthesis was shown to provide a facile route to the tetrahydroquinoxalinones and was therefore the initial method of choice in this study.

The original synthetic procedure consists essentially of two steps; (1) a condensation reaction in which pipecolinic acid is reacted with the appropriately substituted 1-halogeno-2-nitrobenzene in the presence of a base to give N-[2'-nitrophenyl]piperidine-2-carboxylic acid.

(2) a cyclization step in which the methyl ester of the nitro-acid is reductively cyclized using palladium catalyst and cyclohexene.

The catalyst, palladium on carbon is however an expensive reagent and was not available at the onset of this work. This prompted a re-examination of the cyclization step with a view to obtaining a substitute, cheaper reagent.

Adegoke and Alo [83] had reported the use of tin and concen-

trated hydrochloric acid as the reagent for cyclization in the synthesis of 3,3-a dihydrothiazolo[3,4-b]quinoxalin-4-ones. The initial preparations of the tetrahydropyridoquinoxalinone in this work therefore involved the use of this reagent. The yields were however not good and therefore resulted in a waste of the equally expensive pipecolinic acid.

The exposition by Abou-Gharbia and co-workers[35] which appeared during the course of this study (described earlier in the introduction) offered two alternative methods of cyclization as well as a new medium for the condensation reaction which was worth investigating.

2.1.1 Preparation of the N-[2'-nitrophenyl]piperidine-2-carboxylic acid

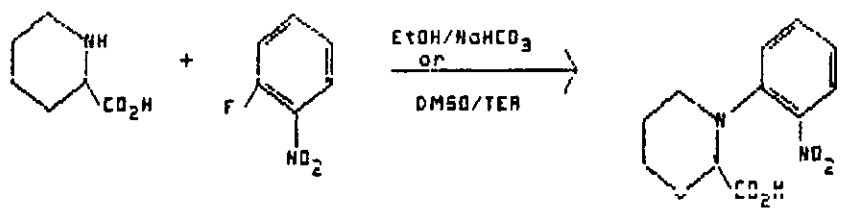
Two methods of condensation were used to prepare N-[2'-nitrophenyl]piperidine-2-carboxylic acid i.e. reaction of pipecolinic acid with 1-fluoro-2-nitrobenzene either in ethanol basified with sodium hydrogen carbonate (Method A) or in dimethylsulphoxide with triethylamine as base (Method B). The results are tabulated below.

TABLE 2

SUMMARY OF RESULTS OBTAINED FOR CONDENSATION OF PIPECOLINIC ACID WITH 1-FLUORO-2-NITROBENZENE

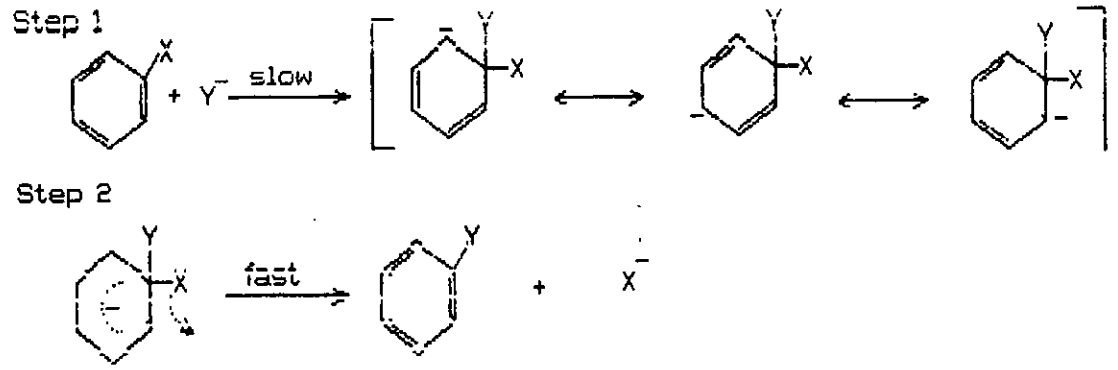
METHOD	SOLVENT	BASE	REACTION Time/hrs	REACTION TEMPERATURE	% YIELD
A	Ethanol	10% aqueous Sodium hydrogen carbonate	5	Reflux	66
B	Dimethyl--sulphoxide	Triethylamine	18	Reflux	42

The equation for this reaction is as follows:



(149)

The reaction is essentially an aromatic nucleophilic substitution and proceeds via the well known SNAr mechanism. This is by far the most important mechanism for nucleophilic aromatic substitution and consists of two steps. The general mechanism of reaction is depicted in scheme 14 below.



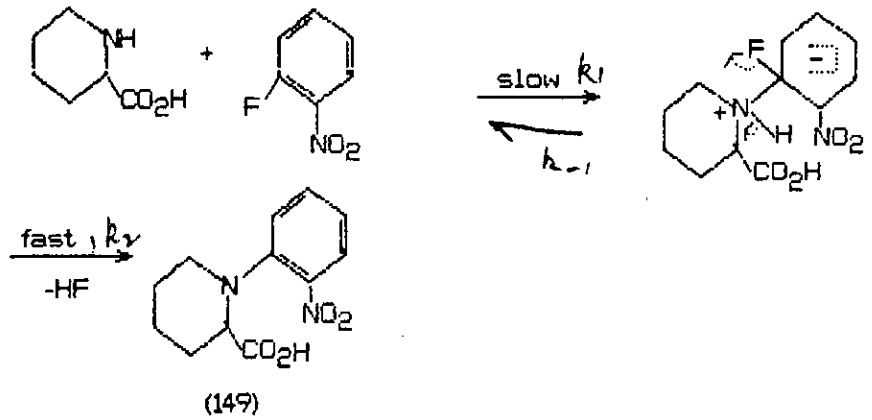
SCHEME 14

The first step is usually, but not always, rate determining. This mechanism greatly resembles the tetrahedral mechanism of aliphatic nucleophilic substitution and in another way the arenium ion mechanism of electrophilic aromatic substitution. In all three cases the attacking species forms a bond with the

substrate, giving an intermediate and then the leaving group departs. The mechanism is referred to as the SNAr mechanism but has also been called by other names including SN2Ar, the addition-elimination and the intermediate complex mechanism.

The reaction of piperidine itself with several 1-substituted 2,4-dinitrobenzenes has been thoroughly investigated by Bunnett and co-workers[84] and provides one of the evidences in support of the SNAr mechanism i.e. evidence from studies of the effect of the leaving group on the reaction.

The mechanism of the reaction between piperidine-2-carboxylic acid and 1-fluoro-2-nitrobenzene can therefore be formulated as follows



(149)

The reaction proceeded smoothly by Method A and within one hour of reaction, the characteristic change in colour, from pale yellow to deep orange/red, which usually accompanies such condensation reactions was observed. The reaction was however monitored by t.l.c and reflux was continued for 5 hrs in order

to obtain optimum yields. The product was obtained initially as an oil on extraction of the reaction mixture with chloroform.

Pipecolinic acid is not readily soluble in sodium hydrogen carbonate. This problem was overcome by using an excess of a 10% solution of the base. In earlier work from this laboratory 2% bicarbonate solutions were used in the preparation of analogous N-[2'-nitrophenyl]pyrrolidine-2-carboxylic acids supposedly in order to avoid the formation of phenols which were obtained at higher base concentrations.

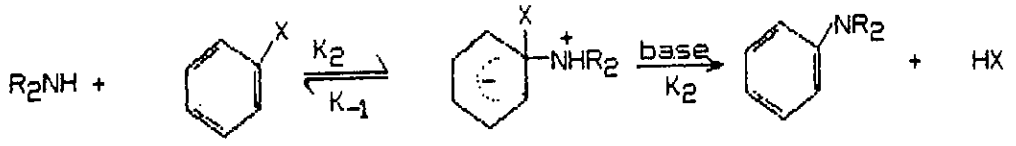
This study has however shown that an increase in base concentration from 2% to 10% resulted in an increase in product yields from 60% as reported in the literature[34] to 66%. Furthermore, formation of phenols was not observed by this author for any of the reactions in this work and solutions of up to 50% concentration of bicarbonate could be used without any decrease in yield.

It is pertinent to note that further increase in % concentration of the base from the 10% solution employed did not give a corresponding increase in yield. This observation is consistent with the fact that for the SNAr mechanism, in cases where bases are catalysts, they catalyze only at low base concentrations: a plot of the rate against the base concentration shows that small increments of base rapidly increase the rate until a certain concentration of base is reached, after which further base addition no longer greatly affects the rate. This behaviour, based on a partitioning effect is also evidence for

S_NAr

the SNAr mechanism and confirms that it is the mechanism operating in this reaction.

Base catalysis is found precisely in those cases where the amine moiety cleaves easily but X does not, so that k_{-1} is large and step 2 is rate determining. This is to be expected in this case where the amine moiety is the large piperidine ring and X is the fluoride ion.



SCHEME 15

At low base concentration, each increment of base, by increasing the rate of step 2 increases the fraction of intermediate that goes to product rather than reverting to reactants. At high base concentration, the process is virtually complete: there is very little reversion to reactants and the rate becomes dependent on step 1. Just how bases catalyze step 2 has been investigated for protic [85-89] as well as aprotic [90,91] solvents, but is not relevant to this study.

In method B, the reaction was carried out in a dipolar aprotic solvent, dimethylsulphoxide, with triethylamine as base. No efforts were made to vary the concentrations of base used in this reaction, as base catalysis in aprotic solvents has been shown to be more complicated [90,91].

A much lower yield of product was obtained by this method. The reaction was initially carried out at 60°C for 18hrs as reported by Abou-Gharbia et al,[35] but t.l.c of the reaction mixture at the end of this time showed no appreciable formation of product. The reaction was repeated at reflux temperature and this time gave better results.

A problem encountered with this method was that of purification of the product which was initially obtained as an oil that would not crystallize. T.l.c. indicated contamination with DMSO and so it was purified by taking the oil up into dichloromethane and extracting with sodium hydrogen carbonate to convert the acid product to its sodium salt. The aqueous layer was collected and the carboxylic acid recovered by re-acidifying with 50% hydrochloric acid followed by extraction with dichloromethane.

In both cases (Methods A and B), the oil obtained on evaporation of solvents crystallized from petroleum ether (40-60°) to give the product :N-[2'-nitrophenyl] piperidine-2-carboxylic acid, as a yellow solid which was recrystallized from ethyl acetate/pentane mixtures to give bright yellow prisms. The melting point of the product obtained by Method B was the same as that recorded in the literature i.e 78-80°C whereas the product from Method A had a melting point of 79-80°C which is suggestive of a purer compound. The infra-red and nuclear magnetic resonance spectra of both products were identical in all respects.

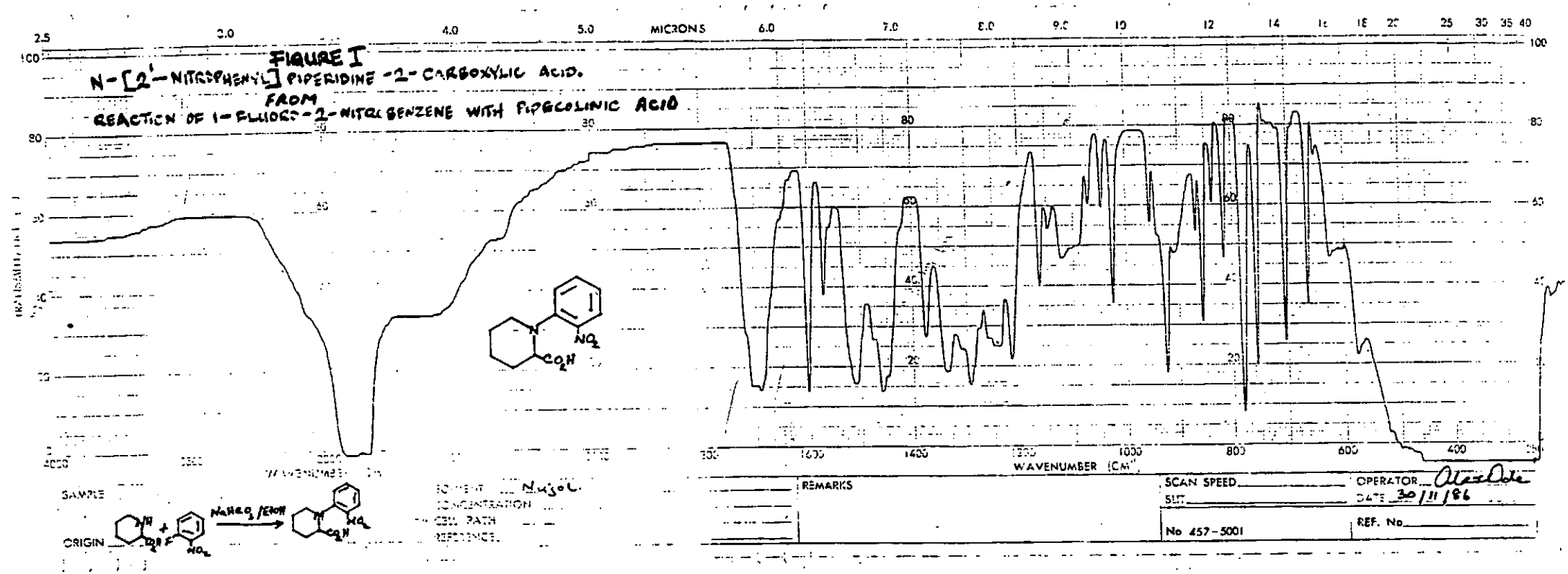
The IR spectrum (Fig I) showed the following characteristic absorptions: The OH stretch of the carboxylic acid

FIGURE I

N-[2'-NITROPHENYL] PIPERIDINE -2- CARBOXYLIC ACID.

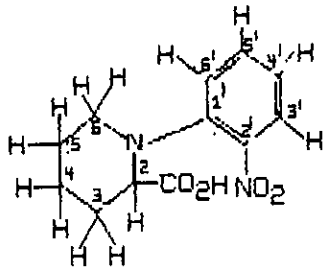
FROM

REACTION OF 1-FLUORO-2-NITROBENZENE WITH PIPECOLINIC ACID



appears as a broad absorption at about 3,000cm^{-1}. The strong carbonyl absorption at 1710cm^{-1} is attributable to the C=O stretch of a carboxylic acid. Other prominent absorption at 1600cm^{-1} and 1520cm^{-1} are attributed to the skeletal C==C stretch of the benzene ring and the stretching vibration of the nitro group respectively. The C-H out of plane deformation mode of the 1,2-disubstitued benzene ring occurs at 750 cm^{-1}.

The pmr resonance spectrum of this compound (FigII) showed the following absorptions in the aliphatic region: a 4H-multiplet at 1.67; a 2H-multiplet at 2.07 ; followed by two sets of 1H-multiplets at 3.05 and 3.46 and finally a 1H -triplet at 4.08, accounting for the nine protons of the piperidine ring.



N-[2'-NITROPHENYL]PIPERIDINE-2-CARBOXYLIC ACID

The lowfield triplet at 4.08 is easily assigned to H-2 which is highly deshielded by the carboxylic acid group as well as the nitrogen atom, and is split by the two adjacent protons on

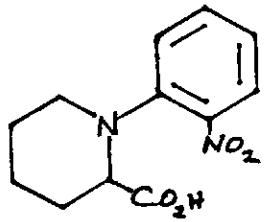
carbon 3 (H-3). The two signals at 3.05 and 3.46 integrate for only one proton each. They are assigned to H-6 as these are the only protons on the same carbon which , owing to the conformation of the molecule, may be chemically non-equivalent: they are borne on a carbon bonded to nitrogen as part of a ring and this may restrict free rotation. The multiplet at 2.07 is assigned to H-3. These protons are deshielded by the adjacent ($CH(N)CO_2H$) grouping and so occur lowfield to H-4 and H-5. The latter protons appear as an unresolved multiplet at 1.67. These protons are not chemically equivalent but their chemical environments are close enough for them to appear as the complex multiplet observed at this field strength.

The aromatic signals of the acid adduct comprise a triplet of doublets at 7.05; J, 5Hz (triplet) and 1.5Hz (doublets); a double-doublet at 7.29; J,4Hz and 1 Hz overlapping with a second double-doublet at 7.48, J,4Hz and 1Hz and a further triplet of doublets at 7.78, J,5Hz (triplet) and 1.5Hz (doublet). These signals are seen more clearly in the spectrum showing the expanded aromatic region of the methyl ester of the carboxylic acid (Fig XIVA).

From the magnitude of the vicinal coupling constants it is clear that the triplets at 7.05 and 7.78 are adjacent protons whilst the two doublets at 7.29 and 7.48 represent the other contiguous protons. The low field triplet is assigned to H-3' which is expected to be deshielded by the adjacent nitro group and so the other triplet at 7.05 must be due to H-4'.

FIGURE II

^1H-NMR Spectrum of N-[2'-Nitrophenyl]piperidine-2-carboxylic acid determined in $CDCl_3$ at 90 MHz.



The line splittings observed in the second doublet of the triplet of doublets at 7.05 are also seen in the doublet at 7.48 and suggest that these proton are coupled (J=1.25Hz). The signal at 7.48 is therefore assigned to H-5': This signal is expectedly low field to H-6' (7.29) because of the nitro group in the para position which has a greater deshielding effect on H-5' than the nitrogen atom of the piperidine ring has on H-6'.

The carboxylic acid proton is observed as a single broad peak at 10.16 which is exchangeable on shaking with deuterium oxide.

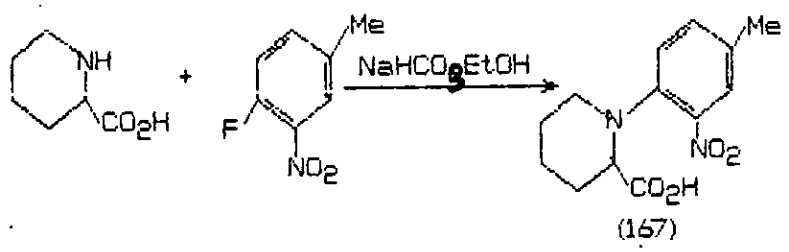
The full assignment of signals is shown in Table 3 (p.113)

On the basis of the results obtained as summarized in Table 2 , condensation of pipecolinic acid with 1-fluoro-2-nitrobenzene in ethanolic sodium hydrogen carbonate solution was clearly the better method for preparation of the nitro-acid. Consequently, this method was used for all preparations of N-[-2'-nitrophenyl] piperidine-2-carboxylic acid and the other substituted derivatives prepared in the course of this study.

Tetrahydropyridoquinoxalines substituted in positions 1-4 were needed for n.O.e. studies (section 2.2) and so attempts were made to obtain N-[2'-nitrophenyl]piperidine-2-carboxylic acids variously substituted in positions 3-6 of the aromatic ring as precursors to these heterotricycles.

Thus reaction of pipecolinic acid with 4-fluoro-3-nitrotoluene for 5hrs. at reflux temperature afforded N-[4'-methyl-2'nitrophenyl] piperidine-2-carboxylic acid as depicted in the following equation

of reaction.



(167)

The product was obtained as an oil which later solidified giving a deep yellow crystalline solid. The new compound was obtained in 50% yield and had a melting point of 85-86 °C. The yield was lower than that obtained for the unsubstituted derivative but this was not unexpected since the methyl substituent is an electron donating group; aromatic nucleophilic substitutions proceeding via the SNAr mechanism are accelerated by electron withdrawing groups especially in positions ortho and para to the leaving group and hindered by electron donating groups. In this case the activation of the ring by the nitro group ortho to the leaving group is reduced by the electron donating effect of the methyl susbtituent at the para position.

The IR spectrum of the acid adduct (Fig III) showed the OH stretch of the carboxylic acid at 3,000cm^{-1}.

A strong absorption at 1700cm^{-1} represents the C=O stretch of the carboxylic acid whilst the aromatic ring absorptions and the absorption due to the nitro group were present at 1620 and 1525cm^{-1} respectively.

The ^{1}H-NMR spectrum at 80MHz (Fig IV)' is expectedly

FIGURE III

N-[4'-METHYL-2'-NITROPHENYL]PIPERIDINE-2-CARBOXYLIC ACID

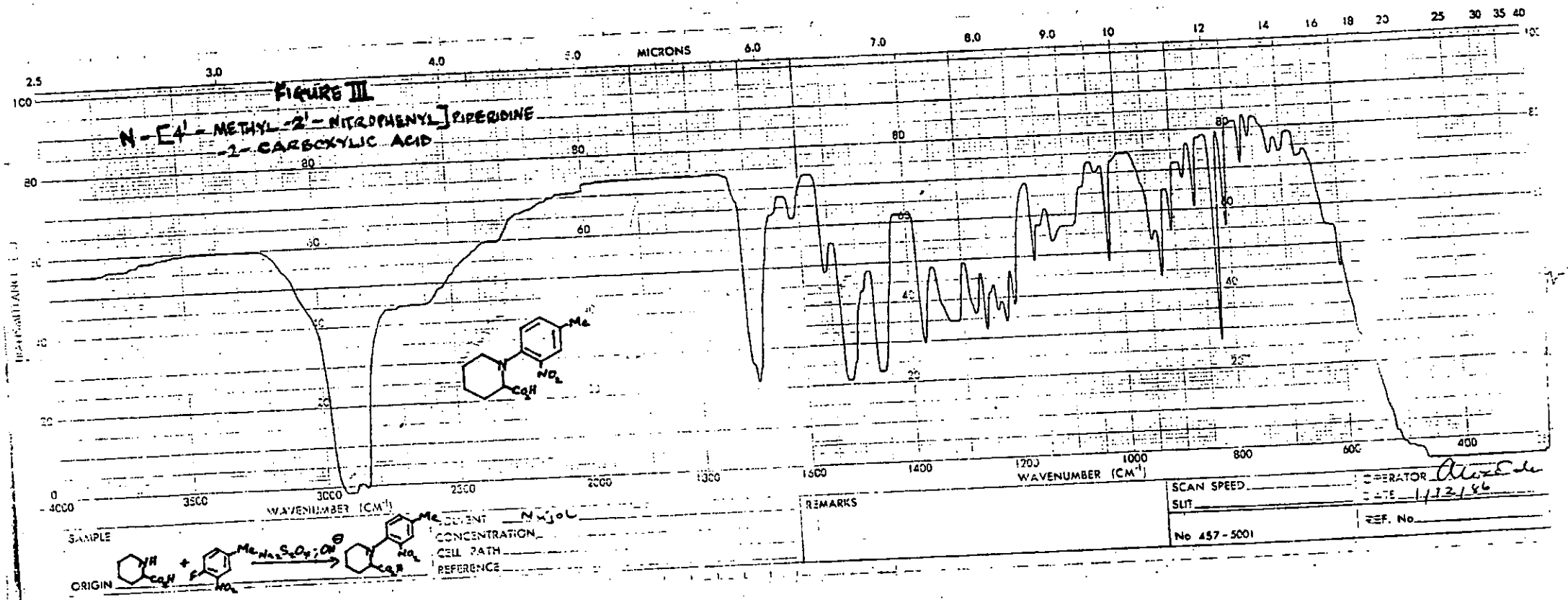
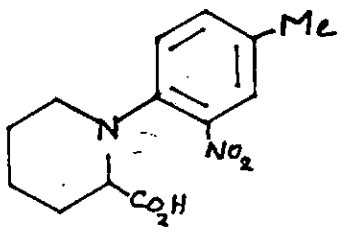


FIGURE IV

^{1}H-NMR Spectrum of
N-[4'-methyl-2'-nitrophenyl] piperidine
-2-carboxylic acid determined in
$CDCl_3$ at 80 MHz.

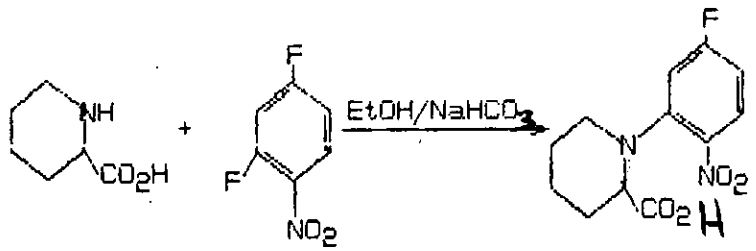


similar in many respects to that of N-[2'-nitrophenyl]piperidine -2-carboxylic acid. H-4 and H-5 again appear as a multiplet shifted 0.07ppm upfield to 1.6 (cf.1.67 for the unsubstituted compound) . This slight upfield shift was present in all the signals compared to the corresponding signals in the unsubstituted compound and is due to the electronic effect of the methyl substituent on the ring (see Table 3). H-3 (CH_2-$CH(N)CO_2$) appears as a 2H multiplet at 2.05 followed at 2.32 by a characteristic 3H singlet due to the ArMe grouping. H-6 (CH_2-N-) again gives rise to two ^1H multiplets at 2.97 and 3.37 . The ^1H triplet at 4.04 is easily assigned to H-2 which is split by the adjacent two protons (H-3).

The aromatic region of the spectrum is much simpler than that of the unsubtituted compound. The signal comprises a 2H multiplet at 7.23 attributed to H-5' and H-6', and a singlet at 7.54 due to H-3' which has no adjacent protons. The carboxylic acid proton appeared at 9.9 as a broad signal which collapses with deuterium oxide (see Table 3 for full assignment).

Elemental analysis, showing a close fit to the calculated values was further corroborating evidence for the structure of the new compound.

N-[5'-fluoro-2'-nitrophenyl]piperidine-2-carboxylic acid (168) was similarly prepared by reaction of pipecolinic acid with 2,4-difluoronitrobenzene (Sanger's reagent). The equation of this reaction is as follows



Sanger's Reagent (168)

The product was initially obtained as an oil which crystallized from n-pentane as yellow crystals with a melting point of 97-98 °C . As expected, the product yield was high (75%) due to the further activation of the aromatic ring by the second fluoro substituent.

? no other product i.e. selectivity

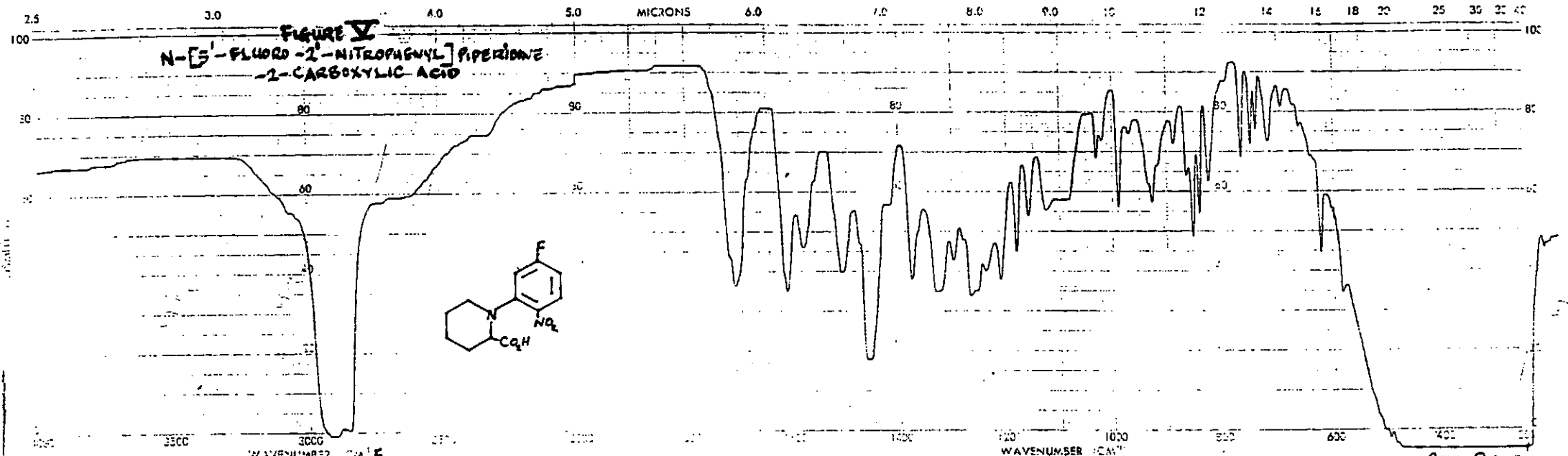
The IR spectrum of this new compound (Fig V) showed absorption at 2800cm^{-1} and 1710cm^{-1} due to the O-H and C=O stretching vibrations respectively . This is consistent with the carboxylic acid structure. The benzene ring absorption was observed at 1610cm^{-1} while the nitro group caused a band at 1530cm^{-1} .

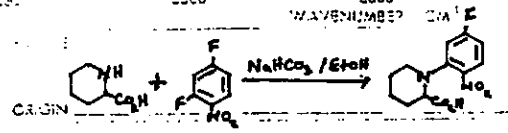
The ^{1}H-NMR spectrum at 80MHz (Fig VI) showed a now familiar set of signals due to the piperidine ring in the aliphatic region of the spectrum but an expected slight downfield shift of all the signals is observed. H-4 and H-5 again appear as an unresolved multiplet at 1.7. The second 2H multiplet at 2.17 is assigned to H-3. The two signals due to H-6 are the two 1-H multiplets at 3.10 and 3.63. H-2 appears as a now familiar triplet at 4.07.

The aromatic region is more complex than that of both the unsubstituted compound and its methyl derivative. This is due to further coupling of the protons to ^{19}F. Three sets of signals are

FIGURE V

N-[5'-FLUORO-2'-NITROPHENYL] PIPERIDINE-2-CARBOXYLIC ACID





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DATE 1/12/86

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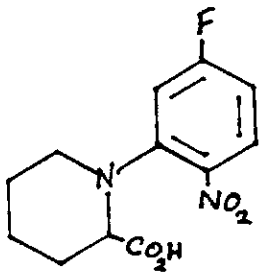
FIGURE VI

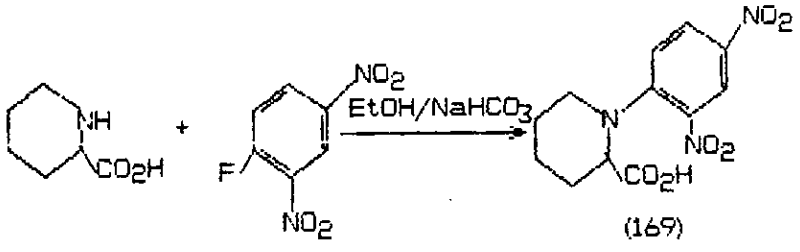
^1H-NMR Spectrum of
N-[5'-fluoro-2'-nitrophenyl] piperidine
-2-carboxylic acid determined in
$CDCl_3$ at 80 mHz.



however observed in this region. H-4′ and H-6′ appear as a 2H multiplet at 6.96 and 6.95 respectively. The signal at 7.90 (1H, multiplet) is assigned to H-3′ which is adjacent to the electronegative nitro group. The carboxylic acid proton appears as a broad signal at 9.45. exchangeable with deuterium oxide. The full assignment of signals is shown in Table 3.

The structure of this new compound was further corroborated by elemental analytical values that were a close fit to theoretical values.

Similarly, the reaction of 2,4-dinitrofluorobenzene with pipecolinic acid gave N-[2′4′-dinitrophenyl]piperidine-2 -carboyxlic acid (169) as depicted in the equation of reaction below.



(169)

The product was obtained in 75% yield. This again is higher than the 70% yield earlier reported from this laboratory. This may also be attributed to the increase in base strength used as discussed earlier. Similarly, the melting point of 134 -135 °C was higher than the reported[33] melting point of 130- 131 °C and may also be attributable to an improved work-up procedure (newly designed) giving a purer compound. The purification procedure used for all the acids in this series was to take up the crude

acid into chloroform or dichloromethane. Addition of sodium hydrogen carbonate solution converted the acid to its sodium salt leaving the organic contaminants i.e unreacted halogeno compounds etc in the organic layer. The aqueous layer was then collected and the acid product recovered by acidification with hydrochloric acid followed by extraction with chloroform. On evaporation of solvent and crystallization with appropriate solvents, a much purer compound was obtained in each case as evidenced from the NMR spectra and elemental analyses.

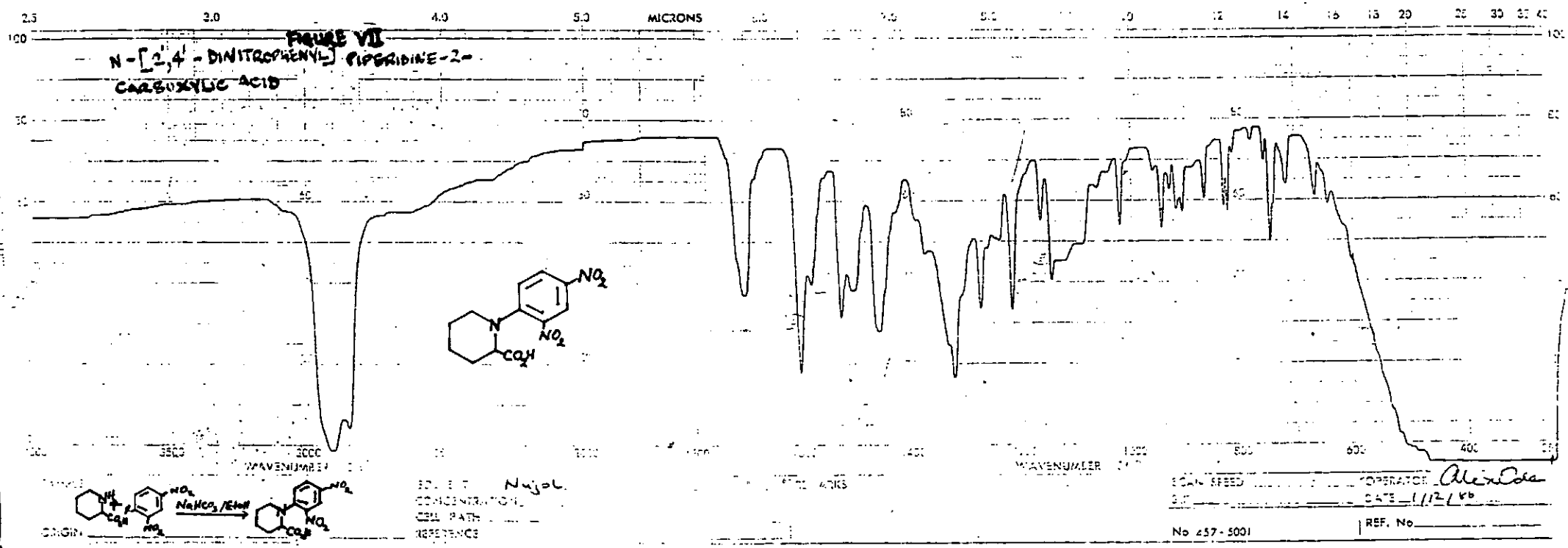
The IR spectrum of N-[2',4'-dinitrophenyl]piperidine-2-carboxylic acid (Fig VII) showed the expected carbonyl absorption of a carboxylic acid at $1710cm^{-1}$. The aromatic ring absorption was seen at $1610cm^{-1}$ and the nitro groups absorbed at 1530 and $1510cm^{-1}$.

In the ^{1}H-NMR spectrum at 80MHz, (Fig VIII) protons H-4 and H-5 appear as a multiplet at 1.8. The down field shift (cf.1.67 for unsubstituted compound) was expected and is due to the deshielding effect of the second nitro group. Similarly, the signal due to H-3 appears as a 2H multiplet shifted slightly downfield to 2.21. The two H-6 protons this time gave only one signal ; a 2H multiplet at 3.40. The base proton of the carboxylic acid group (H-2) appears as a triplet at 4.15 (cf 4.08, unsubstituted compound).

The aromatic protons comprise a 1H-doublet at 7.18 (J= 9Hz); a 1H double-doublet at 8.25 (J=9Hz and 2Hz) and another 1H doublet at 8.68 (J= 2Hz). The lowfield meta coupled doublet at

FIGURE VII

N-[2',4'-DINITROPHENYL] PIPERIDINE-2-CARBOXYLIC ACID



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DATE 1/12/66

No 457-5001

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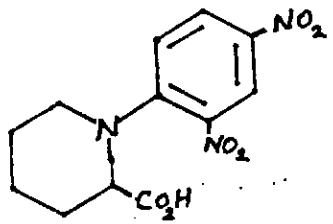
FIGURE VIII

^1H-NMR Spectrum of
N-[2',4'-Dinitrophenyl] piperidine
-2-carboxylic acid determined
in $CDCl_3$ at 80 MHz



8.68 is assigned to H-3 which is expected to be strongly deshielded by the two nitro groups in the ortho-positions to it. H-5' and H-6' are ortho-coupled (J= 9Hz). The lower field signal at 8.25 is assigned to H-5' which is adjacent to the electronegative nitro group and H-6' absorbs at 7.18.

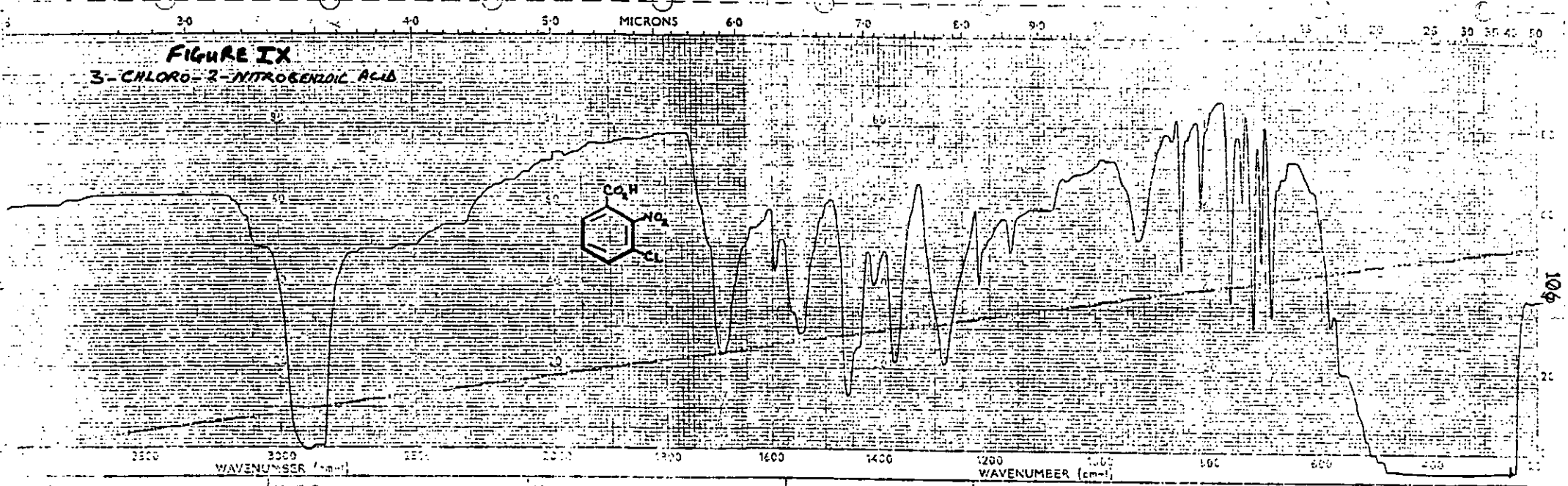
The proton of the carboxylic acid absorbs at 8.84 and is exchangeable with deuterium oxide. It is pertinent to note the upfield shift in the signal of the carboxylic acid proton of the substituted compounds compared to the unsubstituted parent compound (see Table 3). This may be due to conformational requirements in the substituted compounds .

The reactions described above were all successful, giving high yields of the required N-[2'-nitrophenyl]piperidine-2-carboxylic acid substituted in positions 4 and 5 of the aromatic ring. Attempts to obtain the nitro acids substituted in positions 3 and 6 of the aromatic ring either failed completely or were only partially successful. The starting materials in these cases were the commercially available 2,3-dichloronitrobenzene, for preparation of the 6-chloro-substituted acid and 3-chloro-2 nitrobenzoic acid methyl ester for the preparation of the 3-substituted compound.

3-chloro-2-nitrobenzoic acid methylester is not commercially available but was easily prepared from the commercially available acid . Thus 3-chloro-2-nitrobenzoic acid (170) gave 3-chloro-2-nitrobenzoic acid methyl ester (171) on refluxing in anhydrous methanol acidified with concentrated sulphuric acid ,in 85 % yield.

FIGURE IX

3-CHLORO-2-NITROBENZOIC ACID



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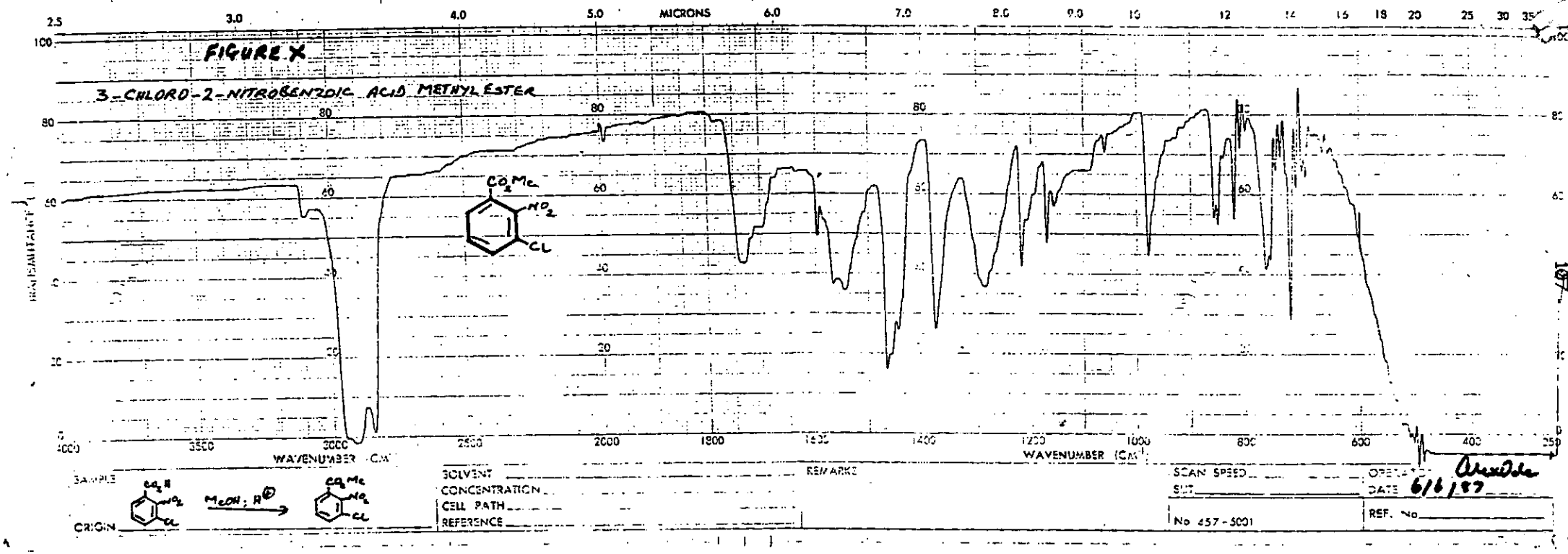
OPERATOR Glenn Dike 6/6/87

FIGURE X

3-CHLORO-2-NITROBENZOIC ACID METHYL ESTER



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OPERATOR Alexander

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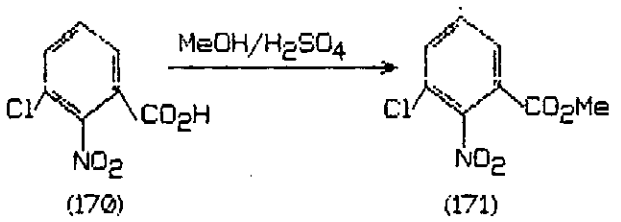
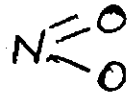
The product was obtained as a dirty white solid on removal of methanol from the reaction mixture . Further, purification gave white crystals with a melting point of 98-100 °C. The lit. ← equation of reaction is given below.

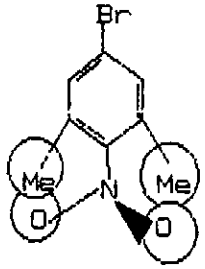


(170) (171)

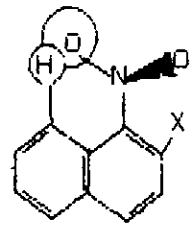
The IR spectra showed a characteristic shift of the carbonyl absorption from 1690cm^{-1} in the carboxylic acid (Fig IX) to 1740cm^{-1} in the ester (Fig X).

This ester was then reacted with pipecolinic acid in the usual manner. After 5hrs, the change in colour of the reaction mixture from light yellow to deep red/orange which is characteristic of these condensation reactions was not observed. T.l.c confirmed that no reaction had occurred. The reaction mixture was therefore kept under reflux for 5 days and constantly monitored by t.l.c. After 5 days, no significant reaction had occurred. The failure of this reaction must be due to steric effects. In bimolecular nucleophilic substitution, activation by a nitro group requires conjugation between the substituent and the reaction site. This in turn requires that the  group becomes nearly coplanar with the benzene ring, and if this is prevented, by bulky ortho-substituents, the susceptibility of

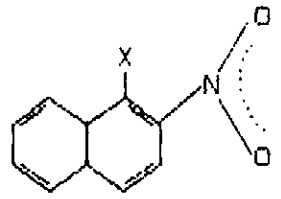
an aromatic halide to bimolecular attack will be drastically reduced. For instance 4-bromo-2,6-dimethylnitrobenzene (172) reacts much less readily than p-bromonitrobenzene with piperidine because the activating nitro group cannot attain coplanarity [92].



(172)



(173)



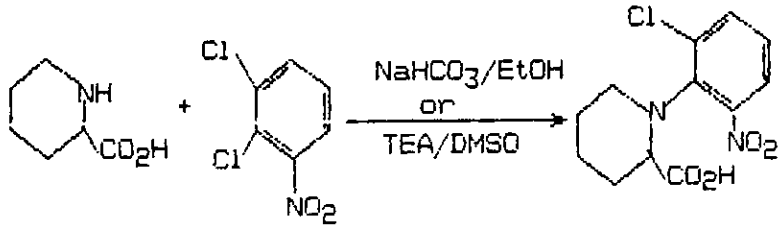
(174)

Similarly, 1-nitro-2-halogenonaphthalenes (173) react less readily than the 2-nitro-1-halogenonaphthalenes (174) since the 1-nitro group suffers steric hindrance from the peri hydrogn i.e the hydrogen at the 8-position [92].

The failure of the reaction between pipecolinic acid and 3-chloro-2-nitrobenzoic acid methyl ester is therefore clearly due to this type of steric effect.

Similar steric effects account for the poor results obtained on reaction of 2,3,-dichloronitrobenzene with pipecolinic acid N-[6'-chloro-2-nitrophenyl]piperidine-2-carboxylic acid (175) was obtained but only in 1% yield.

The equation of this reaction is given below.



(175)

The product was obtained as a light yellow crystalline solid with a melting point of 165-166 °C. The reaction mixture had to be kept under reflux for 5 days and was constantly monitored by t.l.c. Up to 70% of unreacted 2,3-dichloronitrobenzene was recovered on work-up.

The reaction was repeated in dimethylsulphoxide with triethylamine as base with the same results.

The IR spectrum of the this new acid adduct (Fig XI) showed the expected carbonyl absorption of a carboxylic acid at 1715cm^{-1} while the nitro group absorbed at 1540cm^{-1}.

The proton magnetic resonance spectrum (Fig XII) showed protons H-3, H-4 and H-5 of the piperidine nucleus appearing as an unresolved 6H multiplet at 1.57-1.87. The H-6 protons appear as a 2H multiplet at 3.15. The broad signal at 4.02 integrates for one proton only and is assigned to the proton at the base of the carboxylic acid group i.e H-2.

The aromatic signals comprised three sets of multiplets at 7.10, 7.38 and 7.41 The low-field signal at 7.41 is assigned to H-3 which is highly deshielded by the adjacent nitro group. Similarly, the chloro group at position 6' causes a

FIGURE - XI

N-[6'-CHLORO-2'-NITROPHENYL]

PIPERIDINE-2-CARBOXYLIC ACID

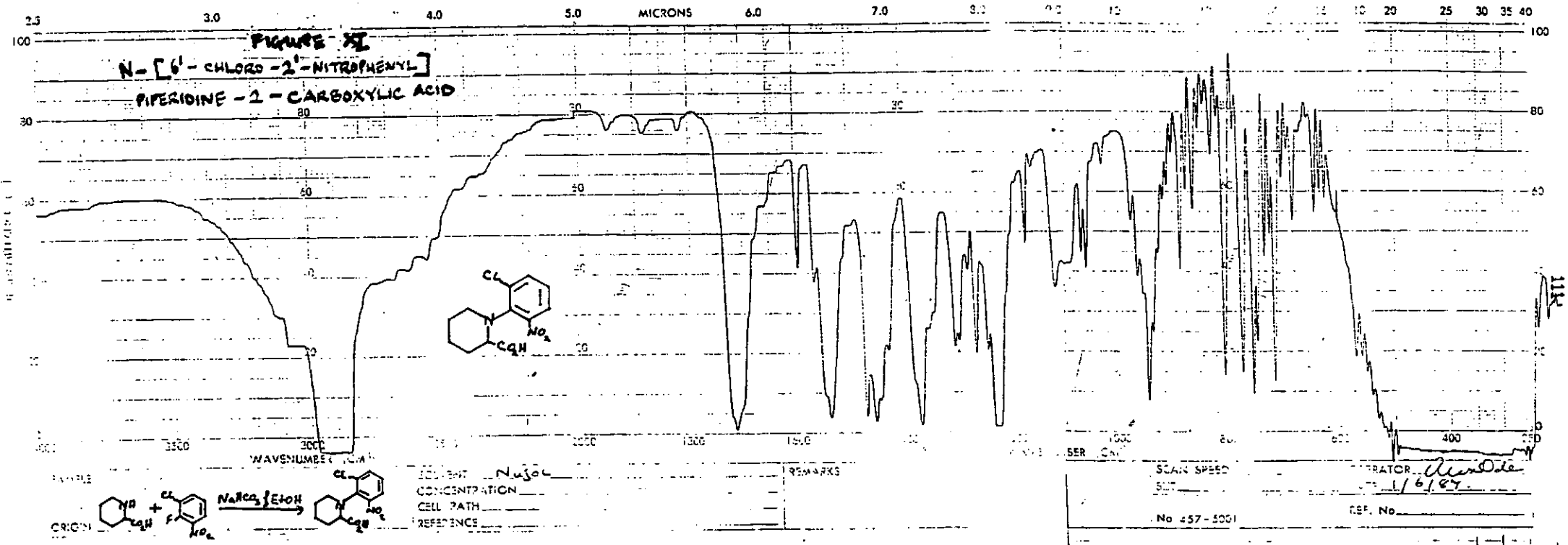


FIGURE XII

^1H-NMR Spectrum of
N-[6'-Chloro-2'-nitrophenyl] piperidine
-2-carboxylic acid determined in
$CDCl_3$ at 80 MH_z.

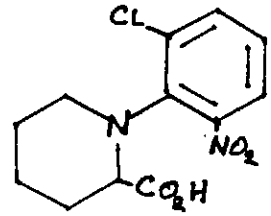
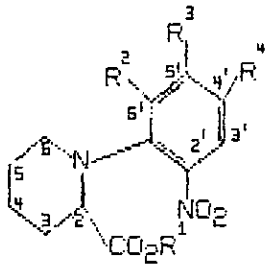


TABLE 3

^{1}H- NMR SPECTRA OF N-[2'-NITROPHENYL] PIPERIDINE-2-CARBOXYLIC ACIDS AND ESTERS (DETERMINED IN DEUTERIOCHLOROFORM AT 80MHz)



PROTON	R^1-R^4=H	R^1-R^3=H R^4=Me	R^1=R^2=R^4=H R^3=F	R^1-R^3=H R^4=NO_2	R^1=R^3=R^4=H R^2=CL	R^1=Me R^2-R^4=H	R^1=Me, R^4=NO_2 R^2=R^3=H
3'-H	7.78	7.54	7.9	8.68	7.41	7.72	8.60
4'-H	7.05		6.96		7.19	7.02	
5'-H	7.48	7.23		8.25	7.38	7.47	8.30
6'-H	7.29	7.23	6.95	7.18		7.29	7.1
2-H	4.08	4.04	4.07	4.15	4.02	4.02	4.13
3-H	2.07	2.05	2.17	2.21	1.57	2.10	2.20
4-H	1.67	1.6	1.7	1.8	1.87	1.7	1.77
5-H							
6-H	3.05 3.46	2.97 3.37	3.10 3.63	3.40	3.15	3.01 3.60	3.37
OMe						3.60	3.72
OH	10.16	9.9	9.45	8.84			
ArMe		2.32					

deshielding of proton H-5' and this absorbs at 7.38 . The signal at 7.19 is assigned to H-4.

Elemental analysis confirmed the structure of this new compound as the results obtained were close to the calculated theoretical values.

2.1.2. Cyclization of N-[2'-nitrophenyl]piperidine-2-carboxylic acids.

Four different methods of reductive cyclization were used to convert N-[2'-nitrophenyl]piperidine-2-carboxylic acid to the desired heterotricycle: 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one. The methods differed in the cyclization reagents employed which are as follows:-

(a) Palladium on carbon

(b) Alkaline sodium dithionite (sodium hydrosulphite)

(c) Tin in concentrated hydrochloric acid

(d) Iron in acetic acid.

The results obtained are summarized in Table 4 below.

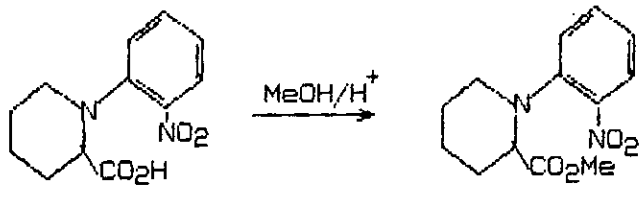
TABLE 4

SUMMARY OF RESULTS OBTAINED FOR CYCLIZATION OF N-[2'-NITROPHENYL] PIPERIDINE-2-CARBOXYLIC ACID

METHOD	REAGENTS FOR CYCLIZATION	REACTION TIME/hrs	TEMPERATURE OF REACTION	%YIELD	MELTING PT. OF PRODUCT/oC
A	Pd/C, C_6H_{10} EtOH	7 (5 + 2)	Reflux	55 (from acid)	188 - 190
B	$Na_2S_2O_4$; NaOH	1.5	Room Temperature	58	190 - 191
C	Sn/ HCL, EtOH	3	Reflux	17	188 - 190
D	Fe; AcOH	3	60 - 65 ^{o}C	23.7	188 - 190 [34]

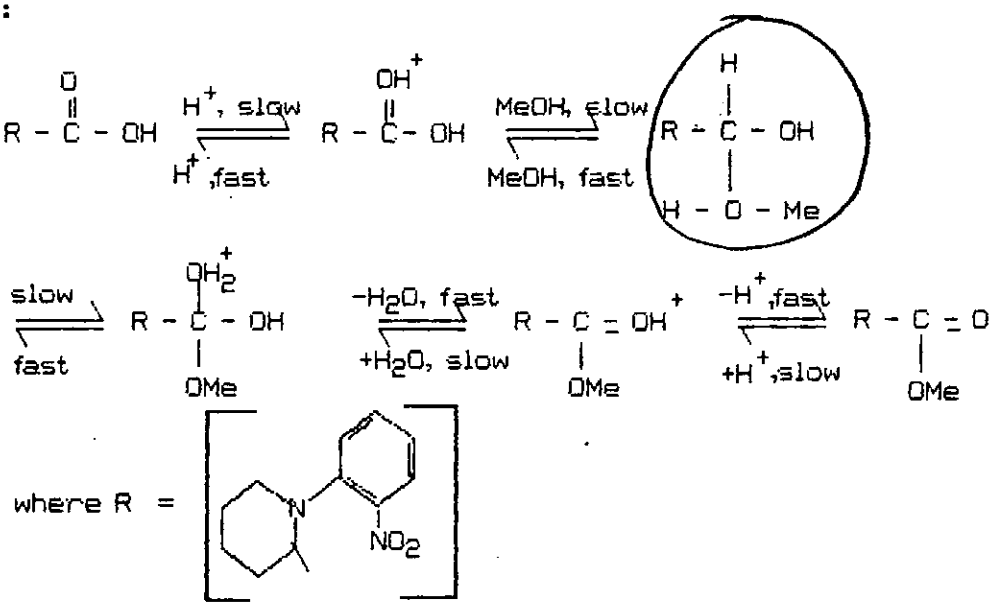
The first method, Method A, was the procedure earlier reported and adopted by our group for the preparation of the heterocycle. This method involves hydrogen transfer reductive cyclization of the methyl ester of the carboxylic acid, achieved by the use of palladium catalyst and cyclohexene [95] according to Braude's earlier method [96].

Esterification of the acid was achieved by refluxing the acid adduct in dry freshly distilled methanol in the presence of concentrated sulphuric acid. The equation of reaction is given below.



(149) (150)

The product was obtained in 95% yield as a thick transparent yellow oil. The mechanism of reaction is as follows:



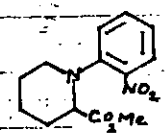
The IR spectrum of the ester (Fig XIII) showed the expected carbonyl abosorption at 1740cm^{-1} (C=O stretch of a carboxylic acid ester). The benzene ring absorptions, still occurred at 1600cm^{-1} . In addition, absorptions due to the stretching vibrations of the nitro group and the C-O group of the ester were present at 1520cm^{-1} and 1340cm^{-1} respectively.

The proton magnetic resonance spectrum (Fig XIV) is similar in many respects to that of the carboxylic acid, the obvious differences being the absence of a carboxylic acid proton and the additional signal due to the methoxy protons (see Table 3) .

Protons H-4 and H-5 of the piperidine ring appeared as the

FIGURE XIII

METHYL N-[2'-NITROPHENYL] PIPERIDINE -2-CARBOXYLATE



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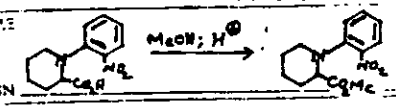

ORIGIN

SOLVENT Neat
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RESOLUTION

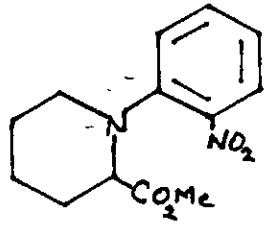
REMARKS

SCAN SPEED
SLIT
No 457-5001

OPERATOR Alan Ode
DATE 12/12/86
REF. No

FIGURE XIV

^1H-NMR Spectrum of Methyl N-[2'-nitrophenyl] piperidine-2-carboxylate determined in $CDCl_3$ at 80 MHz.



usual 4H multiplet at 1.7. The second multiplet at 2.10 was assigned to H-3. H- 6 again appeared as two sets of multiplets at 3.01 and 3.60 but the methoxy protons also absorb at 3.60 and the characteristic 3H singlet appeared above the multiplet of H-6 Proton H -2 appeared as the familiar triplet at 4.02 .

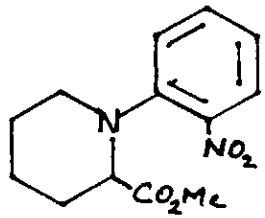
The aromatic region of the spectrum was expanded (Fig XIV A) to aid the assignment of signals. This expanded spectrum also aided the assignment of the signals in the aromatic region of the carboxylic acid itself. The aromatic signals comprise a triplet of doublets at 7.02. J,4.25Hz (triplet) and 1.2Hz (doublets); a double-doublet at 7.29; J,4.5Hz and 1.5Hz respectively, followed by a second double-doublet at 7.47; J,4.25Hz and 1.0Hz respectively and a further triplet of doublets at 7.72; J, 4.25Hz (t) and 1.5Hz (d) . The further splitting (J,1.25Hz) observed in the signals at 7.02 and 7.46 in this spectrum is similar to that observed in the spectrum of the carboxylic acid but is seen more clearly in this expanded spectrum.

As with the carboxylic acid, the lowfield triplet at 7.72 was assigned to H-3' which is adjacent to the electronegative nitro group. The coupling constant values (J,4.25Hz) indicated that this triplet at 7.72 and the triplet at 7.02 belong to adjacent protons, and so the high field triplet was assigned to H-4'.

H-5' is expected to occur lowfield to H-6' because of the nitro group in the para position and so the lower field doublet at 7.47 was assigned to H-5' and the doublet at 7.29 to

FIGURE XIIA

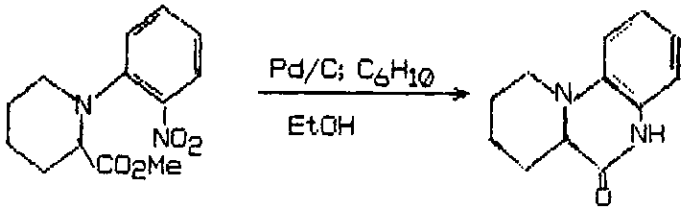
Expanded aromatic region of ^{1}H-NMR Spectrum of Methyl N-[2'- dinitrophenyl] piperidine - 2- carboxylate.



H-6'. This assignment was further corroborated by the additional splitting (J,1.25Hz) which indicate that they belong to adjacent protons i.e. H-4' and H-5'.

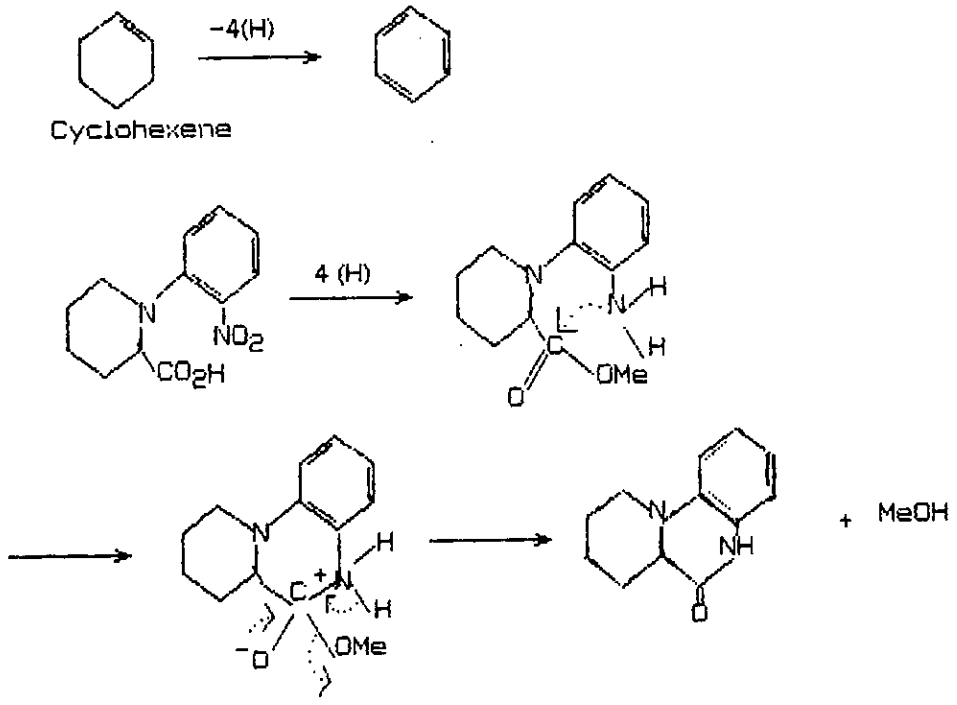
The methyl ester thus obtained was treated with 5% palladium on charcoal in refluxing absolute ethanol and cyclohexene for 2hrs. The ester cyclized under these conditions to give the expected heterocycle. In earlier work in this laboratory, 10% palladium on charcoal was generally used for such cyclizations because initial exploratory work on methyl N-[2,4-dinitrophenyl] glycinate had shown that 5% palladium was ineffective for the cyclization reaction. Cyclization was however achieved on this substrate with 10% palladium and consequently this catalyst was used for the cyclization of several N-[2'-nitrophenyl]cycloamine -2-carboxylic acids. 5% palladium was used here because it was the reagent available owing to the high cost of the 10% reagent. No difficulty was experienced by this author in obtaining the parent heterocycle with this reagent.

The equation for this cylization reaction is given below.



(150) (152)

The reduction is presumed to initially give the N-[2'-aminophenyl] derivative of the cycloamine carboxylic ester. The reduced compound in this case is not isolated but is cyclized in situ intramolecularly to give the desired heterotricycle. Outlined below is the mechanism of this reaction.



Cyclohexene is first oxidized to benzene thus providing nascent hydrogen which effects reduction of the nitro group to give methyl N-[2-aminophenyl]piperidine-2-carboxylate. This hydrogen transfer is catalyzed by palladium. The electrophilic carbonyl carbon in this amino compound is susceptible to attack by the lone pair of electrons on the nitrogen atom of the amino group. The intermediate resulting from such an attack in which a new carbon -nitrogen bond has been formed, loses a molecule of methanol to afford the desired heterotericycle. It is pertinent to note here that the alkyl ester of the carboxylic acid is

preferred for this cyclocondensation reaction because the alcohol is expected to be a better leaving group than water.

The product 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one was obtained in 58% yield. The melting point of 188-190 °C differed greatly from the literature[34] melting point of 148-149 °C. This could be attributed to the improved purification procedure which entailed boiling the product with Norite (decolourizing charcoal) in ethanol several times in order to remove coloured carbon impurities that may have accounted for the lower melting point reported earlier from this laboratory. Even with this treatment, it was not possible to completely remove these impurities from the compound as was evident from the grey colour of the product compared to the white solid later obtained by Method B.

Purification by column chromatography was impracticable as the heterocyle is only soluble in solvents such as dimethylsulphoxide, pyridine and dimethylformamide .

In Method B, N-[2'-nitrophenyl]piperidine-2-carboxylic acid was reductively cyclized directly using alkaline sodium dithionite. The reaction was carried out at room temperature for 1.5hrs. It was found to be an extremely pH sensitive reaction and the pH had to be monitored throughout by the addition of sodium dithionite or sodium hydroxide. Yields varied from 35-58% with varying pH. Optimum yields were obtained at pH 8. The product was obtained as white crystals with a melting point of 190-191 °C.

The mechanism for the cyclization is essentially the same as described for Method A. The aromatic nitro group is reduced to the amino group by sodium dithionite to give the N-[2'-aminophenyl]derivative of the carboxylic acid. Electrophilic attack on the carbonyl carbon by the lone pair of electrons on the nitrogen atom of the new amino group results in the formation of an intermediate which loses a molecule of water to give 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one.

There has been very little study on the mechanism of reduction of nitro groups but like the palladium/cyclohexene system, the reduction in this case is effected by nascent hydrogen which is provided by the powerful reducing agent, sodium dithionite, according to the following equation of reaction

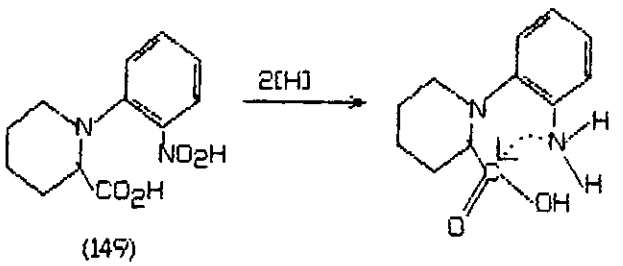
$$Na_2S_2O_4 + 2H_2O \leftrightarrows 2NaHSO_3 + 2[H]$$

Nascent Hydrogen

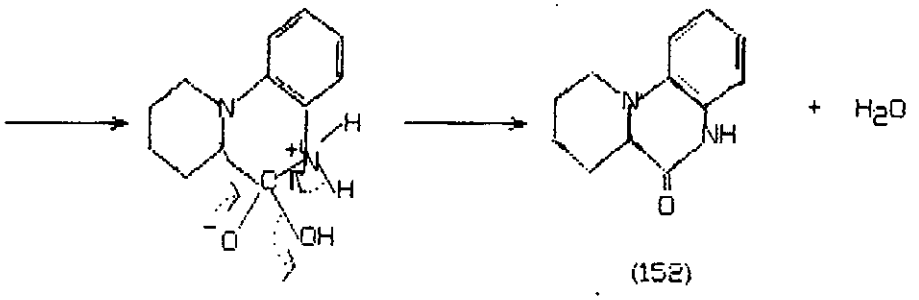
Sodium hydroxide is needed to react with the acidic sodium hydrogen sulphite thus maintaining the neutrality of the reaction medium.

$$NaHSO_3 + NaOH \dashrightarrow Na_2SO_3 + H_2O$$

The mechanism of the reductive cyclization is as follows:



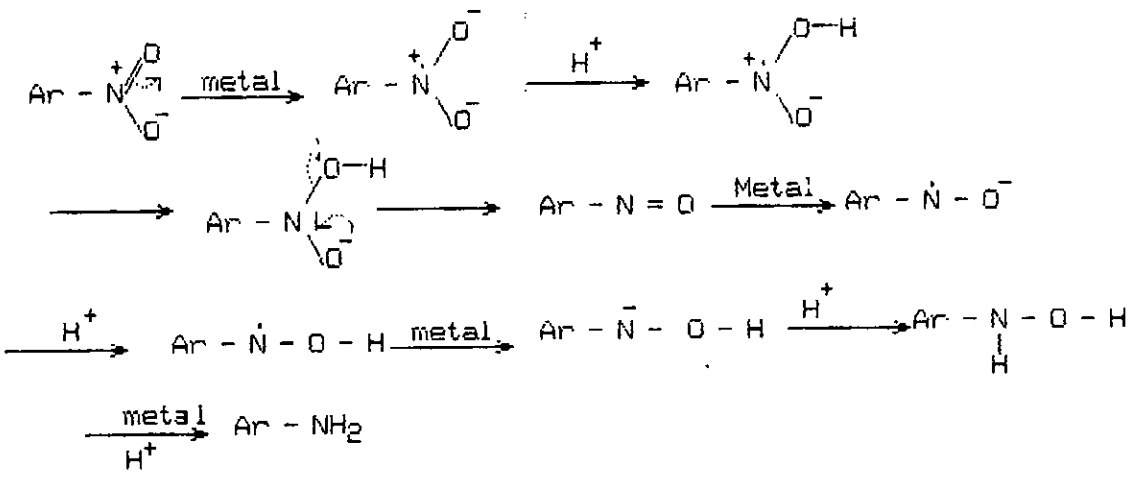
(149)



(152)

The advantage of this method over Method A is that it circumvents the formation of a nitroester precursor before cyclization as with the Braude's palladium on carbon method. The reaction occurs smoothly at room temperature and a much purer product is obtained. This purity is evident from the higher melting point and the clean white crystals obtained which contrast with the coloured compound obtained by Method A. The optimum yield of 58% recorded at pH8 is higher than that of Method A because it is obtained directly from the acid.

The use of metals in acid as reducing agents is intrinsic to methods C and D. The reduction of the aromatic nitro group which precedes the intramolecular cyclization step is achieved by the use of these reagents. As stated above, the mechanisms of the reduction of aromatic nitro compounds have been very little studied though it is usually presumed that, at least with some reducing agents, nitroso compounds and hydroxylamines are intermediates. With metals and acid the following path has been suggested[97].



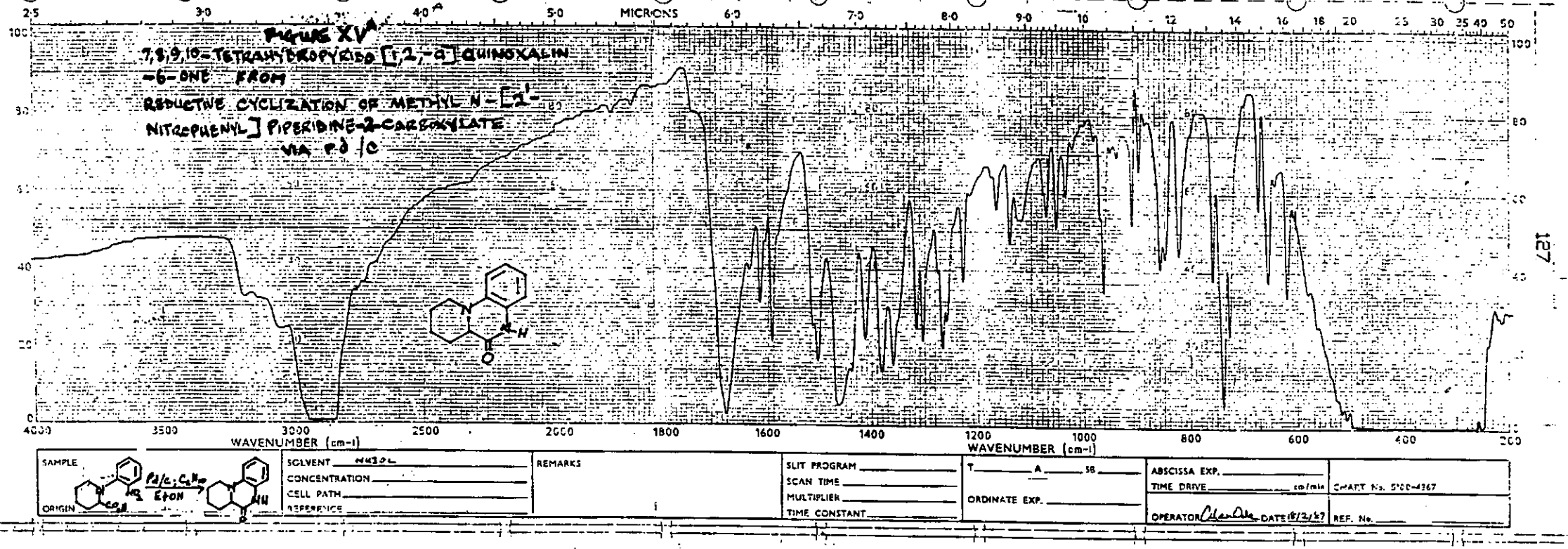
After reduction of the nitro group the mechanism of the cyclization reaction in both cases is identical to that outlined for Method B above.

Both Methods C and D gave poor overall yields of the heterocyclic compound. With tin in hydrochloric acid, a yield of only 17% was recorded whereas with iron in glacial acetic acid, just over 23% yield was obtained. In addition, the product obtained by cyclization with iron in acetic acid was highly coloured and had to be boiled with Norite for 30 mins to remove coloured impurites. In both reactions a greenish brown microcrystalline solid was obtained. This product had a melting point of 188-190 °C.

The infrared and proton magnetic resonance spectra of the products obtained by all four methods of cyclization of the acid were identical in all respects. The infrared spectra (Fig XV A and XV B) show the N-H stretching absorption of the amide at 3400 cm^{-1}. The shift in carbonyl absorption either from 1740 cm^{-1} in the

FIGURE XV

7,8,9,10-TETRAHYDROPYRIDO [1,2,-a] QUINOXALIN -6-ONE FROM REDUCTIVE CYCLIZATION OF METHYL N-[2'-NITROPHENYL] PIPERIDINE-2-CARBOXYLATE VIA Pd/C



SAMPLE

SOLVENT NUJOL
CONCENTRATION
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REFERENCE

REMARKS

SLIT PROGRAM
SCAN TIME
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T A SB
ORDINATE EXP.

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TIME DRIVE cm/min

OPERATOR [illegible] DATE 8/2/57

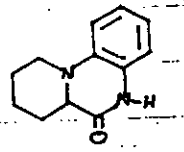
CHART No. 5700-4367

REF. No.

FIGURE XV

7,8,9,10-TETRAHYDROPYRIDO[1,2-a]
QUINOXALIN-6-ONE

FROM REDUCTIVE CYCLIZATION OF N-
[2'-NITROPHENYL] PIPERIDINE-2-
CARBOXYLIC ACID VIA ALKALINE
SODIUM DITHIONITE



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ester or 1700cm^{-1} in the carboxylic acid down to 1675cm^{-1}, due to the lactam formed after cyclization was characteristic.

The proton magnetic resonance spectrum (Fig XVI) determined in pyridine d_5 expectedly show similarities in the aliphatic region to the spectra of the carboxylic acid and ester precursors. Thus, a six proton multiplet is observed at 1.41-1.76 followed by two sets of multiplets at 2.62 and 3.59 overlapping with a one-proton multiplet at 3.63.

The six-proton multiplet is assigned to H-7 ,H-8 and H-9. The $-CH_2-N-$ group i.e H- 10 gives rise to the two sets of signals at 2.62 and 3.59 and the one-proton signal at 3.63 is assigned to H-7.

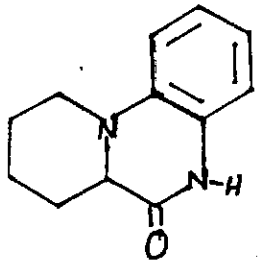
The aromatic signals appear as a complex multiplet at 6.90-7.10 in the spectrum determined in pyridine d_5 at 60, 80 and 90 MHz and were not assigned at this stage. The full assignment of signals was done with the spectrum determined at 360MHz (section 2.2, Table 5).

Further evidence for the structure of the compound was obtained from microanalytical data which gave a close fit to the calculated/expected values for the tetrahydroquinoxalinone.

From the results obtained and summarized in table 4 above, cyclization with alkaline sodium dithionite i.e Method B was clearly the method of choice in this study. In addition to giving a higher overall yield of a purer compound, the reaction proceeds smoothly at room temperature and the reagent is much cheaper. It also has the advantage of circumventing the

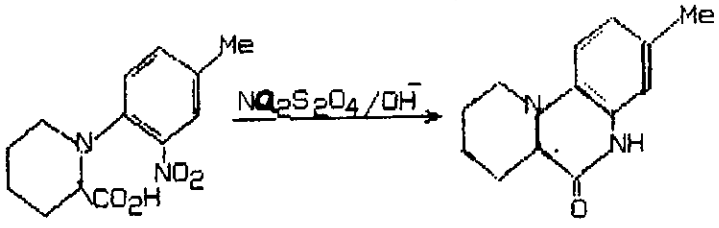
FIGURE XVI

^1H-NMR Spectrum of 7,8,9,10-Tetrahydropyrido[1,2-a]quinoxalin-6-one determined in pyridine d_5 at 80 MHz.



preparation of a nitroester precursor required for cyclization with palladium on carbon. The sodium dithionite method was therefore used for the preparation of the tetrahydropyridoquinoxalinones required for the n.O.e studies.

Thus cyclization of N-[4'-methyl-2'-nitrophenyl]piperidine-2-carboxylic acid gave 7,8,9,10,-tetrahydro-3-methylpyrido[1,2-a] quinoxalin-6-one. The equation of reaction is as follows



(167) (176)

The mechanism of reaction is the same as for the unsubstituted heterocycle. The compound was obtained as a pinkish white crystalline solid in 62% yield. The melting point of this new heterotricycle was 148-150 ^{o}C.

The infrared spectrum (Fig XVII) showed the N-H stretching absorption of the amide at 3260cm^{-1} while the lactam carbonyl absorbed at 1680cm^{-1}.

The proton magnetic resonance spectrum (Fig XVIII) showed the expected series of multiplets in the aliphatic region due to the piperidine ring protons. In addition, the methyl protons on the aromatic ring appear as an expected 3-proton singlet at 2.13. The six proton multiplet at 1.34-1.72 is assigned to protons H-7, H-8

FIGURE XVII

7,8,9,10,-TETRAHYDRO-3-METHYLPYRIDO [1,2,-a] QUINOXALIN-6-ONE

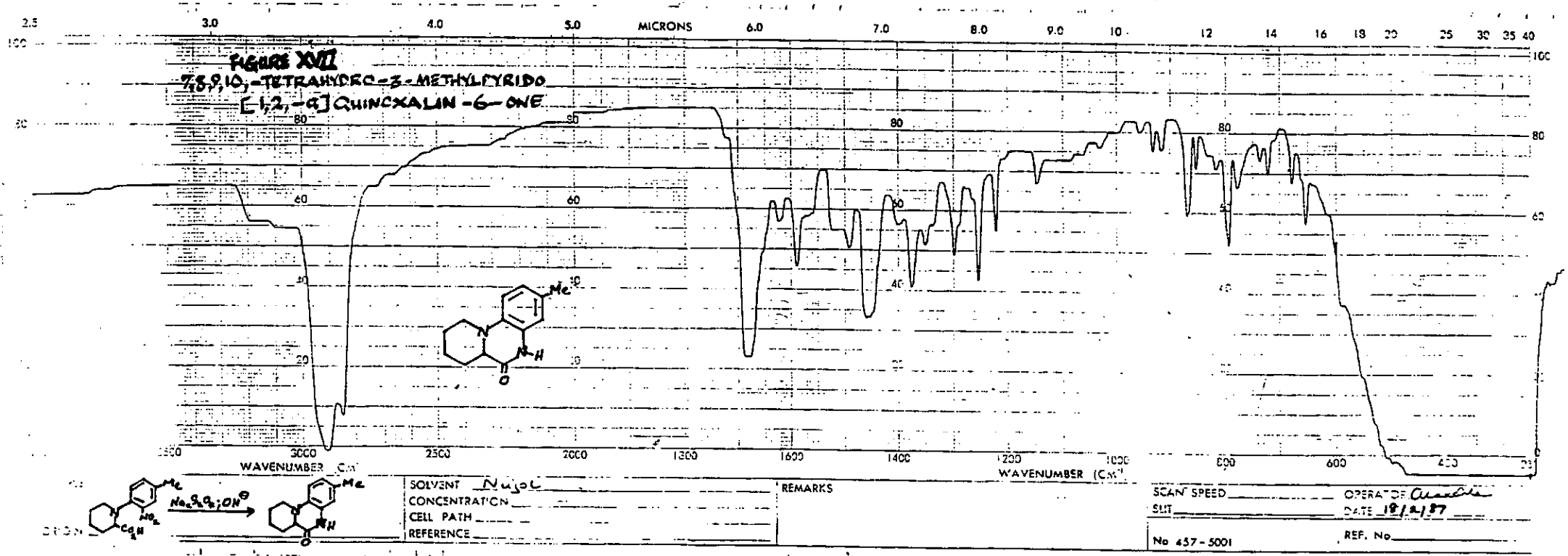
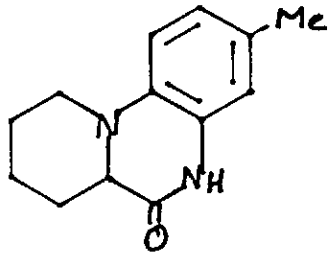


FIGURE XVIII

1H-NMR Spectrum of
7,8,9,10-Tetrahydro-3-Methylpyrido
[1,2-a] quinoxalin-6-one determined
in DMSO-d6 at 80 MHz



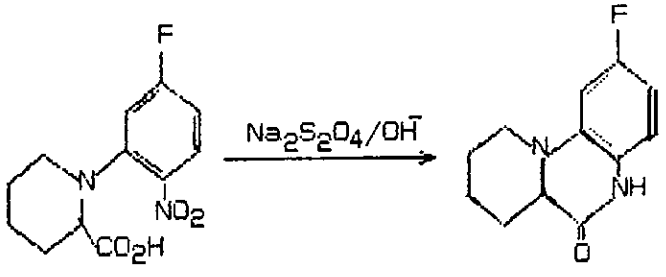
and H-9. H-10 appears as the usual two sets of one -proton multiplets at 2.47 and 3.60. The 7a proton appears as a one - proton multiplet at 3.33.

The aromatic signals at 80MHz comprise a three proton doublet. The spectrum at 360MHz later showed this to be a 2H singlet at 6.69 and a 1-H singlet at 6.61. The full assignment is discussed later in section 2.2 .

The amide proton is seen at 10.40 as a sharp one-proton singlet which disappeared on deuteriation.

Elemental analysis further confirmed the structure of this compound as it analyzed for $C_{13}H_{16}N_2O_2 \cdot 0.5H_2O$.

Similarly 7,8,9,10-tetraydro-2-fluoropyrido[1,2-a] quinoxalin-6-one (177) was obtained on treatment of N-[5'-fluoro-2'-nitrophenyl]piperidine-2-carboxylic acid with alkaline sodium dithionite. The equation of reaction is given below.



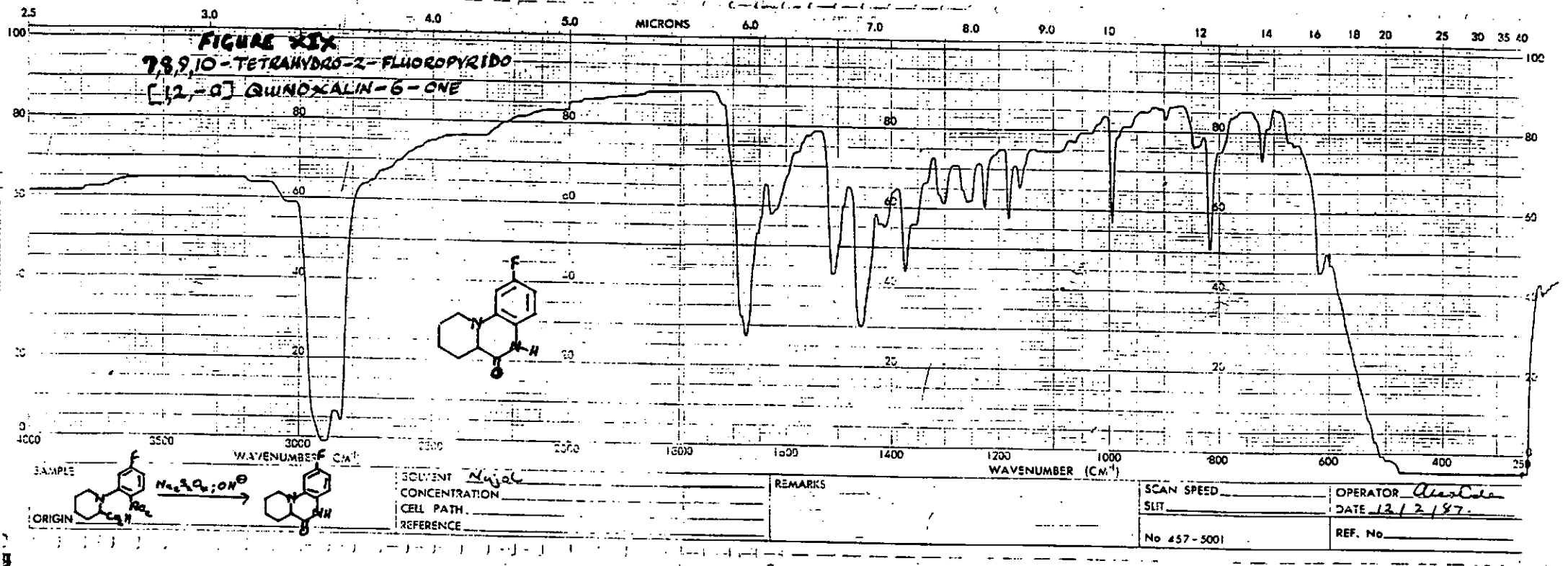
(168) (177)

The mechanism of reaction is as described for the parent heterocycle. This new compound, a grey microcrystalline solid was obtained in 69% yield and had a melting point of 195-196 °C.

The infrared spectrum (Fig XIX) showed the expected N-H

FIGURE XIX

7,8,9,10-TETRAHYDRO-2-FLUOROPYRIDO [1,2-a] QUINOXALIN-6-ONE



SAMPLE

ORIGIN

SOLVENT Nujol

CONCENTRATION

CELL PATH

REFERENCE

REMARKS

SCAN SPEED

SLIT

No 457-5001

OPERATOR Alex Cole

DATE 12/2/87.

REF. No

stretching vibration and the lactam carbonyl absorption at 3100cm^{-1} and 1680 cm^{-1} respectively.

The proton magnetic resonance spectrum at 80MHz (Fig XX) showed the usual sets of multiplets due to the piperidine ring protons in the aliphatic region, and a complex multiplet in the aromatic region.

The six-proton multiplet at 1.40-2.00 is assigned to H-7, H-8 and H-9 protons. The two one-proton multiplets at 2.64 and 3.70 are assigned to H-10 while the 7a-proton absorbs at 3.50. The aromatic protons comprise a 3-proton complex multiplet at 6.6-7.0 whilst the amide proton appears as a singlet at 10.40 exchangeable with deuterium oxide.

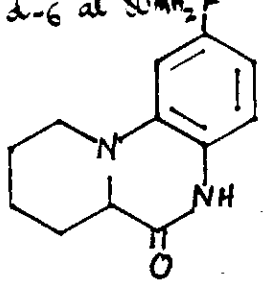
The full assignment of these signals was done with the high field NMR spectrum at 360 MHz as discussed in section 2.2.

Further corroboration of the structure of this compound was obtained from elemental analysis, the values obtained were close to the calculated /expected values for the heterotricycle .

In contrast with the results obtained above for the preparation of these new heterotricycles, attempts made to obtain the 3-nitro derivative of the heterocyle by cyclization of N-[2'4'-dinitrophenyl]piperidine-2-carboxylic acid via sodium dithionite, all failed. An apparently charred material was obtained on every attempt. This was probably due to reduction of both nitro groups by sodium dithionite . Herein lies the advantage of selective hydrogen transfer reductive cyclization with palladium on carbon. The cyclohexene/palladium system has already been

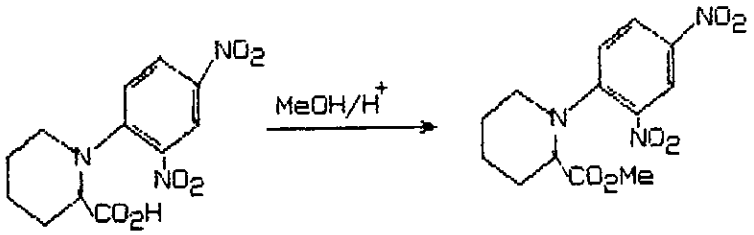
FIGURE XX

^1H-NMR Spectrum of
7,8,9,10-Tetrahydro-2-fluoro-pyrido
[1,2-a] quinoxalin-6-one determined
in DMSO d-6 at 80 MH_2F



established[33] as a selective reducing agent. It has been used for the preparation of the 1-nitro and 3-nitro derivatives of the tetrahydropyridoquinoxaline in which only the 2-nitro group of the dinitroester precursor is selectively reduced, leading to intramolecular cyclization. This method was therefore employed to obtain the 3-nitro derivative.

The nitroester precursor was prepared by refluxing N-[2'4'-dinitrophenyl]piperidine-2-carboxylic acid in dry, freshly distilled methanol containing concentrated sulphuric acid. The equation of reaction is given below.



(169) (178)

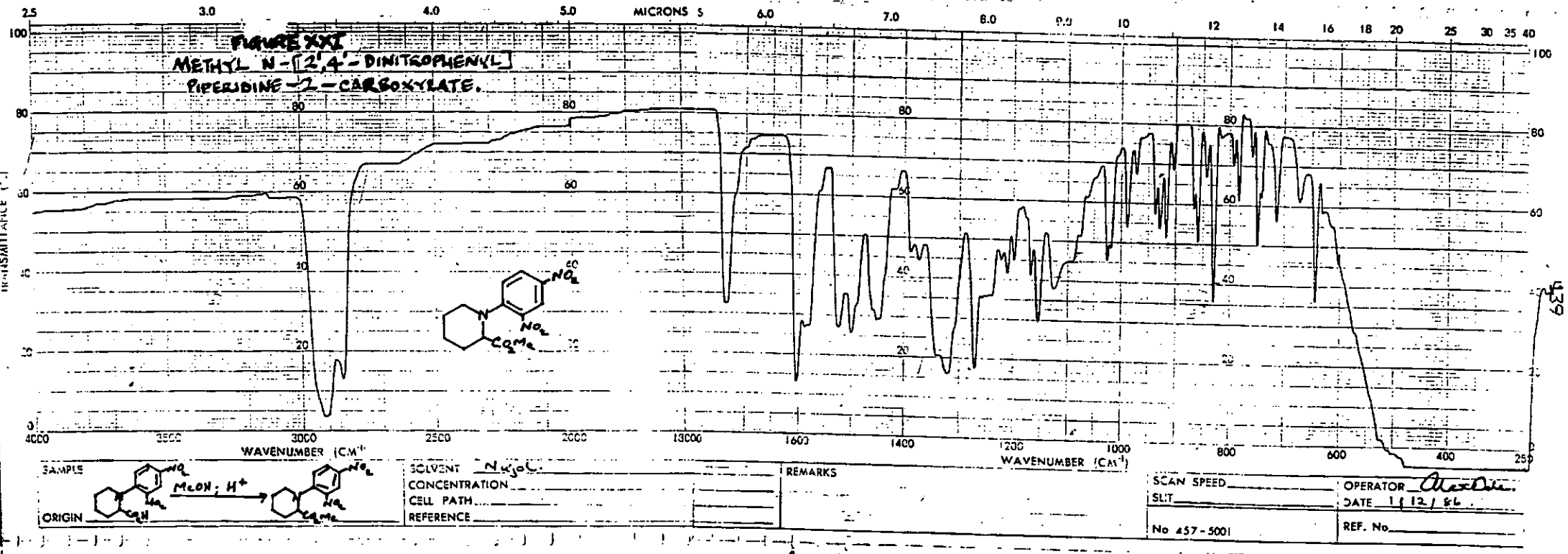
The mechanism of this reaction is the same as described previously for methyl-N-[2'-nitrophenyl]piperidine-2-carboxylate.

The product of reaction, methyl N-[2'4'-dinitrophenyl] piperidine-2-carboxylate (178), was obtained in 95% yield as a bright yellow crystalline solid with a melting point of 86-87 °C (Lit[33] 86- 87 °C).

The infrared spectrum (Fig XXI) showed the expected absorption due to the carbonyl group of a carboxylic acid ester at 1740cm^{-1}. Other prominent absorptions are the bands due to the benzene ring at 1600 cm^{-1} and the stretching vibrations of the two

FIGURE XXI

METHYL N-[2',4'-DINITROPHENYL] PIPERIDINE-2-CARBOXYLATE.



SAMPLE

ORIGIN

SOLVENT Nujol

CONCENTRATION

CELL PATH

REFERENCE

REMARKS

SCAN SPEED

SLIT

No 457-5001

OPERATOR

DATE 1/12/86

REF. No.

439

nitro groups at 1530 and 1510cm^{-1}.

The proton magnetic resonance spectrum (Fig XXII) showed the following absorptions in the aliphatic region :a four proton multiplet at 1.77 followed by two 2-proton multiplets at 2.20 and 3.37 then a 3-proton singlet at 3.72 and finally a 1-proton triplet at 4.13. The multiplet at 1.77 is assigned to H-4 and H-5. The second multiplet at 2.20 is assigned to H-3. As with the carboxylic acid, H-6 gives rise to only one signal, the 2-proton multiplet at 3.37.

The one proton triplet at 4.13 is unambiguously assigned to H-2. Similarly the singlet at 3.72 is assigned to the methoxy protons also confirming that esterification had occurred.

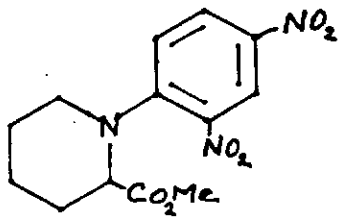
The aromatic signals comprise a 1-proton doublet at 7.0 (J=8Hz) a double-doublet at 8.3 (J=12Hz and 2Hz) and another doublet at 8.60 (J=2Hz).

The high field doublet is assigned to H-6' while the double-doublet is assigned to proton H-5' which is deshielded by the two nitro groups in the ortho and para positions. H-3' is expectedly even more strongly deshielded by the two ortho nitro groups and the low field doublet is assigned to this proton. H-5' is meta-coupled to H-3 (J=2Hz) and this further corroborates the assignments.

The methyl ester thus obtained was treated with 5% palladium on charcoal and cyclohexene in refluxing ethanol for 2hrs .A dark brown microcrystyalline solid was obtained as product. Attempts at recrystallization with ethanol resulted in the separation of two compounds from the reaction product; an ethanol

FIGURE XXII

^1H-NMR Spectrum of Methyl N-[2',4'-dinitrophenyl] piperidine-2-carboxylate determined in $CDCl_3$ at 80 MHz.



insoluble dark brown solid (product I) and an ethanol soluble bright yellow crystalline solid (product II).

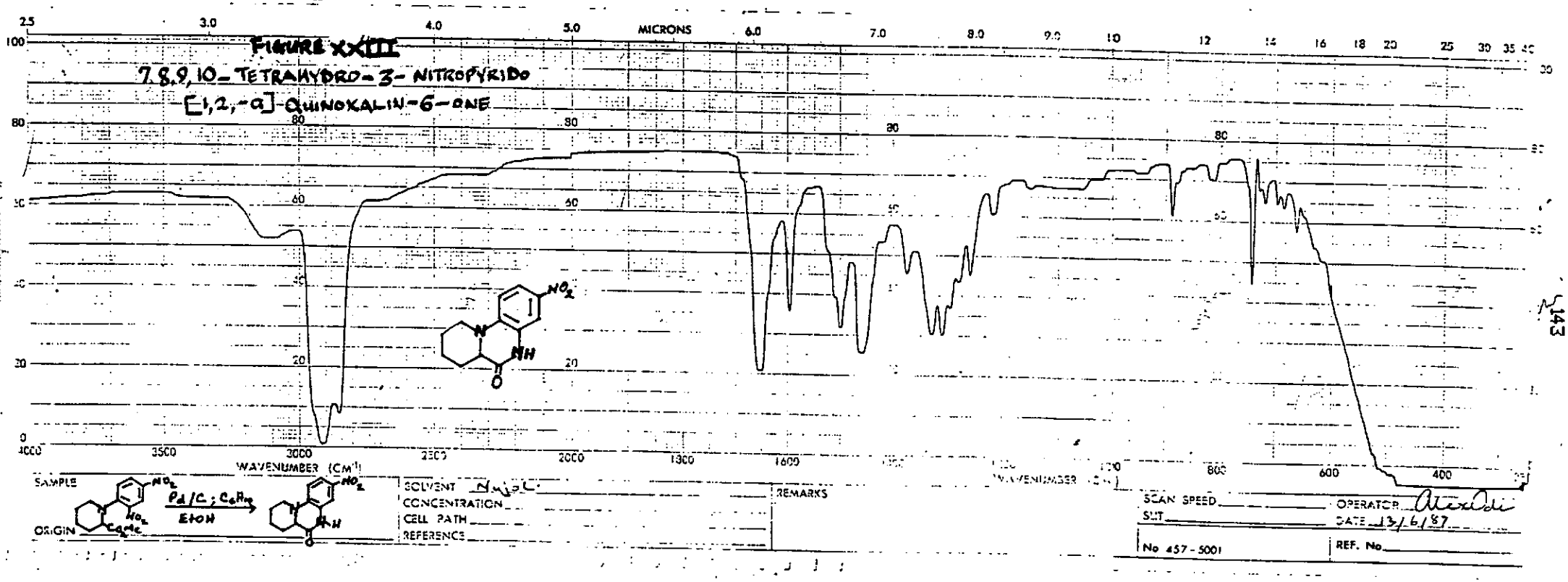
Product I had a melting point of 295°C dec. The reported[33] melting point of the expected 7,8,9,10-tetrahydro-3-nitropyrido[1,2-a]quinoxalin-6-one is 290°C dec and this suggested that product I was the desired compound. However, the infra-red spectrum of this compound was similar to that obtained from attempted cyclization with sodium dithionite; there was no carbonyl absorption. In addition, the proton magnetic resonance spectrum showed no aromatic protons. This evidence ruled out the possibility of the product being the desired lactam.

Product II on the other hand, gave a melting point of 188-190°C. The infra-red spectrum of this compound (Fig XXIII) showed the characteristic absorptions at 3150cm^{-1} and 1660cm^{-1} due to the N-H and C=O stretching absorptions of the cyclic amide suggesting that cyclization to the lactam had indeed occurred. In addition there were absorptions at 1600cm^{-1} and 1500cm^{-1} which are attributed to the benzene ring and the nitro group respectively and indicate that the second nitro group was not reduced to an amino group.

The proton magnetic resonance spectrum (Fig XXIV) showed the usual six -proton multiplet at 1.2-2.0 followed by three multiplets corresponding to one proton each at 2.50, 3.0 and 4.0 respectively. The aromatic protons comprise a one proton doublet at 7.0 (J=10Hz) and a two proton multiplet at 7.8. This is followed by a one-proton singlet at 11.0 exchangeable with deuterium oxide.

FIGURE XXIII

7,8,9,10-TETRAHYDRO-3-NITROPYRIDO [1,2,-a]-QUINOXALIN-6-ONE



SAMPLE

ORIGIN

Pd/C; C_6H_{14} / ETOH

SOLVENT $CHCl_3$

CONCENTRATION

CELL PATH

REFERENCE

REMARKS

SCAN SPEED

SLIT

OPERATOR Alexandri

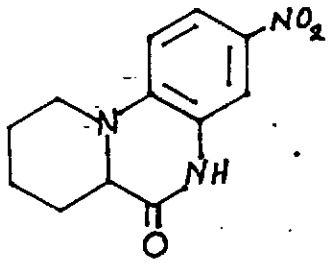
DATE 13/6/87

No 457-5001

REF. No.

FIGURE XXIV

^{1}H-NMR Spectrum of
7,8,9,10-Tetrahydro-3-nitropyrido
[1,2-a] quinazolin-6-one determined
in DMSO-d_6 at 90 MHz



The multiplet at 1.2 - 2.0 is assigned to protons H-7, H-8 and H-9. The remaining three multiplets correspond to those of the two $-CH_2-N-$protons i.e H-10, which as stated earlier are non- equivalent and thus give separate signals at 2.50 and 4.0 and the 7a -proton i.e CH(N)-C=O which appears at 3.0.

The highfield aromatic signal at 7.0 is assigned to H-1. It is ortho-coupled (J=10Hz) to H-2. H-2 and H-4 are expected to be equally deshielded by the nitro group at position 3 although H-4 should also be affected by the amide grouping in its second ortho position. The multiplet at 7.8 is therefore assigned to H-2 and H-4.

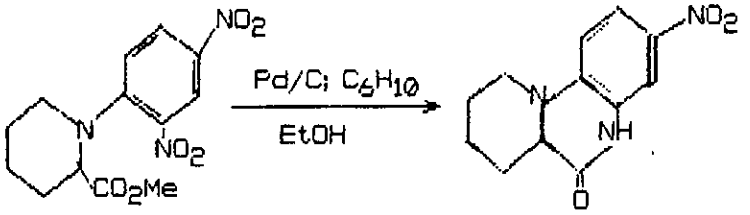
THe presence of the one-proton singlet at 11.0 exchangeable with deuterium on shaking with deuterium oxide confirms the presence of the N-H grouping in the compound. This is also corroborated by the absorption at 3150cm in the infra-red.

From the spectroscopic evidence, it is clear that cyclization of the nitroester occurred under the conditions of the reaction to give the expected tricyclic quinoxalininone (Product II) although reduction of the second nitro group occurred to some extent giving the apparently charred product I.

Although product II had a melting point which differed by as much as 100 °c from the literature[33] melting point, all the spectroscopic evidence indicated that it was the desired heterotricycle, 7,8,9,10-tetrahydro-3-nitropyrido[1,2-a] quinoxalin-6-one. In addition, the compound analyzed for $C_{12}H_{13}N_3O_3.H_2O$ ie the mononitro compound with one molecule of

water of crystallization.

The equation for this reaction is given below.



(178) (179)

The mechanism for this reaction is the same as described for the preparation of the parent heterocycle by this method.

In conclusion, cyclization of N-[2'-nitrophenyl]piperidine-2-carboxylic acids via alkaline sodium dithionite has been demonstrated to be the best method for preparing tetrahydro-pyridoquinoxalinones provided there is no other reducible group in the acid adduct. In this case, selective hydrogen transfer reductive cyclization of the ester of the carboxylic acid using the cyclohexene/palladium catalyst system is the preferred method.

2.2.0 REACTIONS OF 7,8,9,10-TETRAHYDROPYRIDO[1,2,-a] QUINOXALIN-6-ONE WITH ELECTROPHILIC REAGENTS:

2.2.1 Reactions with electrophilic reagents

As the initial object of this study was to investigate the chemistry and properties of the new tetrahydropyridoquinoxalinone skeleton, this aspect of the work therefore commenced with a study of the reactions of the title compound with electrophilic reagents. It was anticipated that the aromatic ring would be susceptible to such reagents just like the parent quinoxaline and the analogous pyrrolo[1,2,-a]quinoxalines.

The heterotricycle however remained unreactive to sulphuric acid even on heating. This is in complete contrast to the pyrroloquinoxalines which are highly reactive towards sulphuric acid giving the corresponding sulphonic acids in good yield at room temperature.

Bromination of the heterocycle was examined under four different conditions viz:

(1) With bromine in water,

(2) With bromine in acetic acid,

(3) With N-bromosuccinimide in 50% sulphuric acid and,

(iv) With bromine in boiling concentrated hydrobromic acid.

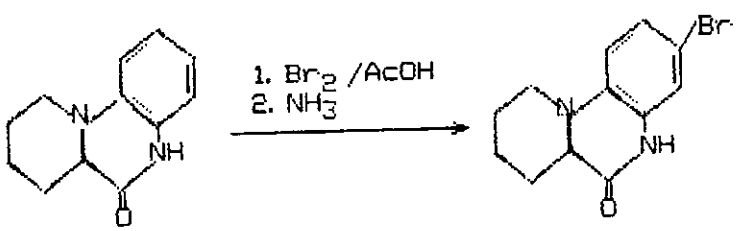
The rationale for the choice of reaction conditions has been discussed in the introduction.

With one mole equivalent bromine in water, over 80% of the starting material was recovered after two days of stirring at room temperature. In addition, a green microcrystalline solid, m.p >

300 °C , which was insoluble even in hot ethanol, was isolated from the reaction. The structure of this compound has not been elucidated yet, but the IR spectrum (Fig XXV) suggests that cleavage of the tricyclic ring occurred to give a carboxylic acid. Thus the O-H and C=O stretching vibrations of a carboxylic acid are present at 3400 and 1700cm^{-1} respectively. Absorptions due to the aromatic ring are still present at 1605 and 1505cm^{-1} indicating that the aromatic ring remained intact.

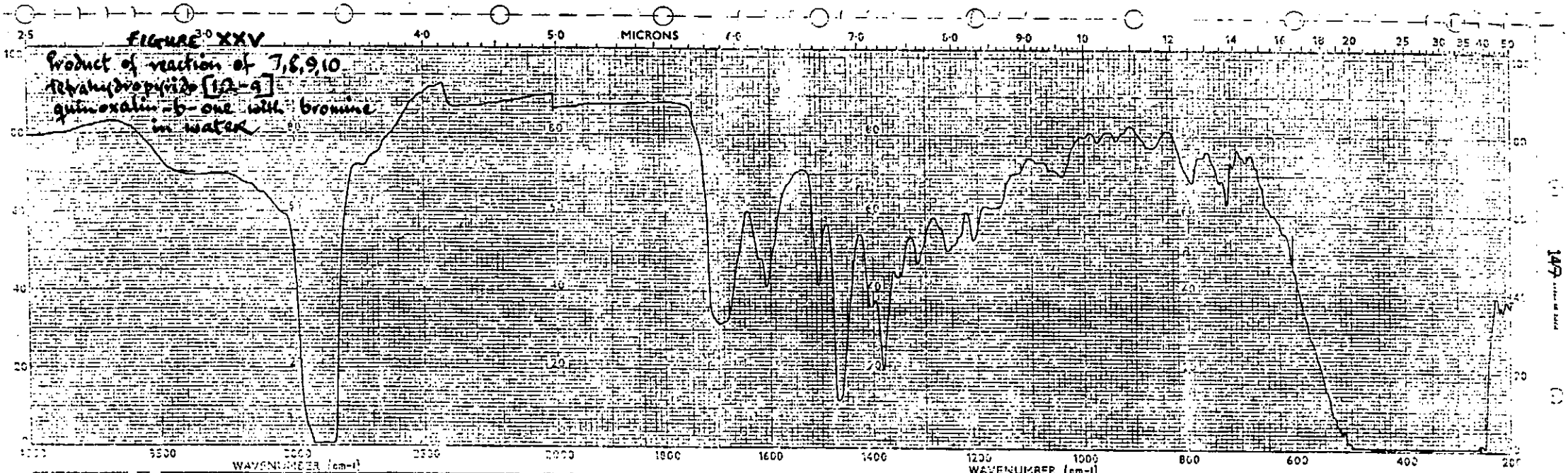
Elemental analysis of the solid gave values for carbon, hydrogen and nitrogen of 46.31% 3.66%, and 3.99% respectively, suggesting the presence of more than one bromine atom in the compound in addition to the carboxylic acid group. Owing to the insolubility of this product in NMR solvents, the p.m.r spectrum gave very broad signals and so no useful information as to the structure of the compound could be derived from it.

Bromination of the heterocycle however occurred smoothly at room temperature with one mole equivalent bromine in acetic acid, giving a monobromo derivative which was unambiguously indentified as the 3-bromo compound from the n.O.e experiments discussed in section 2.2.2. The equation for this reaction is represented below.

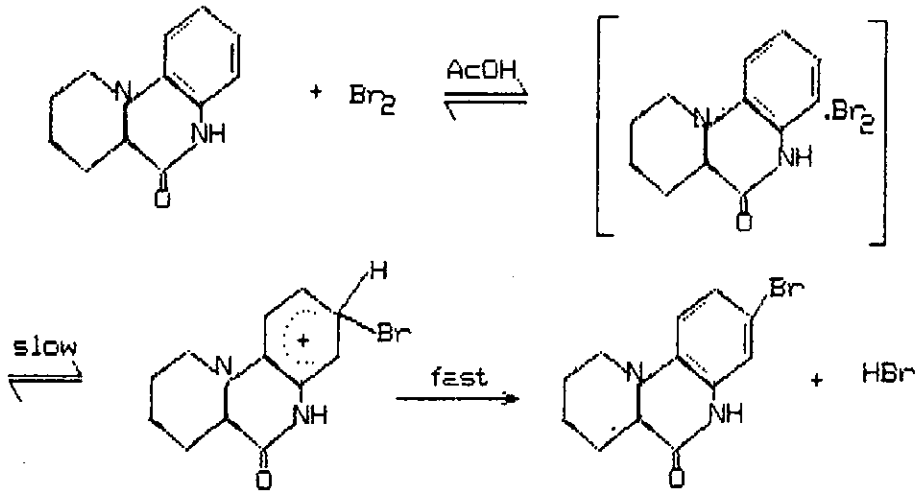


(158) (180)

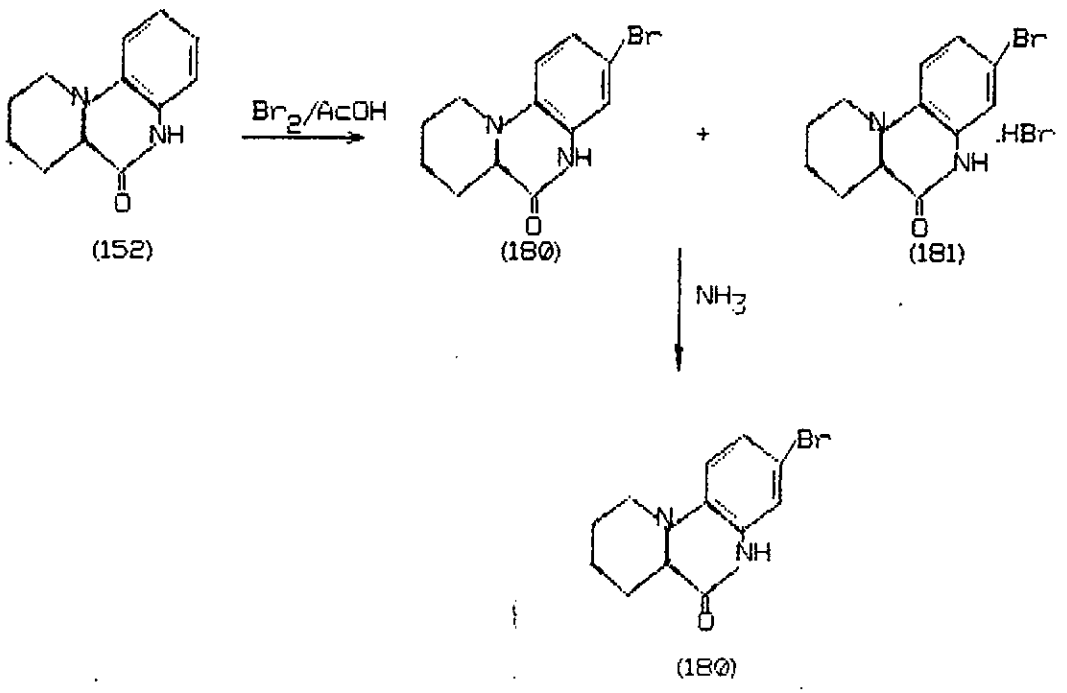
FIGURE XXV


Product of reaction of 7,8,9,10 tetrahydropyrido [1,2-a] quinoxalin-6-one with bromine in water
MICRONS
WAVENUMBER (cm-1)
WAVENUMBER (cm-1)
+ Br2/H2O

Halogenation involving molecular bromine is a bimolecular process in polar solvents (ACOH, $MeNO_2$ etc) and the mechanism of reaction is represented below.



The reaction was however found to go through a suspected mixture of the 3-bromo compound (180) and its hydrobromide salt (181). The free base of the latter compound was liberated on addition of ammonia. The equation of reaction could therefore be represented as:



(152) (180) (181)

(180)

Evidence for this mode of reaction was obtained from the p.m.r. spectrum of the initial product of reaction of bromine in acetic acid, a grey microcrystalline solid, m.p.175-176 °C. The p.m.r spectrum (Fig XXVI) shows in addition to the expected signals in the aliphatic and aromatic regions of the spectrum, two N-H peaks at 10.40 and 10.53. On addition of ammonia to this grey solid, a red brick crystalline solid, the 3-bromo derivative was obtained, m.p 225-226 °C. The p.m.r. spectrum of this latter compound (Fig XLII) (see section 2.2.2) shows a sharp signal at 10.51 due to the N - H grouping i.e one of the N-H signals collapsed on addition of ammonia. The product thus obtained, after recrystallization from aqueous ethanol was analytically pure. The signals in the p.m.r spectrum of the initial product (Fig XXVI) could not be fully assigned since, as mentioned above, it is the spectrum of a mixture of compounds.

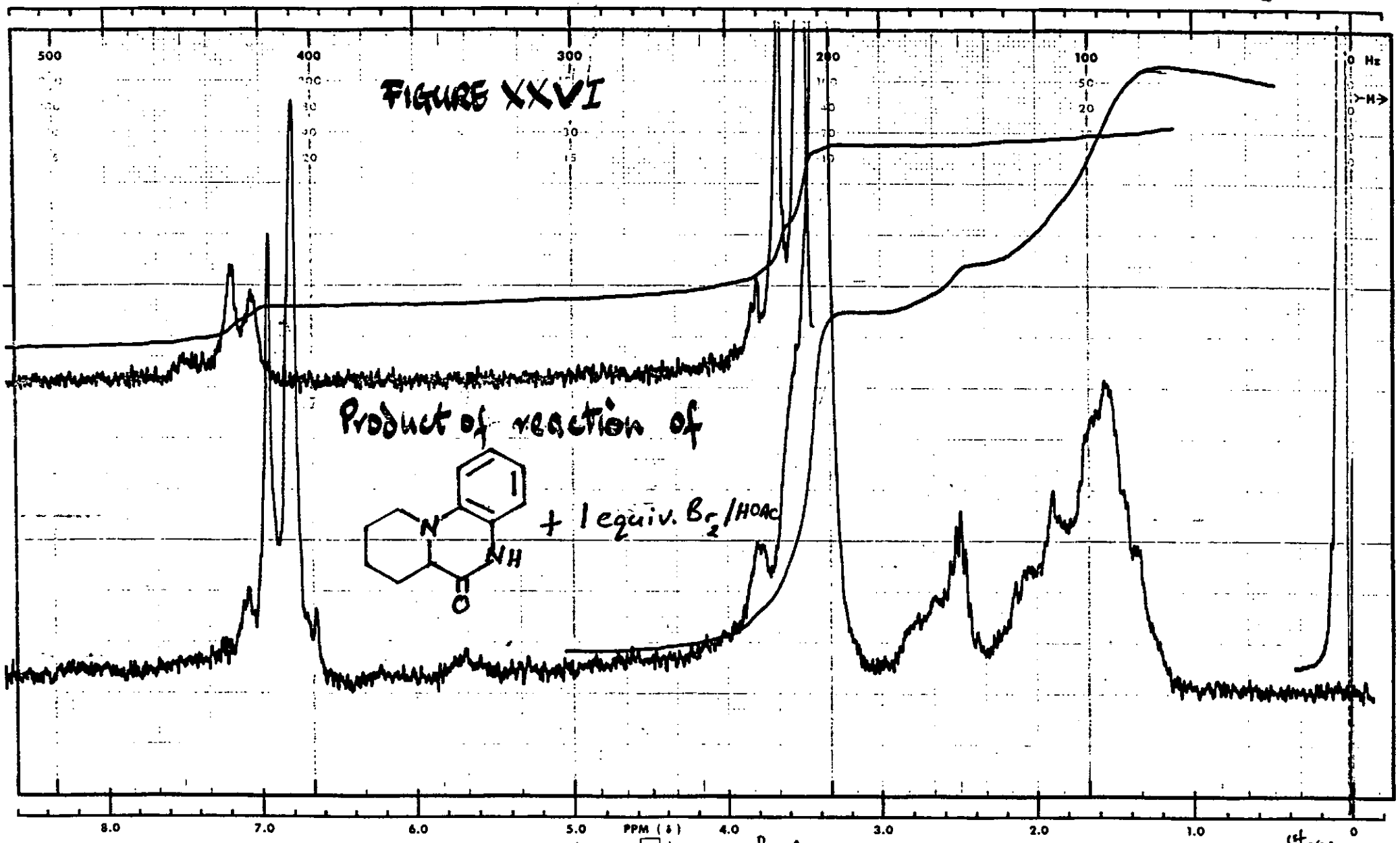
Bromination of tne analogous pyrrolo[1,2-a]quinoxaline according to the same procedure was reported[19] as going through an isolable hydrobromide. The free base was similarly released on treatment with ammonia.

7,8,9,10-Tetrahydro-3-bromopyrido[1,2-a]quinoxalin-6-one (180) was thus obtained on reaction of the parent heterocycle with one mole equivalent bromine in acetic acid, followed by treatment with ammonia. This new compound, a red-brick crystalline solid had m.p.225-226 °C.

The IR spectrum (Fig XXVII) shows the expected N-H and C=O stretching vibrations of the lactam at 3200 and 1680 cm^{-1}

MADE IN U.S.A.

FIGURE XXVI



Product of reaction of

+ 1 equiv. Br_2/HOAc

SWEEP OFFSET (Hz): 250
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: 0.05 (.05)

SAMPLE: Pyrido + 1equiv Br_2/HOAc

SOLVENT: DMSO-d_6

REMARKS: 1st run Hydrobromide + 3-bromo?

mpt. 175-176°

varian analytical instrument division

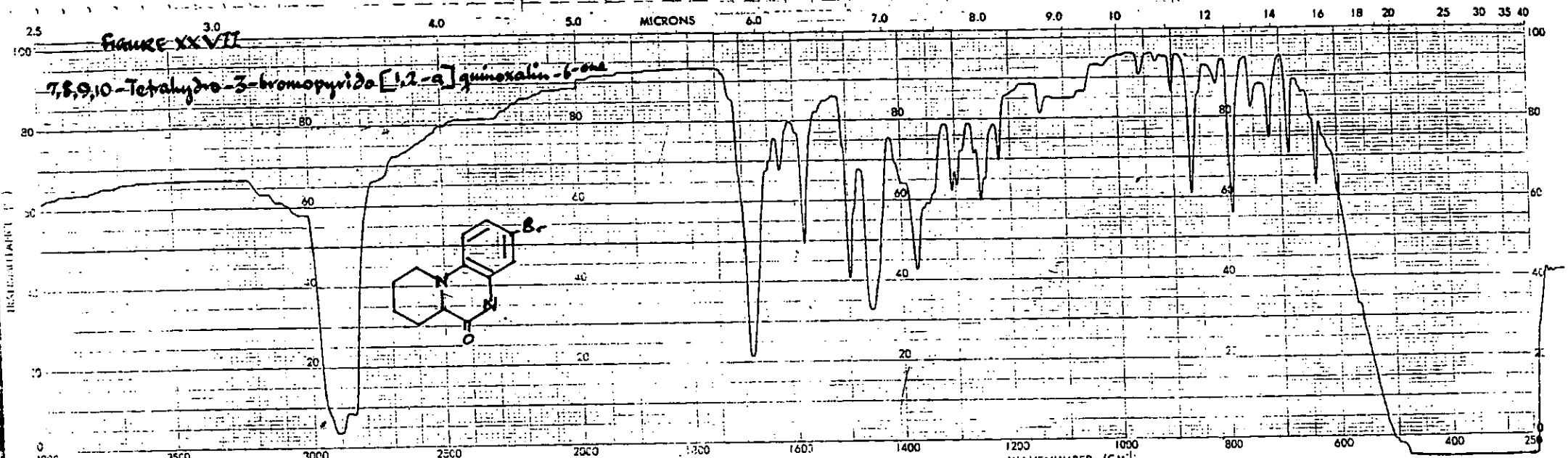
DATE: 12/8/84

OPERATOR: ALD

60 MHz NMR SPECTRUM NO.

Figure XXVII

7,8,9,10-Tetrahydro-3-bromopyrido[1,2-a]quinoxalin-6-one



SAMPLE

(i) 1 equiv. Br_2/HOAc
(ii) NH_3

ORIGIN

WAVENUMBERS (CM⁻¹)

SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

REMARKS

SCAN SPEED
SLIT
No 457-5001

OPERATOR
DATE 11/11/86
REF. No

respectively The skeletal stretch of the aromatic ring was present at 1500cm^{-1} whilst the bands at 870 and 790cm^{-1} are consistent with the 1,2,4-trisubstituted benzene structure.

The assignment of signals in the p.m.r. spectrum of this new heterotricycle is discussed fully in section 2.2.2. The compound analyzed for $C_{12}H_{13}BrN_2O$ thus confirming the monobromo structure.

Reaction of the parent pyridoquinoxalinone with excess bromine in refluxing acetic acid according to the procedure described by Nagarajan et al[19] for the bromination of pyrrolo[1,2-a] quinoxalines did not give the expected dibromo derivative.

Elemental analysis of the crystalline product of this reaction gave values for carbon, hydrogen, and nitrogen which were in close agreement with the calculated /theoretical values for $C_{12}H_{13}BrN_2O$ and therefore suggested a monobromo structure for the product, which differed from that obtained by bromination with one mole equivalent bromine in acetic acid.

The p.m.r. spectrum of this product (FigXXIX) however indicates the presence of a mixture of compounds deduced from the two N-H peaks at 10.45 and 10.78 respectively. This mixture could not be properly separated by the usual laboratory techniques owing to the insolubility of the product in most organic solvents

It is however suggested that from the evidence of elemental analysis and the p.m.r., the product was a mixture of isomeric monobromo derivatives. Since they could not be separated, the p.m.r spectrum could not be adequately interpreted and the n.O.e

FIGURE XXVIII

Product of reaction of 7,8,9,10-Tetrahydropyrido[1,2-a] quinoxalin-6-one with excess bromine in acetic acid.

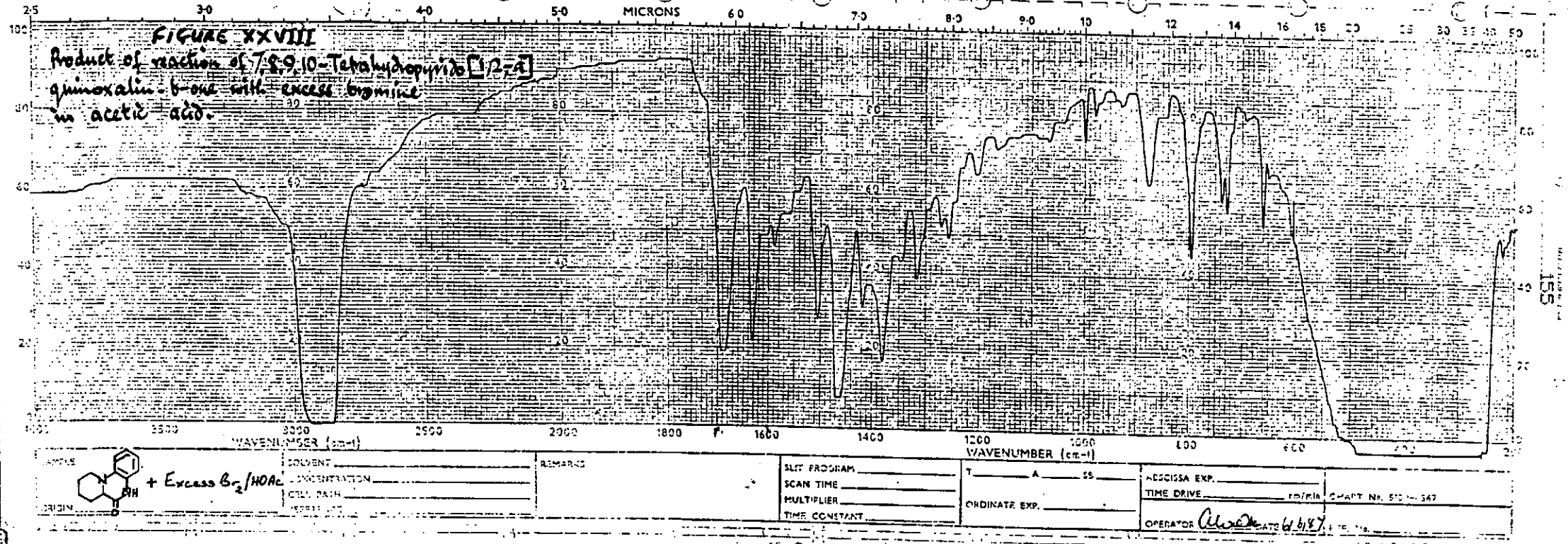
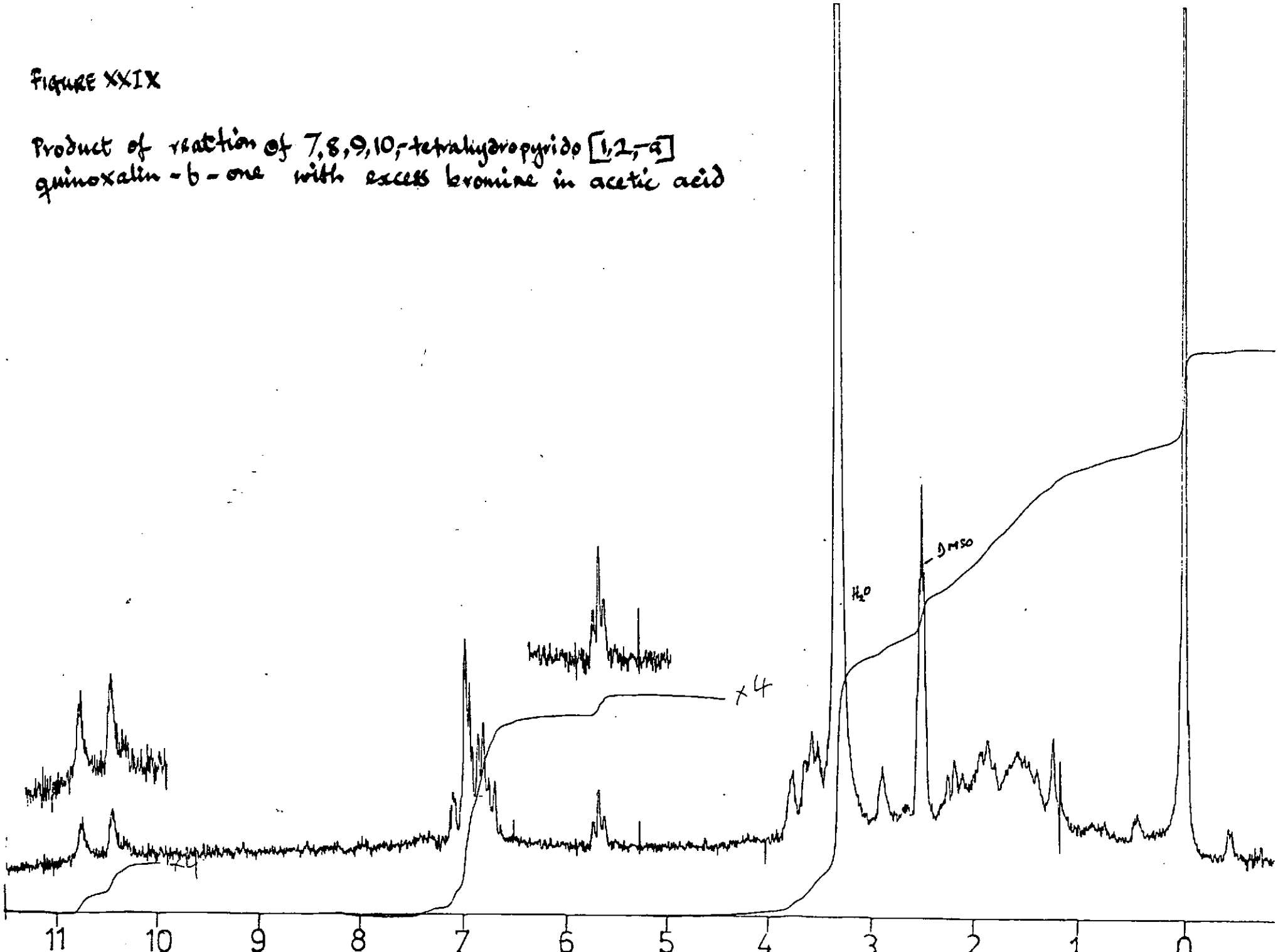
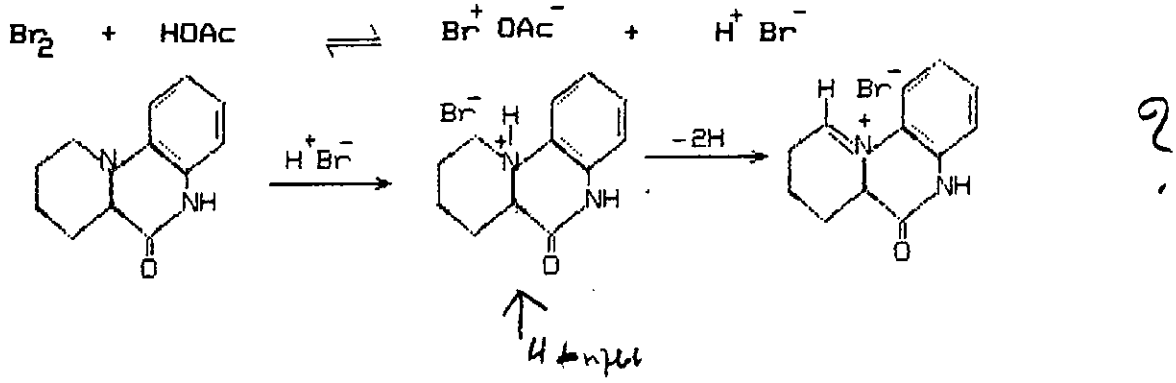


FIGURE XXIX

Product of reaction of 7,8,9,10,-tetrahydropyrido [1,2,-a] quinoxalin-6-one with excess bromine in acetic acid



experiment could not be performed to determine the orientation of bromine in the heterotricyclic products. It is however pertinent to note the presence of an olefinic proton in one of the compounds as seen from a prominent triplet at 5.66. The most plausible explanation for this signal is that deprotonation occurs following quaternization of the base by HBr-:



One of the H-10 protons is thereby lost and the signal due to the second proton is shifted to the olefinic region of the spectrum.

The IR spectrum (Fig XXVIII) further corroborates this iminium salt postulate with the appearance of a sharp band at $1635cm^{-1}$ attributed to the C=N stretching vibration. The N-H absorption as well as the C=O stretch were still present at 3100 and $1690cm^{-1}$ respectively. The skeletal stretching vibration of the aromatic ring was present at $1505cm^{-1}$. The C-H (out of plane) deformation bands present at 875 and $795cm^{-1}$ indicate a 1,2,4-trisubstituted benzene and so at least one of the constituents of

the mixture has bromine in the aromatic ring either at the 2- or 3- position.

Similarly, reaction of the parent heterocycle with N-bromosuccinimide in 50% v/v aqueous sulphuric acid gave a mixture of three mono-bromo derivatives as evidenced from elemental analysis and N.M.R. One of these compounds was successfully separated from the mixture on trituration of the reaction product with ethanol. This compound had identical m.p. and IR and p.m.r spectra as the product of the reaction of the parent heterocycle with one mole equivalent bromine in acetic acid and so was identified as the 3-bromo compound.

The remaining mixture could not be separated and had identical IR (Fig XXX) and p.m.r. spectrum (Fig XXXI) as the mixture of products obtained with excess bromine in acetic acid described above.

High temperature bromination of the parent heterotricycle with excess bromine in boiling hydrobromic acid did not give the expected dibromo derivative but rather gave a yet unidentified monobromo compound which is suspected to be a 2-bromo derivative on the basis of its IR spectrum.

The product was obtained as a brown crystalline solid m.p 278-280 ^{o}C.

The IR. spectrum (Fig XXXII) shows the expected N-H and C=O stretching vibrations of the lactam as bands at 3050 and 1625 cm^{-1} respectively . The sharp absorption band at 1625cm^{-1} is attributed to a C=N stretch and suggests that the usual

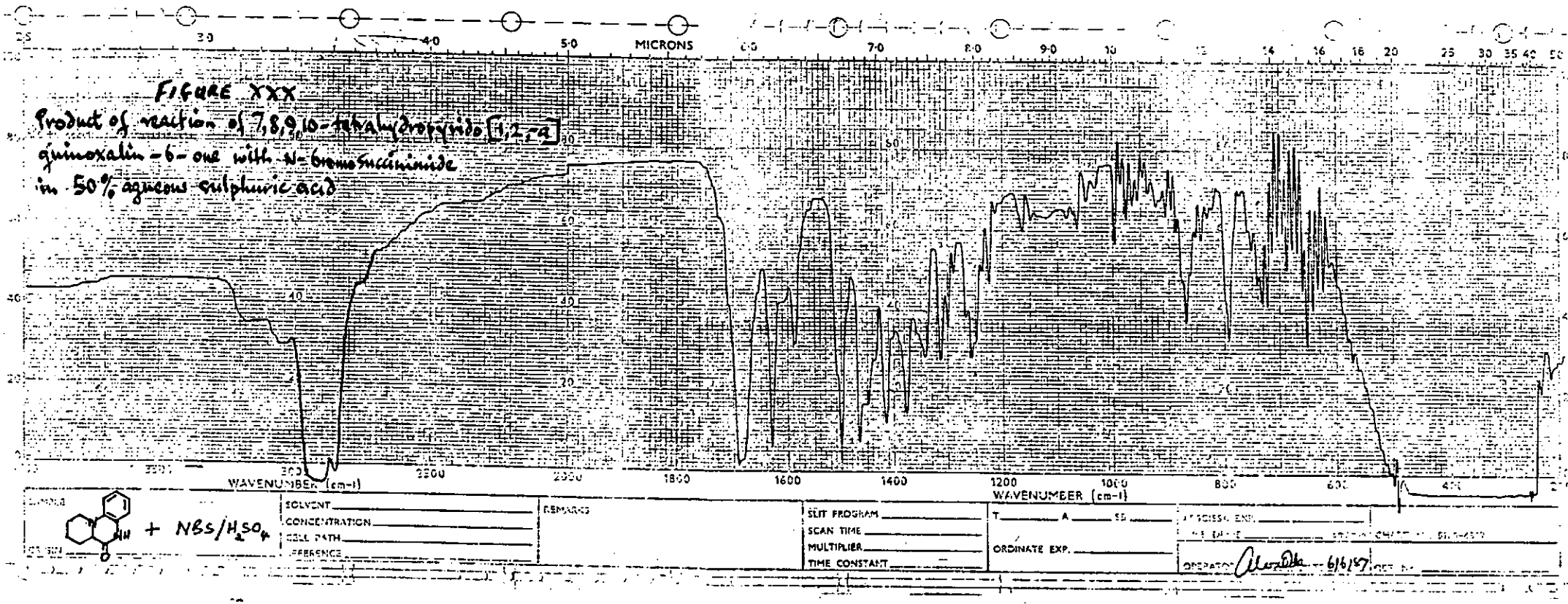
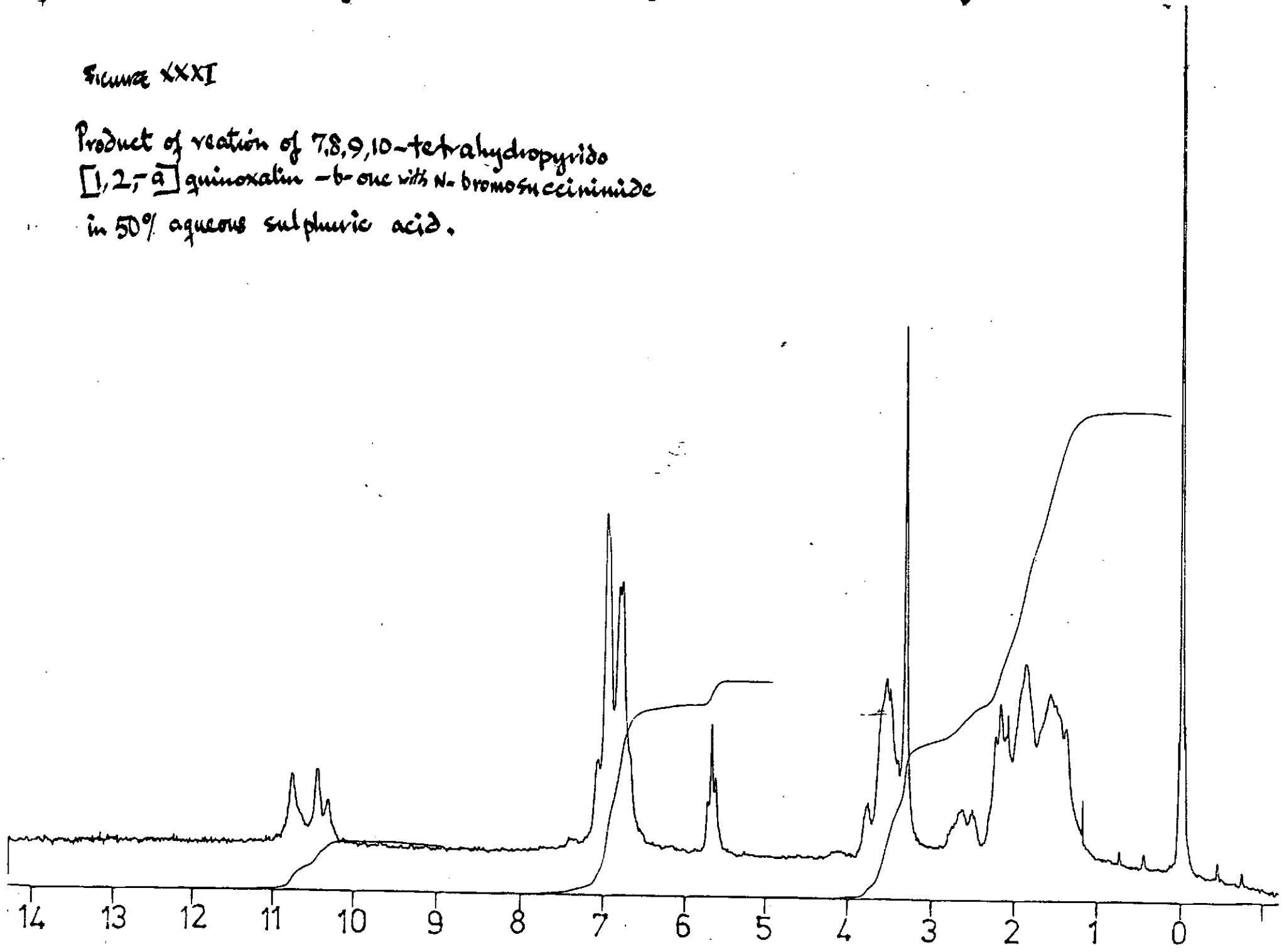


FIGURE XXX

Product of reaction of 7,8,9,10-tetrahydropyrido [1,2-a] quinoxalin-6-one with N-bromosuccinimide in 50% aqueous sulphuric acid

Figure XXXI

Product of reation of 7,8,9,10-tetrahydropyrido [1,2,-a] quinoxalin -6-one with N-bromosuccinimide in 50% aqueous sulphuric acid.



deprotonation discussed earlier occurred at position 10 of the heterocycle under the conditions of the reaction. The skeletal vibration of the aromatic ring appears at 1500cm^{-1}. Other prominent absorptions are the C-H (out of plane) deformation bands at 870 and 790cm^{-1} which indicate a 1,2,4-trisubstituted benzene and suggests that bromination had occurred at either the 2- or 3-position of the heterotricycle.

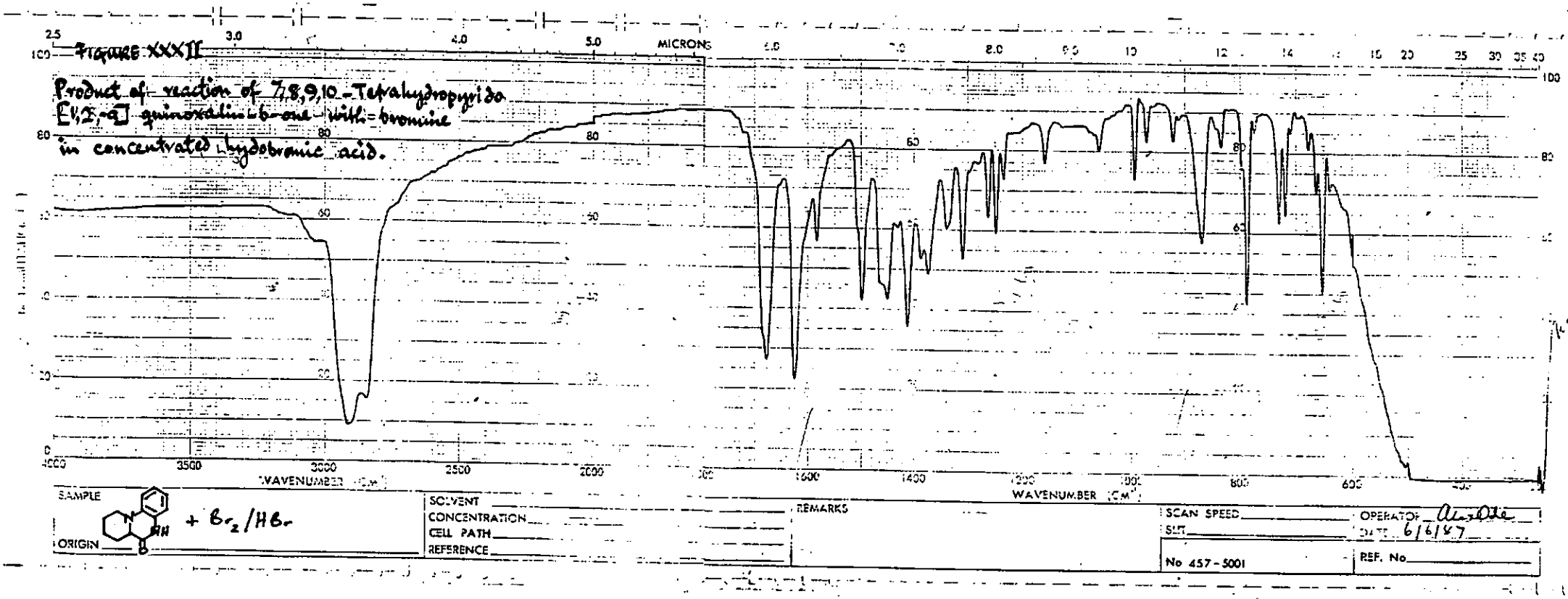
Insolubility of the products in the usual n.m.r solvents did not allow us to obtain an n.m.r spectrum. However, the IR spectrum of this compound (Fig XXXII) as well as other physical characteristics (m.p. and appearance) differed from that of the 3-bromo derivative (IR spectrum, Fig XXVII) obtained from reaction with bromine in acetic acid, and so it was assumed that substitution took place at the 2-position.

This postulate is in accordance with the proposition made in the introduction that under strong acid conditions, the amine nitrogen is fully protonated and the amide directs substitution to the 2- or 4- position. In this case quarternization of the amine nitrogen also leads to deprotonation of one of the H-10 protons thus giving rise to the prominent absorption at 1625cm^{-1} attributed to the C=N stretch resulting from such a deprotonation

The mass spectrum of this new compound (Fig XXXIII) further confirms the presence of bromine as well as the loss of two protons from the parent heterocycle. The spectra of chlorides and bromides are notable for their very characteristic isotope cluster and so the M and M+2 peaks at m/z 279 and m/z 281 with

FIGURE XXXII

Product of reaction of 7,8,9,10-Tetrahydropyrido [1,2,-a] quinoxalin-6-one with bromine in concentrated hydrobromic acid.



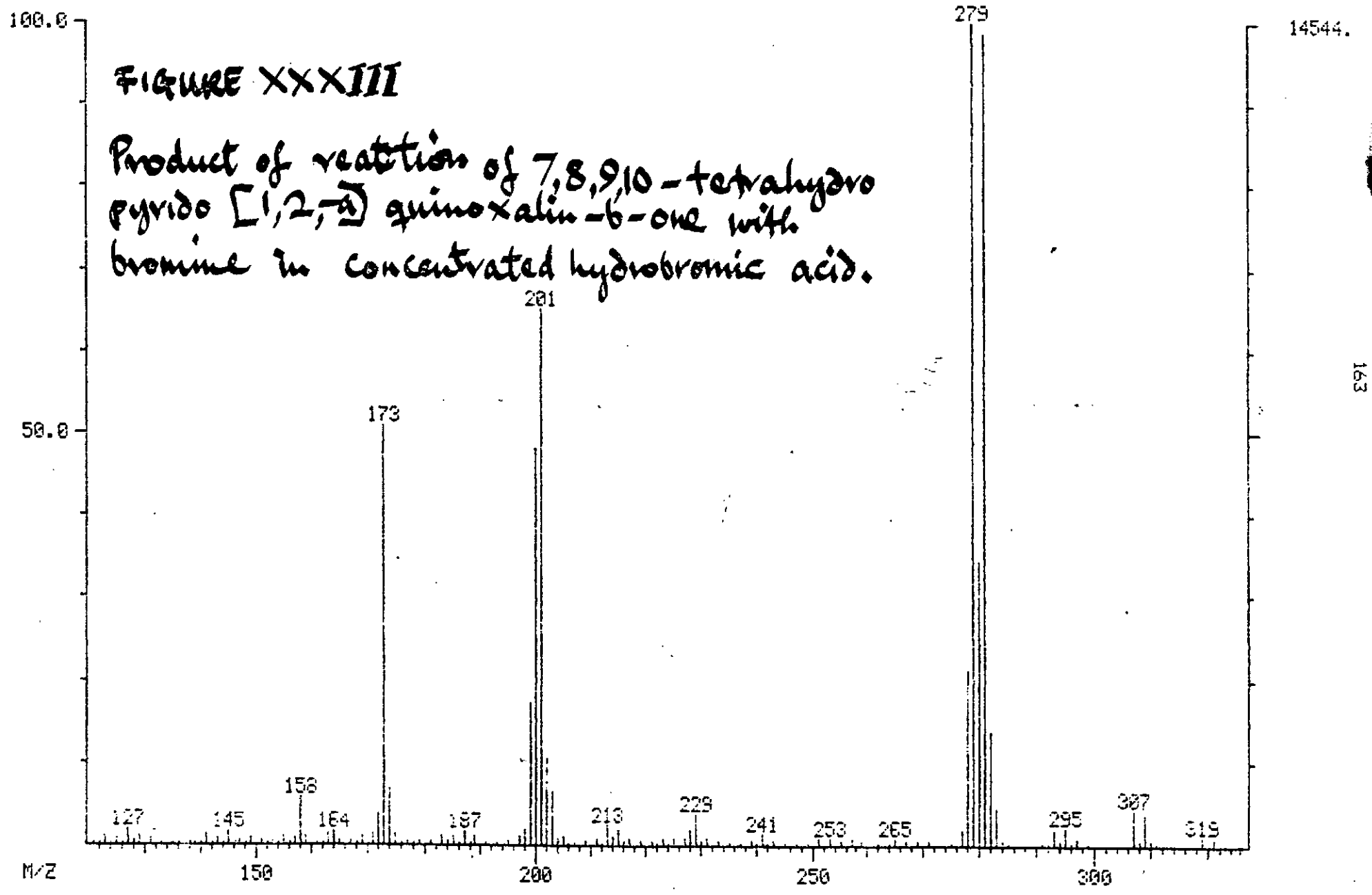


FIGURE XXXIII

Product of reaction of 7,8,9,10-tetrahydro pyrido [1,2,-a] quinoxalin-6-one with bromine in concentrated hydrobromic acid.

the expected intensity ratio of approximately 1:1 is diagnostic for a bromide. The peak at m/z 279 is also the base peak. The parent heterocycle has its molecular ion at m/z 202 (34) and so this peak at m/z 279 represents a molecule in which one bromine atom has been added to the parent heterocycle whilst two protons have been lost. If a simple electrophilic substitution of bromine into the aromatic ring had occurred, the molecular ion would have appeared at m/z 280 with an M+2 peak at m/z 282.

A definite structure for this new compound is however yet to be assigned and will require further investigation.

All attempts at nitration of the title compound with concentrated nitric acid, concentrated, nitric acid in acetic acid, or concentrated nitric acid in nitrous acid (from sodium nitrite in dilute nitric acid) gave ring opened products as evidenced from their IR spectra (Figs. XXXIV-XXXVI). The shift in the carbonyl absorption from 1675cm^{-1} to ca 1700cm^{-1} was characteristic.

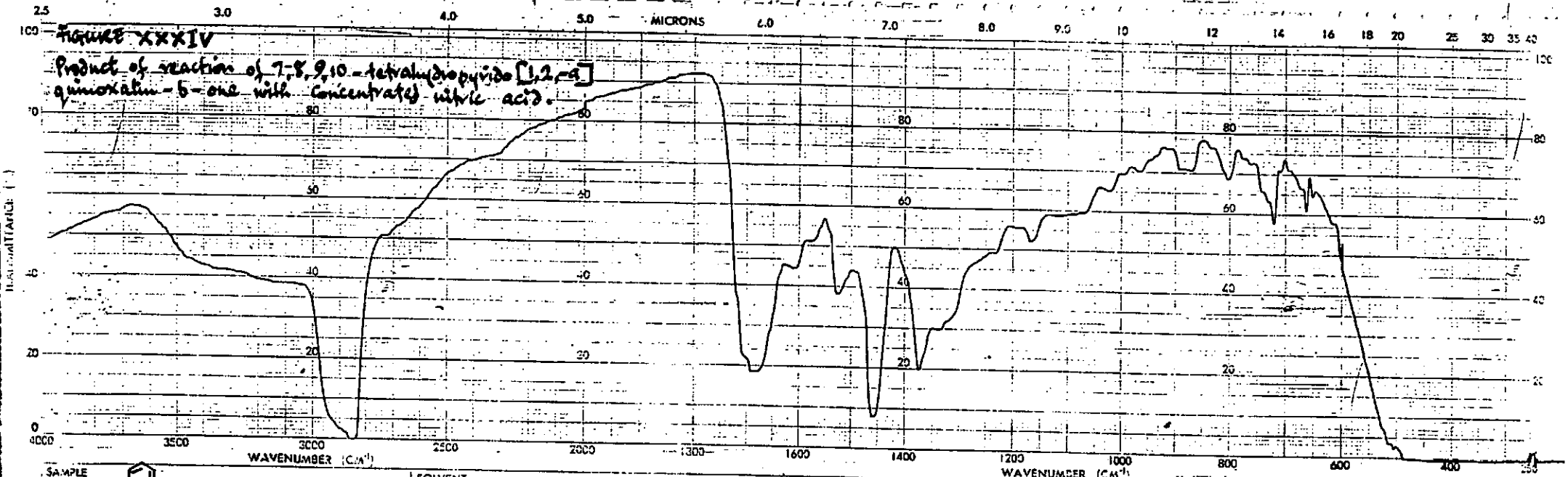
This study has therefore shown that 7,8,9,10-tetrahydropyrido [1,2-a]quinoxalin-6-one is readily cleaved by concentrated nitric acid.

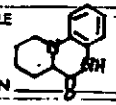
Similarly, attempts at nitrosation with sodium nitrite in dilute hydrochloric acid gave a carboxylic acid resulting from cleavage of the tricyclic ring struture (IR spectrum of product, Fig XXXVII).

The presence of a nitro group in all the products was however evident from elemental analysis which gave higher

Figure XXXIV

Product of reaction of 7,8,9,10-tetrahydropyrido [1,2-a] quinoxalin-6-one with Concentrated nitric acid.



SAMPLE  + c. HNO_3

ORIGIN

SOLVENT

CONCENTRATION

CELL PATH

REFERENCE

REMARKS

SCAN SPEED

SLIT

No 457-5001

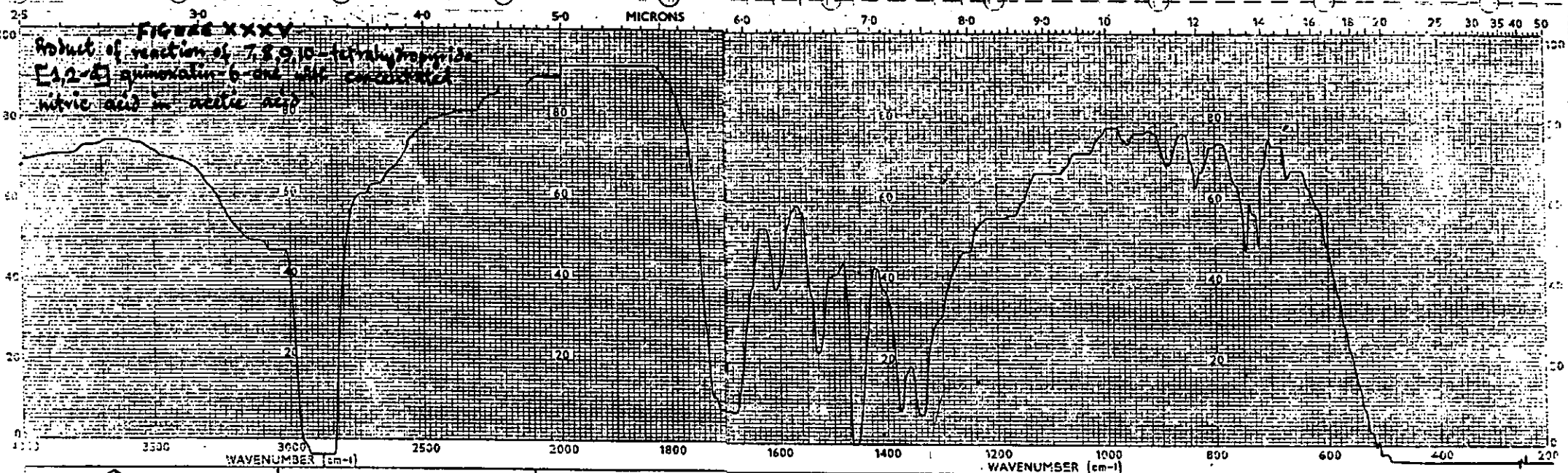
OPERATOR

DATE 12/9/57.

REF. No.

FIGURE XXXV

Product of reaction of 7,8,9,10-tetrahydropyrido [1,2-a] quinoxalin-6-one with concentrated nitric acid in acetic acid



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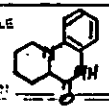

+ $C_6H_6N_2/HOAc$

SOLVENT
CONCENTRATION
CELL PATH
REFERENCE

REMARKS

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SCAN TIME
MULTIPLIER
TIME CONSTANT

T ____ A ____ SB ____
ORDINATE EXP.

ABSCISSA EXP.
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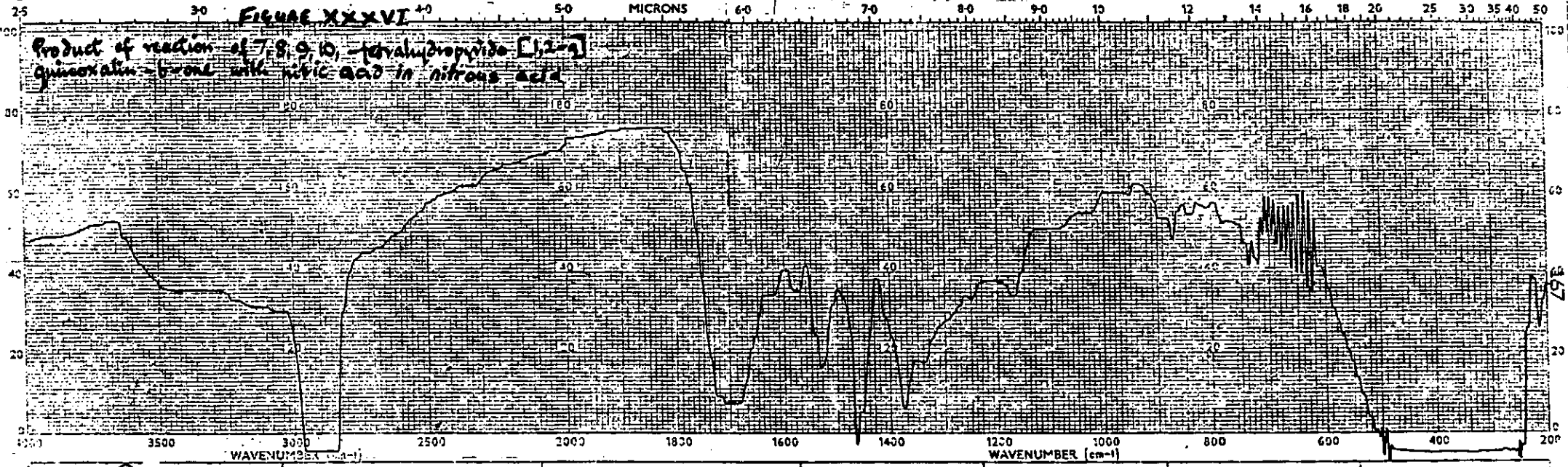
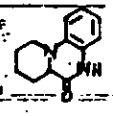
OPERATOR Alan Ok DATE 19/4/87 REF. No.

FIGURE XXXVI

Product of reaction of 7,8,9,10,-tetrahydropyrido [1,2-a] quinoxalin-6-one with nitric acid in nitrous acid



SAMPLE:  + HNO_2/HNO_3

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CONCENTRATION
CELL PATH
REFERENCE

REMARKS

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TIME CONSTANT

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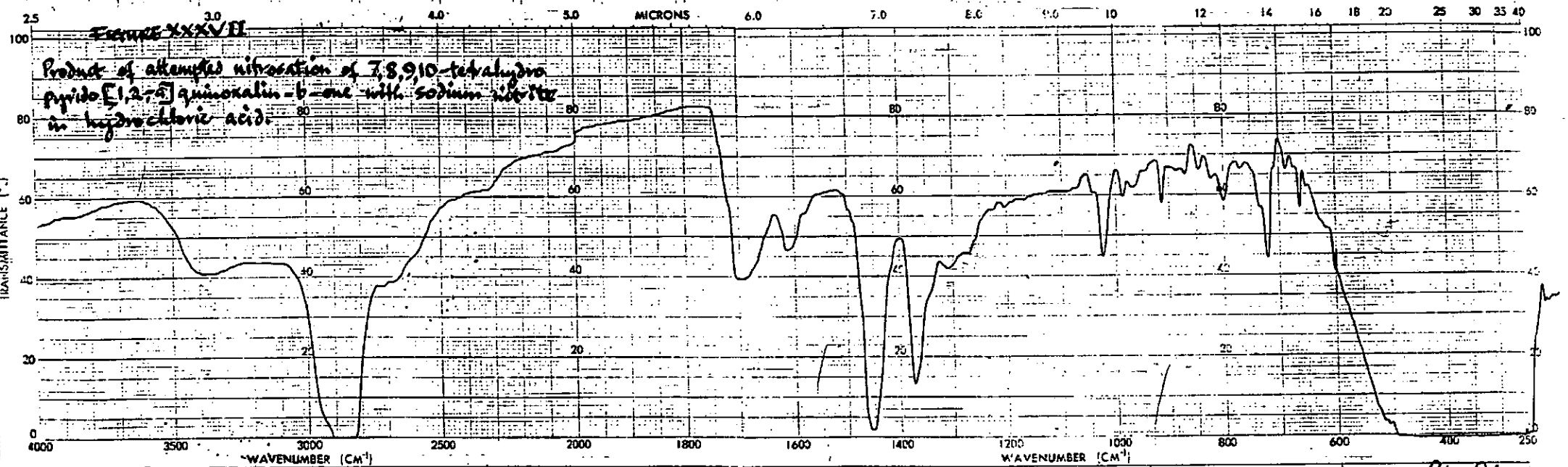
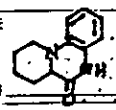
CH-7 No. 5196-4367
REF. No.

Example XXXVII

Product of attempted nitrosation of 7,8,9,10-tetrahydro pyrido[1,2-a]quinoxalin-6-one with sodium nitrite in hydrochloric acid.



SAMPLE  + $NaNO_2$ / HCl

ORIGIN

SOLVENT

CONCENTRATION

CELL PATH

REFERENCE

REMARKS

SCAN SPEED

SLIT

No 457-5001

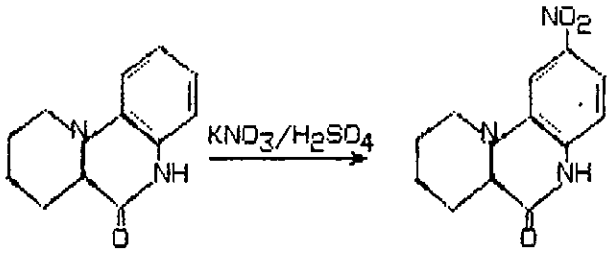
OPERATOR Alex Doe

DATE

REF. No

nitrogen content than the starting material. The products were not characterized in this study.

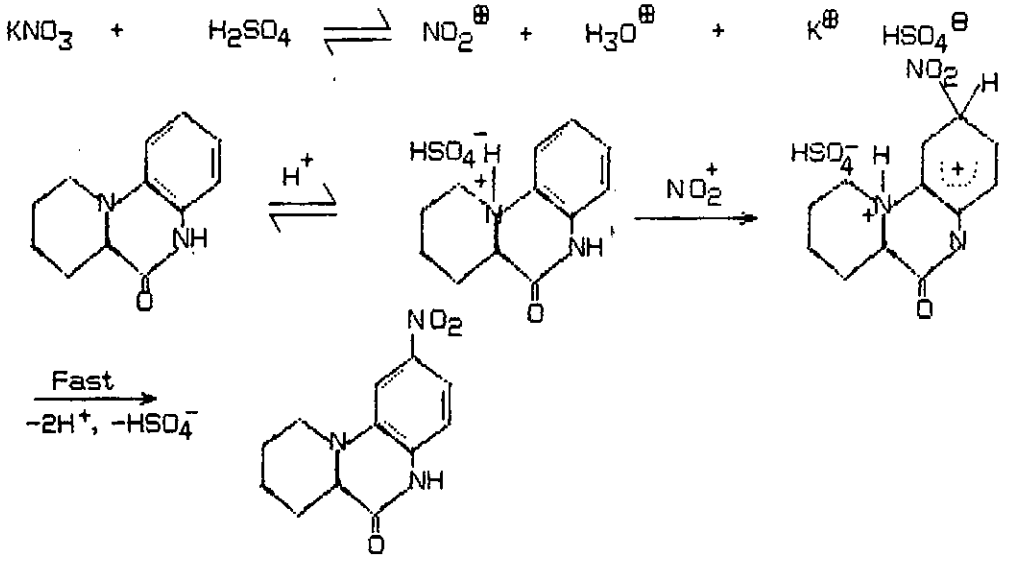
Nitration of the heterotricycle was however achieved using potassium nitrate in cold concentrated sulphuric acid, giving a mononitro derivative which after recrystallization was unambiguously identified as the 2-nitro derivative (182) from the n.O.e studies in section 2.2.2. The equation for this reaction is depicted below.



(152) (182)

The product, a brown crystalline solid, m.p 212-214 °C, was obtained in 61% yield after recrystallization from ethanol.

The mechanism of reaction is represented below:



Thus, under the strong acid conditions of the reaction, the amine nitrogen is protonated and the combined effect of the amide and the quartenary nitrogen atom directs substitution to the 2-position, which is meta to the deactivating protonated amine nitrogen and para to the amide grouping.

Deprotonation of one of the H-10 protons also occurs to some extent as can be seen from the presence of a small triplet, appearing as an impurity in the olefinic region of the p.m.r spectrum (Fig XLIII) .

The full proton spectral assignment is given in section 2.2.2. The IR spectrum of this new heterocycle (Fig XXXVIII) shows the expected N-H and C=O stretches at 3050 and 1680cm^{-1} respectively whilst the nitro group absorbed at 1510cm^{-1} .

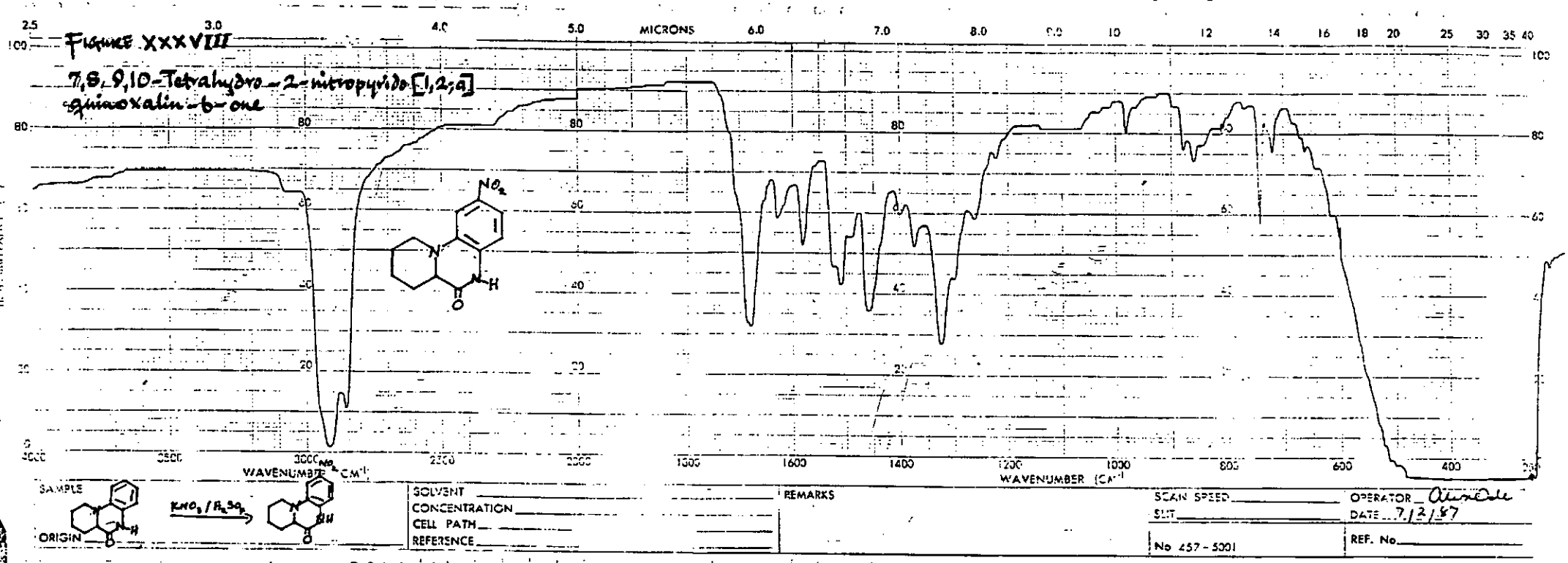
The structure of the compound was further confirmed from elemental analysis which gave values for carbon, hydrogen and nitrogen that were a close fit to the theoretical/calculated values.

Vilsmeier formylation was attempted in a bid to introduce the formyl group into the aromatic ring. Mixtures of phosphoryl chloride in dimethylformamide in varying proprotions were used. In all attempts, intractable mixtures, giving 7-10 spots on t.l.c were obtained.

Although there have been several reports on Vilsmeier formylation of aromatic heterocycles with bridgehead nitrogen atoms, none of these have saturated rings as part of their structure.

Figure XXXVIII

7,8,9,10-Tetrahydro-2-nitropyrido[1,2,a]quinoxalin-6-one



SAMPLE

ORIGIN

KNO_3 / H_2SO_4

SOLVENT

CONCENTRATION

CELL PATH

REFERENCE

REMARKS

SCAN SPEED

SLIT

No 457-5001

OPERATOR Alice Cole

DATE 7/2/87

REF. No

2.2.2 Nuclear Overhauser Enhancement studies.

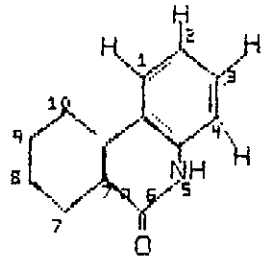
As noted in the introduction, the nuclear Overhauser effect provides a valuable method for interrelating contiguous protons[97]. Its use in heterocyclic systems is however limited to date. Never theless, an n.O.e from an N-H has been used in several instances in amides and peptides for assigning resonances. For example it has been used to assign the amide proton resonances of nicotinamide adenine dinucleotide (NAD) 98. We conjectured therefore that the n.O.e must have considerable potential in heteroaromatic chemistry where a cyclic NH can be identified, especially as such an NH will often exchange relatively slowly on an NMR time scale in solvents such as dimethylsulphoxide, and so in such instances,should be useful as an n.O.e probe .

Successful assignment of the aromatic proton signals of the parent heterocycle was clearly recognised as a pre-requisite for the use of the n.O.e in the determination of orientation of aromatic electrophilic substitution in this compound. In addition, the validity of the method had to be established using at least two other derivatives of the quinoxalinone before it could be applied to the products of reaction of the parent heterocycle with electrophilic reagents. The 3-methyl and 2-fluoro derivatives of the heterotricycle, prepared by direct synthesis as described in section 1.0 were used for this purpose.

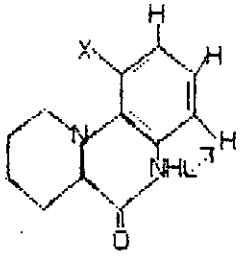
In the tetrahydropyridoquinoxalinones under study, the N-H is adjacent to H-4 of the aromatic ring and so an n.O.e enchancement was expected from N-H to H-4. The position of a substituent X on

the aromatic ring could then be determined using a combination of the coupling pattern and this n.O.e effect (see scheme 16) An n.O.e enhancement was also expected from -N-CH_2 to H-1. This strategy was therefore applied to the determination of the sites of electrophilic aromatic substitution of 7,8,9,10-tetrahydropyrido [1,2,-a]quinoxalin-6-one.

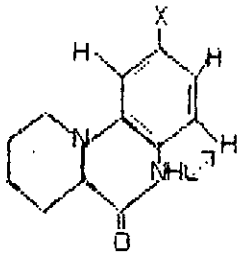
As mentioned above, the validity of this method was established using the unsubstituted heterocycle (152) its 3-methyl (176) and 2-fluoro (177) derivatives. The spectra of these compounds were simplified by running the samples at a higher magnetic field; 360 MHz, and also by selective decoupling of the N-H from the aromatic protons.



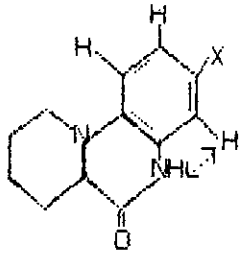
PARENT HETEROCYCLE



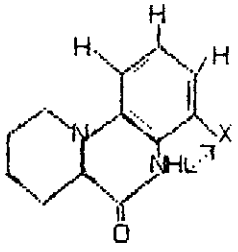
Substitution at position -1
H-4 double-doublet
(ortho + meta coupling)
n.O.e. enhancement



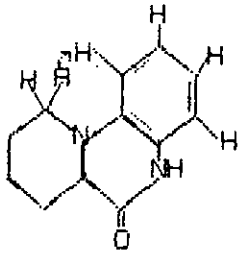
Substitution at position 2
H-4 -doublet (ortho-coupling)
n.O.e enhancement



Substitution at position 3
H-4 = doublet (small J,
meta-coupling)
n.O.e enhancement



Substitution at position 4
No H-4 to show n.O.e. enhancement



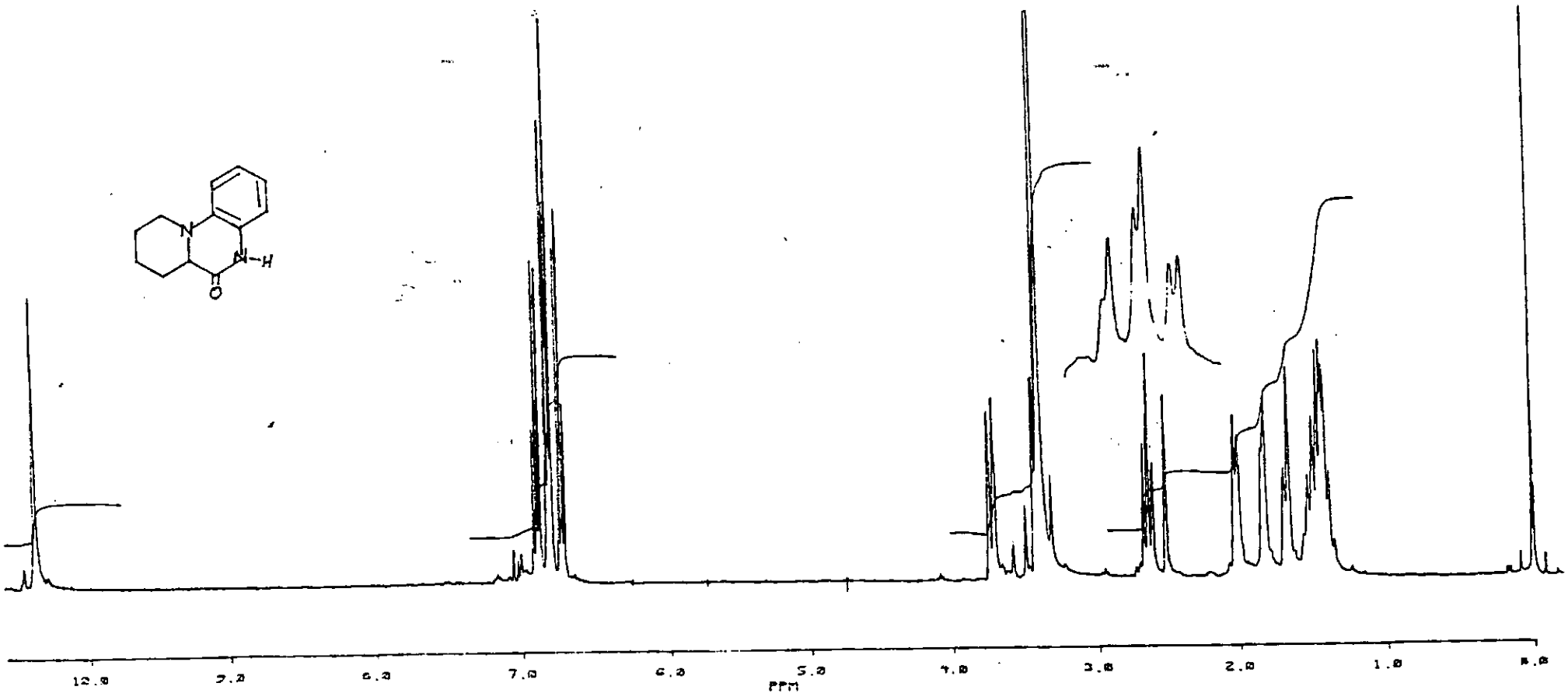
n.O.e enhancement from
N-CH_2 to H-1

SCHEME 16

The aromatic proton signals of the parent compound (152) determined in [$^{2}_{6}$H] dimethylsulphoxide at 360MHz (Fig XXXIX^{A}) comprised a triplet of doublets at 6.72 [J,7.5Hz(t) and 1.5Hz (d)] a double-doublet at 6.80 [J,7.5 and 1.5Hz] overlapping with a second broadened doublet at 6.82 (J,7.5Hz) and a further triplet of doublets at 6.89 [J,7.5Hz(t) and 1.5Hz(d)]. These protons were not distinguishable on the basis of their coupling constant values as the magnitude of the vicinal coupling constants was the same. However the relative intensities of the individual lines showed that the doublet 6.80 and triplet 6.72. arose from adjacent hydrogen atoms whilst the doublet 6.82 and triplet 6.89 represented the other contiguous protons. Irradiation of the N-H singlet (10.37) produced a 15% n.O.e enchancement at 6.80 thus establishing that this signal was due to H-4 hence the triplet at 6.72 was assigned to H-3. Irradiation of the NCH(H) signal (Heq,10-H) at 3.72 on the other hand, produced a 16% enhancement at 6.82 thus establishing that this signal was due to H-1 the triplet at 6.89 was therefore assigned to H-2. The n.O.e effects observed from N-H to H-4 and from N-CH(H) to H-1 thus allowed the assignment of the aromatic proton resonances as seen in Table 5. It is pertinent to note that the n.O.e observed from N-CH(H) to H-1 makes the assignment of the signal at 3.72 to one of the H-10 protons (Heq) unambiguous. In earlier work from this laboratory,[33,34] H-10 was reported as a two-proton multiplet at 3.9 followed by a one-proton multiplet ascribed to the 7a proton. The n.O.e experiments have therefore

FIGURE XXXIX

^{1}H-N.M.R Spectrum of 7, 8, 9, 10-Tetrahydropyrido [1,2-a] quinoxalin-6-one determined in $(CD_3)_2SO$ at 360 mH_z



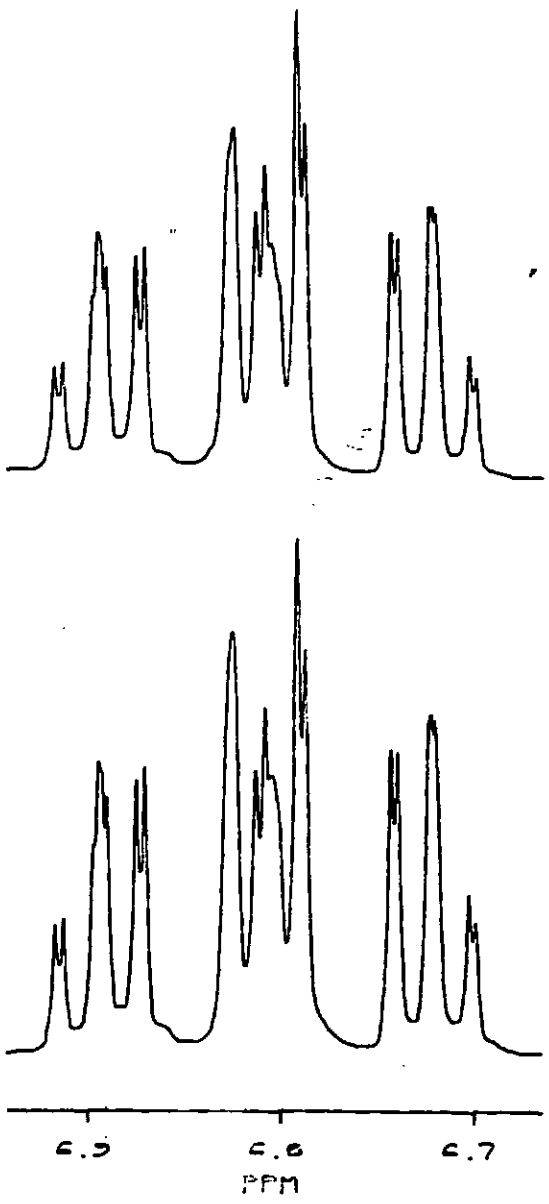
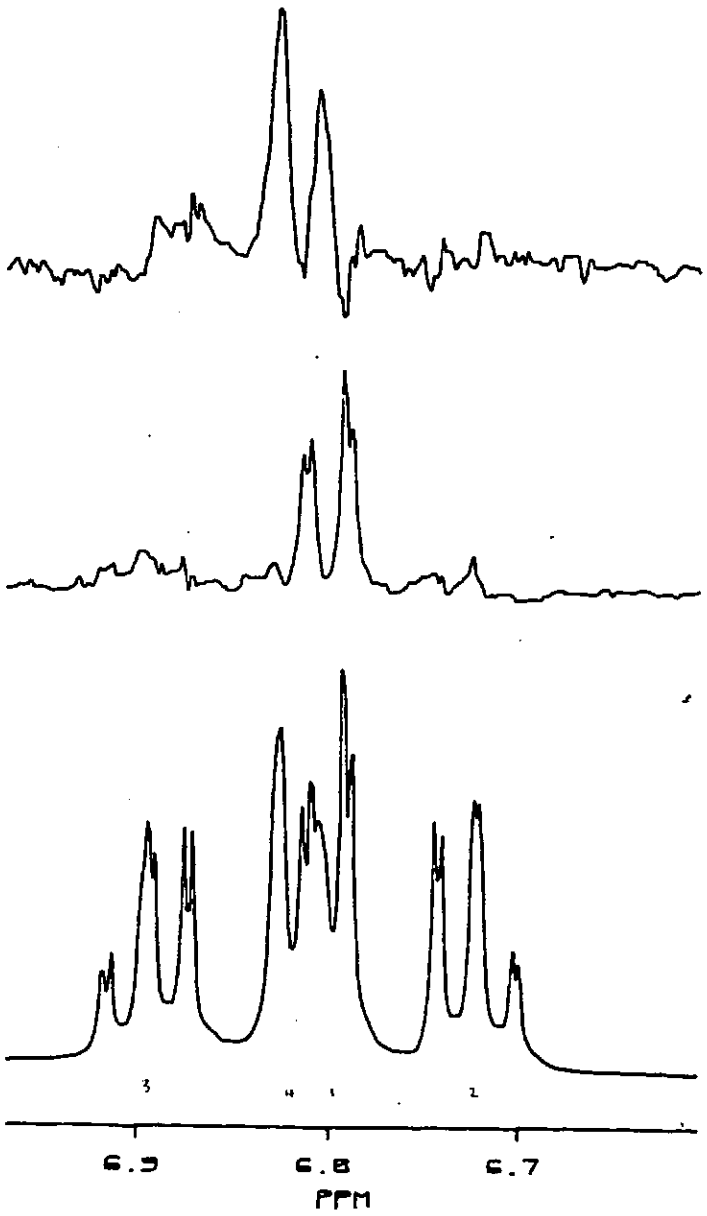


FIGURE XXXIX[A]
Expanded aromatic region of
1H-N.m.r Spectrum of 7,8,9,10-tetrahydro
pyrido [1,2-a] quinoxalin-6-one after
selective decoupling of NH

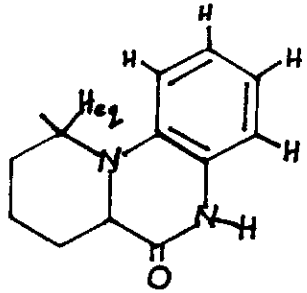
Figure XXXIX[8]

N.O.e experiments on 7,8,9,10-tetrahydro pyrido [1,2-a] quinoxalin-6-one



n.O.e. – Irradiation of Heq doublet (3.72 ppm); 16% enhancement at 6.82 ppm

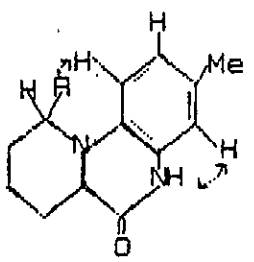
n.O.e. – Irradiation of NH singlet.; 15% enhancement at 6.80 ppm



assisted to unequivocally establish that the signal occurring lowest downfield in the aliphatic region of the spectrum is due to one of the H-10 protons (H eq). As noted in section 1.0, The H-10 protons are non-equivalent due to restricted rotation about the C-N bond. The 7-a proton is expected to be deshielded by the anisotropic effect of the carbonyl group and so the one-proton multiplet at 3.42 was assigned to this proton whilst the signal at 2.62 was assigned to the second H-10 proton.

The remaining six protons due to 7-H, 8-H and 9-H could not be unambiguously assigned at this stage (The full assignments were made by ^{13}C: ^{1}H correlation experiments in section 2.5) The signals comprise a 3-proton multiplet at 1.43 followed by three 1-proton signals at 1.66, 1.82 and 2.00 respectively.

In fully assigning the proton signals of the analogues of the heterotricycle, similar n.O.e experiments as above had to be carried out. The p.m.r. spectrum of the 3-methyl derivative of the heterocycle determined at 360MHz is shown in Figure XL.



n.O.e observed from H-4 to NH and from H-1 to NCH(H).

The aromatic proton signals of this compound comprise a one-proton singlet at 6.61 and a two-proton singlet at 6.69 (cf. a three-proton doublet in the spectrum at 80 MHz, section 1.20. Fig XVII). Irradiation at 6.61 produced a 3.3% n.O.e effect at

FIGURE XL

^1H-N-m.r Spectrum of 7,8,9,10-tetrahydro-3-methyl pyrido [1,2-a] quinoxalin-6-one determined in $(CD_3)_2SO$ at 360 MH_z

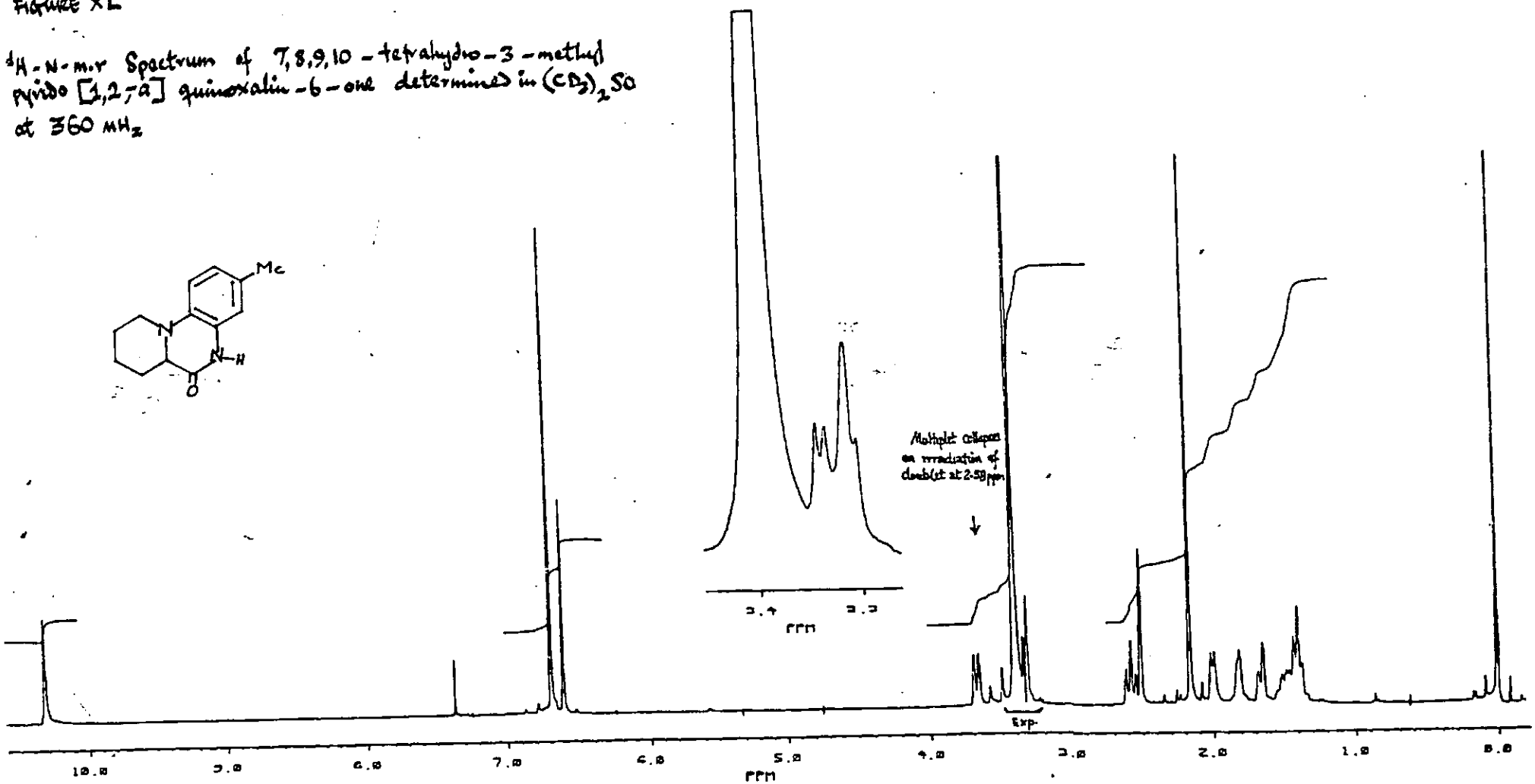
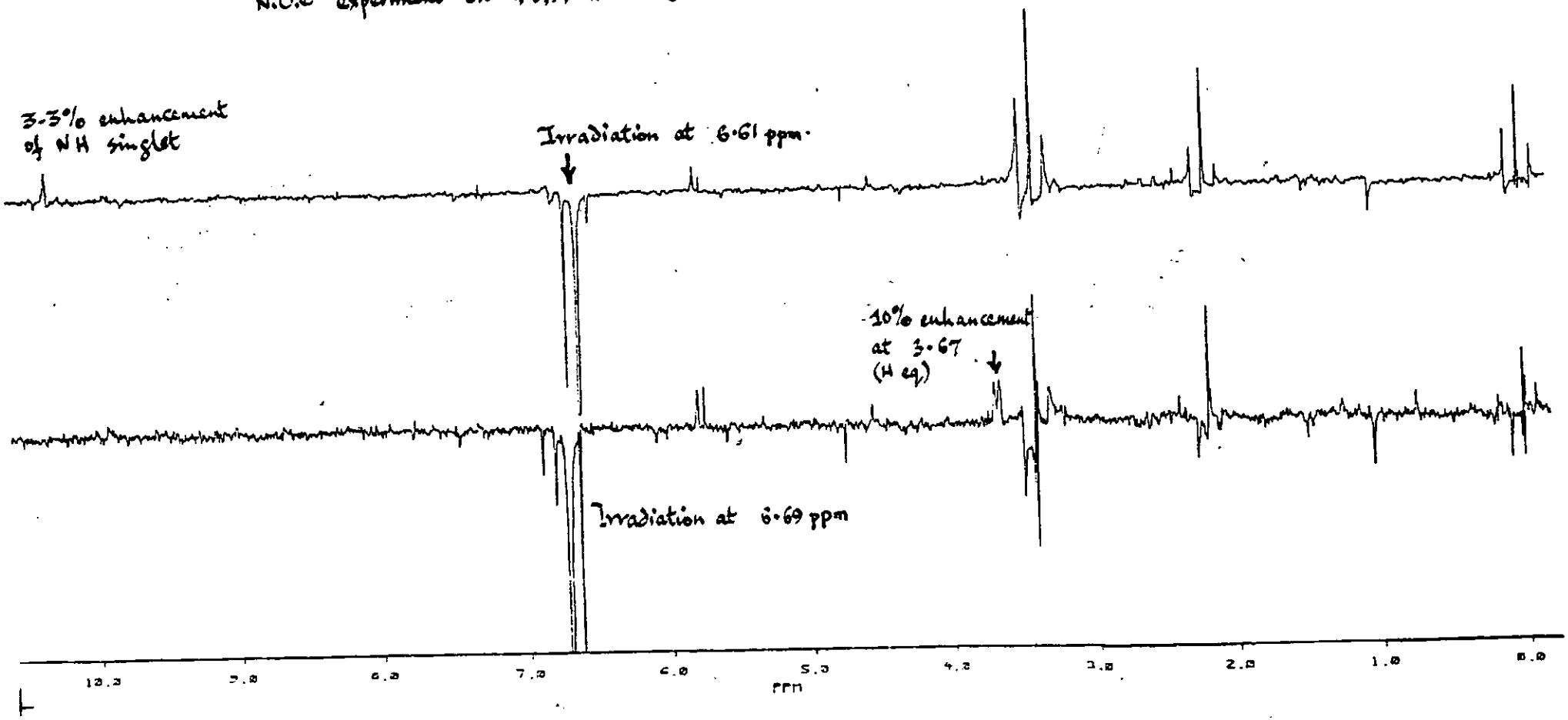


FIGURE XL[A]

N.O.e experiment on 7,8,9,10-tetrahydro-3-methyl[1,2,-a]quinoxalin-6-one

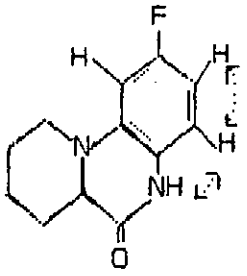


10.32 (N-H) thus establishing that this signal is due to H-4. Irradiation at 6.69 on the other hand produced a 10% n.O.e enhancement at 3.67 (H-10) and therefore this 6.69 signal is assigned to protons H-1 and H-2. Here again, the lowfield signal in the aliphatic region of the spectrum (3.67) is unambiguously assigned to one of the H-10 protons (Heq). Conclusive evidence for this assignment was obtained from the collapse of the multiplet at 3.67 on irradiation of the signal at 2.58. The signal at 3.33 was therefore assigned to the 7-a proton.

This pattern in which the signal due to the 7-a proton occurs in between the two multiplets of the H-10 protons was observed in all the tricyclic quinoxalinones investigated in this study. This is in contrast with what obtains in the N-[2'-nitrophenyl]piperidine-2-carboxylic acids in which the base proton of the carboxylic acid group i.e H-2 expectedly gives a triplet downfield from all the other signals in the aliphatic region of the spectrum (see Tables 3 and 5).

The ArMe grouping of the 3-methyl derivative of the tetrahydropyridoquinoxalinone gives rise to the characteristic 3-proton singlet at 2.16. The remaning four signals assigned to the 7-H, 8-H and 9-H protons comprise a 3-proton multiplet at 1.42 followed by three 1-proton signals at 1.64, 1.80 and 1.99 respectively .

A full assignment was similarly made of the signals in the spectrum of the 2- fluoro derivative of the heterotricycle.



n.O.e observed from H-4 to NH and from H-4 to H-3

The p.m.r. spectrum determined at 360MHz is shown in Figure XLI. The aromatic signals of this compound were rather more complex because of coupling to the ^{19}F. Three sets of signals could however be distinguished (see expansion, inset of Fig XLI): a triplet of doublets at 6.51 followed by a double-doublet at 6.68 and a further triplet at 6.75. Irradiation at 6.75 produced a 16% n.O.e enhancement at 6.51 and a 6% n.O.e enhancement on the N-H signal (10.40). The triplet at 6.75 is therefore unambiguously assigned to H-4 whilst the other triplet at 6.51 represents the adjacent proton i.e H-3 The doublet at 6.68 therefore belongs to H-1. A full assignment of the aromatic protons was therefore done without the observation of an n.O.e from NCH(H) to H-1. It was not necessary to perform this second n.O.e experiment since irradiation of H-4 provided the information needed for a complete assignment of the three aromatic proton signals. The signals at 2.66 and 3.72 were as usual assigned to the two H-10 protons following the pattern already observed in the parent heterocycle and its methyl derivative. Similarly the one-proton multiplet at 3.50 was assigned to the 7-a proton. Again the other signals in the aliphatic region of the spectrum could not be completely assigned; protons 7-H, 8-H

FIGURE XLI

^{1}H-N-m·r Spectrum of 7,8,9,10-tetrahydro-2-fluoropyrido [1,2-a] quinoxalin-6-one determined in $(CD_3)_2SO$ at 360 mH_z

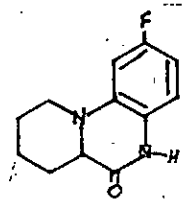
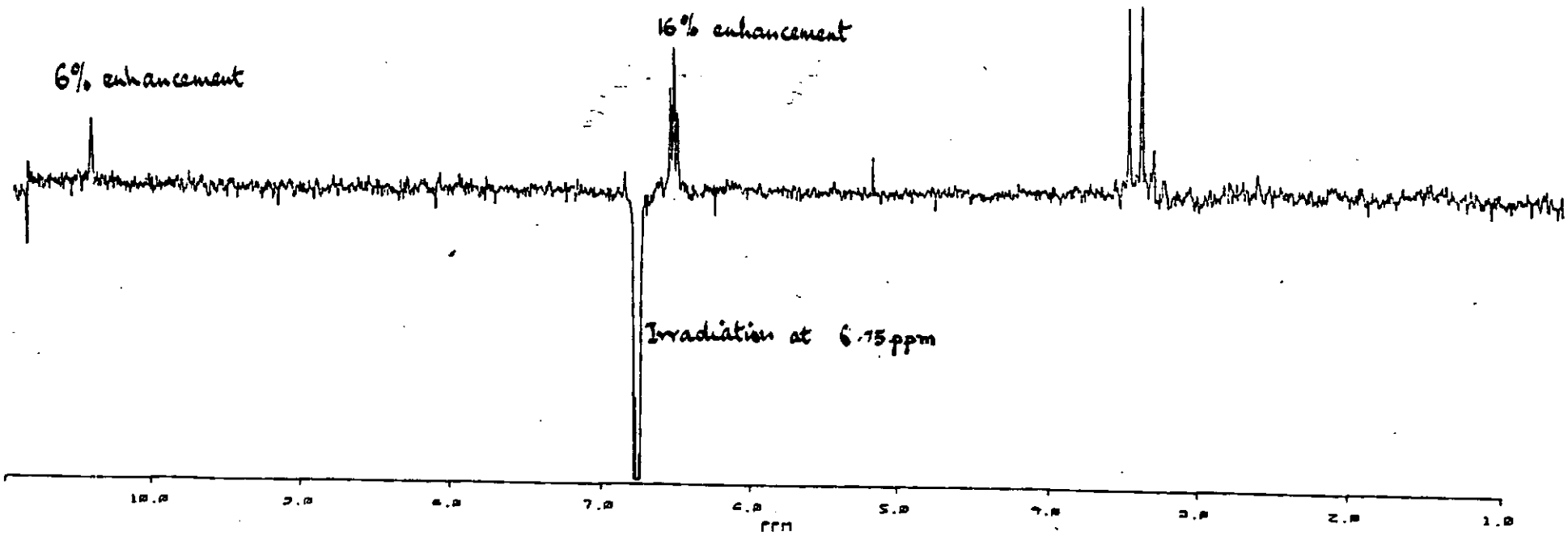


Figure XLI[A]

n.O.e experiment on 7,8,9,10-tetrahydro-2-fluoropyrido [1,2-a] quinoxalin-6-one.



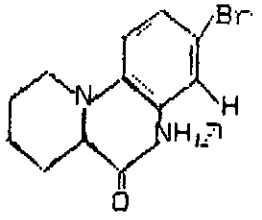
and 9-H give rise to the multiplets at 1.48 and 2.00.

This strategy was then employed to fully characterize two of the products of aromatic electrophilic substitution described above viz:

(i) The product of bromination of the parent heterocycle with one mole equivalent bromine in acetic acid and,

(ii) The product of nitration of the heterotricycle with potassium nitrate in cold concentrated sulphuric acid.

The spectrum of the monobromo compound obtained from the bromination reaction is shown in Figure XLII. The aromatic signals comprised a doublet at 6.76 (J,8.5Hz) another doublet at 6.93 (J,2.2 Hz) followed by a multiplet at 7.02. The 2.2Hz coupling constant of the signal at 6.93 indicates that it belongs to a proton that is meta-coupled. This provides evidence of substitition either at position 2- or 3- of the heterocycle in the same way as the IR spectrum (Fig XXVII) which indicates a 1,2,4-trisubstituted benzene. However on irradiation of this meta-coupled doublet, a 4% n.O.e effect was produced at 10.51 (NH) indicating that this signal is due to H-4 and therefore substitution must have occured at the 3-position.



n.O.e. enhancement of NH on irradiation of H-4 (doublet, 2.2 Hz, meta-coupled)

FIGURE XLII

^{1}H-N.m.r spectrum of 7,8,9,10-tetrahydro-3-bromopyrido [1,2,-a] quinoxalin-6-one determined in $(CD_3)_2SO$ at 360 MHz

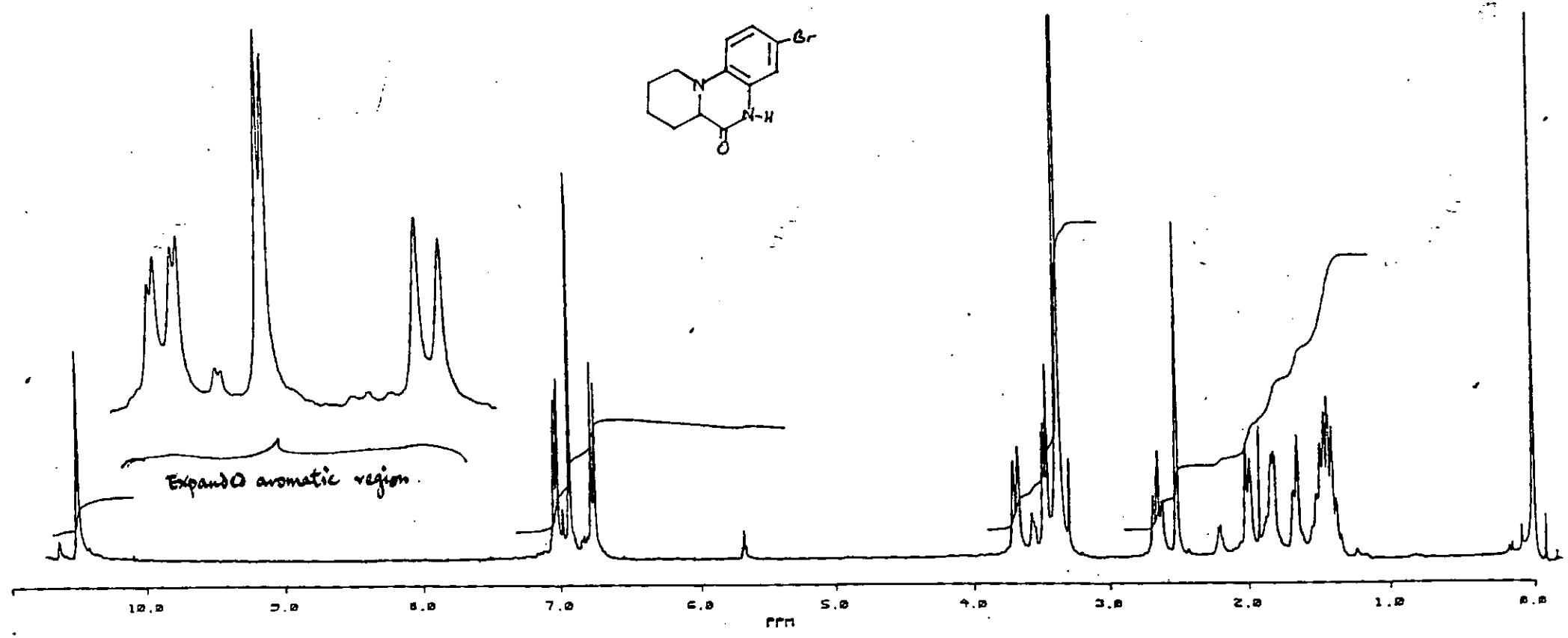
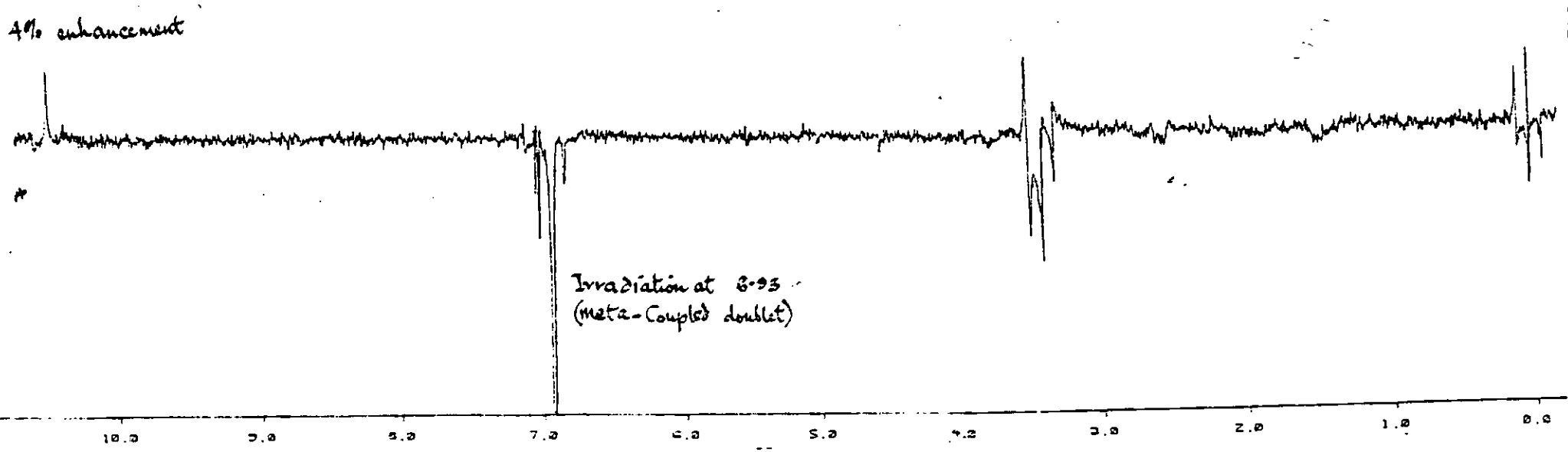


FIGURE XLII[A]

N.O.e experiment on 7,8,9,10-tetrahydro-3-bromopyrido [1,2,-a] quinoxalin-6-one



The low field multiplet at 7.02 was assigned to H-2 which is expected to be deshielded by the adjacent electronegative bromo-substituent and the multiplicity is due to extensive ortho- and meta-coupling. The high field doublet at 6.76 is only ortho-coupled (J,8.5Hz) and was assigned to H-1.

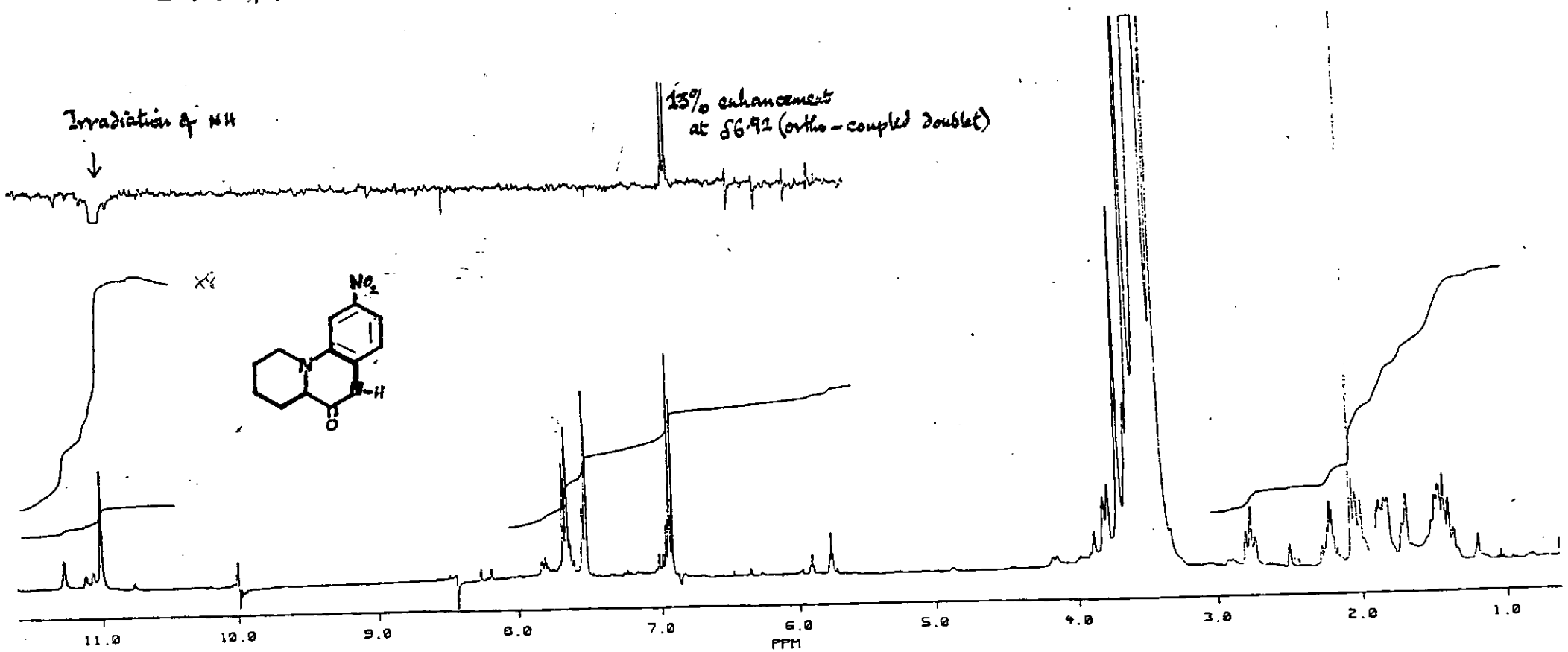
The signals in the aliphatic region of the spectrum were assigned in a similar manner to those of the derivatives already described. Thus the H-10 protons appeared as usual as two sets of multiplets at 2.64 and 3.90 respectively. The one -proton multiplet at 3.48 was assigned to the 7-a proton whilst the remaining sets of multiplets at 1.43, 1.82 and 2.00 account for the other six piperidine ring protons i.e 7-H 8-H and 9-H. Thus, full assignments of the aromatic signals of the bromination product allowed unambiguous identification of this new compound as 7,8,9,10-tetrahydro-3-bromopyrido[1,2,-a]quinoxalin-6-one.

Difficulties were initially experienced in carrying out the n.O.e experiment on the mononitro compound obtained from reaction of the heterocycle with potassium nitrate in cold concentrated sulphuric acid. This problem was however eventually solved by complete degassing of the n.m.r experiment solution with argon in order to remove gaseous paramagnetic impurities. The spectrum is shown in Figure XLIII.

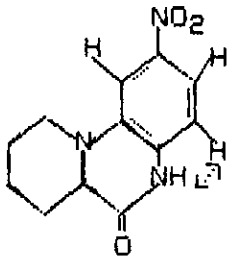
The aromatic signals in this case comprised two sets of multiplets at 7.51 and 7.65 and a doublet (J,8.5Hz) at 6.92. The coupling constant indicates that this proton is ortho-coupled and so substitution again has occurred either at position 2 or

FIGURE XLIII

^{1}H - N.m.r spectrum of 7,8,9,10 – tetrahydro-2-nitropyrido [1,2-a] quinoxalin-6-one and N.O.e experiment.



3. However, irradiation of the N-H signal at 10.40 produced a 13% n.O.e enchancement on this doublet thus confirming that the signal is due to H-4, and hence substition has occurred at position 2.



n.O.e enhancement of H-4 (doublet, ortho coupled) on irradiation of N-H

This experiment therefore proved that this nitro compound which differed from the 3-nitro compound obtained previously by ring synthesis (section 1.2) is 7,8,9,10-terahydro-2-nitropyrido [1,2-a]quinoxalin-6-one.

The aliphatic proton signals were assigned in a similar manner to those previously described for the other derivatives of the heterotricycle. Thus, the signals at 2.75 and 3.70 were assigned to the H-10 protons whilst the 7-a proton appeared at 3.42.

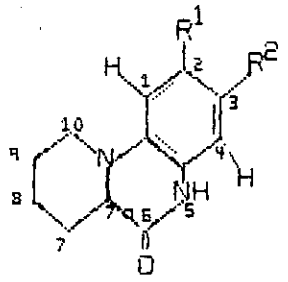
The remaining six piperidine ring protons of 7-H, 8-H and 9-H appeared as multiplets at 1.43, 1.68, 1.84 and 2.00 respectively.

The proton spectral assignments of the parent hetrocycle, its 3-methyl-; 2-fluoro-; 3-bromo-; and 2-nitro- derivatives are given in Table 5.

In conclusion, the original proposition that electrophilic aromatic substitution of the ring system under study may occur either at C-2 or C-4 if the piperidine nitrogen is protonated and

TABLE 5

^{1}H NMR SPECTRA OF 7,8,9,10-TETRAHYDROPYRIDO[1,2-a]QUINOXALIN-6-ONES (DETERMINED IN $(CD_3)_2SO$ AT 360MHz



152; $R^1 = R^2 = H$
176; $R^1 = H$, $R^2 = Me$
177; $R^1 = F$, $R^2 = H$
180; $R^1 = H$, $R^2 = Br$
182; $R^1 = NO_2$, $R^2 = H$

	COMPOUND				
PROTON	(152)	(176)	(177)	(180)	(182)
H-1	6.82	6.69	6.68	6.76	7.51
H-2	6.89	6.69		7.02	
H-3	6.72		6.51		7.65
H-4	6.80	6.61	6.75	6.93	6.92
H-5(NH)	10.37	10.32	10.40	10.51	10.40
H-7a	3.42	3.33	3.50	3.48	3.42
H-7	1.43 1.65	1.42 1.64	1.44	1.43 1.64	1.43 1.68
H-8					
H-9	1.82 2.00	1.80 1.99	2.00	1.82 2.00	1.84 2.00
H-10	2.62 3.72	2.58 3.67	2.66 3.72	2.64 3.70	2.75 3.70
Ar-Me		2.16			

the amide directs substitution or at C-1 or C-3 if sufficient non -protonated material is present, has been substantiated by the results obtained. Hence, under the less strongly acidic conditions of the bromination in acetic acid, the piperidine nitrogen dominates aromatic substitution, whilst under the more strongly acidic conditions in sulphuric acid, this nitrogen atom is protonated and the amide directs substitution. A similar dichotomy has previously been observed by Cheeseman in the nitration of quinoxalin-2-ol[99]. This further confirms the hypothesis that the tetrahydropyrido[1,2-a]quinoxalin-6-one resembles the parent quinoxaline more closely than the analogous pyrrolo[1,2-a] quinoxaliines in its reactions. From the review of pyrrolo[1,2-a] quinoxaline chemistry in the introduction, it is clear that the chemistry of these heterotricycles is dominated by the chemistry of the pyrrole ring. This explains the greater reactivity of the pyrroloquinoxalines towards electrophilic reagents as compared to the pyrido[1,2-a]quinoxalines and in particular, the tetrahydro derivative under study. The effect of the non-aromatic rings is expectedly to reduce the reactivity of the heterocycle and also to increase the possiblity of ring cleavage owing to ring strain.

Furthermore, ^{1}H-N.m.r nuclear Overhauser enhancement studies involving the amide N-H of 7,8,9,10-tetrahydropyrido[1,2-a] quinoxalin-6-ones have been used to identify the aromatic proton resonances of the quinoxalin-6-ones and the applicability of the n.O.e. to the determination of the sites of electrophilic aromatic substitution in heteroaromatic compounds possessing such N-H groups has been demonstrated.

2.3.0 ALKYLATION REACTIONS

One of the major problems encountered in the course of this study was the insolubility of the tetrahydropyridoquinoxalines. All the compounds prepared by direct synthesis as well as the reaction products obtained vide infra (section 2.2) were insoluble in most organic solvents and this prevented their easy purification by the usual methods of column chromatography or preparative t.l.c. As a result, in cases where two or more reaction products were obtained, they could not be adequately separated for unequivocal identification. It was conjectured that these insolubility problems arose from intermolecular hydrogen bonding and could therefore be solved by N-alkylation of the heterocycle. This assumption has now been circumstantiated in this work.

As was highlighted in the review of pyrrolo[1,2-a] quinoxaline chemistry, these heterocycles are known to react readily with various alkylating agents either in dimethylformamide with sodium hydride as base or in methanolic sodium methoxide to give the N-alkyl derivatives in good yields. It was therefore envisaged that the pyridoquinoxalinones under study would react in a similar manner. Working on this presumption, we anticipated obtaining the N-methyl derivative of the parent heterocycle, which would be more soluble, and examining the electrophilic substitution reactions on this compound. In addition to removing the hydrogen bonding that contributes to the relative insolubility of these quinoxalinones, it was also anticipated that the results of these reactions could then be contrasted with the N-methylation products

of compounds derived from direct substition in order to examine the possibility of contributions from N-haloamide rearrangements. Furthermore, the presence of an N-methyl group was expected to afford a very useful ^{1}H-NMR standard which could be used, not only to assess purity but also as a probe for nuclear Overhauser enhancement studies. Preparation of this N-methyl compound however proved more difficult than initially expected.

2.3.1 N-Alkylation with ethyl iodide using 'aged' sodium hydride in dimethylformamide.

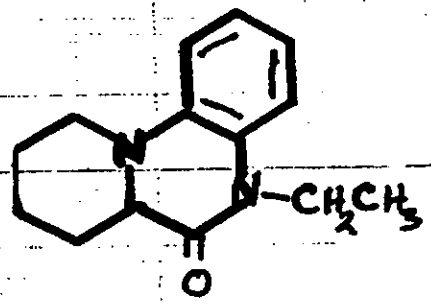
The first attempt to obtain the N-alkyl derivative of the parent pyridoquinoxalinone using ethyl iodide in dimethyl formamide in the presence of an old stock of sodium hydride was successful. T.l.c. of the reaction product showed one major component and some impurities including unreacted starting material . This new compound 7,8,9,10-tetrahydro-5-ethylpyrido[1,2-a]quinoxalin-6-one, was expectedly soluble in almost all organic solvents and so purification was easily done by preparative t.l.c using ethyl acetate/petroleum ether mixtures.

Evidence that alkylation had occured was obtained from the p.m.r. spectrum (Fig XLIV) which showed the characteristic two proton quartet and three proton-multiplet due to the ethyl group. This was further corroborated by the absence of a signal due to N-H. All other signals were consistent with the pyridoquinoxaline structure indicating that the tricyclic ring was intact.

The equation for this reaction is given below

CHART S-60T
MADE IN U.S.A.

FIGURE XLIV



500 400 200 200 100 0 Hz

8.0 7.0 6.0 5.0 PPM (δ) 4.0 3.0 2.0 1.0 0

SWEEP OFFSET (Hz): /
SPECTRUM AMPLITUDE: 10
INTEGRAL AMPLITUDE: 2
SPINNING RATE (RPS): 40

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: Pyridone alkylation product c EtI

REMARKS: after prep t.l.c.

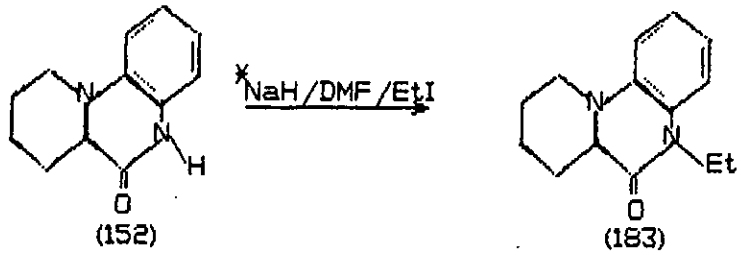
SOLVENT: $CDCl_3$

varian
analytical instrument division

DATE: 15/8/84

OPERATOR: ALO

60 MHz NMR
SPECTRUM NO.



(152) (183)

* The sodium hydride used in this reaction had been stored for a long time and consequently converted to sodium hydroxide on prolonged exposure to air and moisture.

The signals in the aliphatic region of the proton magnetic resonance spectrum (Fig XLIV) comprised a broad, four proton multiplet at 1.2-1.5. assigned to 8-H and 9-H followed by a three proton multiplet at 1.7 assigned to 7-H and one of the 10-H protons. The two further one proton multiplets at 2.0 and 2.5 were assigned to 7a-H and the second 10-H proton respectively. The remaining two signals in this region were unequivocally assigned to the ethyl group and comprised a three proton multiplet at 3.5 and a two-proton quartet at 4.0.

The aromatic signals comprised a three proton multiplet at 6.9 followed by a one proton singlet at 7.15, accounting for the four aromatic protons.

As all attempts to repeat N-alkylation with fresh sodium hydride failed, the success of the reaction was later deduced to be due to the presence of sodium hydroxide (from hydrolysis of sodium hydride on long standing).

2.3.2 Attempted N-Alkylation Reactions

Spurred on by the result obtained above several attempts were made to obtain the N-methyl derivative of 7,8,9,10-tetrahydropyrido[1,2,-a]quinoxalin-6-one by reacting the

heterocycle with methyl iodide in dry dimethylformamide or tetrahydrofuran in the presence of sodium hydride (this time a fresh bottle of an 80% dispersion in oil). In all cases an oily product was obtained which would not crystallize out. The proton magnetic resonance spectrum of this oil did not show the usual set of multiplets expected for the piperidine ring protons and the IR spectrum showed no carbonyl absorptions. This suggested that cleavage of the tricyclic ring had occurred.

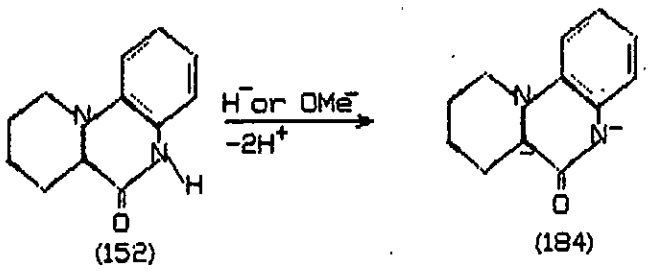
In further attempts to obtain the N-methyl derivative, the pyridoquinoxalinone was reacted with dimethylsulphate in methanolic sodium methoxide according to the procedure described by Cheeseman and Tuck[18] for the methylation of 4-oxopyrrolo [1,2-a]quinoxaline. A brown crystalline solid was obtained which showed no aromatic protons and no carbonyl absorption in the NMR and IR spectra respectively.

The same product was obtained on heating the heterotricycle with methyl iodide in methanolic sodium methoxide. Taylor and Cheeseman[26] had used this method to methylate a 1,5-dihydro-1-oxo derivative of pyrrolo[1,2,-a]quinoxaline,

The NMR data on the products of these reactions suggest that a rupture of the tricyclic ring structure occurred to give either a substituted benzene or an aliphatic compound. The absence of a carbonyl absorption in the IR spectrum is significant and suggests that the cleavage of the ring occurred on either side of the carbonyl group.

The most plausible explanation for these observations is

that deprotonation of both the lactam nitrogen and the 7a-carbon is achieved by the strong base used (sodium hydride or sodium methoxide.)



(152) (184)

A dianion such as (184) is then obtained which leads to two possible attacking atoms aside from the possibility of attack by oxygen. Attack on the alkyl halide by the 7-a carbon anion would be expected to result in cleavage of the already strained pyrido ring. The heterocycle may be compared with 1,3-dicarbonyls which may be deprotonated, if treated with two moles of strong enough base, to give dianions such as:

$$CH_3\text{-}CO\text{-}CH_2\text{-}CO \xrightarrow{\text{2 moles base}} CH^{-}\text{-}CO\text{-}CH^{-}\text{-}CO\text{-}$$

Such dianion synthons (called ambident nucleophiles) may attack in two or more different ways to give different products.

Usually, ambident nucleophiles with two potentially attacking atoms can attack with either of them depending on conditions, and mixtures of products are often obtained.

A useful general principle first reported by Hauser and Harris[100] has been applied successfully several times to obtain the

desired product in such reactions. According to this principle, whenever we desire to remove a proton at a given position for use as a nucleophile but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position since it is the ion of the weaker acid. On the other hand, if it is desired to attack with the more acidic position, all that is necessary is to remove just one proton .

Applying this principle to the quinoxalinone, the N-H group is more acidic than the 7-a C-H group and so on removal of both ions by the strong hydride or methoxide ions, attack on the alkyl halide is by the 7a-carbon anion rather than the N-anion since it is the ion of the weaker acid. This invariably leads to a cleavage of the tricyclic ring rather than the desired N-alkylation. Thus the rationale for the successful N-alkylation of the heterolactam when aged sodium hydride was used, is based on the extensive conversion of the sodium hydride to sodium hydroxide.This weaker base only mono-deprotonated i.e abstracted only one proton, that of the stronger acid (N-H) thereby leading to smooth N-alkylation.

Subsequently the work was directed towards methods of N-alkylation in which a mild base would be used. Two methods were investigated. (1) N-alkylation with methyl iodide in the presence of potassium hydroxide in dimethylsulphoxide. This method had been used for the successful N-alkylation of indole and pyrrole[101] as well as N- and O- alkylation of phenols, alcohols,

amides and acids[102]. (2) Phase transfer catalysis, which has been discussed in the introduction.

Both methods were primarily devised in a bid to ensure a homogeneous reaction mixture. In nucleophilic substitions, the organic substrate is usually insoluble in water and other polar solvents, while the nucleophile is often an anion, which is only soluble in water. Consequently , a dipolar aprotic solvent such as dimethylsulphoxide may serve to dissolve both species or phase transfer catalysis may be employed.

The reaction of the quinoxalinone with methyl iodide in dimethylsulphoxide with potassium hydroxide as base did not give the desired N-alkyl product. The procedure employed as reported by R.A.W. Johnstone et al[102] for the N-alkylation of phenols, alcohols, amides and acids involved the simple addition of the heterocycle, followed immediately by the alkyl halide, to a mixture of powdered potassium hydroxide in dimethylsulphoxide.

The mixture was kept stirring at room temperature and constantly monitored by t.l.c. T.l.c. of the reaction mixture after two hours showed no appreciable formation of product. In earlier published work, alkylations were achieved in high yields after 10-30 minutes.

In the synthesis of N-n-alkylindoles and pyrroles by Heaney and Ley[101] using by this method the reaction was said to proceed via the formation of the potassium salts of indole and pyrrole respectively after interaction with powdered potassium hydroxide in dimethylsulphoxide. Alkylation was then achieved without the

isolation of the potassium salts by addition of an excess of the appropriate n-alkyl halide.

It may be suggested here that the potassium salt of our heterolactam is relatively not easily formed under the conditions of the reaction. This reaction will require further investigation to determine if the potassium salt could be formed on prolonged contact with the base i.e allowing for more time to generate the N-anion before addition of the alkyl halide to the reaction mixture.

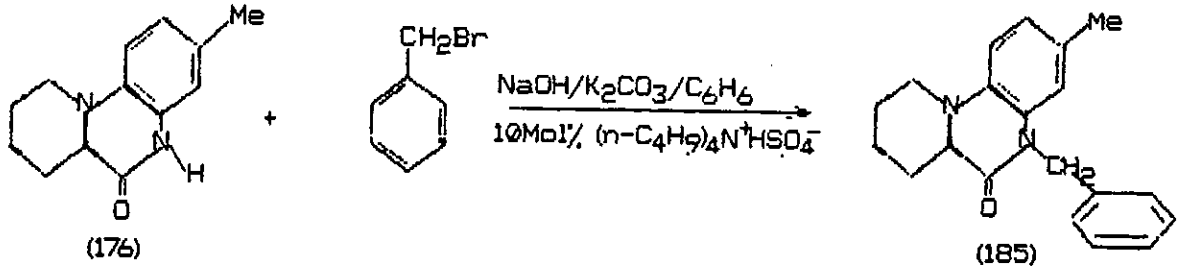
2.3.3 Phase Transfer Catalyzed N- Alkylations

The N-alkylations of the pyridoquinoxalinones were finally achieved by phase transfer catalysis (P.T.C.). As noted in the introduction, P.T.C. is one of the most important recent methodologies developed in organic synthesis which is rapidly gaining popularity in heterocylic chemistry where a wide range of synthetic applications have been reported[82]. Although P.T.C. conditions have been applied to the N-alkylation of some simple lactams[103,104], there is no report of phase transfer catalyzed reactions on any skeleton similar to the one under study. This report on the phase transfer catalyzed N-alkylation of pyrido[1,2-a] quinoxalin-6-ones is therefore a significant addition to the increasing application of phase transfer catalysis in heterocyclic chemistry.

This study has show that N-alkylation of pyrido[1,2-a] quinoxalin-6-ones can be accomplished conveniently in a solid-liquid two phase system consisting of powdered sodium hydroxide/

potassium carbonate suspended in benzene in the presence of a catalytic (about 10 mol-%) amount of tetra-n-butylammonium hydrogen sulphate. The reactions proceeded smoothly at reflux temperature to afford the corresponding N-alkyl cpmpounds in reasonably good yields.

Thus reaction of 7,8,9,10-tetrahydro-3-methylpyrido[1,2-a] quinoxalin-6-one with benzyl bromide under these conditions gave 7,8,9,10-tetrahydro-3-methyl-5-benzylpyrido[1,2-a] quinoxalin-6-one (185) in 57% yield. The equation for this reaction is given below.

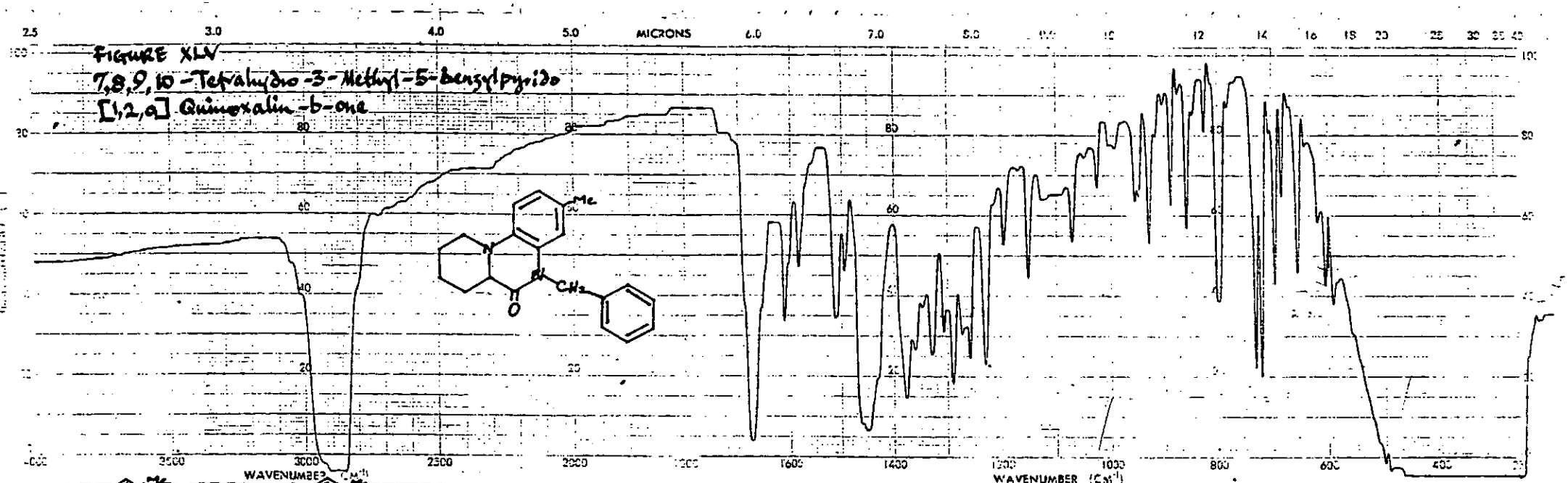


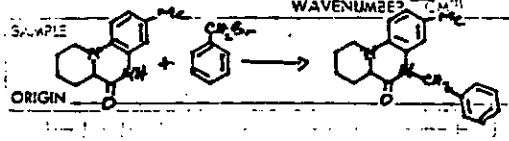
(176) (185)

This new compound, a greenish brown crystalline solid had m.p 140-142 °C. The IR (Fig XLV) showed the expected C=O stretch of the lactam carbonyl at 1675cm^{-1}. Absorption due to the benzene ring were present at 1605cm^{-1} and 1505cm^{-1}. In addition, the strong absorptions at 730cm^{-1} and 720cm^{-1} are attributed to the C-H out of plane deformation bands of the monosubstituted benzyl substituent. The absence of an N-H stretch which was present at 3260cm^{-1} in the starting material suggested that N-alkylation

FIGURE XLV

7,8,9,10 -Tetrahydro-3-Methyl-5-benzylpyrido [1,2,a] Quinoxalin-6-one





SAMPLE

ORIGIN

SOLVENT Nujol

CONCENTRATION

CELL PATH

REFERENCE

REMARKS

SCAN SPEED

SLIT

No 457-5001

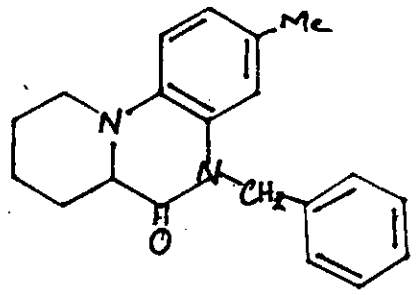
OPERATOR Alex Cole

DATE 1/7/87

REF. No.

FIGURE XLVI

^1H-NMR Spectrum of 7,8,9,10-tetrahydro-3-methyl-5-benzylpyrido [1,2,a] quinoxalin-6-one determined in $CDCl_3$ at 80 MH_z



had occurred.

The p.m.r spectrum (Fig XLVI) gave corroborative evidence for the structure of the product. The signals in the aliphatic region of the spectrum comprised a six proton multiplet at 1.42-2.02 followed by a three-proton singlet at 2.15 and two further multiplets at 2.52 and 3.61 which integrated for one and two protons respectively. A two-proton doublet appeared at 5.15 (J=5.0Hz). This signal has spinning side bands located at equal distances (12.0Hz) on either side of the doublet.

The aromatic signals comprise a three-proton doublet at 6.74 and a five-proton singlet at 7.24. The absence of an N-H signal is significant.

The aliphatic region of the spectrum was expectedly similar to that of 7,8,9,10-tetrahydro-3-methylpyrido[1,2-a]quinoxalin-6-one. The multiplet at 1.42 is attributed to protons H-7, H-8, and H-9 of the piperidine ring. The characteristic three-proton singlet at 2.15 is due to the Ar-Me group. The multiplet at 2.52 is assigned to one of the H-10 protons whilst the second H-10 proton and the base proton [CH(N)CO] account for the two-proton multiplet at 3.61.

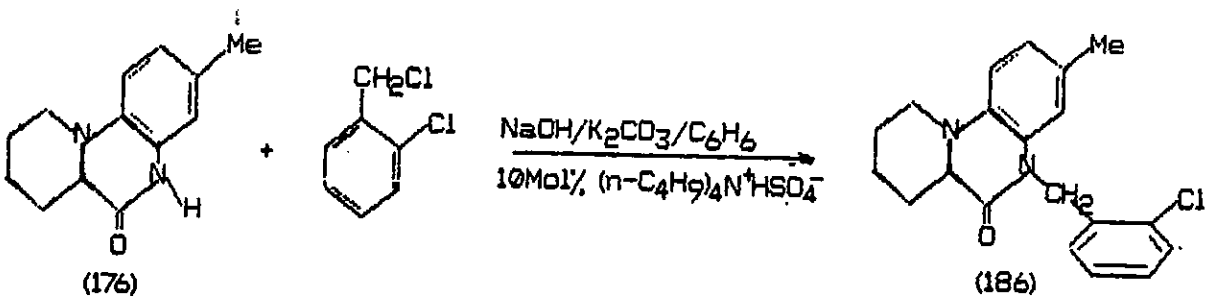
The doublet at 5.15 (J=5Hz) is characteristic for this series of compounds and is due to the -N-CH_2-Ar grouping. The doublet indicates that the two protons are chemically non-equivalent presumably due to restricted rotation about nitrogen. Consequent upon resonance involving the non-bonding electrons on nitrogen, there exists some partial double bond character in the C-N bond

resulting in an increase in the energy barrier to rotation and hence on the rate of rotation. This rate of rotation is sufficiently slow for two different chemical shift signals to arise from the chemically non-equivalent protons.

The three-proton doublet at 6.74 is assigned to the aryl protons of the pyridoquinoxaline skeleton whilst the five-proton singlet at 7.24 is due to the new benzyl substituent.

The structure of this new heterocyclic compound was further confirmed from elemental analysis which gave values for carbon, hydrogen and nitrogen that were in close agreement with the calculated/theoretical values.

Similarly, reaction of 7,8,9,10-tetrahydro-3-methylpyrido [1,2-a]quinoxalin-6-one with 2-chlorobenzylchloride gave the expected N-2-chlorobenzyl derivative of the heterotricycle (186) in very good yields. The equation of reaction is



(176) (186)

The product, a light yellow crystalline solid m.p.116-118 °C, was obtained in 85% yield .

The IR spectrum (Fig XLVII) showed the expected carbonyl

absorption at 1670cm^{-1}. The benzene ring absorptions appeared at 1610cm^{-1} and 1510cm^{-1}. Other intense absorptions at 805cm^{-1} and 755cm^{-1} were attributed to the C-H out of plane deformation bands of the 1,2,4-trisubstituted and 1,2-disubstituted benzene rings respectively.

The p.m.r. spectrum (Fig XLVIII) further corroborated the structure of this new compound . The characteristic doublet due to the N-CH_2-Ar grouping appeared as a two proton singlet with spinning side bands at this field strength (60 MHz).

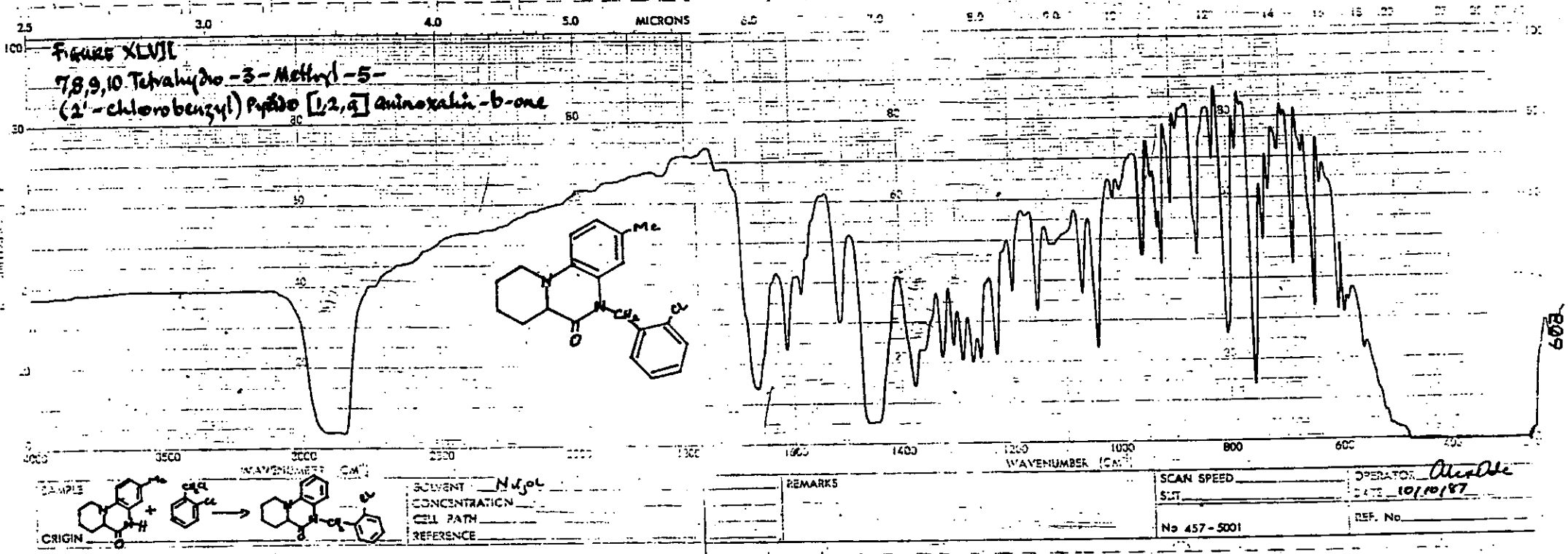
This is comparable to the situation already encountered in which the aromatic protons of 7,8,9,10-tetrahydro-3-methyl pyrido[1,2-a]quinoxalin-6-one appear, as a doublet in the spectra at 60,80 and 90MHz whereas at the higher field strength of 360MHz it was seen to be two singlets.

The signals in the aliphatic region of the spectrum were in accordance with the proposed structure and comprised a six-proton multiplet at 1.6-2.0, a three proton singlet at 2.15 a one-proton multiplet at 2.5 a two-proton multiplet at 3.6 and a two-proton singlet at 5.2.

The six-proton multiplet was assigned to protons H-7,H-8 and H-9 of the piperidine ring. The singlet at 2.15 is characteristic of the Ar-Me group. The one-proton multiplet at 2.5 was assigned to one of the H-10 protons whilst the two-proton multiplet at 3.6 was ascribed to the second H-10 proton and the 7-a proton. The two-proton singlet at 5.2 was assigned to the N-CH_2-Ar grouping as indicated above .

FIGURE XLVII

7,8,9,10 Tetrahydro-3-Methyl-5-(2'-chlorobenzyl) Pyrido [1,2,4] quinoxalin-6-one



SAMPLE

ORIGIN

SOLVENT Nujol

CONCENTRATION

CELL PATH

REFERENCE

REMARKS

SCAN SPEED

SLIT

No 457-5001

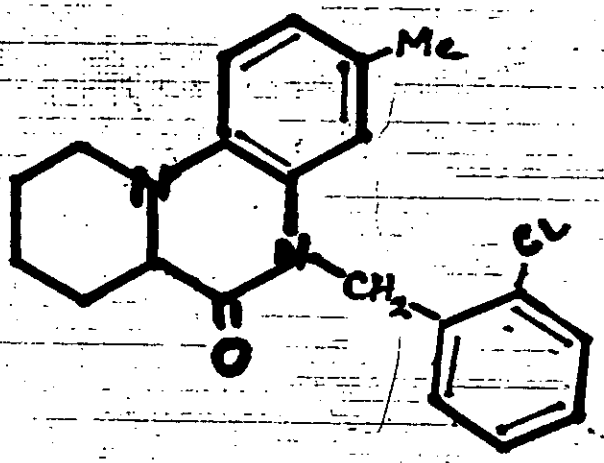
OPERATOR Alexander

DATE 10/10/87

REF. No

669

FIGURE XLVIII



SWEEP OFFSET(Hz): _____
SPECTRUM AMPLITUDE: 10
INTEGRAL AMPLITUDE: 2
SPINNING RATE(RPS): 40

MANUAL ✓
SWEEP TIME(SEC): 50 250
SWEEP WIDTH(Hz): ✓ 75 50 100 250 500 ✓
FILTER: 1 2 3 4 5 6 7 8
RF POWER LEVEL: 0.05

AUTO ☐
(250)
(500)
(2)
(.05)

SAMPLE

REMARKS: 7,8,9,10-TETRAHYDRO-3-METHYL-5-(2'-CHLORO BENZYL)PYRIDO[1,2-a]QUINOXALIN-6-ONE

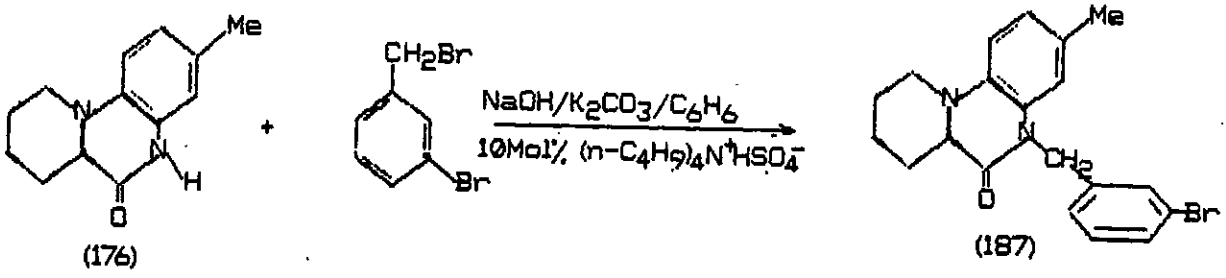
SOLVENT: $CDCl_3$

DATE: 18/10/87 OPERATOR: Alison Lee 60 MHz NMR SPECTRUM NO. _____

GOSS Scientific Instruments Limited

The signals in the aromatic region further confirmed that N-alkylation had occurred as two sets of aryl protons were evident; a three-proton doublet at 6.6 and a four-proton multiplet at 7.0-7.5 due to the aromatic protons of the pyridoquinoxaline and the N-benzyl substituent respectively. The absence of an N-H signal was significant as it indicated that N-alkylation and not O-alkylation had occurred .

Reaction of 7,8,9,10-tetrahydro-3-methylpyrido[1,2-a] quinoxalin-6-one with 3-bromobenzylbromide similarly gave the N-(bromobenzyl) derivative of the heterocycle (187). The equation for this reaction is represented below.

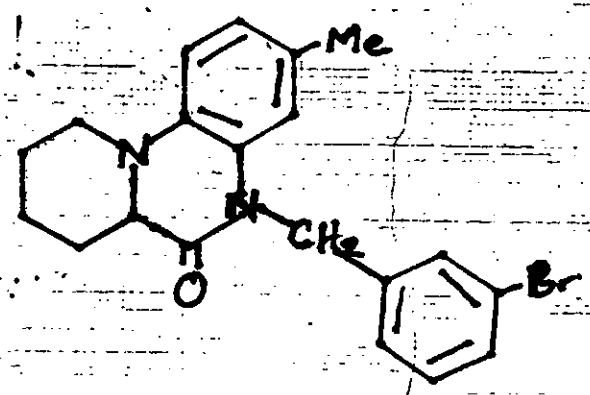


(176) (187)

The product was obtained in 50% yield as a dark green crystalline solid m.p.124-125 ^{o}C. The structure of this new compound was confirmed from the p.m.r spectrum (Fig XLIX) .

The aliphatic proton signals comprised a six-proton multiplet at 1.6-1.9; a three proton singlet at 2.15; a one-proton multiplet at 2.5; a two-proton multiplet at 3.7 and finally a

FIGURE XLIX



500 400 300 200 100 0 Hz

8.0 7.0 6.0 5.0 PPM (δ) 4.0 3.0 2.0 1.0 0

SWEEP OFFSET(Hz): ✓
SPECTRUM AMPLITUDE: 10
INTEGRAL AMPLITUDE: 2
SPINNING RATE(RPS): 40

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
REMARKS: 7,8,9,10-TETRAHYDRO-3-METHYL-5-(3'-BROMOBENZYL) PYRIDO[1,2-a]QUINOXALIN-6-ONE
SOLVENT: $CDCl_3$

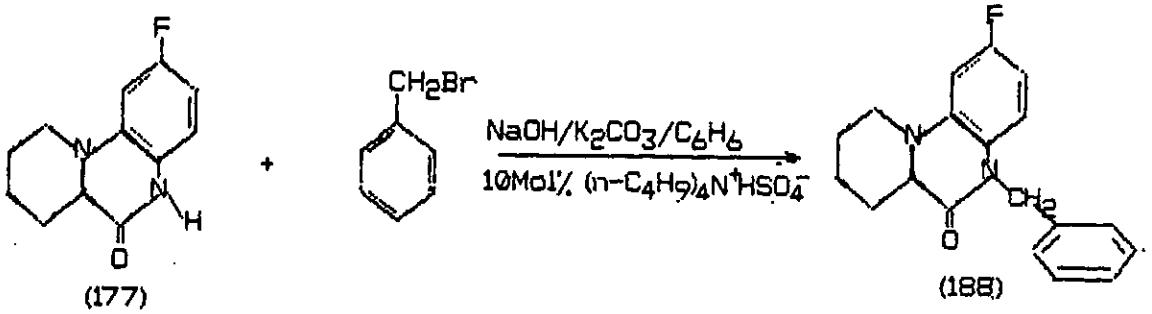
DATE: 17/10/87. OPERATOR: [signature] 60 MHz NMR SPECTRUM NO.

two proton singlet at 5.2.

The six-proton multiplet is attributed to the six piperidine ring protons H-7, H-8 and H-9 whilst the two multiplets at 2.5 and 3.3 account for the remaining three piperidine ring protons i.e H-10 and H-7a The singlet at 2.15 is characteristic for the Ar-Me group. The signal at 5.2 confirms the presence of the $N-CH_2-Ar$ grouping.

The aromatic signals comprise a two proton doublet (J=8Hz) at 6.8 and a four-proton multiplet at 7.35 confirming the presence of two sets of aryl protons in the compound. The protons of the bromobenzyl substituent expectedly occur lower down field to the doublet of the aryl ring of the pyridoquinoxaline skeleton.

7,8,9,10-Tetrahydro-2-fluoropyrido[1,2-a]quinoxalin-6-one was also alkylated under the same conditions with benzyl bromide. The equation of this reaction is given below.



(177) (188)

This new heterocycle, 7,8,9,10-tetrahydro-2-fluoro-5-benzyl pyrido[1,2-a]quinoxalin-6-one (188) was obtained in 50% yield as a light yellow crystalline solid m.p. 107-108 °C.

The IR spectrum (Fig L) showed the expected carbonyl absorption

at 1660cm^{-1}. Absorptions due to the aromatic rings appeared at 1610 and 1510cm^{-1}. The C-H (out of plane) deformation vibrations of the 1,2,4-trisubstituted and the monosubstituted benzene rings were present at 830 and 705cm^{-1} respectively.

The p.m.r. spectrum (Fig LI) showed the usual sets of multiplets accounting for the nine piperidine ring protons in the aliphatic region. These signals are a broad six-proton multiplet at 1.25-1.57 attributed to H-7, H-8 and H-9 of the piperidine ring followed by a one-proton multiplet at 2.8 and a two-proton multiplet at 3.60 assigned to the H-10 protons and the 7-a proton. The characteristic two-proton doublet (J=2Hz) due to the N-CH_2-Ar grouping was present at 5.16.

The presence of two sets of aryl protons in the compound is evident from the aromatic region of the spectrum.The aromatic signals comprised a complex three-proton multiplet 6.3-6.8, attributed to the aryl protons of the pyridoquinoxaline skeleton followed by a five proton singlet (broad at base) at 7.25 due to the protons of the benzyl substituent.

Further evidence for the structure of this compound was obtained from elemental analysis, the values for carbon, hydrogen and nitrogen being in accordance with the proposed structure.

All the N-alkyl derivatives thus prepared were expectedly soluble in most organic solvents and purification (where necessary) was done by column chromatography or preparative t.l.c.

All reactions were carried out in boiling benzene for 4hrs. No efforts were made to optimize yields. This could therefore be

Figure 1

7,8,9,10-tetrahydro-2-fluoro-5-benzylpyrido[1,2,6]quinoxalin-6-one

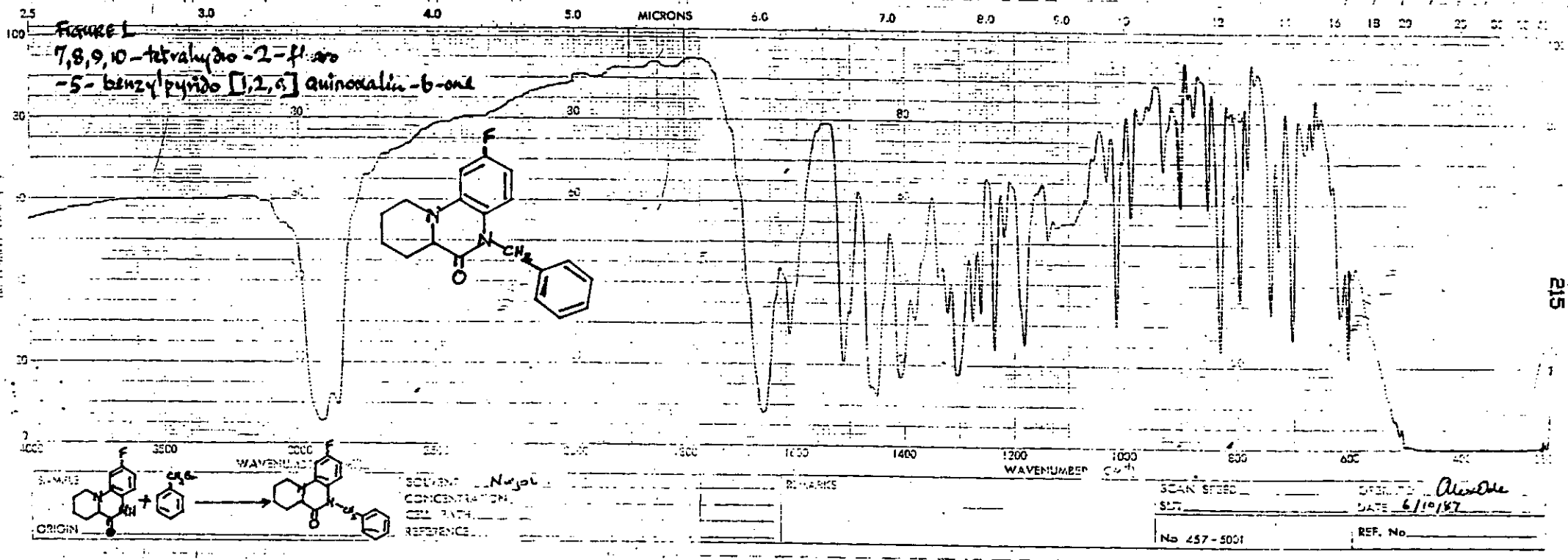
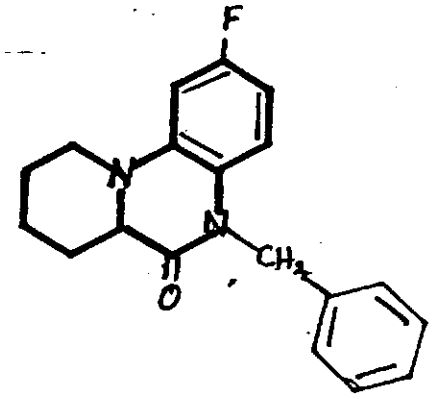


FIGURE L 1
^1H-NMR Spectrum of 7,8,9,10-tetrahydro-2-fluoro-5-benzylpyrido[1,2,a]quinoxalin-6-one determined in $CDCl_3$ at 80 MH_z



a subject for further study.

The use of benzyl bromides and substituted benzylchlorides as substrates was because previous workers had shown[105] that alkyl bromides and allyl type chlorides are the best alkylating agents in similar exploratory N-alkylation reactions.

The use of alkyl iodides is not recommended because the reaction rate is markedly reduced due to the poisoning effect of iodide ion in P.T.C. systems.

In conclusion this work has shown that 7,8,9,10,-tetrayhdropyrido[1,2-a]quinoxalin-6-ones are not alkylated by the conventional methods with alkyl halides in the presence of sodium hydride or sodium methoxide as bases. N-alkylation is however achieved under P.T.C. conditions. Focusing our attention on possible synthetic applications of phase transfer catalysis in heterocyclic chemistry, we have found that effective N-alkylation of the pyridoquinoxalinones under study is achieved under P.T.C. conditions. This method has several advantages viz: (1) The procedure is mild and convenient giving good yields of product. (ii) The entire operation is simple and requires relatively little time. (iii) The use of inflammable and air-sensitive reagents such as sodium metal (for preparation of sodium methoxide), or sodium hydride, is avoided.

2.4.0 ATTEMPTED 6-CHLORINATION AND OXIDATION REACTIONS

2.4.1 Attempted Nucleophilic substitution of the 6-oxo group with chlorine

Investigations also commenced on selective substitution of the carbonyl oxygen in the title compound with chlorine in order to obtain the 6-chloro derivative of the heterotricycle, which was expected to be amenable to nucleophilic substitution reactions as previously described for pyrrolo[1,2-a]quinoxalines.

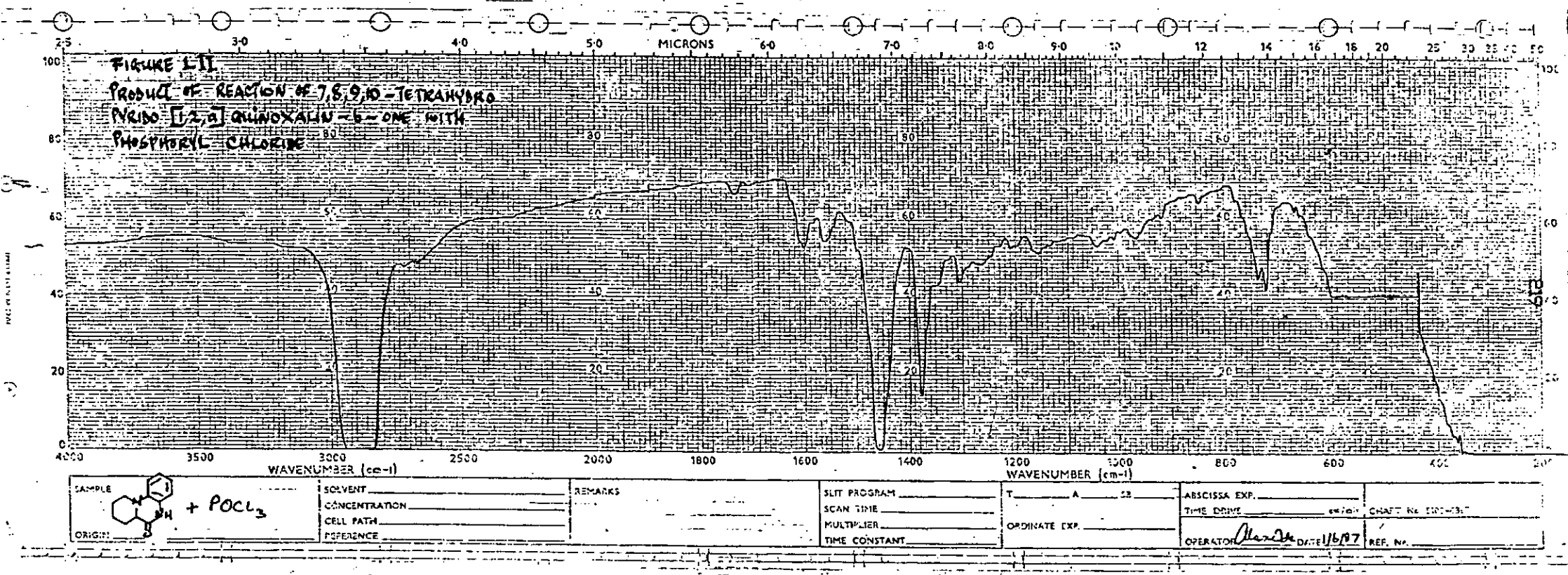
Several attempts at reaction of the heterocycle with either phosphoryl chloride or with mixtures of phosphoryl chloride and pyridine, did not give the desired 6-chloro compound. In all cases, deep purple-black crystalline needles were obtained on work-up after only 10 minutes reaction time. This compound, m.p > 300 °C gave inky solutions in water, ethanol, or chloroform. The IR spectrum (Fig. LII) indicated that the the carbonyl oxygen had been replaced by chlorine as evidenced from the absence of the characteristic carbonyl absorption at 1685cm^{-1}. The p.m.r spectrum (Fig.LIII) showed very broad absorptions and so could not provide useful information for structural elucidation.

Elemental analysis of this compound however suggested that polychlorination had occurred as the values obtained for carbon, hydrogen and nitrogen were 39.3%, 3.6% and 7.4% respectively (cf. starting material: C,71.29%; H,6.93 and N, 13.86%). The presence of aromatic protons in the p.m.r spectrum suggests that chlorination occurred in the piperidine ring.

Although the structure of this compound was not elucidated

FIGURE L II

PRODUCT OF REACTION OF 7,8,9,10-TETRAHYDRO PYRIDO [1,2,a] QUINOXALIN-6-ONE WITH PHOSPHORYL CHLORIDE



SAMPLE + $POCl_3$

ORIGIN:

SOLVENT

CONCENTRATION

CELL PATH

REFERENCE

REMARKS

SLIT PROGRAM

SCAN TIME

MULTIPLIER

TIME CONSTANT

T A SB

ORDINATE EXP.

ABSCISSA EXP.

TIME DRIVE

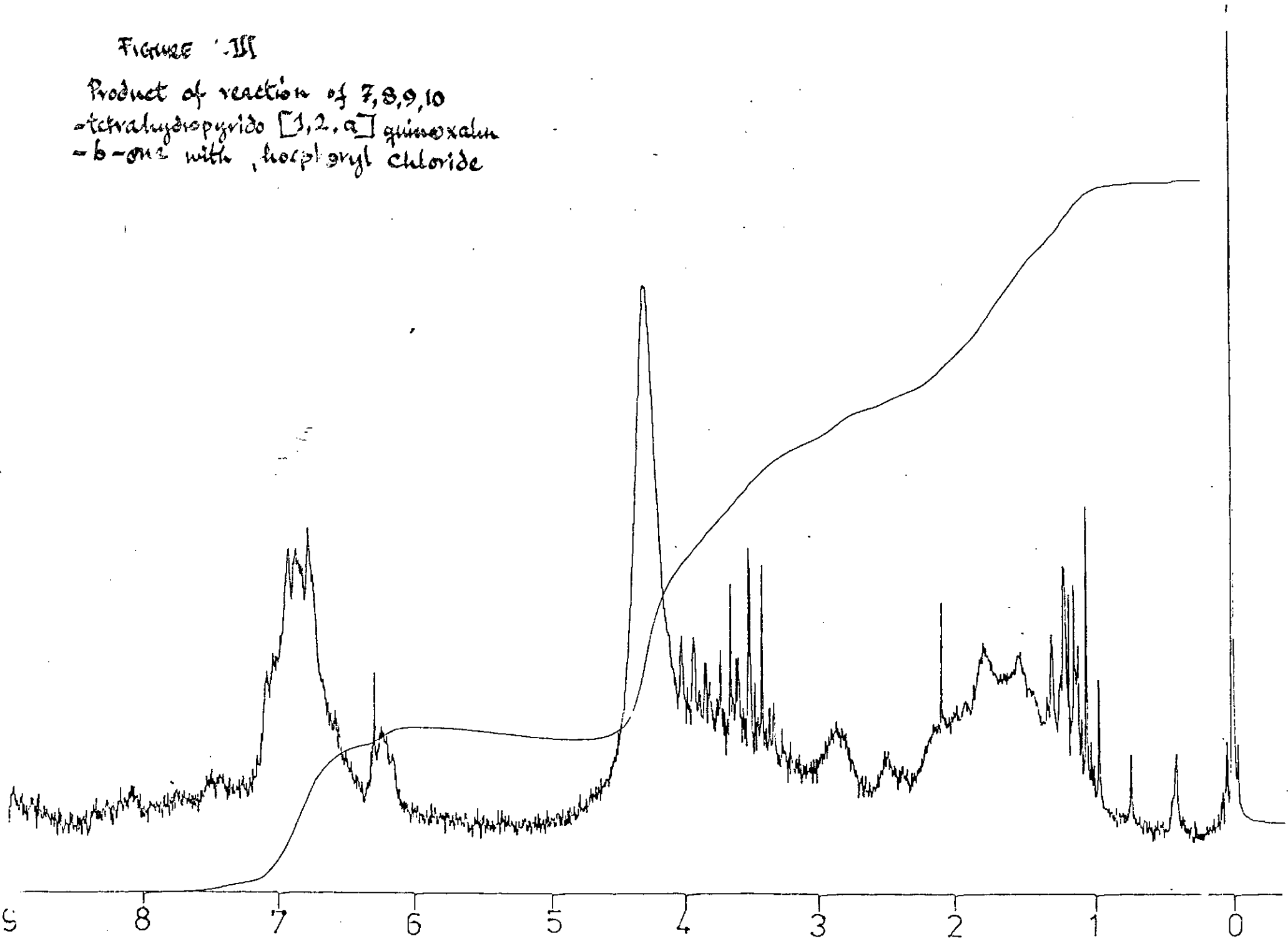
OPERATOR DATE 1/6/87

CHART No.

REF. No.

FIGURE III

Product of reaction of 7,8,9,10
-tetrahydropyrido [1,2,a] quinoxalin
-6-one with thiophenyl chloride



220

in this study, such a polychlorinated product could hardly be used for the type of halogen substitution reactions initially envisaged.

2.4.2 Oxidation Reactions

The heterotricycle, 7,8,9,10-tetrahydropyrido[1,2-a] quinoxalin-6-one was also treated with the oxidizing agents, alkaline potassium ferricyanide and manganese dioxide. Although the products obtained were not fully characterized in this study, preliminary analysis shows that whilst the tricyclic ring skeleton remained intact on treatment with manganese dioxide, the reaction with potassium ferricyanide gave a ring opened product.

Reaction of the heterolactam with 'aged' manganese dioxide initially gave an oil which crystallized from ethylacetate/ petroleum ether mixtures to give a light brown crystalline solid, m.p. 185-187 °C. This compound was soluble in solvents such as chloroform, methanol etc. (cf.insolubility of starting material in these solvents). The p.m.r spectrum of this product (Fig.LV) showed absorptions in the aliphatic and aromatic regions of the spectrum due to the piperidine ring and aromatic protons respectively.

The IR spectrum (Fig.LIV) confirmed that the tricyclic structure was intact from the presence of the N-H and C=O absorptions of the lactam which occurred at 3150 and 1680 cm^{-1} respectively.

Reaction of the heterotricycle with alkaline potassium ferricyanide according to the procedure described by Taylor and

FIGURE LIV

Product of reaction of 7,8,9,10-Tetrahydropyrido [1,2-a] Quinoxalin-6-one with Manganese dioxide.

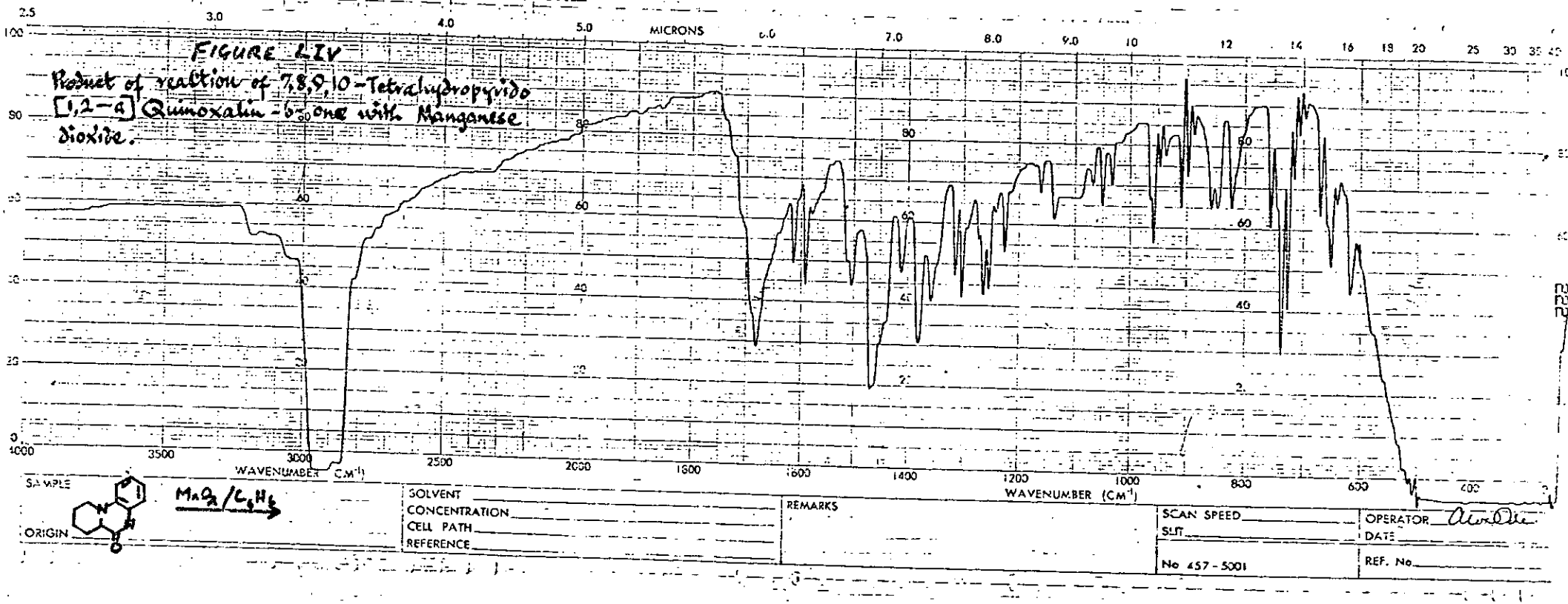
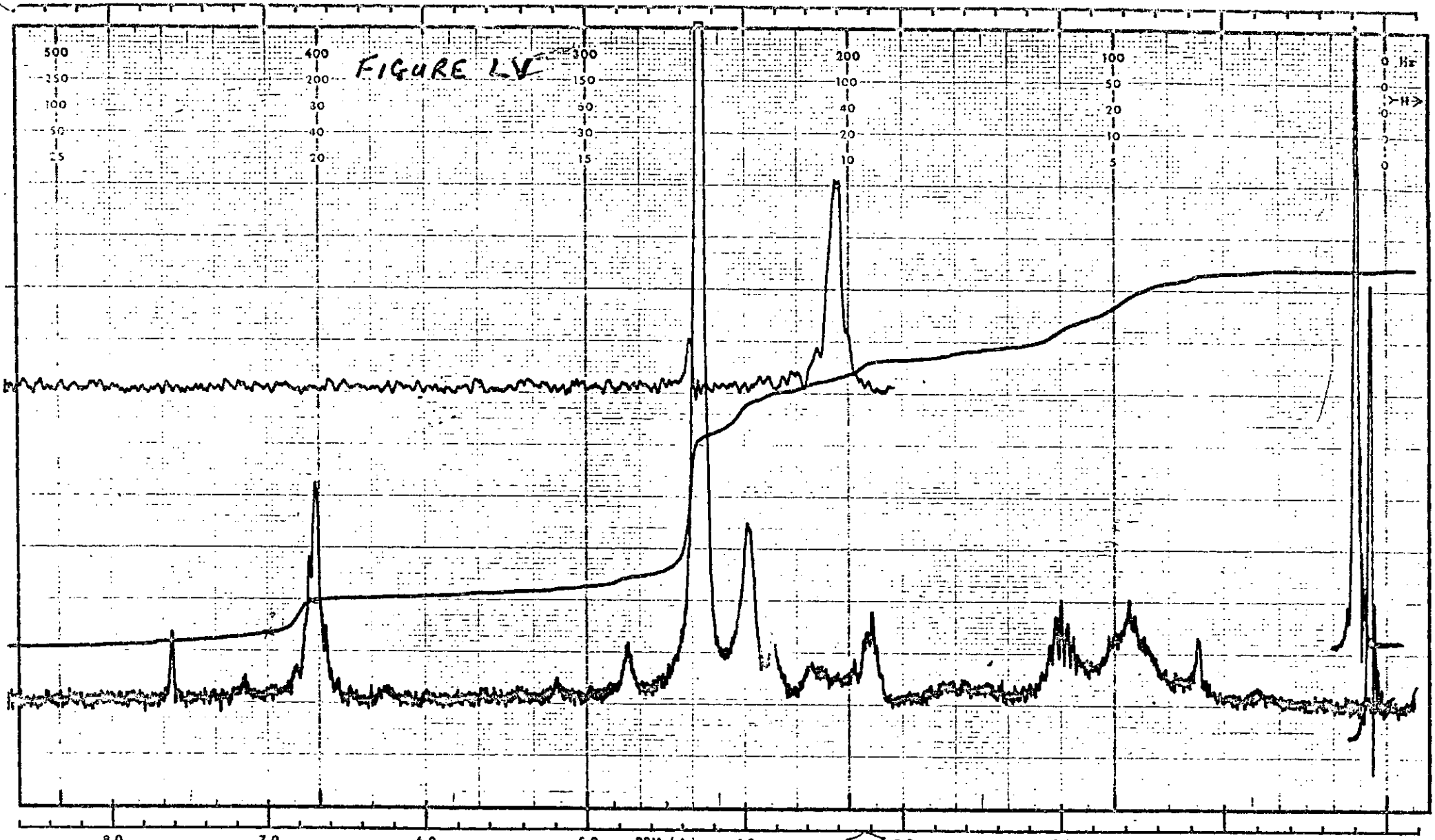


FIGURE LV



SWEEP OFFSET (Hz): 200Hz
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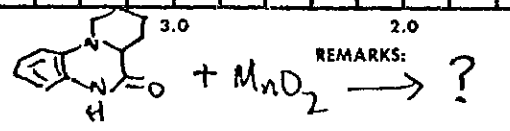
INTEGRAL AMPLITUDE: 2
SPINNING RATE (RPS): 30

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:  + MnO_2 ⟶ ?

REMARKS:

SOLVENT: CD_3OD

varian
analytical instrument division

DATE: 5/2/85 OPERATOR: ALO

60 MHz NMR
SPECTRUM NO.

Hand[24], gave over 60% of the unreacted starting material. A dichloromethane soluble product was however obtained. Evaporation of solvent gave a brown oil. The IR spectrum of this product (Fig LVI) clearly indicates a carboxylic acid from the prominent C=O stretch as well as the O-H stretch of a carboxylic acid at 1730 and 3400cm^{-1} respectively. The skeletal vibrations of the aromatic ring was present at 1600cm^{-1}. This compound could not be fully characterized in this study.

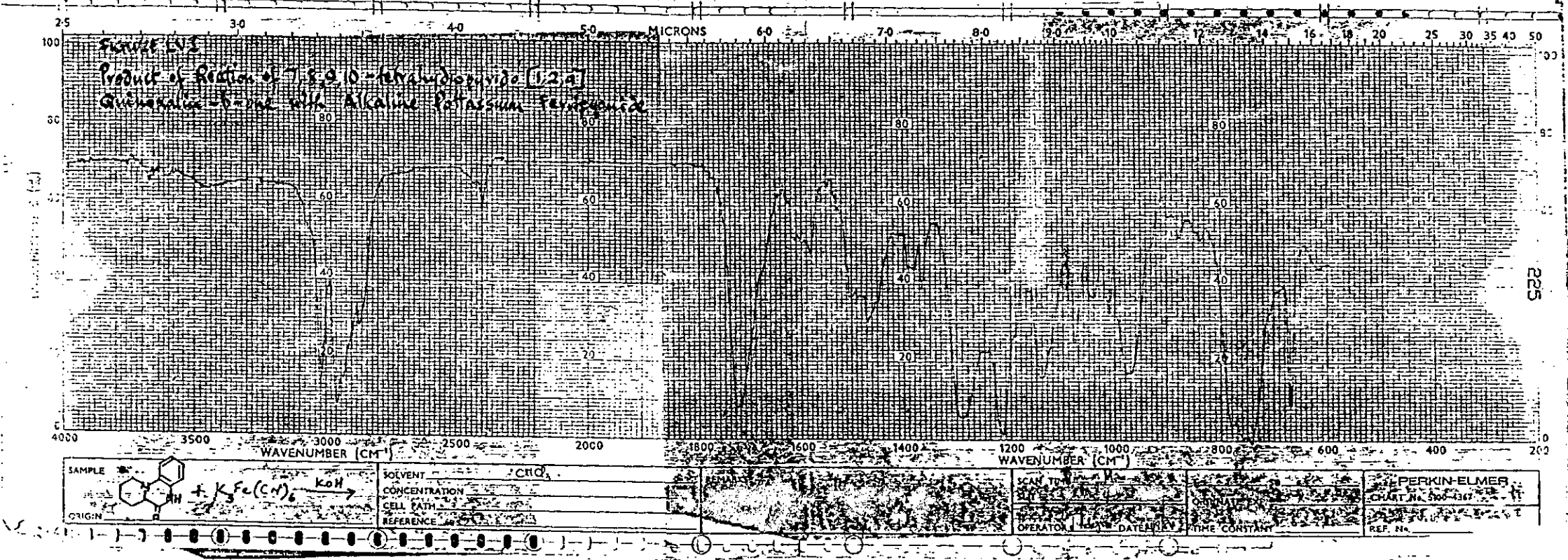


Figure 2.13
Product of Reaction of 7,8,9,10-tetrahydrophenanthrene [1,2,a] Quinoxaline-5-one with Alkaline Potassium Ferricyanide
MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)
SAMPLE
ORIGIN
+ K3Fe(CN)6
KOH
SOLVENT CHCl3
CONCENTRATION
CELL PATH
REFERENCE
PERKIN-ELMER

2.5.0 CARBON-13 N M R STUDIES.

A pre-requisite to this study was a secure assignment of the ^{13}C-NMR signals of the parent heterocycle; 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one , which as far as we are aware has never been done before. This could then be followed by assignments of the signals of the available derivatives viz the 2-fluoro-; 3-methyl-; and 3-bromo compounds.

Figure LVII^{B} is the broad band proton decoupled spectrum of the parent heterocycle. Maximum simplification of carbon-13 spectra is usually achieved by simultaneously decoupling all of the protons from all of their coupling carbon partners. To do this requires a decoupling signal which contains all of the appropriate proton frequencies. The clarity of single line spectra resulting from this decoupling procedure leads to easier analysis. Also the additional factor of greater chemical shift range further enhances the value of the carbon-13 spectrum. In addition such proton-noise decoupled spectra usually exhibit line intensities which are very uneven and this is used to advantage in signal assignment. Thus, with the parent heterocycle, the twelve non-equivalent carbon atoms in the molecule give a twelve line ^{13}C-NMR spectrum (Fig LVII). As expected, there were five lines (signals) in the aliphatic region; at 23.01, 23.23, 26.58, 46.10 and 59.05, representing the five piperidine ring carbons. (The multiplet at 39.5 is due to the solvent, dimethylsulphoxide d_6).

The aromatic carbon signals comprise single lines at 112.14, 114.97 ,119.00, 123.28, 127.09 and 135.44. The signals at

```
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3.2       2.EP                 F1[PPM]=    200.006
F2[PPM]=       .010            HZ/CM=    362.22   PPM/CM=    3.9999
MI=         .637P P 2.PP

 MBC.011
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INTENS. LEVEL  =       .637      NOISE =     .12950    SENS. LEVEL
F1 =    18111.66 HZ =    200.0057 PPM      F2 =          .87 HZ =
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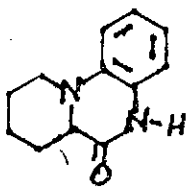
£	CURSOR	FREQUENCY	PPM	INTENSITY
1	5004	15216.104	168.0303	2.272
2	7132	12265.264	135.4444	1.632
3	7677	11509.248	127.0957	2.010
4	7926	11163.882	123.2819	5.769
5	8205	10776.511	119.0042	6.032
6	8468	10411.227	114.9704	5.747
7	8653	10154.968	112.1405	5.899
8	12119	5347.145	59.0481	5.816
9	12964	4175.032	46.1046	5.540
10	13364	3619.875	39.9740	8.000
11	13379	3598.806	39.7413	3.435
12	13395	3577.366	39.5046	3.898
13	13410	3556.749	39.2769	3.463
14	13424	3536.144	39.0494	1.544
15	14238	2407.470	26.5855	5.477
16	14457	2104.080	23.2352	5.594
17	14471	2083.940	23.0128	5.217

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HZ/PT =    1.387     FW =    28500       TE =      297
PD =    2.0000000    PW =         16.0   NS =      192
DS =           0     DW =         22     DE =       11.0
DR CURRENT = 12      SY= 67.4000000      PR =        H 1
RG =       400
NC =           .2    LB =       2.000    GB =       0.0
TM1 =          0     TM2 =         0     F1[PPM]=    200.005
F2[PPM]=        .010           HZ/CM=    362.22   PPM/CM=    3.9999
CX =       50.000    CY =       6.000    MAXY =      20.000
SR =   26223.132     IS =          1     AZFE =         0
NOBC =         0     ISEN =      128     MI =        .637P
PC =       1.000     AI =          0     PC0 =       0.0
PC1 =        0.0     QS          GAMMA =       0.0  ALPHA =       0.0
NZP =          0
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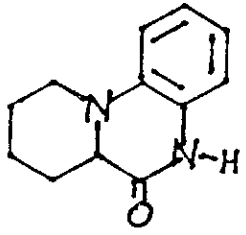
1.EF      1.^        2.EP                  F1[PPM]=    200.005
F2[PPM]=        .010           HZ/CM=    362.22   PPM/CM=    3.9999
OFFSET =      -1.500           MARK SEPARATION    20.00P
MARK CM =       -.300          2.CY =        6.000 0
2.
```

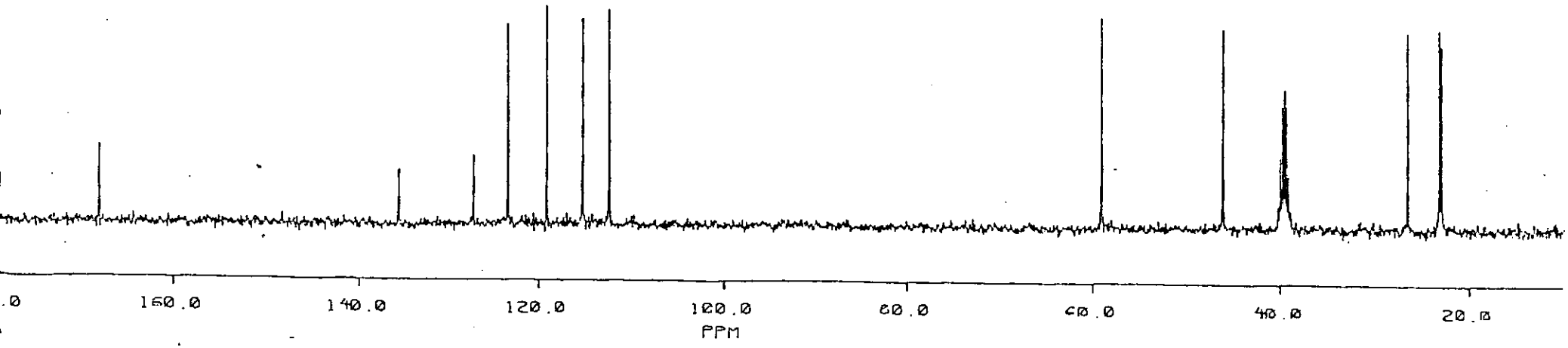
Figure LVIIA

^{13}C-NMR signals of 7, 8, 9, 10-tetrahydopyrido [1,2-a] quinoxalin 6-one

Figure LVIIB

Proton - decoupled ^{13}C - NMR spectrum of 7, 8, 9, 10 - tetrahydropyrido [1, 2 - a] quinoxalin - 6 - one.





127.09 and 135.44 are of much lower intensity and represent carbons bearing groups other than hydrogen i.e carbons 4a and 4b although it was not clear at this stage which resonance was due to 4a or to 4b.

The signal at 168.03 was unambiguously assigned to the carbonyl carbon (i.e C-6) The ability to observe directly the NMR characteristics of carbonyl carbons is a major strength of carbon-13 NMR in chemistry, especially as the carbonyl resonance is usually at a very high frequency , so that it is well separated from interferences and confusion. The ultimate merit lies in the narrow ranges within which different classes appear so that quite fine distinction can be made, in the knowledge that the influence of unaccounted factors will be mininal. Thus, the carbonyl carbon of all amides including lactams absorb in the range 162-184.

The proton decoupled spectrum therefore not only confirms the number of carbon atoms present but also indentifies the carbonyl carbon as well as the non-proton bearing carbons 4a and 4b which give lines of lower intensities.

A full assignment of the carbon-13 resonances of the heterotricycle was however achieved by a careful assignment of the ^{1}H-NMR signals by n.O.e experiments as discussed in 2.2.2., followed by the use of two-dimensional one-bond and long range ^{13}C: ^{1}H chemical shift correlations.

The use of two-dimensional NMR for correlating spectra of coupled heteronuclei was first proposed in 1977[106]. Since then,

a considerable number of papers have appeared describing different techniques for heteronuclear corelation. Whilst broad band decoupled carbon-13 NMR spectra bring the advantage of clarification to the spectroscopist, all of the valuable coupling information is lost. The presentation of data in two dimensions on the other hand allows much more information to be assembled and correlated than would be conceivable in a normal one-dimensional plot.

The mechanism of chemical shift correlation experiments has been extensively discussed in the literature[106-108] and will not be described here. The most widely used method[108] produces a two-dimensional spectrum in which one signal appears for each directly bonded carbon-hydrogen pair in a molecule. This experiment establishes which protons couple with which carbons and so provides information which completely unambiguously establishes the coupling relationships between carbons and protons.

Using this technique of 2D one-bond and long range $^{13}C:{}^{1}H$ chemical shift correlations, the carbon-13 resonances of the parent heterocycle were assigned. All experiments and data acquisition were performed on Fourier transform computers.

The aromatic proton resonances of the parent heterocycle were assigned by n.O.e experiments. Thus irradiation of the amide proton resonance (10.37) led to a 15% enhancement of the H-4 resonance (6.80) whilst irradiation of the N-CH(H) signal (3.72) brought about a 16% enhancement of the H-1 signal(6.82). These resonances showed vicinal couplings (J,7.5Hz) to the H-3 (6.72) and H-2 (6.89) signals. The aliphatic proton

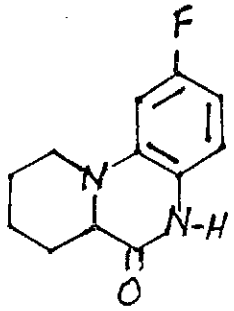
resonances of the piperidine ring were assigned by a COSY experiment and are shown in Table 6 together with the p.m.r. assignments.

The proton-bearing carbon-13 resonances were then assigned by a one-bond $^{13}C:^{1}H$ chemical shift correlation as mentioned above, using the standard sequence [108]. The aromatic region was assigned in a separate experiment in order to obtain the best resolution. The important C-4a and C-4b signals (non-proton bearing) were assigned by a long-range $^{13}C:^{1}H$ chemical shift correlation in which the delay times were set to establish relationships to the meta-oriented proton signals [107]. This correlation also served to confirm the assignments made from the one-bond $^{13}C:^{1}H$ correlation. The results are tabulated.

The assignments were then made for the 2-fluoro-; 3-methyl-; and 3-bromo- derivatives of the heterotricycle. The assignments for the fluoro compound were consistent with the magnitude of the $^{13}C\ ^{19}F$ coupling constants. The spectra are shown in Figures LVIII-LX.

```
MIN. INTENSITY =        .384 P    MAXY  =   20.00000     PP CONSTANT =    1.00000
INTENS. LEVEL  =        .384      NOISE =     .06323     SENS. LEVEL =     .25291
F1 =    18111.66 HZ =   200.0046 PPM      F2 =          .87 HZ =         .0096 PPM
```

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	5050	15153.009	167.3326	1.277
2	5506	14519.974	160.3421	.538
3	5676	14284.092	157.7373	.396
4	7036	12397.875	136.9080	.466
5	7044	12387.168	136.7898	.505
6	7921	11169.740	123.3459	.931
7	8440	10450.167	115.3998	1.733
8	8447	10440.408	115.2920	1.708
9	9160	9450.960	104.3657	1.447
10	9177	9428.190	104.1142	1.394
11	9457	9039.552	99.8225	1.382
12	9477	9011.663	99.5146	1.328
13	12139	5018.931	58.7362	2.749
14	12960	4180.529	46.1650	2.797
15	13349	3640.379	40.2002	1.377
16	13364	3619.634	39.9711	3.026
17	13379	3598.692	39.7399	5.433
18	13395	3577.590	39.5068	6.136
19	13410	3556.549	39.2745	5.288
20	13425	3535.536	39.0424	2.671
21	13440	3514.482	38.8099	.953
22	14232	2416.054	26.6802	3.629
23	14460	2099.697	23.1867	2.978
24	14482	2069.412	22.8522	2.848

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HZ/PT =   1.387    FW =  28500         TE =      297
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DR CURRENT = 12    SY= 67.4000000      PR =        H 1
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NC =         4     LB =     2.000      GB =       0.0
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F2[PPM]=     .010          HZ/CM=    362.22   PPM/CM=    3.9999
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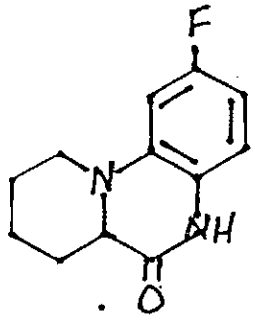
PC1 =      0.0     QS        GAMMA =      0.0   ALPHA =      0.0
MZP =        0
2.EP               F1[PPM]=   200.005          F2[PPM]=      .010
```

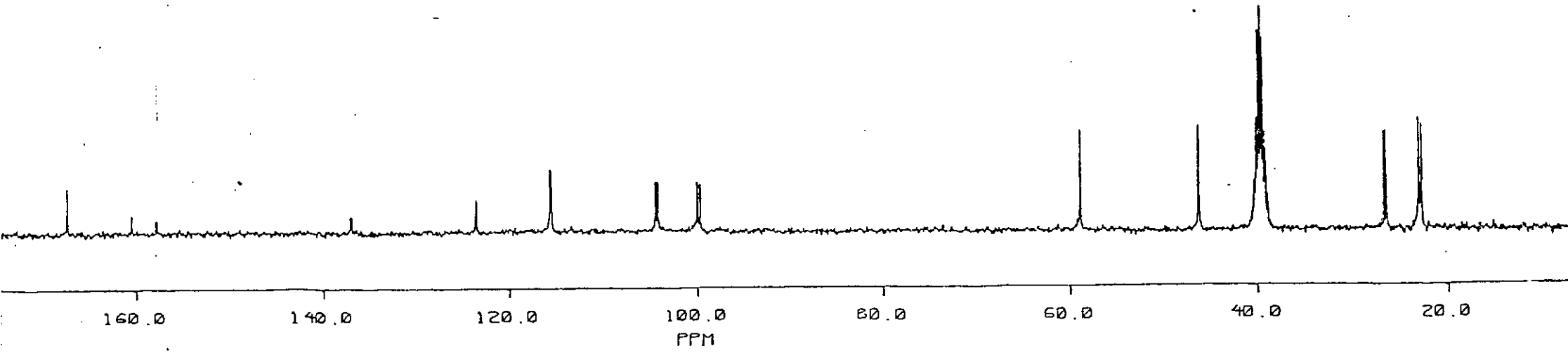
Figure LVIIIA

^{13}C-NMR signals of 7, 8, 9, 10 – tetrahydro – 2-flouropyrido [1, 2-a] quinoxalin – 6 – one.

Figure LVIII B

Proton decoupled ^{13}C-NMR spectrum of 7,8,9,10-tetrahydro-2 fluoropyrido [1,2-a] quinoxalin-6-one





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F1[PPM]=    200.005              F2[PPM]=        .010
HZ/CM=    362.22    PPM/CM=    3.9999  2.1         1.ZG
1.2       2.EP      MI=        4.551P P 2.PP

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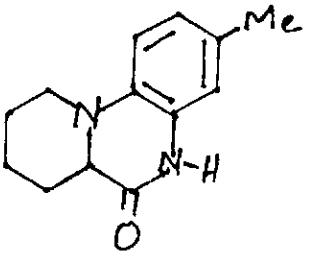
F1 =    18111.66 HZ =    200.0046 PPM      F2 =                .87 HZ =       .0096 PPM
```

L	CURSOR	FREQUENCY	PPM	INTENSITY
1	4992	15220.791	168.0811	5.610
2	7270	12060.682	133.1844	5.736
3	7620	11575.646	127.8283	7.671
4	7677	11496.072	126.9495	6.539
5	7908	11175.727	123.4120	14.648
6	8429	10453.137	115.4325	13.267
7	8652	10143.307	112.0111	12.435
8	12105	5353.665	59.1198	5.904
9	12950	4181.735	46.1783	11.970
10	13340	3640.466	40.2012	8.517
11	13356	3618.796	39.9619	24.229
12	13371	3597.736	39.7293	45.727
13	13386	3576.948	39.4997	52.682
14	13401	3555.770	39.2659	45.494
15	13416	3535.304	39.0399	23.324
16	13431	3514.081	38.8055	7.993
17	14245	2385.158	26.3389	12.780
18	14459	2088.751	23.0658	13.168
19	14468	2076.693	22.9326	12.551
20	14655	1816.120	20.0552	8.337

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'[PPM]=        .010              HZ/CM=   362.22   PPM/CM=    3.9999
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BC =           0    ISEN =     128      MI =       4.551P
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1 =         0.0    QS         GAMMA =       0.0  ALPHA =        0.0
P =           0
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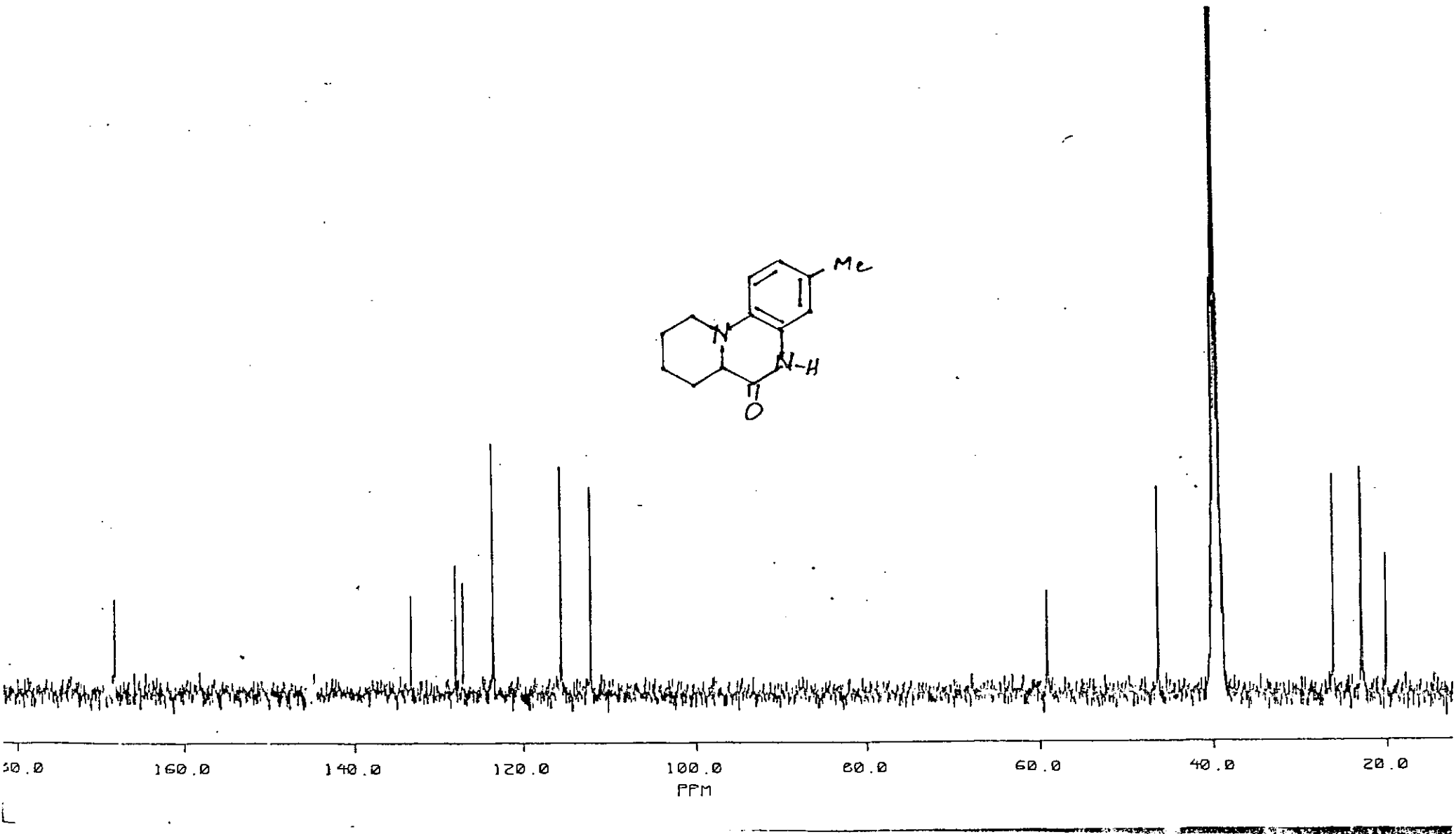
Figure LIX A.

^{13}C-NMR signals of 7, 8, 9, 10-tetrahydro-3-methylpyrido [1, 2-a] quinoxalin-6-one.

Figure LIX B

Proton decoupled ^{13}C-NMR spectrum of 7, 8, 9, 10 - tetrahydro - 3 - bromopyrido[1,2-a] quinoxalin - 6 - one.



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F1 =    13112.18 HZ     200.0103 PPM     F2 =    -362.05 HZ =     -3.9981 PPM
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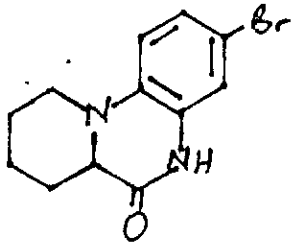
#	CURSOR	FREQUENCY	PPM	INTENSITY
1	5014	15187.790	167.7167	1.666
2	7176	12189.139	134.6030	1.424
3	7569	11643.945	128.5825	1.850
4	7788	11340.239	125.2287	4.109
5	8334	10582.062	116.8562	3.467
6	8538	10299.076	113.7313	3.291
7	8807	9927.063	109.6232	1.481
8	12135	5310.619	58.6444	3.774
9	12960	4164.993	45.9934	3.179
10	13362	3607.507	39.8372	3.623
11	13377	3586.642	39.6068	6.421
12	13392	3565.828	39.3770	7.558
13	13408	3544.596	39.1425	6.479
14	13423	3523.477	38.9093	3.201
15	14238	2393.250	26.4283	3.282
16	14464	2079.041	22.9586	3.342
17	14482	2054.546	22.6881	3.283
18	15963	-.245	-.0027	1.297

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DS =           0     DW =        22      DE =        11.0
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PS =       400
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F2[PPM]=    -3.998           HZ/CM=     362.24   PPM/CM=    4.0002
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PC1 =        0.0     QS          GAMMA =       0.0  ALPHA =        0.0
NZP =          0
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G= 339.4386 0        G=    -.0000 77     3.?        3.1
1.TR =         3     3.EF       3.2       2.EP                F1[PPM]=    200.010
F2[PPM]=    -3.998           HZ/CM=     362.24   PPM/CM=    4.0002
OFFSET =    -1.500           MARK SEPARATION     20.00P
MARK CM =      -.300          2.3       3.EP      3.1
1.RD =    2.0000000 4        1.?       1.2G      1.TR =         3
3.EF       3.EP      3.EP
NO MEMORY FOR OVERLAY         3.EP                F1[PPM]=       .244 130
F2[PPM]=      -.000 127.6     HZ/CM=       3.62   PPM/CM=     \.0400
3.1        1.3       3.1       1.TR =         3    3.EF
3.EP       3.1       1.WR MBC.011 DELETE ON =D1  (Y,N,@)?: Y
      1.3        3.ED AUP3 JMODXH.AU
```

Figure LXA.

^{13}C-NMR signals of 7,8,9,10-tetrahydro-3-bromopyrido [1,2-a] quinoxalin-6-one

Figure LX^{B}.

Proton decoupled ^{13}C-NMR spectrum of 7,8,9,10-tetrahydro-3-bromopyrido[1,2-a] quinoxalin-6-one.

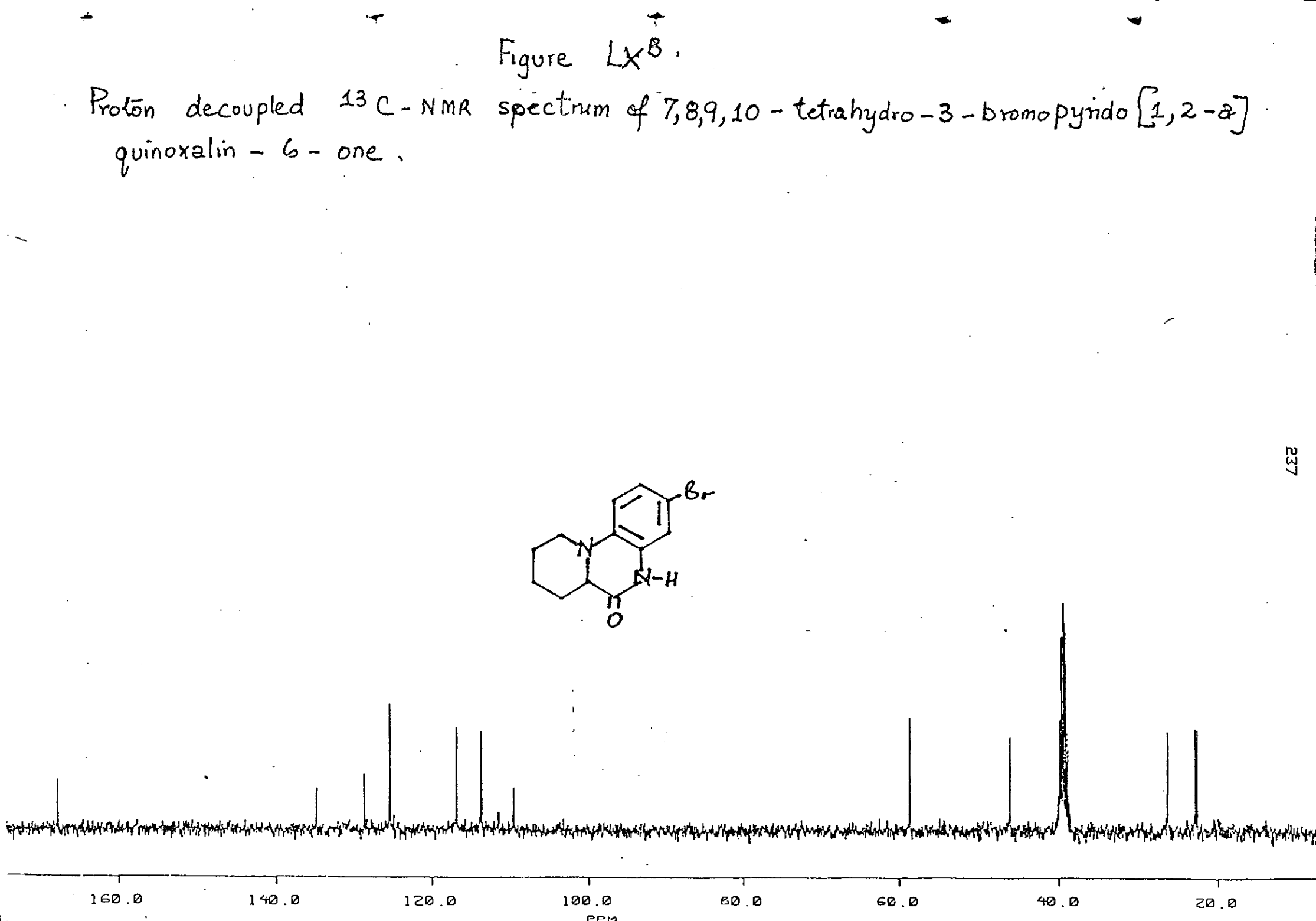
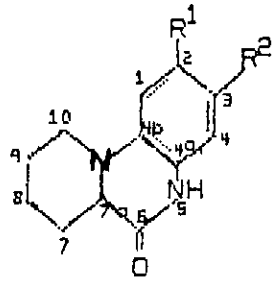


TABLE 6

NMR ASSIGNMENTS OF 7,8,9,10-TETRAHYDROPYRIDO[1,2-a]QUINOXALIN-6-ONES



152; $R^1 = R^2 = H$
176; $R^1 = H$, $R^2 = Me$
177; $R^1 = F$, $R^2 = H$
180; $R^1 = H$, $R^2 = Br$

ATOM NUMBER	(152) ^1H	(152) ^{13}C	(177) ^{13}C	(177) $J^{13}C$; ^{19}F Hz	(176) ^{13}C	(180) ^{13}C
1	6.82	112.14	99.65	27.9	112.01	113.73
2	6.89	123.28	159.03	235.9	123.40	125.23
3	6.72	119.00	104.24	22.8	127.83	109.62
4	6.80	114.97	115.34	9.01	115.43	116.58
4a		127.09	123.34		126.95	128.58
4b		135.44	136.84	10.8	133.18	134.60
5	10.37					
6		163.03	157.33		163.08	157.62
7a	3.42	59.05	58.73		59.12	58.64
7	1.4[m], 1.97	26.58	26.62		26.34	26.42
8	1.4[m], 1.82	23.23	23.19		23.06	22.95
9	1.6[m], 1.4[m]	23.01	22.85		22.93	22.68
10	2.45, 3.72	46.10	46.16		46.18	45.99
Ar-Me					20.05	

2.5.1 Studies on The Magnitude of Deuterium Isotope Effects on Carbon-13 Resonances in 7,8,9,10-Tetrahydropyrido[1,2,a]quinoxalin-6-ones:-

The replacement of hydrogen with deuterium has been known for many years to produce shifts in the position of the neighbouring carbon-13 NMR signals [107]. Recently the magnitude of these effects has been shown to possess a stereochemical dependance [109,110]. The tetrahydropyridoquinoxalin-6-one ring system possesses an amide nitrogen which is of defined geometry relative to the aromatic portion of the molecule. This amide N-H exchanges relatively slowly in DMSO d_{-6} with deuterium. It is possible therefore to observe the carbon-13 NMR signals from both deuteriated and unlabelled species and thus to measure the intrinsic isotope shifts quite accurately. Similar isotope shifts have been observed [111] in the carbon-13 NMR spectra of aromatic amines and correlated with the intramolecular hydrogen bonding.

In this study it has been shown that there is a dependance of the isotope shifts on the geometrical relationship of the carbon concerned to the nitrogen of the amide.

An initial requirement for this study was a secure assignment of the ^{13}C-NMR signals of the parent compound as discussed above. As soon as this was achieved, then attention was directed towards measuring the extents of the shifts of signals of the α-carbon atoms upon exchange of the amide N-H with deuterium. The exchange experiment was carried out by adding one drop of deuterium oxide to the DMSO d_{-6} solutions of the compounds.

Figures LXI - LXIV are spectra showing the deuterium isotope shift experiments on the parent compound, its 2-fluoro-; 3-methyl-; and 3-bromo- derivatives respectively. The coupling of the relevant carbons (4,4a,4b and 6) to deuterium can be seen from the spectra. The magnitudes of the shifts are set out in Table 7.

Table 7

Deuterium Isotope Shifts of Carbon-13 Resonances.

(in ppm x 100)

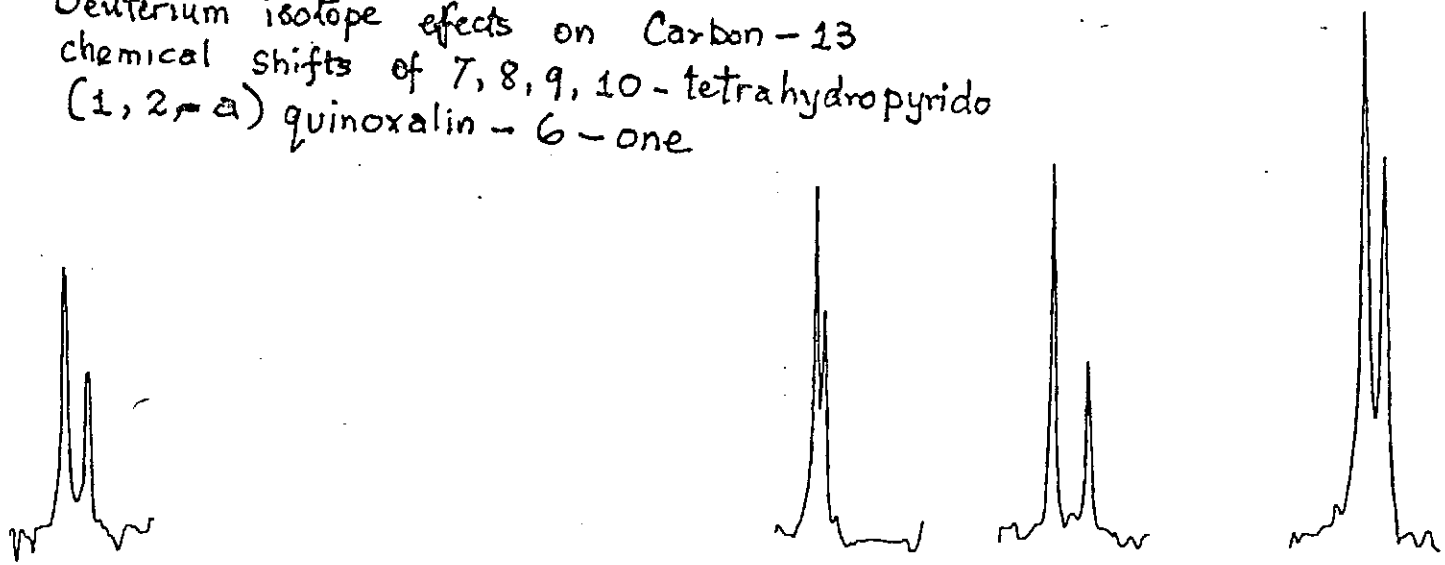
ATOM NUMBER	COMPOUND (152)	(177)	(176))	(180)
4	6.6	6.5	6.0	6.3
4 a	11.8	12.2	11.8	12.7
4 b	2.7	2.8	2.1	2.1
6	7.8	7.9	7.7	7.8

The magnitude of the deuterium isotope effects observed, as shown above, is found to be dependant on the relative orientation of the β - carbon atom to the amide N-H. In the group of compounds of differing substitution pattern studied, there is a consistently greater isotope effect on C-4a compared to that on C-4b which may be related to the geometry of the amide. It will however need a much wider study in order to establish any effects which may arise from substituents and other potential variables such as the nature of the heterocylic ring.

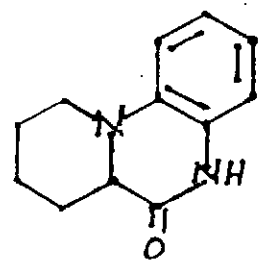
In conclusion, the carbon-13 NMR resonances of 7,8,9,10-

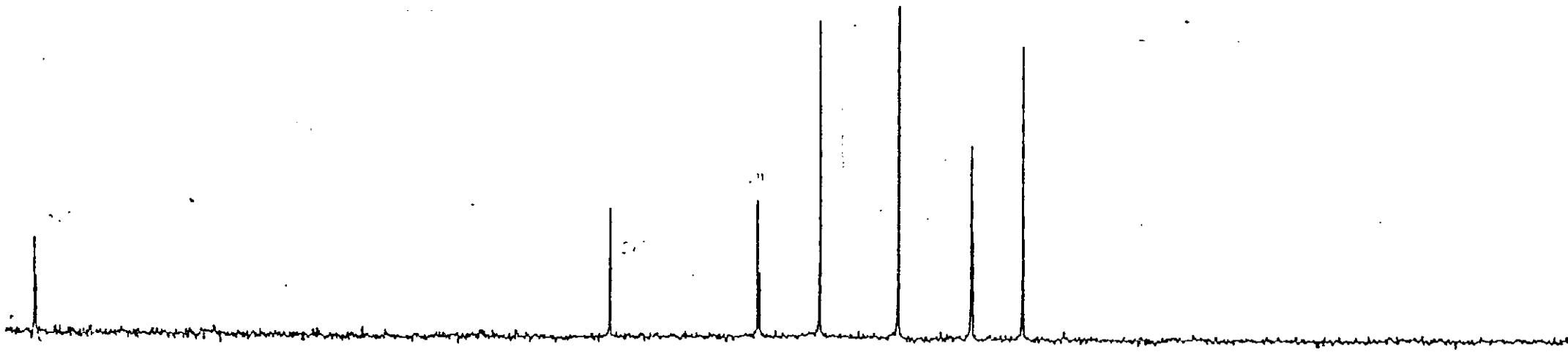
Figure LXI.

Deuterium isotope effects on Carbon-13 chemical shifts of 7,8,9,10-tetrahydropyrido (1,2-a) quinoxalin-6-one



C 2 ppm/cm.





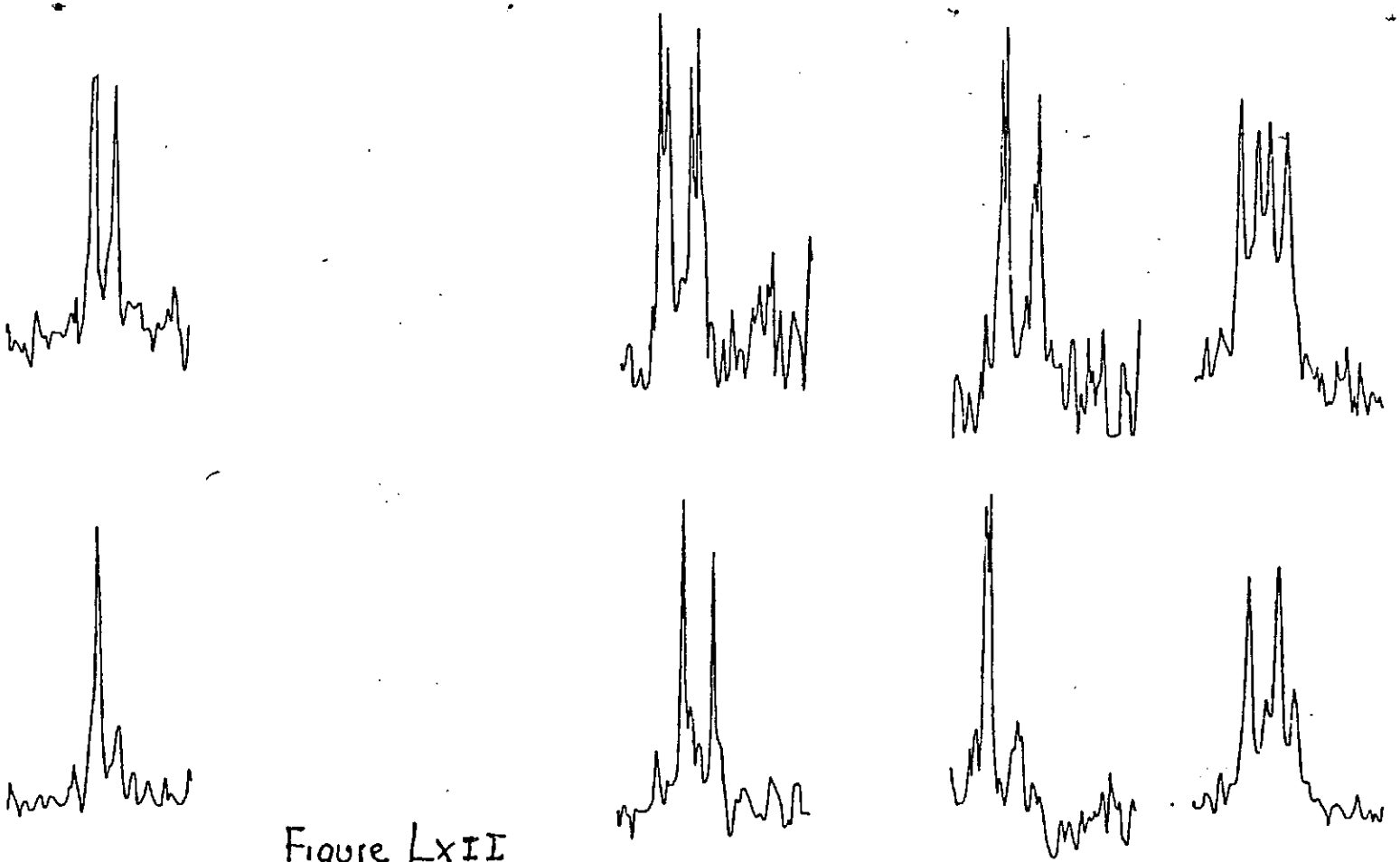
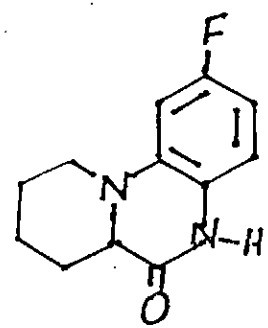


Figure LXII

Deuterium isotope effects on Carbon-13 chemical shifts of 7,8,9,10-tetrahydro-2-fluoro pyrido [1,2-a] quinoxalin-6-one.



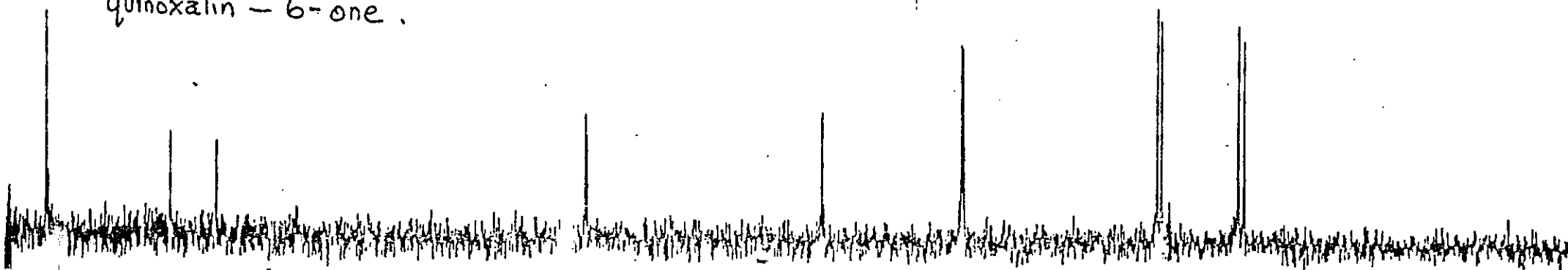
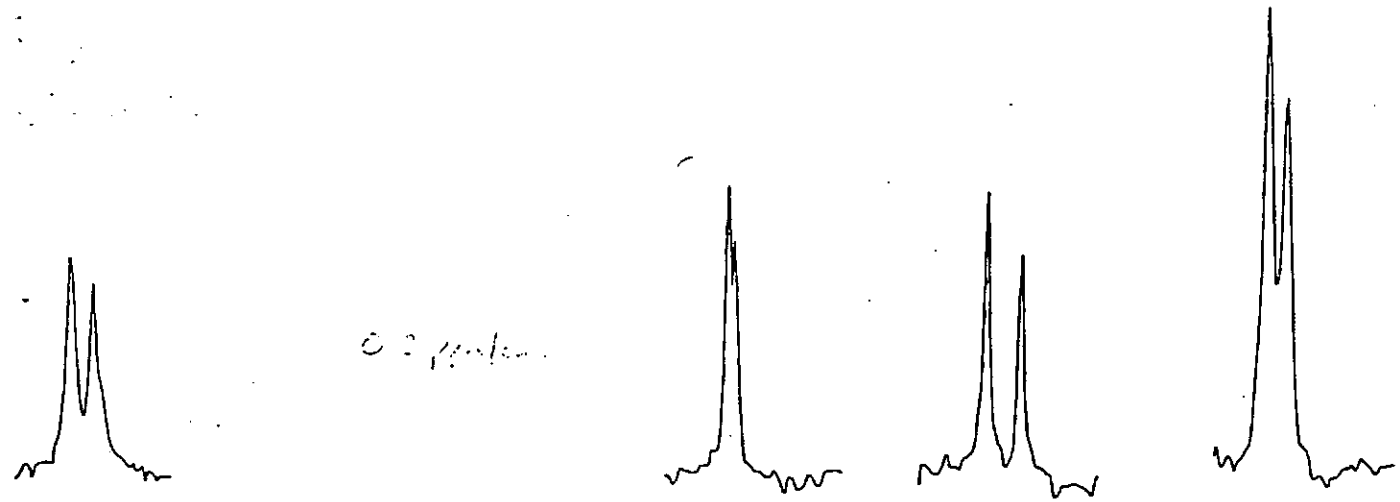
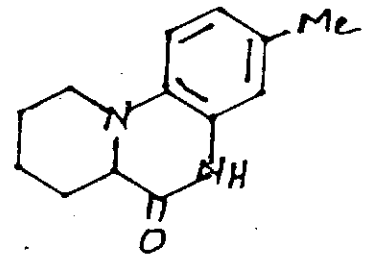


Figure LXIII

Deuterium isotope effects on Carbon-13 chemical shifts of 7, 8, 9, 10 tetrahydro-3-methylpyrido (1, 2-a) quinoxalin-6-one





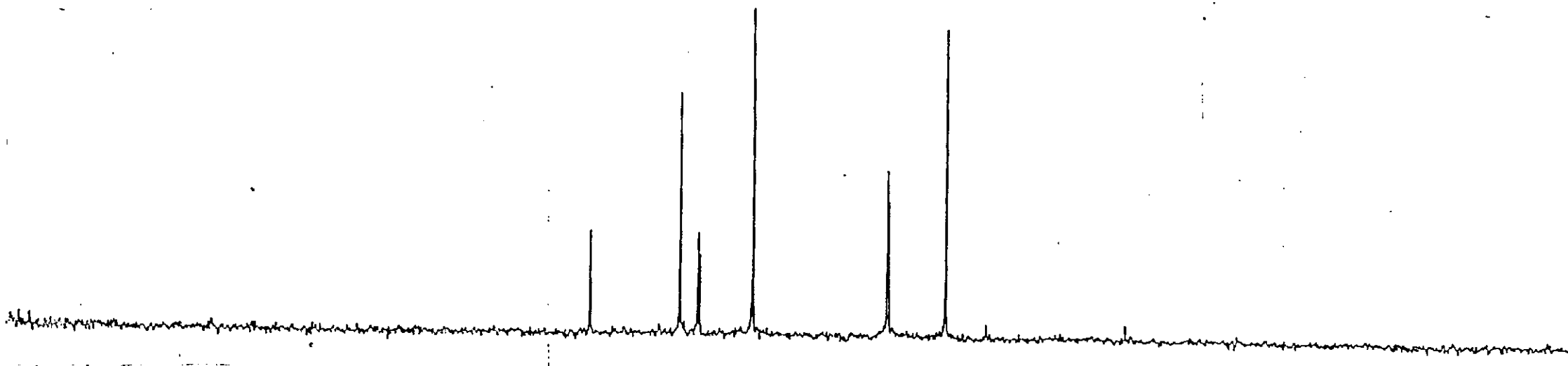
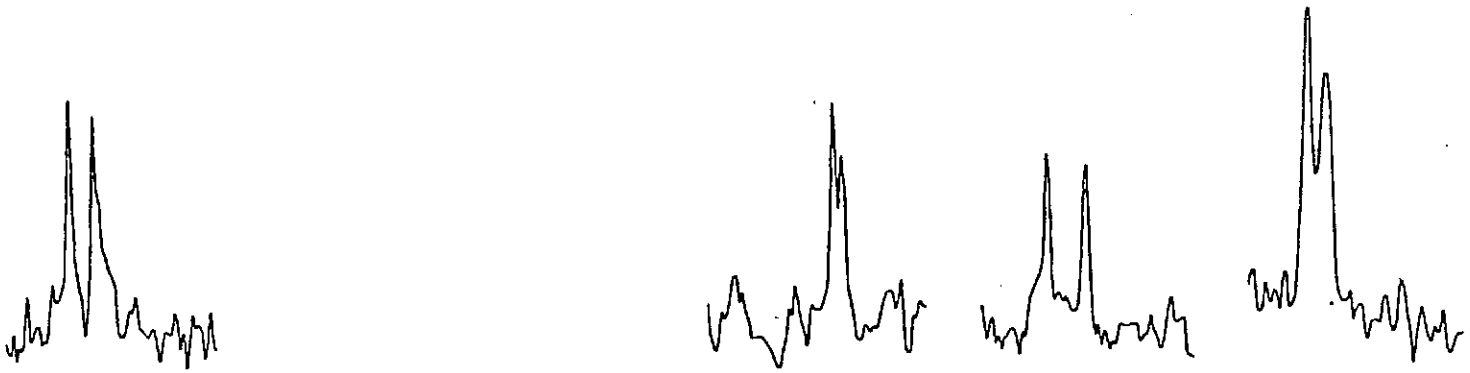
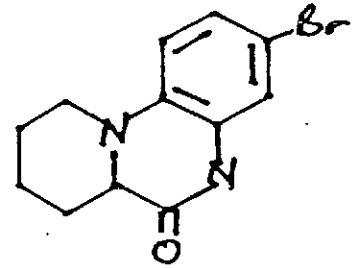
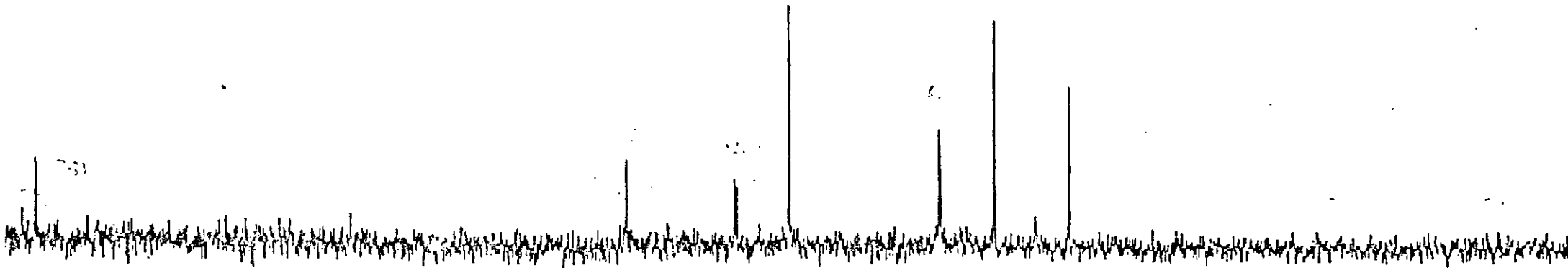


Figure LXIV

Deuterium isotope effects on Carbon-13 Chemical shifts of 7, 8, 9, 10-tetrahydro-3-bromopyrido (1, 2-a) quinoxalin-6-one







tetrahydropyrido[1,2-a]quinoxalin-6-one, its 2-fluoro-;3-methyl-; and 3-bromo- derivatives have been securely assigned in this study. In addition, we have presented evidence to show that the magnitudes of deuterium isotope shifts on the carbon-13 resonances of the α-carbon atoms is dependant on the geometrical relationship of the carbons concerned to the amide.

Prior to this work, there has been no report on ^{13}C-NMR of such compounds and so the results of this study are an important contribution to the ever growing utility of carbon-13 NMR spectroscopy in organic chemistry.

2.6.0 BIOLOGICAL SCREENING:

As noted in the introduction, there is no information on the biological properties of the tetrahydropyridoquinoxalinones under study.

This paucity of information prompted a biological assay of the heterotricycles and their precursors, as regards their possible use for example in agriculture. The following compounds synthesized in this study were sent for biological screening at the Shell Research Centre, Sittingbourne, Kent, U.K. They were screened for antibacterial and antifungal activity in plants and also for possible use as plant growth regulators:-

(i) N-[2'-nitrophenyl]piperidine-2-carboxylic acid (149).

(ii)N-[2',4'-dinitrophenyl]piperidine-2-carboxylic acid (169).

(iii)N-4'- methyl-2'nitrophenyl]piperidine-2-carboxylic acid (167).

(iv) N-[5'-fluoro-2-nitrophenyl]piperidine-2-carboxylic acid (168).

(v) 7,8,9,10-Tetrahydropyrido[1,2-a]quinoxalin-6-one (152).

(vi) 7,8,9,10-Tetrahydro-3-methylpyrido[1,2-a]quinoxalin-6-one(176).

(vii) 7,8,9,10-Tetrahydro-2-fluoropyrido[1,2-a]quinoxalin-6-one (177).

(viii) 7,8,9,10-Tetrahydro-3-methyl-5-benzylpyrido[1,2-a] quinoxalin-6-one (180)

(ix) 7,8,9,10-tetrahydro-3-methyl-5-benzylpyrido[1,2-a]quinoxalin-6-one (185)

(x) 7,8,9,10,- Tetrahydro-2-fluoro-5-benzylpyrido[1,2-a]quinoxalin-6-one(188)

(xi) 7,8,9,10-Tetrahydro-3-methyl-5-(2'-chlorobenzyl)pyrido [1,2-a]quinoxalin-6-one (186)

Of these eleven compounds sent for the biological assay fungicide activity was recorded in seven samples. These are the substituted N-[2'-nitrophenyl]piperidine-2-carboxylic acids [compounds (167),(168) and (169)], the 3-methyl-derivative of the quinoxalinone (176) and the N-benzyl derivatives of the methyl- and fluoro- pyridoquinoxalinones;[compounds (185) and (188)].

These compounds showed activity as a protectant for Vine downy mildew (Plasmopora Viticola). In addition, the N-2'-chlorobenzyl derivative of 7,8,9,10,-tetrahydro-3-methylpyrido [1,2-a]quinoxalin-6-one (186) showed activity as an antisporulant for Plasmopora Viticola as well as against Pyricularia Oryzae (Rice Blast).

No insecticidal or herbicidal activity was detected in any of the compounds.

These initial results suggest that the N-benzyl derivatives of the heterotricycles (especially its methyl derivative) may be useful in agriculture as fungicides. Further investigations however still need to be carried out in this direction. Substitution of the 3-methyl derivative of the tetrahydropyrido quinoxalinone with various substituted benzyl groups and subsequent biological screening of these compounds should provide the appropriate candidates for such future research.

3.0 EXPERIMENTAL

3.1.0 GENERAL EXPERIMENTAL DETAILS

Melting points were determined on a "Kofler hot stage" apparatus and are uncorrected. Infrared spectra were measured for Nujol mulls with a Perkin-Elmer 597 spectrophotometer. ^{1}H-NMR spectra were determined in the indicated solvent with tetramethylsilane (TMS) as the internal standard reference (0.00) at 60MHz with a varian T60 or Perkin-Elmer R12; at 80MHz with a Bruker WP80; at 90MHz with a Perkin-Elmer R32 and at 360MHz with a Bruker WM360 spectrometer. ^{13}C-NMR spectra were measured with Bruker WM360 spectrometer. Mass spectra were measured with a Kratos MS-25 mass spectrometer. Column chromatography was performed as described by W.C. Still (J. Org. Chem; 1978, 43 2923). Reactions were followed by thin layer chromatography (t.l.c), carried out on plastic sheets of silica gel 60 F_{254} Merck Art. 5735, and developed in a solvent system consisting of ethyl acetate in petroleum ether 60-80^{o}. Solvents for chromatography and crystallization were dried and purified prior to use as described by D.D. Perrin, W.L.F. Armarego and D.R. Perrin in "Purification of Laboratory Chemicals" Pergamon Press, 1980. Evaporation of organic extracts in vacuo was done on a Buchi rotary evaporator after drying as specified in each case.

3.2.0 GENERAL PROCEDURE FOR PREPARATION OF N-[2'-NITROPHENYL] PIPERIDINE-2-CARBOXYLIC ACIDS

These compounds were obtained by refluxing equimolar amounts of the appropriate halonitrobenzene and pipecolinic acid in ethanol made alkaline with 10% sodium hydrogen carbonate solution, for 5 hrs. The basic solution in each case was allowed to cool and washed by extraction with ether. The aqueous layer was acidified (2M HCL) and the resulting oil was taken up in chloroform and dried (anhydrous Na_2SO_4).Organic solvents were removed in vacuo, leaving a residue in each case.

3.2.1. N-[2'-NITROPHENYL]PIPERIDINE-2-CARBOXYLIC ACID

Preparation Method A:

A mixture of 1-fluoro-2-nitrobenzene (7.055g; 0.05 moles) in ethanol (210ml) and pipecolinic acid (6.5g, 0.05 moles) in sodium hydrogen carbonate solution was heated under reflux for 5hrs. The reaction was carried out and worked up as described in the general procedure. The residue obtained after removal of chloroform crystallized from petroleum ether 40-60°. Recrystallization from ethyl acetate/pentane gave 7.84g (66.4%) N-[2'-nitrophenyl]piperidine-2-carboxylic acid as bright yellow prisms. m.p. 79-80°C. Lit.[34] m.p. 78-80°C

IR: 3000 (OH),1710 (C=O),1600,1520 (NO_2)750(s) cm^{-1} (Fig.I)

p.m.r ($CDCL_3$): 1.67 (4H, piperidine,m), 2.07 (2H,m,-CH_2 CH(N) CO), 3.05 & 3.46 (2H, m,-CH_2 -N-) 4.08 (1H,t,-CH(N)-CO_2), 7.05 & 7.29 (aromatic 2H,m), 7.48 (ArH,m), 7.78 (ArH) 10.16, (1H, s, broad, exchangeable with D_2O,-COOH). (Fig II)

Anal.Calcd.for $C_{12}H_{14}N_2O_4$: C,57.60; H,5.60; N,11.20.
Found: C, 57.86; H,5.76; N,11.10.

Method B:

A mixture of 1-fluoro-2-nitrobenzene (5.0g, 0.035 moles), pipecolinic acid (4.57g, 0.035 moles), triethylamine (6ml) in dimethylsulphoxide (45ml) was heated under reflux with stirring for 18hrs. The resulting mixture was diluted with cold water (150ml) and washed by extraction with ether. The aqueous layer was acidified to pH3 with conc. HCL and extracted repeatedly with dichloromethane. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The resulting oily product was further purified by taking it up into dichloromethane and extracting with sodium hydrogen carbonate. The aqueous layer was collected and the acid product recovered by re-acidifying the extract and further extraction with dichloromethane. Evaporation of solvent in vacuo left an oily product which crystallized from petroleum ether (40-60°) to give 3.7g (42%) of N-[2'-nitrophenyl] piperidine-2-carboxylic acid. m.p.78-80°C.

All spectral data of this compound were identical with those obtained for the product obtained by Method A.

3.2.2. N-[4'METHYL-2'-NITROPHENYL]-PIPERIDINE-2-CARBOXYLIC ACID:

4-Fluoro-3-nitrotoluene (4.6ml, 5.80g, 37.5mmoles) in ethanol (120ml) was refluxed with pipecolinic acid (4.85g, 37.5mmoles) in sodium hydrogen carbonate solution for 5hrs. The

reaction was worked up as described in the general procedure. After removal of chloroform, an oily product was obtained which later solidified giving a deep yellow crystalline solid, 5.5g (50%).

m.p. 88-89 °C

IR: 2800 (OH),1685 (C=O),1520 (NO_2),825 (s) cm^{-1} (Fig III)

p.m.r ($CDCl_3$): 1.60 (piperidine 4H,m), 2.05 (2H,m,-CH_2-CH(N)-CO-), 2.32 (3H, s, ArMe), 2.97 & 3.37 (2H,m,-CH_2-N-), 4.04 (1H,t,-CH(N)-CO2) 7.23 (aromatic 2H,m), 7.54 (ArH,s), 9.9 (1H,s, broad, exchangeable with D_2O, -COOH) (Fig IV)

Anal.Calcd.for $C_{13}H_{16}N_2O_4$: C,59.09; H,6.06; N,10.60.

Found: C, 59.06; H,6.31; N,10.63.

3.2.3. N-[5'-FLUORO-2-NITROPHENYL]PIPERIDINE-2-CARBOXYLIC ACID

2,4-Difluoronitrobenzene (5.96g, 37.5mmoles) in ethanol (120ml) was reacted with pipecolinic acid (4.85g, 37.5mmoles) according to the general procedure. After removal of chloroform, a product which crystallized from n-pentane as yellow crystals, was obtained; 7.55g (75%)

m.p. 97-98 °C

IR: 2800 (OH),1710 (C=O),1610,1510(NO_2),860 (s) cm^{-1} (Fig V)

p.m.r ($CDCl_3$): 1.7 (piperidine 4H, m), 2.17 (2H,m,-CH_2-CH(N)-CO-), 3.10 & 3.63 (2H,m,-CH_2-N-), 4.07 (1H,t,-CH(N)-CO_2), 6.95 & 6.96 (aromatic 2H,m), 7.90 (ArH, m), 9.45 (1H,s,broad, exchangeable with D_2O,-COOH), (Fig VI).

Anal.Calcd. for $C_{12}H_{13}N_2FO_4$: C, 53.73; H,4.85; N,10.45.

Found: C,53.72; H,4.96; N10.39.

3.2.4 N-[2',4'-DINITROPHENYL]PIPERIDINE-2-CARBOXYLIC ACID:

2,4-Dinitrofluorobenzene (6.98g, 37.5 mmoles) in ethanol (210ml) was reacted with pipecolinic acid (4,85g, 37.5mmoles) in sodium hydrogen carbonate solution according to the general procedure described. After removal of chloroform, a product which crystallized from petroleum ether (40-60 ^{o}) as yellow prisms was obtained (8.33g, 75.3%) m.p. 134-135 ^{o}C. Lit.[33] m.p. 130-131 ^{o}C IR: 1710 (C=O),1610 (s),1530, 1510 (NO_2), 1460, 750 (s) cm^{-1}. (Fig VII)

p.m.r. ($CDCL_3$): 1.80 (piperidine 4H, m), 2.21 (2H,m-CH_2-CH(N)-CO_2), 3.40 (2H,m,-CH_2-N-), 4.15 (1H,t,-CH(N)-CO_2-), 7.18 (aromatic 1H, d, broad at base, J=9Hz), 8.25 (ArH, dd, J=9Hz), 8.68 (ArH,d,J=2Hz), 8.84 (1H,s, broad, exchangeable with D_2O,- COOH). (Fig VIII).

3.2.5 N -[6'-CHLORO-2'-NITROPHENYL] PIPERIDINE-2-CARBOXYLIC ACID.

2,3-Dichloronitrobenzene (4.8g, 25mmoles) in ethanol (150ml) was reacted with pipecolinic acid (3.23g, 25mmoles) in sodium hydrogen carbonate solution according to the general procedure described. After removal of chloroform, 95% of unreacted 2,3-dichloronitrobenzene was recovered.

The reaction was repeated; the mixture was kept under reflux for 5 days and constantly monitored by t.l.c. 0.071g (1%) of N-[6'-Chloro-2'-nitrophenyl]piperidine-2-carboxylic acid was obtained on work-up whilst 3.36g (70%) 2,3-dichloronitrobenzene was recovered. m.p. of product = 165-166 ^{o}C.

IR: 1715 (C=O), 1540 (NO_2), 1370, 945, 810 (s) cm-1 (Fig XI)

p.m.r ($CDCL_3$): 1.57-1.87 (piperidine 6H,m), 3.15 (2H,m,$-CH_2-N-$), 4.02 (1H, m, broad), 7.10,(aromatic 1H,m), 7.38 & 7.4 (aromatic 2H, m), (Fig XII).

Anal.Calcd.for $C_{12}H_{13}N_2CLO_4$: C, 50.70; H,4.58; N,9.85.
Found: C, 50.76; H,4.48; N,9.84 .

B. A mixture of 2,3-dichloronitrobenzene (4.8g, 25mmoles), pipecolinic acid (3.17g, 25mmoles), triethylamine (6 ml), in dimethylsuphoxide (45ml) was heated under reflux with stirring for 18hrs. The resulting mixture was diluted with cold water (150ml) and washed by extraction with ether. The aqueous layer was acidified to pH3 with conc.HCL and extracted with dichloromethane. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The resulting oily product was further purified by taking it up into dichloromethane and extracting with sodium hydrogen carbonate. The aqueous layer was collected, and the acid product recovered by re-acidifying and extracting the aqueous extract with dichloromethane. On evaporation of solvent, an oily product was obtained which crystallized from petroleum ether (40-60^{o}) to give 0.07g (1%) of N-[6'-chloro-2'-nitrophenyl] piperidine-2-carboxylic acid as yellow crystals. All spectral data of this compound were identical with those of the product of condensation in dilute bicarbonate solution.

3.2.6 ATTEMPTED PREPARATION OF N-[3'-CARBOMETHOXY-2'-NITROPHENYL]PIPERIDINE-2-CARBOXYLIC ACID:

(i) 3-Chloro-2-nitrobenzoic acid (5g,25mmoles) was added to anhydrous methanol (250ml) containing concentrated sulphuric acid (4ml). The mixture was kept refluxing overnight. Methanol was then completely removed in vacuo leaving a white crystalline solid. This product was taken up into chloroform and the organic extract successively washed with sodium hydrogen carbonate solution, dilute HCL and water. After drying (Na_2SO_4), the solvent was completely removed in vacuo leaving a white crystalline solid, 3-chloro-2-nitrobenzoic acid methyl ester, (4.58g, 85%), m.p. 98-100 °C.

IR: 1730 (C=O), 1540 (NO_2), 1460, 1375, 1280, 720 cm^{-1} (Fig X).

(ii) 3-Chloro-2-nitrobenzoic acid methyl ester (2.15g, 1mmole) in ethanol (125ml) was mixed with pipecolinc acid (1.93g, 15 mmoles) in sodium hydrogen carbonate solution. The reaction was kept under reflux for 5 days and constantly monitored by t.l.c. After 5 days, no significant reaction had occurred.

3.3.1 7,8,9,10-TETRAHYDROPYRIDO[1,2-a]QUINOXALIN-6-ONE

A. Preparation Method A.

(i) N-[2'-nitrophenyl]piperidine-2-carboxylic acid (10.0g, 0.04moles) was refluxed with anhydrous methanol (400ml) containing concentrated sulphuric acid (6ml) for 5hrs. The mixture was allowed to cool and excess methanol removed in vacuo. The resulting mixture was extracted with chloroform (3x100ml). The organic extract was washed successively with sodium hydrogen

carbonate, dilute HCL and water . After drying (Na_2SO_4), and evaporation of solvents, the product Methyl N-[2'-nitrophenyl] piperidine-2-carboxylate, was obtained as a thick transparent yellow oil (10g, 95%).

IR: 2950 (CH_3), 1740 (C=O), 1600 (s), 1520 (NO_2); 1340(C-O), 750 cm^{-1}. (Fig XIII)

p.m.r. ($CDCL_3$): 1.7 (piperidine 4H,m), 2.10 (2H,m,- CH_2 CH_2 (N)-CO), 3.01 & 3.60 (2H,m,-CH_2 -N),3.60 (3H,S, OMe), 4.02, (1H, t, -CH-CO_2), 7.02 & 7.29 (aromatic 2H, m), 7.47, (ArH, m) 7.72 (ArH,dd, J=7.5 Hz and 1.5 Hz). (Fig XIV)

(ii) To methyl N-[2'-nitrophenyl]piperidine-2-carboxylate (8.0g,0.03 moles) was added dry, freshly redistilled cyclohexene (16ml) and 5% palladium on charcoal (5g), with absolute ethanol (200ml). The mixture was heated under reflux for 2 hrs. The resulting dark mixture was filtered through Celite, after which the solvents were completely removed leaving a dark gum. The gum crystallized from ethanol/diethyl ether mixtures and recrystallization from aqueous ethanol gave 3.5g (58%) of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one as a grey microcrystalline solid m.p 188-190 °C. Lit. mp=148-149 °C

IR: 3400 (N-H), 1675 (lactam C=O),1205 (s),750 cm^{-1} (Fig XV)

p.m.r. (DMSO d_6): 1.43, 1.65, 1.82 & 2.00 (piperidine 6H, m), 2.62 & 3.72 (2H, m,-CH_2 -N) 3.42 (1H,t,-NCH - C=O), 6.72 [aromatic 1H,t of d's; J=7.5Hz (t),and 1.5Hz (d)],6.80 (ArH dd,J=7.5Hz &

1.5 Hz), 6.82 (ArH,d,J=7.5 Hz),6.89 [ArH,t of d's; J=7.5Hz (t), and 1.5Hz (d)], 10.37 (1H, broad, exchangeable with D_2O, N-H). (Figs XVI and XXXIX)

Anal.Calcd.for $C_{12}H_{14}N_2O_2$: C,71.29; H,6.93; N,13.86.
Found: C,70.12; H,6.78; N,13.72.

Method B:

N-[2'-nitrophenyl]piperidine-2-carboxylic acid (2.36g, 10mmoles) was dissolved in water (80ml) and the pH adjusted to 9-10 with 50% sodium hydroxide solution. To this stirred solution was added sodium dithionite (7.0g) in small portions. The pH was monitored during the addition and readjusted to pH 9 when necessary. The reaction mixture was kept stirring for 1.5hrs, cooled, and acidified with conc.HCL to pH2. The separated white solid was filtered, washed with water and dried. Recrystallization from aqueous ethanol gave 1.5g (57.2%)* of a dirty white microcrystalline solid. m.p. 190-191 °C.

The spectral data of this cyclized compound were identical in all respects with those of the product obtained by Method A.

* pH sensitive reaction ! Yield varies from 35-58%

C. Method C.

N-[2'-nitrophenyl]piperidine-2-carboxylic acid (2.36g, 10mmoles) was dissolved in absolute ethanol (60ml) containing conc.HCL (14ml). Tin granules (3.6g) were added and the mixture heated under reflux for 3hrs. Excess ethanol was removed in vacuo

and the residue basified (50% NaOH) and extracted repeatedly with chloroform. The combined chloroform extract was washed with water, dried (Na_2SO_4) and the solvent removed in vacuo leaving a greenish brown microcrystalline solid. Recrystallization from aqueous ethanol gave 0.35g (17%) of 7,8,9,10-tetrahydropyrido [1,2-a]quinoxalin-6-one. m.p. 188-190 °C.

The IR spectrum of this compound was identical to that of products obtained by Methods A and B.

Method D:

To a stirred solution of N-[2'-nitrophenyl]piperidine-2-carboxylic acid (2.36g,10mmoles) in glacial acetic acid (25ml) was added 1.2g iron powder over a period of 15mins. The temperature of the reaction was raised to 80 °C and then the reaction mixture was allowed to stir at 60-65 °C for 3hrs. The mixture was cooled and filtered and the acetic acid was evaporated in vacuo. The remaining slurry was extracted with dichloromethane (3x30ml). The dichloromethane extracts were cooled, dried (Na_2SO_4) and evaporated in vacuo leaving a black crystalline solid. The product was purified by boiling with Norite in ethanol for 30 mins. After filtering, excess ethanol was removed in vacuo leaving a greenish brown crystalline solid (0.48g, 23.7%) m.p. 188-190 °C.

The infrared spectrum of this compound was identical with the spectra of the products obtained by Methods A-C.

3.3.2 7,8,9,10-TETRAHYDRO-3-METHYLPYRIDO[1,2-A]QUINOXALIN-6-ONE:

N-[4'-methyl-2'-nitrophenyl]piperidine-2-carboxylic acid (2.0g, 7.5mmoles) was dissolved in water (80ml) and the pH adjusted to 9-10 with 50% NaOH solution. To this stirred solution was added sodium dithionite (7g), in small portions. The pH was monitored during the addition and readjusted to pH9 when necessary. The reaction mixture was kept stirring at room temperature for 1.5hrs, then cooled and acidified with conc. HCL to pH2. The separated white solid was collected, washed with water and dried. Recrystallization from aqueous ethanol gave 1.01g (62% of 7,8,9,10-tetrahydro-3-methylpyrido[1,2-a]quinoxalin-6-one as a pinkish-white crystalline solid m.p. 148-150 °C

IR: 3260 (N-H), 1680 (C=O), 1460, 790 (s) cm^{-1} (Fig XVII)

p.m.r. (DMSO d_6-): 1.42, 1.64, 1.80, & 1.99 (piperidine 6H,m). 2.16 (3H,s,ArMe), 2.58 & 3.67 (2H,m-CH_2-N), 3.33 (1H, t, -N-CH-C=O), 6.61 (ArH, s), 6.69 (aromatic 2H,m), 10.32 (1H,s, exchangeable with D_2O, N-H). (Fig XVIII & XL)

Anal.Calcd.for $C_{13}H_{16}N_2O.0.5H_2O$: C,69.33; H,71; N,12.44.
Found: C, 69.34; H,6.76; N,12.20.

3.3.3. 7,8,9,10-TETRAHYDRO-2-FLUOROPYRIDO[1,2-A]QUINOXALIN-6-ONE:

N-[5'fluoro-2'-nitrophenyl]piperidine-2-carboxylic acid (2g, 7.46 mmoles) was dissolved in water (80ml) and the pH adjusted to 9-10 with 50% NaOH solution. To this stirred solution was added sodium dithionite, (7.0g) in small portions. The experiment was carried out and worked up as described for

7,8,9,10-tetrahydro-3-methylpyrido[1,2-a]quinoxalin-6-one. The product, a grey microcrystalline solid (1.13g, 69%) was recrystallized from aqueous ethanol, m.p. 195-196 °C.
IR: 3100 (N-H), 1680 (C=O), 1510, 1460, 820 (s) cm^{-1} (Fig XIX)
p.m.r (DMSO d-$_6$): 1.48 & 2.00 (piperidine 6H,m) 2.66 & 3.72 (2H,m, - CH_2 -N), 3.50 (1H,t, -N-CH-C=O), 6.51 (1H, m, ArH), 6.68 & 6.75 (aromatic 2H,m), 10.40 (N-H). (Figs. XX & XLI)
Anal.Calcd. for $C_{12}H_{13}N_2OF$: C,65.45; H,5.90; N,12.72.
Found: C, 65.37; H.5.58; N,12.47.

3.3.4. ATTEMPTED PREPARATION OF 7,8,9,10-TETRAHYDRO-3-NITROPYRIDO[1,2-A]QUINOXALIN-6-ONE BY THE SODIUM DITHIONITE REDUCTIVE CYCLIZATION METHOD:

N-[2',4'-dinitrophenyl]piperidine-2-carboxylic acid (1.48g,5mmoles) was dissolved in water (40ml) and the pH adjusted to 9-10 with 50% NaOH. To this stirred solution was added sodium dithionite (3.5g) in small portions. The pH was monitored during the addition and readjusted to pH9 when necessary. The reaction mixture was stirred for 1.5hrs then cooled, acidified with conc. HCL to a pH of 2. The separated black solid was filtered, washed with water and dried. The infrared of the solid product showed no carbonyl absorption and the p.m.r. spectrum showed no aromatic protons. The reaction was repeated and the same results obtained.

3.3.5. 7,8,9,10-TETRAHYDRO-3-NITROPYRIDO[1,2-a]QUINOXALIN-6-ONE:

(i) N-[2',4'-dinitrophenyl]piperidine-2-carboxylic acid (2g, 6.8mmoles) was added to anhydrous methanol (100ml) containing concentrated sulphuric acid (1.5ml). The mixture was made to reflux for 6hrs. It was then allowed to cool and excess methanol removed in vacuo. The residual mixture was extracted with chloroform (3x100ml). The organic layer was successively washed with sodium hydrogen carbonate, dilute HCL and water, then dried (Na_2SO_4). After removal of chloroform, the product, Methyl-N-[2,4-dinitrophenyl]piperidine-2-carboxylate, was obtained as an oil which later solidified. The yellow crystalline solid (2.8g, 95%) was recrystallized from petroleum ether (60-80 ^{o})/diethyl ether m.p. 86-87 ^{o}C Lit[33] m.p. 86-87 ^{o}

IR: 1740 (C=O), 1600 (s), 1530, 1510 (NO_2), 830, 800 cm^{-1} (Fig XXI)

p.m.r. ($CDCL_3$): 1.77 (piperidine 4H, m), 2.20 (2H, m), 3.37 (2H, m,-CH_2-N), 3.72 (3H,s, OMe) 4.13 (1H, t, H-C-CO_2R) 7.1 (aromatic 1H, d, J=8Hz), 8.3 (ArH, dd,J=12Hz & 2Hz), 8.60 (ArH,d, J=2Hz), (Fig XXII).

(ii) To methyl N-[2'4'-dinitrophenyl]piperidine-2-carboxylate (1.5g),4.85mmoles) was added dried, freshly redistilled cyclohexene (8ml, 0.08 moles), 5% palladium on charcoal (2g) and absolute ethanol (75ml). The mixture was heated under reflux for 2 hrs. The resulting dark mixture was filtered through Celite

after which solvents were completely removed leaving a gum which crystallized from diethyl ether to give a dark brown crystalline solid. Trituration with hot ethanol gave two products :- an ethanol insoluble product,(0.20g) and an ethanol soluble product (0.48g).

The ethanol insoluble product (product I) was a dark brown solid with a melting point of 290°dec (Lit[33] m.p. of 7,8,9,10-tetrahydro-3-nitropyrido[1,2-a]quinoxalin-6-one = 290° dec). The IR spectrum of this product showed no carbonyl absorption and the p.m.r.spectrum showed no aromatic protons.

Product II, a bright yellow crystalline solid had a m.p. of 188-190°C. IR: 3150 (N-H),1670 (C=O),1600,1500 (NO_2),1305,1330, 745cm^{-1} (Fig XXIII).

p.m.r. ($CDCL_3$): 1.2-2.0,(piperidine 6H,m); 2.50 & 4.0 (2H, m, $-CH_2-N$), 3.0 (1H, m, -N-CH-C=O), 7.0, (ArH, d, J=10Hz) 7.8 (aromatic 2H, m), 11.0 (1H, s, -N-H), (Fig XXIV).

Anal.Calcd.for $C_{12}H_{13}N_3O_3$: C,58.30; H,5.26; N,17.01.
Found: C,54.45; H,4.8; N,15.3.

| ct p145

3.4.0 REACTIONS OF 7,8,9,10-TETRAHYDROPYRIDO[1,2-a]QUINOXALIN-6-ONE WITH ELECTROPHILIC REAGENTS

3.4.1. REACTION WITH SULPHURIC ACID :

7,8,9,10-Tetrahydropyrido[1,2-a]quinoxalin-6-one (0.20g,1mmole) was dissolved in conc. sulphuric acid (5ml) and the mixture set aside at room temperature overnight. The solution was poured onto ice (ca10g) and left for 30 mins. Over 80% of the starting material was collected.

The reaction was repeated in refluxing conc. sulphuric acid for 30mins . The same results were obtained.

3.4.2. REACTION WITH BROMINE IN WATER.

A mixture of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one (0.2g,1mmole) and bromine (0.05ml,1mmole) in water (10ml) was kept stirring at room temperature for 2 days. The resulting dark green mixture was filtered and a dark green solid collected. On trituration with hot ethanol, over 80% of the starting material was recovered. In addition, 0.03g of a dark green microcrystalline solid, m.p >300 ^{o}C was isolated. This solid was insoluble even in hot ethanol.

IR: 3400 (OH), 1700 (C=O),1605,1505cm^{-1} ,(Fig XXV).

3.4.3 REACTION WITH ONE MOLE EQUIVALENT BROMINE IN ACETIC ACID :

7,8,9,10- Tetrahydropyrido[1,2-a]quinoxalin-6-one (0.2g, 1mmole) was dissolved in acetic acid (10ml) and cooled in ice. To this stirred solution was added bromine (0.05 ml,1mmole) in

acetic acid (2ml) dropwise. The mixture was kept stirring at room temperature for 1hr., after which the precipitate formed was filtered and washed with water to give a grey microcrystalline solid (mixture of 3-bromo compound and its hydrobromide salt ?) m.p. 175-176 °C.

The p.m.r. spectrum (Fig XXVI) indicates mixture of products as evidenced from the two N-H peaks at 10.4 and 10.53.

The free base, a red brick microcrystalline solid was liberated with conc. ammonia and recrystallized from aqueous ethanol to give 0.20g (71.4%) of 7,8,9,10-tetrahydro-3-bromopyrido [1,2-a]quinoxalin-6-one m.p. 225-226 °C.

IR: 3200 (N-H),1680 (C=O),1500,1460,870,790, cm^{-1} (Fig XXVII).

p.m.r. (DMSOd-$_6$) 1.43,1.64,1.82 & 2.00 (6H,m, piperidine), 2.64 & 3.70 (2H,- CH_2 -N) 3.48 (1H,m CH-C=O), 6.76 (^{1}H, d, J=8.5 Hz), 6.93 (ArH,d,J=2.2Hz), 7.02 (^{2}ArH, dd, J=2Hz and 8Hz), 10.51 (N-H), (Fig XLII).

Anal.Calcd.for $C_{12}H_{13}ON_2Br$: C.51.26; H,4.63; N,9.97.

Found: C,51.66; H,4.78; N,9.65.

3.4.4. REACTION WITH EXCESS BROMINE IN ACETIC ACID:.

7,8,9,10-Tetrahydropyrido[1,2-a]quinoxalin-6-one (0.2g, 1mmole) was dissolved in acetic acid (10 ml) and cooled in ice. To this stirred solution was added bromine (0.15ml,3mmoles) in the same solvent (2ml), dropwise. The mixture was kept stirring at room temperature for 10mins. The bright yellow precipitate formed was filtered, washed with ether, suspended in ethanol

(20ml) and heated under reflux for 15mins. The mixture was cooled and excess aqueous ammonia was then added. The product was collected as a dark brown microcrystalline solid, 0.20g., m.p 240-242 °C.

IR: 3100 (N-H), 1690 (C=O), 1635 (C=N), 1505, 875, 795cm^{-1} (Fig XXVIII).

Anal.Calcd. for C12H13N13N2OBr: C,51.26; H,4.63; N,9.97.

Found : C, 50.9 ; H,4.0 ; N 10.2.

p.m.r spectrum (Fig XXIX) indicated a mixture of products as evidenced from two N-H peaks at 10.45 & 10.78. This mixture could not be separated by the usual laboratory techniques of column chromatography or preparative t.l.c owing to its insolubility in most organic solvents.

3.4.5 REACTION WITH N-BROMOSUCCINIMIDE IN SULPHURIC ACID:

N-Bromosuccinimide (0.9g, 5 mmoles) was added to a stirred solution of 7,8,9,10-tetrahydropyrido[1,2,-a]quinoxalin-6-one (10g, 5 mmoles) in aqueous sulphuric acid (50% v/v;, 30ml) and the mixture stirred until the NBS,had dissolved completely. The reaction mixture was kept stirring at room temperature overnight, then it was poured onto ice and made alkaline with excess conc. ammonia solution. The precipitated grey solid (1.2g) was collected, washed with water and dried. On trituration with ethanol, the 3-bromo derivative of the heterotricycle, 7,8,9,10-tetrahydro-3-bromopyrido[1,2-a]quinoxalin-6-one (0.5g, 35.7 %) was separated as the ethanol soluble portion (identical m.p, i.r and n.m.r as product of reaction of the heterolactam

with equimolar Br_2/AcoH). The ethanol insoluble portion was collected, washed with water and dried to give 0.6g (42.85%) of the mixture of monobromo derivatives obtained from reaction of the heterocycle with excess Br_2 / AcoH: identical m.p, i.r (Fig XXX), p.m.r (Fig XXXI) and analytical data. The mixture proved inseparable by the usual laboratory techniques.

3.4.6 REACTION WITH BROMINE IN CONCENTRATED HYDROBROMIC ACID:

7,8,9,10-Tetrahydropyrido[1,2-a]quinoxalin-6-one (0.20g, 1mmole) was added to a solution of bromine (0.15 ml, 3mmoles) in conc. hydrobromic acid (4 ml). The mixture was heated under reflux for 30mins, cooled and poured onto ice. A slight excess of ammonia was added and the product crystallized out as a dark brown solid which was collected and washed with water. Recrystallization from aqueous ethanol afforded 0.20g (71.4%) of an unidentified mono bromoderivative m.p. 278-280vc.

IR: 3050 (N-H), 1675 (C=O), 1625 (C=N), 1500,870, 790 cm^{-1} (Fig. XXXII).

The mass spectrum had ions at m/z 281 (M+2,98.7%),279 (M^+,100%),201 (64.9%),200 (47.77%),199 (17.19%),174 (7.0%), 173 (50.95%), 158 (5.7%).

Anal.Calcd.for $C_{12}H_{12}N_2OBr$: C,51.61; H,4.30; N,10.00.
Found: C,53.37; H,4.9; N,9.93.

51%

3.4.7 REACTION WITH NITRIC ACID :

Concentrated nitric acid (2ml) was added to a suspension of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one (0.4g,2mmoles) in water(4ml). A dark brown precipitate was immediately formed. The mixture was kept stirring at room temperature for a further 10min. It was then neutralized (ammonia solution) and the precipitate collected, washed and dried to give 0.25g of a brown crystalline solid m.p.> 350 °C dec.
IR: 3400 br,(OH), 1700 (C=O), 1380 cm^{-1} , (Fig XXXIV).
Analytical; found: C,52.5, H, 4.8, N 15.7.

3.4.8 REACTION WITH CONCENTRATED NITRIC ACID IN ACETIC ACID:

(i) Fuming nitric acid (0.1ml, 2mmoles) in acetic acid (1.0ml) was added dropwise to a stirred solution of 7,8,9,10-tetrahydropyrido[1,2,-a]quinoxalin-6-one (0.4g,2mmoles) in acetic acid (10ml) at 18-20 °C. The mixture was kept stirring at room temperature overnight , then poured onto ice-cold water. The resulting dark green precipitate was collected, washed with water and dried. 0.35g (87.5 %) of the starting material was recovered on trituration with ethanol.

(ii) 7,8,9,10-Tetrahydropyrido[1,2-a]quinoxalin-6-one (0.4g, 2mmoles) was dissolved in acetic acid (10ml) and concentrated nitric acid (1.0 ml) was added dropwise. The mixture was kept stirring at room temperature for 1hr. then poured onto ice. The precipitate formed was collected , washed

with water and dried to give 0.3g of a brown crystalline solid, m. p. 258-260 °C.

IR: 1705 (C=O), 1530 (NO_2), 1380, 1340 cm^{-1} (Fig XXXV).

Analytical ; Found: C, 47.2; H, 4.1; N, 15.3.

3.4.9 REACTION WITH NITROUS ACID IN DILUTE NITRIC ACID

7,8,9,10-Tetrahydropyrido[1,2-a]quinoxalin-6-one (0.20g, 1mmole) was dissolved in dilute nitric acid (5ml), cooled to 0-5 °C in an ice -salt bath and then a solution of sodium nitrite (0.14g, 2mmoles) in water (2ml) was added. The mixture was allowed to stir at room temperature for 1hr. The resulting precipitate was filtered, washed with water and dried. Recrystallization from aqueous ethanol gave 0.09g of a brown microcrystalline solid m.p. > 300 °C dec.

IR: 3400, br,(O-H), 1700 (C=O), 1530 (NO_2), 1380 cm^{-1} (Fig XXXVI).

3.4.10 REACTION WITH SODIUM NITRITE IN DILUTE HYDROCHLORIC ACID;

7,8,9,10-Tetrahydropyrido[1,2-a]quinoxalin-6-one (0.4g, 2mmoles) dissolved in a mixture of concentrated hydrochloric acid (0.8 ml) and ice water (0.6 ml), was treated dropwise, at 0 °C with sodium nitrite (0.45g in 3ml water). The temperature was maintained at 0-5 °C during the addition, by external cooling. When evolution of nitrous oxide had subsided, the mixture was allowed to stand at room temperature for a further 1hr. The resulting dark brown precipitate was filtered, washed and dried.

Yield = 0.33g. m.p > 300 °C dec

IR: 3400 br, (O-H), 1700 (C=O), 1610, 1375, 800cm^{-1}

(Fig XXXVII).

3.4.11 REACTION WITH POTASSIUM NITRATE/ CONC. SULPHURIC ACID.

An intimately ground mixture of 7,8,9,10-tetrahydropyrido [1,2-a]quinoxalin-6-one (0.40g,2mmoles) and potassium nitrate (0.20g, 2mmoles) was added, over a 10min. period, to ice-cold, stirred concentrated sulphuric acid (20ml). The reaction mixture was kept stirring at room temperature for 40min. then poured onto ice and the aqueous mixture made alkaline with concentrated ammonia solution. The dark brown precipitate formed was filtered, washed with water and dried. Recrystallization from aqueous ethanol gave 0.30 g (61%) of 7,8,9,10-tetrahydro-2-nitropyrido[1,2-a]quinoxalin-6-one, m.p 212-214 °C

IR: 3050 (N-H), 1680 (C=O), 1510 (NO_2) ,1460, 1325, 740 cm^{-1}

(Fig XXXVIII).

p.m.r. (DMSOd-$_6$): 1.43, 1.68, 1.84, and 2.00 (piperidine 6H, m) 2.75 & 3.70 (2H, m, CH_2-N), 3.42 (1H, m,CH-C=O),6.92 (ArH, m, H-4), 7.51 (ArH, m, H-1), 7.65 (ArH, m, H-3),(Fig XLIII).

Anal. Calcd. for C12H12N3O3: C,58.30; H,5.26; N,17.00.

Found: C, 58.10; H, 5.04; N, 16.87.

3.5.0 N-ALKYLATION REACTIONS

3.5.1 7,8,9,10-TETRAHYDRO-5-ETHYLPYRIDO[1,2-a]QUINOXALIN-6-ONE

*Sodium hydride (0.4g) was washed thoroughly with petroleum ether (5x20ml) and then DMF (20ml) was added. 7,8,9,10-Tetrahydropyrido[1,2-a]quinoxalin-6-one (0.4g, 2 mmoles) was added to this suspension. The mixture was kept stirring at room temperature for 1hr. and ethyl iodide (1ml) was added dropwise . The mixture was kept stirring at room temperature for 24hrs, after which it was poured onto ice. The light brown precipitate formed was collected, washed with water and dried. The major product was separated from impurities, including unreacted starting material, by prep. t.l.c. 0.12g, (26%) of 7,8,9,10-tetrahydro-5-ethylpyrido[1,2-a]quinoxaline-6-one was obtained as a light brown crystalline solid.

p.m.r ($CDCl_3$): 1.2-1.5 (4H,M piperidine), 1.7 (3H,m), 2.0 (1H,m), 2.5 (1H, m), 3.5 (3H, m, CH_3-CH_2-N), 4.0 (2H, q.NCH_2-CH_3), 6.9 (aromatic 3H,m) 7.15 (ArH, s), (Fig XLIV).

* Old stock of sodium hydride used which had been extensively converted to sodium hydroxide on prolonged exposure to air and moisture.

3.5.2 ATTEMPTED N-ALKYLATION WITH METHYL IODIDE IN THE PRESENCE OF SODIUM HYDRIDE:

Sodium hydride (0.5g, 20mmoles of an 80% dispersion in oil) was washed thoroughly with petroleum ether and then dry THF (40 ml) was added. 7,8,9,10-tetahydropyrido[1,2-a]quinoxalin-6-

one was added to this mixture which was kept stirring for 30mins and then methyl iodide (1.8ml ,3mmoles) was added. The reaction mixture was kept stirring for 12hours , constantly monitored by t.l.c, after which it was poured onto ice. No precipitate was formed, so the reaction mixture was extracted repeatedly with chloroform. The combined chloroform extracts was concentrated in vacuo to give a light brown oil.

The infra-red spectrum of this product showed no carbonyl absorptions.

The reaction was repeated using dry DMF as solvent; the same results were obtained.

3.5.3 ATTEMPTED N-ALKYLATION WITH DIMETHYLSULPHATE OR METHYL IODIDE IN METHANOLIC SODIUM METHOXIDE:

Freshly distilled dimethylsulphate (5ml) was added dropwise to a suspension of 7,8,9,10-tetrahydropyrido[1,2-a] quinoxalin-6-one (0.40g 2mmoles) in methanolic sodium methoxide (from 0.5g sodium and 25ml methanol). The mixture was heated under reflux for 6 hrs and then excess methanol evaporated in vacuo. A light brown crystalline residue was obtained. After attempts to take this residue up into chloroform had failed, the product was recrystallized from ethanol/ diethyl ether mixtures to give a light brown crystalline solid.

The IR spectrum of the product showed no carbonyl absorption and the p.m.r spectrum showed no aromatic protons.

The reaction was repeated using methyl iodide in place of dimethylsulphate; the same results were obtained

3.5.4 ATTEMPTED N-ALKYLATION WITH METHYL IODIDE IN DIMETHYLSULPHOXIDE IN THE PRESENCE OF POTASSIUM HYDROXIDE

To dimethylsuphoxide (3ml)was added powdered potassium hydroxide (0.23g, 4mmoles) After stirring for 5 minutes, 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one (0.20g, 1mmole) was added, followed immediately by methyl iodide (0.13ml, 2mmoles). Stirring was continued at room temperature and the reaction was constantly monitored by t.l.c. After 2hrs, there was no appreciable formation of product as evidenced from t.l.c. of the reaction mixture.

GENERAL PROCEDURE FOR PHASE TRANSFER CATALYZED N-ALKYLATION OF 7,8,9,10-TETRAHYDROPYRIDO[1,2-a] QUINOXALIN-6-ONES.

A solution of the alkyl halide (3 mmoles) in benzene (0.5 ml) is added dropwise with efficient stirring to the refluxing mixture of the pyridoquinoxalinone (2 mmoles), finely powdered sodium hydroxide (0.28g), potassium carbonate (0.56g), tetra-n-butyl ammonium hydrogen sulphate (0.068g,0.2 mmoles) and benzene (10ml). Stirring in each case is continued for 4hrs. at reflux temperature. The resultant mixture is cooled to room temperature, diluted with benzene (10ml) and treated with water (20ml) . The organic phase is separated, washed with water, dried over anhydrous sodium sulphate and evaporated in vacuo.

3.5.5 7,8,9,10-TETRAHYDRO-3-METHYL-5-BENZYLPYRIDO [1,2-a]QUINOXALIN-6-ONE.

7,8,9,10-tetrahydro-3-methylpyrido[1,2-a]quinoxalin-6-one (0.43g,2mmoles) was reacted with benzylbromide (0.36ml, 3mmoles) in the manner described. On evaporation of solvents, an oily residue was obtained which crystallized from petroleum ether (60 ^{o} -80 ^{o}). Recrystallization from ethyl acetate/petroleum ether gave a greenish brown crystalline solid, 0.35g, 57% ; m.p. 140-142 ^{o}C.

IR: 1675 (C=0), 1605,1505,1380, 800, 730, 720 (s) cm-1 (Fig.XLV)

p.m.r (CDCl3) 1.4-2.0 (6H, piperidine m) 2.15 (3H,s,ArMe), 2.52 (1H, m),3.61 (2H,m) 5.15 (2H,d,J=5Hz) N-CH_2-Ar),6.74 (aromatic 3H,d) , 7.24, (5H, s,ArH), (Fig.XLVI)

Anal. calcd. for $C_{20}H_{22}N_2O$:,78.43, H, 7.18, N, 9.15
Found : C, 78.97. H,6.90, N,8.89.

3.5.6 7,8,9,10-TETRAHYDRO-3-METHYL-5-(2'-CHLOROBENZYL) PYRIDO[1,2-a]QUINOXALIN-6-ONE.

7,8,9,10-Tetrahydro-3-methylpyrido[1,2-a]quioxalin-6-one (0.43g,2mmoles) was reacted with o-chlorobenzylchloride (0.4 ml, 3 mmoles) according to the general procedure described. On removal of solvents a light yellow crystalline solid was immediately obtained. Recrystallization from ethyl acetate /petroleum ether mixtures gave 0.58g (85%) of the product as a light yellow crystalline soild m.p.116-118 ^{o}C

IR: 1670 (C=0),1610, 1510, 805, 755 (s) cm (Fig.XLVII).

p.m.r. (CDCL3): 1.6-2.0 (6H,piperidine,m) 2.15 (3H,S,ArMe),

2.5 (1H, m) 3.6 (2H,m) 5.2 (2H, N-CH_2-Ar) 6.6 (aromatic 3H, d) 7.0-7.5 (aromatic 4H,m) (Fig.XLVIII).

3.5.7 7,8,9,10-TETRAHYDRO-3-METHYL-5-(3'-BROMOBENZYL) PYRIDO[1,2-a]QUINOXALIN-6-ONE:-

7,8,9,10-Tetrahydro-3-methylpyrido[1,2-a]quinoxalin-6-one 0.43g, 2 mmoles) was reacted with m-bromobenzylbromide (0.75g 3mmoles) in the manner previously described. On evaporation of solvent, an oily residue was obtained. T.l.c showed one major product and some impurities. The product was purified by passing through a short column of silica and eluting with ethyl acetate /petroleum ether mixtures. 0.38g, (50%) of the product was obtained as a green crystalline solid. m.p. 124-125 °C.

p.m.r. ($CDCl_3$): 1.6-1.9 (6H, m, piperidine), 2.15 (3H,s,ArMe), 2.5 (1H,m), 3.7 (2H,m), 5.2 (2H,s,N-CH_2-Ar), 6.8 (aromatic 3H, d), 7.35 (4H,m,ArH), (Fig XLIX).

3.5.8 7,8,9,10-TETRAHYDRO-2-FLUORO-5-BENZYLPYRIDO [1,2-a]QUINOXALIN-6-ONE.

7,8,9,10-Tetrahydro-2-fluoropyrido[1,2-a]quinoxalin-6-one (0.44g, 2mmoles) was reacted with benzyl bromide (0.36ml, 3mmoles) according to the general procedure described. The oily residue obtained after work-up crystallized from n-pentane and was recrystallized from ethyl acetate/pentane mixtures to give a light yellow crystalline solid as product (0.31g, 50%) m.p. 107-108 °C

IR: 1660 (C=O), 1610,1510,1455,830,705 cm^{-1} (Fig L).

p.m.r.($CDCl_3$): 1.25-2.57 (piperidine 6H, m, br), 2.18 (1H ,m),

3.60,(2H,m), 5.16 (2H,d,J=2Hz, -N-CH -Ar), 6.3-6.8 (aromatic
2
3H,m), 7.25 (5H,br,aromatic H), (Fig LI).

Anal.Calcd.for C H N OF: C, 73.55; H,6.10; N,9.0.
19 19 2
Found: C,73.64; 5.99; N, 8.92.

3.6.0 ATTEMPTED 6-CHLORINATION AND OXIDATION REACTIONS

3.6.1 ATTEMPTED 6-CHLORINATION :- REACTION WITH PHOSPHORYL CHLORIDE

(i) A mixture of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one and $POCl_3$ (10ml) was heated under reflux. Within 5-10 mins. of reaction, the mixture had turned black. It was however kept under reflux for 1 hr., after which the dark mixture was extracted repeatedly with dichloromethane. After evaporation of solvent, a product crystallized from ethanol/diethyl ether mixtures as deep purple/black needles m.p. > 300 ^{o}C dec. Yield = 0.15g.

IR: 1605, 1550, 1375, 740, 725 cm^{-1} (Fig LII).

p.m.r spectrum (Fig LIII) showed broad, unresolved, multiplets in both the aliphatic and aromatic regions.

Analytical; Found: C, 36.39; H, 3.52; N, 6.85.

(ii) $POCl_3$ (5ml) was added to a solution of 7,8,9,10-tetrahydro pyrido[1,2-a]quinoxalin-6-one (0.2g, 1mmole) in pyridine (10ml). The mixture was kept under reflux for 15 mins., then cooled, poured onto ice and neutralized with 50% NaOH solution. The inky solution was extracted with dichloromethane. The same results were obtained as in (i) above.

3.6.2 REACTION WITH MANGANESE DIOXIDE

Manganese dioxide (1.0g) was added to a suspension of 7,8,9,10-tetrahydropyrido[1,2,-a]quinoxalin-6-one (0.2g, 1mmole) in benzene (20ml). The mixture was heated under reflux with

stirring for 24hr. and then filtered and the solvent removed in vacuo leaving an oily residue which crystallized from ethyl acetate/petroleum ether mixtures as light brown crystals.

m.p. 185-187 °C.
IR: 3050 (N-H), 1680 (C=O), 1610, 1590, 1500, 790, 775, 650 cm^{-1} (Fig LVI).

p.m.r (CD_3OD): 1.2-2.2, 3.4, 4.0 & 4.7(multiplets,piperidine ring protons), 6.7 (ArH, m), 7.6 (ArH?, s) (Fig. LV).

3.6.3 REACTION WITH ALKALINE POTASSIUM FERRICYANIDE

An aqueous solution of potassium ferricyanide (4.9g, 15 mmoles, in 50ml water) was added slowly with stirring to a suspension of 7,8,9,10-tetrahydropyrido[1,2-a]quinoxalin-6-one (1.0g, 5mmoles) in 15% potassium hydroxide solution (50ml). The mixture was kept stirring at room temperature overnight. It was then filtered and 0.64g (64%) of the starting material was recovered. The filtrate was treated with dilute sulphuric acid to pH 1.0, then the mixture was extracted repeatedly with dichloromethane. The organic extract was washed with water, dried, (Na_2SO_4) and solvent removed in vacuo leaving a light brown oil.

IR: 3400, br, (O-H), 1730 (C=O), 1380, 740 cm^{-1} (Fig LVI).

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Use of the Nuclear Overhauser Effect in the Determination of the Orientation of Aromatic Substitution in Tricyclic Quinoxalinones

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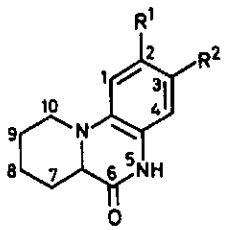
^{1}H N.m.r. nuclear Overhauser enhancement studies involving the amide NH of 7,8,9,10-tetrahydropyrido[1,2-*a*]quinoxalin-6-ones have been used to identify the aromatic proton signals of the quinoxalin-6-ones and to show that bromination with bromine in glacial acetic acid takes place at C-3 whilst nitration with potassium nitrate–concentrated sulphuric acid takes place at C-2.

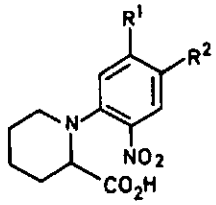
Classical methods for the orientation of groups which have been introduced by substitution onto an aromatic or heteroaromatic ring have often involved lengthy unambiguous syntheses. More recent n.m.r. spectroscopic methods involve chemical-shift and coupling-constant arguments. The nuclear Overhauser effect provides a valuable method for interrelating contiguous protons.[1] An n.O.e. from an NH has been observed on a number of occasions with amides and peptides having been used, for example,[2] to assign the amide proton resonances of NAD. It has considerable potential in heteroaromatic chemistry where a cyclic NH can be identified particularly as an NH will often exchange relatively slowly on an n.m.r. time-scale in solvents such as dimethyl sulphoxide. In this paper we describe the application of this strategy to the determination of the sites of electrophilic aromatic substitution of tetrahydropyrido[1,2-*a*]quinoxalin-6-ones (1).[3,4]

Electrophilic aromatic substitution of this ring system may occur either at C-2 or C-4 if the piperidine nitrogen is protonated and the amide directs substitution or at C-3 if sufficient non-protonated material is present. The position of a substituent X may then be determined using a combination of the coupling pattern and n.O.e. effect from the NH to 4-H (see Scheme). An n.O.e. enhancement will also be observed from the NCH_2 to 1-H.

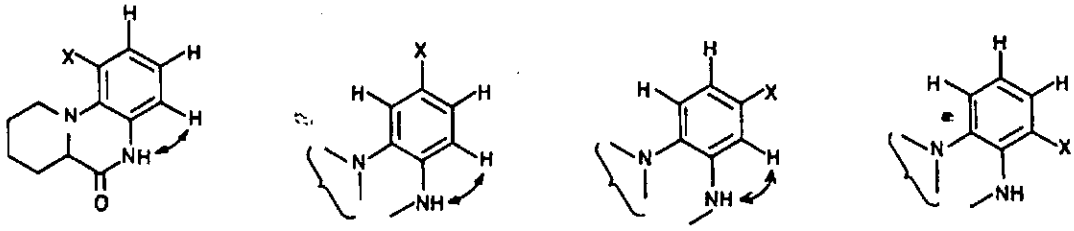
The validity of the method was established using the unsubstituted 7,8,9,10-tetrahydropyrido[1,2-*a*]quinoxalin-6-one (1) and its 3-methyl (2) and 2-fluoro (3) derivatives which were prepared by reductive cyclization[3,5] of the nitro acids (7)—(9) (see Experimental section). The aromatic proton signals of the parent compound (1) determined in [$^2H_6$]dimethyl sulphoxide at 360 MHz comprised: a triplet of doublets at δ 6.72 [*J* 7.5 (t) and 1.5 Hz (d)], a double doublet, at δ 6.80 [*J* 7.5 and 1.5 Hz] overlapping with a second broadened doublet, at δ 6.82 (*J* 7.5 Hz), and a further triplet of doublets at δ 6.89 [*J* 7.5 Hz (t) and 1.5 Hz (d)]. Although the magnitude of the vicinal coupling constants was the same, the relative



(1) $R^1 = R^2 = H$
(2) $R^1 = H, R^2 = Me$
(3) $R^1 = F, R^2 = H$
(4) $R^1 = H, R^2 = Br$
(5) $R^1 = NO_2, R^2 = H$
(6) $R^1 = H, R^2 = NO_2$



(7) $R^1 = R^2 = H$
(8) $R^1 = H, R^2 = Me$
(9) $R^1 = F, R^2 = H$



4-H = double doublet (*ortho* + *meta* coupling) n.O.e. enhancement

4-H = doublet (*ortho* coupling) n.O.e. enhancement

4-H = doublet (small *J*, *meta* coupling) n.O.e. enhancement

No 4-H to show n.O.e. enhancement

Scheme.

intensities of the individual lines showed that the doublet δ 6.80 and triplet δ 6.72 arose from adjacent hydrogen atoms whilst the doublet δ 6.82 and the triplet, δ 6.89 represented the other contiguous protons. Irradiation of the NH singlet (δ 10.37) produced a 15% n.O.e. enhancement at δ 6.80 whilst irradiation of the NCH(H) signal (10-H) produced a 16% enhancement at δ 6.82, thus allowing the assignment of the aromatic proton resonances (see Table 1). The aromatic proton signals of the 3-methyl compound (**2**) comprised a 1 H singlet (δ 6.61) and a 2 H singlet (δ 6.69). Irradiation at δ 6.61 produced a 3.3% n.O.e. effect at δ 10.32 (NH) whilst irradiation at 6.69 produced a 10% n.O.e. enhancement at δ 3.67 (10-H). The aromatic signals of the 2-fluoro compound (**3**) were rather more complex because of coupling to the ^{19}F. However irradiation at δ 6.75 produced a 16% n.O.e. enhancement at δ 6.51 and a 6% n.O.e. enhancement on the NH signal (δ 10.40) again allowing a full assignment.

The monobromo (**4**) and mononitro (**5**) compounds were obtained by bromination in acetic acid and nitration with potassium nitrate–concentrated sulphuric acid respectively. In the case of the bromo compound irradiation of the signal at δ 6.93 (d, *J* 2.2 Hz, *meta* coupling) produced a 4% n.O.e. effect at δ 10.51 (NH). Hence substitution has taken place at the 3-position. On the other hand irradiation of the NH in the nitro compound, produced a 13% n.O.e. enhancement on a doublet (*J* 8.5 Hz) at δ 6.92. Hence this nitro compound, which differed from the product (**6**) obtained previously by ring synthesis,[3] is the 2-nitro compound. The full proton spectral assignments are given in Table 1. Hence under the less strongly acidic conditions of the bromination, the piperidine nitrogen dominates aromatic substitution, whilst under the more strongly acidic conditions in sulphuric acid, this nitrogen atom is protonated and the amide directs substitution. A similar dichotomy has previously been observed[6] in the nitration of quinoxalin-2-ol.

Table 1. ^1H N.m.r. spectra of 7,8,9,10-tetrahydropyrido[1,2-*a*]quinoxalin-6-ones [determined in $(CD_3)_2SO$ at 360 MHz]

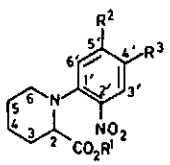
	Compound				
Proton	(1)	(2)	(3)	(4)	(5)
1-H	6.82	6.69	6.68	6.76	7.51
2-H	6.89	6.69		7.02	
3-H	6.72		6.51		7.65
4-H	6.80	6.61	6.75	6.93	6.92
5 (NH)	10.37	10.32	10.40	10.51	10.40
7a-H	3.42	3.33	3.50	3.48	3.42
7-H	1.43	1.42		1.43	1.43
8-H	1.65	1.64	1.48	1.64	1.68
9-H	1.82	1.80	2.00	1.82	1.84
	2.00	1.99		2.00	2.00
10-H	2.62	2.58	2.66	2.64	2.75
	3.72	3.67	3.72	3.70	3.70
ArMe		2.16			

Experimental

^1H N.m.r. spectra were determined on Bruker WP 80 and WH 360 spectrometers and are tabulated. I.r. spectra were determined as Nujol mulls.

Preparation of (2-Nitrophenyl)piperidine-2-carboxylic Acids.—A solution of 1-fluoro-2-nitrobenzene (7.06 g) and piperidine-2-carboxylic acid (9.7 g) in ethanol (210 ml) containing aqueous sodium hydrogen carbonate (100 ml) was heated under reflux for 4 h and then cooled and washed with ether. It was acidified with dilute hydrochloric acid and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to give 1-(2-nitrophenyl) piperidine-2-carboxylic acid (8.4 g) which crystallized from ethyl acetate–light petroleum as bright yellow needles, m.p. 79—80 °C (lit.,[34] 79—80 °C) (Found: C, 57.9; H, 5.8; N, 11.1. Calc. for $C_{12}H_{14}N_2O_4$: C, 57.6; H, 5.6; N, 11.2%); $\nu_{max.}$ 3 000 br, 1 700, 1 610, and 1 520 cm^{-1}. Under similar conditions 4-fluoro-3-nitrotoluene (5.8 g) and piperidine-2-carboxylic acid (4.85 g) gave *N-(4-methyl-2-nitrophenyl)piperidine-2-carboxylic acid* (**8**) (5.5 g), m.p. 85—86 °C (Found: C, 59.1; H, 6.3; N, 10.6. $C_{13}H_{16}N_2O_4$ requires C, 59.1; H, 6.1; N, 10.6%); $\nu_{max.}$ 3 000, 1 700, 1 620, and 1 525 cm^{-1}. 2,4-Difluoronitrobenzene (5.96 g) and piperidine-2-carboxylic acid (4.85 g) similarly gave 1-(*5-fluoro-2-nitrophenyl)piperidine-2-carboxylic acid* (**9**) (7.55 g), m.p. 97—98 °C (Found: C, 53.7; H, 5.0; N, 10.4. $C_{12}H_{13}FN_2O_4$ requires C, 53.7; H, 4.85; N, 10.45%); $\nu_{max.}$ 3 000, 1 715, 1 620, and 1 520 cm^{-1}.

Table 2. ^1H N.m.r. spectra of 1-phenylpiperidine-2-carboxylic acids and esters (determined in $CDCl_3$ at 80 MHz)



	Compound				
Proton	R^1—R^3 = H	R^1 = Me, R^2 = R^3 = H	R^1 = R^2 = H, R^3 = Me	R^1 = R^3 = H, R^2 = F	R^1 = R^2 = H, R^3 = NO_2
3'-H	7.78	7.72	7.54	7.9	8.68
4'-H	7.05	7.02		6.96	
5'-H	7.48	7.47	7.23		8.25
6'-H	7.29	7.29	7.23	6.95	7.18
2-H	4.08	4.02	4.04	4.07	4.15
3-H	2.07	2.10	2.05	2.17	2.21
4-H	1.67	1.7	1.6	1.7	1.8
5-H					
6-H	3.05	3.01	2.97	3.10	3.40
	3.46	3.60	3.37	3.63	
OMe		3.60			
OH	10.16		9.9	9.45	8.84
ArMe			2.32		

2,4-Dinitrofluorobenzene (6.98) and piperidine-2-carboxylic acid (4.85 g) gave 1-(2,4-dinitrophenyl)piperidine-2-carboxylic acid (8.3 g), m.p. 134—135 °C (lit.,[3] 130—131 °C) (Found: C, 49.2; H, 4.6; N, 14.0. Calc. for $C_{12}H_{13}N_3O_6$: C, 48.8; H, 4.4; N, 14.2%); $\nu_{max.}$ 1 710, 1 610, 1 530, 1 460, and 750 cm^{-1}.

Methylation.—1-(2-Nitrophenyl)piperidine-2-carboxylic acid (10 g) was heated under reflux in anhydrous methanol (400 ml) containing concentrated sulphuric acid (6 ml) for 5 h. The solution was concentrated, taken up in chloroform (300 ml), and washed with aqueous sodium hydrogen carbonate, dilute hydrochloric acid, and water, dried (Na_2SO_4) and evaporated to give the ester (10 g) as a thick oil, $\nu_{max.}$ 1 740, 1 610, 1 520, 1 350, and 750 cm^{-1}. Under similar conditions 1-(2,4-dinitrophenyl)piperidine-2-carboxylic acid (2 g) gave its methyl ester (2 g), m.p. 86—87 °C (lit.,[3] 86—87 °C); $\nu_{max.}$ 1 740, 1 600, 1 530, 1 500, and 830 cm^{-1}.

Cyclization Reactions.—Method A. A solution of methyl 1-(2-nitrophenyl)piperidine-2-carboxylate (8.0 g) in ethanol (200 ml) containing freshly redistilled cyclohexene (16 ml) and 5% palladium on charcoal (5 g) was heated under reflux for 2 h. The resulting mixture was filtered through Celite and the filtrate evaporated to give a gum which was recrystallized from ethanol–diethyl ether and aqueous ethanol to afford 7,8,9,10-tetrahydropyrido[1,2-*a*]quinoxalin-6-one (**1**) (3.5 g) as a grey solid, m.p. 189—190 °C (lit.,[3] m.p. 189—190 °C).

Method B.[4] 1-(2-Nitrophenyl)piperidine-2-carboxylic acid (2.36 g) was dissolved in water (80 ml) and the pH was adjusted to 9—10 with 50% aqueous sodium hydroxide. Sodium dithionite (7.0 g) was added in small portions and the pH was maintained at *ca.* 9 by the addition of alkali. After a further 1.5 h, the solution was cooled and acidified to pH 2. The product (1.13 g) was filtered off, washed with water, dried, and recrystallized from aqueous ethanol, m.p. 190—191 °C; it was identical (i.r.) with the previously described material.

Using method B 1-(4-methyl-2-nitrophenyl)piperidine-2-carboxylic acid (2.0 g) gave 7,8,9,10-*tetrahydro*-3-*methylpyrido*[1,2-a]*quinoxalin*-6-*one* (**2**) (0.99 g), m.p. 148—150 °C (Found: C, 69.3; H, 6.8; N, 12.45; $C_{13}H_{16}N_2O \cdot \frac{1}{2}H_2O$ requires C, 69.3; H, 7.1; N, 12.4%); $\nu_{max.}$ 3 260, 1 680, 1 460, and 790 cm^{-1}.

Similarly 1-(5-fluoro-2-nitrophenyl)piperidine-2-carboxylic acid (2 g) gave 2-*fluoro*-7,8,9,10-*tetrahydropyrido*[1,2-a]*quinoxaline*-6-*one* (**3**) (1.13 g), m.p. 195—196 °C (Found: C, 65.4; H, 5.9; N, 12.5. $C_{12}H_{13}FN_2O$ requires C, 65.45; H, 5.9; N, 12.7%); $\nu_{max.}$ 3 100, 1 680, 1 510, 1 460, and 820 cm^{-1}.

Using method A, methyl 1-(2,4-dinitrophenyl)piperidine-2-carboxylate (1.5 g) gave 7,8,9,10-*tetrahydro*-3-*nitropyrido*[1,2-a]*quinoxalin*-6-*one* (**6**) (0.58 g) which crystallized from aqueous ethanol, m.p. 188—190 °C (Found: C, 54.45; H, 4.8; N, 15.3. $C_{12}H_{13}N_3O_3 \cdot H_2O$ requires C, 54.3; H, 5.7; N, 15.9%); $\nu_{max.}$ 3 200, 1 660, 1 600, 1 510, and 880 cm^{-1}.

Bromination of 7,8,9,10-*Tetrahydropyrido*[1,2-a]*quinoxalin*-6-*one.*—The quinoxalin-6-one (**1**) (0.2 g) in glacial acetic acid (10 ml) was cooled in ice and bromine (0.05 ml) in acetic acid (2 ml) was added dropwise. The solution was stirred at room temperature for 1 h after which the product was filtered off and washed thoroughly with water. The free base was liberated with concentrated ammonia and recrystallized from aqueous ethanol to afford 3-*bromo*-7,8,9,10-*tetrahydropyrido*[1,2-a]*quinoxalin*-6-*one* (0.2 g) as a red solid, m.p. 225—226 °C (Found: C, 51.7; H, 4.8; N, 9.6. $C_{12}H_{13}BrN_2O$ requires C, 51.3; H, 4.6; N, 10.0%); $\nu_{max.}$ 3 200, 1 680, 1 500, 1 460, 870, and 790 cm^{-1}.

Nitration of 7,8,9,10-*Tetrahydropyrido*[1,2-a]*quinoxalin*-6-*one.*—The quinoxalin-6-one (**1**) (0.4 g) and potassium nitrate (0.2 g) were intimately ground and added over 10 min to ice-cold concentrated sulphuric acid (20 ml). The mixture was then stirred for 40 min after which it was poured onto ice and made alkaline with concentrated ammonia. The product was collected and crystallized from aqueous ethanol to afford 7,8,9,10-*tetrahydro*-2-*nitropyrido*[1,2-a]*quinoxalin*-6-*one* (**5**) (0.3 g) as a brown solid, m.p. 212—214 °C (Found: C, 58.1; H, 5.0; N, 16.9. $C_{12}H_{13}N_3O_3$ requires C, 58.3; H, 5.3; N, 17.0%); $\nu_{max.}$ 1 680, 1 510, 1 460, and 740 cm^{-1}.

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