

E. A. Adegoke* and Babajide Alo

Department of Chemistry, University of Lagos,
Lagos, Nigeria

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New tricyclic quinoxalinone skeletons with bridge-head nitrogen atoms and containing sulphur in a fully-reduced five-membered ring C were obtained. 3,3a-Dihydrothiazolo[3,4-*a*]quinoxalin-4-ones I-III were prepared by metal-acid reductive cyclisation of *N*-(nitrophenyl)- and *N*-(dinitrophenyl)thiazolidine-4-carboxylic acids IVa,b,c. Attempts to obtain the skeleton by selective hydrogen transfer reductive cyclisation of the corresponding esters Va,b,c were unsuccessful.

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In our recent work [1,2] we highlighted our continuing objective of the synthesis of polycondensed heterocyclic compounds. In pursuance of this, our attention was directed to obtaining another new tricyclic skeleton containing sulphur in a fully reduced ring C. It is expected that the presence of another heteroatom other than nitrogen should produce a skeleton of different physiological properties.

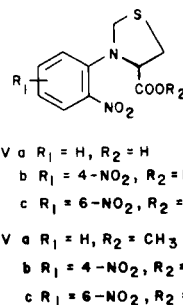
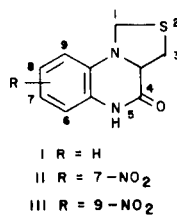
Thiazole or thiazolidine residues fused to a quinoxaline moiety in the 2,3-positions is well documented. Saikachi and Tagami [3] obtained thiazolo[4,5-*b*]quinoxaline and its derivatives by reacting 2-mercapto-3-aminoquinoxalines with acid chlorides. For the synthesis of the same group of compounds Singh and Singh [4] condensed 2,3-dichloroquinoxaline with thioureas. In similar experiments, Ismail and Sauer [5] established that the type of adduct obtained depended upon the nature of the solvent. Equimolecular amounts of 2,3-dichloroquinoxaline and thiourea in dimethyl sulphoxide afforded diquinoxalino[2,3-*b*:2',3'-*e*]1,4-dithiin, while in ethanol 2-imino-2,3-dihydrothiazolo[4,5-*b*]quinoxaline was formed in addition. The imino nature of the latter was confirmed by ready monoacylation and arylsulphonation but no formation of diazonium salts and Schiff bases. The same group of workers obtained 3-amino-2-iminodihydrothiazolo[4,5-*b*]quinoxaline hydrochloride by reacting 2,3-dichloroquinoxaline with acetone thiosemicarbazone in ethanol. The structure of this compound was confirmed by deamination using nitrous acid to give 2-imino-2,3-dihydrothiazolo[4,5-*b*]quinoxaline. Recently Ghadha *et al.* [6] reacted 2,3-dichloroquinoxaline with cyclic thioureas, dithiocarbamates, and thioamides to give similar heterocyclic systems.

Heterocyclic compounds in which a thiazolidine residue is fused to a quinoxalinone nucleus at the 1,2-positions are relatively unknown. The only report as far as we know is that of Talukdar *et al.* [7,8] who obtained some mesoionic thiazolo[3,2-*a*]quinoxalin-4-ones among several other compounds and carried out synthetic studies on their blue colour. Other mesoionic systems could not be prepared be-

cause they were very unstable.

This paper describes the synthesis of 3,3a-dihydrothiazolo[3,4-*a*]quinoxalin-4-ones. Essentially, the work involved a base-catalysed condensation between a nitrohalogenobenzene and a cyclic thioamino acid followed by metal-acid reduction of the nitro adduct to an amino compound that was generally not isolated but allowed to undergo acid-catalysed dehydration to give the tricyclic heterocycle [9]. Contrary to the view of Johnstone *et al.* [10] attempted cyclisation of the sulphur-containing nitroesters through selective hydrogen transfer reduction with cyclohexene in refluxing ethanol using a large quantity of palladium catalyst was unsuccessful in our own case. It seemed that a large quantity of palladium could not overcome the poisoning effect of the sulphur in the ring system.

Condensation between halogenonitrobenzene (2-fluoronitrobenzene, 2,4-dinitrochlorobenzene or 2,6-dinitrochlorobenzene) and thiazolidene-4-carboxylic acid in refluxing dilute sodium hydrogen carbonate solution afforded new acid adducts IVa,b,c. A reaction time of 4 hours was optimum. Above this, the yield depreciated due to production of a yet unidentifiable tarry material. Esterification of the acid, in each case, however, gave compound Va,b,c in very good yield.



The new esters, Va,b,c, were refluxed in boiling ethanol containing cyclohexene and a large quantity of palladised charcoal [10,11]. All the compounds (Va,b,c) did not cyclise to give any of the compounds I-III. Selective reduction

Table

Compound No.	Mp (°C)	ν max cm^{-1}	$^1\text{H-NMR } \delta$	ms % RI
I	280 dec	3420 (N-H) 1680 (lactam C=O)	2.0 (d, thiazolidine, 2H) 2.8 (d, 1H, S-CH-N) 3.6 (d, 1H, S-CH-N) 4.0 (t, 1H, CHC=O) 6.2 (4H, s, broad at base) 9.9 (s, 1H, NH)	205.85 (100) 178.24 (33) 150.20 (98)
II	300° dec	3400 (N-H) 1680 (s, lactam C=O) 1530 (NO_2)	2.0 (d, thiazolidine 2H) 3.0 (d, 1H, S-CH-N) 3.6 (d, 1H, S-CH-N) 4.0 (t, 1H, CHC=O) 6.2 (m, aromatic, 2H) 6.4 (s, 1H, ArH) 8.8 (s, 1H, NH)	250.97 (100) 195.0 (96)
III	291° dec	3460 (N-H) 1660 (s, lactam C=O) 1530 (NO_2)	2.0 (d, thiazolidine 2H) 3.0 (d, 1H, S-CH-N) 3.6 (d, 1H, S-CH-N) 4.0 (t, 1H, CHC=O) 6.3 (d, 1H, ArH) 6.6 (t, 1H, ArH) 6.8 (d, 1H, ArH) 8.8 (s, 1H, NH)	250.96 (100) 223.18 (31) 195.01 (96)

which should be accompanied in the present case by an intramolecular cyclocondensation was attempted by reacting either the acid IV or its ester V with either ammonium polysulphide or methanolic sodium hydrogen sulphide solutions. In most cases a complete obliteration of the acid or ester carbonyl absorption was characteristic of the ir spectrum. This was suggestive of a cleavage of the functional groups by the reagents mentioned. Cyclisation of the nitroacid IV to the expected lactam I-III was however, effected in refluxing ethanol containing tin and concentrated hydrochloric acid [9].

The structures assigned to all the compounds synthesised were based on ir, nmr, mass spectral data and on elemental analysis. Both the acid IV and the ester V were easily characterised by strong carbonyl absorptions at around 1710 and 1740 cm^{-1} respectively in their ir spectra. The shift of the carbonyl absorption from 1710 cm^{-1} in the acid IV to between 1660 and 1680 cm^{-1} in the lactam I-III was generally significant. In the nmr spectrum, a 2H doublet at δ 2.0 and a 2H doublet of a doublet at between δ 2.8 and 3.6 are characteristic of the two thiazolidine methylenes. Also an upfield shift of the aromatic multiplets at between δ 6.9 and 7.9 in compounds IVa,b,c to between δ 6.2 and 6.8 in the tricycles I-III was noteworthy, and indicated a collapse of the nitro group's deshielding effect. The mass spectra of the polycondensed compounds showed abundant molecular ions characteristic of the tricycles earlier reported by us [1].

Formation of the new thiazoloquinoxalinones from the adduct IV appears to arise from a metal-acid reduction of

the nitro group to an amino group whose nitrogen lone pair attacks the electrophilic carbon of the acid carbonyl followed by an acid-catalysed dehydration of the cycloaddition intermediate, thus producing a new carbon-nitrogen-sulphur skeleton.

EXPERIMENTAL

Melting points were determined with a Kofler hot plate apparatus and are uncorrected. Infrared spectra were obtained on a Perkin Elmer 257 using Nujol Muls and potassium bromide discs. The pmr spectra were determined on a Varian 60 MHz instrument and in pyridine- d_5 solutions with trimethylsilane as internal standard. The mass spectra were obtained at 70 eV. Microanalyses were partly carried out at Microanalytical Laboratory of the School of Chemistry, University of Bristol, England. Silica for tlc was Merck Kieselgel HF₂₅₄. Plates were developed in ethyl acetate-benzene mixtures and spots detected in an iodine tank.

N-(2-Nitrophenyl)thiazolidine-4-carboxylic Acid (IVa).

2-Fluoronitrobenzene (2.8 g, 0.02 mole) in ethanol (125 ml) was mixed with thiazolidine-4-carboxylic acid (4.0 g, 0.03 mole) in sodium hydrogen carbonate solution. The mixture was heated under reflux for 4 hours. The basic solution was allowed to cool and was washed by extraction with chloroform. The aqueous solution was acidified (2M hydrochloric acid). The oil which separated was taken up in chloroform. The organic layer was washed with water and dried over magnesium sulphate. After removal of the chloroform, an oily product was left behind, 3.1 g (62%); ir: 3550 (OH), 1720 (s, C=O), 1600 (s), 1530 (s, NO_2), 760 cm^{-1} ; nmr: δ 2.4 (doublet, thiazolidine, 2H), 3.0 (d, 1H, S-CH-N), 3.6 (d, 1H, S-CH-N), 3.9 (t, 1H, HCCOOH), 7.8 (4H, s, broad at base), 8.4 (1H, broad, exchangeable with deuterium oxide).

Anal. Calcd. for $\text{C}_{10}\text{H}_9\text{N}_2\text{O}_4\text{S}$: C, 47.24; H, 3.94; N, 11.02; S, 12.60. Found: C, 47.34; H, 4.34; N, 10.77; S, 12.21.

N-(2,4-Dinitrophenyl)thiazolidine-4-carboxylic Acid (IVb).

1-Chloro-2,4-dinitrobenzene (4 g, 0.02 mole) in ethanol (125 ml) was mixed with thiazolidine-4-carboxylic acid (4.0 g, 0.03 mole) in sodium

hydrogen carbonate solution. The experiment was carried out and worked up as described for *N*-(2-nitrophenyl)thiazolidine-4-carboxylic acid above. The product, 4 g (68%) was a yellow oil (tlc showed one spot); ir: 3500 (OH), 1720 (s, C=O), 1600 (s), 1530 (s, NO₂), 860 (s); nmr: δ 2.4 (doublet, thiazolidine, 2H), 3.0 (d, 1H, S-CH-N), 3.6 (d, 1H, S-CH-N), 3.9 (t, 1H, HCCOOH), 7.4 (m, aromatic, 2H), 7.8 (d, ArH), 8.4 (1H, broad, exchangeable with deuterium oxide).

Anal. Calcd. for C₁₀H₉N₃O₆S: C, 40.13; H, 3.01; N, 14.05; S, 10.70. Found: C, 40.48; H, 3.31; N, 13.69; S, 10.60.

N-(2,6-Dinitrophenyl)thiazolidine-4-carboxylic Acid (IVc).

1-Chloro-2,6-dinitrobenzene (4 g, 0.02 mole) in ethanol (125 ml) was mixed with thiazolidine-4-carboxylic acid (4 g, 0.03 mole) in sodium hydrogen carbonate solution. The experiment was carried out and worked up as described for *N*-(nitrophenyl)thiazolidine-4-carboxylic acid above. After crystallization from petroleum ether (40-60°), the product, 4.2 g (70%) was obtained as yellow prisms, mp 129-130°; ir: 3600 (OH), 1710 (s, C=O), 1610 (s), 1530 (s, NO₂), 810 (s) cm⁻¹; nmr: δ 2.4 (doublet, thiazolidine 2H), 3.0 (d, 1H, S-CH-N), 3.6 (d, 1H, S-CH-N), 3.9 (t, 1H, HCCOOH), 6.9 (q, 1H, ArH), 7.4 (d, 1H, ArH), 7.9 (d, 1H, ArH), 8.4 (1H, broad, exchangeable with deuterium oxide).

Anal. Calcd. for C₁₀H₈N₄O₆S: C, 40.13; H, 3.01; N, 14.05; S, 10.70. Found: C, 39.96; H, 2.74; N, 14.40; S, 10.59.

Methyl *N*-(2-Nitrophenyl)thiazolidine-4-carboxylate (Va).

N-(2-Nitrophenyl)thiazolidine-4-carboxylic acid (2.3 g, 0.009 mole) was added to anhydrous methanol (200 ml) containing concentrated sulphuric acid (1.5 ml). The mixture was heated under reflux for 6 hours. Excess methanol was removed and the residue was taken up in chloroform. The organic layer was successively washed with sodium hydrogen carbonate, 2*M* hydrochloric acid and water. After drying over magnesium sulphate, the chloroform was removed leaving 2.1 g (86%) of a yellow oil (tlc showed one spot); ir: 1750 (s, C=O), 1610 (s), 1530 (NO₂) 730 cm⁻¹; nmr: δ 2.2 (doublet, thiazolidine, 2H), 2.5 (d, 1H, S-CH-N), 2.6 (s, 3H, OCH₃), 3.3 (d, 1H, S-CH-N), 3.8 (t, 1H, HC COOCH₃), 7.6 (4H, s, broad at base); ms: 267.96 (M⁺, 16.23%), 209.15 (M⁺ - 58.81, 100%).

Anal. Calcd. for C₁₁H₁₁N₂O₆S: C, 49.25; H, 4.48; N, 10.45; S, 11.94. Found: C, 48.86; H, 4.75; N, 10.83; S, 11.56.

Methyl *N*-(2,4-Dinitrophenyl)thiazolidine-4-carboxylate (Vb).

N-(2,4-Dinitrophenyl)thiazolidine-4-carboxylic acid (2.7 g, 0.009 mole) was added to anhydrous methanol (200 ml) containing concentrated sulphuric acid (1.5 ml) and the solution kept under reflux for 6 hours. The reaction was worked up as described for methyl *N*-(2-nitrophenyl)thiazolidine-4-carboxylate above. The product afforded 2.4 g (85%) of a yellow oil (tlc showed one spot); ir: 1750 (s, C=O), 1620 (s), 1530 (s, NO₂), 830 cm⁻¹; nmr: δ 2.2 (doublet, thiazolidine, 2H), 2.5 (d, 1H, S-CH-N), 2.6 (s, 3H, OCH₃), 3.3 (d, 1H, S-CH-N), 3.8 (t, 1H, HCCOOCH₃), 7.0 (m, aromatic, 2H), 7.8 (d, ArH); ms: 312.99 (M⁺, 14%), 254.12 (M⁺ - 58.87, 100%).

Anal. Calcd. for C₁₁H₁₁N₃O₆S: C, 42.17; H, 3.51; N, 13.42; S, 10.22. Found: C, 42.36; H, 3.59; N, 13.11; S, 9.82.

Methyl *N*-(2,6-Dinitrophenyl)thiazolidine-4-carboxylate (Vc).

N-(2,6-Dinitrophenyl)thiazolidine-4-carboxylic acid (2.7 g, 0.009 mole) was added to anhydrous methanol (200 ml) containing concentrated sulphuric acid (1.5 ml) and the solution kept under reflux for 6 hours. The reaction was worked up as described for methyl *N*-(2-nitrophenyl)thiazolidine-4-carboxylate above. The product, after recrystallisation from petroleum ether (40-60°)-diethyl ether solution mixtures afforded 2.6 g (92%) of yellow crystals, mp 131-132°; ir: 1750 (s, C=O), 1615 (s), 1530 (s, NO₂), 750 cm⁻¹; nmr: δ 2.2 (doublet, thiazolidine, 2H), 2.5 (d, 1H, S-CH-N), 2.6 (s, 3H, OCH₃), 3.3 (d, 1H, S-CH-N), 3.8 (t, 1H, HCCOOCH₃), 6.9 (q, 1H, ArH), 7.4 (d, 1H, ArH), 7.9 (d, 1H, ArH); ms: 312.99 (M⁺, 14.1%), 254.13 (M⁺ - 58.86, 100%).

Anal. Calcd. for C₁₁H₁₁N₃O₆S: C, 42.17; H, 3.50; N, 13.42; S, 10.22. Found: C, 41.83; H, 3.91; N, 13.14; S, 9.89.

3,3a-Dihydrothiazolo[3,4-*a*]quinoxalin-4-one (I).

To *N*-(2-nitrophenyl)thiazolidine-4-carboxylic acid (2.5 g, 0.01 mole) in ethanol (50 ml) was added granulated tin (1.8 g, 0.015 mole) followed by concentrated hydrochloric acid (10 ml). The mixture was heated under reflux for 1 hour. After removal of excess ethanol, it was allowed to cool. After basification with 2*M* sodium hydroxide, the mixture was extracted with chloroform. The organic layer was washed with water and dried over magnesium sulphate. The chloroform was removed leaving a dark brown oil which crystallized from petroleum ether (40-60°) to give 1.8 g (54%) of a dark brown microcrystalline solid mp 280° dec; ir: 3420 (N-H), 1680 (lactam C=O); nmr: δ 2.0 (doublet, thiazolidine, 2H), 2.8 (d, 1H, S-CH-N), 3.6 (d, 1H, S-CH-N), 4.0 (t, 1H, CHC=O), 6.2 (4H, s, broad at base), 9.9 (s, 1H, NH); ms: 205.85 (M⁺, 100%), 178.24 (M⁺ - 27.61, 33%), 150.20 (M⁺ - 55.65, 98%).

Anal. Calcd. for C₁₀H₁₀N₂OS: C, 58.25; H, 4.85; N, 13.6; S, 15.53. Found: C, 57.89; H, 4.85; N, 13.42; S, 15.29.

3,3a-Dihydro-7-nitrothiazolo[3,4-*a*]quinoxalin-4-one (II).

To *N*-(2,4-Dinitrophenyl)thiazolidine-4-carboxylic acid (3 g, 0.01 mole) in ethanol (50 ml) was added granulated tin (1.8 g, 0.015 mole) followed by concentrated hydrochloric acid (10 ml). The mixture was heated under reflux for 1 hour. The reaction was worked up as described for 3,3a-dihydrothiazolo[3,4-*a*]quinoxalin-4-one above. The work-up afforded a substance which crystallised from ethanol to give 1.6 g (64%) of a dark brown microcrystalline compound mp 300° dec; ir: 3400 (NH), 1680 (s, lactam C=O), 1530 (NO₂) cm⁻¹; nmr: δ 2.0 (d, thiazolidine, 2H), 3.0 (d, 1H, S-CH-N), 3.6 (d, 1H, S-CH-N), 4.0 (t, 1H, CHC=O), 6.2 (m, aromatic, 2H), 6.4 (s, 1H, ArH), 8.8 (s, 1H, NH); ms: 250.97 (M⁺, 100%), 223.19 (M⁺ - 27.78, 31%), 195.0 (M⁺ - 55.97, 96%).

Anal. Calcd. for C₁₀H₉N₃O₃S: C, 47.80; H, 3.59; N, 16.73; S, 12.75. Found: C, 48.12; H, 3.92; N, 16.66; S, 12.36.

3,3a-Dihydro-9-nitrothiazolo[3,4-*a*]quinoxalin-4-one (III).

To *N*-(2,6-dinitrophenyl)thiazolidine-4-carboxylic acid (3 g, 0.01 mole) in ethanol (50 ml) was added granulated tin (1.8 g, 0.015 mole) followed by concentrated hydrochloric acid (10 ml). The mixture was heated under reflux for 1 hour. The reaction was worked up as described for 3,3a-dihydrothiazolo[3,4-*a*]quinoxalin-4-one above. The product obtained crystallised from ethanol to give 1.48 g (59%) of a dark brown microcrystalline material mp 291° dec; ir: 3460 (N-H), 1660 (s, lactam C=O), 1530 (NO₂); nmr: δ 2.0 (d, thiazolidine, 2H), 3.0 (d, 1H, S-CH-N), 3.6 (d, 1H, S-CH-N), 5.6 (t, 1H, CHC=O), 6.3 (d, 1H, ArH), 6.6 (t, 1H, ArH), 6.8 (d, 1H, ArH), 8.8 (s, 1H, NH); ms: 250.96 (M⁺, 100%), 223.18 (M⁺ - 27.7, 31%), 195.01 (M⁺ - 55.95, 96%).

Anal. Calcd. for C₁₀H₉N₃O₃S: C, 47.80; H, 3.59; N, 16.73; S, 12.75. Found: C, 47.65; H, 3.38; N, 16.36; S, 12.35.

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