Synthesis of 4*H*-3,3a-Dihydrothiazolo[4,3-*b*]quinazolines

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Regiospecific synthesis of 4*H*-3,3a-dihydrothiazolo[4,3-*b*]quinazolines and 7-methyl-4*H*-3,3a-dihydrothiazolo[4,3-*b*]quinazolines **IVa** and **IVb** is described. The *N*-substituted thiazolidinecarboxylic acids **Ia** and **Ib** were converted to the corresponding acid chlorides, **IIa** and **IIb** but neither reacted with silver trifluoromethanesulphonate. The carboxylic acids **Ic** and **Id** were however, decarboxylated to the corresponding iminium ions using phosphorus oxychloride and these afforded the nitroamines **IIIa** and **IIIb**. Reductive cyclisation led to the quinazolines **IVa** and **IVb**.

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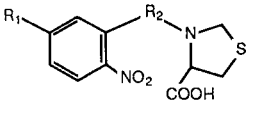
Recently, we reported the synthesis of 1,2,4-benzothiadiazines *via* iminium salts generated readily at room temperature [1]. We therefore, delineated schemes extending this procedure to the synthesis of the new 4*H*-3,3a-dihydrothiazolo[4,3-*b*]quinazolines, derivatives of which have been well identified as antimalarials, antihypotensive agents and as possessing blood platelet aggregation inhibiting activity [2,3,4].

As far as we know, the first and only synthesis of the unsaturated keto analogues of the new compounds was reported recently by Daboun *et al* [5] who condensed anthranilic acid with 5-substituted-4-thioxo-2-thiazolinone and obtained thiazolo[3,2-*b*]quinazolinone and thiazolo[4,3-*b*]-quinazoline-1,9-diones. The pharmacological activity of the group of title compounds prompted us to report this unambiguous and high-yielding route to IVa and IVb.

Two routes were delineated.

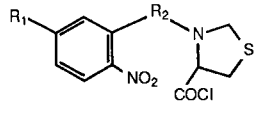


Ia R_1 = H, R_2 = -CO-

b R_1 = CH_3, R_2 = -CO-

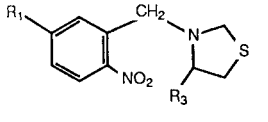
c R_1 = H, R_2 = $-CH_2-$

d R_1 = CH_3, R_2 = $-CH_2-$



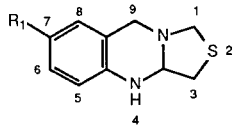
IIa R_1 = H, R_2 = -CO-

b R_1 = CH_3, R_2 = -CO-



IIIa R_1 = H, R_3 = $-NHC_2H_5$

b R_1 = CH_3, R_3 = $-NHC_2H_5$



IVa R_1 = H

b R_1 = CH_3

The first was aimed at converting the acid chlorides **IIa** and **IIb** to the nitroamines followed by reductive cyclisation to the 9-oxo derivative of **IVa** and **IVb**. Lithium aluminium hydride reduction [6] would then convert the oxo compounds to the tricycles **IVa** and **IVb**.

Accordingly, base-catalysed condesation between 2-nitrobenzoyl chlorides and thiazolidine-2-carboxylic acid afforded in quantitative yield the acids **Ia** and **Ib**, which had the expected twin carbonyl absorptions in their ir spectra. Conversion of the acids to the acid chlorides **IIa** and **IIb** was smooth and quantitative. The ir spectra of **IIa** and **IIb** were characterised by the usual shift to 1780 cm^{-1}. Attempted generation of the proposed thiazolidinium salt synthons by reacting silver trifluoromethanesulphonate with either **IIa** or **IIb** was unsuccessful. This seems consistent with an earlier observation on the reaction of the reagent with *N*-trifluoroacetylpyrrolidine-2-carboxylic acid [7].

However, another attempt involving decarboxylation of acids **Ia** and **Ib** using phosphorus oxychloride was prompted by a reported successful conversion of *N*-benzoylpiperidines to *N*-benzylpiperidines *via* iminium salts generated by the oxychloride [8,9]. Reaction of acid **Ia** or **Ib**, with phosphorus oxychloride followed by quenching with either ammonia or ethylamine produced unexpectedly the corresponding arylamides **VIIa-VIId**, and 5-*H*-thiazole, **VIII**. Absorptions at δ 1.2 (3H, t), 3.4 (2H, m), 7.2 (dd) and at 8.0 were characteristic of the nmr spectra of the *N*-ethylbenzamides isolated. Activation of the ring system by a methyl group also resulted in a ready cleavage of the amido carbonyl carbon-nitrogen bond. We propose that the acids **Ia** and **Ib** decarboxylated to the ininium ions **Va** and **Vb** in the presence of the Lewis acid-phosphorus oxychloride. However, the carbonyl carbon acquired a greater electrophilicity than the ring carbon atom in an α-position to the thiazolidium nitrogen. This resulted in a preferential attack of the nucleophile at the carbonyl carbon yielding the transition state structures **VIa-VId**. These all collapsed to give the nitroamides **VIIa-**

Table

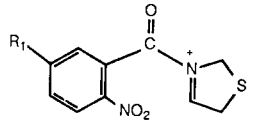
Properties of 4*H*-3,3a-Dihydrothiazolo[4,3-*b*]quinazolines

Compound Number	mp	ν max cm^{-1}	^1H NMR, δ	MS	(% R1)
IVa	179-180°	3360 (NH)	2.10 (s, N-CH_2-S, 2H)	191.99	(100)
		1660 (NH)	2.15 (broad, H-3a, 1H)	—	—
		1600 (benzene ring)	3.60 (d, S-CH_2-C, 2H)	164.94	(37.67)
			3.81 (s, Ar-CH_2-N, 2H), 6.80-7.10 (m, aromatic,	149.96	(26.36)
			4H), 5.50 (broad, NH, 1H, exchanged with deuterium oxide)	83.03	(1.70)
IVb	163-164°	3300 (NH), 1650 (NH),	2.11 (s, N-CH_2-S, 2H), 2.25 (s, CH_3, 3H),	191.99	(100)
		1610 (benzene ring)	2.32 (broad, H-3a, 1H),	165.03	(36.51)
			3.60 (d, S-CH_2-C, 2H),	150.02	(26.43)
			3.70 (s, Ar-CH_2-N, 2H), 6.90-7.30 (broad, aromatic, 3H), 5.21 (broad, NH, 1H, exchanged with with deuterium oxide)	83.02	(39.93)

VIId. Therefore the benzoyl derivatives of thiazolidines could not be used.

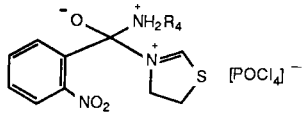
The other route involving benzyl derivatives was successful. Base-catalysed benzylation [10] of the cycloamine carboxylic acid gave adducts with characteristic spectral absorptions for the nitrobenzyl and thiazolidine carboxylic acid residues. In either of the adducts **Ic** and **Id**, decarboxylation, using phosphorus oxychloride, was complete within minutes of reaction. Quenching with anhydrous ethylamine gave the nitroamines **IIIa** and **IIIb**. These were isolated. The ir spectra did not contain any carbonyl absorptions. The nmr spectra of the new amines contained all the expected signals, in addition to ethyl hydrogen absorptions at δ 1.1 (3H) for **IIIa**, 1.2 (3H) for **IIIb** and at 3.0 (2H) for either **IIIa** or **IIIb**.

The mode of heterocyclisation of diamines *via* cyclocondensation in which the amino groups are suitably juxtaposed on adjacent aromatic rings had been established [11]. In earlier studies, however, the fact that the amino group eliminated when one is attached to an aromatic ring and the other to a saturated ring has not been explored. Reductive cyclisation [12] of the nitrocycloamines **IIIa** and **IIIb**, afforded tricyclic compounds **IVa** and **IVb** respectively. Neither cycloamines gave an *N*-ethyl substituted tricyclic compound. Both gave the 4*H*-tricycles. This suggests that it is the ethylamino group attached to the saturated heterocyclic ring that was eliminated during cyclisation. Protonation preceeded formation of the transition state for the cyclisation and proton attack therefore occurred at the more basic nitrogen atom of the saturated cyclic system.



Va $R_1 = H$

b $R_1 = CH_3$

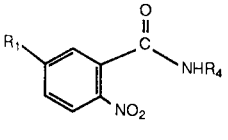


VIa $R_1 = H$, $R_4 = H$

b $R_1 = CH_3$, $R_4 = H$

c $R_1 = H$, $R_4 = C_2H_5$

d $R_1 = CH_3$, $R_4 = C_2H_5$



VIIa $R_1 = H$, $R_4 = H$

b $R_1 = CH_3$, $R_4 = H$

c $R_1 = H$, $R_4 = C_2H_5$

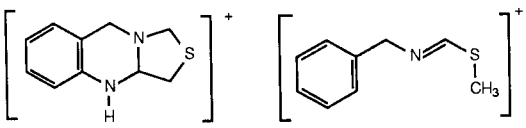
d $R_1 = CH_3$, $R_4 = C_2H_5$

VIII

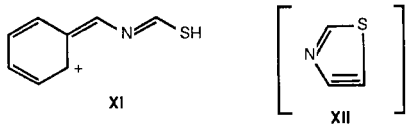
Structures **IVa** and **IVb** assigned to the heterocycles were consistent with ir and nmr spectral data and with elemental analysis.

Corroborating evidence for the tricycle **IVa** was obtained from its mass spectrum. The mother ion m/z 191.99 (100%), fragmented to **X** m/z 165.03 by loss of one hydrogen cyanide molecule. The *S*-methyl ion **X** fragmented further to **X1** by loss of the methyl radical. The presence of an abundant ion at m/z 83.03 indicative of a thiazolyne radical **XII** confirmed the presence of the thiazolidine ring moiety.

In the ms of compound **IVb**, an initial loss of a methyl group prompted by the +I effect of a secondary amino group invoked on it the false molecular ion which appeared at m/z 192 instead of 206. The difference of 14 a.m.u. confirmed the homologous relationship between **IVa** and **IVb**. Thereafter, **IVb** fragmented along a pattern similar to that of **IVa**. In all ions containing the sulphur atom, the expected M + 1 and M + 2 peaks were observed.



IX X



XI XII

EXPERIMENTAL

For general experimental details, see reference [13]. Microanalyses were, however, partly carried out at the Department of Chemistry, U.M.I.S.T., Manchester, England and by C, H, N Analysis Ltd., Leicester, England, Silver trifluoromethanesulphonate, the benzyl bromides and thiazolidine-4-carboxylic acid were all purchased from Aldrich Chemical Co.

N-(2-Nitrobenzoyl)thiazolidine-4-carboxylic Acids **Ia** and **Ib**.

Thiazolidine-4-carboxylic acid 2.3 g (0.017 mole) dissolved in 1 *M* sodium hydroxide solution (100 ml) was treated with the appropriate nitrobenzoyl chloride 2.0 g (0.012 mole) in small portions at room temperature for 2 hours. The solution was kept basic throughout by addition of more 1*M* sodium hydroxide solution. The mixture was filtered and the filtrate washed once with chloroform (50 ml). The aqueous solution was acidified (3*M* hydrochloric acid) and the acidic solution extracted thrice with dichloromethane. The organic solution was dried over magnesium sulphate and the solvent removed to give a solid product.

N-(2-Nitrobenzoyl)thiazolidine-4-carboxylic Acid (**Ia**).

This compound was obtained in 67% yield (2.27 g) as pale yellow crystals mp 138-140°; ir (Nujol): 3240 (OH), 1720 (C=O, acid), 1680 (C=O, amide), 1530 and 1350 cm^{-1} (NO_2); nmr (deuteriochloroform): δ 2.15 (s, -NCH_2-S-, 2H), 3.50 (d, C-CH_2-S, 2H), 4.4 (t, CHC=O, 1H), 7.40-8.38 (m, aromatic, 4H), 9.0 (broad, OH, 1H exchanged with deuterium oxide); ms: 282.03 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_2O_5S$: C, 46.81; H, 3.55; N, 9.93; S, 11.35. Found: C, 46.92; H, 3.73; N, 9.70; S, 11.24.

N-(5-Methyl-2-nitrobenzoyl)thiazolidine-4-carboxylic Acid (**Ib**).

This compound was obtained in 88% yield (3.15 g) of a yellow solid mp 114-115°; ir (Nujol): 3400 (OH), 1760 (C=O acid), 1660 (C=O amide), 1600 (aromatic) 1530 and 1350 cm^{-1} (NO_2); nmr (deuteriochloroform): δ 2.15 (s, -NCH_2-S, 2H), 2.20 (s, CH_3, 3H), 4.0 (d, C-CH_2-S, 2H), 4.6 (t, CHC=O, 1H), 6.7-7.6 (m, aromatic, 3H), 8.0 (broad, OH, 1H exchanged with deuterium oxide); ms: 296.05 (M^+).

Anal. Calcd. for $C_{12}H_{12}N_2O_5S$: C, 48.63; H, 4.05; N, 9.46; S, 10.81. Found: C, 48.76; H, 4.30; N, 9.23; S, 10.67.

N-(2-Nitrobenzyl)thiazolidine-4-carboxylic Acids **Ic** and **Id**.

Thiazolidine-4-carboxylic acid (0.075 mole) and potassium carbonate (1.0 g) were dissolved in 50% aqueous ethanol (20 ml). The mixture was refluxed for 10 minutes after which the appropriate nitrobenzyl bromide (0.046 mole) was added to the reaction mixture. Reflux was continued for a further 4 hours. All solvents were removed at reduced pressure and the residue was washed once with dichloromethane followed by acidification with 5% hydrochloric acid. The product was taken up in dichloromethane and the organic solution was dried over anhydrous magnesium sulphate. After removing the solvent, a red oil was obtained. Chromatography of the oil obtained and elution of the silica gel column with ethyl acetate-benzene (2:1) gave pure **Ic** and **Id** (see below).

N-(2-Nitrobenzyl)thiazolidine-4-carboxylic Acid (**Ic**).

This compound was obtained in a yield of 69% (8.5 g) as a red oil; ir (neat film): 3600 (OH), 1720 (C=O), 1610 (aromatic), 1530 and 1350 (NO_2), 750 cm^{-1} (*O*-disubstituted benzene); nmr (deuteriochloroform): δ 2.15 (8, N-CH_2-S, 2H), 4.0 (m, Ar-CH-N, C-CH_2-S, 4H), 4.20 (t, CHC=O, 1H), 7.40-8.0 (m, aromatic, 4H), 9.10 (broad, OH, 1H exchanged with deuterium oxide); ms: 268.05 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.48; N, 10.45; S, 11.94. Found: C, 49.51; H, 4.51; N, 10.28; S, 11.85.

N-(5-Methyl-2-nitrobenzyl)thiazolidine-4-carboxylic Acid (**Id**).

This compound was obtained in a yield of 88% (11.35 g) as a red oil; ir (neat film): 3640 (OH), 1720 (C=O), 1610 (aromatic), 1530 and 1350 (NO_2), 830, 750 (substitution pattern of benzene); nmr (deuteriochloroform): δ 2.20 (s, N-CH_2-S, 2H), 2.31 (s, CH_3, 3H), 3.20 (d, C-CH_2-S, 2H), 4.0 (s, Ar-CH_2-N, 2H), 4.46 (t, CHC=O, 1H), 7.2-7.8 (m, aromatic 3H), 8.10 (broad, OH, 1H exchanged with deuterium oxide); ms: 282.07 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_2O_4S$: C, 51.06; H, 4.96; N, 9.92; S, 11.35. Found: C, 51.39; H, 5.13; N, 9.67; S, 11.09.

Acid Chlorides **IIa** and **IIb**.

The carboxylic acids **I** (0.02 mole) was stirred with redistilled thionyl chloride (15 ml) at room temperature for 48 hours. Excess thionyl chloride was removed at reduced pressure leaving behind the corresponding acid chloride as a brown oil **IIa** from **Ia** or **IIb** from the acid **Ib**. The yield was quantitative; ir: 1789 (COCl) and 1630 (C=O amide) cm^{-1} were present.

For the attempted conversion of the acid chlorides to the nitroamines using silver trifluoromethanesulphonate to generate the intermediate iminium salt synthons, (see reference [1]).

N-(2-Nitrobenzyl)-4-ethylaminothiazolidines **IIIa** and **IIIb**.

To the appropriate *N*-(2-Nitrobenzyl)thiazolidinecarboxylic acid **Ic** or **Id** (8.80 mmoles) was added phosphorus oxychloride (10 ml). The mixture was heated to 110° and maintained at that temperature for 10 minutes. The reaction mixture was allowed to cool. Dichloromethane (50 ml) and then excess anhydrous ethylamine (20 ml) were injected to the reaction mixture. The mixture was further stirred at room temperature for 1½ hours. The organic mixture was washed severally with water, 2% sodium bicarbonate solution (50 ml × 2) and then once with brine. The organic solution was dried over anhydrous magnesium sulphate and the solvent completely removed affording a brown oil which was purified by passing through a column of silica gel. Elution with ethyl acetate-methanol (9:1) gave the pure amine.

N-(2-Nitrobenzyl)-4-ethylaminothiazolidine (**IIIa**).

This compound was obtained in a yield of 85% (2.0 g) as brown crystals from petroleum ether (40-60°) mp 67-69°; ir: 3360 (NH), 1650 (NH), 1600 (aromatic), 1530, 1350 (NO_2), 750 cm^{-1} (*O*-disubstituted benzene); nmr (deuteriochloroform): δ 1.70 (s, -NCH_2-S-, 2H), 2.0 (t, CH_3, 3H), 3.0 (d, C-CH_2-S, 2H), 4.2 (m, C-CH_2-C, Ar-CH_2-N, 4H), 4.5 (t, N-CH-N, 1H), 7.6-7.9 (m, aromatic, 4H), 5.0 (broad, -NH, 2H exchanged with deuterium oxide); ms: 267.11 (M^+).

Anal. Calcd. for $C_{12}H_{17}N_3O_2S$: C, 53.93; H, 6.37; N, 15.73; S, 11.79. Found: C, 54.09; H, 6.60; N, 15.70; S, 11.73.

N-(5-Methyl-2-nitrobenzyl)-4-ethylaminothiazolidine (**IIIb**).

This compound was obtained in a yield of 55% (1.36 g) as a brown oil; ir (neat film): 3600 (NH), 1665 (NH), 1515 and 1345 (NO_2), 880 and 730 cm^{-1} (benzene substitution), nmr (deuteriochloroform): δ 2.15 (s, N-CH_2-S, 2H), 2.20 (t, -CCH_3, 3H), 2.30 (s, Ar-CH_3, 3H), 3.0 (d, C-CH_2-S, 2H), 4.0 (m, C-CH_2-C, Ar-CH_2-N, 4H), 4.2 (t, N-CH-N, 1H), 7.2-7.8 (m, aromatic, 3H); ms: 281.12 (M^+).

Anal. Calcd. for $C_{13}H_{19}N_3O_2S$: C, 58.43; H, 6.76; N, 14.95; S, 11.39. Found: C, 58.71; H, 6.90; N, 11.67; S, 11.22.

4*H*-3,3a-Dihydrothiazolo[4,3-*b*]quinazolines **IVa** and **IVb**.

The appropriate *N*-(2-nitrobenzyl)-4-ethylaminothiazolidine (1.77 mmoles) in glacial acetic acid (20 ml) was treated under reflux with a mixture of iron filings (0.3 g) and iron dust (0.3 g) in small portions at 130° over 2 hours. After the addition, reflux was continued further for 12 hours. The reaction mixture was poured onto crushed ice and filtered. The precipitate was extracted into dichloromethane and the organic solution washed successively with water, 2% sodium hydrogencarbonate solution (100 ml × 3) and finally with water. The organic solution was dried over anhydrous magnesium sulphate. Removal of solvent afforded a solid purified by passing it through a column of silica gel. Ethyl acetate-methanol (9:1) gave solid products.

4*H*-3,3a-Dihydrothiazolo[4,3-*b*]quinazoline (**IVa**).

This compound was obtained in 72% yield (0.24 g) as a brown microcrystalline solid mp 179-180°; ir (chloroform): 3360 (NH), 1660 (NH), 1600 (aromatic); nmr (deuteriochloroform): δ 2.1 (s, N-CH_2-S, 2H), 2.15 (broad, H-3a, 1H), 3.60 (d, S-CH_2-C, 2H), 3.81 (s, Ar-CH_2-N, 2H), 6.80-7.10 (m, aromatic, 4H), 5.50 (broad, NH, 1H exchanged with deuterium oxide); ms: 192 (M^+, 100), 164.99 (M-27, 37.67); 149.96 (M-42, 26.36); 83.03 (M-109, 1.70).

Anal. Calcd. for $C_{10}H_{12}N_2S$: C, 53.93; H, 6.37; N, 15.73; S, 11.73. Found: C, 54.09; H, 6.60; N, 15.70; S, 11.73.

7-Methyl-4*H*-3,3a-dihydrothiazolo[4,3-*b*]quinazoline (**IVb**).

This compound was obtained in 74% yield (0.27 g) as a brown microcrystalline solid mp 163-164°; ir (chloroform): 3300 (NH), 1650 (NH), 1610 (aromatic); nmr (deuteriochloroform): δ 2.11 (s, N-CH_2-S, 2H), 2.25 (s, CH_3, 3H), 2.32 (broad, H-3, 1H); 3.60 (d, S-CH_2-C, 2H), 3.70 (s, Ar-CH_2-N, 2H), 7.30-6.90 (m, aromatic, 3H), 5.21 (broad, NH, 1H, exchanged with deuterium oxide); ms: 191.99 (M-14, 100), 165.03 (M-41, 36.51), 150.02 (M-56, 26.43), 83.02 (M-123, 39.93).

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.08; H, 6.80; N, 13.59; S, 15.53. Found: C, 64.26; H, 7.12; N, 13.27; S, 15.35.

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