A New Synthetic Route to 3,4-Dihydro-2*H*-1,4-thiazines

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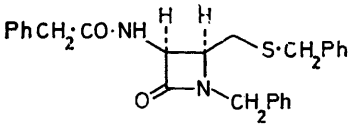
3,4-Dihydro-2*H*-1,4-thiazine-6-carboxylates have been synthesised by reaction of 2-mercaptoethylamine with 2,3-dibromoacrylic esters. Of particular value for the preparation of analogues of the cephalosporins is the direct conversion of 2-mercaptoethylamine into 3,4-dihydro-2*H*-1,4-thiazine-5-carboxylic acids containing 6-carboxylate groups.

THE photolytically induced Wolff rearrangement of 3-diazopyrrolidine-2,4-diones [1] has been used to prepare the intermediate β-lactam (1) from L-cysteine.[2] This intermediate should enable a variety of nuclear analogues of



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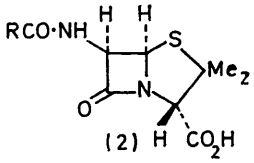

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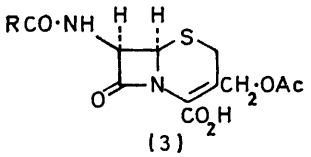

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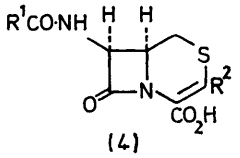

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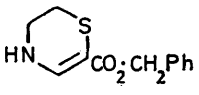

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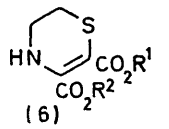

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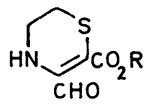


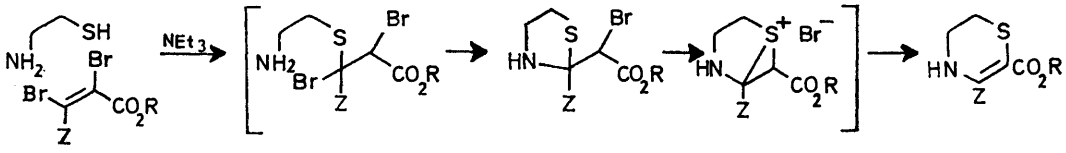
(7)

the penicillins (2) and cephalosporins (3) to be prepared. Compounds with the general structure (4), where R^2 is one of the many groups found useful in this position in the cephalosporins or is an electron-withdrawing group such as carboxylate, would be of particular interest.

Although 3,4-dihydro-2*H*-1,4-thiazines have been obtained by several methods,[3] including the degradation of penicillanic esters,[4] the only method available for synthesis from 2-mercaptoethylamine and related compounds is the reaction with α-bromo-ketones.[5] Although this is a versatile procedure, the problems encountered with the preparation of selectively esterified bromo-oxaloacetic acid led us to consider an alternative route.

Bromopyruvic esters are known to react with 2-mercaptoethylamine and its derivatives to give alkyl 3,4-dihydro-2*H*-1,4-thiazine-5-carboxylates.[5] 2,3-Dibromoacrylic esters, which have the same oxidation level but are more stable intermediates, were expected to react with 2-mercaptoethylamine by addition of the thiol to the double bond; this would labilise both bromine atoms, allowing the subsequent ring closure and elimination to occur rapidly. 2-Mercaptoethylamine reacted smoothly with benzyl 2,3-dibromoacrylate in the presence of triethylamine at 0° to give benzyl 3,4-dihydro-2*H*-1,4-thiazine-6-carboxylate (5). The location of the ester group followed from the observation that the ^1H n.m.r. signal at τ 2·30, due to the olefinic proton, was a doublet (J 7 Hz) which collapsed to a singlet when the labile 1-proton was exchanged with D_2O. The u.v. and n.m.r. spectra were similar to those of the corresponding methyl ester, which had been prepared from 2-mercaptoethylamine and sodium 2-chloromalonaldehydate.[6] If, as expected, the thiolate ion adds initially at the β-carbon atom of the 2,3-dibromoacrylic ester, a subsequent rearrangement must occur which may take place as indicated in the Scheme, leading to 3,4-dihydro-2*H*-1,4-thiazine-6-carboxylates.

If this rearrangement is a general feature of the reaction of 2-mercaptoethylamine with 2,3-dibromoacrylic esters, then the analogous reaction with dibromomaleic half esters should lead directly to the required 5,6-disubstituted 3,4-dihydro-2*H*-1,4-thiazines. Alcoholysis of dibromomaleic anhydride [7] gave the half esters of



SCHEME

[1] G. Lowe and D. D. Ridley, *J.C.S. Chem. Comm.*, 1973, 328; *J.C.S. Perkin I*, 1973, 2024.

[2] J. R. Hlubucek and G. Lowe, *J.C.S. Chem. Comm.*, 1974, 419.

[3] F. Asinger, H. Dien, and W. Schaefer, *Monatsh.*, 1964, **95**, 1335; F. Asinger, H. Offermanns, W. Puerschel, K. H. Lim, and D. Neuray, *ibid.*, 1968, **99**, 2090; F. Asinger, H. Offermanns, and D. Neuray, *Annalen*, 1970, **739**, 32; F. Asinger, H. Offermanns, D. Neuray, and P. Mueller, *Monatsh.*, 1970, **101**, 1295; F. Asinger, A. Saus, H. Offermanns, D. Neuray, and A. Lim, *ibid.*, 1971, **102**, 321, and references cited therein.

[4] I. McMillan and R. J. Stoodley, *Tetrahedron Letters*, 1966, 1205; *J. Chem. Soc.* (*C*), 1968, 2533; R. J. Stoodley, *ibid.*, p. 2891; N. Maggi and G. Cignarella, *Chimica e Industria*, 1970, **52**, 164.

[5] S. Rossi, T. Bacchetti, and S. Maiorana, *Gazzetta*, 1962, **92**, 1367, and references cited therein.

[6] A. R. Dunn, I. McMillan, and R. J. Stoodley, *Tetrahedron*, 1968, **24**, 2985.

[7] B.P. 1,026,442, 1966 (*Chem. Abs.*, 1966, **65**, 2131).

dibromomaleic acid, which when treated with 2-mercaptoethylamine in the presence of triethylamine at room temperature, gave 6-alkoxycarbonyl-3,4-dihydro-2*H*-1,4-thiazine-5-carboxylic acids (6; R^2 = H) in good yield. These products gave a deep brown colour with iron(III) chloride solution, similar to that given by pyrrole-2-carboxylic acid, and its u.v. absorption maximum at 323 nm was not significantly changed when the carboxylic acid was ionised. Thus the carboxylic acid probably has little influence on this electronic transition, which is similar to that found for alkyl 3,4-dihydro-2*H*-1,4-thiazines-6-carboxylates ($\lambda_{max.}$ 316 nm). More conclusive evidence for the arrangement of the carboxylic acid and ester functions was however obtained by thermal decarboxylation; thus the benzyl ester (6; R^1 = CH_2Ph, R^2 = H), when heated in dimethyl sulphoxide at 140—150° for 1 h, gave benzyl dihydro-2*H*-1,4-thiazine-6-carboxylate (5), identical with the specimen prepared from 2-mercaptoethylamine and benzyl dibromoacrylate. Similarly the treatment of the methyl 6-carboxylate (6; R^1 = Me, R^2 = H) gave methyl 3,4-dihydro-2*H*-1,4-thiazine-6-carboxylate.[6]

The carboxylic acid (6; R^1 = CH_2Ph, R^2 = H) was esterified with diazomethane, and also by refluxing with methanol in the presence of concentrated sulphuric acid, to give the diester (6; R^1 = CH_2Ph, R^2 = Me), there being no evidence of ester exchange. The 5-t-butyl ester (6; R^1 = CH_2Ph, R^2 = Bu^t) could likewise be prepared by esterification with isobutene in the presence of concentrated sulphuric acid.

Diethyl 3,4-dihydro-2*H*-1,4-thiazine-5,6-dicarboxylate (6; R^1 = R^2 = Et), prepared by the reaction of 2-mercaptoethylamine with diethyl bromo-oxaloacetate, when hydrolysed with 1 equiv. of sodium hydroxide, gave a compound identical with that obtained by the reaction of 2-mercaptoethylamine with ethyl dibromomaleate, and was thus assigned the structure (6; R^1 = Et, R^2 = H). It appears therefore that the carboxylic acid function at C-6 is much less susceptible to both acid- and base-catalysed reactions than that at C-5. The inertness of ester groups at C-6 in 3,4-dihydro-2*H*-1,4-thiazines towards reduction with lithium borohydride has been noted previously.[8] 6-Benzyloxycarbonyl-3,4-dihydro-2*H*-1,4-thiazine-5-carboxylic acid (6; R^1 = CH_2Ph, R^2 = H) likewise was not reduced by lithium borohydride. Lithium aluminium hydride however reduced the compound to the aldehyde (7), presumably by way of a stable intermediate which generated the aldehyde during the isolation procedure.

This new and direct route for the preparation of 3,4-dihydro-2*H*-1,4-thiazine-5-carboxylic acids should be valuable for the generation of nuclear analogues of the cephalosporins from suitably substituted β-lactams such as (1).

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 257 grating spectrometer, n.m.r. spectra with Perkin-Elmer R10 and R14 spectrometers operating at 60 and 100 MHz, respectively, and mass spectra with A.E.I. MS9 and Varian M.A.T. CH7 instruments. Microanalyses were determined by Dr. Strauss and his staff in this laboratory. Absorbents for t.l.c. and p.l.c. were $HF_{254+366}$ and $PF_{254+366}$ silica gel (Merck), respectively. Anhydrous sodium sulphate was used to dry organic solvents. Light petroleum refers to the fraction of b.p. 60—80°.

Benzyl 2,3-Dibromoacrylate.—A solution of dibromoacrylic acid (2·88 g) (m.p. 85—86°; prepared from propiolic acid [9]) in thionyl chloride (8 g) was heated under reflux for 2·5 h. The excess of thionyl chloride was removed under reduced pressure and a solution of dry benzyl alcohol (5 ml) in dry benzene (20 ml) was added. The solution was refluxed for 20 min, the solvent removed, and the residue fractionally distilled to give *benzyl dibromoacrylate* (2·95 g), b.p. 121—131° at 0·1 mmHg, $\nu_{max.}$ (film) 1720 cm^{-1} (C:O); τ ($CDCl_3$), 1·76 (1H, s, C=CHBr), 2·64 (5H, ArH), and 4·76 (2H, s, CH_2Ph) (Found: C, 37·5; H, 2·6; Br, 49·8. $C_{10}H_8Br_2O_2$ requires C, 37·5; H, 2·5; Br, 50·0%).

Benzyl 3,4-Dihydro-2H-1,4-thiazine-6-carboxylate (5).—Benzyl dibromoacrylate (0·96 g) in chloroform (5 ml) was added dropwise to a stirred solution of 2-mercaptoethylamine hydrochloride (0·34 g) in triethylamine (1·2 g) and chloroform (15 ml) at 0°. The solution was kept at room temperature for 18 h, the solvent was removed, and the residue was dissolved in ethyl acetate and aqueous sodium hydrogen carbonate. The aqueous layer was extracted several times with ethyl acetate and the combined ethyl acetate extracts were dried and evaporated to yield a crystalline mass. Recrystallisation from chloroform–light petroleum gave the *1,4-thiazine* (5) (0·46 g) as needles, m.p. 109—110°, $\lambda_{max.}$ 258 (ε 3570) and 316 nm (11,000); $\nu_{max.}$ ($CHCl_3$) 3470 and 3370 (NH), 1680 (C:O), and 1610 cm^{-1} (C:C); τ ($CDCl_3$) 2·30 (1H, d, *J* 7 Hz, collapsed to a singlet on exchange with D_2O, C=C*H*·NH), 2·61 (5H, ArH), 4·77 (2H, s, CH_2Ph), 5·0br (1H, s, NH), 6·45 (2H, m, NH·CH_2), and 7·20 (2H, m, S·CH_2) (Found: C, 61·5; H, 5·7; N, 5·9%; M^+, 235. $C_{12}H_{13}NO_2S$ requires C, 61·2; H, 5·6; N, 5·9%; *M*, 235).

3-Benzyloxycarbonyl-2,3-dibromoacrylic Acid.—A solution of dibromomaleic anhydride [7] (51·2 g) in dry benzyl alcohol (25 g) was kept at 80° for 2·5 h. On cooling the product crystallised and was recrystallised from chloroform–light petroleum to give the *ester* (57 g) as needles, m.p. 85—86°; $\nu_{max.}$ ($CHCl_3$) 2600br (CO_2H), 1730br (C:O), and 1685 cm^{-1} (C:C); τ ($CDCl_3$) −0·80 (1H, s, CO_2H), 2·62 (5H, ArH), and 4·73 (2H, s, CH_2Ph) (Found: C, 36·5; H, 2·0; Br, 43·5. $C_{11}H_8Br_2O_4$ requires C, 36·3; H, 2·2; Br, 43·9%).

6-Benzyloxycarbonyl-3,4-dihydro-2H-1,4-thiazine-5-carboxylic Acid (6; R^1 = CH_2Ph, R^2 = H).—3-Benzyloxycarbonyl-2,3-dibromoacrylic acid (36·4 g) in chloroform (100 ml) was added to a stirred solution of 2-mercaptoethylamine hydrochloride (11·3 g) in triethylamine (50·6 g) and chloroform (400 ml). After 18 h the solvent was removed below 30°. The residue was dissolved in aqueous potassium carbonate and extracted with benzene. The aqueous solution was acidified with dilute hydrochloric acid and the yellow precipitate was filtered off. The remaining aqueous solution was extracted several times with benzene. The benzene extract was dried and evaporated below 30°, and the residual solid was combined with the yellow precipitate. Recrystallisation from chloroform–light petroleum gave

[8] A. R. Dunn and R. J. Stoodley, *Chem. Comm.*, 1969, 1368.
[9] F. Montanari and A. Negrini, *Gazzetta*, 1957, **87**, 1102.

the 1,4-*thiazine* (5·6 g) as yellow needles, m.p. 156—157° (decomp.), $\lambda_{max.}$ 323 nm (ε 6670); $\nu_{max.}$ ($CHCl_3$) 3380 (NH) and 1710 cm^{-1} (C:O); τ ($CDCl_3$) 2·55 (5H, ArH), 2·82br (1H, s, NH) 4·66 (2H, s, CH_2Ph), 6·20 (2H, m, $NH{\cdot}CH_2$), and 7·15 (2H, m, $S{\cdot}CH_2$) (Found: C, 55·7; H, 4·8; N, 5·0; S, 11·6. $C_{13}H_{13}NO_4S$ requires C, 55·9; H, 4·7; N, 5·0; S, 11·45%).

6-*Benzyl* 5-*Methyl* 3,4-*Dihydro*-2H-1,4-*thiazine*-5,6-*dicarboxylate* (6; $R^1 = CH_2Ph$, $R^2 = Me$).—(*a*) The foregoing half-ester (2·80 g) was added in portions with stirring to an excess of diazomethane in ether (containing 10% methanol) at 0°. Stirring was continued until all the solid had dissolved and the solution was kept overnight at 0°. Acetic acid was added to destroy the excess of diazomethane and the solution was washed with aqueous potassium carbonate, dried, and evaporated. The residual crystalline mass was recrystallised from chloroform–light petroleum to give the *diester* (2·3 g) as small rods, m.p. 97—98°; $\lambda_{max.}$ 324 nm (ε 7050); $\nu_{max.}$ ($CHCl_3$) 3460 (NH) and 1725 and 1690 cm^{-1} (C:O); τ ($CDCl_3$) 2·64 (5H, ArH), 4·80 (2H, s, CH_2Ph), 5·25br (1H, s, NH), 6·36 (3H, s, $CO_2{\cdot}CH_3$), 6·36 (2H, m, $NH{\cdot}CH_2$), and 7·10 (2H, m, $S{\cdot}CH_2$) (Found: C, 57·2; H, 5·0; N, 4·7; S, 11·1. $C_{14}H_{15}NO_4S$ requires C, 57·3; H, 5·1; N, 4·7; S, 10·9%).

(*b*) A solution of the benzyl half-ester (0·40 g) in methanol (20 ml) containing concentrated sulphuric acid (2 drops) was refluxed for 16 h. The solution was partitioned between aqueous sodium hydrogen carbonate solution and ether. The aqueous layer was extracted twice with ether and the combined ethereal extracts were washed with brine and dried. Removal of the solvent left an oil (0·41 g) which crystallised. Recrystallisation from chloroform–light petroleum gave the diester as prisms, m.p. 97—98°, mixed m.p. 97—98°, with the sample obtained in (*a*).

6-*Benzyl* 5-*t-Butyl* 3,4-*Dihydro*-2H-1,4-*thiazine*-5,6-*dicarboxylate* (6; $R^1 = CH_2Ph$, $R^2 = Bu^t$) (with C. B. Hudson).—A suspension of the benzyl half-ester (1·70 g) in dry dioxan (20 ml) was treated with isobutene (15 ml) and concentrated sulphuric acid (0·2 ml), and shaken in a sealed vessel at room temperature for 4 days. The mixture was partitioned between aqueous sodium hydrogen carbonate solution and ether. The aqueous layer was extracted twice with ether and the combined ethereal extracts were washed with brine and dried. Removal of the solvent left an oil which crystallised. Recrystallisation from methylene chloride–light petroleum and benzene–light petroleum (with charcoal) gave the *diester* as off-white needles, m.p. 118°, $\lambda_{max.}$ (EtOH) 323 nm (ε 8530); $\nu_{max.}$ (Nujol) 3335 (NH) and 1730 and 1670 cm^{-1} (C=O); τ ($CDCl_3$) 2·68 (5H, ArH), 4·80 (2H, s, CH_2Ph), 5·39br (1H, s, NH), 6·40 (2H, m, $NH{\cdot}CH_2$), 7·12 (2H, m, $S{\cdot}CH_2$), and 8·52 (9H, s, Bu^t) (Found: C, 61·0; H, 6·4; N, 4·3; S, 9·3. $C_{17}H_{21}NO_4S$ requires C, 60·9; H, 6·3; N, 4·2; S, 9·5%).

Methyl Dibromomaleate.—A solution of dibromomaleic anhydride [7] (25·6 g) in methanol (4·0 ml) and benzene (25 ml) was refluxed for 3 h. The solvent was removed and the residue crystallised on cooling. Recrystallisation from benzene–light petroleum gave *methyl dibromomaleate* (20·0 g) as straw-coloured rods, m.p. 80—81·5°, $\lambda_{max.}$ (EtOH) 258 (ε 3350) and 230 nm (6500); $\nu_{max.}$ (Nujol) 3600—2300 (CO_2H), 1746 (CO_2Me), and 1700 cm^{-1} (CO_2H) (Found: C, 21·1; H, 1·7; Br, 54·8. $C_5H_4Br_2O_4$ requires C, 20·9; H, 1·4; Br, 55·5%).

6-*Methoxycarbonyl*-3,4-*dihydro*-2H-1,4-*thiazine*-5-*carboxylic Acid* (6; $R^1 = Me$, $R^2 = H$).—2-Mercaptoethylamine hydrochloride (1·14 g) was dissolved in a solution of sodium methoxide [from sodium (1·15 g) and methanol (20 ml)] and to this solution at 0° was added methyl dibromomaleate (2·88 g) in methanol (10 ml). The mixture was kept at room temperature for 2 days, and then most of the methanol removed below 30°. The mixture was partitioned between aqueous sodium hydrogen carbonate solution and benzene. The aqueous layer was cooled to 0° and acidified with sulphuric acid. This solution was extracted with benzene and the extract was dried and evaporated to give a crystalline solid (1·01 g). Recrystallisation from chloroform–light petroleum gave the 1,4-*thiazine* as yellow needles, m.p. 146—147° (decomp.); $\lambda_{max.}$ (EtOH) 322 nm (ε 7120); $\nu_{max.}$ (Nujol) 3330 (NH) and 1708 cm^{-1} (C=O); τ ($CDCl_3$) 2·85br (2H, s, NH and CO_2H), 6·18 (3H, s, CO_2Me), 6·20 (2H, m, $NH{\cdot}CH_2$), and 7·12 (2H, m, $S{\cdot}CH_2$) (Found: C, 41·2; H, 4·6; N, 6·9; S, 15·7. $C_7H_9NO_4S$ requires C, 41·4; H, 4·5; N, 6·9; S, 15·7%).

Decarboxylation of 6-*Methoxycarbonyl*-3,4-*dihydro*-2H-1,4-*thiazine*-5-*carboxylic Acid* (6; $R^1 = Me$, $R^2 = H$).—A solution of the acid (85 mg) in dimethyl sulphoxide (3 ml) was kept at 140—150° under nitrogen for 40 min, then cooled, diluted with water (20 ml), and extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate solution, water, and brine, dried, and evaporated. P.l.c. of the residue (55 mg) [acetone–light petroleum (1 : 1)] gave methyl 3,4-dihydro-2*H*-1,4-thiazine-6-carboxylate, m.p. 95—98° (lit.,[6] 100—102°), $\lambda_{max.}$ (MeOH) 313 (ε 9270) and 263 nm (2900); $\nu_{max.}$ ($CHCl_3$) 3470 (NH) and 1695 cm^{-1} (C=O); τ ($CDCl_3$) 2·37 (1H, d, *J* 6 Hz, C=CH), 5·22br (1H, s, NH), 6·26 (3H, s, $CO_2{\cdot}CH_3$), 6·38 (2H, m, $NH{\cdot}CH_2$), and 7·13 (2H, m, $S{\cdot}CH_2$).

Decarboxylation of 6-*Benzyloxycarbonyl*-3,4-*dihydro*-2H-1,4-*thiazine*-5-*carboxylic Acid* (6; $R^1 = CH_2Ph$, $R^2 = H$).—A solution of the acid (0·20 g) in dimethyl sulphoxide was heated at 140—150° for 1 h and the product was isolated as above. After recrystallisation from chloroform–light petroleum the product had m.p. 109—110° and mixed m.p. 109—110° with the specimen obtained from 2-mercaptoethylamine and benzyl dibromoacrylate, and had similar u.v., i.r., and n.m.r. spectra.

Diethyl 3,4-*Dihydro*-2H-1,4-*thiazine*-5,6-*dicarboxylate* (6; $R^1 = R^2 = Et$).—Diethyl bromo-oxalacetate [10] (0·267 g) and 2-mercaptoethylamine hydrochloride (0·114 g) were dissolved in ethanol, and triethylamine (0·202 g, 2 mol. equiv.) was added with stirring. The white precipitate was filtered off and the solvent removed from the filtrate. A portion of the residue (0·2 g) was applied to a p.l.c. plate and the major band (R_F 0·3) was removed to give a yellow oil which crystallised. Recrystallisation from carbon tetrachloride gave the 1,4-*thiazine* (0·094 g) as needles, m.p. 75—77°, $\lambda_{max.}$ 223 (ε 5670) and 324 nm (7080); $\nu_{max.}$ ($CHCl_3$) 3440 (NH), 1730 (CO), and 1595 cm^{-1} (C=C); τ ($CDCl_3$) 5·25br (1H, s, NH), 5·7 (4H, 2q, $O{\cdot}CH_2{\cdot}CH_3$), 6·35 (2H, m, $CH_2{\cdot}N$), 7·07 (2H, m, $CH_2{\cdot}S$), and 8·70 (6H, 2t, $O{\cdot}CH_2{\cdot}CH_3$) (Found: C, 49·0; H, 6·1; N, 5·7; S, 13·0. $C_{10}H_{15}NO_4S$ requires C, 49·0; H, 6·1; N, 5·7; S, 13·0%).

Hydrolysis of Diethyl 3,4-*Dihydro*-2H-1,4-*thiazine*-5,6-*dicarboxylate*.—The diester (0·282 g) was stirred with sodium hydroxide (0·058 g, 1 mol. equiv.) in water (25 ml) at room temperature for 16 h. After being washed with chloroform to remove unchanged thiazine (10 mg), the solution was acidified and extracted with chloroform. The extract was dried and evaporated and the residue triturated with ether to

[10] L. Bauer and C. S. Mahajanshetti, *J. Heterocyclic Chem.*, 1968, **5**, 331.

give crystals. Recrystallisation from carbon tetrachloride gave yellow needles, m.p. 133—137° (decomp.), $\lambda_{max.}$ (EtOH) 223 (ε 6200) and 323 nm (7080); $\nu_{max.}$ ($CHCl_3$) 3350 (NH), 1710 (CO), and 1575 cm^{-1} (C=C); τ ($CDCl_3$) 2·85br (1H, s, NH), 5·63 (2H, q, O·CH_2·CH_3), 6·20 (2H, m, CH_2·N) 7·15 (2H, m, CH_2·S), and 8·60 (3H, t, O·CH_2·CH_3) (Found: C, 44·0; H, 5·1; N, 6·5; S, 14·5. $C_8H_{11}NO_4S$ requires C, 44·2; H, 5·1; N, 6·45; S, 14·7%).

Ethyl Dibromomaleate.—A solution of dibromomaleic anhydride [7] (19·7 g) in dry ethanol (35 ml) was refluxed for 2 h. The ethanol was evaporated off to give *ethyl dibromomaleate* (21·8 g), $\nu_{max.}$ 3000—2400 (CO_2H), 1730 (CO), and 1590 cm^{-1} (C=C); τ ($CDCl_3$) 5·68 (2H, q, O·CH_2·CH_3) and 8·67 (3H, t, O·CH_2·CH_3); *m/e* 300 (M^+, $C_4H_6Br_2O_4$), 272 ($M^+ - C_2H_4$), 256 ($M^+ - CO_2$), and 227 ($M^+ - CO_2Et$) (all peaks $M : M + 2 : M + 4$ in the ratio 1 : 2 : 1 as expected for the bromine isotopes).

6-*Ethoxycarbonyl*-3,4-*dihydro*-2H-1,4-*thiazine*-5-*carboxylic Acid* (6; R^1 = Et, R^2 = H).—Ethyl dibromomaleate (3·0 g) in chloroform (10 ml) was added to a stirred solution of 2-mercaptoethylamine hydrochloride (1·14 g, 1 mol. equiv.) in ethanol (50 ml). An excess of triethylamine (3·03 g) was added and the mixture stirred overnight. The solvent was removed and the residue taken up in sodium hydrogen carbonate solution and washed with chloroform. The aqueous phase was acidified and extracted with chloroform several times. The extract was dried and evaporated. The residual gum crystallised. Recrystallisation from chloroform–light petroleum gave the 1,4-*thiazine* as yellow needles, m.p. 135—137°, mixed m.p. 135—137°, with the sample prepared by hydrolysis of diethyl 3,4-dihydro-2*H*-1,4-thiazine-5,6-dicarboxylate; the u.v., i.r., and n.m.r. spectra were also identical (Found: C, 44·0; H, 5·1; N, 6·5; S, 15·0. $C_8H_{11}NO_4S$ requires C, 44·2; H, 5·0; N, 6·45; S, 14·7%).

Benzyl 5-*Formyl*-3,4-*dihydro*-2H-1,4-*thiazine*-6-*carboxylate* (7; R = CH_2Ph).—To the carboxylic acid (6; R^1 = CH_2Ph, R^2 = H) (0·27 g) in dry ether (200 ml) was added lithium aluminium hydride (0·04 g) in ether (50 ml) with stirring. The mixture was refluxed for 12 h and the solution kept overnight at room temperature. After addition of N-hydrochloric acid (4 ml) and separation of the organic layer, the aqueous phase was extracted with chloroform. The combined organic extracts were washed with water and brine, dried, and evaporated. The residue was purified by p.l.c. with chloroform as eluant. The *aldehyde* was obtained as a yellow oil, $\lambda_{max.}$ (EtOH) 400 nm (ε 1900), 335 (ε 10,120), 250 (ε 5060), and 226 nm (ε 6470); $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1735 (CO_2R), and 1685 cm^{-1} (CHO); τ ($CDCl_3$) −0·38 (1H, s, CHO) 2·63 (5H, ArH), 4·40br (1H, s, NH), 4·75 (2H, s, CH_2Ph) 6·39 (2H, m, NH·CH_2), and 7·12 (2H, m, S·CH_2) (Found: C, 58·7; H, 5·1; N, 5·1%; M^+, 263. $C_{13}H_{13}NO_3S$ requires C, 59·3; H, 5·0; N, 5·3%; *M*, 263).

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