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786. *The Synthesis of Model Intermediates related to Thiamine-catalysed Reactions*

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Reaction of suitably protected carbonyl compounds with 2-lithiothiazoles has led to the synthesis of models related to the intermediates involved in reactions catalysed by thiamine, *e.g.*, active pyruvate, active acetoin, and active glycolaldehyde.

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In view of the suggestion of Breslow [1] that thiamine initiates its catalytic role by attachment of a substrate, *e.g.*, Me·CO·CO_2H, to the 2-position of its thiazolium nucleus, it is of some interest to attempt the synthesis of such postulated intermediates, *e.g.*, "active pyruvate" (I),[2] by an unambiguous route. Preliminary model experiments [3] with 2-lithiothiazole [4] and methyl pyruvate led to the formation of very small amounts of methyl 2-hydroxy-2-(2-thiazolyl)propanoate (II; R = CO_2Me), but on attempted quaternisation with benzyl bromide the residue in the 2-position of the thiazole nucleus was ejected and 3-benzylthiazolium bromide obtained. Conversion of the ester (II; R = CO_2Me) into the corresponding amide (II; R = CO·NH_2), however, allowed of successful quaternisation to yield several salts such as compound (III; R = CO·NH_2, R′ = $PhCH_2$, X = Br), including that derived from the pyrimidyl moiety of thiamine itself, 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide. The quaternised amides showed considerable resistance to acid hydrolysis and to attack by nitrous acid, however, and could not be converted into the required acids as the vigour of treatment required for any reaction at all to take place resulted in more extensive decomposition.

Attention was therefore turned to approaching the desired acid *via* the corresponding aldehyde, which might be obtained from the reaction of 2-lithiothiazole with protected pyruvic aldehydes. Thus, reaction with 1,1-dimethoxy- and 1,1-diethoxy-acetone [5a,b,6] yielded the expected thiazole hydroxy-acetals [II; R = $CH(OMe)_2$ and R = $CH(OEt)_2$, respectively], but both showed unexpected resistance to hydrolysis to yield the free aldehyde; nor could the desired aldehyde (II; R = CHO) be obtained by transacetalisation with *p*-nitrobenzaldehyde. The dimethyl acetal reacted with methyl iodide and with *p*-nitrobenzyl bromide to yield the corresponding quaternary salts [III; R = $CH(OMe)_2$, R′ = Me, X = I, and R = $CH(OMe)_2$, R′ = *p*·NO_2·C_6H_4·CH_2, X = Br, respectively], but attempted hydrolysis of the first of these yielded only a mixture of unchanged starting material and 3-methylthiazolium iodide in which the complete 2-substituent had been expelled.

As this hydrolytic route had proved abortive it was decided to approach the desired carboxyl group through a degradative reaction of the type R·CO·Me ⟶ R·CO_2H. Direct reaction of diacetyl with 2-lithiothiazole can be made to yield a trace of 3-hydroxy-3-(2-thiazolyl)butan-2-one (II; R = CO·Me), but the major product is the diol (IV). It is, therefore, more convenient to proceed *via* the reaction of 2-lithiothiazole with the protected 3,3-dimethoxybutan-2-one [7] to yield compound [II; R = $CMe(OMe)_2$] which, in contrast to the acetals above, undergoes ready hydrolysis to yield the required hydroxyketone (II; R = CO·Me) in high yield. This compound was found to undergo the haloform reaction only to a limited extent under a variety of different conditions, a behaviour paralleled by the closely related 2-phenylacetoin,[8] PhMeC(OH)·CO·Me. In the case of the

[1] R. Breslow, *J. Amer. Chem. Soc.*, 1958, **80**, 5894.
[2] H. Holzer and K. Beaucamp, *Angew. Chem.*, 1959, **71**, 776; *Biochim. Biophys. Acta*, 1964, **46**, 225.
[3] J. E. Downes and P. Sykes, *Chem. and Ind.*, 1959, 1156.
[4] R. P. Kurkjy and E. V. Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 6260.
[5] (*a*) F. Wille, L. Soffer, and W. Weisskopf, *Annalen*, 1950, **568**, 34; (*b*) H. Pasedach, F. Brunnmüller, and R. Oster, G.P. 1,008,276/1957.
[6] E. A. Braude and E. A. Evans, *J.*, 1955, 3324.
[7] E. A. Braude and C. J. Timmons, *J.*, 1953, 3135.
[8] J. Wegmann and H. Dahn, *Helv. Chim. Acta*, 1946, **29**, 101.

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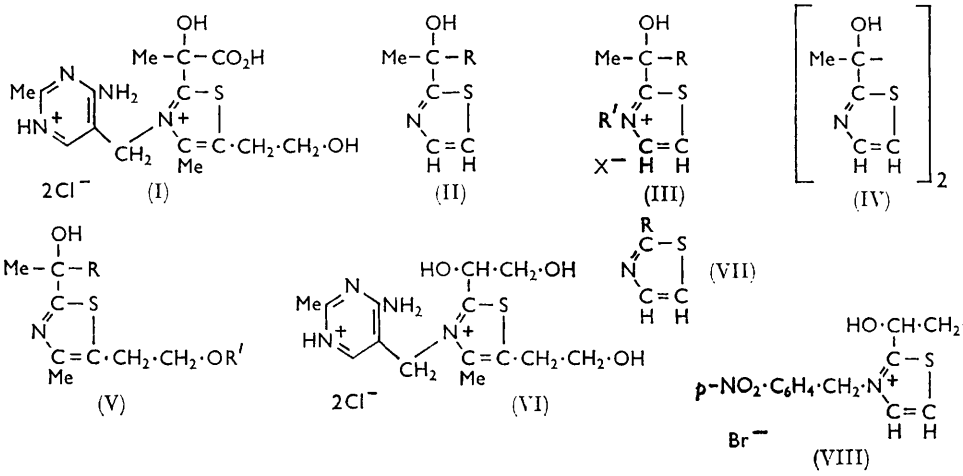
thiazole hydroxy-ketone, this unexpected behaviour appears to be related to the ready decomposition of the compound, resulting in polymer formation, under the highly basic conditions required by the haloform reaction. Reduction of the hydroxy-ketone with sodium borohydride yielded the corresponding 1,2-diol [II; R = CH(OH)·Me] but this too exhibited anomalous behaviour in the haloform reaction and did not yield the desired carboxylic acid. It has also proved possible, by protecting the hydroxyl group of the thiazole 5-substituent, to synthesise analogous derivatives incorporating the B_1-thiazole, 4-methyl-5-2′-hydroxyethylthiazole, itself. Thus, reaction of 2-lithio-4-methyl-5-2′-trityloxyethylthiazole with 3,3-dimethoxybutan-2-one yielded the hydroxy-ketal [V; R = $CMe(OMe)_2$, R′ = CPh_3] which could be hydrolysed to the hydroxy-ketone (V; R = CO·Me, R′ = H), and the latter then reduced to the 1,2-diol [V; R = CH(OH)·Me, R′ = H].

Quaternisation of the simpler thiazole hydroxy-ketone and 1,2-diol with *p*-nitrobenzyl bromide yielded the expected models (III; R = CO·Me, R′ = *p*·NO_2·C_6H_4·CH_2, X = Br) and [III; R = CH(OH)·Me, R′ = *p*·NO_2·C_6H_4·CH_2, X = Br], respectively, related to "active diacetyl" and "active acetoin."[9] The hydroxy-ketal [II; R = $CMe(OMe)_2$], by contrast, suffered expulsion of the 2-substituent on quaternisation to yield 3-4′-nitrobenzylthiazolium bromide; it was found that a similar ejection took place with the hydroxy-ketone above, unless about 10% of the thiazole was converted into the hydrobromide before quaternisation was attempted.



The postulated intermediate in the transketolase reaction catalysed by thiamine is "active glycolaldehyde" (VI).[10] An initial approach to a suitable model was made through 2-bromoacetylthiazole[11] (VII; R = CO·CH_2Br) which could be converted into the corresponding acetate (VII; R = CO·CH_2OAc). Hydrolysis with dilute sulphuric acid yields the hydroxyacetyl compound (VII; R = CO·CH_2OH), which can be reduced with sodium borohydride to the 1,2-diol [VII; R = CH(OH)·CH_2OH]. The latter compound may also be obtained directly by borohydride reduction of the acetate, as the acetyl group is also lost during the reduction. The synthesis is laborious however, its overall yield is low, and the earlier stages were unlikely to be applicable to a similar synthesis with the vitamin B_1-thiazole. Attention was therefore turned to the possible reaction of protected hydroxy-acetaldehydes with 2-lithiothiazole. Tetrahydro-2-pyranyl-[12] and

[9] L. O. Krampitz, I. Suzuki, and G. Greuell, *Fed. Proc.*, 1961, **20**, 971.
[10] H. Holzer, *Angew. Chem.*, 1961, **73**, 721.
[11] H. Erlenmeyer, O. Weber, P. Schmidt, G. Küng, C. Zinnstag, and B. Prijs, *Helv. Chim. Acta*, 1948, **31**, 1142.
[12] I. Iwai, T. Iwashige, M. Asai, K. Tomita, T. Hiraoka, and J. Ide, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 188.

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trityl-oxyacetaldehydes were obtained (the latter from the lead tetra-acetate oxidation of 1-tritylglycerol [13a,b]) and both reacted with 2-lithiothiazole to yield the corresponding 2-substituted thiazoles [VII; R = $CH(OH)\cdot CH_2O\cdot C_5H_9O$ and $CH(OH)\cdot CH_2O\cdot CPh_3$, respectively]. Both can then be hydrolysed to yield the required diol [VII; R = $CH(OH)\cdot CH_2OH$], but the route involving the tetrahydro-2-pyranyl compound is the more satisfactory. Quaternisation of the 1,2-diol with *p*-nitrobenzyl bromide yielded the model intermediate (VIII) related to " active glycolaldehyde."

Tests of the model intermediates for catalytic activity are proceeding.

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Experimental

Methyl 2-Hydroxy-2-(2-thiazolyl)propanoate (II; R = CO_2Me).—2-Bromothiazole (28·3 g.) in ether (30 ml.) was added, with vigorous stirring, to an ethereal solution of butyl-lithium (110 ml., 1·1 mol.; prepared and standardised by the method of Gilman [14a–c]) kept at −40° under a stream of dry nitrogen. After stirring for 15 min., methyl pyruvate (17·6 g.) in ether (20 ml.) was added, the temperature of the mixture being maintained at −30°, and stirred for a further 30 min. The resulting mixture was poured into 3N-hydrochloric acid (60 ml.) and ice. The aqueous layer was separated, brought to pH 5 with sodium hydroxide, and the resulting orange oil extracted with ether (6 × 75 ml.). The combined extracts were dried (Na_2SO_4) and evaporated to yield a brown oil (12 g.). Distillation in a Hickman-type still yielded a fraction b. p. 90° (bath temp.)/6 × 10^{-4} mm., which partly crystallised. Recrystallisation from pentane yielded the *hydroxy-ester* as colourless needles (1·0 g., 3%), m. p. 81° (Found: C, 45·3; H, 4·8; N, 7·5. $C_7H_9NO_3S$ requires C, 45·0; H, 4·8; N, 7·5%), $\nu_{max.}$ 3220 and 1745 $cm.^{-1}$.

Treatment of the above hydroxy-ester with an excess of 3,5-dinitrobenzoyl chloride in pyridine yielded the *3,5-dinitrobenzoate* as pale yellow leaflets, m. p. 126° (Found: C, 44·0; H, 3·2; N, 11·3. $C_{14}H_{11}N_3O_8S$ requires C, 44·1; H, 2·9; N, 11·0%).

Attempted quaternisation of the hydroxy-ester with benzyl bromide (48 hr. at 50° in nitromethane) led to the formation of 3-benzylthiazolium bromide, m. p. and mixed m. p. with authentic material, 155° (Found: C, 46·8; H, 4·9; N, 5·4. Calc. for $C_{10}H_{10}BrNS$: C, 46·9; H, 4·9; N, 5·5%).

2-Hydroxy-2-(2-thiazolyl)propanamide (II; R = $CO\cdot NH_2$).—The above ester (0·2 g.) in dry methanol (5 ml.) was cooled in an ice–salt bath and treated with a stream of dry ammonia for 45 min. The solution was then sealed in the glass tube and set aside for 2 days. Removal of the solvent under reduced pressure gave a crystalline solid which on recrystallisation from dry ether yielded the *hydroxyamide* (0·09 g., 50%) as colourless needles, m. p. 147° (Found: C, 41·9; H, 4·7; N, 16·0. $C_6H_6N_2O_2S$ requires C, 41·9; H, 4·7; N, 16·2%).

3-Benzyl-2-(1-carbamoyl-1-hydroxyethyl)thiazolium Bromide (III; R = $CONH_2$, R′ = $PhCH_2$, X = Br).—The above amide (0·2 g.) and benzyl bromide (0·22 ml., 1·1 mol.) were heated in dry dimethylformamide (2 ml.) for 3 hr. at 95°. Removal of the solvent under reduced pressure, trituration with acetone, and recrystallisation from methanol–ether yielded the *thiazolium bromide* (0·15 g., 38%) as colourless needles, m. p. 160° (Found: C, 45·6; H, 4·3; N, 8·1. $C_{13}H_{15}BrN_2O_2S$ requires C, 45·5; H, 4·4; N, 8·1%).

Similar procedures with methyl iodide and 4-amino-5-bromomethyl-2-methylpyrimidine hydrobromide yielded *2-(1-carbamoyl-1-hydroxyethyl)-3-methylthiazolium iodide* (III; R = $CONH_2$, R′ = Me, X = I) as colourless needles, m. p. 152° (Found: C, 27·1; H, 3·9; N, 9·1. $C_7H_{11}IN_2O_2S$ requires C, 26·8; H, 3·5; N, 8·9%) and *3-(4-amino-2-methyl-5-pyrimidylmethyl)-2-(1-carbamoyl-1-hydroxyethyl)thiazolium bromide hydrobromide* as buff needles, m. p. 170°. (Found: C, 30·8; H, 4·0; N, 14·3. $C_{12}H_{17}Br_2N_5O_2S,H_2O$ requires C, 30·5; H, 4·0; N, 14·8%).

The quaternised amides exhibited surprising resistance to acid hydrolysis and to attack by nitrous acid under a variety of conditions. Under conditions vigorous enough for attack to take place, extensive decomposition occurred and the required acids were not obtained.

[13] (*a*) P. E. Verkade, J. Van Der Lee, and W. Meerburg, *Rec. Trav. chim.*, 1935, **54**, 716; (*b*) H. Bredereck, A. Wagner, and D. Geissel, *Chem. Ber.*, 1961, **94**, 812.

[14] (*a*) H. Gilman and A. H. Houbein, *J. Amer. Chem. Soc.*, 1944, **66**, 1515; (*b*) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *ibid.*, 1949, **71**, 1499; (*c*) H. Gilman and R. G. Jones, *Org. Reactions*, 1951, **6**, 352.

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1,1-*Dimethoxy*-2(2-*thiazolyl*)*propan*-2-*ol* [II; R = $CH(OMe)_2$].—1,1-Dimethoxyacetone [5a,b] (8·1 g.) in ether (30 ml.) was added to a solution of 2-lithiothiazole [from 1·32N-ethereal butyl-lithium (72 ml.) and 2-bromothiazole (11·2 g.)] at −60°. The resultant slurry was warmed to 0° and poured into a slurry of ice (25 g.) and ammonium chloride (3·6 g.). The residue, on evaporation of the dried (Na_2SO_4) ether extract, gave after three distillations the *hydroxy-acetal* as colourless needles, m. p. 59°, b. p. 61° (bath)/5 × 10^{-4} mm. (Found: C, 47·3; H, 6·3; N, 6·9. $C_8H_{13}NO_3S$ requires C, 47·3; H, 6·5; N, 6·9%).

Similar treatment of 1,1-diethoxyacetone [6] yielded 1,1-*diethoxy*-2-(2-*thiazolyl*)*propan*-2-*ol* [II; R = $CH(OEt)_2$], b. p. 75°/0·02 mm. (Found: C, 52·3; H, 7·7; N, 5·7. $C_{10}H_{17}NO_3S$ requires C, 52·0; H, 7·4; N, 6·1%). Treatment with aqueous picric acid yielded a *picrate*, m. p. 122° (from ethyl acetate) (Found: C, 41·5; H, 4·3; N, 12·4. $C_{16}H_{20}N_4O_{10}S$ requires C, 41·8; H, 4·4; N, 12·2%).

Attempts to hydrolyse either acetal directly or by transacetalisation with *p*-nitrobenzaldehyde, or to prepare carbonyl derivatives from the acetals, were without success.

3-*Methyl*-2-(1,1-*dimethoxy*-2-*hydroxyprop*-2-*yl*)*thiazolium Iodide* [III; R = $CH(OMe)_2$, R′ = Me, X = I].—The above thiazole [II; R = $CH(OMe)_2$] (0·21 g.) was heated with methyl iodide (3 ml.) in a sealed tube for 24 hr. at 80°. The red oil which had separated crystallised on trituration with dry acetone. Recrystallisation by dissolving in acetonitrile (10 ml.) and diluting the cold solution with a large volume of ether (*ca.* 100 ml.) yielded the *methiodide*, m. p. 146° (Found: C, 31·4; H, 4·6; N, 4·2; I, 36·4. $C_9H_{16}INO_3S$ requires C, 31·3; H, 4·7; N, 4·1; I, 36·8%).

Similar treatment with *p*-nitrobenzyl bromide followed by recrystallisation from methanol–ether yielded the p-*nitrobenzylthiazolium bromide* [III; R = $CH(OMe)_2$, R′ = p-CH_2-C_6H_4-NO_2, X = Br], m. p. 172° (Found: C, 42·8; H, 4·6; N, 6·7. $C_{15}H_{19}BrN_2O_5S$ requires C, 43·0; H, 4·6; N, 6·7%).

In an attempt at hydrolysis, the methiodide (0·056 g.) was set aside in N-hydrochloric acid (5 ml.) for 4½ days. Paper chromatography of the solution on Whatman No. 1 paper in n-butanol–acetic acid–water (5 : 2 : 3) showed ultraviolet-absorbent spots at R_F 0·74 (very strong) and 0·35 (faint) only, corresponding, respectively, to unchanged starting material and 3-methylthiazolium iodide.[15]

Reaction of 2-*Lithiothiazole with Diacetyl*.—2-Lithiothiazole was prepared from 2-bromothiazole (8·9 g.) and 1·08N-ethereal butyl-lithium (50 ml.). The cold (−60°) solution was then blown over (50 min.) through a capillary into a stirred, cold (−60°) solution of diacetyl (9·3 g., 2 mol.) in ether (60 ml.) under dry nitrogen. The resulting slurry was allowed to warm to 0° and then poured into 3N-hydrochloric acid (40 ml.) containing ice. The mixture was stirred vigorously resulting in the separation of a solid and a brownish oil. Recrystallisation of the solid from propan-2-ol yielded 2,3-*di*-(2-*thiazolyl*)*butane*-2,3-*diol* (IV) (2·5 g.) as colourless needles, m. p. 135° (Found: C, 47·2; H, 5·0; N, 11·1. $C_{10}H_{12}N_2O_2S_2$ requires C, 46·9; H, 4·7; N, 10·9%), $\nu_{max.}$ 3310 $cm.^{-1}$. The brownish oil was extracted with ether (100 ml.), dried (Na_2SO_4), evaporated, and the residue distilled [25° (bath temp.)/10^{-4} mm.] to yield a trace of 3-*hydroxy*-3-(2-*thiazolyl*)*butan*-2-*one* (II; R = CO·Me) as colourless prisms, m. p. 46° (Found: C, 49·0; H, 5·4; N, 8·0. $C_7H_9NO_2S$ requires C, 49·1; H, 5·3; N, 8·2%), $\nu_{max.}$ 3355 and 1710 $cm.^{-1}$.

3,3-*Dimethoxy*-2-(2-*thiazolyl*)*butan*-2-*ol* [II; R = $CMe(OMe)_2$].—2-Lithiothiazole was prepared from 2-bromothiazole (70 g.) in ether (200 ml.) and 1·26N-ethereal butyl-lithium (335 ml.). After the mixture had been set aside for 15 min. at −70°, 3,3-dimethoxybutan-2-one [7] (56 g.) in ether (200 ml.) was added dropwise, the resulting slurry stirred at −70° for 1 hr., and then allowed to warm slowly to 0°. It was poured into aqueous ammonium chloride containing ice, the aqueous layer extracted with ether (2 × 100 ml.), and the combined extracts dried (Na_2SO_4) and evaporated. From the residual oil the *butanol* separated as colourless needles (sublimed at 60°/10^{-5} mm.), m. p. 77° (Found: C, 49·5; H, 6·7; N, 6·3. $C_9H_{15}NO_3S$ requires C, 49·8; H, 6·9; N, 6·5%).

The crude thiazole was set aside overnight in 4% (v/v) sulphuric acid (700 ml.), the solution then made alkaline with sodium carbonate, saturated with salt, and extracted with ether (3 × 200 ml.). Evaporation of the ether followed by sublimation at 40°/0·4 mm. on to a cold-finger yielded 3-hydroxy-3-(2-thiazolyl)butan-2-one (see above, 81% overall yield on 2-bromothiazole). The hydroxy-ketone yielded a 3,5-*dinitrobenzoate* as pale yellow prisms, m. p.

[15] W. Hafferl, R. Lundin, and L. L. Ingraham, *Biochemistry*, 1963, **2**, 1298.

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138° (Found: C, 46·5; H, 3·1; N, 11·7. $C_{14}H_{11}N_3O_7S$ requires C, 46·1; H, 3·0; N, 11·5%) and a *thiosemicarbazone*, m. p. 198° (Found: C, 39·4; H, 5·3; N, 22·8. $C_8H_{14}N_4OS_2$ requires C, 39·4; H, 5·0; N, 23·0%).

Attempts at the haloform reaction under a variety of conditions with the hydroxy-ketone yielded only small amounts of haloform (as did 2-phenylacetoin [8] under the same conditions). Stability experiments in alkaline solution on the hydroxy-ketone showed decomposition to yield polymeric material.

2-(2-Thiazolyl)butane-2,3-diol [II; R = CH(OH)·Me].—3-Hydroxy-3-(2-thiazolyl)butan-2-one (1·0 g.) in methanol (4 ml.) was treated with an excess of solid sodium borohydride. The mixture was set aside for 30 min. at room temperature, then warmed on a water-bath and poured into water. The solution was basified with sodium carbonate, saturated with sodium chloride, and extracted with ether. Evaporation of the dried ethereal extract yielded a solid (0·82 g.) which was sublimed twice (67°/5 × 10^{-3} mm.) to give the *diol*, m. p. 127° (Found: C, 48·8; H, 6·5; N, 7·9. $C_7H_{11}NO_2S$ requires C, 48·6; H, 6·4; N, 8·1%), $\nu_{max.}$ 3360 and 3125 $cm.^{-1}$.

4-Methyl-5-(2-trityloxyethyl)thiazole.—Trityl chloride (19·5 g.) was added to 4-methyl-5-(2-hydroxyethyl)thiazole (10 g.) in dry pyridine (100 ml.), and the mixture heated on a boiling-water bath (4 hr.). The mixture was then poured into ice–water and the separated solid recrystallised from methanol to yield the *trityl ether* as pale yellow needles (20·8 g., 77%), m. p. 124° (Found: C, 77·9; H, 5·7; N, 3·3. $C_{25}H_{23}NOS$ requires C, 78·0; H, 6·0; N, 3·6%). The ether yielded a *picrate* (from ethanol), m. p. 190° (Found: C, 60·4; H, 4·1; N, 9·1. $C_{31}H_{26}N_4O_8S$ requires C, 60·6; H, 4·3; N, 9·1%).

3,3-Dimethoxy-2-(4-methyl-5-trityloxyethyl-2-thiazolyl)butan-2-ol [V; R = $CMe(OMe)_2$, R′ = CPh_3].—4-Methyl-5-(2-trityloxyethyl)thiazole (10 g.) in dry tetrahydrofuran (50 ml.) was added dropwise to a well-stirred solution of lithium-butyl in ether (1·09N; 60 ml., 2·5 equiv.) cooled to −40° under dry nitrogen. A cherry-red solution was obtained to which was slowly added 3,3-dimethoxybutan-2-one (8·6 g., 2·5 mol.) in dry tetrahydrofuran (40 ml.), the temperature being maintained between −40 and −50°. The resulting solution was allowed to warm to 0° and then poured into aqueous ammonium chloride (7%; 50 ml.) containing some ice. The aqueous layer was saturated with sodium chloride and extracted twice with tetrahydrofuran. The dried extract was evaporated and the residue washed with a little methanol to yield a white solid (11·2 g.) which, on recrystallisation from benzene, gave the *thiazole*, m. p. 171° (Found: C, 71·8; H, 7·0; N, 2·9. $C_{31}H_{35}NO_4S$ requires C, 72·0; H, 6·8; N, 2·7%).

3-Hydroxy-3-(5-hydroxyethyl-4-methyl-2-thiazolyl)butan-2-one (V; R = CO·Me, R′ = H).—The above hydroxy-ketal (2·0 g.) was heated under reflux with aqueous acetic acid (80%, 10 ml.) for 10 min., the solution cooled and poured into water (10 ml.). Triphenylmethanol (0·9 g., 98%) was filtered off, the filtrate basified with potassium carbonate, saturated with sodium chloride, and extracted with ether. Removal of the solvent yielded an oil which after twice distilling (110°/10^{-2} mm.), crystallised on standing to give the *hydroxy-ketone*, m. p. 66° (Found: C, 52·1; H, 6·8; N, 6·0. $C_{10}H_{15}NO_3S$ requires C, 52·5; H, 6·6; N, 6·1%).

2-(5-Hydroxyethyl-4-methyl-2-thiazolyl)butane-2,3-diol [V; R = CH(OH)·Me, R′ = H].—The above hydroxy-ketone (1·0 g.) in methanol (10 ml.) was treated with an excess of solid sodium borohydride. The mixture was then heated under reflux (45 min.), cooled, diluted with water (20 ml.), saturated with sodium chloride, and extracted with ether. Evaporation of the extract and two distillations at 130°/5 × 10^{-4} mm. gave the *diol* as a viscous oil (Found: C, 51·8; H, 7·4; N, 6·6. $C_{10}H_{17}NO_3S$ requires C, 52·0; H, 7·4; N, 6·1%).

2-(2,3-Dihydroxybut-2-yl)-3-(4-nitrobenzyl)thiazolium Bromide [III; R = CH(OH)·Me, R′ = p-CH_2·C_6H_4·NO_2, X = Br].—2-(2-Thiazolyl)butane-2,3-diol (1·73 g.) and p-nitrobenzyl bromide (2·30 g.) were melted together on a water-bath for 5 hr. Trituration with dry ether, then dry acetone, gave a solid (2·33 g.) which, on recrystallisation from acetonitrile, yielded the *thiazolium bromide*, m. p. 172° (Found: C, 43·5; H, 4·3; N, 7·4. $C_{14}H_{17}BrN_2O_4S$ requires C, 43·2; H, 4·4; N, 7·2%).

2-(2-Hydroxy-3-oxobut-2-yl)-3-(4-nitrobenzyl)thiazolium Bromide (III; R = CO·Me, R′ = p-CH_2·C_6H_4·NO_2, X = Br).—3-Hydroxy-3-(2-thiazolyl)butan-2-one (0·345 g.), its hydrobromide (obtained as a colourless solid by passing dry, bromine-free hydrogen bromide through a dry ethereal solution of the thiazole, 0·06 g.), and p-nitrobenzyl bromide (0·525 g.) were heated (5 hr.) at 100°. The resulting gum was triturated with dry ether and acetone and recrystallised from acetonitrile to yield the *thiazolium bromide* as pale yellow prisms, m. p. 148° (Found: C,

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43·2; H, 4·2; N, 7·4. $C_{14}H_{15}BrN_2O_4S$ requires C, 43·5; H, 3·9; N, 7·3%), $\nu_{max.}$ 3100 and 1710 cm.$^{-1}$.

Quaternisation in the absence of any thiazole hydrobromide yielded only **3-(4-*nitrobenzyl*)-*thiazolium bromide***, m. p. and mixed m. p. 187° (Found: C, 39·6; H, 3·3; N, 9·1. $C_{10}H_9BrN_2O_2S$ requires C, 39·9; H, 3·0; N, 9·3%). Quaternisation of 3,3-dimethoxy-2-(2-thiazolyl)butan-2-ol yielded only 3-(4-nitrobenzyl)thiazolium bromide.

2-*Bromoacetylthiazole* (VII; R = CO·CH_2Br).—The hydrobromide is recorded [11] as having m. p. 172—174° (decomp.); we found m. p. 186°. The free thiazole is described as a red oil (no analysis); we obtained colourless needles, m. p. 54° (Found: C, 28·9; H, 2·1; N, 6·8. C_5H_4BrNOS requires C, 29·1; H, 2·0; N, 6·8%).

2-*Acetoxyacetylthiazole* (VII; R = CO·CH_2·OAc).—Freshly fused potassium acetate (0·75 g.) in dry ethanol (15 ml.) was added to 2-bromoacetylthiazole hydrobromide (1·0 g.) in dry ethanol (4 ml.) and the mixture heated under reflux (10 min.). The separated potassium bromide (0·8 g.) was filtered off, the filtrate concentrated (5 ml.), made neutral with sodium carbonate, and extracted with ether. The dried ethereal extract yielded, on evaporation, a red oil (0·55 g.) which partly crystallised on standing. Sublimation (60°/0·1 mm.) of the separated crystals gave the ***acetoxy-compound***, m. p. 60° (Found: C, 45·3; H, 3·6; N, 7·4. $C_7H_7NO_3S$ requires C, 45·4; H, 3·8; N, 7·6%).

2-*Hydroxyacetylthiazole* (VII; R = CO·CH_2OH).—The above acetoxy-compound (0·24 g.) was heated under reflux (2 hr.) with methanolic hydrogen chloride (2% w/v; 5 ml.). The solution was then concentrated (1 ml.), water (10 ml.) added, and the solution saturated with potassium carbonate and extracted with ether (3 × 20 ml.). Evaporation of the dried ethereal extract yielded a solid which on sublimation (80°/5 × 10^{-4} mm.) gave **2,2-*dimethoxy*-2-(2-*thiazolyl*)*ethanol*** as colourless prisms, m. p. 148° (Found: C, 44·7; H, 5·7; N, 7·0. $C_7H_{11}NO_3S$ requires C, 44·4; H, 5·8; N, 7·4%). Ready hydrolysis with dilute sulphuric acid (2% v/v) yielded **2-*hydroxyacetylthiazole***, m. p. 132° (Found: C, 42·3; H, 3·6; N, 9·4. $C_5H_5NO_2S$ requires C, 42·0; H, 3·5; N, 9·8%). This could also be obtained directly from the acetoxy-compound on hydrolysis with dilute sulphuric acid.

2-*Thiazolylethylene glycol* [VII; R = CH(OH)·CH_2OH].—2-Acetoxyacetylthiazole (0·265 g.) in methanol (10 ml.) was treated with an excess of sodium borohydride. The solution was heated under reflux (10 min.) to complete the reaction, cooled, and diluted with water (10 ml.). Aqueous sodium carbonate (10%; 5 ml.) was added, the solution saturated with sodium chloride, and extracted continuously with ether (24 hr.). Evaporation of the ethereal extract yielded a yellow oil (0·21 g.) which crystallised on standing. Sublimation (70°/5 × 10^{-4} mm.) yielded the ***diol*** as colourless prisms, m. p. 69° (Found: C, 41·6; H, 5·0; N, 9·5. $C_5H_7NO_2S$ requires C, 41·4; H, 4·9; N, 9·7%). The diol may also be obtained by sodium borohydride reduction of 2-hydroxyacetylthiazole.

Trityloxyacetaldehyde.—Lead tetra-acetate (6·63 g., 1 mol.) was added in small portions to a shaken solution of 1-tritylglycerol [13a,b] (5 g.) in dry benzene (100 ml.). The solution was shaken for a further 2 hr. at room temperature and the mixture poured into water (150 ml.). Benzene (100 ml.) was added, lead dioxide (*ca.* 1 g.) filtered off through Hyflo supercel, the benzene layer washed with water (2 × 50 ml.) and then sodium hydrogen carbonate solution (2 × 50 ml.), and dried. Evaporation of the dried benzene solution, followed by pumping out at 0·1 mm., yielded impure ***trityloxyacetaldehyde*** as a yellow foam, softening at 48°, which could not be further purified. It was used without further treatment.

2-(1-*Hydroxy*-2-*trityloxyethyl*)*thiazole* [VII; R = CH(OH)·CH_2O·CPh_3].—Impure trityloxyacetaldehyde (8·4 g.) in ether (84 ml.) was added to an ethereal solution of 2-lithiothiazole [obtained from 1·1N-ethereal butyl-lithium (25 ml.) and 2-bromothiazole (4·5 g.) in the usual way] at −75°. The slurry obtained was allowed to warm to −20° and then poured into an ice-cold solution of ammonium chloride. The aqueous layer was extracted with ether (50 ml.) and the total ethereal extract dried (Na_2SO_4) and evaporated. The ***thiazole*** was washed with a little dry ether and recrystallised from benzene (6·0 g., 50%), m. p. 173° (Found: C, 74·6; H, 5·7; N, 3·4. $C_{24}H_{21}NO_2S$ requires C, 74·5; H, 5·5; N, 3·6%). Hydrolysis with aqueous acetic acid yielded the thiazolylglycol (13%), m. p. and mixed m. p. 69°.

2-[1-*Hydroxy*-2-(*tetrahydropyran*-2-*yloxy*)*ethyl*]*thiazole* [VII; R = CH(OH)·CH_2O·C_5H_9O].—Tetrahydropyran-2-yloxyacetaldehyde (9·07 g.) [12] in dry ether (50 ml.) was added to an ethereal solution of 2-lithiothiazole [obtained from 1·26N-ethereal butyl-lithium (50 ml.) and 2-bromothiazole (10·3 g.) in dry ether (50 ml.)] at −70°. Working up the mixture as above yielded the

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thiazole as a colourless oil, b. p. 105° (bath)/5 × 10^{-4} mm. (Found: C, 52·5; H, 6·5; N, 6·0. $C_{10}H_{15}NO_3S$ requires C, 52·5; H, 6·6; N, 6·1%). Hydrolysis with dilute sulphuric acid (2% v/v) yielded the thiazolylglycol (39%), m. p. and mixed m. p. 69°.

2-(1,2-*Dihydroxyethyl*)-3-(4-*nitrobenzyl*)*thiazolium Bromide* (VIII).—2-Thiazolylethylene glycol (0·11 g.) and *p*-nitrobenzyl bromide (0·175 g.) in dry nitromethane (3 ml.) were heated under reflux for 11 hr. The separated solid (0·13 g.) was recrystallised from methanol–ether to yield the *thiazolium salt*, m. p. 195° (Found: C, 40·2; H, 3·6; N, 7·6. $C_{12}H_{13}BrN_2O_4S$ requires C, 39·9; H, 3·6; N, 7·8%).

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