23. *Aminoalkyl Esters of Thiazolecarboxylic and Thiazolyl-4-acetic Acids.*

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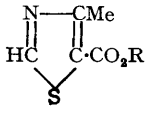
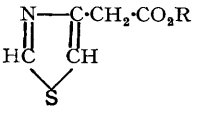
Various alternative routes to the β-diethylaminoethyl ester of 4-methylthiazole-5-carboxylic acid have been investigated. Similar esters of other carboxylic and acetic acids of the thiazole series have been prepared, either by alcoholysis of the ethyl esters or by reaction of the acids with β-chloroethyldiethylamine and potassium carbonate in acetone solution.

Johnson and his co-workers (*J. Amer. Chem. Soc.*, 1929, **51**, 1815; 1930, **52**, 1585, 3724, 4139, 4141; 1931, **53**, 1470, 1475; *Rec. trav. chim.*, 1930, **49**, 1066; 1931, **50**, 72; U.S.Ps. 1,743,083, 1,970,656, 2,014,498, 2,020,650,

2,030,373) were the first to investigate the potentialities of monocyclic thiazoles as chemotherapeutic agents. They were mainly concerned with 2-arylthiazoles but, apart from general statements as to the pharmacological interest or the biological potency of individual or groups of compounds, no detailed pharmacological reports have been published. Similar studies have subsequently been made by other investigators (Niederl *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 707; 1939, **61**, 1145; Adams *et al.*, *ibid.*, 1937, **59**, 2260, 2262; Wetherill and Hann, *ibid.*, 1934, **56**, 970; 1935, **57**, 1752; Rose, Shonle, and Chen, *Pharm. Arch.*, 1940, **11**, 81; Levvy and Nisbet, *J.*, 1938, 1053; U.S.Ps. 2,027,030, 2,242,237; B.P. 549,846) especially with aryl-substituted thiazolines. Erlenmeyer and Meyenburg (*Helv. Chim. Acta*, 1937, **20**, 1389) and Doran and Shonle (*J. Org. Chem.*, 1938, **3**, 193) have synthesised and examined the pharmacological properties of a number of 5 : 5-disubstituted 2 : 4-thiazolidiones (see following paper) and the diethylamides of two thiazolecarboxylic acids have been investigated as analeptics (Erlenmeyer and Meyenburg, *Helv. Chim. Acta*, 1937, **20**, 204; Hoffer and Reinert, *Arch. int. Pharmacodyn.*, 1937, **56**, 211). The incorporation of the thiazole ring system into antibacterial agents of the sulphanilamide series, furnishing substances of considerable clinical value, provides the most familiar example of the utilisation of the thiazole ring system in chemotherapeutic agents. The marked local anæsthetic or spasmolytic properties of the dialkylaminoalkyl esters of aminobenzoic, diphenylacetic, fluorene-9-carboxylic and related acids suggested that the preparation and examination of such derivatives in the thiazole series might yield interesting results.

After considerable activity in the period 1885—1895, the carboxylic acids of the thiazole series received little attention until 1935 when, after the isolation of 4-methylthiazole-5-carboxylic acid (I; R = H) by the degradation of vitamin B_1, interest in these compounds was revived. All the thiazolecarboxylic and the thiazolylacetic acids utilised in the research described in this paper were prepared by the classical method, *i.e.*, the condensation of a halogenated α- or β-keto-ester with either thioformamide or thioacetamide.

The moderately easily accessible acid (I; R = H) was smoothly converted into its β-*diethylaminoethyl* (I; R = $CH_2 \cdot CH_2 \cdot NEt_2$) and related *esters via* the *acid chloride*, and the same route could conveniently be

(I.)  (II.) 

employed to prepare the N-*diethylamide* and analogous compounds. This method was not applicable to the other acids studied, because of the difficulty of obtaining the acid chlorides, and various alternative routes to the above β-diethylaminoethyl ester were investigated in order to establish general methods of synthesis. Treatment of the acid with β-chloroethyldiethylamine in acetone solution in the presence of anhydrous potassium carbonate (cf. Miescher and Hoffman, *Helv. Chim. Acta*, 1941, **24**, 458; Hoffman, *ibid.*, 1941, **24**, 36—40E) gave the desired ester in good yield and alcoholysis of the ethyl ester, simply by heating with β-diethylaminoethyl alcohol, proved equally effective. The latter reaction is readily reversible, refluxing the diethylaminoethyl ester with an excess of alcohol furnishing an excellent yield of the ethyl ester.

The fourth route investigated proved less successful but some interesting points emerged from its study. In the first place β-*chloroethyl acetoacetate* was prepared readily from the ethyl ester by refluxing with ethylene chlorohydrin. Bromination of this ester, followed by condensation with thioformamide, gave β-*chloroethyl 4-methylthiazole-5-carboxylate* (I; R = $CH_2 \cdot CH_2Cl$). Treatment of the latter with diethylamine under widely varying conditions only gave small or negligible yields of the required diethylaminoethyl ester, the main product in most cases consisting of *NN'*-tetra-ethyl-1 : 2-diaminoethane ($Et_2N \cdot CH_2 \cdot CH_2 \cdot NEt_2$). Gilman and Pickles (*J. Amer. Chem. Soc.*, 1925, **47**, 251) had had similar experience and had isolated the same compound when attempting to effect reaction between diethylamine and β-chloroethyl benzenesulphonate.

The β-chloroethyldiethylamine method was employed to prepare the β-*diethylaminoethyl ester* of 2 : 4-*dimethylthiazole-5-carboxylic acid* and the alcoholysis route was applied to produce a similar ester from *ethyl 2-methylthiazole-4-carboxylate*. Despite the statement of Steude (*Annalen*, 1891, **261**, 27) and more recently of Erlenmeyer and Heitz (*Helv. Chim. Acta*, 1942, **25**, 832) that the latter ethyl ester cannot be obtained by condensation of ethyl bromopyruvate with thioacetamide, it was found that this reaction could be effected smoothly in alcoholic solution.

Ethyl thiazolyl-4-acetate (II; R = Et) was prepared in *ca.* 30% yield from ethyl γ-bromoacetoacetate and thioformamide, and hydrolysis with potassium hydroxide gave the corresponding *acid* (II; R = H). It may be noted here that the employment of potassium rather than sodium hydroxide for the hydrolysis of esters in this series of compounds results in remarkably improved yields of acidic products; in some cases no acid at all could be isolated after hydrolysis with sodium hydroxide. The alcoholysis method furnished excellent yields of the β-*diethylaminoethyl esters* of both *thiazolyl-* and *2-methylthiazolyl-4-acetic acids*.

None of the methods outlined above could be applied successfully to prepare the *diethylaminoethyl ester* of *2-amino-4-methylthiazole-5-carboxylic acid*. It was eventually produced by the following synthesis. Alcoholysis of ethyl acetoacetate with β-diethylaminoethyl alcohol gave a 25% yield of β-*diethylaminoethyl acetoacetate*, and bromination followed by condensation of the brominated product with thiourea yielded the required ester.

All the aminoalkyl esters examined pharmacologically exhibited spasmolytic and analeptic properties, as was to be expected from their resemblance to β-diethylaminoethyl diphenylacetate hydrochloride (Trasentin) and β-diethylaminoethyl 1-*cyclo*hexyl-1-phenylacetate hydrochloride (Trasentin 6H). The neurotropic action

was less marked than the musculotropic action; thus, whereas the ability of various aminoalkyl esters of 4-methylthiazole-5-carboxylic acid (I) to inhibit the contractions produced by acetylcholine was only about one-thousandth that of Trasentin, the effect of the most potent compound, the diethylaminoethyl ester, in relaxing histamine spasm was one-quarter that of Trasentin 6H. The diethylaminoethyl esters of the thiazolylacetic acids exhibited only a fraction of the musculotropic action of the corresponding esters of 4-methylthiazole-5-carboxylic acid and the introduction of the 2-amino group into the latter markedly reduced the activity. The dimethyl- and the diethyl-aminoethyl esters of (I) produced convulsions in doses equal to one-quarter to one-sixth of the dose required with Trasentin 6H, and one-sixth to one-eighth of that required with 1 : 2-pentamethylenetetrazole (Leptazol). Only the diethylaminoethyl ester of (I) was effective in antagonising a lethal dose of a short-acting barbiturate; none of the esters was effective against the long-acting variety. The diethylaminoethyl ester of the amino-acid, which might have been expected to show local anæsthetic properties, was practically devoid of activity. The *N*-diethylamide of (I) and analogous compounds had analeptic properties and caused convulsions, but had no action on the heart comparable with that of *N*-diethylnicotinamide (Nikethamide, Coramine).

Experimental.

Derivatives of 4-Methylthiazole-5-carboxylic Acid.—The condensation of thioformamide with ethyl α-bromoacetoacetate (Kharasch, Sternfield, and Mayo, *J. Amer. Chem. Soc.*, 1937, **59**, 1655) was effected according to Erlenmeyer and Meyenburg (*Helv. Chim. Acta*, 1937, **20**, 204; cf. Harington and Moggridge, *J.*, 1939, 443). The *picrate* of the *ethyl ester* formed yellow prismatic needles from alcohol, m. p. 110° (Found : N, 14·15. $C_{13}H_{12}O_9N_4S$ requires N, 14·0%).

The acid was obtained in practically theoretical yield by heating the ethyl ester (20 g.) on the steam bath with aqueous potassium hydroxide (150 c.c., 10%) for 30 mins. (cf. the 75% yield of Clarke and Gurin, *J. Amer. Chem. Soc.*, 1935, **57**, 1876). The *quinine salt* was prepared by refluxing an alcoholic solution of equimolecular quantities of the acid and base for several hours, evaporating to dryness and crystallising from ethyl acetate. This procedure gave needles, m. p. 189·5° (decomp.) (Found : C, 64·15; H, 6·6. $C_{25}H_{29}O_4N_3S$ requires C, 64·2; H, 6·25%). The acid (22 g.), after being refluxed with thionyl chloride (40 c.c.) for 3 hours, removing the excess of the latter under reduced pressure and subliming the product at 40—55° (bath temp.)/10^{-4} mm., yielded the *acid chloride* (20 g.) in short hexagonal prisms, m. p. 64° (Found : C, 37·3; H, 2·45. C_5H_4ONClS requires C, 37·15; H, 2·5%).

β-Diethylaminoethyl Ester.—(*a*) The acid chloride (3 g.) in dry acetone (25 c.c.) was treated with diethylaminoethyl alcohol (2·2 g.) and the mixture refluxed for 6 hours (A). The crystalline solid which separated on cooling was recrystallised from alcohol–acetone giving the *hydrochloride* of the *diethylaminoethyl ester* (75—80% yield) as needles, m. p. 167° (Found : C, 47·6; H, 7·1. $C_{11}H_{19}O_2N_2ClS$ requires C, 47·4; H, 6·85%). When the acetone solution (A) was evaporated and the residue treated with sodium bicarbonate and extracted with ether the *diethylaminoethyl ester* (85% yield) was obtained as a viscous oil, m. p. *ca.* 1—2°, b. p. 80° (bath temp.)/10^{-4} mm., $n_D^{24°}$ 1·5060 (Found : C, 54·75; H, 7·95. $C_{11}H_{18}O_2N_2S$ requires C, 54·5; H, 7·5%). On shaking this water insoluble ester with 2N-sodium hydroxide solution for 5 minutes, practically quantitative yields of 4-methylthiazole-5-carboxylic acid and diethylaminoethyl alcohol were produced. (The *picrate* of *diethylaminoethyl alcohol*, yellow crystals from acetone, has m. p. 79° (Found : N, 15·9. $C_{12}H_{18}O_8N_4$ requires N, 16·2%).) With a deficiency of picric acid the diethylaminoethyl ester gives a *monopicrate* as yellow crystals from acetone, m. p. 132° (Found : N, 14·7. $C_{17}H_{21}O_9N_5S$ requires N, 14·85%), and with an excess of the reagent a *dipicrate* is formed. This can also be obtained from the monopicrate. It separates as yellow crystals from acetone, m. p. 125—126° (Found : N, 15·7. $C_{23}H_{24}O_{16}N_8S$ requires N, 16·0%). The *methiodide* of the ester, obtained after standing for some days at 20° with an excess of the reagent, formed hexagonal leaflets from acetone–alcohol, m. p. 195° (Found : N, 7·15. $C_{12}H_{21}O_2N_2IS$ requires N, 7·3%).

(*b*) A mixture of 4-methylthiazole-5-carboxylic acid (3 g.), anhydrous potassium carbonate (2 g.) and β-chloroethyldiethylamine (4·3 g., 1·5 mol.) in acetone (100 c.c.) was refluxed for 4 hours. The mixture was filtered, the filtrate evaporated and the residue distilled, giving the diethylaminoethyl ester (2·9 g., 60%), m. p. 3°, b. p. 162—163°/12 mm., $n_D^{19°}$ 1·5106, which formed the same dipicrate, m. p. 126° (mixed m. p.), and gave the same hydrolysis products as the sample prepared by method (*a*).

(*c*) A solution of ethyl 4-methylthiazole-5-carboxylate (2·6 g.) in diethylaminoethyl alcohol (8 g., 4 mols.) was heated for 20 hours at 170—175° using a short reflux condenser through which the ethyl alcohol produced could be eliminated. Distillation gave the diethylaminoethyl ester (2·5 g., 70%), b. p. 165—166°/15 mm., $n_D^{13·5°}$ 1·5102 (dipicrate). Neither increasing the time of reaction nor the proportion of the diethylaminoethyl alcohol employed caused any increase in yield. On heating the ester (1·9 g.) with alcohol (40 c.c.) under reflux for 6½ hours, diethylaminoethyl alcohol (0·5 g., 55%), b. p. *ca.* 60°/15 mm., $n_D^{21°}$ 1·4413, and ethyl 4-methylthiazole-5-carboxylate (1·2 g., 90%), b. p. 110—115°/15 mm., $n_D^{21°}$ 1·5058 (picrate), were obtained on distillation.

β-Dimethylaminoethyl Ester Hydrochloride.—Prepared in 80% yield according to method (*a*) above, from dimethylaminoethyl alcohol, it formed prisms from alcohol–acetone, m. p. 202° (Found : C, 42·9; H, 5·75. $C_9H_{15}O_2N_2ClS$ requires C, 43·1; H, 6·05%).

β-Piperidinoethyl Ester Hydrochloride.—Method (*a*) employing β-piperidinoethyl alcohol (Blicke and Maxwell, *J. Amer. Chem. Soc.*, 1942, **64**, 429) gave a 65% yield of silky needles, from alcohol–acetone, m. p. 190° (decomp.) (Found : C, 49·95; H, 6·4. $C_{12}H_{19}O_2N_2ClS$ requires C, 49·55; H, 6·6%).

β-Morpholinoethyl Ester Hydrochloride.—Prepared by route (*a*) in 85% yield. The crystals from alcohol have m. p. 207° (decomp.) (Found : C, 45·35; H, 6·05. $C_{11}H_{17}O_3N_2ClS$ requires C, 45·1; H, 5·85%).

β-Diethylaminopropyl Ester Hydrochloride.—The alcohol was prepared from propylene oxide and diethylamine according to Goldfarb (*J. Amer. Chem. Soc.*, 1941, **63**, 2280) except that little reaction appeared to ensue with completely anhydrous reagents. After adding a little water a smooth reaction occurred giving a 75% yield of the alcohol. The ester hydrochloride, prepared by (*a*) above in 75% yield, formed needles from alcohol–ligroin (b. p. 60—80°), m. p. 156·5° (Found : C, 49·5; H, 7·55. $C_{12}H_{21}O_2N_2ClS$ requires C, 49·2; H, 7·25%).

γ-Diethylaminopropyl Ester Hydrochloride.—The method of Hromatka (*Ber.*, 1942, **75**, 136) for the amino-alcohol was found unsatisfactory and that due to Campbell and Campbell (*Proc. Indiana Acad. Sci.*, 1939, **49**, 101) was employed. Using method (*a*) and crystallising first from alcohol–acetone and then from alcohol–ligroin (b. p. 60—80°) the hydrochloride was obtained in 40% yield in needles, m. p. 153° (Found : C, 49·15; H, 7·05. $C_{12}H_{21}O_2N_2ClS$ requires C, 49·2; H, 7·25%).

β-Chloroethyl Ester.—A solution of thioformamide (9·3 g.) in alcohol (20 c.c.) was cooled to 8° and the α-bromocompound (30·8 g.) from β-chloroethyl acetoacetate (see below, for preparation) in alcohol (10 c.c.) was added over 7 mins. with stirring and cooling, the temperature being allowed to rise only to 30°. After standing overnight and diluting with water (200 c.c.), concentrated hydrochloric acid (50 c.c.) was added, non-basic material was removed with ether and,

after addition of excess solid sodium bicarbonate, isolation with ether gave the ester (6 g., 25%), b. p. 150—160°/20 mm., as a yellow oil which solidified on keeping. Recrystallisation from ligroin (b. p. 40—60°) gave needles, m. p. 59° (Found : C, 40·85; H, 4·05. $C_7H_8O_2NClS$ requires C, 40·9; H, 3·9%). Hydrolysis with 10% aqueous potassium hydroxide gave 4-methylthiazole-5-carboxylic acid (quinine salt, m. p. and mixed m. p.). The *picrate* crystallised from alcohol in yellow plates, m. p. 115° (Found : N, 12·85. $C_{13}H_{11}O_9N_4ClS$ requires N, 12·9%). Attempts to convert the above ester into the diethylaminoethyl ester were unsuccessful, except when the chloro-ester was made into the iodo-ester and the latter was heated in a sealed tube at 130° with a large excess of diethylamine. In most of the numerous experiments carried out, *NN'*-tetraethyl-1 : 2-diaminoethane, b. p. 78—80°/20 mm., $n_D^{20°}$ 1·4366 (Found : N, 16·15. Calc. for $C_{10}H_{24}N_2$: N, 16·25%), was obtained in varying amounts. Its dihydrochloride had m. p. 190—191° (Gilman and Pickles, *J. Amer. Chem. Soc.*, 1925, **47**, 251, give b. p. 70—72°/10 mm. for the base and m. p. 187° for the dihydrochloride). The *dipicrate* crystallised from acetone in yellow plates, decomp. at 243° (Found : C, 41·95; H, 4·95. $C_{22}H_{30}O_{14}N_8$ requires C, 41·9; H, 4·8%).

Diethylamide.—(*a*) (cf. method of Erlenmeyer and Meyenburg, *loc. cit.*). A mixture of the acid chloride (3 g.) and diethylamine hydrochloride (2·1 g.) was heated for 2 hours at 160°, occasionally returning the sublimate to the melt. The residue was treated with sodium hydroxide solution and isolation with ether gave the *diethylamide* (2·2 g., 60%) as a pale yellow oil, completely miscible with water, b. p. 287° (slight decomp.), 169—170°/23 mm., 85—90° (bath temp.)/10^{-4} mm., $n_D^{25°}$ 1·5240 (Found : C, 54·0; H, 7·25. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1%). The *picrate* formed yellow crystals from acetone, m. p. 118° (Found : N, 16·15. $C_{15}H_{17}O_8N_5S$ requires N, 16·4%).

(*b*) The acid chloride (10 g.) and diethylamine (9·8 g.) were mixed in cold ether (300 c.c.). After 5 mins. the diethylamine hydrochloride was separated and evaporation and distillation of the residue gave the diethylamide (10·3 g., 85%), having constants as above.

Dimethylamide.—Method (*a*) gave only a 15% yield, but a 90% yield was obtained by method (*b*). It is a water-soluble mobile oil, b. p. 164°/23 mm., 80—85° (bath temp.)/10^{-4} mm., $n_D^{22°}$ 1·5460 (Found : C, 49·85; H, 6·1. $C_7H_{10}ON_2S$ requires C, 49·4; H, 5·9%). The *picrate* formed yellow crystals, m. p. 109°, from acetone (Found : N, 17·5. $C_{13}H_{13}O_8N_5S$ requires N, 17·55%).

Piperidino-amide.—Method (*a*) failed to give more than a 15% yield but method (*b*) gave an 80% yield of amide with b. p. 197°/23 mm., 90° (bath temp.)/10^{-4} mm., $n_D^{21°}$ 1·5634 (Found : C, 57·5; H, 6·8. $C_{10}H_{14}ON_2S$ requires C, 57·1; H, 6·7%). The *picrate* crystallised from alcohol in yellow needles, m. p. 148·5° (Found : N, 15·7. $C_{16}H_{17}O_8N_5S$ requires N, 15·95%).

Morpholino-amide.—Prepared in 75% yield by method (*b*) this had b. p. 206°/23 mm., 100° (bath temp.)/10^{-4} mm., $n_D^{21°}$ 1·5649. It gradually solidified on keeping and after crystallisation from ligroin (b. p. 80—100°) it was obtained in prisms, m. p. 54—55° (Found : C, 51·3; H, 5·45. $C_9H_{12}O_2N_2S$ requires C, 50·95; H, 5·7%). It is highly hygroscopic. The *picrate* crystallised from acetone, m. p. 181·5° (slight decomp.) (Found : N, 16·0. $C_{15}H_{15}O_9N_5S$ requires N, 15·85%).

Derivatives of 2 : 4-*Dimethylthiazole-5-carboxylic Acid.*—*β-Diethylaminoethyl ester.* The acid (12 g.; Erlenmeyer *et al.*, *Helv. Chim. Acta*, 1938, **21**, 1020) was treated with β-chloroethyldiethylamine (13 g.) and anhydrous potassium carbonate (6 g.) in dry acetone (400 c.c.) as described above. The *ester* (15·3 g., 80%) had b. p. 121—124°/3 mm., $n_D^{21°}$ 1·5071 (Found : C, 56·25; H, 7·85. $C_{12}H_{20}O_2N_2S$ requires C, 56·25; H, 7·85%). Hydrolysis of the ester by refluxing for 30 mins. with 10% aqueous potassium hydroxide gave a 65% yield of the parent acid, m. p. 233°, undepressed on admixture with an authentic specimen. The *dipicrate* of the *diethylaminoethyl ester* formed fine yellow needles, m. p. 163°, on crystallisation from acetone (Found : N, 15·45. $C_{24}H_{26}O_{16}N_8S$ requires N, 15·7%). The *amide*, prepared from the ethyl ester by treatment with 0·880 ammonia, crystallised from alcohol–ligroin (b. p. 60—80°) as plates or needles, m. p. 140° (Found : N, 17·55. $C_6H_8ON_2S$ requires N, 17·95%).

Derivatives of 2-*Methylthiazole-4-carboxylic Acid.*—When a solution of thioacetamide (4 g., 1·3 mol.) in alcohol (25 c.c.) was treated with ethyl bromopyruvate (7·8 g.; Ward, *J.*, 1923, 2210; Steude, *Annalen*, 1891, **261**, 25) a yellow colour developed rapidly and the temperature of the reaction mixture rose to 60°. After standing overnight at 20° 2N-hydrochloric acid was added and the solution was extracted with ether to remove non-basic material. Isolation of the product with ether after treatment with an excess of bicarbonate gave *ethyl* 2-*methylthiazole-4-carboxylate* (5 g., 75%) which sublimed at about 70° (bath temp.)/10^{-4} mm. Crystallisation from ligroin (b. p. 60—80°) gave prismatic needles, m. p. 58° (Found : C, 49·0; H, 5·35. $C_7H_9O_2NS$ requires C, 49·1; H, 5·3%). With methyl alcohol as solvent for the condensation, poorer yields (60%) were obtained and on using chloroform as solvent the hydrobromide (m. p. *ca.* 120°) of a water-soluble base (m. p. 74°), which could not be investigated further, was obtained. Reaction of the ester with hydrogen chloride or picric acid gave only intractable gums, but the *amide* was obtained with 0·880 ammonia. After crystallisation from alcohol–ligroin (b. p. 60—80°) it had m. p. 152° (Found : N, 19·5. $C_5H_6ON_2S$ requires N, 19·7%).

The ethyl ester (10 g.) in diethylaminoethyl alcohol (40 g.) was refluxed gently for 36 hours in a flask fitted with a short air condenser. Fractionation of the residual liquid gave the water-soluble *β-diethylaminoethyl ester* (9·9 g., 70%), b. p. 140°/3·5 mm., $n_D^{19°}$ 1·5170 (Found : C, 54·15; H, 8·05. $C_{11}H_{18}O_2N_2S$ requires C, 54·5; H, 7·5%). The *monopicrate* was crystallised from aqueous acetone and had m. p. 74—76° (after sintering at *ca.* 70°) (Found : N, 14·85. $C_{17}H_{21}O_9N_5S$ requires N, 14·85%).

Derivatives of Thiazolyl-4-acetic Acid.—Many attempts to prepare the ester gave unsatisfactory yields. The following is a description of the procedure which gave the best results. Ethyl γ-bromoacetoacetate (28·7 g.; Conrad and Schmidt, *Ber.*, 1896, **29**, 1043) in alcohol (50 c.c.) was treated with a solution of thioformamide (11 g.) in alcohol (15 c.c.), the latter being added in small portions with stirring so that the temperature did not rise above 40°. After the addition, the mixture was heated under reflux for 15 minutes when ammonium bromide (6—7 g.) separated. Following extensive dilution with 2N-hydrochloric acid and ether extraction, the aqueous portion was mixed with excess of sodium bicarbonate and isolation with ether followed by fractionation gave the *ethyl ester* (5·6 g., 25%), b. p. 122°/15 mm., $n_D^{17°}$ 1·5115 (Found : C, 48·65; H, 5·2. $C_7H_9O_2NS$ requires C, 49·1; H, 5·3%). The *picrate* separated from alcohol in silky yellow needles, m. p. 112° (Found : N, 13·7. $C_{13}H_{12}O_9N_4S$ requires N, 14·0%).

The ester (3·4 g.) was hydrolysed almost immediately on shaking with 10% aqueous potassium hydroxide (20 c.c.) giving *thiazolyl-4-acetic acid* (2 g.), in long needles from benzene, m. p. 139° (Found : C, 42·1; H, 3·6. $C_5H_5O_2NS$ requires C, 41·95; H, 3·5%). It sublimes unchanged at 60—75° (bath temp.)/10^{-4} mm. With thionyl chloride it develops a blue colouration, changing to bluish-red. Light absorption in alcohol : Maximum, 2400A., ε = 3500. The *amide* (75% yield), prepared from the ester with 0·880 ammonia, crystallised from alcohol–ligroin (b. p. 60—80°) in plates, m. p. 124° (Found : N, 19·45. $C_5H_6ON_2S$ requires N, 19·7%).

A solution of ethyl thiazolyl-4-acetate (8·6 g.) in diethylaminoethyl alcohol (15 g., 2·5 mols.) was refluxed for 24 hours in a flask fitted with a short air condenser. Distillation then gave the *β-diethylaminoethyl ester* (11·1 g., 90%), as a pale yellow water-soluble oil, b. p. 186°/29 mm., 80—90° (bath temp.)/10^{-4} mm., $n_D^{21°}$ 1·5048 (Found : C, 54·5; H, 7·65. $C_{11}H_{18}O_2N_2S$ requires C, 54·5; H, 7·5%). The *dipicrate* crystallised from ethyl acetate or chloroform–acetone and had m. p. 102° (Found : N, 15·95. $C_{23}H_{24}O_{16}N_8S$ requires N, 16·0%). On hydrolysis of the ester with 10% aqueous potassium hydroxide, thiazolyl-4-acetic acid (m. p. and mixed m. p.) was obtained.

Derivatives of 2-*Methylthiazolyl-4-acetic Acid.*—The following procedure represents an improvement upon the method

of Steude (*Annalen*, 1891, **261**, 40). Ethyl γ-bromoacetoacetate (9 g., distilled) was dissolved in alcohol and thioacetamide (3·2 g.) was added with gentle stirring. Some heat was evolved and after a few minutes a clear yellow solution was obtained. This was allowed to remain undisturbed for some 16 hours. Six such reaction mixtures were mixed together, treated with 2N-hydrochloric acid (500 c.c.) and extracted with ether. The aqueous portion was mixed with excess sodium bicarbonate and isolation by means of ether gave the ethyl ester (35 g., 75%), b. p. 127°/13 mm., $n_D^{21°}$ 1·5020. The *picrate* crystallises from either alcohol or acetone as needles, m. p. 98° or 105°, independent of the solvent employed (Found: N, 13·75. $C_{14}H_{14}O_9N_4S$ requires N, 13·55%). Hydrolysis with aqueous potassium hydroxide gave the acid (60—80% yield), which separated from water or benzene as thick needles, m. p. 124° (Steude, *loc. cit.*, gives m. p. 121°). It sublimed unchanged at 85—95° (bath temp.)/10^{-4} mm. Light absorption in alcohol: Maximum, 2420A., ε = 4500. The *amide*, prepared from ester with 0·880 ammonia, formed plates or needles, m. p. 141°, from alcohol–ligroin (b. p. 60° 80°) (Found: N, 18·2. $C_6H_8ON_2S$ requires N, 17·95%).

β-Diethylaminoethyl Ester.—(*a*) The acid (10·7 g.) was refluxed with β-chloroethyldiethylamine (15 g., 1·5 mol.) and anhydrous potassium carbonate (20 g.) in dry acetone (200 c.c.) for 4 hours. This gave the *β-diethylaminoethyl ester* (12 g., 70%), b. p. 131°/4 mm., 70—80° (bath temp.)/10^{-4} mm., $n_D^{19°}$ 1·5001 (Found: C, 56·3; H, 8·1. $C_{12}H_{20}O_2N_2S$ requires C, 56·25; H, 7·85%). The *dipicrate*, crystallised from acetone, had m. p. 126° (Found: C, 40·4; H, 3·8. $C_{24}H_{26}O_{16}N_8S$ requires C, 40·35; H, 3·65%).

(*b*) The ethyl ester (5·5 g.) and β-diethylaminoethyl alcohol (10 g.) were refluxed gently for 32 hours in a flask fitted with a short air condenser. This gave the diethylaminoethyl ester (4 g.; 55%), b. p. 184—185°/22 mm., $n_D^{17°}$ 1·5029 (dipicrate). Hydrolysis of either sample of ester gave β-diethylaminoethyl alcohol (picrate) and the thiazolylacetic acid (m. p. and mixed m. p.).

β-Chloroethyl Ester.—Bromine (15·05 c.c.) was added during 30 minutes to a solution of β-chloroethyl acetoacetate (49·4 g.; for preparation, see below) in carbon disulphide (58 c.c.) and chloroform (20 c.c.). After standing overnight, the solution was washed several times with water, dried and evaporated at 50—55°/20 mm. to give the crude γ-bromo-compound (61·3 g., 85%) as a pale brown liquid. Five portions (10·5 g. each) of this product were each treated with thioacetamide (3·25 g.) as for the ethyl ester preparation already described. Fractionation of the crude product gave the *β-chloroethyl ester* (23·5 g., 50%), b. p. *ca.* 170°/20 mm., 110°/4 mm., $n_D^{18°}$ 1·5266 (Found: C, 43·75; H, 4·8. $C_8H_{10}O_2NClS$ requires C, 43·75; H, 4·6%). Hydrolysis with 10% aqueous potassium hydroxide was very rapid at 20° and gave the 2-methylthiazolyl-4-acetic acid (m. p. and mixed m. p.). The *picrate* crystallised from aqueous alcohol in yellow needles, m. p. 103—104° (Found: C, 37·7; H, 3·25. $C_{14}H_{13}O_9N_4ClS$ requires C, 37·45; H, 2·9%).

Derivatives of 2-Amino-4-methylthiazole-5-carboxylic Acid.—*β-Diethylaminoethyl ester.* A mixture of β-diethylaminoethyl acetoacetate (24 g.; $n_D^{19°}$ 1·4489; for preparation, see below) and water (125 c.c.) and 2N-hydrochloric acid (75 c.c.) was stirred and cooled (ice) while bromine (19·2 c.c.) was added during 20 minutes. After stirring at 0° for a further 2 hours, treatment with potassium acetate (24 g.) in water (24 c.c.) was followed by the addition of a suspension of thiourea (10 g.) in water (25 c.c.). The solution was stirred during some 16 hours at 20°, filtered, extracted with ether and then made alkaline with ammonia solution. Isolation with ether and purification by crystallisation from alcohol–ligroin (b. p. 60—80°) and sublimation at 110—120° (bath temp.)/10^{-4} mm., gave the *β-diethylaminoethyl ester* (5·5 g., 20%) as glistening plates, m. p. 121° (Found: C, 51·5; H, 7·3. $C_{11}H_{19}O_2N_3S$ requires C, 51·35; H, 7·45%).

β-Chloroethyl ester. The α-bromo-compound (62 g.) from β-chloroethyl acetoacetate was added with shaking to an ice-cold solution of thiourea (22 g.) in water (300 c.c.). A precipitate of the hydrobromide was obtained after some hours. A small portion of this, on crystallisation from alcohol–ligroin (b. p. 60—80°), gave the *hydrobromide* of the *β-chloroethyl ester*, m. p. 210° (decomp.) (Found: N, 9·4. $C_7H_{10}O_2N_2ClBrS$ requires N, 9·3%). The reaction mixture was warmed with an equal volume of water to dissolve the hydrobromide, filtered to remove a small residue, and then basified with ammonia solution. The precipitate was crystallised from aqueous alcohol giving the *β-chloroethyl ester* (54 g.; 95%) as fine needles, m. p. 164—165° (Found: C, 38·4; H, 4·1. $C_7H_9O_2N_2ClS$ requires C, 38·1; H, 4·1%).

Preparation of Intermediates.—*β-Chloroethyl acetoacetate.* Ethyl acetoacetate (130 g.) was refluxed gently with ethylene chlorohydrin (80·5 g.) in a flask fitted with an air condenser, so arranged that the ethyl alcohol produced escaped from the condenser. After 3—4 hours the liquid temperature had risen from 140° to 195°. Fractionation of the product gave *β-chloroethyl acetoacetate* (84 g., 45%) as a mobile liquid, b. p. 120—121°/19 mm., $n_D^{17°}$ 1·4542 (Found: Cl, 21·6. $C_6H_9O_3Cl$ requires Cl, 21·55%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in deep yellow needles, m. p. 100° (Found: N, 16·55. $C_{12}H_{13}O_6N_4Cl$ requires N, 16·25%). α-Bromination of this ester was effected in the same manner as for the ethyl ester (Kharasch, Sternfield, and Mayo, *J. Amer. Chem. Soc.*, 1937, **59**, 1655) and the crude product, obtained in 80% yield, had $n_D^{18°}$ 1·4919.

β-Diethylaminoethyl acetoacetate. A mixture of ethyl acetoacetate (39 g.) and β-diethylaminoethyl alcohol (35 g.) was refluxed for 5—6 hrs. in such a manner that the alcohol formed escaped from the system. Careful fractionation gave the *β-diethylaminoethyl ester* (15 g., 25%) as a pale yellow oil, b. p. 83°/5 mm., $n_D^{18°}$ 1·4481 (Found: N, 7·35. $C_{10}H_{19}O_3N$ requires N, 6·95%). The ester was miscible with water. The *picrate* crystallised from alcohol–ethyl acetate in yellow leaflets, m. p. 70° (Found: N, 13·05. $C_{16}H_{22}O_{10}N_4$ requires N, 13·0%).

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