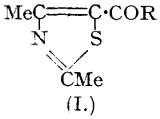
162. *The Action of Thionyl Chloride on 2 : 4-Dimethylthiazole-5-carboxylic Acid.*

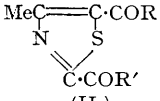
By W. R. Boon.

When **2 : 4**-dimethylthiazole-5-carboxylic acid (I; R = OH) is heated under reflux with an excess of thionyl chloride the main product is *4-methylthiazole-2 : 5-dicarboxylic acid dichloride* (II; R = R′ = Cl). The normal acid chloride (I; R = Cl) is obtained by the action of 1 mol. of thionyl chloride in presence of pyridine.

In an attempt to prepare **2 : 4**-dimethylthiazole-5-carboxylic acid chloride (I; R = Cl) by heating the acid under reflux with an excess of thionyl chloride, an acid chloride was obtained which, owing to difficulties of purification and its extreme sensitivity, did not give satisfactory analytical results, but nevertheless appeared to be a methylthiazole-dicarboxylic acid dichloride. Confirmation of this was obtained by converting it into a series of *diamides* [II; R = R′ = NH_2, NHMe, NHEt, $N(Me)_2$, $N(Et)_2$, or $N<C_4H_8>O$].

Of the two possible methylthiazole-dicarboxylic acids, 2-methylthiazole-4 : 5-dicarboxylic acid (III) has been described (Roubleff, *Annalen*, 1890, **259**, 253). Hydrolysis of the dichloride with water, instead of giving a dicarboxylic acid, led to formation of 4-methylthiazole-5-carboxylic acid (IV), identical (m. p. and mixed m. p. of acids and of ethyl esters) with that described by Wohmann (*ibid.*, p. 277).


(I.)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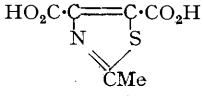
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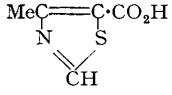
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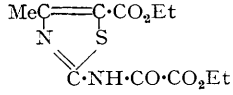
(V.)

Final confirmation of the structure of the acid chloride was obtained by the synthesis of *ethyl 4-methylthiazole-2 : 5-dicarboxylate* (II; R = R′ = OEt), and its conversion into the same diamide (II; R = R′ = NH_2) as that obtained from the dichloride. The synthesis of this ester was effected by condensing ethyl monothio-oxamate, $NH_2 \cdot CS \cdot CO_2Et$, with ethyl α-chloroacetoacetate. Hydrolysis of the ester with dilute sodium hydroxide, followed by acidification, gave an excellent yield of 4-methylthiazole-5-carboxylic acid, carbon dioxide being lost very readily even if the acidification was effected at 1°. This lability, which appears

to be a general property of thiazole-2-carboxylic acids (see B.P. 546,994), makes ethyl monothio-oxamate a useful intermediate for the preparation of thiazoles unsubstituted in position 2.

Reaction of ethyl 4-methylthiazole-2 : 5-dicarboxylate with 2·5 mols. of hydrazine hydrate (5%) at room temperature gave, in addition to the *dihydrazide* (II; R = R′ = NH·NH_2), *ethyl 4-methylthiazole-2-carboxyhydrazide-5-carboxylate* (II; R = OEt, R′ = NH·NH_2). The configuration of the latter was confirmed by converting it by Curtius's method into *ethyl 5-carbethoxy-4-methylthiazole-2-carbamate* (V), identical with the product obtained by reaction between ethyl 2-amino-4-methylthiazole-5-carboxylate and ethyl chloroformate.

The exact mechanism of the conversion of 2 : 4-dimethylthiazole-5-carboxylic acid into *4-methylthiazole-2 : 5-dicarboxylic dichloride* by means of thionyl chloride is unknown. It appears, however, to be a direct oxidation of the 2-methyl group by the thionyl chloride, since it occurs even when the latter has been rigorously purified and when the reaction is effected in an atmosphere of nitrogen; further, considerable quantities of sulphur chloride can be isolated as a by-product of the reaction. Oxidation of a suitable methyl group to a carboxy-chloride by means of thionyl chloride is not unknown, since (D.R.-P. 282,133; Friedländer, Vol. 12, p. 171) 2 : 4-dichlorobenzoyl chloride can be made by heating the sodium salt of either 2-chlorotoluene-4- or 4-chlorotoluene-2-sulphonic acid with thionyl chloride. 2 : 4-Dimethylthiazole-5-carboxylic acid chloride (I; R = Cl) can be made by reaction between 1 mol. each of the acid and thionyl chloride in presence of pyridine; it is unstable, resinifying on attempted distillation. Solutions are, however, readily prepared for use, *e.g.*, in the preparation of amides, a number of which are described.

The amides made in this investigation were examined for respiratory stimulant activity at Edinburgh University through the kindness of the late Professor A. J. Clark. Few of the substances examined showed any marked activity of this nature, the most active being 2 : 4-dimethylthiazole-5-carboxdiethylamide (I; R = NEt_2), which possesses the same order of activity as " Nikethamide." A similar result was reported by Heffer and Reinert (*Arch. Int. Pharm. Ther.*, **1937**, **56**, 211) during the course of this investigation. The only other substances which approached this in activity were 2 : 4-dimethylthiazole-5-carboxyhydrazide (I; R = NH·NH_2) and 4-methylthiazole-2 : 4-dicarboxydiamide (II; R = R′ = NH_2), which were approximately half as active.

Experimental.

Ethyl 2 : 4-dimethylthiazole-5-carboxylate and the corresponding acid were prepared by Hantzsch's method (*Annalen*, 1889, **250**, 260). The methyl ester was made by reaction of the acid with methanol and hydrogen chloride; m. p. 8·8°, b. p. 125°/26 mm., $n^{20°}$ 1·524. This ester forms a *monohydrate*, m. p. 35·5° (Found: N, 7·3. $C_7H_{11}O_3NS$ requires N, 7·4).

4-Methylthiazole-2 : 5-dicarboxydichloride.—2 : 4-Dimethylthiazole-5-carboxylic acid (80 g.) was heated under reflux for 72 hours with pure thionyl chloride (550 c.c.), and the reaction mixture filtered through sintered glass to remove 7·8 g. of an amorphous, orange product. After the thionyl chloride had been removed by distillation at ordinary pressure, the residue was fractionated under reduced pressure, giving sulphur chloride (67 g.) and the *acid dichloride* (86 g.; 78%), b. p. 166—168°/32 mm. (90°/1 mm.) (Found: C, 30·55; H, 1·4; N, 6·15; Cl, 36·2. $C_6H_3O_2NCl_2S$ requires C, 32·1; H, 1·34; N, 6·25; Cl, 31·7%). Prolonged heating is necessary to obtain a high yield, 4, 40, and 72 hrs.' heating giving yields of 48, 59, and 76%, respectively.

The thionyl chloride used above was freed from sulphuryl chloride by heating under reflux with sulphur and aluminium chloride. The product was then fractionated, and freed from traces of sulphur chloride by distillation from a mixture of linseed oil and bee's wax. For ordinary preparative purposes technical thionyl chloride is satisfactory.

2 : 4-Dimethylthiazole-5-carboxychloride.—2 : 4-Dimethylthiazole-5-carboxylic acid (15·9 g.) was suspended in dry ether (100 c.c.), pyridine (8 g.) added, and the whole cooled to − 5°. Thionyl chloride (12 g.) was then added slowly with stirring so that the temperature did not rise above 0°. After standing for 1 hour, the precipitated pyridine hydrochloride was filtered at the pump and rapidly washed with a little dry ether. The acid chloride was obtained by evaporation of the ether and sulphur dioxide, care being taken that the residue was not heated above 45°. The identity of the product was proved by conversion into the amide.

Ethyl monothio-oxamate was prepared by the following modification of the recorded method (cf. Weddige, *J. pr. Chem.*, 1874, **9**, 133). A solution of ethyl cyanoformate (218 g.) in benzene (250 c.c.) was cooled to 0° and saturated with dry hydrogen sulphide; diethylamine (2 g.) was then added, and the passage of hydrogen sulphide continued until the temperature, which rose to 30—35°, had fallen to 15—20°. After standing overnight, the precipitated thio-oxamate was filtered off, washed with a small quantity of benzene, and dried at 45° (yield, 237 g.). A further quantity (25 g.) was obtained by evaporating the filtrate to dryness and triturating the residue with a little benzene. Total yield 86%, m. p. 64—65°. The use of alcohols as solvents during the reaction is to be avoided, since they produce intractable, evil-smelling oils.

Ethyl 4-Methylthiazole-2 : 5-dicarboxylate.—Ethyl α-chloroacetoacetate (257 g.) and ethyl monothio-oxamate (200 g.) were mixed and warmed gently to initiate the reaction; the source of heat was then removed, and after the reaction had moderated the mixture was heated on a steam-bath for 12 hours, then poured into water, neutralised with sodium bicarbonate, and extracted with ether. The *ester*, recovered by distillation from the dried ethereal solution, had b. p. 208°/50 mm.; m. p. 59° after crystallisation from petrol (b. p. 60—80°); yield 160 g. (43%) (Found: C, 49·3; H, 5·3; N, 5·75. $C_{10}H_{13}O_4NS$ requires C, 49·4; H, 5·35; N, 5·76%).

4-Methylthiazole-2 : 5-dicarboxydiamide.—The foregoing ethyl ester (24 g.) was suspended in ammonia (*d* 0·880; 200 c.c.) and kept for 5 days. The solid was then filtered off and crystallised first from ethanol and then from dioxan; m. p. 200° (Found: C, 39·0; H, 3·63; N, 22·4. $C_6H_7O_2N_3S$ requires C, 38·9; H, 3·78; N, 22·7%). This *amide* was also made from 4-methylthiazole-2 : 5-dicarboxydichloride by adding it to an excess of ice-cold ammonia.

The following amides of 4-methylthiazole-2 : 5-dicarboxylic acid were made from the acid chloride. *Bismethylamide*, m. p. 217° (Found: C, 45·3; H, 5·6; N, 19·1. $C_8H_{11}O_2N_3S$ requires C, 45·1; H, 5·2; N, 19·7%); *bisethylamide*, m. p. 158° (Found: C, 49·6; H, 6·15; N, 17·0. $C_{10}H_{15}O_2N_3S$ requires C, 49·7; H, 6·23; N, 17·4%); *bisdimethylamide*, b. p. 152—154°/0·1 mm. (Found: C, 49·3; H, 6·25; S, 13·3. $C_{10}H_{15}O_2N_3S$ requires C, 49·7; H, 6·23; S, 13·3%); *bisdiethylamide*, b. p. 173°/0·4 mm. (Found: C, 56·4; H, 7·4; N, 14·2; S, 11·15. $C_{14}H_{23}O_2N_3S$ requires C, 56·6; H, 7·7; N, 14·1; S, 10·8%); *bismorpholide*, m. p. 118° (Found: C, 52·4; H, 5·75; N, 12·8. $C_{14}H_{19}O_4N_3S$ requires C, 52·0; H, 5·84; N, 12·9%).

Ethyl 4-Methylthiazole-2-carboxyhydrazide-5-carboxylate and 4-Methylthiazole-2 : 5-dicarboxydihydrazide.—Ethyl 4-methylthiazole-2 : 5-dicarboxylate (20 g.) was suspended in a mixture of 50% hydrazine hydrate (15 c.c.) and water

(50 c.c.) and kept for 5 days. The *ethyl* ester was then filtered off, and crystallised first from water and then from ethanol; m. p. 166° (Found : C, 41·8; H, 5·0; N, 18·45. $C_8H_{11}O_3N_3S$ requires C, 41·9; H, 4·8; N, 18·3%). On concentrating the mother-liquors, the *dihydrazide*, m. p. 243°, was obtained (Found : C, 35·4; H, 4·7. $C_6H_9O_2N_5S$ requires C, 35·3; H, 4·8%). Only the latter was obtained by heating under reflux for 18 hours a mixture of ethyl 4-methylthiazole-2 : 5-dicarboxylate (15 g.), 50% hydrazine hydrate (20 c.c.), and water (20 c.c.).

Ethyl 5-Carbethoxy-4-methylthiazole-2-carbamate.—Ethyl 4-methylthiazole-2-carboxyhydrazide-5-carboxylate (2·3 g.) was dissolved in an excess of 10% hydrochloric acid and allowed to react for 10 minutes at 0° with a solution of sodium nitrite (10 g.) in water (15 c.c.). The reaction mixture was extracted with ether, the ethereal solution washed with sodium carbonate solution, dried over calcium chloride, filtered, and mixed with absolute alcohol (150 c.c.). The bulk of the ether was distilled off, and the residual solution heated under reflux for 3 hours. After evaporation of the alcohol, the residue was recrystallised from aqueous alcohol; yield 1·9 g. (80%) (Found : C, 46·8; H, 5·4; N, 10·8. $C_{10}H_{14}O_4N_2S$ requires C, 46·5; H, 5·4; N, 10·9%). This *ester* was also made by warming a mixture of ethyl 2-amino-4-methylthiazole-5-carboxylate (Zurcher, *Annalen*, 1889, **250**, 281) (1·9 g.) with ethyl chloroformate (0·5 g.) for 1 hour, extracting the unchanged amine with dilute hydrochloric acid, and recrystallising the residue.

4-Methylthiazole-5-carboxylic Acid.—(a) *From ethyl 4-methylthiazole-2 : 5-dicarboxylate.* The ester (21 g.) was dissolved in a mixture of industrial ethanol (150 c.c.) and 32% sodium hydroxide (30 c.c.). After being heated under reflux for 4 hours, the mixture was evaporated to dryness, the residue dissolved in water, and concentrated hydrochloric acid added until the solution was faintly acid to Congo-red; during this addition there was a brisk evolution of carbon dioxide. The precipitated acid was filtered off, but as it was appreciably soluble in water and heavily contaminated with organic matter, the filtrate was evaporated to dryness, and the residue, together with the crude acid, was extracted with ethanol, from which the acid crystallised (11·2 g.; 88%), m. p. 260° (decomp.) [Wohmann, *loc. cit.*, gives m. p. 257° (decomp.)]. (b) *From 4-methylthiazole-2 : 5-dicarboxydichloride.* The chloride was shaken in the cold with a slight excess of N-sodium hydroxide for 3 hours, and the product isolated as above. In both cases the identity of the acid was proved by conversion into its known ethyl ester (Wohmann, *loc. cit.*).

The following amides of 2 : 4-dimethylthiazole-5-carboxylic acid were made by standard methods from either (*a*) the methyl or ethyl ester or (*b*) the acid chloride.

(*a*) Amide, as *dihydrate*, m. p. 81·5° (Found : loss at 100°, 19·4. $C_6H_8O_2N_2S,2H_2O$ requires $2H_2O$, 20·1%); anhydrous *amide*, m. p. 137° (Found : C, 37·9; H, 6·25; N, 15·0; S, 16·8. $C_6H_8O_2N_2S$ requires C, 37·5; H, 6·25; N, 14·6; S, 16·7%). *Hydrazide*, m. p. 138—139° from ethyl acetate (Found : C, 42·0; H, 5·4; N, 24·8. $C_6H_9ON_2S$ requires C, 42·0; H, 5·27; N, 24·6%). Methylamide, very hygroscopic; *picrate*, from methanol, m. p. 141—142° (Found : C, 39·4; H, 3·15; N, 18·0. $C_{13}H_{13}O_8N_5S$ requires C, 39·2; H, 3·15; N, 17·6%). *Ethylamide*, m. p. 69°, from ethyl acetate (Found : C, 52·0; H, 6·7; N, 15·2; S, 17·55. $C_8H_{12}ON_2S$ requires C, 52·1; H, 6·52; N, 15·2; S, 17·4%).

(*b*) n-*Propylamide*, m. p. 39·5°, b. p. 195°/24 mm. (Found : C, 53·9; H, 7·05; N, 14·45; S, 16·3. $C_9H_{14}ON_2S$ requires C, 54·4; H, 7·05; N, 14·2; S, 16·2%). n-*Butylamide*, m. p. 17·6°, b. p. 190°/14 mm. (Found : C, 56·1; H, 7·65; N, 13·5; S, 14·8. $C_{10}H_{16}ON_2S$ requires C, 56·5; H, 7·55; N, 13·2; S, 15·1%). n-*Amylamide*, b. p. 116°/0·83 mm. (Found : C, 57·8; H, 8·1; N, 12·4; S, 14·35. $C_{11}H_{18}ON_2S$ requires C, 58·2; H, 7·96; N, 12·4; S, 14·16%). *Benzylamide*, m. p. 102° (Found : C, 63·5; H, 5·7; N, 11·1; S, 13·3. $C_{13}H_{14}ON_2S$ requires C, 63·4; H, 5·68; N, 11·4; S, 13·0%). *Dimethylamide*, b. p. 169°/25 mm. (Found : C, 52·7; H, 6·8; N, 14·8; S, 17·3. $C_8H_{12}ON_2S$ requires C, 52·3; H, 6·52; N, 15·2; S, 17·4%). *Diethylamide*, b. p. 174°/15 mm. (Found : C, 56·7; H, 7·5; N, 13·2; S, 14·8. $C_{10}H_{16}ON_2S$ requires C, 56·6; H, 7·54; N, 13·2; S, 15·1%). *Piperidide*, b. p. 192°/14 mm. (Found : C, 58·8; H, 7·05; N, 12·1. $C_{11}H_{16}ON_2S$ requires C, 58·9; H, 7·14; N, 12·5%). *Morpholide*, m. p. 66° (Found : C, 52·65; H, 6·4; N, 12·0. $C_{10}H_{14}O_2N_2S$ requires C, 53·0; H, 6·19; N, 12·3%).

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[*Received, February 9th*, 1945.]