263. *The Conversion of Sucrose into Thiazole Derivatives. Part II. 2 : 4-Dimethylthiazole Derivatives and 2 : 4 : 5-Trimethylthiazole.*

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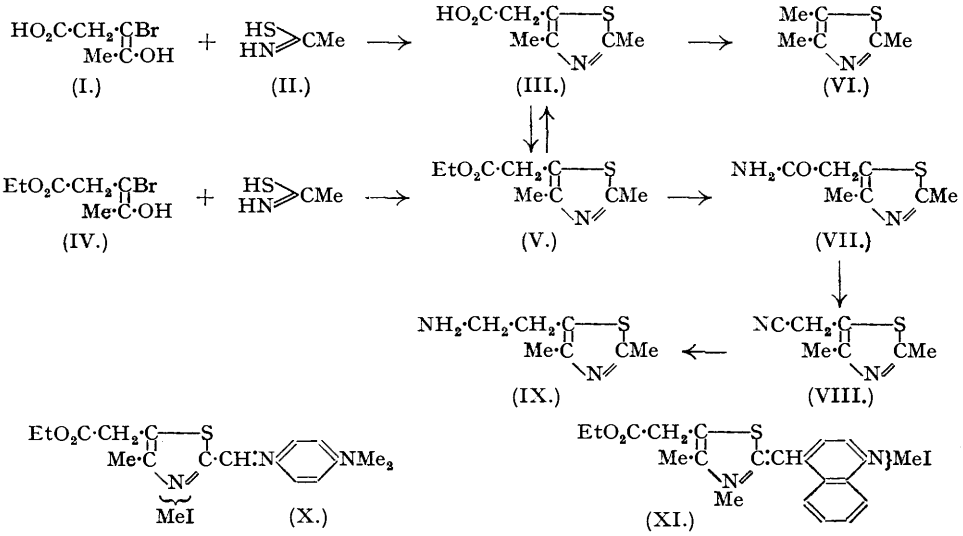
Condensation of β-bromolævulic acid and its ethyl ester with thioacetamide yields 2 : 4-*dimethylthiazole-5-acetic acid* and *ethyl* 2 : 4-*dimethylthiazole-5-acetate* respectively. Several derivatives of the latter product are described, and decarboxylation of 2 : 4-dimethylthiazole-5-acetic acid affords a convenient method for the preparation of 2 : 4 : 5-trimethylthiazole.

SUCROSE can be readily transformed into lævulic acid, and in Part I (this vol., p. 590) we described several sulphanilamidothiazoles, which were obtained through the condensation of β-bromolævulic acid and its ethyl ester with thiourea. Continuing this theme, we have now investigated the condensation of β-bromolævulic acid (I) with thioacetamide (II), whereby 2 : 4-*dimethylthiazole-5-acetic acid hydrobromide* is obtained; this is readily converted into 2 : 4-dimethylthiazole-5-acetic acid (III). The latter, on esterification, gave ethyl 2 : 4-dimethylthiazole-5-acetate (V), identical with the product of the condensation of ethyl β-bromolævulate (IV) with thioacetamide.



Decarboxylation of 2 : 4-dimethylthiazole-5-acetic acid was effected smoothly to give an 80% yield of 2 : 4 : 5-trimethylthiazole (VI). Hitherto, this trimethylthiazole has only been prepared by the condensation of thioacetamide with methyl 1-chloroethyl ketone (Roubleff, *Annalen*, 1890, **259**, 258).

Treatment of the thiazole ester with concentrated aqueous ammonia gave the corresponding *amide* (VII) which was readily dehydrated with phosphorus oxychloride to 2 : 4-*dimethyl-5-cyanomethylthiazole* (VIII). The latter, on catalytic hydrogenation over Raney nickel, was converted into 2 : 4-dimethyl-5-2′-aminoethylthiazole (IX) which, however, was unstable and could only be isolated as the *dipicrate*. In view of the previous work of Hinegardner and Johnson (*J. Amer. Chem. Soc.*, 1930, **52**, 3724), this compound should exhibit some physiological activity as a sympathomimetic agent.

It has been shown previously by Mills and Smith (*J.*, 1922, **121** 2724) that the activity of the substituent methyl group in the thiazole ring depends upon its position. Thus, whereas 4-phenyl-2-methylthiazole will condense readily with benzaldehyde and phthalic anhydride, and its quaternary ammonium salts couple with *p*-dimethylaminobenzaldehyde, its isomer, 2-phenyl-4-methylthiazole, undergoes none of these reactions. In this work we found that *ethyl* 2 : 4-*dimethylthiazole-5-acetate methiodide* underwent reaction with only 1 mole of *p*-nitrosodimethylaniline to form 4-*methyl-5-carbethoxymethylthiazole-2-aldehyde* p-*dimethylaminoanil methiodide* (X) which was a brownish-green crystalline compound with a bluish-green metallic reflex, giving rise to deep purple aqueous solutions. Similarly, ethyl 2 : 4-dimethylthiazole-5-acetate methiodide condensed with 1 mole of quinoline methiodide to give a deep red crystalline compound which, by analogy to 4-phenyl-3-methyl-2-thiazolenyl-4-quinolylmethane methiodide of Mills and Smith (*loc. cit.*), must be 3 : 4-*dimethyl-5-carbethoxymethyl-2-thiazolenyl-4-quinolylmethane methiodide* (XI).

EXPERIMENTAL.

Ethyl 2 : 4-*Dimethylthiazole-5-acetate*.—To ethyl β-bromolævulate (20·8 g.) dissolved in ethyl alcohol (20 c.c.), thioacetamide (7·0 g.) was slowly added in small portions; an exothermic reaction occurred with formation of a yellow solution. After 12 hours at room temperature, the alcohol was removed and the thick yellow syrup thus obtained dissolved in water, a few drops of hydrochloric acid (5N) were added, and the solution was extracted with ether to remove any unchanged starting materials. Ammonia (5N) was added to the aqueous solution at 0° until the solution was slightly alkaline (litmus);

a yellow oil then separated. The crude product was extracted with ether, and the ethereal layer was washed with water and dried ($MgSO_4$), and the ether removed. The residual liquid was distilled in a vacuum; *ethyl* 2 : 4-*dimethylthiazole* 5-*acetate* was thus obtained as a pale yellow liquid, b. p. 142°/15 mm, 212°/756 mm., $n_D^{18°}$ 1·4942. Yield, 11·6 g. (62·5%) (Found : C, 53·9; H, 6·1; N, 7·2; OEt, 23·1. $C_9H_{13}O_2NS$ requires C, 54·2; H, 6·5; N, 7·0; OEt, 22·6%). The *picrate* was obtained as a yellow, crystalline solid, m. p. 168° (Found : C, 42·4; H, 3·4; N, 13·1. $C_{15}H_{16}O_9N_4S$ requires C, 42·1; H, 3·7; N, 13·1%).

Condensation of β-Bromolævulic Acid with Thioacetamide.—Thioacetamide (1·0 g.) was added in portions to β-bromolævulic acid (2·25 g.) at 80°. After a few minutes, an exothermic reaction occurred, and when the mixture had cooled to room temperature, a partly solid product was obtained. This was pressed on a porous pile, and colourless crystals isolated, which were recrystallised from acetone ethyl alcohol–light petroleum (b. p. 40—60°). After two recrystallisations, pure 2 : 4-*dimethylthiazole*-5-*acetic acid hydrobromide* was obtained as colourless crystals, m. p. 183°. Yield, 1·78 g. (61·2%) (Found : C, 33·7; H, 4·3. $C_7H_{10}O_2NBrS$ requires C, 33·4; H, 4·0%).

The free base was obtained from the hydrobromide (1·5 g.) by dissolving it in water (6 c.c.) and heating under reflux for 15 minutes. The strongly acid solution was cooled, and a concentrated aqueous solution of potassium hydroxide added carefully, until, when the solution was still acid to litmus, crystals separated. These were filtered off and recrystallised from hot water; m. p. 185°. Yield, 0·93 g. (91·4%).

Esterification of 2 : 4-*Dimethylthiazole*-5-*acetic Acid.*—The acid (2·0 g.) was heated under reflux with 2% ethyl-alcoholic hydrogen chloride (50 c.c.) for 6 hours. The resulting solution was neutralised with barium carbonate, the barium salts were filtered off, and the alcoholic solution was evaporated to dryness under reduced pressure. The residue was extracted with ether, and the ethereal extract evaporated to a brown liquid which was subsequently distilled; b. p. 212°/745 mm., $n_D^{20°}$ 1·4943 (Found : OEt, 22·9. Calc. for $C_9H_{13}O_2NS$: OEt, 22·6%). Yield of ethyl 2 : 4-dimethylthiazole-5-acetate, 1·46 g. (62·7%).

2 : 4 : 5-*Trimethylthiazole.*—2 : 4-Dimethylthiazole-5-acetic acid (0·8 g.) was heated on an oil-bath in a distillation flask. At 190° (bath temp.) the crystals melted; at 235° (bath temp.) carbon dioxide was evolved and a colourless, pungent smelling liquid distilled, b. p. 164—166° (vapour temp.), $n_D^{18°}$ 1·5060. Yield of 2 : 4 : 5-trimethylthiazole, 0·49 g. (82·5%). On treatment with one mol. of picric acid, yellow needles of 2 : 4 : 5-trimethylthiazole picrate were obtained, m. p. 133—134° (Found : C, 40·4; H, 3·7. Calc. for $C_{12}H_{12}O_7N_4S$: C, 40·4; H, 3·4%). Roubleff (*loc. cit.*) gives m. p. 133°.

2 : 4-*Dimethylthiazole*-5-*acetamide.*—Ethyl 2 : 4-dimethylthiazole-5-acetate (1·0 g.) was suspended in concentrated ammonia solution (*d* 0·88; 5 c.c.), and the mixture shaken for 2 hours; a clear yellow solution was then obtained. After several hours at 0°, colourless needles separated. More crystals were obtained by concentration of the mother liquors. The total crude product recrystallised from ethyl alcohol–ether in feathery, colourless needles of 2 : 4-*dimethylthiazole*-5-*acetamide*, m. p. 173°. Yield, 0·72 g. (84·3%) (Found : C, 49·4; H, 5·5; N, 17·1. $C_7H_{10}ON_2S$ requires C, 49·4; H, 5·9; N, 16·5%). On treatment with picric acid, long needles of the *picrate* were obtained, m. p. 185° (Found : C, 39·4; H, 3·5; N, 17·4. $C_{13}H_{13}O_8N_5S$ requires C, 39·1; H, 3·3; N, 17·5%).

2 : 4-*Dimethyl*-5-*cyanomethylthiazole.*—2 : 4-Dimethylthiazole-5-acetamide (1·3 g.) was heated with phosphorus oxychloride (freshly distilled; 5 c.c.) on an oil-bath for 45 minutes at 105—115°. The phosphorus oxychloride was then removed on a water-bath at 50° under reduced pressure. To the dark syrupy residue, crushed ice was added, then solid sodium carbonate until the solution was alkaline (litmus). The dark brown solution was then exhaustively extracted with ether, the ethereal extract dried ($MgSO_4$), and the ether removed by evaporation. The crystalline residue was recrystallised from hot water to give needles of 2 : 4-*dimethyl*-5-*cyanomethylthiazole*, m. p. 87°. Yield, 1·0 g. (86%) (Found : C, 54·9; H, 4·9; N, 17·8. $C_7H_8N_2S$ requires C, 55·3; H, 5·2; N, 18·1%). The *picrate* was obtained as a yellow crystalline solid, m. p. 125° (Found : C, 40·9; H, 3·2. $C_{13}H_{11}O_7N_5S$ requires C, 40·9; H, 2·9%).

Reduction of 2 : 4-*Dimethyl*-5-*cyanomethylthiazole.*—2 : 4-Dimethyl 5-cyanomethyl thiazole (0·95 g.) was dissolved in methyl alcohol (40 c.c.) and hydrogenated over Raney nickel at room temperature. When approximately the theoretical amount of hydrogen had been absorbed and no further absorption occurred, the catalyst was filtered off and the methyl alcohol evaporated under reduced pressure in an atmosphere of nitrogen. The product decomposed on keeping but was characterised as the dipicrate. A solution of the syrup (0·2 g.) in alcohol was added to a hot concentrated aqueous solution of picric acid (0·6 g.). On cooling, an oil separated, which eventually solidified and recrystallised from hot water ln yellow crystals, m. p. 169°. It was 2 : 4-*dimethyl*-5-2′-*aminomethylthiazole dipicrate* (Found : C, 37·3; H, 3·0; N, 17·9. $C_{19}H_{18}O_{14}N_8S$ requires C, 37·1; H, 2·9; N, 18·2%).

Condensation of Ethyl 2 : 4-*Dimethylthiazole*-5-*acetate Methiodide with* p-*Nitrosodimethylaniline.*—Ethyl 2 : 4-dimethylthiazole-5-acetate (1·0 g.) was kept with methyl iodide (100% excess) at room temperature for 24 hours. The methyl iodide was then evaporated under reduced pressure. A yellow oil was obtained which slowly crystallised; it recrystallised from alcohol in colourless prisms, m. p. 133°, which decomposed too rapidly for analytical figures to be obtained.

To an alcoholic solution of ethyl 2 : 4-dimethylthiazole-5-acetate methiodide (crude oil; 1·0 g.) was added an alcoholic solution of *p*-nitrosodimethylaniline (0·5 g.), whereby a bright green solution was obtained. Piperidine (2 drops) was added; the colour changed to reddish brown, and the solution was heated under reflux for 15 minutes; a purple colouration had then developed. On cooling, crystals separated and were filtered off (0·3 g.). The solution was again heated for a further 2 hours, and on cooling, more crystals were obtained (0·2 g.). The crude product was recrystallised from aqueous methyl alcohol, and 4-*methyl*-5-*carbethoxymethylthiazole*-2-*aldehyde* p-*dimethylaminoanil methiodide* was obtained as a brownish-green crystalline compound with a bluish-green metallic reflex, m. p. 208°. In dilute aqueous or alcoholic solution the crystals gave a deep purple colouration, which was easily discharged by acids and regenerated by alkali (Found : C, 45·9; H, 5·5. $C_{18}H_{24}O_2N_3IS$ requires C, 45·7; H, 5·1%).

Condensation of Ethyl 2 : 4-*Dimethylthiazole*-5-*acetate Methiodide with Quinoline Methiodide.*—To ethyl 2 : 4-dimethylthiazole-5-acetate methiodide (crude oil; 1·0 g.) dissolved in ethyl alcohol (10 c.c.) was added an alcoholic solution of quinoline methiodide (1·7 g.; 100% excess) and sodium hydroxide (0·17 g.). The solution was heated under reflux for 30 minutes; a vivid red colouration had then developed. On cooling, a semi-solid product separated, which was recrystallised from methyl alcohol to give 3 : 4-*dimethyl*-5-*carbethoxymethyl*-2-*thiazolenyl*-4-*quinolylmethane methiodide* as dark red crystals with a bright green, metallic reflex, m. p. 200°. Yield, 0·35 g. (Found: C, 50·3; H, 5·1; N, 6·2. $C_{20}H_{23}O_2N_2IS$ requires C, 49·8; H, 4·8; N, 5·8%).

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