

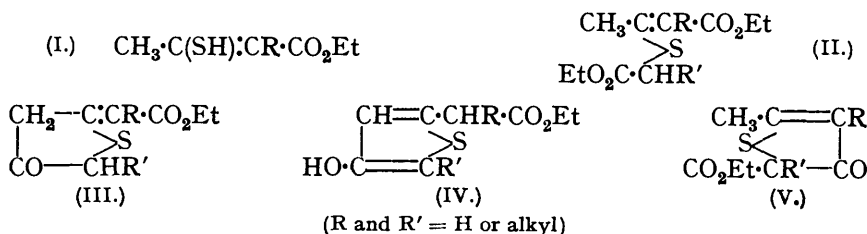
261. *Preparation of Thiophen Derivatives. Part II.*

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Thioethers formed by the condensation of β -thioketonic esters with α -halogenated fatty esters have been utilised in the synthesis of hydroxythiophens.

ETHYL carbethoxylævulate cyclises easily to the thiophen derivative during thionation (Mitra, Chakrabarty, and Mitra, J., 1939, 1116). Similar results have been obtained with

unsubstituted and $\alpha\beta$ -substituted lævulates but in a low yield. An alternative route to thiophen derivatives starts from β -thioketonic esters (I; R = H or alkyl) :



The condensation of an α -halogenated fatty ester with the sodio-derivative of (I) yields the thioether (II) (cf. Mitra, *J. Indian Chem. Soc.*, 1938, 15, 31). In presence of emulsified sodium (II) gives the ketone (III), which undergoes internal rearrangement to the hydroxythiophen (IV). The carbethoxy-group of the crotonic residue in (II) does not take part in the cyclisation, since (II; R = H, R' = Me) gives the hydroxythiophen (IV; R = H, R' = Me) and not the ketone (V; R = H, R' = Me), as the product gives a coloration with ferric chloride. One of the malonic carbethoxy-groups in the thioether (II; R' = Me; R = CO₂Et) is eliminated during ring formation and the hydroxythiophen (IV; R = H, R' = Me) is formed. These hydroxythiophens are markedly more acidic than phenols, readily giving alkali-metal salts and forming intense violet colorations with ferric chloride. Treatment with thionyl chloride readily replaces hydroxyl by chlorine; the chloro-compounds, unlike chlorobenzene, are hydrolysed like acid chlorides on boiling with water. They are etherified by normal methods.

EXPERIMENTAL.

Preparation of Thiophencarboxylic Acids from Lævulates.—The thionation of the lævulate was carried out as described by Mitra, Chakrabarty, and Mitra (*loc. cit.*). The oil obtained on removal of the benzene was hydrolysed with excess of baryta, and the material obtained on acidification crystallised from alcohol. Yield, 20—25%. The hydroxythiophen first formed reacted with the alcoholic solvent to give the corresponding ether.

5-Ethoxy-2-methyl-4-ethylthiophen-3-carboxylic acid, from ethyl β -carbethoxy- α -ethyl-lævulate, formed colourless needles, m. p. 105° (Found: S, 15.3. C₁₀H₁₄O₃S requires S, 14.9%). Ethyl $\alpha\beta$ -dicarbethoxylævulate lost the α -carbethoxy-group during thionation, since the thiophen obtained was identical with 5-ethoxy-2-methylthiophen-3-carboxylic acid (*loc. cit.*). *5-Ethoxy-2:4-dimethylthiophen-3-carboxylic acid*, from ethyl β -carbethoxy- α -methyl-lævulate, formed colourless needles, m. p. 125° (Found: S, 16.1. C₉H₁₂O₃S requires S, 16.0%); on de-ethylation with hydrobromic acid (*d* 1.8) it gave *5-hydroxy-2:4-dimethylthiophen-3-carboxylic acid*, which formed colourless needles, m. p. 140° (Found: S, 19.0. C₇H₈O₃S requires S, 18.6%).

5-Ethoxy-2-methylthiophen.—Lævulic acid (25 g.) was dissolved in absolute alcohol (200 c.c.) saturated with dry hydrogen chloride at 0°, and hydrogen sulphide passed in for 24 hours. The mixture was poured on ice and extracted with benzene. The portion, b. p. 120°/6 mm., of the product responded to the indophenin test and did not give a coloration with ferric chloride (Found: S, 23.0. C₇H₁₀OS requires S, 22.5%).

Thioethers (II).—The thioketonic ester (I) was dissolved in benzene and added slowly to emulsified sodium in benzene suspension at 0°. The sodio-derivative was left at 25° for 8 hours, the α -halogenated fatty ester then added, and the mixture refluxed for 6 hours. The ether was extracted with benzene and distilled under reduced pressure.

Ethyl β -(α' -carbethoxyethylthio)crotonate (II; R = H, R' = Me), from ethyl thioacetoacetate (25 g.) and ethyl α -bromopropionate (30 g.), had b. p. 124°/5 mm. (Found: S, 13.3. C₁₁H₁₈O₄S requires S, 13.0%). *Ethyl α -(α' -carbethoxyethylthio)ethylidenemalonate* (II; R = CO₂Et, R' = Me), from ethyl thioacetylmalonate (I; R = CO₂Et) (30 g.) and α -bromopropionic ester (30 g.), had b. p. 125°/5 mm. (Found: S, 9.8. C₁₄H₂₂O₆S requires S, 10.1%). *Ethyl β -carbethoxy-methylthiocrotonate* (II; R = R' = H), from ethyl thioacetoacetate (50 g.) and ethyl chloroacetate (42 g.), had b. p. 116°/9 mm. (Found: S, 14.2. C₁₀H₁₆O₄S requires S, 13.8%).

Hydroxythiophens.—The thioether (II) was dissolved in dry benzene (6 vols.) containing a few drops of alcohol. A small portion of the mixture was added to emulsified sodium (1 mol.) suspended in dry benzene (25°). After the reaction had abated, the mixture was kept at 0°,

the remaining thioether gradually added, and the whole kept (8 hours) until the sodium had dissolved. After addition of aqueous alcohol the precipitate was filtered off, washed with alcohol and benzene and acidified, and the liberated hydroxythiophen extracted with benzene.

Ethyl 3-hydroxythiophen-5-acetate (IV; R = R' = H), obtained from (II; R = R' = H) (25 g.), had b. p. 96°/5 mm. (Found: C, 51.3; H, 5.5; S, 17.4. C₈H₁₀O₃S requires C, 51.6; H, 5.4; S, 17.2%). *Ethyl 3-hydroxythiophen-5- α -propionate* (IV; R = Me, R' = H), obtained from (II; R = Me, R' = H) (18 g.), had b. p. 116°/5 mm. and solidified in colourless cubes, m. p. 53° (Found: C, 54.3; H, 6.0; S, 15.7. C₉H₁₂O₃S requires C, 54.0; H, 6.0; S, 16%). *Ethyl 3-hydroxy-2-methylthiophen-5-acetate* (IV; R = H, R' = Me), from (II; R = H, R' = Me) (25 g.), was a pale yellow oil, b. p. 104°/5 mm. (Found: S, 15.5. C₉H₁₂O₃S requires S, 16.0%). The corresponding acid was also obtained from the thioether (II; R = CO₂Et, R' = Me) (10 g.).

Ethyl 3-Chlorothiophen-5-acetate.—The thiophen (IV; R = R' = H) (7 g.) was dissolved in thionyl chloride (15 c.c.) and left at 25° for 12 hours. On removal of thionyl chloride under reduced pressure a yellow oil, b. p. 128°/8 mm., remained (Found: Cl, 17.17. C₈H₉O₂ClS requires Cl, 17.35%).

Ethyl 3-Ethoxythiophen-5-acetate.—The thiophen (IV; R = R' = H) (10 g.), dissolved in dry benzene (50 c.c.), was gradually added to emulsified sodium (1.8 g. in 100 c.c. of benzene) and kept at 25° for 6 hours. Ethyl iodide (33.5 g.) was added, and the mixture refluxed for 8 hours. The benzene extract gave an oil, b. p. 102°/5 mm. (Found: S, 14.5. C₁₀H₁₄O₃S requires S, 14.9%).

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