

161. The Acylation of 4-Hydroxy-3-carbethoxy-2-methylthiophen.

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An acyl group can be readily introduced into 4-hydroxy-3-carbethoxy-2-methylthiophen by the Friedel-Crafts method.

THE introduction of an acyl group into the thiophen nucleus under Friedel-Crafts conditions has been described only for the parent compound and its simple homologues. It is of interest to record an application of the reaction to a more highly substituted thiophen nucleus, namely, 4-hydroxy-3-carbethoxy-2-methylthiophen ($R = C_2H_5$; $R' = H$). This substance reacts with acid chlorides in the presence of aluminium chloride in nitrobenzene to give the corresponding 5-acyl derivatives. In this way 5-aceto-, 5-chloroaceto-, and 5-stearo-4-hydroxy-3-carbethoxy-2-methylthiophen ($R = C_2H_5$; $R' = Ac, Cl\cdot CH_2\cdot CO\cdot$, and $C_{17}H_{35}\cdot CO\cdot$) have been prepared.

4-Hydroxy-3-carbethoxy-2-methylthiophen itself, by reacting possibly in the keto-form, undergoes considerable resinification on treatment with alkalis (Benary and Baravian, *Ber.*, 1915, **48**, 593). No tendency to polymerize, however, is shown by the 5-aceto- and 5-stearo-derivatives, and these are readily hydrolysed with aqueous alcoholic potassium hydroxide in almost quantitative yield to 5-aceto-, and 5-stearo-4-hydroxy-3-carboxy-2-methylthiophen ($R = H$; $R' = Ac$; and $C_{17}H_{35}\cdot CO$). With the 5-chloroaceto-derivative, as is to be expected from the reactivity of the substituent group, a complex reaction occurs with alkalis, and the acid could not be obtained by hydrolysis. An acid which on analysis appeared to be the monohydrate of 4-hydroxy-3-carboxy-5-chloroaceto-2-methylthiophen ($R = H$; $R' = ClCH_2\cdot CO$) was isolated as a by-product of the Friedel-Crafts reaction. The molecule of water could not be removed from the acid, but the latter yielded an ethyl ester identical with that described above.

EXPERIMENTAL.

4-Hydroxy-3-carbethoxy-5-aceto-2-methylthiophen.—Aluminium chloride (40.2 g., 3 mol.) in nitrobenzene (200 c.c.) was added to 4-hydroxy-3-carbethoxy-2-methylthiophen (18.6 g., 1 mol.) (Benary and Baravian, *loc. cit.*) and acetyl chloride (11.8 g., 1.5 mol.) in nitrobenzene (100 c.c.). The mixture was heated on a boiling water bath for 4 hours and, when cool, was poured on to a mixture of crushed ice (600 g.) and concentrated sulphuric acid (30 c.c.). The nitrobenzene, together with some of the unchanged thiophen ester, was removed with steam. The residue was crystallised from alcohol (charcoal) to give colourless prisms (10 g.), m. p. 101—102° (Found: C, 53.0; H, 5.4; S, 14.1. $C_{10}H_{12}O_4S$ requires C, 52.6; H, 5.3; S, 14.05%).

4-Hydroxy-3-carboxy-5-aceto-2-methylthiophen.—The above ester (1 g.) in alcohol (40 c.c.) was refluxed with potassium hydroxide (0.8 g.) in water (3 c.c.) for 15 minutes. After acidification with hydrochloric acid, the whole was poured into water and the solid product collected and dried (wt., 0.85 g.). The acid was insoluble in alcohol, ligroin, benzene, chloroform, and ethyl acetate, but crystallised from glacial acetic acid in colourless prisms, m. p. ca. 265° (decomp.) (Found: C, 47.9; H, 4.25; S, 15.8. $C_8H_8O_4S$ requires C, 48.0; H, 4.0; S, 16.0%).

4-Hydroxy-3-carbethoxy-5-chloroaceto-2-methylthiophen.—Aluminium chloride (24 g., 3 mol.) in nitrobenzene (100 c.c.) was added to 4-hydroxy-3-carbethoxy-2-methylthiophen (11.2 g., 1 mol.) and chloroacetyl chloride (8.2 g., 1.2 mol.) in nitrobenzene (50 c.c.). The mixture was heated on a boiling water bath for 6 hours, and when cool, poured on to crushed ice (400 g.) and concentrated sulphuric acid (15 c.c.). The nitrobenzene was removed with steam and the residue triturated with 2N sodium carbonate solution (20 c.c.), collected, and washed with water. The material, containing much

tarry impurity, was crystallised twice from alcohol (charcoal) giving colourless needles (2.5 g.), m. p. 145° (Found: C, 45.7; H, 4.2; S, 12.2; Cl, 13.45. $C_{10}H_{11}O_4S$ requires C, 45.7; H, 4.2; S, 12.2; Cl, 13.5%).

4-Hydroxy-3-carboxy-5-chloroaceto-2-methylthiophen.—The sodium carbonate extract of the above ester was acidified with hydrochloric acid and the precipitate collected. The product was crystallised twice from aqueous alcohol (charcoal) to give colourless needles (1.5 g.), m. p. ca. 195° (decomp.). This is probably the monohydrate of *4-hydroxy-3-carboxy-5-chloroaceto-2-methylthiophen* (Found: C, 38.4; H, 3.5; S, 12.8; Cl, 14.1. $C_8H_7O_4S \cdot H_2O$ requires C, 38.0; H, 3.6; S, 12.7; Cl, 14.1%). Neither crystallisation from benzene, nor sublimation at 150°/10⁻⁵ mm. served to remove a molecule of water from the acid.

The acid was converted to its ester as follows. A small amount of the substance was heated to ca. 60° with thionyl chloride. After a few minutes the excess thionyl chloride was boiled off and the residual acid chloride decomposed with alcohol. The product, recrystallised from alcohol, had m. p. 145°, not depressed by admixture with authentic 4-hydroxy-3-carboxy-5-chloroaceto-2-methylthiophen.

Attempts to hydrolyse the latter ester were unsuccessful. Little reaction occurred on shaking the compound with 3 equivalents of *N* NaOH at room temperature for 48 hours; heating with alkalis gave only resinous products.

4-Hydroxy-3-carbethoxy-5-stearo-2-methylthiophen.—Aluminium chloride (40.2 g., 3 mol.) in nitrobenzene (200 c.c.) was added to 4-hydroxy-3-carbethoxy-2-methylthiophen (18.6 g., 1 mol.) and stearyl chloride (30.2 g., 1 mol.—from stearic acid, m. p. 69°) in nitrobenzene (100 c.c.). The mixture was heated at 105–110° for 2½ hours and when cool, the product was poured on to crushed ice (600 g.) and concentrated sulphuric acid (30 c.c.). The nitrobenzene was removed with steam and the residue was crystallised from glacial acetic acid (70 c.c.), yielding a mixture (32 g.) of stearic acid and the desired compound. The crystals were dissolved in alcohol (400 c.c.) and calcium chloride (8 g.) in alcohol (200 c.c.) was added. The solution was then made just alkaline to litmus by the dropwise addition of ammonium hydroxide solution (0.880) and the precipitate of calcium stearate was collected. The filtrate was evaporated to a small bulk under reduced pressure, diluted with water and the separated solid collected. After drying in a vacuum desiccator, the two products were combined and extracted with hot ligroin (b. p. 60–80°) and then with benzene. (Treatment of the solid with benzene without the initial ligroin extraction caused gel formation.) The extracts were combined and the solvent evaporated. The solid residue (13 g.) would not crystallise satisfactorily (due probably to contamination with calcium salts) until it had been boiled for a few minutes with dilute hydrochloric acid, after which it separated from ligroin (b. p. 60–80°) in well-formed crystals. Two crystallisations from this solvent and one from alcohol gave colourless prisms (9 g.), m. p. 61–62° (Found: C, 68.6; H, 9.4; S, 7.3. $C_{26}H_{44}O_4S$ requires C, 69.0; H, 9.8; S, 7.1%).

4-Hydroxy-3-carboxy-5-stearo-2-methylthiophen.—The above ester (7 g.) in alcohol (100 c.c.) was refluxed with potassium hydroxide (2.5 g.) in water (10 c.c.) for 30 minutes. Water (100 c.c.) was added, and the refluxing continued for a further 30 minutes, when a clear solution was obtained. The hot solution was acidified with hydrochloric acid and the whole poured into water. The solid was collected and dried (wt., 6.3 g.) m. p. 128–131°. Crystallisation from benzene gave colourless plates (6 g.) m. p. 132–133° (Found: C 67.8; H 8.9; S, 7.6. $C_{24}H_{40}O_4S$ requires C, 67.9; H, 9.4; S, 7.6%).

Each of the above 3-carbethoxy- and 3-carboxy-4-hydroxy-5-acyl-2-methylthiophens gave an intense violet colour with alcoholic ferric chloride. The enol group of the 5-aceto- and 5-stearo-esters is titratable in alcoholic solution with standard sodium hydroxide solution, using phenolphthalein as indicator. With the 5-chloroaceto-ester the end-point is obscured by the formation of colour attending the resinification of the compound.

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