203. *Aluminium Chloride, a New Reagent for the Condensation of β-Ketonic Esters with Phenols. Part II. The Condensation of 2 : 4-Dihydroxy-5-ethylbenzoic Acid and its Methyl Ester with Ethyl Acetoacetate.*

By S. M. SETHNA and R. C. SHAH.

Ethyl acetoacetate condenses with 2 : 4-dihydroxy-5-ethylbenzoic acid and its methyl ester in presence of aluminium chloride to give 5-*hydroxy*-4-*methyl*-8-*ethylcoumarin*-6-*carboxylic acid* and its *methyl* ester respectively, thus supporting by analogy the constitutions assigned to the condensation products of β-resorcylic acid and methyl β-resorcylate with ethyl acetoacetate (this vol., p. 228).

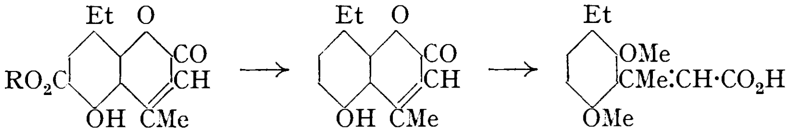
IN continuation of the work described in Part I (this vol., p. 228) we have condensed ethyl acetoacetate with methyl 2 : 4-dihydroxy-5-ethylbenzoate and obtained *methyl* 5-*hydroxy*-4-*methyl*-8-*ethylcoumarin*-6-*carboxylate* (I, R = Me). This ester on hydrolysis gave an acid, $C_{13}H_{12}O_5$ (I, R = H), m. p. 242°, which on decarboxylation gave a *compound*,

$C_{12}H_{12}O_3$, m. p. 212—213°. The decarboxylated product was converted into a *methylated cinnamic acid*, $C_{14}H_{18}O_4$ (III), by a modification of Robertson and Canter's method (J., 1931, 1875), and was thus shown to be a derivative of coumarin, not of chromone.

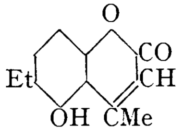
Of the two alternative constitutions for the decarboxylated product, namely, (II) and (IV), the latter is excluded because the substance is not identical with 5-hydroxy-4-methyl-6-ethylcoumarin, m. p. 174—175°, obtained by the Clemmensen reduction of 5-hydroxy-6-acetyl-4-methylcoumarin (Sethna, Shah, and Shah, this vol., p. 228). This leads to the constitutions (I, R = Me) and (I, R = H) for the ester and the acid respectively, thus definitely showing that the 4-hydroxyl group of the benzoic acid derivative takes part in the ring closure. This supports by analogy the constitutions assigned to the condensation products of methyl β-resorcylate and β-resorcylic acid with ethyl acetoacetate described in Part I (*loc. cit.*).

When 2 : 4-dihydroxy-5-ethylbenzoic acid was condensed with ethyl acetoacetate in the presence of aluminium chloride, 5-*hydroxy*-4-*methyl*-8-*ethylcoumarin*-6-*carboxylic acid* (I, R = H) was obtained.

When the preceding condensations were effected with sulphuric acid instead of aluminium chloride, the same products were obtained, but in inferior yields.



(I.) (II.) (III.)



(IV.)

EXPERIMENTAL.

2 : 4-*Dihydroxy*-5-*ethylbenzoic Acid and its Methyl Ester*.—The acid was prepared from 4-ethylresorcinol by Shah and Samant's method (unpublished work; cf. Desai and Hamid, *Proc. Indian Acad. Sci.*, 1937, **6**, *A*, 287). A mixture of 4-ethylresorcinol (100 g.), potassium hydrogen carbonate (500 g.), and water (1000 c.c.) was heated on a water-bath for 2½ hours and then on a wire gauze for ½ hour, cooled, and neutralised with concentrated hydrochloric acid. The product crystallised from water in long needles (40 g.), m. p. 187—188° (efferv.).

The methyl ester was prepared by refluxing the acid (18 g.), methyl alcohol (75 c.c.), and sulphuric acid (5 c.c.) for 24 hours on a water-bath. It crystallised from aqueous methyl alcohol in clusters of tiny needles (12 g.), m. p. 127—128°.

Methyl 5-*Hydroxy*-4-*methyl*-8-*ethylcoumarin*-6-*carboxylate* (I, R = Me).—Methyl 2 : 4-dihydroxy-5-ethylbenzoate (11·5 g.; 1 mol.) and ethyl acetoacetate (10 g.; 1·3 mols.) were dissolved in hot dry nitrobenzene (20 c.c.), a solution of anhydrous aluminium chloride (16 g.; 2 mols.) in hot nitrobenzene (60 c.c.) added, and the mixture heated at 130—140° for about an hour, the evolution of hydrogen chloride then being negligible. The product was cooled, ice and concentrated hydrochloric acid (10 c.c.) added, and the nitrobenzene distilled in steam. The residual brown mass crystallised from rectified spirit in pale yellow needles (7·5 g.), m. p. 186—187° (Found : C, 64·1; H, 5·4. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·3%). The *ester* was sparingly soluble in alcohols and in 10% sodium hydroxide solution. It gave with alkali a deep yellow colour without fluorescence, characteristic of 5-hydroxycoumarins (Collie and Chrystall, J., 1907, **91**, 1804; Dey, J., 1915, **107**, 1614, 1621), and an intense violet coloration with alcoholic ferric chloride.

The *acetyl* derivative, prepared by refluxing the ester (0·5 g.) with sodium acetate (1 g.) and acetic anhydride (3 c.c.) for 3 hours, crystallised from rectified spirit in pointed needles, m. p. 183—185° (Found : C, 63·8; H, 5·3. $C_{16}H_{16}O_6$ requires C, 63·2; H, 5·3%). The *benzoyl* derivative, prepared by the pyridine–benzoyl chloride method, crystallised from alcohol in colourless needles, m. p. 154—156° (Found : C, 68·8; H, 5·0. $C_{21}H_{18}O_6$ requires C, 68·9; H, 4·9%). The *methyl* ether, prepared by refluxing a solution of the ester in acetone (50 c.c.) for 24 hours with fused potassium carbonate (1 g.) and methyl iodide (3 c.c.), crystallised from dilute alcohol in needles, m. p. 87—88° (Found : C, 65·1; H, 5·9. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%).

5-*Hydroxy*-4-*methyl*-8-*ethylcoumarin*-6-*carboxylic Acid* (I, R = H).—(A) The ester (1 g.) was heated in a sealed tube at 125—130° for 3 hours with glacial acetic acid (10 c.c.) and concentrated hydrochloric acid (10 c.c.). The product crystallised from rectified spirit in faint yellow needles, m. p. 242° (efferv.) (Found : C, 62·8; H, 5·0. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%).

(B) The ester (0·5 g.) was shaken with sodium hydroxide solution (10%; 20 c.c.) and kept for 60 hours, the solution then obtained was acidified with concentrated hydrochloric acid, and the product crystallised from rectified spirit, forming needles (0·25 g.), m. p. and mixed m. p. with the product from (A) 242° (efferv.).

The *phenyl* ester was prepared by refluxing the *acid* (1 g.), phenol (1 g.), and acetic anhydride (8 c.c.) for 3½ hours on a wire gauze. The product obtained on addition of the mixture to water was washed with dilute sodium hydroxide solution and crystallised from rectified spirit, forming tiny colourless needles (0·3 g.), m. p. 134—135° (Found : C, 70·0; H, 4·9. $C_{19}H_{16}O_5$ requires C, 70·4; H, 4·9%). It was insoluble in alkali and gave a violet coloration with alcoholic ferric chloride.

5-*Hydroxy*-4-*methyl*-8-*ethylcoumarin* (II).—(A) The ester (I, R = Me) (2 g.) was heated in a sealed tube with glacial acetic acid (15 c.c.), water (15 c.c.), and concentrated hydrochloric acid (10 c.c.) at 170—180° for 6—7 hours. The product crystallised from 60% alcohol (charcoal) in colourless tiny needles (1 g.), m. p. 212—213° (Found : C, 69·8; H, 5·8. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). A mixture with 5-hydroxy-4-methyl-6-ethylcoumarin, m. p. 174—175° (Sethna, Shah, and Shah, *loc. cit.*), melted below 160°. 5-*Hydroxy*-4-*methyl*-8-*ethylcoumarin* dissolved in alkali to an intense yellow solution. It did not give a ferric chloride coloration.

(B) The acid (I, R = H) (0·5 g.) was heated with water (40 c.c.) in a sealed tube for 7 hours at 180—185°. The brown product crystallised from 60% alcohol (charcoal) in colourless tiny needles, m. p. and mixed m. p. with (A) 212—213°.

(C) The acid (I, R = H) was quantitatively and conveniently decarboxylated at its m. p.

The *acetyl* derivative, prepared by refluxing (II) (0·5 g.) with sodium acetate (1 g.) and acetic anhydride (2 c.c.) for 3 hours, crystallised from 60% alcohol in tiny needles, m. p. 112—114° (Found : C, 68·0; H, 5·7. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). The *benzoyl* derivative, prepared by the pyridine–benzoyl chloride method, crystallised from rectified spirit in long colourless needles, m. p. 173—174° (Found : C, 73·9; H, 5·2. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%). The *methyl* ether, prepared by means of methyl sulphate and cold sodium hydroxide solution, crystallised from dilute alcohol in clusters of tiny needles, m. p. 107—109° (Found : C, 71·1; H, 6·3. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%).

2 : 6-*Dimethoxy*-β-*methyl*-3-*ethylcinnamic Acid* (III).—Attempts to obtain the cinnamic acid derivative by Robertson and Canter's method (*loc. cit.*), by heating the substance in an alkaline solution for a few minutes and then adding methyl sulphate, were unsuccessful. The following modified method was therefore used with good results. 5-Hydroxy-4-methyl-8-ethylcoumarin (0·5 g.) was dissolved in acetone, methyl sulphate (2 c.c.) added, and the mixture heated on a boiling water-bath. Sodium hydroxide (5%; 20 c.c.) was then added gradually with constant shaking, followed by more methyl sulphate and sodium hydroxide, the heating being continuous. The *product* obtained on acidification crystallised from water, containing a little alcohol, in tiny silky needles, m. p. 119—121°. It decolourised bromine water and dilute potassium permanganate solution (Found : C, 67·0; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

The methylated cinnamic acid derivative obtained from 5-hydroxy-4-methyl-6-ethylcoumarin by the same method melted at 119—120° and did not depress the m. p. of the preceding compound.

Condensation of 2 : 4-*Dihydroxy*-5-*ethylbenzoic Acid with Ethyl Acetoacetate in Presence of Aluminium Chloride.*—The acid (5 g.; 1 mol.), ethyl acetoacetate (4·5 g.; *ca.* 1·3 mols.), and aluminium chloride (8 g.), dissolved in dry nitrobenzene (40 c.c.), were heated for an hour at 120—130°, and the reaction mixture worked up as in the case of methyl 2 : 4-dihydroxy-5-ethylbenzoate. The product crystallised from rectified spirit (charcoal) in pale yellow needles (1·6 g.), m. p. and mixed m. p. with the acid obtained by the hydrolysis of (I, R = Me) 242° (efferv.).

Condensation of 2 : 4-*Dihydroxy*-5-*ethylbenzoic Acid and its Methyl Ester with Ethyl Acetoacetate in Presence of Sulphuric Acid.*—(a) To a mixture of methyl 2 : 4-dihydroxy-5-ethylbenzoate (5 g.) and ethyl acetoacetate (4 g.), sulphuric acid (80%; 30 c.c.) was gradually added with shaking and after 40 hours the mixture was poured into ice-cold water. The product was treated with sodium bicarbonate solution; the insoluble portion crystallised from rectified spirit in clusters of tiny needles (1·6 g.), m. p., and mixed m. p. with methyl 5-hydroxy-4-methyl-8-ethylcoumarin-6-carboxylate obtained by the aluminium chloride method, 186—187°. The sodium bicarbonate solution on acidification with concentrated hydrochloric acid gave 5-hydroxy-4-methyl-8-ethylcoumarin-6-carboxylic acid, which crystallised from rectified spirit in needles (1·5 g.), m. p. and mixed m. p. 242° (efferv.).

(b) 2 : 4-Dihydroxy-5-ethylbenzoic acid (3 g.) was mixed with ethyl acetoacetate (2·5 g.), and concentrated sulphuric acid (15 c.c.) gradually added with shaking. The mixture was kept for 50 hours and then poured into ice-cold water. The product crystallised from rectified spirit in needles (0·6 g.), m. p., and mixed m. p. with 5-hydroxy-4-methyl-8-ethylcoumarin-6-carboxylic acid obtained from the aluminium chloride experiment, 242° (efferv.).

All the analyses recorded are microanalyses by Dr. Schoeller.

ROYAL INSTITUTE OF SCIENCE, BOMBAY.
ISMAIL COLLEGE, ANDHERI, BOMBAY.

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