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Studies in the Synthesis of Cyclohexenocoumarins. Part I

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β-(2:4-Dihydroxybenzoyl) propionic acid obtained from resorcinol on succinoylation and Clemmensen reduction has yielded butyric acid derivative. This on Pechmann reaction with ethyl acetoacetate, has furnished 7-hydroxy-4-methylcoumarin-6-butyric acid. The methyl ether has been cyclised to 7-methoxy-4-methyl-4'-ketocyclohexeno (5', 6'-5, 6)coumarin in poor yield using polyphosphoric acid or anhydrous aluminium chloride as cyclising agents.

Sen and Basu[1] condensed different phenols with ethyl cyclohexanone-2-carboxylate in the presence of conc. sulphuric acid and obtained corresponding cyclohexeno (1',2'-4,3)-coumarin derivatives. Chowdhry and Desai[2] prepared different cyclohexenocoumarins by the condensation of phenols with cyclic β-ketonic esters using phosphorus oxychloride, anhydrous aluminium chloride and sulphuric acid as condensing agents. It was thought of interest to synthesise different cyclohexenocoumarins in which cyclohexene ring is fused in 5,6-positions of the coumarin ring systems.

Resorcinol on succinoylation at room temperature gave β-(2,4-dihydroxybenzoyl)-propionic acid[3] which on Clemmonsen reduction afforded γ-(2,4-dihydroxyphenyl)butyric acid[4,5]. The above acid on Pechamann reaction with ethyl acetoacetate and sulphuric acid gave 7-hydroxy-4-methylcoumarin-6-butyric acid and its ethyl ester. The structure of the latter was proved by esterification of the former with ethanol and sulphuric acid as also by hydrolysis. This ester on methylation gave ethyl 7-methoxy-4-methylcoumarin-6-butyrate which on treatment with sodium hydroxide solution and excess of dimethyl sulphate furnished the corresponding cinnamic acid, thus confirming the coumarin structures assigned to these products.

This is a unique case of esterification taking place during the Pechmann condensation. The Pechmann condensation of β-resorcylic acid with ethyl acetoacetate and sulphuric acid as condensing agent gave the decarboxylated product rather than the esterfied one.[6] In order to study this esterification process further, the acid was condensed with ethyl benzoyl acetate in the presence of sulphuric acid when it gave 7-hydroxy-4-phenyl-coumarin-6-butyric acid and its ethyl ester. Similar condensation with methyl acetoacetate afforded 7-hydroxy-4-methylcoumarin-6-butyric acid and its methyl ester. The structure of the methyl ester was proved by hydrolysis to the above acid and also by esterification of the acid with methanol and concentrated sulphuric acid.

1. Sen and Basu, *this Journal*, 1928, **5**, 467.
2. Chowdhry and Desai, *Proc. Indian Acad. Sci.*, 1938, **8A**, 1.
3. Desai and Shroff, *J. Uni. Bombay*, 1941, **10**, 397.
4. Desai and Figueredo, *Proc. Indian Acad. Sci.*, 1941, **14A**, 605.
5. Brown *et al.*, *Ber.*, 1941, **74B**, 1772.
6. Shah, *et al.*, *this Journal* 1937, **14**, 717.

7-Hydroxy-4-methylcoumarin-6-butyric acid on methylation gave methyl-7-methoxycoumarin-6-butyrate which on hydrolysis with 6% sodium hydroxide solution yielded 7-methoxy-4-methylcoumarin-6-butyric acid. This acid on cyclisation furnished 7-methoxy-4-methyl-4'-ketocyclohexeno(5',6'-5,6)coumarin in very poor yield by using either polyphosphoric acid or by Johnson's inverse process of cyclisation with phosphorus pentachloride and anhydrous aluminium chloride[7].

EXPERIMENTAL

γ-(2,4-Dihydroxyphenylbutyric Acid.—β-(2,4-Dihydroxybenzoyl) propionic acid was prepared by succinoylation of resorcinol according to Desai and Shroff[3].

The above acid (10 g.) was heated with zinc amalgam (30 g.) and hydrochloric acid (conc. 75 ml) for 15 hr. γ-(2,4-Dihydroxyphenyl) butyric acid was extracted with ether and crystallised from benzene as colorless crystals, m.p. 111°. Julis *et al.*[5] have reported the reduced acid as a viscous oil but Desai and Figueredo[4] have reported m.p. 105°.

7-Hydroxy-4-methylcoumarin-6-butyric Acid and its Ethyl Ester.—γ-(2,4-Dihydroxyphenyl)butyric acid (6 g.) was mixed with ethyl acetoacetate (6 g.) and 80% sulphuric acid (25 ml) in the cold. Next day it was poured on ice water. The product was treated with bicarbonate solution and filtered. The filtrate on acidification gave an *acid* which was crystallised from acetic acid in shining needles, m.p. 230°, yield 5.4 g. (Found : C, 64.25; H, 5.47. $C_{14}H_{14}O_5$ requires C, 64.11 ; H, 5.38%). The residue was found to be *ethyl 7-hydroxy-4-methylcoumarin-6-butyrate* which was crystallised from dil. ethanol in shining plates, m.p. 153°, yield 0.2 g. (Found : C, 66.19 ; H, 6.25. $C_{16}H_{18}O_5$ requires C, 66.2 ; H, 6.2%). The ester (0.5 g.) was hydrolysed whith 6% sodium hydroxide solution (15 ml). Next day it was filtered and acidified. It was crystallised from acetic acid in shining needles; m.p. of this acid and the acid prepared as above was identical. This ester was also prepared by refluxing the above acid with ethanol and concentrated sulphuric acid for 3 to 4 hr. M.p. and mixed m.p. were 153°. *Acetyl derivative*, prepared as usual, had m.p. 124°. (Found : C, 64.48 ; H, 5.77. $C_{18}H_{20}O_6$ requires C, 65.0 ; H, 6.0%). *Methoxy derivative*, prepared as usual, had m.p. 116°. (Found : C, 67.45 ; H, 6.45. $C_{17}H_{20}O_5$ requires C, 67.1 ; H, 6.5%).

Methyl 7-Methoxy-4-methylcoumarin-6-butyrate.—7-Hydroxy-4-methylcoumarin-6-butyric acid (1 g.) was mixed with dry acetone (30 ml), anhydrous potassium carbonate (1 g.), dimethyl sulphate (1 g.) and refluxed on a water bath for 6 to 7 hr. The residue, on evaporation of acetone, was washed with dil. sodium hydroxide solution and crystallised from ethanol in colorless plates, m.p. 118°, yield 0.6 g. (Found : C, 66.45; H, 6.21. $C_{16}H_{18}O_5$ requires C, 66.19 ; H, 6.26%).

7-Methoxy-4-methylcoumarin-6-butyric Acid.—Methyl-7-methoxy-4-methylcoumarin-6-butyrate (1 g.) was mixed with 6 % sodium hydroxide solution (25 ml). Next day it was filtered, acidified and crystallised from dil. ethanol in shining needles, m.p. 176°, yield 0.5 g. (Found : C, 65.48 ; H, 5.85. $C_{15}H_{16}O_5$ requires, C, 65.21 ; H, 5.84%.).

7-Methoxy-4-methyl-4'-ketocyclohexene (5', 6'-5,6) coumarin.—7-Methoxy-4-methylcoumarin-6-butyric acid (3.0 g.) was mixed with phosphorus pentachloride (4 g.) and dry

7. Johnson and Glenn, *J. Amer. Chem. Soc.*, 1949, 71, 1012.

benzene (20 ml). The mixture was refluxed on a water bath for 6 to 7 hr. Benzene, phosphorus pentachloride and volatile matter were removed by applying vacuum at 60° to 70°. Benzene (15-20 ml) was added and the process repeated. The acid chloride was dissolved in benzene and added slowly to the mixture of anhydrous aluminium chloride (3 g.) and dry benzene (40 ml) in cold condition. It was stirred for 2 to 3 hr. and about 50 ml of ether was added with stirring. The organic layer was washed with hydrochloric acid, sodium bicarbonate solution and potassium hydroxide solution. On evaporation of the ether the *coumarin* was obtained which was crystallised from benzene light-petroleum (m.p. 160°.) (Found: C, 69.56; H, 5.21. $C_{15}H_{14}O_4$ requires C, 69.76; H, 5.42%).

It was also prepared by heating the mixture of the acid (1 g.) and polyphosphoric acid (10 g.) at 170° for 30 min. The mixture was added to ice-water, filtered and washed with sodium hydroxide solution. The compound was crystallised from benzene-light-petroleum. m.p. and mixed m.p. with above sample was 160°.

7-Hydroxy-4-phenylcoumarin-6-butyric Acid and its Ethyl Ester.—γ-(2,4-Dihydroxyphenyl) butyric acid (5 g.) was mixed with ethyl benzoylacetate (5 g.) and 80% sulphuric acid (20 ml). Next day the mixture was poured on ice water, and worked up as above. The acid was crystallised from ethanol in rosey plates, m.p. 235°, yield 4.2 g. (Found: C, 70.39; H, 4.72. $C_{19}H_{16}O_5$ requires C, 70.36; H, 4.95%).

Ethyl 7-Hydroxy-4-phenylcoumarin-6-butyrate was crystallised from ethanol in shining plates, m.p. 156°, yield, 0.1 g. (Found: C, 72.2; H, 5.63. $C_{21}H_{20}O_5$ requires C, 71.9; H, 5.69%).

7-Hydroxy-4-methylcoumarin-6-butyric Acid and its Methyl Ester.—γ-(2,4-Dihydroxyphenyl) butyric acid (2 g.) was mixed with methyl acetoacetate (2 g.) and 80% sulphuric acid (10 ml) and worked up as above. 7-Hydroxy-4-methylcoumarin-6-butyric acid was crystallised from ethanol in colorless crystals, m.p. 230°, yield, 1.5 g. *Methyl-7-hydroxy-4-methylcoumarin-6-butyrate* was crystallised from ethanol in shining plates, m.p. 154°. (Found: C, 65.57; H, 5.90. $C_{15}H_{16}O_5$ requires C, 65.21; H, 5.84%).

2,4-Dimethoxy-5-carboxypropyl-β-methylcinnamic Acid.—Ethyl 7-methoxy-4-methylcoumarin-6-butyrate (0.5 g.) was heated with 5% sodium hydroxide solution (15 ml) for 15 min. Dimethyl sulphate (2 ml) was then added with constant shaking. More sodium hydroxide and dimethyl sulphate were added and the mixture was heated for a few minutes. The alkaline solution was left overnight. It is filtered and the filtrate on acidification gave the above product which was crystallised from ethanol in colorless crystals, m.p. 195°, yield, 0.1 g. (Found: C, 61.84; H, 6.42. $C_{16}H_{20}O_6$ requires C, 62.33; H, 6.49%).

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