

Studies in the Synthesis of Coumarino- α -pyrones and Furocoumarins.

Part XII: Synthesis of 4-Hydroxy-2-oxo-2H-furo (2,3-f)

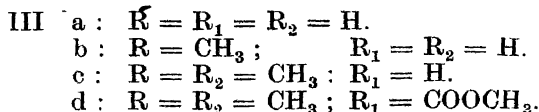
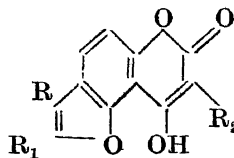
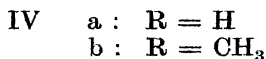
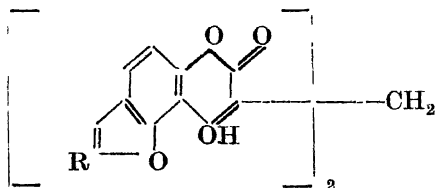
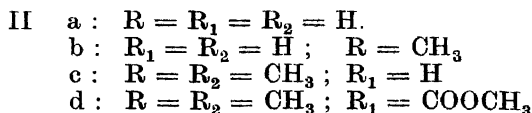
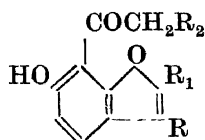
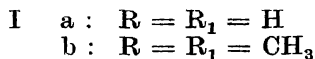
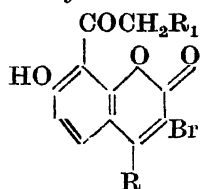
Benzopyran Derivatives

Y. A. Shaikh and K. N. Trivedi

7-Hydroxy-8-acetylcoumarin on bromination and hydrolysis gave 6-hydroxy-7-acetylbenzofuran, which on heating with sodium and ethyl carbonate afforded 4-hydroxy-2-oxo-2H-furo (2,3-f) benzopyran (IIIa). 4-Hydroxy-7-methyl-2-oxo-2H-furo (2,3f) benzopyran, 4-hydroxy-3,7-dimethyl-2-oxo-2H-furo (2,3-f) benzopyran, 6-carbomethoxy-4-hydroxy-3,7-dimethyl-2-oxo-2H-furo (2,3-f) benzopyran and 4-hydroxy-5,9-dimethyl-2-oxo-2H-furo (2,3-h) benzopyran were synthesised by a similar procedure from 6-hydroxy-7-acetyl-3-methyl benzofuran, 7-hydroxy-8-propionyl-4-methylcoumarin and 3-chloro-5-hydroxy-6-acetyl-4, 7-dimethylcoumarin respectively.

Furo-4-hydroxycoumarin derivatives, on treatment with formalin, gave the corresponding methylene bis derivatives (IVa), (IVb) and (VIII).

In continuation of our work on the synthesis of furocoumarins¹, we report here the synthesis of 4-hydroxy-2-oxo-2H-furo (2,3-f) benzopyran derivatives. These were prepared from corresponding *o*-hydroxy-acyl benzofurans, obtained by the alkaline hydrolysis of the corresponding *o*-hydroxy-acyl-3-bromo-coumarin derivatives. 4-Hydroxy- α -pyrone ring was then built upon these *o*-hydroxy-acyl-benzofurans by the action of sodium and ethyl carbonate according to Boyd and Robertson².

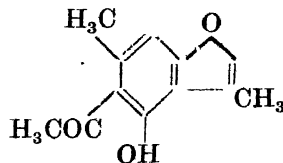
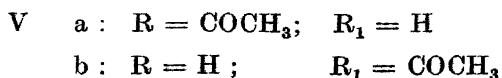
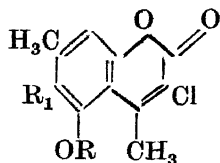


1. V. N. Dholakia and K. N. Trivedi, *J. Indian Chem. Soc.*, 1970, **47**, 1058; Parts VIII, IX, X, XI (in press).
2. Boyd and Robertson, *J. Chem. Soc.*, 1948, 174.

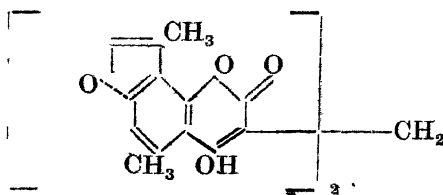
7-Hydroxy-8-acetylcoumarin³ on bromination with bromine in acetic acid gave the 3-bromo derivative (Ia), which on hydrolysis with 10% sodium carbonate yielded 6-hydroxy-7-acetylbenzofuran (IIa). (IIa) and 6-hydroxy-7-acetyl-3-methylbenzofuran⁴ (IIb) on heating with sodium and ethyl carbonate gave 4-hydroxy-2-oxo-2H-furo(2,3-f) benzopyran (IIIa) and 4-hydroxy-7-methyl-2-oxo-2H-furo(2,3-f) benzopyran (IIIb) respectively. 7-Hydroxy-8-propionyl-4-methyl-coumarin on bromination with bromine in acetic acid afforded 3-bromo-7-hydroxy-8-propionyl-4-methylcoumarin (Ib). This on hydrolysis with aqueous sodium carbonate underwent ring contraction to yield a mixture of 6-hydroxy-7-propionyl-3-methylbenzofuran (IIc) and the corresponding 2-carboxylic acid derivative which on esterification with dimethylsulphate in the presence of sodium bicarbonate gave Me-6-hydroxy-7-propionyl-3-methylbenzofuran-2-carboxylate (IId). (IIc) and (IId) on condensation with sodium and ethylcarbonate according to Boyd and Robertson's method afforded 4-hydroxy-3,7-dimethyl-2-oxo-2H-furo(2,3-f) benzopyran (IIIc) and 6-carbomethoxy-4-hydroxy-3,7-dimethyl-2-oxo-2H-furo(2,3-f) benzopyran (IIId).

An alternative route to the synthesis of 4-hydroxy-2-oxo-2H-furo(2,3-h) benzopyran derivatives was also explored. 3-Chloro-5-hydroxy-4,7-dimethylcoumarin⁵ on acetylation with acetic anhydride in the presence of sulphuric acid gave 3-chloro-5-acetoxy-4,7-dimethylcoumarin (Va), which on Fries migration furnished 3-chloro-5-hydroxy-6-acetyl-4,7-dimethylcoumarin (Vb). (Vb) on hydrolysis with 10% sodium carbonate afforded 4-hydroxy-5-acetyl-3,6-dimethylbenzofuran (VI). (VI) on heating with sodium and ethylcarbonate gave 4-hydroxy-5,9-dimethyl-2-oxo-2H-furo (2,3-h) benzopyran (VII)

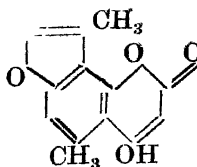
Furo-4-hydroxycoumarin derivatives (IIIa), (IIIb) and (VII) on treatment with formaldehyde gave the corresponding methylene bis derivatives (IVa), (IVb) and (VIII).



VI



VIII



VII

3. D. B. Limaye and N. R. C. Sathe, *Chem. Abst.*, 1937, **31**, 2212.
4. D. B. Limaye and M. C. Joshi, *Rasayanam*, 1941, **1**, 225.
5. D. Chakravarti, *J. Indian Chem. Soc.*, 1931, **8**, 407.

EXPERIMENTAL

3-Bromo-7-hydroxy-8-acetylcoumarin (Ia) : 7-Hydroxy-8-acetylcoumarin³ (4.0 g.) was dissolved in hot acetic acid and bromine in acetic acid (16 ml.; 20%; 0.01 mole) was added with shaking. After cooling it was poured in water. The product which separated was filtered and washed with water. It crystallised from acetic acid, m.p. 198°. Yield 3.0 g. (Found : Br, 28.62%; $C_{11}H_7O_4Br$ requires Br, 28.27%).

6-Hydroxy-7-acetylbenzofuran (IIa) : 3-Bromo-7-hydroxy-8-acetylcoumarin (3.0 g.) was refluxed with sodium carbonate solution (30 ml., 10%) for 1 hr. The reaction mixture was filtered hot. The filtrate on acidification gave a solid, which was treated with sodium bicarbonate solution. The insoluble solid was filtered, washed with water and dried. It crystallised from alcohol, m.p. 110°. Yield 0.3 g. (Found : C, 68.30; H, 4.42%. $C_{10}H_8O_3$ requires C, 68.19; H, 4.44%).

4-Hydroxy:2-oxo-2H-furo(2,3-f)benzopyran (IIIa) : 6-Hydroxy-7-acetylbenzofuran (1.0 g.), ethylcarbonate (10 ml.) were mixed and the solution was added to pulverised sodium (2 g.). The reaction mixture was heated on a steam bath for 6 hr. and treated with alcohol to decompose excess of sodium. The contents were poured into water and extracted with ether. The alkaline aqueous layer on acidification gave the product which was filtered and purified by taking in sodium bicarbonate solution. The insoluble part was removed by filtration and the filtrate on acidification gave the pure product. It crystallised from alcohol, m.p. 249°. Yield 0.3 g. (Found : C, 65.21; H, 2.67%. $C_{11}H_6O_6$ requires C, 65.34; H, 2.97%).

3,3'-Methylene-bis-(4-hydroxy-2-oxo-2H-furo(2,3-f) benzopyran (IVa) : 4-Hydroxy-2-oxo-2H-furo(2,3-f)benzopyran (0.1 g.) was dissolved in ethanol (5 ml.). To the filtered solution, formalin (0.3 ml.; 40% solution) was added and the reaction mixture was refluxed in a water bath for 20 minutes. The separated product was filtered hot and dried. It crystallised from nitrobenzene, m.p. 312°. Yield 0.1 g. (Found : C, 66.42; H, 3.29%. $C_{23}H_{12}O_8$ requires C, 66.34; H, 2.88%).

4-Hydroxy-7-methyl-2-oxo-2H-furo(2,3-f)benzopyran (IIIb) : A mixture of 6-hydroxy-7-acetyl-3-methylbenzofuran⁴ (1.0 g.), ethyl carbonate (10 ml.) and pulverised sodium (1 g.) was heated on a steam bath for 6 hr. The unreacted sodium was decomposed with little alcohol and the reaction mixture was poured into ice water. It was extracted with ether to remove unreacted products and the alkaline aqueous layer was acidified. The product which separated was filtered and purified as described before. It crystallised from alcohol, m.p. 245°. Yield 0.7 g. (Found : C, 66.28; H, 3.71%. $C_{12}H_8O_4$ requires C, 66.67; H, 3.70%).

3,3'-Methylene-bis-(4-hydroxy-7-methyl-2-oxo-2H-furo(2,3-f) benzopyran (IVb) : 4-Hydroxy-7-methyl-2-oxo-2H-furo(2,3-f)benzopyran (0.1 g.) was dissolved in alcohol (15 ml.), to which formalin (0.3 ml.; 40% solution) was added. The reaction mixture was refluxed for 20 minutes, the separated product was filtered hot. It crystallised from nitrobenzene, m.p. 308°. Yield 0.1 g. (Found : C, 67.75; H, 3.67%. $C_{25}H_{16}O_8$ requires C, 67.56; H, 3.60%).

3-Bromo-7-hydroxy-8-propionyl-4-methylcoumarin (Ib) : 7-Hydroxy-8-propionyl-4-methylcoumarin (4.6 g.) was dissolved in hot acetic acid and to the hot solution bromine in acetic acid (18 ml.; 20%; 0.01 mole) was added with stirring. The product which separated after 10 minutes was filtered and dried. It crystallised from acetic acid, m.p. 214°. Yield 3.0 g. (Found : Br, 26.11%. $C_{13}H_{11}O_4$ requires Br, 25.72%.)

6-Hydroxy-7-propionyl-3-methylbenzofuran(IIc) and Me 6-hydroxy-7-propionyl-3-methyl benzofuran-2-carboxylate (IIId) : 3-Bromo-7-hydroxy-8-propionyl-4-methylcoumarin (3 g.) was refluxed with sodium carbonate solution (30 ml; 7%) for 1 hr. The reaction mixture was filtered hot and allowed to cool. The product which separated was filtered and washed with sodium bicarbonate solution followed by water. It crystallised from alcohol, m.p. 92°. Yield 0.5 g. (Found : C, 70.60; H, 5.78%. $C_{12}H_{12}O_5$ requires C, 70.47; H, 5.40%). The filtrate on acidification gave a mixture of (IIc) and the corresponding 2-carboxylic acid derivative which was separated by treating the mixture with sodium bicarbonate solution. The acid derivative (1 g.) was esterified by refluxing it with dimethyl sulphate (1 ml.) in acetone in the presence of sodium bicarbonate (2 g.) for 6 hr. The reaction mixture was filtered hot, acetone was evaporated and the product which separated was treated with sodium bicarbonate solution, filtered, washed and dried. It crystallised from alcohol, m.p. 154°. (Found : C, 63.84; H, 5.11%. $C_{14}H_{14}O_5$ requires C, 64.12; H, 5.34%).

4-Hydroxy-3,7-dimethyl-2-oxo-2H-furo(2,3-f)benzopyran (IIIc) : A solution of 6-hydroxy 7-propionyl-3-methylbenzofuran (1.5 g.), diethyl carbonate (10 ml.) was poured into pulverised sodium (2 g.) and was heated in a water bath for 5 hr. The reaction mixture was cooled, unreacted sodium was decomposed with alcohol (20 ml.) and it was poured into water. The clear solution was ether extracted to remove unreacted substances and the aqueous layer was acidified. The separated product was filtered and purified by treating it with sodium bicarbonate solution. The insoluble part was removed by filtration and the filtrate on acidification gave the pure product which was filtered, washed and dried. It crystallised from alcohol, m.p. 194°. Yield 0.4 g. (Found : C, 68.22; H, 4.25%. $C_{13}H_{10}O_4$ requires C, 67.82; H, 4.34%).

6-Carbomethoxy-4-hydroxy-3,7-dimethyl-2-oxo-2H-furo(2,3-f) benzopyran (IIId) : Me 6 hydroxy-7-propionyl-3-methylbenzofuran-2-carboxylate (0.8 g.) was dissolved in ethyl carbonate (7 ml.). The solution was carefully poured into pulverised sodium (2 g.) and heated on a steam bath for 6 hr. The reaction was worked out as usual. The product obtained was taken in sodium bicarbonate solution and filtered. The filtrate on acidification gave the product which crystallised from acetic acid, m.p. 315°. Yield 0.2 g. (Found : C, 62.38; H, 3.96%. $C_{15}H_{12}O_6$ requires C, 62.53; H, 4.13%).

3-Chloro-5-acetoxy-4,7-dimethylcoumarin (Va) : A mixture of 3-chloro-5-hydroxy-4,7-dimethylcoumarin (5 g.), acetic anhydride (15 ml.) and con. sulphuric acid (few drops) was carefully refluxed on a sand bath for 30 minutes. The reaction mixture was poured into crushed ice. The solid which separated was filtered and washed with dilute sodium hydroxide solution to remove unreacted product, and then by water. It crystallised from acetic acid, m.p. 166°. Yield 3.5 g. (Found : C, 58.48; H, 3.87; Cl, 13.41%. $C_{13}H_{11}O_4Cl$ requires C, 58.53; H, 4.12; Cl, 13.23%).

3-Chloro-5-hydroxy-6-acetyl-4,7-dimethylcoumarin (Vb): A mixture of 3-chloro-5-acetoxy-4,7-dimethylcoumarin (4 g.) and anhydrous aluminium chloride (12 g.) was heated in an oil bath for 2 hr. at 140°. The reaction mixture was cooled externally in ice and was decomposed by slow addition of cold hydrochloric acid (25 ml., 1 : 1). The solid which separated was filtered and washed with water. It crystallised from acetic acid, m.p. 230°. Yield, 0.2 g. It developed purple colour with alcoholic ferric chloride solution and was soluble in alkali solution in cold (Found : C, 58.83; H, 3.95; Cl, 13.29%. $C_{13}H_{11}O_4Cl$ requires C, 58.53; H, 4.12; Cl, 13.32%).

4-Hydroxy-5-acetyl-3,6-dimethylbenzofuran (VI): 3-Chloro-5-hydroxy-6-acetyl-4,7-dimethylcoumarin (3 g.) was refluxed with sodium carbonate solution (30 ml., 10%) for 2 hr. The solution was filtered hot. On cooling the product which separated was filtered and washed with sodium bicarbonate solution. It crystallised from alcohol, m.p. 117°. Yield 0.3 g. (Found : C, 70.76; H, 5.80%. $C_{12}H_{12}O_3$ requires C, 70.60; H, 5.88%).

4-Hydroxy-5,9-dimethyl-2-oxo-2H-furo(2,3-h)benzopyran (VII): 4-Hydroxy-5-acetyl-3,6-dimethylbenzofuran (1 g.) was dissolved in ethyl carbonate (10 ml.). The solution was slowly added to pulverised sodium (2 g.) and the reaction mixture was heated in a water bath for 6 hr. After cooling, the excess of sodium was decomposed by slow addition of alcohol (15 ml.). The reaction mixture was further diluted with water and ether extracted to remove unreacted products. The aqueous layer on acidification gave a solid which was filtered and treated with sodium bicarbonate solution. The insoluble solid was removed by filtration and the filtrate on acidification gave the product which crystallised from alcohol, m.p. 295°. Yield 0.2 g. (Found : C, 67.70; H, 4.16%. $C_{13}H_{10}O_4$ requires C, 67.82; H, 4.34%).

3,3'-Methylene-bis(4-hydroxy-5,9-dimethyl-2-oxo-2H-furo(2,3-h)benzopyran (VIII) 4-Hydroxy-5,9-dimethyl-2-oxo-2H-furo(2,3-h) benzopyran (0.1 g.) was dissolved in alcohol (5 ml.) and filtered hot. Formalin (0.3 ml, 40% solution) was added and the mixture was refluxed in a water bath for 30 minutes. The product which separated was filtered and dried, m.p. 310°. Yield 0.1 g. (Found : C, 68.20; H, 4.16%. $C_{27}H_{20}O_3$ requires C, 68.64; H, 4.23%).

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