[Contribution from the Chemistry Department, M.S. University of Baroda]

Synthesis of Some 4-Hydroxycoumarin Derivatives

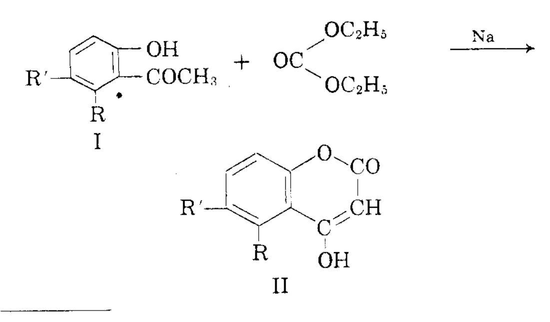
N. J. DESAI and SURESH SETHNA

Received October 9, 1956

The synthesis of 4,5-dihydroxy-, 4,5-dihydroxy-6-methoxy-, and 4,7,8-trihydroxycoumarin has been described. The Elbs persulfate oxidation of 4,7,8-trimethoxy and 4,7-dimethoxycoumarin gave 2,5-dihydroxy-3,4-dimethoxyacetophenone and 2,5-dihydroxy-4-methoxyacetophenone respectively instead of the expected 6-hydroxycoumarin derivatives. The action of sodium hydroxide on some 4-hydroxy- and 4-methoxycoumarin derivatives has been studied and it has been found that either a benzoylacetic acid derivative or an *o*-hydroxyketone is formed. Hydrochloric acid has been found to demethylate 4-methoxycoumarins to 4-hydroxycoumarins.

The present work was undertaken with a view to synthesizing various 4-hydroxycoumarin derivatives with one or more hydroxyl groups in the benzenoid part of the molecule as only a few of these are known. The syntheses have been achieved either by condensing the appropriately substituted phenol with cyanoacetic ester under the conditions of the Hoesch reaction according to Sonn,[1] or by the condensation of an appropriately substituted *o*-hydroxyketone with ethyl carbonate in the presence of sodium metal according to Boyd and Robertson.[2]

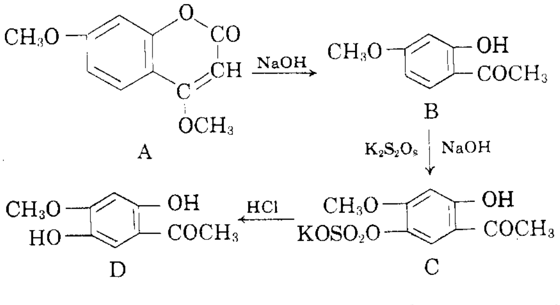
2-Hydroxy-6-methoxyacetophenone (I, R = OCH_3; R′ = H) on reaction with ethyl carbonate gave 4-hydroxy-5-methoxycoumarin (II, R = OCH_3; R′ = H), which on demethylation gave 4,5-dihydroxycoumarin (II, R = OH; R′ = H). 2-Hydroxy-5,6-dimethoxyacetophenone (I, R = R′ = OCH_3) on a similar condensation gave 4-hydroxy-5,6-dimethoxycoumarin (II, R = R′ = OCH_3). On treating this with anhydrous aluminum chloride, a product was obtained, the analysis of which showed that only partial demethylation had taken place. Further, the product gave a bluish violet color with alcoholic ferric chloride similar to the one given by 4,5-dihydroxycoumarin. Baker[3] has reported that in the demethylation of 5,6-dimethoxyflavone with anhydrous aluminum chloride, under mild conditions, 5-hydroxy-6-methoxyflavone was formed. On the basis of all this evidence the 4,5-dihydroxy-6-methoxycoumarin (II, R = OH; R′ = OCH_3) structure is assigned to the partially demethylated product. For want of material demethylation with hydriodic or hydrobromic acid could not be studied.



4,7,8-Trihydroxycoumarin has been synthesized by the condensation of cyanoacetic ester with pyrogallol under the conditions of the Hoesch reaction. It has also been obtained by the condensation of 2-hydroxy-3,4-dimethoxyacetophenone with ethyl carbonate and subsequent demethylation of the 4-hydroxy-7,8-dimethoxycoumarin obtained.

Some of the above 4-hydroxycoumarin derivatives have been condensed with formaldehyde according to Sullivan *et al.*[4] and the 3,3′-methylene bis-4-hydroxycoumarin derivatives obtained.

Various 6-hydroxycoumarin derivatives have been synthesized by previous workers by the Elbs persulfate oxidation of coumarins.[5] The oxidation of 4,7,8-trimethoxycoumarin by this method to 6-hydroxy-4,7,8-trimethoxycoumarin and its subsequent demethylation was thought of as a convenient method for the synthesis of 4,6,7,8-tetrahydroxycoumarin, but the product obtained in the oxidation was found on direct comparison to be 2,5-dihydroxy-3,4-dimethoxyacetophenone. 4,7-Dimethoxycoumarin on similar oxidation gave 2,5-dihydroxy-4-methoxyacetophenone. The formation of 2,5-dihydroxyacetophenone derivatives in the above reaction can be explained on the basis of the coumarin derivative (A) decomposing to the *o*-hydroxyacetophenone derivatives (B) in the presence of alkali and the subsequent oxidation of this ketone through (C) to yield (D).



The action of alkali on 4-hydroxycoumarin

---

(1) Sonn, *Ber.*, **50**, 1292 (1917).

(2) Boyd and Robertson, *J. Chem. Soc.*, 174 (1948).

(3) Baker, *J. Chem. Soc.*, 956 (1939).

(4) Sullivan, Huebner, Stahmann, and Link, *J. Am. Chem. Soc.*, **65**, 2288 (1943).

(5) Sethna, *Chem. Revs.*, **49**, 91 (1951).

derivatives has been studied by Anschutz and Scholl.[6] These workers obtained *o*-hydroxyacetophenone and its derivatives upon hydrolysis of 4-hydroxycoumarin and its derivatives with potassium hydroxide solution at 180–200°. They were not able to isolate the intermediate *o*-hydroxybenzoylacetic acids. Iguchi and Utsugi[7] treated 4,7-dihydroxy-5-methylcoumarin with hot 10% potassium hydroxide and obtained orcacetophenone. Garden *et al.*[8] have very recently reported that in the hydrolysis of 4,6-dihydroxycoumarin, besides 2,5-dihydroxyacetophenone, 2,5-dihydroxybenzoic acid was also obtained. In the present work, 4,7-dimethoxycoumarin when heated with sodium hydroxide solution under comparatively mild conditions gave an acid to which the 2-hydroxy-4-methoxybenzoylacetic acid structure has been assigned, for it gave: a reddish brown color with alcoholic ferric chloride; 4-hydroxy-7-methoxycoumarin on heating with dilute hydrochloric acid; and a mixture of 4-hydroxy-7-methoxycoumarin and 2-hydroxy-4-methoxyacetophenone on boiling with water. For similar reasons the product obtained on heating 4,7,8-trimethoxycoumarin with alkali is assigned the 2-hydroxy-3,4-dimethoxybenzoylacetic acid structure.

4-Hydroxy-7,8-dimethoxy- (I), 4,7,8-trihydroxy- (II), and 4,7-dihydroxycoumarin (III) on heating with 10% alkali on a steam bath for 0.5 hr. gave the original coumarins back. However, on heating under reflux for 3 hr. (I) gave 2-hydroxy-3,4-dimethoxyacetophenone as seen by direct comparison with an authentic specimen, but (II) and (III) did not undergo decomposition.

The action of hot hydrochloric acid on some 4-methoxycoumarin derivatives has also been studied. 4,7-Dimethoxy-, 4,7,8-trimethoxy-, and 4,6-dimethoxycoumarin on heating with hydrochloric acid on a steam bath gave the corresponding 4-hydroxycoumarins in all cases as seen by direct comparison. Arndt *et al.*[9] have also noted the demethylation of 3-bromo-4-methoxycoumarin on heating with hydrochloric acid.

EXPERIMENTAL

All the melting points are uncorrected.

4-Hydroxy-5-methoxycoumarin (II, R = OCH_3; R' = H). 2-Hydroxy-6-methoxyacetophenone[3] (1 g.) was mixed with ethyl carbonate (10 ml.) in the presence of pulverized sodium (1.5 g.). After the initial vigorous reaction had subsided the reaction mixture was heated on a steam bath for an hour. Alcohol was then added to destroy the excess of sodium and the excess of ethyl carbonate was removed with ether. The product obtained on acidification, crystallized from dilute alcohol in colorless needles (0.5 g.), m.p. 155°. It dissolved in sodium bicarbonate solution with effervescence. It did not give any color with alcoholic ferric chloride.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.5; H, 4.2. Found: C, 62.4; H, 4.0.

4,5-Dimethoxycoumarin. Methylation of the above coumarin (0.5 g.) was carried out with dimethyl sulfate (0.32 g.) and anhydrous potassium carbonate (1.5 g.) in boiling acetone during 2 hr. The product obtained crystallized from aqueous alcohol in needles, m.p. 179–180°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.9. Found: C, 63.9; H, 4.9.

4,5-Dihydroxycoumarin (II, R = OH; R' = H). A mixture of 4-hydroxy-5-methoxycoumarin (0.5 g.) and anhydrous aluminum chloride (1 g.) was heated at 145–150° for 3 hr. Ice and hydrochloric acid were then added and the product obtained crystallized from dilute alcohol in colorless needles (0.3 g.), m.p. 221° (dec.). It was soluble in sodium bicarbonate solution with effervescence. It gave a bluish violet color with alcoholic ferric chloride.

Anal. Calcd. for $C_9H_6O_4$: C, 60.7; H, 3.4. Found: C, 60.9; H, 3.9.

3,3'-Methylene bis-(4-hydroxy-5-methoxycoumarin). To a hot solution of 4-hydroxy-5-methoxycoumarin (0.5 g.) in dilute alcohol, formaldehyde (0.5 ml.) was added and the mixture heated under reflux for an hour when a white crystalline product separated. It crystallized from alcohol in white needles, m.p. 251–252° (dec.).

Anal. Calcd. for $C_{21}H_{16}O_8$: C, 63.6; H, 4.1. Found: C, 63.4; H, 4.1.

4-Hydroxy-5,6-dimethoxycoumarin (II, R,R' = OCH_3). This was prepared from 2-hydroxy-5,6-dimethoxyacetophenone[3] (0.5 g.), ethyl carbonate (10 ml.) and pulverized sodium (0.5 g.). It crystallized from dilute alcohol in white needles, m.p. 114°. It dissolved in sodium bicarbonate solution with effervescence.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.5; H, 4.5. Found: C, 59.6; H, 4.7.

4,5-Dihydroxy-6-methoxycoumarin (II, R = OH; R' = OCH_3). A mixture of 4-hydroxy-5,6-dimethoxycoumarin (0.3 g.) and anhydrous aluminium chloride (1 g.) was heated at 145–150° for 3 hr. The product obtained crystallized from dilute alcohol in colorless needles, m.p. 194° (dec.). It dissolved in sodium bicarbonate solution and gave a bluish violet color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.7; H, 3.9. Found: C, 57.6; H, 4.0.

4,7,8-Trihydroxycoumarin. Pyrogallol (6 g.) was dissolved in dry ether and cyanoacetic ester (6 g.) and anhydrous zinc chloride (10 g.) added. The mixture was slowly saturated with dry hydrogen chloride gas for 4 hr. when a brown oil separated. Next day the ether was removed and the oil poured into water. On standing, the ketimine hydrochloride deposited as a white mass. It was hydrolyzed with 50% sulfuric acid by heating on a steam bath for 2 hr. The reaction mixture was added to a large quantity of water when the crude coumarin was precipitated. It crystallized from boiling water in colorless needles, m.p. 258° (dec.). It gave a dirty bluish green color with alcoholic ferric chloride and dissolved in sodium bicarbonate solution with effervescence.

Anal. Calcd. for $C_9H_6O_5$: C, 55.7; H, 3.1. Found: C, 55.6; H, 3.4.

The trimethyl ether gave white needles from dilute alcohol, m.p. 178°.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 61.2; H, 4.6.

4-Hydroxy-7,8-dimethoxycoumarin was prepared from 2-hydroxy-3,4-dimethoxyacetophenone[10] (1 g.), ethyl carbonate, and pulverized sodium (1 g.), and gave from alcohol stout needles (0.8 g.), m.p. 242° (dec.). It was soluble in sodium bicarbonate solution with effervescence.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.5; H, 4.5. Found: C, 59.6; H, 4.3.

---

(6) Anschutz and Scholl, *Ann.*, **379**, 333 (1911).

(7) Iguchi and Utsugi, *J. Pharm. Soc. Japan*, **73**, 1290 (1953).

(8) Garden, Hayes, and Thomson, *J. Chem. Soc.*, 3315 (1956).

(9) Arndt, Loewe, Un, and Ayca, *Ber.*, **84**, 319 (1951).

(10) Baker, *J. Chem. Soc.*, 667 (1941).

Methylation of this coumarin yielded the same trimethyl ether as above. M.p. and mixed m.p. 178°.

Demethylation of the dimethoxycoumarin (0.5 g.) with hydriodic acid (5 ml.; 1.7 d.) by refluxing for 2 hr. in acetic anhydride solution (5 ml.) gave 4,7,8-trihydroxycoumarin. M.p. and mixed m.p. with the product described above was 258° (dec.).

3,3'-Methylene bis-(4-hydroxy-7,8-dimethoxycoumarin). White needles from cyclohexanone, m.p. 288° (dec.).

Anal. Calcd. for $C_{23}H_{20}O_{10}$: C, 60.5; H, 4.4. Found: C, 60.8; H, 4.4.

Elbs persulfate oxidation of 4,7,8-trimethoxycoumarin. 4,7,8-Trimethoxycoumarin (1 g.) was dissolved in sodium hydroxide (10%; 20 ml.) by heating on a steam bath. The solution was then cooled and potassium persulfate (1.5 g. in 30 ml. water) was added gradually during 3 hr. The solution was mechanically stirred and the temperature was not allowed to rise above 10°. The reaction mixture was left overnight and next day it was just acidified with hydrochloric acid and extracted with ether. The ether on evaporation gave negligible product. To the aqueous layer more concentrated hydrochloric acid (30 ml.) was added and the solution heated on a steam bath for 4 hr. It was then extracted with benzene in the cold. The product obtained on removal of benzene crystallized from water in pale yellow prisms, m.p. 119°. Mixed melting point with an authentic specimen of 2,5-dihydroxy-3,4-dimethoxyacetophenone[10] was not depressed.

Elbs persulfate oxidation of 4,7-dimethoxy coumarin. 4,7-Dimethoxycoumarin[1] on similar oxidation gave a product m.p. 164°. Mixed m.p. with an authentic specimen of 2,5-dihydroxy-4-methoxyacetophenone[11] was not lowered.

2-Hydroxy-4-methoxybenzoylacetic acid. 4,7-Dimethoxycoumarin (0.5 g.) was heated with sodium hydroxide solution (10%; 20 ml.) on a steam bath for 30 min. The resulting solution was then cooled and acidified with dilute ice cold hydrochloric acid. The precipitated solid (0.35 g.) melted at 126–128° (effervescence). It dissolved in sodium bicarbonate solution with effervescence. It gave a reddish brown color with alcoholic ferric chloride.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.1; H, 4.8. Found: C, 57.5; H, 4.9.

(a) The above acid (0.3 g.) was heated for 15 min. on a water bath with hydrochloric acid (1:1) and the product obtained crystallized from dilute alcohol in needles, m.p. 256°. Mixed m.p. with 4-hydroxy-7-methoxycoumarin[2] was not lowered. (b) The above acid (0.3 g.) was heated with water (20 ml.) on a steam bath for 2 hrs. The reaction mixture was cooled and extracted with ether (40 ml.). The ether extract was washed with sodium bicarbonate solution (5%; 20 ml.). The sodium bicarbonate solution on acidification gave 4-hydroxy-7-methoxycoumarin. The ether on evaporation gave 2-hydroxy-4-methoxyacetophenone as seen by direct comparison.

2-Hydroxy-3,4-dimethoxybenzoylacetic acid. Obtained from 4,7,8-trimethoxycoumarin by the action of alkali as above, m.p. 123°. It dissolved in sodium bicarbonate solution with effervescence. It gave a reddish brown color with alcoholic ferric chloride.

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 55.0; H, 5.0. Found: C, 54.9; H, 4.7.

On heating with hydrochloric acid (1:1) it gave 4-hydroxy-7,8-dimethoxycoumarin and on heating with water on a steam bath for 2 hr. it gave two products: 4-hydroxy-7,8-dimethoxycoumarin and 2-hydroxy-3,4-dimethoxyacetophenone.[10]

Action of hydrochloric acid on various 4-methoxycoumarin derivatives. (a) A mixture of 4,7-dimethoxycoumarin (0.3 g.) and hydrochloric acid (1:1; 10 ml.) was heated on a steam bath for 0.5 hr. The product obtained on cooling crystallized from dilute alcohol in needles, m.p. 256°. Mixed m.p. with 4-hydroxy-7-methoxycoumarin[2] was not depressed.

(b) 4,7,8-Trimethoxycoumarin (0.3 g.) on similar treatment with hydrochloric acid (1:1; 10 ml.) gave 4-hydroxy-7,8-dimethoxycoumarin as seen by direct comparison with the product described above.

(c) 4,6-Dimethoxycoumarin[8] (0.3 g.) on similar treatment with hydrochloric acid (1:1; 10 ml.) gave 4-hydroxy-6-methoxycoumarin[8] as seen by direct comparison.

Acknowledgment. One of us (N. J. D.) thanks the government of India for the award of a research scholarship.

BARODA 1, INDIA

---

[11] Bargellini and Aureli, *Atti. accad. Lincei*, 20 (*ii*), 118 (1911).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF TEMPLE UNIVERSITY]

Substituted 1,10-Phenanthrolines. X. Ethyl Derivatives[1]

FRANCIS H. CASE, ZELDA B. JACOBS, RICHARD S. COOK, AND JACK DICKSTEIN

Received October 11, 1956

The preparation of the following compounds, together with necessary intermediates, is described: 3-, 4-, and 5-ethyl-1,10-phenanthrolines; 3,8-; 4,6-; 4,7-; and 5,6-diethyl-1,10-phenanthrolines.

In view of the results of recent analytical tests on methyl-1,10-phenanthrolines[2] it was considered of interest to prepare some of the homologous ethyl derivatives.

The use of 1-chloropentanone-3, $ClCH_2CH_2COC_2H_5$, in the synthesis of a quinoline was first reported by Blaise and Maire,[3] who prepared 4-ethylquinoline from aniline and aniline hydrochloride in ethanol solution using this reagent. We have found that it may be used satisfactorily as component B in a modified Skraup reaction (Yale[4] method) for the preparation of 4-ethyl-

---

[1] This work was supported by a grant from the Committee on Research and Publications of Temple University.

[2] W. W. Brandt and G. F. Smith, *Anal. Chem.*, **21**, 1313 (1949).

[3] E. E. Blaise and N. Maire, *Bull. soc. chim. France*, [4] **3**, 662, 667 (1908).

[4] H. L. Yale and J. Bernstein, *J. Am. Chem. Soc.*, **70**, 254 (1948).