g. (0.100 mole) of magnesium and 8.86 g. (0.081 mole) of ethyl bromide in 100 cc. of ether there was added a solution of 5.2 g. (0.020 mole) of 9-(β-dimethylaminoethyl)-9-cyanofluorene in a mixture of 100 cc. of ether and 150 cc. of xylene. The solution was heated to 120–130° for three hours, during which the greenish-black solution turned yellow. The reaction mixture was decomposed with dilute ammonia, the organic layer was separated, dried and the solvent was evaporated to leave a residue which practically all distilled at 159–161° (2 mm.) and analyzed for **9-(β-dimethylaminoethyl)-fluorene.**

Anal. Calcd. for $C_{17}H_{19}N$: C, 86.05; H, 8.07; N, 5.90. Found: C, 85.16; H, 8.12; N, 6.11.

The hygroscopic hydrochloride melted at 172–174°.

Anal. Calcd. for $C_{17}H_{19}N{\cdot}HCl$: N, 5.20. Found: N, 4.85.

The perchlorate was prepared by adding 10 cc. of hot 5% perchloric acid to a solution of 1 g. of the material in 5 cc. of alcohol. It melted, after three recrystallizations from dioxane, at 207–208°.

Anal. Calcd. for $C_{17}H_{19}N{\cdot}HClO_4$: C, 60.44; H, 5.97 N, 4.15. Found: C, 60.75; H, 5.78; N, 4.41.

The picrate melted at 181–183°.

Anal. Calcd. for $C_{17}H_{19}N{\cdot}C_6H_3N_3O_7$: C, 59.22; H, 4.76; N, 12.01. Found: C, 59.22; H, 4.81; N, 11.73.

NEW YORK 11, NEW YORK

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, M. R. SCIENCE INSTITUTE, GUJARAT COLLEGE, AHMEDABAD]

Synthesis of Flavone- and Flavonol-6-carboxylic Acid and Related Derivatives

BY D. N. SHAH, S. K. PARIKH AND N. M. SHAH

RECEIVED OCTOBER 18, 1954

Using 2-hydroxy-5-carboxyacetophenone as starting material, flavone- and flavonol-6-carboxylic acids and their various derivatives have been synthesized for the first time.

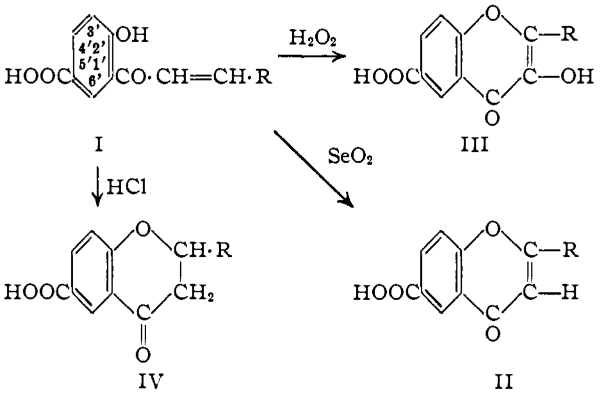
In connection with their work on the Fries migration of *p*-acetoxybenzoic acid, Shah and Shah[1] obtained 2-hydroxy-5-carboxyacetophenone, a substance of much potential value for synthetic work. Its easy accessibility opens the way for the synthesis of chromones, flavones and related substances containing the carboxyl group. A perusal of the literature shows that several chromonecarboxylic acids are known, but such carboxylated flavonoid compounds have not been described except the recently reported 3′,4′-dihydroxy-6-carboxyflavonol.[2]

The present work was undertaken as a part of a systematic study of such heterocyclic compounds and synthesis of flavone-6-carboxylic acid, flavonol-6-carboxylic acid and several of their derivatives is described in this paper. That such compounds may possess vitamin-p like activity adds to the interest of this work.

The Kostanecki–Robinson acetylation of 2-hydroxy-5-carboxyacetophenone or its methyl ester was fruitless and failed to yield 2-methylchromone-6-carboxylic acid. It has been observed in other instances also that the carboxyl group inhibits or hinders the above acetylation. Efforts to synthesize the above chromone acid by other methods are in progress. Hence attention was diverted to the building of the heterocyclic ring by other methods.

When 2′-hydroxy-5′-carboxychalcone (I) and its 4-methoxy and 3-hydroxy derivatives, previously prepared[3] by the condensation of 2-hydroxy-5-carboxyacetophenone and the appropriate aldehyde with ethanolic potassium hydroxide, were oxidized with selenium dioxide in amyl alcohol according to Venkataraman,[4] flavone-6-carboxylic acid (II) and its 4′-methoxy and 3′-hydroxy derivatives, respectively, were obtained. When these three chalcones and in addition the 4-hydroxy derivative were subjected to the Algar–Flynn oxidation[5] with hydrogen peroxide in the presence of cold alkali, flavonol-6-carboxylic acid (III) and its derivatives were obtained in good yield.

The *p*-methoxychalcone was isomerized also by dilute alcoholic hydrochloric acid treatment to the corresponding flavanone (IV).



R = either C_6H_5, $-C_6H_4OH$-*p*, $-C_6H_4OCH_3$-*p* or $-C_6H_4OCH_3$-*m*

It is evident from the above results that a carboxyl group in the benzene nucleus does not exert any retarding influence on the above reactions for the ring formation.

Experimental

Flavone-6-carboxylic Acid.—Selenium dioxide (1 g.) was added to 2′-hydroxy-5′-carboxychalcone (1 g.) dissolved in dry amyl alcohol (30 ml.) and the mixture was refluxed at 140–150° for about 12 hours ($CaCl_2$ guard-tube). The precipitated selenium then was filtered off and the filtrate was subjected to steam distillation. After the removal of amyl alcohol, the solid that separated in the flask was collected and crystallized from acetic acid as small white granules, m.p. 302°, yield 0.4 g. It dissolves in sodium bicarbonate solution with effervescence and in alkali solution with yellow color.

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[4] K. Venkataraman, *et al.*, *J. Chem. Soc.*, 866 (1935); 569 (1936); D. Chakravarti and J. Dutta, *J. Indian Chem. Soc.*, **16**, 639 (1939).

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Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.76; neut. equiv., 266.0. Found: C, 71.70; H, 3.70; neut. equiv. (by titration), 265.2.

The methyl ester prepared by the methanol–sulfuric acid method, crystallized from dilute ethanol as needles, m.p. 139°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.3. Found: C, 72.51; H, 4.2.

4′-Methoxyflavone-6-carboxylic Acid.—A mixture of 2′-hydroxy-5′-carboxy-4-methoxychalcone (1 g.) dissolved in dry amyl alcohol (80 ml.) and selenium dioxide (1 g.), protected from moisture by a $CaCl_2$ guard-tube, was refluxed at 160–165° for 12 hours as before. On working it up similarly, the product obtained was dried and treated with benzene. The yellow solid that separated was collected and crystallized from ethanol as yellow granules, m.p. 328–330° dec., yield 0.3 g. It is soluble in hot acetic acid, sparingly so in hot ethanol, dissolves in $NaHCO_3$ with effervescence, and its sulfuric acid solution exhibits green fluorescence.

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.9; H, 4.05; neut. equiv., 296. Found: C, 68.7; H, 3.90; neut. equiv. (by titration), 298.4.

3′-Hydroxyflavone-6-carboxylic Acid.—2′-Hydroxy-5′-carboxy-3-hydroxychalcone (0.5 g.) in dry amyl alcohol (15 ml.) was treated with selenium dioxide (0.5 g.) at 150–160° for 12 hours, as above. The product isolated as above crystallized from acetic acid as reddish-brown crystals, m.p. 302° dec., yield 0.1 g. It dissolves in $NaHCO_3$ with effervescence and in alkali with yellow color.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.54. Found: C, 67.82; H, 3.35.

4′-Methoxyflavanone-6-carboxylic Acid.—2′-Hydroxy-5′-carboxy-4-methoxychalcone (0.5 g.) dissolved in ethanol (90 ml.) was mixed with hydrochloric acid (25 ml. 10%) when a slight precipitate was formed. It was dissolved by adding a little more ethanol, and the solution refluxed on steam-bath for nearly 50 hours, the excess of ethanol then distilled off and the residual liquid left at room temperature until a pale yellow solid separated which was collected and crystallized from ethanol, pale yellowish granules, m.p. 217°.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.79; neut. equiv., 298. Found: C, 68.28; H, 4.81; neut. equiv. (by titration), 295.5.

Flavonol-6-carboxylic Acid.—2′-Hydroxy-5′-carboxychalcone (1 g.) was dissolved in ethanol (25 ml.) and sodium hydroxide solution (25 ml., 5%) added and the alkaline solution cooled in ice-bath; it turned red. To this solution, hydrogen peroxide (6 ml., 16.5%) was added. The reaction mixture was kept in ice-bath for 3 hours and then left at room temperature overnight for 24 hours. The red solution turned slowly to pale yellow. When it was diluted with ice-water and acidified (HCl 1:1) a yellow solid separated. This was collected, washed with water and crystallized from nitrobenzene as yellow needles, m.p. 313° dec. It gives Wilson's boric acid test and brown color with alcoholic ferric chloride. It dissolves in alkali with yellow color and is insoluble in acetone.

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.1; H, 3.54; mol. wt., 282. Found: C, 68.0; H, 3.45%; mol. wt. (Ag salt method), 278.6.

The acetoxy derivative, prepared by acetic anhydride–NaAc method, crystallized from ethanol, pale yellow needles, m.p. 237–238°.

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.68; H, 3.70. Found: C, 66.48; H, 3.61.

4′-Methoxyflavonol-6-carboxylic Acid.—2′-Hydroxy-5′-carboxy-4-methoxychalcone (1 g.) was treated with hydrogen peroxide similarly as in the previous case. The product isolated as before, crystallized from nitrobenzene as yellow lustrous needles, m.p. 327° dec. It gives green fluorescence in concentrated sulfuric acid and dissolves in alkali with a yellow color.

Anal. Calcd. for $C_{17}H_{12}O_6$: C, 65.4; H, 3.85; mol. wt., 312. Found: C, 65.3; H, 3.72; mol. wt. (Ag. salt method), 308.5.

The acetoxy derivative, prepared as before, crystallized from ethanol as lemon-yellow needles, m.p. 220°.

Anal. Calcd. for $C_{19}H_{14}O_7$: C, 64.4; H, 3.95. Found: C, 64.2; H, 3.78.

3′-Hydroxyflavonol-6-carboxylic Acid.—2′,3-Dihydroxy-5′-carboxychalcone (0.5 g.) was subjected to hydrogen peroxide treatment as before. The product isolated similarly crystallized from ethanol as yellow needles, m.p. 311°.

Anal. Calcd. for $C_{16}H_{10}O_6$: C, 64.43; H, 3.36. Found: C, 64.21; H, 3.17.

4′-Hydroxyflavonol-6-carboxylic Acid.—2′-Hydroxy-5′-carboxy-4-hydroxychalcone (0.5 g.) was treated with hydrogen peroxide as before. The product obtained similarly was collected and crystallized from dilute alcohol as pale yellow needles, m.p. 241°; in concentrated H_2SO_4 solution it gives pale green fluorescence.

Anal. Calcd. for $C_{16}H_{10}O_6$: C, 64.43; H, 3.36. Found: C, 64.31; H, 3.40.

AHMEDABAD, INDIA

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF SCHERING CORPORATION]

11-Oxygenated Steroids. XI. The Synthesis of 17α-Hydroxycorticosterone (Compound F) 21-Acetate from Pregnane-11β,17α-diol-3,20-dione

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The conversion of pregnane-11β,17α-diol-3,20-dione to 17α-hydroxycorticosterone 21-acetate has been accomplished in several ways from the following intermediates: a, 3,3-dimethoxypregnane-11β,17α-diol-20-one; b, pregnane-11β,17α-diol-3,20-dione 3-ethylene ketal; c, 4-bromopregnane-11β,17α-diol-3,20-dione *via* the 3,20-bis-ethylene ketal; d, 4-bromopregnane-11β,17α-diol-3,20-dione *via* the 3-ethylene ketal.

The chemical synthesis of 17α-hydroxycorticosterone (Kendall's Compound F) has been accomplished from cortisone,[1] 20-cyano-Δ^{17}-pregnen-21-ol-3,11-dione,[2] Δ^4-pregnene-11α,17α,21-triol-3,20-dione (11-epi-17α-hydroxycorticosterone),[3] pregnane-3α,11α,17α-triol-20-one and pregnane-3α,17α-diol-11,20-dione[4] and from pregnane-3α,11β,17α-triol-20-one.[5] This paper describes

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