

Chromone and Flavone-7-carboxylic Acids

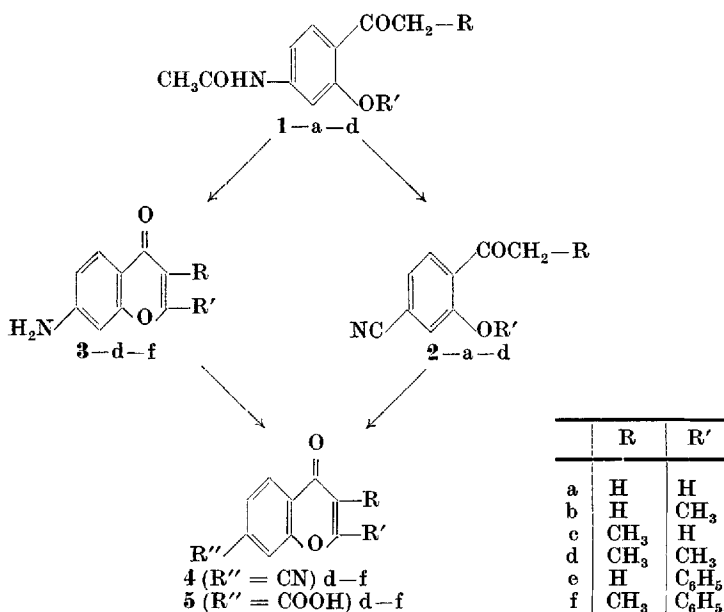
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Summary

The synthesis of some hitherto unknown chromone and flavone-7-carboxylic acids is reported.

The knowledge of chromone and flavone (ring A) carboxylic acids seems at present to be limited to the 2¹⁾, 6^{2a-e)} and 8^{2a-e)} 3) isomers, some derivatives of which possess interesting pharmacological properties. The basic ester of 3-methylflavone-8-carboxylic acid⁴⁾ are, e. g., valuable antispasmodics, particularly the piperidinoethyl ester⁵⁾, and more recently, interesting anticoagulants have been found among chromone-2-carboxamides⁶⁾. As a contribution to the knowledge of the lacking isomers, we wish to report the synthesis of chromone and flavone 7-carboxylic acids.

As starting materials, o-hydroxyarylalkylketones bearing an amino or cyano group in the 4 position, were used as in the following scheme:



¹⁻⁶⁾ s. S. 37.

The key intermediates 4-acetamido-2-hydroxy, or methoxy, aceto (**1 a, b**) and propiophenone (**1 c, d**) were prepared according to CHEN⁷). Flavone-7-carboxylic acid (**5 e**) was synthesised by two routes differing in that the carboxylic function was introduced, as a cyano group, before or after the formation of the γ -pyrone ring.

Thus 4-amino-2-methoxyacetophenone, obtained from acid hydrolysis of compound **1 b**, through the SANDMEYER reaction followed by aluminum trichloride demethylation, furnished 4-cyano-2-hydroxy-acetophenone (**2 a**), that *via* the oxydative cyclization with selenium dioxide of the corresponding chalcone derivative, i. e. 4'-cyano-2'-hydroxychalcone, afforded the 7-cyanoflavone (**4 e**). Hydrolysis of compound **4 e** gave flavone -7-carboxylic acid (**5 e**) which was characterized as chloride and ethyl ester. In the second route 7-aminoflavone (**3 e**), prepared either according to BAPAT and VENKATARAMANN⁸) or *via* the oxydative cyclization with selenium dioxide of 2'-hydroxy-4'-acetamidochalcone, obtained from **1 a**, gave by means of the SANDMEYER reaction the 7-cyanoflavone (**4 e**) as above.

2,3-Dimethylchromone and 3-methylflavone-7-carboxylic acids (**5 d** and **5 f**) were preferably prepared through the 7-amino corresponding derivatives (**3 d** and **3 f**) because of difficulties encountered in the preparation of the intermediate 4-cyano-2-hydroxypropiophenone (**2 e**). The KONSTANECKI-ROBINSON acylation of the 4-acetamido-2-hydroxypropiophenone (**1 c**) with acetic anhydride and sodium acetate or with benzoyl chloride and sodium benzoate gave the corresponding 7-acetamido-2,3-dimethylchromone and 7-benzamido-3-methylflavone.

After acid hydrolysis, the resulting 7-amino derivatives (**3 d** and **3 f**) subjected to the SANDMEYER reaction furnished the wanted 7-cyano derivatives

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⁴) P. DA RE, L. VERLICCHI and I. SETNIKAR, J. Med. Pharm. Chem. **2**, 263 (1960).

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⁶) P. TRONCHE, J. COUQUELET and P. JOLLAND, Ann. Pharm. Franc. **23**, 573 (1965).

⁷) F. C. CHEN and C. T. CHANG, J. chem. Soc. London 2663 (1961).

⁸) Proc. Indian Acad. Sci. **42 A**, 336 (1955).

(4d and 4f), and then a final hydrolysis yielded the 2,3-dimethylchromone and 3-methylflavone-7-carboxylic acids, 5d and 5f, which were characterized as chlorides and ethyl esters.

Experimental

2-Methoxy-4-cyanoacetophenone (2b). Compound 1b (4 g) was boiled with 16 ml of 2.1% hydrochloric acid for 1 hr and the resulting solution, after cooling, was diazotized at 0–5° with sodium nitrite (1.35 g) in 10 ml water. The solution of diazonium salt, cautiously neutralized (litmus paper) by adding dry sodium carbonate, was added with stirring to a solution of cuprous cyanide (prepared from 4.82 g crystallized copper sulfate and 4.82 g of sodium cyanide in 50 ml water) at 50°. The reaction mixture was left to stand overnight, then filtered and the crude product extracted with chloroform and dried. Removal of the solvent left a solid which on crystallizing from ligroin gave 1.8 g bright yellow product, m. p. 109–111°.

Anal. Calcd. for $C_{10}H_9NO_2$: C 68.55; H 5.17; N 7.99. Found: C 68.40; H 5.21; N 8.10.

2-Hydroxy-4-cyanoacetophenone (2a). To one gram of compound 2b in 15 ml of benzene, 1.5 g of aluminium trichloride were added and the mixture was refluxed for 1 hr. Removal of the solvent left a solid which was decomposed with ice-water and dilute hydrochloric acid. The crude product was filtered, washed with water and dried. On crystallizing from ligroin, a yellow crystalline solid (0.4 g) was obtained, m. p. 97–99°.

Anal. Calcd. for $C_9H_7NO_2$: C 67.07; H 4.38; N 8.69. Found: C 66.94; H 4.49; N 8.86.

2'-Hydroxy-4'-cyanochalcone. To compound 2a (1.1 g) and 0.7 g of benzaldehyde in 20 ml 95% ethanol, 11 ml 10% sodium hydroxide were added, under stirring, and the mixture was left to stand 12 hr. After careful acidification the separated solid was collected by filtration, washed with water and dried. On crystallizing from dilute acetic acid, the yield was 0.8 g of yellow product, m. p. 157–160°.

Anal. Calcd. for $C_{16}H_{11}NO_2$: C 77.09; H 4.44; N 5.62. Found: C 76.72; H 4.32; N 5.79.

7-Cyanoflavone (4e). A mixture of 0.7 g of 2'-hydroxy-4'-cyanochalcone, 30 ml amyl alcohol and 0.9 g of selenium dioxide was kept at 145° for 12 hr. After cooling the separated solid was collected and extracted with chloroform; after evaporation of the solvent the residue was crystallized from ethyl acetate to give 0.5 g of white solid, m. p. 225–227°.

Anal. Calcd. for $C_{16}H_9NO_2$: C 77.72; H 3.66; N 5.66. Found: C 77.49; H 3.76; N 5.83.

The same compound was prepared by applying the SANDMEYER reaction to 7-amino-flavone⁸⁾ (3e). A mixture melting point of this derivative with a sample of compound 4e, was not depressed.

Flavone-7-carboxylic acid (5e). Compound 4e (2.47 g) and 30 ml 70% sulfuric acid were refluxed for 1 hr. The reaction mixture was then poured into ice-water and the separated solid was collected by filtration. Crystallization of the crude product from ethyl acetate gave 1.5 g of white crystalline solid, m. p. 299–301°.

Anal. Calcd. for $C_{16}H_{10}O_4$: C 72.17; H 3.81. Found: C 72.07; H 3.83.

Chloride: pale yellow crystals, from ligroin, m. p. 185–188°.

Anal. Calcd. for $C_{16}H_9ClO_3$: C 67.50; H 3.19; Cl 12.44. Found: C 67.41; H 3.27; Cl 12.55.

Ethyl ester: white needles from aqueous ethanol, m. p. 184–186°.

Anal. Calcd. for $C_{18}H_{14}O_4$: C 73.46; H 4.79. Found: C 73.20; H 4.78.

2'-Hydroxy-4'-acetamidochalcone. Compound 1a (3.86 g) and 2.12 g of benzaldehyde in 30 ml 95% ethanol were added of 40 ml 10% sodium hydroxide and the solution kept at room temperature for 12 hr. After cautious acidification with dilute hydrochloric

acid, the precipitated solid was collected by filtration, washed with water and dried. Crystallization of the crude product from aqueous acetic acid, gave 4.5 g of yellow solid, m. p. 186—189°.

Anal. Calcd. for $C_{17}H_{15}NO_3$: N 4.98. Found: N 4.89.

7-Acetamidoflavone. A mixture of 2.07 g of 2'-hydroxy-4'-acetamidochalcone and 2.2 g selenium dioxide in 60 ml amyl alcohol was refluxed at 145° for 12 hr. The reaction mixture was filtered and the filtrate was distilled in steam. The residue collected by filtration was crystallized from ethyl acetate giving 1.1 g of crystalline compound, m. p. 275—276°.

Anal. Calcd. for $C_{17}H_{13}NO_3$: C 73.10; H 4.69; N 5.01. Found: C 72.97; H 4.69; N 5.13.

A mixture melting point of this compound with a sample of that prepared according to BAPAT and VENKATARAMANN⁶) was not depressed.

7-Acetamido-2,3-dimethylchromone. A mixture of 9.5 g of compound 1c, 4.5 g of anhydrous sodium acetate and 8 ml acetic anhydride was refluxed at 170° for 6 hr. By pouring the reaction mixture in water, the chromone derivative was isolated. On crystallizing from ethanol, 7 g of white product were obtained, m. p. 225—227°.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C 67.61; H 5.67; N 6.07. Found: C 67.60; H 5.73; N 5.96.

7-Amino-2,3-dimethylchromone (3d). The preceding compound (6 g) was refluxed with 40 ml concentrated hydrochloric acid for 1 hr. The reaction mixture was poured into water, alkalinized with potassium carbonate and the separated solid, collected by filtration, on crystallizing from benzene gave 4 g of white product, m. p. 210—212°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C 69.83; H 5.86; N 7.40. Found: C 69.54; H 5.77; N 7.45.

7-Cyano-2,3-dimethylchromone (4d). A suspension of compound 3d (1.66 g) in 25 ml 10% hydrochloric acid was diazotized at 0—5° with sodium nitrite (0.61 g) in 10 ml water. The solution of the diazonium salt, cautiously neutralized (litmus paper) by adding dry sodium carbonate, was filtered and the filtrate was added, under stirring, to a solution of cuprous cyanide (prepared from 2.17 g crystallized copper sulfate and 2.17 g sodium cyanide in 50 ml of water) and the mixture was left to stand overnight. The separated solid was extracted with chloroform, dried and the solvent removed. The residue was crystallized from ligroin: 0.8 g of pale yellow solid, m. p. 201—202°.

Anal. Calcd. for $C_{12}H_9NO_2$: C 72.40; H 4.56; N 7.04. Found: C 72.31; H 4.60; N 7.02.

The same compound was obtained by means of the KOSTANECKI-ROBINSON acylation of the crude 2c.

2,3-Dimethylchromone-7-carboxylic acid (5d). Compound 4d (0.5 g) was refluxed with 10 ml 70% sulfuric acid for 1 hr. By pouring the reaction mixture in water the separated solid was collected by filtration and purified by double precipitation. After crystallization from 95% ethanol, 0.3 g of white crystalline compound, m. p. 270—272°, was obtained.

Anal. Calcd. for $C_{12}H_{10}O_4$: C 66.05; H 4.62. Found: C 66.19; H 4.67.

Chloride: white needles from ligroin, m. p. 98—100°.

Anal. Calcd. for $C_{12}H_9ClO_3$: C 60.90; H 3.84; Cl 14.97. Found: C 61.09; H 3.69; Cl 15.11.

Ethyl ester: white crystals from ethanol, m. p. 78—79°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C 68.28; H 5.73; Found: C 68.15; H 5.43.

4-Cyano-2-methoxypropiofenone (2d). By the procedure outlined for compound 2b, 4 g of 4-acetamido-2-methoxypropiofenone (1d) gave 1.4 g of the cyano derivative 2d, as a yellow crystalline product (from ligroin) m. p. 90—91°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C 69.90; H 5.86; N 7.42. Found: C 69.78; H 5.86; N 7.45.

The demethylation of compound **2d** yielded the corresponding 2-hydroxy-4-cyanopropiophenone (**2d**) which was difficult to crystallize (it was characterized as benzoyl derivative m. p. 170–171°) but was employed successfully in the KOSTANECKI-ROBINSON acylation to give compound **4d**.

3-Methyl-7-benzamidoflavone. A mixture of compound **1c** (10 g), benzoyl chloride (20 g) and sodium benzoate (30 g) was heated at 180–190° for 6–8 hr. After cooling the resulting product was triturated in a mortar with four portions of 100 ml 10% sodium hydroxide, filtering each time through a filter plate, then washing with water until the alkaline reaction disappeared. The crude product on crystallizing from ethanol gave 8 g of crystalline solid, m. p. 255–258°.

Anal. Calcd. for $C_{23}H_{17}NO_3$: C 77.73; H 4.25; N 3.94. Found: C 77.55; H 4.86; N 3.97.

3-Methyl-7-aminoflavone (3f). A mixture of 3-methyl-7-benzamidoflavone (2 g) in 20 ml of 70% sulfuric acid was refluxed for 1 hr. The reaction mixture was diluted with ice-water, alkalized with potassium carbonate and the separated solid was filtered.

The crude product was crystallized from benzene affording 1.1 g of white compound, m. p. 210–212°.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C 76.46; H 5.21; N 5.57. Found: C 76.23; H 5.22; N 5.61.

3-Methyl-7-cyanoflavone (4f): A suspension of 2 g compound **3f** in 30 ml 15% hydrochloric acid, was diazotized at 0–5° with 0.56 g sodium nitrite in 10 ml water. By the procedure described for compound **4d**, 0.7 g of the nitrile derivative **4f** was obtained, m. p. 209–211° (from isopropyl alcohol).

Anal. Calcd. for $C_{17}H_{11}NO_2$: N 5.36. Found: N 5.48.

3-Methylflavone-7-carboxylic acid (5f). Compound **4f** (1 g) and 15 ml 70% sulfuric acid, were refluxed for 1 hr. By pouring the reaction mixture in ice-water the carboxylic acid was isolated by filtration and purified by double precipitation. On crystallizing from benzene, 0.5 g of white crystalline product, m. p. 230–232°, were obtained.

Anal. Calcd. for $C_{17}H_{12}O_4$: C 72.85; H 4.32. Found: C 72.65; H 4.28.

Chloride: crystals from ligroin: m. p. 130°.

Anal. Calcd. for $C_{17}H_{11}ClO_3$: C 68.35; H 3.71; Cl 11.87. Found: C 68.50; H 3.71; Cl 11.78.

Ethyl ester: white crystalline product, from ethanol, m. p. 154–155°.

Anal. Calcd. for $C_{19}H_{16}O_4$: C 74.09; H 5.23. Found: C 73.92; H 5.26.

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