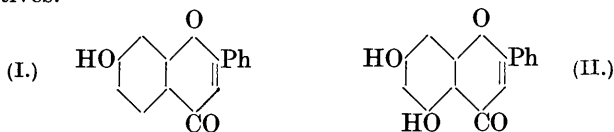


CCCXI.—*A Synthesis of Acacetin and Certain Other Derivatives of Flavone.*

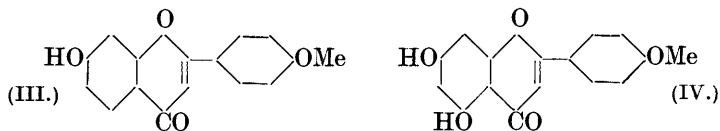
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THE direct acylation of derivatives of *o*-hydroxyacetophenone has hitherto been utilised for the synthesis of 3-substituted flavones only, and in order to extend the scope of this very convenient method we have carefully studied the conditions under which 7-hydroxyflavone (I) and chrysin (II) may best be obtained by benzylation of resacetophenone and phloracetophenone respectively. Satisfactory yields are obtainable, but relatively more benzoic anhydride and longer

heating are required than with the earlier preparations of flavonol derivatives.



When resacetophenone was treated with anisic anhydride and sodium anisate and the product hydrolysed, 7-hydroxy-4'-methoxyflavone (III) was obtained.



This substance closely resembles *pratol*, a naturally occurring hydroxymethoxyflavone with which it is very probably identical. *Pratol* was isolated by Power and Salway (J., 1910, 97, 231) from *Trifolium pratense*, the common red clover, and Rogerson (*ibid.*, p. 1006) also noted its occurrence among the constituents of *Trifolium incarnatum*, the carnation or crimson-flowered clover. Unfortunately, as the result of a fire all authentic specimens of *pratol* have been lost, and a direct comparison could not be made. The anisoylation of phloracetophenone and hydrolysis of the product yields acacetin (IV). This flavone was first isolated from the leaves of *Robinia pseudacacia*, Linn., by A. G. Perkin (J., 1900, 77, 430), who considered that it was probably identical with von Gerichten's apigenin monomethyl ether, prepared by hydrolysis of methylated apiin (*Ber.*, 1900, 33, 2908). More recently, Hattori (*Acta Phytchim.*, 1925, 2, No. 3, 105) isolated *acaciin* from the leaves of *Robinia pseudacacia* and showed that the substance is acacetin 7-diglucoside since it could not be methylated by methyl iodide under the usual conditions. The synthetical material was proved, by direct comparison and the method of mixed m. p.'s, to be identical with the natural product derived from *acaciin*.

EXPERIMENTAL.

7-Hydroxyflavone (I).—A mixture of resacetophenone (5 g.), benzoic anhydride (30 g.) and sodium benzoate (6 g.) was heated at 180—185° for 4 hours, and after cooling, the pale brown mass was broken up and added to alcohol (160 c.c.). The mixture was boiled during the gradual addition of potassium hydroxide (18 g.) dissolved in water (20 c.c.) and then for 30 minutes under reflux. After removal of the greater part of the alcohol by distillation, the residue

was dissolved in water, the filtered solution saturated with carbon dioxide and the precipitated light brown, crude product isolated (5.5 g.). After repeated crystallisation from acetic acid (charcoal) and ethyl acetate, 7-hydroxyflavone was obtained in long, colourless needles, m. p. 240° (Found : C, 75.5; H, 4.3. Calc. for $C_{15}H_{10}O_3$: C, 75.6; H, 4.2%). The yellow solution in sulphuric acid exhibited a blue fluorescence and the acetyl derivative crystallised from alcohol in colourless needles, m. p. 129—130°. The properties of the substance agreed closely with those which Emilewicz and Kostanecki (*Ber.*, 1898, **31**, 703) ascribed to 7-hydroxyflavone.

7-Hydroxy-4'-methoxyflavone (III).—The starting materials were resacetophenone (4 g.), anisic anhydride* (40 g.), and sodium anisate (4 g.), and hydrolysis was effected by means of potassium hydroxide (20 g.) dissolved in alcohol (200 c.c.). The crude product (3.9 g.) was boiled with an excess of acetic anhydride for 2 hours and on fractional crystallisation of the acetylated material from alcohol three substances (*a*, *b*, *c*.) were isolated. On account of its sparing solubility (*b*) was readily separated from (*a*) and (*c*) and, of these, (*c*) was the more sparingly soluble. The main product (*a*) was repeatedly crystallised from alcohol and 7-acetoxy-4'-methoxyflavone was obtained in small, colourless needles, m. p. 165—166° after sintering at 160° (Found : C, 69.4; H, 4.8. $C_{18}H_{14}O_5$ requires C, 69.7; H, 4.5%). The substance is readily soluble in hot ethyl alcohol, somewhat less readily in hot methyl alcohol, and moderately readily in benzene. On hydrolysis with 10% alcoholic potassium hydroxide, it yields 7-hydroxy-4'-methoxyflavone which crystallises from aqueous alcohol, m. p. 262° (Found : C, 71.2; H, 4.7. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%). On acetylation and crystallisation of the product from a mixture of ethyl acetate and alcohol, clusters of colourless, feathery needles, m. p. 167—168°, were obtained and found to be identical with (*a*). The second product (*b*) is sparingly soluble in hot alcohol and crystallised from ethyl acetate in colourless, slender, rectangular prisms, m. p. 208° (Found : C, 69.8; H, 4.7%). It appears to be isomeric with 7-acetoxy-4'-methoxyflavone, but on hydrolysis it gave rise to two substances. The first and more sparingly soluble of these crystallised from alcohol in bundles of microscopic needles, m. p. 290—291°, dissolving in sulphuric acid to a non-fluorescent, greenish-yellow solution, whilst

* Anisic acid (100 g.) boiled for 24 hours with acetic anhydride (300 g.) furnished 70 g. of the crystallised anhydride, m. p. 99°. Anisic acid (50 g.) was converted into the chloride by thionyl chloride and then allowed to react in benzene solution with anisic acid (45 g.) and pyridine (80 g.). There resulted 75 g. of the crystallised anhydride. The first method is a little more convenient and the second method gives a slightly better yield.

the second substance—long, colourless needles, m. p. 261—262°, from alcohol—was identical with 7-hydroxy-4'-methoxyflavone (Found : C, 71.3; H, 4.8%). The third substance (c) from the acetylation of the crude product crystallised in orange-yellow (sometimes almost colourless), large, rhombohedral prisms or decahedra, m. p. 171—172° (Found : C, 69.0; H, 4.5%).

Power and Salway (*loc. cit.*) state that pratol crystallises from alcohol in needles, m. p. 253°, having a talon-like shape with curved edges, and that acetylpratol forms colourless needles, m. p. 166°. Our 7-hydroxy-4'-methoxyflavone crystallised at first in the characteristic form described for pratol, but on recrystallisation very long, straight, colourless needles were obtained. It has frequently been observed that the m. p.'s of flavone and flavonol derivatives synthesised in the present series of investigations were higher than those recorded for the specimens of natural origin. This was the case, e.g., with myricetin and datisctin (compare *isorhamnetin*, previous communication) and, from this point of view, the recorded m. p.'s of pratol (253°) and acetylpratol (166°), when compared with those of 7-hydroxy-4'-methoxyflavone (262°) and its acetyl derivative (167—168°), suggest identity. The reactions of the hydroxy-methoxyflavone correspond closely with those of pratol. They are : a pale yellow solution in aqueous alkalis ; no coloration with alcoholic ferric chloride ; a yellow coloration on the addition of a drop of sulphuric acid to an acetic anhydride solution ; and, finally, solubility relations. The solution in sulphuric acid exhibits a greenish-blue fluorescence which becomes vivid blue in a short time. Power and Salway have not recorded this behaviour in the case of pratol.

Chrysin (II).—A mechanically-stirred mixture of phloracetophenone* (5 g.), benzoic anhydride (50 g.) and sodium benzoate (6 g.) was heated at 180—185° for 6 hours and, for hydrolysis, alcohol (300 c.c.) and potassium hydroxide (32 g.) in water (20 c.c.) were employed. The crude product was isolated in the usual manner but in this case yellow, crystalline flakes (7.5 g.) were obtained. The material was acetylated by means of an excess of boiling acetic anhydride and a drop of pyridine in 2 hours, and the diacetylchrysin was crystallised from alcohol (charcoal), from benzene—light petroleum, and once again from alcohol in clusters of colourless needles, m. p. 192° (Found : C, 67.5; H, 4.1. Calc. for C₁₅H₁₄O₆ : C, 67.5; H, 4.1%). Kostanecki (*Ber.*, 1893, 26, 2901) states that diacetylchrysin has m. p. 185°. On hydrolysis with 10% alcoholic potassium hydroxide (slightly in excess of theoretical) on

* In the preparation of this substance by the method of Hoesch (*Ber.*, 1915, 48, 1122) it is advantageous to add zinc chloride and to keep the reaction mixture in an ice-chest for a few days.

the steam-bath for 30 minutes and subsequent acidification, chrysin was obtained. The flavone was twice crystallised from methyl alcohol; yellow prisms, m. p. 275° (Found: C, 70.9; H, 3.7. Calc. for $C_{15}H_{10}O_4$: C, 70.9; H, 3.9%). This m. p. is in agreement with that given in the literature and the properties of the substance corresponded closely with those of chrysin as described by Piccard (*Ber.*, 1873, **6**, 884, 1160; 1874, **7**, 888; 1877, **10**, 176), Kostanecki (*loc. cit.*), and Emilewicz, Kostanecki and Tambor (*Ber.*, 1899, **32**, 2448). On methylation in the known manner (Kostanecki, *loc. cit.*), the monomethyl ether, tectochrysin, was obtained. The substance crystallised from alcohol in yellow, hexagonal prisms with pointed ends, m. p. 163° (Found: C, 71.3; H, 4.3. Calc. for $C_{16}H_{12}O_4$: C, 71.6; H, 4.5%). Kostanecki (*loc. cit.*) states that tectochrysin occurs in long needles, m. p. 163°, whilst Piccard (*loc. cit.*) describes hemi-pyramids on a prismatic base and quotes the m. p. 164°.

Acacetin (IV).—The condensation of phloracetophenone (5 g.) with anisic anhydride (50 g.) in presence of sodium anisate (6 g.) and the subsequent hydrolysis were carried out as in the case last described. The crude product (5.8 g.) was crystallised from a mixture of acetic acid and alcohol (charcoal), and recrystallised from 95% alcohol, finally in pale yellow, woolly needles, m. p. 261° (Found: C, 67.5; H, 4.5. Calc. for $C_{16}H_{12}O_5$: C, 67.6; H, 4.2%). A mixture with natural acacetin, m. p. 258—259°, melted at 258—260°, and direct comparison showed that the two specimens were identical in every respect. (We are greatly indebted to Dr. Shizuo Hattori for kindly sending us a specimen of acacetin from acaciin.) The diacetyl derivative of the synthetic flavone was prepared in the usual manner and, as stated by Hattori (*loc. cit.*) for the natural product, it crystallised from alcohol in lustrous needles, m. p. 203° (Found: C, 65.3; H, 4.2. Calc. for $C_{20}H_{16}O_7$: C, 65.2; H, 4.3%).

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