256. *Synthetical Experiments in the Chromone Group. Part VIII. Derivatives of* o-*Hydroxy-, 2 : 5-Dihydroxy-, and 2 : 4 : 5-Trihydroxyacetophenone.*

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An earlier statement of Bhullar and one of us (J., 1931, 1165), that Robinson's chromone condensation is inapplicable to *o*-hydroxyacetophenone, must be modified because the action of benzoic anhydride and trimethylgallic anhydride on the ketone has now given small amounts of flavone and 3′ : 4′ : 5′-trimethoxyflavone respectively. More satisfactory results were obtained with 2 : 5-dihydroxyacetophenone : benzoylation, anisoylation, and trimethylgalloylation, followed by vigorous hydrolysis, led to 6-hydroxyflavone, 6-*hydroxy*-4′-*methoxyflavone*, and 6-*hydroxy*-3′ : 4′ : 5′-*trimethoxyflavone* respectively. Demethylation of the last compound gave 6 : 3′ : 4′ : 5′-*tetrahydroxyflavone*. Similarly, by the action of benzoic anhydride on 2 : 4 : 5-trihydroxyacetophenone, was obtained 6 : 7-dihydroxyflavone, very pale cream-coloured needles, m. p. 254°, described by Reigrodski and Tambor (*Ber.*, 1910, **43**, 1964) as microscopic prisms, m. p. 135° (with loss of $1H_2O$), and by Hattori (*Acta Phytochim.*, 1932, **6**, 131) as melting at 250°. Primetin, its 5 : 6-isomeride, has been isolated from *Primula modesta* by Nagai and Hattori (*ibid.*, 1930, **5**, 1).

For reasons explained in Part VII (J., 1932, 1108) the dyeing properties and colour reactions of 6 : 3′ : 4′ : 5′-tetrahydroxy- and 6 : 7-dihydroxy-flavone are recorded. Although the dihydroxyflavone is a definitely weaker dye than the 7 : 8-isomeride (J., 1929, 2219), doubtless owing to the proximity to the pyrone oxygen of the hydroxyls of the latter, its dyeing properties compare favourably with those of 6 : 3′ : 4′ : 5′-tetrahydroxyflavone, which has two more hydroxyls: hydroxyl groups in the fused benzene ring in a flavone appear to have greater auxochromic effect than hydroxyls in the 2-phenyl ring.

2 : 4 : 5-Trihydroxyacetophenone, previously prepared by Bargellini and Avrutin (*Gazzetta*, 1911, **40**, ii, 342, 347), and Badhwar and Venkataraman (J., 1932, 2420), has now been obtained by the methods of (*a*) Hoesch, (*b*) Friedel and Crafts, (*c*) Nencki. Mauthner (*J. pr. Chem.*, 1933, **136**, 213) has prepared it by the Fries and by the Hoesch method, but has ascribed to it the structure of 2 : 3 : 5-trihydroxyacetophenone. It is undoubtedly the 2 : 4 : 5-trihydroxy-compound, because (1) quinol does not undergo the Hoesch or the Nencki reaction (we have found that the interaction of quinol with acetic acid and zinc chloride, in the presence or absence of acetic anhydride, leads only to the *O*-diacetyl derivative; see also Baker and Eastwood, J., 1929, 2900), and (2) the Robinson reaction with the ketone yields a flavone which has the properties of a catechol derivative and is rightly represented as 6 : 7-dihydroxyflavone.

The possibility of 3-acylation during the Robinson reaction with hydroxyphenyl methyl ketones has been the source of confusion and experimental difficulty in recent syntheses of chromones (Bhullar and Venkataraman, *loc. cit.*; Anderson, *Canadian J. Research*, 1932, **7**, 285). In order, therefore, to devise a modification of the procedure which would preclude 3-acylation and to provide incidentally a preliminary test of the commonly assumed mechanism of the reaction (see also Wittig, Baugert, and Richter, *Annalen*, 1925, **446**, 155), attempts were made to effect closure to the γ-pyrone ring in *O*-acyl derivatives of 2-acetyl-1-naphthol. Heating 2-acetyl-1-naphthyl benzoate with sodium benzoate or with zinc chloride did not lead to any crystalline material. 2-Acetyl-1-naphthol was recovered after hydrolysis when its benzoate was treated with phosphorus oxychloride and chloroform or heated with (*a*) sodium acetate and (*b*) acetic anhydride and sodium acetate. On treatment of the benzoate with sodium benzoate and benzoic anhydride, 3-benzoyl-α-naphthaflavone was obtained. 2-Phenylacetyl-1-naphthyl acetate, in which the ω-phenyl may be expected to facilitate chromone formation (Cheema and Venkataraman, J., 1932, 918), gave no chromone on treatment with zinc chloride, was unchanged by acetic anhydride, and was converted into 2-phenylacetyl-1-naphthol by sodium acetate. Other negative results obtained with a variety of dehydrating agents and experimental conditions are not recorded.

EXPERIMENTAL.

2 : 4 : 5-*Trihydroxyacetophenone*.—(*a*) Dry hydrogen chloride was passed for 8 hours into a mixture of hydroxyquinol (2·4 g.), acetonitrile (1 g.), zinc chloride (1 g.), and dry ether (20 c.c.) cooled in ice. After 4 days' keeping at 0°, the ether was decanted, and the solid washed with ether and boiled with water (50 c.c.) for 2 hours in a current of carbon dioxide. From the cooled solution, ether extracted 2 : 4 : 5-trihydroxyacetophenone, which crystallised from water in golden-yellow, stout, long, prismatic needles (0·8 g.), m. p. 206—207° (Bargellini and Avrutin, 200—202°; Mauthner, 206—207°) (Found: C, 57·0; H, 4·8. Calc.: C, 57·1; H, 4·8%). The triacetyl derivative crystallised from alcohol in colourless needles, m. p. 110° (Mauthner, 106—107°) (Found: C, 57·0; H, 4·6. Calc.: C, 57·2; H, 4·8%).

(*b*) To a mechanically stirred mixture of hydroxyquinol triacetate (15 g.), aluminium chloride (15 g.), and nitrobenzene (100 g.), heated on the steam-bath till no more hydrogen chloride was evolved and then cooled to room temperature, acetyl chloride (5 g.) was added drop by drop. The mixture was finally heated on the steam-bath for 4 hours, cooled, and treated with ice–hydrochloric acid, and the nitrobenzene removed by steam-distillation. The ketone was isolated from the aqueous residue as in the previous case (3 g.).

(*c*) Fused powdered zinc chloride (6 g.) was dissolved in acetic acid (8 g.) at 140°, and acetic anhydride (8 g.) added, followed by hydroxyquinol (10 g.). The solution was kept at 145—150° for 1 hour, finally becoming claret-red, and was then poured into a saturated solution of sodium hydrogen sulphite. Ether (250 c.c.) extracted the trihydroxyacetophenone, which was crystallised from sulphurous acid and then from water (yield, 4·2 g.).

Flavone.—*o*-Hydroxyacetophenone (2 g.), benzoic anhydride (20 g.), and sodium benzoate (4 g.) were heated together at 180—185° for 6 hours, the product boiled with 10% alcoholic potassium hydroxide (100 c.c.) for ½ hour, most of the alcohol removed in a vacuum, and the residue poured into water. Pale yellow needles (0·3 g.), m. p. 99°, from light petroleum (b. p. 30—50°) (Found: C, 81·2; H, 4·4. Calc. for $C_{15}H_{10}O_2$: C, 81·1; H, 4·5%).

3′ : 4′ : 5′-*Trimethoxyflavone.*—This was prepared from trimethylgallic anhydride by the above method. The product was dissolved in hot acetic acid, and a few drops of concentrated sulphuric acid and then hot water added. Repeated crystallisation from alcohol gave a very small amount of pale yellow needles, m. p. 150—151° [Found (microanalysis by Schoeller): C, 61·9; H, 5·9; loss at 120°, 10·5. Calc. for $C_{18}H_{16}O_5,2H_2O$: C, 62·1; H, 5·7; H_2O, 10·4%]. The m. p. of the dehydrated substance was 174—175° (Hattori, *Acta Phytochim.*, 1932, **6**, 131, gives m. p. 174—175°).

6-Hydroxyflavone, prepared from 2 : 5-dihydroxyacetophenone (4 g.), benzoic anhydride (35 g.), and sodium benzoate (7 g.) and purified through the acetyl derivative (1·8 g.), m. p. 159°, formed colourless needles, m. p. 234° (Kostanecki, Levi, and Tambor, *Ber.*, 1899, **32**, 331, describe dark yellow needles, m. p. 231—232°) (Found: C, 75·5; H, 4·3. Calc. for $C_{15}H_{10}O_3$: C, 75·6; H, 4·2%).

6-*Hydroxy*-4′-*methoxyflavone*, prepared from 2 : 5-dihydroxyacetophenone (1·5 g.), anisic anhydride (10 g.), and sodium anisate (3 g.), formed, after two crystallisations from alcohol, long colourless needles (0·6 g.), m. p. 249° (Found: C, 71·6; H, 4·5. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%). The yellow solution in sulphuric acid has a green fluorescence, and an alcoholic solution gives no coloration with ferric chloride. The *acetyl* derivative crystallises from alcohol in colourless needles, m. p. 161° (Found: C, 69·7; H, 4·4. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%).

6-*Hydroxy*-3′ : 4′ : 5′-*trimethoxyflavone.*—The product obtained from 2 : 5-dihydroxyacetophenone (5 g.), trimethylgallic anhydride (40 g.), and sodium trimethylgallate (7 g.), after alkaline hydrolysis and precipitation with carbon dioxide, was redissolved in cold 3% aqueous sodium hydroxide (charcoal; ½ hour) and again precipitated by carbon dioxide. The *acetyl* derivative, after repeated crystallisation from alcohol, formed colourless needles (0·4 g.), m. p. 185° [Found (micro): C, 64·9; H, 5·0. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%]. Hydrolysis with 5% alcoholic potassium hydroxide and acidification, followed by two crystallisations from aqueous alcohol, gave very pale orange plates, m. p. 232—233° [Found (micro): C, 65·5; H, 4·8. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%]. The bright yellow solution in sulphuric acid has a weak green fluorescence, and an alcoholic solution gives no coloration with ferric chloride.

6 : 3′ : 4′ : 5′-*Tetrahydroxyflavone.*—The preceding acetate was demethylated with boiling hydriodic acid–acetic anhydride. The crude product was purified *via* the *acetyl* derivative, which crystallised from alcohol–acetic acid in colourless needles, m. p. 258—259° [Found (micro): C, 60·6; H, 4·1. $C_{23}H_{18}O_{10}$ requires C, 60·8; H, 4·0%]. Hydrolysis with alcoholic potassium hydroxide and crystallisation from aqueous alcohol gave 6 : 3′ : 4′ : 5′-tetrahydroxyflavone in yellow needles, m. p. 347° [Found (micro): C, 55·6; H, 4·4; loss at 150°, 11·3. $C_{15}H_{10}O_6,2H_2O$ requires C, 55·9; H, 4·3; H_2O, 11·2%]. The substance forms a bright yellow, non-fluorescent solution in sulphuric acid and a bright red solution in aqueous sodium hydroxide; an alcoholic solution gives an intense green colour with ferric chloride (changing to reddish-brown with aqueous ammonia), a deep yellow with magnesium and hydrochloric acid, and a deep reddish-brown (changing slowly to pale greenish-brown and finally to a brown precipitate) with sodium amalgam. The shades produced on wool mordanted with aluminium, chromium, iron, and tin are cream, yellowish-brown, dark green, and lemon-yellow respectively.

6 : 7-*Dihydroxyflavone.*—The crude flavone (1·1 g.), obtained from 2 : 4 : 5-trihydroxyacetophenone (2 g.), benzoic anhydride (25 g.), and sodium benzoate (4 g.), was boiled with 5% aqueous sodium hydroxide for 20 minutes (in order to eliminate a by-product, isolable by fractional crystallisation; m. p. 278—281°, probably the 3-benzoyl derivative), and carbon dioxide passed through the deep orange solution. The orange-brown precipitate, after two crystallisations from aqueous acetic acid–alcohol (charcoal), formed very pale cream-coloured, silky needles, m. p. 254° [Found (micro): C, 70·7; H, 4·1. Calc. for $C_{15}H_{10}O_4$: C, 70·9; H, 3·9%]. The substance gives a colourless non-fluorescent solution in sulphuric acid (Reigrodski and Tambor, *loc. cit.*, record green colour and green fluorescence) and a bright yellow solution in

aqueous sodium hydroxide. An alcoholic solution gives an intense green colour with ferric chloride (turning violet-brown with aqueous ammonia), a bright yellow with magnesium and hydrochloric acid, a pale orange with sodium amalgam, and a greenish-yellow gelatinous precipitate with lead acetate. With aluminium, chromium, iron, and tin mordants, the shades produced on wool are cream, yellowish-brown, chocolate, and pale yellow respectively.

The acetyl derivative crystallised from aqueous alcohol in colourless needles, m. p. 201° (Reigrodski and Tambor give 195°) [Found (micro) : C, 67·2; H, 4·1. Calc. for $C_{19}H_{14}O_6$: C, 67·5; H, 4·1%].

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