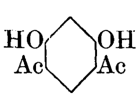
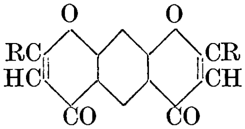
CCCXXV.—*Synthetical Experiments in the Chromone Group. Part III. Diflavones.*

By KHUSHHAL CHAND GULATI and KRISHNASAMI VENKATARAMAN.

THE Allan–Robinson method of heating aromatic hydroxy-ketones with acid anhydrides to obtain chromone derivatives (J., 1924, **125**, 2192) has proved so valuable for the synthesis of naturally occurring flavone pigments that the possibilities of the reaction for the preparation of various types of substituted γ-pyrone appear to be worth study. Two such applications, one giving chromones derived from pyrogallol and the other pyrones derived from α-naphthol, have been reported (Venkataraman, J., 1929, 2219; Bhullar and Venkataraman, this vol., p. 1165). The preparation of dichromones by the action of acid anhydrides on 4 : 6-diacetylresorcinol (I) is now described. Diflavone (II; R=Ph) has been prepared by Ryan and O'Neill (*Proc. Royal Irish Acad.*, 1915, **32**, 48) by two methods different from ours. Ryan and others (*ibid.*, 1915, **32**, 167, 185, 193; 1930, **39**, 425) found that the ester and chalkone methods were not applicable to the synthesis of substituted diflavones; the former did not proceed and the latter led to the isomeric dicoumaranones. Other members of the dichromone series are dichromone, 2 : 2′-dibenzyldichromone (Algar, Fogarty, and Ryan, *ibid.*, 1924, **36**, 315), 2 : 2′ : 3 : 3′-tetramethyldichromone and 3 : 3′-dimethyldiflavone (Wittig, *Ber.*, 1926, **59**, 116). Wittig used the Robinson method.

The condensation of 4 : 6-diacetylresorcinol with benzoic anhydride and sodium benzoate led to a mixture of diflavone (II; R=Ph) and an alkali-soluble substance whose constitution as 7-*hydroxy*-6-*acetylflavone* (III; R=Ph) was obvious from its properties and the mode of isolation. By using anisic anhydride and sodium anisate, 4′ : 4″-*dimethoxydiflavone* (II; R = C_6H_4·OMe) and 7-*hydroxy*-4′-*methoxy*-6-*acetylflavone* (III; R = C_6H_4·OMe) were obtained. Demethylation of the former with hydriodic acid gave the 4′ : 4″-*dihydroxydiflavone* (II; R = C_6H_4·OH). The action of veratric and trimethylgallic anhydrides respectively on diacetylresorcinol led only to the corresponding 7-hydroxy-6-acetylflavones [III; R = $C_6H_3(OMe)_2$ and $C_6H_2(OMe)_3$]. Finally, as in the case of certain other polyhydroxy-ketones, the action of acetic anhydride and sodium acetate on diacetylresorcinol yielded a mixture of products somewhat difficult to purify. The alkali-insoluble substance obtained in the reaction appeared from its analysis to be *diacetyldimethyldichromone* (IV); the amount was insufficient for fuller investigation. The alkali-soluble substance corresponded in its properties to the alkali-soluble substances obtained in the preceding reactions and has therefore been formulated as 7-*hydroxy*-6-*acetyl*-2-*methylchromone* (III; R = Me). An attempt to prepare dimethyldichromone (II; R = Me), for comparison with (IV), by heating diacetylresorcinol with ethyl acetate and sodium gave only the unchanged diketone.


(I.)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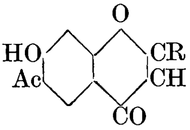
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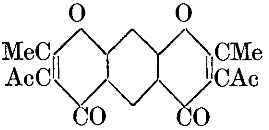
During trials of different methods for the conversion of resorcinol diacetate into 4 : 6-diacetylresorcinol, one of the products obtained was *resacetophenone* 2-*monoacetate* (V). (By the partial acetylation of resacetophenone, Tahara, *Ber.*, 1892, **25**, 1300, obtained the 4-monoacetate.) This conversion involves *p*-migration of an acetyl group; the Fries reaction on phenyl acetate, however, yields *o*-hydroxyacetophenone (Freudenberg and Orthner, *Ber.*, 1922, **55**, 1748).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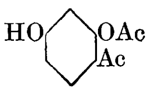
(V.)

EXPERIMENTAL.

4 : 6-*Diacetylresorcinol* (I).—Treatment of resacetophenone with zinc chloride, glacial acetic acid, and phosphorus oxychloride (Torrey and Kipper, *J. Amer. Chem. Soc.*, 1908, **30**, 850) and of resorcinol diacetate with zinc chloride (Eijkmann, *Centr.*, 1904, I, 1597; 1905, I, 814) led to unsatisfactory results. The following modification of Heller's method (*Ber.*, 1912, **45**, 418) gave comparatively good yields. Dry redistilled resorcinol diacetate (100 g.) and sublimed ferric chloride (44 g.) were mixed and heated at 180° for 3 hours in an atmosphere of carbon dioxide. The product, treated with very dilute hydrochloric acid and crystallised from alcohol (charcoal) and then from benzene, gave colourless needles (15 g.), m. p. 182°.

The process was repeated under widely varying conditions, but the yield of a pure colourless product could not be improved. When a solution of resorcinol diacetate (5·0 g.) and ferric chloride (4·2 g.) in glacial acetic acid (10 c.c.) was boiled for 6 hours, and the reaction mixture poured into hot water, the product (2·3 g.) obtained crystallised from boiling water in colourless needles, m. p. 119—120°, and was identified as *resacetophenone* 2-*monoacetate* (V) (Found : C, 61·7 ; H, 5·2. $C_{10}H_{10}O_4$ requires C, 61·8 ; H, 5·1%). Heated with ferric chloride (2·1 g.) for 3 hours at 180°, the substance (5·0 g.) gave diacetylresorcinol (0·6 g.). When the substance was boiled with 50% hydrochloric acid for 1 hour, and the solution salted out after cooling, resacetophenone was obtained. An alcoholic solution of the substance gave with ferric chloride a bright orange-red colour : resacetophenone 4-monoacetate melts at 74° (Tahara, *loc. cit.*) and gives a violet colour with ferric chloride.

Following Wittig (*loc. cit.*) for the preparation of dipropionylresorcinol, resorcinol diacetate (10·0 g.) was heated to 130° (thermometer in the liquid), finely powdered zinc chloride (3·0 g.) added with stirring, and the mixture carefully heated until there was a sudden and rapid rise of temperature. The mixture was allowed to cool and ground with aqueous methyl alcohol; the residue, crystallised from benzene, gave resacetophenone (4·1 g.), m. p. 142°.

When resorcinol diacetate was heated with aluminium chloride under different conditions, two substances were isolated. One was resacetophenone monoacetate. The other, obtained in minute amount, crystallised from hot water in colourless needles, m. p. 83—84° (Found : C, 60·9 ; H, 5·1%) ; in alcoholic solution it gave no coloration with ferric chloride.

Diflavone (II ; R = Ph).—An intimate mixture of 4 : 6-diacetylresorcinol (4·0 g.), benzoic anhydride (60 g.), and sodium benzoate (12·0 g.) was heated at 180—185° for 8 hours. The product was ground, boiled with 10% alcoholic caustic potash (340 c.c.) for 30 minutes, and poured into a large excess of water. The precipitate was washed with water and crystallised from dilute acetic acid, giving long colourless needles (1·2 g.), m. p. 281—282° (Ryan and O'Neill give m. p. 281—282°, after softening at 275°) (Found : C, 78·7 ; H, 3·5. Calc. for $C_{24}H_{14}O_4$: C, 78·6 ; H, 3·5%). The pale yellow solution in concentrated sulphuric acid exhibited a faint green fluorescence : before crystallisation the material gave a brown solution and a violet fluorescence. According to Ryan and O'Neill, diflavone gives with sulphuric acid a pale yellow solution and a brilliant blue fluorescence.

7-*Hydroxy*-6-*acetylflavone* (III ; R = Ph).—The alkaline filtrate (above) after removal of the diflavone was saturated with carbon dioxide. The brown powder precipitated (1·0 g.) was crystallised repeatedly from dilute acetic acid, giving colourless needles, m. p. 123° (Found : C, 72·9 ; H, 4·3. $C_{17}H_{12}O_4$ requires C, 72·8 ; H, 4·3%), which gave a faint blue fluorescence in sulphuric acid and an orange coloration with alcoholic ferric chloride.

4′ : 4″-*Dimethoxydiflavone* (II; R = $C_6H_4{\cdot}OMe$).—The condensation was carried out in the above way with diacetylresorcinol (5·0 g.), anisic anhydride (Robinson and Venkataraman, J., 1926, 2345) (58 g.), and sodium anisate (10·0 g.). The *product* (2·9 g.) insoluble in the alkali hydroxide crystallised from aqueous pyridine in yellow needles, m. p. 192° (decomp.) (Found: C, 73·1; H, 4·2. $C_{26}H_{18}O_6$ requires C, 73·2; H, 4·2%). It was sparingly soluble in the common organic solvents, gave no ferric chloride reaction, and its bright red solution in sulphuric acid exhibited a violet fluorescence.

4′ : 4″-*Dihydroxydiflavone* (II; R = $C_6H_4{\cdot}OH$).—Crude dimethoxydiflavone (1·9 g.) was dissolved in acetic anhydride (20 c.c.), and hydriodic acid (*d* 1·7; 20 c.c.) added. When the reaction had moderated, the whole was boiled for 2 hours and poured into ice-cold saturated sodium bisulphite solution. The reddish precipitate was crystallised twice from alcohol, giving colourless needles (0·8 g.), m. p. 317° (Found: C, 72·3; H, 3·2. $C_{24}H_{14}O_6$ requires C, 72·4; H, 3·5%). 4′ : 4″-*Dihydroxydiflavone* assumes an intense red colour in contact with sulphuric acid, and the pale orange solution in sulphuric acid has a faint green fluorescence. The substance gives in aqueous caustic soda a magenta solution. An alcoholic solution gives hardly any coloration with ferric chloride; turns yellow on the addition of potassium acetate solution and deposits yellow needles after a moment; and gives a very pale yellow curdy precipitate with lead acetate solution. A solution of the substance in absolute alcohol gives with sodium amalgam a bright magenta colour, which slowly becomes dirty brown and finally brownish-green; with magnesium and hydrochloric acid it gives a pink coloration. The substance is sparingly soluble in boiling glacial acetic acid, but readily forms a yellow solution on the addition of a drop of sulphuric acid; no mineral acid compound, however, is deposited on cooling.

When the dihydroxy-compound was boiled with acetic anhydride and a few drops of pyridine during 2 hours, and the product crystallised from alcohol, colourless needles, m. p. 204—205°, were obtained (Found: C, 69·7; H, 3·7. $C_{28}H_{18}O_8$ requires C, 69·7; H, 3·7%).

7-*Hydroxy*-4′-*methoxy*-6-*acetylflavone* (III; R = $C_6H_4{\cdot}OMe$).—The alkaline filtrate after removal of the dimethoxydiflavone (above) was saturated with carbon dioxide. The precipitate obtained crystallised from dilute acetic acid in flesh-coloured needles (0·3 g.), m. p. 160—161° (Found: C, 69·7; H, 4·5. $C_{18}H_{14}O_5$ requires C, 69·6; H, 4·5%). The red solution of the *substance* in sulphuric acid showed a weak violet fluorescence. An alcoholic solution gave a brown colour with ferric chloride.

7-Hydroxy-3′ : 4′-dimethoxy-6-acetylflavone [III; R = $C_6H_3(OMe)_2$].—Diacetylresorcinol (5·0 g.), veratric anhydride (Allan and Robinson, J., 1926, 2334) (61 g.), and sodium veratrate (10·0 g.) were heated together at 190° for 6 hours, and the product was boiled with alcoholic potash. When the solution was poured into water, no diflavone separated. Carbon dioxide was passed through the clear liquid for several hours, and the precipitate collected (4·3 g.). After repeated crystallisation from glacial acetic acid, the *substance* was obtained as minute yellow needles, m. p. 182° (Found: C, 67·1; H, 4·7. $C_{19}H_{16}O_6$ requires C, 67·0; H, 4·7%). It gave a yellow solution in aqueous caustic soda, a red solution with a faint violet fluorescence in sulphuric acid, and a weak orange coloration with alcoholic ferric chloride. The *acetyl* derivative melted at 141° (Found: C, 65·6; H, 4·7. $C_{21}H_{18}O_7$ requires C, 65·9; H, 4·9%).

3′ : 4′ : 5′ : 3″ : 4″ : 5″ - *Hexamethoxydiflavone*. — *Trimethylgallic anhydride* (compare Fischer and Freudenberg, *Ber.*, 1913, **46**, 1129; Kalff and Robinson, J., 1925, **127**, 181). To a mixture of trimethylgallic acid (" Organic Syntheses," **6**, 96) (80 g.), pyridine (35 g.), and toluene (115 c.c.), cooled in ice and mechanically stirred, a 20% solution of carbonyl chloride in toluene (115 c.c.) was added during 2 hours. After 2 hours' further stirring, ice-cold dilute hydrochloric acid was introduced, the mixture stirred, and the product collected, and washed successively with water, sodium carbonate solution and water, and dried in a desiccator. The substance (62 g.), m. p. 153—156°, was used directly for the chromone synthesis.

Diacetylresorcinol (2·0 g.), trimethylgallic anhydride (12·0 g.), and sodium trimethylgallate (4·0 g.) were heated together at 200° for 4 hours. The mass was then boiled with 10% aqueous caustic potash (50 c.c.) for a few minutes and cooled; the dark brown residue, repeatedly crystallised from dilute acetic acid, gave a minute amount of yellow needles, m. p. 134—136° (decomp.).

7 - *Hydroxy* - 3′ : 4′ : 5′ - *trimethoxy* - 6 - *acetylflavone* [III; R = $C_6H_2(OMe)_3$].—The alkaline filtrate (above) was saturated with carbon dioxide, and the precipitate obtained crystallised from aqueous acetic acid, forming long yellow needles (0·65 g.), m. p. 224—225° (Found: C, 65·0; H, 4·9. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%). The pale brown solution of the substance in sulphuric acid had a weak violet fluorescence. The alcoholic solution gave a dark red colour with ferric chloride. The *acetyl* derivative melted at 156—157° (Found: C, 64·2; H, 4·8. $C_{22}H_{20}O_8$ requires C, 64·1; H, 4·8%).

3 : 3′-*Diacetyl*-2 : 2′-*dimethyldichromone* (IV).—A mixture of diacetylresorcinol (5·0 g.), fused sodium acetate (10·0 g.), and acetic anhydride (50 g.) was vigorously boiled under reflux during 8 hours.

The excess of acetic anhydride was then distilled off, and the residue treated with boiling alcoholic caustic potash (100 c.c.) for a few minutes. After dilution with much water, the precipitate was collected, dissolved in glacial acetic acid (charcoal), poured into water, and finally crystallised from molten naphthalene. The light brown plates (0·3 g.) obtained melted at 261—264° (decomp.) (Found : C, 66·4; H, 4·5. $C_{18}H_{14}O_6$ requires C, 66·2; H, 4·3%). The *dichromone* forms in sulphuric acid a red solution with a green fluorescence.

7-*Hydroxy*-6-*acetyl*-2-*methylchromone* (III; R = Me).—Acidification of the alkaline filtrate and crystallisation of the precipitate from dilute acetic acid gave small needles (1·4 g.), m. p. 134—135° (after sintering at 104°) (Found : C, 65·8; H, 4·8. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·5%). The pale orange solution of the *chromone* in sulphuric acid has a violet fluorescence. The alcoholic solution gives with ferric chloride a reddish-violet colour.

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