A New Synthesis of Flavonols.

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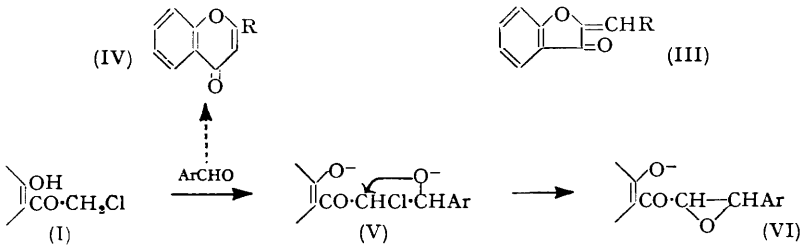
Flavonols (II) are obtained in yields of up to 35% by the condensation of ω-chloro-*o*-hydroxyacetophenones (I) with aromatic aldehydes in the cold in presence of ethanolic alkali.

Kostanecki and his collaborators (Woker, Kostanecki, and Tambor, *Ber.*, 1903, **36**, 4235; Kostanecki, *Bull. Soc. chim. France*, 1903, **29**, Appendix, 1) showed that Friedländer (*e.g.*, Brüll and Friedländer, *Ber.*, 1897, **30**, 297; Simonis, *Z. angew. Chem.*, 1926, **39**, 1461) had obtained 2-arylidenecoumaran-3-ones (III) and not, as he thought, flavones (IV), by the reaction of ω-halogeno-*o*-hydroxyacetophenones (I) with aromatic aldehydes in presence of alkali. It has now been found, unexpectedly,* that if the condensation is carried out in the cold in presence of excess of alkali, the corresponding flavonol (II) is generally obtained in a yield of up to 35% calculated on (I). Twelve flavonols have been prepared in this way (Experimental, section A). With increase in temperature or a deficiency in alkali

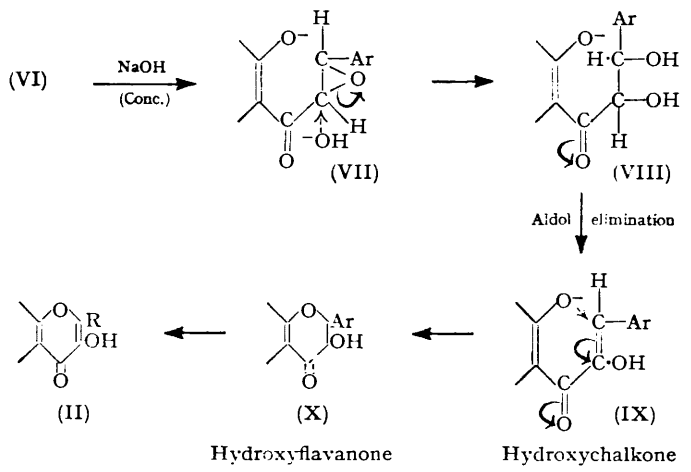
* See Hayden, O'Sullivan, Philbin, and Wheeler (*Research*, 1952, **5**, 396); the first observation was made by O'Sullivan (M.Sc. Thesis, National University of Ireland, 1951) in other work on derivatives of ω-chloro-*o*-hydroxyacetophenones (Philbin, O'Sullivan, and Wheeler, *J.*, 1954, 4174).

2-arylidenecoumaran-3-ones (III), hitherto the only known products, are obtained [Experimental, sections B and C; see also A (13)]. 3-Hydroxyflavanones (X) have also been isolated and are probably intermediate in the production of (II) (Experimental, section C).



The mechanism suggested for the production of (II) and (III) from (I) is based on the formation of the intermediate keto-epoxide (VI) (cf. Widman, *Ber.*, 1916, **49**, 477). The conversion of (VI) into (II) and (III) in the presence of alkaline hydrogen peroxide has been discussed by Geissman and Fukushima (*J. Amer. Chem. Soc.*, 1948, **70**, 1686; cf. Anand, Iyer, and Venkataraman, *Proc. Indian Acad. Sci.*, 1949, **29**, *A*, 203; Gripenberg, *Acta Chem. Scand.*, 1953, **7**, 1323). In the present instance the transformation of (VI) into (X) in excess of alkali is considered in view of the high concentration of OH^- to involve the external S_N2 reaction (VII ⟶ VIII) (see Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Sons, Ltd., London, 1953, p. 341). This is followed by an aldol elimination of water (VIII ⟶ IX) and a chalkone–flavanone rearrangement (IX ⟶ X). The reactivity of epoxychalkones is such that alternative reaction mechanisms are possible.

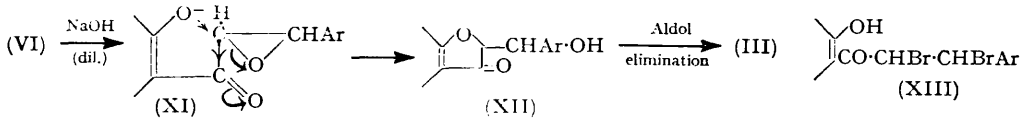
Geissman (personal communication) has suggested that the oxidation of (X) to (II) is effected by a portion of the epoxide (VI). As an alternative, Marathe, Chandorkar, and Limaye (*Rasāyanam*, 1952, **2**, 48; cf. Gripenberg, *loc. cit.*) have shown that 3-hydroxyflavanones (X) disproportionate in alkali in the absence of oxygen to form flavonols among other products; the reduced product is the corresponding flavanone (Marathe, *Science and Culture*, 1954, **19**, 516). When the amount of alkali present is reduced, the internal S_N2 reaction (XI ⟶ XII) predominates, and (XII) forms (III) by an aldol elimination. It



will be observed that compound (XII) is a probable intermediate in the synthesis of (III) by the condensation of an aromatic aldehyde with a coumaran-3-one (Gripenberg, *loc. cit.*).

Hayden, O'Sullivan, Philbin, and Wheeler (*Research*, 1952, **5**, 396) suggested that the new synthesis of (II) from (I) is analogous to the Rasoda reaction (Limaye, *Rasāyanam*,

1950, **2**, 1) for the production of flavonols by the action of water on 2′-hydroxychalkone dibromides (XIII) followed by treatment of the product (V; Cl replaced by Br) with alkali. The reaction scheme here discussed is similar to that established by Limaye and his collaborators for the Rasoda reaction (see Marathey, Ph.D. Thesis, Poona, 1952; *Science and Culture*, 1954, **20**, 135; Marathe, Ph.D. Thesis, Poona, 1953, and *loc. cit.*).



In some of the condensation reactions small quantities of complex products were obtained. Investigation of these products is in hand.

Experimental

Crystallisation was from ethanol unless otherwise stated.

(A) *Synthesis of Flavonols : Use of Excess of Cold Ethanolic Alkali.*—A mixture of the ω-chloro-2-hydroxyacetophenone (1 mol.; 1 pt.) and the aldehyde (2 mols.) in ethanol (5 pts.) was treated at below room temperature (ice-water cooling) with aqueous sodium hydroxide (50%; 3·5 mols. of NaOH) in ethanol (4 pts.). The precipitate of the sodium salt of the flavonol was collected after 3 hr. and decomposed by 10% hydrochloric acid to give the substantially pure flavonol (m. p. *ca.* 3° low). The pure product was obtained after one crystallisation, with a loss in yield of about 8%. No change in yield was obtained by increasing the proportion of aldehyde or alkali, or by carrying out the reaction in nitrogen or in presence of a trace of quinol. Addition of the ketone–aldehyde mixture to the ethanolic alkali reduced the yield. The following 12 flavonols were prepared in this way. The yield shown is of pure product (one crystallisation) calculated on the chloro-ketone.

(1) ω-Chloro-2-hydroxyacetophenone (ketone 1) (Fries and Pfaffendorf, *Ber.*, 1910, **43**, 212; Auwers, *Ber.*, 1926, **59**, 2899) and benzaldehyde gave flavonol (30%), pale yellow needles, m. p. 169—170°, not depressed by addition of an authentic sample (Algar and Flynn, *Proc. Roy. Irish Acad.*, 1934, **42**, *B*, 5) [acetate, m. p. 109° (Found : C, 72·4; H, 4·6. Calc. for $C_{17}H_{12}O_4$: C, 72·9; H, 4·3%)]. Kostanecki and Szabrański (*Ber.*, 1904, **37**, 2820) give m. p. 169—170° for the flavonol and 110—111° for the acetate. *3-Benzoyloxyflavone* formed needles (from methanol), m. p. 159—160° (Found : C, 77·1; H, 4·3. $C_{22}H_{14}O_4$ requires C, 77·2; H, 4·1%).

(2) Ketone (1) and *p*-anisaldehyde gave 4′-methoxyflavonol (31%), yellow prisms (from chloroform), m. p. 233—234°, not depressed by addition of an authentic sample (Algar and Flynn, *loc. cit.*) [acetate, m. p. 132—133° (Found : C, 69·5; H, 4·8. Calc. for $C_{18}H_{14}O_5$: C, 69·7; H, 4·6%)]. Algar and Flynn (*loc. cit.*) give m. p. 235° for the flavonol. Edelstein and Kostanecki (*Ber.*, 1905, **38**, 1507) give m. p. 138—139° for the acetate. *3-Benzoyloxy-4′-methoxyflavone*, needles (from methanol), m. p. 149—150° (Found : C, 74·1; H, 4·4. $C_{23}H_{16}O_5$ requires C, 74·2; H, 4·3%).

(3) Ketone (1) and veratraldehyde gave 3′ : 4′-dimethoxyflavonol (30%), yellow needles, m. p. 201—202° (Found : C, 68·7; H, 4·9. Calc. for $C_{17}H_{14}O_5$: C, 68·5; H, 4·7%) [acetate, m. p. 112—113° after two crystallisations (Found : C, 67·0; H, 4·7. Calc. for $C_{19}H_{16}O_6$: C, 67·0; H, 4·7%)]. Berstein, Fraschina, and Kostanecki (*Ber.*, 1905, **38**, 2177) give m. p. 199—200° for the flavonol and 130—131° for the acetate—the discrepancy in the m. p. of the acetate cannot be explained.

(4) ω-Chloro-2-hydroxy-4-methoxyacetophenone (ketone 2) (Auwers and Pohl, *Annalen*, 1914, **405**, 264; Sonn, *Ber.*, 1917, **50**, 1268) and benzaldehyde gave 7-methoxyflavonol (33%), pale yellow needles, m. p. 179—180° (Found : C, 72·0; H, 4·5. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%) [acetate, m. p. 177—178° (Found : C, 69·4; H, 4·4. Calc. for $C_{18}H_{14}O_5$: C, 69·7; H, 4·5%)]. Auwers and Pohl (*loc. cit.*, p. 271) give m. p. 177—178° for the flavonol and 176° for the acetate.

(5) Ketone (2) and *p*-anisaldehyde gave 7 : 4′-dimethoxyflavonol (13%), yellow needles, m. p. 192—193° (Found : C, 68·4; H, 4·7. Calc. for $C_{17}H_{14}O_5$: C, 68·5; H, 4·7%) [acetate, m. p. 193° (Found : C, 66·8; H, 4·9. Calc. for $C_{19}H_{16}O_6$: C, 67·1; H, 4·8%)]. Juppen and Kostanecki (*Ber.*, 1904, **37**, 4162) give m. p. 196—197° for the flavonol and 193—194° for the acetate.

(6) Ketone (2) and veratraldehyde gave 7 : 3′ : 4′-trimethoxyflavonol (fisetin 7 : 3′ : 4′-trimethyl ether) (20%), yellow needles, m. p. 186—187° (Found : C, 66·2; H, 5·0. Calc. for $C_{18}H_{16}O_6$: C, 65·9; H, 4·9%) [acetate, m. p. 169—170° (Found : C, 64·9; H, 5·0. Calc. for $C_{20}H_{18}O_7$: C, 64·9; H, 4·9%)]. Kostanecki and Nitkowski (*Ber.*, 1905, **38**, 3588) give m. p. 186° for the flavonol and 170° for the acetate. It was necessary in the preparation of this flavonol to increase the quantity of sodium hydroxide to 5 mols. in order to reduce the formation of benzylidenecoumaranone. For purification, the crude material obtained by decomposition of the sodium salt was extracted from benzene by aqueous sodium hydroxide (2%), and the flavonol was precipitated by acidification of the alkaline solution, and was crystallised.

(7) ω-Chloro-2-hydroxy-5-methylacetophenone (ketone 3) (Fries and Finck, *Ber.*, 1908, **41**, 4276; Auwers, *Annalen*, 1909, **364**, 164) and benzaldehyde gave 6-methylflavonol (33%), light brown needles, m. p. 198—199° (Found : C, 76·1; H, 4·8. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8%) [benzoate (from methanol), m. p. 168—169° (Found : C, 77·3; H, 4·7. Calc. for $C_{23}H_{16}O_4$: C, 77·5; H, 4·5%)]. Auwers and Müller (*Ber.*, 1908, **41**, 4239) give m. p. 196—197° for the flavonol and 167—168° for the benzoate. *3-Acetoxy-6-methylflavone*, needles, m. p. 109—110° (Found : C, 73·9; H, 5·0. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%).

(8) Ketone (3) and *o*-anisaldehyde gave little precipitate of the sodium salt of the flavonol by the standard procedure. The solution was filtered and acidified with 10% hydrochloric acid, and, next day, the precipitate of *2′-methoxy-6-methylflavonol* (24%) was collected. It formed prisms, m. p. 201—202° (from aqueous methanol followed by chloroform–ligroin) (Found : C, 72·7; H, 5·2. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%). The ethanolic ferric colour was purple, and the fluorescence in sulphuric acid blue. *3-Acetoxy-2′-methoxy-6-methylflavone* separated as a powder, m. p. 156—157° (Found : C, 70·8; H, 5·3. $C_{19}H_{16}O_5$ requires C, 70·4; H, 5·0%).

In a preliminary experiment under the conditions described at (A) above, but without cooling, ketone (3) and *o*-anisaldehyde gave a precipitate of *2-o-anisylidene-5-methylcoumaran-3-one* (3%), yellow powder (Found : C, 76·5; H, 5·2. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%), m. p. 187—188° (from aqueous ethanol), not depressed by addition of a sample, m. p. 189—190°, prepared by the general method of Auwers and Müller (*loc. cit.*) from *o*-anisaldehyde and 5-methylcoumaran-3-one. This compound gave a red solution in sulphuric acid which did not fluoresce in ultra-violet light. The isomeric 2′-methoxy-6-methylflavone has m. p. 110° (Baker and Besly, *J.*, 1940, 1106).

(9) Ketone (3) and *p*-anisaldehyde gave 4′-methoxy-6-methylflavonol (35%), yellow needles, m. p. 192—193° (Found : C, 72·0; H, 4·9; OMe, 11·6. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 5·0; 1OMe, 11·0%) [acetate, m. p. 137—138° (Found : C, 70·9; H, 5·0; OMe, 9·6. Calc. for $C_{19}H_{16}O_5$: C, 70·4; H, 5·0; 1OMe, 9·6%)]. Limaye (*Rasāyanam*, 1950, **2**, 5) gives m. p. 191—192° for the flavonol and 136—137° for the acetate. *3-Benzoyloxy-4′-methoxy-6-methylflavone* formed needles, m. p. 171—172° (Found : C, 74·1; H, 4·7. $C_{24}H_{18}O_5$ requires C, 74·6; H, 4·7%).

(10) Ketone (3) and piperonaldehyde gave 6-methyl-3′ : 4′-methylenedioxyflavonol (25%), pale yellow needles, m. p. 196—197° (Found : C, 68·8; H, 4·2. Calc. for $C_{17}H_{12}O_5$: C, 68·9; H, 4·1%). Ozawa, Okuda, Kawanishi, and Fujii (*J. Pharm. Soc. Japan*, 1951, **71**, 1178; *Chem. Abs.*, 1952, **46**, 6124) give m. p. 195—196°. *3-Acetoxy-6-methyl-3′ : 4′-methylenedioxyflavone* formed pale pink needles, m. p. 168—169° (Found : C, 67·3; H, 4·2. $C_{19}H_{14}O_6$ requires C, 67·5; H, 4·2%).

(11) Ketone (3) and 2 : 4-dimethoxybenzaldehyde (Cullinane and Philpott, *J.*, 1929, 1763) gave *2′ : 4′-dimethoxy-6-methylflavonol* (18%; two crystallisations), yellow prisms, m. p. 230—231° (Found : C, 69·2; H, 5·1. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). The flavonol gave a dark green ethanolic ferric colour and exhibited a blue ultra-violet fluorescence in sulphuric acid solution. *3-Acetoxy-2′ : 4′-dimethoxy-6-methylflavone* formed pale yellow prisms, m. p. 134—135° (Found : C, 68·3; H, 5·2. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

In a preliminary experiment under the standard conditions (A above), but without cooling, ketone (3) and 2 : 4-dimethoxybenzaldehyde gave a small precipitate of *2-(2 : 4-dimethoxybenzylidene)-5-methylcoumaran-3-one*, yellow prisms, m. p. 192—193° (Found : C, 73·2; H, 5·5. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%) The compound formed in sulphuric acid a red non-fluorescent solution characteristic of 2-benzylidenecoumaran-3-ones.

(12) Ketone (3) and veratraldehyde gave *3′ : 4′-dimethoxy-6-methylflavonol* (33%), yellow needles (from aqueous ethanol), m. p. 200—201° (Found : C, 69·1; H, 5·2. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). The ethanolic ferric colour was violet and the ultra-violet fluorescence in sulphuric acid solution was yellow. *3-Acetoxy-3′ : 4′-dimethoxy-6-methylflavone* formed needles, m. p. 146—147° (Found : C, 68·2; H, 5·3. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

(13) Ketone (3) and *p*-hydroxybenzaldehyde gave only a trace of precipitate when mixed

with ethanolic alkali as described at (A) above. The solution was filtered and acidified with concentrated hydrochloric acid. Next day the precipitate of 2-*p*-hydroxybenzylidene-5-methylcoumaran-3-one was collected and crystallised from aqueous acetic acid. It formed an orange powder (18%), m. p. 252—254° (decomp.). Auwers and Müller (*Ber.*, 1908, **41**, 4238) give m. p. 254—255°. Methylation of the coumaranone by methyl sulphate and potassium carbonate in acetone gave 2-*p*-anisylidene-5-methylcoumaran-3-one, yellow needles (from methanol), m. p. 153—154°, not depressed by addition of a sample prepared by Auwers and Müller's method (*loc. cit.*) from *p*-anisaldehyde and 5-methylcoumaran-3-one (cf. Auwers and Anschütz, *Ber.*, 1921, **54**, 1556).

(B) *Production of Benzylidenecoumaranones: Use of Excess of Hot Ethanolic Alkali.*—The following 2-benzylidenecoumaran-3-ones were precipitated when ketone (2) and the corresponding aldehyde were mixed with concentrated ethanolic alkali as described at (A), but at about 70°. Yields calculated on the chlorohydroxy-ketone are given in parentheses.

2-Benzylidene-6-methoxycoumaran-3-one separated in needles (50%), m. p. 145—146° (Found: C, 75·8; H, 4·6. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8%). Auwers and Pohl (*Annalen*, 1914, **405**, 268) give the same m. p. The isomeric 7-methoxyflavone has m. p. 110—111° (Emilewicz and Kostanecki, *Ber.*, 1899, **32**, 312).

2-*p*-Anisylidene-6-methoxycoumaran-3-one crystallised in yellow needles (60%), m. p. 134—135° (Found: C, 72·4; H, 5·3. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 5·0%). Panse, Shah, and Wheeler (*J. Univ. Bombay*, 1941, **10**, 83) give m. p. 134°. The isomeric 7 : 4′-dimethoxyflavone has m. p. 143—144° (Tambor, *Ber.*, 1916, **49**, 1710).

Methoxy-2-veratrylidene-6-coumaran-3-one formed pale yellow needles (70%), m. p. 185—186° (Found: C, 69·7; H, 5·4. Calc. for $C_{18}H_{16}O_5$: C, 69·2; H, 5·1%). Auwers and Pohl (*loc. cit.*) give m. p. 183—184°. The solution in sulphuric acid was deep red with a weak orange-red fluorescence. The isomeric 7 : 3′ :4′-trimethoxyflavone had m. p. 177° (Dr. A. Schiavello, personal communication; cf. Schiavello and Sebastiani, *Gazzetta*, 1949, **79**, 912).

(C) *Production of 3-Hydroxyflavanones and of 2-Benzylidenecoumaran-3-ones: Use of Less than 0·5 Mol. of Sodium Hydroxide.*—A mixture of chlorohydroxy-ketone (1 mol.; 1 pt.), aldehyde (1·5 mol.), aqueous sodium hydroxide (5%; 0·35 mol. of NaOH), and ethanol (10 pts.) was shaken for 3 hr. and, next day, was diluted with water (75 pts.) and extracted with ether. The extract was washed successively with aqueous sodium hydrogen sulphite, aqueous sodium hydroxide (4%), and water, and dried. The residue obtained on evaporation of the solvent was crystallised. The yields shown are calculated on sodium hydroxide which was in deficit.

3-Hydroxyflavanones. Ketone (1) and benzaldehyde gave 3-hydroxyflavanone (20%), prisms, m. p. 175—177°, raised by crystallisation from methanol to 182—183° (Found: C, 75·3; H, 5·0. Calc. for $C_{15}H_{12}O_3$: C, 75·0; H, 5·0%). The product did not depress the m. p. of an authentic sample (Reichel and Steudel, *Annalen*, 1942, **553**, 90). Oyamada (*Bull. Chem. Soc. Japan*, 1941, **16**, 411; *Chem. Abs.*, 1947, **41**, 3797) gives m. p. 183—184° for the hydroxyflavanone.

Ketone (1) and veratraldehyde gave 3-hydroxy-3′ : 4′-dimethoxyflavanone (3%), needles (from methanol), m. p. 157—158° (Found: C, 68·4; H, 5·4. Calc. for $C_{17}H_{16}O_5$: C, 68·0; H, 5·4%). Oyamada (*J. Chem. Soc. Japan*, 1943, **64**, 335; *Chem. Abs.*, 1947, **41**, 3798) gave m. p. 155—157°.

2-Benzylidenecoumaran-3-ones. Ketone (1) and *p*-anisaldehyde gave 2-*p*-anisylidenecoumaran-3-one (11%), yellow needles, m. p. 138—139°, not depressed by addition of a sample prepared from the corresponding coumaranone and aldehyde (cf. Auwers and Anschütz, *Ber.*, 1921, **54**, 1558, 3331) (Found: C, 76·6; H, 5·1. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8%).

Ketone (3) and benzaldehyde gave 2-benzylidene-5-methylcoumaran-3-one (40%), pale yellow prisms (from methanol), m. p. 119°, not depressed by addition of an authentic sample (Auwers and Müller, *Ber.*, 1908, **41**, 4238) (Found: C, 81·9; H, 5·2. Calc. for $C_{16}H_{12}O_2$: C, 81·3; H, 5·1%).

Ketone (3) and *p*-anisaldehyde gave 2-*p*-anisylidene-5-methylcoumaran-3-one (30%), yellow needles (from methanol), m. p. 152—153°, not depressed by addition of an authentic sample (Auwers and Anschütz, *loc. cit.*, p. 1556).

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