813. *The Synthesis of Flavan-2 : 3-diols (Dihydro-α : 2-dihydroxychalcones).*

By J. W. GRAMSHAW, A. W. JOHNSON, and T. J. KING.

The products of reduction of luteolinidin and apigeninidin chlorides by lithium aluminium hydride are shown to be flav-2-enes. Hydroxylation of 5 : 7 : 3′ : 4′-tetramethoxyflav-2-ene yields a flavan-2 : 3-diol which exists almost entirely as the open-chain tautomer, a dihydro-α : 2-dihydroxychalcone. Treatment of this diol with acid yields cyanidin chloride tetramethyl ether which has been synthesised by an independent route.

MOST of the *leuco*anthocyanins of known structure are derivatives of flavan-3 : 4-diol (I) and the chemistry of these substances is summarised in recent reviews.[1] Nearly all the syntheses of flavan-3 : 4-diols reported so far have involved the reduction of either a flavonol [2,3,4] or a flavanonol [5,6,7,8] but the syntheses are complicated by the existence of four racemic forms resulting from asymmetric centres at positions 2, 3, and 4. Thus two racemates of 3′ : 4′ : 7 : 8-tetramethoxyflavan-3 : 4-diol were obtained by reduction of the corresponding flavanonol with lithium aluminium hydride and hydrogenation over a platinum catalyst respectively,[6] and each differed from the racemate, the (—)-form of which was identical with tetra-*O*-methylmelacacidin, prepared by hydrogenation of the

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[1] Swain and Bate-Smith, " The Chemistry of Vegetable Tannins," Soc. Leather Trades Chemists, Croydon, 1956, p. 109; King, *Sci. Proc. Royal Dublin Soc.*, 1955, **27**, 87.

[2] Mozingo and Adkins, *J. Amer. Chem. Soc.*, 1938, **60**, 669.

[3] Bauer, Birch, and Hillis, *Chem. and Ind.*, 1954, 757.

[4] King and Clark-Lewis, *J.*, 1955, 3384.

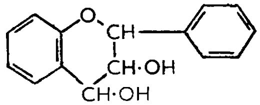
[5] Swain, *Chem. and Ind.*, 1954, 1144; Freudenberg and Roux, *Naturwiss.*, 1954, **41**, 450.

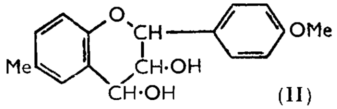
[6] Joshi and Kulkarni, *Chem. and Ind.*, 1954, 1421, 1456; 1956, 124.

[7] Bognar and Rakosi, *ibid.*, p. 188.

[8] Keppler, *J.*, 1957, 2721.

corresponding flavonol.[4] Joshi and Kulkarni [6] have also synthesised three of the four racemates (II).


(I)


(II)

Although some speculations were made concerning the conformations of the heterocyclic-ring substituents, generalisations on the orientations of hydroxyl groups produced by the reductions of cyclic ketones by different methods were somewhat complicated by the observation [7] that the same isomer (I) is produced by reduction of flavanonol with lithium aluminium hydride and by hydrogenation over platinum, although the product differed from that obtained by hydrogenation of flavonol over copper oxide.[2]

The hydroxylation of flav-3-enes seemed to offer an alternative and stereospecific approach to the flavan-3 : 4-diol system and a study of the reaction was undertaken in order to augment the previous views on the stereochemistry of the products and to correlate the conformations of the *leuco*anthocyanins with those of the catechins.[9] Flav-3-enes containing 3-oxygenated substituents were claimed by Karrer and Seyhan [10] as the products obtained from the reduction of the corresponding flavylium salts with lithium aluminium hydride, although in a later study of the reaction [11] it was pointed out that flav-2-ene structures were not excluded for the products. On the other hand flav-2-enes can be obtained by dehydration of *epi*catechins [12,13] and other methods,[14] the structures being assigned on the basis of the method of preparation and chemical properties.[15] Thus, although a dihydro-2-hydroxychalcone was obtained after hydrolysis with dilute acetic acid, the possibility of prototropic rearrangement of the flav-3-ene to the 2-isomer was ignored. We have prepared luteolinidin tetramethyl ether [16] (III) by condensation of 3 : 4-dimethoxyphenyl ethynyl ketone with phloroglucinol dimethyl ether following Johnson and Melhuish's method,[17] and have confirmed the identity of the product by the preparation of derivatives and by ring fission under acetylating conditions whereby 2-acetoxy-4 : 6 : 3′ : 4′-tetramethoxychalcone (IV) was obtained. Reduction of the flavylium chloride (III) with lithium aluminium hydride gave the flav-2-ene (V), the formulation of which is based upon the presence of a free methylene group in the molecule as determined by the measurement of the nuclear magnetic resonance spectrum. We are very grateful to Dr. N. Sheppard who performed this experiment. In a similar series of transformations, condensation of phloroglucinol dimethyl ether and ethynyl *p*-methoxyphenyl ketone gave apigeninidin chloride, which by reduction with lithium aluminium hydride formed 5 : 7 : 4′-trimethoxyflav-2-ene. The flav-2-ene (V) has been prepared previously by Freudenberg and his co-workers [12] by the action of hydrazine on the toluene-*p*-sulphonate of 5 : 7 : 3′ : 4′-tetramethyl*epi*catechin, and acid hydrolysis of (V) gave the dihydrochalcone (VI), tautomeric with the 2-hydroxyflavan (VII). By analogy with the Δ^2-structure of the flavene (V) it is probable that the 3-methoxyflavenes prepared by Karrer and Seyhan [10] are also Δ^2-compounds.

Thus our original objective, the preparation of 3 : 4-dihydroxyflavans, was not possible by this approach but we have been able to utilise the flav-2-ene (V) to prepare and examine

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[9] Whalley, "The Chemistry of Vegetable Tannins," Soc. Leather Trades Chemists, Croydon, 1956, p. 109; Birch, Clark-Lewis, and Robertson, *J.*, 1957, 3586.

[10] Karrer and Seyhan, *Helv. Chim. Acta*, 1950, **33**, 2209.

[11] Freudenberg and Weinges, *Annalen*, 1954, **590**, 140.

[12] Freudenberg, Fikentscher, and Harder, *ibid.*, 1925, **441**, 157.

[13] King, Clark-Lewis, and Forbes, *J.*, 1955, 2948.

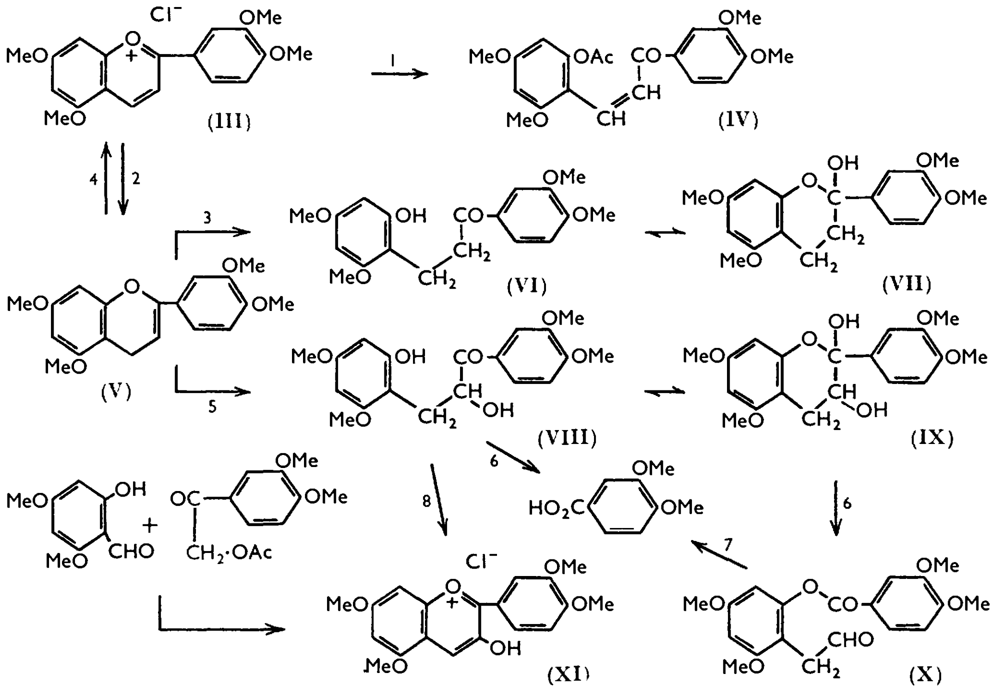
[14] Shah, Kulkarni, and Joshi, *J. Sci. Ind. Res., India*, 1954, **13**, *B*, 186; Shriner, "The Roger Adams Symposium," John Wiley and Sons, Inc., New York, 1955, p. 103.

[15] Freudenberg *et al.*, *Annalen*, 1925, **442**, 309; 1926, **446**, 87.

[16] Pratt, Robinson, and Williams, *J.*, 1924, **125**, 199.

[17] Johnson and Melhuish, *J.*, 1947, 346.

the properties of a compound of the isomeric 2 : 3-dihydroxyflavan structure. Such compounds are as yet unknown although Karrer and Fatzer[18] suggested that they might cyclise readily to benzoylcoumarans, a prediction which we have not substantiated. Like all simple 2-hydroxyflavans, the product of hydroxylation of the flav-2-ene exhibited ring-chain tautomerism and in fact existed largely as the dihydro-2 : α-dihydroxychalcone



Reagents: 1, Pyridine–Ac_2O. 2, $LiAlH_4$. 3, 50% AcOH. 4, Dry HCl in C_6H_6. 5, OsO_4. 6, HIO_4. 7, 20% KOH. 8, Conc. HCl in Pr^iOH.

(VIII), as shown by its physical properties, particularly the ultraviolet and infrared spectra. The hydroxylation of the flavene (V) was best effected with osmium tetroxide; an oxidation with monoperphthalic acid gave a mixture of the epoxide, the diol, and (probably) a little of the 3-oxoflavan. Treatment of this mixture with acetic acid followed by acetic anhydride and pyridine gave the crystalline diacetate of compound (VIII), from which the αβ-dihydro-α : 2-dihydroxychalcone (VIII), identical with that obtained after oxidation with osmium tetroxide, was obtained by hydrolysis. Some evidence for the existence of compound (VIII) in the flavan-2 : 3-diol form (IX) was obtained from the results of periodate oxidation. Veratric acid was formed (from the open-chain form, VIII) together with smaller quantities of an ester, presumably (X) (from the cyclic form, IX) which gave more veratric acid after hydrolysis. A further product isolated from the perphthalic oxidation of (VIII) has been formulated tentatively as the dioxo-alcohol (XII). The dihydro-α : 2-dihydroxychalcone (VIII), the corresponding diacetate, and the crude epoxide all gave cyanidin chloride 5 : 7 : 3′ : 4′-tetramethyl ether (XI) on treatment with hydrogen chloride. This anthocyanidin, which has been prepared by Karrer and his co-workers[19] as well as by Hayashi,[20] has been synthesised by condensation of phloroglucinaldehyde dimethyl ether and ω-acetoxyacetoveratrone and the product shown to

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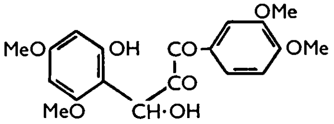
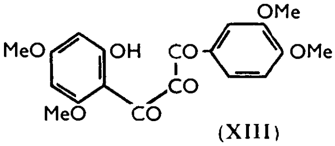
[18] Karrer and Fatzer, *Helv. Chim. Acta*, 1942, **25**, 1129.
[19] Karrer, Widmer, Helfenstein, Hürlimann, Nievergelt, and Monserrat-Thoms, *ibid.*, 1927, **10**, 729.
[20] Hayashi, *Acta Phytochim.* (*Japan*), 1934, **8**, 65.

be identical with that derived from dihydro-α : 2-dihydroxy-4 : 6 : 3′ : 4′-tetramethoxychalcone. The flavan-2 : 3-diols or dihydro-α : 2-dihydroxychalcones may thus be regarded as another type of *leuco*anthocyanin, and the original formulation [21] of *leuco*-anthocyanins as flavan-2 : 3 : 4-triols is of interest in this connection. The flavan-3 : 4-diols are probably only one of several groups of *leuco*anthocyanins.



(XII)



(XIII)

Aerial oxidation of compound (VIII) gave a product which from analytical evidence appeared to be 1-(3 : 4-dimethoxyphenyl)-3-(2-hydroxy-4 : 6-dimethoxyphenyl)propane-1 : 2 : 3-trione (XIII), a structure which is consistent with the physical evidence. This product failed to yield cyanidin chloride 5 : 7 : 3′ : 4′-tetramethyl ether on treatment with hydrochloric acid in propan-2-ol.

EXPERIMENTAL

Ultraviolet absorption spectra were determined in 95% ethanol except where otherwise stated.

3-(3 : 4-*Dimethoxyphenyl)prop-2-yn-1-ol.*—A suspension of sodium acetylide in liquid ammonia (600 c.c.) was prepared from sodium (13·6 g.) in the usual manner. Redistilled veratraldehyde (83 g.) in purified dioxan (55 c.c.) was added to the sodium acetylide during 1½ hr. while a stream of acetylene was passed through the stirred suspension. The passage of acetylene was continued for another 6 hr., after which ammonium chloride (35 g.) was added and the ammonia allowed to evaporate. The residue was triturated with water and the alcohol (90 g., 94%), m. p. 97—98°, collected by filtration and used in the next stage without further purification. For analysis, the product was sublimed at 90°/0·1 mm. and afforded white needles, m. p. 99·5—100° (lit.,[22] 99°) (Found: C, 68·5; H, 5·95. Calc. for $C_{11}H_{12}O_3$: C, 68·7; H, 6·3%).

3 : 4-*Dimethoxyphenyl Ethynyl Ketone.*—The foregoing alcohol (28·8 g.) in cooled acetone (200 c.c.) was stirred under nitrogen while chromium trioxide (12·45 g.) in water (42 c.c.) and concentrated sulphuric acid (10·5 c.c.) was added at 5° during 1½ hr. After about 1 hr. a crystalline product separated and at this stage acetone (50 c.c.) was added. After the addition of the chromium trioxide, the reaction mixture was stirred for a further 30 min. and then diluted with water (1 l.). The *ketone* which separated was removed by filtration and after crystallisation from aqueous methanol formed colourless needles, m. p. 118·5—119·5° (26·5 g., 93%). For analysis a sample was sublimed at 100°/0·2 mm., forming needles, m. p. 119·5—120° (Found: C, 69·7; H, 5·2. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%), $\lambda_{max.}$ 216, 293, and 329 mμ (log ε 4·11, 3·95, and 4·04 respectively), $\lambda_{min.}$ 209, 259, and 306 mμ (log ε 4·10, 3·13, and 3·92 respectively).

Luteolinidin Tetramethyl Ether.—Concentrated sulphuric acid (19 c.c.) was added dropwise to a mixture of phloroglucinol dimethyl ether [23] (11·6 g.) and 3 : 4-dimethoxyphenyl ethynyl ketone (14·3 g.) in glacial acetic acid (190 c.c.). The solution rapidly became dark red and after 4 days a dark red precipitate of the sulphate of luteolinidin tetramethyl ether (28·4 g.) had separated and was removed by filtration. It was converted into the corresponding chloride by 2 crystallisations from 6N-hydrochloric acid. The chloride formed orange needles (24·8 g.), m. p. 161—162° (decomp.; rapid heating) (lit.,[24] m. p. 161—162°) (Found, on a sample dried *in vacuo* at room temperature over solid sodium hydroxide: C, 51·0; H, 6·0; Cl, 9·75; loss in wt. at 120° *in vacuo*, 19·0. Calc. for $C_{19}H_{19}O_5Cl,4{\cdot}5H_2O,0{\cdot}25HCl$: C, 50·4; H, 6·3; Cl, 9·8; loss of H_2O and HCl, 19·9%), $\lambda_{max.}$ in ethanol containing 1% of 0·1N-hydrochloric acid: 203, 242, 280, 370, and 492 mμ (log ε 4·54, 4·17, 4·28, 3·70, and 4·62 respectively); $\lambda_{min.}$ 237, 257, 339, and

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[21] Robinson and Robinson, *Biochem. J.*, 1933, **27**, 206.
[22] Clapperton and MacGregor, *J. Amer. Chem. Soc.*, 1949, **71**, 3234.
[23] Pratt and Robinson, *J.*, 1924, **125**, 188.
[24] Baker, *J.*, 1929, 1593.

387 mμ (log ε 4·16, 3·94, 3·40, and 3·66 respectively). A further quantity of the product was obtained by dilution of the acetic acid mother-liquors with ether, a gum being precipitated which was treated with boiling ethanol (50 c.c.). The ethanolic solution was decanted from undissolved material, cooled, and saturated with hydrogen chloride. The precipitated solid was separated and crystallised from 6N-hydrochloric acid, giving luteolinidin chloride tetramethyl ether (2 g.), m. p. 161—162° (decomp.).

The ferrichloride formed silky orange-brown needles (from acetic acid), m. p. 206·5—207·5° (lit.,[16] m. p. 206—207°) (Found: C, 43·7; H, 3·9; Fe, 11·4. Calc. for $C_{19}H_{19}O_5Cl_4Fe$: C, 43·5; H, 3·65; Fe, 11·3%), $\lambda_{max.}$ 242, 279, 324, 368, and 492 mμ (log ε 4·32, 4·35, 3·89, 3·96, and 4·58 respectively), $\lambda_{min.}$ 235, 258, 316, 338, and 401 mμ (log ε 4·30, 4·15, 3·88, 3·83, and 3·80 respectively).

2-*Acetoxy*-4 : 6 : 3′ : 4′-*tetramethoxychalcone*.—Luteolinidin tetramethyl ether (1·0 g. of the chloride hydrate) was warmed in pyridine (15 c.c.) for 1 hr. on the water bath. The orange-red solution was cooled, acetic anhydride (15 c.c.) was added, and the mixture kept overnight at room temperature. It was then poured into water (500 c.c.) and after some hours the slightly sticky solid which had separated was collected, washed with water, and dried. Repeated crystallisation from ethanol (charcoal) gave the *chalcone* as pale yellow leaflets (450 mg.), m. p. 154—155°, not depressed on admixture with an authentic specimen prepared by acetylation of 2-hydroxy-4 : 6 : 3′ : 4′-tetramethoxychalcone,[16] m. p. 178—179° (Found: C, 65·0; H, 5·95. $C_{21}H_{22}O_7$ requires C, 65·2; H, 5·75%), $\lambda_{max.}$ 204, 247, and 360 mμ (log ε 4·71, 4·24, and 4·48 respectively), $\lambda_{min.}$ 238 and 271 mμ (log ε 4·11 and 3·60).

5 : 7 : 3′ : 4′-*Tetramethoxyflav*-2-*ene*.—Cooled tetrahydrofuran (300 c.c.) was added to a mixture of luteolinidin chloride tetramethyl ether (13·63 g.; dried at 65° *in vacuo* for 24 hr.) and lithium aluminium hydride (6·62 g.) at −70° and stirring was commenced immediately. The flavylium salt was decolorised rapidly and the temperature of the stirred suspension was slowly raised, until the solvent boiled. The mixture was heated under reflux for 2 hr. After removal of solvent (200 c.c.), the residue was cooled and the excess of lithium aluminium hydride destroyed by the addition of wet ether (300 c.c.). The product was then shaken with 25% aqueous sodium potassium tartrate (200 c.c.), and the aqueous layer removed and repeatedly extracted with 50 c.c. portions of ether. The combined ethereal fractions were washed with aqueous sodium potassium tartrate (3 × 50 c.c.) and then dried and the solvent removed to give a pink residue (10·6 g.). Crystallisation from ether gave pink needles (8·23 g.), m. p. 114—116° raised to 118·5—119° after two further crystallisations from ethanol. Careful purification of material obtained from mother-liquors gave the product as pinkish blades (total yield, 9·03 g., 73%). Sublimation at 105—107°/0·05 mm. gave colourless prisms, m. p. 119·5° (lit.,[12] m. p. 119°), which were crystallised from ethanol before analysis (Found: C, 69·4; H, 6·3. Calc. for $C_{19}H_{20}O_5$: C, 69·5; H, 6·15%), $\lambda_{max.}$ 209, 247, 273, and 292 mμ (log ε 4·73, 4·29, 3·90, and 3·82 respectively), $\lambda_{min.}$ 241 and 290 mμ (log ε 4·28 and 3·81).

αβ-*Dihydro*-2-*hydroxy*-4 : 6 : 3′ : 4′-*tetramethoxychalcone*.—A solution of 5 : 7 : 3′ : 4′-tetramethoxyflav-2-ene (300 mg.) in aqueous acetic acid (15 c.c. of 50%) was heated on the water bath for 2 hr., then cooled, and the crystalline product (285 mg.) separated and crystallised from ethanol to give the dihydrochalcone as colourless needles, m. p. 137·5—138° (lit., 137°) undepressed on admixture with a sample prepared as described by Freudenberg *et al.*[25] (Found: C, 66·0; H, 6·4. Calc. for $C_{19}H_{22}O_6$: C, 65·9; H, 6·4%), $\lambda_{max.}$ 206, 227, 273, and 303 mμ (log ε 4·81, 4·54, 4·08, and 3·94 respectively), $\lambda_{min.}$ at 221, 246, and 292 mμ (log ε 4·43, 3·54, and 3·90 respectively). The infrared spectrum of a solution in chloroform showed bands in the carbonyl region at 1592, 1621, 1659, and 1716 (w) cm.$^{-1}$. The methyl ether, 2 : 4 : 6 : 3′ : 4′-pentamethoxydihydrochalcone (obtained by use of methyl sulphate and potassium carbonate in acetone), formed colourless needles, m. p. 113·5—114° (lit.,[25] 113—114°), from methanol (Found: C, 66·9; H, 6·8. Calc. for $C_{20}H_{24}O_6$: C, 66·7; H, 6·7%), $\lambda_{max.}$ 207, 228, 273, and 303 mμ (log ε 4·72, 4·40, 4·10, and 3·93 respectively), $\lambda_{min.}$ 219, 248, and 292 mμ (log ε 4·30, 3·60, and 3·89 respectively). The *acetyl derivative* (prepared by acetic anhydride–pyridine) formed white felted needles, m. p. 126·5—127° (from methanol) (Found: C, 65·3; H, 6·2; Ac, 11·8. $C_{19}H_{21}O_6\cdot CO\cdot CH_3$ requires C, 64·9; H, 6·2; Ac, 11·1%), $\lambda_{max.}$ 204, 228, 274, and 303 mμ (log ε 4·65, 4·38, 4·08, and 3·88 respectively), $\lambda_{min.}$ 217, 246, 293 mμ (log ε 4·26, 3·40, and 3·85 respectively). The infrared spectrum of a chloroform solution showed bands at 1595, 1620, 1671, and 1762 cm.$^{-1}$.

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[25] Freudenberg, Fikentscher, and Wenner, *Annalen*, 1925, **442**, 309.

Formation of Flavylium Salts from 5 : 7 : 3′ : 4′-*Tetramethoxyflav-2-ene*.—(*a*) A solution of ferric chloride (500 mg.) in concentrated hydrochloric acid (1·5 c.c.) was added to a solution of the flavene (110 mg.) in glacial acetic acid (5 c.c.). After 2 days at room temperature, the crystalline precipitate was collected and crystallised from acetic acid to yield luteolinidin tetramethyl ether ferrichloride (72·4 mg., 41%), m. p. alone and mixed with the sample described above, 206·5—207·5°. (*b*) A solution of the flavene (100 mg.) in benzene (2 c.c.) was saturated with dry hydrogen chloride and kept at room temperature for 3 days. The orange-red precipitate was collected and crystallised from 6N-hydrochloric acid to yield luteolinidin tetramethyl ether chloride (40 mg.), m. p. and mixed m. p. 161—162°.

Apigeninidin Chloride Trimethyl Ether; 5 : 7 : 4′-*Trimethoxyflavylium Chloride*.—Ethynyl *p*-methoxyphenyl ketone, m. p. 87—88° (Found: C, 74·9; H, 4·9. Calc. for $C_{10}H_8O_2$: C, 74·9; H, 5·1%), $\lambda_{max.}$ 223 and 305 mμ (log ε 4·00 and 4·23), was prepared by the method of Irving and Johnson [26] by oxidation of 3-*p*-methoxyphenylprop-2-ynol, m. p. 36—37°. Concentrated sulphuric acid (18 c.c.) was added dropwise to a solution of phloroglucinol dimethyl ether (12·4 g.) and ethynyl *p*-methoxyphenyl ketone (11·5 g.) in cooled (10°) glacial acetic acid (180 c.c.). The solution rapidly became dark red, and after 5 days the dark red precipitate of apigeninidin sulphate trimethyl ether (34·2 g.) was collected, washed with ether, and twice crystallised from 6N-hydrochloric acid to yield the corresponding chloride (22·8 g.) as orange needles, m. p. 135—136°, of a *hydrate* which still contained hydrogen chloride (Found: C, 55·6; H, 5·95; Cl, 11·4; loss at 100° *in vacuo*, 15·0. $C_{18}H_{17}O_4Cl,2{\cdot}5H_2O,0{\cdot}25HCl$ requires C, 55·9; H, 5·8; Cl, 11·5; loss of H_2O and HCl, 15·5%). King *et al.*[13] record m. p. 159—160° (decomp.), for a pentahydrate. Light absorption in ethanol containing 1% of N-hydrochloric acid: max. at 205, 242, 277, 325, and 474 mμ (log ε 4·55, 3·96, 4·29, 3·72, and 4·59 respectively); min. at 236, 249, 303, and 346 mμ (log ε 3·94, 3·92, 3·54, and 3·12 respectively). The ferrichloride separated from acetic acid as red-brown prisms, m. p. 185—186° (with sintering at 181°) (lit.,[16] 187° with sintering at 180°) (Found: C, 43·5; H, 3·6; Fe, 10·6. Calc. for $C_{18}H_{17}O_4Cl_4Fe$: C, 43·7; H, 3·5; Fe, 10·6%), $\lambda_{max.}$ 204, 242, 277, 326, and 475 mμ (log ε 4·59, 4·23, 4·38, 3·99, and 4·54 respectively), $\lambda_{min.}$ 234, 251, 305, and 345 mμ (log ε 4·21, 4·18, 3·88, and 3·80).

5 : 7 : 4′-*Trimethoxyflav-2-ene*.—Apigeninidin trimethyl ether (hydrated salt dried at 65° *in vacuo* for 24 hr.; 4·05 g.) in tetrahydrofuran (120 c.c.) was treated with lithium aluminium hydride (2·02 g.) and the mixture worked up essentially as described above for the preparation of 5 : 7 : 3′ : 4′-tetramethoxyflav-2-ene. Removal of solvent at 15° under reduced pressure in a stream of nitrogen afforded a pink solid which was treated with boiling light petroleum in a nitrogen atmosphere, the suspension cooled at 0° for 4 hr., and the insoluble material (50 mg.) separated. The solvent was removed from the filtrate to give a pink residue (3·02 g.) which separated from ethanol as an amorphous solid, m. p. 119—123°. Repeated purification of this material from ethanol followed by sublimation (120°/1 mm. for 4 days) gave colourless prisms, m. p. 130·5—131° (sintering at 128°) (lit.,[13] 129—130°) which was not raised after further crystallisation from ethanol (Found: C, 72·5; H, 6·1. Calc. for $C_{18}H_{18}O_4$: C, 72·5; H, 6·1%). A mixture of this product with a sample kindly supplied by Dr. J. W. Clark-Lewis had m. p. 128—130°. Light absorption max. were at 204, 222, 247, and 272 mμ (log ε 4·68, 4·41, 4·40, and 3·90 respectively) and min. at 218, 235, and 266 mμ (log ε 4·41, 4·33, and 3·89). The infrared spectrum of a solution in carbon tetrachloride showed max. at 3066, 2997, 2951, 2911, 2865, 2842, 1467, 1458, 1440, 1419, 1346, 1331, and 1305 cm.$^{-1}$. Another determination (KBr disc) gave a spectrum which was identical with that of the authentic specimen.

5 : 7 : 3′ : 4′-*Tetramethoxyflavan*-2 : 3-*diol*; αβ-*Dihydro*-α : 2-*dihydroxy*-4 : 6 : 3′ : 4′-*tetramethoxychalcone*.—(*a*) A solution of 5 : 7 : 3′ : 4′-tetramethoxyflav-2-ene (540 mg.) in dry benzene (12 c.c.) was added to a solution of osmium tetroxide (420 mg.) in a mixture of benzene (6 c.c.) and pyridine (0·6 c.c.). The solution darkened and a slight precipitate was observed after 2 hr. The mixture was kept in the dark until deposition of solid had ceased (5 days), then it was diluted with ether (25 c.c.) and kept overnight and the light brown crystalline complex separated and washed with ether. This complex was dissolved in warm methylene dichloride (25 c.c.), and the solution cooled and shaken with 2% aqueous potassium carbonate solution (100 c.c.) containing mannitol (10 g.) until the colour of the organic phase ceased to fade (48 hr.). The aqueous phase was then replaced by fresh potassium carbonate–mannitol reagent, and agitation continued until the organic phase was colourless (24 hr.). Ether (150 c.c.) was added and the aqueous layer removed. This was extracted with ether (2 × 25 c.c.), and the combined

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[26] Irving and Johnson, *J.*, 1948, 2037.

organic layers were washed and dried. Removal of the solvent at <28° under reduced pressure in an atmosphere of nitrogen left a residue which was treated with ether and most of the ether removed to give αβ-*dihydro*-α : 2-*dihydroxy*-4 : 6 : 3′ : 4′-*tetramethoxychalcone* (474 mg., 78%) as pale yellow crystals, m. p. 111—113°. The ethereal mother-liquors were clarified with charcoal and cautiously diluted with light petroleum (b. p. 60—80°) to give a further quantity of the product (60 mg.) as colourless needles, m. p. 111—113°. It recrystallised from benzene–light petroleum as colourless leaflets, m. p. 88—90° (with previous darkening), which contained solvent of crystallisation (Found: C, 65·7; H, 6·15. $C_{19}H_{22}O_7,\frac{1}{2}C_6H_6$ requires C, 65·8; H, 6·3%). Slow crystallisation from ethyl acetate–light petroleum, chloroform–light petroleum, or ether–light petroleum afforded white felted needles, m. p. 113—114° (sintering >110°), which after further crystallisation from cold aqueous methanol gave the product as colourless silky needles, m. p. 114·5—115° (Found: C, 62·9; H, 6·15. $C_{19}H_{22}O_7$ requires C, 63·0; H, 6·12%), $\lambda_{max.}$ 207, 229, 276, and 307 mμ (log ε 4·73, 4·37, 4·00, and 3·88 respectively), $\lambda_{min.}$ 220, 249, and 294 mμ (log ε 4·30, 3·59, and 3·83 respectively). The infrared spectrum of a solution in chloroform showed main max. at 3324, 3070, 2986, 2941, 2839, 1673, 1628, and 1601 cm.$^{-1}$, and of the solid (KBr disc) at3503, 3413, 3293, 3092, 2930, 2832, 1653,1624, 1590, and 1518 cm.$^{-1}$. The product was readily soluble in the common organic solvents, except light petroleum in which it was sparingly soluble. It dissolved completely in dilute aqueous sodium hydroxide to give a colourless solution which soon became yellow and after warming changed to a pale orange colour. Heating an ethanolic solution with concentrated hydrochloric acid gave a bright cherry-red colour which is attributed to anthocyanidin formation. A bright red colour was also obtained with the vanillin reagent.[27]

(*b*) αβ-Dihydro-α : 2-diacetoxy-4 : 6 : 3′ : 4′-tetramethoxychalcone monohydrate (264 mg.; see below), anhydrous potassium acetate (3·0 g.), and oxygen-free absolute methanol (30 c.c.) were heated under reflux in an atmosphere of nitrogen for 14 hr. The yellow solution was evaporated under reduced pressure at 25—28° and the residue shaken with water (30 c.c.) and ether (100 c.c.). The aqueous layer was separated, washed with ether (2 × 10 c.c.), and then rejected; the combined ethereal extracts were washed and dried and the solvent was removed under reduced pressure as in the previous experiment. The residual bright yellow solid was treated with a small amount of methanol and filtered from a small quantity of a yellow oxidation product (0·8 mg.; see below), and the filtrate diluted with ether and evaporated as above. Crystallisation of the residue thrice from benzene–light petroleum (charcoal) and once from chloroform–light petroleum yielded αβ-dihydro-α : 2-dihydroxy-4 : 6 : 3′ : 4′-tetramethoxychalcone as white felted needles (39 mg., 18%), m. p. 113—114° alone and when mixed with the product from the previous experiment.

(*c*) A portion of the solid (100 mg.) obtained from the action of monoperphthalic acid on 5 : 7 : 3′ : 4′-tetramethoxyflav-2-ene (see below) was dissolved in benzene (2 c.c.), the solution clarified with charcoal, and the hot solution diluted with light petroleum (2 c.c.). The colourless solution was decanted from the precipitated gum and slowly diluted with an equal volume of light petroleum. The solid so obtained was collected and after crystallisation from ether–light petroleum gave αβ-dihydro-α : 2-dihydroxy-4 : 6 : 3′ : 4′-tetramethoxychalcone as colourless needles, m. p. 113—114°, identical with the products of the two previous experiments.

α : 2-*Diacetoxy*-αβ-*dihydro*-4 : 6 : 3′ : 4′-*tetramethoxychalcone*.—(*a*) The product of the foregoing experiment was acetylated with acetic anhydride and pyridine at room temperature to yield the *diacetyl derivative* as colourless needles, m. p. 148·5—149°, of the monohydrate (Found: C, 59·5; H, 5·95; loss on drying at 65° *in vacuo*, 3·4. $C_{23}H_{26}O_9,H_2O$ requires C, 59·5; H, 6·05; H_2O, 4·5. Found, on a sample dried at 65° *in vacuo*: C, 61·6; H, 5·7. $C_{23}H_{26}O_9$ requires C, 61·9; H, 5·8%), $\lambda_{max.}$ 204, 229, 278, and 307 mμ (log ε 4·73, 4·41, 4·13, and 3·95 respectively), $\lambda_{min.}$ 218, 249, and 296 mμ (log ε 4·30, 3·54, and 3·92 respectively). The infrared spectrum of a chloroform solution showed bands in the carbonyl region at 1600, 1622, 1686, 1742, and 1765 cm.$^{-1}$

(*b*) An ethereal solution of monoperphthalic acid (832 mg.; 3 mol.) was added to 5 : 7 : 3′ : 4′-tetramethoxyflav-2-ene (500 mg.) in ether (150 c.c.), and the solution diluted with dry ether (to 250 c.c.) and kept at 18° with occasional shaking for 80 min. Acidic material was removed by shaking the mixture with the calculated quantity of aqueous sodium hydrogen carbonate, and the resulting ethereal layer was separated and dried. The solvent was removed at room temperature under reduced pressure in an atmosphere of nitrogen. The residue (480 mg.),

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[27] Bate-Smith and Swain, *Chem. and Ind.*, 1953, 377.

which rapidly assumed a bright orange-red colour when exposed to air, was dissolved in acetic acid (5 c.c.) containing anhydrous potassium acetate (300 mg.) and acetic anhydride (1 c.c.). This solution was kept at room temperature overnight, then cooled (ice), and pyridine (10 c.c.) and acetic anhydride (4 c.c.) were added. After a further 24 hr. at room temperature, the solution was poured into cold water and the precipitated solid collected. After two crystallisations from methanol, α : 2-diacetoxy-αβ-dihydro-4 : 6 : 3′ : 4′-tetramethoxychalcone (469 mg., 69%) formed colourless needles, m. p. 148·5—149°, identical with the product of the previous experiment. It gave a bright cherry-red colour with the vanillin reagent [27] or when warmed with concentrated hydrochloric acid.

Periodate Oxidation of αβ-Dihydro-α : 2-dihydroxy-5 : 7 : 3′ : 4′-tetramethoxychalcone.—5% Aqueous sodium metaperiodate (3·28 c.c.) was added in small quantities during 36 hr. to αβ-dihydro-α : 2-dihydroxy-5 : 7 : 3′ : 4′-tetramethoxychalcone (VIII) (300 mg.) dissolved in methanol (7 c.c.), and the mixture kept overnight at room temperature. The product was diluted with water (10 c.c.) and exhaustively extracted with ether. The ethereal extract was shaken with sodium hydrogen carbonate solution and from the ethereal layer phenolic and neutral fractions were isolated in the usual manner. The crystalline solid obtained by acidification of the sodium hydrogen carbonate layer was collected and crystallised from water, to give veratric acid (73 mg.) as colourless needles, m. p. and mixed m. p. 179—180°. A further quantity of veratric acid (15 mg.) was obtained by ether-extraction of the mother-liquors and vacuum-sublimation of the product.

The neutral fraction from the oxidation was obtained as a partially crystalline colourless gum (79 mg.) which was hydrolysed by warm 20% aqueous potassium hydroxide (5 c.c.) in an atmosphere of nitrogen until dissolution was complete. The orange-red solution was cooled and the acidic material isolated in the usual manner. The crude veratric acid thus obtained was purified as above and afforded the pure acid (35 mg.) as colourless prisms, m. p. 179—180°. The overall yield of veratric acid was thus 123 mg. (81%).

Cyanidin Chloride 5 : 7 : 3′ : 4′-Tetramethyl Ether.—(*a*) αβ-Dihydro-α : 2-dihydroxy-5 : 7 : 3′ : 4′-tetramethoxychalcone (25 mg.) was heated in propan-2-ol–concentrated hydrochloric acid (19 : 1; 25 c.c.) in a sealed tube for 1½ hr. The product was cooled, diluted with ether (75 c.c.), and then brought on to a cellulose (Solka-Floc) column (170 × 20 mm.). Preliminary elutions were carried out with propan-2-ol–ether (1 : 4; 250 c.c.) containing concentrated hydrochloric acid (5 c.c.) and then ether (100 c.c.) containing saturated methanolic hydrogen chloride (3 c.c.). The main product was eluted from the column with the upper phase of butan-1-ol–2N-hydrochloric acid (1 : 1) and after an initial pale purple eluate of phlobaphene had been obtained and rejected the main fraction of anthocyanidin plus phlobaphene (*ca.* 20 c.c.) was collected and combined with that obtained from a second similar experiment starting from 25 mg. of the dihydrochalcone. The solvent was removed from the combined eluates under reduced pressure at 18° as rapidly as possible, care being taken to ensure that an excess of hydrogen chloride was always present by the frequent additions of small amounts of saturated methanolic hydrogen chloride. The residue was again chromatographed on a cellulose column (180 × 20 mm.), the butanol–hydrochloric acid upper phase being used for elution as before. After separation of the purple phlobaphene band, the anthocyanidin was eluted as a broad red band. It was diluted (to 50 c.c.) with concentrated hydrochloric acid (2·5 c.c.) and the hydrochloric acid–butanol upper layer, and a determination of the light absorption of the resulting solution and comparison with a standard solution indicated that the anthocyanidin content was 2·44 mg. Removal of the solvent gave a red residue which showed R_F values identical with those of authentic cyanidin chloride 5 : 7 : 3′ : 4′-tetramethyl ether when subjected to chromatography on paper. A further quantity of the product was isolated from the propanol–ether eluates of the two reaction products, and the total yield of the anthocyanidin was 4·1 mg. (6·8%). The acid solutions of the anthocyanidin faded rapidly and as a result a spectrophotometric determination gives a minimum figure.

Similar reactions were carried out on α : 2-diacetoxy-αβ-dihydro-4 : 6 : 3′ : 4′-tetramethoxychalcone, and the crude product from the action of monoperphthalic acid on 5 : 7 : 3′ : 4′-tetramethoxyflav-2-ene (above). The products were shown to be identical with cyanidin 5 : 7 : 3′ : 4′-tetramethyl ether by chromatography on paper. Streaks at the solvent fronts caused by the presence of traces of phlobaphene were observed. Formation of the anthocyanidin was slightly faster from the diol than from its diacetate, and considerably faster from the crude oxide than from the diol.

(*b*) A cooled (0°) solution of 2-hydroxy-4 : 6-dimethoxybenzaldehyde (1·01 g.) and ω-acetoxy-3 : 4-dimethoxyacetophenone (below) (1·15 g.) in dry ethyl acetate (12·5 c.c.) and dry ethanol (3 c.c.) was saturated with hydrogen chloride during 3 hr. and the dark red solution stored in the dark at room temperature for 7 days. Ether (17 c.c.) was then added cautiously and the mixture kept in the refrigerator for 14 days. The trihydrate of cyanidin chloride 5 : 7 : 3′ : 4′-tetramethyl ether was obtained as black prisms with a green reflex, m. p. 192—196° with previous sintering (Found: C, 54·5; H, 6·0; Cl, 8·8; loss at 100° *in vacuo*, 11·8. Calc. for $C_{19}H_{19}O_6Cl,3H_2O$: C, 54·7; H, 6·0; Cl, 8·5; H_2O, 13·0%). After crystallisation from ethanol–concentrated hydrochloric acid (1 : 1) the trihydrate was obtained as small felted carmine needles, m. p. 201—202° with previous sintering (Found: C, 54·8; H, 5·7; Cl, 8·4; loss at 100° *in vacuo*, 13·8%). Hayashi [20] records decomp. 200° for a dihydrate. Light absorption: (i) in ethanol containing 1% of N-hydrochloric acid, max. at 270, 335, 385, and 535 mμ (log ε 4·38, 3·55, 3·63, and 4·60 respectively) with a shoulder at 320—355 mu [log ε (mean) 3·57], min. at 250, 352, and 400 mμ (log ε 4·26, 3·33, and 3·61 respectively); (ii) in the butan-1-ol–2N-hydrochloric acid (1 : 1) upper layer containing 5% of concentrated hydrochloric acid, max. at 276, 385, and 532 mμ (log ε 4·28, 3·59, and 4·54 respectively), min. at 345 and 397 mμ (log ε 3·44 and 3·60). After this solution had been kept in the dark for 3 days the intensity (log ε) of the max. at 532 mμ had dropped to 4·42. The perchlorate formed fine purple-red needles, m. p. 255—256° (decomp.) (from glacial acetic acid) (Found: C, 51·5; H, 4·3. $C_{19}H_{19}O_{10}Cl$ requires C, 51·5; H, 4·4%).

Phloroglucinaldehyde 2 : 4-*Dimethyl Ether*.—A stirred and cooled (−10°) mixture of phloroglucinol dimethyl ether (10·2 g.) and zinc cyanide [28] (12 g.) in anhydrous ether (250 c.c.) was saturated with dry hydrogen chloride during 3 hr. and then allowed to warm to room temperature. Next day the sticky imine hydrochloride was collected, washed with ether, and triturated with water (50 c.c.). The resulting amorphous precipitate was separated, washed with a little water, then ether, and dissolved in boiling 50% v/v aqueous methanol (450 c.c.). After filtration, the solution was heated to *ca.* 65° for ½ hr., then cooled, and the crystalline precipitate which separated was collected and twice recrystallised from aqueous methanol to yield the product (8·24 g.) as colourless needles, m. p. 71°. The combined aqueous methanol mother-liquors were reduced to *ca.* 300 c.c. under reduced pressure, then cooled, and the precipitated solid was collected. This was treated with a small quantity of ether, the insoluble material was separated, and after removal of the solvent the residue was distilled in steam. The colourless needles which were obtained in the distillate were separated and crystallised from aqueous methanol to give a further quantity (1·92 g.) of the aldehyde (total yield, 10·16 g., 83%; lit.,[13] 30%) (Found: C, 59·3; H, 5·75. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%).

ω-*Diazo*-3 : 4-*dimethoxyacetophenone*.—Freshly prepared veratroyl chloride (13·5 g.) in dry chloroform (25 c.c.) was added dropwise during 1 hr. to a cooled (5°) solution of diazomethane (from 42 g. of *N*-nitrosomethylurea) in ether (300 c.c.). When evolution of nitrogen had ceased, the yellow silky needles (10·1 g.), m. p. 76—77° (decomp.), were collected, and light petroleum (500 c.c.) was added to the filtrate which was then evaporated at room temperature to small volume in a stream of air. The yellow solid which separated was collected and crystallised twice from light petroleum to give a further quantity (2·5 g.), m. p. 77—78° (decomp.), of ω-*diazo*-3 : 4-*dimethoxyacetophenone* (total yield, 12·6 g., 91%). For analysis, a small quantity was recrystallised from light petroleum to give the product as pale yellow silky needles, m. p. 77·5—78° (Found: C, 58·2; H, 4·8; N, 13·0. $C_{10}H_{10}O_3N_2$ requires C, 58·2; H, 4·9; N, 13·6%).

ω-*Acetoxy*-3 : 4-*dimethoxyacetophenone*.—The foregoing diazo-ketone (5·05 g.) and glacial acetic acid (35 c.c., containing 0·5 g. of fused potassium acetate) were heated, with frequent shaking, at 70° until evolution of nitrogen ceased. The golden-brown solution was poured into water (150 c.c.), and the clear solution was extracted with ether. The ethereal extract was shaken with aqueous sodium hydrogen carbonate solution, dried, and evaporated. The residual gum was triturated with methanol in order to induce crystallisation. The solid product was collected, and crystallised from methanol, then ether, to yield colourless rhombs of ω-acetoxy-3 : 4-dimethoxyacetophenone (4·82 g., 83%), m. p. 85·5—86·5°, raised to 86—87° by further crystallisation from ether or methanol (values between 82·5—83·5 and 91—92° have been recorded for the m. p.) (Found: C, 60·3; H, 5·9. Calc. for $C_{12}H_{14}O_5$: C, 60·5; H, 5·9%).

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[28] Adams and Levine, *J. Amer. Chem. Soc.*, 1923, **45**, 2373.

1 - (3 : 4 - *Dimethoxyphenyl*) - 3 - (2 - *hydroxy* - 4 : 6 - *dimethoxyphenyl*)*propane* - 1 : 2 : 3 - *trione*.—5 : 7 : 3′ : 4′-Tetramethoxyflav-2-ene (570 mg.) was treated with osmium tetroxide (398 mg.) as described above. The resulting complex was decomposed in the same manner as previously and the colourless ether–methylene dichloride solution of the dihydrodihydroxychalcone separated and kept in the dark for 24 days, during which it became yellow. The solvent was removed at <25° under reduced pressure in a stream of nitrogen and the pale yellow residue triturated with methanol (3 c.c.). The undissolved solid was separated, washed with methanol, and crystallised from ethanol to give the presumed *trione* (8 mg.) as bright yellow leaflets, m. p. 197·5—199° (Found, on a sample dried at 130° *in vacuo*: C, 61·5; H, 5·0. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·85%), $\lambda_{max.}$ (in dioxan) 231 and 281 mμ (log ε 4·19 and 4·30), $\lambda_{min.}$ 247 mμ (log ε 3·52). Intense bands in the infrared spectrum (KBr) in the carbonyl region were observed at 1592, 1606, 1634, 1645, 1663, and 1687 cm.$^{-1}$. An ethanolic solution of the oxidation product gave an orange-brown colour when heated with concentrated hydrochloric acid and the resulting solution was shown not to contain cyanidin chloride tetramethyl ether by paper chromatographic examination. Small yields of the same oxidation product have been isolated from an oxidation of the flavene (V) with monoperphthalic acid, from an aerial oxidation of an ethereal solution of the αβ-dihydro-α : 2-dihydroxychalcone (VIII), and from the deacetylation of α : 2-diacetoxy-αβ-dihydro-4 : 6 : 3′ : 4′-tetramethoxychalcone with potassium acetate (see above).

3 - *Hydroxy* - 1 - (3 : 4 - *dimethoxyphenyl*) - 3- (2-*hydroxy* - 4 : 6 - *dimethoxyphenyl*)*propane* - 1 : 2 - *dione*.—An ethereal solution of monoperphthalic acid (1·36 g., 5 mol.) was added to 5 : 7 : 3′ : 4′-tetramethoxyflav-2-ene (500 mg.; 1 mol.) in anhydrous ether, and the mixture diluted with ether (to 250 c.c.) and cooled in the refrigerator. After 7 and 14 days, further quantities of monoperphthalic acid (278 mg., 1 mol.) were added, and after 3 weeks the ethereal solution was decanted from the solid which was dissolved in chloroform (10 c.c.), and the combined solutions were washed with aqueous sodium hydrogen carbonate and dried. The solvent was removed at <25° at reduced pressure in an atmosphere of nitrogen to leave a sticky product which was triturated with methanol and washed with methanol to remove all soluble products. The yellow residue (116 mg.) was fractionally crystallised from small quantities of ethanol–chloroform to yield sparingly soluble bright yellow leaflets and moderately soluble pale yellow needles. The former product was identical with that described in the foregoing experiment. The mother-liquors from the crystallisation, after evaporation to small bulk, yielded a further quantity of the second product which was mixed with the main crop and crystallised from ethanol to give the *hydroxy-diketone* (51·6 mg.) as pale yellow needles, m. p. 174—175° (Found: C, 61·0; H, 5·65. $C_{19}H_{20}O_8$ requires C, 60·65; H, 5·35%). The intensities of the light absorption bands varied rapidly on keeping but the following are the highest values observed: max. at 203—206, 228, and 282—284 mμ (log ε 4·60, 4·40, and 4·37 respectively) with min. at 219—220 and 250 mμ (log ε 4·31 and 3·84). Prominent bands in the infrared spectrum ($CHCl_3$ solution) were obtained at 1606, 1649, and 1685 cm.$^{-1}$. An ethanol solution of the compound gave a cerise colour when treated with magnesium and concentrated hydrochloric acid but not with the acid alone. A low yield of the same compound has also been isolated after reaction of perbenzoic acid with 5 : 7 : 3′ : 4′-tetramethoxyflav-2-ene.

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