219. *Derivatives of Hydroxyquinol. Part I. Compounds Related to 3 : 4 : 6-Trimethoxy-2-propenylacetophenone.*

By F. M. Dean, D. R. Randell, and Graham Winfield.

The preparation and properties of several 5 : 6-disubstituted derivatives of hydroxyquinol related to certain fungal metabolites are described.

Apart from the 5-substituted derivatives, the chemistry of hydroxyquinol has not been systematically studied in spite of its importance in fungal metabolites [1] and depsidones: [2] this paper describes a general route to 5 : 6-disubstituted hydroxyquinols required for synthetical studies of citromycetin,[3] fulvic acid,[4] and ustic acid.[5]

Of the published routes [6-8] to ethers of 3 : 4 : 6-trihydroxyphthalic acid, that of MacKenzie and Robertson [8] employing the intermediate indanone (I; R = H) seemed suitable for extension, but the butyric acid (III), prepared from the æsculetin derivative [9] (II), gave only the dihydrocoumarin (IV) when attempts were made to convert it into the indanone (I; R = Me). Resistance to substitution in the 6-position of the hydroxyquinol nucleus was also evident in the phenolic ketone (V) (see below), this being inert in the Gattermann, Kolbe, and Reimer–Tiemann reactions and destroyed rather than nitrated by nitric acid. A similar resistance has already been noted [3] in the hydroxy-acid (VI) to Hoesch, Gattermann, and Friedel–Crafts conditions. Fortunately, the Claisen rearrangement, in which ionic demands are small,[10] is successful.

When modified by the use of boron trifluoride instead of aluminium chloride to induce the Fries rearrangement in the diacetate (VII), Mauthner's [11] preparation of 2 : 5-dihydroxy-4-methoxyacetophenone (VIII; R = H) from vanillin gave excellent yields of this phenol or of its monoacetate (VIII; R = Ac). Methylation and then hydrolysis of the acetate supplied the unreactive phenol (V). Selective alkylation of the quinol (VIII; R = H) to the benzyl ether (VIII; R = CH_2Ph), followed by treatment of the derived acetate with sodium hydride, furnished a β-diketone (IX) cyclised by hydrochloric acid to the chromone (X; R = CH_2Ph). More vigorous treatment of this chromone with hydrochloric acid supplied the corresponding 6-hydroxychromone (X; R = H) which was, however, more easily prepared by controlled hydrolysis of its 3-acetyl derivative (XI) obtained directly from the diacetate of 2 : 5-dihydroxy-4-methoxyacetophenone (VIII; R = H) by treatment with sodium hydride followed by acetic acid. The allyl ether (X; R = CH_2·CH·CH_2) of this hydroxychromone rearranged readily when heated, giving the desired 5-allyl-6-hydroxy-7-methoxy-2-methylchromone (XII; R = H). Unfortunately, the allyl group could not be isomerised into a propenyl group because the methyl ether (XII; R = Me) was destroyed by bases, and with acids suffered demethylation and cyclisation to the γ-pyronocoumaran (XIII).

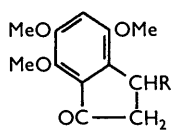
Claisen rearrangement of the monoallyl ether (XIV; R = H) of 2 : 5-dihydroxy-4-methoxyacetophenone readily gave 2-allyl-3 : 6-dihydroxy-4-methoxyacetophenone (XV; R = H), and thence 3 : 6-dihydroxy-4-methoxy-2-propylacetophenone by hydrogenation. Monomethylation of this allylquinol was unusual because the chelated hydroxyl group was attacked preferentially, giving (XV; R = Me). This result may not be due entirely to

[1] Bracken, "The Chemistry of Micro-Organisms," Pitman, London, 1955.
[2] Asahina, in Zechmeister (Ed.), "Fortschritte der Chemie organischer Naturstoffe," Vol. 8, Springer-Verlag, Vienna, 1951.
[3] Robertson, Whalley, and Yates, *J.*, 1951, 2013.
[4] Dean, Eade, Moubasher, and Robertson, *J.*, 1957, 3497.
[5] Raistrick and Stickings, *Biochem. J.*, 1950, **48**, 53.
[6] Faltis and Kloiber, *Monatsh.*, 1929, **53**, 631.
[7] Bargellini, *Gazzetta*, 1914, **44**, I, 187.
[8] MacKenzie and Robertson, *J.*, 1949, 497.
[9] Vliet, in Gilman and Blatt (Ed.), "Organic Syntheses," Wiley and Sons, Inc., New York, 1941, Coll. Vol. I, p. 360.
[10] Tarbell, "Organic Reactions," Wiley and Sons, Inc., New York, 1944, **2**, 1.
[11] Mauthner, *J. prakt. Chem.*, 1933, **136**, 205.

the hindered nature of the surviving hydroxyl group because some reduction in the stability of the chelated system must follow the partial rotation of the acetyl group necessary to accommodate the allyl substituent [see (XV)]. Vigorous alkylation of the quinol (XV; R = H) furnished the dimethyl ether, isomerised by bases into 3 : 4 : 6-trimethoxy-2-propenylacetophenone (XVI; R = Me).

Similarly, benzylation and rearrangement of the allyl ether (XIV; R = H) led to the allylphenol (XVII; R = H), the methyl ether (XVII; R = Me) of which gave with bases 6-benzyloxy-3 : 4-dimethoxy-2-propenylacetophenone (XVI; R = CH_2Ph). This resinified in acid-catalysed debenzylation, but in catalytic hydrogenation gave 6-hydroxy-3 : 4-dimethoxy-2-propylacetophenone (XVIII).

The oxidation of the two propenylacetophenones (XVI; R = Me or CH_2Ph) was studied. The latter was destroyed by ozone, but the former gave a stable *iso*ozonide (XIX), the structure of which was inferred from its elementary analysis, the presence of two *C*-methyl groups (Kuhn–Roth), and the infrared spectrum, which indicated the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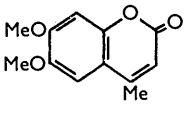
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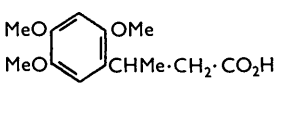
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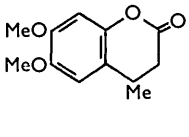
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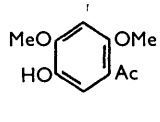
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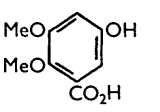
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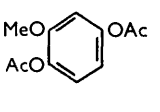
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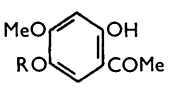
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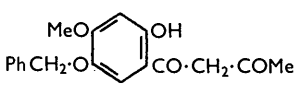
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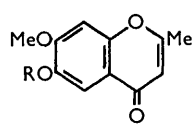
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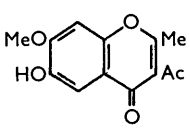
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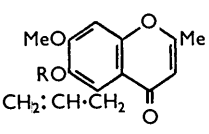
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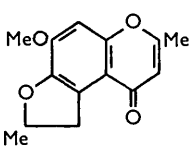
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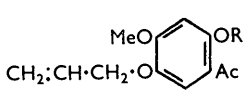
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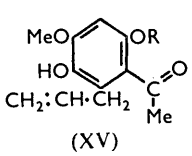
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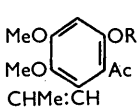
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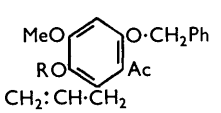
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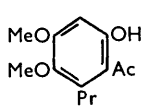
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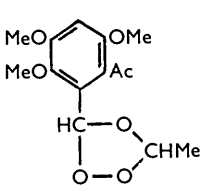
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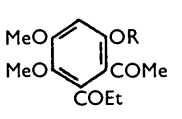
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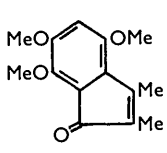
(XXI)

presence of an acetophenone-type carbonyl group (1692 cm.$^{-1}$) (not reactive to hydroxylamine) and the absence of hydroxyl groups. Related compounds, *e.g.*, (XVIII), have three intense absorption bands, near 220, 270, and 300 mμ, but the *iso*ozonide has but one, at 303 mμ. This difference may have a stereochemical origin since models show that the

acetyl group in (XIX) cannot become coplanar with the benzene ring, and the crowding of the acetyl group and the *iso*oozonide system could account for the unusual stability of both. Under forcing conditions of either hydrolysis or reduction this *iso*oozonide gave resins only.

Both propenylacetophenones (XVI; R = Me or CH_2Ph) gave adducts with osmium tetroxide, but fission of these was accompanied by dehydration, resulting in a purple resin and the diketones (XX; R = Me or CH_2Ph), which gave a positive reaction (green turning violet) in the aniline acetate test [12] for *o*-diacylbenzenes, and phthalazines with hydrazine. Dehydration of (XX; R = Me) usually gave dark resins, but on one occasion gave a brick-red indenone (XXI) (C:O band at 1704 cm.$^{-1}$) thus confirming structures (XX; R = Me or CH_2Ph) for these diketones, both of which exhibited a single carbonyl band at 1700 cm.$^{-1}$.

Experimental

β-2 : 4 : 5-*Trimethoxyphenylbutyric Acid* (III).—A solution of 4 : *O* : *O*-trimethylæsculetin (10 g.) in 5% aqueous sodium hydroxide (100 ml.) was shaken under hydrogen with Raney nickel (5 g.) until colourless (~3 hr.). Liberated from the filtrate by hydrochloric acid and isolated with ether, β-2-*hydroxy*-4 : 5-*dimethoxyphenylbutyric acid* was obtained in needles (10 g.), m. p. 134°, from alcohol [Found: C, 59·9; H, 6·5; OMe, 25·7. $C_{10}H_{10}O_3(OMe)_2$ requires C, 60·0; H, 6·7; OMe, 25·8%]. Methyl sulphate (15·8 g.) was added with vigorous stirring to this acid (10 g.) in 10% aqueous sodium hydroxide (100 ml.) during ½ hr., and the whole boiled for 1 hr. Acidification of the cooled solution and extraction of the product into ether furnished β-2 : 4 : 5-*trimethoxyphenylbutyric acid*, crystallising from ether–light petroleum (b. p. 60—80°) in needles (9·5 g.), m. p. 102° [Found: C, 61·3; H, 7·1; OMe, 36·5, 36·6. $C_{10}H_9O_2(OMe)_3$ requires C, 61·4; H, 7·1; OMe, 36·6%]. This acid was hardly affected by polyphosphoric acid at 70°, by phosphoric oxide in boiling benzene, or by sulphuric acid monohydrate at 0°.

3 : 4-*Dihydro*-6 : 7-*dimethoxy*-4-*methylcoumarin* (IV).—The trimethoxy-butyric acid (III) (5 g.) was kept with phosphorus pentachloride (3·5 g.) in chloroform (75 ml.) for ¼ hr. at room temperature and then at 65° for ½ hr. The solvent was removed, and the residue freed from phosphorus oxychloride by repeated distillation of the benzene solution. The crude acid chloride was treated in stirred benzene (20 ml.) with powdered, freshly sublimed aluminium chloride (4·0 g.) at 30° and then kept at 80° for ½ hr. The mixture was decomposed with crushed ice (400 g.) and 2N-hydrochloric acid (200 ml.) and the product, isolated by repeated extraction with light petroleum, was purified from ether–light petroleum (b. p. 60—80°), giving 3 : 4-*dihydro*-6 : 7-*dimethoxy*-4-*methylcoumarin* in feathery rosettes (0·5 g.), m. p. 84°; ester absorption at 1740 cm.$^{-1}$ (Found: C, 64·9; H, 6·4. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%). Under milder conditions, only the butyric acid was recovered. Hydrolysis of the dihydrocoumarin by hot 2N-sodium hydroxide and acidification of the resulting solution with 0·5N-hydrochloric acid furnished β-2-hydroxy-4 : 5-dimethoxyphenylbutyric acid, m. p. and mixed m. p. 134°.

5-*Acetoxy*-2-*hydroxy*-4-*methoxyacetophenone* (VIII; R = Ac).—Vanillin (30 g.) in stirred N-sodium hydroxide (175 ml.) was cautiously oxidised with hydrogen peroxide (100-vol.; 30 ml.) in water (70 ml.). After 1½ hr. 10N-sodium hydroxide (60 ml.) and crushed ice (300 g.) were added, followed by acetic anhydride (50 ml.) with vigorous agitation. Methoxyquinol diacetate separated as a brown powder which, when purified from methanol, formed needles (33 g.), m. p. 94°, with a strong infrared absorption band (Nujol) at 1789 (phenolic acetate) (Found: C, 59·0; H, 5·5. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%). Acetic acid (80 ml.) containing this diacetate (20 g.) was saturated with boron trifluoride and poured into water (300 ml.), whereupon 5-*acetoxy*-2-*hydroxy*-4-*methoxyacetophenone* slowly crystallised and was obtained by recrystallisation from alcohol as needles (18 g.), m. p. 104°, soluble in 2N-sodium hydroxide and having a purple ferric reaction in alcohol [Found: C, 58·6; H, 5·4; OMe, 14·0; OAc, 29·5. $C_8H_6O_2(OAc)(OMe)$ requires C, 58·9; H, 5·4; OMe, 13·9; OAc, 18·2%]. When the boron trifluoride reaction mixture was poured into 5N-hydrochloric acid (200 ml.) and boiled for ¼ hr., the cold solution deposited a brown powder, which, when crystallised from alcohol, gave 2 : 5-dihydroxy-4-methoxyacetophenone (VIII; R = H) in yellow needles (15·7 g.), m. p. 166°, having a green ferric reaction and infrared absorption bands (Nujol) at 3400 (C–OH) and 1675 cm.$^{-1}$ (chelated C:O)

[12] Weygand, Weber, and Maekawa, *Chem. Ber.*, 1957, **90**, 1879.

[Found: C, 59·4; H, 5·7; OMe, 17·3. Calc. for $C_8H_7O_3(OMe)$: C, 59·3; H, 5·5; OMe, 17·0%]. The *diacetate* formed needles, m. p. 130°, from a large volume of alcohol [Found: C, 58·7; H, 5·4; OMe, 12·0. $C_{12}H_{11}O_7(OMe)$ requires C, 58·6; H, 5·3; OMe, 11·7%].

5-Hydroxy-2 : 4-dimethoxyacetophenone (V).—5-Acetoxy-2-hydroxy-4-methoxyacetophenone (20 g.), potassium carbonate (20 g.), and methyl sulphate (10 ml.) were heated in boiling acetone (250 ml.) until a test sample gave no ferric reaction (~ 12 hr.). Evaporation of the hot filtrate to a small bulk (40 ml.) and addition of water (100 ml.) induced separation of the product which was purified from alcohol, giving *5-acetoxy-2 : 4-dimethoxyacetophenone* in prisms (20 g.), m. p. 123° [Found: C, 60·8; H, 6·1; OMe, 26·2. $C_{10}H_8O_3(OMe)_2$ requires C, 60·5; H, 5·9; OMe, 26·1%]. Hydrolysed in ½ hr. at 40° by sodium hydroxide (10 g.) in water (50 ml.), this acetate (7 g.) in alcohol (50 ml.) supplied the crude *phenol*, liberated by concentrated hydrochloric acid and purified from alcohol, forming prisms (5·5 g.), m. p. 154°, devoid of a ferric reaction [Found: C, 61·1; H, 5·8; OMe, 31·8. $C_8H_6O_2(OMe)_2$ requires C, 61·2; H, 6·2; OMe, 31·6%]. This phenol was unaffected by (i) hydrogen cyanide and zinc chloride (or aluminium chloride) in ether saturated with hydrogen chloride, (ii) aqueous potassium hydrogen carbonate at the b. p. for 1½ hr., (iii) sodium hydroxide and carbon tetrachloride under reflux for 18 hr.

5-Benzyloxy-2-hydroxy-4-methoxybenzoylacetone (IX).—Interaction of 2 : 5-dihydroxy-4-methoxyacetophenone (20 g.) and benzyl bromide (18·8 g.) in boiling acetone (350 ml.) containing potassium carbonate (20 g.) for 4 hr. gave *5-benzyloxy-2-hydroxy-4-methoxyacetophenone*, which was isolated in the usual way and then crystallised from chloroform–light petroleum, forming needles (20 g.), m. p. 151°, $\lambda_{max.}$ (in ethanol) 237, 277, 343 mμ (log ε 4·23, 4·05, 3·84), with a blue-green ferric reaction and giving a yellow solid with 2N-sodium hydroxide [Found: C, 70·4; H, 5·6; OMe, 11·5. $C_{15}H_{13}O_3(OMe)$ requires C, 70·6; H, 5·9; OMe, 11·4%]. With methyl sulphate and potassium carbonate in acetone, this phenol gave the 2 : 4-*dimethoxy-compound*, crystallising from aqueous alcohol in soft laminæ, m. p. 80°, turning pink in sunlight [Found: C, 71·3; H, 6·4; OMe, 21·8. $C_{15}H_{12}O_2(OMe)_2$ requires C, 71·3; H, 6·3; OMe, 21·7%]. The *acetate* formed needles, m. p. 100° from methanol [Found: C, 69·1; H, 5·9; OMe, 10·5. $C_{17}H_{15}O_4(OMe)$ requires C, 68·8; H, 5·7; OMe, 9·9%].

With sodium hydride (0·38 g.) in boiling pyridine (25 ml.) for ½ hr., 2-acetoxy-5-benzyloxy-4-methoxyacetophenone (5 g.) formed a solution which, when poured on ice (80 g.) containing a slight excess of acetic acid, gave a brown solid that separated from aqueous methanol, giving *5-benzyloxy-2-hydroxy-4-methoxybenzoylacetone* as needles (3·5 g.), m. p. 124°, soluble in dilute sodium hydroxide and having an olive-green ferric reaction (Found: C, 68·1; H, 5·6. $C_{18}H_{18}O_5$ requires C, 68·0; H, 5·3%). This diketone (6 g.) also resulted when 5-benzyloxy-2-hydroxy-4-methoxyacetophenone (10 g.) was refluxed with ethyl acetate (15 ml.) and sodium (8 g.) for 6 hr.

3-Acetyl-6-hydroxy-7-methoxy-2-methylchromone (XI).—The brown solution obtained from sodium hydride (0·4 g.) and 2 : 5-diacetoxy-4-methoxyacetophenone (5 g.) in boiling pyridine in ½ hr. was mixed with ice (100 g.) and acidified with acetic acid. The crystalline deposit was purified from methanol–benzene, giving the *3-acetylchromone* in needles (3 g.), m. p. 232°, soluble in dilute sodium hydroxide but devoid of a ferric reaction (Found: C, 61·7; H, 4·7. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·9%). The *acetate* separated from alcohol in needles, m. p. 210° (Found: C, 62·1; H, 5·0. $C_{15}H_{14}O_6$ requires C, 62·1; H, 4·9%), and the methyl ether in prisms, m. p. 192°, from benzene–light petroleum. Obtained by the potassium carbonate–acetone method, the *benzyl ether* crystallised from methanol–benzene in long needles, m. p. 179° (Found: C, 71·1; H, 5·5. $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·3%), and when warmed on the steam-bath with acetic acid containing an equal volume of concentrated hydrochloric acid it regenerated the parent 3-acetylchromone, m. p. and mixed m. p. 232°.

6-Hydroxy-7-methoxy-2-methylchromone (X; R = H).—(i) The above 3-acetylchromone (XI) (1 g.) was heated under reflux for 3 hr. with 5% aqueous sodium carbonate (100 ml.). Liberated by dilute hydrochloric acid, *6-hydroxy-7-methoxy-2-methylchromone* crystallised from alcohol in needles (0·75 g.), m. p. 235° (Found: C, 64·1; H, 5·0. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%), giving the *acetate* as prisms, m. p. 162—164°, from alcohol (Found: C, 63·2; H, 4·9. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·9%).

(ii) When boiled vigorously for 2 min., diluted with water (20 ml.), and cooled, a solution of 5-benzyloxy-2-hydroxy-4-methoxybenzoylacetone (2 g.) in alcohol (20 ml.) containing concentrated hydrochloric acid (6 drops) slowly deposited *6-benzyloxy-7-methoxy-2-methylchromone*, which formed prisms (1·6 g.), m. p. 140°, from benzene–light petroleum [Found: C, 73·1; H, 5·8; OMe, 9·3. $C_{17}H_{13}O_3(OMe)$ requires C, 73·0; H, 5·4; OMe, 10·5%]. A mixture of this

chromone (0·25 g.), concentrated hydrochloric acid (4 ml.), and acetic acid (4 ml.) was kept at 90° for 1½ hr. and diluted with water. The product was purified from alcohol, giving the 6-hydroxychromone in needles (0·15 g.), m. p. and mixed m. p. 235°.

5-Allyl-6-hydroxy-7-methoxy-2-methylchromone (XII; R = H).—By means of allyl bromide (6·5 g.) and potassium carbonate (10 g.) in boiling acetone (125 ml.), 6-hydroxy-7-methoxy-2-methylchromone (10 g.) was converted into *6-allyloxy-7-methoxy-2-methylchromone* which, isolated by evaporation of the filtered solution and purified from aqueous methanol, formed pale yellow rhombs (11·5 g.), m. p. 125°, $\lambda_{max.}$ (in ethanol) 233, 280, 317 mμ (log ε 4·38, 3·95, 4·03) (Found: C, 68·3; H, 5·7. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). When cooled, a solution of this 6-allyloxychromone (10 g.) in glycerol (100 ml.) which had been kept at 200° under nitrogen for ½ hr. deposited a solid which was recrystallised from alcohol giving *5-allyl-6-hydroxy-7-methoxy-2-methylchromone* in needles (9·6 g.), m. p. 216°, $\lambda_{max.}$ (in ethanol) 236, 281, 326 mμ (log ε 4·39, 3·94, 3·93) (Found: C, 68·1; H, 6·0. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). The *acetate* (XII; R = Ac) formed silky needles, m. p. 125°, from aqueous alcohol (Found: C, 66·5; H, 5·5. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). The *methyl ether* (XII; R = Me) (methyl sulphate–potassium carbonate) formed needles, m. p. 97°, from aqueous methanol, $\lambda_{max.}$ (in ethanol) ~230, 276, 307 mμ (log ε 4·41, 4·06, 3·96) (Found: C, 69·2; H, 6·1. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%).

7-Methoxy-2 : 6′-dimethyl-γ-pyrono(2′ : 3′-5 : 4)coumaran (XIII).—A rapid stream of hydrogen bromide was passed through 5-allyl-6 : 7-dimethoxy-2-methylchromone (500 mg.) in acetic acid (5 ml.). White crystals appeared after 1 hr.: these gradually redissolved. After 2 hr. the mixture was poured into water and neutralised with sodium hydrogen carbonate. The product (300 mg.) crystallised from aqueous methanol, giving the *γ-pyronocoumaran* in tiny prisms, m. p. 139°, $\lambda_{max.}$ (in ethanol) 218, 239, 336 mμ (log ε 4·36, 4·41, 3·87), insoluble in aqueous alkali, and inert to alcoholic ferric chloride and bromine in acetic acid [Found: C, 68·3; H, 5·9; OMe, 11·8; *C*-Me, 13·3. $C_{13}H_{11}O_3(OMe)$ requires C, 68·3; H, 5·7; OMe, 12·6; 2*C*-Me, 12·2%]. The same coumaran resulted when the allyldimethoxychromone was kept overnight at 0° in chloroform saturated with hydrogen bromide, and when 5-allyl-6-hydroxy-7-methoxy-2-methylchromone (XII; R = H) was treated with hydrogen bromide in acetic acid.

5-Allyloxy-2-hydroxy-4-methoxyacetophenone (XIV; R = H).—A mixture of 2 : 5-dihydroxy-4-methoxyacetophenone (20 g.), potassium carbonate (20 g.), and allyl bromide (13·6 g.) in acetone (250 ml.) was kept at the b. p. for 9 hr., then filtered and evaporated. The residue was recrystallised from light petroleum, giving *5-allyloxy-2-hydroxy-4-methoxyacetophenone* (XIV; R = H) in needles (20 g.), m. p. 80°, having a green ferric reaction (Found: C, 65·2; H, 6·5. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·4%). The *benzoate* (benzoyl chloride in 10% aqueous sodium hydroxide) crystallised in needles, m. p. 104°, from alcohol (Found: C, 69·9; H, 5·4. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·6%). The *acetate* (XIV; R = Ac) separated from benzene–light petroleum in needles, m. p. 116° (Found: C, 63·3; H, 5·9. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%), and the *methyl ether* (XIV; R = Me) (12 hours' alkylation by methyl sulphate–potassium carbonate) crystallised from the same solvent in needles, m. p. 81° (Found: C, 66·3; H, 7·0. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

2-Allyl-3-hydroxy-4 : 6-dimethoxyacetophenone (XV; R = Me).—(i) 5-Allyloxy-2 : 4-dimethoxyacetophenone (10 g.) was isomerised in boiling quinoline (50 ml.) during 40 min. and the product was isolated by dilution with ether (100 ml.), removal of quinoline by repeated washing with 5N-hydrochloric acid, and extraction into 2N-sodium hydroxide. Acidification of the extract and purification of the precipitate from benzene–light petroleum gave *2-allyl-3-hydroxy-4 : 6-dimethoxyacetophenone* (XV; R = Me) as needles (6·5 g.), m. p. 110° (Found: C, 65·9; H, 7·0. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). A better yield (8·7 g.) resulted when the isomerisation was in glycerol at 200° and the product was isolated by addition of water.

(ii) Isomerisation of 5-allyloxy-2-hydroxy-4-methoxyacetophenone (10 g.) in glycerol (50 g.) as in (i) above but in a nitrogen atmosphere furnished *2-allyl-3 : 6-dihydroxy-4-methoxyacetophenone* (XV; R = H), crystallising from benzene–light petroleum in pale yellow needles (8·1 g.), m. p. 114°, having a transient green ferric reaction (Found: C, 65·0; H, 6·5. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·4%). Alkylation of this quinol (3 g.) with methyl iodide (1 mol.) and potassium carbonate in acetone gave 2-allyl-3-hydroxy-4 : 6-dimethoxyacetophenone (1·3 g.), m. p. and mixed m. p. 110°. Hydrogenation of this quinol (1 g.) in methanol (100 ml.) containing palladium–charcoal (0·5 g.) in the usual way supplied *3 : 6-dihydroxy-4-methoxy-2-propylacetophenone*, separating from aqueous alcohol in lime-green prisms (1 g.), m. p. 118°, $\lambda_{max.}$ (in ethanol)

237, 277, 320 mμ (log ε 3·93, 3·59, 3·55) [Found: C, 64·1; H, 7·3; OMe, 14·1. $C_{11}H_{13}O_3(OMe)$ requires C, 64·3; H, 7·1; OMe, 13·8%].

3 : 4 : 6-*Trimethoxy-2-propenylacetophenone* (XVI; R = Me).—Methylation of either 2-allyl-3 : 6-dihydroxy-4-methoxyacetophenone or its 6-methyl ether (10 g.) with methyl sulphate and potassium carbonate gave 2-*allyl*-3 : 4 : 6-*trimethoxyacetophenone* as an oil (10 g.), b. p. 110°/0·05 mm. (Found: C, 67·4; H, 7·0. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·3%). At 130° for 1 hr. in 25% methanolic potassium hydroxide followed by dilution with water (150 g.) this oil (10 g.) produced 3 : 4 : 6-*trimethoxy-2-propenylacetophenone*, which crystallised from light petroleum in needles (9·4 g.), m. p. 80° [Found: C, 67·3; H, 7·3; OMe, 36·4. $C_{11}H_9O(OMe)_3$ requires C, 67·2; H, 7·3; OMe, 37·2%].

2-*Allyl*-6-*benzyloxy*-3-*hydroxy*-4-*methoxyacetophenone* (XVII; R = H).—Isolated in the usual way from a mixture of 5-allyloxy-2-hydroxy-4-methoxyacetophenone (20 g.), benzyl bromide (8 ml.), and potassium carbonate (10 g.) which had been kept in boiling acetone for 12 hr., 5-*allyloxy*-2-*benzyloxy*-4-*methoxyacetophenone* separated from light petroleum in needles (20 g.), m. p. 82°, $\lambda_{max.}$ (in ethanol) 235, 270, 328 mμ (log ε 4·35, 4·03, 3·91) (Found: C, 73·1; H, 6·4. $C_{19}H_{20}O_4$ requires C, 73·0; H, 6·3%), and when subjected (10 g.) to the Claisen rearrangement as for the analogues (XIV; R = H or Me) but in " Carbitol " at the b. p. for 1 hr. supplied 2-*allyl*-6-*benzyloxy*-3-*hydroxy*-4-*methoxyacetophenone* as needles (8·9 g.), m. p. 116°, from benzene–light petroleum, soluble in 2N-sodium hydroxide [Found: C, 72·9; H, 6·3; OMe, 9·0. $C_{18}H_{17}O_3(OMe)$ requires C, 73·0; H, 6·3; OMe, 9·9%]. The *methyl ether* (XVII; R = Me) crystallised from light petroleum in soft plates, m. p. 50°, $\lambda_{max.}$ (in ethanol) 265, 296 mμ (log ε 3·58, 3·57), $\nu_{max.}$ 1689 (acetophenone C:O), 1645 and 1595 cm.$^{-1}$ (aromatic and double-bond) (Found: C, 73·9; H, 6·9. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

6-*Benzyloxy*-3 : 4-*dimethoxy*-2-*propenylacetophenone* (XVI; R = CH_2Ph).—2-Allyl-6-benzyloxy-3 : 4-dimethoxyacetophenone (5 g.) was heated in 25% methanolic potassium hydroxide (100 ml.) at 130° for 1 hr. The oil which separated when the mixture was poured on ice (180 g.) and kept, gradually solidified and could then be crystallised from aqueous methanol giving 6-*benzyloxy*-3 : 4-*dimethoxy*-2-*propenylacetophenone* in rhombs (4·5 g.), m. p. 80°, $\lambda_{max.}$ (in ethanol 217, 235 (infl.), 309 mμ (log ε 4·53, 4·3, 3·58) [Found: C, 74·0; H, 7·2; OMe, 19·6. $C_{18}H_{16}O_2(OMe)_2$ requires C, 73·6; H, 6·8; OMe, 19·0%], with infrared absorption bands (Nujol) at 1695 (acetophenone C:O) and 1654 and 1595 cm.$^{-1}$ (aromatic and double-bond).

6-*Hydroxy*-3 : 4-*dimethoxy*-2-*propylacetophenone* (XVIII).—(i) Uptake of hydrogen ceased after absorption of 2 mol. when 6-benzyloxy-3 : 4-dimethoxy-2-propenylacetophenone (1 g.) in methanol (10 ml.) containing palladium–charcoal (0·5 g.) was shaken in this gas. Evaporation of the filtrate gave 6-*hydroxy*-3 : 4-*dimethoxy*-2-*propylacetophenone* as a pale yellow oil, b. p. 160°/0·2 mm., $\lambda_{max.}$ (in ethanol) 218, 268, 306 mμ (log ε 4·12, 3·67, 3·60) [Found: C, 65·2; H, 7·7; OMe, 25·8. $C_{11}H_{12}O_2(OMe)_2$ requires C, 65·5; H, 7·6; OMe, 26·1%]. This phenol gave an intense green ferric reaction.

(ii) ¼ Hr. after the gradual addition of 6-benzyloxy-3 : 4-dimethoxy-2-propenylacetophenone (1 g.) in ether (50 ml.) to calcium (0·5 g.) in liquid ammonia, ammonium chloride was added and the solvents were allowed to evaporate. The phenolic fraction of the residual brown gum was purified from benzene on neutral alumina, giving 6-hydroxy-3 : 4-dimethoxy-2-propylacetophenone, identified by means of its infrared spectrum with a specimen from (i).

3 : 4 : 6-*Trimethoxy*-2-*propenylacetophenone* iso*Ozonide* (XIX).—A stream of ozonised oxygen was passed into 3 : 4 : 6-trimethoxy-2-propenylacetophenone (3 g.) in ethyl acetate (90 ml.) at 0° for 2 hr. Removal of the solvent *in vacuo* left a gum which was unaffected by water and gave no reaction in the starch–iodide test but crystallised from aqueous methanol in plates (2·4 g.). Purified from benzene–light petroleum, this solid furnished the iso*ozonide* in prisms, m. p. 116—118°, $\lambda_{max.}$ (in ethanol) 303 mμ (log ε 3·66), insoluble in 2N-sodium hydroxide, devoid of a ferric reaction, and inert to alkaline silver oxide [Found: C, 56·4, 56·4, 56·4; H, 6·3, 6·4, 6·1; OMe, 30·9; *C*-Me (Kuhn–Roth), 9·5. $C_{14}H_{18}O_7$ requires C, 56·4; H, 6·1; OMe, 31·2; 2*C*-Me, 10·1%].

3 : 4 : 6-*Trimethoxy*-2-*propionylacetophenone* (XX; R = Me).—The adduct which separated overnight from mixed solutions of osmium tetroxide (3·5 g.) in ether (50 ml.) and of 3 : 4 : 6-trimethoxy-2-propenylacetophenone (3·5 g.) was decomposed in aqueous methanol (50 ml.) by sulphur dioxide. Filtered through charcoal, the solution was concentrated under reduced pressure and extracted continuously with ether, from which evaporation left a gum; purification from a little methanol and then light petroleum gave the *propionylacetophenone* as prisms,

m. p. 94—97°, $\lambda_{max.}$ (in ethanol) 215, 230, 270, 321 mμ (log ε 4·16, 4·14, 3·92, 3·91) (Found: C, 63·5; H, 6·9. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%).

With hydrazine hydrochloride (100 mg.) and sodium acetate (150 mg.) in water (1 ml.) at 80° for 10 min., this diketone (100 mg.) in alcohol (2 ml.) gave a solid, which, when treated with 2N-aqueous sodium hydroxide and crystallised from aqueous methanol, furnished *4-ethyl-5 : 6 : 8-trimethoxy-1-methylphthalazine* in needles, m. p. 120° (Found: C, 64·0; H, 7·0; N, 10·6. $C_{14}H_{18}O_3N_2$ requires C, 64·1; H, 6·9; N, 10·7%).

6-Benzyloxy-3 : 4-dimethoxy-2-propionylacetophenone (XX; R = CH_2Ph).—As with the trimethoxy-analogue, 6-benzyloxy-3 : 4-dimethoxy-2-propenylacetophenone (2 g.) formed with osmium tetroxide an adduct which, when decomposed by sulphur dioxide in 80% alcohol containing charcoal, gave a reddish solid. Extraction of this solid with ether left a gum from which boiling light petroleum (b. p. 60—80°) isolated material which, purified from benzene–light petroleum, gave *6-benzyloxy-3 : 4-dimethoxy-2-propionylacetophenone* in prisms (800 mg.), m. p. 111° [Found: C, 70·3; H, 6·3; OMe, 13·6; *C*-Me (Kuhn–Roth), 7·8. $C_{18}H_{16}O_3(OMe)_2$ requires C, 70·2; H, 6·4; OMe, 18·0; 2*C*-Me, 8·8%]. This diketone with hydrazine gave *8-benzyloxy-4-ethyl-5 : 6-dimethoxy-1-methylphthalazine*, crystallising from benzene in needles, m. p. 137° (Found: C, 71·1; H, 6·6. $C_{20}H_{22}O_3N_2$ requires C, 71·0; H, 6·5%).

4 : 6 : 7-Trimethoxy-2 : 3-dimethylindenone (XXI).—Heating of 3 : 4 : 6-trimethoxypropionylacetophenone (2 g.) with acetic anhydride (35 ml.) and sodium acetate (2·5 g.) in the steam-bath for 1½ hr. gave a dark solution which was poured into water (80 ml.). Next day the residual red gum solidified in contact with ether and when crystallised from benzene–light petroleum supplied the *indenone* in massive red prisms, m. p. 174° (Found: C, 68·0; H, 6·4. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%). Small quantities of this indenone often accompanied the diketone formed by decomposition of the osmic ester, but no conditions have been found in which the cyclisation occurs reliably.

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