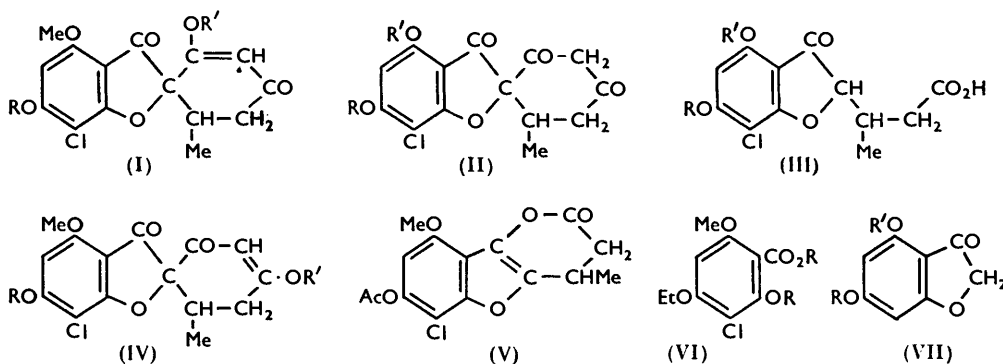


705. Griseofulvin. Part XII.* Position of the Aryl Methyl Ether Linkage, Labile to Aqueous Alkali.

By L. A. DUNCANSON, JOHN FREDERICK GROVE, J. MACMILLAN,
and T. P. C. MULHOLLAND.

Degradative and spectroscopic evidence is presented showing that it is the 6- and not the 4-methyl ether linkage in griseofulvin (and certain derivatives) which is hydrolysed by aqueous alkali. The stability to aqueous alkali of the methyl ether linkage in several model compounds, related to the aromatic ring in griseofulvin, has been investigated; ethers *para* to the carbonyl group in a 7-chlorocoumaranone are labile but those similarly situated in an acetophenone are stable. The methyl ethers of 4:6-dihydroxycoumaranone have been orientated unambiguously; the ultraviolet and infrared spectra of these compounds and of several derivatives of griseofulvin are discussed.

IN griseofulvin (I; R = R' = Me) and certain of its derivatives one of the aryl methyl ether linkages is hydrolysed by boiling aqueous alkali to give the corresponding phenol. Thus,^{1,2} griseofulvin and 7-chloro-4:6-dimethoxy-2'-methylgrisan-3:4':6'-trione (II; R = R' = Me) with 0.5*N*-sodium hydroxide yield the phenol, 7-chloro-4(or 6)-hydroxy-6-(or 4)-methoxy-2'-methylgrisan-3:4':6'-trione (II; R = H or Me, R' = Me or H).³ Similarly ⁴ β-(7-chloro-4:6-dimethoxy-3-oxocoumaran-2-yl)butyric acid (III; R = R' =



Me), an oxidation product of griseofulvin, yields with 3*N*-sodium hydroxide the phenolic acid (III; R = H or Me, R' = Me or H), an oxidation product of the phenolic trione (II; R = H or Me, R' = Me or H). Degradative and spectroscopic evidence is now presented showing that these phenols are 6-hydroxycoumaranones. The tentative suggestion in Part IV³ that they were the 4-hydroxy-derivatives was first doubted when these phenols were found to give negative reactions with methanolic titanous chloride; the model 4-hydroxycoumaranones, described below, gave red colours with this reagent.

Degradative Evidence.—The phenolic trione (II; R = H, R' = Me) with diazoethane yielded two isomeric diethyl ethers (I and IV; R = R' = Et), distinguished by their ultraviolet light absorption.^{2,3} The diethyl ether (I; R = R' = Et) on permanganate oxidation gave 3-chloro-4-ethoxy-2-hydroxy-6-methoxybenzoic acid (VI; R = H) whose structure was established by methylation to an ester ether (VI; R = Me) identical with

* Part XI, *J.*, 1957, 3124.

¹ Oxford, Raistrick, and Simonart, *Biochem. J.*, 1939, **33**, 240.

² Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.

³ *Idem*, *J.*, 1952, 3977.

⁴ Grove, Ismay, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3958.

an authentic specimen prepared by ethylation of methyl 3-chloro-4-hydroxy-2:6-dimethoxybenzoate.⁵

The phenolic trione derived from griseofulvin by aqueous alkaline hydrolysis is therefore (II; R = H, R' = Me). It follows that the phenolic acid, derived from (III; R = R' = Me), is (III; R = H, R' = Me) and that the neutral lactonic acetate⁴ formed therefrom is (V).

Ultraviolet and infrared spectra confirm the degradative conclusions. The model compounds were prepared by recorded methods except 4-hydroxy-6-methoxycoumaranone (VII; R = Me, R' = H) which was prepared by the following adaption of Shriner and Witte's method⁶ for 4-hydroxycoumaranone. 2:6-Dihydroxy-4-methoxyacetophenone⁷ was converted *via* the diacetyl derivative into ω -bromo-2:6-dihydroxy-4-methoxyacetophenone which, on ring closure, afforded the coumaranone (VII; R = Me, R' = H). This unambiguous synthesis finally establishes that the monomethyl ether, obtained by monomethylation of 4:6-dihydroxycoumaranone (VII; R = R' = H) with diazomethane,⁸ and also by ring closure of the Hoesch reaction product of chloroacetonitrile and phloroglucinol monomethyl ether,^{8,9} is the 4-methyl ether (VII; R = H, R' = Me). Attempts

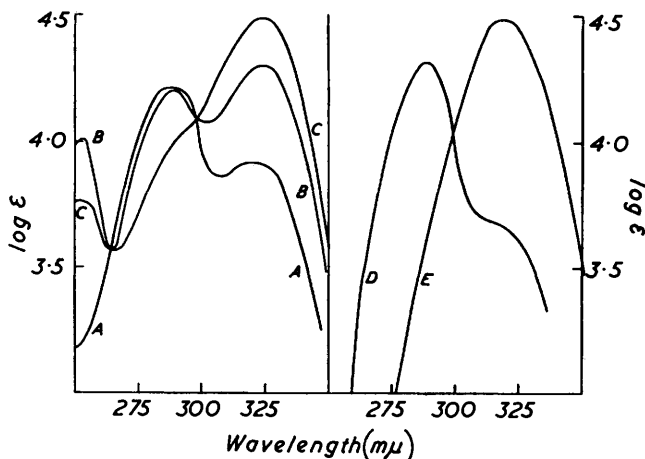


FIG. 1. Ultraviolet absorption of the acid (III; R = H, R' = Me).

In EtOH, (A) 1.66×10^{-3} M, (B) 2.16×10^{-4} M, and (C) 2.16×10^{-5} M. (D) In EtOH containing 2% of HCl. (E) In 0.1N-NaOH.

to prepare the 6-methyl ether by methylation of the diphenol with methyl sulphate as reported by Balakrishna, Rao, and Seshadri¹⁰ were unsuccessful.

Ultraviolet Absorption Spectra.—Cram and Cranz¹¹ have shown that *o*- and *p*-hydroxyacetophenones can be distinguished by comparing their ultraviolet light absorption in ionising and non-ionising media. For *o*-hydroxy-derivatives, the *K*-band of both the anion and the undissociated molecule have maxima of similar intensity at about the same wavelength. In the *p*-hydroxy-series, the *K*-band of the anion occurs at a much longer wavelength and is more intense than that of the undissociated molecule. The model hydroxycoumaranones behaved in the same way (Table 1).

The 4-hydroxy-compound (VII; R = Me, R' = H) absorbed at 280 m μ (*K*-band) as the undissociated molecule and at 285 m μ as the anion, a shift of only 5 m μ ; with the 6-hydroxy-compound (VII; R = H, R' = Me) there was a corresponding shift of 34 m μ . The phenolic acid (III; R = H, R' = Me) showed absorption typical of a 6-hydroxycoumaranone. The spectrum of the phenolic trione (II; R = H, R' = Me) is complicated

⁵ Grove, MacMillan, Mulholland, and Zealley, *J.*, 1952, 3967.

⁶ Shriner and Witte, *J. Amer. Chem. Soc.*, 1939, **61**, 2328.

⁷ Sönn and Bülow, *Ber.*, 1925, **58**, 1691.

⁸ Geissman and Hinreiner, *J. Amer. Chem. Soc.*, 1951, **73**, 782.

⁹ Gruber and Horvarth, *Monatsh.*, 1949, **80**, 563.

¹⁰ Balakrishna, Rao, and Seshadri, *Proc. Indian Acad. Sci.*, 1949, **29**, 394.

¹¹ Cram and Cranz, *J. Amer. Chem. Soc.*, 1950, **72**, 595.

TABLE I. Ultraviolet-light absorption of hydroxycoumaranones (λ_{\max} in $m\mu$).

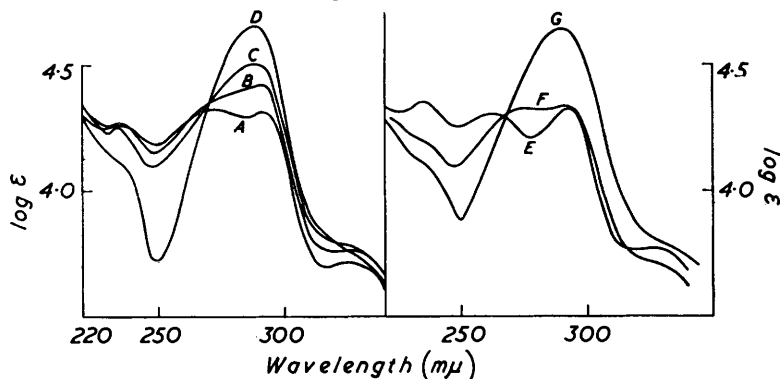
Compound	In ethanol + 2% HCl				In 0.1N-sodium hydroxide			
	K-band		B-band		K-band		B-band	
	λ_{\max}	log ϵ	λ_{\max}	log ϵ	λ_{\max}	log ϵ	λ_{\max}	log ϵ
VII; R = Me, R' = H	280	4.31	~315	3.63	285	4.35	346	3.81
VII; R = H, R' = Me	284	4.35	~315	3.78	318	4.53		
VII; R = R' = H	283	4.30	~312	3.83	306	4.51	~345	3.70
VII; R = R' = Me	282	4.33	~318	3.72 *				
III; R = H, R' = Me	289	4.32	~320	3.68	320	4.52		
II; R = H, R' = Me	292	4.30	~325	3.70 †	327	4.65		
II; R = R' = Me	292	4.34	~330	3.70 †	291	4.65	~330	3.80

* In ethanol.

† In ethanol-McIlvaine buffer pH 2.1 (1 : 1).

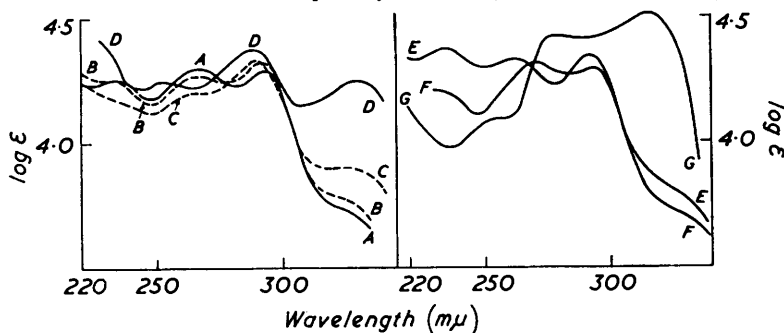
by the presence of the cyclic 1 : 3-dione chromophore (see Fig. 3 and below); however, the high-intensity band at 327 $m\mu$ in alkaline solution, absent from the spectrum of (II;

FIG. 2. Ultraviolet absorption of the trione (II; R = R' = Me).



In EtOH, (A) $1.216 \times 10^{-4}M$, (B) $6.08 \times 10^{-5}M$, (C) $3.04 \times 10^{-5}M$, and (D) $1.216 \times 10^{-6}M$. (E) In EtOH containing 2% of HCl. (F) In 1 : 1 EtOH-McIlvaine buffer (pH 2.1), and in 0.5N-ethanolic HCl (pH 1.5). (G) In 0.1N-NaOH.

FIG. 3. Ultraviolet absorption of the trione (II; R = H, R' = Me).



In EtOH, (A) $1.28 \times 10^{-4}M$, (B) $1.28 \times 10^{-5}M$, (C) $6.4 \times 10^{-6}M$, and (D) $1.28 \times 10^{-6}M$. (E) In EtOH containing 2% of HCl. (F) In 1 : 1 EtOH-McIlvaine buffer (pH 2.1). (G) In 0.1N-NaOH.

R = R' = Me) in alkaline solution (Fig. 2), clearly demonstrates the presence of a 6-hydroxycoumaranone chromophore.

In ethanol, the absorption of the 6-hydroxy- but not the 4-hydroxy-coumaranones was dependent on concentration. The curves obtained at various concentrations lay between those of the anion and the undissociated molecule and showed a sharp isosbestic point. The curves (Fig. 1) for (III; R = H, R' = Me) are typical; similar families of curves were obtained for (VII; R = H, R' = Me, and R = R' = H).

The enolised cyclic 1 : 3-dione chromophore in (II; R = R' = Me) showed concentration-dependent absorption in ethanol (Fig. 2);¹² in dilute solution the anion absorption band at 285 m μ (cf. dimedone, 280 m μ) reinforced that due to the substituted coumaranone chromophore, giving a broad peak of high intensity. There was no sharp isosbestic point. Curves for (II; R = H, R' = Me) (Fig. 3) also showed concentration-dependent absorption in ethanol but in this case the effect was complicated by the presence of the 6-hydroxy-coumaranone chromophore. Both triones (II; Me and H, R' = Me) possessed absorption maxima at 267–275 m μ in ethanol in concentrated solution (cf. dimedone, 255 m μ), in aqueous-ethanolic hydrochloric acid, and in ethanolic McIlvaine buffer pH 2.1, and thus exist in these solvents mainly as the enols (IV; R = Me and H, R' = H) corresponding to the methyl ether (IV; R = R' = Me) and not as the enols (I; R = Me and H, R' = H) corresponding to griseofulvin. After subtraction of absorption due to the coumaranone chromophore, the 1 : 3-dione enol methyl ether chromophore absorbs at 250 m μ in griseofulvin (cf. dimedone methyl ether, 249 m μ) and at 259 m μ in the isomeric (IV; R = R' = Me). The bathochromic shift in the latter compound is unexpected but may be due to interaction between the two carbonyl groups at the 3- and 2'-positions; Cram and

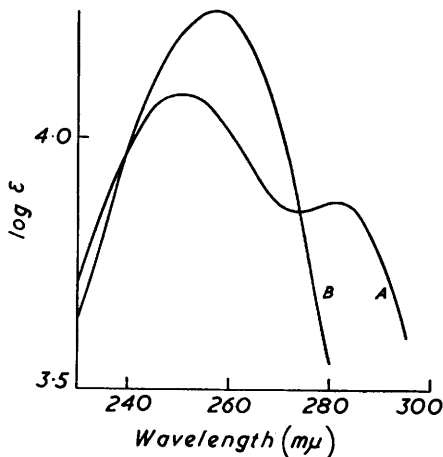


FIG. 4. Ultraviolet absorption of dimedone.

(A) In MeOH containing 2% of HCl. (B) As (A) but after dilution with an equal volume of water.

Steinberg¹³ have suggested that the anomalous absorption of 1 : 6-dioxospiro[4 : 4]nonane might be due to such an interaction.

In ethanol containing 2% of hydrogen chloride, the triones (II; R = R' = Me, and R = H, R' = Me) display absorption almost identical with that of (IV; R = Me, R' = Et).³ This result suggests that rapid ethylation of the triones occurs in this solvent. Similarly, dissolution of griseofulvin in methanol containing 2% of hydrogen chloride appears to cause rapid conversion into the isomeric methyl ether (IV; R = R' = Me) since the absorption spectrum in this solvent is identical with that of (IV; R = R' = Me) in the same solvent.² It is of interest that dimedone is not methylated after three days at room temperature with methanol-2% hydrogen chloride; the absorption (Fig. 4) in this solvent shows reduced intensity at 250 m μ (undissociated enol chromophore) and an absorption maximum at 280 m μ (conjugate acid chromophore), indicating an equilibrium between the undissociated enol and the conjugate acid.¹⁴ On dilution of this solution with water, the band at 280 m μ disappears and the band at 250 m μ increases in intensity.

The absorption data presented for (II; R = R' = Me), (II; R = H, R' = Me), and (III; R = H, R' = Me) correct those published in Parts I² and II⁴ of this series.

¹² Meek, Turnbull, and Wilson, *J.*, 1953, 2891.

¹³ Cram and Steinberg, *J. Amer. Chem. Soc.*, 1954, **76**, 2753.

¹⁴ Eistert, Merbel, and Reiss, *Chem. Ber.*, 1954, **87**, 1513.

Infrared Absorption.—Duncanson, Grove, and Zealley¹⁵ have shown that 4- and 7-hydroxyphthalides can be distinguished by their infrared spectra in dilute solution; the weak intramolecular hydrogen bonding in the 7-hydroxy-derivatives causes a characteristic lowering of the carbonyl frequency by about 20 cm.⁻¹. This work has been extended to hydroxycoumaranones where, in model compounds, it was found that a 4-hydroxy-substituent lowers the carbonyl frequency by about 20 cm.⁻¹ (Table 2).

Farmer, Hayes, and Thomson¹⁶ have quoted the data for (VII; R = R' = H; R = H, R' = Me; and R = Me, R' = H); these measurements were obtained by us on specimens prepared for this investigation in these laboratories.

The trione (II; R = H, R' = Me) and acid (III; R = H, R' = Me) showed carbonyl absorption typical of a 6-hydroxycoumaranone in accord with the assigned structures.

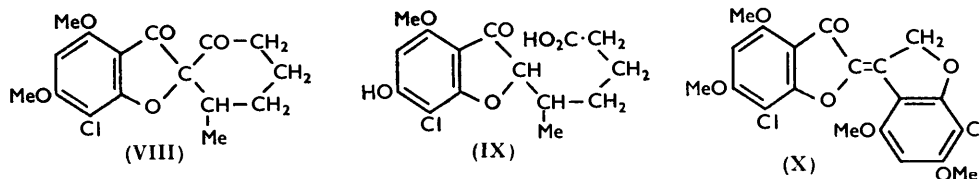
TABLE 2. Carbonyl stretching frequency of hydroxycoumaranones in chloroform solution.

Compound	ν (cm. ⁻¹)	Compound	ν (cm. ⁻¹)	Compound	ν (cm. ⁻¹)
VII; R = R' = H ...	1679	III; R = H, R' = Me	1708	II; R = H, R' = Me	1701
VII; R = Me, R' = H	1682	III; R = R' = Me ...	1704	II; R = R' = Me	1701
VII; R = H, R' = Me	1698			IX	1701
VII; R = R' = Me ...	1700				

The phenolic acid, obtained¹⁷ by alkaline hydrolysis of the reduction product (VIII) of the isomer (IV; R = R' = Me) of griseofulvin, is clearly not a 4-hydroxycoumaranone and must be the 6-hydroxy-compound (IX).

Model Compounds.—Although the 6-methyl ether linkage in the diether (II; R = R' = Me) is readily hydrolysed by aqueous alkali, it is stable to much more vigorous treatment with mineral acid. Thus the ether was recovered in 55–70% yield after 24 hours' refluxing with 6*N*-sulphuric acid, and no phenolic products could be isolated.

The stability of the methyl ether groups in several model compounds, structurally related to the aromatic ring in griseofulvin, was determined by refluxing with 0.5–3*N*-sodium hydroxide. All models contained a chloro-substituent since it has been shown¹⁸ that the 6-methoxyl substituent in dechlorogriseofulvin is stable to alkali.



Of the models examined, only (\pm)- β -(7-chloro-4 : 6-dimethoxy-3-oxocoumaran-2-yl)-butyric acid (III; R = R' = Me) and 7-chloro-4 : 6-dimethoxycoumaranone possessed methyl ether linkages which were split with aqueous alkali. The former, whose synthesis will be described in a later paper, gave the corresponding (\pm)-6-hydroxy-derivative (III; R = H, R' = Me). The latter yielded the self-condensation product (X) in high yield together with uncharacterised phenolic material (5%); more vigorous treatment with aqueous alkali caused extensive decomposition without increasing the yield of phenolic material.

The following derivatives of acetophenone were unaffected: 3-chloro-4-methoxy, 5-chloro-2-methoxy, 3-chloro-2 : 4 : 6-trimethoxy, and 3-chloro-2-hydroxy-4 : 6-dimethoxy. The last mentioned compound was prepared by a Friedel-Crafts reaction between 2-chloro-3 : 5-dimethoxyphenol and acetyl chloride; the methyl ether, 3-chloro-2 : 4 : 6-trimethoxyacetophenone, was prepared by methylation with methyl iodide and potassium carbonate.

¹⁵ Duncanson, Grove, and Zealley, *J.*, 1953, 1331.

¹⁶ Farmer, Hayes, and Thomson, *J.*, 1956, 3600.

¹⁷ Mulholland, *J.*, 1952, 3994.

¹⁸ MacMillan, *J.*, 1953, 1697.

Among other model compounds methyl 3-chloro-2 : 4 : 6-trimethoxybenzoate was quantitatively hydrolysed by alkali to the corresponding benzoic acid. 8-Chloro-5 : 7 : 4'-trimethoxyflavone, suggested by Dr. W. D. Ollis, Bristol University, as a possible model, was split into 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid and 4-methoxyacetophenone. The flavone was prepared from buddleoflavanolide by hydrolysis to acacetin¹⁹ followed successively by chlorination and methylation.

Attempts to prepare 3 : 5-dichloro-2 : 4 : 6-trimethoxyacetophenone by a Friedel-Crafts reaction on 2 : 4-dichloro-1 : 3 : 5-trimethoxybenzene were unsuccessful. From reactions in carbon disulphide 3 : 3'-dichloro- and 3 : 3' : 5-trichloro-2 : 2' : 4 : 4' : 6 : 6'-hexamethoxydiphenyl were obtained (the latter by methylation of a phenolic fraction), together with the acetate of 2 : 6-dichloro-3 : 5-dimethoxyphenol.⁵

It is notable that the 2-hydroxy-derivative of (III; R = R' = Me) which exists in alkaline solution in the open-chain 1 : 2-dione form does not suffer hydrolysis of the 6-methyl ether linkage with aqueous alkali although it undergoes a benzilic acid rearrangement. This fact, and the above model experiments show that an aryl methyl ether linkage, situated *para* to the carbonyl group in a 7-chlorocoumaranone is readily hydrolysed by dilute aqueous alkali whereas a methoxyl group similarly situated in an acetophenone is stable. Substitution of the coumaranone in the 2-position prevents preferential self-condensation.

EXPERIMENTAL

Microanalyses are by Messrs. W. Brown and A. G. Olney. M. p.s are corrected. In chromatography, B.D.H. alumina was rendered alkali-free (pH 4) and activated at 250°/15 mm. Ultraviolet light absorption was measured with a Unicam S.P. 500 spectrophotometer. The infrared spectra were measured with a Grubb-Parsons S 3A spectrometer fitted with a rock-salt prism.

Ethylation of 7-Chloro-6-hydroxy-4-methoxy-2'-methylgrisan-3 : 4' : 6'-trione (II; R = H, R' = Me).—The trione (1.17 g.), suspended in ethanol (15 ml.), was treated overnight with diazoethane (from 10 g. of 4-ethylamino-4-methyl-3-nitrosopentan-2-one) in ether (200 ml.). The recovered gum in benzene (30 ml.) was adsorbed on alumina (28 × 1.5 cm.), and the band of general adsorption (blue in ultraviolet light) was eluted with benzene. The recovered colourless gum, on treatment with ether, deposited *7-chloro-6 : 2'-diethoxy-4-methoxy-6'-methylgrisan-2'-en-3 : 4'-dione* (I; R = R' = Et) which crystallised from ethanol in needles (420 mg.), m. p. 174—175° (Found : C, 59.9; H, 5.4; Cl, 8.9; Oalk as OMe, 24.5. C₁₉H₂₁O₆Cl requires C, 59.9; H, 5.6; Cl, 9.3; Oalk as OMe, 24.4%), λ_{max.} (in EtOH) ~323, 292, ~255, 235 mμ (log ε 3.75, 4.36, 4.18, 4.34 respectively). The infrared spectrum of a "Nujol" mull showed absorption max. at 1705 and 1654 cm.⁻¹ in the double-bond stretching region.

The ether mother-liquors, cooled in acetone-solid carbon dioxide, deposited *7-chloro-6 : 4'-diethoxy-4-methoxy-6'-methylgrisan-3'-en-3 : 2'-dione* (IV; R = R' = Et) which crystallised from ethanol in needles (460 mg.), m. p. 205° (Found : C, 59.4; H, 5.3; Oalk as OMe, 25.4%), λ_{max.} (in EtOH) ~320, 292, 260, 236 mμ (log ε 3.78, 4.23; 4.23; 4.30 respectively).

In some preparations the diethyl ether (IV; R = R' = Et) could not be obtained solid.

Oxidation of 7-Chloro-6 : 2'-diethoxy-4-methoxy-6'-methylgrisan-2'-en-3 : 4'-dione (I; R = R' = Et).—To the diethyl ether (250 mg.) in acetone (40 ml.) was added powdered potassium permanganate (1.0 g.). After 16 hr. at room temperature, the precipitated manganese salts were collected, washed with acetone, and extracted with dilute aqueous ammonia. Acidification of the alkaline extract gave *3-chloro-4-ethoxy-2-hydroxy-6-methoxybenzoic acid* which crystallised from ethyl acetate in needles (11 mg.), m. p. 179—181° (decomp.) (Found : C, 48.4; H, 4.5. C₁₆H₁₁O₅Cl requires C, 48.7; H, 4.5%). The methyl ether methyl ester, obtained with diazomethane, crystallised from diethyl ether in plates, m. p. 120—122° and was identical (mixed m. p. and infrared spectrum) with a synthetic specimen of *methyl 3-chloro-4-ethoxy-2 : 6-dimethoxybenzoate*, prisms, m. p. 122—124° [from light petroleum (b. p. 40—60°)] (Found : C, 52.8; H, 5.3; Cl, 12.8. C₁₂H₁₅O₆Cl requires C, 52.5; H, 5.5; Cl, 12.9%), prepared by treatment of methyl 3-chloro-4-hydroxy-2 : 6-dimethoxybenzoate with diazoethane.

4 : 6-Dihydroxycoumaranone, prepared by the method of Drumm, MacMahon, and Ryan,²⁰

¹⁹ Baker, Hemming, and Ollis, *J.*, 1951, 691.

²⁰ Drumm, MacMahon, and Ryan, *Proc. Roy. Irish Acad.*, 1924, **36**, 149.

had m. p. 255° (decomp.), p*K* 6.2. It gave a reddish colour with methanolic titanous chloride.

6-Hydroxy-4-methoxycoumaranone was prepared by methylation of 4:6-dihydroxycoumaranone as described by Geissman and Hinreiner.⁸ The product, crystallised from dioxan, had m. p. 299—300°, p*K* 6.0 (Geissman and Hinreiner recorded m. p. 290—292°; Gruber and Horvarth⁹ give m. p. 262—269°) (Found: C, 59.9; H, 4.5. Calc. for C₉H₈O₄: C, 60.0; H, 4.5%). It gave no colour with methanolic titanous chloride and gave a violet colour with concentrated nitric acid.

4-Hydroxy-6-methoxycoumaranone.—(a) 2:6-Diacetoxy-4-methoxyacetophenone. 2:6-Dihydroxy-4-methoxyacetophenone⁷ (4.0 g.) and acetic anhydride (20 ml.) were heated under reflux for 24 hr. then poured into ice-water. An ethereal extract of the precipitated solid was washed with 0.25*N*-sodium hydroxide and with water; concentration of the dried solution, after treatment with charcoal, gave the *diacetate* (4.4 g.), m. p. 73—75°. It formed prisms m. p. 76°, from benzene-light petroleum (b. p. 40—60°) (Found: C, 58.5; H, 5.4. C₁₃H₁₄O₆ requires C, 58.6; H, 5.3%).

(b) 2:6-Diacetoxy- ω -bromo-4-methoxyacetophenone. The above acetate (6.0 g.) in carbon disulphide (350 ml.) was stirred at room temperature during the addition (5 hr.) of bromine (3.74 g.) in carbon disulphide (62 ml.). The product separated towards the end of the addition and after being kept at 0° for 0.5 hr. was collected. The filtrate, to which ether was added, was washed with water and the dried solution was evaporated to dryness *in vacuo* at low temperature. The residual *bromo-compound* was washed with a little ether, combined with the first crop, and crystallised from benzene-light petroleum (b. p. 60—80°) in needles (5.2 g.), m. p. 94—96°. A pure specimen had m. p. 96—97° (Found: C, 44.95; H, 4.0; Br, 23.05. C₁₃H₁₃O₆Br requires C, 45.2; H, 3.8; Br, 23.2%).

(c) ω -Bromo-2:6-dihydroxy-4-methoxyacetophenone. The foregoing bromo-compound (3.8 g.) in ethanol (80 ml.) was heated under reflux for 20 min. with 16% aqueous hydrogen bromide (100 ml.). After dilution with water, the mixture was concentrated *in vacuo* at room temperature. The crude product (2.7 g.) separated as a yellow gum (which soon solidified), followed by pale yellow needles of almost pure *product*. The latter crystallised from benzene in almost colourless needles, m. p. 139.5—140.5 (decomp.) (Found: C, 42.0; H, 3.7; Br, 30.5. C₉H₉O₄Br requires C, 41.4; H, 3.5; Br, 30.6%).

(d) 4-Hydroxy-6-methoxycoumaranone. The crude dihydroxy-compound (2.5 g.) and sodium acetate trihydrate (2.5 g.) in ethanol (110 ml.) were heated under reflux for 1 hr. The residue obtained on evaporation *in vacuo* was washed with water, dried, and sublimed *in vacuo*, giving 4-hydroxy-6-methoxy-coumaranone as a colourless solid (0.97 g.). It crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 144°, p*K* 6.64 (Found: C, 60.0; H, 4.6; OMe, 16.8. Calc. for C₉H₈O₄: C, 60.0; H, 4.5; 1 OMe, 17.2%). Methylation, with diazomethane, gave 4:6-dimethoxycoumaranone, m. p. and mixed m. p. 136—138°.

4-Hydroxy-6-methoxycoumaranone was slightly soluble in cold dilute sodium hydroxide but readily soluble on heating, the sodium salt separating on cooling. It gave a brown colour with methanolic ferric chloride, a red colour with methanolic titanous chloride, and a violet colour with concentrated nitric acid. The 2:4-*dinitrophenylhydrazone*, crystallised from nitrobenzene, decomposed at 220° (Found: C, 49.9; H, 3.4; N, 15.1. C₁₅H₁₂O₇N₄ requires C, 50.0; H, 3.4; N, 15.55%). A crystalline benzylidene derivative could not be prepared.

Balakrishna *et al.*¹⁰ reported the preparation of 4-hydroxy-6-methoxycoumaranone by partial methylation of the parent 4:6-dihydroxy-compound and gave m. p. 147—148°; in our hands this preparation was unsuccessful.

3-Chloro-2-hydroxy-4:6-dimethoxyacetophenone (With Mr. A. W. DAWKINS).—A mixture of 2-chloro-3:5-dimethoxyphenol (25 g.), redistilled nitrobenzene (35 g.), and acetyl chloride (20 g.) was treated with powdered aluminium chloride (35 g.) during 1 hr. with cooling, then kept at room temperature for 72 hr. and diluted with water (250 ml.), followed by concentrated hydrochloric acid (30 ml.). After removal of the nitrobenzene in steam the black solid was collected and triturated with ether. The yellow powder (29 g.) so obtained crystallised from a large volume of methanol, yielding the required *acetophenone* as yellow needles (26.5 g.), m. p. 191—192° (Found: C, 52.1; H, 4.5; Cl, 15.4. C₁₀H₁₁O₄Cl requires C, 52.1; H, 4.8; Cl, 15.4%). The phenol gave a brown colour with ethanolic ferric chloride and a green colour with methanolic titanous chloride. The infrared spectrum showed an absorption band at 1625 cm.⁻¹ due to the chelated and unsaturated carbonyl group.

The *methyl ether*, prepared by boiling the phenol (100 mg.) in acetone (10 ml.) for 6 hr. with methyl iodide (0.5 ml.) and potassium carbonate (1.0 g.) and pouring the mixture into water (10 ml.), was obtained in colourless needles (90 mg.) and was purified by sublimation at $70^{\circ}/10^{-2}$ mm.; it had m. p. 74° (Found: C, 54.4; H, 5.25; Cl, 13.9; OMe, 33.05. $C_{11}H_{13}O_4Cl$ requires C, 54.0; H, 5.3; Cl, 14.5; 3OMe, 38.0%). It gave no colour with methanolic titanous chloride.

8-Chloro-5:7:4'-trimethoxyflavone (With Miss M. T. KENNEDY).—5:7-Dihydroxy-4'-methoxyflavone (200 mg.; m. p. 263° ; prepared by hydrolysis of buddleoflavanolide¹⁹) in acetic acid (75 ml.) was treated with sulphuryl chloride (164 mg.) in acetic acid (15 ml.) (immediate separation of yellow needles). After 1 hr. at room temperature, the *8-chloro-derivative* (180 mg.) was collected and recrystallised from ethanol in yellow needles, m. p. $306-308^{\circ}$ (Found: C, 60.7; H, 4.05; Cl, 10.3. $C_{16}H_{11}O_5Cl$ requires C, 60.3; H, 3.5; Cl, 11.1%). The acetic acid mother-liquors, after 18 hr. at 0° , deposited a pale yellow *substance* (60 mg.), m. p. 246° (Found: C, 46.95; H, 2.7; Cl, 25.4. $C_{16}H_9O_5Cl_3 \cdot H_2O$ requires C, 47.3; H, 2.7; Cl, 26.2%).

The foregoing 8-chloro-derivative (160 mg.) in acetone (75 ml.) was heated under reflux for 16 hr. with methyl iodide (4 ml.) and potassium carbonate (10 g.). The precipitate obtained on pouring the mixture into water was collected and recrystallised (charcoal) from methanol in cream-coloured needles (100 mg.), m. p. $218-220^{\circ}$, of *8-chloro-5:7:4'-trimethoxyflavone* (Found: C, 62.5; H, 4.3; Cl, 9.9. $C_{16}H_{15}O_5Cl$ requires C, 62.3; H, 4.3; Cl, 10.2%).

Attempted Nuclear Acetylation of 2:4-Dichloro-1:3:5-trimethoxybenzene (With Miss D. ISMAY).—(a) The dichloro-compound was recovered unchanged after treatment with acetyl chloride and concentrated sulphuric acid in ether at room temperature, with acetyl chloride and aluminium chloride in boiling carbon disulphide for 12 hr., and with acetic anhydride and aluminium chloride in boiling ether for 2 hr. Treatment with acetic anhydride and aluminium chloride in nitrobenzene at 200° led to extensive decomposition.

(b) Powdered aluminium chloride (3.34 g., 0.025 mole) was added to the dichlorotrimethoxybenzene (2.38 g., 0.01 mole) in carbon disulphide (25 ml.); acetic anhydride (1.02 g., 0.01 mole) was added dropwise to the boiling solution and heating under reflux was continued for 2 hr. The solvent was removed by distillation and the brown residue was treated with ice and concentrated hydrochloric acid. An ether extract of the resulting orange solution was extracted with 3*N*-sodium hydroxide and washed with water. Recovery of the neutral fraction afforded a brown solid which on crystallisation from methanol yielded (1) 3:3'-*dichloro-2:2':4:4':6:6'-hexamethoxydiphenyl*, needles (70 mg.), m. p. $193-204^{\circ}$, raised by repeated recrystallisation from methanol to $206-208^{\circ}$ [Found: C, 53.4; H, 5.2; Cl, 17.4%; *M* (Rast), 382. $C_{18}H_{20}O_6Cl_2$ requires C, 53.6; H, 5.0; Cl, 17.6%; *M*, 403] (no infrared bands attributable to carbonyl groups), and (2) a solid (1.7 g.), m. p. $84-94^{\circ}$, which, after adsorption on alumina (12×1.5 cm.) from benzene and elution of the band fluorescing blue in ultraviolet light, yielded 2:6-*dichloro-3:5-dimethoxyphenyl acetate* (710 mg.), needles, m. p. $127-129^{\circ}$ (Found: C, 45.4; H, 3.9; Cl, 26.3. $C_{10}H_{10}O_4Cl_2$ requires C, 45.3; H, 3.8; Cl, 26.8%). It was identical (mixed m. p.) with a specimen prepared from 2:6-dichloro-3:5-dimethoxyphenol⁶ with acetic anhydride and pyridine. The infrared spectrum showed an absorption band at 1780 cm.^{-1} characteristic of a phenyl acetate.

The alkaline extract on acidification gave a solid (70 mg.), m. p. $150-173^{\circ}$, which was combined with a solid (60 mg.) obtained by ether-extraction of the mother-liquors and was methylated with diazomethane, giving 3:3'-*dichloro-2:2':4:4':6:6'-hexamethoxydiphenyl* (85 mg.), m. p. and mixed m. p. $201-203^{\circ}$, after crystallisation from methanol.

(c) When experiment (b) was repeated with 10 g. of the dichloro-compound the neutral fraction (5.0 g.) had m. p. $100-109^{\circ}$. Recrystallisation from methanol gave pale yellow needles (4.1 g.), m. p. $112-127^{\circ}$, which were adsorbed on alumina (18×1.5 cm.) from a benzene solution (20 ml.). Elution of the lowest band (mauve fluorescence in ultraviolet light) with benzene and recovery yielded 2:6-*dichloro-3:5-dimethoxyphenyl acetate* (2.94 g.), m. p. $115-121^{\circ}$ raised by two recrystallisations followed by sublimation at $60^{\circ}/10^{-3}$ mm. to $127-129^{\circ}$.

The alkali-soluble fraction, on trituration with methanol, gave a solid, m. p. $182-189^{\circ}$, which with diazomethane yielded 3:3':5-*trichloro-2:2':4:4':6:6'-hexamethoxydiphenyl*, prisms (from ethyl acetate), m. p. $176-179^{\circ}$ [Found: C, 49.6; H, 4.25; Cl, 24.2%; *M* (Rast), 414. $C_{18}H_{19}O_6Cl_3$ requires C, 49.4; H, 4.4; Cl, 24.3%; *M*, 438]. The infrared spectrum showed no bands due to carbonyl or hydroxyl groups.

Alkaline Hydrolysis Experiments with Model Compounds.—(a) 3-Chloro-4-methoxyacetophenone,²¹ m. p. 71—73°, was recovered in 97% yield after treatment with boiling 0.5N-sodium hydroxide for 5 hr.

(b) 5-Chloro-2-methoxyacetophenone, prepared by Wittig's method,²² had m. p. 34°. The 2 : 4-dinitrophenylhydrazone formed orange needles, m. p. 226°, from benzene (Found : C, 49.3; H, 3.6; N, 15.7. $C_{15}H_{13}O_5N_2Cl$ requires C, 49.4; H, 3.6; N, 15.4%). The acetophenone was recovered in 95% yield after 5 hours' boiling with 0.5N-sodium hydroxide.

(c) Methyl 3-chloro-2 : 4 : 6-trimethoxybenzoate (100 mg.) was heated under reflux for 5 hr. with 0.5N-sodium hydroxide. Acidification afforded 3-chloro-2 : 4 : 6-trimethoxybenzoic acid (80 mg.), needles, m. p. 186—188° (decomp.) (from aqueous methanol) (Found : C, 48.5; H, 4.6. Calc. for $C_{10}H_{11}O_5Cl$: C, 48.8; H, 4.5%).

(d) 3-Chloro-2-hydroxy-4 : 6-trimethoxyacetophenone (104 mg.) was heated under reflux for 5 hr. with 0.5N-sodium hydroxide in a stream of nitrogen. Acidification and recovery of the precipitated solid gave starting material (101 mg.), m. p. 189—192°. Recrystallisation from ethanol gave needles (94 mg.), m. p. and mixed m. p. 190—192°.

(e) 3-Chloro-2 : 4 : 6-trimethoxyacetophenone (100 mg.) was treated with 0.5N-sodium hydroxide (10 ml.) as in (d). Filtration gave starting material (75 mg.), m. p. and mixed m. p. 73°.

After 3 or 36 hours' boiling with 3N-sodium hydroxide recovery was 35% or 5% respectively. No alkali-soluble material was obtained in the former case, while in the latter, 25% of an intractable solid, m. p. >300°, was isolated.

(f) 8-Chloro-5 : 7 : 4'-trimethoxyflavone. (i) The flavone (60 mg.) and 0.5N-sodium hydroxide (25 ml.) were heated under reflux for 6 hr. Acidification of the filtrate with 3N-hydrochloric acid, after removal of some starting material, gave a yellow solid (6 mg.) which crystallised from methanol (charcoal) in colourless needles, m. p. and mixed m. p. with 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid, 210°.

Extraction of the acidic mother-liquors with ether and recovery gave a brown oil which with Brady's reagent yielded an orange solid, m. p. 218°, raised by recrystallisation from ethanol to 220° and undepressed on admixture with 4-methoxyacetophenone 2 : 4-dinitrophenylhydrazone.

(ii) The flavone (52 mg.) in methanol (30 ml.) containing 0.5N-sodium hydroxide (50 ml.) was heated under reflux for 6 hr. Working up as before yielded 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid, m. p. 216—218°, identified by infrared spectrum and mixed m. p. (Found : C, 46.9; H, 4.3. Calc. for $C_9H_9O_5Cl$: C, 46.5; H, 3.9%), and 4-methoxyacetophenone 2 : 4-dinitrophenylhydrazone, m. p. 212°.

(g) 7-Chloro-4 : 6-dimethoxycoumaranone²³ (100 mg.), suspended in 0.5N-sodium hydroxide (10 ml.), was heated under reflux for 3 hr. in a stream of nitrogen. After cooling to 0°, the solid was collected and the filtrate which darkened rapidly in air was acidified with concentrated hydrochloric acid and extracted with ether. The neutral solid (75 mg.) was adsorbed on alumina (3 × 1.5 cm.) from benzene and the least strongly adsorbed band which fluoresced bright yellow in ultraviolet light was collected. Recovery gave a colourless solid (26 mg.) which crystallised from benzene in prisms, m. p. 249—250°, of 7-chloro-2-(7-chloro-4 : 6-dimethoxycoumaran-3-ylidene)-4 : 6-dimethoxycoumaranone (Found : C, 55.0; H, 3.5. $C_{20}H_{16}O_7Cl_2$ requires C, 54.7; H, 3.7%), λ_{max} . (in EtOH) 326, 287.5, 263.5, 239 m μ (log ϵ 3.55, 4.13, 4.12, 4.21). The remaining yellow bands, on elution with benzene-methanol (99 : 1), gave intractable orange gums (3.4 mg.)

The ether extract (10 mg.), a brown amorphous material, was dissolved in benzene (30 ml.) and chromatographed on alumina (3 × 1.5 cm.). A colourless band, fluorescing dark blue in ultraviolet light, was eluted with benzene and furnished orange prisms (1 mg.), m. p. 288—290° (decomp.) (from benzene-methanol). A yellow band with a yellow fluorescence in ultraviolet light, eluted with benzene-methanol (99 : 1), gave yellow prisms (5 mg.), m. p. 294—295°, of a phenol [Found : C, 48.9; H, 3.6; OMe, 9.8. $C_{18}H_{16}O_9Cl_2$ ($C_{18}H_{12}O_7Cl_2 \cdot 2H_2O$) requires C, 48.4; H, 3.6; 2OMe, 13.9%]; this gave a positive Millon test but no colour with methanolic ferric or titanous chlorides.

Similar results were obtained by heating under reflux for 8—12 hr. with N-sodium hydroxide

²¹ Nguyen-Hoan and Buu-Hoi, *Compt. rend.*, 1947, **224**, 1363.

²² Wittig, *Ber.*, 1924, **57**, 88.

²³ MacMillan, Mulholland, Dawkins, and Ward, *J.*, 1954, 429.

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in the presence or absence of ethanol. Boiling with 3N-sodium hydroxide for 8 hr. led to extensive decomposition.

(h) (\pm)- β -(7-Chloro-4 : 6-dimethoxy-3-oxocoumaran-2-yl)butyric acid (234 mg.) in 3N-sodium hydroxide (10 ml.) was heated under reflux for 4 hr. in a current of nitrogen. The cooled solution was filtered from gelatinous material and acidified at 0°. After 24 hr. the cream-coloured solid (123 mg.) was collected and crystallised twice from ethyl acetate, giving (\pm)- β -(7-chloro-6-hydroxy-4-methoxy-3-oxocoumaran-2-yl)butyric acid as colourless ill-defined prisms, m. p. 212—214° (decomp.) (Found: C, 51.9; H, 4.4; Cl, 11.1. C₁₃H₁₃O₆Cl requires C, 51.9; H, 4.3; Cl, 11.8%). Ferric chloride and titanous chloride tests were negative.

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