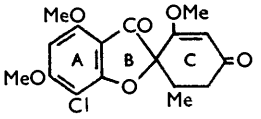
440. *Griseofulvin. Part XVII.*[1] *Synthesis of 7-Chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione.*

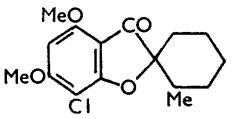
By A. W. Dawkins and T. P. C. Mulholland.

The synthesis is described of grisan and coumaran-3-one *spirocyclo*pentane analogues of some griseofulvin derivatives, and of racemates of the griseofulvin degradation products, (*l*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one * (II) and (*d*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (III).

The preceding paper[1] described a synthesis of the racemate of (*l*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one * (II), the racemate of a product obtained from (*l*,*d*)-griseofulvin (I). In the present paper details are given of a second route[3] which led to the synthesis of the racemates of the (*l*,*d*)-ketone (II) and of (*d*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (III). This route was based on reports[4,5] that the usnolic acid analogue (IV; R = R′ = Me) obtained by ring closure of the keto-ester (V; R = R′ = Me) with sulphuric acid[4,5,6] was a spiran rather than a dihydrodibenzofuran derivative. Ozonolysis of the ester (IV; R = R′ = Me) gave formaldehyde and a compound shown to be a coumaranone ester[5] (VI; R = R′ = Me, R″ = CO_2Et) by spectroscopy and oxidation to a salicylic acid. Since grisans containing a *C*-methyl group in the correct position for derivatives of griseofulvin might be obtained by this route, it was further investigated.



(I)



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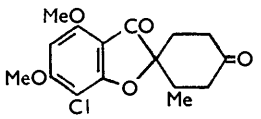

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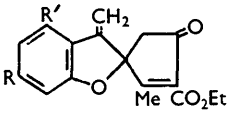

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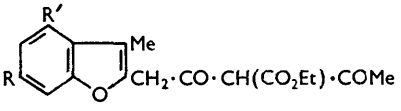
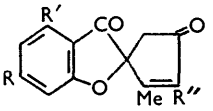


(V)



(VI)

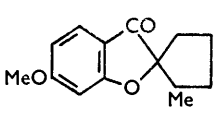
(i) The synthesis[6] of the ester (IV; R = OMe, R′ = H) was extended to give the spiran (VII). The orientation of the formyl group in the intermediate aldehyde (VIII; R = R′ = H, R″ = CHO), previously[6] based on a mixed decomposition point of the corresponding acid (VIII; R = R′ = H, R″ = CO_2H), was confirmed by comparison of its ethyl ester with an authentic specimen of ethyl 6-methoxy-3-methylcoumaranone-2-carboxylate. The keto-ester (V; R = OMe, R′ = H) obtained[6] from the above aldehyde was cyclised with sulphuric acid to the spiran (IV; R = OMe, R′ = H) either directly[6] or through its copper chelate. The spiran showed strong absorption at 328 mμ (log ε 3·98), assumed to be due to the exocyclic methylene group conjugated with the aromatic ring. In this it resembled the analogue (IV; R = R′ = Me). The dihydro-derivative (IX) showed only weak absorption (C=C–C=O, R band) at 321 mμ. Ozonolysis of the ester (IV; R = OMe, R′ = H) gave formaldehyde and the coumaranone ester (VI; R = OMe, R′ = H, R″ = CO_2Et), which no longer showed absorption at 1649 cm.$^{-1}$ (=CH_2) but

* Concerning (*l*,*d*) see footnote, p. 2203, and ref. 2.

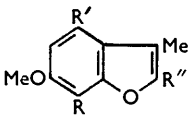
[1] Part XVI, Dawkins and Mulholland, preceding paper.
[2] MacMillan, *J.*, 1959, 1823.
[3] Dawkins and Mulholland, XVIth Internat. Congr. Pure Appl. Chem., Paris, 1957.
[4] Dean, *Sci. Prog.*, 1952, **40**, 653.
[5] Dean, Halewood, Mongkolsuk, Robertson, and Whalley, *J.*, 1953, 1250.
[6] Foster, Robertson, and Healy, *J.*, 1939, 1594.

possessed an additional band at 1715 cm.$^{-1}$ ascribed to the chemically unreactive carbonyl group of a coumaran-3-one. The ultraviolet spectrum was almost identical with that of 6-methoxycoumaran-3-one. Oxidation of this ester (VI; R = OMe, R′ = H, R″ = CO_2Et) gave 2-hydroxy-4-methoxybenzoic acid, and acidic hydrolysis gave the acid (VI; R = OMe, R′ = H, R″ = CO_2H) which was decarboxylated to the unsaturated ketone (VI; R = OMe, R′ = R″ = H). Hydrogenation of the latter with a palladium–carbon catalyst gave a low yield of the *cyclo*pentane (VII). This was identical with the racemate of 6-methoxy-3-oxocoumaran-2-*spiro*-1′-(2′-methyl*cyclo*pentane) obtained previously [1] by condensation of 6-methoxycoumaranone with 1 : 4-dibromopentane.

(ii) *Grisans.* For the synthesis of grisans the required 2-propionic acid (VIII; R = R′ = H, R″ = $[CH_2]_2{\cdot}CO_2H$) was obtained directly from 6-methoxy-3-methylcoumarone [6] with β-propiolactone. The entering group was shown to occupy the 2-position by chain-lengthening of the known 6-methoxy-3-methylcoumarone-2-acetic acid (VIII; R = R′ = H, R″ = $CH_2{\cdot}CO_2H$).



(VII)



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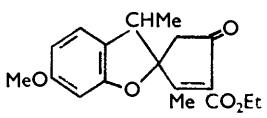
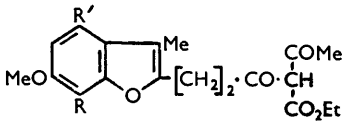
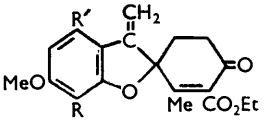


(IX)

Condensation of the acid chloride of the 2-propionic acid with ethyl ethoxymagnesio-acetoacetate (cf. ref. 5) gave a mixture of the ester (VIII; R = R′ = H, R″ = $[CH_2]_2{\cdot}CO_2Et$) and the required keto-ester (X; R = R′ = H). The latter was cyclised by sulphuric acid [6] or, better, polyphosphoric acid to the methylenespiran ester (XI; R = R′ = H) which resembled its analogue (IV; R = OMe, R′ = H) chemically and showed strong absorption at 326 mμ. Ozonolysis of the methylene ester gave the coumaran-one (XII; R = R′ = H, R″ = CO_2Et) which showed ultraviolet absorption very similar to that of 6-methoxycoumaranone. Acidic hydrolysis of the ester with simultaneous decarboxylation gave the non-crystalline unsaturated ketone (XII; R = R′ = R″ = H) characterised as the 2 : 4-dinitrophenylhydrazone. Hydrogenation of this ketone gave an intractable product.



(X)



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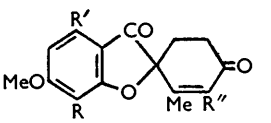

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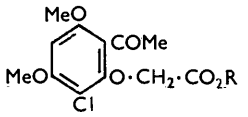

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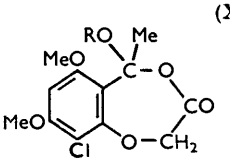

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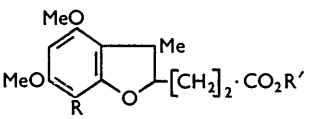
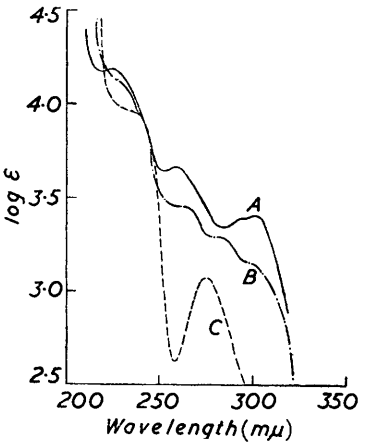


(XV)

For grisans more closely related to griseofulvin, 3-chloro-2-hydroxy-4 : 6-dimethoxy-acetophenone [7] was used as starting material. Condensation with the appropriate chloro- or bromo-ester gave the phenoxyacetates (XIII; R = Et, and R = Me). Acidic hydrolysis of the phenoxyacetates gave one of two isomeric acids $C_{12}H_{13}O_6Cl$ (XIII and XIV; R = H) both with m. p. 144°, or an inseparable mixture of the two (m. p. 119—120°). Ethanolic sulphuric acid gave the open form (XIII; R = H); with 3N-hydrochloric acid the product consisted of the cyclic form (XIV; R = H). Hydrolysis with N-hydrochloric

acid gave a substance shown to be a 1 : 1 mixture of the two acids by analysis and spectroscopy. The ultraviolet spectra of the two forms of the acid were distinct (see Figure), the acetophenone chromophore of diminished intensity shown by acid (XIII; R = H) being absent from the spectrum of the cyclic form. Although the infrared spectra of the cyclic acid and its esters showed only a single C=O band [*e.g.*, (XIV; R = Me), 1742 cm.$^{-1}$], the open form [*e.g.*, (XIII; R = Et)] showed, besides absorption at 1648 cm.$^{-1}$ (acetophenone C=O), a doublet both as a solid (1763, 1753 cm.$^{-1}$) and, at a higher frequency, in solution. Investigation of model compounds [8] showed that the doublet occurred generally in substituted phenoxy- and alkoxy-acids and their esters.

Dehydration of both forms of the acid gave the coumarone (VIII; R = Cl, R′ = OMe, R″ = H) which condensed with β-propiolactone to give the required 2-propionic acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$), but the yield was low and could not be improved. Attempts to orientate the entering group by two Arndt–Eistert syntheses from the carboxylic acid (VIII; R = Cl, R′ = OMe, R″ = CO_2H) failed, but a better synthesis of the 2-propionic acid which served for orientation was as follows. Reaction of the coumarone with hydrogen cyanide gave the 2-formyl derivative (VIII; R = Cl, R′ = OMe, R″ = CHO) whose structure was proved by oxidation and esterification to



Ultraviolet absorption spectra of (*A*) *compound* (XIII; R = H), (*C*) *compound* (XIV; R = H), *and* (*B*) *a* 1 : 1 *mixture thereof.*

ethyl 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-carboxylate (VIII; R = Cl, R′ = OMe, R″ = CO_2Et) identical with authentic material obtained by ring closure of the ester (XIII; R = Et). The aldehyde was converted into the 2-acrylic acid (VIII; R = Cl, R′ = OMe, R″ = $CH{:}CH{\cdot}CO_2H$) which was selectively reduced to the 2-propionic acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$) identical with material prepared by the first method.

Selective hydrogenation of the 2-acrylic acid was first accomplished in the presence of a nickel catalyst,[9] but the insolubility of the acid in organic solvents made this method impracticable on a larger scale. Hydrogenation of the sodium salt of the acid in aqueous solution with a palladium–strontium carbonate catalyst [10] gave satisfactory results in early experiments, but later, from the purified acid, it gave a complex mixture from which, besides the desired product, its dechloro-analogue (VIII; R = H, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$) and the coumarans (XV; R = Cl, R′ = H; and R = R′ = H) were also isolated. Both the coumaran acid (XV; R = R′ = H) and the corresponding ester (XV; R = H, R′ = Me) were dehydrogenated to the corresponding coumarones with sulphur and chloranil respectively. The required selective reduction was shown to occur if a little piperidine was added to the pure acid. Presumably piperidine was present in

[8] Dawkins and Duncanson, unpublished work.
[9] Burdick and Adkins, *J. Amer. Chem. Soc.*, **1934**, **56**, 438.
[10] Martin and Robinson, *J.*, **1943**, 491.

the acid obtained from the Doebner condensation, but the addition of piperidine to the pure acid did not give yields as high as those which had been obtained from the impure acid.

The 2-propionyl chloride (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2$·COCl) condensed with ethyl ethoxymagnesioacetoacetate, giving the keto-ester (X; R = Cl, R′ = OMe). Since direct cyclisation of the keto-ester with sulphuric or polyphosphoric acid failed, it was treated with cupric acetate, giving a mixture of the isomeric α- (80—90%) and β-copper chelates. The β-chelate (m. p. 98—100°) was converted into the α-chelate (m. p. 164°) when heated at 120—130°. The ester carbonyl band (1739 cm.$^{-1}$ in the keto-ester) was absent from the infrared spectra of both chelates, suggesting that this group acted in a donor capacity in both cases together with one of the carbonyl groups. A band at 1623 cm.$^{-1}$, present in both the chelates and the keto-ester, is evidently due to bonded carbonyl as in acetylacetone.[11] Cyclising the β-chelate with polyphosphoric acid at room temperature, or the α-chelate at 70—80°, gave the methylenespiran ester (XI; R = Cl, R′ = OMe) in *ca.* 40% yield. When the α-chelate was treated with polyphosphoric acid at room temperature none of the required ester was obtained, the product containing starting material (30%), (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2$·CO_2H) (30%), the corresponding ethyl ester (10%) and traces of the ketone (VIII; R = Cl, R′ = OMe, R″ = CH_2·COMe).

The properties of the methylenespiran ester were consistent with the structure assigned to it. As with other members of the chlorine-containing series, the ultraviolet spectra showed a bathochromic shift compared with the 6-methoxy-analogues. Ozonolysis and reduction of the ozonide with zinc–acetic acid gave a mixture of starting material (5%), 3-chloro-2-hydroxy-4 : 6-dimethoxyacetophenone (40%), a chlorine-free acidic fraction (30%) and, surprisingly, the crystalline coumaranone (XII; R = Cl, R′ = OMe, R″ = H) (4%). The infrared spectrum [1718 cm.$^{-1}$ (coumaranone CO) and 1684 cm.$^{-1}$ (C=C–CO)] and ultraviolet spectrum were consistent with this structure. Hydrolysis of the ozonide with water gave the coumaranone ester (XII; R = Cl, R′ = OMe, R″ = CO_2Et) which, however, could not be hydrolysed to the free acid. The ready hydrolytic decarboxylation occurring during hydrolysis of the ozonide with zinc–acetic acid is unexplained.

Hydrogenation of the coumaranone (XII; R = Cl, R′ = OMe, R″ = H) with a palladium–carbon catalyst gave an alcohol fraction (which was not investigated owing to the stereochemical complications due to the presence of three asymmetric centres), a monoketone, and a diketone. The monoketone was identical with the synthetic racemate[1] of (*l*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one (II). On the other hand the infrared spectrum of the diketone in solution was distinct from that of (*l*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione[12] (III) but was identical with that of the (*d*,*d*)-diketone[13] (III). The synthetic diketone is therefore the racemate of the latter. It is presumed that the formation of only one racemate of (II) and (III), but of different configuration, must be due to simultaneous competing reduction mechanisms.

Experimental

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney. Absorption spectra (in ethanol) and alumina for chromatography were obtained as described previously.[1] Unless otherwise stated, infrared spectra were determined for Nujol " mulls "; chromatography was carried out in ultraviolet light; light petroleum had b. p. 40—60°.

Ethyl 6-hydroxy-3-methylcoumarone-2-carboxylate, prepared (60% yield) by Hantszch's method,[14] formed prisms, m. p. 179°, from ethanol (lit., m. p. 178°) (Found: C, 65·4; H, 5·6. Calc. for $C_{12}H_{12}O_4$: C, 65·4; H, 5·5%), $\nu_{max.}$ 1700 cm.$^{-1}$, $\lambda_{max.}$ 313, 282, 241, 210 mμ (log ε 4·30, 4·07, 3·90, 4·24).

[11] Gordy, *J. Chem. Phys.*, 1940, **8**, 516.
[12] Dawkins and Mulholland, *J.*, 1959, 1830.
[13] Mulholland, *J.*, 1952, 3994.
[14] Hantszch, *Ber.*, 1886, **19**, 292.

Treatment with dimethyl sulphate gave the methoxy-acid (VIII; R = R′ = H, R″ = CO_2H) (30%) and the corresponding ethyl ester (25%). The latter formed needles, m. p. 74—75°, from ethanol (lit.,[14] m. p. 74°) (Found: C, 66·5; H, 6·1. Calc. for $C_{13}H_{14}O_4$: C, 66·65; H, 6·0%), $\nu_{max.}$ 1700 cm.$^{-1}$, $\lambda_{max.}$ 312, 285, 243 mμ (log ε 4·44, 4·13, 3·97). The methoxy-acid, m. p. 184°, was identical (infrared spectrum) with the oxidation product of 2-formyl-6-methoxy-3-methylcoumarone, and esterification gave the above ethyl ester, m. p. 74°.

Ethyl α-acetyl-β-oxo-6-methoxy-3-methylcoumarone-2-γ-butyrate[6] (V; R = OMe, R′ = H) prepared from 6-methoxy-3-methylcoumarone-2-acetyl chloride and ethyl ethoxymagnesioacetoacetate,[5] was an orange-red oil, $\nu_{max.}$ 1714, 1623, and 1587 cm.$^{-1}$. The *copper derivative*, obtained by shaking an ethereal solution of the keto-ester with aqueous cupric acetate, formed greenish-blue plates, m. p. 175°, from methanol (Found: C, 68·4; H, 5·8. $C_{36}H_{38}O_6Cu$ requires C, 68·6; H, 6·1), $\nu_{max.}$ 1715, 1692, 1671, and 1587 cm.$^{-1}$.

Ethyl 6-Methoxy-3-methylenecoumaran-2-spiro-1′-(2′-*methyl*-4′-*oxo*cyclo*pent*-2′-*en*-3′-*carboxylate*) (IV; R = OMe, R′ = H).—A mixture of the above keto-ester (7 g.) and concentrated sulphuric acid (15 ml.) was kept at −5° for 3 days, then diluted with water (50 ml.) and extracted with ether. Extraction of the ethereal solution with sodium hydrogen carbonate solution and acidification of the alkaline extract gave 6-methoxy-3-methylcoumarone-2-acetic acid (200 mg.), m. p. 139—140°, identified by mixed m. p., analysis, and spectra. Recovery from the ether extract gave a pale yellow oil, which after passage through a charcoal column in ethanol, was obtained crystalline by prolonged trituration under light petroleum (b. p. 80—100°) at −50°. Further recrystallisation at room temperature gave the methylene ester as needles (2·8 g.), m. p. 122° (lit.,[5] m. p. 122°) (Found: C, 68·7; H, 6·0; OMe, 19·1. Calc. for $C_{18}H_{18}O_5$: C, 68·8; H, 5·8; OAlk as OMe, 19·5%), $\nu_{max.}$ 1745, 1707, 1649, 1615, 1595 cm.$^{-1}$, $\lambda_{max.}$ 327, 263, 231, 214 mμ (log ε 3·98, 4·12, 4·35, 4·31). The ester gave an intense positive Ehrlich reaction, and decolorised permanganate. The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 175—176°, from benzene–light petroleum (b. p. 60—80°) (Found: N, 11·1. $C_{24}H_{22}O_8N_4$ requires N, 11·3%). The methylene ester was obtained in slightly higher yield (*ca.* 45%) by cyclisation of the copper derivative with sulphuric acid. Attempts to hydrolyse the ester with alcoholic hydrochloric acid failed.

Hydrogenation of the Ester (IV; R = OMe, R′ = H).—One mol. of hydrogen was absorbed when the ester (150 mg.) was hydrogenated at room temperature and pressure with a catalyst prepared *in situ* from palladium chloride (7 mg.) and charcoal (75 mg.) in acetic acid (10 ml.). The recovered gum was chromatographed in ether on alumina (pH 7; 10 × 0·5 cm.). Elution with ether and repeated trituration of the product under light petroleum at 0° gave plates (105 mg.) of *ethyl 6-methoxy-2-methylcoumaran*-2-spiro-1′-(2′-*methyl*-4′-*oxo*cyclo*pent*-2′-*en*-3′-*carboxylate*) (IX), m. p. 77—78° after recrystallisation from the same solvent (Found: C, 68·6; H, 6·35. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%), $\nu_{max.}$ 1738, 1698, 1610 cm.$^{-1}$, $\lambda_{max.}$ 320, 302, 281, ~263, 228 mμ (log ε 2·78, 3·45, 3·59, 3·72, 4·25). The compound did not give a blue colour with Ehrlich's reagent and was unsaturated to neutral permanganate. The 2 : 4-*dinitrophenylhydrazone* formed orange plates, m. p. 160°, from benzene–light petroleum (Found: N, 11·1. $C_{24}H_{24}O_8N_4$ requires N, 11·3%).

Ethyl 6-Methoxy-3-oxocoumaran-2-spiro-1′-(2′-*methyl*-4′-*oxo*cyclo*pent*-2′-*en*-3′-*carboxylate*) (VI; (R = OMe, R′ = H, R″ = CO_2Et).—A stream of ozone–oxygen was passed into a solution of the preceding ester (500 mg.) in carbon tetrachloride (30 ml.) until the solution became opaque. Evaporation of the filtered solution *in vacuo* gave a gum which was mixed with cold water (25 ml.) and kept for 24 hr. Distillation of the aqueous fraction into a saturated solution of dimedone in 10% aqueous ethanol gave the derivative of formaldehyde as needles, m. p. and mixed m. p. 191—192° : (infrared spectrum). An ethereal solution of the residual gum was chromatographed on alumina (pH 7; 15 × 1 cm.). The lowest bright-blue fluorescent band was eluted with ether and recovered, the product giving rosettes (110 mg.) when boiled with light petroleum. The following band fluorescing greenish-blue gave slightly impure material (100 mg.). Recrystallisation of the combined product from light petroleum (b. p. 60—80°) gave the *ester* (VI; R = OMe, R′ = H, R″ = CO_2Et) (200 mg.), m. p. 115—117° (Found: C, 64·5; H, 5·3. $C_{17}H_{16}O_6$ requires C, 64·55; H, 5·1%), $\nu_{max.}$ 1751, 1715, and 1701 cm.$^{-1}$, $\lambda_{max.}$ 321, 275, 232 mμ (log ε 3·98, 4·21, 4·23). The compound gave an orange-red nitroprusside and a negative Ehrlich reaction: it reduced Fehling's solution and gave no blue colour with concentrated nitric acid. The *mono*-2 : 4-*dinitrophenylhydrazone* formed yellow plates, m. p. 243° (decomp.), from benzene–light petroleum (b. p. 60—80°) (Found: N, 11·1. $C_{23}H_{20}O_9N_4$

requires N, 11·3%). Oxidation of the ester (100 mg.) with Fehling's solution (cf. ref. 5) gave 2-hydroxy-4-methoxybenzoic acid (25 mg.), m. p. 154—155° (lit.,[15] m. p. 152—154°).

6-Methoxy-3-oxocoumaran-2-spiro-1'-(2'-methyl-4'-oxocyclopent-2'-ene-3'-carboxylic Acid) (VI; R = OMe, R' = H, R'' = CO_2H).—The ester (VI; R = OMe, R' = H, R'' = CO_2Et) (70 mg.) was heated under reflux for 6 hr. with 2N-hydrochloric acid (17·5 ml.) and ethanol (14 ml.) under nitrogen. On cooling, the pale yellow product separated (15 mg.). Removal of ethanol *in vacuo* gave more product (15 mg.) together with starting material (30 mg.). Purification of the product by way of the sodium salt and recrystallisation from ethanol gave colourless needles (23 mg.) of the *acid*, m. p. 175—177° (Found: C, 62·5; H, 4·0%; equiv., 284. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2%; *M*, 288), $\nu_{max.}$ 1716, and 1697 cm.$^{-1}$, $\lambda_{max.}$ 318, 273, 232, 210 mμ (log ε; 4·05, 4·25, 4·30, 4·45).

6-Methoxy-3-oxocoumaran-2-spiro-1'-(2'-methylcyclopent-2'-en-4'-one) (VI; R = OMe, R' = R'' = H).—The above acid (70 mg.) was heated in a modified sublimation tube at 190—200° in a stream of nitrogen for 10 min. Sublimation of the residue *in situ* at 190°/10^{-4} mm. gave the cyclo*pentenone* (VI; R = OMe, R' = R'' = H), which formed pale yellow needles (40 mg.), m. p. 193—195° from aqueous acetone (Found: C, 68·9; H, 5·2. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·95%), $\nu_{max.}$ 1713 cm.$^{-1}$, $\lambda_{max.}$ 320, 273, 232, 209 mμ (log ε 3·92, 4·07, 4·16, 4·40). The 2 : 4-*dinitrophenylhydrazone* formed orange-red plates, m. p. 238—240°, from ethyl acetate (Found: N, 13·1. $C_{20}H_{16}O_7N_4$ requires N, 13·2%). Decarboxylation was also carried out in *p*-cymene at the b. p. for 1 hr.

Reduction of the cyclo*Pentenone* (VI; R = OMe, R' = R'' = H).—The ketone (15 mg.) in ethyl acetate (1·5 ml.) was added to a previously reduced catalyst prepared from palladium chloride (10 mg.) and charcoal (40 mg.) in water (1 ml.), and the mixture was shaken at room temperature and pressure in an atmosphere of hydrogen until absorption ceased (2·4 mol. in 5 min.). Recovery gave a pale yellow gum (13 mg.) which was chromatographed in benzene on alumina (pH 4; 4 × 0·5 cm.).

A bright blue-fluorescent band was eluted with benzene and gave a colourless glass (2 mg.) on recovery. Sublimation followed by crystallisation from light petroleum gave prisms (0·8 mg.), m. p. 167—168°, of *6-methoxy-3-oxocoumaran-2-spiro-1'-(2'-methylcyclopentane*) (VII), identical (mixed m. p. and infrared spectrum) with the product from condensation of 6-methoxycoumaran-3-one and 1 : 4-dibromopentane.[1]

6-Methoxy-3-methylcoumarone-2-β-propionic Acid (VIII; R = R' = H, R'' = $[CH_2]_2{\cdot}CO_2H$).—(i) A mixture of β-propiolactone (7·5 ml., 8·64 g.) and 6-methoxy-3-methylcoumarone (19·44 g.) was heated under reflux for 6 hr. at 200°. The cooled residue was ground with sodium carbonate solution. The mixture was filtered, the ether-washed filtrate was acidified, and the precipitated product (5·3 g.) collected. Sublimation at 130°/10^{-4} mm. and crystallisation from dilute ethanol gave the *acid* (4·9 g.) as colourless plates, m. p. 137° (Found: C, 66·5; H, 6·2%; equiv., 231. $C_{13}H_{14}O_4$ requires C, 66·65; H, 6·0%; *M*, 234), $\nu_{max.}$ 1707 cm.$^{-1}$, $\lambda_{max.}$ 292, 253 mμ (log ε 3·80, 4·16). The acid gradually gave a red-violet colour in concentrated sulphuric acid. Starting material (10 g.) was recovered from the carbonate-insoluble fraction.

(ii) 6-Methoxy-3-methylcoumarone-2-acetic acid (440 mg.) and redistilled thionyl chloride (1 ml.) were warmed gently together until a clear solution was obtained. Volatile products were removed *in vacuo* below 30° and the residual red oil in ether (10 ml.) was added at 0° to a 3-fold excess of diazomethane in ether (15 ml.) and kept at 0° for 24 hr. Removal of the ether *in vacuo* gave pale yellow needles of the diazo-ketone, m. p. 118—123°.

The crude product in dioxan (10 ml.) was added dropwise to a mechanically stirred suspension of freshly prepared silver oxide (2 g.) in a solution of sodium thiosulphate (1 g.) and potassium carbonate (1 g.) in water (20 ml.) at 50—60°. Nitrogen was evolved and after 20 min. the temperature was raised to 70° for 10 min., then to 90° for 5 min. After filtration, acidification with dilute nitric acid caused separation of a brown oil, which partly solidified on trituration with water. Sublimation of the semisolid material at 100—130°/10^{-4} mm., followed by crystallisation of the sublimate from dilute ethanol, gave the acid (60 mg.), m. p. 137—138°, identical (mixed m. p. and infrared spectrum) with material obtained by method (i) (Found: C, 66·5; H, 6·3%).

Ethyl 6-Methoxy-2'-methyl-3-methylene-4'-oxogris-2'-en-3'-carboxylate (XI; R = R' = H).—The above acid was converted into the green oily acid chloride with phosphorus pentachloride

[15] Kostanecki and Tambor, *Ber.*, 1895, **28**, 2307.

by the method described above. The *amide* formed plates from benzene–light petroleum (b. p. 60—80°) (Found: N, 6·1. $C_{13}H_{15}O_3N$ requires N, 6·0%).

A solution of the acid chloride in ether (500 ml.) was mixed with a suspension of ethyl ethoxymagnesioacetoacetate [from acetoacetic ester (2·7 g.), ethanol (1·2 ml.), and magnesium (0·48 g.) in ether (50 ml.)] and heated under reflux for 24 hr. Excess of dilute acetic acid was added and the separated ethereal layer was washed with sodium hydrogen carbonate solution, giving 6-methoxy-3-methylcoumarone-2-β-propionic acid (200 mg.) on acidification.

Recovery of the ethereal solution gave an orange oil (4·2 g.) which was chromatographed in benzene on alumina (pH 4; 15 × 1 cm.). Elution with the same solvent removed: (i) a narrow highly fluorescent band giving a colourless oil (90 mg.) on recovery, and (ii) a greenish-red fluorescent band giving a pale orange oil (3·1 g.). Product (i) was crystallised from light petroleum and from methanol giving plates (60 mg.), m. p. 51—52°, of *ethyl 6-methoxy-3-methylcoumarone-2-β-propionate* (VIII; R = R′ = H, R″ = $[CH_2]_2{\cdot}CO_2Et$), identical (mixed m. p. and infrared spectrum) with material obtained by esterification of the free acid (Found: C, 68·3; H, 7·4. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%), $\nu_{max.}$ 1737, 1624, 1594 cm.$^{-1}$. Product (ii) was heated at 100—110°/10^{-4} mm. for 4 hr. to remove acetoacetic ester; the non-volatile oil (2·2 g.) consisted essentially of the required keto-ester; it gave an intense ferric reaction in ethanol and formed a copper chelate.

Cyclisation.—(i) *Sulphuric acid.* The crude keto-ester (X; R = R′ = H) (12 g.) in concentrated sulphuric acid (25 ml.) was kept at 0° for 8 days, then worked up as described for the lower homologue (see above).

Acidification of the alkaline extract gave a flocculent yellow precipitate which decomposed to a tar on filtration. The unfiltered mixture was extracted with benzene, and the extract passed through silica (pH 6·75; 10 × 1 cm.). Elution with benzene gave 6-methoxy-3-methylcoumarone-2-β-propionic acid (600 mg.), m. p. 133—135°, identified by the infrared spectrum. Recovery of the ethereal solution gave an orange oil (4·5 g.) with an intense Ehrlich reaction. Chromatography in ether on alumina (pH 7; 15 × 1·5 cm.) and elution with ether removed, first, a narrow fluorescent band, giving ethyl 6-methoxy-3-methylcoumarone-2-β-propionate (20 mg.) on recovery, and then a pale blue-fluorescent band which, on recovery, gave a pale yellow oil (4·1 g.), with an intense Ehrlich reaction. The oil crystallised with difficulty from ethanol and on recrystallisation from aqueous ethanol gave needles (3·8 g.), m. p. 97—98°, of the *methylene ester* (XI; R = R′ = H) (Found: C, 69·6; H, 6·2. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%), $\nu_{max.}$ 1728, 1668, 1641, 1614 cm.$^{-1}$, $\lambda_{max.}$ 326, 316, 273, 260, 233, 215 mμ (log ε 4·05, 4·09, 4·18, 4·43, 4·37). The 2 : 4-*dinitrophenylhydrazone* formed orange-red plates, m. p. 182° (decomp.), from acetic acid–ethanol (Found: C, 59·3; H, 4·7; N, 10·7. $C_{25}H_{24}O_8N_4$ requires C, 59·05; H, 4·8; N, 11·0%).

(ii) *Polyphosphoric acid.* The keto-ester (1·5 g.) was mixed with polyphosphoric acid (20 g.) and kept at room temperature for 4 days. Recovery gave the methylene ester (700 mg.), the ethyl ester [VIII; R = R′ = H, R″ = $[CH_2]_2{\cdot}CO_2Et$) (30 mg.), and no acidic product. This method gave a cleaner product than (i).

Ethyl 6-Methoxy-2′-methyl-3 : 4′-dioxogris-2′-en-3′-carboxylate (XII; R = R′ = H, R″ = CO_2Et).—The above methylene ester (1 g.) in carbon tetrachloride (30 ml.) was ozonised as for the lower homologue, formaldehyde being isolated as the methone derivative. Chromatography of the product in ether on alumina gave a pale yellow gum (510 mg.) which solidified under ethanol when seeded with material recovered from attempted hydrolysis of the crude ester (see below). Recrystallisation from dilute ethanol gave the *coumaranone ester* (XII; R = R′ = H, R″ = CO_2Et) as needles, m. p. 110—111° (Found: C, 65·4; H, 5·6. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5%), $\nu_{max.}$ 1735 (ester C=O), 1704 (coumaranone C=O), 1686 cm.$^{-1}$ (conjugated 6-ring C=O), $\lambda_{max.}$ 320, 272, 231, 208 mμ (log ε 3·95, 4·12, 4·17, 4·42). It gave an intractable red precipitate with Brady's reagent and no Ehrlich reaction.

6-Methoxy-2′-methylgris-2′-en-3 : 4′-dione (XII; R = R′ = R″ = H).—The coumaranone ester (3 g.) was heated under reflux with ethanol (300 ml.) and 2N-hydrochloric acid (350 ml.) for 4 hr. in nitrogen. Carbon dioxide (0·6 mol.) was evolved. The solution was concentrated *in vacuo*, and the aqueous residue was extracted with ether. Extraction of the ethereal solution with aqueous sodium hydrogen carbonate and recovery gave only a trace of acidic gum. Recovery from the ethereal extract gave a brown oil (1·6 g.) which was chromatographed in ether on alumina (pH 4; 10 × 1 cm.). Elution of the column with ether gave a pale blue fluorescent band, giving a pale yellow gum (1·5 g.) on recovery, and a dark blue fluorescent

band which on recovery gave the crystalline ester (XII; R = R′ = H, R″ = CO_2Et) (20 mg.).

The gum, consisting essentially of (XII; R = R′ = R″ = H), was neutral and unsaturated to permanganate but did not crystalline; it had $\nu_{max.}$ 1713 and 1667 cm.$^{-1}$ and $\lambda_{max.}$ 318, 272, 232, 209 mμ (log ε 3·98, 4·13, 4·22, 4·45). The 2 : 4-*dinitrophenylhydrazone* formed orange-red prisms, m. p. 230°, from ethyl acetate (Found: C, 57·4; H, 4·2; N, 12·6. $C_{21}H_{18}O_7N_4$ requires C, 57·5; H, 4·1; N, 12·8%).

Ethyl 2-*Acetyl*-6-*chloro*-3 : 5-*dimethoxyphenoxyacetate* (XIII; R = Et).—3-Chloro-2-hydroxy-4 : 6-dimethoxyacetophenone (46·0 g.), redistilled ethyl bromoacetate (66·4 g.), and anhydrous potassium carbonate (56·0 g.) were heated together under reflux in acetone (700 ml.) for 72 hr. Filtration and removal of acetone *in vacuo* gave a yellow oil, which was precipitated from ethanol (200 ml.) by ether, giving prisms (58 g.). Recrystallisation from ethanol gave the *ester* as needles (56·6 g.), m. p. 72° (Found: C, 53·3; H, 5·6; Cl, 11·3. $C_{14}H_{17}O_6Cl$ requires C, 53·1; H, 5·4; Cl, 11·2%), $\nu_{max.}$ 1763, 1735 (doublet; oxyacetate C=O), 1684 cm.$^{-1}$ (acetyl C=O), $\lambda_{max.}$ 305, 292, 258, 223 mμ (log ε 3·35, 3·43, 3·70, 4·21). The 2 : 4-*dinitrophenylhydrazone* formed yellow prisms, m. p. 136°, from ethyl acetate (Found: N, 11·3. $C_{20}H_{21}O_9N_4Cl$ requires N, 11·3%).

The *methyl ester* (XIII; R = Me), prepared from methyl bromoacetate as above, formed prisms, m. p. 103—104°, from methanol (Found: C, 51·7; H, 5·1; Cl, 12·0. $C_{13}H_{15}O_6Cl$ requires C, 51·6; H, 5·0; Cl, 11·7%), $\nu_{max.}$ 1760 (broad), 1680 cm.$^{-1}$, $\lambda_{max.}$ ~305, 293, 268, 233 mμ (log ε 3·35, 3·42, 3·66, 4·20).

2-*Acetyl*-6-*chloro*-3 : 5-*dimethoxyphenoxyacetic Acid* (XIII; R = H).—A solution of the above ethyl ester (47·4 g.) in ethanol (200 ml.), water (300 ml.), and sulphuric acid (14 ml.) was heated under reflux for 4 hr., diluted with water until cloudy, and kept overnight at 5°. The precipitate was washed with sodium carbonate solution; starting material (19·7 g.) remained.

Acidification of the alkaline extract gave the *acid* (XIII; R = H) (19·1 g.), needles, m. p. 144° (from benzene or water) (Found: C, 50·0; H, 4·6; OMe, 21·7%; equiv., 290. $C_{12}H_{13}O_6Cl$ requires C, 49·9; H, 4·5; 2OMe, 21·5%; *M*, 287·5), $\nu_{max.}$ 1751 (carboxyl C=O) and 1659 cm.$^{-1}$ (acetyl C=O), $\lambda_{max.}$ 301, 292, 258, 224 mμ (log ε 3·42, 3·39, 3·66, 4·19).

2-*Acetyl*-6-*chloro*-3 : 5-*dimethoxyphenoxyacetic Acid* (*Lactol Form*) (XIV; R= H).—The methyl ester (XIII; R = Me) (500 mg.) was heated under reflux with 3N-hydrochloric acid (20 ml.) for 6·5 hr. The solid product was filtered off, dissolved in warm sodium carbonate solution, treated with charcoal, filtered, and acidified at 0°, giving the *acid* (XIV; R = H) (311 mg.), m. p. 133—137°. It formed needles, m. p. 143—144°, from dilute ethanol (Found: C, 49·8; H, 4·6; Cl, 12·2. $C_{12}H_{13}O_6Cl$ requires C, 49·9; H, 4·5; Cl, 12·3%), $\nu_{max.}$ 1746 cm.$^{-1}$ (lactone C=O), $\lambda_{max.}$ 275, 240 mμ (log ε 3·09, 3·95). Mixtures with the acid (XIII; R = H) of m. p. 144° had m. p.s between 115° and 140°. A 1 : 1 mixture melted sharply at 119—120°, behaved as a pure compound, and was identical with material obtained as described below.

The methyl ester (XIII; R = Me) (1·5 g.) was heated under reflux for 4 hr. with N-hydrochloric acid (75 ml.). Recovery gave an *acid* (1·1 g.), m. p. *ca.* 115°, which formed needles (920 mg.), m. p. 119—120°, from benzene (Found: C, 49·6; H, 4·7; Cl, 13·6; OMe, 22·9%), $\nu_{max.}$ *ca.* 1749 (broad monomeric carboxyl CO and lactol CO), 1659 cm.$^{-1}$ (acetyl C=O). The ultraviolet spectrum was identical with that calculated for and determined with a 1 : 1 mixture of the two acids.

Methylation of the Isomeric Acids (XIII and XIV; R = H).—(i) A suspension of the acid (XIV; R = H) (29 mg., 1 mol.) in ether (5 ml.) was treated overnight with diazomethane (1 mol.) in ether (5 ml.). Recovery gave the *ester* (XIV; R = Me) (29·5 mg.), needles (from methanol) (24 mg.), m. p. 97° (Found: C, 51·6; H, 5·4. $C_{13}H_{15}O_6Cl$ requires C, 51·6; H, 5·0%), $\nu_{max.}$ 1742 cm.$^{-1}$, $\lambda_{max.}$ ~275, 235 mμ (log ε 3·07, 3·98). A mixture with the isomeric methyl ester (XIII; R = Me) had m. p. 78—85°.

(ii) The acid (XIII; R = H) gave the corresponding ester (XIII; R = Me), m. p. 103—104°, identical (mixed m. p., infrared and ultraviolet spectra) with the product from the methyl chloroacetate reaction.

7-*Chloro*-4 : 6-*dimethoxy*-3-*methylcoumarone* (VIII; R = Cl, R′ = OMe, R″ = H).—A mixture of 2-acetyl-6-chloro-3 : 5-dimethoxyphenoxyacetic acid (either form; 17·3 g.), fused sodium acetate (34 g.), and acetic anhydride (100 ml.) was heated under reflux until carbon dioxide evolution ceased (30 min.).

The cooled solution was diluted and made alkaline with sodium carbonate. The product (16 g.), m. p. 143—144°, was filtered off, passed through a column of alumina (pH 4; 50 g.) in benzene (3 l.), recovered, and crystallised from ethanol, giving the *coumarone* (VIII; R = Cl, R′ = OMe, R″ = H) as needles (14 g.), m. p. 148° (Found: C, 58·2; H, 5·0; Cl, 15·5; OMe, 27·6. $C_{11}H_{11}O_3Cl$ requires C, 58·3; H, 4·9; Cl, 15·6; 2OMe, 27·3%), $\nu_{max.}$ 1626, 1611, 1591 cm.$^{-1}$, $\lambda_{max.}$ 320, ~275, 263, 220, 216 mμ (log ε 2·42, 4·00, 4·19, 4·56, 4·56). The coumarone sublimed at 130°/10^{-4} mm., formed an unstable red picrate, gave no colour with alcoholic ferric chloride, formed a cherry-red solution in cold sulphuric acid, and like the 6-methoxy-analogue, did not decolorise permanganate in acetone.

Ethyl 7-Chloro-4 : 6-dimethoxy-3-methylcoumarone-2-carboxylate (VIII; R = Cl, R′ = OMe, R″ = CO_2Et).—Ethyl 2-acetyl-6-chloro-3 : 5-dimethoxyphenoxyacetate (XIII; R = Et) (15·8 g.) was heated under reflux for 1 hr. in a solution of sodium (1 g.) in ethanol (50 ml.). The cooled solution was diluted with water (750 ml.), and the *coumarone-carboxylate* (2·7 g.) was filtered off and crystallised from ethanol in needles, m. p. 172—173° (Found: C, 56·1; H, 5·1; Cl, 11·95. $C_{14}H_{15}O_5Cl$ requires C, 56·3; H, 5·1; Cl, 11·9%), $\nu_{max.}$ 1712 cm.$^{-1}$, $\lambda_{max.}$ 312, 298, 245, 230 mμ (log ε 4·32, 4·37, 4·34, 4·30). Acidification of the filtrate with dilute hydrochloric acid gave 2-acetyl-6-chloro-3 : 5-dimethoxyphenoxyacetic acid (XIII; R = H) (11·2 g.), m. p. 143°. In some experiments the acidic product consisted of the 1 : 1 mixture of (XIII and XIV; R = H).

7-Chloro-4 : 6-dimethoxy-3-methylcoumarone-2-carboxylic Acid (VIII; R = Cl, R′ = OMe, R″ = CO_2H).—The above ester (895 mg.) was warmed at 40° with sodium hydroxide (6 g.) in 50% aqueous ethanol (100 ml.) for 10 min. Dilution with ice and water and acidification afforded the *acid* (790 mg.), m. p. 283—286°. Sublimation at 150°/10^{-5} mm. gave plates, m. p. 310° (decomp.) (Found: C, 53·4; H, 4·3%; equiv., 273. $C_{12}H_{11}O_5Cl$ requires C, 53·3; H, 4·1%; *M*, 271), $\nu_{max.}$ 1671 cm.$^{-1}$, $\lambda_{max.}$ 293, 238 mμ (log ε 4·26, 4·31).

The *methyl ester*, prepared with diazomethane, crystallised from methanol in plates, m. p. 196° (Found: C, 54·4; H, 4·6; OMe, 33·0. $C_{13}H_{13}O_5Cl$ requires C, 54·85; H, 4·6; 3OMe, 32·7%), $\nu_{max.}$ 1713 cm.$^{-1}$. Hydrolysis of the ester (600 mg.) for 30 min. at 60° with sodium hydroxide (3 g.) in 1 : 1 aqueous ethanol (50 ml.) regenerated the free acid (500 mg.). Treatment of the acid chloride, obtained from the carboxylic acid and thionyl chloride in pyridine as an orange gum, with ethereal diazomethane yielded the *diazo-ketone* (VIII; R = Cl, R′ = OMe, R″ = $CO{\cdot}CHN_2$) which formed pale yellow needles, m. p. 118—120°, from ether (Found: C, 52·6; H, 3·6; N, 9·6. $C_{13}H_{11}O_4N_2Cl$ requires C, 53·0; H, 3·8; N, 9·5%).

Attempted Wolff rearrangement of the diazo-ketone (600 mg.) by the method used previously gave only 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-carboxylic acid (VIII; R = Cl, R′ = OMe, R″ = CO_2H) (530 mg.), m. p. 250—260° (decomp.).

Heating the acid (200 mg.) in quinoline (0·5 ml.) with copper bronze (100 mg.) at 190—195° for 5 min., followed by recovery of the product in ether, gave 7-chloro-4 : 6-dimethoxy-3-methylcoumarone (150 mg.), m. p. 143°, identical (mixed m. p. and infrared spectrum) with material prepared above.

7-Chloro-2-formyl-4 : 6-dimethoxy-3-methylcoumarone (VIII; R = Cl, R′ = OMe, R″ = CHO).—Anhydrous hydrogen cyanide (200 ml.) was added to a solution of 7-chloro-4 : 6-dimethoxy-3-methylcoumarone (142 g.) in ether (6 l.) at 0°. A fast stream of dry hydrogen chloride was passed into the mixture at 0—5° until absorption ceased (6 hr.). The solution was kept at 0° overnight; the green aldimine hydrochloride was filtered off, washed with ether, and hydrolysed with water (10 l.) at 100°. Filtration gave the *aldehyde* (110 g.), m. p. *ca.* 140°. After 24 hr. a second crop of the aldimine hydrochloride separated from the ethereal mother-liquors, giving a further 27 g. of aldehyde on hydrolysis. The yellow colour was removed by passing a benzene solution of the aldehyde through alumina (pH 4; 60 × 2 cm.), and the product was crystallised from benzene, ethanol, or acetone. Sublimation at 130°/10^{-4} mm. and recrystallisation from acetone gave prisms, m. p. 183° (Found: C, 56·7; H, 4·45; Cl, 13·7; OMe, 24·15. $C_{12}H_{11}O_4Cl$ requires C, 56·6; H, 4·45; Cl, 14·9; 2OMe, 24·35%), $\nu_{max.}$ 1662 cm.$^{-1}$, $\lambda_{max.}$ 341, 312, 253 mμ (log ε 4·24, 4·16, 4·28). The 2 : 4-*dinitrophenylhydrazone* formed crimson plates, m. p. 312°, from acetone (Found: C, 49·4; H, 3·7; N, 12·8. $C_{18}H_{15}O_7N_4Cl$ requires C, 49·7; H, 3·5; N, 12·9%).

The *azlactone*, prepared by the method of Foster *et al.*,[6] formed crimson needles, m. p. 235°, from ethyl acetate (Found: C, 63·0; H, 4·3; N, 3·5; Cl, 8·7. $C_{21}H_{16}O_5NCl$ requires C, 63·3; H, 4·0; N, 3·5; Cl, 8·9%). Alkaline hydrolysis of the azlactone gave, after clearing with

sulphur dioxide and acidification, not the expected pyruvic acid, but 7-*chloro*-4 : 6-*dimethoxy*-2 : 3-*dimethylcoumarone* (VIII; R = Cl, R′ = OMe, R″ = Me), which formed plates, m. p. 290°, from methanol (Found: C, 59·6; H, 5·2; OMe, 25·3. $C_{12}H_{13}O_3Cl$ requires C, 59·9; H, 5·45; 2OMe, 25·7%), $\nu_{max.}$ 1621 (aromatic) and 1596 cm.$^{-1}$ (C=C). Oxidation of the aldehyde with potassium permanganate in aqueous acetone gave 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-carboxylic acid (VIII; R = Cl, R′ = OMe, R″ = CO_2H), m. p. 310° (decomp.), identical (infrared spectrum) with the acid obtained by hydrolysis of the ethyl ester.

7-*Chloro*-4 : 6-*dimethoxy*-3-*methylcoumarone*-2-β-*propionic Acid* (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$).—(i) The above coumarone (2·26 g., 1 mol.) and β-propiolactone (720 mg., 1 mol.) were heated together under reflux for 4 hr. The cake formed on cooling was dissolved in ether (200 ml.); the solution was filtered and extracted with sodium carbonate solution. Acidification of the extract gave a brown acidic product (720 mg.), m. p. 118—128°, which was chromatographed on silica (10 g.; pH 7) in benzene, giving a cleaner product (630 mg.), m. p. 119—130°, raised to 123—130° by recovery from the silver salt.

An ethereal solution of a sample of the acid with diazomethane gave the *methyl ester* which formed prisms, m. p. 102°, from methanol (Found: C, 57·9; H, 5·6. $C_{15}H_{17}O_5Cl$ requires C, 57·6; H, 5·5%), $\nu_{max.}$ 1739 cm.$^{-1}$ (ester C=O), $\lambda_{max.}$ 320, 294, 278, 265, 226, 223, 219 mμ (log ε 2·61, 3·30, 4·05, 4·27, 4·53, 4·52, 4·52). The remaining acid (500 mg.) was methylated as above and chromatographed in benzene on alumina (pH 4; 10 × 1 cm.). Elution of the pale-blue-fluorescent band with ether gave the pale yellow ester (350 mg.). Hydrolysis with N-ethanolic hydrochloric acid regenerated the acid as pale brown plates. Sublimation at 120—125°/10^{-4} mm. and recrystallisation from aqueous ethanol gave the *acid* as prisms, m. p. 134—135° (Found: C, 56·2; H, 5·1; Cl, 11·9%; equiv., 293. $C_{14}H_{15}O_5Cl$ requires C, 56·3; H, 5·1; Cl, 11·9%; *M*, 299), $\nu_{max.}$ (Nujol " mull ") doublet, 1722, 1706 cm.$^{-1}$; (in $CHCl_3$) 1716 cm.$^{-1}$.

(ii) *Through* 7-*chloro*-4 : 6-*dimethoxy*-3-*methylcoumarone*-2-*acrylic Acid* (VIII; R = Cl, R′ = OMe, R″ = $CH{:}CH{\cdot}CO_2H$).—A mixture of 7-chloro-2-formyl-4 : 6-dimethoxy-3-methylcoumarone (4 g.), malonic acid (6·7 g.), piperidine (330 mg.), and pyridine (17 ml.) was heated at 100° for 1 hr., and at 120° for 10 min. Acidification of the cooled solution gave a precipitate (6·1 g.; m. p. 230—240°), extraction of which with sodium carbonate solution left a residue of 7-chloro-4 : 6-dimethoxy-3-methylcoumarone (1·3 g.). Acidification of the alkaline extract precipitated the *acrylic acid* (4·75 g.), m. p. 243—247°, which formed yellow needles, m. p. 252°, from benzene (Found: C, 56·9; H, 4·6; Cl, 11·9. $C_{14}H_{13}O_5Cl$ requires C, 56·7; H, 4·4; Cl, 11·95%), $\nu_{max.}$ 1692, 1676 cm.$^{-1}$ (doublet) (this acid was insoluble in the solvents used for infrared spectra in this region), $\lambda_{max.}$ 329, 255 mμ (log ε 4·44, 4·04).

The *methyl ester*, prepared with methanolic sulphuric acid or with diazomethane in benzene followed by chromatography, formed prisms, m. p. 179°, from methanol (Found: C, 57·8; H, 5·1; OMe, 29·5. $C_{15}H_{15}O_5Cl$ requires C, 57·95; H, 4·9; 3OMe, 29·9%), $\nu_{max.}$ 1709 cm.$^{-1}$.

Reduction of the Acrylic Acid.—(*a*) The once crystallised acid (102 mg.) in acetic acid (50 ml.) was added to a suspension of Raney nickel (*ca.* 0·2 g.) in ethanol (2 ml.) and hydrogenated at room temperature and pressure until absorption ceased (1 mol. in 8 hr.). Filtration gave a green solution which was concentrated to *ca.* 5 ml. *in vacuo*. Water (100 ml.) was added and, after storage at 5° overnight, the pink solid (60 mg.), m. p. >360°, was collected. It was stirred with cold dilute hydrochloric acid for 1 hr., and the mixture filtered, giving a pale yellow acid (35 mg.), m. p. 90—95°. Purification through the sodium salt and crystallisation from light petroleum (b. p. 60—80°) gave 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-β-propionic acid, identical (mixed m. p. and infrared spectrum) with the product obtained by method (i).

(*b*) A solution of the crude acrylic acid (93 g.) in 0·1N-sodium hydroxide (3·5 l.) was hydrogenated at room temperature and pressure in the presence of 5% palladium–strontium carbonate (50 g.). Absorption ceased after 8 hr. (0·64 mol.). Charcoal (10 g.) was added and the filtered solution was acidified, giving a pale brown solid (38 g.) and sticky material which was reprecipitated from sodium hydroxide solution, giving more product (5 g.). The product was chromatographed in benzene on silica (pH 7; 20 × 1·5 cm.), giving the acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$) (39 g.), m. p. 133—135°, identical (mixed m. p. and infrared spectrum) with material obtained as described above.

(*c*) A solution of the pure acrylic acid (56 g.; m. p. 252°) in 0·1N-sodium hydroxide (2·3 l.) was hydrogenated as in (*b*). Absorption (2 mol.) was complete in 1 hr. Extraction of the acidified solution with ether and with chloroform and recovery from the extracts gave intractable solids, m. p. 88—95° (42 g.) and 82—87° (7·8 g.) severally. Methylation of the combined

products with ethereal diazomethane gave a pale yellow oil (50·7 g.), which was chromatographed in benzene on alumina (30 × 2·5 cm.). The single bright blue band was fractionally eluted with benzene, giving as main fractions colourless needles (6·3 g.), m. p. 104—106°, from benzene–light petroleum (b. p. 60—80°), and colourless prisms (A) (3·6 g.), m. p. 98—100°, from methanol. Further elution gave colourless gums (37 g.) (B).

The needles crystallised from methanol as prisms, m. p. 107—108°, of *methyl 7-chloro-4 : 6-dimethoxy-3-methylcoumaran-2-β-propionate* (XV; R = Cl, R′ = Me) (Found: C, 57·0; H, 6·2; Cl, 11·5. $C_{15}H_{19}O_5Cl$ requires C, 57·2; H, 6·1; Cl, 11·25%), $\nu_{max.}$ 1731 cm.$^{-1}$.

Hydrolysis of the above ester (203 mg.) with boiling N-sodium hydroxide (1·5 hr.) gave laths (190 mg.), m. p. 147—148°, of *7-chloro-4 : 6-dimethoxy-3-methylcoumaran-2-β-propionic acid* (XV; R = Cl, R′ = H) (Found: C, 55·7; H, 5·7; Cl, 11·4; OMe, 20·9. $C_{14}H_{17}O_5Cl$ requires C, 55·9; H, 5·7; Cl, 11·8; 2OMe, 20·6%), $\nu_{max.}$ 1716 cm.$^{-1}$.

The material (A) recrystallised from methanol in prisms (2·7 g.), m. p. 102°, identical (mixed m. p. and infrared spectrum) with methyl 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-β-propionate (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2Me$). Alkaline hydrolysis as above gave the corresponding acid (1·9 g.). Material (B) gave an intense blue colour with nitric acid. It was rechromatographed and the single band was eluted in 10 equal fractions with benzene; fractions 2 and 8 were again chromatographed. Fraction 2 gave an uncrystallisable gum consisting essentially of *methyl 4 : 6-dimethoxy-3-methylcoumaran-2-β-propionate* (XV; R = H, R′ = Me) (Found: C, 64·1; H, 7·0; OMe, 32·8. $C_{15}H_{20}O_5$ requires C, 64·25; H, 7·2; 3OMe, 33·2%), $\nu_{max.}$ 1728 cm.$^{-1}$. Hydrolysis as above yielded *4 : 6-dimethoxy-3-methylcoumaran-2-β-propionic acid* (XV; R = R′ = H) as prisms, m. p. 114°, from ether–light petroleum (1 : 1) (Found: C, 63·2; H, 6·8; OMe, 21·8%; equiv., 265. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8; 2OMe, 23·3%; *M*, 266), $\nu_{max.}$ 1716 cm.$^{-1}$.

Material from fraction 8 was hydrolysed as described above, giving a product which crystallised from 1 : 1 ether–light petroleum. Hand-picking of crystals followed by recrystallisation gave *4 : 6-dimethoxy-3-methylcoumarone-2-β-propionic acid* (VIII; R = H, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$), m. p. 124° (Found: C, 63·5; H, 5·9; OMe, 22·9. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·05; 2OMe, 23·5%).

When pyridine was added in increments of 0·5% to the pure acrylic acid before reduction, the catalyst was poisoned before dechlorination could be eliminated.

When <1% of piperidine was added, dechlorination and reduction to coumarans was inhibited, but reduction was incomplete, giving the acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$) (40%) and some starting material.

Dehydrogenation.—(i) The coumaran acid (XV; R = R′ = H) (2 g.) was heated with sulphur (200 mg.) at 220° for 20 min. and at 280° for 5 min. Continuous extraction of the gummy black acidic fraction with light petroleum followed by hand-picking of the crystallised extract gave starting material (320 mg.), m. p. 110—112°, and the required coumarone-propionic acid (VIII; R = H, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$) (540 mg.), m. p. and mixed m. p. 124°.

(ii) The gummy coumaran ester (XV; R = H, R′ = Me) (157 mg.) and *o*-chloranil (135 mg.) in chloroform (5 ml.) were stored in the dark for 1·5 hr. The recovered product in benzene was passed through a column of alumina (10 × 0·7 cm.), and the pale blue band eluted with benzene, giving a colourless glass (135 mg.) which formed prisms (115 mg.), m. p. 115—117°, from 1 : 1 ether–light petroleum. Further recrystallisation from methanol raised the m. p. of the *coumarone–tetrachlorocatechol complex* to 117° (Found: C, 48·15; H, 3·7; Cl, 26·85; OMe, 18·6. $C_{15}H_{17}O_5Cl,C_6H_2O_2Cl_4$ requires C, 48·0; H, 3·7; Cl, 27·1; 3OMe, 17·7%). Alkaline hydrolysis of the complex gave an acidic gum, which formed plates of the coumarone-propionic acid (VIII; R = H, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$), m. p. 122—124° (from 1 : 1 ether–light petroleum).

Ethyl α-Acetyl-β-oxo-7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-γ-valerate (X; R = Cl, R′ = OMe).—A solution of 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-β-propionic acid (23·5 g.) in dry chloroform (500 ml.) was treated with phosphorus pentachloride (20 g.) and heated under reflux for 0·5 hr. Volatile products were removed at 30° *in vacuo* and the residue kept at 12 mm. for 4 hr. Ethyl ethoxymagnesioacetoacetate (12 g.) was added to a solution of the residue in ether (1·5 l.), and the mixture was boiled for 24 hr. 40% Acetic acid (250 ml.) was added and the ethereal layer was washed with sodium carbonate solution, from which the propionic acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$) (5·9 g.) was obtained.

Recovery of the ethereal solution gave a fluorescent orange oil (25 g.) which was chromatographed in ether on alumina (15 × 1·5 cm.) and gave the following bands on elution, first, a bright blue-fluorescing band giving the ester (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2 \cdot CO_2Et$) (800 mg.) as rosettes, m. p. 74—76°, from ethanol, and then an orange-red band with intense green fluorescence, giving an orange oil (18 g.). Heating at 110°/10^{-4} mm. for 2 hr. removed excess of ethyl acetoacetate, leaving a gum (14 g.), $\nu_{max.}$ 1737, 1718, 1621, 1600 $cm.^{-1}$, which gave a cherry-red colour with ethanolic ferric chloride and formed no stable ketonic derivatives. The gum (12 g.) in ether (100 ml.), when shaken with saturated aqueous copper acetate, deposited blue crystals (2·8 g.), m. p. 159—162°. These, combined with a further 6 g. obtained as below, crystallised from chloroform in pale blue prisms, m. p. 164°, of the *α-copper derivative* of the required keto-ester (X; R = Cl, R′ = OMe) [Found: C, 54·0; H, 5·2; Cl, 8·2. $(C_{20}H_{22}O_7Cl)_2Cu$ requires C, 54·3; H, 5·0; Cl, 8·05%].

Evaporation of the ether layer gave a green gum which was fractionally crystallised from methanol, giving the α-chelate (6 g., see above) and the *β-derivative* (1·8 g.) as green prisms, m. p. 98—100° (from ethanol) (Found: C, 54·1; H, 5·1; Cl, 7·85%). On continued heating at 120—130° it was converted into the α-isomer.

Ethyl 7-Chloro-4 : 6-dimethoxy-2′-methyl-3-methylene-4′-oxogris-2′-en-3′-carboxylate (XI; R = Cl, R′ = OMe).—(*a*) A mixture of the β-copper derivative (1·4 g.) and polyphosphoric acid (20 g.) was kept at room temperature for 10 days, diluted with ice and water (50 ml.), and extracted with ether. The dried ethereal extract was washed with sodium carbonate solution, then evaporated to a brown gum (1·18 g.). The gum was chromatographed in benzene on alumina (16 × 1·5 cm.), and the column was eluted with benzene, giving the following fluorescent bands: (i) A narrow blue band, giving ethyl 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-β-propionate (5 mg.), m. p. 72—73°, on recovery. (ii) A greenish-blue band, giving a yellow gum; when this was kept in ethanol pale yellow rosettes (175 mg.), m. p. 137°, separated. (iii) A blue band; the yellow gum recovered from it partly crystallised when kept with light petroleum, giving rosettes (278 mg.), m. p. 129—131°.

Products (ii) and (iii) were recrystallised from ethanol, giving rosettes (410 mg.). Sublimation (120—130°/10^{-4} mm.) and recrystallisation from methanol gave needles, m. p. 137°, of the *methylene ester* (Found: C, 60·9; H, 5·3; OMe, 21·65; Cl, 8·9. $C_{20}H_{21}O_6Cl$ requires C, 61·1; H, 5·4; OAlk as OMe, 21·05; Cl, 9·0%), $\nu_{max.}$ 1731 (ester C=O), 1680 (conjugated *cyclo*hexenone C=O), 1638 (=CH_2), 1610 $cm.^{-1}$ (aromatic ring), $\lambda_{max.}$ 282, ~275, and 253 mμ (log ε 4·30, 4·28, 4·57). The ester gave a very intense blue Ehrlich reaction and decolorised permanganate.

(*b*) The α-copper derivative (500 mg.) and polyphosphoric acid (20 g.) were heated at 70—80° for 1 hr. Recovery as described above gave the required methylene ester (210 mg.), m. p. 137°.

(*c*) A mixture of the α-derivative (1·8 g.) and polyphosphoric acid (30 g.) was kept at room temperature for 10 days and worked up as above. Acidification of the alkaline extract gave the coumarone-2-β-propionic acid (600 mg.). No methylene ester was formed (negative Ehrlich test), and some copper derivative (600 mg.) was regenerated by shaking the acid with aqueous cupric acetate. Chromatography of the remaining gum (320 mg.) gave the ethyl coumarone-2-β-propionate (120 mg.) and a trace of an unidentified compound (5 mg.), m. p. 181—182° (after 2 recrystallisations from methanol) (Found: C, 61·1; H, 5·7. $C_{15}H_{17}O_4Cl$ requires C, 60·7; H, 5·8%). Infrared maxima at 1713, 1640, and 1614 $cm.^{-1}$ support its assignment as *7-chloro-4 : 6-dimethoxy-3-methyl-2-3′-oxobutylcoumarone* (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2 \cdot COMe$).

Attempted cyclisation of the crude free keto-ester (1·0 g.) with polyphosphoric acid (10 g.) at room temperature for 1 hr. and then at 70—80° for 3 min. gave the acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2 \cdot CO_2H$) (900 mg.) as the only isolable product. Similar results were obtained at room temperature (24 hr.) and at 80° (0·5 hr.).

7-Chloro-4 : 6-dimethoxy-2′-methylgris-2′-en-3 : 4′-dione (XII; R = Cl, R′ = OMe, R″ = H).—(*a*) The above methylene ester (248 mg.) in carbon tetrachloride (15 ml.) was ozonised for 8 min. at room temperature (ozone output *ca.* 4 mg./min.). Solvent was removed *in vacuo*, and the residue in ether (20 ml.) and acetic acid (10 ml.) was cooled in ice during the addition of water (2 ml.) and zinc dust (100 mg.). After 12 hr., water (20 ml.) was added, and the ether layer was separated, combined with ether-washings of the aqueous layer, and extracted with sodium hydrogen carbonate solution.

The gum recovered from the ethereal extract was chromatographed in benzene on alumina (15 × 0·8 cm.). Elution gave the following fluorescent bands: (i) A lower pale blue band

which was eluted with benzene, giving starting material (12 mg.), m. p. 134—136°. (ii) A blue band; elution with benzene–methanol (100 : 1) gave a gum which crystallised from methanol in rosettes (10 mg.), m. p. 164—167°, which, recrystallised from ethanol, gave the *coumaranone* (XII; R = Cl, R′ = OMe, R″ = H) as rosettes (8 mg.), m. p. 167—168° (Found: C, 59·4; H, 4·5; Cl, 11·1. $C_{16}H_{15}O_5Cl$ requires C, 59·5; H, 4·7; Cl, 11·0%), $\nu_{max.}$ 1718 and 1683 cm.$^{-1}$, $\lambda_{max.}$ 323, 291, 235, 213 mμ (log ε 3·70, 4·30, 4·19, 4·42). (iii) A blue band, eluted with benzene–methanol (20 : 1), gave a gum which when sublimed then crystallised from methanol afforded 3-chloro-2-hydroxy-4 : 6-dimethoxyacetophenone (100 mg.). Recovery from the sodium hydrogen carbonate extract of the reaction product gave chlorine-free acidic gums (2 mg.).

(*b*) A solution of the methylene ester (137 mg.) in carbon tetrachloride was ozonised for 0·5 hr. (ozone output 0·6 mg./min.). Removal of solvent *in vacuo* gave a gum which was kept under water (25 ml.) overnight. The product was extracted with ether, and the extract was shaken with sodium hydrogen carbonate and with sodium hydroxide solution. Acidification of the alkaline extracts, and recovery, gave a chlorine-free solid (10 mg.) and 3-chloro-2-hydroxy-4 : 6-dimethoxyacetophenone (30 mg.) respectively. The gum obtained from the ethereal solution was chromatographed in benzene on alumina (20 × 0·5 cm.). Fractional elution of the broad band gave: (i) starting material (6 mg.), m. p. 134—136° (eluted by benzene). (ii) a colourless gum (27 mg.) (eluted by benzene–methanol 200 : 1), and (iii) a pale yellow gum (21 mg.) (eluted by benzene–methanol 40 : 1). Crystallisation of product (iii) gave needles (1·2 mg.), m. p. 143—149°, which were not further investigated. Product (ii) crystallised from methanol, giving rosettes (13 mg.) of *ethyl 7-chloro-4 : 6-dimethoxy-3 : 4′-dioxogris-2′-en-3′-carboxylate* (XII; R = Cl, R′ = OMe, R″ = CO_2Et), m. p. 168—171°, raised to 174° by crystallisation from ethanol (Found: C, 57·5; H, 4·9; OMe, 21·3. $C_{19}H_{19}O_7Cl$ requires C, 57·8; H, 4·85; OAlk as OMe, 20·9%), $\nu_{max.}$ 1739, 1705, 1684, 1623, 1593 cm.$^{-1}$. The ester was not hydrolysed with boiling 1—10N-hydrochloric acid, and alkaline hydrolysis caused degradation.

Reduction of 7-Chloro-4 : 6-dimethoxy-2′-methylgris-2′-en-3 : 4′-dione (XII; R = Cl, R′ = OMe, R″ = H).—The dione (10 mg.) in ethyl acetate (1 ml.) was added to a previously reduced catalyst prepared from palladium chloride (5 mg.) and charcoal (20 mg.) in water (1 ml.). The mixture was shaken in hydrogen at room temperature and pressure for 6 hr. (absorption complete in 3 hr.). The recovered gum (9 mg.) in benzene (0·5 ml.) was chromatographed on alumina (20 × 0·2 cm.). Elution of the column removed the following fluorescent bands (eluant in parentheses): (i) a bright blue forerun (benzene); (ii) a darker blue band (ether); (iii) a top bright blue band (benzene–methanol, 50 : 1). The gums recovered from each fraction were chromatographed on circular papers (Whatman No. 1). The spot containing fraction (i) was developed with ether–methanol (1 : 1), giving an inner stationary ring and a mobile outer ring. The latter was cut from the paper in ultraviolet light and eluted with ether–methanol, giving a gum, which was crystallised twice from methanol, giving prisms (0·6 mg.), m. p. 150—154°, identical (mixed m. p. and infrared spectrum) with the racemate of (*l,d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one (II). The central spot on the paper yielded a trace of gummy alcohol (infrared spectrum).

Product (ii) was chromatographed as above. A narrow mobile outer ring was identified as the racemate of (*l,d*)-ketone (II) (0·5 mg.). The central spot was cut out and eluted with methanol, giving a cluster of prisms (0·9 mg.), m. p. 170—175°, of the racemate of (*d,d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (III). The infrared spectrum in chloroform was identical with that of the (*d,d*)(*i.e.*, 2*R* : 2′*R*)-diketone (III) [13] and distinct from that of the (*l,d*)(*i.e.*, 2*S* : 2′*R*)-form.[12]

The authors are indebted to Imperial Chemical Industries Limited, General Chemicals Division, Widnes, for chlorinating the phloroglucinol dimethyl ether, Dr. L. A. Duncanson for the infrared spectra, Mr. J. F. Grove for initiating this work and for his continued interest in it, and to several colleagues for valuable discussion.

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