439. *Griseofulvin. Part XVI.* Synthesis of Compounds related to Griseofulvin.*

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Racemic spirans related to griseofulvin have been prepared by condensation between coumaranones and dibromoalkanes. The presence of the grisan ring system in griseofulvin has been confirmed by synthesis of 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one, which is shown to be the racemate of the (*l*,*d*)-stereoisomer,† obtained by degrading the (*l*,*d*)-diastereoisomer of griseofulvin.

The synthesis of racemates of some non-spiran oxidation products, and improved preparations of certain dibromoalkanes, are also described.

The structures (I; R = Cl and H) proposed for griseofulvin [1] and dechlorogriseofulvin [2] respectively were supported by syntheses [3] of several non-spiran degradation products.

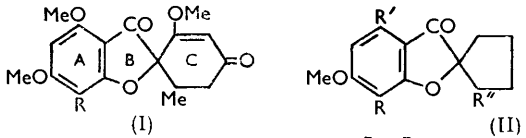
The preparation of further non-spiran degradation products is described in this paper

* Part XV, *J.*, 1959, 1830.

† The prefixes denote the configuration of the two asymmetric centres, the spiran centre preceding. Griseofulvin is defined (Part XIV) as the (*d*,*d*)-stereoisomer; inversion of the spiran centre yields the (*l*,*d*)-diastereoisomer.

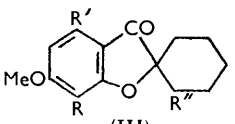
[1] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977.
[2] MacMillan, *J.*, 1953, 1697.
[3] MacMillan, Mulholland, Dawkins, and Ward, *J.*, 1954, 429.

together with the synthesis of a racemate of a spiran degradation product, thus confirming the presence of the grisan ring system in griseofulvin.



(I)

(II)



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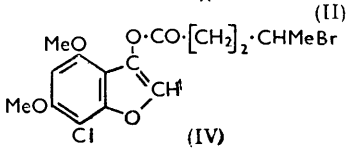


(IV)

Three routes to spirocyclic derivatives of griseofulvin were investigated: (*a*) Condensation of appropriate coumaranones and dibromoalkanes, (*b*) ester syntheses from 2 : 2-disubstituted coumaranones, and (*c*) a modification of the Dean and Robertson synthesis of usnolic acid analogues.[4] The last route is described in the following paper.

(a) *Dibromoalkane Syntheses.*—In this method, briefly reported elsewhere,[5] condensation of suitable dibromoalkanes with coumaran-3-ones in the presence of potassium *tert.*-butoxide (but not ethoxide or methoxide) gave spirans (see Table 1). The yields were low but the method was simple and the starting materials were readily prepared.

TABLE 1.

Coumaranone	Halide	Product
6-Methoxy-	1 : 4-Dibromopentane	II; R = R′ = H, R″ = Me
7-Chloro-4 : 6-dimethoxy-	1 : 4-Dibromobutane	II; R = Cl, R′ = OMe, R″ = H
,, ,,	1 : 5-Dibromopentane	III; R = Cl, R′ = OMe, R″ = H
,, ,,	1 : 5-Dibromohexane	III; R = Cl, R′ = OMe, R″ = Me

The condensation failed with a bromoacyl bromide; γ-bromovaleroyl bromide and 7-chloro-4 : 6-dimethoxycoumaranone gave the coumaronyl ester (IV).

The synthetic racemates (II; R = R′ = H, R″ = Me) and (III; R = Cl, R′ = OMe, R″ = Me) behaved as single racemates. The m. p. of the latter was depressed by mixture with (*d*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan (Product C, m. p. 147—148°) obtained [6] from griseofulvin and the infrared spectra in solution differed; but the m. p. was not depressed on admixture with the (*l*,*d*)-stereoisomer [7] and the infrared spectra were identical. The synthetic product was therefore the racemate of the latter and the presence of the grisan ring system in griseofulvin was confirmed.

It was necessary to develop improved syntheses of 1 : 4-dibromopentane and 1 : 5-dibromohexane since published methods gave low yields, *e.g.*, for the latter [8] only 1%. Fission of heterocyclic compounds gave good results. 1 : 4-Dibromopentane was prepared in 90% yield by treating tetrahydro-2-methylfuran with sodium bromide and concentrated sulphuric acid. 1 : 5-Dibromohexane was prepared in 61% yield by treating 1-benzoyl-2-methylpiperidine with phosphorus tribromide and bromine.[9]

Contrary to Slater and Stephen's findings,[10] methylation of 6-hydroxycoumaranone gave the 6-methoxy-compound.

(b) *Ester Syntheses.*—Although this route did not yield spirocyclic compounds, it led to racemates of several oxidation products of griseofulvin and dechlorogriseofulvin.

Methyl crotonate and 7-chloro-4 : 6-dimethoxycoumaran-3-one gave the ester (V; R = Cl, R′ = H, R″ = Me) which was separated into two racemates, α and β, by

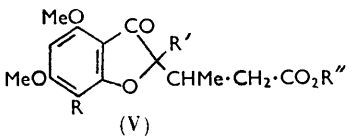
[4] Dean, *Sci. Progr.*, 1952, **40**, 653.
[5] Dawkins and Mulholland, XVIth Internat. Congr. Pure Appl. Chem., Paris, 1957.
[6] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.
[7] Dawkins and Mulholland, *J.*, 1959, 1830.
[8] Perkin, *J.*, 1887, **51**, 702.
[9] von Braun, *Ber.*, 1904, **37**, 2915.
[10] Slater and Stephen, *J.*, 1920, **117**, 309.

crystallisation. The m. p. (83—86°) of the latter was not depressed on admixture with material of $[\alpha]_D$ −19°, m. p. 96—98°, obtained by degradation of griseofulvin *via* the trione (VI; R = Cl, R′ = R″ = OMe),[11] and the infrared spectra in chloroform solution were identical.

Acidic hydrolysis of either ester gave the same acid (V; R = Cl, R′ = R″ = H) which regenerated a mixture of the esters on methylation. A mixture of the esters was obtained by heating either of the pure esters with potassium carbonate in acetone.

Alkaline hydrolysis of the synthetic acid (V; R = Cl, R′ = R″ = H), like that of the optically active material,[11] gave the phenolic acid (VII), which was shown to be the 6-hydroxy-compound by the infrared spectrum in dilute chloroform solution (C=O, 1701 cm.$^{-1}$).[12]

The acid (V; R = Cl, R′ = R″ = H) with alkaline permanganate gave the hydroxy-acid (V; R = Cl, R′ = OH, R″ = H) whose infrared spectrum in Nujol "mull" was identical with that of material of $[\alpha]_D$ −17° (in acetone) from griseofulvin.[11,13] Dehydration gave the lactone (VIII; R = Cl) which could not be separated into two racemates. Its infrared spectrum in Nujol mull, m. p., and mixed m. p. were identical with those of lactone A.[11]



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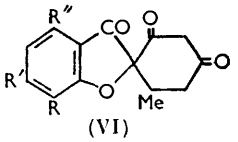

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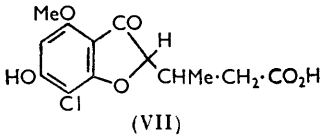

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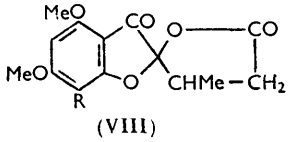

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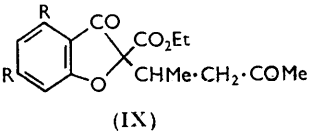

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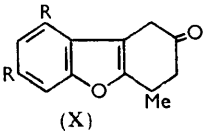

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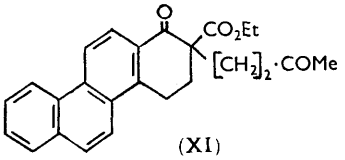

(XI)

In the dechlorogriseofulvin series the synthetic ester (V; R = R′ = H, R″ = Me) was obtained as a mixture of two isomeric forms, probably corresponding to the two racemates (cf. above). Only one form crystallised. Acidic hydrolysis of the mixture of non-crystalline ethyl esters (V; R = R′ = H, R″ = Et) gave a gum consisting essentially of the acid (V; R = R′ = R″ = H) but containing varying amounts of a phenolic impurity which was eliminated during oxidation to the crystalline hydroxy-acid (V; R = R″ = H, R′ = OH). This was less stable than the chlorine-containing analogue and it was not obtained in pure form from dechlorogriseofulvin.[2] The synthetic acid often contained the lactone (VIII; R = H) into which it was converted easily. The lactone was also obtained directly, but in low yield, by oxidation of ethyl 4 : 6-dimethoxy-3-oxocoumaran-2-β-butyric acid (V; R = R′ = H, R″ = Et). The m. p. of the lactone was not depressed on admixture with the lactone prepared from dechlorogriseofulvin, and the infrared spectra were identical.

Attempts to prepare the triones (VI; R = H, R′ = R″ = OMe; and R = R′ = R″ = H) from the available 3-oxocoumaran-2-carboxylates[3] failed. In particular the esters (IX; R = H, and R = OMe) could not be cyclised to spirans although they gave the corresponding dibenzofurans (X; R = H and R = OMe) when heated with aqueous

[11] Grove, Ismay, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3958.
[12] Duncanson, Grove, MacMillan, and Mulholland, *J.*, 1957, 3555.
[13] MacMillan, *J.*, 1959, 1823.

alkali.[3] Under basic conditions a reverse Michael reaction often occurred, giving the oxocoumaran-2-carboxylates, and in acidic media starting material or intractable products resulted. The ester (XI) similarly fails to cyclise to a spiran.[14]

Experimental

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney. Alumina (B.D.H. or Peter Spence Type H) was (*a*) used without further treatment (pH 10), (*b*) rendered alkali-free [15] and activated at 250°/17 mm. for 3 hr. (pH 4; Grade II), or (*c*) washed with water after treatment with nitric acid and then treated with methanol and activated (pH 7; Grade II). Silica was material of large pore-size (<100 B.S.S.; pH 6·75). Chromatography was carried out in ultraviolet light. Ultraviolet spectra (ethanol solutions) and infrared spectra (Nujol mulls unless stated otherwise) were obtained as described previously.[16] Light petroleum had b. p. 40—60°.

1 : 4-*Dibromopentane*.—A solution of sodium bromide (109 g.) and concentrated sulphuric acid (137 ml.) in water (125 ml.) was kept at 30° during the gradual addition of tetrahydro-2-methylfuran (43 g.). The mixture was boiled for 2 hr. and steam-distilled. The product recovered from the distillate by ether-extraction was fractionally distilled, giving the dibromo-compound (103 g.), b. p. 98—99°/25 mm., n_D^{15} 1·516 (lit., b. p. 104—106°/30 mm.,[17] n_D^{15} 1·515 [18]).

1 : 5-*Dibromohexane*.—(i) Perkin's method,[8] starting from ethyl acetoacetate and 1 : 3-dibromopropane, gave the following yields: ethyl 5 : 6-dihydro-2-methylpyran-3-carboxylate (62%); the corresponding acid (34%); 6-hydroxyhexan-2-one (69%); hexane-1 : 5-diol (50%); and 1 : 5-dibromohexane (b. p. 153—155°/100 mm.) (17%, overall 1·2%). The physical constants agreed with those reported.

(ii) Phosphorus tribromide (182 g.) and then bromine (120 g.) were added in portions to 1-benzoyl-2-methylpiperidine (140 g.; m. p. 46°; lit., m. p. 44—45° [19]) at 0° with shaking. The product was distilled at *ca.* 20 mm. until the distillate became yellow. Phosphoryl bromide was removed by shaking the distillate with ice (500 g.), and the mixture was extracted with light petroleum. The petroleum extract was washed with sodium carbonate, water, and concentrated sulphuric acid until the washings were colourless. Recovery from the petroleum extract and distillation of the residue gave 1 : 5-dibromohexane (103 g.), b. p. 121—124°/23 mm., which darkened in light. The recorded b. p.[20] was 120—122°/20—25 mm. Use of phosphorus pentabromide gave lower yields.

ω-*Chlororesacetophenone*.—Dry hydrogen chloride was passed into a solution of resorcinol (72·0 g.), chloroacetonitrile (48 g.),[21] and zinc chloride (48 g.) in dry ether for 2 hr. at room temperature. After 1 hr., the ketimine hydrochloride was filtered off, washed with ether, and hydrolysed at 70° with water (5 l.) for 1 hr. The product, which separated on cooling, crystallised from toluene, giving the phenol as nearly colourless needles (85 g.), m. p. 132—133 [lit.,[22] m. p. 131° (uncorr.)].

2-*Chloroacetyl*-5-*methoxyphenol*.—(*a*) The above phenol (30 g.) in ether (300 ml.) with ethereal diazomethane gave a precipitate of the monomethyl ether which crystallised from ethanol in needles (31 g.), m. p. 116—117° (lit.,[23] 116°) (Found: C, 53·6; H, 4·6; Cl, 17·8. Calc. for $C_9H_9O_3Cl$: C, 53·9; H, 4·5; Cl, 17·7%).

(*b*) Powdered aluminium chloride (9 g.) was added to 1 : 3-dimethoxybenzene (8·0 g.) and chloroacetyl chloride (6·5 g.) in carbon disulphide (30 ml.). After 1 hr. the solvent was decanted from the red oil, and the latter was treated with ice-cold water (30 ml.) and concentrated hydrochloric acid (20 ml.). The steam-volatile part of the product was recovered in ether, giving the phenol (3·9 g.), m. p. 111—114°, raised to 116—117° by recrystallisation.

[14] Nasipuri, *Chem. and Ind.*, 1956, 795.
[15] Prins and Shoppee, *J.*, 1946, 494.
[16] Mulholland and Ward, *J.*, 1954, 4676.
[17] Grishkewitsch-Trochimowski, *J. Russ. Phys. Chem. Ges.*, 1916, **40**, 916.
[18] Paul, *Ann. Chim.* (*France*), 1932, **18**, 303.
[19] Bunzel, *Ber.*, 1889, **22**, 1053.
[20] Solonina, *Chem. Zentr.*, 1899, I, 25.
[21] Scholl, *Ber.*, 1896, **29**, 2415; Steinkopf, *Ber.*, 1908, **41**, 2541.
[22] Sonn, *Ber.*, 1917, **50**, 1262.
[23] von Auwers and Pohl, *Annalen*, 1914, **405**, 264.

6-*Methoxycoumaran*-3-*one*.—(*a*) A mixture of 6-hydroxycoumaran-3-one (5·0 g.) in benzene (2 l.) and excess of ethereal diazomethane was kept for 18 hr. Recovery of the neutral product gave the coumaranone (4·2 g.), m. p. 123—125°, which crystallised from ethanol in prisms, m. p. 124—125° (lit.,[24] 125°) (Found: C, 65·7; H, 5·0. Calc. for $C_9H_8O_3$: C, 65·85; H, 4·9%), $\nu_{max.}$ 1710 cm.$^{-1}$, $\lambda_{max.}$ 318, 268, 233, 208 mμ (log ε 4·00, 4·12, 4·05, 4·29).

(*b*) 2-Chloroacetyl-5-methoxyphenol (3·0 g.) was heated with sodium acetate (3·0 g.) in ethanol (150 ml.) for 2 hr. Crystallisation of the recovered product gave the coumaranone (2·2 g.), m. p. 124—125°.

6-*Methoxy*-3-*oxocoumaran*-2-spiro-1′-(2′-*methyl*cyclo*pentane*) (II; R = R′ = H, R″ = Me).—A slurry of 6-methoxycoumaran-3-one (0·82 g.) in benzene (50 ml.) was added simultaneously with 1 : 4-dibromopentane (1·15 g.) in benzene (50 ml.) to a stirred suspension of potassium *tert.*-butoxide (1·4 g.) in benzene (50 ml.) boiling under reflux. When addition was complete (30 min.) the mixture was heated under reflux for 3 hr. The cooled, filtered solution was washed with sodium hydroxide solution and water and evaporated and the residue was chromatographed in benzene on alumina (pH 4; 20 × 1 cm.). Elution of the blue fluorescent band with benzene and recovery gave an oil (300 mg.) containing unchanged dibromide. Rechromatography in light petroleum and elution with ether–light petroleum (20 : 1) gave a gum (42 mg.) which crystallised from light petroleum in prisms (36 mg.) of the *spiran*, m. p. 164—167°, raised to 167—168° by sublimation *in vacuo* and recrystallisation from ethanol (Found: C, 72·1; H, 6·9. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%), $\nu_{max.}$ 1712 cm.$^{-1}$; $\lambda_{max.}$ 318, 267, 233, 208 mμ (log ε 4·01, 4·12, 4·05, 4·29).

7-*Chloro*-4 : 6-*dimethoxy*-3-*oxocoumaran*-2-spirocyclo*pentane* (II; R = Cl, R′ = OMe, R″ = H).—The procedure described above was applied to a slurry of 7-chloro-4 : 6-dimethoxycoumaran-3-one [3] (2·29 g.) in benzene (50 ml.), a solution of 1 : 4-dibromobutane (2·16 g.) in benzene (50 ml.) and potassium *tert.*-butoxide (2·8 g.) in benzene (50 ml.). Heating under reflux for 5 hr. and filtration of the cooled suspension gave a yellow filtrate which was extracted with sodium hydroxide solution. Acidification of the alkaline extract gave 3-chloro-2-hydroxy-4 : 6-dimethoxyacetophenone (60 mg.), m. p. 189—191° after crystallisation, identical with authentic material.[13]

The semi-solid product recovered from the neutral fraction was repeatedly extracted with light petroleum. Recovery from the extract gave a solid (400 mg.), m. p. 182—186°. Sublimation at 110°/10^{-4} mm. followed by crystallisation from ethanol gave prisms, m. p. 192—193°, of the *spiran* (Found: C, 59·1; H, 5·4; Cl, 12·2; OMe, 21·4. $C_{14}H_{15}O_4Cl$ requires C, 59·4; H, 5·35; Cl, 12·55; 2OMe, 21·9%), $\nu_{max.}$ 1717 cm.$^{-1}$; $\lambda_{max.}$ 331, 322, 289, 238, 213 mμ (log ε 3·68, 3·69, 4·30, 4·20, 4·37).

Purification of the petroleum-insoluble neutral fraction by chromatography and sublimation gave starting material (1·08 g.), m. p. 212—214°.

7-*Chloro*-4 : 6-*dimethoxygrisan*-3-*one* (III; R = Cl, R′ = OMe, R″ = H).—7-Chloro-4 : 6-dimethoxycoumaran-3-one (2·29 g.) in benzene (50 ml.) was condensed with 1 : 5-dibromopentane (2·31 g.) in benzene (50 ml.) in the presence of potassium *tert.*-butoxide (2·8 g.) in benzene (50 ml.) as described above. Treatment of the residual orange gum with benzene–light petroleum precipitated a solid (120 mg.). Sublimation of this at 130°/10^{-4} mm. and recrystallisation from ethanol gave prisms (70 mg.) of the *grisan*, m. p. 176—177° (Found: C, 60·5; H, 5·9. $C_{15}H_{17}O_4Cl$ requires C, 60·7; H, 5·8%), $\nu_{max.}$ 1715 cm.$^{-1}$.

Unchanged coumaranone (1·20 g.) was recovered from the benzene–petroleum mother-liquor.

7-*Chloro*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3-*one* (III; R = Cl, R′ = OMe, R″ = Me).—7-Chloro-4 : 6-dimethoxycoumaran-3-one (2·90 g.) was condensed with 1 : 5-dibromohexane (2·44 g.) in the presence of potassium *tert.*-butoxide (2·80 g.) as described in the preceding experiments, identical quantities of benzene being used, but when addition was complete the mixture was heated under reflux for 1·5 hr. The cooled, filtered, sodium hydroxide-washed solution was concentrated to *ca.* 5 ml., diluted with light petroleum (5 ml.), and kept at 0°. Prisms (112 mg.) (A), m. p. 142—146°, separated. The gum recovered from the mother-liquor was chromatographed in benzene on alumina (pH 4; 20 × 0·5 cm.).

Elution with benzene removed a yellow non-fluorescent band (i) followed by a blue band (ii). Further elution with benzene–methanol (50 : 1) removed a second blue band (iii). Recovery and purification of fraction (iii) gave starting material (850 mg.), m. p. 200—203°.

[24] Blom and Tambor, *Ber.*, 1905, **38**, 3589.

Fraction (i) gave a gum (40 mg.) which was sublimed (120—130°/10^{-4} mm.) and crystallised from ethanol in prisms, m. p. 146—150° (25 mg.) (B). The gum (340 mg.) recovered from fraction (ii) crystallised from benzene–light petroleum (b. p. 60—80°) in prisms, m. p. 140—147° (295 mg.) (C). Sublimation of the combined products, A, B, and C at 110—120°/10^{-4} mm. followed by crystallisation from ethanol gave the *grisan* as stout needles (405 mg.), m. p. 157—158° (Found: C, 61·8; H, 6·3; Cl, 11·1; OMe, 20·0. $C_{16}H_{19}O_4Cl$ requires C, 61·8; H, 6·1; Cl, 11·5; 2OMe, 20·0%), $\lambda_{max.}$ 331, 322, 289, 238, 212 mμ (log ε 3·67, 3·70, 4·33, 4·20, 4·41). In an attempt to separate an analytically pure specimen into two racemates recrystallisation was repeated 36 times but no change in m. p. or infrared spectrum occurred.

The m. p. of the racemate was not depressed on admixture with the (*l*,*d*)-stereoisomer (*i.e.*, 2*S* : 2′*R*; m. p. 152—153°) obtained by degradation [7] of the (*l*,*d*)-diastereoisomer of griseofulvin, and the infrared spectra in chloroform were identical. The (*d*,*d*)-stereoisomer [6] (*i.e.*, 2*R* : 2′*R*; m. p. 147—148°, " Product C ") obtained from griseofulvin was distinct. The infrared spectrum in chloroform was different and the m. p. was depressed on admixture with the (*l*,*d*)-stereoisomer or the synthetic racemate.

Attempts to obtain the 2′-hydroxy-derivative of the racemate by oxidation with potassium permanganate in acetone–sodium carbonate solution failed.

Attempted Synthesis of 7-Chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′-dione.—A slurry of 7-chloro-4 : 6-dimethoxycoumaran-3-one (11·45 g.) in benzene (200 ml.) was condensed with 1 : 4-dibromopentan-1-one (12·25 g.) in benzene (100 ml.) in the presence of potassium *tert.*-butoxide (14 g.) in benzene (100 ml.) as described above. Working up gave a red filtrate from which an intractable brown tar (6 g.) was removed by extraction with sodium hydroxide solution. Evaporation of the benzene solution gave a gum which was chromatographed on alumina (25 × 1·5 cm.) giving the following bands: (i) eluted by benzene–methanol (100 : 1), a bright blue fluorescent band; and (ii) eluted by benzene–methanol (25 : 1), a broad pale blue band.

Recovery of material from band (i) gave a gum (1·8 g.) which crystallised from ethanol in prisms (1·3 g.), m. p. 124°, of *7-chloro-4 : 6-dimethoxycoumaron-3-yl γ-bromovalerate* (IV) (Found: C, 46·05; H, 4·4; Cl, 8·9; Br, 20·0; OMe, 15·6. $C_{15}H_{16}O_5ClBr$ requires C, 46·05; H, 4·1; Cl, 9·1; Br, 20·4; OMe, 15·85%), $\nu_{max.}$ 1760, 1623, 1609 cm.$^{-1}$; $\lambda_{max.}$ 265, 219 mμ (log ε 4·18, 4·62), unsaturated to permanganate in acetone and darkening in sunlight. Band (ii) gave starting material (8 g.).

Methyl 7-Chloro-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyrate (V; R = Cl, R′ = H, R″ = Me).—7-Chloro-4 : 6-dimethoxycoumaran-3-one (4·2 g.) in dioxan (200 ml.) at 46° was treated with methyl crotonate (2·1 g.) and N-methanolic sodium methoxide (8·0 ml.). After storage at 55—60° for 6 hr. and at room temperature for 2 days, the filtered mixture was treated with acetic acid (5 ml.) and charcoal, filtered, and evaporated *in vacuo*. A solution of the residue in benzene (150 ml.) was washed with water, dried, and chromatographed on alumina (25 × 2·5 cm.). Elution with benzene–methanol (100 : 1) removed a blue fluorescent band. The recovered product was distilled at 170—200°/10^{-4} mm. on to a cold finger and then crystallised from benzene, giving material (A), m. p. 143—150° (1·0 g.). Extraction of material recovered from the mother-liquor with acetone gave a residue (B), m. p. 138—150° (0·5 g.). Materials (A) and (B) were washed with acetone, giving the *α-ester* (1·00 g.), m. p. 152—154°, which crystallised from benzene–light petroleum (b. p. 60—80°) in needles (Found: C, 54·85; H, 5·2; Cl, 10·9; *C*-Me, 5·35. $C_{15}H_{17}O_6Cl$ requires C, 54·8; H, 5·2; Cl, 10·8; 1*C*-Me, 4·6%).

The gum obtained from the mother-liquors was fractionally crystallised from ether, giving impure material (0·8 g.) and the *β-ester* (0·90 g.) as needles, m. p. 83—86° (Found: C, 54·5; H, 5·4; Cl, 10·9; *C*-Me, 5·6%). The m. p. was not depressed on admixture with optically active methyl 7-chloro-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyrate (see below) prepared from griseofulvin; in chloroform the infrared spectra were identical, and distinct from the spectrum of the α-ester.

Interconversion of the esters. The β-ester (100 mg.), anhydrous potassium carbonate (0·5 g.), and acetone (10 ml.) were heated together under reflux for 7 hr. Recovery and fractional crystallisation from benzene–light petroleum (b. p. 60—80°) gave the α-ester (36 mg.), m. p. 138—147°, raised to 150—152° by further crystallisation. Crystallisation of the more soluble fractions from ether gave the β-ester (41 mg.), m. p. 83—85°.

Similar results were obtained with the α-ester. The esters were not interconverted by seeded crystallisation or in toluene under reflux for 5 hr.

7-Chloro-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyric Acid (V; R = Cl, R′ = R″ = H).—(i) The above α-ester (561 mg.) was boiled with N-hydrochloric acid (25 ml.) for 3 hr., water (20 ml.) being added after 2·5 hr. The filtered, water-washed product (495 mg.), m. p. 154—162° (decomp.), was used for further work. A specimen was crystallised from toluene, precipitated from solution in sodium hydrogen carbonate by acidification with hydrochloric acid, and recrystallised, giving the *acid* as needles, m. p. 151—154° (decomp.), the decomp. point depending on the rate of heating and not being depressed on admixture with the optically active acid from griseofulvin [11] (Found: C, 53·2; H, 5·05; Cl, 11·3; OMe, 20·4%; equiv., 305. $C_{14}H_{15}O_6Cl$ requires C, 53·45; H, 4·75; Cl, 11·3; 2OMe, 19·7%; *M*, 315).

(ii) Hydrolysis of the β-ester (500 mg.) in the same way gave the same acid (460 mg.), m. p. and mixed m. p. 150—157° (Found: C, 53·5; H, 5·0; Cl, 11·4; OMe, 19·1%). The infrared spectra of the acids from (i) and (ii) were identical.

The acid (100 mg.) from (i) with diazomethane gave a mixture separated into the α-ester (47 mg.; m. p. 142—150°) and the β-ester (38 mg.; m. p. 82—85°) by crystallisation.

Methylation of the acid from (ii) gave similar results.

7-Chloro-6-hydroxy-4-methoxy-3-oxocoumaran-2-β-butyric Acid (VII).—7-Chloro-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyric acid (234 mg.) was boiled with N-sodium hydroxide (10 ml.) for 4 hr. After cooling, filtration, and acidification of the filtrate, the precipitated solid (123 mg.) was collected and crystallised from ethyl acetate in prisms of the phenolic acid, m. p. 212—214° (decomp.), not depressed on admixture with material prepared from griseofulvin [11] (Found: C, 51·9; H, 4·4; Cl, 11·1; OMe, 10·3. $C_{13}H_{13}O_6Cl$ requires C, 51·9; H, 4·3; Cl, 11·8; OMe, 10·3%), $\nu_{max.}$ (dilute chloroform solution) 1701 (C=O), 1737 cm.$^{-1}$ (shoulder, monomeric CO_2H).

7-Chloro-2-hydroxy-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyric Acid (V; R = Cl, R′ = OH, R″ = H).—A solution of 7-chloro-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyric acid (134 mg.) in N-sodium carbonate (10 ml.) was treated with 4·5% aqueous potassium permanganate (3·0 ml.) at 1—2° during 1·5 hr. The mixture was kept at 0° for 1·5 hr., excess of permanganate decomposed with sulphur dioxide, and the filtered solution acidified with hydrochloric acid. The gummy product, recovered in ether, was treated with a little ether, and the resultant solid [85 mg.; m. p. 179—182° (decomp.)] crystallised from ethyl methyl ketone–light petroleum (b. p. 60—80°) in needles of the *hydroxy-acid*, m. p. 189—190° (decomp.) (Found: C, 51·1; H, 4·6; Cl, 10·65. $C_{14}H_{15}O_7Cl$ requires C, 50·8; H, 4·6; Cl, 10·7%). The m. p. was not depressed on admixture with a specimen of the acid obtained from griseofulvin as described previously [11,12] and the infrared spectra of the two products were identical.

Dehydration.—The above hydroxy-acid (85 mg.) was kept with acetic anhydride (0·3 ml.) and pyridine (0·7 ml.) at 35° for 3 days. The product obtained by dilution with water at 0° was washed with sodium hydrogen carbonate solution and with water, giving the *lactone* (VIII; R = Cl) (61 mg.). It crystallised from ethyl acetate as needles, m. p. 223—224°, not depressed on admixture with lactone (A) obtained from griseofulvin [11] (Found: C, 53·6; H, 4·2; Cl, 11·4. $C_{14}H_{13}O_6Cl$ requires C, 53·7; H, 4·2; Cl, 11·3%). The infrared spectrum was indistinguishable from that of lactone (A). The lactone was also obtained by sublimation of the hydroxy-acid at 190—210°/10^{-4} mm.

Methyl 4 : 6-Dimethoxy-3-oxocoumaran-2-β-butyrate (V; R = R′ = H, R″ = Me).—N-Methanolic sodium methoxide (2·0 ml.) was added to 4 : 6-dimethoxycoumaranone (1·94 g.) and methyl crotonate (1·00 g.) in dioxan (40 ml.) at 24°. After 24 hr. the mixture was acidified with acetic acid and evaporated *in vacuo*. An ethereal solution of the residue was washed with sodium hydrogen carbonate solution and with water, and the oily product recovered by evaporation was chromatographed on alumina (22 × 1·5 cm.) in ether. A band fluorescing blue was eluted with ether–methanol (100 : 1), giving, on recovery, a syrup (1·7 g.). The syrupy ester (2·3 g.) from several experiments was kept with ether, giving a solid (1·0 g.) which crystallised from benzene–ether in prisms, m. p. 88—89°, of the *α-ester* (Found: C, 61·2; H, 6·2; OMe, 30·8. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·2; 3OMe, 31·6%).

The syrup recovered from the ethereal mother-liquor did not crystallise and distilled as a very pale yellow syrup (180—210°/10^{-3} mm.) (Found: C, 61·1; H, 6·2%). It is considered to consist essentially of the β-ester.

Ethyl 4 : 6-Dimethoxy-3-oxocoumaran-2-β-butyrate (V; R = R′ = H, R″ = Et).—2N-Ethanolic sodium ethoxide (0·43 ml.) was added to 4 : 6-dimethoxycoumaran-3-one (1·00 g.) and ethyl crotonate (0·59 g.) in dioxan (18 ml.) at 20°. After 48 hr. a little tar was filtered off;

the filtrate was acidified with acetic acid, and the product recovered and chromatographed (elution of a purple-fluorescing band) as described above for the methyl ester. The *ester* was obtained as an oil (1·00 g.) which was distilled at 190°/10^{-3} mm. (Found: C, 62·1; H, 6·6; *C*-Me, 8·1. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·5; 2*C*-Me, 9·8%).

4 : 6-*Dimethoxy*-3-*oxocoumaran*-2-β-*butyric Acid* (V; R = R′ = R″ = H).—The above ester (1·50 g.) was boiled with 3N-hydrochloric acid (20 ml.) for 5 hr. The cooled mixture was made alkaline, washed with ether, and acidified. The crude orange gummy product (1·19 g.) recovered in ether was distilled (200°/10^{-3} mm.), giving a pale yellow hygroscopic glass which consisted essentially of the required acid but contained a phenolic impurity (ferric reaction) (Found: C, 60·3; H, 5·7; OMe, 18·2. Calc. for $C_{14}H_{16}O_6$: C, 60·0; H, 5·75; 2OMe, 22·1%).

Hydrolysis with weaker hydrochloric acid lessened but did not eliminate the formation of the impurity.

The ethyl ester (Found: C, 62·5; H, 6·8. Calc. for $C_{16}H_{20}O_6$: C, 62·3; H, 6·5%) was identical (infrared spectrum) with material prepared as described above.

2-*Hydroxy*-4 : 6-*dimethoxy*-3-*oxocoumaran*-2-β-*butyric Acid* (V; R = R″ = H, R′ = OH).—The above acid (350 mg.) in N-sodium carbonate (22 ml.) was treated with 4·5% potassium permanganate solution (7·6 ml.) at 1—2° during 2 hr. After 4 hr. at 0° the product was recovered as described for the chlorine-containing analogue, giving a solid (193 mg.) which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) in needles (70 mg.) of the *hydroxy-acid*, m. p. 169—173° (decomp.) (Found: C, 56·9; H, 5·7; OMe, 21·4%; equiv., 276. $C_{14}H_{16}O_7$ requires C, 56·75; H, 5·4; 2OMe, 20·9%; *M*, 296). The acid gave no colour with ferric chloride.

Dehydration of the hydroxy-acid (112 mg.) as described for the chlorine-containing analogue gave the *lactone* (VIII; R = H) (85 mg.), prisms (from ethyl acetate–light petroleum), m. p. 150—151° (Found: C, 60·3; H, 5·4; OMe, 22·6. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·1; 2OMe, 22·3%). The m. p. was not depressed by mixture with the lactone obtained from dechlorogriseofulvin,[2] and the infrared spectra of the two products were indistinguishable.

Alkaline Oxidation of Ethyl 4 : 6-*Dimethoxy*-3-*oxocoumaran*-2-β-*butyrate*.—An ice-cold stirred suspension of the ester (525 mg.) in N-sodium carbonate (30 ml.) was treated dropwise with 5% potassium permanganate solution, but only a few drops were decolorised. After the addition of dioxan (25 ml.) addition of the permanganate was continued (10·0 ml., in 1 hr.). The mixture was kept overnight at 0°, then decolorised with sulphur dioxide and filtered. The filtrate and acetone washings of the cake were evaporated *in vacuo*, sodium hydroxide solution was added, and starting material (0·2 g.) was recovered in ether. The aqueous fraction was acidified; the product recovered by ether-extraction crystallised from ether, giving the lactone (VIII; R = H) (45 mg.), m. p. 141—142°, raised to 150—151° (34 mg.) by crystallisation from ethyl methyl ketone. The lactone was identical (mixed m. p. and infrared spectrum) with material obtained as described above.

Attempted Ring Closure of Ethyl 4 : 6-*Dimethoxy*-2-(1-*methyl*-3-*oxobutyl*)-3-*oxocoumaran*-2-*carboxylate* (IX; R = R′ = OMe).—Attempted ring closure with sodium ethoxide in the absence or presence of ethanol, sodium, triphenylmethylsodium, sodamide, potassium *tert.*-butoxide, concentrated sulphuric acid, or polyphosphoric acid failed. Similar results were obtained with the analogue (IX; R = R′ = H).

(−)7-*Chloro*-4 : 6-*dimethoxy*-3-*oxocoumaran*-2-β-*butyric Acid*.—The optically active acid obtained from griseofulvin [11] gave the *methyl ester* as prisms, m. p. 96—98° (from ether), $[\alpha]_D^{22}$ −19° ± 3° (*c* 0·84 in acetone) (Found: C, 55·0; H, 5·4; Cl, 10·8. $C_{15}H_{17}O_6Cl$ requires C, 54·8; H, 5·2; Cl, 10·8%).

The authors are indebted to Dr. L. A. Duncanson and Mr. M. B. Lloyd for the infrared spectra, to Mr. J. F. Grove for initiating this work and interest in it, to several colleagues for helpful discussion, and to Mr. G. Ward for technical assistance.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, AKERS RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS. [*Received, January 13th*, 1959.]