361. *Griseofulvin. Part XIV.* Some Alcoholytic Reactions and the Absolute Configuration of Griseofulvin.*

By J. MacMillan.

Racemisation of the asymmetric spiran centre of griseofulvin takes place on treatment with 0·5N-sodium methoxide, and probably with 0·04N-sodium ethoxide. In contrast, the corresponding trione (II; R = R′ = Me) is stable to both 0·5N-sodium methoxide and ethoxide. In both compounds sodium ethoxide causes replacement of methoxyl by ethoxyl groups.

The absolute configuration of griseofulvin is deduced as (2*S* : 6′*R*)-7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione.

In Part IV [1] of this series some alcoholytic reactions of griseofulvin (I; R = R′ = R″ = Me) and of the parent trione (II; R = R′ = Me) were mentioned briefly. Further investigation of these reactions is now reported.

The product, m. p. 239—240°, obtained [1] from griseofulvin and boiling 0·5N-sodium methoxide was found to be a mixture of griseofulvin (40%) and a diastereoisomer (60%). This mixture was separated by chromatography on alumina or by fractional crystallisation of the mixed triones obtained by acid hydrolysis. Methylation of the diastereoisomeric trione (II; R = R′ = Me) afforded the diastereoisomer of griseofulvin and of the isomeric enol ether (III; R = R′ = R″ = Me).

The constitution of the diastereoisomer of griseofulvin was established as follows. First, it was converted by boiling 0·5N-sodium methoxide into griseofulvin *via* the above diastereoisomeric mixture. Secondly, oxidation with zinc permanganate [2] to the acid (IV),

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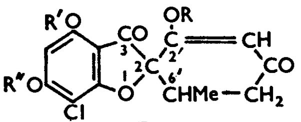
* Part XIII, *J.*, 1958, 2929.

[1] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977.

[2] Grove, Ismay, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3958.

and periodate cleavage of the latter, gave (+)-methylsuccinic acid which was also obtained from griseofulvin.[3] It follows that the spiran and not the 6'-centre (CHMe) is inverted in the formation of the diastereoisomer.

The acid (IV), as isolated by oxidation of the diastereoisomer, had $[\alpha]_D$ −31° (in ethanol), lowered to −19° by dissolution in 3N-sodium hydroxide and recovery: the acid (IV) from griseofulvin had $[\alpha]_D$ −19° (in ethanol), unchanged by treatment with 3N-sodium hydroxide.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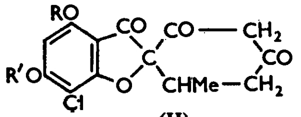
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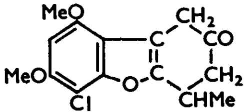
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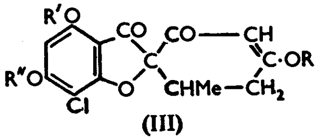
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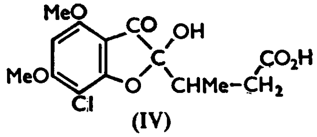
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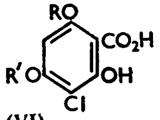
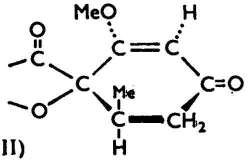

(VI)

Thus the acid (IV), as normally prepared from griseofulvin, appears to be the equilibrium mixture of $C_{(2)}$-diastereoisomers, accounting for the observed formation of two diastereoisomeric lactones.[3]

Since (+)-methylsuccinic acid has been related to D-glyceraldehyde,[4] the absolute configuration at position 6' in both griseofulvin and the diastereoisomer is fixed as in (VII) and (VIII). The configuration of the spiran centre relative to the 6'-centre may be deduced as follows. From optical-rotation data the equilibrium mixture of diastereoisomers, obtained from both griseofulvin and the diastereoisomer, contains only 40% of griseofulvin. The latter is therefore assigned the sterically less favoured configuration (VII) where the 3-carbonyl and the 6'-methyl groups are *cis*; the diastereoisomer would then be (VIII). On the nomenclature system of Cahn, Ingold, and Prelog,[5] griseofulvin and the diastereoisomer are, respectively, (2*S* : 6'*R*)- and (2*R* : 6'*R*)-7-chloro-4 : 6 : 2'-trimethoxy-6'-methylgris-2'-en-3 : 4'-dione. With this system, correlation of configuration in a series of related compounds is not always evident. To overcome this difficulty here and in subsequent papers it is proposed, by agreement with the Editor, to designate the two asymmetric centres by *d* and *l* (though, for bibliography, the *R*,*S* designations will also be noted at appropriate places); thus griseofulvin is prefixed by (*d*,*d*) and the diastereoisomer by (*l*,*d*), the spiran centre being that first mentioned.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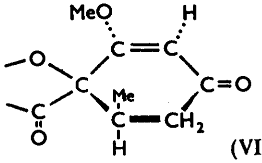
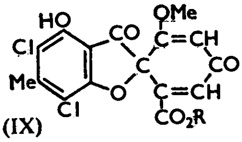

(VIII)

Barton and Scott[6] have reported recently that the spiran centres in geodin (IX; R = H) and erdin (IX; R = Me) are racemised at room temperature in dioxan containing 2% of hydrogen chloride, and these authors suggest a mechanism involving the intermediate keten-ketone (X). In the present case racemisation could proceed by nucleophilic attack of methoxide ion at position 3 (see XI) or at 2' (see XII). The latter seems less likely since it implies rupture of ring C, and this ring has been shown[1] to survive as orcinol monomethyl ether in the cleavage of griseofulvin by 2N-sodium methoxide.

[3] Grove, MacMillan, Mulholland, and Zealley, *J.*, 1952, 3967.
[4] Klyne, " Progress in Stereochemistry," Butterworths, London, 1951, Vol. I, Chapter 5.
[5] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[6] Barton and Scott, *J.*, 1958, 1767.

Unlike their methyl ethers, both the (*d,d*)- and the (*l,d*)-trione (II; R = R′ = Me) are stable to boiling 0·5N-sodium methoxide (cf. usnic acid [7]). With 0·5N-sodium hydroxide the (*l,d*)-trione, like the (*d,d*)-trione,[8] gave the dibenzofuran (V), although in very low yield. In contrast to (*d,d*-I; R = R′ = R″ = Me) which also gives the dibenzofuran (V) with 0·5N-sodium hydroxide, the (*l,d*)-diastereoisomer yielded the salicylic acid (VI; R = R′ = Me); this result may reflect the greater accessibility of the 3-carbonyl group in the (*l,d*)-diastereoisomer (see VIII).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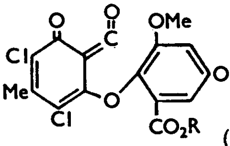
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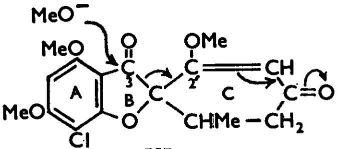
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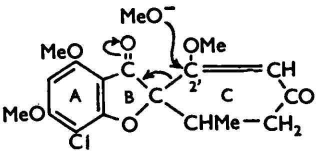
(XII)

In Part IV,[1] the (*d,d*)-trione (II; R = R′ = Me) and boiling 0·5N-sodium ethoxide were stated to yield a compound $C_{17}H_{17}O_6Cl$ by replacement of the alkali-labile aryl-methoxyl group by an ethoxyl group. This conclusion has been shown to be incorrect by the non-identity of this product and the (*d,d*)-trione (II; R = Me, R′ = Et), derived from the (*d,d*)-ethyl ether (I; R = R″ = Et, R′ = Me) of established structure.[9] Further elementary analyses of the alcoholysis product (and methyl and ethyl ethers) established the formula $C_{18}H_{19}O_6Cl$, and alkoxyl determinations confirmed the absence of methoxyl groups but the presence of two ethoxyl groups. These facts suggested structure (II; R = R′ = Et) which was confirmed by oxidation to the salicylic acid (VI; R = R′ = Et). The latter compound was identified by conversion into the ethyl ether ethyl ester, identical with a synthetic specimen prepared by chlorination of ethyl 2 : 4 : 6-triethoxybenzoate. The trione (II; R = R′ = Et) had the same molecular rotation as the (*d,d*)-trione (II; R = R′ = Me). Thus treatment of the latter compound with boiling 0·5N-sodium ethoxide replaces both methoxyl groups by ethoxyl without causing racemisation.

Griseofulvin and boiling 0·04N-sodium ethoxide gave a complex mixture. Chromatography of the neutral fraction gave the alcoholysis product, described in Part IV,[1] in low yield but with a higher m. p. (210—212°); the (*d,d*)-triethyl ether (I; R = R′ = R″ = Et) and traces of an unidentified substance, m. p. 200°, were also isolated. The acidic fraction, after ethylation and chromatography, gave the (*d,d*)-triethyl ether (III; R = R′ = R″ = Et) and an unidentified substance, m. p. 173—175°. The product of m. p. 210—212°, appears to be isomeric with, but possesses half the molecular rotation of, (*d,d*)-7-chloro-6 : 2′-diethoxy-4-methoxy-6′-methylgris-2′-en-3 : 4′-dione (I; R = R″ = Et, R′ = Me),[9,10] one of the alternative structures suggested for it in Part IV;[1] it may therefore be a mixture of the (*d,d*)- and the (*l,d*)-diastereoisomer of (I; R = R″ = Et, R′ = Me).

EXPERIMENTAL

For general experimental details see Duncanson *et al.*[9] In chromatography columns were eluted in ultraviolet light. Unless otherwise stated, ultraviolet absorption spectra were determined for ethanol solutions, and infrared spectra for Nujol mulls.

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[7] MacKenzie, *J. Amer. Chem. Soc.*, 1955, **77**, 2214.
[8] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.
[9] Duncanson, Grove, MacMillan, and Mulholland, *J.*, 1957, 3555.
[10] Duncanson, Grove, and Jeffs, *J.*, 1958, 2929.

(l,d)(i.e., 2R : 6′R)-7-*Chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (I; R = R′ = R″ = Me).—(A) *Preparation of the mixture of* (l,d *and* d,d)-*diastereoisomers.* The (*d,d*)-compound (I; R = R′ = R″ = Me) (1·3 g.) was boiled for 5 hr. with sodium (1·5 g.) in methanol (130 ml.). The reaction mixture which had $[\alpha]_D^{17}$ +178° was worked up as described previously,[1] giving the mixture (821 mg.) of (*d,d* and *l,d*)-isomers (I; R = R′ = R″ = Me); crystallisation from benzene–light petroleum (b. p. 60—80°) gave needles, m. p. 240—242°, $[\alpha]_D^{20}$ +179° (*c* 1·0 in 0·5N-sodium methoxide), +181° (*c* 1·1 in acetone), +202° (*c* 0·96 in chloroform) (Found: C, 57·8; H, 4·9; Cl, 10·0; OMe, 25·8. Calc. for $C_{17}H_{17}O_6Cl$: C, 57·9; H, 4·85; Cl, 10·1; 3OMe, 26·4%), $\nu_{max.}$ 1717, 1705, ~1670, 1655 cm.$^{-1}$, (in ethylidene chloride) 1714 and 1667 cm.$^{-1}$. The specific rotation was unchanged after heating of the product under reflux for a further 20 hr. in 0·5N-sodium methoxide.

(B) *Separation of the diastereoisomeric mixture.* (i) The mixture (2·0 g.) in benzene (150 ml.) was adsorbed on alumina (40 × 1·5 cm.) and eluted with benzene–methanol (199 : 1). In a typical experiment the band fluorescing blue was 26 cm. long and was collected in 13 fractions, comprising a fore-run, then 6 × 1 cm., 5 × 3 cm. and finally 1 × 5 cm. lengths of the band. The following fractions were obtained (specific rotations in chloroform in parentheses): (1) Fore-run 211 mg.; (2) 66 mg.; (3) 48 mg.; (4) 42 mg. (1—4 having $[\alpha]_D$ < +100°); (5) 40 mg. (+111°); (6) 78 mg. (+140°); (7) 128 mg. (+148°); (8) 257 mg. (+162°); (9) 253 mg. (+191°); (10) 173 mg. (+236°); (11) 270 mg. (+274°); (12) 152 mg. (+301°); (13) 182 mg. (+305°).

In this way 18·0 g. were chromatographed in 2·0 g. batches, giving: (*a*) 3·2 g., $[\alpha]_D$ <100°; (*b*) 2·0 g., $[\alpha]_D$ >300°; and (*c*) 11·8 g. of intermediate $[\alpha]_D$; crystallisation of (*b*) from ethanol gave the (*d,d*)-isomer (I; R = R′ = R″ = Me) as needles (1·375 g.), m. p. 219—222°, $[\alpha]_D^{20}$ +342° (*c* 1·57 in chloroform). Crystallisation of (*a*) from benzene gave the (*l,d*)-diastereoisomer, (2R : 6′R)-7-*chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (I; R = R′ = R″ = Me), in needles (2·64 mg.), m. p. 214—216°, $[\alpha]_D^{22}$ +88° (*c* 0·99 in chloroform), 78° (*c* 0·97 in acetone) (Found: C, 57·5, 57·6; H, 4·85, 4·8; Cl, 10·0; OMe, 25·9. $C_{17}H_{17}O_6Cl$ requires C, 57·9; H, 4·85; Cl, 10·1; 3OMe, 26·4%), $\lambda_{max.}$ 323, 290, ~252, 236 mμ (log ε 3·78, 4·41, 4·25, 4·46), $\nu_{max.}$ 1718 and 1667 cm.$^{-1}$, (in ethylidene chloride) 1719 and 1670 cm.$^{-1}$, (in chloroform) 1718 and 1660 cm.$^{-1}$. The corresponding $\nu_{max.}$ for the (*d,d*)-isomer were: 1705 and 1658; 1715 and 1669; 1708 and 1655 cm.$^{-1}$.

A mixture (2 : 3) of the pure (*d,d*)- and (*l,d*)-diastereoisomers, once crystallised from benzene–light petroleum (b. p. 60—80°), and the mixture of diastereomers, described in (A), had identical infrared spectra. An approximate m. p.–composition curve is shown in the Figure.

(ii) The diastereoisomeric mixture (3·0 g.) in methanol (600 ml.) was hydrolysed with 2N-hydrochloric acid (750 ml.) as described for (*d,d*-I; R = R′ = R″ = Me),[8] and the crude solid product (2·7 g.) was extracted with sodium carbonate solution. A solution of the neutral fraction in ether was combined with ether-washings of the sodium carbonate extract; recovery yielded a gum, a warm ether extract of which deposited long needles (63 mg.) of (*l,d*)-7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione (III; R = R′ = R″ = Me) (see below).

The recovered acidic fraction (1·96 g.), decomp. 250—255°, $[\alpha]_D^{18}$ +227° (*c* 1·08 for the sodium salt in water), was fractionally crystallised from acetic acid, giving (i) the less soluble (*d,d*)-7-chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′ : 4′-trione, prisms (305 mg.), decomp. 260—263°, $[\alpha]_D^{18}$ +414° (*c* 1·04 for the sodium salt in water), and (ii) (l,d)(i.e., 2R : 6′R)-7-*chloro*-4 : 6-*dimethoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione* (II; R = R′ = Me), prisms (689 mg.), decomp. 219—223°, $[\alpha]_D^{15}$ +111° (*c* 1·06 for the sodium salt in water) [Found: (sample crystallised from acetic acid and dried over potassium hydroxide at 140°/0·1 cm. for 7 hr.) C, 56·4; H, 4·7; Cl, 10·0; OMe, 17·2%; (sample crystallised from ethyl methyl ketone and dried in the same way) C, 55·6; H, 4·5; Cl, 10·4; OMe, 18·1%; equiv. (phenolphthalein) 346. $C_{16}H_{15}O_6Cl$ requires C, 56·7; H, 4·5; Cl, 10·5; 2OMe, 18·3%, *M*, 338·5]. Consistently low carbon values were obtained irrespective of the mode of preparation or conditions of drying. $\nu_{max.}$ were at 1673, 1605 (broad), 1511, 3195, and 3545 cm.$^{-1}$.

Methylation.—The (*l,d*)-trione (100 mg.) was treated with diazomethane. Several crystallisations of the product from methanol gave needles (57 mg.), m. p. 180—185°. Adsorption on alumina (8 × 1·5 cm.) from benzene (5 ml.) and fractional elution with ether–methanol (99 : 1) gave (*a*) (*l,d*)-7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione (I; R = R′ = R″ = Me), needles (21 mg.), m. p. 213—215° (from methanol), identified by mixed m. p. and infrared spectrum, (*b*) mixed fractions (20 mg.), m. p. 170—180°, and (*c*) (l,d)(i.e., 2R : 6′R)-7-*chloro*-4 : 6 : 4′-*trimethoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione* (III; R = R′ = R″ = Me), long needles

(7 mg.), m. p. 200—202° (from methanol), $[\alpha]_D^{18}$ +92° (*c* 1·02 in acetone) (Found: C, 57·9; H, 5·0; Cl, 10·3; OMe, 26·0. $C_{17}H_{17}O_6Cl$ requires C, 57·9; H, 4·85; Cl, 10·1; OMe, 26·4%), $\lambda_{max.}$ 325, 290, 262, ~225 mμ (log ε 3·76, 4·35, 4·30, 4·30), $\nu_{max.}$ 1719, 1645, 1608, ~1592, 1506 cm.$^{-1}$

Reactions of (l,d)(i.e., 2R′ : 6′R)-7-*Chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (I; R = R′ = R″ = Me).—(a) *Treatment with* 0·5N-*sodium methoxide.* The compound (50 mg.) was boiled for 4·5 hr. with sodium (57 mg.) in magnesium-dried methanol (50 ml.). Dilution with ice-water gave the mixture of (*d,d*)- and (*l,d*)-isomers (I; R = R′ = R″ = Me), needles (30 mg.), m. p. 240—242° [from benzene–light petroleum (b. p. 60—80°)], $[\alpha]_D^{19}$ +203° (*c* 0·99 in chloroform), showing infrared absorption identical with that of the mixture obtained from the (*d,d*)-isomer.

(b) *Aqueous alkaline hydrolysis.* The compound (215 mg.) was boiled for 4·5 hr. in nitrogen with freshly prepared 0·5N-sodium hydroxide which had previously been boiled for 1 hr. in nitrogen. After filtration from a trace of solid, the alkaline filtrate was extracted with ether, then saturated with carbon dioxide, re-extracted with ether (2 mg. of intractable gum), and acidified. The resultant solid (148 mg.) was collected and sublimed at 160°/10^{-2} mm. Crystallisation of the sublimate from ethyl acetate gave 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid as needles (18 mg.), m. p. 220—222° (decomp.), identified by infrared spectrum and by methylation to the methyl ether methyl ester, m. p. and mixed m. p. 127—128°.

Mixed m. p. diagram for (l,d)- (*scale A*) *and* (d,d)-*griseofulvin* (*scale B*).

(c) *Zinc permanganate oxidation.* The compound (2·88 g.) in acetone (910 ml.) was treated with 2% aqueous zinc permanganate (340 ml.) in five portions during 0·5 hr. After 4 hr. (occasional shaking) excess of permanganate was destroyed with ethanol, and the mixture filtered. The filtrate and acetone washings were worked up as described [2] for the zinc permanganate oxidation of griseofulvin, giving (i) starting material, needles (414 mg.) (from ethanol), m. p. and mixed m. p. 211—213°, (ii) an acidic gum (1·5 g.) which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) in needles (520 mg.), m. p. 181—184° not depressed on admixture with 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid (m. p. 180—184°) obtained from (*d,d*)-griseofulvin (Found: C, 51·3, 51·2; H, 4·7, 4·9. Calc. for $C_{14}H_{15}O_7Cl$: C, 50·8; H, 4·6%), $\nu_{max.}$ 1706, 1623, 1593, 1506 cm.$^{-1}$, $[\alpha]_D^{20}$ −31° (*c* 1·32 in ethanol), −19° (*c*, 1·01 in 0·1N-sodium hydroxide), and, after dissolution in 3N-sodium hydroxide (3 min.) and recovery, $[\alpha]_D^{20}$ −21° (*c* 1·01 in ethanol) and −22° (*c* 1·06 in acetone). 7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid, obtained by oxidation of (*d,d*)-griseofulvin with zinc permanganate, had $[\alpha]_D^{19}$ −19° (*c* 1·04 in ethanol), unchanged by treatment with cold 3N-sodium hydroxide, and $[\alpha]_D^{22}$ −18·5° (*c* 1·06 in 0·1N-sodium hydroxide). The manganese dioxide, worked up as described previously [2] for the oxidation of (*d,d*)-griseofulvin, gave 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid, needles (64 mg.), m. p. 215—218° (decomp.) (from ethyl acetate).

Periodate Oxidation of 7-*Chloro*-2-*hydroxy*-4 : 6-*dimethoxycoumaran*-3-*one*-2-β-*butyric Acid* (IV).—The following improved procedure [3] was used. (*a*) The finely-powdered butyric acid {730 mg.; $[\alpha]_D^{20}$ −19° (*c* 1·1 in ethanol)}, from (*d,d*)-griseofulvin, was shaken in water (120 ml.) with 0·09M-sodium periodate (200 ml.) at 23° for 8 days. 3-Chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (420 mg., 85%) was collected and crystallised from ethyl acetate in needles (340 mg.), m. p. and mixed m. p. 219—222° (decomp.). The aqueous filtrate (titration of an aliquot part showed consumption of 2·06 mol. of periodate) was extracted continuously for 5 days with ether. Recovery gave a gum (480 mg.) which, after sublimation at 80—90°/10^{-3} mm. and crystallisation from benzene, afforded (+)-methylsuccinic acid as needles (340 mg.), m. p. 111—112°, $[\alpha]_D^{22}$ +9·0° (*c* 2·04 in water) (Found: C, 45·7; H, 6·2. Calc. for $C_5H_8O_4$: C, 45·45; H, 6·1%); the anhydride, prepared with a mixture of acetyl chloride and thionyl chloride, crystallised from benzene–light petroleum (b. p. 60—80°) in plates, m. p. 67—69°, $[\alpha]_D^{20}$ +31° (*c* 3·53 in ethanol) (Found: C, 52·8; H, 5·4. Calc. for $C_5H_6O_3$: C, 52·6; H, 5·3%).

(*b*) The butyric acid {330 mg.; $[\alpha]_D^{20}$ −31° (*c* 1·32 in ethanol)}, derived from (*l,d*)-griseofulvin, was oxidised as in (*a*) with sodium periodate (2·1 g.) in water (160 ml.), giving (i) 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (183 mg., 82%), m. p. and mixed m. p. 217—219° (decomp.), and (ii) (+)-methylsuccinic acid (86 mg.), m. p. 111—112°, $[\alpha]_D^{20}$ +8·0° (*c* 1·89 in water) (Found: C, 43·6; H, 6·2%); the anhydride had m. p. 67—69° and $[\alpha]_D^{21}$ +31° (*c* 1·7 in ethanol).

The (+)-methylsuccinic acid and anhydride obtained in (*a*) and (*b*) were identified by direct comparison (mixed m. p. and infrared spectrum) with specimens prepared by resolution of (±)-methylsuccinic acid *via* the strychnine salt.[11]

Reactions of (l,d)(i.e., 2R : 6′R)-7-*Chloro*-4 : 6-*dimethoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione* (II; R = R′ = Me).—(a) *With* 0·5N-*sodium hydroxide*. The (*l,d*)-trione (150 mg.) was boiled for 5·5 hr. in nitrogen in 0·5N-sodium hydroxide (25 ml.) which had previously been boiled for 1 hr. in nitrogen. The solid neutral fraction (26 mg.) was collected and adsorbed on alumina (7 × 1 cm.) from a benzene solution (5 ml.). Elution with benzene (150 ml.) and recovery gave 8-chloro-1 : 2 : 3 : 4-tetrahydro-3-oxo-5 : 7-dimethoxy-1-methyldibenzofuran (V) which, after sublimation at <130°/10^{-3} mm., crystallised from methanol in needles (5 mg.), m. p. and mixed m.p. 136—138°, $[\alpha]_D^{18}$ −26° (*c* 0·45 in acetone).

Acidification of the aqueous alkaline filtrate from the reaction mixture afforded a gum which gave no 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid on sublimation.

(b) *With* 0·5N-*sodium methoxide*. The (*l,d*)-trione (102 mg.) and sodium (230 mg.) in methanol (20 ml.) were boiled for 5 hr. in nitrogen. Dilution with water, acidification, and removal of methanol *in vacuo* gave a precipitate which was collected; dissolution in sodium carbonate solution (ether washing) and recovery gave unchanged (*l,d*)-trione (100 mg.), crystallising from acetic acid in prisms (70 mg.), decomp. 216—218°, identified by its infrared spectrum and optical rotation.

As shown previously,[1] identical treatment of the (*d,d*)-trione (1 g.) gave starting material (860 mg.), crystallising from acetic acid in prisms (720 mg.) identified by infrared spectrum, optical rotation, and methylation to (*d,d*)-griseofulvin.

(d,d)(i.e., 2S : 6′R)-7-*Chloro*-4 : 6-*diethoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione* (II; R = R′ = Et).—(a) *Preparation*. Treatment of (*d,d*)-7-chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′ : 4′-trione (500 mg.) with sodium (550 mg.) in ethanol (50 ml.) as previously described [1] gave the (d,d)-4 : 6-*diethoxy-homologue* (II; R = R′ = Et), crystallising from acetic acid in needles (350 mg.), decomp. 226—228°, $[M]_D^{20}$ +1457° (*c* 1·0 for the sodium salt in water) [Found: C, 58·6; H, 5·1; Cl, 9·7; OEt, 24·2%; equiv. (phenolphthalein), 345. $C_{18}H_{19}O_6Cl$ requires C, 58·9; H, 5·2; Cl, 9·7; 2OEt, 24·5%; *M*, 368], $\nu_{max.}$ 1708, 1650, and 3040 (broad) $cm.^{-1}$.

The neutral fraction of the crude product crystallised from ethanol in needles, m. p. 177—179°, identical (m. p. and mixed m. p.) with (*d,d*)-7-chloro-4 : 6 : 4′-triethoxy-6′-methylgris-3′-en-3 : 2′-dione (III; R = R′ = R″ = Et) (see below).

(b) *Ethylation*. The product from the 4 : 6-diethoxy-trione (775 mg.) and excess of diazoethane was chromatographed in benzene (50 ml.) on alumina (30 × 1 cm.), giving: (i) a lower band fluorescing blue. Elution with benzene and recovery yielded (d,d)-7-*chloro*-4 : 6 : 4′-*triethoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione* (III; R = R′ = R″ = Et), needles (350 mg.), m. p. 180—181° (from ethanol) (Found: C, 60·6; H, 5·85; Cl, 9·2; OEt, 33·7. $C_{20}H_{23}O_6Cl$ requires C, 60·8; H, 5·9; Cl, 9·0; 2OEt, 34·2%), $\lambda_{max.}$ ~324, 293, 264, 237 mμ (log ε 3·86, 4·33, 4·35, 4·4), $\nu_{max.}$ 1704 and 1655 $cm.^{-1}$; and (ii) an upper band fluorescing blue. Elution with benzene–methanol (99 : 1) gave the isomeric (d,d)-7-*chloro*-4 : 6 : 2′-*triethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (I; R = R′ = R″ = Et) which crystallised from benzene–light petroleum (b. p. 60—80°) in needles (240 mg.), m. p. 173—175°, $[\alpha]_D^{20}$ +297° (*c* 0·85 in acetone) (Found: C, 60·7; H, 6·0; Cl, 8·9%), $\lambda_{max.}$ ~323, 292·5, ~256, 237 mμ (log ε 3·79, 4·38, 4·19, 4·33), $\nu_{max.}$ 1696 and 1657 $cm.^{-1}$.

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[11] Ladenberg, *Ber.*, 1895, **28**, 1170.

Oxidation of the latter compound (97 mg.) in acetic acid (1·5 ml.) with chromium trioxide (300 mg.) in acetic acid (1·5 ml.) and water (0·6 ml.) as described [1] for 7-chloro-2′-ethoxy-4 : 6-dimethoxy-6′-methygris-2′-en-3 : 4′-dione (I; R = Et, R′ = R″ = Me) gave 3-ethoxy-2 : 5-toluquinone (1 mg.), m. p. and mixed m. p. 54—56°.

Each of the isomeric ethyl ethers with boiling 2N-hydrochloric acid in ethanol, as for the acid hydrolysis of griseofulvin,[8] gave the parent trione, identified by infrared spectrum and elementary analysis.

(c) *Methylation.* The product from the 4 : 6-triethoxy-trione (775 mg.) and excess of diazomethane was chromatographed on alumina (21 × 1·5 cm.), giving: (i) a lower band fluorescing blue; elution with benzene yielded (d,d)-7-*chloro*-4 : 6-*diethoxy*-4′-*methoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione* (III; R = Me, R′ = R″ = Et), needles, m. p. 218—219° (from methanol) (Found: C, 59·6; H, 5·6; Cl, 9·4. $C_{19}H_{21}O_6Cl$ requires C, 59·9; H, 5·5; Cl, 9·3%), $\lambda_{max.}$ 320, 292, 263, 235 mμ (log ε 3·76, 4·27, 4·27, 4·31), $\nu_{max.}$ 1704 and 1662 cm.$^{-1}$; and (ii) an upper band fluorescing blue; elution with benzene–methanol (99 : 1) gave the isomeric (d,d)-7-*chloro*-4 : 6-*diethoxy*-2′-*methoxy*-6′-*methylgris*-2′-*en*-3 : 4-*dione* (I; R = Me, R′ = R″ = Et), crystallising from ethanol in prisms, m. p. 208—212° (Found: C, 59·7; H, 5·8; Cl, 9·3%), $\lambda_{max.}$ ~325, 292, 255, 233 mμ (log ε 3·87, 4·46, 4·29, 4·48), $\nu_{max.}$ 1707 and 1673 cm.$^{-1}$.

(d) *Oxidation.* The 4 : 6-diethoxy-trione (200 mg.) in acetone (50 ml.) was treated with powdered potassium permanganate (800 mg.). After 16 hr. at room temperature, the precipitated manganese salts were collected and extracted with dilute aqueous ammonia; acidification gave 3-*chloro*-4 : 6-*diethoxy*-2-*hydroxybenzoic acid* (VI; R = R′ = Et), crystallising from ethyl acetate in needles (12 mg.), m. p. 171° (decomp.) (Found: C, 51·0; H, 5·1; Cl, 14·0. $C_{11}H_{13}O_5Cl$ requires C, 50·7; H, 5·0; Cl, 13·6%), $\nu_{max.}$ 1660 and 3200 cm.$^{-1}$.

The ethyl ether ethyl ester, prepared with diazoethane, crystallised from light petroleum (b. p. 40—60°) in plates, m. p. 65—67°, identical (mixed m. p. and infrared spectrum) with the synthetic specimen described below.

Ethyl 3-*Chloro*-2 : 4 : 6-*triethoxybenzoate.*—*Ethyl* 2 : 4 : 6-*triethoxybenzoate,* obtained from 2 : 4 : 6-trihydroxybenzoic acid (2·0 g.) and diazoethane, crystallised from light petroleum (b. p. 40—60°) in plates (1·8 g.), m. p. 88—89° (Found: C, 64·1; H, 8·1; OEt, 60·5. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·85; 4OEt, 63·7%). This ester (286 mg.) in carbon tetrachloride (15 ml.) was treated slowly with chlorine (78 mg.) in carbon tetrachloride (6·3 ml.). After 12 hr. at room temperature the mixture was washed with water, dried, and evaporated, giving *ethyl* 3-*chloro*-2 : 4 : 6-*triethoxybenzoate,* needles (200 mg.), m. p. 67—68° [from light petroleum (b. p. 40—60°)] (Found: C, 57·1; H, 6·8; Cl, 11·6. $C_{15}H_{21}O_5Cl$ requires C, 56·9; H, 6·7; Cl, 11·2%).

(d,d)(i.e., 2S : 6′R)-7-*Chloro*-6-*ethoxy*-4-*methoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione* (II; R = Me, R′ = Et).—7-Chloro-6 : 2′-diethoxy-4-methoxy-6′-methylgris-2′-en-3 : 4′-dione [9] (45 mg.) in ethanol (5 ml.) and 2N-hydrochloric acid (5 ml.) was hydrolysed as for griseofulvin,[8] giving (d,d)-7-*chloro*-6-*ethoxy*-4-*methoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione,* stout needles, decomp. 234—236° (Found: C, 57·9; H, 5·1; Cl, 10·0. $C_{17}H_{17}O_6Cl$ requires C, 57·9; H, 4·85; Cl, 10·1%). The infrared spectrum (bands at 1708, 1651, and ~3125 cm.$^{-1}$) was very similar to, but distinct from, that of 7-chloro-4 : 6-diethoxy-6′-methylgrisan-2 : 2′ : 4′-trione (see above).

Action of 0·04N-*Sodium Ethoxide on* (d,d)-*Griseofulvin.*—Griseofulvin (2·0 g.) was heated under reflux for 5 hr. with sodium (0·8 g.) in ethanol (800 ml.). After dilution with water (400 ml.) and acidification, the ethanol was removed *in vacuo,* giving a gum (A; 1·2 g.) which was collected after 18 hr. at 0°. After storage at 0° for several days, a second fraction (B; 200 mg.) was collected.

A solution of fraction (A) in ether was extracted with sodium carbonate solution, and the recovered neutral fraction in benzene (15 ml.) was chromatographed on alumina (20 × 1·5 cm.), giving: (*a*) a narrow band fluorescing blue; elution with benzene gave an oil (5 mg.) which was discarded; (*b*) a broad band fluorescing blue; elution with benzene gave a solid (35 mg.), crystallising from ethanol in needles, m. p. 174—178°, identical (mixed m. p. and infrared spectrum) with (*d,d*)-7-chloro-4 : 6 : 4′-triethoxy-6′-methylgris-3′-en-3 : 2′-dione (III; R = R′ = R″ = Et); and (*c*) upper broad band fluorescing blue; elution with benzene–methanol (99 : 1) gave a gum (400 mg.) which yielded a solid (130 mg.), m. p. 175—200°, on treatment with ethanol. This solid from fraction (*c*), combined with a similar fraction (20 mg.), m. p. 170—190°, from (*b*), was washed with ether and crystallised from ethanol to constant m. p. (210—212°), giving prisms of the (?) mixture of (*d,d*)- and (*l,d*)-7-chloro-6 : 2′-diethoxy-6′-methylgris-2′-en-3 : 4′-dione (I; R = R″ = Et, R′ = Me), $[M]_D^{20}$ +308° (*c* 0·82 in acetone)

(Found: C, 59·3, 59·3; H, 5·8, 5·9, 5·9; Cl, 9·2. Calc. for $C_{19}H_{21}O_6Cl$: C, 59·9; H, 5·6; Cl, 9·3. Calc. for $C_{20}H_{23}O_6Cl$: C, 60·8; H, 5·9; Cl, 9·0%); analysis of the alkyl iodide, obtained by the Zeisel method, by gas chromatography as described by Haslam, Hamilton, and Jeffs,[12] indicated the presence of methoxyl and ethoxyl in the approximate ratio of 1 : 1·6. The ultraviolet absorption spectra, as described by Grove *et al.*[3], of this solid showed $\nu_{max.}$ 1718 and 1667 cm.$^{-1}$.

The ether-soluble fraction of the solid, m. p. 175—200°, obtained from band (*c*) was chromatographed in ether on alumina, giving two bands fluorescing blue: (i) A lower band eluted with ether gave an unidentified solid which, after repeated crystallisation from methanol, was obtained as needles (2 mg.), m. p. 200°, $\lambda_{max.}$ ~325, 291, 263, 233 ($E^{1\%}_{1\,cm.}$ 153, 444, 566, 578), $\nu_{max.}$ 1700 and 1653 cm.$^{-1}$: this compound was distinct (mixed m. p.) from (*d,d*)- and (*l,d*)-7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione (III; R = R′ = R″ = Me) and the (*d,d*)-4′-ethoxy-homologue (III; R = Et, R′ = R″ = Me) and from the 2′-ethoxy-homologue of (*d,d*)-griseofulvin. (ii) An upper band, elution of which with ether–methanol (99 : 1) yielded a little more of the (?) mixture of (*d,d*)- and (*l,d*)-diastereoisomers of the homologue (I; R = R″ = Et, R′ = Me).

The acidic gum (600 mg.), recovered from the sodium carbonate extract of fractions A and B, was treated with excess of diazoethane and then chromatographed on alumina (30 × 2 cm.) in ether. A narrow band fluorescing blue, eluted with ether and discarded, was followed by a broad band fluorescing blue which was fractionally eluted as follows: (*x*) ether (50 ml.) eluted (*d,d*)-7-chloro-4 : 6 : 4′-triethoxy-6′-methylgris-3′-en-3 : 2′-dione (III; R = R′ = R″ = Et), needles (30 mg.), m. p. and mixed m. p. 177—180°; (*y*) ether (3 × 100 ml.) eluted gums (267 mg.); and (*z*) ether–ethanol (99 : 1) (100 ml.) eluted an unidentified compound, crystallising from ethanol in needles, m. p. 173—175°, $\lambda_{max.}$ ~323, 290, ~252, 236 ($E^{1\%}_{1\,cm.}$ 146, 579, 359, 589), $\nu_{max.}$ 1716 and 1665 cm.$^{-1}$. This compound depressed the m. p.s of the 6 : 2′-diethoxy- and the 4 : 6 : 2′-triethoxy-homologue of (*d,d*)-griseofulvin.

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[12] Haslam, Hamilton, and Jeffs, *Analyst*, 1958, **83**, 66.