351. *Griseofulvin. Part VII.* Dechlorogriseofulvin.*

By J. MacMillan.

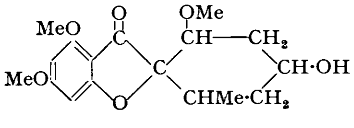
Dechlorogriseofulvin, $C_{17}H_{18}O_6$, the dechloro-derivative of griseofulvin, has been isolated from the culture filtrates of *Penicillium griseofulvum* Dierckx and certain strains of *Penicillium janczewskii* Zal. The chemistry of this new metabolite is described, together with a sensitive colour test for its detection in the presence of griseofulvin.

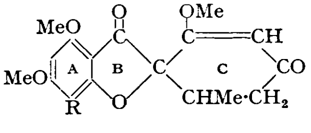
DECHLOROGRISEOFULVIN was isolated, together with griseofulvin, from the culture filtrates of *Penicillium griseofulvum* Dierckx and certain strains of *Penicillium janczewskii* Zal. [= *P. nigricans* (Bainier) Thom] (MacMillan, *Chem. and Ind.*, 1951, 719). Both species are known to produce griseofulvin (Oxford, Raistrick, and Simonart, *Biochem. J.*, 1939, **33**, 240; Brian, Curtis, and Hemming, *Trans. Brit. Mycol. Soc.*, 1946, **29**, 173; 1949, **32**, 30).

The fungi were grown and the culture filtrates extracted as described by Brian *et al.* (*loc. cit.*). Dechlorogriseofulvin and griseofulvin were isolated from the crude solid extract by chromatography on alumina or by fractional crystallisation from methanol or benzene. Dechlorogriseofulvin was obtained in yields of 30—50 mg. per l. from the culture filtrates of *P. griseofulvum* Dierckx, together with griseofulvin (60—100 mg. per l.), but several morphologically identical strains of *P. janczewskii* Zal., isolated from Wareham Heath soil, differed in their ability to produce dechlorogriseofulvin (see Experimental section). Although griseofulvin occurs both in the mycelium and culture filtrates of *P. griseofulvum* and *P. janczewskii*, dechlorogriseofulvin was isolated only from the culture filtrate.

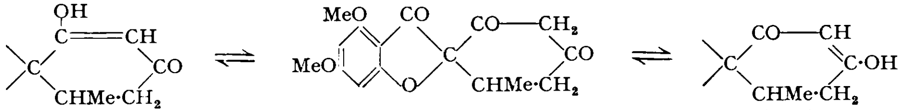
Dechlorogriseofulvin, $C_{17}H_{18}O_6$, was shown to be the dechloro-analogue of griseofulvin by catalytic reduction to 4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (I), obtained by reductive dechlorination of griseofulvin (Part V, *J.*, 1952, 3987). Dechlorogriseofulvin is therefore 4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione (II; R = H) (cf. Part IV, *J.*, 1952, 3977). The ultra-violet and infra-red spectra closely resemble those of griseofulvin. The ultra-violet curve (see Figure) showed an expected small shift to shorter wave-length. The infra-red indicated the presence of two carbonyl groups, but only one of these was chemically reactive.

(I)



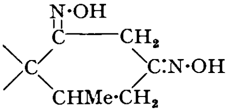


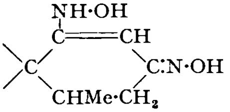
(II)



(III*a*) (III) (III*b*)

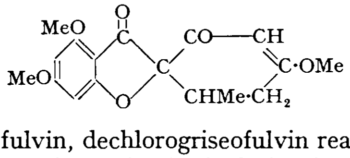
(IV)

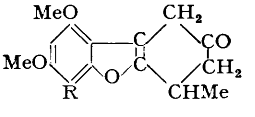




(V)

(VI)





(VII)

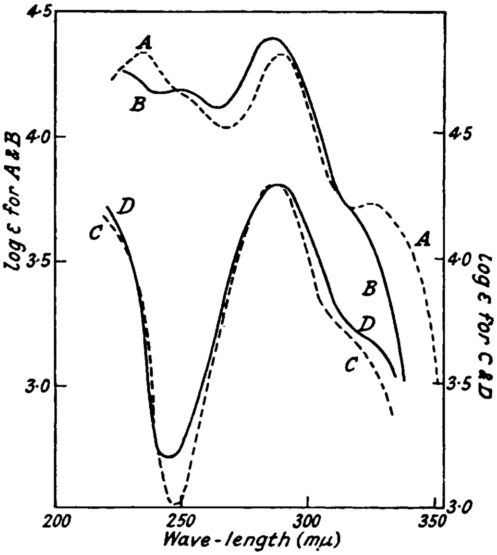
Like griseofulvin, dechlorogriseofulvin reacted with semicarbazide in pyridine and with methanolic ammonia to give basic derivatives (cf. Part I, *J.*, 1952, 3949).

---

* Part VI, *J.*, 1952, 3994.

Hydrolysis of dechlorogriseofulvin with dilute mineral acid gave the 1 : 3-diketone (III*a* $\rightleftharpoons$ III $\rightleftharpoons$ III*b*). With hydroxylamine at pH 5—6 this gave a derivative considered to be the dioxime (IV) rather than (V) since it was saturated to neutral permanganate. Methylation of (III) afforded dechlorogriseofulvin (II; R = H) and the isomeric (VI). Derivatives of all three tautomers of (III) have thus been prepared.

With 0·5N-sodium hydroxide, dechlorogriseofulvin yielded (III) and 1 : 2 : 3 : 4-tetrahydro-3-keto-5 : 7-dimethoxy-1-methyldibenzofuran (VII; R = H) whose structure and mode of formation were inferred by analogy with its counterpart (VII; R = Cl) in the griseofulvin series (cf. Part IV, *loc. cit.*). In this reaction, hydrolysis of one of the methoxyl groups in ring A did not take place; the only acidic product was (III). In this respect, dechlorogriseofulvin differs from griseofulvin; the lability of one of the aryl methoxyl groups in the latter towards alkali must be directly due to activation by the chloro-substituent.

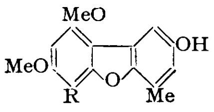


A, Griseofulvin in methanol.
B, Dechlorogriseofulvin in methanol.
2-Carbomethoxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid, (C) in ethanol, and (D) in 0·1N-sodium hydroxide.

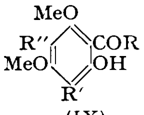
Both dechlorogriseofulvin and (III) were oxidised with alkaline yellow mercuric oxide to 3-hydroxy-5 : 7-dimethoxy-1-methyldibenzofuran (VIII; R = H) which was also obtained by catalytic dehydrogenation of (VII; R = H). Catalytic dechlorination of the methyl ether of the corresponding griseofulvin oxidation product (VIII; R = Cl) (Part II, *J.*, 1952, 3958) gave the methyl ether of (VIII; R = H).

Zinc permanganate oxidation of dechlorogriseofulvin furnished the expected 2-hydroxy-4 : 6-dimethoxybenzoic (IX; R = OH, R′ = R″ = H) and 2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid (X), the latter isolated only as the lactone. A monobasic trimethoxy-acid, $C_{16}H_{18}O_8$, was also isolated, whose ultra-violet absorption (see Figure) showed that the coumaranone ring system was still present and that phenolic and enolic hydroxyl groups were absent (no shift in 0·1N-sodium hydroxide). The infra-red spectrum revealed the presence of a saturated ester group (band at 1740 cm.$^{-1}$); this group was hydrolysed by hot 3N-hydrochloric acid; methanol and carbon dioxide (1·3 moles) were evolved with the formation of a hygroscopic acid which could not be characterised but yielded the lactone of (X) on oxidation with zinc permanganate. These facts are consistent with structure (XI; R = H) for the third oxidation product whose formation from dechlorogriseofulvin is readily accounted for by oxidation at the double bond in ring C.

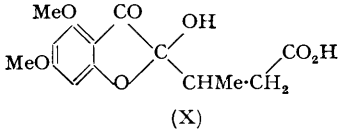
The infra-red spectrum of the acid (XI; R = H) in the solid state is noteworthy, showing only two bands in the double-bond stretching region (at 1740 and 1685 cm.$^{-1}$) and an OH band at 3120 cm.$^{-1}$. The frequency of the latter is much higher than that normally found in solid (dimeric) acids and suggests that (XI; R = H) exists in the solid as a monomer with intra- or inter-molecular bonding between the hydroxyl group and the coumaranone-carbonyl group. On this basis, the band at 1685 cm.$^{-1}$ could be assigned to the coumaranone-carbonyl group and the fairly broad band at 1740 cm.$^{-1}$ could contain the ester- and carboxyl-carbonyl bands. In 0·12M-dioxan solution, (XI; R = H) showed carbonyl absorption bands at 1755, 1735, and 1715 cm.$^{-1}$. The band at 1735 cm.$^{-1}$ corresponds to the frequency found for saturated carboxylic acids in dioxan solution by Flett (*J.*, 1951, 962) and those at 1755 and 1715 cm.$^{-1}$ could be due to ester- and coumaranone-carbonyl respectively. In 0·02M-ethylene dichloride, only two carbonyl bands were distinguished (at 1755 and 1715 cm.$^{-1}$); the former could contain the ester- and carboxyl-carbonyl bands and the latter may be the coumaranone-carbonyl band. If these assignments are correct, the rise in frequency of the coumaranone-carbonyl band, from 1685 cm.$^{-1}$ in the solid to 1715 cm.$^{-1}$ in a non-polar solvent, indicates that it is intermolecular bonding which takes place in the solid between the coumaranone-carbonyl and the hydroxyl group. The spectrum of the liquid methyl ester (XI; R = Me) possessed three carbonyl absorption bands—coumaranone-carbonyl at 1703 cm.$^{-1}$, and a very broad ester-carbonyl band at about 1740 cm.$^{-1}$ just resolvable into two maxima at about 1745 and 1735 cm.$^{-1}$.



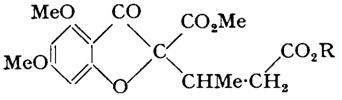
(VIII)



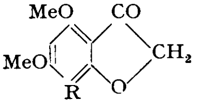
(IX)



(X)



(XI)



(XII)

As expected, the degradation products formed from ring C of griseofulvin were also obtained from dechlorogriseofulvin. Potassium hydroxide fusion and chromic oxide oxidation gave 5-methylresorcinol and 3-methoxy-2 : 5-toluquinone, respectively.

Dechlorogriseofulvin gives an intense blue-violet colour with nitric acid (*d* 1·42) at room temperature, whereas griseofulvin gives a pale yellow colour. This provides a sensitive test for dechlorogriseofulvin and can be used to disclose 1 μg. in a solid mixture. The colour is also produced in acetic acid solution but requires a large ratio of nitric to acetic acid. The violet colour was also given by the isomeric methyl ether (VI) and by the triketone (III) but not by the corresponding griseofulvin derivatives. That the reaction reflects the absence of the chloro-substituent in ring A was shown by the results obtained with a number of derivatives of phloroglucinol dimethyl ether. These results indicate that production of a violet colour with nitric acid may be diagnostic of the system (IX; R′ = R″ = H). For instance, the compounds (IX; R = OH, R′ = Cl, R″ = H; R = OH, R′ = H, R″ = Cl; R = OMe, R′ = Cl, R″ = H; and R = R″ = H, R′ = Me) and (XII; R = Cl) did not respond to the test whereas the corresponding compounds without the chloro- or methyl substituent did. Compounds without the COR grouping (phloroglucinol dimethyl ether, and the 2- and 4-chloro- and 2-methyl-derivatives) gave negative results. With phloroglucinol trimethyl ether derivatives corresponding to (IX; R′ = R″ = H), there was a colour shift to green.

EXPERIMENTAL

Some microanalyses were carried out by Mr. W. Brown of these laboratories.

In chromatography, B.D.H. alumina was rendered alkali-free (Prins and Shoppee, *J.*, 1946, 498) and activated for 3 hr. at 250°/17 mm.

4 : 6-Dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (III) was identified throughout by infra-red spectroscopy and its *X*-ray powder diagram.

Isolation of Dechlorogriseofulvin.—The crude material obtained by chloroform-extraction of the culture filtrates of *P. griseofulvum* and the dechlorogriseofulvin-producing strains of

P. janczewskii was provided by P. J. Curtis, C. H. Unwin, and G. L. F. Norris of these laboratories. The following are typical of many experiments.

(*a*) Crude solid extract (19·0 g.), from the culture filtrate of *P. janczewskii* (No. 571), in benzene (4 l.) was chromatographed on alumina (135 × 3·5 cm.). Development with ether–light petroleum (b. p. 40—60°) (1 : 1) gave a yellow band which was rapidly eluted and discarded. Continued development (3 days) afforded (i) a lower band fluorescing mauve in ultra-violet light, not completely separated from (ii) an upper broad band fluorescing blue. Elution of (i) yielded dechlorogriseofulvin (2·4 g.), m. p. 179—181°, after crystallisation from methanol. Band (ii) was eluted first with ether–light petroleum (b. p. 40—60°) (1 : 1) and then with benzene–ethanol (99 : 1), giving griseofulvin (8·1 g.), m. p. 218—220°, after several crystallisations from ethanol. The overlap between bands (i) and (ii) was fractionally eluted with the ether–light petroleum, giving fractions, m. p. 160—200° and 200—212°. Rechromatography of the former gave griseofulvin (710 mg.) and dechlorogriseofulvin (270 mg.); the latter yielded griseofulvin (1·5 g.), m. p. 212—216° after recrystallisation from ethanol.

Culture No. 250, the strain employed in earlier work in these laboratories on griseofulvin (Brian *et al.*, *loc. cit.*), produced no dechlorogriseofulvin. Cultures no. 571 and 573 afforded 15—30 mg. per l. of dechlorogriseofulvin together with griseofulvin (60—120 mg. per l.). Intermediate were cultures no. 963 and 964 from which only small amounts (3—5 mg. per l.) of dechlorogriseofulvin were obtained in addition to griseofulvin (60—100 mg. per l.).

(*b*) Crude solid extract (10·5 g.) from the culture filtrate of *P. griseofulvum* in benzene (2 l.) was freed from coloured contaminants by filtration through alumina (6 × 2·5 cm.). The broad colourless band fluorescing blue was eluted with benzene; the eluate and filtrate were concentrated stepwise, giving (i) griseofulvin (3·0 g.), m. p. 218—220° after several recrystallisations from ethanol, (ii) 4·15 g., m. p. 180—200°, (iii) 2·0 g., m. p. 169—174°, and (iv) 0·6 g., m. p. 170—180°. The combined fractions (iii) and (iv), after several crystallisations from methanol, afforded dechlorogriseofulvin in needles (1·9 g.), m. p. 179—181°.

Dechlorogriseofulvin crystallised from benzene or methanol in needles, m. p. 179—181°, raised to 180—210° on admixture with griseofulvin, $[\alpha]_D^{19}$ +390° (*c*, 1·0 in $COMe_2$) [Found: C, 64·4, 64·4, 64·2; H, 5·6, 5·4, 5·7; OMe, 27·0, 27·2%; *M* (Rast), 306. $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·7; 3OMe, 29·2%; *M*, 318]. Light absorption in MeOH: Max. ~325, 286, 250 (log ε 3·62, 4·39, 4·18).

Derivatives. The 2 : 4-*dinitrophenylhydrazone* formed red needles, decomp. 264—266° (from nitrobenzene–methanol) (Found: C, 55·5; H, 4·1; N, 11·15. $C_{23}H_{22}O_9N_4$ requires C, 55·4; H, 4·4; N, 11·15%).

With 1 mol., and also with excess, of hydroxylamine, only amorphous nitrogen-containing compounds were obtained.

Treatment with semicarbazide hydrochloride in pyridine for 2 days at room temperature followed by dilution gave the (?) *pyrazoline*, buff needles, decomp. 240—242° (from ethanol) (Found: C, 57·2; H, 5·7; N, 11·2; OMe, 28·2. $C_{18}H_{21}O_6N_3$ requires C, 57·6; H, 5·6; N, 11·2; 3OMe, 25·0%). It was basic and in ethanol gave a wine-red ferric chloride colour discharged on addition of water. The Knorr pyrazoline test was negative. Its mineral acid solutions slowly deposited an unsaturated, nitrogen-containing compound which gave 4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione with warm mineral acid.

The *amine*, obtained as for griseofulvamine (Part I, *loc. cit.*), crystallised from aqueous methanol in needles, m. p. 198—200° (Found: C, 59·7; H, 5·9; N, 4·6; OMe, 21·4. $C_{16}H_{17}O_5N,H_2O$ requires C, 59·8; H, 5·9; N, 4·4; 2OMe, 19·3%). It was basic, gave the same ferric chloride colour reaction as the pyrazoline and was hydrolysed with warm mineral acid to 4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione; it did not react with Brady's reagent. Its *monoacetyl* derivative crystallised from ethanol in needles, m. p. 247—249° (Found: C, 62·4; H, 5·4; N, 3·6. $C_{18}H_{19}O_6N$ requires C, 62·6; H, 5·5; N, 4·0%). The 2 : 4-*dinitrophenylhydrazone* of the acetyl derivative crystallised from nitrobenzene–methanol in red needles, decomp. 287—289° (Found: C, 54·9; H, 4·4; N, 13·5. $C_{24}H_{23}O_9N_5$ requires C, 54·9; H, 4·4; N, 13·3%).

4′-*Hydroxy*-4 : 6 : 6′-*trimethoxy*-2′-*methylgrisan*-3-*one* (I).—Dechlorogriseofulvin (200 mg.) in acetic acid (10 ml.) was hydrogenated in the presence of Adams's catalyst (100 mg.) (2 mols. absorbed in 1·5 hr.). Removal of the catalyst and solvent gave 4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (120 mg.) (Part V, *loc. cit.*), m. p. 222° (corr.), identified by mixed m. p., analysis, and infra-red spectrum.

Hydrolysis of Dechlorogriseofulvin.—(a) *Acid.* The compound (1·3 g.) in methanol (200 ml.) was heated under reflux for 6 hr. with 2N-hydrochloric acid (250 ml.). Removal of the methanol gave 4 : 6-*dimethoxy*-2′-*methylgrisan*-3 : 4′ : 6′-*trione*, prisms (1·1 g.), decomp. 248—250° (from acetic acid), $[\alpha]_D^{21}$ +480° (*c*, 1·0; Na salt in H_2O) [Found: C, 63·2, 63·1; H, 5·3, 5·2; OMe, 20·1, 19·0%; equiv. (potentiometric), 290. $C_{16}H_{16}O_6$ requires C, 63·2; H, 5·3; 2OMe, 20·4%; equiv., 304]. The *dioxime*, prepared by heating the trione (320 mg.) under reflux with hydroxylamine hydrochloride (500 mg.) and 0·116N-sodium hydroxide (6·3 ml.), crystallised from 2-methoxyethanol in needles, decomp. 231—233° (Found: C, 57·25; H, 5·5; N, 8·5. $C_{16}H_{18}O_6N_2$ requires C, 57·5; H, 5·4; N, 8·4%).

(b) *Alkaline.* Dechlorogriseofulvin (1·3 g.) was heated under reflux for 5 hr. in nitrogen with 0·5N-sodium hydroxide. After complete dissolution (1 hr.), a yellow oil separated which solidified on cooling and was collected; it sublimed at 70—80°/10^{-4} mm., giving 1 : 2 : 3 : 4-*tetrahydro*-3-*keto*-5 : 7-*dimethoxy*-1-*methyldibenzofuran*, needles (230 mg.), m. p. 99—100° (from methanol), $[\alpha]_D^{21}$ −25° (*c*, 1·0 in $COMe_2$) (Found: C, 69·2, 68·9; H, 6·2, 6·2; OMe, 21·9. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2; 2OMe, 23·8%). Light absorption in EtOH: Max. 256, 216 mμ (log ε 4·14, 4·47). The *dinitrophenylhydrazone* crystallised in red needles (from nitrobenzene–methanol), decomp. 247—248° (Found: C, 57·1; H, 4·7; N, 12·9. $C_{21}H_{20}O_7N_4$ requires C, 57·3; H, 4·6; N, 12·7%).

The acidic fraction, recovered from the alkaline mother-liquors, was fractionally crystallised from acetic acid but the sole product was the trione (III) (600 mg.), decomp. 240—242°. The most soluble fraction was also identified by analysis [Found: C, 63·0; H, 5·4; OMe, 19·0%; equiv. (potentiometric), 300]. The reaction was less clean in air but gave similar results.

Methylation of 4 : 6-*Dimethoxy*-2′-*methylgrisan*-3 : 4′ : 6′-*trione*.—The acid (880 mg.), suspended in ether (100 ml.) and methanol (20 ml.), was treated overnight with excess of diazomethane, and the recovered gum was chromatographed on alumina (35 × 1·0 cm.) from its benzene solution. The lower broad band, fluorescing light blue in ultra-violet light, was eluted with benzene–ether (4 : 1), giving 4 : 6 : 4′-*trimethoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione* as a gum (270 mg.) which could only be obtained solid by adding its methanolic solution to a large volume of water (Found: C, 63·8; H, 5·9; OMe, 28·6. $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·7; 3OMe, 29·2%). Light absorption in EtOH: Max. $\sim$323, 286, 266 mμ (log ε 3·7, 4·425, 4·424). The upper band, fluorescing blue, was eluted with benzene containing 1% of methanol, and gave dechlorogriseofulvin (305 mg.) which, after crystallisation from methanol, had m. p. and mixed m. p. 177—179°.

Oxidation of Dechlorogriseofulvin.—(a) *Chromic oxide.* The compound (250 mg.) in acetic acid (4 ml.) was treated dropwise with chromic oxide (750 mg.) in acetic acid (4 ml.) and water (1·5 ml.). After the vigorous reaction, induced by gentle warming, had subsided (10 min.), the mixture was heated under reflux for ½ hr. Dilution and extraction with benzene gave 3-methoxy-2 : 5-toluquinone, separated from starting material by sublimation at 95°/10^{-4} mm. and identified by mixed m. p. (147—148°) after crystallisation from methanol.

(b) *Mercuric oxide.* Dechlorogriseofulvin (1·6 g.), suspended in 0·67N-sodium hydroxide, was oxidised with yellow mercuric oxide (2·5 g.) and worked up as described for griseofulvin (Part II), giving 3-*hydroxy*-5 : 7-*dimethoxy*-1-*methyldibenzofuran*, needles (200 mg.), m. p. 169—171° (from benzene) (Found: C, 69·5, 69·7; H, 5·3, 5·2; OMe, 26·0. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4; 2OMe, 24·0%). Light absorption in MeOH: Max. 314, 285, 264, 230 mμ (log ε 4·02, 4·2, 4·24, 42·9); its *picrate* formed red needles, m. p. 155°, from benzene (Found: C, 51·9; H, 3·1; N, 8·65. $C_{15}H_{14}O_4,C_6H_3O_7N_3$ requires C, 51·8; H, 3·5; N, 8·6%). The phenol gave no ferric chloride colour reaction.

The *methyl ether*, obtained with methyl sulphate and alkali, crystallised from methanol in prisms, m. p. 118° (Found: C, 71·0; H, 5·8; OMe, 32·7. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9; 3OMe, 34·2%). Light absorption in MeOH: Max. 311, 285, 264, 230 mμ (log ε 4·13, 4·29, 4·36, 4·66); it gave a *picrate* as red needles, m. p. 148—149°, from methanol (Found: C, 52·7; H, 3·8. $C_{16}H_{16}O_4,C_6H_3O_7N_3$ requires C, 52·7; H, 3·7%).

Oxidation of 4 : 6-dimethoxy-2′-methylgrisan-3 : 4′ : 6′-trione (800 mg.) in the same way gave the dibenzofuran (250 mg.) and 300 mg. of recovered starting material.

(c) *Zinc permanganate.* Dechlorogriseofulvin (2·37 g.) in alcohol-free acetone (850 ml.) was treated slowly (¾ hr.) with 1% aqueous zinc permanganate (500 ml.). After 2 hr. at room temperature with occasional shaking, the manganese dioxide was filtered off, washed with acetone, and extracted with dilute aqueous ammonia. Acidification of the ammoniacal extract, extraction with ether, and recovery gave 2-hydroxy-4 : 6-dimethoxybenzoic acid (95 mg.), m. p. 157—159°, identical (mixed m. p.) with a synthetic specimen.

The aqueous-acetone mother-liquors and washings were concentrated to *ca.* 300 ml. and then extracted with ethyl acetate, and the ethyl acetate extract in turn was extracted with sodium hydrogen carbonate. Recovery of the ethyl acetate layer gave the *lactone* of 2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid as needles (275 mg.), m. p. 170—171° (from methanol or ethyl acetate–light petroleum), $[\alpha]_D^{18}$ $-23\cdot5°$ (*c*, 0·72 in $COMe_2$) (Found : C, 61·0, 60·9; H, 5·3, 5·1; OMe, 21·9. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·1; 2OMe, 22·0%). It slowly dissolved in warm dilute sodium hydroxide and hydrogen carbonate to a yellow solution, acidification of which discharged the colour and gave a mixture of the lactone and the free acid.

The sodium hydrogen carbonate extract, on acidification and recovery, afforded a gum, trituration of which with benzene gave the *acid* (XI; R = H) as plates (220 mg.), m. p. 213—215°, from aqueous methanol (prisms from ethyl acetate) [Found : C, 56·9; H, 5·4; OMe, 27·5%; equiv. (potentiometric), 324. $C_{16}H_{18}O_8$ requires C, 56·8; H, 5·3; 3OMe, 27·5%; equiv., 338]. Light absorption max. : in EtOH, ~323, 288, ~235 mμ (log ε 3·66, 4·3, 3·7), in 0·1N-NaOH, ~325, 288, ~230 mμ (log ε 3·66, 4·3, 3·97). Recovery of the benzene filtrate from the acid (XI; R = H) afforded a gum which was heated for 3 days at 35° with acetic anhydride (1 ml.) in pyridine (0·5 ml.). Dilution gave a solid which was separated by sodium hydrogen carbonate extraction into the above lactone (375 mg.) and the acid (XI; R = H) (88 mg.).

The *methyl* ester (XI; R = Me), obtained with diazomethane, distilled at 120° (bath-temp.)/10^{-4} mm. (Found : C, 58·1; H, 6·0; OMe, 33·2. $C_{17}H_{20}O_8$ requires C, 58·0; H, 5·7; 4OMe, 35·2%).

Conversion of 2-*Carbomethoxy*-4 : 6-*dimethoxycoumaran*-3-*one*-2-β-*butyric Acid* (XI; R = H) *into the Lactone of* 2-*Hydroxy*-4 : 6-*dimethoxycoumaran*-3-*one*-2-β-*butyric Acid.*—The acid (XI; R = H) (100 mg.), heated under reflux in nitrogen with 3N-hydrochloric acid (baryta trap), dissolved in 1 hr. with liberation of 1·3 mols. of carbon dioxide and methanol (chromotropic acid test). Extraction of the cooled solution with ether and recovery gave a gummy hygroscopic acid (53 mg.) which was treated at 0° in N-sodium carbonate (5 ml.) with 1% zinc permanganate (9 ml., 4·5 atoms of O). Decolorisation with sulphur dioxide, addition of 3N-hydrochloric acid, and extraction with ether gave a gum. Treatment of the latter in pyridine with acetic anhydride for 3 days at 35°, dilution, and extraction with ethyl acetate afforded the lactone of 2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid, m. p. 166—168°, identified by mixed m. p. and infra-red spectrum.

Dehydrogenation of 1 : 2 : 3 : 4-*Tetrahydro*-3-*keto*-5 : 7-*dimethoxy*-1-*methyldibenzofuran.*—The compound (100 mg.) in 2-methylnaphthalene (5 ml.) was heated under reflux in nitrogen for 6 hr. with 5% palladium–charcoal (100 mg.). After addition of ether, filtration, and removal of ether, water (10 ml.) and 3N-sodium hydroxide (1 ml.) were added and the 2-methylnaphthalene removed by steam-distillation. Acidification of the filtered alkaline solution gave 3-hydroxy-5 : 7-dimethoxy-1-methyldibenzofuran (43 mg.), m. p. and mixed m. p. 170—171° (picrate, m. p. and mixed m. p. 156—157°).

Dechlorination of 8-*Chloro*-3 : 5 : 7-*trimethoxy*-1-*methyldibenzofuran.*—The compound (45 mg.) (Part II) in ethanol containing 10% ethanolic potassium hydroxide (2·5 ml.) was shaken in hydrogen for 6 hr. with 2% palladised strontium carbonate (300 mg.). The filtered solution was diluted with water and neutralised, and the ethanol removed at 40° *in vacuo*. Ether-extraction and recovery gave 3 : 5 : 7-trimethoxy-1-methyldibenzofuran (36 mg.), m. p. and mixed m. p. 118—119° (picrate, m. p. and mixed m. p. 148—149°).

Fusion of Dechlorogriseofulvin with Potassium Hydroxide.—Carried out as described for griseofulvin (Oxford *et al.*, *loc. cit.*), this gave 5-methylresorcinol (0·7 mol.).

The author is indebted to Mr. J. F. Grove and Dr. L. A. Duncanson for determining and discussing the infra-red spectra; to Dr. A. F. Wells, Imperial Chemical Industries Limited, Dyestuffs Division, for *X*-ray powder comparisons; to Mr. D. Gardner and Miss D. Ismay for technical assistance; and to many colleagues for suggestions and criticisms.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, BUTTERWICK RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS.
[*Received, January 10th*, 1953.]