763. *Griseofulvin. Part V.* Catalytic Reduction.*

By T. P. C. MULHOLLAND.

Hydrogenation of griseofulvin may take three routes, *viz.*: (*a*) reduction of the double bond only, to give a product which on further hydrogenation undergoes reduction of the reactive keto-group and hydrogenolysis of the chlorine; (*b*) reduction to an alcohol and saturation of the ethylenic linking; or (*c*) reduction of the keto-group to an alcohol group which is hydrogenolysed to methylene, followed by reduction of the ethylenic linking. Hydrogenation of *iso*griseofulvin follows mainly route (*b*).

THE present paper describes the reduction of griseofulvin (I) and *iso*griseofulvin (VI). The chemistry of the products is described in Part VI (following paper).

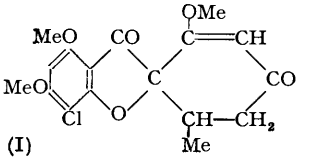
Griseofulvin.—In the first two experiments with palladised charcoal, reduction was slow, as described by Oxford, Raistrick, and Simonart (*Biochem. J.*, 1939, **33**, 240), giving dihydrogriseofulvin $C_{17}H_{19}O_6Cl$ (40%), and tetrahydrodeoxygriseofulvin $C_{17}H_{21}O_5Cl$ (26%), together with small amounts of two new products, $C_{17}H_{21}O_6Cl$ and $C_{17}H_{22}O_6$. In subsequent experiments, *ca.* 1·5 mols. of hydrogen were rapidly absorbed after which reduction became very slow. Interruption at the end of the rapid phase gave dihydrogriseofulvin (57%) as before. Only a small amount (3%) of tetrahydrodeoxygriseofulvin was formed and, instead, a third new compound $C_{17}H_{19}O_5Cl$ was obtained (26%). The reason for this is obscure. The change from slow to rapid initial reduction coincided with the use of fresh batches of materials in the catalyst.

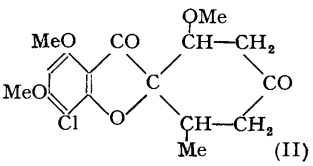
Reduction with a platinic oxide catalyst gave mainly the compound $C_{17}H_{21}O_6Cl$ and a small amount of tetrahydrodeoxygriseofulvin.

On further reduction with the palladised charcoal catalyst used for the second series of experiments, dihydrogriseofulvin gave only the chlorine-free compound, $C_{17}H_{22}O_6$.

* Part IV, preceding paper.

Only the starting material was isolated when the compound $C_{17}H_{21}O_6Cl$ was reduced, although the colour reaction with nitric acid suggested that some dechlorination may have occurred. The compound $C_{17}H_{19}O_5Cl$ gave tetrahydrodeoxygriseofulvin on reduction. Microhydrogenation of the latter with a platinic oxide catalyst did not reveal further ethylenic unsaturation.


(I)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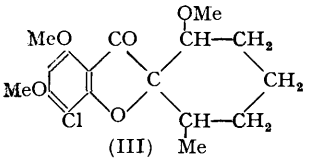
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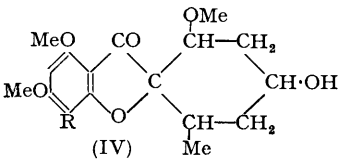
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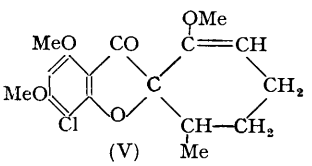

(V)

The ultra-violet absorption spectra showed that the main absorption bands, at 291 and 324 mμ, of griseofulvin were not affected by reduction, the carbonyl group conjugated with the aromatic ring remaining intact in the reduction products (Fig. 1). The presence of this carbonyl group in all the reduction products was confirmed by the infra-red spectra (Fig. 2); a band absorbing at *ca.* 1690—1700 cm.$^{-1}$ persisted in all the compounds except the compound $C_{17}H_{22}O_6$ in which the frequency was lowered to 1670 cm.$^{-1}$. In addition, the infra-red spectra showed that the compounds $C_{17}H_{22}O_6$ and $C_{17}H_{21}O_5Cl$ contained hydroxyl groups.

Oxidation of the latter substance gave dihydrogriseofulvin.

Clearly in dihydrogriseofulvin $C_{17}H_{19}O_6Cl$, tetrahydrodeoxygriseofulvin $C_{17}H_{21}O_5Cl$, and the compounds $C_{17}H_{21}O_6Cl$ and $C_{17}H_{22}O_6$, the ethylenic bond has been saturated. In addition, one of the carbonyl groups has been reduced to CH·OH in the last two compounds and to methylene in tetrahydrodeoxygriseofulvin. These compounds must therefore be represented by the structures tabulated below and derived from (I).

Formula	Name employed by Oxford *et al.* (*loc. cit.*)	New name	Structure
$C_{17}H_{19}O_6Cl$	Dihydrogriseofulvin	7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione	(II)
$C_{17}H_{21}O_5Cl$	Tetrahydrodeoxygriseofulvin	7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one	(III)
$C_{17}H_{21}O_6Cl$	—	7-Chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one	(IV; R = Cl)
$C_{17}H_{22}O_6$	—	4′-Hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one	(IV; R = H)

The presence of an αβ-unsaturated ketone system explains the formation of 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (III) and the failure to obtain this compound from the reduction of 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (II), the ketone in the latter case being reduced to the chlorine-free alcohol (IV; R = H) but without subsequent hydrogenolysis. Similarly, 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = Cl) does not undergo hydrogenolysis on further reduction.

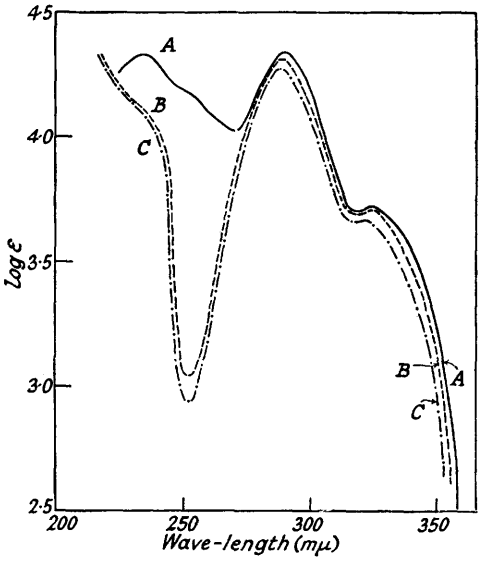
The formation of the compound $C_{17}H_{19}O_5Cl$ is of considerable interest because the analysis and properties indicate that, while the carbonyl group has undergone complete reduction to methylene, the ethylenic bond remains intact and is responsible for weak absorption in the infra-red at 1667 cm.$^{-1}$ (Fig. 2*e*). This compound is therefore 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one (V). As expected, it gives the fully saturated compound (III) on further reduction and is clearly the only precursor of the latter. Comparison of the yields in the first and the second series of experiments with palladium catalysts show that (V) is not formed at the expense of (II) and thus the course of the

reaction is the same in both series, but in the second the formation of (II) and (V) is much increased, while saturation of the latter remains a comparatively slow reaction.

The isolation of 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one appears not to have close analogies in the literature; although there are records of preferential reduction of the carbonyl group in unsaturated aldehydes, subsequent hydrogenolysis does not take place without simultaneous saturation of the ethylenic bond.

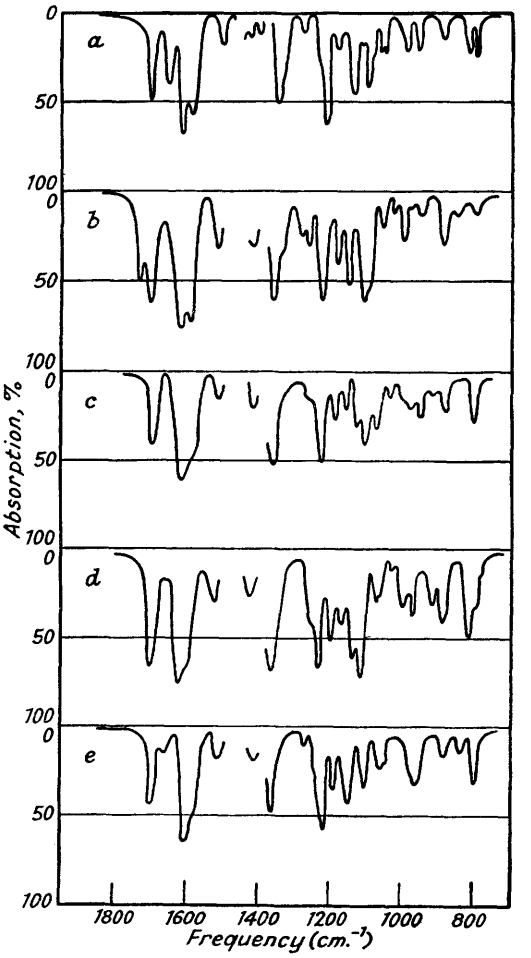
Griseofulvin (I) may thus be considered to undergo reduction in three ways: (i) Reduction of the double bond to give 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione

FIG. 1.



A, Griseofulvin.
B, Dihydrogriseofulvin.
C, Tetrahydrodeoxygriseofulvin.

FIG. 2.

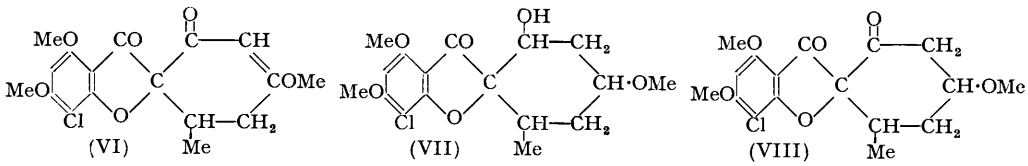


a, Griseofulvin (I); *b, dihydrogriseofulvin* (II); *c, 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one* (IV; R = Cl); *d, tetrahydrodeoxygriseofulvin* (III); *e, 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one* (V).

(II) which undergoes further reduction to 4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = H) and presumably 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = Cl). (ii) Reduction of the carbonyl to an alcohol group with saturation of the double bond, giving 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = Cl). (iii) Reduction of the carbonyl group followed by hydrogenolysis, giving 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one (V) and then by saturation of the double bond to give 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (III).

Thus all the theoretically possible products from reduction of the αβ-unsaturated ketone system in the hydroaromatic ring have been isolated, with the exception of the unsaturated alcohol; and there are indications that an unsaturated alcohol may be present

in the reduction products of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione (VI) (see Part VI).



7-Chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione (iso*Griseofulvin*) (VI).—In the presence of a palladium–charcoal catalyst, as with griseofulvin, there was a rapid absorption of two mols. of hydrogen, followed by slow uptake of a third mol. When hydrogenation was allowed to go to completion, no pure product could be obtained and analysis showed that extensive dechlorination had taken place.

When the reduction was stopped at the end of the rapid phase, the main product was 7-chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one (VII). There were also obtained, in small amounts, 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione, m. p. 275° (decomp.), and a ketonic gum from which both 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione and 7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione, m. p. 177°, were obtained by acid hydrolysis. The evidence for the structure allotted to these compounds is discussed in Part VI. They are regarded as having been derived from acid-unstable reduction products which partly decomposed under the influence of the acid present during reduction and chromatography of the products.

Reduction of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione with Raney nickel gave a complex mixture from which only a small amount of 7-chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one and unchanged starting material were isolated.

Oxidation of 7-chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one (VII) gave the corresponding ketone, 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione $C_{17}H_{19}O_6Cl$ (VIII), which could not be obtained by direct catalytic reduction of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione. The ketone (VIII) resembles the isomeric ketone (II) in properties, but, although the infra-red spectrum shows the presence of two carbonyl groups, the compound does not form a dinitrophenylhydrazone. In this respect the ketone (VIII) resembles (VI) from which it is derived, while the reactivity of the ketone (II) is paralleled by that of griseofulvin (Part I). The existence of chemically distinct isomeric reduction products provides further evidence that the isomerism present in griseofulvin and the isomeric compound is positional and due to the 1 : 3-diketone enol ether structure (see Part I).

Experimental

M. p.s are corrected. The absorption spectra are given in Figs. 1 and 2 and the Tables below. Infra-red absorption spectra were obtained as described in Part I. Microanalyses are by Drs. Strauss and Weiler, Oxford (who determined some of the ultra-violet absorption spectra), Mr. W. Brown, Imperial Chemical Industries Limited, Butterwick Research Laboratories, and the Analytical Department, Imperial Chemical Industries Limited, Dyestuffs Division.

Reductions were carried out at room temperature and pressure.

In chromatography, except where stated, B.D.H. or Peter Spence's alumina (type H) was washed with 2N-nitric acid and with water, refluxed with methanol, and activated *in vacuo* for 3 hours at 250°, giving material of pH 4 and activity grade II (Brockmann and Schodder, *Ber.*, 1941, **74**, 73). Elution of the fluorescent bands was followed by intermittent inspection in ultra-violet light. The bands were colourless in daylight.

Griseofulvin. Reduction in Presence of Palladium.—(*a*) *Slow reduction.* Griseofulvin (4·0 g.) in ethyl acetate (400 ml.) was hydrogenated with a catalyst prepared from palladium chloride (2·5 g.), charcoal (8 g.), and water (150 ml.) as described by Oxford *et al.* (*loc. cit.*). Reduction was stopped after 13 hours (1·4 mols. of hydrogen absorbed). The crude product (3·5 g.) in carbon tetrachloride (150 ml.) was chromatographed on alumina (21·5 × 2·5 cm.) and the following bands collected. (i) Violet fluorescing band. Elution with ether–light petroleum (1 : 1) gave 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (III) (1·0 g., 26%), colourless

needles (from ethanol), m. p. 181°, $[\alpha]_D^{22}$ −34° (*c.* 1·0 in acetone) (Found: C, 59·9; H, 6·1; Cl, 10·4; OMe, 26·6. Calc. for $C_{17}H_{21}O_5Cl$: C, 59·9; H, 6·1; Cl, 10·4; 3OMe, 27·3%). It was saturated to neutral permanganate, and microhydrogenation in acetic acid with Adams's catalyst did not reveal further ethylenic unsaturation.

Ultra-violet absorption spectra (in methanol).

Compound	$\lambda_{max.}$	log ε
7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (III)	322	3·68
	287	4·28
	~234	4·10
7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (II)	323	3·70
	288	4·31
	~234	4·10
4′-Hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = H)	~314	3·69
	282	4·31
7-Chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one (V)	325	3·71
	288	4·32
	236	4·16
7-Chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = Cl)	323	3·67
	287	4·29
	~230	4·11
7-Chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one (VII)	322	3·70
	289	4·33
	~240	4·07
7-Chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione (VIII)	323	3·73
	289	4·20
	~242	3·99

Infra-red absorption spectra.

Compound	Frequency assignments (cm.$^{-1}$) CO	OH
7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (III)	1700	—
7-Chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (II)	1725, 1700	—
4′-Hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = H)	1670	3448
7-Chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one (V)	1702	—
7-Chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (IV; R = Cl)	1695	3425
7-Chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one (VII)	1690	3450
7-Chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione (VIII)	1730, 1693	—

Of the above, only (V) had ethylenic C=C absorption [at 1667 (weak)].

(ii) Violet fluorescing band. Elution with ether + 1% of methanol gave 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (II) (1·6 g., 40%), colourless needles (from ethanol), m. p. 198°, $[\alpha]_D^{22}$ −20° (*c.* 1·0 in acetone). Some specimens from subsequent experiments (see below) had m. p. 206—208° (Found: C, 57·4; H, 5·3; Cl, 9·55; OMe, 25·3. Calc. for $C_{17}H_{19}O_6Cl$: C, 57·5; H, 5·4; Cl, 10·0; 2OMe, 26·2%). The *oxime* crystallised from dilute ethanol in plates, m. p. 255—256° (decomp.) (Found: C, 55·2; H, 5·5; N, 3·8. $C_{17}H_{20}O_6NCl$ requires C, 55·2; H, 5·45; N, 3·8%). As reported by Oxford *et al.* (*loc. cit.*), the dione (II) gave a precipitate with Brady's reagent but no satisfactory analyses could be obtained for this derivative.

(iii) Streaky green band. Elution with ether + 3% of methanol gave a solid crystallising from ethanol in colourless needles (0·07 g.), m. p. 180—190°. The product contained solvent of crystallisation, lost on heating. It was rechromatographed and the middle fraction (58 mg.) crystallised from benzene in prisms, m. p. 185—188°, identical (mixed m. p. and infra-red spectrum) with 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (see below).

(iv) Narrow purple fluorescing band. Elution with ether + 3% of methanol gave 4′-*hydroxy*-4 : 6 : 6′-*trimethoxy*-2′-*methylgrisan*-3-*one* (IV; R = H), colourless needles (from ethanol), m. p. 222—223°, $[\alpha]_D^{22}$ −10° (*c*, 0·5 in acetone) (Found: C, 62·9; H, 6·7; Cl, nil; OMe, 28·0. $C_{17}H_{22}O_6$ requires C, 63·3; H, 6·9; 3OMe, 28·8%). It did not react with neutral permanganate or Brady's reagent and, unlike the chlorine-containing derivatives of griseofulvin, gave an intense violet colour with concentrated nitric acid.

(*b*) *Rapid reduction.* Griseofulvin (2·0 g.) in ethyl acetate (200 ml.) was reduced as before with a catalyst prepared from a fresh batch of palladium chloride (1·0 g.), water (90 ml.), and charcoal (4·0 g.). Hydrogen was absorbed rapidly during 10 minutes (*ca.* 1·6 mols. of hydrogen) and then more slowly. After 15 minutes (1·7 mols. of hydrogen) the reaction was stopped. The crude product, in benzene (70 ml.), was chromatographed on alumina (21·5 × 2·5 cm.). The first two violet bands were eluted as in the previous experiment. Recovery gave colourless solids. The first (0·75 g.), on fractional crystallisation from ethanol and benzene–light petroleum, gave 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one, m. p. 180° (0·06 g., 3%) and the less soluble 7-*chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3-*one* (V) (0·5 g., 26%) which crystallised from ethanol or from benzene-light petroleum in long slender colourless needles, m. p. 194—195°,

$[\alpha]_D^{20}$ +155° (*c*, 1·0 in acetone) [Found: C, 60·2, 60·4; H, 5·65, 5·7; Cl, 10·4, 10·7; OMe, 26·2; *M* (Rast), 305. $C_{17}H_{19}O_5Cl$ requires C, 60·3; H, 5·65; Cl, 10·5; 3OMe, 27·5%; *M*, 358]. This compound did not react with Brady's reagent. Although it did not react with bromine in chloroform in the cold, and was attacked very slowly by neutral permanganate, the presence of unsaturation was shown by catalytic reduction to 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (see below).

The second solid was 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione (1·15 g., 57%). Rechromatography, followed by crystallisation from ethanol, gave colourless needles, m. p. 202—203° (0·9 g.).

A similar result was obtained in all subsequent experiments, the ratio of 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione to 7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one approximating to 5 : 2. The purest specimens of the former, m. p. 206—208°, were obtained when the chromatographic separation was carried out as rapidly as possible and with the minimum of exposure to ultra-violet light.

Griseofulvin. Reduction in Presence of Platinum Oxide.—(a) *Partial reduction.* Hydrogenation of griseofulvin (3·34 g.) in glacial acetic acid (300 ml.) in the presence of Adams's catalyst (500 mg.) was stopped after hydrogen (1·3 mols.) had been absorbed in 18 minutes. The crude solid (3·55 g.) obtained on removal of the catalyst and solvent was chromatographed in benzene on alumina (19·6 × 2·5 cm.) and the following bands collected. (i) Violet fluorescing band eluted with benzene. Recovery gave a solid (315 mg.), which, after crystallising from benzene–light petroleum, had m. p. 174—175°, not depressed by mixture with 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one.

(ii–iv) A blue band followed by an interband and a violet band were eluted with benzene followed by ether + 1% of methanol and gave intractable products (798 mg.).

(v) Violet band. Elution with ether + 2% of methanol gave unchanged griseofulvin (1·33 g.), m. p. and mixed m. p. 217—219°.

(vi) The remaining band was cut from the extruded column and extracted with methanol. Recovery gave *7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one* (IV; R = Cl)) (174 mg.) which crystallised from benzene in prisms, m. p. 197—198°, containing solvent of crystallisation, lost on heating, $[\alpha]_D^{22}$ −17° (*c*, 1·0 in acetone) (Found: C, 57·5; H, 5·9; Cl, 9·6; OMe, 24·1. $C_{17}H_{21}O_6Cl$ requires C, 57·2; H, 5·9; Cl, 9·9; 3 OMe, 26·1%). This compound was identical (mixed m. p. and infra-red spectrum) with impure material obtained by reduction with palladium. It did not react with Brady's reagent, Fearon and Mitchell's reagent, or ferric chloride, or give an alkali xanthate. It was saturated to neutral permanganate.

The *monoacetyl* derivative (acetic anhydride in pyridine at 34° for 4 days) crystallised from ethanol in colourless crystals, m. p. 208—209° (Found: C, 56·6; H, 5·75. $C_{19}H_{23}O_7Cl$ requires C. 57·2; H, 5·8%).

(b) *Complete reduction.* Hydrogenation of griseofulvin (1·43 g.) in acetic acid (100 ml.) with the catalyst recovered from (*a*) was allowed to go to completion (3 mols. in 1 hour). The product (1·55 g.) in benzene (25 ml.) was chromatographed on alumina (pH 8) (14 × 2·0 cm.). Development with benzene gave a blue fluorescing band of general absorption and an upper fluorescing band. The lower band was eluted with benzene, giving a solid (674 mg.) which on repeated crystallisation from benzene and aqueous methanol gave a little 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one. The same substance (222 mg.) was obtained by elution of the upper band with benzene + 1% of methanol. The solid (630 mg.), recovered from the crystallisation mother-liquors, was rechromatographed in the same way on alumina (15·5 × 2·0 cm.) and eluted with benzene. The lower band (violet fluorescence) gave 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (204 mg.), identified by analysis and infra-red spectrum. The upper violet fluorescing band gave the alcohol (IV; R = Cl) (113 mg.), m. p. 194—196°. A colourless interband gave intractable material (250 mg.).

7-Chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one.—(i) *Oxidation.* The compound (120 mg.) in acetic acid (2·5 ml.) was treated in portions with chromic oxide (234 mg.) in acetic acid (0·9 ml.) and water (0·4 ml.). After each addition the mixture was warmed until the chromic oxide was consumed and when addition was complete the mixture was heated under reflux (1 minute), cooled, diluted with water (25 ml.), and extracted with benzene. The extract, after being washed with water and evaporated, gave a gum which solidified on trituration with ether. After being washed with ether, the solid (5 mg.) crystallised from benzene–light petroleum in microcrystalline clumps, m. p. 203—205°, identified as 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3 : 4′-dione by mixed m. p. and infra-red spectrum.

(ii) *Reduction.* The compound (343 mg.) in ethyl acetate (30 ml.) was hydrogenated with a

catalyst prepared from palladium chloride (0·2 g.), water (12 ml.), and charcoal (0·75 g.). Hydrogen (*ca.* 0·9 mol.) was absorbed in 2 days. Chromatography of the product yielded only intractable fractions in addition to unchanged starting material (0·22 g.), m. p. and mixed m. p., 190—193°, after crystallisation from benzene. Material from the mother-liquor gave a blue colour with concentrated nitric acid indicating that some dechlorination had occurred (see Part VII).

Reductive Dechlorination of 7-*Chloro*-4 : 6 : 6′-*trimethoxy*-2′-*methylgrisan*-3 : 4′-*dione*.—The compound (0·5 g.) in ethyl acetate (40 ml.) was hydrogenated in the presence of a catalyst prepared from palladium chloride (0·5 g.), water (35 ml.), and charcoal (1·8 g.). Absorption proceeded slowly and was not accelerated by addition after 1 hour of 3N-hydrochloric acid (1 ml.). After 19 hours (1·5 mols. absorbed), the crude product was obtained in the usual way and chromatographed in benzene (10 ml.) on alumina (15·5 × 2·0 cm.); giving (*a*) an ill-defined violet fluorescing band which gave a few mg. of a colourless solid, m.p . 142—144°, (*b*) a broad violet fluorescing band, from which ether + 2% of methanol gave starting material (90 mg.), m. p. and mixed m. p. after crystallisation, 198°, (*c*) an interband with little fluorescence giving a solid (85 mg.), which after crystallisation from benzene–light petroleum had m. p. 205—210°, not depressed on admixture with fraction (*d*), and (*d*) a dull violet band, from which ether + 10% of methanol gave 4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one (100 mg.), colourless plates (from benzene), m. p. 220—222° (Found: C, 63·3; H, 6·8; Cl, nil. Calc. for $C_{17}H_{22}O_6$: C, 63·3; H, 6·9%).

Reduction of 7-*Chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3-*one*.—The compound (358 mg.) in ethyl acetate (30 ml.) was hydrogenated in the presence of a catalyst prepared from palladium chloride (0·2 g.), water (12 ml.), and charcoal (0·75). After 3 hours (1·0 mol. absorbed) the crude product was isolated and crystallised from ethanol, giving a solid A (0·12 g.) from which unchanged starting material, m. p. and mixed m. p. 192—193°, was recovered by repeated crystallisation from benzene–light petroleum. Evaporation of the ethanolic mother-liquor from (A) gave a solid (0·13 g.) which, after crystallisation from benzene–light petroleum and from ethanol, was obtained with m. p. 181° and identified as 7-chloro-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one by mixed m. p., infra-red spectrum, and analysis.

Reduction of 7-*Chloro*-4 : 6 : 4′-*trimethoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione* (VI).—A solution of the compound (2·0 g.) in ethyl acetate (200 ml.) was reduced in the presence of a catalyst prepared from palladium chloride (1·0 g.), water (120 ml.), and charcoal (4·0 g.). Reduction was stopped after 20 minutes (2·0 mols. absorbed), when the rate of the reduction had become very slow. The crude product in benzene (100 ml.) was chromatographed on alumina (21 × 3·0 cm.). Elution with ether + 1% of methanol gave a violet band with a bright lower fringe. Elution of the violet fringe gave a colourless solid, m. p. 240—°260 (14 mg.), which was not ketonic to Brady's reagent. This fraction was rechromatographed and from the middle fraction 3 mg. of colourless material were obtained, having m. p. 268—270° (decomp.) and identified by mixed m. p. and infra-red spectrum as 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione, m. p. 275—277° (decomp.), obtained by a different method (Part VI). A violet band gave a gum (*ca.* 0·4 g.) separated by trituration with ether into two intractable fractions (A, 60 mg., m. p. 50—60°; and B, a gum; each of these fractions was submitted to acid hydrolysis as described below). A large band, eluted with ether + 5% of methanol, gave a gum (1·0 g.) which was washed with ether and crystallised from ethanol as colourless needles, m. p. 228—230°, $[\alpha]_D^{19}$ −29° (*c.* 0·85 in acetone) of 7-*chloro*-6′-*hydroxy*-4 : 6 : 4′-*trimethoxy*-2′-*methylgrisan*-3-*one* (VII) (Found: C. 57·5; H, 6·0; Cl, 10·3; OMe, 26·2. $C_{17}H_{21}O_6Cl$ requires C, 57·2; H, 5·9; Cl, 9·9; 3OMe, 26·1%). The properties closely resembled those of 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one.

Hydrolysis of fractions A and B. *A*. The solid (0·12 g.) in acetic acid (2·0 ml.) and water (0·4 ml.) was heated under reflux for 2 hours. The gum obtained by evaporation to dryness was chromatographed on alumina (6 × 1·0 cm.) from its benzene solution (3 ml.). The following fractions were eluted with ether + 1% of methanol: (*a*) narrow band with violet fluorescence giving a trace of solid, m. p. 220—230°; (*b*) a band with faint fluorescence yielding a solid (6 mg.) which crystallised from ethanol in colourless needles, m. p. 262—266° (decomp.), not depressed on admixture with 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-en-3 : 2′-dione, m. p. 274° (decomp.) (see Part VI); and (*c*) a diffuse violet fluorescing band which gave a trace of gum.

B. The gum, in acetic acid (5 ml.) and concentrated hydrochloric acid (0·5 ml.), was heated under reflux (5 minutes) and diluted with water. The precipitated gummy solid was chromatographed in benzene on alumina (12·5 × 1·0 cm.), and the following fractions collected: (a) a violet fluorescing band which, when eluted with ether, gave a solid (9 mg.), m. p. 170—172°;

(*b*) a band, eluted with ether, giving a solid (10 mg.), m. p. 170—174°; and (*c*) a violet fluorescing band eluted with ether + 1% of methanol, giving a solid (2 mg.), m. p. 263—270° after softening from 220°. It was non-ketonic to Brady's reagent and probably was impure 7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-ene-3 : 2′-dione. The combined solids from (*a*) and (*b*) crystallised from benzene–light petroleum in colourless microcrystalline clumps, m. p. 173—174°, identical (mixed m. p. and infra-red spectrum) with 7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione, described in Part VI.

When hydrogenation of 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione was conducted as in the previous experiment for 2 days, *ca.* 3 mols. of hydrogen were absorbed but the product, m. p. 181—182°, obtained by chromatography and subsequent crystallisation gave a blue colour with concentrated nitric acid indicating that dechlorination had occurred (see above). Analysis confirmed the loss of chlorine (Found: Cl, 3·7. Calc. for $C_{17}H_{21}O_5Cl$: Cl, 9·9%).

Reduction of this compound in ethanol with Raney nickel resulted in the uptake of *ca.* 3 mols. of hydrogen in 2 hours. Chromatography showed the product to be very complex, and the only compounds identified were a little unchanged starting material and 7-chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one. Addition of chloroform (2%) inhibited reduction.

Oxidation of 7-Chloro-6′-hydroxy-4 : 6 : 4′-trimethoxy-2′-methylgrisan-3-one.—The compound (400 mg.), dissolved in warm acetic acid (8 ml.), was oxidised by dropwise addition of chromic acid (760 mg.) in acetic acid (3 ml.) and water (1·2 ml.). The procedure previously described for the oxidation of 7-chloro-4′-hydroxy-4 : 6 : 6′-trimethoxy-2′-methylgrisan-3-one was followed, giving a gum. When scratched with ether (3 ml.), *7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgrisan-3 : 2′-dione* (VIII) (89 mg.) crystallised. After being washed with ether, it crystallised from ethanol in colourless plates, m. p. 177—178° (Found: C, 57·4; H, 5·6; Cl, 10·4; OMe, 25·9. $C_{17}H_{19}O_6Cl$ requires C, 57·5; H, 5·4; Cl, 10·0; 3OMe, 26·2%). The compound did not react with Brady's reagent and was not attacked by neutral permanganate. It was insoluble in cold 3N-sodium hydroxide but decomposed when warmed, giving a yellow solution.

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