

764. *Griseofulvin. Part VI.* Chemistry of the Reduction Products.*

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The chemistry of the reduction products of griseofulvin and the isomeric 7-chloro-4 : 6 : 4'-trimethoxy-6'-methylgris-3'-en-3 : 2'-dione (*isogriseofulvin*) is described. The reactions are consistent with the formulæ proposed for these compounds in Part V and provide conclusive proof for the orientation of the two isomers. The compound $C_{16}H_{19}O_5Cl$ (product B) obtained by catalytic reduction of 7-chloro-4 : 6-dimethoxy-2'-methylgrisan-3 : 4' : 6'-trione (griseofulvic acid) (Part I, *J.*, 1952, 3949) is shown to be 7-chloro-6'-hydroxy-4 : 6-dimethoxy-2'-methylgrisan-3-one (XVIII).

IN the preceding paper it was shown that catalytic reduction of griseofulvin (I) gave five products, *viz.*: (II), (III; $R' = Cl$), (III; $R' = H$), (IV), and (V). On the other hand, reduction of *isogriseofulvin* (VI) gave mainly (VII), isomeric with (III; $R' = Cl$). The corresponding ketone (VIII), isomeric with (IV), was prepared by oxidation of (VII). In the present paper, an account is given of the chemistry of these products. The relations between the more important compounds discussed are outlined in the annexed scheme.

The stability of (V) to acid and alkaline hydrolysis (Oxford *et al.*, *loc. cit.*) was confirmed. The reduction product (III; $R' = Cl$) showed a similar stability. The compounds (III; $R' = H$) and (VII) were not attacked by aqueous 3N-sodium hydroxide. These results,

* Part V, preceding paper.

although incompatible with the ester structure proposed for griseofulvin by Oxford *et al.* (*loc. cit.*), are consistent with the structures (I) and (VI) proposed in Part IV (*J.*, 1952, 3977) for griseofulvin and the isomeric *isogriseofulvin* respectively since these show the reduction products as saturated ethers.

Now, if griseofulvin and *isogriseofulvin* are respectively (I) and (VI), and not *vice versa*, the corresponding dihydro-derivatives are (IV) and (VIII). Then (IV), as a saturated ether, should resist alkaline hydrolysis, like the corresponding alcohol (III; R' = Cl). On the other hand, (VIII), as a 1 : 3-diketone, should be susceptible to alkaline hydrolysis. It should thus be possible to test the structural assignments.

As expected, the dihydro-derivative of (VI) was unstable to alkali, but the small amount of material available prevented the characterisation of the products. However, the dihydro-derivative of (I) was also unstable to alkali, and hydrolysis in an inert atmosphere gave 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (IX), an intractable neutral fraction, and a phenolic fraction. Examination of the infra-red spectrum of the phenolic fraction by Mr. T. A. Kletz, Imperial Chemical Industries Limited, Billingham Division, disclosed that it consisted of *m*-cresol containing about 10% of 2 : 5-dihydroxytoluene. A study of the behaviour of (IV) towards acid hydrolysis provided an explanation of this unexpected cleavage.

In dilute ethanolic sulphuric acid, (IV) lost the elements of methanol, affording a neutral unsaturated dimethoxy-compound, C₁₆H₁₅O₅Cl (X), which contained a chemically reactive carbonyl group. Infra-red analysis showed the presence of two carbonyl groups. As in griseofulvin and the reduction products, the coumaranone-carbonyl group was still present, absorbing at 1697 cm.⁻¹ The second carbonyl group absorbed at 1670 cm.⁻¹, compared with 1725 cm.⁻¹ in (IV) and 1650 cm.⁻¹ in griseofulvin. The lowered frequency in the ketone (X) and in griseofulvin is consistent with the presence of an αβ-unsaturated carbonyl group in both compounds. The ketone (X) is thus the vinylogue of a 1 : 3-diketone and as expected is broken down by alkali to the acid (IX), an unresolved neutral fraction, and a phenolic fraction similar to the phenolic fraction obtained by alkaline hydrolysis of (IV). The formation of the same products from (IV) and (X) suggests that the latter is an intermediate in this reaction. Easy degradation of (IV) to the acid (IX) and *m*-cresol by alkali is therefore to be expected. The formation of 2 : 5-dihydroxytoluene is probably due to the presence of enough oxygen to cause part of the intermediate (XI) to undergo oxidative degradation instead of dehydration to *m*-cresol.

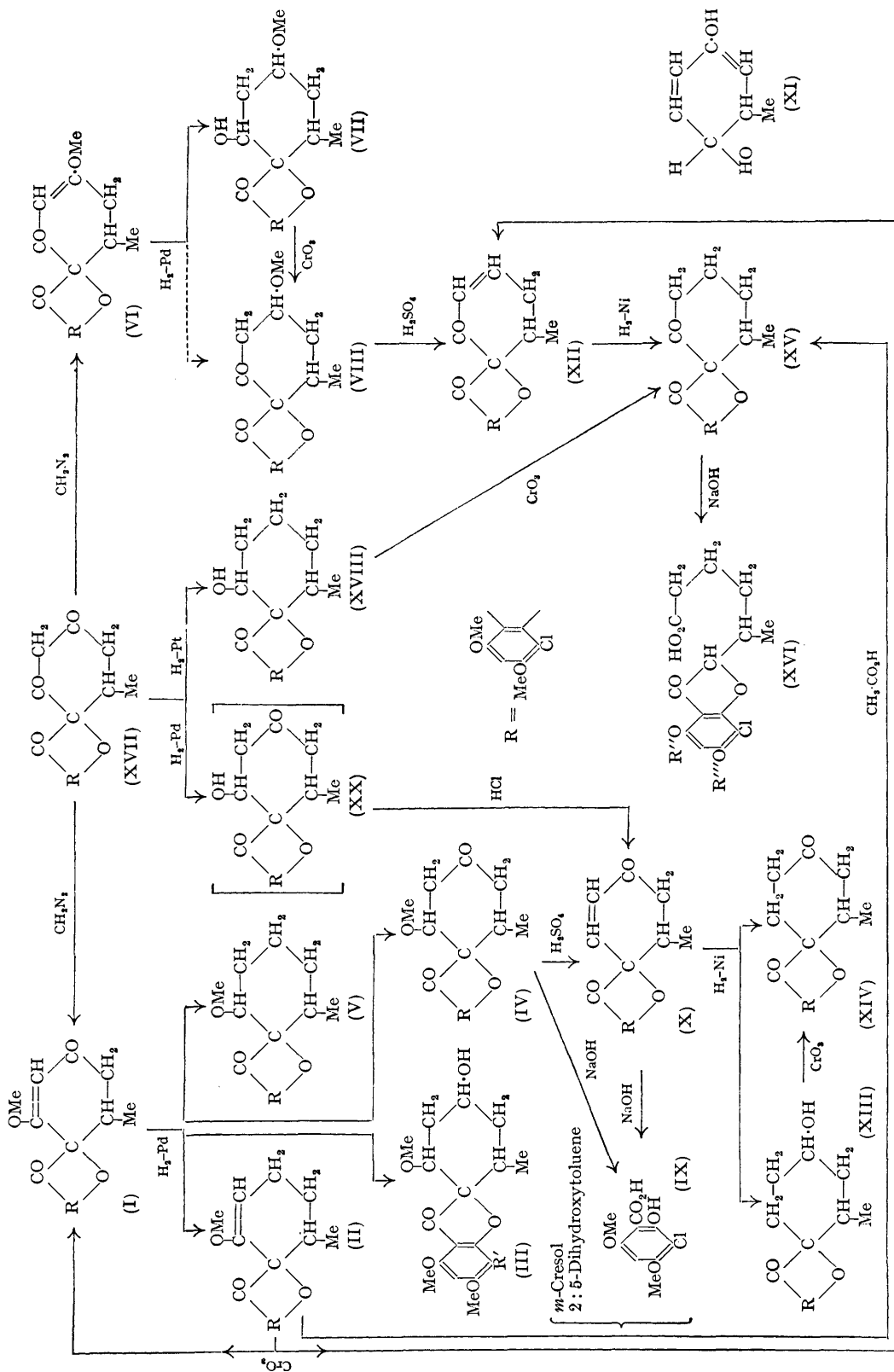
During acid hydrolysis of (IV), traces of a saturated ketone C₁₈H₂₁O₆Cl were isolated, resembling (IV) in its properties. It was probably formed by replacement of a methoxyl substituent by ethoxyl.

Acid hydrolysis of (VIII) gave an alkali-unstable unsaturated ketone (XII), isomeric with (X). The infra-red spectrum showed that this also contained two carbonyl groups, one of which was αβ-unsaturated, but the ketone did not form a dinitrophenylhydrazone. The formation of (XII) is considered to involve the loss of the elements of methanol from (VIII), as in the formation of (X) from (IV).

The desired proof of structures (I) and (VI) respectively was obtained by reduction of the ketones (X) and (XII) to the corresponding saturated ketones which showed the expected differences in stability to hydrolysis.

Catalytic reduction of the ketone (X), derived from griseofulvin, in the presence of Raney nickel gave the saturated alcohol (XIII) which was oxidised to the corresponding ketone (XIV); the latter was obtained also directly when a small amount of chloroform was present during the reduction (*cf.* Cornubert and Phélisse, *Compt. rend.*, 1948, 227, 1131). Similar reduction of the ketone (XII), derived from (VI), in the presence of Raney nickel gave an intractable product but addition of chloroform led to the saturated ketone (XV).

The compound (XIV) is neither a 1 : 3-diketone nor the vinylogue of a 1 : 3-diketone and should be stable to alkali; but (XV) is a 1 : 3-diketone and should be split. This proved to be the case, (XIV) being stable to 3*N*-sodium hydroxide, and (XV) breaking down under much milder conditions to give an acid C₁₅H₁₇O₆Cl. This acid is phenolic and is therefore considered to be 7-chloro-4(or 6)-hydroxy-6(or 4)-methoxycoumaran-3-one-2-5'-



hexanoic acid (XVI; $R' = H$, $R'' = Me$ or *vice versa*). The ready hydrolysis of an aryl methyl ether, though unusual, takes place with a number of griseofulvin derivatives (see Parts I and II).

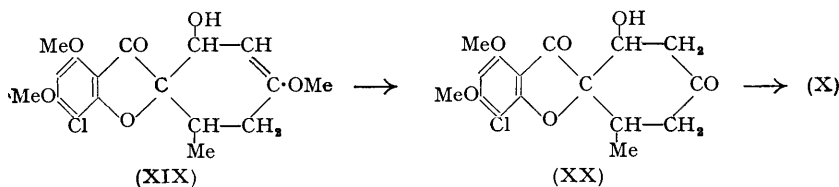
7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-3 : 2'-dione (XV) is identical with the ketone obtained by the chromic acid oxidation of the compound B, $C_{16}H_{19}O_5Cl$, one of the reduction products of 7-chloro-4 : 6-dimethoxy-2'-methylgrisan-3 : 4' : 6'-trione (griseofulvic acid) (XVII) (see Part I). Therefore the product B is (XVIII), and not (XIII).

Whereas griseofulvin and the ketones (X) and (XIV) react readily with carbonyl reagents, 7-chloro-4 : 6 : 4'-trimethoxy-6'-methylgris-3'-en-3 : 2'-dione and the ketones (XII) and (XV) derived from it do not, probably owing to steric hindrance. It may also be noted that the specific rotations of 7-chloro-4 : 6 : 4'-trimethoxy-6'-methylgris-3'-en-3 : 2'-dione and of 7-chloro-4 : 6-dimethoxy-6'-methylgris-3'-en-3 : 2'-dione are considerably lower than those of griseofulvin and 7-chloro-4 : 6-dimethoxy-6'-methylgris-2'-en-3 : 4'-dione respectively.

The chemistry of the compound $C_{17}H_{19}O_5Cl$ (II), obtained by reduction of griseofulvin, is consistent with the structure proposed in Part V. As an enol ether it is stable to aqueous alkali, but is converted into 7-chloro-4 : 6-dimethoxy-6'-methylgrisan-3 : 2'-dione (XV) by dilute acetic acid. If no rearrangement has taken place, the compound $C_{17}H_{19}O_5Cl$ must be 7-chloro-4 : 6 : 2'-trimethoxy-6'-methylgris-2'-en-3-one (II). That this is so was shown by oxidation of (II) to griseofulvin by chromic acid. A second oxidation product is 7-chloro-4 : 6-dimethoxy-6'-methylgris-3'-ene-3 : 2'-dione (XII) and the probable sequence of reactions leading to the formation of this compound is discussed below.

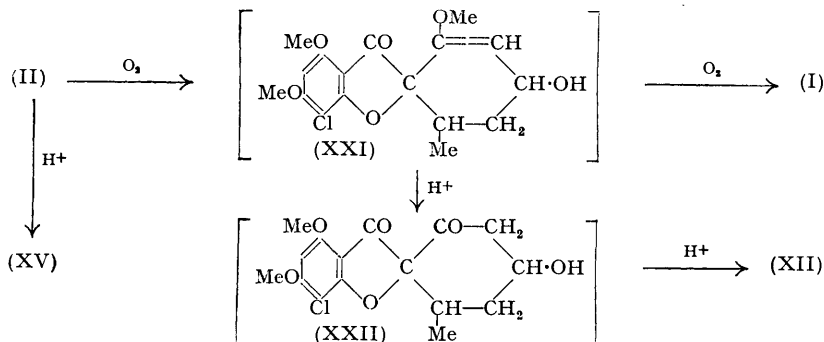
Although (II) is stable to aqueous sodium hydroxide in concentrations up to 25%, 20% alcoholic potassium hydroxide brings about exchange of ethoxyl for methoxyl, leaving the main skeleton of the molecule unchanged. The crude product is a mixture of at least two and probably three compounds, of which one is a diethoxy- and another a monoethoxy-compound, whilst the third is probably an isomeric monoethoxy-compound. The infra-red spectra of all those compounds are almost identical with that of 7-chloro-4 : 6 : 2'-trimethoxy-6'-methylgris-2'-en-3-one. Sodium ethoxide has a similar effect on other compounds of the griseofulvin series (see Part IV).

Two points call for further explanation. (i) It has been shown in Part V that both 7-chloro-4 : 6-dimethoxy-6'-methylgris-2'-en-3 : 4'-dione (X) and 7-chloro-4 : 6-dimethoxy-6'-methylgris-3'-en-3 : 2'-dione (XII) are obtained on reduction of 7-chloro-4 : 6 : 4'-trimethoxy-6'-methylgris-3'-en-3 : 2'-dione (VI). Since (XII) can also be obtained by the action of acid on 7-chloro-4 : 6 : 4'-trimethoxy-6'-methylgrisan-3 : 2'-dione (VIII), it is assumed that some of the latter compound was formed during the reduction but was decomposed by the acid present during chromatography of the product. The formation of (X) is more difficult to explain. It is possible that the unsaturated alcohol (XIX) is formed, which, in the presence of acid, gives 7-chloro-6'-hydroxy-4 : 6-dimethoxy-2'-methylgrisan-3 : 4'-dione (XX), whence (X) would result by loss of water. This mechanism receives some support from the partial reduction of 7-chloro-4 : 6-dimethoxy-2'-methylgrisan-3 : 4' : 6'-trione (XVII) with a palladium catalyst to a gum from which 7-chloro-4 : 6-dimethoxy-6'-methylgris-2'-en-3 : 4'-dione was obtained by hydrolysis. Similarly, Auterinen (*Suomen Kemi.*, 1937, 10, B, 22; *Chem. Abs.*, 1938, 32, 509) has shown that the dimedone reduction product 3-hydroxy-5 : 5-dimethylcyclohexanone is unstable and readily loses water to give 5 : 5-dimethylcyclohex-2-enone.



(ii) Oxidation of (II) to griseofulvin and 7-chloro-4 : 6-dimethoxy-6'-methylgris-3'-en-3 : 2'-dione (XII) (see above) is most readily explained by a similar series of reactions.

The issue is complicated by the possibility of simultaneous hydrolysis. However, hydrolysis of (II) without oxidation gives 7-chloro-4 : 6-dimethoxy-6'-methylgrisan-3 : 2'-dione (XV); this cannot be an intermediate in the formation of (XII) as it does not yield (XII) when oxidised under identical conditions. It is possible that the methylene group, activated by the adjacent double bond, is oxidised, giving the unsaturated alcohol (XXI) which (a) gives griseofulvin (I) on further oxidation, or (b), as an enol ether, is hydrolysed by acid to (XXII), which yields (XII) by dehydration under the influence of acid.



7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-3'-en-3 : 2'-dione (XII) was first isolated by Dr. M. A. T. Rogers by reduction of griseofulvin with aluminium isopropoxide. The results were not always reproducible and in some experiments only unchanged starting material was recovered. The mode of formation of (XII) in this reaction remains obscure, but it is likely that the unsaturated alcohol (XXI) figures as an intermediate also in this reaction.

EXPERIMENTAL

M. p.s are corrected. Absorption spectra are collected in Tables 1 and 2. Infra-red spectra were obtained as described in Part I. Microanalyses are by Drs. Strauss and Weiler, Oxford, who determined the ultra-violet spectra, and Mr. W. Brown, Imperial Chemical Industries Limited, Butterwick Research Laboratories. For chromatography, see Part V. Almost all the compounds gave rise to bands of blue to violet fluorescence.

Attempted Hydrolysis.—(i) 7-Chloro-4 : 6 : 6'-trimethoxy-2'-methylgrisan-3-one (V). Only starting material was recovered after being heated under reflux with *n*-ethanolic sulphuric

TABLE 1.

Compound	Frequency assignments (cm. ⁻¹)		
	CO	C=C ethylenic	OH
7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-2'-en-3 : 4'-dione (X) ...	1697, 1760	—	—
7-Chloro-4'-hydroxy-4 : 6-dimethoxy-2'-methylgrisan-3-one (XIII)	1690	—	3346
7-Chloro-4 : 6-dimethoxy-2'-methylgrisan-3 : 4'-dione (XIV)	1713, 1703	—	—
7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-3 : 2'-dione (XV)	1728, 1700	—	—
7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-3'-en-3 : 2'-dione (XII)...	1690, 1667	—	—
7-Chloro-4(or 6)-hydroxy-6(or 4)-methoxycoumaran-3-one-2-(5'- hexanoic acid (XVI)	1702, 1670	—	2660b
Compound A	1708	1672w	—
Compound B	1707	1670w	—
Compound C	1707	1670w	—

w = weak, b = broad.

acid (6 hours), 24% aqueous sodium hydroxide (3 hours), or 20% aqueous alcoholic potassium hydroxide (3 hours).

(ii) 7-Chloro-4'-hydroxy-4 : 6 : 6'-trimethoxy-2'-methylgrisan-3-one (III; R' = Cl). The compound was recovered unchanged after being heated under reflux with aqueous *N*-sodium hydroxide (3 hours) or with ethanolic *N*-sulphuric acid (6 hours).

(iii) 4'-Hydroxy-4 : 6 : 6'-trimethoxy-2'-methylgrisan-3-one (III; R = H). This was insoluble in boiling 3*N*-sodium hydroxide.

TABLE 2. *Ultra-violet absorption spectra (in methanol).*

Compound	$\lambda_{\max.}$ (m μ)	log ϵ	Compound	$\lambda_{\max.}$ (m μ)	log ϵ
7-Chloro-4 : 6-dimethoxy-2'-methylgrisan-3-one (XIII)	324 287 ~238	3.71 4.37 4.08	7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-3'-en-3 : 2'-dione (XII)	326 290 228	3.69 4.27 4.40
7-Chloro-4 : 6-dimethoxy-2'-methylgrisan-3 : 4'-dione (XIV)	324 288 ~238 213	3.71 4.37 4.08 4.35	Compound A	327 289 ~228	3.74 4.39 4.33
7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-3 : 2'-dione (XV)	~326 291 ~239 216	3.69 4.28 3.98 4.24	7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-2'-en-3 : 4'-dione (X)	326 291 220	3.70 4.32 4.35

7-Chloro-4 : 6 : 6'-trimethoxy-2'-methylgrisan-3 : 4'-dione (IV).—(a) *Alkaline hydrolysis.* A solution of the compound (200 mg.) in sodium hydroxide (15 ml.; N) and ethanol (10 ml.) was heated under reflux in nitrogen for 3 hours. The tar obtained by concentration and cooling was collected (43 mg.; A). After extraction with benzene, the filtrate was saturated with carbon dioxide and diluted. A phenolic gum (ca. 10 mg.; B) was recovered in ether. Acidification of the aqueous layer with hydrochloric acid caused separation of fraction C (75 mg.).

The neutral fraction A, m. p. 115—200°, contained chlorine but was intractable.

Distillation of the fraction B *in vacuo* gave an oil with a strong phenolic smell. It gave a blue colour with Gibbs' reagent and was shown by Mr. T. A. Kletz, Imperial Chemical Industries Limited, Billingham Division, using a reflecting microscope attached to an infra-red spectrometer, to consist of *m*-cresol mixed with about 10% of 2 : 5-dihydroxytoluene.

Fraction C, crystallised from ethyl acetate or ethyl methyl ketone in colourless needles, m. p. 220—221° (decomp.), identified as 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid by mixed m. p., infra-red absorption spectrum, and X-ray powder diagram (Found : C, 46.8; H, 4.05; Cl, 14.95. Calc. for C₉H₉O₅Cl : C, 46.45; H, 3.9; Cl, 15.25%).

(b) *Acidic hydrolysis.* The compound (5.3 g.) was heated under reflux with sulphuric acid (635 ml.; 2N) and ethanol (480 ml.) for 6 hours. The solid (3.0 g.), obtained by concentration *in vacuo* and filtration, was chromatographed in benzene (100 ml.) on alumina (27 × 3 cm.). The following fractions were eluted with ether + 1% of methanol : (i) A band with violet fluorescence. The solid (?) *ethoxy-ketone* (43 mg.) remaining after recovery and washing with ether crystallised from benzene—light petroleum in colourless crystals, m. p. 156—157° (Found : C, 58.3; H, 5.6; Cl, 9.6. C₁₈H₂₁O₆Cl requires C, 58.6; H, 5.7; Cl, 9.6%). It gave a precipitate with Brady's reagent on warming, was saturated to neutral permanganate, and, although insoluble in cold 3N-sodium hydroxide, partly dissolved on warming to give a yellow solution. (ii) A dark band, giving 7-chloro-4 : 6-dimethoxy-6'-methylgrisan-2'-en-3 : 4'-dione (X) (2.5 g.), which crystallised from ethanol in colourless needles, m. p. 177—178°, [α]_D²⁵ + 442° (c. 0.96 in acetone) (Found : C, 59.6; H, 4.85; Cl, 10.65; OMe, 19.5. C₁₆H₁₅O₅Cl requires C, 59.5; H, 4.7; Cl, 11.0; 2OMe, 19.2%). The *dinitrophenylhydrazone* crystallised from light petroleum—acetic acid in orange yellow needles, m. p. 282—283° (decomp.) (Found : N, 11.0. C₂₂H₁₉O₅N₄Cl requires N, 11.15%). The ketone was unsaturated to neutral permanganate and bromine water, but did not reduce Fehling's solution or give a colour with ferric chloride. It was insoluble in cold 3N-sodium hydroxide but partly dissolved when heated giving a yellow colour, discharged on acidification.

Alkaline Hydrolysis of 7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-2'-en-3 : 4'-dione.—The ketone (230 mg.), sodium hydroxide (50 ml.; N), and enough methanol to give a homogeneous solution were heated under reflux for 6 hours in nitrogen, cooled, and filtered, giving an intractable solid (49 mg.). After extraction with benzene, the filtrate was acidified. The precipitate (100 mg.) was filtered and crystallised from ethyl methyl ketone in colourless needles, m. p. 219—222° (decomp.) not depressed by mixture with 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid. Ether-extraction of the aqueous acid filtrate and recovery gave a gum with a phenolic smell. Distillation *in vacuo* followed by extraction with boiling light petroleum gave a soluble phenolic fraction which gave a blue colour with Gibbs' reagent.

Attempted oxidation of 7-chloro-4 : 6 : 6'-trimethoxy-2'-methylgrisan-3 : 4'-dione and 7-chloro-4 : 6-dimethoxy-6'-methylgrisan-2'-en-3 : 4'-dione with chromic acid failed. Small amounts of unchanged starting materials were the only compounds isolated.

Catalytic Reduction of 7-Chloro-4:6-dimethoxy-6'-methylgris-2'-en-3:4'-dione.—(a) The ketone (322 mg.) in ethanol (30 ml.) was hydrogenated with Raney nickel (*ca.* 1.0 g.) in an atmosphere of hydrogen at room temperature and pressure (absorption: 2 mols. in 20 minutes). The gummy product obtained by removal of the catalyst and solvent was chromatographed in benzene (50 ml.) on alumina (10×2.5 cm.) and fractions showing fluorescence were collected. After two small fractions, ether + 3% of methanol (blue fluorescence) removed 7-chloro-4'-hydroxy-4:6-dimethoxy-2'-methylgrisan-3-one (XIII) (150 mg.) which crystallised from benzene-light petroleum in colourless prisms, m. p. 160° (Found: C, 58.8; H, 5.8; Cl, 10.4. $C_{16}H_{19}O_5Cl$ requires C, 58.8; H, 5.9; Cl, 10.9%). The alcohol was saturated to neutral permanganate, did not react with Brady's reagent, and was insoluble in boiling 3N-sodium hydroxide.

(b) The ketone (569 mg.) in ethanol containing 1% of chloroform (40 ml.) was reduced in the presence of Raney nickel (*ca.* 1.0 g.) in ethanol (30 ml.) as described above (absorption: 1 mol. in 50 minutes). The crude product, isolated as described in (a), contained a proportion of a nickel complex insoluble in benzene, which was decomposed by shaking it with benzene and dilute sulphuric acid. The organic layer, after concentration to 20 ml., was chromatographed on alumina (10×2.5 cm.) and the fluorescent bands were eluted with ether. This yielded 7-chloro-4:6-dimethoxy-2'-methylgrisan-3:4'-dione (XIV) (408 mg.) which crystallised from benzene-light petroleum in colourless needles, m. p. 178–179° (Found: C, 59.3; H, 5.1; Cl, 10.7. $C_{16}H_{17}O_5Cl$ requires C, 59.2; H, 5.3; Cl, 10.9%). The ketone gave a precipitate with Brady's reagent on warming and was saturated to neutral permanganate. It was recovered unchanged after 1 hour's heating with 3N-sodium hydroxide. An increase in the concentration of chloroform led to slower reduction and lower yields.

Oxidation of 7-Chloro-4'-hydroxy-4:6-dimethoxy-2'-methylgrisan-3-one.—The alcohol (40 mg.) in acetic acid (1 ml.) was oxidised by dropwise addition of chromic acid (50 mg.) in acetic acid (0.25 ml.) and water (0.1 ml.). The mixture was warmed on the steam-bath between additions of the reagent, and finally, after one hour at room temperature, was diluted with water (10 ml.) and filtered. Crystallisation of the product (18 mg.) from benzene-light petroleum gave 7-chloro-4:6-dimethoxy-2'-methylgrisan-3:4'-dione, m. p. 176–178° not depressed by mixture with material obtained in the previous experiment.

7-Chloro-4:6:2'-trimethoxy-6'-methylgris-2'-en-3-one (II).—(i) *Alkaline hydrolysis.* (a) No reaction took place in refluxing 25% sodium hydroxide (3 hours).

(b) The compound (274 mg.) and 20% aqueous alcoholic potassium hydroxide (40 ml.) were heated together under reflux in nitrogen for $6\frac{1}{2}$ hours. After cooling, the neutral product (188 mg.) was filtered off and the filtrate, after extraction with benzene and ethyl acetate, was acidified with hydrochloric acid. Extraction with benzene and recovery gave an acid (5 mg.), m. p. 205–209° (decomp.), depressed to 191–192° by mixture with 3-chloro-2-hydroxy-4:6-dimethoxybenzoic acid [m. p. 210–215° (decomp.)]. The neutral product was chromatographed in benzene (15 ml.) on alumina (15.5×2 cm.). On elution with ether-light petroleum (1:1) a band of violet fluorescence separated and was collected (eluate I), followed by one of little fluorescence (eluate II). A second violet band was eluted with ether (eluate III). On evaporation the eluates gave (all crystallised from light petroleum): (I) *compound A* (44 mg.), rods and needles, m. p. 165–166° [Found: C, 62.2, 62.5; H, 6.4, 6.5; Cl, 10.7, 8.4; OAlkyl, calc. as OMe, 24.7. $C_{19}H_{23}O_5Cl$ requires C, 62.2; H, 6.3; Cl, 9.7; apparent OMe (2OEt, 1OMe), 25.2%]; (II) *compound B* (20 mg.), cubes, m. p. 172–173° (Found: C, 61.3; H, 6.0; Cl, 10.1. $C_{18}H_{21}O_5Cl$ requires C, 61.3; H, 6.0; Cl, 10.05%); and (III) *compound C* (51 mg.), needles, m. p. 162–163°, $[\alpha]_D^{25} +134^\circ$ (*c.* 0.6 in acetone) [Found: C, 61.3; H, 6.0; Cl, 9.5; OAlkyl calc. as OMe, 24.35. $C_{18}H_{21}O_5Cl$ requires C, 61.3; H, 6.0; Cl, 10.05; apparent OMe (1OEt, 2OMe), 26.1%].

A mixture of compounds B and C melted at 168–172° but the m. p. of compound C could not be raised above 162°. Material of m. p. 172° was obtained from only two of three experiments and it is probable that compounds B and C are isomeric monoethoxy-derivatives. The infra-red spectra of compounds B and C (see Table I) were indistinguishable and almost identical with the infra-red spectrum of 7-chloro-4:6:2'-trimethoxy-6'-methylgris-2'-en-3-one. The spectrum of compound A showed slight differences. The products were stable to alkali, saturated to neutral permanganate and not ketonic to Brady's reagent.

(ii) *Acidic hydrolysis.* (a) Hydrolysis with ethanolic N-sulphuric acid gave an intractable gum which was shown to be a mixture by the infra-red spectrum.

(b) The compound (500 mg.) was heated under reflux with acetic acid (40 ml.) and water (10 ml.) for 2 hours. Evaporation *in vacuo* gave a solid (334 mg.) which was chromatographed in benzene (20 ml.) on alumina (8×1.5 cm.). A blue fluorescent band was eluted with benzene + 1% of methanol and gave on evaporation 7-chloro-4:6-dimethoxy-6'-methylgrisan-3:2'-dione

(XV) (261 mg.) which crystallised from benzene–light petroleum in colourless needles, m. p. 204–205° (Found: C, 59.5; H, 5.2; Cl, 11.1; OMe, 21.1. $C_{16}H_{17}O_5Cl$ requires C, 59.2; H, 5.3; Cl, 10.9; 2OMe, 19.1%). The compound was saturated to neutral permanganate and insoluble in cold sodium hydroxide. It dissolved on warming (see below). It was identical (mixed m. p. and infra-red spectrum) with the ketone $C_{16}H_{17}O_5Cl$ (XVIII) recorded in Part I.

(iii) *Oxidation.* (a) The compound was not attacked by alkaline hydrogen peroxide at room temperature or at 100°.

(b) A warm solution of the compound (500 mg.) in acetic acid (9 ml.) was treated in portions with chromic oxide (1.5 g.) in acetic acid (9 ml.) and water (4 ml.) (spontaneous refluxing). When addition was complete the solution was heated under reflux for 5 minutes, cooled, diluted with water (20 ml.), and extracted with benzene. The extract was washed with sodium carbonate solution and evaporated, giving a gum which was washed with a little ether, thus yielding a solid (52 mg.). The solid was chromatographed in benzene (3 ml.) on alumina (10 × 1.0 cm.). A narrow band with violet fluorescence was eluted with ether and discarded. Further elution with ether + 1% of methanol eluted first a faint dark violet fluorescing band, giving on evaporation 7-chloro-4 : 6-dimethoxy-6'-methylgris-3'-en-3 : 2'-dione (XII) (30 mg.) and then a band of blue fluorescence which on evaporation gave griseofulvin (9 mg.), identified by mixed m. p. and infra-red spectrum.

The dione (XII) crystallised from ethanol in colourless needles. The purest specimens obtained by this method melted at 273° (decomp.) although material of higher m. p. was obtained by a different method (see below) [Found: C, 59.7; H, 4.8; Cl, 10.6; OMe, 16.0%; *M* (micro-Rast), 328. $C_{16}H_{15}O_5Cl$ requires C, 59.5; H, 4.7; Cl, 11.0; 2OMe, 19.2%; *M*, 322.5). The dione did not react with Brady's reagent and was unsaturated to neutral permanganate. It was insoluble in cold 3*N*-sodium hydroxide but decomposed on warming therein.

7-Chloro-4 : 6-dimethoxy-6'-methylgris-3'-en-3 : 2'-dione was also obtained by acid hydrolysis of 7-chloro-4 : 6 : 4'-trimethoxy-6'-methylgrisan-3 : 2'-dione (see below) and as a minor product from the reduction of 7-chloro-4 : 6 : 4'-trimethoxy-6'-methylgris-3'-en-3 : 2'-dione (Part V). The m. p.s of mixtures were not depressed and the infra-red spectra were identical. They were also identical with a specimen obtained by reduction of griseofulvin with aluminium isopropoxide (see below).

Alkaline Hydrolysis of 7-Chloro-4 : 6-dimethoxy-6'-methylgrisan-3 : 2'-dione.—The ketone (240 mg.) was refluxed with *N*-sodium hydroxide (20 ml.) in nitrogen for 2 hours. After cooling, undissolved material (16 mg.) was rejected, and the filtrate was acidified with concentrated hydrochloric acid. After storage of the solution in the refrigerator, the sticky solid was filtered off, washed with water, and dissolved in benzene. Recovery gave 7-chloro-4(or 6)-hydroxy-6(or 4)-methoxycoumaran-3-one-2'-5'-hexanoic acid (XVI) as a colourless solid (184 mg.) which after repeated crystallisation from ethyl methyl ketone–light petroleum had m. p. 177–179° [Found: C, 54.3, 55.1; H, 5.2, 5.5; Cl, 11.0; OMe, 12.2%; equiv. (potentiometric titration), 150. $C_{15}H_{17}O_6Cl$ requires C, 54.8; H, 5.2; Cl, 10.8; 1OMe, 9.4%; equiv. (dibasic acid), 164]. The acid was soluble in aqueous sodium hydrogen carbonate, and gave a weak brown colour with ferric chloride, intensified by addition of water. It gave a positive Millon's but negative Gibbs' reaction, did not couple with diazotised amines, and was slowly attacked by neutral permanganate. It did not react with Brady's reagent.

7-Chloro-4 : 6 : 4'-trimethoxy-6'-methylgrisan-3 : 2'-dione (VIII).—(a) The ketone was insoluble in cold 3*N*-sodium hydroxide but partly dissolved when heated, giving a yellow solution.

(b) *Acid hydrolysis.* The ketone (60 mg.), ethanol (12 ml.), and 2*N*-sulphuric acid (15 ml.) were heated under reflux for 6 hours. The solid [18 mg.; m. p. ca. 240° (decomp.)], obtained by concentration *in vacuo* and filtration, was further purified by passage of a solution in benzene through a short column of alumina, elution being completed with ether + 1% of methanol. Crystallisation of the recovered material from ethanol gave 7-chloro-4 : 6-dimethoxy-6'-methylgris-3'-en-3 : 2'-dione as colourless needles, m. p. 275–277° (decomp.). The identity with material obtained by oxidation of 7-chloro-4 : 6 : 2'-trimethoxy-6'-methylgris-2'-en-3-one was confirmed by mixed m. p. and the infra-red spectrum.

7-Chloro-6'-hydroxy-4 : 6 : 4'-trimethoxy-2'-methylgrisan-3-one (VII).—This was insoluble in boiling 3*N*-sodium hydroxide.

Reduction of 7-Chloro-4 : 6-dimethoxy-6'-methylgris-3'-en-3 : 2'-dione.—(a) In the presence of Raney nickel in ethanol, hydrogen (3 mols.) was absorbed during 10 minutes at room temperature and pressure, but the product could not be purified.

(b) A solution of the ketone (45 mg.) in ethanol (40 ml.) containing chloroform (1%) was shaken with hydrogen in the presence of Raney nickel (ca. 1.0 g.) in ethanol (40 ml.) at room

temperature and pressure. Hydrogen (1.5 mols.) was absorbed in 5 minutes. At this stage, rapid gas evolution began and the reaction was stopped. After filtration and recovery, the crude product which was only partly soluble in benzene, was shaken with benzene and dilute sulphuric acid. The solid (12 mg.) obtained from the benzene layer by evaporation and trituration of the resultant gum with ether crystallised from ethyl acetate in colourless prisms, m. p. 200—201°, identical (mixed m. p. and infra-red spectrum) with 7-chloro-4 : 6-dimethoxy-6'-methylgrisan-3 : 2'-dione.

Hydrogenation of 7-Chloro-4 : 6-dimethoxy-2'-methylgrisan-3 : 4' : 6'-trione in the Presence of Palladium Black [Dr. J. MACMILLAN].—The trione (1.0 g.) in acetic acid (50 ml.) was hydrogenated in presence of palladium black at room temperature and pressure (1.5 mols. absorbed in 2½ hours). After filtration and recovery the residual colourless gum, on trituration with light petroleum, gave a gum which could not be crystallised or purified by chromatography. It was neutral, ketonic, and unsaturated to potassium permanganate. The crude product (200 mg.) was dehydrated by heating it under reflux for 2 minutes with concentrated hydrochloric acid (0.2 ml.) and acetic acid (2.0 ml.). Subsequent dilution with water gave a solid which, crystallised from dilute ethanol, had m. p., alone or mixed with 7-chloro-4 : 6-dimethoxy-6'-methylgris-2'-en-3 : 4'-dione, 178° (Found: C, 59.55; H, 5.0. Calc. for C₁₆H₁₅O₅Cl: C, 59.5; H, 4.7%). The dinitrophenylhydrazone crystallised from nitrobenzene-methanol in orange needles, m. p. and mixed m. p. with 7-chloro-4 : 6-dimethoxy-6'-methylgris-2'-en-3 : 4'-dione dinitrophenylhydrazone, 283—284° (decomp.) (Found: C, 53.0; H, 3.9; N, 11.5. Calc. for C₂₂H₁₉O₈N₄Cl: C, 52.9; H, 3.8; N, 11.1%).

Reduction of Griseofulvin with Aluminium isoPropoxide [Dr. M. A. T. ROGERS].—Griseofulvin (0.5 g.) was reduced with isopropyl alcohol (50 ml.; dried by distillation from aluminium isopropoxide) and aluminium isopropoxide (1.0 g.). After 6 hours the solvent was removed, the residue was stirred with 2N-hydrochloric acid, and the residual solid was washed and dried (0.4 g.; m. p. 216—240°). Crystallisation from ethanol gave colourless needles, m. p. 275° (slow decomp.), and from toluene-light petroleum long flattened needles, $[\alpha]_D^{21} + 281^\circ$ (ca. 0.98 in chloroform), identical (mixed m. p. and infra-red spectrum) with 7-chloro-4 : 6-dimethoxy-6'-methylgris-3'-en-3 : 2'-dione prepared by other methods. These results were not always reproducible and sometimes griseofulvin was recovered unchanged.

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