

**244.** *Griseofulvin Analogues. Part IV.<sup>1</sup> The Preparation and Properties of Some Chlorides.*

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Griseofulvic acid (I; R = H) is converted by phosphoryl chloride in the presence of water and lithium chloride into a mixture of the 2'- and the 4'-chloride (II; R = H, R' = Cl and III; R = H, R' = Cl, respectively); 3'-substituted griseofulvic acids with the same reagents give predominantly 4'-chlorides. However, 4'-amines (III; R' = NH<sub>2</sub>) and some 4'-ethers give 2'-chlorides under these conditions, whereas 2'-amines and ethers give predominantly 4'-chlorides. 2'- and 4'-Chlorides react under alkaline conditions with thiols to give 2'- and 4'-S-alkyl compounds, and with phenol and lower alcohols to give 2'- and 4'-ethers. Chlorides of both series react with ammonia and other bases to give the corresponding amines.

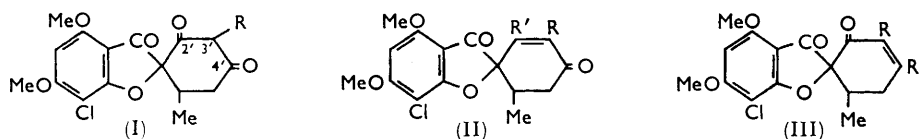
In order to replace by other groups the 2'-substituent in griseofulvin or 3'-halogeno- and 3'-alkyl-griseofulvins (II; R' = OMe), we required a series of compounds containing a functional group at position 2' that could be displaced by treatment with nucleophilic reagents. Ethers (II; R' = OAlkyl) homologous with griseofulvin can be made by treating griseofulvic acid (I; R = H) with diazoalkanes,<sup>2</sup> with alcohols in the presence of acids,<sup>2</sup> or with alkyl halides in the presence of potassium carbonate or silver oxide.<sup>3</sup>

<sup>1</sup> Part III, preceding paper.

<sup>2</sup> Duncanson, Grove, and Jeffs, *J.*, 1958, 2929.

<sup>3</sup> Gregory, Holton, Robinson, and Walker, *J.*, 1962, 1269.

All these methods have the disadvantage that some of the 4'-ether is produced at the same time. Moreover, griseofulvic acid and its 3'-substituted derivatives are not particularly suitable starting materials for S-alkyl compounds. We therefore explored routes to 2'-chlorides (II; R' = Cl), from which we expected to be able to prepare a variety of 2'-substituted derivatives.



3-Chlorocyclohex-2-enone has been prepared by treating cyclohexane-1,3-dione with phosphorus trichloride.<sup>4</sup> Griseofulvic acid, however, was not affected by phosphorus trichloride in refluxing benzene; with phosphorus pentachloride in chloroform it gave only a mixture of the 4'-chloride and degradation products, but a suspension of griseofulvic acid in phosphoryl chloride gradually dissolved when warmed on the steam-bath, giving a mixture of the 2'- and the 4'-chloride (II and III respectively: R = H, R' = Cl). Attempts to repeat this experiment gave variable results; freshly distilled phosphoryl chloride reacted more slowly than old, undistilled samples. Moreover, treatment of griseofulvic acid on the steam-bath for 90 minutes with freshly distilled phosphoryl chloride left about 10% of starting material, but when 1% by volume of water was added to the same batch of distilled phosphoryl chloride the griseofulvic acid was completely consumed in 30 minutes; prolonged heating caused destruction of the product. As a useful preparative method we heated griseofulvic acid for 20 minutes with phosphoryl chloride containing 1% of water and isolated starting material (15–20%) and the isomeric chlorides (about 25% each). The latter were separated, at first by chromatography, but later by Girard P reagent, with which the more hindered carbonyl group of the 4'-chloride did not react.

Griseofulvic acid reacted smoothly with phosphoryl chloride in dimethylformamide (but not in dimethylacetamide), to give excellent yields of the 4'-chloride. The absence of the isomeric 2'-chloride may have been due to steric hindrance, for chlorinations of this type probably proceed through a bulky phosphorus-containing intermediate.<sup>5</sup> The course of this reaction was little affected by the addition of lithium chloride (see below).

At the suggestion of Dr. V. M. Clark of Cambridge University we next heated griseofulvic acid on the steam-bath with moist \* phosphoryl chloride in the presence of lithium chloride for 20 minutes. Infrared analysis<sup>6</sup> showed that the product consisted of the 2'- (60%) and the 4'-chloride (40%); no starting material could be detected. The pure 2'-chloride was isolated from this mixture in 50% yield by treatment with Girard P reagent.

When 3'-bromogriseofulvic acid was heated with moist phosphoryl chloride and lithium chloride, only the 4'-chloride (III; R = Br, R' = Cl) was formed; and 3'-benzylgriseofulvic acid heated with moist phosphoryl chloride gave only a mixture of starting material and the 4'-chloride (III; R = CH<sub>2</sub>Ph, R' = Cl). It seemed unlikely, therefore, that 2'-chlorides could be prepared from 3'-substituted griseofulvic acids, and we turned our attention to other starting materials. It was evident that compounds lacking the symmetry of the griseofulvic acids were required, so that there would be only one course for the reaction to take even though this course might be opposed by steric hindrance. Ethers of the types (II and III; R' = OMe) were available; such ethers can be converted

\* The optimum ratio of water to phosphoryl chloride for a particular griseofulvic acid, ether, or amine is usually 1–2%, but may be as high as 4%. The ratios recorded in the Experimental section are usually those found by small-scale trials to give the best results.

<sup>4</sup> Crossley and Haas, *J.*, 1903, 494.

<sup>5</sup> Bosshard, Mory, Schmid, and Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1653; Bosshard and Zollinger, *ibid.*, p. 1659.

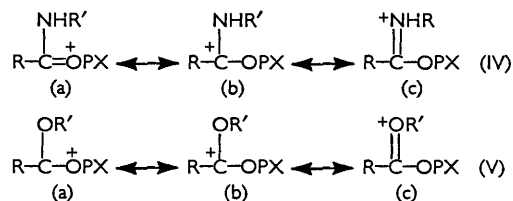
<sup>6</sup> Page and Staniforth, following paper.

by ammonia into the corresponding amines. We have studied also the chlorination of these ethers and amines.

Griseofulvamine (II;  $R = H, R' = NH_2$ ), when heated with freshly distilled phosphoryl chloride and lithium chloride, gave the 4'-chloride in >65% yield, 7% of recovered griseofulvic acid, and an acid extract that at room temperature slowly deposited more of the pure 4'-chloride. The reaction of the isomeric amine (III;  $R = H, R' = NH_2$ ) with moist phosphoryl chloride in the presence of lithium chloride gave >90% of the 2'-chloride. Griseofulvin gave under the conditions just described an almost quantitative yield of the 4'-chloride (although only degradation products were formed in the absence of lithium chloride); and isogriseofulvin, when heated for 10 minutes with phosphoryl chloride containing 2% of water in the presence of lithium chloride, gave the 2'-chloride in excellent yield.

The conversion of 4'-amines into 2'-chlorides proceeded satisfactorily also for the 3'-bromo-, 3'-chloro-, 3'-benzyl, and 3'-propyl derivatives, but reaction of 3'-substituted isogriseofulvins was not always in the desired direction, for 3'-chloroisogriseofulvin (III;  $R = Cl, R' = OMe$ ) gave only the 4'-chloride, and 3'-benzylisogriseofulvin gave the 2'- (about 60% yield) and the 4'-chloride (about 6% yield) (the last-mentioned compound, however, was easily removed by chromatography).

The mechanism of these transformations merits attention. It is obvious that our reagent is not simply phosphoryl chloride, and in the following discussion we use the symbol PX to represent the phosphorus-containing part of the molecule.



In general, esters of carboxylic acids are not converted into acid chlorides by phosphorus halides, although phosphorus pentachloride (which is usually more reactive than phosphoryl chloride) converts esters of oxalic acid and enolisable  $\beta$ -keto-esters into acid chlorides.<sup>7</sup> Amides, moreover, are not converted into acid chlorides by phosphorus halides, although they sometimes react in other ways, as in the preparation of nitriles from aromatic amides<sup>8</sup> and in the Bischler-Napieralski reaction. The difference in reactivity towards phosphorus halides between amides and esters can probably be explained by consideration of the resonance forms (IV) and (V).

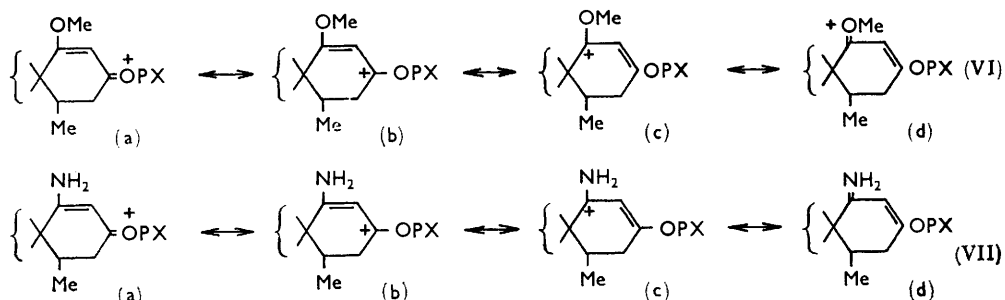
If we assume that a reactive phosphorus-containing compound initially attacks the oxygen of a carbonyl group, then (IV) and (V) represent the possible resonance structures of the ionic intermediates. Form (IVc) contributes much more to stability than form (Vc), so that the intermediate from the amine is available for further reaction, whereas that from the ester may not exist. However, if the group R is  $R'O\cdot CO-$  or  $\cdot CH_2C<$ , then additional resonance forms are available. The reactions of oxalic and acetoacetic esters with phosphorus halides can be explained in this way. The relevant intermediates in the chlorination of griseofulvin and griseofulvamine can be written as in the partial formulæ (VI) and (VII), respectively. Similar resonance forms can be written for the 4'-substituted series.

Griseofulvin and isogriseofulvin should, therefore, be more reactive than esters of carboxylic acids to phosphorus-containing reagents, and amines of the type (II and III;  $R' = NH_2$ ) should be more reactive than griseofulvin and isogriseofulvin, respectively,

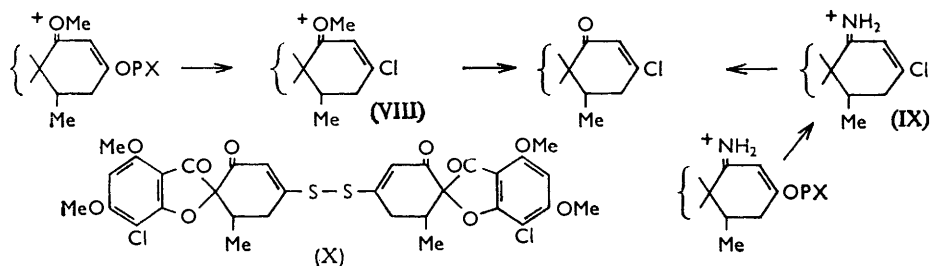
<sup>7</sup> Houben-Weyl, "Methoden der organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th edn., 1952, Vol. VIII, p. 466.

<sup>8</sup> Kirsanov and Makitra, *Zhur. obschei Khim.*, 1956, **28**, 907 (*Chem. Abs.*, 1956, **50**, 14,633 <sup>4</sup>).

as indeed they are. The next stage is probably attack by a chloride ion; hydrolysis of the intermediate (IX), or loss of Me<sup>+</sup> from (VIII), completes the reaction.



For 3'-unsubstituted compounds the mechanism seems to be exclusively that suggested above; similar reasoning can be applied to account for the production of the 2'-chloride from isogriseofulvin and from isogriseofulvamine. However, the inductive effect of a 3'-halogen atom could lead to altered contributions from the various resonance



forms. Consequently the intermediate from a 3'-halogenoisogriseofulvin might be attacked at position 4' by a halide ion, whereas the more powerful contribution from the resonance form similar to (VIId), derived from a 3'-halogenoisogriseofulvamine, would overcome the inductive effect of the halogen atom and a 2'-chloride would be obtained. Steric effects may also be involved, for 3'-chlorogriseofulvin gives the expected 4'-chloride, and 3'-benzylisogriseofulvin gives the 2'-chloride as the major product, as well as a small amount of the 4'-chloride.

The suggested mechanism helps to explain some other observations. It is probable that attack by a large phosphorus-containing reagent would be faster at the 4'- than at the hindered 2'-position, and in fact griseofulvin and griseofulvamine react more quickly than isogriseofulvin and isogriseofulvamine, respectively.

When isogriseofulvin was treated with moist phosphoryl chloride and lithium chloride, and the reaction was not allowed to go to completion, a substantial amount of griseofulvic acid was isolated. Griseofulvic acid is rapidly destroyed under these conditions (see before) and cannot have been present as such in large amounts in the reaction mixture. Nor can it have been formed by hydrolysis of a chloride during the working-up, for reactions that have gone to completion do not produce any griseofulvic acid, and in any event the chlorides are not readily hydrolysed by acid. The griseofulvic acid must, therefore, have been formed by hydrolysis of a reactive intermediate such as (VIId).

We reported above that griseofulvamine, when treated with phosphoryl chloride and lithium chloride, gave an acid-soluble by-product that was gradually converted by dilute acid into the 4'-chloride. We even found it necessary to carry out a final acid hydrolysis in order to obtain reasonable yields of 2'-chlorides from the corresponding 4'-amines (III; R = Br or Cl, R' = NH<sub>2</sub>). These facts indicate the presence of the postulated intermediate (IX).

We prepared many compounds from 2'- and 4'-chlorides by nucleophilic displacement of chlorine. In general, 4'- were more reactive than 2'-chlorides, but they were more extensively decomposed under strongly alkaline conditions. In the 2'-series, the 3'-halogeno-compounds were more reactive, and the 3'-propyl compound less reactive, than the unsubstituted and the 3'-benzyl compound. The 2'-chlorides reacted readily with methanol under basic conditions to give substituted griseofulvins (proof of orientation was often obtained in this way), but with ethanol and propanol more drastic conditions were necessary. The chloride (II; R = R' = Cl) was converted into the corresponding phenyl ether by sodium phenoxide in acetone, and the chloride (III; R = H, R' = Cl) into the corresponding phenyl ether by phenol in the presence of potassium carbonate. The chlorides (II and III; R = H, R' = Cl) both reacted with benzenethiol in acetone containing triethylamine, to give the corresponding phenylthio-derivatives.

With hydrogen sulphide in acetone containing triethylamine, the chloride (III; R = H, R' = Cl) gave the thiol (III; R = H, R' = SH); this was not obtained pure. It was S-methylated by diazomethane, and with iodine monochloride or bromine in dimethylformamide containing potassium acetate it gave the disulphide (X).

The 2'-S-alkyl compounds and the S-aryl compound recorded in Table I were prepared by treating the chlorides with appropriate thiols in ketonic solvents containing triethylamine. The conditions required for almost complete reaction varied from a few minutes at room temperature [methanethiol and the chloride (II; R = R' = Cl)] to several days at 100° in a sealed tube [butanethiol and the chloride (II; R = Pr<sup>n</sup>, R' = Cl)]. Care had to be taken to avoid loss of bromine from the chloride (II; R = Br, R' = Cl) during reaction with thiols. In the presence of trimethylamine we obtained the methylthio-compound (II; R = Br, R' = SMe), but the higher homologues were not obtained analytically pure. We prepared the compounds (III; R = H, R' = SEt, SPh, S·CH<sub>2</sub>Ph, and S·CH<sub>2</sub>·CH<sub>2</sub>·NEt<sub>2</sub>) from the chloride (III; R = H, R' = Cl) by standard methods.

The 2'-chloride (II; R = H, R' = Cl) reacted with some amines in aqueous dioxan at room temperature in the presence of sodium hydroxide at pH 11–12 (pH-meter), giving substituted griseofulvamines. This reaction proceeded smoothly with 2-diethylaminoethylamine, 3-dimethylaminopropylamine, and 3-diethylaminopropylamine, but gave unidentified products with ethanolamine and diethanolamine. The isomeric 4'-chloride (III; R = H, R' = Cl) gave the expected isogriseofulvamines with 2-diethylaminoethylamine in the presence of added alkali, and with piperidine and pyrrolidine.

#### EXPERIMENTAL

Unless otherwise stated, rotations refer to acetone solutions (*c* 1), and "alumina" means Woelm Grade II (acid) alumina. Phosphoryl chloride was distilled just before use.

*Reaction of Griseofulvic Acid with Phosphoryl Chloride.*—Water (0.95 ml.) was added to phosphoryl chloride (95 ml.). When the reaction had subsided, griseofulvic acid<sup>3</sup> (16.15 g.; 60-mesh) was added and the mixture heated on the steam-bath for 20 min. with occasional shaking. Most of the phosphoryl chloride was removed under reduced pressure and the residual gum cooled and treated with water. Extraction with chloroform gave a solution which was washed with water, 2*N*-sodium carbonate, and water, dried (MgSO<sub>4</sub>), and evaporated, leaving a mixture of chlorides (13.5 g.). This was chromatographed in benzene (350 ml.) on alumina, elution being carried out with benzene-ethyl acetate (20:1 v/v) and finally with benzene-ethyl acetate (4:1 v/v). The earlier fractions left a solid (5.37 g.) which was recrystallised from acetic acid (45 ml.), giving 7,4'-dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (4.73 g.), m. p. 248–250.5°, [α]<sub>D</sub><sup>20</sup> +278° (Found: C, 53.4; H, 3.95; Cl, 19.5. C<sub>16</sub>H<sub>14</sub>Cl<sub>2</sub>O<sub>5</sub> requires C, 53.8; H, 3.95; Cl, 19.85%). The later fractions gave 7,2'-dichloro-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (4.20 g.), m. p. 197.5–199.5° (from carbon tetrachloride), [α]<sub>D</sub><sup>20</sup> +370° (Found: C, 53.95; H, 4.0; Cl, 19.5%). The chloride was converted into griseofulvin when refluxed with methanol and aqueous sodium carbonate.

*Reaction of Griseofulvic Acid with Phosphoryl Chloride and Lithium Chloride.*—Lithium chloride (17.0 g.) was cautiously added to phosphoryl chloride (100 ml.) containing 1% of water.

Griseofulvic acid (17.0 g.) was added, and after a few min. the whole was heated on the steam-bath for 20 min. The mixture was worked up as in the previous experiment, giving mixed chlorides (17.7 g.) and a negligible amount of acidic material. A portion of the mixed chlorides (5.0 g.) was refluxed for 15 min. in ethanol (50 ml.) containing acetic acid (5 ml.) and Girard P reagent (2.1 g.). The cooled mixture was poured into aqueous sodium hydrogen carbonate (10 g. in 300 ml.) and extracted three times with ethyl acetate. The ethyl acetate solution was washed with water and evaporated, leaving a yellow solid (1.8 g.), m. p. 232—237°, shown by infrared analysis to be crude 7,4'-dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione. The aqueous layer, when acidified with 2N-sulphuric acid and then stirred and extracted during 4 hr. with ethyl acetate (400 ml.), gave 7,2'-dichloro-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (2.40 g.), m. p. 195—197.5°, raised to 200—201.5° by recrystallisation from carbon tetrachloride or ethanol.

*Reaction of Griseofulvic Acid with Phosphoryl Chloride in Dimethylformamide.*—Phosphoryl chloride (2.0 ml.) was added during 1 min., with cooling in water, to a solution of griseofulvic acid (1.7 g.) in dimethylformamide (20 ml.). The solution became yellow, and after 1 hr., when the rotation was constant, water (80 ml.) was added with cooling. 7,4'-Dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (1.75 g.) separated, having m. p. 241—244°.

*Reaction of 3'-Bromogriseofulvic Acid with Phosphoryl Chloride in Dimethylformamide.*—Phosphoryl chloride (2.0 g.) was added to a cooled solution of 3'-bromogriseofulvic acid<sup>9</sup> (2.0 g.) in dimethylformamide (15 ml.). After 40 min. the mixture was worked up as just described. The solid obtained (2.0 g.) was washed in ethyl acetate with aqueous sodium carbonate, then with water, and the solution was dried (MgSO<sub>4</sub>) and evaporated. Recrystallisation of the residue from acetic acid gave 3'-bromo-7,4'-dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (0.76 g.), m. p. 213—216°,  $[\alpha]_D^{20} + 212^\circ$  (c 0.66) (Found: C, 44.15; H, 3.0; Hal., 33.2. C<sub>18</sub>H<sub>13</sub>BrCl<sub>2</sub>O<sub>5</sub> requires C, 44.0; H, 3.0; Hal., 34.6%).

*Reaction of 3'-Bromogriseofulvic Acid with Phosphoryl Chloride and Lithium Chloride.*—Lithium chloride (1.7 g.) was added to phosphoryl chloride (10 ml.) containing water (0.1 ml.). 3'-Bromogriseofulvic acid (2.05 g.) was added, and the mixture refluxed for 25 min., then worked up as in the corresponding reaction of griseofulvic acid, giving a neutral solid (2.3 g.), m. p. 185—205°, shown by infrared analysis to contain ca. 90% of 3'-bromo-7,4'-dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione.

*Reaction of 3'-Chlorogriseofulvic Acid with Phosphoryl Chloride in Dimethylformamide.*—3'-Chlorogriseofulvic acid<sup>9</sup> (1.87 g.), treated with phosphoryl chloride (20 ml.) in dimethylformamide (20 ml.) as in the preceding experiment, gave 7,3',4'-trichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (0.80 g.), m. p. 235.5—237.5° (from acetic acid),  $[\alpha]_D^{20} + 258^\circ$  (Found: C, 49.5; H, 3.4; Cl, 27.2. C<sub>16</sub>H<sub>13</sub>Cl<sub>3</sub>O<sub>5</sub> requires C, 49.1; H, 3.3; Cl, 27.2%).

*Reaction of 3'-Benzylgriseofulvic Acid with Phosphoryl Chloride.*—3'-Benzylgriseofulvic acid<sup>9</sup> (2.14 g.) was heated on the steam-bath for 10 min. with phosphoryl chloride (10 ml.) containing water (0.1 ml.). The mixture was worked up and chromatographed as in the corresponding reaction of griseofulvic acid; elution was with benzene-ethyl acetate (95 : 5 v/v). The solid (0.72 g.) recrystallised from propan-2-ol, giving 3'-benzyl-7,4'-dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (0.52 g.), m. p. 170.5—171.5°,  $[\alpha]_D^{20} + 158^\circ$  (Found: C, 61.7; H, 4.4; Cl, 15.9. C<sub>23</sub>H<sub>20</sub>Cl<sub>2</sub>O<sub>5</sub> requires C, 61.75; H, 4.5; Cl, 15.85%). Acidification of the alkaline extract gave crude 3'-benzylgriseofulvic acid (1.04 g.).

*Reaction of Griseofulvin with Phosphoryl Chloride and Lithium Chloride.*—Griseofulvin (1.7 g.) was added to phosphoryl chloride (10 ml.) containing water (0.1 ml.) and lithium chloride (1.7 g.), and the mixture heated on the steam-bath for 1 hr., then worked up as in the preceding experiment (chromatography was omitted), giving 7,4'-dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (1.74 g.), m. p. 239—244°.

*Reaction of 3'-Chlorogriseofulvin with Phosphoryl Chloride and Lithium Chloride.*—3'-Chlorogriseofulvin (0.49 g.) was treated with phosphoryl chloride (5.0 ml.) containing water (0.2 ml.) and lithium chloride (0.49 g.), and heated on the steam-bath for 5 hr. The mixture was worked up as in the preceding experiment, giving a solid (0.48 g.) which was recrystallised from acetic acid. The resulting 7,3',4'-trichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione had m. p. 231.5—233°, identical (infrared) with the product described below. This chloride, refluxed for 10 min. with methanol and potassium carbonate, gave 3'-chloroisogriseofulvin (infrared), m. p. 250—255°.

<sup>9</sup> Walker, Warburton, and Webb, *J.*, 1962, 1277.

*Reaction of Isogriseofulvin with Phosphoryl Chloride and Lithium Chloride.*—Isogriseofulvin (1.76 g.) was treated with phosphoryl chloride (10 ml.) containing water (0.2 ml.) and lithium chloride (1.76 g.) as in the corresponding reaction of griseofulvic acid. The mixture was worked up in the same way (treatment with Girard reagent was omitted), giving 7,2'-dichloro-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (1.70 g.), m. p. 191—191.5°.

*Reaction of 3'-Chloroisogriseofulvin with Phosphoryl Chloride and Lithium Chloride.*—3'-Chloroisogriseofulvin<sup>9</sup> (0.97 g.) was heated with phosphoryl chloride (10 ml.) containing water (0.4 ml.) and lithium chloride (0.97 g.), on the steam-bath for 5 hr. Working up as in the preceding experiment gave a solid (0.84 g.), m. p. 211—216°, shown by infrared analysis to contain ca. 70% of the 4'-chloride and 30% of starting material. The alkaline extract contained ca. 0.2 g. of 3'-chlorogriseofulvic acid. The neutral product was heated on the steam-bath for 30 min. with acetic acid (4.0 ml.) and 2*N*-sulphuric acid (0.8 ml.) to hydrolyse starting material, and the resulting 3'-chlorogriseofulvic acid (0.19 g.) was removed from an ethyl acetate solution of the product with 2*N*-sodium carbonate. The ethyl acetate solution gave 7,3',4'-trichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione, m. p. 229—231°, identical (infrared) with the material described above.

*Reaction of 3'-Benzylisogriseofulvin with Phosphoryl Chloride and Lithium Chloride.*—3'-Benzylisogriseofulvin<sup>3</sup> (6.6 g.) was treated with phosphoryl chloride (60 ml.) containing water (2.4 ml.) and lithium chloride (5.1 g.) and left overnight, then heated on the steam-bath. Working up as in the corresponding reaction of isogriseofulvin gave a colourless glass (6.0 g.). This was chromatographed on alumina containing increasing amounts (1—5%) of ether. The rotation of the eluates was measured. The earlier fractions contained the 4'-chloride (0.35 g.) (infrared). The later fractions contained the 2'-chloride (3.6 g., 60%), which was pure enough for use. A sample crystallised when moistened with ethanol, giving 3'-benzyl-7,2'-dichloro-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione, m. p. 123—125°,  $[\alpha]_D^{20} + 279^\circ$  (Found: C, 60.7; H, 4.7; Cl, 15.8.  $C_{23}H_{20}Cl_2O_5, \frac{1}{2}H_2O$  requires C, 60.5; H, 4.6; Cl, 15.5%).

*4'-Amino-7-chloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (Isogriseofulvamine).*—Isogriseofulvin (2.0 g.) was suspended in dry methanol (200 ml.) and a stream of ammonia passed into the suspension for 1½ hr. The solution was taken to dryness under reduced pressure, leaving a pale yellow solid (1.2 g.), m. p. 316—318°. Two recrystallisations from methanol gave *isogriseofulvamine* (0.41 g.), m. p. 321—322°,  $[\alpha]_D^{25} + 359^\circ$  (in methanol) (Found: C, 54.9; H, 5.2; Cl, 9.9; N, 3.8.  $C_{16}H_{14}ClNO_5, MeOH$  requires C, 55.2; H, 5.45; Cl, 9.95; N, 3.7%).

*3'-Chloroisogriseofulvamine.*—(a) From 7,3',4'-trichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione. The chloride (0.71 g.) in dry methanol (35 ml.), treated with gaseous ammonia for 30 min., gave 4'-amino-7,3'-dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (0.65 g.), m. p. 320° (decomp.) (from nitromethane),  $[\alpha]_D^{20} + 285^\circ$  (Found: C, 51.5; H, 4.05; Cl, 18.65; N, 3.9.  $C_{16}H_{13}Cl_2NO_5$  requires C, 51.7; H, 4.05; Cl, 19.05; N, 3.8%). (b) From 3'-chloroisogriseofulvin. 3'-Chloroisogriseofulvin,<sup>9</sup> treated with ammonia as described for *isogriseofulvamine*, gave the amine in 85% yield, with m. p. 320° (decomp.), identical (infrared) with the material just described.

Similar reactions gave: from 3'-bromoisogriseofulvin,<sup>9</sup> 4'-amino-3'-bromo-7-chloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (81%), m. p. 290—295° (decomp.) (from methanol),  $[\alpha]_D^{20} + 227^\circ$  (Found: C, 45.3; H, 3.6; Hal, 27.65; N, 3.4.  $C_{16}H_{13}BrClNO_5, \frac{1}{2}MeOH$  requires C, 45.9; H, 3.95; Hal, 26.7; N, 3.2%); from 3'-benzylisogriseofulvin,<sup>3</sup> 4'-amino-3'-benzyl-7-chloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (90%), m. p. 183—185° (from methanol),  $[\alpha]_D^{20} + 196^\circ$  (Found: C, 63.7; H, 5.5; Cl, 8.2; N, 3.4.  $C_{23}H_{22}ClNO_5, \frac{1}{2}H_2O$  requires C, 63.2; H, 5.3; Cl, 8.1; N, 3.2%); and from 3'-*n*-propylisogriseofulvin,<sup>3</sup> 4'-amino-7-chloro-4,6-dimethoxy-6'-methyl-3'-*n*-propylgris-3'-en-3,2'-dione (87%), m. p. 145—150° (from methanol and ether),  $[\alpha]_D^{20} + 225^\circ$  (Found: C, 60.15; H, 5.9; Cl, 9.35; N, 3.7.  $C_{19}H_{22}ClNO_5$  requires C, 60.0; H, 5.8; Cl, 9.3; N, 3.8%).

*Reaction of Griseofulvamine with Phosphoryl Chloride and Lithium Chloride.*—Griseofulvamine<sup>10</sup> (1.7 g.) was added to anhydrous phosphoryl chloride (10 ml.) containing lithium chloride (1.7 g.). The mixture was heated on the steam-bath for 15 min. and worked up as in the corresponding reaction of griseofulvin, giving 7,4'-dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,4'-dione (1.05 g.), m. p. 239—247°,  $[\alpha]_D^{20} + 282^\circ$ . Acidification of the sodium carbonate extract gave griseofulvic acid (100 mg.), and the hydrochloric acid extract, left for a few hours at room temperature, deposited more of the crystalline 4'-chloride.

<sup>10</sup> Grove, Macmillan, Mulholland, and Rogers, *J.*, 1952, 3949.

*Reaction of Isogriseofulvamine with Phosphoryl Chloride and Lithium Chloride.*—Isogriseofulvamine (80 g., solvated with one mole of methanol) was cautiously added to phosphoryl chloride (400 ml.) containing water (4.0 ml.) and lithium chloride (80 g.). The mixture was heated on the steam-bath for 75 min., then most of the phosphoryl chloride was removed under reduced pressure and the residual oil slowly treated in a cooling-bath with 2N-hydrochloric acid (800 ml.). The mixture was heated on the steam-bath for 1 hr. and cooled, then worked up as in the corresponding reaction of griseofulvin, giving 7,2'-dichloro-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (64.5 g., 84%), m. p. 192—194° (corr.) (from ethanol),  $[\alpha]_D^{20} +370^\circ$ . A second crop (5.15 g., 6.5%) had m. p. 189—194° (corr.). Griseofulvic acid (6.5 g.) was recovered from the alkaline extracts. In a small-scale experiment (1.7 g. of the amine) in which the acid hydrolysis was omitted, the chloride (0.89 g.) was obtained from the ethyl acetate extract, and the acid layer, after 3 hr. at room temperature, deposited more (0.45 g.) of the pure chloride.

*Reaction of 3'-Benzylisogriseofulvamine with Phosphoryl Chloride and Lithium Chloride.*—The amine (1.0 g.) was heated on the steam-bath for 3 hr. with phosphoryl chloride (10 ml.) containing water (0.2 ml.) and lithium chloride (1.0 g.), and the product was worked up as in the corresponding reaction of griseofulvin; it gave 3'-benzyl-7,2'-dichloro-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (0.8 g.), m. p. 122—125°, identical (infrared) with that described earlier.

*Reaction of 3'-Chloroisogriseofulvamine with Phosphoryl Chloride and Lithium Chloride.*—The amine (15.0 g.) was heated on the steam-bath for 5 hr. with phosphoryl chloride (150 ml.) containing water (3.0 ml.) and lithium chloride (15.0 g.) and worked up as in the preceding experiment. The residue was heated on the steam-bath for 2 hr. in acetic acid (150 ml.) and 2N-sulphuric acid (15 ml.). The solvent was removed under reduced pressure and the residue in acetic acid washed with water, 2N-sodium carbonate, and water, and dried (MgSO<sub>4</sub>). The ethyl acetate was removed, and the residue recrystallised from acetic acid, giving 7,2',3'-trichloro-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (8.7 g., 56%), m. p. 212.5—215° and 221—224.5°,  $[\alpha]_D^{20} +335^\circ$  (Found: C, 48.8; H, 3.3; Cl, 27.3. C<sub>18</sub>H<sub>13</sub>Cl<sub>3</sub>O<sub>5</sub> requires C, 49.1; H, 3.3; Cl, 27.2%).

*Reaction of 3'-n-Propylisogriseofulvamine with Phosphoryl Chloride and Lithium Chloride.*—The amine (10.5 g.) was heated on the steam-bath for 4 hr. with phosphoryl chloride (100 ml.) containing water (2.0 ml.) and lithium chloride (10.0 g.), and worked up as in the preceding experiment. The final ethyl acetate solution was passed through a short column of kieselguhr, and the solvent removed, giving 7,2'-dichloro-4,6-dimethoxy-6'-methyl-3'-n-propylgris-2'-en-3,4'-dione (8.23 g., 74%), m. p. 196—198°,  $[\alpha]_D^{20} +307^\circ$  (Found: C, 56.9; H, 5.15; Cl, 17.6. C<sub>19</sub>H<sub>20</sub>Cl<sub>2</sub>O<sub>5</sub> requires C, 57.1; H, 5.1; Cl, 17.8%).

*7-Chloro-4'-mercapto-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione.*—A solution of 7,4'-dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione (3.6 g.) in dry acetone was treated at room temperature with hydrogen sulphide in acetone (2.3% w/v; 200 ml.). Triethylamine (3.0 ml.) was added, and after 4 days the solution was evaporated under reduced pressure and the residue in ethyl acetate was washed with 2N-hydrochloric acid, water, N-sodium carbonate, and water. The alkaline extract was freed from acetone under reduced pressure, then acidified with 2N-hydrochloric acid. The precipitate was washed with water and dried, giving material (2.58 g.) that softened at 235°. A sample, when boiled with acetic acid, partly dissolved and crystallised, giving the thiol, m. p. 244—245.5° (decomp.). The infrared spectrum of this compound, which was not obtained pure, showed a strong band at 2550 cm.<sup>-1</sup> in Nujol (SH).

*7-Chloro-4'-methylthio-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione.*—The crude thiol (0.71 g.) from the preceding experiment, suspended in dry acetone, was treated with triethylamine (0.31 ml.), giving a yellow solution, which was treated with an excess of ethereal diazomethane. The product in ethyl acetate was washed with 2N-hydrochloric acid, water, 2N-sodium carbonate, and water. The solution was dried (MgSO<sub>4</sub>) and evaporated, and the residue washed with ether and recrystallised from acetonitrile, giving the *methylthio-compound* (0.35 g.), m. p. 229.5—232.5° (Found: C, 55.5; H, 4.9; Cl, 9.7. C<sub>17</sub>H<sub>17</sub>ClO<sub>5</sub>S requires C, 55.4; H, 4.65; Cl, 9.6%).

*Di-(7-chloro-4,6-dimethoxy-6'-methyl-3,2'-dioxogris-3'-en-4-yl) Disulphide.*—A cooled solution of the crude thiol (III; R = H, R' = SH) (1.78 g.) in dimethylformamide (25 ml.) was treated with potassium acetate (1.08 g.), then with bromine (0.30 ml.), and after 10 min. poured into water. The pH was adjusted to 1 and a little sodium hydrogen sulphite solution added. The solid (1.50 g.) recrystallised from dimethylformamide, giving the *disulphide* (0.95 g.), m. p.



289° (decomp.) (Found: C, 54.1; H, 4.0; Cl, 10.2; S, 8.6.  $C_{32}H_{28}Cl_2O_{10}S_2$  requires C, 54.3; H, 4.0; Cl, 10.0; S, 9.1%).

*Reaction of 7,4'-Dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione with Phenol.*—The chloride was refluxed in ethyl methyl ketone for 4 hr. with a large excess of phenol and potassium carbonate, giving 7-chloro-4,6-dimethoxy-6'-methyl-4'-phenoxygris-3'-en-3,2'-dione (75%), m. p. 207—208.5° (from ethyl acetate),  $[\alpha]_D^{20} + 93.5^\circ$  ( $c$  0.5) (Found: C, 63.7; H, 4.9; Cl, 8.6.  $C_{22}H_{19}ClO_6$  requires C, 63.7; H, 4.6; Cl, 8.55%).

*Reaction of 7,4'-Dichloro-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione with Thiols.*—Treatment of the 4'-chloride in acetone with the appropriate thiol in the presence of triethylamine at room temperature for 24 hr., as described below for the isomeric 2'-chloride, gave the following *gris-3'-en-3,2'-diones*: 7-Chloro-4'-ethylthio-4,6-dimethoxy-6'-methyl- (60%), m. p. 177—179° (from nitromethane),  $[\alpha]_D^{20} + 236^\circ$  (Found: C, 56.4; H, 4.95; Cl, 9.35.  $C_{18}H_{19}ClO_6S$  requires C, 56.45; H, 5.0; Cl, 9.3%). 7-Chloro-4,6-dimethoxy-6'-methyl-4'-phenylthio- (60%), m. p. 229—231° and 244—245° (from nitromethane),  $[\alpha]_D^{20} + 110^\circ$  ( $c$  0.5) (Found: C, 61.0; H, 4.6; S, 7.4.  $C_{22}H_{18}ClO_6S$  requires C, 61.3; H, 4.4; S, 7.4%). 4'-Benzylthio-7-chloro-4,6-dimethoxy-6'-methyl- (40%), m. p. 145—147° (from methanol),  $[\alpha]_D^{20} + 181^\circ$  ( $c$  0.2) (Found: C, 61.8; H, 4.8; Cl, 8.0.  $C_{23}H_{21}ClO_6S$  requires C, 62.1; H, 4.8; Cl, 8.0%). 7-Chloro-4'-(2-dimethylaminoethylthio)-4,6-dimethoxy-6'-methyl- [20% yield after purification as the hydrochloride, and finally, by chromatography on alumina (Grade IV)], m. p. 97—102° (from propan-2-ol) (Found: C, 57.9; H, 6.1; Cl, 7.9; N, 3.0; S, 7.1.  $C_{23}H_{23}ClNO_6S$  requires C, 58.2; H, 6.2; Cl, 7.8; N, 3.1; S, 7.1%). 7-Chloro-4'-(2-hydroxyethyl)-4,6-dimethoxy-6'-methyl- (57%), m. p. 138—140° (from benzene-ether),  $[\alpha]_D^{20} + 232^\circ$  (Found: C, 54.25; H, 4.9; Cl, 9.0; S, 8.4.  $C_{18}H_{19}ClO_6S$  requires C, 54.2; H, 4.8; Cl, 8.9; S, 8.0%) {acetylation with acetic anhydride in pyridine at 25° for 65 hr. gave the *acetate* (85% yield), m. p. 162—163° (from ethanol),  $[\alpha]_D^{20} + 196^\circ$  (Found: C, 54.1; H, 4.9; Cl, 8.3; S, 7.1.  $C_{20}H_{21}ClO_6S$  requires C, 54.5; H, 4.8; Cl, 8.1; S, 7.3%)}

*Reaction of 7,2'-Dichloro-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione with Alcohols.*—The chloride (1.0 g.) was refluxed for 45 min. with potassium carbonate (1.0 g.) in dry ethanol (30 ml.), and the solvent removed. The residue in ethyl acetate was passed through an alumina column, and the solid remaining after removal of the solvent was washed with ether and recrystallised from ethanol, giving 7-chloro-2'-ethoxy-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione (0.4 g.), m. p. 203—206°,  $[\alpha]_D^{20} + 317^\circ$ , identical (infrared) with material prepared by known methods.<sup>2</sup>

Treating the chloride for 15.5 hr. as just described with propan-1-ol gave 7-chloro-4,6-dimethoxy-6'-methyl-2'-n-propoxygris-2'-en-3,4'-dione (50%), m. p. 158—160°,  $[\alpha]_D^{20} + 288^\circ$ , identical (infrared) with material prepared by known methods.<sup>2</sup>

*Reaction of 7,2',3'-Trichloro-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione with Sodium Phenoxide.*—Treatment of the chloride (1.0 g.) for 10 min. at room temperature with sodium phenoxide (1.0 g.) in dry acetone (25 ml.) gave 7,3'-dichloro-4,6-dimethoxy-6'-methyl-2'-phenoxygris-2'-en-3,4'-dione (50%), m. p. 260—262° (from acetonitrile),  $[\alpha]_D^{20} + 171^\circ$  (Found: C, 58.9; H, 4.0; Cl, 16.3.  $C_{22}H_{18}Cl_2O_6$  requires C, 58.8; H, 4.0; Cl, 15.8%).

*Preparation of 2'-Thiols from Chlorides.*—The *thiols* shown in the Table were prepared as follows: The 2'-chloride (*ca.* 1 g.) in an anhydrous ketone (20—50 ml.) was treated in a stoppered flask or sealed tube with the appropriate thiol (*ca.* 1 ml.) and triethylamine (*ca.* 1 ml.) for the time and at the temperature specified. The mixture was evaporated to dryness and the residue treated with water and extracted with ethyl acetate. The ethyl acetate solution was washed with water, 2N-sodium carbonate, water, 2N-hydrochloric acid, and water, dried ( $MgSO_4$ ), and evaporated. The residue was chromatographed in benzene-ethyl acetate on alumina if necessary, then recrystallised.

*Reaction of 7,2'-Dichloro-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione with Amines.*—The chloride (4.0 g.) in pure dioxan (150 ml.) and water (30 ml.) was stirred under nitrogen. 2-Diethylaminoethylamine (6.5 g., 2 equiv.) was added, and after 45 min. the pH, which had fallen to 9.8, was adjusted to 11—12 with 2N-sodium hydroxide and kept in that range for *ca.* 7 hr. After 13 ml. of sodium hydroxide had been added, the pH remained constant. Acetic acid was added until the pH was 6.5 and the solution concentrated to a small volume under reduced pressure. The residue was shaken with 2N-hydrochloric acid and ethyl acetate; a colourless solid separated. Filtration gave the *hydrochloride* (8.5 g.), m. p. 229—231° (from water), raised to 230—232° by recrystallisation from ethanol (Found: C, 56.1; H, 6.6; Cl, 15.0; N, 5.5.  $C_{22}H_{20}Cl_2N_2O_6$  requires C, 55.8; H, 6.4; Cl, 15.0; N, 5.9%).

2'-Thiols (II; R' = SR<sup>a</sup>).

R	R''	Time (hr.)	Temp.	Solvent	Yield (%)	M. p.	[α] <sub>D</sub> <sup>b</sup>	Formula	C	H	Cl	S	Found (%)	Required (%)
H	Me	40	25°	Me <sub>2</sub> CO	65	251-253 <sup>c,f</sup>	500°	C <sub>22</sub> H <sub>17</sub> ClO <sub>5</sub> S	55.1	4.5	9.8	8.3	55.4	4.65
H	Et	40	25	Me <sub>2</sub> CO	40	185-187 <sup>g</sup>	475	C <sub>23</sub> H <sub>19</sub> ClO <sub>5</sub> S	56.2	5.1	9.3	8.3	56.45	5.0
H	Pr <sup>n</sup>	24	80	COMeEt	30 <sup>e</sup>	166.5-168 <sup>h</sup>	459	C <sub>24</sub> H <sub>21</sub> ClO <sub>5</sub> S	57.8	5.3	9.0	8.3	57.5	5.3
H	Bu <sup>n</sup>	24	56	Me <sub>2</sub> CO	35 <sup>e</sup>	154.5-156.5 <sup>g</sup>	429	C <sub>25</sub> H <sub>23</sub> ClO <sub>5</sub> S	58.6	5.95	8.6	7.9	58.5	5.6
H	CH <sub>3</sub> CH <sub>2</sub> OH	220	25	Me <sub>2</sub> CO	83	181-183 <sup>i</sup>	373	C <sub>26</sub> H <sub>25</sub> ClO <sub>5</sub> S	54.0	5.0	9.0	7.9	54.2	4.8
H	CH <sub>3</sub> CH <sub>2</sub> X <sup>e</sup>	110	25	Me <sub>2</sub> CO	47 <sup>e</sup>	204-206 <sup>g</sup>	350 <sup>i</sup>	C <sub>26</sub> H <sub>25</sub> ClNO <sub>2</sub> S <sup>n</sup>	59.2	4.4	6.7	5.8	59.1	4.2
H	Y <sup>b</sup>	10	78	EtOH	42 <sup>g</sup>	215-216 <sup>j</sup>	360 <sup>i</sup>	C <sub>26</sub> H <sub>25</sub> Cl <sub>2</sub> NO <sub>2</sub> S <sup>l,o</sup>	49.5	4.6	15.6	6.7	49.8	4.4
H	Ph	0-17	25	Me <sub>2</sub> CO	50	229-231 <sup>k</sup>	110	C <sub>24</sub> H <sub>19</sub> ClO <sub>5</sub> S	61.0	4.6	7.4	7.4	61.3	4.4
H	Et <sub>2</sub> N-CH <sub>2</sub> -CH <sub>3</sub>	24	25	Me <sub>2</sub> CO	70 <sup>d</sup>	244-245 <sup>l</sup>	378 <sup>g</sup>	C <sub>23</sub> H <sub>20</sub> ClNO <sub>2</sub> S <sup>p</sup>	57.8	6.3	7.9	7.8	58.2	6.2
H	CH <sub>2</sub> Ph	16	25	Me <sub>2</sub> CO	40	210-212 <sup>i</sup>	336	C <sub>23</sub> H <sub>19</sub> ClO <sub>5</sub> S	61.9	4.8	7.9	7.8	62.1	4.8
H	Allyl	16	25	Me <sub>2</sub> CO	65	153-154 <sup>g</sup>	443	C <sub>24</sub> H <sub>21</sub> ClO <sub>5</sub> S	57.7	4.8	9.3	7.7	57.8	4.85
Br	Me	0-33	25	Me <sub>2</sub> CO	54	190-193 <sup>h</sup>	408	C <sub>21</sub> H <sub>15</sub> BrClO <sub>5</sub> S	46.0	3.6	25.7 <sup>r</sup>	7.8	45.6	3.6
Cl	Me	18	25	Me <sub>2</sub> CO	65	192.5-195 <sup>h</sup>	471	C <sub>21</sub> H <sub>15</sub> Cl <sub>2</sub> O <sub>5</sub> S	50.6	4.2	17.7	7.7	51.8	4.0
Cl	Et	18	25	Me <sub>2</sub> CO	66	184.5-186.5 <sup>g</sup>	385	C <sub>24</sub> H <sub>19</sub> Cl <sub>2</sub> O <sub>5</sub> S	51.6	4.45	17.0	7.7	51.8	4.35
Cl	Pr <sup>n</sup>	18	25	Me <sub>2</sub> CO	70	135-137 <sup>h</sup>	373	C <sub>25</sub> H <sub>21</sub> Cl <sub>2</sub> O <sub>5</sub> S	53.0	4.85	16.3	7.3	52.9	4.7
Cl	Bu <sup>n</sup>	18	25	Me <sub>2</sub> CO	55 <sup>e</sup>	103.5-106.5 <sup>k</sup>	350	C <sub>26</sub> H <sub>23</sub> Cl <sub>2</sub> O <sub>5</sub> S	54.2	5.0	16.05	6.7	53.9	5.0
Cl	Allyl	18	25	Me <sub>2</sub> CO	20 <sup>e</sup>	133.5-135.5 <sup>g</sup>	342	C <sub>24</sub> H <sub>19</sub> Cl <sub>2</sub> O <sub>5</sub> S	52.9	4.2	16.7	7.2	53.15	4.2
Cl	CH <sub>2</sub> Ph	18	25	Me <sub>2</sub> CO	30	136.5-138.5 <sup>h</sup>	202.5	C <sub>23</sub> H <sub>18</sub> Cl <sub>2</sub> O <sub>5</sub> S <sup>m</sup>	57.3	4.2	15.1	6.7	57.6	4.2
CH <sub>2</sub> Ph	Me	24	40	Me <sub>2</sub> CO	62	219-220 <sup>g</sup>	455	C <sub>23</sub> H <sub>18</sub> ClO <sub>5</sub> S	62.3	5.2	7.7	6.4	62.3	5.4
CH <sub>2</sub> Ph	Et	96	40	Me <sub>2</sub> CO	63	178-180 <sup>g</sup>	465	C <sub>24</sub> H <sub>20</sub> ClO <sub>5</sub> S	63.3	5.4	7.9	6.2	63.5	5.3
CH <sub>2</sub> Ph	Pr <sup>n</sup>	22	100	Me <sub>2</sub> CO	67	115-116 <sup>k</sup>	451	C <sub>24</sub> H <sub>20</sub> ClO <sub>5</sub> S	63.8	5.5	7.3	6.1	64.1	5.6
CH <sub>2</sub> Ph	Bu <sup>n</sup>	60	40	Me <sub>2</sub> CO	60 <sup>e</sup>	—	390	C <sub>27</sub> H <sub>23</sub> ClO <sub>5</sub> S <sup>m</sup>	63.6	6.3	7.3	5.8	64.2	6.2
CH <sub>2</sub> Ph	Allyl	48	40	Me <sub>2</sub> CO	55	127-129 <sup>k</sup>	465	C <sub>24</sub> H <sub>20</sub> ClO <sub>5</sub> S	63.9	5.1	7.3	6.1	64.4	5.2
CH <sub>2</sub> Ph	CH <sub>2</sub> Ph	48	40	Me <sub>2</sub> CO	40	159-161 <sup>g</sup>	337	C <sub>23</sub> H <sub>19</sub> ClO <sub>5</sub> S	66.3	5.1	6.6	6.1	66.2	5.2
Pr <sup>n</sup>	Me	60	40	Me <sub>2</sub> CO	78	119-121 <sup>g</sup>	457	C <sub>23</sub> H <sub>19</sub> ClO <sub>5</sub> S	58.15	5.5	9.1	7.4	58.5	5.6
Pr <sup>n</sup>	Pr <sup>n</sup>	54	100	Et <sub>2</sub> CO	60	112-113 <sup>g</sup>	423	C <sub>23</sub> H <sub>19</sub> ClO <sub>5</sub> S	60.0	6.1	8.35	7.1	60.2	6.2
Pr <sup>n</sup>	Bu <sup>n</sup>	100	100	Et <sub>2</sub> CO	40	90-91 <sup>g</sup>	402	C <sub>23</sub> H <sub>19</sub> ClO <sub>5</sub> S	8.0	6.8	8.0	6.8	7.8	7.1
Pr <sup>n</sup>	Allyl	70	50	Me <sub>2</sub> CO	36	109-110 <sup>g</sup>	425	C <sub>23</sub> H <sub>19</sub> ClO <sub>5</sub> S	60.15	5.7	8.2	7.2	60.5	5.8
Pr <sup>n</sup>	CH <sub>2</sub> Ph	40	100	Et <sub>2</sub> CO	57	132-133 <sup>h</sup>	254	C <sub>23</sub> H <sub>19</sub> ClO <sub>5</sub> S	7.4	6.2	7.4	6.2	7.3	6.6

<sup>a</sup> X = Phthalimido. <sup>b</sup> Y = 2-(2-Imidazolyl). <sup>c</sup> Purified by chromatography before crystallisation. <sup>d</sup> Washing with acid omitted. <sup>e</sup> From MeNO<sub>2</sub>. <sup>f</sup> From EtOH. <sup>g</sup> From MeOH. <sup>h</sup> From EtOAc. <sup>i</sup> Hydrochloride, cryst. from EtOH-COMe<sub>2</sub>; [α]<sub>D</sub> is for H<sub>2</sub>O soln. <sup>j</sup> From Pr-OH. <sup>k</sup> In H<sub>2</sub>O. <sup>l</sup> +0.5EtOH. <sup>m</sup> Found: N, 2.7%. <sup>n</sup> Found: N, 2.8. <sup>o</sup> Found: N, 6.0. <sup>p</sup> Found: N, 6.1%. <sup>q</sup> Found: N, 3.1%. <sup>r</sup> Found: N, 3.1%. <sup>s</sup> c 0.5 as hydrochloride in water. <sup>t</sup> Hydrochloride, m. p. 231-233° (Found: C, 54.3; H, 6.2; Cl, 14.5. C<sub>23</sub>H<sub>19</sub>Cl<sub>2</sub>NO<sub>2</sub>S requires C, 53.9; H, 6.0; Cl, 14.5%). <sup>u</sup> Total halogen.

The hydrochloride was shaken with ethyl acetate and sodium carbonate solution, and the ethyl acetate layer worked up to give 7-chloro-2'-(2-diethylamino)-4,6-dimethoxy-6'-methylgris-2'-en-3,4'-dione, m. p. 132—134° (from acetone and hexane),  $[\alpha]_D^{20} + 421^\circ$  (Found: C, 61.0; H, 6.8; Cl, 8.2; N, 6.3.  $C_{22}H_{29}ClN_2O_5$  requires C, 60.5; H, 6.7; Cl, 8.1; N, 6.4%).

The following substituted griseofulvamines were similarly prepared: 7-Chloro-4,6-dimethoxy-2'-(3-dimethylaminopropylamino)-6'-methyl-, m. p. 236° (decomp.) (from ethanol),  $[\alpha]_D^{20} + 338^\circ$  (in water) (Found: C, 54.4; H, 6.6; Cl, 14.7; N, 6.1.  $C_{21}H_{28}Cl_2N_2O_5$  requires C, 54.9; H, 6.1; Cl, 15.5; N, 6.1%), and 7-chloro-2'-(3-diethylaminopropylamino)-4,6-dimethoxy-6'-methyl-gris-2'-en-3,4'-dione hydrochloride, m. p. 217—220° (from ethanol and ether),  $[\alpha]_D^{20} + 366^\circ$  (Found: C, 56.4; H, 6.8; Cl, 14.4; N, 5.5.  $C_{23}H_{32}Cl_2N_2O_5$  requires C, 56.7; H, 6.7; Cl, 14.6; N, 5.75%).

7-Chloro-4'-diethylaminoethylamino-4,6-dimethoxy-6'-methylgris-3'-en-3,2'-dione.—The chloride (10.0 g.) in dioxan (250 ml.) and water (50 ml.), treated as in the preceding experiment with 2-diethylaminoethylamine (6.5 g.), at pH 9.2—10 during 5 hr., gave the amine, which was not obtained pure and was characterised as the hydrogen oxalate, m. p. 202—205° (decomp.) (from ethanol),  $[\alpha]_D^{20} + 244^\circ$  (in water) (Found: C, 54.1; H, 6.2; Cl, 6.6; N, 5.0.  $C_{24}H_{31}ClN_2O_6$  requires C, 54.7; H, 5.9; Cl, 6.7; N, 5.3%).

7-Chloro-4,6-dimethoxy-6'-methyl-4'-piperidinogris-3'-en-3,2'-dione.—The 4'-chloride (5.0 g.) was dissolved in piperidine (50 ml.) and left overnight at room temperature. The mixture was poured into 2N-hydrochloric acid (250 ml.); a solid (5.8 g.) separated. Extraction of the filtrate with ethyl acetate gave an additional 1.0 g. The combined solids crystallised from ethanol, giving the amine (4.4 g., 80%), m. p. 185—190°,  $[\alpha]_D^{20} + 415^\circ$  (Found: C, 61.9; H, 6.05; Cl, 8.6; N, 3.1.  $C_{21}H_{24}ClNO_5$  requires C, 62.1; H, 6.0; Cl, 8.7; N, 3.45%).

7-Chloro-4,6-dimethoxy-6'-methyl-4'-(1-pyrrolidinyl)gris-3'-en-3,2'-dione.—Treatment of the 4'-chloride with pyrrolidine instead of piperidine, as in the preceding experiment, gave the amine (48% yield), m. p. 248—253°,  $[\alpha]_D^{20} + 319^\circ$  (Found: C, 61.0; H, 6.2; N, 3.2.  $C_{20}H_{22}ClNO_5$  requires C, 61.3; H, 6.2; N, 3.2%).