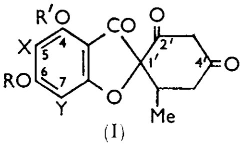
301. *Griseofulvin Analogues. Part VI.*[1] *Dechlorogriseofulvin and Some of its Derivatives.*

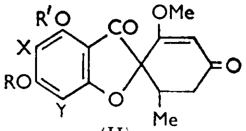
By V. Arkley, G. I. Gregory, and T. Walker.

Catalytic reduction of griseofulvic acid (I; R = R′ = Me, X = H, Y = Cl) gave the dechloro-triketone (I; R = R′ = Me, X = Y = H), which on methylation gave dechlorogriseofulvin (II; R = R′ = Me, X = Y = H) and dechloroisogriseofulvin (III; R = R′ = Me, X = Y = H). Nitration of the last two compounds gave the corresponding 5- and 7-nitro-compounds, which were reduced to the amines. Nitration of griseofulvic acid gave a 3′-nitro-compound (V; X = NO_2, Y = Cl), which was reduced to the 3′-amino-compound (V; X = NH_2, Y = Cl) or the corresponding dechloro-compound. Attempts to prepare 7-fluorogriseofulvin from the corresponding amine were unsuccessful. 5-Nitrogriseofulvin (II; R = R′ = Me, X = NO_2, Y = Cl) was demethylated at both positions 4 and 6 by lithium iodide.

As part of the programme for modifying griseofulvin (II; R = R′ = Me, X = H, Y = Cl) described in earlier papers,[1] we have examined the replacement of the 7-chlorine atom by other groups. A previous worker[2] has shown that some dechlorination takes place during the hydrogenation of griseofulvin in presence of palladium, but ring C was reduced in the resulting products which were therefore of little value for preparation of griseofulvin analogues. Attempts to dechlorinate the bisketal[3] (IV; R = Me, X = Cl) by hydrogenolysis in the presence of palladium–carbon were unsuccessful. However hydrogenolysis of griseofulvic acid (I; R = R′ = Me, X = H, Y = Cl), by use of palladium–carbon under alkaline conditions, gave the dechloro-triketone (I; R = R′ = Me, X = Y = H) in good yield. Treatment with diazomethane and separation of the ethers with Girard's reagent P,[3] or by chromatography,[4] then gave dechlorogriseofulvin (II; R = R′ = Me, X = Y = H) and dechloroisogriseofulvin (III; R = R′ = Me, X = Y = H); the former was identical with what MacMillan[5] obtained by fermentation.



(I)



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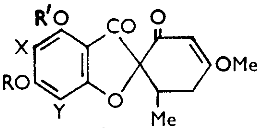

(III)

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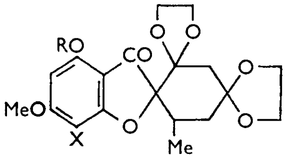
[1] Part V, *J.*, 1962, 1292.
[2] Mulholland, *J.*, 1952, 3987.
[3] Arkley, Attenburrow, Gregory, and Walker, *J.*, 1962, 1260.
[4] Duncanson, Grove, and Jeffs, *J.*, 1958, 2929.
[5] MacMillan, *J.*, 1953, 1697.

Before undertaking the nitration of dechlorogriseofulvin, nitration of griseofulvin and griseofulvic acid was studied. Fuming nitric acid in acetic acid–acetic anhydride readily gave 5-nitrogriseofulvin (II; R = R′ = Me, X = NO_2, Y = Cl). Hydrolysis of this compound gave the 5-nitro-triketone (I; R = R′ = Me, X = NO_2, Y = Cl). Reduction of 5-nitrogriseofulvin with iron in acetic acid[6] gave 5-aminogriseofulvin (II; R = R′ = Me, X = NH_2, Y = Cl). The optical rotation of 5-nitrogriseofulvin was lower than that expected on the basis of a comparison by molecular weight with griseofulvin. This was also true of the 5-amine when measured as the hydrochloride. Nitration of griseofulvic acid with fuming nitric acid in acetic acid gave the 3′-nitro-triketone (V; X = NO_2, Y = Cl). Catalytic reduction of this under alkaline conditions gave the 3′-amino-triketone (V; X = NH_2, Y = Cl), accompanied, especially under more alkaline conditions and on longer hydrogenation, by the 3′-amino-7-dechloro-triketone (V; X = NH_2, Y = H). These amino-triketones were isolated as their *N*-benzoyl derivatives (V; X = Bz·NH, Y = Cl or H). With diazomethane the 3′-nitro-triketone (V; X = NO_2, Y = Cl) gave a mixture of labile neutral ethers that reverted to the triketone on alumina. Crystallisation of the mixture gave a pure compound, which was assigned the 2′-methyl ether structure (VI; R = Me, X = NO_2, Y = Cl) by comparing its ultraviolet ($\lambda_{max.}$ 292 mμ) and infrared spectra [$\nu_{max.}$ 1702—1686 (ketones), 1534 + 1348 cm.$^{-1}$ (NO_2)] with those of the 3′-substituted griseofulvins described previously.[7] The 3′-benzamido-triketone (V; X = Bz·NH, Y = Cl) with diazomethane gave three products, which were separated by chromatography on alumina: two of these had the spectroscopic properties expected for the 2′- and the 4′-methyl ether (VI and VII; R = Me, X = Bz·NH, Y = Cl); the least polar compound contained four methoxy-groups and is assigned structure (VIII) on the basis of its analysis, infrared spectrum (lack of NH band and bands at *ca.* 1350, 1225, and 1282 cm.$^{-1}$ favour the 2′-ether [1]), ultraviolet spectrum ($\lambda_{max.}$ 290 mμ), and behaviour on chromatography. A similar sequence of reactions was used to prepare the 3′-acetamido-ether (VI; R = Me, X = Ac·NH, Y = Cl).



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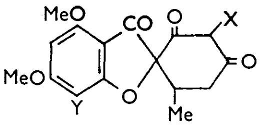
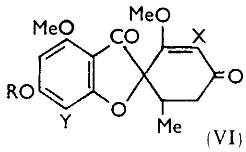


(V)



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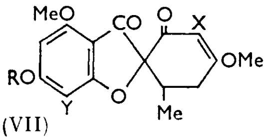

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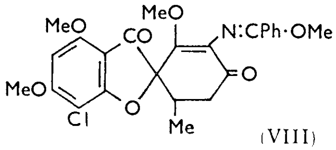

(VIII)

Nitration of dechlorogriseofulvin, in acetic acid containing acetic anhydride, gave a mixture of the 5- and the 7-nitro-compound (II; R = R′ = Me, X = NO_2, Y = H; and Y = NO_2, X = H), which were separated by chromatography on alumina into crystalline solids with specific rotations of +281° and +392°, respectively. Since neither isomer gave the blue colour with concentrated nitric acid characteristic of dechlorogriseofulvin[5] and usually associated with the absence of a substituent at position 7, we assigned their structure on the basis of the chemical evidence. Reduction of both nitro-compounds to the corresponding amines (II; R = R′ = Me and X = NH_2, Y = H; or X = H, Y = NH_2) was accomplished with iron in acetic acid, and the amine from the nitro-compound with the lower rotation was converted into the corresponding *N*-benzoyl derivative. This compound was also prepared by catalytically reducing 5-nitrogriseofulvic acid (I;

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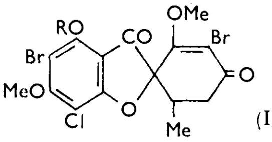
[6] Béchamp, *Annalen*, 1854, **92**, 401; Witt, *Ber.*, 1912, **45**, 2380.

[7] Gregory, Holten, Robinson, and Walker, *J.*, 1962, 1269.

$R = R' = Me$, $X = NO_2$, $Y = Cl$) under alkaline conditions, chlorine being lost to give 5-aminodechlorogriseofulvic acid (I; $R = R' = Me$, $X = NH_2$, $Y = H$), which was isolated as its *N*-benzoyl derivative (I; $R = R' = Me$, $X = Bz{\cdot}NH$, $Y = H$). Methylation of this triketone and separation of the 2'- and the 4'-methyl ether by chromatography on alumina gave 5-benzamidodechlorogriseofulvin (II; $R = R' = Me$, $X = Bz{\cdot}NH$, $Y = H$), thus establishing the structure of the 5- and 7-nitro-compounds. These assignments were supported by spectroscopic results and by comparing the optical rotations of these nitro-compounds with that of 5-nitrogriseofulvin.

One object of the work was to prepare an analogue of griseofulvin in which the 7-chlorine atom was replaced by fluorine. Attempts to apply the Baltz–Schiemann reaction[8] to 7-aminogriseofulvin (II; $R = R' = Me$, $X = H$, $Y = NH_2$) were unsuccessful. Diazotisation in presence of butyl nitrite[9] or tetrahydrofuran[10] gave a water-soluble diazonium fluoroborate, which could not be pyrolysed to fluorogriseofulvin. Attempted catalysed decomposition of the diazonium salt with copper or copper salts[11] led to rapid deamination and recovery of dechlorogriseofulvin. A recent note[12] had described the total synthesis of racemic 7-fluorodechlorogriseofulvin (II; $R = R' = Me$, $X = H$, $Y = F$) and the conversion of norgriseofulvic acid (I; $R = H$, $R' = Me$, $X = H$, $Y = Cl$) into "*d,d*"-fluorogriseofulvin in a series of reactions with perchloryl fluoride as the fluorinating agent.

As part of this work, we wished to see whether a 5-nitrogriseofulvin could be easily demethylated. Previously[13] 5,3'-dibromogriseofulvin (IX; $R = Me$) was demethylated with lithium bromide to the 4-phenol (IX; $R = H$), whereas griseofulvin did not react. It has now been shown that treatment of 5-nitrogriseofulvin (II; $R = R' = Me$, $Y = NO_2$, $Y = Cl$) with lithium iodide gave a phenol shown to be the 4,6-dihydroxy-compound (II; $R = R' = H$, $X = NO_2$, $Y = Cl$), as its hydrolysis with mineral acid gave a product that contained no methoxy-groups (Zeisel). The 4- and the 6-methoxy-group in 5-nitrogriseofulvic acid were shown to be stable to acid hydrolysis.



(IX)

The phenol (II; $R = R' = H$; $X = NO_2$, $Y = Cl$) had an anomalous carbonyl band (1728 cm.$^{-1}$) in its infrared spectrum and this was associated with changes in bands in the aromatic region. It seemed possible that in this compound ring A exists in a keto-form.[12] An examination of the ultraviolet absorption spectrum provided some extra evidence as the spectrum of the compound did not resemble that of the phenol (II; $R = Me$, $R' = H$, $X = H$, $Y = Cl$) or that of the 6-hydroxy-compound (II; $R = H$, $R' = Me$, $X = H$, $Y = Cl$). Methylation of the "phenol" (II; $R = R' = H$, $X = NO_2$, $Y = Cl$) with diazomethane gave 5-nitrogriseofulvin, identified by its infrared spectrum.

EXPERIMENTAL

M. p.s are corrected. Solvents (except when otherwise stated) were acetone for optical rotations, measured at 20—23° (c 1 ± 0·3%), ethanol for ultraviolet absorption spectra, and bromoform for infrared spectra. Solutions in organic solvents were dried over magnesium sulphate before evaporation. Alumina for chromatography was Woelm's material of pH 4 and Brockmann grade II or III. Thin-layer chromatography was carried out on Merck's "Kieselgel G" in 1 : 1 benzene–ethyl acetate.

4,6-*Dimethoxy*-6'-*methylgrisan*-3,2',4'-*trione* (I; $R = R' = Me$, $X = Y = H$). Griseofulvic acid (I; $R = R' = Me$, $X = H$, $Y = Cl$) (100 g.) was dissolved in water (3 l.) containing sodium carbonate (78 g., 5 equiv.) and shaken with hydrogen at room temperature and pressure

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[8] Roe, in "Organic Reactions," John Wiley and Sons, Inc., New York, 1949, Vol. V, p. 193.
[9] Gadeker, Frederick, Semb, and Vaughan, *J. Org. Chem.*, 1961, **26**, 468.
[10] Fletcher and Namkung, *Chem. and Ind.*, 1961, 179.
[11] Bergmann, Berkovic, and Ikan, *J. Amer. Chem. Soc.*, 1956, **78**, 6037.
[12] Taub, Kuo, and Wendler, *Chem. and Ind.*, 1962, 557.
[13] Walker, Warburton, and Webb, *J.*, 1962, 1277.

in presence of 10% palladised charcoal (10 g.). After 7 hr., 8½ l. of hydrogen had been absorbed (theory 7 l.) and a sample was withdrawn. Neutral material was removed by extraction with ethyl acetate, and the acidic fraction was isolated and analysed for chlorine (Cl, 0·42%); it had m. p. 238—240°, $[\alpha]_D$ +455° (*c* 0·9 in $NaHCO_3$). The main batch was shaken with hydrogen for a further hour, then filtered and extracted with ethyl acetate (500 ml.). The aqueous layer was freed from solvent and acidified. The precipitated dechlorogriseofulvic acid (I; R = R′ = Me, X = Y = H) (86 g., 96%) was crystallised from acetic acid, to give the pure sample, m. p. 244—247°, $[\alpha]_D$ +449° (*c* 0·995 in $NaHCO_3$) {MacMillan [5] gives m. p. 248—250° (decomp.), $[\alpha]_D$ +480° (*c* 1·0, as Na salt in H_2O); McMaster *et al.*[14] report m. p. 245—248°, $[\alpha]_D$ +420° (*c* 0·25 in 2N-NaOH)}, $\lambda_{max.}$ (in 0·1N-NaOH) 284 mμ (ε 47,100), $\nu_{max.}$ (in Nujol) 1660 cm.$^{-1}$ (CO·C:C· and bonded ketone) (Found: C, 63·0; H, 5·45; Cl, 0·0; OMe, 20·0. Calc. for $C_{16}H_{16}O_6$: C, 63·2; H, 5·3; Cl, 0·0; OMe, 20·4%).

The dechlorination was also carried out with aqueous triethylamine instead of sodium carbonate solution.

Treatment of the trione with boron trifluoride–ether complex and ethane-1,2-diol, under the standard conditions [3] gave *2′,4′-bisethylenedioxy-4,6-dimethoxy-6′-methylgrisan-3-one* (IV; R = Me, X = H) (100%), m. p. 182—183° (from ethanol), $[\alpha]_D$ −97°, $\lambda_{max.}$ 282 mμ (ε 21,200), $\nu_{max.}$ 1700 cm.$^{-1}$ (C=O) (Found: C, 61·2; H, 6·3; Cl, 0·0. $C_{20}H_{24}O_8$ requires C, 61·2; H, 6·2%). Treatment of the bisketal with magnesium iodide–ether complex [3] gave *2′,4′-bisethylenedioxy-4-hydroxy-6-methoxy-6′-methylgrisan-3-one* (IV; R = X = H) (43%), m. p. 229° (from acetone), $[\alpha]_D$ −115°, $\lambda_{max.}$ 281 mμ (ε 22,500), $\nu_{max.}$ 1675 cm.$^{-1}$ (CO·C:C·) (Found: C, 60·5; H, 6·0; Cl, 0·0. $C_{19}H_{22}O_8$ requires C, 60·3; H, 5·9%). Mineral-acid hydrolysis of the bisketal (IV; R = Me, X = H) regenerated dechlorogriseofulvic acid with identical physical constants with the earlier specimen.

4,6,2′-Trimethoxy-6′-methylgris-2′-en-3,4′-dione (II; R = R′ = Me, X = Y = H).—Dechlorogriseofulvic acid (I; R = R′ = Me, X = Y = H) (1·0 g.) in methanol (20 ml.) and triethylamine (0·3 ml.) was treated with an excess of ethereal diazomethane, the excess of which was later destroyed with acetic acid. The solvents were removed *in vacuo*. The residue was dissolved in ethyl acetate (50 ml.) and extracted with N-sodium carbonate (2 × 50 ml.) then water (2 × 50 ml.), and the solvent removed. The residual enol-ethers were separated by the Girard reagent as described earlier,[3] to give dechlorogriseofulvin (0·25 g., 24%), m. p. 177—179° (from ethanol), $[\alpha]_D$ +382°, $\lambda_{max.}$ 249 (ε 15,800) and 285 mμ (ε 25,900) {MacMillan [5] reports m. p. 179—181°, $[\alpha]_D$ +390°, $\lambda_{max.}$ (in MeOH) 250 (ε 15,140), 286 (ε 24,550), and ~325 (ε 4169)} (Found: C, 64·1; H, 5·7; Cl, 0·0; OMe, 29·4. Calc. for $C_{17}H_{18}O_6$: C, 64·2; H, 5·7; OMe, 29·2%).

The fraction which did not form a Girard derivative gave dechloroisogriseofulvin (0·4 g., 38%), m. p. 153° (from methanol), $[\alpha]_D$ +249°, $\lambda_{max.}$ 261 (ε 21,200) and 285 mμ (ε 21,400) [MacMillan [5] reports $\lambda_{max.}$ 266 (ε 26,550) and 286 mμ (ε 26,610)] (Found: C, 64·0; H, 5·7. Calc. for $C_{17}H_{18}O_6$: C, 64·2; H, 5·7%).

7-Chloro-4,6,2′-trimethoxy-6′-methyl-5-nitrogris-2′-en-3,4′-dione (II; R = R′ = Me, X = NO_2, Y = Cl).—Griseofulvin (25·0 g.) in glacial acetic acid (350 ml.) and acetic anhydride (100 ml.) at 30—35° was treated with fuming nitric acid (25 ml.) without external cooling. After 18 hr. at room temperature the mixture was poured into ice–water (3 l.) with stirring and the precipitated solid was collected and washed with water. The crude nitro-compound was dissolved in ethyl acetate (300 ml.), washed successively with sodium hydrogen carbonate solution and water, then dried, and the solvent was removed to give *5-nitrogriseofulvin* (II; R = R′ = Me, X = NO_2, Y = Cl) (16·0 g., 71%), m. p. 199—201° (from ethyl acetate), $[\alpha]_D$ +248°, $\lambda_{max.}$ 236 (ε 27,000), 277 (infl.) (ε 16,300), and 332 mμ (ε 4900), $\nu_{max.}$ 1718 (ketone), 1660 (COC:C·), and 1542 + 1350 cm.$^{-1}$ (NO_2) (Found: C, 51·3; H, 4·25; N, 3·1; Cl, 8·9. $C_{17}H_{16}ClNO_8$ requires C, 51·3; H, 4·05; N, 3·5; Cl, 8·9%). Hydrolysis of 5-nitrogriseofulvin with sulphuric acid in acetic acid [3] gave *5-nitrogriseofulvic acid* (I; R = R′ = Me, X = NO_2, Y = Cl) (85%), m. p. 210° (from methanol), $[\alpha]_D$ +178°, $\lambda_{max.}$ 266 (ε 28,400) and 333 mμ (ε 4500), $\nu_{max.}$ (in Nujol) 1708 (ketone), 1664 (CO·C:C·), and 1538 + 1368 cm.$^{-1}$ (NO_2) (Found: C, 49·8; H, 3·8; Cl, 9·2; N, 3·4. $C_{16}H_{14}ClNO_8$ requires C, 50·1; H, 3·7; Cl, 9·2; N, 3·65%).

5-Amino-7-chloro-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione (II; R = R′ = Me, X = NH_2, Y = Cl).—5-Nitrogriseofulvin (II; R = R′ = Me, X = NO_2, Y = Cl) (4·0 g.) was

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[14] McMaster, Scott, and Trippett, *J.*, 1960, 4628.

dissolved in acetic acid (120 ml.) and the mixture diluted with water (12 ml.). Iron filings (8·0 g.) were added gradually to the stirred solution and the mixture was stirred for 5½ hr. The mixture was filtered and diluted with water (1 l.), then extracted with ethyl acetate (3 × 100 ml.). Removal of the solvent from the dried ethyl acetate extract left the crude amine as a yellow foam (3·4 g.). Chromatography on alumina (200 g., grade II) and elution with benzene containing 5% and then 10% v/v of ethyl acetate gave *5-aminogriseofulvin* (II; R = R′ = Me, X = NH_2, Y = Cl) (0·4 g., 11%), m. p. 122—123° (EtOH), $[\alpha]_D$ +396°, $[\alpha]_D$ +295° (in 2N-HCl), $\lambda_{max.}$ 248 (ε 23,600), 285 (ε 11,300), and 397 mμ (ε 3190), $\lambda_{max.}$ (in 0·1N-HCl) 274 (ε 18,200) and 337 mμ (ε 4250), $\nu_{max.}$ 3470 + 3390 (NH_2), 1706 (C=O), 1656 cm.$^{-1}$ (CO·C:C·) (Found: C, 55·5; H, 5·1; Cl, 9·7; N, 3·8. $C_{17}H_{18}ClNO_6$ requires C, 55·5; H, 4·9; Cl, 9·65; N, 3·8%).

7-Chloro-4,6-dimethoxy-6′-methyl-3′-nitrogrisan-3,2′,4′-trione (V; X = NO_2, Y = Cl) (with R. F. K. MEREDITH).—Griseofulvic acid (10 g.) was suspended in glacial acetic acid (200 ml.) and treated with fuming nitric acid (10 ml.). The mixture was stirred at room temperature for 2 hr. and the solid was collected (11·75 g.) and washed with ether. Crystallisation from acetone gave *3′-nitrogriseofulvic acid* (V; X = NO_2, Y = Cl) (9·7 g., 86%), m. p. 258°, $[\alpha]_D$ +257° (*c* 1·0 as Na salt in H_2O), $\lambda_{max.}$ (in 0·1N-NaOH) 232 (infl.) (ε 17,200), 290·5 (ε 26,800), and 327 mμ (infl.) (ε 8200), $\nu_{max.}$ (in Nujol) 2600 (bonded OH), 1684 (bonded ketone ?), 1620 (bonded CO·C:C·), 1530 + 1344 cm.$^{-1}$ (NO_2) (Found: C, 50·0; H, 3·6; Cl, 9·2; N, 3·6. $C_{16}H_{14}ClNO_8$ requires C, 50·1; H, 3·7; Cl, 9·2; N, 3·65%).

7-Chloro-4,6,2′-trimethoxy-6′-methyl-3′-nitrogris-2′-en-3,4′-dione (VI; R = Me, X = NO_2, Y = Cl).—3-Nitrogriseofulvic acid (V; X = NO_2, Y = Cl) (3·8 g.) in acetone (500 ml.) was treated with ethereal diazomethane (N.B.: no excess). Evaporation left a foam which was dissolved in ethyl acetate (200 ml.) and washed successively with 2N-sodium carbonate (250 ml.) and water (4 × 200 ml.). Removal of the solvent left a gum which crystallised, to give the enol ether (1·33 g., 43%), m. p. 101—103°, $[\alpha]_D$ +228°. Recrystallisation from ethanol and then ethyl acetate gave *7-chloro-4,6,2′-trimethoxy-6′-methyl-3′-nitrogris-2′-en-3,4′-dione* (VI; R = Me, X = NO_2, Y = Cl), m. p. 172—174°, $\lambda_{max.}$ 292 (ε 20,400) and 324 mμ (ε 5100), $\nu_{max.}$ 1702—1686 (ketones), 1534 + 1348 cm.$^{-1}$ (NO_2) (Found: C, 51·6; H, 4·5; Cl, 8·7; N, 3·5; OMe, 22·1. $C_{17}H_{16}ClNO_8$ requires C, 51·3; H, 4·05; Cl, 8·9; N, 3·5; OMe, 23·4%).

3′-Benzamido-7-chloro-4,6-dimethoxy-6′-methylgrisan-3,2′,4′-trione (V; X = Bz·NH, Y = Cl) (with R. F. K. MEREDITH).—3′-Nitrogriseofulvic acid (0·96 g.) in water (50 ml.) containing sodium carbonate (0·18 g., 1·5 equiv.) was shaken with hydrogen at room temperature and pressure in presence of 5% palladised charcoal (0·1 g.). After 21 hr. when 3 mol. of hydrogen (197 ml.) had been absorbed, the solution was filtered and more sodium carbonate (5·0 g.) was added. The mixture was shaken with benzoyl chloride (0·37 ml., 1·25 mol.) until all the benzoyl chloride had reacted and then extracted with ethyl acetate. The aqueous layer was acidified and extracted with ethyl acetate. Evaporation of the extract gave the *3′-benzamido-triketone* (0·65 g., 57%), m. p. 179—181° (from ethanol), $[\alpha]_D$ +191°, $\lambda_{max.}$ 288 mμ (ε 36,700), $\lambda_{max.}$ (in 0·1N-NaOH) 291·5 mμ (ε 44,000), $\nu_{max.}$ (in Nujol) 3340 (NH), 1706 (C=O), 1620 + 1540 cm.$^{-1}$ (CO·NH) (Found: C, 60·3; H, 4·45; Cl, 7·6; N, 2·9. $C_{23}H_{20}ClNO_7$ requires C, 60·3; H, 4·4; Cl, 7·75; N, 3·05%).

Substituting acetic anhydride for the benzoyl chloride in the above reaction gave *3′-acetamido-7-chloro-4,6-dimethoxy-6′-methylgrisan-3,2′,4′-trione* (V; X = Ac·NH, Y = Cl) (11%); m. p. 141—143°, $\lambda_{max.}$ (in 0·1N-NaOH) 291 mμ (ε 39,800), $\nu_{max.}$ 3350 (NH), 1702 (C=O) and 1620 + 1530 cm.$^{-1}$ (CO·NH) (Found: C, 53·2; H, 5·0; Cl, 8·7; N, 3·1. $C_{18}H_{18}ClNO_7,\frac{1}{2}H_2O$ requires C, 53·4; H, 4·7; Cl, 8·8; N, 3·5%).

By increasing the concentration of alkali to 2·4 equiv. during the hydrogenation of the 3′-nitro-triketone, it was possible to carry the hydrogenation further and to isolate *3′-benzamido-4,6-dimethoxy-6′-methylgrisan-3,2′,4′-trione* (V; X = Bz·NH, Y = H), m. p. 226—227°, $[\alpha]_D$ +230°, $\lambda_{max.}$ 292 (ε 25,300) and 324 mμ (ε 7130), $\nu_{max.}$ 3340 (NH), 1702 (C=O), 1620 + 1538 cm.$^{-1}$ (CO·NH) (Found: C, 65·5; H, 4·6; N, 3·0. $C_{23}H_{21}NO_7$ requires C, 65·25; H, 5·0; N, 3·35%), as the least soluble component of a mixture.

Catalytic reduction of the nitro-group and subsequent acylation could also be carried out in pyridine instead of aqueous sodium carbonate.

Treating 3′-benzamidogriseofulvic acid (V; X = BzNH, Y = Cl) (20 g.) with diazomethane and chromatography of the neutral mixture of ethers on alumina (1 kg.; grade II) gave 3 fractions. The least polar fraction, eluted with benzene, yielded *7-chloro-4,6,2′-trimethoxy-3′-α-methoxybenzylideneamino-6′-methylgris-2′-en-3,4′-dione* (VIII) (1·68 g.), m. p.

186—187° (from ethanol), $[\alpha]_D$ +308°, $\lambda_{max.}$ 290·5 mμ (ε 34,000), $\nu_{max.}$ 1702 (C=O), 1674 cm.$^{-1}$ (CO·C:C·) (Found: C, 61·4; H, 5·2; Cl, 7·2; N, 2·9; OMe, 25·2. $C_{25}H_{24}ClNO_7$ requires C, 61·8; H, 5·0; Cl, 7·3; N, 2·9; OMe, 25·5%).

The second fraction, eluted with benzene containing 25% v/v ethyl acetate, gave a product which after further chromatography yielded *3′-benzamido-7-chloro-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione* (VI; R = Me, X = BzNH, Y = Cl) (1·5 g.), m. p. 212—213° (from benzene), $[\alpha]_D$ +101°, $\lambda_{max.}$ 290·5 (ε 28,300) and 320 mμ (infl.) (ε 6120), $\nu_{max.}$ 3400 (NH), 1698 (C=O), 1698 + 1486 (CO·NH), and (1668 cm.$^{-1}$) (CO·C:C) (Found: C, 60·9; H, 5·0; Cl, 7·6; N, 2·7. $C_{24}H_{22}ClNO_7$ requires C, 61·1; H, 4·7; Cl, 7·5; N, 3·0%). This was followed by a fraction, eluted with ethyl acetate, which gave *3′-benzamido-7-chloro-4,6,4′-trimethoxy-6′-methylgris-3′-en-3,2′-dione* (VII; R = Me, X = Bz·NH, Y = Cl) (1·5 g.), m. p. 241—243° (from ethanol), $[\alpha]_D$ +158°; $\lambda_{max.}$ 284 (ε 30,100) and 320 mμ (ε 6700), $\nu_{max.}$ 3400 (NH), 1690 (C=O), 1660 (CO·C:C·), and 1680 + 1488 cm.$^{-1}$ (CO·NH) (Found: C, 61·1; H, 5·0; Cl, 7·4; N, 2·8%).

Similarly, methylation of 3′-acetamidogriseofulvic acid (V; X = Ac·NH, Y = Cl) gave *3′-acetamido-7-chloro-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione* (VI; R = Me, X = AcNH Y = Cl) (18%), m. p. 221—223° (from acetone), $[\alpha]_D$ +134°, $\lambda_{max.}$ 232 (infl.) (ε 17,200), 290·5 (ε 26,300), and 320 mμ (infl.) (ε 5650), $\nu_{max.}$ 3400 (NH), 1700 (C=O), 1700 + 1496 (CO·NH) and 1668 cm.$^{-1}$ (CO·C:C·) (Found: C, 55·9; H, 5·0; Cl, 8·8; N, 3·3. $C_{19}H_{20}ClNO_7$ requires C, 55·7; H, 4·9; Cl, 8·65; N, 3·4%).

4,6,2′-Trimethoxy-6′-methyl-7-nitrogris-2′-en-3,4′-dione (II; R = R′ = Me, X = H, Y = NO_2).—Dechlorogriseofulvin (2·5 g.) was dissolved in acetic acid (35 ml.) and acetic anhydride (10 ml.) at 30° and fuming nitric acid (2·5 ml.) was gradually added. After 16 hr. at room temperature the mixture was poured into water (500 ml.) and extracted with ethyl acetate (250 ml.). The extract was washed with N-sodium carbonate (2 × 250 ml.), then with water (2 × 250 ml.), and the solvent was removed. The residue was chromatographed on alumina (100 g.; grade III). Elution with benzene (250 ml.) gave a fast-running fraction (0·27 g.) which was rejected, and elution with benzene–ethyl acetate (19 : 1, then 9 : 1) gave 2 components. These were shown to be single discreet compounds by thin-layer chromatography (seen as quenching spots in ultraviolet light). The less polar fraction was assigned the structure *4,6,2′-trimethoxy-6′-methyl-5-nitrogris-2′-en-3,4′-dione* (II; R = R′ = Me, X = NO_2, Y = H) and had m. p. 196—199° (from ethanol), $[\alpha]_D$ +291°, $\lambda_{max.}$ 264 (broad) (ε 23,600) and 319 mμ (ε 5600), $\nu_{max.}$ 1710 (C=O), 1658 (CO·C:C·), and 1538 + 1355 cm.$^{-1}$ (NO_2) (0·583 g., 20%) (Found: C, 54·7; H, 4·9; N, 3·9; OMe, 24·7. $C_{17}H_{17}NO_8,\frac{1}{2}H_2O$ requires C, 54·8; H, 4·9; N, 3·8; OMe, 25·0%).

The more polar fraction gave *4,6,2′-trimethoxy-6′-methyl-7-nitrogris-2′-en-3,4′-dione* (II; R = R′ = Me, X = H, Y = NO_2) (0·98 g., 34%), m. p. 165—167° (from ethanol), $[\alpha]_D$ +392°, $\lambda_{max.}$ 275—281 (infl.) (ε 26,200) and 272—274 mμ (ε 26,300), $\nu_{max.}$ 1708 (C=O) 1654 (CO·C:C·) and 1526 + 1330 cm.$^{-1}$ (NO_2) (Found: C, 56·0; H, 4·8; N, 4·1; OMe, 26·3. $C_{17}H_{17}NO_8$ requires C, 56·2; H, 4·7; N, 3·9; OMe, 25·6%).

Similarly, dechloroisogriseofulvin (III; R = R′ = Me, X = Y = H) gave *4,6,4′-trimethoxy-6′-methyl-5-* (9%), m. p. 164—165° (from ethanol), $[\alpha]_D$ +206°, $\lambda_{max.}$ 264 (ε 30,600) and 318—319 mμ (ε 5150), $\nu_{max.}$ 1704 (C=O), 1654 (CO·C:C·), and 1540 + 1334 cm.$^{-1}$ (NO_2) (Found: C, 55·9; H, 4·8; N, 3·6; OMe, 26·0%), and *-7-nitrogris-3′-en-3,2′-dione* (29%), m. p. 203° (from ethanol), $[\alpha]_D$ +337°, $\lambda_{max.}$ 266 (ε 30,800), 280—286 (ε 22,750), and 308—326 mμ (infl.) (ε 6400), $\nu_{max.}$ 1706 (C=O) 1660 (CO·C:C), and 1530 + 1330 cm.$^{-1}$ (NO_2) (Found: C, 56·0; H, 4·9; N, 3·9; OMe, 25·9%).

7-Amino-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione (II; R = R′ = Me, X = H, Y = NH_2).—Dechloro-7-nitrogriseofulvin (II; R = R′ = Me, X = H, Y = NO_2) (1·6 g.) was dissolved in warm methanol (40 ml.) and added slowly to a stirred mixture of reduced iron powder (4·0 g.), acetic acid (8 ml.), and water (72 ml.) at 60° under nitrogen. The mixture was stirred for 1 hr. at 60°, set aside at room temperature overnight, and filtered. The residual salts were washed with methanol (2 × 50 ml.), and the washings and filtrate evaporated *in vacuo* at room temperature until all the methanol had been removed. The solution was acidified with 2N-hydrochloric acid and extracted with ethyl acetate (2 × 100 ml.). Then the aqueous layer was adjusted to pH 10—11 with 2N-sodium hydroxide. The mixture was shaken with ethyl acetate (2 × 500 ml.) and filtered through kieselguhr. The ethyl acetate layer was separated, washed with water (2 × 100 ml.), and evaporated. Trituration of the residue with ether gave *7-amino-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione* (II; R = R′ = Me, X = H, Y = NH$_2$) (0·82 g., 56%), m. p. 192—194° (decomp.) (from ethanol), $[\alpha]_D$ +360° (*c* 0·545), $\lambda_{max.}$ 251 (ε 25,800), 294 (ε 18,900), and 363 mμ (ε 4700), $\nu_{max.}$ 3430 + 3350 (NH$_2$), 1700 (C=O), and 1650 cm.$^{-1}$ (CO·C:C) (Found: C, 61·0; H, 5·8; N, 4·2; OMe, 27·2. $C_{17}H_{19}NO_6$ requires C, 61·3; H, 5·8; N, 4·2; OMe, 27·9%).

Reduction of 4,6,2′-trimethoxy-6′-methyl-5-nitrogris-2′-en-3,4′-dione by the same method gave 5-*amino*-4,6,2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3,4′-*dione* (II; R = R′ = Me, X = NH$_2$, Y = H) (52%), m. p. 176—179° (from ethanol), $[\alpha]_D$ +380°, $\lambda_{max.}$ 249 (ε 30,400) and 284 mμ (ε 17,700), $\nu_{max.}$ 3450 + 3360 (NH$_2$), 1694 (C=O), and 1652 cm.$^{-1}$ (CO·C:C·) (Found: C, 61·0; H, 5·9; N, 4·2; OMe, 28·4%). The N-*benzoyl derivative* had m. p. 286—289° (from ethanol), $[\alpha]_D$ +259°, $\lambda_{max.}$ 235 (ε 31,800), 282 (ε 25,400), and 322—324 mμ (ε 5200), $\nu_{max.}$ 3430 (NH), 1706 (C=O), 1662 (CO·C:C·), and 1678 + 1488 cm.$^{-1}$ (CO·NH?) (Found: C, 65·9; H, 5·3. $C_{24}H_{23}NO_7$ requires C, 65·8; H, 5·3; N, 3·2%).

Reduction of 4,6,4′-trimethoxy-6′-methyl-7-nitrogris-3′-en-3,2′-dione gave 7-*amino*-4,6,4′-*trimethoxy*-6′-*methylgris*-3′-*en*-3,2′-*dione* (40%), m. p. 198° (from ethanol), $[\alpha]_D$ +280° (*c* 0·416), $\lambda_{max.}$ 252 (ε 25,900), 295 (ε 14,900), and 363 mμ (ε 4000), $\nu_{max.}$ 3350 + 3420 (NH$_2$), 1692 (C=O), and 1650 cm.$^{-1}$ (CO·C:C·) (Found: C, 61·1; H, 5·8; N, 4·3; OMe, 27·3%).

5-*Benzamido*-4,6-*dimethoxy*-6′-*methylgrisan*-3,2′,4′-*trione* (I; R = R′ = Me, X = Bz·NH, Y = H).—5-Nitrogriseofulvic acid (I; R = R′ = Me, X = NO$_2$, Y = Cl) (1·0 g.) was dissolved in water (70 ml.) containing sodium carbonate (1·4 g.) and shaken with 10% palladised charcoal (0·35 g.) and hydrogen at room temperature and pressure. After 2½ hr. hydrogenation had virtually ceased and the mixture was filtered and extracted with ethyl acetate (2 × 75 ml.). The aqueous layer (which gave no precipitate on acidification) was shaken with benzoyl chloride (1·5 ml.) and sodium carbonate (3·5 g.) was added. After 24 hr. the solution was filtered and acidified. The precipitated 5-benzamido-triketone (2·4 g., solvated) gave, on reprecipitation, a powder, m. p. 195—196°, $[\alpha]_D$ +260° (*c* 0·08 in 2N-Na$_2$CO$_3$), $\lambda_{max.}$ 270 (ε 30,000) and 320 mμ (ε 5200), $\nu_{max.}$ 1740 + 1690 (C=O), 1690 + 1490 cm.$^{-1}$ (CO·NH) (Found: Cl, 0·0). Treatment of the 5-benzamido-triketone (5·85 g.) with diazomethane and separation of the mixed enol ethers by the Girard reagent gave 5-benzamido-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione (0·151 g., 2·5%), m. p. 282—284° (from ethanol), $[\alpha]_D$ +257°, $\lambda_{max.}$ 235 (ε 31,900), 281 (ε 28,000), and 323 mμ (ε 5500). The infrared spectrum was identical with that of the previous sample prepared from 5-aminodechlorogriseofulvin (Found: C, 66·0; H, 5·2; N, 3·3%). The fraction which did not react with the Girard reagent gave 5-*benzamido*-4,6,4′-*trimethoxy*-6′-*methylgris*-3′-*en*-3,2′-*dione* (III; R = R′ = Me, X = Bz·NH, Y = H) (1·14 g., 19%) as a foam. Treatment with benzene gave a crystalline product (0·8 g., 13%), m. p. 278—279°, $[\alpha]_D$ +176° (*c* 0·08), $\lambda_{max.}$ 224—228 (ε 14,600), 261 (ε 14,200), and 279 mμ (ε 11,500), $\nu_{max.}$ 3420 (NH), 1690 (C=O), 1660 (CO·C:C), and 1660 + 1484 cm.$^{-1}$ (CO·NH) (Found: C, 65·6; H, 5·6; N, 2·9%).

Attempts to Prepare 7-*Fluorogriseofulvin* (II; R = R′ = Me, X = H, Y = F).—7-Aminodechlorogriseofulvin (II; R = R′ = Me, X = H, Y = NH$_2$) (0·5 g.) was dissolved in tetrahydrofuran (5 ml.) and 40% fluoroboric acid (0·5 ml.) at −10°. n-Butyl nitrite (0·2 ml.) in tetrahydrofuran (2 ml.) was added gradually and the mixture was kept for 10 min. at −10°, then diluted with cold anhydrous ether (100 ml.). After 30 min. the *diazonium salt* was collected (0·7 g.); it had m. p. 170° (decomp.), $\nu_{max.}$ (in Nujol) 2230 (N:N), 1728 (C=O), and 1660 cm.$^{-1}$ (CO·C:C) (Found: N, 6·0. $C_{17}H_{17}BF_4N_2O_6$ requires N, 6·5%).

The diazonium salt was (*a*) heated under reflux with xylene for 3 days but did not dissolve and produced no fluorogriseofulvin, and (*b*) heated at 220°/4·79 × 10^{-5} mm. in a sublimation apparatus but gave only a trace of sublimate; and (*c*) the diazonium salt generated in aqueous solution from the amine (0·5 g.) was treated with acetone and cuprous chloride. The neutral fraction from this catalytic decomposition was shown to be crude dechlorogriseofulvin (0·187 g.), m. p. 164° (Found: F, 0·0%) by its infrared spectrum; it gave an intense blue colour with nitric acid.

7-*Chloro*-4,6-*dihydroxy*-2′-*methoxy*-6′-*methyl*-5-*nitrogris*-2′-*en*-3,4′-*dione* (II; R = R′ = H, X = NO$_2$, Y = Cl).—5-Nitrogriseofulvin (II; R = R′ = Me, X = NO$_2$, Y = Cl) (3·0 g.) was boiled with lithium iodide (6·0 g.) in dry acetone (100 ml.) for 3 hr. The mixture was cooled and the precipitated salt collected. The filtrate was evaporated and the residue and the salt were combined, dissolved in water (100 ml.), and acidified. The mixture was extracted with ethyl acetate (2 × 250 ml.), and the ethyl acetate solution was back-extracted with 2N-sodium carbonate (2 × 250 ml.) and water (2 × 250 ml.). The total aqueous extracts were acidified and extracted with ethyl acetate (2 × 250 ml.). This extract was washed with water (2 × 250 ml.) and evaporated. The residue, on trituration with ether, gave the *phenol* (1·7 g., 61%), m. p. 212° (from aqueous acetic acid), $[\alpha]_D$ +291°, $\lambda_{max.}$ (in 0·1N-NaOH) 298 (ε 23,300) and 330 mμ (infl.) (ε 13,750), $\nu_{max.}$ 1728 (C=O), 1660 (CO·C:C·), and 1562 + 1355 cm.$^{-1}$ (NO_2) (Found: C, 48·7; H, 3·2; N, 3·5; Cl, 9·2; OMe, 8·1. $C_{15}H_{12}ClNO_8$ requires C, 48·8; H, 3·3; N, 3·8; Cl, 9·6; OMe, 8·4%). The phenol with diazomethane in ether gave 5-nitrogriseofulvin which had an infrared spectrum identical with that of the authentic specimen prepared earlier.

7-*Chloro*-4,6-*dihydroxy*-6′-*methyl*-5-*nitrogrisan*-3,2′,4′-*trione* (I; R = R′ = H, X = NO_2, Y = Cl).—The preceding phenol (0·41 g.) was heated at 100° with 2N-sulphuric acid (0·41 ml.) and acetic acid (2 ml.). After 1½ hr. the solution was cooled and the *triketone* (I; R = R′ = H, X = NO_2, Y = Cl) collected by filtration (0·38 g., 96%); it had m. p. 197—199° (from aqueous acetic acid), $[\alpha]_D$ +241°, $\lambda_{max.}$ 267 (ε 27,000) and 310 mμ (ε 17,500), $\lambda_{max.}$ (in 0·1N-NaOH) 288 (ε 38,500) and 320 mμ (ε 14,500), $\nu_{max.}$ (in Nujol) 1712—1702 (C=O), 1642 (CO·C:C·), and 1550 + 1310 cm.$^{-1}$ (NO_2) (Found: C, 47·5; H, 3·1; N, 3·9; Cl, 9·7; OMe, 0·14. $C_{14}H_{10}ClNO_8$ requires C, 47·2; H, 2·8; N, 4·0; Cl, 10·0; OMe, 0·0%).

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