243. *Griseofulvin Analogues. Part III.*[1] *Halogen Derivatives of Griseofulvin.*

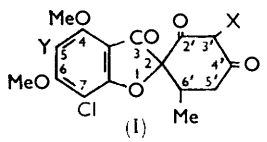
By T. Walker, W. K. Warburton, and G. B. Webb.

The six halogenated triones [I; (*a*) X = Cl, Br, or I; Y = H; (*b*) X = H, Y = Cl or Br; (*c*) X = Y = Cl] have been prepared from griseofulvic acid and converted into the corresponding ethers (II) and (III) (R = Me) related to griseofulvin and isogriseofulvin, respectively. Several homologous ethers of the 3′-halogenogriseofulvic acids were also prepared.

Griseofulvin in acetic acid did not react with bromine alone, but in the presence of mercuric acetate gave 5,3′-dibromo- (II; R = Me, X = Y = Br) and 5-bromo-griseofulvin (II; R = Me, X = H, Y = Br). Similar bromination of 3′-bromogriseofulvic acid gave the tribromo-derivative (V; X = Br).

Continuing our studies of griseofulvin analogues, we report here the preparation of derivatives containing additional halogen atoms.

When griseofulvin (II; R = Me, X = Y = H) in chloroform was treated with an excess of bromine, as described by Grove, MacMillan, Mulholland, and Rogers,[2] the only product isolated, in small yield, was 3′-bromogriseofulvic acid (I; X = Br, Y = H). Simple cyclic β-diketones are readily halogenated,[3] so we investigated the halogenation of griseofulvic acid (I; X = Y = H). With bromine in a variety of solvents (preferably dimethylformamide) it gave excellent yields of 3′-bromogriseofulvic acid and no evidence of further halogenation.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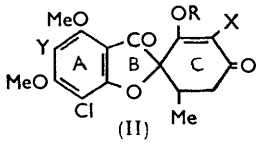
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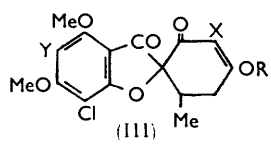
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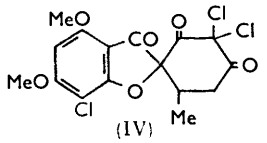
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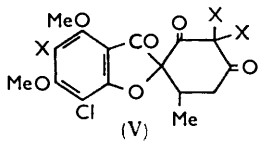
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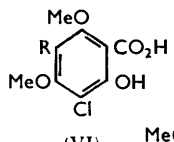
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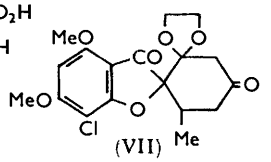
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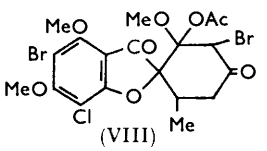
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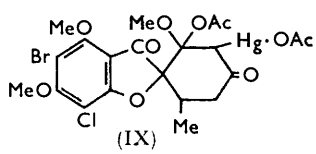
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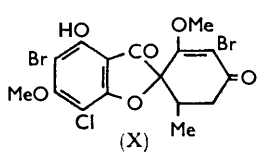
(X)

Griseofulvic acid in dimethylformamide was not attacked by iodine, but in the presence of two equivalents of potassium acetate one equivalent of iodine was rapidly consumed. Acidification of the reaction mixture, to obtain the 3′-iodo-acid, caused partial reversal of the reaction, owing to the presence of iodide ions, but the use of iodine monochloride instead of iodine prevented this.

The 3′-chloro-derivative (I; X = Cl, Y = H) was prepared in high yield by adding one mol. of chlorine in carbon tetrachloride to a solution of griseofulvic acid in dimethylformamide containing potassium acetate. With two mol. of chlorine, the product was a

[1] Part II, preceding paper.
[2] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.
[3] Vorlander and Kohlmann, *Annalen*, 1902, **322**, 246; Norris and Thorpe, *J.*, 1921, 1202; Voitila, *Ann. Acad. Sci. Fennicae, A* 49, No. 1, 110, *Chem. Abs.*, 1939, **33**, 7242; Blout, Eager, and Silverman, *J. Amer. Chem. Soc.*, 1946, **68**, 566.

mixture of the 3′-chloro-acid (I; X = Cl, Y = H) and neutral material that could not be purified. The latter contained some of the *gem*-dichloro-derivative (IV), since it liberated iodine from acidic potassium iodide at room temperature [3] with the formation of some of the 3′-chloro-acid. A similar experiment, in the absence of potassium acetate, gave 30% of starting material and a neutral crystalline compound containing three additional atoms of chlorine. This was best prepared (75% yield) by chlorination of griseofulvic acid in carbon tetrachloride with 3·3 mol. of chlorine and was shown to have structure (V; X = Cl). As this compound was neutral, two of the additional chlorine atoms must be in the 3′-position. Consistently with this,[3] treatment with potassium iodide in acetic acid at room temperature or with chromous chloride in acetone removed one atom of chlorine and gave the 5,3′-dichloro-acid (I; X = Y = Cl). Then potassium iodide, in acetic acid at 100°, eliminated a second chlorine atom and gave a monochlorogriseofulvic acid (I; X = H, Y = Cl) that differed from the 3′-chloro-derivative and therefore contained a chlorine atom in the 5- or 5′-position. The ultraviolet absorption spectra of these compounds, their enol methyl ethers, and the trichloro-compound (V; X = Cl) showed a small maximum at *ca.* 347 mμ in addition to the main absorption peaks. Griseofulvin, however, has a similar small maximum at 324 mμ attributed [2] to the ring A chromophore in conjugation with the 3-carbonyl group, and we concluded that our compounds must have an additional bathochrome in ring A, namely, a chlorine atom in the 5-position, and this was proved by the degradation of a suitable derivative and isolation of a fragment containing ring A of the molecule.

The chlorinated salicylic acid (VI; R = H) obtained [4,5] by refluxing griseofulvin with 2N-sodium methoxide was chlorinated under mild conditions to give the known dichlorosalicylic acid [4] (VI; R = Cl). This acid was obtained in poor yield by a similar degradation of the enol ether (II; R = Me, X = Y = Cl), confirming the presence of a 5-chlorine atom in compounds of this series.

All the halogenated griseofulvic acid derivatives so far described were converted into ethers (II and III) by standard methods (see Experimental section). As these methods have the disadvantage of producing mixtures of the ethers, frequently with the biologically less interesting 4′-ethers (III) predominating, we reinvestigated the direct bromination of griseofulvin.

Griseofulvin did not react with bromine in acetic acid. In the presence of mercuric acetate,* however, instantaneous absorption of bromine occurred. The reaction was not merely catalytic, as titration experiments showed that bromine was consumed in the ratio of one mol. of bromine to 0·5 mol. of mercuric acetate and that no more than 2 mol. of bromine could be caused to react. Treating griseofulvin with two mol. of bromine in the presence of at least one mol. of mercuric acetate gave a non-crystalline froth A, whose structure is described below.

The substance A, in benzene, when passed through a column of alumina, was converted into 5,3′-dibromogriseofulvin (II; R = Me, X = Y = Br). Hydrolysis of this ether gave 5,3′-dibromogriseofulvic acid (I; X = Y = Br), and the dibromo-acid was smoothly reduced to 5-bromogriseofulvic acid (I; X = H, Y = Br) by acidic potassium iodide. When griseofulvin was treated with one mol. of bromine in the presence of 0·5 mol. of mercuric acetate and the product chromatographed, 5-bromogriseofulvin (II; R = Me, X = H, Y = Br) contaminated with a little of the 5,3′-dibromo-compound was obtained. All these compounds were readily identified by the similarity of their infrared and ultraviolet spectra to those of the corresponding chloro-compounds. 3′-Bromogriseofulvic acid (I; X = Br, Y = H), with an excess of mercuric acetate, consumed two mol. of bromine and gave a product that we could neither crystallise nor obtain analytically pure.

* We are grateful to Professor D. H. R. Barton, F.R.S., for suggesting use of this reagent.

[4] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977.
[5] Birch, Massy-Westropp, Rickards, and Smith, *J.*, 1958, 360.

Its negligible optical activity and spectra similar to those of the corresponding trichloro-derivative (V; X = Cl) indicated that it was substantially the tribromo-compound (V; X = Br). An attempt to remove stepwise the halogen atoms from this with acidic potassium iodide, as for the trichloro-compound, failed, 0·9 mol. of potassium iodide giving a mixture of mono-, di-, and tri-bromo-compounds; this reaction was not studied further, as both 5,3′-dibromo- and 5-bromo-griseofulvic acid were obtainable from the corresponding ethers.

The substance A was a colourless glass having a high negative rotation, unchanged by chromatography on silica gel but decomposed by alumina to 5,3′-dibromogriseofulvin with the normal, high positive rotation. Analysis showed the presence of three methoxyl groups and one *O*-acetyl group; a band in the infrared spectrum (at 1755 cm.$^{-1}$), at first ascribed to enol acetate, was considered to be equally consistent with a 2′-acetoxy-group, provided that there was a second substituent at the 2′-position, as Page [6] has shown that *gem*-diacetoxy-groups absorb at a higher frequency (about 1760 cm.$^{-1}$) than a monoacetoxy-group (about 1730 cm.$^{-1}$). The ketal (VII),[7] also, has a high negative rotation, and accordingly we assigned the structure (VIII) to the substance A.

Mercuration of aromatic compounds with mercuric acetate and subsequent displacement of the acetoxymercuri-group by electrophilic reagents being a well-known reaction, clearly ring A of griseofulvin is attacked first in this way.

The overall reaction may be written $ArH + Hg(OAc)_2 + Br_2 = \frac{1}{2}HgBr_2 + \frac{1}{2}Hg(OAc)_2$, and the stoicheiometry observed is explained. Any mercuric acetate in excess of 0·5 mol. can then add across the double bond in ring C to give the hypothetical intermediate (IX), and further reaction with bromine gives the 2′-acetoxy-compound (VIII), which is sufficiently stable to be isolated (not quite pure) but readily eliminates the elements of acetic acid under feebly alkaline conditions.

When 5,3′-dibromogriseofulvin was refluxed with lithium bromide in acetone (conditions that do not change griseofulvin) the phenol (X) was formed.

Experimental

For general directions see Part II.[1]

3′-Bromogriseofulvic Acid (I; X = Br, Y = H).—Bromine (3·0 ml.) was added, with stirring, to a solution of griseofulvic acid (17·0 g.) in dimethylformamide (400 ml.) which was then kept at room temperature for 16 hr. Water (800 ml.) was added, the excess of bromine destroyed with sodium metabisulphite, and the mixture cooled in the refrigerator. The crystalline *3′-bromo-7-chloro-4,6-dimethoxy-6′-methylgrisan-3,2′,4′-trione* was collected (19·1 g., 91%); it had m. p. 248—250° (after earlier decomp.), $[\alpha]_D$ +263° (*c* 1·0 in 0·1N-Na_2CO_3) (Found: C, 46·4; H, 3·6; Hal, 27·7. $C_{16}H_{14}BrClO_6$ requires C, 46·0; H, 3·4; Hal, 27·6%).

3′-Iodogriseofulvic Acid (I; X = I, Y = H).—Iodine monochloride (0·85 g.) in dimethylformamide (5·0 ml.) was added to a solution of griseofulvic acid (1·7 g.) in dimethylformamide (10·0 ml.) containing potassium acetate (1·08 g.). The solution was poured into water (*ca.* 60 ml.) and acidified to pH 1·0 with hydrochloric acid, and the yellow precipitate collected, air-dried, and warmed with ethyl acetate (20 ml.). The *3′-iodo-acid* separated on cooling (1·74 g., 75%), having m. p. 206° (decomp.). A sample recrystallised from acetonitrile gave prisms, m. p. 209° (decomp.), $[\alpha]_D$ +188° (*c* 1·0 in 0·1N-Na_2CO_3) (Found: C, 41·2; H, 3·1; I, 27·4. $C_{16}H_{14}ClIO_6$ requires C, 41·4; H, 3·05; I, 27·3%).

3′-Chlorogriseofulvic Acid (I; X = Cl, Y = H).—A solution of griseofulvic acid (1·7 g.) in dimethylformamide (15·0 ml.) containing potassium acetate (1·08 g.) was cooled in water, and chlorine in carbon tetrachloride (2·27N; 4·85 ml.) added. The mixture was diluted with water (150 ml.), the pH adjusted to about 8·5 with 2N-sodium carbonate, and the solution extracted with chloroform. The aqueous layer was freed from chloroform *in vacuo* and acidified with 2N-sulphuric acid, giving the crude acid, 1·7 g. (91%), m. p. 282—286° (decomp.).

[6] Page, *J.*, 1955, 2017.
[7] Part I, *J.*, 1962, 1260.

Crystallisation from acetonitrile gave pure *7,3′-dichloro-4,6-dimethoxy-6′-methylgrisan-3,2′,4′-trione*, m. p. 286° (decomp.), $[\alpha]_D$ +331° (*c* 1·0 in 0·2N-Na_2CO_3) (Found: C, 51·35; H, 3·9; Cl, 18·95. $C_{16}H_{14}Cl_2O_6$ requires C, 51·5; H, 3·8; Cl, 19·0%).

5,3′,3′-Trichlorogriseofulvic Acid (V; X = Cl).—Chlorine in carbon tetrachloride (6·78% w/v; 115 ml.) was added to a stirred suspension of powdered griseofulvic acid (11·3 g.) in carbon tetrachloride (250 ml.). After 24 hr. the unchanged acid (0·18 g.) was filtered off and the solution washed with water (twice), sodium hydrogen carbonate solution (twice), and water. Evaporation of the dried solution under reduced pressure and trituration of the residue with ether (40 ml.) gave the *trichloro-derivative* (10·9 g., 74%), m. p. 151—153°. It recrystallised from acetic acid as prisms, m. p. 153—155°, $[\alpha]_D$ −3·3° (Found: C, 43·75; H, 2·75; Cl, 31·85. $C_{16}H_{12}Cl_4O_6$ requires C, 43·45; H, 2·75; Cl, 32·1%).

5,3′-Dichlorogriseofulvic Acid (I; X = Y = Cl).—Potassium iodide (20·0 g.) in water (20 ml.) and acetic acid (30 ml.) was added to a solution of the trichloro-derivative (V; X = Cl) (11·05 g.) in acetic acid (150 ml.). Iodine was liberated instantly and 10 min. later the solution was poured into a solution of sodium metabisulphite (12·5 g.) in water (1·5 l.). The precipitated *dichloro-acid* (9·57 g., 92%), when recrystallised from benzene, had m. p. 214·5—216·5°, $[\alpha]_D$ +220° (Found: C, 47·7; H, 3·5; Cl, 26·25. $C_{16}H_{13}Cl_3O_6$ requires C, 47·2; H, 3·2; Cl, 26·1%).

5-Chlorogriseofulvic Acid (I; X = H, Y = Cl).—Potassium iodide (25 g.) in water (100 ml.) was added to a solution of 5,3′-dichlorogriseofulvic acid (11·15 g.) in hot acetic acid (400 ml.), and the mixture heated on the water-bath for 4 hr. The solution was decolorised with sodium hydrogen sulphite solution and concentrated to ~100 ml. under reduced pressure before being poured into water (1·7 l.). The crude product was dried [9·47 g.; m. p. 225—230° (decomp.)], and extracted twice with boiling ether (2 × 100 ml.), and the extracts were discarded. The residue crystallised from 1 : 1 dimethylformamide–water, giving *5-chlorogrisefulvic acid* (5·56 g., 55%), m. p. 243° (decomp.). Recrystallised from nitromethane it had m. p. 243° (decomp.), $[\alpha]_D$ +372° (*c* 0·35 in 0·2N-Na_2CO_3) (Found: C, 51·4; H, 3·75; Cl, 18·65%).

Degradation of 5,3′-Dichlorogriseofulvin (II; R = Me, X = Y = Cl).—5,3′-Dichlorogriseofulvin (1·0 g.) was refluxed for 5 hr. with a solution of sodium methoxide (from 4·6 g. of sodium and 100 ml. of methanol). After evaporation, the residue was poured into water, and the aqueous solution extracted three times with ether and acidified with dilute sulphuric acid. The brown solid that separated was discarded, and the filtrate extracted with ethyl acetate. The residue obtained on evaporation of the organic solvent was triturated with hot cyclohexane–benzene, tar was filtered off, the filtrate evaporated, and the residue crystallised from benzene, to give 3,5-dichloro-2-hydroxy-4,6-dimethoxybenzoic acid (VI; R = Cl), m. p. 181—182·5°, identical (mixed m. p. and infrared spectrum) with an authentic sample.

Preparation of Ethers (II *and* III) *of Halogen-substituted Griseofulvic Acids* (I).—*General methods.* (1) The substituted griseofulvic acid was treated in acetone containing triethylamine (1·1 mol.) with an excess of the appropriate diazoalkane in ether. The excess of diazoalkane was destroyed with a little acetic acid, and the solvents were removed under reduced pressure. The residue in ethyl acetate was washed with dilute hydrochloric acid, dilute sodium carbonate solution, and water, and dried. Removal of the solvent gave a mixture of the ethers that was separated either (*a*) by chromatography on alumina [the 4′-ethers (III) were eluted first] or (*b*) by extraction with ether [the 2′-ethers (II) were the more soluble].

(2) The substituted griseofulvic acid (10 g.), toluene-*p*-sulphonic acid (1 g.), and allyl alcohol (20 ml.) in benzene (200 ml.) were refluxed for 16 hr. in a Dean and Stark apparatus. The mixture was washed with 2N-sodium carbonate and water, dried, and evaporated, and the residue of the 4′-ether was crystallised.

(3) A suspension of the substituted griseofulvic acid (10 g.), dry potassium carbonate (20 g.) and either benzyl or allyl bromide (10 ml.) in acetone (500 ml.) was refluxed for 6 hr. The solid was filtered off and washed with acetone and the combined filtrate and washings were evaporated. The residue, in benzene, was washed with sodium carbonate solution and water and dried. Evaporation of the solvent gave the crude ethers, separated in the case of the benzyl ethers by crystallisation or chromatography. Allyl bromide gave exclusively the 4′-ethers.

The products are recorded in the Table.

2′-Acetoxy-5,3′-dibromo-7-chloro-4,6,2′-trimethoxy-6′-methylgrisan-3,4′-dione (VIII) (with Mr. L. Stephenson).—Bromine (1·5 g.), griseofulvin (1·0 g.), and mercuric acetate (1·0 g.) in acetic acid (35 ml.) were kept for 16 hr. at room temperature. The mercuric bromide was filtered off

Ethers (II) and (III).

	R	X	Y	Method	Solvent	M. p.	$[\alpha]_D$	Formula	Found (%) C	H	Hal	Required (%) C	H	Hal
II	Me	Br	H	1 (*b*)	MeOH	187—189°	+250°	$C_{17}H_{16}BrClO_6$	47·3	4·0	26·85	47·3	3·75	26·7
III	,,	,,	,,	1 (*b*)	MeCN	246—249 †	+264	,,	47·3	3·8	26·2	,,	,,	,,
II	Et	Br	H	1 (*a*)	MeOH	144—146	+243	$C_{18}H_{18}BrClO_6$	49·0	4·45	25·4	48·5	4·05	25·85
III	,,	,,	,,	1 (*a*)	MeOH	204—207	+199	,,	48·2	4·1	—	,,	,,	,,
II	Pr^n	Br	H	1 (*a*)	EtOH	160—161	+220	$C_{19}H_{20}BrClO_6$	49·7	4·6	24·95	49·65	4·4	25·1
III	,,	,,	,,	1 (*a*)	EtOH	219	+240	,,	49·6	4·4	25·35	,,	,,	,,
II	Bu^n	Br	H	1 (*a*)	EtOH	181—182	+215	$C_{20}H_{22}BrClO_6$	50·8	4·7	24·1	50·7	4·7	24·35
III	,,	,,	,,	1 (*a*)	C_6H_6	188—190	+225	,,	50·6	4·95	24·0	,,	,,	,,
III	Allyl	Br	H	2	MeOH	193—194	+253	$C_{19}H_{18}BrClO_6$	49·9	4·1	—	49·9	4·0	—
II	CH_2Ph	Br	H	3	MeOH	211 †	+191	$C_{23}H_{20}BrClO_6$	54·4	4·1	22·7	54·4	4·0	22·7
III	,,	,,	,,	3	MeOH	221—223 †	+208	,,	54·95	4·1	22·5	,,	,,	,,
II	Me	I	H	1 (*b*)	MeOH	193·5—195	+235	$C_{17}H_{16}ClIO_6$	42·8	3·55	34·4	42·65	3·35	33·9
III	,,	,,	,,	1 (*b*)	$MeNO_2$	240 †	+192	,,	42·7	3·4	34·5	,,	,,	,,
II	Et	I	H	1 (*b*)	EtOH	174—176·5	+233	$C_{18}H_{18}ClIO_6$	43·85	3·8	32·9	43·85	3·7	32·95
III	,,	,,	,,	1 (*b*)	$MeNO_2$	229—230	+194	,,	44·0	3·65	32·5	,,	,,	,,
II	Pr^n	I	H	1 (*a*)	EtOH	140—141	+216	$C_{19}H_{20}ClIO_6$	45·0	4·3	32·4	45·05	4·0	32·05
III	,,	,,	,,	1 (*a*)	EtOH	225 †	+192	,,	45·1	3·9	31·95	,,	,,	,,
II	Bu^n	I	H	1 (*a*)	EtOH	177—178	+206	$C_{20}H_{22}ClIO_6$	46·1	4·3	31·8	46·1	4·25	31·2
III	,,	,,	,,	1 (*a*)	EtOH	200—201	+176	,,	46·1	4·5	31·0	,,	,,	,,
III	Allyl	I	H	3	MeOH	188—190	+186·5	$C_{19}H_{18}ClIO_6$	45·8	3·7	—	45·2	3·6	—
II	CH_2Ph	I	H	3	C_6H_6	179—181	+138	$C_{23}H_{20}ClIO_6,C_6H_6$	54·8	4·15	—	55·0	4·15	—
III	,,	,,	,,	3	MeOH	188—190	+165	$C_{23}H_{20}ClIO_6$	49·85	3·4	—	49·8	3·65	—
II	Me	Cl	H	1 (*b*)	MeOH	188·5—190	+278	$C_{17}H_{16}Cl_2O_6$	52·5	4·1	18·25	52·75	4·15	18·3
III	,,	,,	,,	1 (*b*)	MeOH–EtOAc	257—259·5	+334	,,	52·95	4·1	18·25	,,	,,	,,
II	Et	Cl	H	1 (*a*)	MeOH	149—152	+241	$C_{18}H_{18}Cl_2O_6$	53·75	5·0	17·1	53·9	4·5	17·65
III	,,	,,	,,	1 (*a*)	MeOH	213—216	+315	,,	53·8	4·55	17·8	,,	,,	,,
II	Pr^n	Cl	H	1 (*a*)	EtOH	146—148	+235	$C_{19}H_{20}Cl_2O_6$	54·5	5·1	16·6	54·95	4·85	17·1
III	,,	,,	,,	1 (*a*)	EtOH	200—201	+309	,,	54·6	4·6	17·1	,,	,,	,,
II	Bu^n	Cl	H	1 (*a*)	EtOH	175	+232	$C_{20}H_{22}Cl_2O_6$	55·8	5·3	17·0	55·95	5·15	16·5
III	,,	,,	,,	1 (*a*)	EtOH	182—184	+296	,,	55·9	5·2	16·5	,,	,,	,,
III	Allyl	Cl	H	2	MeOH	194—195	+311	$C_{19}H_{18}Cl_2O_6$	55·1	4·4	17·7	55·2	4·4	17·15
II	CH_2Ph	Cl	H	3	MeOH	209 †	+190	$C_{23}H_{20}Cl_2O_6$	59·35	4·25	15·45	59·65	4·35	15·3
III	,,	,,	,,	3	Me_2CO	245—247 †	+251	,,	60·0	4·4	15·0	,,	,,	,,
II	Me	Cl	Cl	1 (*b*)	MeCN	169—171	+221	$C_{17}H_{15}Cl_3O_6$	48·2	3·7	25·3	48·4	3·6	25·25
III	,,	,,	,,	1 (*b*)	AcOH	222·5—224·5	+289	,,	48·4	3·7	25·75	,,	,,	,,
II	Me	H	Cl	1 (*a*)	Pr^i_2O	90—93	—	$C_{17}H_{16}Cl_2O_6$	52·95	4·25	18·5	52·75	4·15	18·3
III	,,	,,	,,	1 (*a*)	MeOH–EtOAc	188·5—190·5	—	,,	52·75	4·2	18·35	,,	,,	,,

† Decomp.

and the filtrate poured into a dilute solution of sodium hydrogen sulphite. The colourless precipitate was collected, dissolved in ethyl acetate, washed with 2N-sodium carbonate and water, dried, and evaporated, giving a froth of the acetoxy-compound, $[\alpha]_D$ −122° (Found: C, 41·3; H, 3·6; Hal, 33·9; OMe, 15·9; OAc, 9·3. Calc. for $C_{19}H_{19}Br_2ClO_8$: C, 40·0; H, 3·35; Hal, 34·2; OMe, 16·3; OAc, 10·3%).

5,3′-Dibromogriseofulvin (II; R = Me, X = Y = Br) (with Mr. L. Stephenson).—The acetoxy-compound (1·28 g.) in benzene was passed through a column of alumina (50 g.). Evaporation of the benzene left crystals (1·12 g.), m. p. 186—187°, $[\alpha]_D$ +174°. Recrystallisation from propan-2-ol gave pure *5,3′-dibromo-7-chloro-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione*, m. p. 188—190°, $[\alpha]_D$ +180° (Found: C, 40·3; H, 3·1; Br, 31·5; Cl, 6·6; OMe, 18·2. $C_{17}H_{15}Br_2ClO_6$ requires C, 40·0; H, 3·0; Br, 31·3; Cl, 6·9; OMe, 18·2%).

5,3′-Dibromogriseofulvic Acid (I; X = Y = Br).—A mixture of 5,3′-dibromogriseofulvin (0·75 g.), acetic acid (4·0 ml.), and 2N-sulphuric acid (0·75 ml.) was heated on a water-bath for 40 min. The cooled solution was poured into water, and the solid that separated (0·72 g.) recrystallised from propan-2-ol–isopropyl ether, giving *5,3′-dibromo-7-chloro-4,6-dimethoxy-6′-methylgrisan-3,2′,4′-trione* (0·44 g.), m. p. 200—202°, $[\alpha]_D$ +163° (Found: C, 39·1; H, 2·9; Hal, 39·0. $C_{16}H_{13}Br_2ClO_6$ requires C, 38·7; H, 2·6; Hal, 39·3%).

5-Bromogriseofulvic Acid (I; X = H, Y = Br).—Potassium iodide (130 mg.) in water (1·0 ml.) and acetic acid (1·0 ml.) was added to 5,3′-dibromogriseofulvic acid (200 mg.) in acetic acid (3·0 ml.). Iodine was liberated at once, and after 1·5 hr. the solution was poured into dilute sodium hydrogen sulphite solution, and the white solid which separated was collected (160 mg.). Recrystallisation from carbon tetrachloride containing a trace of chloroform gave *5-bromo-7-chloro-4,6-dimethoxy-6′-methylgrisan-3,2′,4′-trione*, m. p. 237° (decomp.), $[\alpha]_D$ +310° (*c* 1·0 in 2N-Na_2CO_3) (Found: C, 46·1; H, 3·4; Hal, 27·4. $C_{16}H_{14}BrClO_6$ requires C, 46·0; H, 3·4; Hal, 27·6%).

5-Bromogriseofulvin (II; R = Me, X = H, Y = Br).—A solution of griseofulvin (1·0 g.) and mercuric acetate (0·466 g.; 0·5 mol.) in acetic acid (20 ml.) was treated with bromine (9·235 g.) in acetic acid (100 ml.) until a faint brown colour persisted for more than 2 min.; 5·34 ml. of the bromine solution (1·07 mol.) were used. After 20 min. the solution was poured into water (200 ml.), and the solid (930 mg.; m. p. 65—150°, $[\alpha]_D$ +165°) that separated was collected. The crude product (900 mg.) in benzene was adsorbed on alumina (50 g.). Elution with benzene gave slightly impure 5,3′-dibromogriseofulvin (0·07 g.), m. p. 185—188°, mixed m. p. 188·5—191°, and elution with benzene containing 5% of ether gave crude 5-bromogriseofulvin (0·50 g.). Crystallisation from methanol gave *5-bromo-7-chloro-4,6,2′-trimethoxy-6′-methylgris-2′-en-3,4′-dione* (0·35 g.), m. p. 112—115°, $[\alpha]_D$ +249° (Found: C, 47·0; H, 3·8; Hal, 26·4. $C_{17}H_{16}BrClO_6$ requires C, 47·3; H, 3·75; Hal, 26·7%). A mixture of 5-bromogriseofulvin (250 mg.), acetic acid (2·0 ml.), and 2N-sulphuric acid (0·25 ml.) was refluxed for 1 hr. and then poured into water. The solid that separated (200 mg.) was 5-bromogriseofulvic acid, m. p. and mixed m. p. 237° (decomp.).

5,3′,3′-Tribromo-7-chloro-4,6-dimethoxy-6′-methylgrisan-3,2′,4′-trione (V; X = Br).—Bromine (1·0 g.) in acetic acid (10 ml.) was added slowly with stirring to a suspension of 3′-bromogriseofulvic acid (2·0 g.) in acetic acid (18 ml.) containing mercuric acetate (1·0 g.). After 3 hr. the mixture was made alkaline with 2N-sodium carbonate and acidified to pH 5 with 2N-hydrochloric acid. The crude tribromo-derivative separated (2·2 g.; m. p. 98—101°, $[\alpha]_D$ 0°) but decomposed on attempted purification. A sample was dried at room temperature under reduced pressure and analysed (Found: C, 30·0; H, 2·4; Hal. 44·1. Calc. for $C_{16}H_{12}Br_2ClO_6,3H_2O$: C, 30·5; H, 2·85; Hal, 43·7%).

5,3′-Dibromo-7-chloro-4-hydroxy-6,2′-dimethoxy-6′-methyl-gris-2′-en-3,4′-dione (X).—A mixture of 5,3′-dibromogriseofulvin (0·5 g.), lithium bromide (0·5 g.), and acetone (15 ml.) was refluxed for 2 hr. Most of the solvent was removed and the residue in water acidified to pH 1 with dilute hydrochloric acid. The solid that separated was reprecipitated from dilute sodium carbonate solution with acid, to give the *phenol* (X) (0·32 g.), m. p. 215° (decomp.), $[\alpha]_D$ +172°, $\nu_{max.}$ 3450 (bonded OH) (Found: C, 38·7; H, 2·8; OMe, 10·4. $C_{16}H_{13}Br_2ClO_6$ requires C, 38·7; H, 2·6; OMe, 12·5%).

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