Synthesis in the Griseofulvin Series. III. Chloro Analogs and 6′-Demethylgriseofulvin[1]

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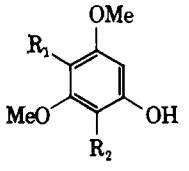
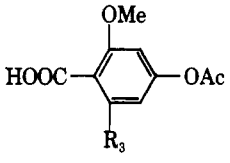
Total syntheses of (±)-7-dechlorogriseofulvin (Va), (±)-5-chloro-7-dechlorogriseofulvin (Vb), and (±)-6′-demethylgriseofulvin (Vc) are described. Monochlorination of Va led to Vb and to (±)-griseofulvin (Vd), thereby completing an additional synthetic route to the latter. Mono- and dichlorination products of (+)-griseofulvin have been obtained and interrelated.

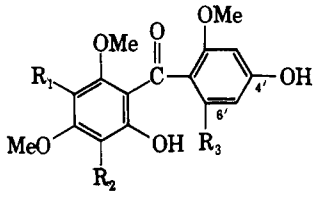
With the development of total syntheses of the mold metabolite and antifungal agent, griseofulvin,[2] interest has focused on related synthetic compounds of possible physiological utility. Following synthesis of the fully active 7-fluoro-7-dechlorogriseofulvin V (R_1 = H, R_2 = F, R_3 = Me),[3] we directed our attention to the preparation of the analogs Va, Vb, and Vc. The key step in our approach, which parallels our griseofulvin synthesis,[2c] was the oxidative radical coupling of the properly constituted dihydroxybenzophenones[2b,4] III to give the respective dienones IV.



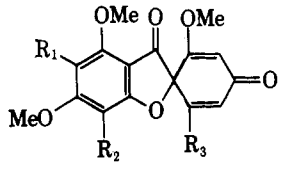
Ia, R_1 = R_2 = H
Ib, R_1 = Cl; R_2 = H
Ic, R_1 = H; R_2 = Cl



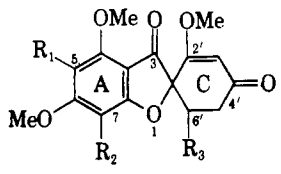
IIa, R_3 = Me
IIb, R_3 = H



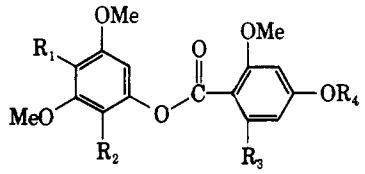
IIIa, R_1 = R_2 = H; R_3 = Me
IIIb, R_1 = Cl; R_2 = H; R_3 = Me
IIIc, R_1 = H; R_2 = Cl; R_3 = H



IVa, R_1 = R_2 = H; R_3 = Me
IVb, R_1 = Cl; R_2 = H; R_3 = Me
IVc, R_1 = H; R_2 = Cl; R_3 = H



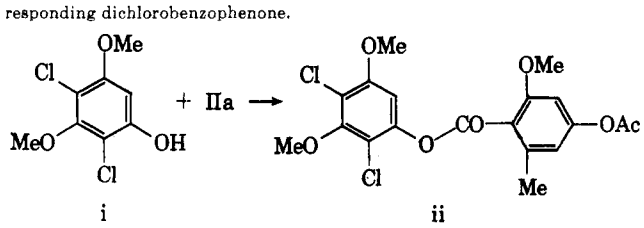
Va, R_1 = R_2 = H; R_3 = Me
Vb, R_1 = Cl; R_2 = H; R_3 = Me
Vc, R_1 = H; R_2 = Cl; R_3 = H
Vd, R_1 = H; R_2 = Cl; R_3 = Me



VIa, R_1 = Cl; R_2 = H; R_3 = Me; R_4 = Ac
VIb, R_1 = Cl; R_2 = H; R_3 = Me; R_4 = H
VIc, R_1 = H; R_2 = Cl; R_3 = H; R_4 = H

For the synthesis of (±)-dechlorogriseofulvin (Va),[5] phloroglucinol dimethyl ether (Ia) was condensed with 2-methoxy-4-acetoxy-6-methylbenzoic acid (IIa) in trifluoroacetic anhydride[2c,3] to give the benzophenone monoacetate (IIIa, 4′-OAc), m.p. 158–160°, which was readily saponified (also in part by alkaline extraction during the work-up) to the benzophenone IIIa, m.p. 180–182° (~50–60%). In the ultraviolet, IIIa possessed intense maximum at 297 mμ (ε 19,700) and shoulder near 328 mμ (ε 7100) typical of similarly constituted benzophenones.[2c,3] In the infrared, the strongly H-bonded *o*-hydroxybenzophenone carbonyl group showed the characteristic shift of the 6.0-μ band to 6.2 μ. The oxidative ring closure of compound IIIa with potassium ferricyanide[2b] by a modified technique[2c] provided the dienone IVa, m.p. 241–244°, in quantitative yield. Hydrogenation of the latter over 10% palladium on charcoal in 1,2-dimethoxyethane proceeded with minimal hydrogenolysis[2c] to give (±)-dechlorogriseofulvin (Va),[6] m.p. 218–219°, in ~70% yield and a minor amount of the corresponding 2′,3′-dihydrodechlorogriseofulvin, m.p. 169–171°.

By contrast with the predominance of C-acylation in the condensation of Ia with IIa in trifluoroacetic anhydride, reaction of 4-chloro-3,5-dimethoxyphenol (Ib) with IIa led primarily to the phenol ester VIa.[7,8] Although the benzophenone IIIb could be isolated by



i ii

Evidently, introduction of an electron-attracting function *para* to the phenolic hydroxol group deactivates the aromatic ring to electrophilic attack. Whether the C-acylated products are formed directly or by Fries rearrangement of phenolic ester intermediates has not been determined.

(1) Preliminary accounts of this work appeared in *Chem. Ind.* (London), 1617 (1962), and *Angew. Chem.*, **74**, 586 (1962). For part II of this series, see ref. 3.

(2) Total syntheses of griseofulvin have been reported by (a) A. Brossi, M. Baumann, M. Gerecke, and E. Kyburz, *Helv. Chim. Acta*, **43**, 1444, 2071 (1960); (b) A. C. Day, J. Nabney, and A. I. Scott, *Proc. Chem. Soc.*, 284 (1960); *J. Chem. Soc.*, 4067 (1961); (c) D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Chem. Ind.* (London), 1627 (1960); *Tetrahedron*, **19**, 1 (1963); (d) G. Stork and M. Tomasz, *J. Am. Chem. Soc.*, **84**, 310 (1962). For a review of griseofulvin chemistry, see J. F. Grove, *Quart. Rev.* (London), **17**, 1 (1963).

(3) D. Taub, C. H. Kuo, and N. L. Wendler, *Chem. Ind.* (London), 557 (1962); *J. Org. Chem.*, in press.

(4) For a recent review and leading references of intramolecular radical coupling of phenols, see C. H. Hassall and A. I. Scott, "Chemistry of Natural Phenolic Compounds," W. D. Ollis, Ed., Pergamon Press, Oxford, 1961, p. 119.

(5) M. Gerecke, E. Kyburz, C. v. Planta, and A. Brossi, *Helv. Chim. Acta*, **45**, 2241 (1962), utilizing another route,[2a] have independently obtained Va, Vb, and Vc, among other synthetic analogs.

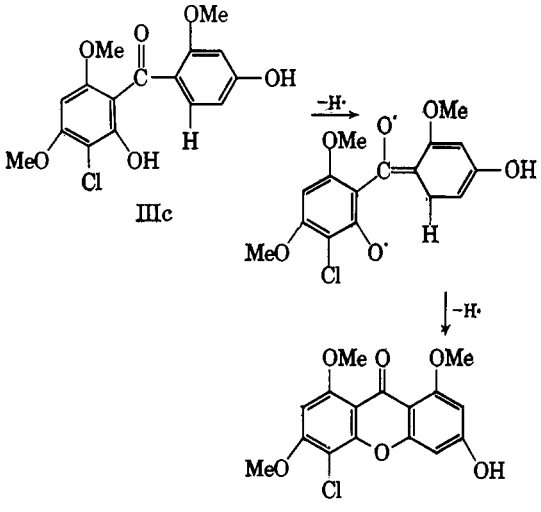
(6) For (+)-dechlorogriseofulvin, see J. MacMillan, *J. Chem. Soc.*, 1697 (1953); V. Arkley, G. I. Gregory, and T. Walker, *ibid.*, 1603 (1963).

(7) C-Acylation predominated in reaction of IIa with 2-chloro-3,5-dimethoxyphenol[2c] and 2-fluoro-3,5-dimethoxyphenol,[3] respectively, but 2,4-dichloro-3,5-dimethoxyphenol (i) reacted with IIa to give almost exclusively the corresponding ester (ii) and only trace amounts of the corresponding dichlorobenzophenone.

(8) O-Acylation of phenols in trifluoroacetic anhydride is described by E. J. Bourne, N. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949); J. M. Tedder, *Chem. Rev.*, **55**, 787 (1955); see also, C. J. Brown, D. E. Clark, W. D. Ollis, and P. L. Veal, *Proc. Chem. Soc.*, 393 (1960).

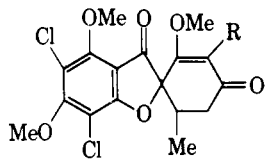
fractional crystallization of the alkaline extract, it proved more efficient to submit the hydrolyzed mixture of benzophenone IIIb and ester VIb to the oxidative coupling reaction, wherein only benzophenone reacted to give neutral dienone IVb, easily separable from unchanged alkali-soluble ester VIb. Hydrogenation of IVb proceeded without difficulty to give (±)-5-chloro-7-dechlorogriseofulvin (Vb), m.p. 213–214°, together with the corresponding 2′,3′-dihydro compound, m.p. 173–174°, as a minor by-product.

The synthesis of 6′-demethylgriseofulvin (Vc) was investigated next. The absence of an alkyl substituent at C-6′ in the pertinent benzophenone IIIc introduces a point of difference with regard to the radical coupling reaction. As an alternative to spirodienone formation, cyclization to a xanthone is a formal possibility. The required benzophenone IIIc was prepared as previously

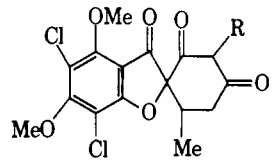


described by acylation of 2-chloro-3,5-dimethoxyphenol (Ic) with 2-methoxy-4-acetoxybenzoic acid (IIb) in trifluoroacetic anhydride. In this example also, the corresponding ester predominated. On alkaline extraction of the reaction mixture and crystallization, benzophenone IIIc, m.p. 217–220°, was obtained in 10% yield, whereas saponification of the neutral fraction and fractional crystallization gave ester VIc, m.p. 192–196°, in 40% yield. Fries rearrangement of the ester VIc utilizing titanium tetrachloride in nitrobenzene[2c,9] produced additional IIIc (30–35%) as well as trace amounts of the phenol Ic. Attempted conversion of IIIc to 6′-demethyldehydrogriseofulvin IVc by the alkaline ferricyanide procedure (see preceding) was a striking failure. The yield of IVc in several attempts was ~1% with no other recognizable product. However, by using heterogenous conditions, lead dioxide–50% ether–acetone,[10] IIIc was converted to IVc, m.p. 345–350°, in 90% yield. The concluding hydrogenation proceeded as in the preceding cases to give predominantly 6′-demethylgriseofulvin, m.p. 227–228°, and a minor amount of the corresponding dihydro compound, m.p. 191–193°.

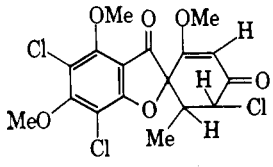
With (±)-dechlorogriseofulvin (Va) now available, its behavior on chlorination was studied. Treatment of Va with one equivalent of chlorine in methylene chloride produced essentially equal amounts of (±)-griseofulvin (Vd) and (±)-5-chloro-7-dechlorogriseofulvin (Vb). This route constitutes an additional synthesis of (±)-griseofulvin. It is of interest that chlorine reacts preferentially by substitution in ring A rather than at the double bond in ring C. By contrast, the β-diketone griseofulvic acid is chlorinated in ring C and, in fact, twice at position 3′ before position 5 in ring A is attacked.[11]



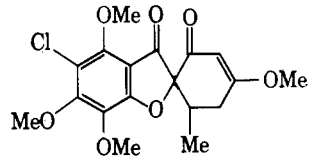
VIIa, R = H
VIIb, R = Cl



VIIIa, R = H
VIIIb, R = Cl



IX



X

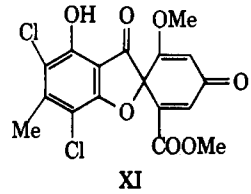
Chlorination of (+)-griseofulvin (Vd) with one equivalent of chlorine gave as the principal product (+)-5-chlorogriseofulvin (VIIa). The n.m.r. spectrum of VIIa lacked the band at 3.9 τ ascribed to the C-5 proton in the griseofulvin structure[12] but did have a band at 4.42 τ associated with the C-3′ proton. The ultraviolet spectrum showed the marked hypsochromic shift (λ_{max} 297 → λ_{max} 273 mμ) shown by other 5-chlorogriseofulvin analogs (see Experimental) and the infrared spectrum showed the unmodified ring C unsaturated carbonyl group (λ_{max} 6.01, 6.18 μ). Also formed was a small quantity of a dichlorogriseofulvin which was the major product (60–70%) of dichlorination of griseofulvin. This substance, 3′,5-dichlorogriseofulvin (VIIb), lacked both aromatic and vinyl proton n.m.r. bands, absorbed in the ultraviolet at 275 mμ and, in the infrared, the ring C unsaturated carbonyl group absorption was shifted to 5.91 μ. This hypsochromic shift of 0.09 μ is noteworthy and is ascribed to interaction of the coplanar C-3′–Cl and C-4′ = 0 groupings analogous to α-equatorial halogen–carbonyl interaction.[13] A second dichlorogriseofulvin, m.p. 158–160°, was formed in minor amount. The latter absorbed in the ultraviolet at 275 mμ indicating the presence of chlorine at C-5 (compare Vb, VIIa, and VIIb) and the ring C carbonyl group absorbed in the infrared at 5.95 μ indicating the presence of adjacent equatorial chlorine. By elimination, this second chlorine should be placed on C-5′ (compare IX). The n.m.r. spectrum (see Experimental) is more in accord with formulation IX than with other possibilities. The positions of the 4- and

(9) N. M. Cullinane and B. F. R. Edwards, *J. Chem. Soc.*, 3016 (1957).
(10) *Cf.* C. H. Hassall and J. R. Lewis, *ibid.*, 2312 (1961).
(11) Halogenated analogs of griseofulvin (including VIIa, VIIb, and X) have been obtained independently by halogenation of griseofulvic acid and conversion to mixtures of the corresponding 2′- and 4′-enol ethers [T. Walker, W. K. Warburton, and G. B. Webb, *ibid.*, 1277 (1962)].
(12) The n.m.r. spectral data for compounds in this series are recorded and discussed by B. H. Arison, N. L. Wendler, D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, and N. R. Trenner, *J. Am. Chem. Soc.*, **85**, 627 (1963). See also ref. 5.
(13) Infrared spectra of griseofulvin analogs are discussed in detail by J. E. Page and S. E. Staniforth, *J. Chem. Soc.*, 1292 (1962). The carbonyl band of 4-chloro-Δ⁴-3-keto steroids occurs at 1690 cm.⁻¹ (5.91 μ) [G. Roberts, B. S. Gallagher and R. N. Jones, "Infrared Absorption Spectra of Steroids," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1958, p. 24]. See also E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).

6-methoxyl bands at 5.85 and 5.94 τ are in agreement only with analogs containing a 5-chlorine (compare Vb, VIIa, and VIIb[12]). The 2'-methoxyl band at 6.30 τ would be shifted to near 5.97 if the 3'-proton (4.30 τ) were replaced by chlorine (compare VIIb[12]). The one proton doublet (4.86, 5.07 τ) is assigned to the 5'-proton coupled to the 6'-proton (both protons are probably diaxial). Multiplets in the 6.9–7.2-τ region are ascribed to the 6'-proton coupled to the 6'-methyl group and the 5'-proton. Finally, the doublet at 8.82 is assigned to the 6'-methyl group.

3',5-Dichlorogriseofulvin (VIIb) was converted into 5-chlorogriseofulvin (VIIa) as follows. Hydrolytic cleavage of the enol ether function of VIIb[14] led in high yield to the corresponding 3',5'-dichlorogriseofulvic acid (VIIIb), m.p. 208–210°. The 3'-chlorine atom, on the α-carbon of the ring C β-dicarbonyl system of VIIIb, was reductively removed by sodium iodide in acetic acid[15] to give 5-chlorogriseofulvic acid (VIIIa), m.p. 227–235°, identical with material obtained by hydrolysis of VIIa. Diazomethane methylation of VIIIa led to VIIa and the isomeric enol ether, 5-chloroisogriseofulvin (X).

The chlorination experiments indicate that available positions in ring A will be chlorinated in preference to possible sites in ring C. It may be advantageous in planning syntheses of related chlorine-containing mold metabolites (*e.g.*, geodin XI[16]) by radical coupling of a phenolic benzophenone precursor to introduce chlorine at the final stage, since its presence earlier might impede benzophenone formation (see ref. 7).



XI

By disk plate assays employing *Botrytis allii* as the test organism, compounds Vb, Vc, VIIa, VIIb, IX, and X were found to be greatly reduced in activity relative to griseofulvin.[17]

Experimental[18]

2-Hydroxy-4'-acetoxy-4,6,2'-trimethoxy-6'-methylbenzophenone (IIIa, 4'-OAc).—To a stirred solution of 2.70 g. of 2-methoxy-4-acetoxy-6-methylbenzoic acid (IIa) in 20 ml. of trifluoroacetic anhydride at 10° was added 1.85 g. of 3,5-dimethoxyphenol (Ia). The mixture was kept at 25–30° overnight and then concentrated to dryness in a stream of nitrogen. The residue was taken up in ether and the latter solution washed successively with 5% potassium bicarbonate solution (acidification of this extract gave a small amount of recovered IIa), 5% potassium hydroxide solution (acidification gave 700 mg. of crude IIIa), and saturated sodium chloride solution. The ether extract was dried over magnesium sulfate and concentrated to dryness under vacuum. Crystallization of the residue (3.50 g.) from ether–petroleum ether (b.p. 30–60°) gave the 2-hydroxy-4'-acetoxybenzophenone (IIIa, 4'-OAc), 1.43 g. (40%), m.p. 153–158°; analytical sample from acetone–ether, m.p. 158–160°; λ_{max} 298 (21,000), sh 335 mμ (ϵ 7450); λ_{max}^{chf} 5.71, 6.15, 6.30 μ.

Anal. Calcd. for $C_{19}H_{20}O_7$: C, 63.32; H, 5.59. Found: C, 62.83; H, 5.51.

The neutral mother liquors (2.0 g.) contained *ca.* 30% additional IIIa, 4'-OAc as indicated by the ultraviolet spectrum, λ_{max} 297 mμ (ϵ 7500), and by hydrolysis to the 2,4'-dihydroxybenzophenone IIIa.

2,4'-Dihydroxy-4,6,2'-trimethoxy-6'-methylbenzophenone (IIIa).—Basic hydrolysis of IIIa, 4'-OAc (1.30 g.), in 100 ml. of methanol and 80 ml. of 5% aqueous sodium hydroxide at room temperature under nitrogen for 2 hr. gave the dihydroxybenzophenone IIIa (960 mg.), m.p. 180–182° (from ethyl acetate); λ_{max} 297 (19,700), sh 328 mμ (ϵ 7100); λ_{max}^{chf} 2.75, 3.04, 6.19, 6.25 μ.

Anal. Calcd. for $C_{17}H_{18}O_6$: C, 64.13; H, 5.70. Found: C, 64.27; H, 6.00.

Similar hydrolysis of the benzophenone acetate mother liquors (2.0 g.) gave additional benzophenone IIIa (400 mg.), m.p. 180–182°.

4,6,2'-Trimethoxy-6'-methylgris-2',4'-diene-3,4'-dione (IVa).—To a solution of 850 mg. of the dihydroxybenzophenone IIIa in 25 ml. of *t*-butyl alcohol was added 15 g. of potassium carbonate in 100 ml. of water. The *t*-butyl alcohol was removed by concentration under vacuum and 3.40 g. of potassium ferricyanide in 40 ml. of water was added dropwise (during 5 min.) to the stirred solution to give a heavy precipitate. After 1 hr., ethyl acetate was added (the precipitate dissolved) and the mixture was washed with cold 5% sodium hydroxide, salt solution, and dried over magnesium sulfate. The neutral residue (760 mg., m.p. 233–240°) was recrystallized from acetone–ether to give IVa, m.p. 241–244°; λ_{max} 288 (32,400), 225 mμ (ϵ 24,000); λ_{max}^{chf} 5.85, 6.00, 6.15, 6.25, 6.63 μ.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.38; H, 5.02.

(±)-4,6,2'-Trimethoxy-6'-methylgris-2'-ene-3,4'-dione (Dechlorogriseofulvin, Va) and 2',3'-Dihydrodechlorogriseofulvin.—A solution of 395 mg. of the dienone IVa in 30 ml. of 1,2-dimethoxyethane was added to a stirred suspension of 900 mg. of 10% palladium–Darco catalyst (pre-reduced) in 20 ml. of 1,2-dimethoxyethane in an atmosphere of hydrogen. Within 5 min., 0.9 equivalent of hydrogen was absorbed, the reaction was stopped, the catalyst was filtered, and the solvent removed under vacuum. The residue in 20 ml. of acetic acid was stirred with 800 mg. of zinc dust for 10 min. to convert any remaining IVa to base-soluble benzophenone IIIa. The zinc was removed by filtration, water was added, and the mixture extracted with chloroform. The latter extract was washed with dilute sodium hydroxide (acidification of the basic extract and chloroform extraction gave ~30 mg. of recovered benzophenone IIIa), salt solution, and dried over magnesium sulfate to give 380 mg. of crystalline neutral material. Thin layer chromatography (benzene–chloroform, 1:1) showed this to consist of Va and a small amount of the corresponding more mobile 2',3'-dihydro compound.

Column chromatography of the neutral material on 40 g. of neutral alumina gave (±)-dechlorogriseofulvin Va from the 50% benzene–chloroform eluates (250 mg., needles from acetone–ether, first crop 150 mg.), m.p. 218–219°; λ_{max} infl 323 (4700), 286 (25,000), 249 mμ (ϵ 15,200); λ_{max}^{chf} 5.76, 6.00, 6.14, 6.22, 6.61 μ.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.13; H, 5.70. Found: C, 64.11; H, 5.71.

Combination of the benzene–5% benzene–chloroform eluates and crystallization from acetone–ether gave 2',3'-dihydrodechlorogriseofulvin (47 mg.), m.p. 169–171°; λ_{max} infl 312 (5200), 284 mμ (ϵ 22,000); λ_{max}^{chf} 5.80, 5.92, 6.15, 6.24, 6.63 μ.

Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.73; H, 6.30. Found: C, 63.35; H, 6.21.

The intermediate benzene–chloroform fractions contained additional Va and 2',3'-dihydro Va with the former predominating.

5-Chloro-2,4'-dihydroxy-4,6,2'-trimethoxy-6'-methylbenzophenone (IIIb).—To a stirred solution of 2.92 g. of 2-methoxy-4-acetoxy-6-methylbenzoic acid (IIa) in 20 ml. of trifluoroacetic

(14) Procedure of V. Arkley, J. Attenburrow, G. I. Gregory, and T. Walker, *J. Chem. Soc.*, 1260 (1962).

(15) *Cf.* F. Kröhnke and H. Timmler, *Ber.*, **69**, 614 (1936); see also ref. 11.

(16) H. Raistrick and G. Smith, *Biochem. J.*, **30**, 1315 (1936); D. H. R. Barton and A. I. Scott, *J. Chem. Soc.*, 1767 (1958).

(17) The authors are indebted to H. Wallick of these laboratories for performing this assay.

(18) Melting points were taken on a microscope hot-stage apparatus and are corrected. Ultraviolet spectra were determined in methanol and rotations measured with a Zeiss photoelectric precision polarimeter employing a 0.2-dm. tube. Whatman No. 4 paper was utilized for paper chromatography and thin layer chromatography (t.l.c.) was carried out on glass plates coated with alumina according to Stahl [E. Stahl, *Chemiker-Ztg.*, **82**, 323 (1958); *Angew. Chem.*, **73**, 646 (1961)].

anhydride at 10° was added 2.20 g. of 4-chloro-2,5-dimethoxyphenol[19] (Ib) and the mixture was allowed to warm to room temperature. A white precipitate of the phenolic ester acetate VIa formed; λ_{max}^{MeOH} 268 (3300), 229 mμ (ε 8900); λ_{max}^{chf} 5.66, 5.75 μ. An additional 20 ml. of trifluoroacetic anhydride was added and the stirred mixture was refluxed gently overnight (~40°). The mixture was filtered, the precipitate (3.40 g. of ester VIa) washed with cold ether, and the filtrate taken to dryness. Thin layer chromatography (t.l.c.) (benzene–chloroform, 9:1) showed two spots: major, benzophenone acetate IIIb, 4'-OAc; and minor, ester VIa. The residue was taken up in 1:1 benzene–ether, washed with 5% potassium bicarbonate, 5% sodium hydroxide, saturated salt solution, and dried over magnesium sulfate. The neutral residue (1.41 g.) containing both IIIb, 4'-OAc and VIa was saponified in 10 ml. of methanol and 20 ml. of 5% aqueous sodium hydroxide for 90 min. at room temperature. Acidification followed by chloroform extraction led to 980 mg. of yellow amorphous solid (mixture of benzophenone IIIb and partially saponified phenolic ester VIb) which was oxidized directly (see next experiment). Acidification of the original basic extract and extraction with chloroform led to crude *p*-chlorobenzophenone IIIb (280 mg.) which was crystallized from acetone–ether to yield yellow prisms, m.p. 199–202°; λ_{max}^{MeOH} 340 (8200), 285 mμ (ε 15,500); λ_{max}^{chf} 2.74, 3.05, 6.17, 6.25, 6.77 sh μ.

Anal. Calcd. for $C_{17}H_{17}O_6Cl$: C, 57.88; H, 4.86. Found: C, 57.40; H, 4.75.

5-Chloro-4,6,2'-trimethoxy-6'-methylgris-2',4'-diene-3,4'-dione (IVb).—To a solution of crude 4-chlorobenzophenone (970 mg.) containing phenolic ester VIb (see preceding experiment) in 20 ml. of *t*-butyl alcohol was added 12.5 g. of potassium carbonate in 90 ml. of water. The *t*-butyl alcohol was removed under vacuum and 2.80 g. of potassium ferricyanide in 35 ml. of water was added dropwise to the stirred mixture. After 30 min., the reaction mixture was extracted with ethyl acetate, the latter extract washed with cold 5% sodium hydroxide, saturated salt solution, and dried over magnesium sulfate. Crystallization of the neutral residue (600 mg.) from acetone–ether gave the 5-chlorodienone IVb (250 mg.), m.p. 202–206°; λ_{max}^{MeOH} 330 (5800), 283 (26,000), 223 mμ (ε 31,000); λ_{max}^{chf} 5.82, 6.00, 6.19, 6.30, 6.65 μ.

Anal. Calcd. for $C_{17}H_{15}O_6Cl$: C, 58.21; H, 4.31. Found: C, 58.00; H, 4.27.

5-Chloro-4,6,2'-trimethoxy-6'-methylgris-2'-ene-3,4'dione (5-Chloro-7-dechlorogriseofulvin, Vb) and 2',3'-Dihydro-5-chloro-7-dechlorogriseofulvin.—The 5-chlorodienone IVb (150 mg.) was hydrogenated over 300 mg. of 10% palladium–Darco in 22 ml. of 1,2-dimethoxyethane and worked up as described for the preparation of Va. Treatment with 300 mg. of zinc dust in 5 ml. of acetic acid yielded 53 mg. of base-soluble benzophenone and 95 mg. of neutral material. The latter was chromatographed over 9 g. of neutral alumina. Crystallization of the single spot (t.l.c., benzene–chloroform 2:1), 100% benzene–50% chloroform–benzene fractions (53 mg.) from acetone–ether, gave pure Vb as hexagonal prisms, m.p. 213–214°; λ_{max}^{MeOH} 331 (5600), 280 (16,000), 237 (23,600), 216 mμ (ε 21,500); λ_{max}^{chf} 5.88, 6.04, 6.20, 6.30, 6.63 μ.

Anal. Calcd. for $C_{17}H_{17}O_6Cl$: C, 57.88; H, 4.85; Cl, 10.05. Found: C, 57.82; H, 4.82; Cl, 9.86.

The combined single spot (t.l.c.), benzene–petroleum ether, 3:1 fractions (25 mg.), gave pure 2',3'-dihydro-Vb; needles from acetone–ether, m.p. 173–174°; λ_{max}^{MeOH} 330 (5200), 272 (15,400), sh 230 mμ (ε 18,500); λ_{max}^{chf} 5.81, 5.92, 6.19, 6.28, 6.74 μ.

Anal. Calcd. for $C_{17}H_{19}O_6Cl$: C, 57.54; H, 5.40. Found: C, 57.35; H, 5.33.

2-Methoxy-4-acetoxybenzoic Acid (IIb).—This acid was prepared by potassium permanganate oxidation of 2-methoxy-4-acetoxybenzaldehyde[20] in aqueous acetone containing magnesium sulfate by the procedure utilized for the preparation of IIa[2c]; yield, 45–50%; plates from ether–hexane, m.p. 92–94°; λ_{max}^{MeOH} 290 (3800), 237 mμ (8900); λ_{max}^{chf} 3.05, 5.70, 5.78, 6.17, 6.26, 6.67 μ.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.47; H, 5.15.

3-Chloro-2,4'-dihydroxy-4,6,2'-trimethoxybenzophenone (IIIc) and 2-Chloro-3,5-dimethoxyphenyl 2'-Methoxy-4'-hydroxybenzoate (VIc). A. Trifluoroacetic Anhydride Procedure.—To a stirred solution of 3.57 g. of 2-methoxy-4-acetoxybenzoic acid (IIb) in 40 ml. of trifluoroacetic anhydride was added (10°) 3.18 g. of 2-chloro-3,5-dimethoxyphenol (Ic)[19] and the mixture kept at room temperature overnight. Considerable precipitate (ester) had formed. Trifluoroacetic anhydride was removed in a stream of nitrogen. Iced water was added cautiously followed by 1:1 ether–ethyl acetate and the mixture was partitioned into acidic (soluble in 5% sodium hydroxide) and neutral fractions. The acidic residue (1.12 g.) on crystallization from acetone–ether gave 330 mg. of benzophenone IIIc, yellow prisms, m.p. 217–220; λ_{max}^{MeOH} 300 (13,600), sh 325 mμ (ε 10,500); λ_{max}^{Nujol} 3.05–3.15, 6.15, 6.22, 6.35, 6.65 μ.

Anal. Calcd. for $C_{16}H_{15}O_6Cl$: C, 56.74; H, 4.47. Found: C, 56.44; H, 4.25.

The neutral fraction (4.95 g.) was saponified in 40 ml. of methanol and 40 ml. of 5% aqueous sodium hydroxide for 2 hr. at room temperature. Crystallization of the product from acetone–ether gave 2.30 g. of ester VIc, m.p. 192–196°; λ_{max}^{chf} 2.80, 3.05, 5.80 μ.

Anal. Calcd. for $C_{16}H_{15}O_6Cl$: C, 56.74; H, 4.47. Found: C, 56.47; H, 4.41.

B. Benzophenone IIIc by Fries Rearrangement of VIc.—To a stirred solution of 2.20 g. of the 6'-demethyl ester VIc in 22 ml. of nitrobenzene (10°) was added dropwise 1.43 ml. (2.47 g.) of titanium tetrachloride. After 17 hr. at room temperature, the reaction mixture was added slowly to a mixture of 500 ml. of ice and 2 *N* hydrochloric acid and 100 ml. of methylene dichloride. The mixture was extracted several times with methylene dichloride and the latter extract in turn was extracted with cold 5% sodium hydroxide. Acidification with dilute hydrochloric acid and extraction with methylene chloride gave, following drying and evaporation of solvent, 1.82 g. of yellow amorphous material. Crystallization from acetone–ether gave 530 mg. of benzophenone IIIc, m.p. 213–216°. Chromatography of the mother liquors on 35 g. of neutral alumina gave from the 50% chloroform–acetone fractions an additional 210 mg. of IIIc, m.p. 212–215°. From the 35% chloroform–benzene fractions *ca.* 10 mg. of phenol Ic, m.p. 55–57° (undepressed on admixture with an authentic sample), was obtained.

7-Chloro-4,6,2'-trimethoxygris-2',4'-diene-3,4'-dione (IVc).—A solution of 550 mg. of benzophenone IIIc in 25 ml. of acetone and 25 ml. of ether was stirred overnight with 6.0 g. of freshly prepared lead dioxide.[10] The reaction mixture was filtered and the filter cake washed with acetone. Evaporation of the filtrate gave 410 mg. of single spot (t.l.c., chloroform–benzene, 5:1) dienone IVc. An additional 90 mg. of IVc was obtained by eluting the filter cake with methanol. The analytical sample was crystallized from methylene chloride–ethyl acetate, m.p. 345–350°; λ_{max}^{MeOH} 325 (4200), 292 (23,000), 231 infl mμ (15,800); λ_{max}^{chf} 5.80, 6.00, 616, 6.25, 6.63 μ.

Anal. Calcd. for $C_{16}H_{13}O_6Cl$: C, 57.09; H, 3.89. Found: C, 56.90; H, 4.13.

When 100 mg. of benzophenone IIIc was treated with potassium ferricyanide in aqueous potassium carbonate by the procedure used for the preparation of IVa and IVb, *ca.* 1–2 mg. of crude IVc, m.p. 300–310°, was obtained on crystallization of the neutral extract (*ca.* 10 mg.) of the reaction mixture from acetone–ether.

7-Chloro-4,6,2'-trimethoxygris-2'-ene-3,4'-dione (6'-Demethylgriseofulvin, Vc) and 2',3'-Dihydro-6'-demethylgriseofulvin.—The dienone IVc (150 mg.) was dissolved in 20 ml. of methylene dichloride. Ethyl acetate (40 ml.) was added and the methylene dichloride removed by distillation until the vapor temperature reached 75°. The solution was carefully cooled to room temperature and added to a pre-reduced suspension of 300 mg. of 10% palladium–Darco in 10 ml. of ethyl acetate in a hydrogen atmosphere. Following uptake of one equivalent of hydrogen (3 min.), the reaction was worked up and treated with zinc dust as described for the preparation of Va to yield 50 mg. of recovered benzophenone IIIc and 90 mg. of neutral solid. The latter was chromatographed over 6 g. of neutral alumina. Combination of the 2%–30% chloroform–benzene fractions (67 mg.) and crystallization twice from benzene gave 6'-demethylgriseofulvin (26 mg.), m.p. 227–228°; λ_{max}^{MeOH} 321 (4800), 289 (20,800), 236 mμ (ε 23,000); λ_{max}^{chf} 5.84, 6.00, 6.15, 6.24, 6.60 μ; slightly

(19) J. F. Grove, J. MacMillan, T. P. C. Mulholland, and J. Zealley, *J. Chem. Soc.*, 3967 (1952).

(20) F. Tiemann and A. Parrisius, *Ber.*, **13**, 2375 (1880), first prepared 2-methoxy-4-acetoxybenzaldehyde and oxidized it with aqueous permanganate. However, they saponified the acetoxy group of their product *in situ* and isolated 2-methoxy-4-hydroxybenzoic acid [β-resorcylic acid-2-methyl ether]. The corresponding acetate IIb does not appear to have been reported.

more polar on paper (R_f 0.50) than griseofulvin (R_f 0.65)—benzene–cyclohexane 5:1–formamide system.

Anal. Calcd. for $C_{16}H_{15}O_6Cl$: C, 56.74; H, 4.47. Found: C, 56.59; H, 4.41.

Rechromatography of the mother liquors (40 mg.) on 4 g. of neutral alumina and crystallization from benzene of the single-spot 20%–40% chloroform–benzene eluates gave an additional 12 mg. of pure Vc.

Combination of the pertinent benzene fractions from both chromatograms and crystallization from acetone–ether gave 2′,3′-dihydro-6′-demethylgriseofulvin, m.p. 191–193°; λ_{max}^{MeOH} 320 (4350), 287 (18,500), 235 mμ (ε 12,300); λ_{max}^{chf} 5.79, 5.86, 6.16, 6.24, 6.62 μ.

Monochlorination of (±)-Dechlorogriseofulvin (Va) to Yield (±)-Griseofulvin (Vd) and (±)-5-Chloro-7-dechlorogriseofulvin (Vb).—(±)-Dechlorogriseofulvin (V, 64 mg., 0.20 mmole) was dissolved in 2 ml. of methylene chloride. At 10°, 14 mg. of chlorine (0.2 mmole) in 0.5 ml. of carbon tetrachloride, diluted to 3 ml. with methylene chloride, was added dropwise with stirring. After 10 min. the reaction mixture was concentrated *in vacuo* to a partly crystalline residue which by t.l.c. (benzene–chloroform 2:3) consisted of essentially equal amounts of Vb and Vd and a trace of the 5,7-dichloro compound Xa. This was chromatographed on 6 g. of neutral alumina. From the 2% chloroform–benzene eluates there was isolated (±)-5-chloro-7-dechlorogriseofulvin (Vb), m.p.213–216°, identical with material obtained by total synthesis by mixture melting point and infrared criteria. From the 35% chloroform–benzene eluates, 12 mg. of crude (±)-griseofulvin (Vd) was isolated, purified further by preparative paper chromatography (Whatman No. 4 paper, benzene–cyclohexane 1:1–formamide system), m.p. 222–224° (from acetone–ether); identical with an authentic sample of (±)-Vd by mixture melting point and infrared criteria.

Monochlorination of (+)-Griseofulvin (Vd) to Yield 5-Chlorogriseofulvin (VIIa) and 5,3′-Dichlorogriseofulvin (VIIb).—A solution of 144 mg. of chlorine (2 mmoles) in 4 ml. of carbon tetrachloride was added dropwise at room temperature to a stirred solution of 706 mg. (2 mmoles) of (+)-griseofulvin (Vd) in 20 ml. of methylene chloride (6 min.). After an additional 20 min., the reaction mixture was concentrated *in vacuo* to a partly crystalline residue. Ether was added and the crystals removed by filtration (recovered Vd, *ca.* 400 mg.). The filtrate was concentrated *in vacuo* to 300 mg. of oil which was chromatographed on 30 g. of neutral alumina. From the 50% benzene–petroleum ether eluates, 5,3′-dichlorogriseofulvin (VIIb) was obtained, 5.1 mg., m.p. 161–163°, after recrystallization from ether–petroleum ether. From the benzene and benzene–chloroform eluates, 198 mg. of 5-chlorogriseofulvin (VIIa) was obtained as an amorphous solid[21], $[\alpha]_D^{chf}$ +278°; λ_{max}^{MeOH} 345 (4100), 273 (14,500), 231 mμ (ε 26,500); λ_{max}^{chf} 5.83, 6.01, 6.18, 6.34 μ.

Anal. Calcd. for $C_{17}H_{16}O_6Cl_2$: C, 52.73; H, 4.17; Cl, 18.32. Found: C, 53.01; H, 4.09; Cl, 18.28.

Hydrolysis of VIIa by the sulfuric–acetic acid procedure[14] afforded 5-chlorogriseofulvic acid (VIIIa), m.p. 229–238°, identical with material prepared by partial dechlorination of VIIb.

Dichlorination of (+)-Griseofulvin (Vd) to Yield 5,3′-Dichlorogriseofulvin (VIIb) and 5,5′-Dichlorogriseofulvin (IX).—(+)-Griseofulvin (Vd, 10.6 g., 30 mmoles) was dissolved in 312 ml. of methylene chloride and 4.32 g. (60 mmoles) of chlorine in 120 ml. of carbon tetrachloride was added with stirring at 25° over a period of 2.5 hr. After one additional hour, the reaction mixture was concentrated *in vacuo* to an oil which was chromatographed on 600 g. of neutral alumina to give, from the hexane–benzene eluates, 7.73 g. (62% plus additional material in the mother liquors) of 5,3′-dichlorogriseofulvin (VIIb), m.p. 167–168°, $[\alpha]_D^{chf}$ +226°; λ_{max}^{MeOH} 346 (4400), 275 (21,500), 220 mμ (ε 26,800); $\lambda_{max}^{CHCl_3}$ 5.80, 5.91, 6.21, 6.34 μ.

Anal. Calcd. for $C_{17}H_{15}O_6Cl_3$: C, 48.42; H, 3.59; Cl, 25.23. Found: C, 48.39; H, 3.63; Cl, 25.27.

From the benzene eluates was obtained 150 mg. of 5,5′-dichlorogriseofulvin (IX), m.p. 158–160°; λ_{max}^{MeOH} 345 (3900), 275 (15,200), 223 mμ (ε 27,300); $\lambda_{max}^{CHCl_3}$ 5.80, 5.95, 6.15, 6.21, 6.33 μ.

N.m.r. spectra showed 4.30 (3′-H), 4.86, 5.07 (doublet 5′-H), 5.85 (4-CH_3O), 5.94 (6-CH_3O), 6.30 (2′-CH_3O), 6.96, 7.16 (centers of overlapping quartets 6′-H), 8.82 τ (doublet 6′-CH_3).

Anal. Calcd. for $C_{17}H_{15}O_6Cl_3$: C, 48.42; H, 3.59; Cl, 25.23. Found: C, 48.27; H, 3.70; Cl, 25.05.

5,3′-Dichlorogriseofulvic Acid (VIIIb).—Two grams of 5,3′-dichlorogriseofulvin (VIIb) was heated with 90 ml. of acetic acid and 18 ml. of 2 *N* sulfuric acid[14] on the steam bath for 3 hr. The reaction mixture was cooled to room temperature, saturated with salt, and extracted with ethyl acetate. The organic phase was extracted with aqueous potassium bicarbonate and the bicarbonate solution was acidified with hydrochloric acid. The acidified reaction mixture was extracted with ethyl acetate and the organic extract was washed with salt water, dried over magnesium sulfate, and concentrated *in vacuo* to crystalline 5,3′-dichlorogriseofulvic acid (VIIIb) which was triturated with acetone–ether to afford a first crop of 1.5 g., m.p. 208–210°; second crop (from acetone–ether) of 0.31 g., m.p. 206–209° (total yield, 94%); λ_{max}^{MeOH} 346 (4400), 280 (27,200), 221 mμ (ε 24,600); $\lambda_{max}^{pyridine}$ 5.86, 6.2, 6.5 μ; λ_{max}^{Nujol} 5.95, 6.1, 6.35, 6.43 μ.

Anal. Calcd. for $C_{16}H_{13}O_6Cl_3$: C, 47.14; H, 3.21; Cl, 26.09. Found: C, 47.27; H, 3.23; Cl, 25.88.

5-Chlorogriseofulvic Acid (VIIIa).—A solution of 4.75 g. of sodium iodide in 35 ml. of acetic acid was added to 2.37 g. of VIIIb in 60 ml. of acetic acid and the reaction mixture was warmed on the steam bath for 4 hr. The iodine color was discharged with aqueous sodium thiosulfate and the resulting colorless solution was extracted with ethyl acetate. The organic phase was washed neutral with salt water, dried over magnesium sulfate, and concentrated *in vacuo*. Crystallization of the residue from acetone–ether gave 688 mg. of crystalline 5-chlorogriseofulvic acid (VIIIa), m.p. 229–238°, with evolution of gas; λ_{max}^{MeOH} 346 (4200), 274 (27,100), 223 mμ (ε 23,200); λ_{max}^{Nujol} 5.94, 6.31, 6.46 μ; $\lambda_{max}^{pyridine}$ 3.0, 4–4.2, 5.3, 5.87, 6.06, 6.21 μ.

Anal. Calcd. for $C_{16}H_{14}O_6Cl_2$: C, 51.45; H, 3.75; Cl, 19.00. Found: C, 51.31; H, 3.66; Cl, 18.57.

5-Chlorogriseofulvin (VIIa) and 5-Chloroisogriseofulvin (X) from 5-Chlorogriseofulvic Acid (VIIIa).—A 600-mg. sample of VIIIa was methylated in 50 ml. of methanol by adding diazomethane in ether to the cold solution until the yellow diazomethane color persisted. The reaction mixture was concentrated to dryness at room temperature and the residue was chromatographed on 80 g. of neutral alumina. From the 5% chloroform–benzene eluates 5-chloroisogriseofulvin (X) was isolated; thin plates from acetone–ether (130 mg.), m.p. 175–177°, $[\alpha]_D^{chf}$ +194°; λ_{max}^{MeOH} 348 (4200), 264 (23,500), 223 mμ (ε 26,000); λ_{max}^{chf} 5.89, 6.04, 6.2–6.24, 6.34 μ.

Anal. Calcd. for $C_{17}H_{16}O_6Cl_2$: C, 52.73; H, 4.17; Cl, 18.32. Found: C, 52.77; H, 4.00; Cl, 18.88.

From the 50% chloroform–benzene fractions, 186 mg. of 5-chlorogriseofulvin (VIIa) was obtained of identical infrared spectrum and paper chromatographic mobility as VIIa obtained by monochlorination of griseofulvin.

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(21) Walker, *et al.*[11] report m.p. 90–93° for VIIa.