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A TOTAL SYNTHESIS OF GRISEOFULVIN AND ITS OPTICAL ANTIPODE[1]

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Abstract—An efficient total synthesis of (±) griseofulvin and its optical antipode, (−) griseofulvin, is described. Several aspects of the chemistry of this substance, its precursors and transformation products are discussed.

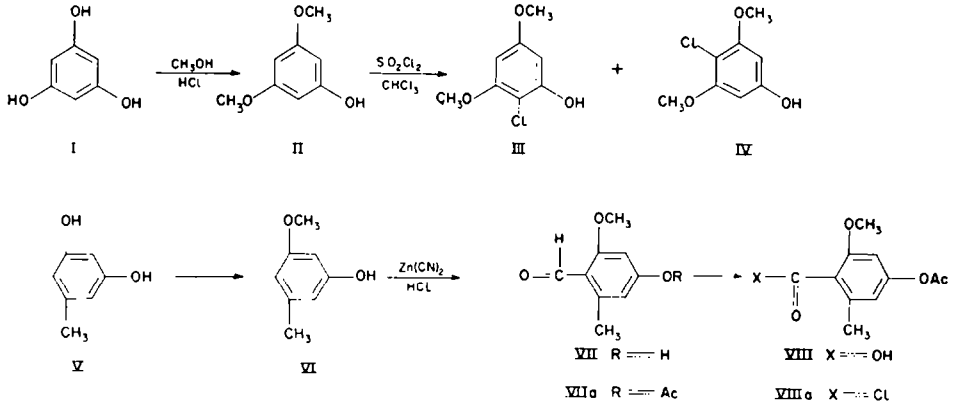
THE chemistry of the important antifungal agent griseofulvin[2] finds its most significant expression in the outstanding structural studies by the British chemists at Imperial Chemical Industries. These studies culminated in 1952 with the establishment of the structure of this substance;[3] in 1959 the stereochemical details were defined and the absolute configuration set forth.[4] Shortly thereafter and in rapid succession, total syntheses were reported by Brossi *et al.*[5] in Switzerland as well as by Day *et al.*[6] in England and subsequently by ourselves.[1] In very recent times an additional synthesis has been recorded.[7]

Our approach to the synthesis of griseofulvin was independently conceived in consideration of the synthesis of usnic acid,[8] a structure which like certain griseofulvin derivatives contains a semibenzenoid system and one which in turn is accessible by oxidative phenolic coupling. It revealed itself subsequently that Scott[9] had been diligently pursuing this route to the same objective. There are, however, certain important differences between our experiences and those reported by Scott *et al.* and these will be treated in turn in the course of the ensuing discussion.

The first stage of the synthesis as projected, required the condensation of a phenolic with an acidic component. Preparation of the phenolic component (III) was effected essentially in accordance with published procedures[10] whereby phloroglucinol, (I) was first converted to its dimethyl ether with methanolic hydrogen chloride followed by nuclear chlorination with sulfuryl chloride in chloroform solution. The mixture of 2-chloro-3,5-dimethoxy phenol (III) and 4-chloro-3,5-dimethoxy phenol (IV) thus produced was easily separated by steam distillation whereby III was the volatile component. The acidic moiety (VIII) was prepared from orcinol which, in the form of its

[1] A preliminary account of this work appeared in part in *Chem. & Ind.* 1627 (1960).
[2] Griseofulvin was first isolated from *Penicillium griseofulvum* and its structure partially defined by A. E. Oxford, H. Raistrick and P. Simonart, *Biochem. J.* **33**, 240 (1939).
[3] J. F. Grove, J. MacMillan, T. P. C. Mulholland and M. A. T. Rogers, *J. Chem. Soc.* 3977 (1952) and related papers.
[4] J. MacMillan, *J. Chem. Soc.* 1823 (1959).
[5] A. Brossi, M. Baumann, M. Gerecke and E. Kyburz, *Helv. Chim. Acta* **43**, 1444, 2071 (1960).
[6] A. C. Day, J. Nabney and A. I. Scott, *Proc. Chem. Soc.* 284 (1960; *J. Chem. Soc.* 4067 (1961).
[7] G. Stork and M. Tomasz, *J. Amer. Chem. Soc.* **84**, 310 (1962).
[8] D. H. R. Barton, A. M. Deflorin and O. E. Edwards, *J. Chem. Soc.* 530 (1956).
[9] A. I. Scott, *Proc. Chem. Soc.* 195 (1958); see also D. H. R. Barton and T. Cohen, *Festschrift A. Stoll* p. 117. Birkhauser, Basel (1957).
[10] J. F. Grove, J. MacMillan, T. P. C. Mulholland and J. Zealley, *J. Chem. Soc.* 3967 (1952).

monoethyl ether (VI)[11] was converted by the Gattermann reaction chiefly to iso-everninaldehyde (VII).[12] The latter on acetylation followed by permanganate oxidation provided 4-acetoxy-2-methoxy-6-methylbenzoic acid (VIII). The corresponding acid chloride (VIIIa) was formed from VIII with thionyl chloride.

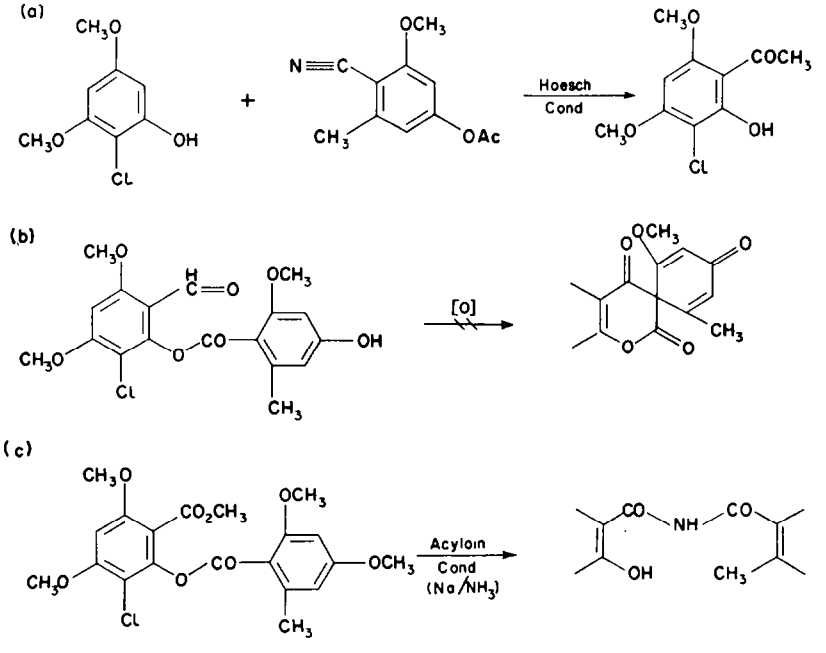


Initial attempts to effect Friedel-Crafts coupling between the phenol (III) and the acid chloride (VIIIa) in nitrobenzene, afforded only the ester IX which was identical with material prepared from the two components in pyridine solution.[1,13] Subsequently we found that under conditions of higher component concentration nuclear

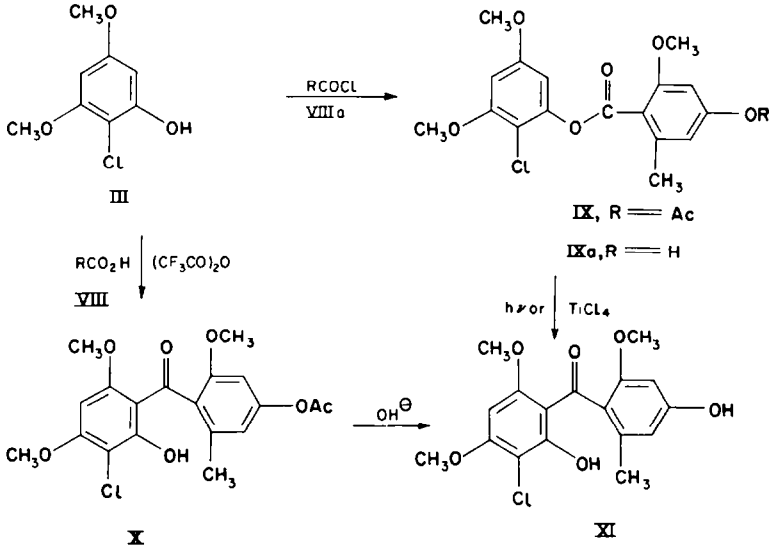
[11] F. Henrich and G. Nachtigall, *Ber. Dtsch. Chem. Ges.* **36,** 889 (1903).

[12] A. St. Pfau, *Helv. Chim. Acta* **11,** 876 (1928); K. Hoesch, *Ber. Dtsch. Chem. Ges.* **46,** 886 (1913); F. W. Canter, A. Robertson and R. B. Waters, *J. Chem. Soc.* 493 (1933).

[13] Several alternative approaches designed to give the benzophenone (XI) directly or indirectly were investigated with the following results:



acylation did occur to the extent of 30–35% in conformity with previous report.[6] At the time of our initial communication[1] we had achieved the synthesis of the benzophenone (XI) by a photo-induced Fries rearrangement on the half ester IXa according to the technique employed by Anderson and Reese[14,14a] for the transformation of catechol monoacetate to 3,4-dihydroxy acetophenone. In the interim we have found that the rearrangement of the half-ester (IXa) to benzophenone (XI) can be effected in 40–50% yield by means of titanium tetrachloride[15] in nitrobenzene solution. Aluminum chloride, on the other hand, was found to promote rearrangement to an extent not greater than 5%, fragmentation into its components being the dominant transformation as evidenced by recovery of 2-chloro-3,5-dimethoxy phenol (III) in 45–50% yield. The best method in our experience for preparing the benzophenone (XI), consisted in allowing the free acid (VIII) to react with the phenolic component (III) in trifluoracetic anhydride at 25°, whereby IX and benzophenone (X) were formed concomitantly.[16] The ester IX (25–30%) being insoluble in trifluoracetic anhydride, separated and was removed by filtration at the conclusion of the reaction; from the filtrate, in turn, the benzophenone (XI) could be isolated, after hydrolysis, in ca. 50% yield. Conversion of IX in turn by mild hydrolysis to half-ester IXa and Fries rearrangement of the latter in the presence of titanium tetrachloride gave additional XI to provide an overall yield of benzophenone of ca. 65%. The formation of XI in this reaction is noteworthy inasmuch as in the previous employment of trifluoracetic anhydride as a catalyst for *phenolic* acylations, only ester products have been reported.[17]



[14] J. C. Anderson and C. B. Reese, *Proc. Chem. Soc.* 218 (1960).

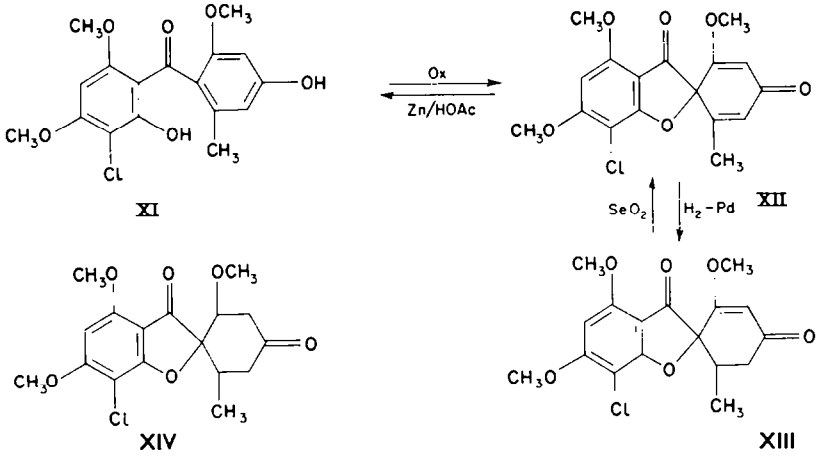
[14a] Irradiation of the ester (IXa) in dry benzene resulted in fragmentation with deposition of the acid (VIII).

[15] N. M. Cullinane and B. F. R. Edwards, *J. Chem. Soc.* 3016 (1957); N. M. Cullinane, R. A. Woolhouse and B. F. R. Edwards, *Ibid.* 3842 (1961).

[16] D. Taub, C. H. Kuo and N. L. Wendler, *Chem. & Ind.* 557 (1962).

[17] E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.* 2976 (1949); see also: C. J. Brown, D. E. Clark, W. D. Ollis and P. L. Veal, *Proc. Chem. Soc.* 393 (1960). See, however, L. I. Woods, *J. Org. Chem.* **27**, 696 (1962).

The conversion of natural (+) griseofulvin, (XIII), to dehydrogriseofulvin (XII) by selenium dioxide and thence by hydrogenolytic cleavage to the benzophenone, (XI), had beenp reviously described by Scott.[9] Our own attempts, in contrast, to effect hydrogenolysis of dehydrogriseofulvin (XII) to benzophenone, (XI), resulted largely in reversion to griseofulvin itself together with the formation of only about 20% of XI. The directional course of the hydrogenation of dehydrogriseofulvin was subsequently recognized as possessing a sensitive catalyst–solvent dependency (see later discussion). On the other hand, it was found that chromous chloride or better, zinc in acetic acid were excellent reagents for affecting the conversion XII → XI. By means of the latter reagent, essentially quantitative yields of benzophenone were obtained from dehydrogriseofulvin in a matter of minutes. Benzophenone (XI), prepared either by synthesis (III → XI) or by degradation from griseofulvin, was obtained as a pale yellow crystalline solid m.p. 210–212°, $\lambda_{max}^{CH_3OH}$ 297 mμ (18,500) 332 mμ (6,200) exhibiting a strongly hydrogen-bonded carbonyl group at 6·19 μ ($CHCl_3$).



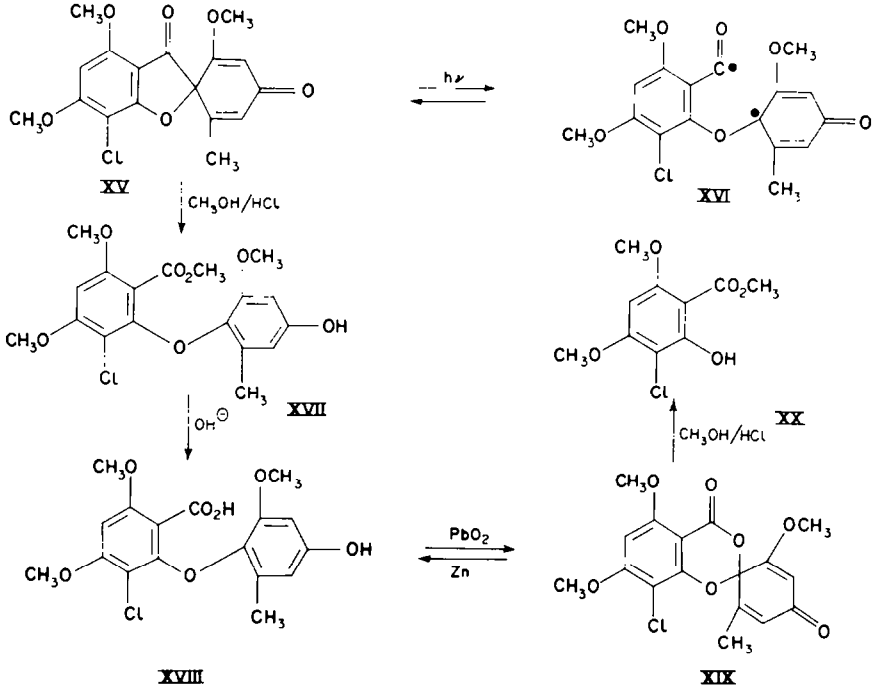
The selenium dioxide dehydrogenation of griseofulvin to dehydrogriseofulvin (XIII → XII) did not, in our experience, proceed to completion in one pass despite prolonged exposure to excess reagent. Likewise, the separation of pure dehydrogriseofulvin from a mixture containing griseofulvin by chromatography was not found possible practically. Griseofulvin, which has essentially the same paper-strip mobility (benzene–cyclohexane–formamide system) as dehydrogriseofulvin, could be readily detected in a mixture of the two substances by its extremely sensitive fluorescence[18] in UV light subsequent to paper-strip chromatography. This characteristic was not exhibited by dehydrogriseofulvin. Griseofulvin and dehydrogriseofulvin likewise did not exhibit discrete separation on alumina by thin layer chromatography but instead behaved in the same manner as on paper. In order to secure pure dehydrogriseofulvin free from griseofulvin, it was found expedient to repeat the selenium dioxide treatment on the isolated dehydrogenation product (see Experimental). In this manner pure dehydrogriseofulvin free of griseofulvin by fluorescence and NMR criteria was obtained.

Optically active dehydrogriseofulvin was found to be slowly racemized on irradiation with uv light in acetonitrile solution. The great insolubility of the inactive (±)

[18] S. H. Cowdry, D. Gardner, J. F. Grove and D. Palmer, *J. Exp. Bot.* **6**, 371 (1955) and later papers.

isomer permitted its separation from solution and subsequent isolation free from contamination by active material. This isomerization allows ready access to the (±) isomer, alternatively available by the preferred synthetic route. Racemization about the spiranic center bears a formal analogy to the case of usnic acid[19] and may be considered to result in virtue of the process XV → XVI with contributions from electron delocalized species of the latter. Griseofulvin is recovered essentially unchanged after irradiation in acetonitrile solution; in methanol solution, however, griseofulvin is converted to an equilibrium mixture of griseofulvin and isogriseofulvin (XIII → XXII); in ethanol solution the ethyl analog of XXII is correspondingly formed.

Dehydrogriseofulvin, being an extended β-diketone, is prone to B-ring cleavage and gives the methyl ester (XVII) on treatment with methanolic hydrogen chloride or aqueous methanolic potassium hydroxide.[20] Prolonged refluxing of the methyl ester with 30% aqueous methanolic potassium hydroxide afforded the free acid (XVIII). Other natural occurring spiranic dieneones have been found to undergo similar cleavage to diaryl ether systems.[21] Oxidation of the acid (XVIII), with lead dioxide[22] afforded a neutral compound formulated as the spiranic lactone (XIX). Confirmation of structure XIX was derived from its IR spectrum (λ_{max} 5·72, 5·95, 6·05 and 6·2 μ) as well as its NMR spectrum. This lactone reverted to the acid XVIII on reduction with zinc



[19] D. H. R. Barton and G. Quinkert, *J. Chem. Soc.* 1 (1960); see also the acid catalyzed racemization of (+) geodin D. H. R. Barton and A. I. Scott, *Ibid.* 1767 (1958).

[20] E. Kyburz, J. Wursch, and A. Brossi [*Helv. Chim. Acta* **45**, 813 (1962)] also observed the transformation XV → XVII with sodium methoxide.

[21] R. F. Curtis, C. H. Hassall, D. W. Jones and T. W. Williams, *J. Chem. Soc.* 4838 (1960).

[22] C. H. Hassall and J. R. Lewis, *J. Chem. Soc.* 2312 (1961).

in acetic acid and was cleaved with methanolic hydrogen chloride to methyl 2-hydroxy-3-chloro-4,6-dimethoxy benzoate (XX).[10]

Oxidative ring closure of the benzophenone (XI) to (±) dehydrogriseofulvin (XII) with potassium ferricyanide, when carried out under the usual conditions,[8] produces 50–60% of dieneone together with large amounts of unoxidized benzophenone (compare also ref. 6). By the simple expedient of reversed addition, nearly quantitative yields of dieneone can be realized. This homogenous oxidative coupling (XI → XII) can also be effected in small yield with lead tetraacetate in acetic acid solution as well as by ceric ammonium sulfate (compare ref. 22). Alternatively, the oxidative ring closure (XI → XII) can be elegantly effected by heterogenous means. Employing lead dioxide in ether–acetone solution, the benzophenone (XI) is quantitatively (100%) transformed to (±) dehydrogriseofulvin. Manganese dioxide in the same reaction produces 95–100% XII, whereas silver oxide affords only 5–10% of dienone.[23]

The hydrogenation of dehydrogriseofulvin had been studied and the course of reaction determined at a very early stage of our synthetic work. At the same time the importance of a high catalyst-substrate ratio (2:1) and the use of a relatively non-polar solvent (EtOAc) were recognized. The hydrogenation occurred rapidly at room temperature and atmospheric pressure and was interrupted after approximately 90% of one mole of hydrogen had been absorbed. The amount of benzophenone produced thereby through hydrogenolysis, as determined both by alkaline extraction and direct chromatography, was found to be consistently ca. 20% for many runs. The presence of unchanged (±) dehydrogriseofulvin (5–10%), together with (±) griseofulvin (55–60%) and a more mobile entity, (±) dihydrogriseofulvin (10–15%), was established by paper-strip chromatography (benzene–cyclohexane formamide system) as well as by isolation. By exploiting the earlier finding that dehydrogriseofulvin is rapidly and quantitatively converted to benzophenone (XI) by zinc in acetic acid, a method was provided for the easy isolation of the (±) griseofulvin. Thus, the hydrogenation product was stirred for 10 minutes at room temperature with zinc and acetic acid whereby all unreacted dehydrogriseofulvin was converted to benzophenone which was extracted by alkali. The benzophenone (25–30%) thus recovered is equivalent to dehydrogriseofulvin in light of the quantitative conversion of the former to the latter (see above). IR analysis of the neutral material demonstrated that it contained 85–90% of griseofulvin (XIII) and 10–15% dihydrogriseofulvin (XIV) conveniently separated chromatographically on Florisil or neutral alumina. The (±) griseofulvin thus obtained melted at 223–225° and was identical with natural griseofulvin in its IR and NMR spectra as well as by paper-strip and thin layer chromatography (Al_2O_3). The conversion yield in the hydrogenation of dehydrogriseofulvin to griseofulvin is, therefore, of the order of 85–90%, representing an overall realizable yield of griseofulvin from starting components (III and VIII) of about 55–60%.

Hydrogenation of optically active dehydrogriseofulvin afforded in addition to (+) griseofulvin as the major product, (+) dihydrogriseofulvin (XIV) identical by physical constant comparison with that obtained earlier from the hydrogenation of (+) griseofulvin.[24] It is significant that the hydrogenation of XII proceeds exclusively from

[23] In view of the remarkable susceptibility of the benzophenone (XI) to oxidative ring closure by a variety of reagents it is surprising that an alkaline solution (K_2CO_3) of this substance appears to be completely stable to air-oxidation for a prolonged period of time even in the presence of Fe^{++}.

[24] T. P. C. Mulholland, *J. Chem. Soc.* 3994 (1952).

one side of the molecule, namely that adjacent to the ether oxygen.[25,26] There was no evidence for the formation of epigriseofulvin[4] from any of the hydrogenations carried out, an observation also made by the English group.[6] As has been noted by others[5] as

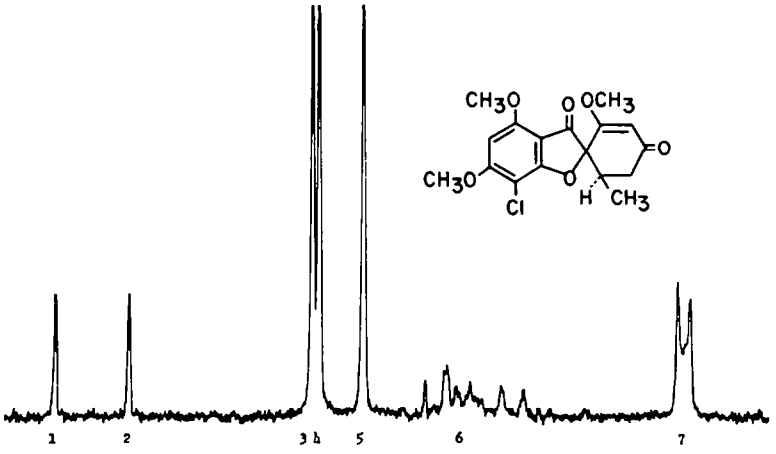


FIG. 1

NMR Spectrum of Griseofulvin (5% in $CDCl_3$)

Band	τ value[a]	Functionality
1	3·86	aromatic H
2	4·50	vinyl H
3	5·97	aromatic OCH_3
4	6·03	aromatic OCH_3
5	6·39	vinyl OCH_3
6	6·93–7·72	CH_2—CH
7	9·04 (doublet)	C—CH_3

[a] Tetramethylsilane = 10·0. For detailed discussion and an NMR study of related compounds see ref. 25*b*.

well, griseofulvin and epigriseofulvin differ unmistakably in their respective mobilities on thin layer chromatography. Furthermore, the IR and particularly the NMR spectra of the two substances are characteristically different. The NMR spectra of griseofulvin

[25a] For configurational assignment see ref. 4; [b] See also 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.*, in press for configurational confirmation by NMR.

[26] It is not obvious from an inspection of the model of dehydrogriseofulvin how such a high degree of stereoselectivity in the hydrogenation could be attributed to steric factors alone. It would rather appear suggested that possible orbital overlap of the π-electrons of the carbonyl group with those of the dieneone system, in a manner similar to that suggested by Stork and Tomasz (cf. ref. 7) in a related connection, or, an intramolecular π-complex (Compare R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron* **2**, 1 (1958); C. P. Kugatova-Shemyakina and Y. A. Ouchinnikov, *Ibid.* **18**, 697 (1962) may play a decisive role. In this same connection it may be mentioned that the orientation of the 6′-methyl group in griseofulvin (*cis* with resepct to the 3 C=O) (Fig. 1) has not been unequivocally determined but rather deduced from equilibrium studies[4] which in turn were dependent on the relative steric evaluation of the 3-carbonyl *vs.* the cyclic ether function. The results of the hydrogenation studies do, however, in light of the above considerations, support this assignment as well as the orientation *cis-syn-cis* (6′-CH_3-3 C=O-2′-OCH_3) for dihydrogriseofulvin XIV.

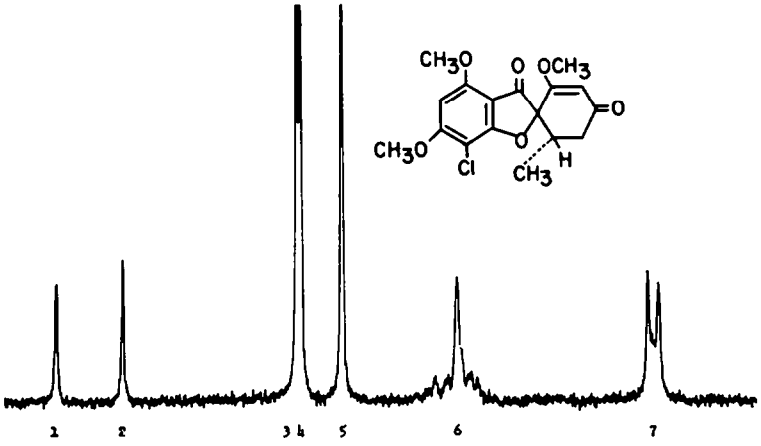


FIG. 2

NMR Spectrum of Epigriseofulvin (5% in $CDCl_3$)

Band	τ value	Functionality
1	3·87	aromatic H
2	4·44	vinyl H
3	5·99	aromatic OCH_3
4	6·02	
5	6·40	vinyl OCH_3
6	7·33–7·62	CH_2—CH
7	9·12 (doublet)	C—CH_3

and epigriseofulvin (Fig. 1 & 2) differ in the coupling pattern of the —CH_2—CH— moiety (6·9–7·7 τ region) which so specifically designates the region of difference.[25b]

In subsequent hydrogenation experiments it was found that when the catalyst to substrate ratio falls below 2:1, increasing amounts of benzophenone (XI) are formed at the expense of griseofulvin. Likewise when methanol was substituted for ethyl acetate as solvent, hydrogenolysis was the preponderant course of reaction (compare ref. 6). Solvents of intermediate polarity such as dioxane gave intermediate results. Hydrogen-transfer type reductions employing palladium-α-phellandrene[27] or diimide (N_2H_4-$Cu(OAc)_2$-air)[28] resulted in exclusive formation of the benzophenone (XI) from dehydrogriseofulvin with the former reagent and the hydrazide of the acid XVIII with the latter. Attempts to effect hydrogenation under conditions of asymmetric induction employing palladium on cellulose catalyst were abortive.

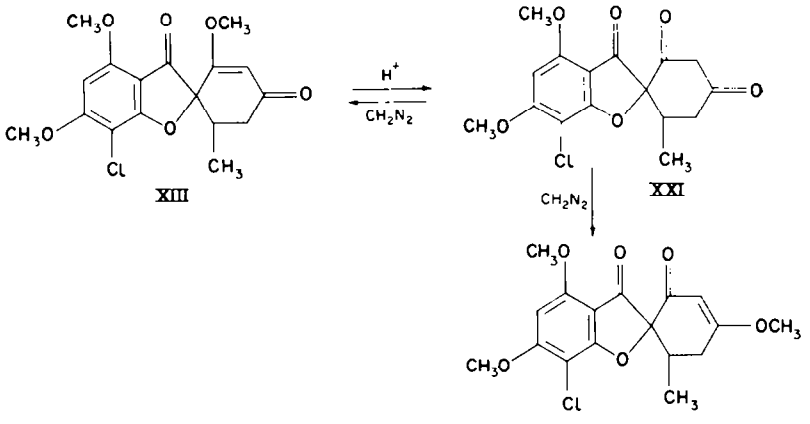
For the optical resolution of (+) griseofulvin, the latter was hydrolysed to (±) griseofulvic acid by heating with a mixture of acetic and sulfuric acids.[29] Attempts to resolve (±) griseofulvic acid as well as (±) griseofulvin by spontaneous resolution techniques were only partially successful in the latter case resulting in ca. 3–4% enrichment of the (+) isomer in two successive crystallizations from acetone–hexane seeded with (+) isomer. By employing cinchonine methohydroxide, (±) griseofulvic

[27] R. Plilland and H. A. Hoa, *C.R. Acad. Sci. Paris.* **252,** (19) 2896 (1961).

[28] E. J. Corey, W. L. Mack and D. J. Pasto, Tetrahedron Letters, 347 (1961); S. Hünig, H. R. Müller and W. Thier, *ibid.* 353 (1961); E. E. van Tamelen, R. S. Dewey and R. J. Timmons, *J. Am. Chem. Soc.*, **83,** 3725 (1961); E. Schmitz and R. Ohme, *Angew. Chem.* **73,** 807 (1961).

[29] Procedure of Belgian Patent 597,963, Glaxo Laboratories, Ltd.; V. Arkley, J. Attenburrow, G. I. Gregory and T. Walker, *J. Chem. Soc.*, 1260 (1962).

acid was converted to a mixture of diastereoisomeric salts from which the salt of (+) griseofulvic acid separated in excellent yield from acetone solution, m.p. 230–231°, $[\alpha]_D$ +314°. This salt was converted with dilute hydrochloric acid to (+) griseofulvic acid (XXI), m.p. 259–263°, $[\alpha]_D^{Pyr}$ +201°; the latter was methylated with diazomethane and chromatographed to provide (+) isogriseofulvin (XXII), m.p. 197–198° $[\alpha]_D$ +215° and (+) griseofulvin (XIII), m.p. 215–216°, $[\alpha]_D$ +339°. The latter was identical in all respects with natural griseofulvin.



XIII XXI XXII

The amorphous mother liquors from the resolution were acidified to provide (−) griseofulvic acid in ca. 20% yield after crystallization from methanol, m.p. 260–264°, $[\alpha]_D^{Pyr.}$ −201°. Methylation of (−) griseofulvic acid and separation on alumina provided (−) isogriseofulvin, m.p. 196–197° $[\alpha]_D$ −216° and (−) griseofulvin, m.p. 216–217°, $[\alpha]_D$ −341°.[30,30a]

By a disc plate assay employing *Botrytis allii* as the test organism, (−) griseofulvin was found to be inactive relative to its natural (+) antipode.[31]

EXPERIMENTAL[32]

2-Methoxy-4-acetoxy-6-methylbenzoic acid (VIII)

To a stirred solution of VIIa[12] (2·0 g; 9·6 mmoles) in 40 ml acetone was added a solution of 5·4 g (34 mmoles) potassium permanganate and 4·61 g (38 mmoles) anhydrous magnesium sulfate in 60 ml water over 1½ hr.[33] After an additional 2½ hr (total time 4 hr), the reaction mixture was chilled in ice and sulfur dioxide was bubbled in until decolorization was complete. The mixture was concentrated *in vacuo* to remove acetone. Water was added to the residue and extraction effected with chloroform. The organic phase was washed with 5% sodium bicarbonate and the latter extract was acidified with hydrochloric acid and the mixture saturated with salt and extracted with chloroform. The chloroform

[30] The (−) antipode is convertible *via* XII to the benzophenone XI and can thence be reintroduced into the cycle leading to (−) griseofulvin.

[30a] *Note added in Proof*
Since this MS was submitted, an article by A. Brossi, M. Baumann and F. Burkhardt [*Helv. Chim. Acta*, **45** 1292 (1962)] appeared describing the synthesis of (—)griseofulvin by another route.

[31] The authors are indebted to H. Wallick of these Laboratories for performing this assay.

[32] The UV spectra were determined in methanol and the rotations measured with a Zeiss photoelectric precision polarimeter employing a 0·2 decimeter tube. Whatman #4 filter paper was utilized for paper chromatography and thin layer chromatography [alumina] was carried out according to Stahl [E. Stahl, *Chem. Z.* **82**, 323 (1958) *Angew. Chem.* **73**, 646 (1961)].

[33] Modified procedure of K. Hoesch, *Ber. Dtsch. Chem. Ges.* **46**, 886 (1913).

extract was washed with water, saturated salt solution, dried ($MgSO_4$) and concentrated to give 1·23 g of VIII as a crystalline residue, m.p. 112–113·5. Crystallization from acetone–ether gave an analytical sample, m.p. 113–114°, λ_{max} 280 mμ (ε, 2,110); $\lambda_{max}^{CHCl_3}$ 2·8–4·3, 5·73, 5·88, 6·22 and 8·0 μ. (Found: C, 58·79; H, 5·28; Calc. for $C_{11}H_{12}O_5$: C, 58·94; H, 5·39%).

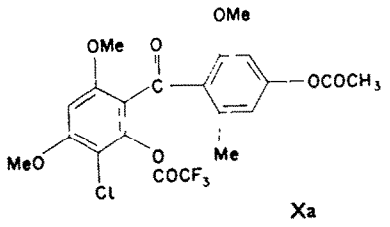
Saponification of VIII (50 mg) in 4 ml methanol and 2 ml 10% aqueous sodium hydroxide at 25° for 2 hr led to *isoeverninic acid* (*2-methoxy-4-hydroxy-6-methylbenzoic acid*), m.p. 189–191° with gas evolution,[34] λ_{max} 282 mμ (ε, 2,600), 246 mμ (ε, 4,200); λ_{max}^{Chf} 2·81, 3·00 (broad), 5·84, 6·20 μ.

3-Chloro-2,4′-dihydroxy-4,6,2′-trimethoxy-6′-methylbenzophenone (XI)

(A) $AlCl_3$-*Catalyzed Friedel-Crafts reaction.* A solution of 3·0 g VIII in 10 ml thionyl chloride (protected from moisture) was kept at 50–60° for 2 hr. Volatile material was removed *in vacuo* leaving a crystalline residue of *4-acetoxy-2-methoxy-6-methylbenzoyl chloride* (VIIIa), m.p. 60–62°; λ_{max}^{Nujol} 5·65, 5·73 μ. The latter (2·95 g) was dissolved in 5 ml nitrobenzene, and to the stirred solution was added 1·89 g *o*-chlorophenol (III)[10] and 3·0 g anhydrous aluminum chloride. After 20 hr the reaction mixture was added dropwise to 100 ml cold 1N HCl. The mixture was extracted with 1:1 benzene–ethyl acetate and the latter in turn was extracted thoroughly with cold 5% sodium hydroxide solution. Acidification, followed by ethyl acetate extraction, drying ($MgSO_4$) and removal of solvent *in vacuo* led to a crystalline residue of benzophenone (XI) 1·2 g (35%), m.p. 209–212°. Crystallization from acetone–benzene gave material with m.p. 210–212°, undepressed with XI obtained from dehydrogriseofulvin (see below). The respective IR spectra were identical.

From the neutral benzene–ethyl acetate layer was obtained 1·0 g (25%) 2-chloro-3,5-dimethoxyphenyl-2′-methoxy-4′-acetoxy-6′-methylbenzoate (IX), m.p. 145–148°. This material was identical with a sample prepared by reaction of III and VIIIa in pyridine (see below).

(B) *Trifluoracetic anhydride.* To a stirred solution of 2·90 g VIII in 20 cc trifluoracetic anhydride at 10° was added 2·20 g phenol III. The latter dissolved producing a deep red solution, from which in ca. 30 min a colorless solid precipitated. After 18 hr at 20°, the precipitate was filtered and washed with a minimum amount of ether to yield 1·2 g (25%) acetoxy ester IX, m.p. 145–150°; raised to 149–152° on crystallization from acetone–ether. This material was identical with an authentic sample by mixed m.p. and IR criteria. The filtrate was concentrated to dryness, the residue taken up in ether and the latter solution extracted with cold 5% sodium hydroxide. Acidification (dil HCl) of the basic extract followed by ether extraction and washing the ether extract with dil potassium bicarbonate solution led to 900 mg phenolic material. Crystallization from ether afforded 600 mg benzophenone (XI). The residue (2·60 g) from the original ether layer gave on fractional crystallization from ether 665 mg benzophenone monoacetate (X), m.p.199–203° (see below) and 960 mg of a new substance, evidently *3-chloro-2-trifluoracetoxy-4′-acetoxy-4,6,2′-trimethoxy-6′-methylbenzophenone* (Xa) prisms from ether–acetone, m.p. 116–120°; λ_{max} 300 mμ (ε, 11,500) shd. 275 mμ (ε, 8,250); λ_{max}^{Chf} 5·54,



Xa

5·71, 5·99, 6·21, 6·85 μ. (Found: C, 52·05; H, 3·77; F, 10·8; Calc. for $C_{21}H_{16}O_8ClF_3$: C, 51·39; H, 3·70; F, 11·6%).

In each case basic hydrolysis of the ester functions in 2·5% aqueous methanolic sodium hydroxide at 25° produced benzophenone (XI) in quantitative yield. The total yield of XI was 2·2 g (50%) with additional material in the mother liquors. In subsequent experiments, continued base extraction of the original ether solution of the reaction mixture resulted in extraction of all benzophenone into the basic layer, from which on acidification it was obtained as the dihydric phenol (XI).

(C) *Light-catalyzed Fries rearrangement.* A solution of 250 mg phenolic ester IXa in 2·5 ml ethanol in a quartz tube was irradiated with UV light [Hanovia Type 16A13 broad spectrum low

[34] E. Fischer and K. Hoesch, *Liebigs. Ann.* **391,** 347 (1912) report m.p. 175° (dec).

pressure light source] at 40° for 66 hr. Chromatography of the residue on 45 g florisil and crystallization of the 5–10% methanol–chloroform eluates from ether gave 42 mg crude XI further purified by crystallization from acetone–ether, 20 mg, m.p. 212·5–215°, plus additional material in the mother liquors, identical with an authentic sample by mixed m.p., paper chromatographic mobility (R_f 0·40 benzene–cyclohexane 5:1 formamide) UV and IR criteria.

When the phenolic ester IXa (25 mg) was irradiated in benzene (2 ml) for 18 hr at 40°, an acidic substance m.p. 180–190° with gas evolution (10 mg) precipitated from solution. This was identified as 2-*methoxy*-4-*hydroxy*-6-*methylbenzoic acid* by mixed m.p. and IR comparison with an authentic sample (see above).

(D) *Titanium tetrachloride-catalyzed Fries rearrangement.* To a solution of 240 mg phenolic ester IXa in 2·7 ml nitrobenzene was added 290 mg titanium tetrachloride under anhydrous conditions. After 18 hr at 20° cold 2N HCl (75 ml) and ether were added. The ether extract was in turn extracted with cold 5% sodium hydroxide solution. The latter was acidified with dil hydrochloric acid and extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and concentrated to dryness *in vacuo*. Crystallization of the residue (175 mg) from ether–acetone gave 60 mg XI, m.p. 209–212°. Paper chromatography (benzene) indicated the mother liquors to consist primarily of XI. This was confirmed by the UV spectrum, λ_{max} 297 mμ (ε, 11,000), shd. 330 mμ (ε, 6,000). The extinction at 296 mμ indicated 60% benzophenone XI. Overall yield of XI ~50%.

(E) *Aluminum chloride-catalyzed Fries rearrangement.* To a stirred solution of 490 mg IXa in 5·00 ml nitrobenzene was added 380 mg anhydrous aluminum chloride. After 20 hr at room temp the reaction mixture was worked up as under (D) to give 420 mg phenolic yellow oil which was chromatographed on 10 g neutral alumina. From the benzene to benzene–30% chloroform eluates was was obtained 115 mg (~45%) of single-spot 2-chloro-3,5-dimethoxyphenol (III), m.p. 57–58°, identical with authentic material by mixed m.p. and IR criteria. Ether crystallization of the 50% acetone–chloroform to 100% acetone eluates gave 25 mg (~5%) of XI, m.p. 205–209°.

2-*Chloro*-3,5-*dimethoxyphenyl*-2′-*methoxy*-4′-*acetoxy*-6′-*methylbenzoate* (IX)

To the acid chloride VIIIa, from 800 mg VIII (see above), in 10 ml pyridine was added 625 mg 2-chloro-3,5-dimethoxyphenol (III). The mixture was warmed on the steam bath for 2 min and kept at 25° for 18 hr. Chloroform was added and the mixture extracted with cold dil hydrochloric acid, cold dil sodium hydroxide solution, saturated salt solution and dried ($MgSO_4$). Crystallization of the residue from ether gave 880 mg IX, m.p. 152–155°; λ_{max} 281 mμ (ε, 4,150); λ_{max}^{Chf} 5·75, 5·80 μ. (Found: C, 57·58; H, 4·66; Cl, 8·88; Calc. for $C_{19}H_{19}O_7Cl$: C, 57·79; H, 4·85; Cl, 8·89%).

2-*Chloro*-3,5-*dimethoxyphenyl*-2′-*methoxy*-4′-*hydroxy*-6′-*methylbenzoate* (IXa)

A solution of 870 mg IX in 60 ml methanol and 40 ml aqueous 10% sodium hydroxide was kept at 25° for 4 hr. The methanol was removed under vacuum and the reaction mixture extracted with chloroform. The aqueous phase was acidified with dil hydrochloric acid extracted with chloroform and the latter extract washed with salt solution and dried ($MgSO_4$). Crystallization from ether gave 615 mg IXa, m.p. 142–144°; λ_{max} 283 mμ (ε, 5,700), 261 mμ (ε, 6, 800), λ_{max}^{Chf} 2·76, 3·00, 5·74 μ. (Found: C, 58·11; H, 5·11; Calc. for $C_{17}H_{17}O_6Cl$: C, 57·89; H, 5·85%).

(−) *Dehydrogriseofulvin* XII *by Selenium dioxide dehydrogenation of* (+) *griseofulvin*

A solution of 30 g (+) griseofulvin and 30 g selenium dioxide in 1·5 l. t-butanol was refluxed for 65 hr. The hot reaction mixture was filtered through celite and the filtrate concentrated to a red oil, which crystallized on adding 150 ml benzene to give 11 g crude dehydrogriseofulvin (XII). The latter by NMR analysis contained ca. 10% griseofulvin. The benzene filtrate was washed with water, dried ($MgSO_4$) and concentrated to dryness. Trituration of the residue with ether led to 14·2 g of comparable crude XII which also contained ca. 10% griseofulvin. In both samples the latter was also detected by its fluorescence on paper chromatography (formamide benzene–cyclohexane 2:1). Two grams of the above crude dehydrogriseofulvin was retreated with selenium dioxide (2 g) in 100 ml refluxing t-butanol for 65 hr and worked up as before. Trituration of the residue with benzene gave a yellow-crystalline solid which was purified further by crystallization from benzene–ether; 1·6 g XII m.p. 271–274° with phase change at 260°. This material was free of griseofulvin as shown by the absence of fluorescence and by NMR analysis. The analytical sample was freed from small amounts of colored (selenium) impurities by chromatography on florisil and crystallization from benzene (80% recovery),

m.p. 276–279° with phase change at 260°; $([\alpha]_D^{acetone} -31{\cdot}6°)$; λ_{max} infl 320 mμ (ε, 6,800); 292 mμ (ε, 33,000), infl 230 (ε, 25,000). (Found: C, 57·94; H, 4·73; Cl, 10·12; Calc. for $C_{17}H_{15}O_6Cl$: C, 58·21; H, 4·31, Cl, 10·11%).

2,4′-Dihydroxy-4,6,2′-trimethoxy-6′-methyl-3-chlorobenzophenone XI *by reductive fission of dehydrogriseofulvin*

(A) *Zinc and acetic acid.* Dehydrogriseofulvin, 1·0 g in 100 ml acetic acid, was treated with stirring at room temp portionwise with 4·0 g zinc dust. The reaction mixture was stirred for 30 min at room temp. The zinc was then filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in methylene chloride and extracted 4 times with ice-cold 2% aqueous potassium hydroxide. The yellow alkaline extracts were acidified with dil sulfuric acid and the precipitated product isolated by extraction with chloroform. The chloroform extracts were washed neutral with water, dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The residue was crystallized from acetone–benzene to afford 980 mg XI, m.p. 210–212°, λ_{max} 297 mμ (ε, 18,500) and 332 mμ (ε, 6, 200). (Found: C, 58·11; H, 4·93; Cl, 9·82; Calc. for $C_{17}H_{17}O_6Cl$: C, 57·88; H, 4·86; Cl, 10·05%).

Paper strip chromatographic analysis showed complete disappearance of dehydrogriseofulvin after 10 min under these reaction conditions.

(B) *Chromous chloride.* To a solution of 100 mg dehydrogriseofulvin in 15 ml acetic acid layered with pet ether was added 4 mmoles chromous chloride in 4 ml aqueous solution. The reaction mixture was stirred at room temp for 16 hr. Paper strip chromatographic analysis indicated essentially complete disappearance of dehydrogriseofulvin in ca. 2 hr. The dark green reaction mixture was diluted with a large volume of chloroform and washed with cold aqueous 2% sodium bicarbonate, cold dil hydrochloric acid, water and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded, after crystallization from acetone–benzene, 41 mg XI, m.p. 210–212°, identical with that described in (A) above.

Benzophenone-4′-monoacetate (X)

To a solution of 2·0 g XI in 20 ml pyridine at 0° was added 0·60 g (1 molar equivalent) acetic anhydride. After 18 hr at 0° ice water was added and the mixture extracted with chloroform. The latter was washed with dil hydrochloric acid, dil sodium bicarbonate solution, and dried ($MgSO_4$). Removal of the solvent gave a residue which crystallized from acetone–ether in pale yellow prisms (1·47 g) m.p. 203–204°; λ_{max} 298 mμ (ε, 18,500); λ_{max}^{Chf} 5·70, 6·20 (broad) μ. (Found: C, 57·75; H, 4·66; Cl, 9·15; Calc. for $C_{19}H_{19}O_7Cl$: C, 57·89; H, 4·85; Cl, 8·90%).

Benzophenone 2,4′-diacetate

A solution of XI was acetylated in 10 ml pyridine with 4 ml acetic anhydride at 25° for 18 hr. The reaction mixture was worked up as above. Crystallization of the residue from ether gave 1·19 g nearly colorless needles, m.p. 159–161°; λ_{max} 308 mμ (ε, 6,600), 273 mμ (ε, 8, 500), 226 mμ (ε, 22,000) λ_{max}^{Chf} 5·69, 6·01, 6·25 μ. (Found: C, 58·27; H, 5·01; Calc. for $C_{21}H_{21}O_8Cl$: C, 57·80; H, 4·84%).

(±)-*Dehydrogriseofulvin by oxidative ring closure of the benzophenone* (XI)

(A) *Potassium ferricyanide.* A 1 g sample of XI was dissolved in 10–15 ml t-butyl alcohol and treated with a solution of 17·5 g potassium carbonate in 125 ml water. The t-butyl alcohol was subsequently evaporated *in vacuo* and the resultant alkaline solution of the benzophenone added dropwise to a stirred solution of 4 g potassium ferricyanide dissolved in 50 ml water. Immediate formation and precipitation of (±)-dehydrogriseofulvin occurred as the addition proceeded. The final reaction mixture was allowed to stir for 18 hr and filtered. The collected dehydrogriseofulvin was washed thoroughly with water and dried to give 900 mg XII. This material was essentially single spot by paper chromatography in a formamide 5:1 benzene–cyclohexane system. The IR spectrum was the same as that of a reference specimen of dehydrogriseofulvin. (±)-Dehydrogriseofulvin prepared and isolated in this manner was employed directly in the hydrogenation to (±)-griseofulvin (see below). A sample crystallized from acetone–ethyl acetate for analysis melted at 288–290° with phase change at 270°. (Found: C, 58·20; H, 4·35; Cl, 10·10; Calc. for $C_{17}H_{15}O_6Cl$: C, 58·21; H, 4·31; Cl, 10·11%).

(B) *Ceric sulfate.* A 100 mg sample of XI dissolved in a solution of 1·75 g potassium carbonate in 12·5 ml water was added with stirring to a solution of 1 g ammonium ceric sulfate dihydrate in 10 ml water. Heavy precipitation of ceric ion resulted which was probably responsible for poor oxidation.

Stirring was permitted to continue for 18 hr. At the end of this time the reaction mixture was extracted with methylene chloride and the extract washed free of unchanged benzophenone with 20% aqueous potassium hydroxide. Evaporation of the solvent *in vacuo* afforded 10 mg dehydrogriseofulvin with the same IR spectrum as a reference sample.

(C) *Lead tetraacetate.* To a stirred solution of 1·00 g XI in 30 ml acetic acid was added 3·5 g lead tetraacetate. After 18 hr at 25° the reaction mixture was concentrated to near dryness *in vacuo*, and partitioned between water and methylene chloride. The organic phase was washed with cold 2% potassium hydroxide solution. Acidification of the alkaline extract afforded 120 mg recovered XI. The methylene chloride layer was washed with salt water, dried ($MgSO_4$) and concentrated to dryness to give 810 mg amorphous residue. This was chromatographed on 30 g neutral alumina. From the 50% chloroform–benzene eluates was obtained 80 mg dehydrogriseofulvin m.p. 271–276°.

Eluates from the early part of the chromatogram (75% pet ether–25% benzene) gave 13 mg of a new compound, m.p. 195–199°; λ_{max} sh 320 mμ (ε, 6,700), 290 mμ (ε, 25,000), 232 mμ (ε, 20,000); λ_{max}^{Chf} 5·69, 5·81, 6·15, 6·25, 7·40 μ. On the basis of the absence of OH functionality in the IR (bonded and non-bonded) and the overall similarity of the UV spectrum to that of dehydrogriseofulvin, the substance is probably a dehydrogriseofulvin analogue acetoxylated in ring C. The 5·81 μ carbonyl band is intense and broad and probably is on unresolved doublet involving the 3 and 4′-carbonyl groups; the band position of the latter being shifted to lower wavelengths by interaction with the presumed adjacent acetoxyl group.

(D) *Lead dioxide.* A solution of 100 mg XI in 4 ml acetone and 4 ml ether was stirred for 18 hr with 1·00 g freshly prepared lead dioxide (cf. ref. 22). The reaction mixture was then filtered and the lead dioxide thoroughly washed with acetone. Evaporation of the combined filtrates gave 100 mg dehydrogriseofulvin, m.p. 283–287°. This material was single spot by thin layer chromatography (Al_2O_3–$CHCl_3$) and identical in the IR with an authentic specimen.

(E) *Manganese dioxide.* A solution of 170 mg XI in 10 ml acetone was oxidized with 1·7 g manganese dioxide.[35] The oxidation was followed by thin layer chromatography (Al_2O_3–$CHCl_3$) and found to be complete in 10 min. The reaction mixture was worked up in the same manner as (A) to give 160–170 mg of a nearly colorless solid, essentially single spot by thin layer chromatography (Al_2O_3–$CHCl_3$) although a very slight trailing impurity was indicated by iodine-vapor development. The IR spectrum of this product was essentially the same as that of a reference specimen of dehydrogriseofulvin.

(F) *Silver oxide.* A 100 mg sample of XI was oxidized in 10 ml acetone with 1 g freshly prepared silver oxide. After stirring for 18 hr, the reaction product was filtered, the filtrate concentrated and the residue dissolved in methylene chloride. Unreacted XI was extracted with alkali. Concentration of the solvent afforded 10–15 mg somewhat impure dehydrogriseofulvin.

Dehydrogriseofulvin by light-catalyzed racemization of (−) dehydrogriseofulvin

A solution of 1·40 g (+) dehydrogriseofulvin in 20 ml acetonitrile in a quartz flask was irradiated with UV light (t = 40°). A colorless crystalline precipitate began to form within 30 min. After 60 hr the product (918 mg; $[\alpha]_D^{Dioxane}$ +9°) was filtered and recrystallized from acetonitrile to give (±) dehydrogriseofulfin m.p. 288–290° $[\alpha]_D^{Dioxane}$ 0°, identical with a reference sample by mixed m.p., and IR spectral comparisons.

Under identical conditions except for the absence of light (−) dehydrogriseofulvin was unchanged.

(+) Isogriseofulvin by irradiation of (+) griseofulvin in methanol

A stirred suspension of 200 mg (+) griseofulvin in 5 ml methanol in a quartz flask was irradiated with UV light at 40–45°. The material dissolved within 1 hr. Thin layer chromatography (Al_2O_3-benzene–chloroform 1:1) showed the formation of a second substance with the same mobility as isogriseofulvin. After 24 hr the solvent was removed *in vacuo*. TLC indicated the residue to consist mainly of isogriseofulvin with griseofulvin as a minor component together with small amounts of polar impurities. Chromatography of the residue on 20 g neutral alumina and combination of the single spot [TLC] benzene eluates gave 43 mg of (+) isogriseofulvin; needles from ether, m.p.197–199°; identical with an authentic sample[36] by mixed m.p. and IR spectral comparison.

Under the same conditions except for the absence of light, griseofulvin was recovered unchanged.

[35] Prepared according to J. Attenburrow *et al. J. Chem. Soc.* 1094 (1952).

[36] J. F. Grove, J. MacMillan, T. P. C. Mulholland and M. A. F. Rogers, *J. Chem. Soc.* 3949 (1952).

Evaporation of the methanolic solution led to the recovery of pure (+) griseofulvin. Similarly (+) griseofulvin was recovered unchanged on irradiation in acetonitrile solution.

Irradiation of isogriseofulvin (20 mg) in 2·5 ml methanol led to a mixture of griseofulvin and isogriseofulvin as shown by TLC.

Irradiation of (+) *griseofulvin in ethanol*

Irradiation of 200 mg (+) griseofulvin in 7 ml ethanol and chromatography of the product on 20 g florosil led to the ethyl homolog (+) *7-chloro-4,6-dimethoxy-4'-ethoxy-6'-methylgris-3'-ene-3,2'dione*. m.p. 166–169; λ_{max}^{MeOH} 325 mμ (ε, 3,400), 291 mμ (ε, 13,600), 264 mμ (ε, 13,800), 233 mμ (13,200), identical with a sample prepared by treatment of griseofulvic acid with ethanolic hydrogen chloride.[8]

Epigriseofulvin

This was prepared according to the method of MacMillan.[4] Chromatography on neutral alumina and elution with mixtures of benzene and chloroform afforded material which crystallized from benzene, m.p. 213–214° $[\alpha]_D$ + 83° (c = 1·0, Chf). (Reported m.p. 214–216° $[\alpha]_D^{Chf}$ + 88°). (Found: C, 57·81; H, 4·73; Calc. for $C_{17}H_{17}O_6Cl$: C, 57·88; H, 4·85%).

Thin layer chromatography on silica gel–EtOAc or on paper strip (formamide 5:1 benzene–cyclohexane) failed to separate griseofulvin from epigriseofulvin to any significant extent. Thin layer chromatography on alumina with chloroform or 1:1 chloroform–benzene as mobile phase, however, produced discrete separation. The NMR spectrum of epigriseofulvin (Fig. 2) is distinct from that of griseofulvin (Fig. 1) in the 6·93–7·72 region.

Hydrolytic cleavage of dehydrogriseofulvin

(A) *Methanolic hydrogen chloride.* A suspension of 1 g (+) dehydrogriseofulvin in 20 ml methanol was treated with a gentle stream of dry hydrogen chloride gas for 4 hr without external cooling. The reaction mixture was passed through a sintered glass funnel and concentrated to a low volume. Crystallization by addition of ether gave XVII (850 mg) which recrystallized from acetone–ether, m.p. 193–193·5°, λ_{max} 283 mμ (ε, 5,200); λ_{max} 3·05 μ (OH); 5·89 μ (C=O); 6·34, and 6·65 μ (aromatic). (Found: C, 56·30; H, 4·78; Cl, 9·16; Calc. for $C_{18}H_{19}O_7Cl$: C, 56·47; H, 4·97; Cl, 9·28%).

(B) *Sodium methoxide in methanol.* A sample of (+) dehydrogriseofulvin (200 mg) in 20 ml 2·5 N MeONa in methanol was refluxed for 5 hr. The reaction mixture was concentrated *in vacuo*, diluted with water, acidified with 2·5 N HCl and extracted with ether. The extracts after washing drying and concentration yielded 190 mg XVII, m.p. 190–194°, identical by IR and UV spectra with that obtained above.

The ester XVII was also produced when dehydrogriseofulvin was refluxed for a short period with 10% potassium hydroxide in 70% methanol–water.

Saponification of XVII *to* XVIII

A solution of 700 mg XVII in 10 ml methanol was treated with 3 g potassium hydroxide dissolved in 3 ml water and refluxed for 5 hr. The reaction mixture was concentrated on a steam bath *in vacuo*. The residue was acidified and filtered leaving a solid which was dissolved in 10% aqueous potassium bicarbonate solution and filtered. The filtrate was acidified and extracted with ethyl acetate and the extract dried ($MgSO_4$) and concentrated. The residue was crystallized from acetone–ether to give XVIII (580 mg), m.p. 219–222° (dec). Recrystallized m.p. 220–223·1°, λ_{max}^{Nujol} 2·86, 2·95 μ (OH): 5·95 (C=O), 6·2, 6·34 μ (aromatic). (Found: C, 55·62; H, 4·79; Cl, 9·42; Calc. for $C_{17}H_{17}O_7Cl$: C, 55·36; H, 4·61; Cl, 9·63%).

Griseolactone (XIX)

A 370 mg sample of XVIII was dissolved in 3:1 chloroform–acetone and stirred for 18 hr with 10 g freshly prepared lead dioxide. The reaction mixture was then filtered, the filtrate concentrated and the residue taken up in ethyl acetate. The extract was washed with aqueous potassium bicarbonate solution, the solvent dried and concentrated and the residue crystallized from ethyl acetate, and finally aqueous acetone to give griseolactone (XIX), m.p. 178–181°, λ_{max} 228 mμ (42,000), 274 mμ (13,600) and 315 mμ (7700); $\lambda_{max}^{CHCl_3}$ 5·71 μ (lactone) 5·95 (C=O). (Found: C, 55·40; H, 4·10; Cl, 9·38; Calc. for $C_{17}H_{15}O_7Cl$: C, 55·66; H, 4·10; Cl, 9·70%).

Another sample of this compound showed polymorphism with m.p. 234–240° and phase change at 200°. The two samples were essentially the same in the IR.

Cleavage of griseolactone to XVIII *with zinc in acetic acid*

Trituration of XIX (10 mg) in acetic acid (0·5 ml) with zinc dust (20 mg) for 10 min followed by workup and crystallization from acetone–ether gave XVIII m.p. 214–220° dec, mixed m.p. with authentic XVIII 216–220° (dec). IR spectrum of this material indicated slightly impure XVIII.

Cleavage of griseolactone to methyl-2-hydroxy-3-chloro-4,6-dimethoxybenzoate XX

(A) *Methanolic hydrogen chloride.* A solution of 20 mg XIX in 10 ml methanol was saturated with dry hydrogen chloride at 0° and allowed to stand at room temp for 18 hr. Concentration and crystallization afforded XX m.p., 183–185° (reported m.p., 186–187 ref. 10). Mixed m.p. with an authentic sample prepared by methanol–hydrogen chloride methylation of 2-hydroxy-3-chloro-4,6-dimethoxy benzoic acid[87] was 183–185°. The IR spectra of the two samples were the same.

(B) *Methanolic potassium hydroxide.* A 10 mg sample of XIX was dissolved in 3 ml methanol, treated with 50 mg KOH in 1 ml water and warmed a few min on the steam bath. The methanol was blown off in a stream of nitrogen and the residue extracted with ethyl acetate. The residue, on removal of the ethyl acetate, crystallized on treatment with methanol, m.p. 183–185°.

Hydrogenation of (±) *dehydrogriseofulvin* (± *griseofulvin*)

(±) Dehydrogriseofulvin, 2·0 g, was dissolved in a minimum volume of methylene chloride, diluted with 250 ml ethyl acetate and the solution concentrated on the steam cone to ca. 220 ml. This solution was added to a stirred suspension of 4·0 g pre-reduced 10% palladium on charcoal catalyst[88] in 50 ml ethyl acetate and hydrogenated at atm. press. and 23°. The hydrogen absorption was rapid and was stopped just short of 1 mole (6 min). The catalyst was removed by filtration and the filtrate concentrated *in vacuo* to a buff-colored foam. The latter was dissolved in 20 ml acetic acid, treated with 2·4 g zinc dust and stirred at room temp for 10 min. The zinc was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in methylene chloride and extracted with cold 2% aqueous potassium hydroxide. The yellow alkaline extracts, after acidification with dil sulfuric acid and extraction with chloroform, yielded 500 mg XI. The neutral material, from the methylene chloride solution after washing with water, drying ($MgSO_4$) and concentrating *in vacuo*, amounted to 1·5 g. Analysis of the neutral material by IR spectroscopy showed, in addition to griseofulvin, the presence of 10–15% dihydrogriseofulvin.

The neutral products from 2 typical hydrogenations were combined, chromatographed on 200 g neutral alumina and eluted with benzene and benzene–chloroform mixtures. The fractions corresponding to 20% benzene–chloroform through 100% chloroform yielded, after crystallization from acetone–Skellysolve B, 1·8 g (±) griseofulvin, m.p. 220–222°. The analytical sample, recrystallized from the same solvents, had m.p. 222–223·5°. (Found: C, 57·81; H 5·05; Cl, 10·02; Calc for $C_{17}H_{17}O_6Cl$: C, 57·88; H, 4·86; Cl, 10·05%).

The IR, UV and NMR spectra as well as the mobility on alumina of this material were identical with that of (·) griseofulvin.

The early chromatographic fractions (benzene) yielded, after crystallization from acetone–hexane, 120 mg ± dihydrogriseofulvin, m.p. 216–217·5°; λ_{max} 287 mμ (ε = 21,300), 321 mμ (ε = 4,970), λ_{min} 250 mμ (ε = 700). (Found: C, 57·85; H, 5·36; Cl, 10·09; Calc. for $C_{17}H_{16}O_6Cl$: C, 57·54; H, 5·41; Cl, 9·99%).

The course of the hydrogenation showed a dependence on solvent and on catalyst ratio with respect to the degree of hydrogenolysis to the benzophenone. In dioxane and 1,2-dimethoxy ethane hydrogenolysis amounted to 40–50% and in ethanol 90%. A catalyst to compound ratio of 2:1 was found to be optimal: ratios of 1:1 and 1:2 gave markedly slower hydrogenation rates and increasingly larger proportions of benzophenone and dihydrogriseofulvin as adjudged by paper strip chromatographic analysis.

Reduction of dehydrogriseofulvin with α-phellandrene

To a solution of 100 mg dehydrogriseofulvin in 10 ml diethyleneglycoldimethyl ether was added

[87] This acid was prepared by R. D. Hoffsommer of these Laboratories by permanganate oxidation of the corresponding aldehyde obtained through the Gatterman reaction with 2-chloro-3,5-dimethoxyphenol.

[88] The catalyst was prepared according to *Organic Synthesis* Coll. Vol. III; p. 687. John Wiley, New York (1955) employing Darco-G-60 as support.

5·0 ml α-phellandrene and 100 mg 5% palladium on carbon catalyst. The reaction mixture was stirred under reflux for 18 hr and sampled periodically for paper strip chromatographic analysis (benzene–cyclohexane 5:1 vs. formamide system). The reaction was complete in 3 hr as evidenced by complete disappearance of the dehydrogriseofulvin spot and the appearance of a new single spot corresponding to XI. The reaction mixture was filtered, diluted with methylene chloride and extracted with cold 2% potassium hydroxide solution. The extracts were washed with ether, acidified with cold hydrochloric acid, and extracted with methylene chloride. The dried methylene chloride extracts yielded, after crystallization from benzene, 65 mg XI m.p. 209–212°.

Reaction of ± dehydrogriseofulvin with "diimide"

To a solution of 100 mg ± dehydrogriseofulvin in 30 ml ethyl acetate was added 0·2 ml anhydrous hydrazine and 5 ml methanol containing 2 mg cupric acetate (the 0 system of Corey *et al.*[37]). The reaction mixture was stirred vigorously in an open flask at 22° for 18 hr. The separated solid was isolated by filtration. Paper strip chromatography showed complete absence of griseofulvin and dehydrogriseofulvin in both the solid product and the filtrate. The solid product, m.p. 212–218° (dec) λ_{max} 283 mμ (4300), which decomposed on attempted recrystallization, was refluxed in acetone for 15 min and crystallized twice from acetone–hexane to afford the acetone derivative of the acid hydrazide of XVIII, m.p. 226–228° λ_{max} 282 mμ (5860). (Found: C, 57·06; H, 5·53; N, 6·69; Cl, 8·46; Calc. for $C_{20}H_{23}O_6N_2Cl$: C, 56·80; H, 5·48; N, 6·63; Cl, 8·46%).

Partial resolution of (±) griseofulvin by preferential crystallization

(±) Griseofulvin (200 mg) was dissolved in 4·0 ml acetone and then diluted with 4·0 ml hexane. To the resultant clear solution at room temp was added one seed crystal of (−) griseofulvin which had been crystallized from acetone–hexane. The mixture was allowed to stand at room temp for 72 hr. The crystals that formed were isolated by filtration and washed with a small volume of cold 1:1 acetone–hexane and dried *in vacuo* at 100°, yielding 94·3 mg material, $[\alpha]_D^{Chf}$ +8·9°. The filtrate and washings were combined and concentrated *in vacuo* to a foam which showed a rotation of $[\alpha]_D^{Chf}$ −6·3°. The positive rotating product, 90 mg, was retreated proportionately as above, yielding 37·5 mg crystalline product, $[\alpha]_D^{Chf}$ +13·2°.

(±) *Griseofulvic acid* XXI

A 500 mg sample of (±) griseofulvin in 5 ml hot acetic acid containing 1 ml 2 N H_2SO_4 was heated on a steam bath for 1 hr. Thin layer chromatography (Al_2O_3–$CHCl_3$) showed hydrolysis to be complete in this period. The reaction mixture was watered out and crystallized from methanol to give 430 mg (±) griseofulvic acid, m.p. 241–243°; pK_a 4·3. The IR spectrum in pyridine solution was the same as that of griseofulvic acid prepared from natural griseofulvin. (Found: C, 56·59; H, 4·46; Cl, 10·78; Calc. for $C_{16}H_{13}O_6Cl$: C, 56·73; H, 4·47; Cl, 10·78%).

Resolution of (±) griseofulvic acid

A solution of 390 mg (±) griseofulvic acid in 10 ml methanol was treated with 10·65 ml 0·108 N cinchonine N-methohydroxide[39] and the solution subsequently evaporated to dryness *in vacuo* and flushed several times with ethanol followed by benzene. The amorphous mixed salts were dissolved in a small volume methanol and the latter displaced with acetone in the hot to the point of near turbidity. The solution was seeded at this point with N-methyl cinchonine salt prepared from (+) griseofulvic acid and allowed to crystallize for 3–4 days. The deposited N-methylcinchonine salt of (+) griseofulvic acid was filtered and washed with acetone; 305 mg, m.p. 228–230°. Recrystallization afforded 230 mg, m.p. 230–232·5°. Further crystallization did not raise the m.p. further. A mixed m.p. with a sample of N-methylcinchonine salt prepared from (+) griseofulvic acid showed no depression and the IR spectra of the two samples were the same. $[\alpha]_D^{24°}$ +314 (c = 1·02, CH_3OH). (Found: C, 66·87; H, 6·10; N, 4·05; Cl, 5·36; Calc. for $C_{36}H_{35}N_2O_7Cl$: C, 66·77; H, 6·03; N, 4·33; Cl, 5·49%).

[39] Prepared by a modification of the method of R. Major and J. Finkelstein (*J. Amer. Chem. Soc.* **63**, 1368 (1947) wherein the N-methiodide of cinchonine is prepared in tetrahydrofuran solution. Care must be exercised that the cinchonine methochloride precursor of the hydroxide base does not contain sodium chloride since otherwise it will provide sodium hydroxide in the silver oxide reaction and precipitate the sodium salt of griseofulvic acid in the resolution step.

A second resolution with 430 mg ± griseofulvic acid in 20 ml ethanol and 11·8 ml 0·10 N cinchonine N-methohydroxide yielded 290 mg recrystallized (+) salt, m.p. 228–230°.

(+) *Griseofulvic acid* XXI *from its N-Methyl cinchonine salt*

A 400 mg sample of the N-methyl cinchonine salt of (+) griseofulvic acid was dissolved in 25 ml hot water and acidified with 2·5 N HCl. The precipitated (+) griseofulvic acid was crystallized from methanol (160 mg), m.p. 259–261°, $[\alpha]_D^{24°}$ +201° (c = 0·99 pyridine). (Found: C, 56·86; H, 4·30; Cl, 10·30; Calc. for $C_{16}H_{15}O_6Cl$: C, 56·73; H, 4·47; Cl, 10·47%).

(+) *Griseofulvin* XIII *and* (+) *isogriseofulvin* (XXII)

(+) Griseofulvic acid (150 mg) in 50 ml methanol was treated with ethereal diazomethone[40] at 0–5° until the solution was just yellow and immediately concentrated *in vacuo*. The resulting mixture of (+) griseofulvin and (+) isogriseofulvin was chromatographed on 5 g neutral alumina and eluted with benzene–chloroform. The single spot material by thin layer chromatography (Al_2O_3–$CHCl_3$) which was eluted with benzene–1% chloroform in benzene gave 35 mg (+) *isogriseofulvin* as needles from methanol, m.p. 196–197°. $[\alpha]_D^{24°}$ +215° (c = 0·989, $CHCl_3$). A mixed m.p. with authentic (+) isogriseofulvin was not depressed and the IR spectra of the two samples were identical. The single spot material by thin layer chromatography (Al_2O_3–$CHCl_3$) which was eluted with chloroform and 50% benzene in chloroform gave (+) *griseofulvin* (60 mg) as prisms from acetone–hexane, m.p. 216–218°, $[\alpha]_D^{24}$ +339° (c = 1·03 $CHCl_3$). This (+) griseofulvin was identical in all respects with natural griseofulvin.

An alternate and direct procedure for separating griseofulvin from isogriseofulvin consisted in allowing the mixture of the two components in dioxane to reflux for 30 min with M/10 sodium carbonate solution.[41] In this way all of the isogriseofulvin was converted to base soluble griseofulvic acid whereas a significant amount of griseofulvin remained unchanged and could be isolated directly from the neutral layer.

(−) *Griseofulvic acid* (XXI)

The mother liquors from the resolutions after separation of all possible (+) salt, remained amorphous despite attempts to induce crystallization of a (−) salt. These mother liquors were decomposed with excess 2·5 N HCl and the precipitated material extracted with ethyl acetate, which was evaporated and the residue crystallized from methanol, m.p. 252–256°. Recrystallization from methanol gave material with m.p. 261·5–263°; (80 mg) $[\alpha]_D^{24}$ −201 (c = 0·093, pyridine). The IR spectrum was identical with that of (+) griseofulvic acid in pyridine solution. (Found: C, 56·76; H, 4·34; Cl, 10·47; Calc. for $C_{16}H_{15}O_6Cl$: C, 56·73; H, 4·47; Cl, 10·47%).

(−) *Griseofulvin* (XIII) *and* (−) *isogriseofulvin* (XXII)

A 60 mg sample of (−) griseofulvic acid was methylated with diazomethane, as described for (+) griseofulvic acid. Separation on alumina afforded (−) isogriseofulvin (10 mg), m.p. 196–197°, $[\alpha]_D^{24}$ −216° (c = 0·953, $CHCl_3$) and (−) griseofulvin (20 mg), m.p. 216–217·5°, $[\alpha]_D^{24}$ = −341° (c = 1·03, $CHCl_3$). The latter was crystallized to constant m.p. and constant rotation. Both the (−) isogriseofulvin and (−) griseofulvin were identical with their respective optical antipodes in the IR.

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[40] Cf. ref. 2 and 3.

[41] A. Brossi *et al.*,[3] designed a method for converting griseofulvin to griseofulvic acid by first isomerizing the former to isogriseofulvin with methanolic hydrogen chloride followed by 15 min reflux of the isomerized product in dioxane solution with M/10 sodium carbonate solution. In repeating this procedure and following the course of hydrolysis by paper strip chromatography we found that at the end of 15 min substantial amounts of isogriseofulvin still remained unhydrolyzed. In our hands it was found necessary to extend the duration of hydrolysis to a least 30 min before quench and workup in order to assure complete hydrolysis.