lized. Recrystallization from aqueous methanol gave 1.01 g (59%) of material: mp 79–80° (lit. mp 79,[2b] 80–81°[2a]); $[\alpha]^{28}D$ +140° (C=O, 557, ethanol) (reported +137°,[2b] +140°[2a]). An additional 0.01 g (0.6%) of material, mp 73–76°, could be obtained by concentration of the mother liquors. The infrared spectrum of this material, mp 79–80°, was identical with that of an authentic sample: lit.[11] mp 78.5–79.5°; mmp 79–80°. The nmr spectrum of the ester showed signals at 1.03 (s, C-10 methyl), 1.22 (d, J = 7 Hz, isopropyl), 1.27 (s, H-18), 3.67 (s, CO_2CH_3), 6.91 (br s, H-14), 7.00 (q, J_{ortho} = 7.5 Hz, J_{meta} = 2 Hz, H-12), and 7.24 (d, J = 7.5 Hz, H-11).

Registry No.—**1**, 18045-62-0; **6**, 25356-78-9; **7**, 25454-68-6; **8**, 18045-63-1.

Griseofulvin Analogs. VII.[1] 5′-Formyl-, 5′-Alkoxalyl-, and 5′-Halogriseofulvins

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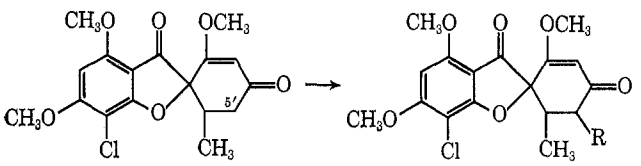
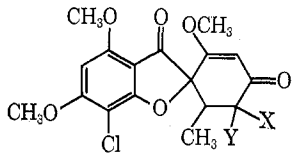
Although a large number of griseofulvin analogs have been prepared involving a variety of positions,[2,3] the 5′ position has not heretofore been manipulated except for the preparation of 5′-hydroxygriseofulvin by microbiological oxidation[4a] and 5,5′-dichlorogriseofulvin.[4b] We have now succeeded in activating the 5′ position of griseofulvin (**1**) by formylation in very high yield (and in much inferior yield by alkoxalylation) thus making it amenable to extensive manipulation. We describe here the preparation of the bromo, chloro, iodo, and fluoro derivatives and present some interesting aspects of their chemistry.

Formylation of griseofulvin (**1**) to form the 5′-formyl derivative **2** was accomplished in 94% yield by simply stirring griseofulvin in a large excess of neat methyl formate in the presence of a molar excess of sodium methoxide for 40 hr. Although methoxalylation and ethoxalylation of the 5′ position were also effected to give **3** and **4**, respectively, the poor yields in which they were obtained precluded their suitability for further transformations.



1 → **2**, R = CHO; **3**, R = $COCO_2CH_3$; **4**, R = $COCO_2Et$

The formyl derivative **2** underwent facile bromination with N-bromosuccinimide in chloroform at room temperature to give 5′-bromo-5′-formyl griseofulvin (**5**) as a mixture of isomers A and B separable by fractional crystallization.[5] The bromo–formyl mixture **5** underwent rapid deformylation to the 5′-bromo derivative **6**



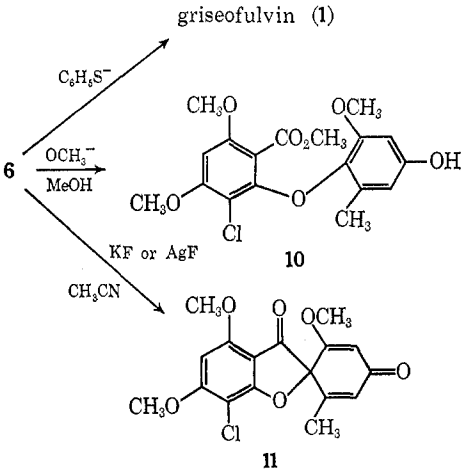
5a, X = Br; Y = CHO
5b, X = CHO; Y = Br
6, X = Br; Y = H
7, X = Cl; Y = H
8, X = I; Y = H
9, X = F; Y = H

with methanolic methoxide. In fact, the two steps could be conveniently combined and **6** isolated directly. In a similar manner, using N-chlorosuccinimide and N-iodosuccinimide, the corresponding 5′-chloro analog **7** and 5′-iodo analog **8** were prepared.

The 5′-fluoro derivative **9** was obtained by treating the sodium salt of **2** in methanol with perchloryl fluoride. Formation of **9** was accompanied by hydrolysis of the enol ether moiety to give 5′-fluorogriseofulvic acid (**9a**) (OH in place of OCH_3 on ring C in **9**) in *ca.* equivalent yield.[6,7]

It has been anticipated that 5′-bromogriseofulvin (**6**) would be a most suitable substrate for introducing a variety of substituents *via* simple displacement. It, however, quickly became apparent that this was not to be the case.

Thus, with even as ideal a nucleophile as thiophenolate ion, **6** underwent preferential reduction to griseofulvin (**1**) rather than displacement. With methoxide in methanol, **6** was converted to the diphenyl ether **10**[8] and with potassium fluoride or silver fluoride in acetonitrile to dehydrogriseofulvin **11**.[9]



(1) See ref 3 for previous papers in this series.

(2) J. F. Grove, *Progr. Chem. Org. Natur. Prod.*, **22**, 203 (1964).

(3) H. Newman and R. B. Angier, *J. Org. Chem.*, **34**, 3484 (1969), and previous publications cited there.

(4) (a) W. Andres, W. McGahren, and M. Kunstmann, *Tetrahedron Lett.*, 3777 (1969). See also the patent application filed July 1, 1968 (Serial No. 741,328), by H. Newman, P. Shu, and W. Andres in which the microbiological reduction of the ring B sulfur analog of dehydrogriseofulvin[4c] is described. The products obtained there were the ring B sulfur analog of griseofulvin and the ring B sulfur analog of 5′-hydroxygriseofulvin, the latter presumably arising by the microbiological oxidation of the former. (b) D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **28**, 3344 (1963). (c) H. Newman and R. B. Angier, *ibid.*, **34**, 1463 (1969); see ref 11 cited there.

(5) The very much lower optical rotation exhibited by isomer A compared with isomer B and the other 5′-halogriseofulvins (see Experimental Section) would appear to suggest that the configuration of the halogen in A is different than it is in the others. Nmr spectroscopy indicates a *trans* diequatorial relationship between the 6′-CH_3 and the 5′-halogen in the 5′-halogriseofulvins (*cf. ca.* 13 Hz coupling constant between the 6′ and 5′ protons). In isomer A, therefore, these substituents would appear to be *cis* oriented.

(6) It is extremely unlikely that fluorination followed hydrolysis, since the expected product would then be the 3′-fluoro derivative.

(7) See, W. A. Sheppard, *Tetrahedron Lett.*, 83 (1969), for a discussion of the mechanism of fluorination with perchloryl fluoride.

(8) E. Kyburz, J. Wursch, and A. Brossi, *Helv. Chem. Acta*, **45**, 813 (1962).

(9) D. Taub, C. H. Kuo, H. L. Slates, and N. C. Wendler, *Tetrahedron*, **19**, 1 (1963).

TABLE I[a,b]

Compd	Aromatic H	Vinyl H	Aromatic OCH_3	Vinyl OCH_3	5′-H	6′-H	6′-CH_3	Other
5′-Formyl **2**	6.13	5.52	4.02, 3.95	3.67	None	3.42 m	1.05 d, J = 6 Hz	OH ← 13.9 d, J = 11 Hz; =C; H ← 7.08 d, J = 11 Hz
5′-Methoxalyl **3**	6.15	5.50	4.03, 3.98	3.65	4.85 d, J = 13 Hz	Not clearly delineated	0.88 d, J = 6 Hz	$-COCOOCH_3$ ← 3.90
5′-Ethoxalyl **4**	6.15	5.51	4.03, 3.98	3.65	4.85 d, J = 13 Hz	Not clearly delineated	0.88 d, J = 6 Hz	4.33 q, 1.38 t; $-COCOOCH_2CH_3$
5′-Bromo-5′-formyl **5a**	6.18	5.70	4.03, 3.98	3.70	None	Not clearly delineated	1.23 d, J = 6 Hz	−CHO 9.58
5′-Bromo-5′-formyl **5b**	6.18	5.80	4.03, 3.98	3.68	None	3.32 m	1.33 d, J = 6 Hz	−CHO 9.52
5′-Bromo **6**	6.15	5.67	4.05, 4.02	3.67	5.20 d, J = 13 Hz	3.2–2.7 m	1.17 d, J = 6 Hz	
5′-Chloro **7**	6.15	5.67	4.05, 4.02	3.67	5.10 d, J = 12 Hz	3.1–2.7 m	1.17 d, J = 6 Hz	
5′-Iodo **8**	6.15	5.67	4.05, 3.99	3.66	5.47 d, J = 13 Hz	3.2–2.9 m	1.18 d, J = 6 Hz	
5′-Fluoro **9**[c]	6.35	5.60[d]	4.05, 4.02	3.70	5.3[e]	Not clearly delineated	1.03 d, J = 6 Hz	
5′-Fluorogriseofulvic acid **9a**[f]	6.50	5.42[d]	4.07, 3.95	None	5.4[g]	Not clearly delineated	0.99 d, J = 6 Hz	
5′-Tosyloxy **12**	6.15	5.47	4.03, 3.99	3.60	5.70 d, J = 12 Hz	Not clearly delineated	1.00 d, J = 6 Hz	7.85 d, ⟶H; H ⟵ 7.30 d, J=9 Hz; J=6 Hz; $-OSO_2$; CH_3; 2.43; H H

[a] Chemical shift values are in ppm (δ) from tetramethylsilane. Spectra were determined in chloroform unless otherwise indicated. [b] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. [c] Solvent $CDCl_3$–d_6-DMSO. [d] Poorly resolved doublet, J_{HF} = 2 Hz. [e] The C-5′-H was just barely discernible as a quartet centered about δ 5.3, $J_{5'H,F}$ = 26 Hz, $J_{5'H,6'H}$ = *ca.* 12 Hz. [f] Solvent d_6-DMSO. [g] The C-5′-H appeared as a quartet with further fine splitting centered about 5.4, $J_{5'H,F}$ = 26 Hz, $J_{5'H,6'H}$ = 10 Hz.

The possibility of displacing halogen in the 5′-chloro and 5′-iodo derivatives (**7** and **8**, respectively) was also briefly investigated with the following results: **7** was recovered unchanged from the reaction with thiophenolate under conditions which converted **6** to **1**. **8** was converted to **1** exclusively with thiophenolate, at a rate much faster than **6**.

8 was recovered virtually unchanged from 17 hr of refluxing with potassium acetate in acetone and was, quite unexpectedly, converted to griseofulvin **1** when heated under reflux (6 hr) in potassium acetate in acetic acid.

The result of the reaction of **6** with thiophenolate in which reduction was found to be favored over displacement made it of interest to investigate a case in which the former reaction pathway is significantly suppressed relative to the latter, thus creating a more favorable situation for observing the latter. 5′-Tosyloxygriseofulvin (**12**) was therefore prepared (from 5′-hydroxygriseofulvin and tosyl chloride–pyridine), since it is known that tosylate and bromide exhibit roughly equivalent leaving potentials.[10] Reaction of **12** with sodium thiophenolate under the conditions employed for **6** except that the reaction time was doubled, left it unchanged.

The resistance to displacement exhibited by the 5′-halo griseofulvin derivatives and 5′-tosyloxygriseofulvin while initially unexpected is, in retrospect, not too surprising. The halogen substituent in these derivatives is in an extremely hindered environment both sterically and electronically. There is a π-electron cloud positioned in close proximity on the opposite side of the 6-membered ring, an axial substituent in a 1,3 relationship (the spiro junction) and an equatorial substituent in a 1,2 relationship (6′-CH_3) to it. A displacement reaction, which would necessarily involve an even greater increase in the steric and electronic crowding is thus disfavored in competition with reaction pathways which can relieve this strain such as reduction to griseofulvin, elimination to dehydrogriseofulvin, and ring opening of ring B.

Nmr Spectra.—In Table I are listed the nmr spectral data of the various 5′-griseofulvin analogs discussed above.

Experimental Section[11]

5′-Formylgriseofulvin (2).—Sodium methoxide (4.3 g, 80 mmol) was cautiously added, with stirring and external cooling, to 150 ml of methyl formate. Griseofulvin (14.0 g, 40 mmol) was added portionwise over a 15-min period and the resultant thick white slurry was stirred at room temperature. After 1 hr the reaction mixture began turning yellow. After 40 hr the bright yellow reaction mixture was concentrated to dryness *in vacuo*. The residual solid was thoroughly mixed with 150 ml of water and

(10) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 82. See also, H. M. R. Hoffman, *J. Chem. Soc.*, 6753, 6762 (1965).

(11) Melting points are uncorrected. The nmr spectra were determined on a Varian A-60 spectrometer. Ultraviolet spectra were measured on a Cary 11MS spectrophotometer. Magnesium sulfate was used for drying. Thin layer chromatograms were run on phosphor-containing silica gel plates (Anal. Tech. Wilmington, Del.) using benzene–ethyl acetate (1:1) for development; thick layer chromatograms were run on 2-mm silica gel plates (E. Merck Agr., Darmstadt, Germany; distributed by Brinkmann Instrument Inc., Westbury, N. Y.).

filtered. The insoluble material (5.1 g) was identified by tlc (PhH–EtOAc 1:1) and infrared as unreacted griseofulvin. The alkaline filtrate was cooled in an ice bath and 10 ml of glacial acetic acid was added with vigorous stirring. The pale yellow crystals which precipitated were collected by filtration, washed with water, and dried *in vacuo* over P_2O_5 at 60°. The yield of analytically pure 5′-formylgriseofulvin (based on unrecovered starting material) was 9.0 g (94.1%): mp 192°; λ_{max}^{MeOH} 291 nm (ϵ 24,765); λ_{max}^{KBr} 5.81, 6.17, and 6.27 μ; $[\alpha]^{25}D$ +199° (c, 1.01 in $CHCl_3$).

Anal. Calcd for $C_{18}H_{17}ClO_7$ (380.8): C, 56.78; H, 4.62; Cl, 9.11. Found: C, 56.77; H, 4.50; Cl, 9.31.

5′-Methoxalylgriseofulvin (3).—Sodium hydride (50% suspension in oil, 1.6 g, 32 mmol) was added to a slurry of griseofulvin (5.6 g, 16 mmol) in 40 ml of sodium-dried benzene. After 30 min., dimethyl oxalate (3.8 g, 32 mmol) was added and the reaction mixture was stirred at room temperature for 72 hr. The yellow slurry was diluted with 60 ml of benzene, cooled in an ice bath, and acidified by the cautious addition of 6 ml of glacial acetic acid. Unreacted starting material (identified by tlc and ir) was removed by filtration and the yellow filtrate was extracted thrice with 30-ml portions of 1 *N* sodium hydroxide. The combined alkaline extracts were washed with ether and acidified by the addition of 12 ml of glacial acetic acid. The gummy pale yellow solid which precipitated was extracted into methylene chloride. The methylene chloride solution was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to a yellow solid *in vacuo*. Recrystallization from methanol yielded 560 mg of white, crystalline 5′-methoxalylgriseofulvin: mp 205–208; λ_{max}^{KBr} 5.73, 5.82, 6.02, 6.15, and 6.25 μ; λ_{max}^{MeOH} 325 nm (ϵ 7240) and 292 (25,900); $[\alpha]^{25}D$ +312° (c 0.51 in $CHCl_3$).

Anal. Calcd for $C_{20}H_{19}ClO_9$ (438.8): C, 54.79; H, 4.37; Cl, 8.12. Found: C, 54.51; H, 4.34; Cl, 8.42.

5′-Ethoxalylgriseofulvin (4).—The 5′-ethoxalyl derivative was obtained essentially as described in the previous experiment using diethyl oxalate. The analytical sample obtained by recrystallization from methanol melted at 209–212: λ_{max}^{KBr} 5.75 (sh), 5.83, 6.02, 6.18, and 6.27 μ; λ_{max}^{MeOH} 330 nm (ϵ 6100) and 291 (18,500); $[\alpha]^{25}D$ +302 (c 0.64 in $CHCl_3$).

Anal. Calcd for $C_{21}H_{21}ClO_9$ (452.8): C, 55.70; H, 4.67; Cl, 7.83. Found: C, 55.81; H, 4.53; Cl, 7.89.

5′-Bromo-5′-formylgriseofulvin (5).—N-Bromosuccinimide (2.92 g, 16.4 mmol) was added to a solution of 5′-formylgriseofulvin (5.71 g, 15 mmol) in 45 ml of chloroform. An exothermic reaction occurred and the solution was cooled to room temperature and stirred for 40 min. The small amount of white solid which had precipitated was removed by filtration and discarded. The filtrate was washed twice with water, dried over anhydrous sodium sulfate and concentrated *in vacuo* to an off-white solid. The crude product was crystallized in the following manner. The total crude was refluxed in 200 ml of *ethanol* for 15 min. The suspension was filtered while hot and the white crystalline bromoaldehyde (isomer A) was dried *in vacuo* at 60° over P_2O_5: yield 450 mg, mp 228–229° w/evol of gas; λ_{max}^{KBr} 5.77, 6.01 (w), 6.14, and 6.25 μ; λ_{max}^{MeOH} 325 nm (ϵ 5750) and 291 (26,450); $[\alpha]^{25}D$ +93° (c 0.45 in $CHCl_3$).

Anal. Calcd for $C_{18}H_{16}BrClO_7$ (459.7): C, 47.03; H, 3.51; Br, 17.38; Cl, 7.71. Found: C, 47.38; H, 3.65; Br, 17.50; Cl, 7.76.

The filtrate from isomer A was concentrated to 30 ml and cooled in an ice bath. The white crystals which separated were collected on a filter and dried *in vacuo* at 60° over P_2O_5. The nmr spectrum of this material (1.09 g, mp 213–218° w/evol of gas) indicated that it was a mixture of the isomeric bromoaldehydes.

In another run, the total crude product (324 mg from 381 mg of 5′-formylgriseofulvin) was recrystallized from 5 ml of *methanol* to yield 135 mg of pure isomer B: mp 218–220° w/evol of gas; λ_{max}^{KBr} 5.85, 6.17, and 6.24 μ; λ_{max}^{MeOH} 325 nm (ϵ 5750) and 292 (25,300); $[\alpha]^{25}D$ +241° (c 0.48 in $CHCl_3$).

Anal. Calcd for $C_{18}H_{16}BrClO_7$ (459.7): C, 47.03; H, 3.51; Br, 17.38; Cl, 7.71. Found: C, 46.65; H, 3.70; Br, 17.74; Cl, 7.87.

We thus have the interesting situation of a change in relative solubilities of the two isomers in going from ethanol to methanol.

5′-Bromogriseofulvin (6).—A solution of 1.9 g (0.0050 mol) of 5′-formylgriseofulvin in 15 ml of chloroform was treated with 0.98 g (0.0055 mol) of N-bromosuccinimide at room temperature. After keeping at room temperature for 1 hr, ice and water were added, followed by some 2 *N* NaOH and methylene chloride. The organic phase was extracted to remove the succinimide formed, dried, and concentrated to small volume. Methanol (10 ml) was added, followed by 1.0 ml of 1 *M* methanolic sodium methoxide. A new solid rapidly separated. After stirring the suspension at room temperature for 15 min, the solid was collected by filtration and washed with methanol, yield (colorless solid) 1.4 g (64%), mp 193–196°. Recrystallization from methanol furnished the analytical sample: mp 207–210°; λ_{max}^{KBr} 5.85 (s), 5.93 (m), and 6.20 μ (vs); λ_{max}^{MeOH} 325 nm (plateau) (ϵ 6500), 293 (28,000), 252 (plateau) (17,000), 235 (22,800), 217 (infl) (25,000), and 210 (27,000); $[\alpha]^{25}D$ +322° (c 0.37 in $CHCl_3$). (The nmr spectra of the product before and after recrystallization were identical.)

Anal. Calcd for $C_{17}H_{16}ClBrO_6$ (431.67): C, 47.29; H, 3.72; Br, 18.51; Cl, 8.21. Found: C, 47.23; H, 3.72; Br, 18.73; Cl, 8.31.

5′-Chlorogriseofulvin (7).—A solution of 1.9 g (0.0050 mol) of 5′-formylgriseofulvin in 15 ml of chloroform was treated with 0.7 g (0.0053 mol) of N-chlorosuccinimide, and the reaction mixture was processed as described for the preparation of the 5′-bromo analog. A 1.45 g (76%) yield of crude product was obtained as a colorless solid melting at 198–203°. Recrystallization from methanol furnished the analytical sample: mp 203–207°; λ_{max}^{KBr} 5.83 (s), 5.91 (m), and 6.20 μ (vs); λ_{max}^{MeOH} 328 nm (plateau) (ϵ 5800), 293 (27,000), 250 (infl) (17,500), 236 (23,000), 217 (23,000), and 210 (24,000); $[\alpha]^{25}D$ +354° (c 0.41 in $CHCl_3$).

Anal. Calcd for $C_{17}H_{16}Cl_2O_6$ (387.21): C, 52.73; H, 4.17; Cl,18 .31. Found: C, 52.76; H, 4.19; Cl, 18.46.

5′-Iodogriseofulvin (8).—A solution of 1.9 g (0.005 mol) of 5′-formylgriseofulvin and 1.3 g (0.0058 mol) of N-iodosuccinimide in 15 ml of chloroform was kept for 1 hr and then diluted with methylene chloride and washed with cold dilute sodium hydroxide. The organic solution was washed, dried, and concentrated to small volume. Methanol (10 ml) was added, followed by 2 ml of 1 *M* methanolic sodium methoxide. (In contrast to the preparation of the 5′-bromo and 5′-chloro analogs, the addition of 1 ml of the methanolic methoxide raised the pH of the medium only to *ca.* 8, which was not basic enough for rapid deformylation.) The solid which separated was collected after 15 min and washed with methanol, yield (ivory colored solid) 1.5 g (63%), mp 214–219° dec. The analytical sample was obtained by heating the product partially suspended in boiling methanol: mp 216–220° dec; λ_{max}^{KBr} 5.85 (s), 6.10 (w), and 6.2 μ (vs); λ_{max}^{MeOH} 327 nm (plateau) (ϵ 6400), 293 (28,500), 255 (plateau) (15,000), 233 (plateau) (21,500), 217 (infl) (27,400), and 210 (28,500); $[\alpha]^{25}D$ +303° (c 0.61 in $CHCl_3$).

Anal. Calcd for $C_{17}H_{16}ClIO_6$ (478.66): C, 42.65; H, 3.37; Cl, 7.41, I, 26.51. Found: C, 42.30; H, 3.25; Cl, 7.44; I, 26.63.

5′-Fluorogriseofulvin (9) and 5′-Fluorogriseofulvic Acid (9a).—A methanolic solution of 0.0026 mol of the sodium salt of 5′-formylgriseofulvin [prepared from 1 g (0.0026 mol) of **2**, 2.6 ml of 1 *M* methanolic sodium methoxide (0.0026 mol) in 20 ml of methanol] was cooled (ice–water) and a rapid stream of perchloryl fluoride was bubbled through for *ca.* 30 sec. The pH of the solution at this point was essentially neutral. Gas passage was discontinued and the metanolic solution was immediately poured into ice–water. The colorless solid which separated was collected by filtration, washed with water, and while still wet, was transferred to a beaker and stirred with cold dilute ($\leq$2 *N*) NaOH for 5 min, and then collected by filtration. (The filtration proceeded slowly because of the fine particle size of product; it took *ca.* 10–15 min to separate the basic supernatant.) The yield of dull white solid obtained was 260 mg (27%). It showed a single spot, R_f *ca.* 0.5, on tlc (silica gel, PhH-EtOAc 1:1). Recrystallization from MeOH–CH_2Cl_2 furnished analytically pure 5′-fluorogriseofulvin: mp 231–233° (wetting 228°); λ_{max}^{KBr} 5.82 (s), 5.98 (s), 6.15, and 6.3 μ (s); λ_{max}^{MeOH} 372 nm (plateau) (ϵ 5900), 292 (25,000), 250 (infl) (17,500), 236 (24,000), 217 (pleateau) (22,000), and 210 (23,000); $[\alpha]^{25}D$ +283° (c 0.08 in $CHCl_3$).

Anal. Calcd for $C_{17}H_{16}ClFO_6$ (370.76): C, 55.07; H, 4.35; Cl, 9.56; F, 5.12. Found: C, 54.86; H, 4.32; Cl, 9.91; F, 4.87.

Acidification of the original filtrate from which the initial colorless solid was separated gave 260 mg (28%) of yellow solid which was converted to the colorless crystalline 5′-fluorogriseofulvic acid (9a): mp 270–272° dec (with effervescence) on trituration with methanol; λ_{max}^{KBr} 2.9 (m), 5.85 (m–s), 5.95 (m–s), 6.02 (s),

and 6.17 μ (vs); λ_{max}^{MeOH} 325 nm (plateau) (ϵ 5500), 291 (29,000), 235 (18,000), and 211 (23,000). **9a** was soluble in aqueous bicarbonate.

Anal. Calcd for $C_{16}H_{14}ClFO_6$ (356.73): C, 53.90; H, 3.96; Cl, 9.94; F, 5.33. Found: C, 53.56; H, 3.72; Cl, 9.77; F, 4.92.

5'-Tosyloxygriseofulvin (12).—A mixture (suspension) of 369 mg (0.001 mol) of 5'-hydroxygriseofulvin[4a,12] and 380 mg (0.002 mol) of tosyl chloride in 2.5 ml of dry pyridine was stirred at room temperature for 27 hr. An additional 190 mg (0.001 mol) of tosyl chloride was then added to the still heterogeneous reaction mixture and stirring continued for another 25 hr. A completely homogeneous reaction mixture formed which was poured into ice–water to precipitate the solid 5'-tosyloxy derivative. The aqueous mixture was made strongly basic (pH $\geq$ 13) with 2 *N* NaOH and stirred at room temperature for 20 min (to destroy excess tosyl chloride) before collecting the product, yield 410 mg (79%), mp 207–212°. Heating the mixture suspended in boiling methanol raised the melting point to 211–214°, λ_{max}^{KBr} 5.85 μ.

Anal. Calcd for $C_{24}H_{23}O_9SCl$ (522.95): C, 54.12; H, 4.43; Cl, 6.78; S, 6.13. Found: C, 54.45; H, 4.30; Cl, 7.08; S, 6.11.

Dehydrogriseofulvin (11) from 5'-Bromogriseofulvin and Silver Fluoride or Potassium Fluoride in Acetonitrile.—A solution of 0.59 g (0.0013 mol) of 5'-bromogriseofulvin in 10 ml of acetonitrile was heated under reflux (protected from light by wrapping the flask in aluminum foil) with 0.5 g (0.004 mol) of AgF (Alfa Inorganic Inc., Beverly, Mass.) for 17 hr and then filtered through Celite. The filtrate was evaporated and 200 mg of the residue obtained was thick-layer chromatographed (developing solvent PhH–EtOAc 1:1). Two somewhat overlapping zones were obtained which were eluted with acetone containing some MeOH. The faster of the two (37 mg) was identified as starting 5'-bromogriseofulvin by melting point and ir and tlc. The slower one (58 mg, mp 270–274° dec) was recrystallized from methanol to give material melting at 282–285° dec.

Anal. Calcd for $C_{17}H_{15}ClO_6$ (350.75): C, 58.17; H, 4.31; Cl, 10.10. Found: C, 57.49; H, 4.47; Cl, 10.36.

The infrared and nmr spectra of the compound were identical with those of authentic dehydrogriseofulvin.

Dehydrogriseofulvin was also the exclusive product obtained from the treatment of 5'-bromogriseofulvin with a large excess of potassium fluoride dihydrate in refluxing acetonitrile (18 hr).

Treatment of 5'-Bromogriseofulvin with Methanolic Methoxide. Formation of 2-Carbomethoxy-2',3,5-trimethoxy-4'-hydroxy-6-chloro-6'-methyldiphenyl Ether (10).—A suspension of 100 mg (0.23 mmol) of 5'-bromogriseofulvin in 1 ml of methanol was treated with 0.23 ml of *ca.* 1 *M* sodium methoxide in methanol (0.23 mmol), and the mixture was stirred at room temperature for 16 hr. Ice–water and methylene chloride were added and the mixture was extracted with dilute sodium hydroxide. Acidification of the basic extract gave 34 mg of a colorless solid A. Drying and evaporating the methylene chloride solution gave 24 mg of a yellow solid B.

Solid A melted at 195–199°. The analytical sample, obtained by recrystallization from methanol, melted at 194–199°: λ_{max}^{KBr} 3.0 (m), 5.75 (sh, m), and 5.85 μ (s); λ_{max}^{MeOH} 285 nm (ϵ 5400).

Anal. Calcd for $C_{18}H_{19}O_7Cl$ (382.79): C, 56.48; H, 5.00; Cl, 9.26. Found: C, 56.20; H, 4.82; Cl, 9.55.

The physical constants cited are in excellent agreement with those reported for **10** by Kyburz, *et al.*[3]

Solid B was identified as starting 5'-bromogriseofulvin (after recrystallization from MeOH) by melting point and mixture melting point, and tlc and infrared spectroscopy.

10 was also the exclusive transformation product when the reaction was conducted in refluxing methanol (1 hr).

Reaction of 5'-Bromogriseofulvin (6) and Sodium Thiophenolate.—To a solution of 0.46 mmol of sodium thiophenolate in 3 ml of methanol [prepared by adding 70 mg (0.64 mmol) of thiophenol to 0.46 ml of 1 *M* sodium methoxide in methanol] was added 0.2 g (0.46 mmol) of 5'-bromogriseofulvin **6**. The resulting suspension was stirred at room temperature for 26 hr and diluted with water, and the solid was collected, yield 110 mg, mp 120–197°. Tlc and nmr spectroscopy indicated the product to be mainly griseofulvin contaminated by some unreacted **6**.

(12) Prepared by Mr. M. Dann of these laboratories.

Registry No.—**2**, 25357-21-5; **3**, 25357-22-6; **4**, 25357-23-7; **5**, 25350-64-5; **6**, 25350-65-6; **7**, 25350-66-7; **8**, 25350-67-8; **9**, 25350-68-9; **9a**, 25350-69-0; **10**, 25357-24-8; **11**, 25357-25-9; **12**, 25357-26-0.

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Structure of Kutkin, the Bitter Glucoside of *Picrorhiza kurroa* Royle ex Benth

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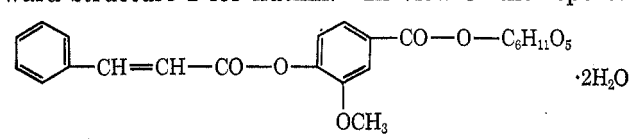
Picrorhiza kurroa Royle ex Benth (Scrophulariaceae)[1c] is a wild plant which grows from Kashmir to Sikkim at an altitude of 5000 to 10,000 ft. The roots are extremely bitter and extensively used in the indigenous system of medicine as an antiperiodic, stomachic, cathartic, and cholagogue. Rastogi, *et al.*,[2,3] previously isolated from the roots a bitter glucoside, kutkin, $C_{23}H_{24}O_{10}\cdot 2H_2O$, mp 211°, $[\alpha]^{41}D$ −165°, together with D-mannitol, vanillic acid, and several uncharacterised products. Kutkin, on hydrolysis, yielded vanillic acid, cinnamic acid, and glucose, on the basis of which they put forward structure I for kutkin. In view of the reported



I

uses of the drug in the indigenous and modern systems of medicine,[4,5] we became interested in the chemistry of kutkin which appeared to be the active principle of the drug. Moreover, the structure I proposed for kutkin by Rastogi, *et al.*, is not consistent with the biogenetic principles applicable to lignins,[6] known to be derived from C_6–C_3 and D-glucose precursors. Again, the facile hydrolysis of kutkin to glucose and other fragments in protic solvents, even at ordinary temperatures, also militates against the assumption[2] that the phenolic and sugar entities are joined in an ester linkage as shown in I.

Experimental Section

Kutkin, isolated from the roots of *Picrorhiza kurroa* (3 kg) following essentially the method of Rastogi, *et al.*,[2] crystallized

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