Griseofulvin Analogs. III. Synthesis of the Ring-B Carbon Analogs of Griseofulvin and Isogriseofulvin

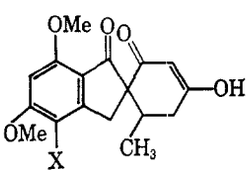
HOWARD NEWMAN AND ROBERT B. ANGIER

Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York

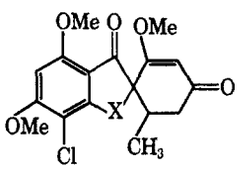
Received November 22, 1965

The preparation of the title compounds is described and their nmr spectra are discussed.

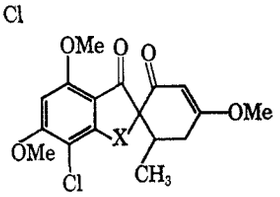
In our previous paper[1] we described the stereospecific synthesis of 5′,7′-dimethoxy-6-methyl-spiro-[cyclohexane-1,2′-indan]-1′,2,4-trione (**1**, X = H). We now report the synthesis of the 4′-chloro analog **2** (X = Cl) *via* the previously developed route and



1, X = H
2, X = Cl



3



4

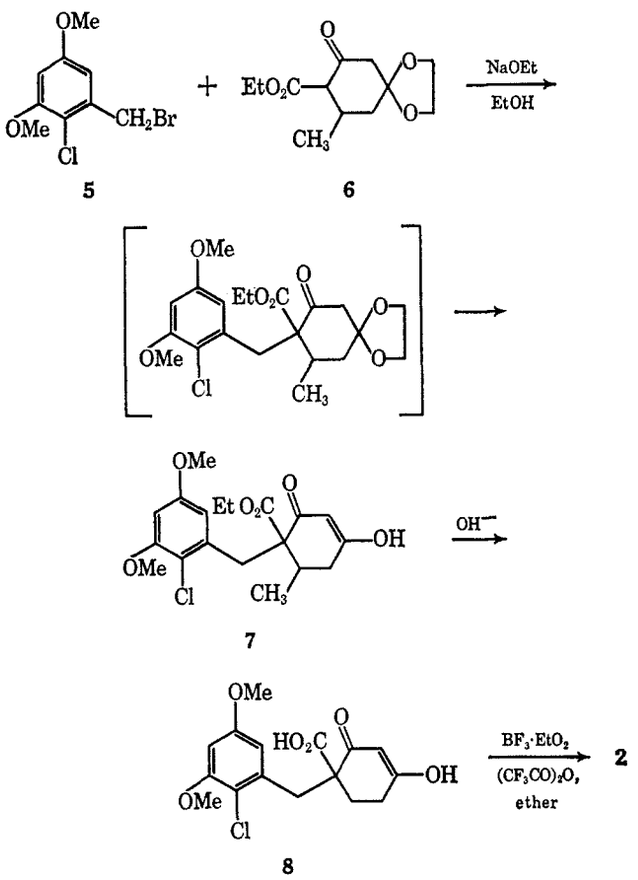
describe its conversion to **3** (X = CH_2) and **4** (X = CH_2) the ring B carbon analogs (gross structure) of griseofulvin **3** (X = O) and isogriseofulvin **4** (X = O), respectively.

The reaction sequence employed to synthesize **2** is outlined in Scheme I; a more detailed discussion of the various steps involved can be found in our previous paper.[1]

The benzyl bromide **5** was obtained by chlorination of 3,5-dimethoxybenzyl alcohol with N-chlorosuccinimide in carbon tetrachloride to give the 2-chlorobenzyl alcohol followed by treatment with hydrogen bromide in benzene. That **5** rather than the 4-chlorodimethoxybenzyl alcohol was obtained follows from the aromatic proton resonances of the product. These appeared as two 1-proton doublets (J = 3 cps) at δ 6.66 and 6.22 as would be expected for two unsymmetrical *meta*-oriented protons.[2a] (The symmetrical 4-analog would be expected to show a single 2-proton peak.)

Methylation of **2** with diazomethane gave a mixture of two isomers present in roughly equal amounts (*cf.* methylation of griseofulvic acid[3]) which was readily resolved by partition chromatography. The structures assigned to the isomers obtained was based on a comparison of their nmr spectra with those of griseofulvin and isogriseofulvin. Table I lists the proton resonances of isomer A (lower chromatographic retention time)

SCHEME I



5 **6** **7** **8**

and isomer B, along with those of the corresponding protons in isogriseofulvin and griseofulvin.[4]

TABLE I[a]

COMPARISON OF THE CHEMICAL SHIFT VALUES OF VARIOUS PROTONS IN **3**, **4**, GRISEOFULVIN, AND ISOGRISEOFULVIN

	Isomer A	Isogriseofulvin	Griseofulvin	Isomer B
Aromatic H	6.41	6.07	6.15	6.55
Vinyl H	5.45	5.40	5.52	5.57
Aromatic OCH_3	4.00	4.01	4.04	4.05
	3.89	3.90	3.99	4.00
Vinyl OCH_3	3.77	3.78	3.63	3.63
Benzyl CH_2	2.91[b]			3.03[b]
CH_2–CH	2.61–2.08			2.83–2.08
$-CH_3$	0.97	1.04	0.98	0.88

[a] Chemical shift values are in parts per million from tetramethylsilane (internal standard); solvent, $CDCl_3$. [b] The half-width of this peak is 4 cps and presumably represents two of the four-line AB spin pattern expected for these protons. The other two are presumably too weak to distinguish from the background noise.

(1) H. Newman and R. B. Angier, *J. Org. Chem.*, **31**, 1456 (1966).

(2) (a) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 96; (b) *ibid.*, p 27.

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

(4) 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).

It is apparent that except for the aromatic proton resonances, the proton chemical shift values in the carbon series are extremely close to those of their counterparts in the oxygen series. The differences observed in the case of the aromatic protons would be expected in view of the substituent change on the ring from oxygen to methylene.

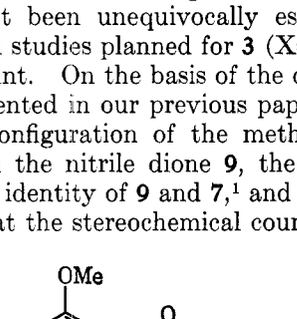
As can be seen, the signals for the aromatic, vinyl, aromatic methoxyl, and methyl protons appear at higher field in isogriseofulvin than in griseofulvin. The vinyl methoxyl protons, on the other hand, resonate at *lower* field in isogriseofulvin. A corresponding pattern is clearly discernable in the proton chemical shifts in isomers A and B. All the protons of isomer A with the exception of the vinyl methoxyl protons resonate at higher field than do the corresponding protons in isomer B. The vinyl methoxyl protons in *A* resonate at *lower* field than do those in B.

The higher field position of the vinyl methoxyl protons in griseofulvin and isomer B could reasonably be attributed to the anisotropy of the ring-B carbonyl group[2b] and the location of the vinyl methoxyl substituent in the region of positive shielding as a consequence of the perpendicular relationship of rings B and C resulting from the spiro junction.

There is a further correspondence in the magnitude of the chemical shift *difference* between the aromatic methoxyl protons of isogriseofulvin and isomer A on the one hand and griseofulvin and isomer B on the other, the difference being larger in the case of the former two (Δ = 0.11 ppm for isogriseofulvin and 0.06 ppm for isomer A) than for the latter (Δ = 0.05 ppm for griseofulvin and 0.03 ppm for isomer B).

The correlation of chemical shift patterns of isogriseofulvin and isomer A and those of griseofulvin and isomer B strongly suggests that each pair is structurally (and conformationally) related, isomer A corresponding to **4** (X = CH_2) and isomer B to **3** (X = CH_2).

The relative stereochemistry of the substituents at the spiro junction and C_6 of ring C in isomer A (and B) has not as yet been unequivocally established. X-Ray diffraction studies planned for **3** (X=CH_2) should resolve this point. On the basis of the conformational argument presented in our previous paper[1] which suggested a *cis* configuration of the methyl and nitrile substituents in the nitrile dione **9**, the demonstrated stereochemical identity of **9** and **7**,[1] and the reasonable assumption that the stereochemical course of the reaction between **5** and **6** parallels that of dechloro **5** and **6**, we favor a *cis* configuration for the C_6-methyl and indanone carbonyl in **3** and **4** (X = CH_2) corresponding to that found in griseofulvin (and isogriseofulvin).



9

The fact that the $-CH_2-CH-$ multiplet in the nmr spectra of **3** (X = CH_2) and **4** (X = CH_2) appears as a rather broad signal (see Table I) as does this corresponding multiplet in griseofulvin (**3**, X = O),[4] but contrasts with the relative sharpness of this absorption in *epi*-griseofulvin[4] (**3**, X = O; C_6-methyl, ring-B carbonyl *trans*) also appears to suggest a stereochemical correspondence between **3** and **4** (X = CH_2) and griseofulvin.

Biological Data.—Both **3** and **4** (X = CH_2) were tested *in vitro vs. Microsporum gypseum* and *in vivo vs. M. canis*. Griseofulvin standards were employed for comparison in both tests. Compound **3** (X = CH_2) showed marginal activity (*ca.* 5% that of griseofulvin) in the *in vitro* test while **4** (X = CH_2) was inactive. Both **3** and **4** (X = CH_2) were inactive *in vivo*.

Experimental Section[5]

2-Chloro-3,5-dimethoxybenzyl Alcohol.—A mixture of 2.0 g (0.012 mole) of 3,5-dimethoxybenzyl alcohol[6] and 1.6 g (0.012 mole) of N-chlorosuccinimide in 15 ml of carbon tetrachloride was stirred and heated under reflux for 12 hr while being irradiated with a 150-w incandescent bulb placed close to the reaction flask. Aluminum foil which surrounded the back and sides of the flask served as a reflector. The reaction mixture was filtered to separate the insoluble succinimide which formed and the filtrate was diluted with ether, washed with dilute aqueous sodium bisulfite, water, dried, and evaporated to yield 2.2 g of a colorless solid which melted at *ca.* 80°. The product was heated in boiling petroleum ether (bp 30–60°) and collected: yield, 2 g (82%); mp 81–85°. Recrystallization from hexane–ethyl acetate furnished the analytical sample, mp 87–88.5°.

Anal. Calcd for $C_9H_{11}ClO_3$ (202.64): C, 53.51; H, 5.49; Cl, 17.55. Found: C, 53.26; H, 5.58; Cl, 17.31.

The nmr spectrum of the product in deuteriochloroform showed two 1-proton doublets at δ 6.66 (J = 3 cps) and δ 6.22 (J = 3 cps) (aromatic protons), a 2-proton singlet at δ 4.70 (Ar CH_2OH), two 3-proton singlets at δ 3.80 and 3.76 (aromatic methoxyls), and a broad exchangeable 1-proton singlet at δ 2.66 (hydroxyl proton).

2-Chloro-3,5-dimethoxybenzyl Bromide (**5**).—The general procedure of Haworth and Perkin[7] was followed. Gaseous hydrogen bromide was bubbled through a cooled (ice–water) solution of 1.7 g (0.0084 mole) of 2-chloro-3,5-dimethoxybenzyl alcohol in 25 ml of anhydrous benzene for 30 min. The flask was stoppered and kept at room temperature for an additional 1.5 hr. Most of the excess hydrogen bromide was removed in a stream of nitrogen, ether was added, and the mixture poured into cold water. The organic phase was washed with cold aqueous bicarbonate and water, then dried, and evaporated to yield a solid residue which was collected after triturating with petroleum ether: yield (pale green solid), 1.5 g (67%); mp 95–99°. The analytical sample was obtained by percolating an ethereal solution of a portion of the product through a short column of Woelm nonalkaline, almost neutral alumina, activity I. Evaporation of the etheral eluate left a colorless solid, mp 97.5–98.5° after recrystallization from cyclohexane.

Anal. Calcd for $C_9H_{10}BrClO_2$ (264.54): C, 40.71; H, 3.80; Br, 30.10; Cl, 13.32. Found: C, 40.58; H, 3.83; Br, 30.04; Cl, 13.70.

1-Carbethoxy-1-(2-chloro-3,5-dimethoxybenzyl)-6-methyl-2,4-cyclohexanedione (**7**).—The general procedure previously outlined for the preparation of the dechloro analog[1] was followed. To 3.7 ml of a cooled (ice–water) 0.68 *N* solution (determined titrimetrically) of sodium ethoxide in absolute[8] ethanol (0.0025 mole) (prepared from metallic sodium) was added 0.6 g (0.0025 mole) of the monoketal 6[1] (actually contaminated with *ca.* 30%

(5) Melting points were taken in a Hershberg apparatus using a 3-in. immersion thermometer. Infrared spectra were determined either neat (liquids or oils) or in Nujol (solids) on a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were measured in methanol on a Cary Model 11MS spectrophotometer. Magnesium sulfate was used for drying.

(6) R. Adams, M. Harfenist, and S. Loewe, *J. Am. Chem. Soc.*, **71**, 1624 (1949).

(7) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **I**, 1434 (1925).

(8) L. F. Fieser, "Experiment sin Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1957, 3rd ed, p 285, method (A).

of its positional isomer[1]) followed by 0.67 g (0.0025 mole) of 2-chloro-3,5-dimethoxybenzyl bromide. The resulting suspension was permitted to warm to room temperature (the reaction mixture did not become homogeneous as it did in the case of the dechloro analog) and stirred for 65 hr. Water was added and the organic product extracted with ether. The ethereal extracts were dried and evaporated, and the yellow liquid residue was heated under reflux for 1 hr in dilute ethanolic–aqueous hydrochloric acid to hydrolyze the ketal function. More water was added, the mixture extracted with ether, and the ethereal extracts, in turn, extracted with bicarbonate solution. A gum separated upon acidification of the bicarbonate extracts which solidified after a short while. The nearly colorless solid was collected, washed with water, and air dried on filter paper to give 0.31 g [33% based on the gross weight of monoketal **6** used or 46% on the basis of the estimated net weight (0.6 × 0.7 = 0.42 g) of **6** present in the mixture] of product, mp 164.5–168°. The analytical sample, mp 167.5–170°, was obtained by suspending a portion of the product in ethanol overnight at room temperature, collecting, washing with ether and drying at 80° *in vacuo* over phosphorus pentoxide for 9 hr: λ_{max}^{Nujol} 5.75 μ; λ_{max}^{MeOH} 290 (sh) (ϵ 7100), 265 (ϵ 13,500), and 230 mμ (ϵ 10,500).

Anal. Calcd for $C_{19}H_{23}ClO_6$ (382.83): C, 59.61; H, 6.06; Cl, 9.26. Found: C, 59.49; H, 6.23; Cl, 9.48.

1-Carboxy-1-(2-chloro-3,5-dimethoxybenzyl)-6-methyl-2,4-cyclohexanedione (**8**).—A suspension of 0.3 g (0.8 mmole) of the dione ester **7** in 3 ml of 30% aqueous sodium hydroxide was heated and stirred at 100° (oil bath temperature) for 15 hr. (During the initial stages of the reaction the suspended material was an oil which was subsequently converted to a fine white solid.) The reaction mixture was cooled in Dry Ice–acetone, some water was added, and the mixture acidified with concentrated hydrochloric acid. The colorless gum which separated was extracted into methylene chloride and the latter extract was dried and evaporated to yield an oily residue which solidified on trituration with ether. The colorless solid obtained, 0.18 g (62%), melted at 84–85° eff, λ_{max}^{Nujol} 5.75, 5.85 μ.

In a larger scale run, 5.2 g (0.014 mole) of ester dione **7** was heated and stirred at 100° in 40 ml of 30% aqueous sodium hydroxide for 12.5 hr. Acidification as above gave a nearly colorless gum which very quickly solidified. The product was collected, washed with water and air dried on filter paper: yield, 3.3 g (69%); mp 68–77° eff (softens *ca.* 58°). In contrast with the product obtained in the small-scale run, this material showed a single peak in the carbonyl region in the infrared at 5.85 μ. The fingerprint region of the spectra of the two preparations also differed, presumably because of a difference in crystalline form. A portion of the product was further purified by suspending in methylene chloride, warming briefly, and keeping at room temperature for *ca.* 3 hr: mp 82.5–84° eff.

Anal. Calcd for $C_{17}H_{19}O_6Cl$ (354.78): C, 57.55; H, 5.40. Found: C, 56.56; H, 5.76.

In view of the nature of the compound (β-keto acid) these figures were considered close enough and further purification attempts were not made. The compound is not stable for prolonged periods.

4′-Chloro-5′,7′-dimethoxy-6-methyl-spiro[cyclohexane-1,2′-indan]-1′,2,4-trione (**2**).—A solution of 2.8 g (0.0079 mole) of the acid dione **8** in a mixture of 15 ml of trifluoroacetic anhydride and 20 ml of anhydrous ether was kept at room temperature for 30 min, 0.6 ml of boron trifluoride etherate was added and the reaction mixture was kept at room temperature for 35.5 hr. Most of the excess trifluoroacetic anhydride–ether was removed *in vacuo* and cold water was added to the residue. After 8 hr at room temperature, the mixture was made basic (pH 8–9) by adding the appropriate amount of sodium hydroxide in pellet form and was extracted twice with methylene chloride and once with ether. A pale yellow solid separated upon acidification of the aqueous phase with concentrated hydrochloric acid which was collected after 45 min. After drying at 80° over phosphorus pentoxide *in vacuo* for 1 hr, the product (1.5 g) melted at 215–228° dec. The compound was further purified by heating it suspended in boiling acetone and collecting after an additional hour at room temperature. The colorless solid obtained, 0.87 g (33%), melted at 244–245° dec. For analysis the compound was dried at 100° over phosphorus pentoxide *in vacuo* for 17 hr: mp 244–245° dec; λ_{max}^{Nujol} 3.02, 6.00, 6.15, and 6.30 μ; λ_{max}^{MeOH} 315 (ϵ 9200), 273 (ϵ 25,200), and 235 mμ (ϵ 28,000).

Anal. Calcd for $C_{17}H_{17}ClO_5$: (336.77): C, 60.63; H, 5.09; Cl, 10.53. Found: C, 60.83; H, 5.42; Cl, 10.50.

4′-Chloro-2,5′,7′-trimethoxy-6-methylspiro[2-cyclohexene-1,2′-indan]1′,4-dione (**3**) **and 4′-Chloro-4,5′,7′-trimethoxy-6-methylspiro[3-cyclohexene-1,2′-indan]-1′,2-dione** (**4**).—The trione **2** (0.5 g, 0.0015 mole) was suspended in methanol; the mixture was cooled (ice–water) and treated with an excess of ethereal diazomethane (from N-methyl-N-nitrosourea). The reaction mixture which was now homogeneous was stirred in the cold for an additional 45 min, the excess diazomethane was destroyed with acetic acid, and the mixture was diluted with methylene chloride. The solution was washed with aqueous bicarbonate, water, dried, and evaporated to yield 0.5 g of a colorless glass whose nmr spectrum indicated it to be a mixture of two components present in roughly equal amounts. The components were separated by partition chromatography on Celite 545 using heptane–ethyl acetate–methanol–water, 80:20:17:4. The faster moving component, component A, was obtained initially as a pale yellow crystalline solid (0.222 g) which after heating partially suspended in boiling ethanol gave 0.162 g of a colorless solid: mp 213–216° (softens *ca.* 203°); λ_{max}^{Nujol} 5.92 and 6.11 μ; λ_{max}^{MeOH} 318 (ϵ 8900), 266 (ϵ 20,400), and 234 mμ (ϵ 27,400).

Anal. Calcd for $C_{18}H_{19}ClO_5$: (350.79): C, 61.63; H, 5.46; Cl, 10.11. Found: C, 61.33; H, 5.55; Cl, 10.20.

After eluting component A, component B was washed off the column with methanol. The crude solid residue obtained by evaporating the methanol was taken up in methylene chloride, filtered through Celite, and the filtrate evaporated to give 0.212 g of a crystalline solid which was further purified by heating partially suspended in boiling ethanol: yield, 0.158 g; mp 233–235°; λ_{max}^{Nujol} 5.92 and 6.09 μ; λ_{max}^{MeOH} 315 (ϵ 9600), 275 (ϵ 19,500), and 235 mμ (ϵ 27,400).

Anal. Found: C, 61.72; H, 5.56; Cl, 10.10.

The nmr spectra of the two isomers are presented in the Discussion section and, as indicated there, served as the basis for structure assignment (components B and A were assigned structures **3** and **4**, respectively).

Acknowledgments.—Analyses were performed by L. Brancone and staff; ultraviolet and nmr spectra were determined by W. Fulmor and staff; chromatography were determined by C. Pidaks and staff. Biological test data were supplied by Messrs. A. C. Dornbush and F. Popken.