The Preparation of 5′-Hydroxydehydrogriseofulvin

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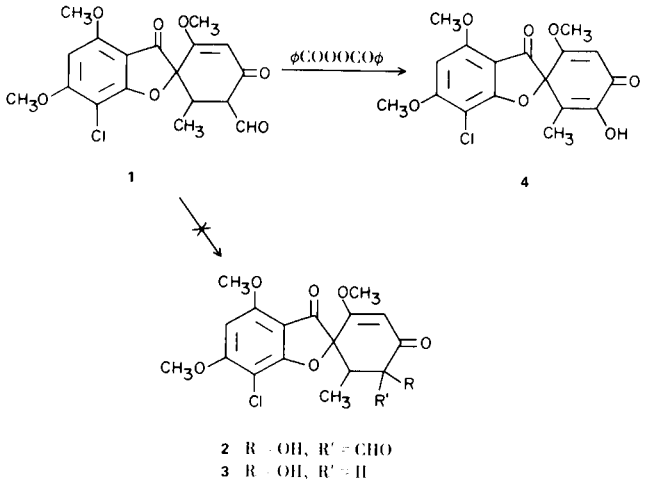
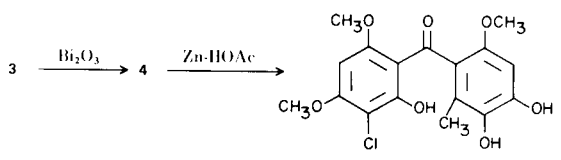
The antifungally active 5′-hydroxygriseofulvin (**3**) has been prepared by the microbiological oxidation of griseofulvin (1), but the poor yield of this conversion and the tedious isolation procedure involved made this route rather unattractive. In an attempt to produce this compound chemically, 5′-formyl griseofulvin (**1**), the preparation of which was recently accomplished simply and in very high yield (2), as its sodium salt in methanol was allowed to react with benzoyl peroxide (3). However, instead of the desired 5′-formyl-5′-hydroxygriseofulvin (**2**) or 5′-hydroxygriseofulvin (**3**) (1), the product isolated in 37% yield was 5′-hydroxydehydrogriseofulvin (**4**).



1 4

2 R = OH, R' = CHO
3 R = OH, R' = H

The structure of **4** follows from its spectral data (see Experimental), its reduction to the benzophenone **5** with zinc in acetic acid and its preparation from 5′-hydroxygriseofulvin by oxidation with bismuth trioxide.



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An attempt to reduce the acetate of **4** to 5′-acetoxygriseofulvin (1), using the hydrogenation condition which effectively transformed dehydrogriseofulvin (**6**) to griseofulvin (4), left it unchanged. (The reduction was not attempted on **4** itself because of its insolubility in the usual organic solvents).

Since further biological evaluation (*in vitro* and *in vivo*) indicated **3** to be less active than the very potent antifungal drug griseofulvin, further attempts to convert **1** to **3** were not made. However, it still remains a very attractive intermediate for this purpose.

EXPERIMENTAL (5)

5′-Hydroxydehydrogriseofulvin (**4**).

A methanolic solution of the sodium salt of 5′-formylgriseofulvin (**1**) was prepared by treating a suspension of 5 g. (0.013 mole) of **1** (2) in 100 ml. of methanol with 13 ml. (0.013 mole) of 1*M* methanolic sodium methoxide, the solution cooled (ice-water) and 3.15 g. (0.013 mole) of benzoyl peroxide added. The resulting suspension was stirred at room temperature. After *ca.* 15 minutes a homogeneous solution was obtained and after *ca.* another 10 minutes a new colorless solid began separating. (In a separate experiment this was shown to be **4**). Stirring at room temperature was continued for 27 hours before collecting the solid, m.p. 257-260° dec. without melting (to a black solid). An additional 0.3 g. of product (dec. without melting 262-265°) separated from the filtrate on further (20 hours) standing giving a total yield of 1.9 g. (37%). The combined fractions were heated, suspended in boiling methanol (in which the product was quite insoluble) and filtered hot to give 1.7 g. of colorless solid which decomposed without melting 260-265°.

An analytical sample, m.p. 275-280° dec. without melting, was obtained by heating a portion of the product suspended in boiling glacial acetic acid and filtering the hot suspension; λ max (potassium bromide), 2.9 (m), 5.85 (s), 6.1 (sh, s), 6.2 (v.s.) and 6.3 (v.s.); λ max (methanol), 320 (plateau) (ε, 10,000), 292 (ε, 35,000), 255 (ε, 16,000), 235 (ε, 25,000) and 214 nm (ε, 37.000); δ (d_6DMSO) (TMS) 9.13 (1-proton, exchangeable, O*H*), 6.57 (aromatic H), 5.90 (vinyl H), 4.12, 4.04 (aromatic OCH_3's) 3.72 (vinyl OCH_3), 1.52 (sharp singlet C-6′-CH_3); m/e 366, 368 (3:1) (M^+) (base peak).

Anal. Calcd. for $C_{17}H_{15}ClO_7$ (366.75): C, 55.67; H, 4.13; Cl, 9.67. Found: C, 55.47; H, 4.07; Cl, 9.62.

Formation of **4** by Bismuth Trioxide Oxidation of 5′-Hydroxygriseofulvin (**3**).

A mixture of 185 mg. (0.5 mmole) of 5′-hydroxygriseofulvin

(**3**) (1), (prepared by Mr. M. Dann of these laboratories) 260 mg. (0.6 mmole) of bismuth trioxide in 10 ml. of glacial acetic acid was heated and stirred at 100° (oil bath temperature) for 15 hours. The colorless solid was collected by filtration and dried, m.p. 275-280° dec. without melting to a black solid. Its i.r., u.v., n.m.r. and mass spectra were identical with those of **4** obtained above.

Acetate of **4**.

Treatment of 340 mg. of **4** with 5 ml. of pyridine and 2.5 ml. of acetic anhydride gave, after 15 minutes a homogeneous solution which was poured into ice-water after standing at room temperature for 3 hours. The solid which separated was collected, washed well with water and air dried to constant weight to yield 360 mg. of the colorless acetate, m.p. 197-200° (deep orange melt); λ max (potassium bromide), 5.70 (OAc), 5.84 (ring B⟩C=O) and 6.05 μ; δ (deuteriochloroform + d_6DMSO) (TMS), 6.26 (aromatic H), 5.68 (vinyl H), 4.06, 4.00 (aromatic OCH_3's) 2.28 (acetyl) CH_3), 1.65 (C-6′-CH_3). All the signals were sharp singlets.

Anal. Calcd. for $C_{19}H_{17}ClO_8$ (408.79): C, 55.82; H, 4.19; Cl, 8.67. Found: C, 55.27; H, 4.23; Cl, 9.02.

(Attempts to recrystallize the acetate from ethyl acetate or methanol gave material with a broadened melting point range. The product appears to be unstable to heat).

Reduction of **4** with Zinc in Acetic Acid. Formation of 2,4,2′-Trimethoxy-6,4,5′-trihydroxy-5-chloro-6-methylbenzophenone (**5**).

Heating a suspension of 0.2 g. of **4** in 5 ml. of glacial acetic acid and 1 ml. of water in the presence of 2 g. of zinc dust on the steam bath with glass rod manipulation produced a yellow solution within 3 minutes. After heating for a total of 5 minutes the solution was decanted from the zinc salts into ice-water and the yellow solid which separated was collected, yield 119 mg., m.p. 208-218°. Recrystallization from methanol furnished the analytical sample, m.p. 215-217.5°; λ max (potassium bromide), 2.9 (OH) and 6.2 μ ⟩C=O + aromatic unsaturation); λ max (methanol), 330 (ε, 6,500), 293 (ε, 24,000), 233 (ε, 18,500) and 210 nm (ε, 31,000); δ (deuteriochloroform-d_6DMSO) (TMS), 6.40, 6.00 (aromatic H′S)[6], 3.96, 3.59 and 3.49 (aromatic OCH_3's), 2.03 (aromatic CH_3). All signals were sharp singlets.

Anal. Calcd. for $C_{17}H_{17}ClO_7$ (368.77): C, 55.37; H, 4.65; Cl, 9.62. Found: C, 55.11; H, 4.64; Cl, 9.65.

Triacetate of **5**.

A solution of *ca.* 100 mg. of **5** in 1.5 ml. of acetic anhydride and 1.5 ml. of pyridine was kept at room temperature for 15 hours then poured into ice-water. The colorless solid which separated was collected, yield 87 mg., m.p. 177-179° (with partial melting and resolidification at *ca.* 90°); λ max (potassium bromide), 5.6 (s, poorly resolved doublet, OAc) and 5.98 μ (m) (Ar-*CO*-Ar); δ (deuteriochloroform-d_6DMSO) (TMS), 6.62, 6.45 (aromatic H′S), 3.96, 3.66, 3.59 (aromatic OCH_3's), 2.32, 2.29, 2.18 (acetyl CH_3's), 2.06 (aromatic CH_3). All the signals were sharp singlets.

Anal. Calcd. for $C_{23}H_{23}O_{10}Cl$ (494.87): C, 55.82; H, 4.68; Cl, 7.17. Found: C, 55.96; H, 4.70; Cl, 7.10.

Acknowledgements.

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REFERENCES

(1a) W. Andres, W. McGaren and M. Kuntsmann, *Tetrahedron Letters*, 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 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) See also ref. 11 in a paper by H. Newman and R. B. Angier, *J. Org. Chem.*, 34, 1463 (1969).

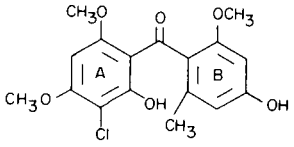
(2) H. Newman and T. Fields, *ibid.*, in press.

(3) G. Allen Jr. and M. J. Weiss, *ibid.*, 27, 4681 (1962).

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

(5) Melting points are uncorrected. The nmr spectra were determined on a Varian A-60 spectrometer, the mass spectra on an AEI MS-9 spectrometer. Magnesium sulfate was used for drying.

(6) Based on the aromatic H signals of the Benzophenone i



i

(4) which appear in a ratio of 2:1 at 6.30 and 5.93 δ (unpublished observations) the 6.40 and 6.00 δ signals in **4** are assigned to the ring B and ring A protons respectively. (nmr spectra of **4** and i were measured in the same solvent system).

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