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THE CONFORMATION OF GRISEOFULVIN. APPLICATION OF AN NMR SHIFT REAGENT

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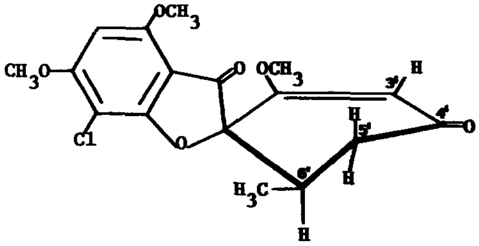
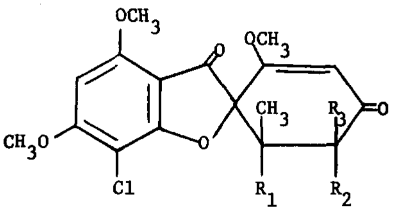
In continuation of previous stereochemical studies[1] in the griseofulvin series we have now found evidence that the preferred conformation of the parent compound in solution is that given in stereostructure I. Our conclusion is based on the finding of relatively strong coupling (J = 13.5 Hz) between the 6'α- and 5'β-protons. This nmr parameter could not be extracted from the nmr spectrum[2] of griseofulvin itself which presents the 6'α-,5'β-, and 5'α-protons at 2.3-3.1δ as a complex and closely spaced three-proton multiplet, involving further coupling to the 6'-methyl substituent[3]. Our present work relies on the application of an nmr "shift reagent," tris-(dipivalomethanato)europium[4] [Eu(DPM)$_3$], to the spectrum of a partially deuterated sample of griseofulvin.

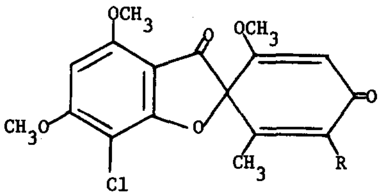


I

The chemical shifts of the three ring C hydrogen substituents were first determined. A solution of griseofulvin (1) in $CH_3CH_2C(CH_3)_2OD$, containing $CH_3CH_2C(CH_3)_2ONa$, heated at reflux for 16 hours gave griseofulvin-5',5'-d$_2$ (2)[5]. In its nmr spectrum, this substance exhibited only one aliphatic proton (other than the expected methyl signals), which appeared as a quartet (1H) at 2.75δ and must be assigned to the 6'α-proton. Selenium dioxide dehydrogenation of 2 gave dehydrogriseofulvin-5'-d (6)[5,6] which was converted to griseofulvin-5'β-d (3)[5] by catalytic hydrogenation with 10% palladium on charcoal. The 5'α- and 6'α-protons of 3 were visible at 2.29 and 2.75δ as a doublet and rough quintet, respectively. Homogeneous catalytic reduction of dehydrogriseofulvin (7) with deuterium and tris(triphenylphosphine)rhodium (I) chloride[7,8] provided griseofulvin-5'α,6'α-d_2 (4)[5] in which the 5'β-proton appeared as a singlet at 2.84δ.



1 $R_1 = R_2 = R_3 = H$
2 $R_1 = H, R_2 = R_3 = D$
3 $R_1 = R_2 = H, R_3 = D$
4 $R_1 = R_2 = D, R_3 = H$
5 $R_1 = R_3 = H, R_2 = D$



6 R = D
7 R = H

Griseofulvin-5',5'-d_2 (2) on being stirred in chloroform solution for 16 hours with neutral alumina (Woelm, activity II) underwent stereoselective partial replacement of the 5'β-deuterium substituent by hydrogen. The product, a mixture[9] of starting material (2) and griseofulvin-5'α-d (5) was free of absorption in the region of 2.3δ (5α-H) but exhibited a complex band at 2.7-2.9δ (1.4H) (Figure 1) representing the coupled and closely spaced 5'β- and 6'α-proton signals. A solution of 5 (0.17M) and $Eu(DPM)_3$ (0.07M) in $CDCl_3$ gave rise to a strikingly altered nmr spectrum (Figure 2) in which proton signals are shifted downfield in general proportion to their closeness to the C-4 carbonyl oxygen[10]. The signals due to 6'-CH_3 (1.48δ), 6'α-H (∿3.9δ), and 5'β-H (5.3δ) now constitute a first order (A_3MX) system in which the doublet[11] at 5.3δ gives $J_{5'\beta-6'\alpha} \sim 13.5$ Hz. A vicinal coupling of this magnitude must be due to trans, diaxial hydrogen substituents and requires conformation I for griseofulvin[12]. The same half-chair ring C conformation has been found for crystalline 5-bromogriseofulvin by X-ray diffraction methods[13,14].

The stereoselectivity of proton exchange reactions at the 5'-methylene group is under further investigation.

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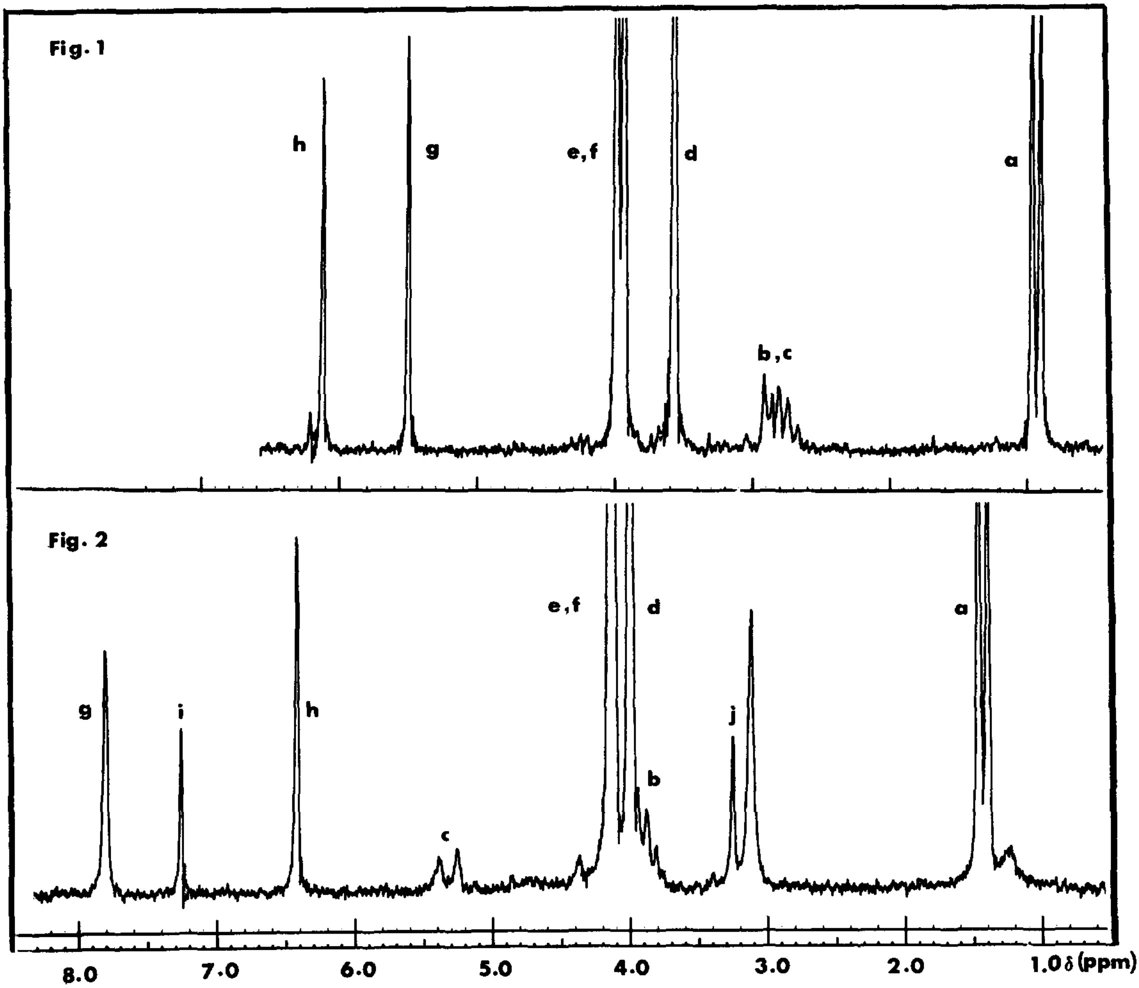

Fig. 1 Nmr spectrum (100) of 5 (+ 2) in $CDCl_3$.

Fig. 2 Nmr spectrum (100) of 5 (+ 2) and 0.4 molar equivalent of $Eu(DPM)_3$ in $CDCl_3$.

PROTON ASSIGNMENTS

a. 6'-CH_3
b. 6'-H
c. 5'β-H
d. 2'-OCH_3
e,f. Ar-OCH_3
g. 3'-H
h. Ar-H
i. $CHCl_3$
j. bands due to $Eu(DPM)_3$[16]

REFERENCES AND FOOTNOTES

1. S. G. Levine and Ronald E. Hicks, *Tetrahedron Letters*, 5409 (1968).
2. All nmr spectra were obtained on a Varian HA-100 spectrometer.
3. We did not succeed in simplifying this spectrum through double irradiation experiments or changes in solvent.
4. (a) C. C. Hinckley, *J. Am. Chem. Soc.*, 91, 5160 (1969); (b) J. K. M. Sanders and D. H. Williams, *Chem. Comm.*, 422 (1970); (c) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Am. Chem. Soc.*, 92, 5734, 5737 (1970).
5. All partially deuterated samples of griseofulvin and dehydrogriseofulvin gave satisfactory results in melting point, optical rotation, and mass spectral determinations.
6. D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, 19, 1 (1963).
7. C. Djerassi and J. Gutzwiller, *J. Am. Chem. Soc.*, 88, 4537 (1966).
8. Hydrogenation of dehydrogriseofulvin using either catalyst gave griseofulvin uncontaminated by isomers. The homogeneous catalyst led to much slower reaction and more extensive hydrogenolysis; it was employed for deuterium addition since the palladium catalyst contains adsorbed hydrogen.
9. Mass spectral analysis of this product gave 2.4% d_0, 39.6% d_1, and 58.0% d_2 species.
10. Some degree of $Eu(DPM)_3$ association presumably occurs at other basic centers as well. The significant downfield shift of the aromatic proton may be due to complexation occurring with the adjacent ether oxygen atoms.
11. This doublet is broadened, as expected, by geminal coupling to the 5'α-deuterium. In samples obtained after longer exposure to alumina, this signal was less distinct due to partial incorporation of protons at the 5'α-position.
12. Our conclusion relies on the assumption that the conformation of griseofulvin is not altered by complexation with $Eu(DPM)_3$. This seems likely since the doublet spacing of the 5'β-proton of 5 (+ 2) does not vary with concentration of the shift reagent.
13. W. A. C. Brown and G. A. Sim, *J. Chem. Soc.*, 1050 (1963).
14. The Merck group has previously proposed[15] conformation I for griseofulvin based on a comparison of its nmr spectrum with that of epigriseofulvin (epimeric at the spiro center). The wider absorption band for the aliphatic ring C protons in the case of griseofulvin was ascribed to the downfield shift of the 5'β proton due to its proximity to the ring B carbonyl oxygen in conformation I.
15. 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, 267 (1963).
16. The bands at approximately 3.2δ are present in the spectrum of $CDCl_3$ solutions of $Eu(DPM)_3$ alone and do not appear to be due to an impurity. These bands are diminished or absent in spectra of solutions of alcohols[4] which associate strongly with $Eu(DPM)_3$. They tend to be present, however, in spectra of ketones. We thank Professor E. Wenkert for helping us to clarify this situation by reference to some of his unpublished work.