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CONFORMATIONAL PREFERENCE IN THE GRISEOFULVIN SERIES. GRISEOFULVOL

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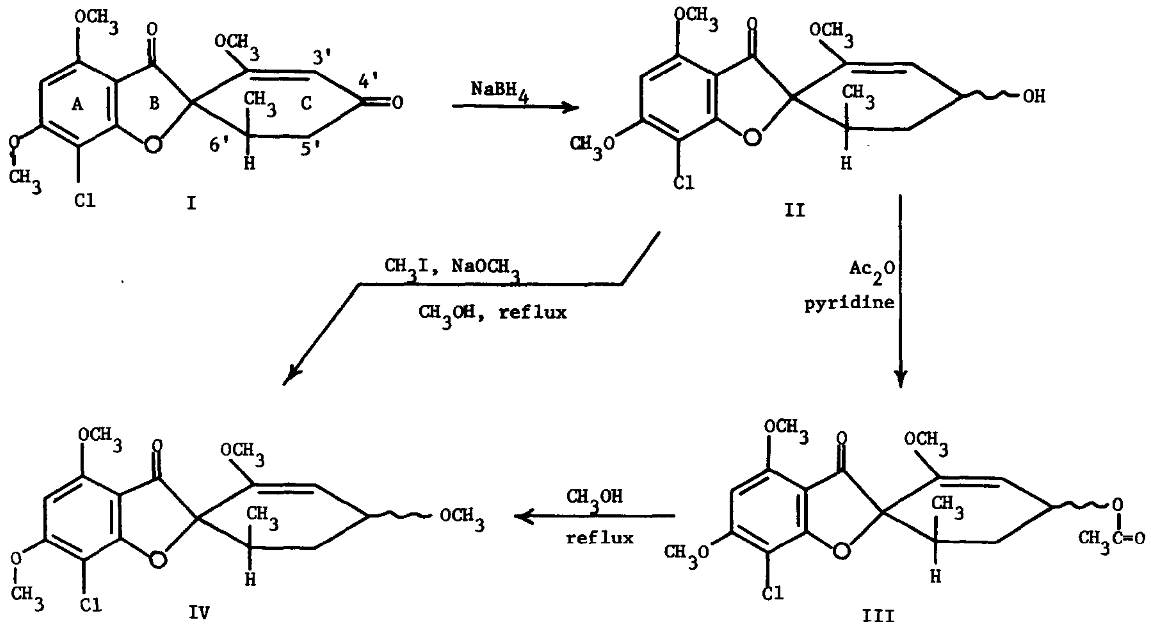
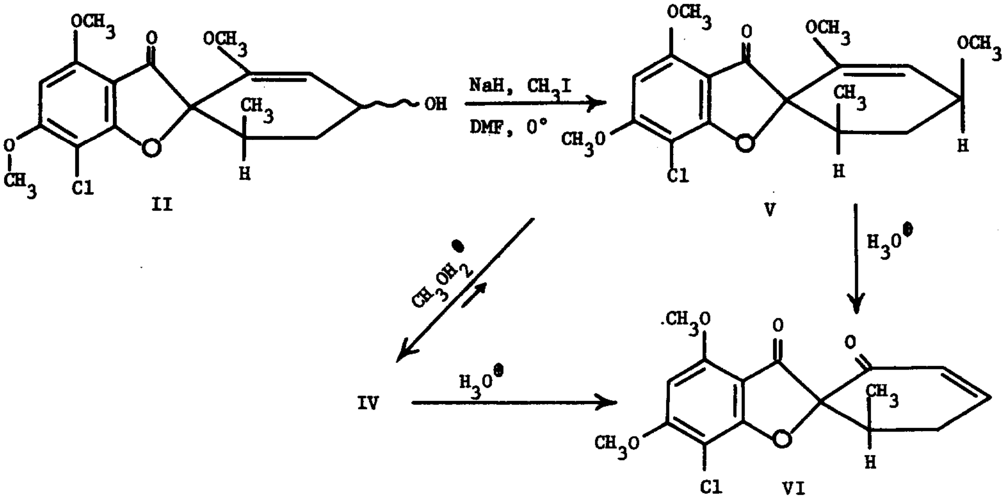
Kyburz and co-workers (2) have reported that reduction of griseofulvin (I) with NaBH$_4$ takes place exclusively at the C(4')-carbonyl group and leads (Scheme I) to a single allylic alcohol, griseofulvol (II), of undetermined C(4')-configuration. It was further found that griseofulvol acetate (III) undergoes solvolysis in boiling methanol to produce the methyl ether (IV), m.p. 201-203°. The latter product was also synthesized by direct methylation (CH$_3$I, NaOCH$_3$/CH$_3$OH) of griseofulvol, implying that the solvolytic replacement had occurred with retention of configuration. We have reinvestigated these reactions as part of a larger study of griseofulvin chemistry designed to elucidate the conformational characteristics of ring C. We report here our findings regarding (a) the C(4')-configuration of griseofulvol and (b) the preferred ring C conformation in griseofulvol and related substances.



SCHEME I

Griseofulvol (II) and the methyl ether IV were prepared according to the published procedures (3) and their properties were in agreement with those already recorded (2). We were surprised to find that the NMR spectra (4) of these two products are strikingly different as shown in Fig. 1 and 2, respectively. In particular, those signals (1.5-3.0δ) which should be associated with the three protons directly attached to positions 5' and 6' of IV appear over a chemical shift range almost double that of the corresponding signals from griseofulvol (II). Our consequent suspicion that these substances do not differ simply as a secondary alcohol and the corresponding methyl ether was experimentally verified.

A solution of griseofulvol in DMF, treated for two hours at 0° with NaH and CH_3I, yielded a methylation product, m.p. 179-182° to which we assign (*vide infra*) structure V (Scheme II). The elemental analysis and spectral properties of V were consistent with its formulation as the simple methylation product of griseofulvol. In particular, the NMR spectrum of V was similar to that of griseofulvol (II) excepting those changes expected for replacement of OH by OCH_3. Both methyl ethers IV and V, on treatment with aqueous acid, gave the known (5) conjugated ketone VI which had previously been obtained (2) by similar treatment of griseofulvol. Either of the methyl ethers, when heated under reflux in CH_3OH containing a trace of HOAc, yielded the same equilibrium mixture of these two substances in which IV is the major constituent. It is evident that the griseofulvol acetate methanolysis product IV is epimeric with griseofulvol at C(4') and that its formation by methylation of griseofulvol (in CH_3OH) also entails inversion at this center (6).



SCHEME II

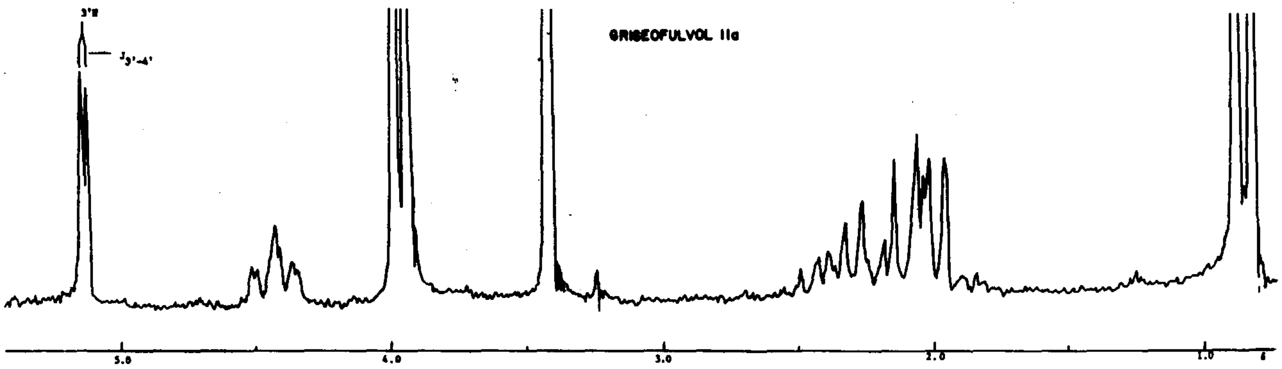


Fig. 1. Partial NMR spectrum of Griseofulvol (IIa) in $CDCl_3$ at 100 Mc./sec.

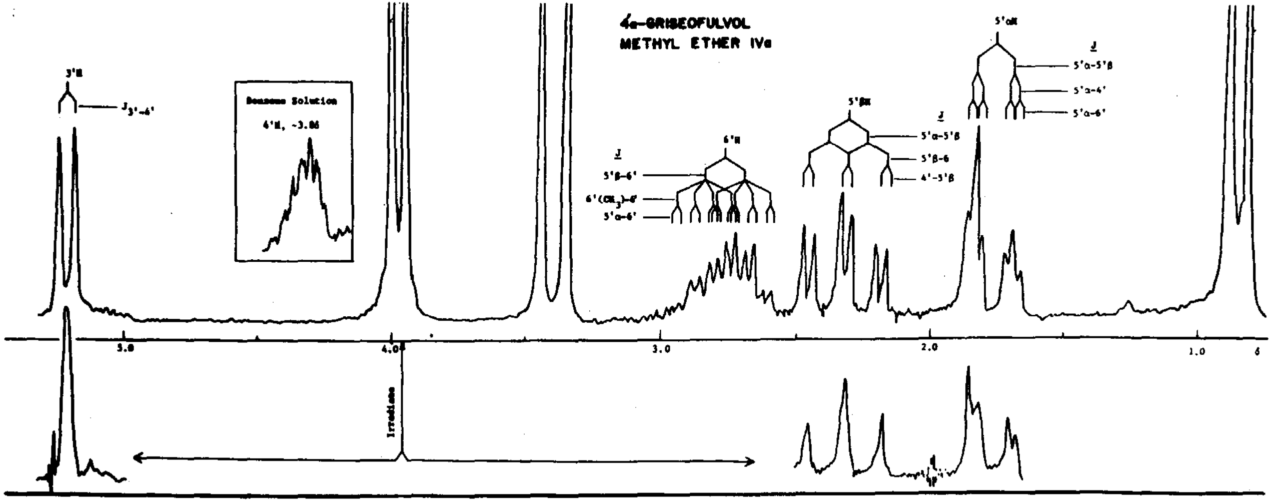


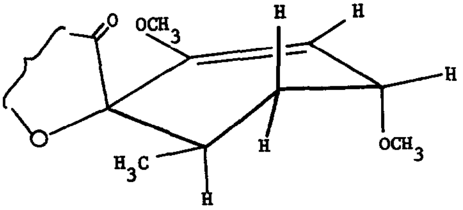
Fig. 2. Partial NMR spectrum of 4'α-Griseofulvol Methyl Ether in $CDCl_3$ at 100 Mc./sec.

The NMR spectrum of IV proved to be strikingly informative, allowing us to deduce the conformation of ring C as well as the C(4')-configuration (7). The wide separation of all ring C proton signals justified a first-order analysis leading to the chemical shifts and coupling constants tabulated below.

	δ ppm
3'-H	5.19
4'β-H	~3.90
5'α-H	1.78
5'β-H	2.32
6'α-H	2.77

	|J|
3'-4'β	5.5
4'-5'α	3
4'-5'β	3.5
5'α-5'β	14
5'α-6'α	3
5'β-6'α	14
6'α-6CH_3	6.5

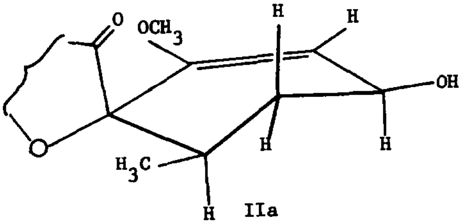
The "triplet of doublets" at 2.32δ has an intensity of 1H and must be identified with one of the C-5 methylene protons, all other assignments being ruled out by chemical shift or multiplicity considerations. Since two large (14 cps) J values are required for this splitting pattern, it follows that a 1,2-*trans*, diaxial coupling (9) is present in addition to the geminal coupling. This vicinal interaction can not involve the C(4')-proton which must be equatorial to account for the 5.5 cps splitting of the C(3')-vinyl proton (10). By inference, the second 14 cps coupling is with the 6α-H. We may conclude that the 2.32δ resonance is due to the C(5'β)-H, *and that the C(6α)-H is axial*. The latter condition requires that the ring C conformation of IV be represented as in IVa and on this basis, the quasi-equatorial C(4')-proton has the β-configuration as shown. The various other J value assignments are consistent with the complete stereostructure IVa. The low-field position of the axial (6'α)-H is accounted for (11) by its proximity to the quasi-axial C(4'α)-OCH_3. The "missing" 4'β-proton resonance is hidden under the aromatic OCH_3 signals in the 400 cps region. Its location was disclosed by integration and verified by a double resonance



IVa

experiment; irradiation at 3.90δ led to the anticipated simplification of signals from adjacent protons at C(3'), C(5'α), and C(5'β). The C(4'β)-proton signal became separately visible when the spectrum was rerun in benzene.

Since griseofulvol is epimeric at C(4') with the methyl ether IVa, it can now be represented by the C(4'β)-alcohol structure IIa. The narrow (2 cps) splitting of the vinyl proton in IIa indicates that the C(4'α)-proton is axial (10); this identifies the ring C conformation of griseofulvol as analogous to that of IVa.



IIa

It is interesting to note that the conformation deduced above places the C(3)-carbonyl as a quasi-axial substituent with respect to ring C. This is also the case for 5-bromogriseofulvin in the crystalline state as determined by X-ray crystallography (12). In further studies, we hope to determine the ring C conformation of griseofulvin in solution and to identify the structural features which govern ring C conformation in this spirocyclic system (13).

REFERENCES AND FOOTNOTES

1. National Defense Education Act Fellow.
2. E. Kyburz, H. Geleick, J. R. Frey, and A. Brossi, *Helv. Chim. Acta*, **43**, 2083 (1960).
3. The methyl ether IV was prepared by methanolysis of griseofulvol acetate rather than by the methylation procedure. See footnote (6).
4. NMR spectra were run at 100 Mc/sec. and are calibrated in ppm (δ) from TMS. Except where noted, solutions were in $CDCl_3$.
5. T. P. C. Mulholland, *J. Chem. Soc.*, 3994 (1952).
6. Kyburz and co-workers (2) report that this methylation reaction gave IV in "ca.20% yield" after chromatography of the total products. Our repetition of their procedure led to a complex product mixture consisting largely of the conjugated ketone VI. A small amount of IV was detected by thin layer chromatography but could not be obtained pure; its formation *via* a solvolysis pathway can not be excluded since all traces of alkali were consumed by the end of the half hour reflux period.

7. Ring C substituents which are *cis* to the ring B ether linkage are designated as α; those *cis* to the ring B carbonyl groups are termed β (8).

8. 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).

9. A value of 14 cps is unusually large even for 1,2-*trans*, diaxial coupling. This is probably due to the absence of electronegative substituents on either of the adjacent carbon atoms. For another example of this type see H.A.P. De Jongh and H. Wynbert, *Tetrahedron*, **21**, 515 (1965).

10. For a very recent application of vinyl-allylic proton spin couplings and references to earlier studies see J. P. Kutney, G. Eigendorf and J. E. Hall, *Tetrahedron*, **24**, 845 (1968).

11. (a) K. Tori and T. Komeno, *Tetrahedron*, **21**, 309 (1965).

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12. W. A. C. Brown and G. A. Sim, *J. Chem. Soc.*, 1050 (1963).

13. We are very grateful to Dr. H. Herzog of the Schering Corporation for providing the supply of griseofulvin which was used in this work.