

Communications to the Editors

STEREOCHEMICAL
CHARACTERISTICS OF
VARIOTIN AS DEDUCED FROM
THE NUCLEAR OVERHAUSER
EFFECT IN THE NMR SPECTRA

Sir :

Variotin, an antifungal antibiotic produced by *Paecilomyces varioti* BAINIER var. *antibioticus*, has the molecular formula $C_{17}H_{25}O_3N^{1,2}$. From chemical and nmr spectroscopic properties the structure of N-(8'-R-hydroxy-6'-methyl-*trans-trans-cis*-dodeca-2', 4', 6'-trienoyl)-2-pyrrolidone was proposed for variotin^{3,4,5}.

Variotin has a conjugated triene system in its molecule. Coupling constants in the nmr spectrum indicated a *trans-trans* configuration in the 2' and 4' double bonds. The configuration of the 6' double bond could not be assigned from the nmr, because there is no proton at the 6' position.

Reaction of variotin with maleic anhydride by refluxing in toluene resulted in a DIELS-ALDER type adduct, consuming one mole of the maleic anhydride. The product obtained as white needles ($C_{21}H_{27}O_6N$), is a monocarboxylic acid (pK_{mcs} 9.75) with no free hydroxyl in the 8' position. From chemical and spectroscopic studies, lactone formation between the 8' hydroxy and a carboxyl group of one of two carboxyls in the adduct was confirmed. Ozonolysis of the adduct yielded D- α -hydroxy caproic acid as was obtained from variotin. Thus the 6' double bond must not have been affected. Accordingly, the authors concluded that the 6' double bond must have a *cis* configuration⁵.

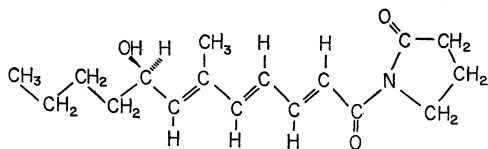
The intramolecular nuclear OVERHAUSER effect (NOE) in the nmr spectrum has now been utilized to determine the configuration of the 6' double bond in variotin. The application of the NOE technique to natural products was evaluated by WOODS and others⁶. Calculating from a DREIDING model with the *cis* configuration at 6', the distance between the 13' methyl and the 7' olefinic proton is

approximately 2.3 Å. Irradiation of one of these protons should increase the intensity or area of the signal of the proximal protons. On the other hand, because of the distance from the 13' methyl to the 8' proton in the *cis* structure, a significant NOE would not be expected with these protons. With a *trans* configuration at 6', the distance between the 13' methyl and the 7' proton is approximately 3.4 Å, and the distance from the 13' methyl to the 8' proton is about 1.6 Å, thus the NOE would be expected with the protons in the 13' methyl and the 8' proton.

To determine the NOE of variotin, the nmr spectra were taken at 100 MC and a concentration of 100 mcg/ml in deuterated benzene using tetramethylsilane (TMS) for frequency lock. By the irradiation of the 13' allylic methyl signal at 1.65 ppm from TMS, the increase in the integrated area due to the 7' doublet at 3.1 ppm was insignificant. On the contrary, the integrated intensity of the quartet signal due to the 8' was increased about 12 % and the total area of signals due to the 4' which overlapped with 5' the olefinic proton at 6.4 ppm was increased about 9 % by the same irradiation.

From the results of NOE values it is concluded that the 8' proton is closer than the 7' proton to the 13' methyl group. Accordingly, the configuration of the 6' double bond of variotin should be assigned as the *trans* form.

The results obtained from the intramolecular NOE in variotin is contrary to the previous chemical result. The authors consider that such a discrepancy may arise by stereochemical change at the 6' double bond during the DIELS-ALDER reaction. The structure of variotin is thus revised to N-(8'-R-hydroxy-6'-methyl-*trans-trans-trans*-dodeca-2', 4', 6'-trienoyl)-2-pyrrolidone.



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