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STEREOCHEMISTRY OF VARIOTIN

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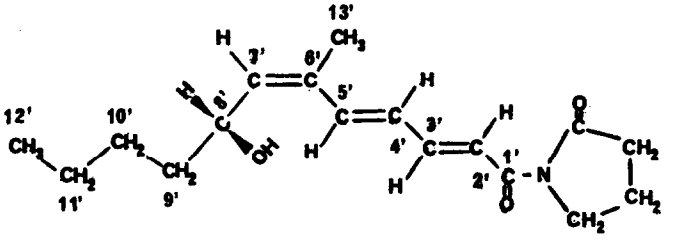
Variotin[1,2], an antifungal antibiotic produced by Paecilomyces varioti Bainier var. antibioticus , has the molecular formula of $C_{17}H_{25}O_3N$. The chemical structure of variotin has been previously reported by the authors[3,4].

From the evidences based on the chemical reactions and n.m.r. spectrometric analyses, we would like to present the configuration of variotin as shown in Fig. I.

Fig. I

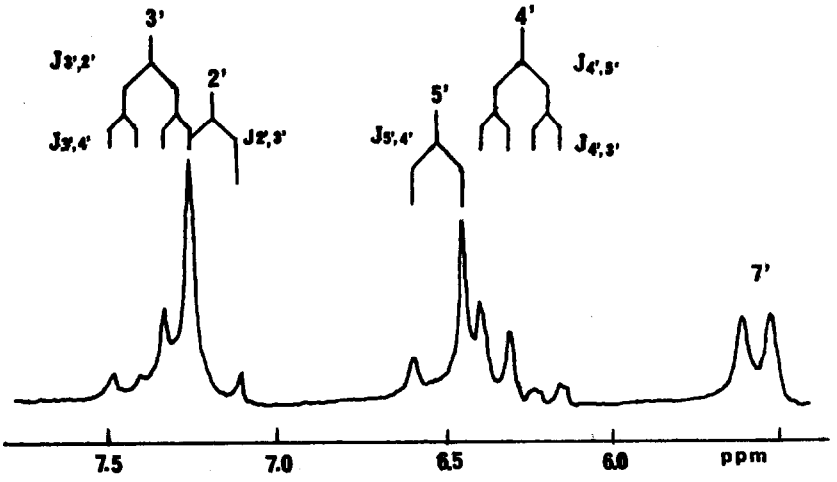


Ozonolysis of variotin only afforded valeraldehyde or valeric acid due to the allylic 8' hydroxy group. However, ozonolysis of acetylvariotin in chloroform followed by oxidative degradation with silver oxide in 1 N sodium

hydroxide gave α-hydroxycaproic acid. The optical rotation of $(\alpha)_D^{25}$ -1.46° (c, 7.2 in ethanol) indicated that the acid belonged to the D series[5], and consequently, the configuration at the 8' position is R.

Information concerning the configurations of the 2' and 4' double bonds was obtained from the n.m.r. spectrum (Fig.2). The signals due to the four olefinic protons appearing in the region 6.0-8.0 ppm can be assigned as follows: 7.4 ppm (H-3', $J_{3,2}$,=15.5 cps, $J_{3,4}$,=9.5 cps), 7.2 ppm (H-2', $J_{2,3}$,=15.5 cps) 6.55 ppm (H-5', $J_{5,4}$,=15.5 cps) and 6.3 ppm (H-4', $J_{4,5}$,=15.5 cps, $J_{4,3}$,=9.5 cps). Spin decoupling experiments showed that

Fig. 2 *



* 100 Mc, in $CDCl_3$, TMS as internal reference.

the two quartets at 7.4 and 6.3 ppm were mutually coupled. The coupling constants revealed a trans-trans configuration

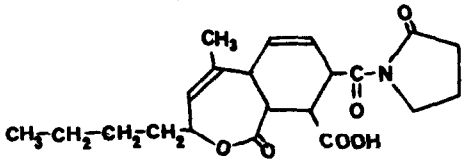
for 2' and 4' double bonds.

The long range interaction between the 7' proton and the 13' methyl group was indefinite and therefore the configuration of the 6' double bond could not be assigned by n.m.r. .

Reaction of variotin with excess maleic anhydride by reflux in toluene for 3 hrs. gave the Diels-Alder type adduct, consuming one mole of the anhydride. In the same reaction at room temperature, 0.34 mole of maleic anhydride was consumed after 18 hrs., and 0.60 mole after 66 hrs.. Relatively ready formation of the adduct with maleic anhydride reconfirmed the presence of trans-trans configuration in the conjugated system. Recrystallization of the adduct from hot iso-propanol yielded white needles; m.p. 137-137.5°, $C_{21}H_{27}O_6N$ (m.w. 389.43), pKmcs 9.75 (mono-carboxylic acid), which showed no characteristic UV absorption band. The infrared spectrum exhibited a lactone at 1780 cm^{-1}, but no band due to the hydroxy group. The adduct showed a positive color reaction for esters, but was negative for acid anhydrides. Ozonolysis of the adduct afforded α-hydroxycaproic acid, indicating that the 6' double bond remained unaffected under the Diels-Alder reaction and that the 8' hydroxy group had been acylated. The signal of the 8' proton observed at 4.35 ppm (quartet) in variotin was shifted to 4.85 ppm (quartet) in the n.m.r. spectrum of the adduct.

From the evidences described above, the lactone formation between the 8' hydroxy group and a carboxyl group of the adduct was confirmed, and the structure can be illustrated as shown in Fig. 3. This fact indicates that the 6' double bond must adapt a cis configuration.

Fig. 3



In conclusion, the stereochemical structure for variotin is N-(8'-R-hydroxy-6'-methyl-trans-trans-cis-dodeca-2',4',6'-trienoyl)-2-pyrrolidone.

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