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STRUCTURE OF VIRANTMYCIN, A NOVEL ANTIVIRAL ANTIBIOTIC

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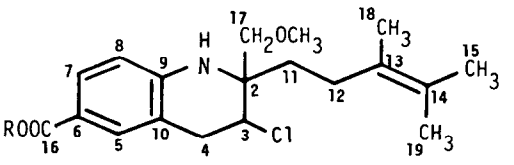
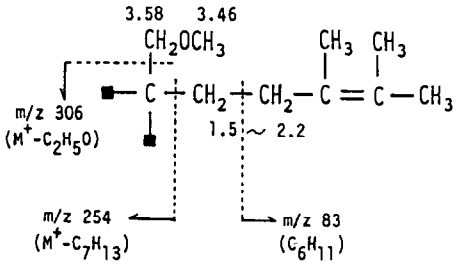
Summary The structure of virantmycin, a novel antiviral antibiotic, isolated from Streptomyces, has been established by chemical and spectroscopic evidences.

Virantmycin (1), an antibiotic active against RNA and DNA viruses has been isolated from the fermentation broth of Streptomyces nitrosporeus[1]. This communication deals with the structural elucidation of 1. The antibiotic, 1, mp. 59°C, $[\alpha]_D^{18}$ -0.05° (c 1, $CHCl_3$) gave the following spectral data: UV λ_{max}^{EtOH} 306 nm (ε, 8100), IR $\nu_{max}^{CCl_4}$ 3440 (NH), 3400-2400 (carboxy OH), 1687 (carboxy CO), 1603 cm^{-1} (C=C). The mass spectrum of 1 showed M^+ m/z 351 ($C_{19}H_{26}NO_3Cl$) and characteristic fragment peaks at m/z 316 (M^+-Cl), 306 (M^+-CH_2OCH_3), 270 (M^+-CH_2OCH_3-HCl), 254 (M^+-C_7H_{13}) and 83 (C_6H_{11}). The ^1H and ^{13}C nmr spectra[2] of 1 and the selective $^{13}C\{^1H\}$ decoupling experiments exhibited the presence of three-substituted aromatic ring (δ_H 6.56 d, J= 8.5 Hz, δ_H 7.78 d, J=3.0 Hz and δ_H 7.82, dd, J=8.5, 3.0 Hz), a carboxyl carbon (δ_C 171.9), a methine (δ_H 4.36 t, J=6.0 Hz; δ_C 56.2) coupled with a methylene (δ_H 3.40 dd, J=16.4, 6.0 Hz and δ_H 3.08 dd, J=16.4, 6.0 Hz; δ_C 33.5), a methoxy methylene (δ_H 3.46 s; δ_C 59.4 for OCH_3 and δ_H 3.58 s; δ_C 74.1 for CH_2), two adjacent methylenes (δ_H 1.6 m; δ_C 27.8 and δ_H 2.0 m; δ_C 33.5), a quaternary carbon (δ_C 58.0) and three methyls (δ_H 1.60 s; δ_C 20.6, 19.9 and 18.4),

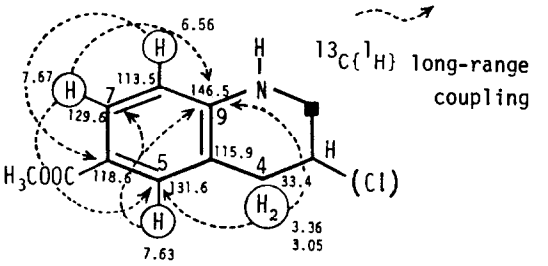


	R
1	H
2	CH_3

which are attached to an isolated double bond (δ_C 124.8 and 126.5). Furthermore, two broad signals in the ^{1}H-nmr spectrum were assigned to be a carboxylic (δ 8.0) and NH (δ 4.7) protons, which disappeared by addition of D_2O. The resonance of the aromatic proton in higher magnetic field at δ 6.56 suggests the location of a NH group on the aromatic carbon at its α-position. The spectral evidences described above characterized the existence of the p-aminobenzoic acid skeleton as the chromophore and alkyl side chain moiety [I] in 1.



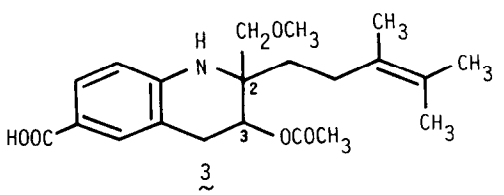
[I]



[II]

The substitution pattern on the isolated double bond [I] and the aromatic ring [II] were well supported by the application of $^{13}C\{^1H\}$ long-range decoupling (LSPD) technique to the methyl ester, 2 [mp. 118°C, $[\alpha]_D^{18}$ -0.10° (c 1, $CHCl_3$), $C_{20}H_{28}NO_3Cl$ (M^+ m/z 365), λ_{max}^{EtOH} 308 nm (ε, 9200), δ_H 3.80 ($COOCH_3$), δ_C 167.2 (ester CO)], which was obtained by treatment of 1 with CH_2N_2. LSPD of methylene signal (C-4, δ_H 3.34 corresponding to δ_C 33.4) collapsed C-9 aromatic carbon (δ_C 146.5, broad triplet) to a sharp triplet ($^3J_{CH}$=9.0 Hz) and the C-5 aromatic carbon (δ_C 131.6, broad doublet) to a sharp double of doublet ($^1J_{CH}$=160.0 Hz, $^3J_{CH}$=6.4 Hz), Irradiation of two aromatic protons (δ_H 7.63 and 7.67) collapsed the C-5 and the C-9 aromatic signals to a broad singlet, and the C-7 (δ_C 129.6, $^1J_{CH}$=163.0 Hz, $^3J_{CH}$=7.1 Hz) to a singlet, respectively. These spectral data indicated that the C-4 methylene protons must be three bonds away from the C-5 and C-9 aromatic carbons. Another, two olefinic carbon signals at δ 124.8 and 126.5 collapses from broad singlet to sharp one upon irradiating the methyl and methylene protons at δ 1.60 and 1.5-2.0, simultaneously, confirming that two methylene groups should be located adjacent to a double bond substituted with three methyl groups. Taking into consideration two structural units [I] and [II] in addition to the location of a chlorine atom at the C-3 methine, we proposed the most suitable structure 1 for virantmycin.

The validity of the structure was also confirmed by its chemical reactions. The treatment of 1 with Zn dust in AcOH (or AcONa in AcOH) afforded the dechloro acetoxyl compound 3 [mp. 62°C, $[\alpha]_D^{18}$ -0.8° (c 1, $CHCl_3$), $C_{21}H_{29}NO_5$ (M^+ m/z 375), δ_H 2.03 (3-acetoxyl methyl) and δ_H 5.23 (C-3 methine t, J=4.5 Hz)]. $LiAlH_4$ reduction of 1 afforded the compound 4 [mp. 68°C $[\alpha]_D^{18}$ +1.4° (c 1, $CHCl_3$), $C_{19}H_{27}NO_2$ (M^+ m/z 301)] characterized with an azirizine ring formed between 1 and 3-positions (δ_H 2.80). Ozonolysis of 1 in $CHCl_3$ (-12°C) gave a 5-membered ring



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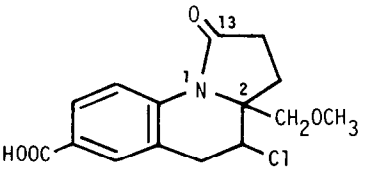

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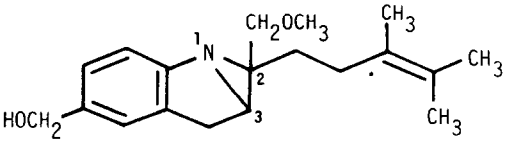

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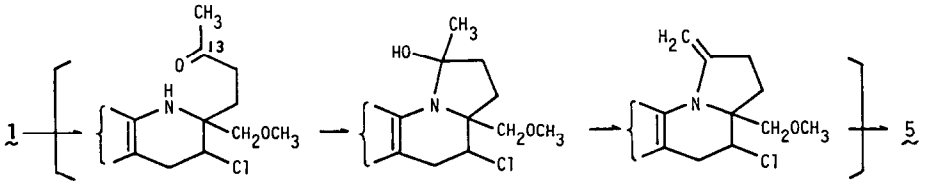
lactam, 5 [mp. 188°C, $C_{15}H_{16}NO_4Cl$, M^+ m/z 309, λ_{max}^{EtOH} 272.5 nm (ε, 9800), IR $\nu_{max}^{CHCl_3}$ 1700 (CO), 1687 cm^{-1} (COOH), δ_C 175.4 (lactam CO)]. Unusual formation of 5-membered ring lactam can be speculated to proceed via an enamine intermediate. The structure of 5 was evidenced by the ^1H-nmr spectral data (C-3, δ_H 4.20 dd, J=3.5, 5.2 Hz, C-4, δ_H 3.18 and 3.25, C-17, δ_H 3.44 and 3.76 d, J=5.0 Hz) and the LSPD.



The ^{13}C chemical shift assignment of compounds 1, 2, 4 and 5 by means of selective $^{13}C\{^1H\}$ decoupling and LSPD experiments is shown in Table 1.

Determination of the absolute configuration of the C-2 and C-3 in 1 is now in progress by X-ray crystallography of 2.

Table 1. ^{13}C Chemical shifts of compounds 1, 2, 4 and 5

Carbon No.	1 (Mult.)*	2	4	5**
-NH-				
2	58.0 (s)	57.9	49.8	66.6
3	56.2 (d)	56.4[b]	50.1	61.2
4	33.5 (t)	33.4[b]	30.2	35.8
5	132.4 (d)	131.6	122.6	131.3
6	117.7 (s)	118.6	138.0	126.8
7	130.4 (d)	129.6	126.2	129.3
8	113.5 (d)	113.5	120.7	119.8
9	147.2 (s)	146.5	150.1	125.5
10	116.0 (s)	115.9[b]	139.5	139.3
11	33.5 (t)	33.6[b]	30.2	28.4
12	27.8 (t)	27.8	33.9	32.4
13	124.8 (s)	124.6	124.2	175.4
14	126.5 (s)	126.5	127.1	
15	18.8 (q)[a]	19.9[a]	20.0[a]	
16	171.9 (s)	167.2	64.5	167.9
17	74.1 (t)	73.9	66.4	72.3
17-OCH_3	59.4 (q)	73.9[a]	58.8[a]	60.3
18	18.4 (q)	18.4[a]	18.3[a]	
19	20.6 (q)[a]	20.6[a]	20.6[a]	
OCH_3		51.5		

*Multiplicity; s=singlet, d=doublet, t=triplet, q=quartet.
**, Compound, 5 was measured in DMSO-d_6.
ab; These assignments within any vertical column may be reversed.

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References and Notes

1) S. Ōmura, A. Nakagawa, H. Hashimoto, R. Ōiwa, Y. Iwai, A. Hirano, N. Shibukawa and Y. Kojima. J. Antibiotics 33(11), 1395 (1980).

2) ^{1}H and ^{13}C-nmr spectra were measured on JNM-PS-100 and JNM-PFT-100 spectrometers, respectively, with $CDCl_3$ as solvent and TMS as internal standard.

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