

STRUCTURE OF PYRROLOMYCIN B,
A CHLORINATED NITRO-PYRROLE
ANTIBIOTIC

Sir:

The two new chlorinated nitro-pyrrole antibiotics, pyrrolomycin A and B, were isolated from the culture broth of *Streptomyces* strain SF-2080.¹⁾

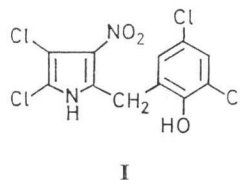
In this communication, we wish to describe the structure of pyrrolomycin B examined by spectroscopic means and X-ray crystallographic analysis, its complete structure being established by the latter method.

Pyrrolomycin B (I), yellow thin plates, mp. 222~225°C, had a molecular formula C₁₁H₆N₂O₃Cl₄ which was derived from the elemental analysis and the high resolution mass spectrum (M⁺ *m/z* 353.9104; Calcd. 353.9132). The IR spectrum of I suggested it to be an aromatic compound with an -NH- function (3200 cm⁻¹), a nitro group (1575, 1350 cm⁻¹) and a hydroxyl group (3500 cm⁻¹). The presence of an aromatic nitro group was also shown by the mass fragment ions at *m/z* 337 (M⁺-OH), 324 (M⁺-NO) and 308 (M⁺-NO₂).²⁾ The PMR spectrum of I in acetone-d₆ showed the presence of one methylene group probably sandwiched between two aromatic systems (δ 4.42, 2H, s), and two aromatic protons at *meta* positions [δ 7.32, 7.16 (1H each, both d, *J*=2.5 Hz)] which might be located on a benzene ring judging from their chemical shifts. Therefore, the other aromatic system, consisting of the remaining C₄NH unit, might correspond to a fully substituted pyrrole ring. Furthermore, a broad proton signal which appeared at δ 8.3~6.8 as a swell of the base line and disappeared by addition of D₂O in the PMR spectrum of I, could be attributed to the -NH- group of the pyrrole ring.

On standing in pyridine and acetic anhydride overnight, pyrrolomycin B yielded a mono-*O*-acetyl derivative (II), almost colorless needles, mp. 180~181°C (benzene), M⁺ at *m/z* 396. Its IR spectrum had absorption bands due to an -NH- function (3250 cm⁻¹), an acetoxy (1735, 1220 cm⁻¹) and a nitro group (1570, 1360 cm⁻¹), while the absorption band near 3500 cm⁻¹ of I attributable to a hydroxyl group was absent in the IR spectrum of II.

From these findings, pyrrolomycin B was believed to have a pyrrole ring and a benzene ring which were linked together by a methylene group,

Fig. 1. Chemical structure of pyrrolomycin B.



and to be substituted with four chlorine, one nitro and one hydroxyl groups on the two aromatic nuclei so that two protons might be located at *meta* positions to each other on the benzene ring. In addition, the nitro group is probably adjacent to the methylene group substituent because of the existence of the intense mass fragment ion peak [M⁺-OH]²⁾ as described above.

The complete structure of pyrrolomycin B has been established as I (Fig. 1) by X-ray crystallographic analysis.

Single crystals of I, suitable for X-ray analysis, were obtained as yellow thin plates by recrystallization from methanol.

Crystal data: Pyrrolomycin B, C₁₁H₆N₂O₃Cl₄, MW=355.8, monoclinic, space group P2₁, *a*=11.305 (2), *b*=13.470 (3), *c*=4.538 (1) Å, β =92.03 (2)°, *Z*=2, *U*=690.6 Å³, *D*_x=1.71 g·cm⁻³.

The intensity data were measured on a Philips PW 1100 four-circle diffractometer with graphite-monochromated CuK α radiation using the θ - 2θ scan method with a scan speed of 2° min⁻¹ in θ . Out of the total of 1,535 independent reflections within a 2θ level of 156°, 1,352 reflections having intensities above 2 σ (I) level were used for the structure determination and refinement. During the data collection, the intensities of three standard reflections, chosen in different regions of reciprocal space and measured every 120 minutes, remained almost constant throughout. The intensities were corrected for Lorentz-polarization factors and were placed on an absolute scale by WILSON's method. No absorption correction was made. The size of the crystal used for the data collection was about 0.3×0.15×0.05 mm.

The structure was determined by the direct method using the MULTAN program.³⁾ The E map revealed 13 of the 20 non-hydrogen atoms, including four chlorine atoms. The remaining seven atoms were located by successive use of difference Fourier and least-squares methods. After block-diagonal least-squares refinement

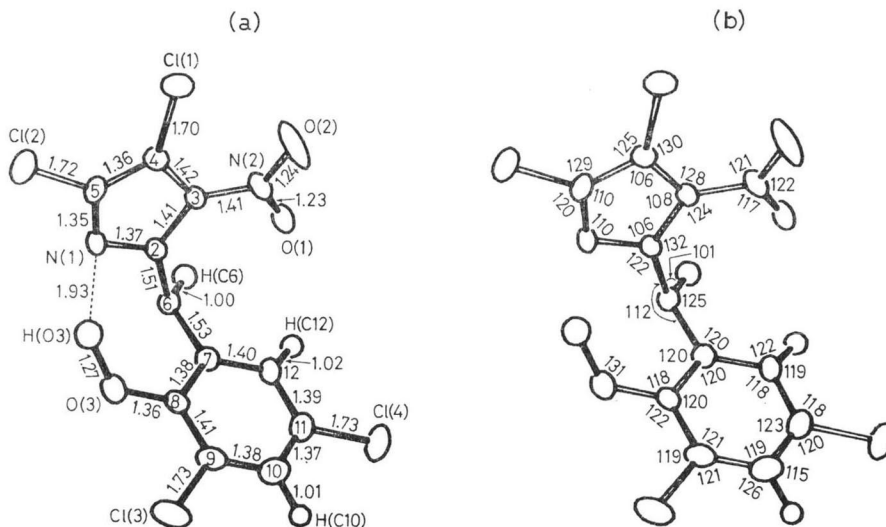
with anisotropic temperature factors and the correction terms for anomalous dispersion of C, O, N and Cl atoms, four hydrogen positions were located on the difference electron density maps. Unfortunately, however, the remaining two hydrogen atoms could not be found at all. The final R factor was 0.079, based on the 1,352 observed reflections, including anisotropic thermal parameters for the non-hydrogen atoms and isotropic ones for the hydrogen atoms. The final atomic coordinates are listed in Table 1.

Thus, the chemical structure of pyrrolomycin B has been determined to be 2-(3,5-dichloro-2-hydroxybenzyl)-4,5-dichloro-3-nitropyrrole as shown in Fig. 1. A perspective drawing of the molecule produced by the ORTEP program⁴⁾ is shown in Fig. 2, which also presents bond lengths and angles. The standard deviations are estimated to be about 0.01 Å for bonds between non-hydrogen atoms, 0.08 Å for C-H bonds, 0.6° for angles among non-hydrogen atoms and 5° for C-C-H and C-O-H angles. These bond lengths and angles are consistent with the chemical structure. The hydroxyl group O(3)H forms an intramolecular hydrogen bond to the N(1) of the pyrrole ring as is seen in Fig. 2 [H(O3)—N(1), 1.93 Å; O(3)—N(1), 2.961(8) Å]; this bond constrains the conformation around the C—CH₂—C axis, so that **I** exhibits chirality in the crystal in the space group P2₁. The following two intermolecular hydrogen bonds link the molecules in the

Table 1. The final atomic coordinates (the estimated standard deviations in parentheses) for non-hydrogen atoms ($\times 10^4$) and hydrogen atoms ($\times 10^3$).

	x	y	z
N (1)	-620 (5)	4675 (0)	2916 (14)
C (2)	-126 (5)	3838 (5)	4138 (15)
C (3)	-755 (6)	3032 (5)	2878 (14)
C (4)	-1639 (6)	3422 (6)	885 (15)
C (5)	-1508 (6)	4425 (6)	976 (18)
C (6)	899 (6)	3888 (6)	6354 (15)
C (7)	2078 (6)	3666 (5)	4932 (15)
C (8)	2545 (6)	4348 (6)	3034 (15)
C (9)	3645 (6)	4168 (7)	1789 (16)
C (10)	4281 (7)	3323 (8)	2512 (18)
C (11)	3814 (7)	2666 (7)	4475 (18)
C (12)	2715 (6)	2804 (6)	5682 (16)
N (2)	-518 (6)	2033 (5)	3574 (14)
O (1)	182 (7)	1814 (4)	5601 (17)
O (2)	-1010 (11)	1393 (5)	1987 (16)
O (3)	1913 (5)	5187 (4)	2435 (12)
Cl(1)	-2682 (2)	2816 (2)	-1201 (5)
Cl(2)	-2312 (2)	5327 (2)	-856 (6)
Cl(3)	4193 (2)	5041 (2)	-617 (5)
Cl(4)	4618 (2)	1632 (2)	5568 (7)
H(C10)	513 (6)	319 (6)	202 (14)
H(O3)	82 (10)	531 (12)	176 (23)
H(C12)	246 (6)	233 (6)	728 (15)
H(C6)	57 (8)	351 (8)	804 (16)

Fig. 2. Stereoscopic drawing of the molecule showing (a) bond lengths (Å) and (b) bond angles (°). The broken line in (a) indicates an intramolecular hydrogen bond.



crystal: N(1) (H) at x, y, z —O(1) at $-x, 1/2+y, 1-z, 2.996(6) \text{ \AA}$; O (2) at x, y, z —O (3) at $-x, -1/2+y, -z, 2.750(10) \text{ \AA}$ [O(2)—H(O3), 2.26 \AA]. The two aromatic rings, the pyrrole ring and the benzene ring, are both, of course, very planar with an average deviation of $\pm 0.009 \text{ \AA}$ and $\pm 0.036 \text{ \AA}$, respectively, and the dihedral angle between the two rings is 72.2° . Although the positions of two hydrogen atoms of the pyrrole NH and one of the benzyl methylene CH_2 group could not unfortunately be found in the present X-ray analysis, their existence proved to be unambiguous as judged by the spectroscopic data described above, and by the bond lengths and angles, planarity, and presence of several intra- and intermolecular hydrogen bonds clarified by this X-ray analysis.

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