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THE CRYSTAL AND MOLECULAR STRUCTURE OF 7-CON-O-METHYLNOGAROL

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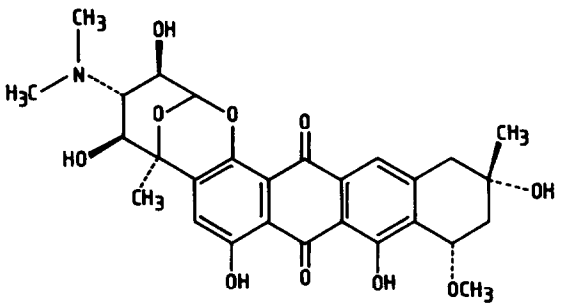
ABSTRACT: A crystal structure analysis for 7-con-O-methylnogarol free base, a promising antitumor antibiotic of the nogalamycin family, has been carried out with low temperature X-ray diffraction data. The relative configuration of the anthracycline moiety is C7(S) and C9(S); the sugar moiety is an α-D-3,6-dideoxy-3-dimethylaminoglucose.

The anthracycline 7-con-O-methylnogarol (1), 7-con-OMeN, an analog of the antitumor antibiotic nogalamycin, has been found to be superior to its parent compound in tests of its antitumor activity thus far conducted. It was



7-CON-OMeN

highly active against six mouse tumor systems and marginally active against a seventh, Table I (2). Activity was substantially greater than the parent compound in most tumor systems (2). Its activity against mouse leukemias was somewhat superior to that of adriamycin, the presently most widely used antitumor antibiotic, while it was less than one-fifteenth as potent as adriamycin in inducing cardiotoxicity in rabbits (3). Consequently, 7-con-OMeN can be regarded as a potentially important chemotherapeutic agent.

We report the preliminary results of a crystal structure determination for 7-con-OMeN in the free base form and, thereby, the complete relative

Table I[a] 7-Con-OMeN Antitumor Activity

Tumor System	Site	Dose (mg/kg/d)	% ILS
P388	IP	12.5	197
L1210	IP	12.5	140
Colon 26	IP	25	106
Lewis Lung	IV	12.5	28
B16	IP	12.5	109
			T/C[b]
Colon 38	SC	25	21
CD8F1 Mammary	SC	25	1

[a]Doses were usually administered on the first day after tumor injection and daily for 9 days.

[b]Ratio of median tumor weights of treated and control groups multiplied by 100.

stereochemistry of the antibiotic.

Crystals of 7-con-OMeN were obtained by slow evaporation of an ethanol solution. They were found to display space-group symmetry C2 with two molecules of the anthracycline and a molecule of ethanol per asymmetric unit: $(C_{28}H_{31}NO_{10})_2 \cdot C_2H_5OH$. Lattice parameters for a crystal at *ca.* 120 K are: $\underline{a}$ = 25.274(4), $\underline{b}$ = 8.927(2), $\underline{c}$ = 26.310(7) Å and β = 120.37(2) degrees. All crystallographic measurements were carried out with the cooled crystal and with monochromatized Mo K_α radiation. Intensities, measured in an ω-scan mode, were corrected for Lorentz and polarization effects.

The initial structural model was determined by application of vector search techniques (4) and a translation function (5) coupled with tangent refinement (6). At present, the refinement by block diagonal least squares techniques (anisotropic temperature factors for nonhydrogen atoms) stands at R = 0.072 with 3647 contributing data. Not all hydrogen atoms have been located.

The conformations of the two independent molecules are very similar; the molecular conformation is illustrated in stereoscopic projection (7) below for one molecule (the applicable atom labeling scheme is also illustrated). The A-rings (the nonaromatic ring of the anthracycline moiety) show the same conformation as that reported for crystalline daunomycin hydrochlorides (8-10) and for carminomycin (11).

The absolute stereochemistry is not determinable from the present crystallographic study because of lack of a suitable anomalous scattering atom but

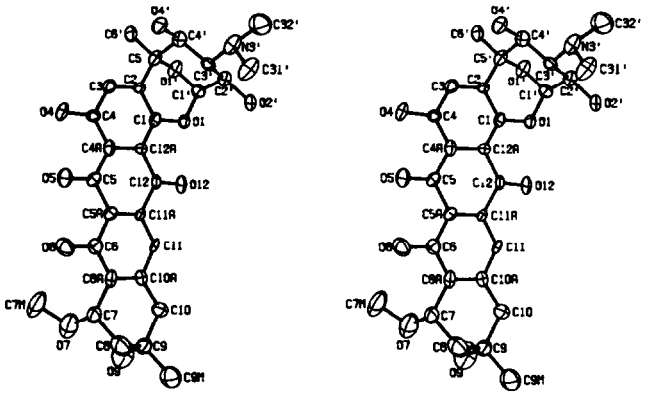


Figure 1. A steresocopic representation of the conformation of one of the two independent molecules of 7-con-OMeN in the crystalline free base. Atom labels follow the convention for the anthracyclines. Hydrogen atoms have not been included.

the identity of the conformation and relative configuration of the A-ring in the enantiomer presented in Figure 1 and that of daunomycin suggest that the absolute stereochemistry is as depicted. In this configuration, the stereochemistry is C7(S) and C9(S) in the A-ring. The sugar moiety fused to the D-ring is an α-D-3,6-dideoxy-3-dimethylaminoglucose. There is, however, evidence derived from circular dichroism (12) that C7 is R, thus indicating the mirror image for the absolute configuration of 7-con-OMeN. Further crystallographic studies to resolve this question are being pursued.

Two intramolecular hydrogen bonds are apparent from the orientation of substituents in both 7-con-OMeN molecules. One, that between the hydroxyl group at C9 and the oxygen atom of the methoxy group at C7, appears to be a common feature in the conformation of the anthracyclines (8-11). The other is between the hydroxyl at C4' of the sugar and the neighboring N atom of the dimethylamino moiety. Further analysis of hydrogen bonding will be presented in a subsequent report after refinement has been completed.

The ethanol of solvation molecule is disordered about a crystallographic two-fold symmetry axis.

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