X-Ray Structure of Ro 21-6150, a Polyether Antibiotic Related to *Dianemycin*

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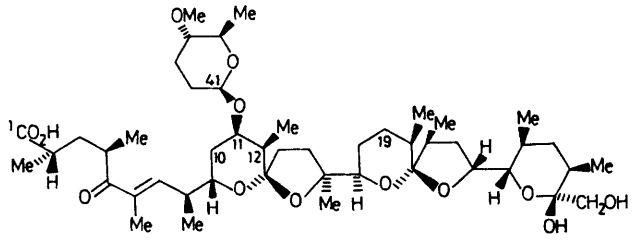
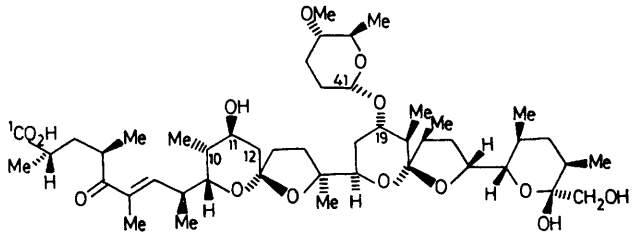
Summary The constitution and absolute configuration of the polyether antibiotic Ro 21-6150 have been established by *X*-ray crystallographic analysis of the silver salt ($C_{47}H_{77}O_{13}Ag$).

POLYETHER antibiotics are monocarboxylic acid ionophores which render cations lipid-soluble and so enable them to pass through membranes.[1] The following polyethers have been reported earlier: lasalocid (X-537A),

nigericin (X-464),[3] X-206,[4] grisorixin,[5] monensin,[6] salinomycin,[7] septamycin,[8] A204A,[9] and most recently lysocellin.[10] As well as being active *in vitro* against gram-positive bacteria and mycobacteria, several polyethers have also been reported[11] to be effective anticoccidial agents. We have now isolated† a novel polyether antibiotic, Ro 21-6150 and its structure (I) has been determined by *X*-ray analysis of the silver salt.



(I)



(II)

Ro 21-6150 was isolated from a culture of *Streptomyces hygroscopicus* strain X-14563, as a sodium salt, m.p. 235 °C, $[\alpha]_D$ + 95° (*c* 1, $CHCl_3$), ν_{max} ($CHCl_3$) 1560 (CO_2^-) and 1650 cm^{-1} (C=C–C=O); λ_{max} (EtOH) 235 nm (ϵ 14,000). The presence in the n.m.r. spectrum ($CDCl_3$) of a C=CMe singlet at δ 1·88 and peaks at δ 2·58 (1H, m, C=CHC*H*) and 6·65 (1H, d, C=C*H*CH, *J* 10 Hz) indicated the same chromophore for (I) as that reported earlier for dianemycin (II).[12] A molecular ion at *m/e* 872 for the sodium salt of (I) however suggested that one of the oxygen atoms present in (II; $C_{47}H_{78}O_{14}$) was missing in (I, $C_{47}H_{78}O_{13}$).

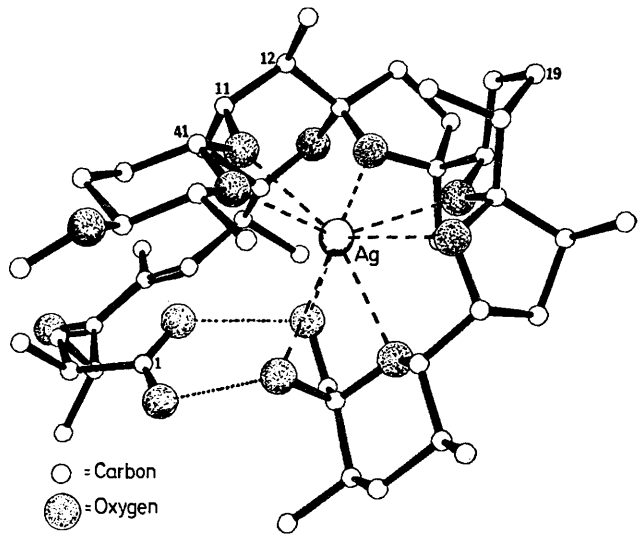
The similarity of (I) and (II) was confirmed by *X*-ray analysis of the silver salt of Ro 21-6150 ($C_{47}H_{77}O_{13}Ag$), m.p. 166—168°C, $[\alpha]_D$ + 91° (*c* 0·6, $CHCl_3$). The conformation of the silver salt in the crystalline form is illustrated in the Figure.

The differences in structure between Ro 21-6150 and dianemycin are at C-10, -11, -12, -19, and -41. The C-10 Me in (I) is absent in (II) but the latter has a methyl group at C-12 which is not found in (I). The sugar-like unit (2,3,6-trideoxy-4-*O*-methyl-D-erythrohexapyranose) is attached as a β-glycoside (C-41) in (I) to the oxygen at C-11, whereas in (II) the same unit is linked as an α-glycoside to the oxygen at C-19, which is the missing oxygen atom in (I).

There is a similar relationship between septamycin[8] and antibiotic A204A[9] to that between (I) and (II).

Crystals of the silver salt of Ro 21-6150 ($C_{47}H_{77}O_{13}Ag$, *M* 958·0) are orthorhombic, space group $P2_12_12_1$, with a = 9·541(7), b = 18·084(10), c = 28·183(20) Å, and Z = 4. The intensity data were measured on a Hilger-Watts four-circle diffractometer (θ–2θ scans, Ni-filtered Cu-K_α radiation). Of the 5527 accessible reflections with $\theta < 76°$, 4863 were considered observed [$I > 2{\cdot}5\sigma(I)$]. The data were corrected for absorption (μ 39·0 cm^{-1}).

The structure was solved by the heavy-atom method. The absolute stereochemistry was established by refining both antipodes (Ag anisotropic, C,O isotropic). The absolute configuration was taken as the one corresponding to the lower weighted *R* value (0·0948 and 0·1242). The final refinement was done by block-diagonal least-squares with the matrix partitioned into five blocks. The hydrogen atoms were included at their calculated positions but were not refined. The final *R* value is 0·044 (hydrogens isotropic, heavier atoms anisotropic).



FIGURE

The co-ordination about the silver ion is irregular. There are eight Ag–O contacts which are less than 3·01 Å. The two oxygen atoms attached to C-41 are both co-ordinated to the silver ion in (I) whereas in (II), none of the three oxygen atoms of the sugar-like unit are involved in the co-ordination of the metal ion. The tertiary hydroxy-group of the terminal ring is hydrogen-bonded (2·65 Å) to one of the oxygen atoms of the carboxylate group and the primary hydroxy-group is hydrogen bonded (2·59 Å) to the other carboxylate oxygen atom. The carboxylate does not bond directly to the cation.

Ro 21-6150 is the seventh of the polyether antibiotics shown to contain a carbon backbone of 30 atoms. This in turn indicates that the aglycone part of the molecule is biosynthesized from a 15-unit polyketide precursor in contrast to the 12-unit precursor established for lasalocid.[13]

† The fermentation production, isolation, and biological properties of Ro 21–6150 will be presented elsewhere.

In addition, Ro 21-6150 represents the fourth polyether shown to contain 2,3,6-trideoxy-4-*O*-methyl-D-erythro-hexapyranose. As in septamycin,[8] this sugar-like unit is attached as a β-glycoside in Ro 21-6150 whereas in antibiotic A204A[9] and dianemycin[12] the linkage is α-glycosidic.

Following completion of these studies, we obtained a sample of antibiotic A-130-A (Shionogi & Co., Ltd.) and found it identical to Ro-6150 by i.r. and n.m.r. criteria.

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