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THE STRUCTURE OF ANHYDRO ERYTHROMYCIN A CARBONATE

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Among the semisynthetic derivatives of an important antibiotic, erythromycin A, its cyclic carbonate exhibits the unique property of being more active against bacteria than the parent antibiotic[1,2]. In the hypothetical structure of the compound postulated by Eli Lilly group, the substitution by carbonate moiety occurred at 9 and 11 carbon atoms of the macrolide ring[1].

We have elucidated the molecular and crystal structure of N-methyl iodide derivative of erythromycin A carbonate. The results obtained indicate that the carbonate moiety is combined with C_{11} and C_{12} (I). The compound is the 8,9-anhydro derivative of the 6,9-hemiketal form of erythromycin A cyclic carbonate N-methyl iodide. The 8,9-anhydro form of the compound is the result of dehydration which occurred during the iodo-methylation process[3,4].

Crystals of the compound suitable to X-ray work were grown from methanol-ethyl acetate-water in the form of colourless prisms elongated in the b-axis direction. Preliminary crystallographic investigations were performed on a precession camera.

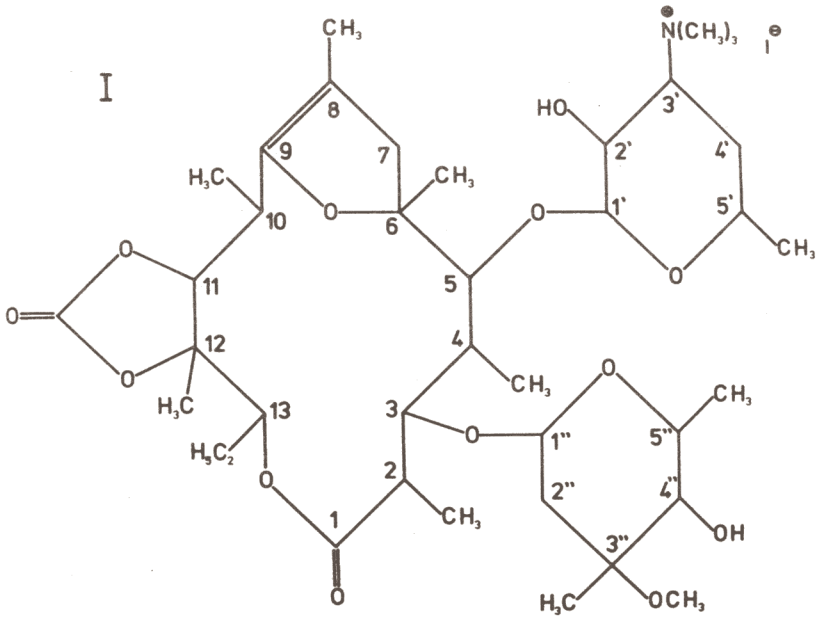
Crystal data: anhydro erythromycin A carbonate N-methyl iodide $C_{39}H_{66}O_{13}NI \cdot CH_3OH$; Mol.wt.=900; m.p. 226-228°C. Monoclinic, Space Group $P2_1$; a=14.35, b=14.38, c=10.91 Å, β=96.10°, V=2241 Å^3, D_m=1.36, D_x=1.39 g/cm^3, Z=2, F_{000}=978.

A crystal with dimensions 0.4 x 1.0 x 0.5 mm was used to collect intensities on a Hilger-Watts four circle fully automatic diffractometer with graphite monochromated CuK_α radiation. Of the 2388 reflections which were measured by the $\theta - 2\theta$ scan technique, 2194 had measurable intensities by the criterion $I > 3\sigma(I)$[5]. During data collection routine repetition of one standard reflection every hour showed that the crystal was stable as the maximum intensity variation was 0.9% from its mean value. Lorentz and polarization factors were applied to give relative structure factors. No absorption corrections were made. Throughout the computations NRC crystallographic programmes system adapted on an ICL 4-70 was used[6]. The structure was solved by the heavy-atom method. The position of the iodine atom was found from the Harker section $P(u,\frac{1}{2},w)$ of the Patterson function to be (x=0.049, y=0.250 free choice, z=0.116). A mirror plane of symmetry was introduced into the first electron density distribution. Several attempts to destroy the pseudo-symmetry by selecting reasonable atomic positions using a bond scan, structure factor and electron density calculation allowed to choose atoms from only one enantiomer. Having all atoms of the molecule, two cycles of least squares block diagonal isotropic approximation were made giving R=17.9%. A difference map at this stage was performed and the methanol molecule was located. Two more cycles of block diagonal least squares isotropic approximation were computed and R index reduced to R=16%. The next, 4 cycles of block diagonal anisotropic approximation were calculated giving R= 7.5% for 1529 reflections. Based on the known absolute configuration of cladinose and desosamine[7,8], the structure is as shown in (II) which illustrates the b-axis projection of the molecule. The Y direction points upwards.

The absolute configurations of the asymmetric centres are consistent with those established for erythromycin A[9].

The details of this work and the crystal structure of the examined compound will be published elsewhere.

I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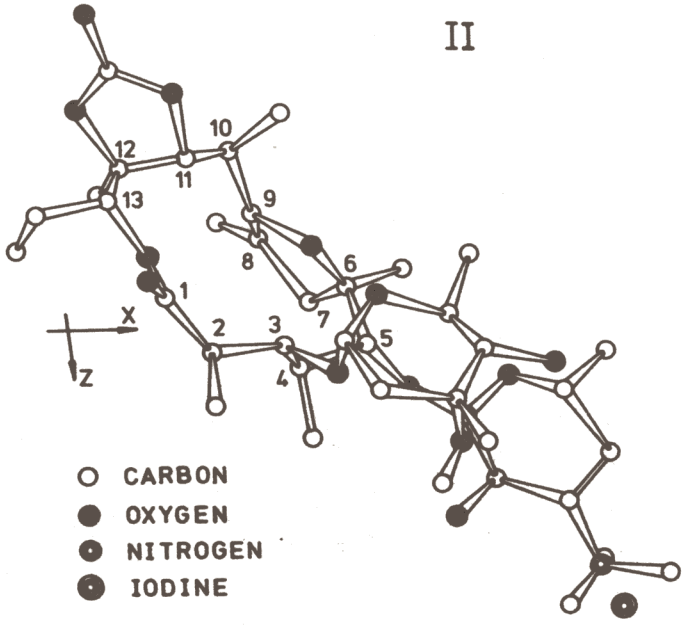
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CARBON
OXYGEN
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IODINE

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