# The Structure of Polyetherin A

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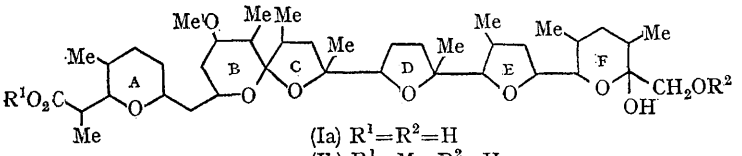
POLYETHERIN A, m.p. 183—185°, $[\alpha]_D$ +36·2° ($CHCl_3$), was isolated earlier[1] as a major antibiotic from cultures of *Streptomyces hygroscopicus* E-749. This paper describes the assignment of structure (Ia) to the antibiotic.

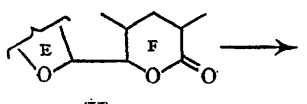
Polyetherin A (Ia), $C_{40}H_{68}O_{11}$ (*M*, 724),† has been characterised[1] as a polycyclic polyether having vicinal primary and tertiary hydroxy-groups a carboxy-group, and a methoxy-group. The remaining six oxygen atoms were assumed to exist as ether functions. The methyl ester (Ib),‡ $M^+$ 738, reacted with 1 mol. of periodate, giving a δ-lactone (II) and formaldehyde. Saponification of (II) followed by methylation and

† The formula was previously[1] represented as $C_{42-43}H_{72-74}O_{12}$.

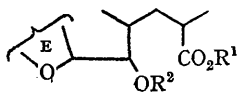
‡ The compounds, which were given molecular formulae, gave satisfactory elemental analyses. The other compounds were amorphous and their homogeneities were checked by t.l.c. and spectra (mass, i.r., and n.m.r.). I.r. spectra were taken in $CHCl_3$ and n.m.r. spectra, unless otherwise stated, were recorded in $CDCl_3$ at 60 Mc./sec.



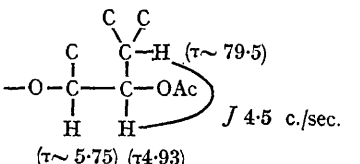
(Ia) $R^1=R^2=H$
(Ib) $R^1=Me$, $R^2=H$
(Ic) $R^1=Me$, $R^2=Ac$



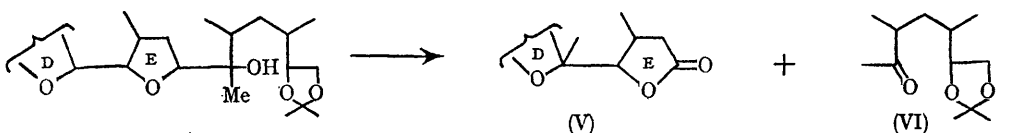
(II)



(IIIa) $R^1=R^2=H$
(IIIb) $R^1=Me$, $R^2=Ac$

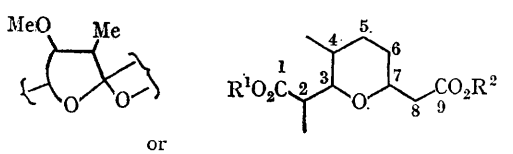


(IIIb')

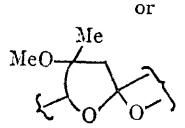


(IV) (V) (VI)

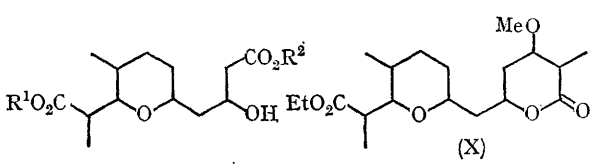
acetylation yielded an acetoxy-dimethyl ester (IIIb). The n.m.r. spin-decoupling study (100 Mc./sec. in $C_6D_6$) inferred that the environment of the acetoxy-group is as shown in (IIIb').



(VIIIa) $R^1=R^2=Me$
(b) $R^1=Et$, $R^2=Me$
(c) $R^1=R^2=H$



(VII)



(IXa) $R^1=Et$, $R^2=Me$
(b) $R^1=R^2=H$

(X)

On the other hand, dehydration of acetylpolyetherin A methyl ester (Ic)[1] with thionyl chloride afforded an anhydride, which has a vinylic methyl ($\tau$ 7·95, 3H, s) and an acetoxymethyl ($\tau$ 5·45, 2H, bs) group but no olefinic proton.

Reduction of (Ib) with sodium borohydride followed by treatment with acetone and toluene-*p*-sulphonic acid yielded a hydroxy-acetonide, which was oxidised by dimethyl sulphoxide–acetic anhydride[2] to give an acetonide-ketone. Grignard reaction of the ketone with methylmagnesium iodide afforded a methylcarbinol (IV), with simultaneous conversion of the methoxycarbonyl group into dimethylcarbinol. Oxidation of (IV) with chromic acid in aqueous acetic acid gave a $\gamma$-lactone (V), *m/e* 576 ($M^+ - H_2O$), $\nu_{max}$ 1775 cm.$^{-1}$, and a methyl ketone (VI), $M^+$ 214, $\nu_{max}$ 1707 cm.$^{-1}$. The n.m.r. spectrum of (V) showed a doublet signal at $\tau$ 5·68 (1H, $J$ 5 c./sec.) as a proton on the carbon bearing the oxygen atom in the lactone ring, and the mass spectrum indicated that the lactone ring consists of $C_5H_7O_2$.

Treatment of the $\delta$-lactone (II) with sulphuric acid in aqueous methanol afforded a product in which the methoxy-group was missing and the n.m.r. spectrum ($C_6D_6$) showed an olefinic proton ($\tau$ 4·33, $W_{\frac{1}{2}}$ 0·8 c./sec.) and a vinylic methyl ($\tau$ 8·33) as well as two methoxycarbonyls ($\tau$ 6·32 and 6·35) indicating methanolysis of the lactone. Acetylation followed by hydroxylation with osmium tetroxide and glycol cleavage with lead tetra-acetate gave a methyl oxo-aldehyde, ($\tau$ 7·60,

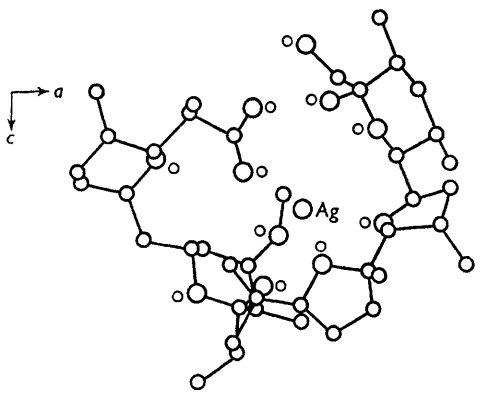
3H, s and $\tau$ 0·12, 1H, m), with the preservation of the two methoxycarbonyls and the acetoxy-group. The smooth formation of the olefin with acid suggested the presence of a spiro-acetal (VII) in polyetherin A.

Oxidation of the methyl ester-lactone (II) with chromic acid afforded, after methylation, a dimethyl ester (VIIIa), $M^+$ 258, which on saponification gave a diacid (VIIIc), $C_{11}H_{18}O_5$, m.p. 188—190°, $[\alpha]_D$ −32·2° (EtOH). The results of the n.m.r. spin-decoupling (100 Mc./sec. in $C_6D_6$) of the dimethyl ester (VIIIa) were in good agreement with the assigned structure. The oxidation of the corresponding ethyl ester-lactone afforded a methyl ethyl diester (VIIIb) and the mass spectrum (*m/e* 272, 199, and 171) confirmed that the carboxy-group originally existed on polyetherin A. Further examination of the oxidation products yielded two additional products. One, isolated from methylation of an acidic fraction, was identified as having the structure (IXa), and on hydrolysis it gave the free acid (IXb), $C_{13}H_{22}O_6$, m.p. 158—161°. The other product was neutral (X), $C_{19}H_{32}O_6$, m.p. 156—159°.

The n.m.r. spectrum of the aforementioned $\gamma$-lactone (V) showed the presence of five secondary methyl ($\tau$ 9·33—8·92) and four tertiary methyl [$\tau$ 8·85 (6H), 8·82, and 8·77] groups. Of these, one secondary and two tertiary methyl groups can be now assigned for rings C and D. The result, coupled with the mass-spectral data, suggested that rings C and D are tetrahydrofuran rings having a tertiary and a secondary methyl, and a tertiary methyl, respectively.

The complete structure of polyetherin A has been determined by three-dimensional *X*-ray diffraction studies of its silver salt, which was crystallised from aqueous ethanol. There are four molecules in the unit cell, $a = 23{\cdot}762$, $b = 14{\cdot}591$, $c = 12{\cdot}080$ Å, with space group $P2_12_12_1$.

Intensity data for approximately 2000 independent reflections ($\theta$ 24·5) were collected with a Hilger and Watts Y 290 automatic diffractometer using Mo–$K_\alpha$ radiation and the $\theta$—$2\theta$ step-scan method.




FIGURE

The structure was solved by the heavy-atom method and refined by the block-diagonal least-squares method. At the present stage of refinement, the *R* factor is 8·5%. The arrangement of atoms within the molecule as seen when viewed along the *b*-axis is shown in the Figure.§

(*Received, September 9th*, 1968; *Com.* 1217.)

§ Monensic acid has recently been described as the only example having this type of structure (A. Agrarap, J. W. Chamberlin, M. Pinkerton, and L. Steinrauf, *J. Amer. Chem. Soc.*, 1967, **89**, 5737).

[1] J. Shoji, S. Kozuki, S. Matsutani, T. Kubota, H. Nishimura, M. Mayama, K. Motokawa, Y. Tanaka, N. Shimaoka, and H. Otsuka, *J. Antibiotics*, 1968, **21**, 402.
[2] J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, 1967, **89**, 2416.