A NOVEL INTRAMOLECULAR DISPLACEMENT REACTION OF 5-O-DESOSAMINYLERYTHRONOLIDE A OXIME

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We recently reported the cleavage of cladinose from erythromycin A oxime to provide 2'-acetyl-5-O-desosaminylerythronolide A acetoxime (1)[1]. In order to provide an intermediate useful for the preparation of a 2, 3-unsaturated macrolide, **1** was treated with methanesulfonyl chloride in pyridine to yield the 3-mesylate (**2**). The nmr spectrum of crude **2** revealed a methanesulfonate peak at δ 3.15. Although the low resolution mass spectrum did not give a molecular ion peak, the highest observed mass at *m/e* 656 corresponds to loss of methanesulfonic acid from **2**.

Compound **2** was heated with lithium chloride in DMF at 100°C to give a new compound (**3**, mp 148~152°C) which did not exhibit methanesulfonate or olefinic proton absorption in the nmr spectrum. The highest observed peak in the mass spectrum was again at *m/e* 656. Microanalytical data for **3** were consistent with an empirical formula of $C_{33}H_{56}N_2O_{11}$. The structure was determined by X-ray analysis carried out on the methiodide derivative (mp 163~169°C) of **3**. Heating **2** in pyridine solution also gave **3**.

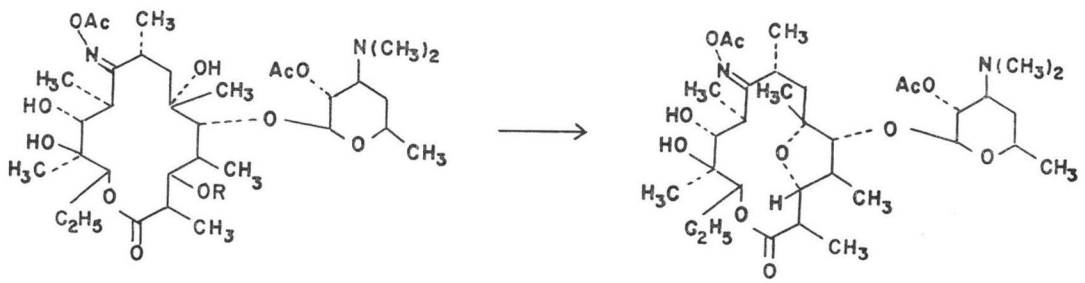
X-ray Diffraction Analysis of 3

Thin plates of **3** were obtained upon crystallization from acetone-hexane. The crystals are orthorhombic, space group $P2_12_12_1$, with a=9.40(2), b=17.63(2), c=27.81(3) Å, and $d_{calc}=1.150\ g\ cm^{-3}$ for Z=4. The diffraction data were measured on a Hilger-Watts four-circle diffractometer (θ-2θ scans, Ni-filtered Cu Kα radiation, pulse height discrimination). The size of the crystal used for data collection was 0.04×0.5×0.5 mm. Of the 4898 accessible reflections with $2\theta<140°$, 2821 had intensities which were significantly greater than background. The reflection data were corrected for absorption ($\mu=59.7\ cm^{-1}$).

The structure was solved by PATTERSON and FOURIER methods and all refinements were carried out by full-matrix least squares. In the preliminary refinement the imaginary part of the anomalous dispersion correction for iodine ($\Delta f''$) was set to zero. Structure factors were then calculated, including the contribution of $\Delta f''$, for the structure and its antipode. The configuration corresponding to the lower weighted R value (0.204 and 0.224) was taken as the absolute configuration. Since this configuration was the same (except at C-3) as that reported for erythromycin A[2], no further verification of the absolute configuration was made. In the following refinements the full anomalous dispersion correction was included. The final discrepancy index was R=0.096 for the 2821 observed reflections (iodine anisotropic, lighter atoms isotropic, no hydrogens). A stereodrawing of **3** is presented in Fig. 1.

Biological Activity

Compound **3** was inactive when tested in an *in vitro* agar diffusion disc assay against *Staphylococcus aureus* 82 and *Bacillus subtilis*

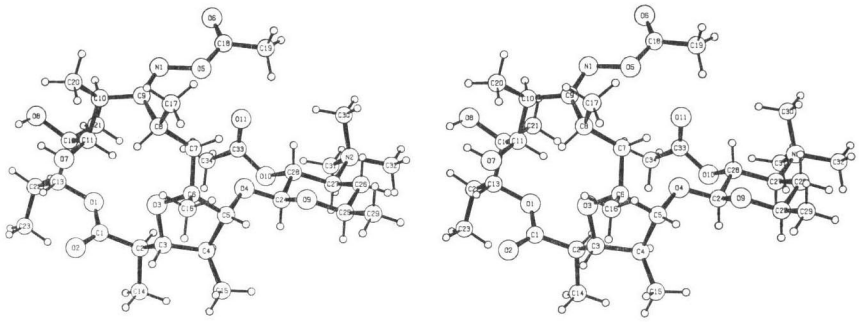


1 R = H

2 R = SO_2CH_3

3

Fig. 1. A stereoscopic view of **3** showing its conformation and absolute configuration



558 at 1 mg/ml, the maximum level tested. It was also inactive *in vivo* against *Streptococcus pyogenes* in mice at 100 mg/kg both subcutaneously and orally.

References

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