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CHEMICAL DEGRADATION AND X-RAY CRYSTAL STRUCTURE OF ROSARAMICIN

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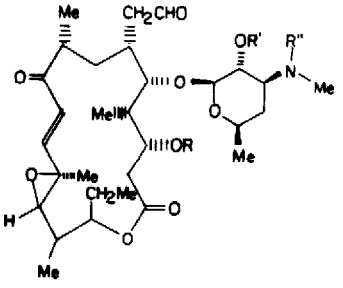
Abstract: The X-ray crystal structure of rosaramicin is reported.

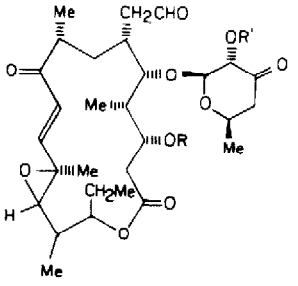
Rosaramicin (1), a novel 16-membered ring macrolide antibiotic, is produced[1] by Micromonospora rosaria. It possesses[2] high activity against gram positive, gram negative and anaerobic bacteria. The superiority of rosaramicin in its spectrum and potency of activity over erythromycin and other macrolide antibiotics has been verified in a number of clinical[3] trials. Rosaramicin is also well tolerated in man. In an earlier study,[4] the structure of rosaramicin was elucidated on the basis of spectroscopic data and a few chemical degradations. Biosynthesis of (1) has also been investigated.[5] We now describe a sequence of reactions which allow one to obtain the algycone portion of (1). In addition, we report the results of a single-crystal X-ray analysis of a derivative of (1) which confirm the previously assigned structure, define the absolute stereochemistry at all asymmetric centers and, in particular, provide details of the solid-state conformation.

A methanolic solution of rosaramicin (1) on treatment with 30% aqueous hydrogen peroxide gave the N-oxide. Upon subsequent treatment of the N-oxide with pyridine and acetic anhydride at room temperature overnight, compounds (2), (3), (4), and (5)[6] were obtained; the proportion of (2) and (3) changed if this reaction was carried out at 50°C for 1.5 h. On treatment with acetic anhydride in $CHCl_3$ solution at room temperature for 8 h, the N-oxide rearranged to (6) and (7).[7]

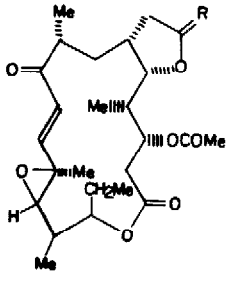
Although rosaramicin could be recyrstallized from a number of solvents, the crystals thus obtained proved to be unsuitable for single-crystal X-ray structural studies. However, suitable crystals were formed by the rosaramicin derivative, compound (8) ($C_{35}H_{59}N_3O_{10}S$, M^+ 713, $[\alpha]_D$ -29.10) which was prepared by reacting (1) with the hydrazine (9) in ethanol solution at room temperature overnight; derivative (8) possesses antibacterial activity of the same order as the parent compound (1).



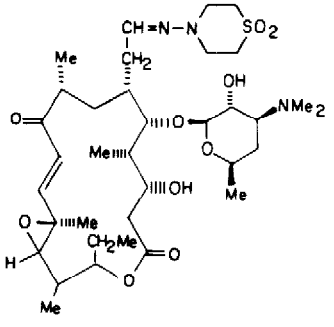
(1) R = R' = H; R'' = Me
(2) R = R' = R'' = COMe
(6) R = H; R' = R'' = COMe



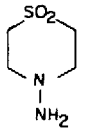
(3) R = R' = COMe
(7) R = H; R' = COMe



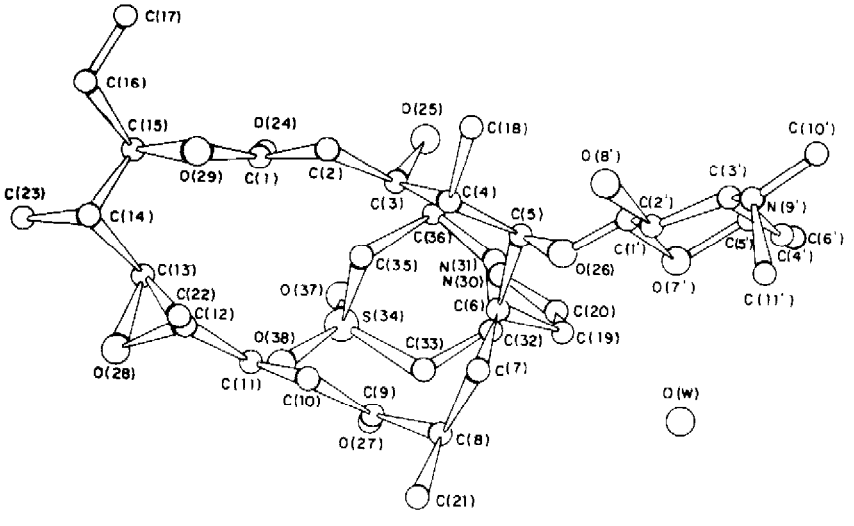
(4) R = H, OCOMe
(5) R = O



(8)



(9)



Crystals of (8), in the form of very fine needles of the monohydrate, were grown from methanol/water. The crystals belong to the orthorhombic system, space group $P2_12_12_1$, with a = 13.92(1), b = 29.23(1), c = 9.93(1) Å, Z = 4. Intensity data to $\theta = 60^\circ$ for one octant, recorded on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu-K_α radiation, λ = 1.5418 Å; θ-2θ scans), yielded only 892 statistically significant $I \geq 2\sigma(I)$ reflections out of a total of 2696 independent measurements.[8] The structure was solved by direct methods by use of MULTAN.[9] Atomic positional and thermal parameters for the non-hydrogen atoms[10] were refined by least-squares calculations to R = 0.08. The absolute configuration, represented by structure (8), was established by use of the anomalous scattering of sulfur.

A view of the solid-state conformation of (8) is shown in the Figure. The conformation of the 16-membered lactone ring is characterized by endocyclic torsion angles $\omega_{1,2}$ 149, $\omega_{2,3}$ -165, $\omega_{3,4}$ 178, $\omega_{4,5}$ -57, $\omega_{5,6}$ -73, $\omega_{6,7}$ 165, $\omega_{7,8}$ -51, $\omega_{8,9}$ -69, $\omega_{9,10}$ -171, $\omega_{10,11}$ -170, $\omega_{11,12}$ 143, $\omega_{12,13}$ -160, $\omega_{13,14}$ 101, $\omega_{14,15}$ -60, $\omega_{15,29}$ 112, $\omega_{29,1}$ 177°. Comparison of the values with the corresponding angles defining the analogous ring in demycarosyl leucomycin A_3 hydrobromide[11] (65, 177, -170, -55, -61, 156, -61, -90, 174, 180, 180, -74, 78, -84, 170, -173°) reveals that the twelve carbon chain from C(1) to C(12) has a very similar conformation in both compounds. However, geometrical constraints imposed by the presence of the epoxide at C(12)-C(13) in (8) result in significant conformational differences in the remaining regions of the rings in these two compounds. Also noteworthy is the virtually identical orientation of the C(6) substituent in both compounds, the C(6)-C(19)-C(20)-N(30) torsion angle in (8) being 6° while the corresponding C-C-C=O angle in demycarosyl leucomycin A_3 hydrobromide is 13°. Although this conformation places the bulky aldehyde derivative underneath the macrocyclic ring in (8), the similarity of the torsion angles in the C(4)...C(9) fragments of both compounds indicates that the derivative is sufficiently remote that it does not significantly perturb the macrolide ring conformation.

References

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6. Compound (2), $C_{36}H_{55}NO_{12}$ (M^+ 693) showed one N-methyl, two-$OCOCH_3$ and one -$NCOCH_3$ group. Compound (3), $C_{33}H_{48}O_{12}$ (M^+ 636) showed the presence of two-$OCOCH_3$ groups. Compound (4), $C_{27}H_{40}O_9$ (M^+ 508), mp 167°, [θ]237 (-18200), δ 5.0 (Broad quartet, H_3), 6.22 (t, H_{20}), 3.66 (dd, H_5). Compound (5), $C_{25}H_{36}O_8$ (M^+ 464), [θ]330 (-1300), δ 4.10 (dd, H_5), 5.06 (H_3)

7. Compound (6), $C_{34}H_{53}O_{11}N$ (M^+ 651), $[\theta]241$ (-14700), showed presence of $N\text{-}CH_3$, $-N\text{-}COCH_3$ and $-OCOCH_3$ groups. Compound (7), $C_{31}H_{46}O_{11}$ (M^+ 594), $[\theta]241$ (-17200), showed absence of $-N(CH_3)_2$ and presence of an $-OCOCH_3$ group.

8. For full details see e.g. R.W. Miller and A.T. McPhail, J. Chem. Soc. Perkin Trans., 2, 1527 (1979).

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10. Hydrogen atoms were included in the structure-factor calculations at their calculated positions but were not refined. Atomic co-ordinates for the non-hydrogen atoms are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

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