Tetrahedron Letters No. 43, pp 3825 - 3828, 1977. Pergamon Press. Printed in Great Britain.

MIMOSAMYCIN, A NOVEL ANTIBIOTIC PRODUCED BY STREPTOMYCES LAVENDULAE No. 314: STRUCTURE AND SYNTHESIS

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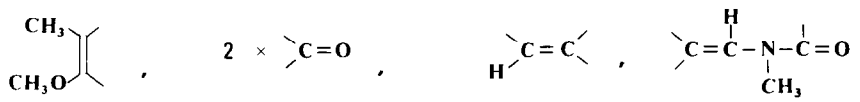
(Received in Japan 17 August 1977; received in UK for publication 5 September 1977)

Streptomyces lavendulae No. 314 produces mimosamycin, which is responsible for the antibiotic activity on mycobacteria including streptomycin-resistant strains of human tubercle bacilli, in addition to chlorocarcins A, B, and C.[1,2]

This paper deals with the structure and total synthesis of mimosamycin, mp. 219-20°, which was shown to have the molecular formula $C_{12}H_{11}NO_4$ on the basis of its elementary analysis and high resolution mass spectrum.[1]

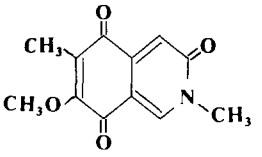
The presence of the following grouping in the molecule was indicated on the basis of spectroscopic data and these groupings account for all elements of mimosamycin.



The joining of these groupings may lead to many possible structures of a new type of heterocyclic quinone[3] but a definite conclusion could not be

reached. The complete structure was established by an X-ray crystallographic study. The crystals have strong twinning forms and were hard to separate as a single crystal. The space group is $P2_1/c$, with a=10.79, b=14.27, c=6.90 Å; β=100.3°, Z=4. Using this twinning crystal, the intensity data for 614 reflections were collected on a Rigaku automatic four circle diffractometer using Mo-K_α radiation and the θ-2θ scan technique up to 2θ=45°. Since some of the hk2 reflections are multiplied with the relevant reflections of other twinning crystal, their intensities are ambiguous. The structure was solved by Patterson and trial-and-error methods and refined to R index of 21.6%.[4]

Spectroscopic data[1] are in agreement with the structure determined as:



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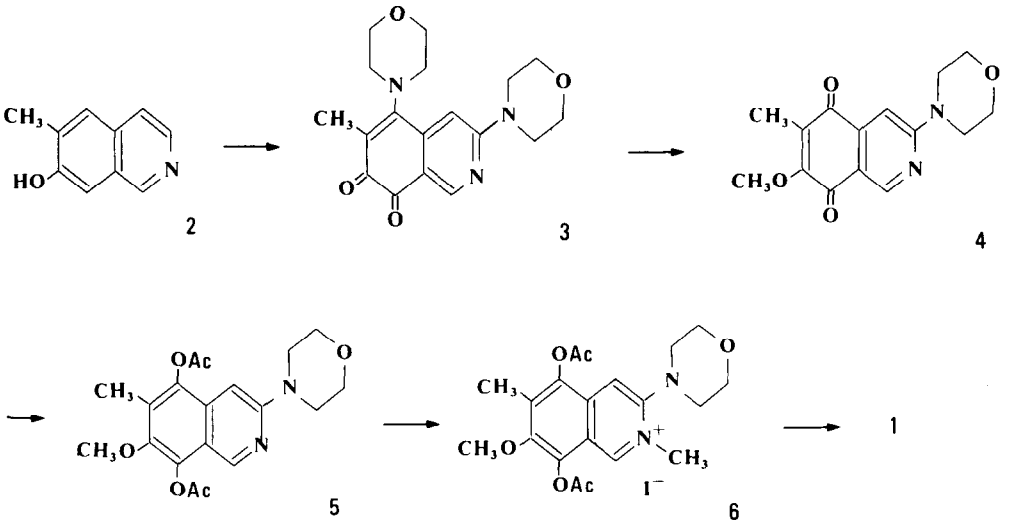
The structure of mimosamycin is that of an unusual heterocyclic quinone[3] proposed as 3,5,8-isoquinolinetrione and finally confirmed by total synthesis as indicated in Scheme 1.

Scheme 1.



An easily accessible starting material, 6-methyl-7-isoquinolinol (2), mp. 177-79°, could be prepared in 80% over-all yield in five steps from m-methoxytolualdehyde[5] by Jackson's method.[6] Oxidation of 2 with oxygen[7] in the presence of cupric acetate and morpholine gave o-quinone (3), mp. 220-21°, in 50% yield, with the expected spectral behavior: IR(KBr) 1665, 1638, 1622 cm^{-1}; UV λ_{max}^{EtOH} 245, 317, 427 nm (log ε 4.33, 3.98, 4.19); NMR (δ , $CDCl_3$) 2.10 (s, 3H), 3.2-3.4 (m, 4H), 3.7-4.0 (m, 12H), 3.83 (s, 3H), 6.92 (s, 1H), 8.78 (s, 1H). By this aerobial oxidation, the potential necessities of all functional groups for this synthesis were provided in one-step at the desired C-3, 5, and 8 positions.

Upon treatment with aqueous sodium hydroxide followed by diazomethane, the o-quinone (3) was converted to methoxy p-quinone (4): mp. 168-70°, UV λ_{max}^{EtOH} 252, 322, 470 nm (log ε 4.40, 4.11, 3.71), in 60% yield. The presence of a morpholine group at the C-3 position in 4 was shown by the proton signal at δ 3.82 (br. s, 3H) in the NMR spectrum of 4.[7]

Methylation of 4 with various methylating agents (methyl iodide, methyl p-toluenesulfonate, methyl fluorosulfonate) was attempted but didn't give rise to any quaternary salt even under forced conditions, presumably because of the weak basicity of 4. This problem was circumvented by the reduction of the p-quinone to its hydroquinone derivative.

Reductive acetylation of 4 with zinc-acetic acid and acetic anhydride afforded, in 92% yield, hydroquinone diacetate (5), mp. 172-74°, which was found to undergo facile N-methylation reaction. Treatment of 5 with excess methyl iodide led quantitatively to monomethiodide (6), mp. 178-79°. The proton signal (3.2-3.6 ppm) of two methylene groups adjacent to morpholine nitrogen in 6 shifted upfield as large as 0.2 ppm relative to that of 5 and the proton signal, which was assigned to the hydrogen at the C-1 position, appeared at δ 9.03 and 10.18 in 5 and 6, respectively. By the displacement of the signal downfield due to the hydrogen at the C-1 position, it is evident that N-methylation of 5 occurred preferentially at the isoquinoline nitrogen. Contrary to the case of 2-dimethylaminopyridine,[8] no concurrent N-methylation

of morpholine nitrogen was observed.

In order to convert 6 into mimosamycin (1), three reactions are still required: i) hydrolysis of the acetoxyl groups, ii) oxidation of the resultant hydroquinone, and iii) substitution of the morpholine group with a hydroxyl group. Treatment of 6 with silver oxide afforded in one-step 2,6-dimethyl-7-methoxy-3,5,8-isoquinolinetrione, which was identified with a sample of natural mimosamycin by mixed mp. and the comparison of IR, UV, NMR, and MS spectra.

References and notes

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