Structure of Antibiotic M139603; X-Ray Crystal Structure of the 4-Bromo-3,5-dinitrobenzoyl Derivative

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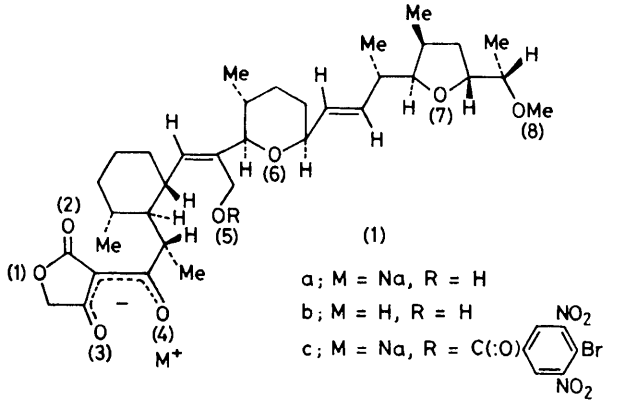
Summary The molecular structure of antibiotic M 139603 has been determined from an *X*-ray crystallographic analysis of the 4-bromo-3,5-dinitrobenzoyl derivative.

THE aerobic fermentation of *Streptomyces longisporoflavus* NCIB 11426 furnishes antibiotic M 139603,[1] a novel antibacterial agent which can be conveniently isolated as the crystalline sodium salt (**1a**) $C_{35}H_{53}O_8.Na$,† *m/e* 624 (M^+), m.p. 176—178 °C;‡ $[\alpha]_D^{23}$ −82 °(*c* 0·2, MeOH); u.v. λ_{max} (EtOH) 234 (ε 13,000) and 270 n.m. (11,000). Compound (**1a**) is soluble in most organic solvents but insoluble in water and can be readily converted into the non-crystalline free acid (**1b**), $C_{35}H_{54}O_8$, ν_{max} (Nujol) 3500, 1765, 1685, and 1650 cm^{-1}, by treatment with 0·1 M HCl. The absence of a carboxylate peak in the i.r. spectrum of (**1a**) [ν_{max} (Nujol) 3300, 1725, and 1645 cm^{-1}], together with the single pK_a value of 1·8 ± 0·3 (spectroscopic titration in MeOH–H_2O, 1 : 9) ruled out lipophilic antibiotics of the monensin type.[2,3] Antibiotic M 139603 is different from all previously known ionophores in that the molecule has been shown to possess a biosynthetically rare acidic grouping in the form of an acyl tetronic acid moiety.



The ^1H n.m.r. spectrum ($CDCl_3$) of (**1a**) revealed the presence of a *trans*-double bond with signals at δ 5·5 (1H, dd, *J* 15 and 9 Hz) and 6·1 (1 H, dd, *J* 15 and 10 Hz) indicating the fragment *trans*-$R^1R^2CHCH{=}CHCHR^3R^4$. Another signal at δ 5·15 (1 H, d, *J* 10 Hz) suggested the existence of a hydrogen on a trisubstituted double bond further coupled to a methine hydrogen, *i.e.* $R^5R^6C{=}CHCHR^7R^8$. The ^{13}C n.m.r. spectrum of (**1a**) was consistent with these data, showing 4 double-bond carbons which, under single-frequency off-resonance decoupling (SFORD) conditions, produced three doublets at δ 130·6, 140·8, and 141·5 and one singlet at δ 130·4 p.p.m. The presence of a methoxy-group in (**1a**) was shown by the ^1H and ^{13}C n.m.r. spectra with peaks at δ 3·3 (3 H, s) and δ 57·5 p.p.m. (q by SFORD), respectively. Treatment of (**1a**) with 4-bromo-3,5-dinitrobenzoyl chloride in dichloromethane followed by chromatography on silica plates (p.l.c.) gave the ester (**1c**), $C_{42}H_{54}BrN_2O_{13}.Na$, m.p. 159—160 °C, $[\alpha]_D^{25}$ − 92° (*c* 0·2 MeOH) which on slow recrystallisation from methanol yielded crystals containing one molecule of water of adequate quality for *X*-ray studies.

Crystal data: $C_{42}H_{54}BrN_2O_{13}Na$, H_2O, M = 915·8, monoclinic, space group $P2_1$, a = 10·533(2), b = 10·737(2), c = 20·577(3) Å, β = 90·80(1)°, U = 2326·9 Å^3, D_c = 1·307, D_m = 1·30 g cm^{-3}, Z = 2, $F(000)$ = 958, Cu-K_α radiation (Ni filter) = 1·5418 Å, μ = 19·7 cm^{-1}.

The cell parameters were determined by least-squares from the setting angles of 25 reflections on a Nonius CAD-4 diffractometer using Cu-$K\alpha$ radiation. Intensities were measured for $\theta \leqslant 60°$; 3696 reflections were scanned and 2515 of these were deemed observed [$I \geqslant 3\sigma(I)$] and were used in the refinement. Absorption corrections were not made. A difference map phased on the bromine atom (located by Patterson synthesis) did not reveal any chemically sensible fragments. Application of MULTAN, however, showed a connected fragment of 22 atoms as well as the bromine atom. Using these as input, successive structure-factor Fourier calculations revealed all the atoms, including a previously unsuspected atom (assumed to be the oxygen of water) co-ordinated to the central sodium. After the refinement had converged isotropically it was continued

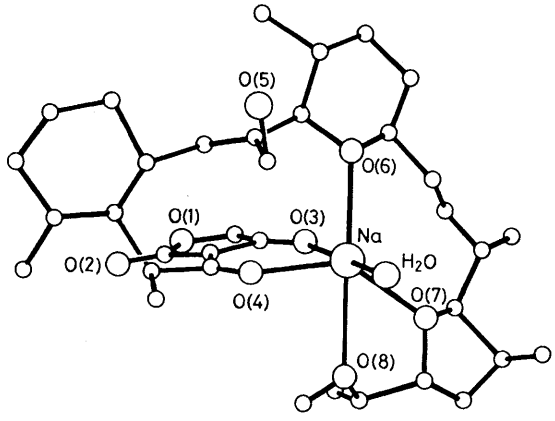


FIGURE. Perspective view of the crystal structure of (**1c**).

† Satisfactory elemental analyses have been obtained for all compounds whose molecular formulae are given.

‡ Sample dried at 25 °C and 0·1 mmHg. Prolonged heating at 100 °C and 0·1 mmHg. raised the m.p. to 239—241 °C.

anisotropically in three blocks. Hydrogen atoms were eventually included in calculated positions (most were detectable in a difference map) but were not refined.§

The absolute configuration was determined by use of the Hamilton statistical method (Br and Na anomalous, Hamilton R-ratio 1·024) and then by comparison of the observed intensities of those 100 Friedel pairs with $\theta \leqslant 40°$ selected to show the greatest intensity difference for the enantiomorphs. Ninety-nine of these pairs differed significantly in the correct sense; one pair had effectively equal intensities. The final conventional R-value (unit weights) at convergence (max. shift/standard deviation, 0·04) was 4·55%.

The Figure shows a perspective view of the molecule (with the acyl group omitted for clarity). The sodium is six-co-ordinate through O(3), O(4), O(6), O(7), O(8), and the solvent molecule, the ligands forming a very distorted octahedron. Bond lengths and angles are within the normal range except for the O–Me distance which is too short. However, this methyl is probably disordered (unreasonably high temperature factor).

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§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

[1] U.K. Pat. Appl. 2,027,013 A.
[2] M. Gorman, J. W. Chamberlin, and L. Hamill, *Antimicrob. Agents Chemother.*, 1968, **363**, 1967.
[3] J. W. Westley, 'Polyether antibiotics: Encyclopedia of Chemical Technology,' 3rd edn., Wiley, New York, 1978, vol. 3, p. 47.