

An X-Ray Determination of the Structure of an Antibacterial Compound from the Sponge, *Ianthella ardis*

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Summary The molecular structure of an antibacterial agent from the sponge *Ianthella ardis* was confirmed by single crystal X-ray analysis as 3,5-dibromo-1(*ax*),6(*ax*)-dihydroxy-4-methoxycyclohexa-2,4-diene-1-acetonitrile (I).

THE structure (I) of the (–)-isomer of an enantiomorph pair of antibacterial compounds isolated from *Ianthella ardis* was described by Fulmor *et al.*,¹ from a study of the physical and chemical properties which also indicated that the (+)-isomer is aeropylsinin-I.^{2†} An X-ray analysis was undertaken to confirm both the stereochemical assignments and the absolute configuration.¹

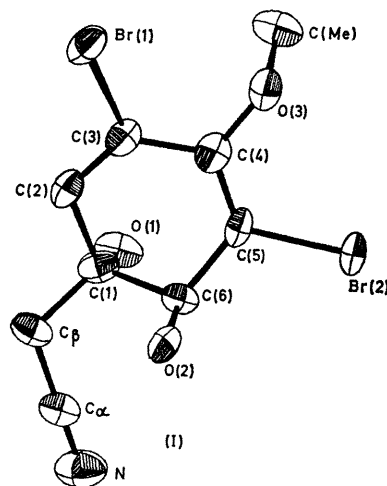
Both enantiomorphs of (I) crystallized from cyclohexane-ethyl acetate‡ in the hexagonal system and appear to be isomorphous. The (–)-isomer has cell dimensions $a = b = 8.676$ (1), $c = 25.980(9)$ Å, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$, with D_m 1.968 g cm⁻³ (floatation in xylene-tetrabromoethane), D_c 1.993 g cm⁻³ for C₉H₉Br₂O₃N with $Z = 6$. The space group, determined subsequently from the anomalous dispersion of the bromines, is $P6_1$; 1011 independent reflections, to $\theta = 67^\circ$, of which 827 were above background, $I > 2.5\sigma(I)$, were measured on a CAD-3 Enraf-Nonius automatic diffractometer in the $\theta-2\theta$ scan mode with Ni-filtered Cu- K_α radiation. The structure was solved by the heavy-atom method and was refined by block-diagonal least-squares in space group $P6_1$.³ With anisotropic thermal parameters ascribed to all atoms except hydrogens, which were not included in the refinement at this stage, the discrepancy index was 5.0%; the stereochemistry of the structure determined for (I) is in complete agreement with that suggested by Fulmor *et al.*, with the *trans* hydroxy-groups assuming the axial-axial configuration and the cyanomethyl group equatorial.

To determine the space group and, hence, the absolute configuration of the molecule, calculations with the imaginary terms for bromine dispersion as $+\Delta f''$ and $-\Delta f''$ were made to obtain structure factors in $P6_1$ and $P6_5$, respectively. The reliability indices for all data were 6.08% ($P6_1$) and 6.27% ($P6_5$); the Hamilton significance test⁵ allowed the rejection of $P6_5$ at the 0.5% significance level. When a set of reflections sensitive to dispersion effects was used the reliability indices were 6.05% for $P6_1$ and 6.58% for $P6_5$ with rejection of the latter at a significance level $\ll \ll 0.5\%$. The determination of the space group as $P6_1$ uniquely defines the absolute configuration which is in agreement with that assigned by Fulmor *et al.*,¹ on the basis of the negative Cotton effect.

The structure was refined anisotropically in $P6_1$ with the bromine dispersion correction using full-matrix least-squares⁶ to $R = 4.5\%$ to remove polar dispersion errors.⁷ (A similar refinement in $P6_5$ yielded $R = 4.8\%$, a further

confirmation that $P6_1$ is the correct space group). A difference Fourier at this stage revealed four C–H protons but not the hydrogens on the methyl or the two hydroxy-groups. In final full-matrix refinement, with the four hydrogens included but not refined, R dropped to 4.2%.⁸

A view of the structure (I) projected on the *ab* plane is shown in the Figure. The individual bond lengths are



FIGURE

$C_\alpha-N$, 1.118; $C_\alpha-C_\beta$, 1.494; $C_\beta-C(1)$, 1.491; $C(1)-C(2)$, 1.530; $C(2)-C(3)$, 1.330; $C(3)-C(4)$, 1.461; $C(4)-C(5)$, 1.309; $C(5)-C(6)$, 1.514; $C(6)-C(1)$, 1.550; $C(1)-O(1)$, 1.427; $C(6)-O(2)$, 1.446; $C(4)-O(3)$, 1.384; $O(3)-C(Me)$, 1.426; $C(3)-Br(1)$, 1.910; $C(5)-Br(2)$, 1.893 Å; the average e.s.d. for the bond lengths is 0.017 Å. The bond angles are unexceptional and there are no unusual intermolecular interactions; the packing is a result of van der Waals' forces only.

The dihedral angle around the twisted diene chromophore is $17.3 \pm 1.0^\circ$ and describes a left-handed helix in agreement with the c.d. Cotton effect¹ which is $[\theta]_{282} -4900$. There are few existing correlations between Cotton effects and experimental results from X-ray data for skewed dienes to confirm the helicity rule.⁸ Only three previous reports are known to us and these include inferential data for dethioglotoxin,⁹ a lumisterol study using X-ray data with unrefined positional parameters,¹⁰ and a structure which does not obey the helicity rule.¹¹ (–)-Aeropylsinin-I, containing only the skewed diene chromophore, provides a clear-cut example in which the helicity rule is

† Mr. W. Fulmor and staff have found that a sample of the (+)-isomer of (I) is indistinguishable from aeropylsinin-I, supplied by Dr. E. Fattorusso,² when compared by mixture m.p. and i.r. analysis.

‡ The samples were crystallized and prepared for the analysis by Messrs. R. D. Mills and R. W. Broschard.

§ A list of the observed and calculated structure factors may be obtained from the authors upon request.

confirmed and furnishes accurate parameters to begin sign of Cotton effects and the magnitude and chirality of possible correlation studies between the magnitude and the diene twist.

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- ¹ W. Fulmor, G. E. Van Lear, G. O. Morton, and R. D. Mills, *Tetrahedron Letters*, 1970, 4551.
- ² E. Fattorusso, L. Minale, and G. Sodano, *Chem. Comm.*, 1970, 751.
- ³ F. R. Ahmed, S. R. Hall, M. E. Pippy, and C. P. Saunderson, "NRC Crystallographic Program for the IBM/360 System," National Research Council, Ottawa, 1968.
- ⁴ S. Neidle and D. Rogers, *Nature*, 1970, **225**, 376.
- ⁵ W. C. Hamilton, *Acta Cryst.*, 1965, **18**, 502.
- ⁶ D. W. Cruickshank and W. S. McDonald, *Acta Cryst.*, 1967, **23**, 9.
- ⁷ G. M. Stewart, F. A. Kundell, and J. C. Baldwin, The X-ray System, 1970, Computer Science Center, University of Maryland.
- ⁸ A. Moscovitz, E. Charney, U. Weiss, and H. Ziffer, *J. Amer. Chem. Soc.*, 1961, **83**, 4661.
- ⁹ H. Ziffer, U. Weiss, and E. Charney, *Tetrahedron*, 1967, **23**, 3881.
- ¹⁰ E. Charney, *Tetrahedron*, 1965, **21**, 3127; D. C. Hodgkin and D. Sayre, *J. Chem. Soc.*, 1952, 4561.
- ¹¹ D. R. Pollard and F. R. Ahmed. Abstracts Summer Meeting of the American Crystallographic Association, Ottawa, 1970, L 8.