The Absolute Configuration of Cervicarcin; Application of the Aromatic Chirality Method

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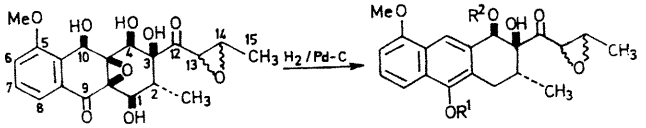
Summary The Aromatic Chirality Method has been applied to establish the absolute configuration of cervicarcin as (I).

THE absolute configuration of cervicarcin (I),[1,2] an antitumour antibiotic produced by *Streptomyces ogaensis*, has been determined by application of the aromatic chirality method.[3-5] Cervicarcin (I) was hydrogenolysed with Pd–C in EtOH–AcOH to give alcohol (II), which was methylated with diazomethane to afford (III).[2] Differentiation between C-1 and C-4 for the hydrogenolysed hydroxy-group was based on 220 MHz n.m.r. measurements and 100 MHz n.m.r. decoupling studies on the methyl ester (III) in C_5D_5N; 1·22(11-CH_3, d, $J_{2a,Me}$ 6·6 Hz), 1·38(15-CH_3, d, $J_{14,Me}$ 5·5 Hz), 2·74 (2-H_{ax}, d, d, q, $J_{1a,2a}$ 11·2, $J_{1e,2a}$ 7·0, $J_{Me,2a}$ 6·6 Hz), 3·13 (1-H_{ax}, d, d, $J_{1a,1e}$ 17·5, $J_{1a,2a}$ 11·2 Hz), 3·33 (1-H_{eq}, d, d, $J_{1e,1a}$ 17·5, $J_{1e,2a}$ 7·0 Hz), 3·41 (14-H, d, q, $J_{14,Me}$ 5·5, $J_{14,13}$ 2·0 Hz), 3·81 (5-OCH_3, 9-OCH_3, s), 4·62 (13-H, d, $J_{13,14}$ 2·0 Hz), 5·75 (4-H, s, long range coupling with 10-H), 6·83(6-H, d, $J_{6,7}$ 7·1 Hz), 7·45(7-H, *ca.* t), 7·81(8-H, d, $J_{7,8}$ 8·0 Hz), and 8·99 (10-H, s). Thus it is the C-1 hydroxy-group that is eliminated by hydrogenolysis. *para*-Chlorobenzoylation by the usual method yielded the monobenzoate (IV), m.p. 187—191°, molecular ion at *m/e* 510·1389 (calc. for $C_{28}H_{27}{}^{35}ClO_7$ 510·1443).



(I)

(II) $R^1 = R^2 = H$
(III) R^1 = Me, $R^2 = H$
(IV) R^1 = Me, R^2 = *p*-Cl·C_6H_4CO

The conformation of the *p*-chlorobenzoate (IV) in $CDCl_3$ differed from that of the alcohol (III) in pyridine; $J_{1e,1a}$ 16·5, $J_{1e,2e}$ 0, $J_{1a,2e}$ 5·5 Hz.

The u.v. spectrum of the alcohol (III) shows a pattern typical of α-substituted naphthalenes,[3] in which the two

longer wavelength transitions [$^1A \rightarrow {}^1L_a$ (short axis), and $^1A \rightarrow {}^1Lb$ (long axis)] overlap with each other. Since the band at 234·5 nm, $^1A \rightarrow {}^1B_b$ (long axis) transition, has a very large absorption coefficient, strong Cotton effects due to interaction with the naphthalenoid chromophore were expected in the *p*-chlorobenzoate (IV).[4] In fact, the c.d. spectrum indicated this prediction to be correct; the c.d. spectrum of *p*-chlorobenzoate (IV) showed two very strong Cotton effects ($\Delta\epsilon_{242} = +76{\cdot}6$, $\Delta\epsilon_{228} = -46{\cdot}2$) while the alcohol (III) exhibited only a simple Cotton effect ($\Delta\epsilon_{230} = +6{\cdot}0$).

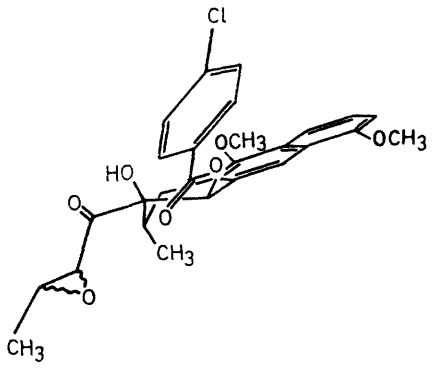


FIGURE. *The positive chirality of* p-*chorobenzoate* (IV).

The positive first Cotton effect sign indicates that the chirality between the long axes of the naphthalene and the *p*-chlorobenzoate chromophores is positive. That is, the benzoyloxy-group adopts a β-configuration, in which the chirality between two long axes is always positive irrespective of the conformation of the cyclohexane ring. From this the absolute configuration of cervicarcin is represented by (I).

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[1] S. Marumo, K. Sasaki, and S. Suzuki, *J. Amer. Chem. Soc.*, 1964, **86**, 4507.
[2] S. Marumo, K. Sasaki, K. Ohkura, K. Anzai, and S. Suzuki, *Agric. and Biol. Chem.* (*Japan*), 1968, **32**, 209.
[3] N. Harada and K. Nakanishi, *Accounts Chem. Res.*, submitted for publication.
[4] N. Harada, K. Nakanishi, and S. Tatsuoka, *J. Amer. Chem. Soc.*, 1969, **91**, 5896.
[5] N. Harada and K. Nakanishi, *J. Amer. Chem. Soc.*, 1969, **91**, 3989.