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THE STEREOCHEMISTRY OF ALBOFUNGIN

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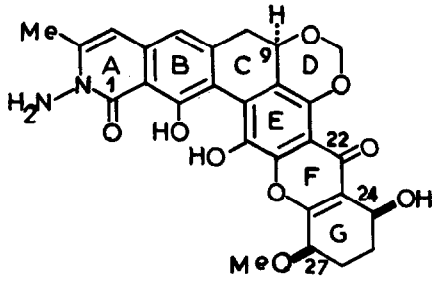
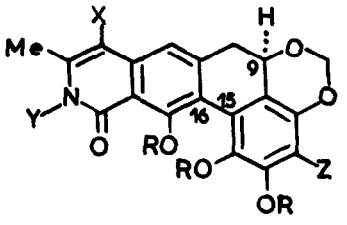
Albofungin, an antibiotic from Actinomyces albus var. fungatus (1), had recently been shown to have the structure I (2). Now we have found it to possess the absolute stereochemistry depicted by formula I.

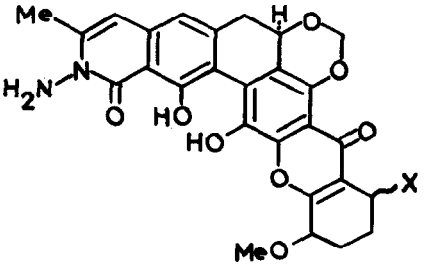


(I)

The helicity of the BCE ring system of the antibiotic and hence the configuration of the C-9 centre was determined from CD spectra of albofungin and its degradation products, especially albofungol (IIa), in a manner similar to the exciton chirality method of Harada and Nakanishi (3). The inherently dissymmetric chromophore of albofungol (IIa) comprises a benzenoid and an isoquinoline moiety (the E and AB rings); although virtually conjugated, these could be treated separately to a first approximation as acetophenone and naphthalene-like chromophores, respectively. The CD curves of albofungin and albofungol (Fig.1) and of various derivatives (II) exhibit several Cotton effects among which a negative effect at 250-260 nm and a positive effect at 220-230 nm are the only ones common to all the compounds tested, irrespective

of their substitution pattern. These effects were attributed to the dipole-dipole interaction of the intramolecular charge-transfer transition of the E ring chromophore with a $^1A \rightarrow {}^1B_b$ type $\pi \rightarrow \pi^*$ transition of the AB system. According to the aromatic chirality rule (3), it is the sign of the first of the split-type Cotton effects which is indicative of the chirality. Therefore left-hand helicity about the C_{15}-C_{16} axis was deduced for the chromophore of albofungol, which implies a R configuration for the C-9 centre.





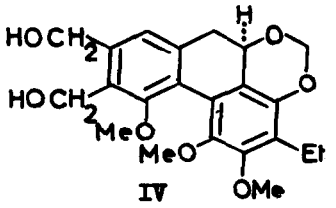
II: X = H, Cl, Br, or $O_2NC_6H_4N_2$;
Y = NH_2, H, Me, N=CHPh, or NAc_2;
Z = Ac, Et, or OH; R = H, Me, or Ac

IIa: X = R = H, Y = NH_2, Z = Ac

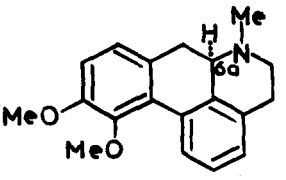
IIb: X = R = H, Y = H, Z = Et

IIIa: X = Cl

IIIb: X = OH



IV



V

This conclusion was verified by converting 2-deamino-22-deoxoalbofungol (IIb, m.p. 295-297°) on methylation with MeI+NaH followed by $KMnO_4$ oxidation and $LiAlH_4$ reduction into a diol (IV; diacetate: m.p. 196-197°) whose chromophore closely resembles that of apomorphine dimethyl ether (V). Since apomorphine has been chemically correlated to R-aspartic acid (4) and as the CD spectra of the two compounds (Fig.2) are very similar, the C-9 centre of albofungin must also have the R configuration.

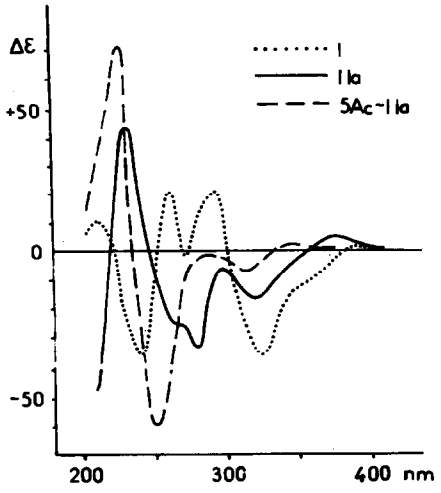


Figure 1. CD spectra of albofungin (I), albofungol (IIa), and pentaacetyl albofungol (5Ac-IIa) in ethanol.

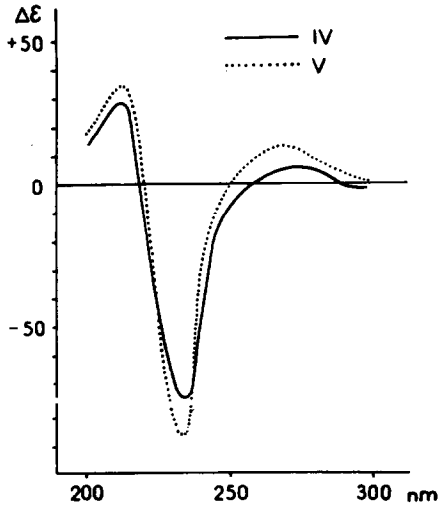


Figure 2. CD spectra of the diol (IV) and apomorphine dimethyl ether (V) in ethanol.

The stereochemistry of the C-24 and C-27 centres was elucidated by oxidative cleavage of the F and G rings after protection of the 24-hydroxyl (methylation by MeI+NaH, then oxidation by $KMnO_4$+$NaIO_4$). With albofungin itself (I), this degradation yielded meso-2,5-dimethoxyadipic acid (identified as dianilide, m.p. 229-230°), thus demonstrating cis position of the substituents in the G ring but giving no information on their absolute configuration. Hence racemisation of the C-24 centre was effected by dissolution of albofungin (I) in conc. HCl to form 24-epimeric chlorides (IIIa). The chlorides, without separation, were converted into albofungin and 24-epi-albofungin (IIIb) by treatment with AcONa followed by mild hydrolysis with 0.2 N Me_4NOH. Subsequent O-methylation and oxidation by $KMnO_4$+$NaIO_4$ resulted in a mixture of meso and (-)-2,5-dimethoxyadipic acids. The latter was shown to be the 2R,5R enantiomer by comparison with the 2S,5S-acid synthesized from D-mannitol.

Thus the 9R,24S,27R configuration (I) has been demonstrated for albofungin.

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