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THE STRUCTURE OF FLAVOFUNGIN

R.Bognár,[a] B.O.Brown,[b] W.J.S.Lockley,[b] S.Makleit,[a] T.P.Toube,[b]
B.C.L.Weedon,[b] and K.Zsupán,[a]

[a]Institute of Organic Chemistry, L.Kossuth University, Debrecen, Hungary.

[b]Department of Chemistry, Queen Mary College, Mile End Road, London, E.1.

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Flavofungin, an antifungal antibiotic from Streptomyces flavofungini,[1] was characterised as a polyhydroxy polyene macrolide by Bognár et al.[2] We have now shown it to be a mixture (ca. 10:1) of (1a) and (1b).

The spectral properties of flavofungin ($\nu_{C=O}^{KBr}$ 1680 cm^{-1}; λ_{max}^{EtOH} 261 and 364 nm, ε = 8,200 and 56,500 respectively), its perhydro-derivative ($\nu_{C=O}^{KBr}$ 1730 cm^{-1}), and $LiAlH_4$ reduction product (λ_{max}^{EtOH} 348, 331, and 317 nm), reveal the conjugated pentaene lactone chromophore. The mass spectrum of peracetylflavofungin, m.p.151°, shows a molecular ion at m/e 986 from which eight successive acetic acid fragments (8 x 60 a.m.u.) are lost. High resolution measurements on m/e 686 (M-5x60), 806 (M-3x60), 866 (M-2x60), and 926 (M-60) indicate a molecular formula $C_{52}H_{74}O_{18}$. The pertrimethylsilyl ether of flavofungin clearly shows the loss of at least six Me_3SiOH fragments from the molecular ion, m/e 1226. Thus flavofungin has the molecular formula $C_{36}H_{58}O_{10}$ and contains eight hydroxyl groups. The perhydro-derivative (m.p.150°) does not react with periodate; accordingly there is no 1,2-diol. Its peracetate and pertrimethylsilyl ether give molecular ions 12 a.m.u. higher than those of the corresponding flavofungin derivatives. The n.m.r. spectrum ($CDCl_3$) of peracetyl-flavofungin shows 12 olefinic protons (τ 2.6-4.7), 24 acetoxy protons (τ 7.9), and 12 C-CH_3 protons (τ 8.9-9.3), but no cyclopropyl protons. Flavofungin therefore contains six carbon-carbon double bonds and four methyl groups.

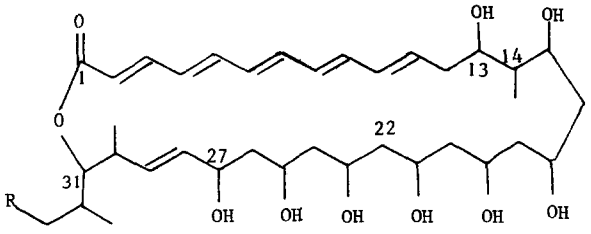
Alkali fusion of flavofungin gives no high molecular weight product, but that of the perhydro-derivative gives tridecane-1,13-dioic acid in good yield together with traces of dodecanoic acid. This establishes all structural features from C-1 to C-13 and the presence of a hydroxyl at C-15.[3] Careful ozonolysis of flavofungin or its peracetate, and treatment of the crude product with base, affords the aldehyde (2a). The same compound is produced on permanganate oxidation of flavofungin.

Perhydroflavofungin was converted ($LiAlH_4$; P/HI; $LiAlH_4$; H_2/Pt) into the parent C_{36}-hydrocarbon. This exhibited an (M-2) ion at m/e 504 and appreciably intense ions at m/e 323, 211, 210, and 85, indicating structure (3a) or (3b).[4] Repetition of the reaction sequence using $LiAlD_4$ for the initial reduction gave the d_2-hydrocarbon (3c); m/e 506, 323, 213, 212, and 85. Perhydroflavofungin was also converted by a decarboxylation procedure (KOH; Ac_2O; $Pb(OAc)_4/I_2/h\nu$; P/HI; $LiAlH_4$; H_2/Pt) into the C_{35}-hydrocarbon (3d); m/e 490, 323, 197, 196, and 85. The parent C_{36}-hydrocarbon is therefore (3a).

Hydrogenation (Pt/HOAc) of o taacetylflavofungin yields the perhydro-derivative and (30%) a heptaacetate, $C_{50}H_{84}O_{16}$ (isolated by t.l.c.; M^+ 940; the loss of seven acetic acid units from the molecular ion is observable). Flavofungin therefore has an allylic hydroxyl group at C-27, although all attempts to oxidise this function selectively failed. These results, together with steric considerations, show that lactonisation is at C-31.

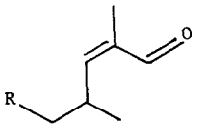
In the mass spectra of the peracetyl and pertrimethylsilyl derivatives of flavofungin and of perhydroflavofungin, peaks are observed which indicate the presence of small amounts (ca. 8%, assuming similar volatility) of a homologue with a molecular ion 14 a.m.u. above those of the major component. In the n.m.r. and mass spectra of the 2,4-dinitrophenylhydrazone of (2a) there are also peaks due to ca. 8% of the homologue (2b). Thus flavofungin is a mixture of (1a) and (1b) in the approximate proportions 10:1.

Mycoticin, an antibiotic from S.ruber,[5] was recently shown by Wasserman et al.[6] to consist of approximately equimolar amounts of two compounds for which structures (1a) and (1b) were proposed. In direct comparisons of flavofungin (m.p. 210°) and mycoticin (m.p. 220°)* no differences are observed in the following: i.r. (CsBr disc) and u.v. (95% EtOH) spectra of the antibiotics and their peracetates; mass spectra of the peracetates and pertrimethylsilyl ethers (except for relative intensities of peaks due to the two homologues); n.m.r. ($CDCl_3$) spectra of the peracetates; t.l.c. (silica gel, 3-4 solvent systems) of the perhydro-derivatives, the peracetates, and perhydro-peracetates; hydrogenolysis of the antibiotics (Pt/EtOH). However the X-ray powder photographs of the two antibiotics show significant differences, the pattern for flavofungin being more clearly defined than that of the less homogeneous mycoticin. Furthermore flavofungin in dioxane is laevorotatory whereas mycoticin is dextrorotatory.[6] We conclude that, apart possibly for absolute configuration at one or more asymmetric centres, the two antibiotics are mixtures of the same two compounds in different proportions. The position of lactonisation in flavofungin is therefore confirmed by



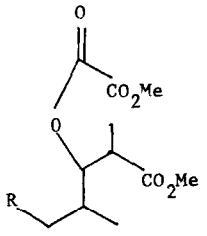
1a, R=H

1b, R=Me



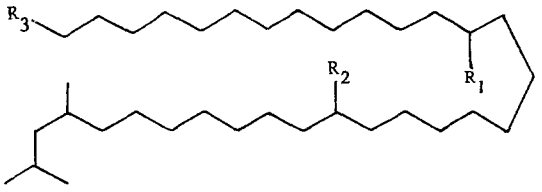
2a, R=H

2b, R=Me



4a, R=H

4b, R=Me



3a, R_1=Me, R_2=H, R_3=Me

3b, R_1=H, R_2=Me, R_3=Me

3c, R_1=Me, R_2=H, R_3=CHD_2

3d, R_1=Me, R_2=H, R_3=H

the degradation of mycoticin to (4a) and (4b).[6] The results now reported on flavofungin confirm the location in mycoticin of a methyl at C-14 rather than C-22, the location of the polyhydroxy system at C-13 to C-27, and the presence of an allylic hydroxyl.

Flavofungin may be identical with flavomycoin from S.roseflavus.[7]

Footnote and References

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