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THE STRUCTURE OF ABIKOVIROMYCIN

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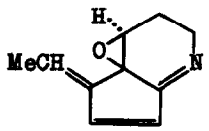
Abikoviromycin (1,2), $C_{10}H_{11}NO$, is an optically active antiviral antibiotic from Streptomyces abikoensis with basic properties. It is highly unstable and polymerizes promptly on isolation even at -50°; however it can be handled in dilute solutions and in the form of its salts (acid sulfate: dec.140-141°, $[\alpha]_D$ +24° (c 1, water); picrate: dec.137-140°). We have shown that this antibiotic is (4S,4aR)-5-ethylidene-2,3-dihydro-1,5-pyrindine 4,4a-oxide I.



I

Abikoviromycin is readily reduced by $NaBH_4$ into a crystalline dihydro compound, $C_{10}H_{13}NO$ (m.p. 60-61°), which is a secondary amine of pK_a 8.07. Dihydro abikoviromycin contains one active hydrogen atom but no carbonyl, whereas the original antibiotic is devoid of hydrogen exchangeable for deuterium on dissolving in D_2O. Hence the oxygen in abikoviromycin must be ethereal and the nitrogen in $>C=N-$ grouping.

As can be seen from its empirical formula the antibiotic should possess six double bond increments. On hydrogenation with PtO_2 it consumes about 5 moles of H_2 and yields three stereoisomeric saturated secondary amines, $C_{10}H_{19}N$ (3,5-dinitrobenzoates: m.p. 128-130°, 105-106°, 152-153°). It thus follows that abiko-

viromycin has three double bonds and three rings of which one contains oxygen capable of hydrogenolysis in the presence of platinum.

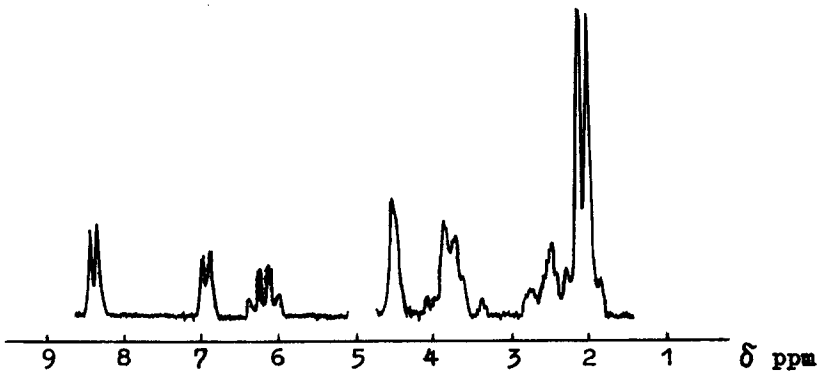
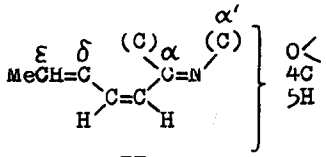
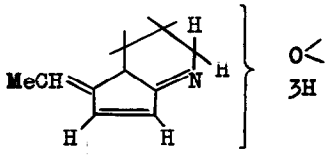


FIG.1. NMR spectrum of abikoviromycin acid sulfate (60 Mc, in D_2O)

The antibiotic displays a characteristic UV absorption undergoing a considerable bathochromic shift upon acidification (in neutral EtOH or in 0.1 N KOH: λ_{max} 218, 244, 289 mμ (lg ε 3.83, 3.99, 3.94); in 0.1 N HCl: λ_{max} 236, 341 mμ (lg ε 3.99, 4.05)). The NMR spectrum of abikoviromycin (Fig.1) is indicative of the presence of an ethylidene group (three-proton doublet at 2.10 and one-proton quartet at 6.18 ppm with J 7 cps) and a cis-disubstituted ethylene group (two one-proton doublets at 6.95 and 8.42 ppm with J 6 cps). Judging by the chemical shifts and the λ_{max} values, these olefinic groups and the imino group are conjugated forming the chromophore II (calc. λ_{max}^{EtOH} = 215 (C=C-C=N) + 30 (add.C=C) + 5 (exo pos.C=C) + 5 (α-alk.) + 2 x 18 (δ- and ε-alk.) = 291 mμ, $\Delta\lambda_{N \rightarrow NH^+}$ ca.50 mμ; cf (3)). The possibility of the oxygen atom being in the α- and/or α'-position is excluded by the pK_a value of dihydro abikoviromycin since amino acetals are of far less basicity.



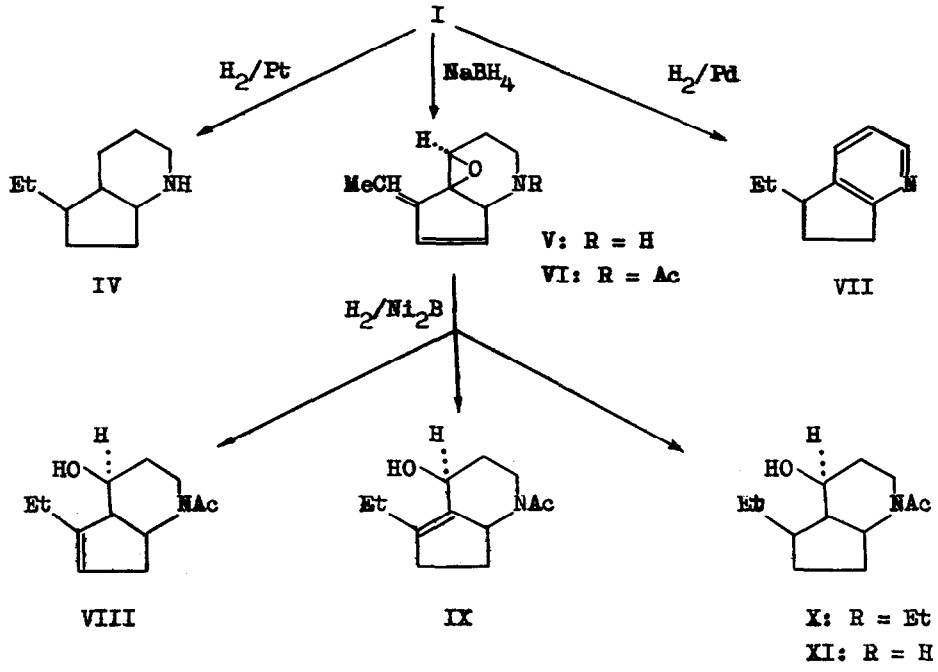
II



III

On catalytic hydrogenation in the presence of palladium black abikoviromycin yields among other products a tertiary base, $C_{10}H_{13}N$ (picrate: m.p.108-109°).

The latter contains an ethyl group and displays UV, IR and NMR spectra characteristic of 2,3-dialkyl pyridines (UV in EtOH: λ_{max} 268 infl., 272, 279 infl. mμ (lg ε 3.64, 3.68, 3.56); NMR in CCl_4: δ 1.00 (3H, t, J 7), 6.93 (1H, q, J_1 5, J_2 8), 7.37 (1H, d, J 8), 8.22 (1H, d, J 5)). Since the α,δ-branched grouping II is present in the parent compound these data bear evidence of the ethyldihydropyrindine structure IV for the abikoviromycin hydrogenolysis product. Therefore the antibiotic possesses the hydropyrindine skeleton III, the oxygen atom being present as an oxide bridge located in the six-membered ring.



The NMR spectrum of abikoviromycin indicates the presence of only one methine bound to the oxygen atom: so the oxide bridge must be attached on one side to a tertiary carbon, i.e. to the C-4a atom. In the spectrum of the antibiotic itself the methine signal is a rather broad singlet (4.54 ppm) but in the NMR spectrum of the N-acetyl dihydro derivative of the antibiotic (m.p. 50-51°) it becomes a distinct quartet at 3.08 ppm with J_1 5 and J_2 3 cps. This quartet shows the oxide bridge to be located at position 4,4a (VI), rather then 3,4a, so that abikoviromycin possesses structure I.

Hydrogenation of dihydro abikoviromycin V in the presence of nickel boride catalyst resulted in cleavage of the oxide ring and (complete or partial) saturation of the double bonds to form three amino alcohols isolated as N-acetyl derivatives VIII - X (VIII: m.p. 124–125°; IX: m.p. 91–92°; X: m.p. 126–127°). The mass spectrum of the saturated alcohol X displays a fragmentation pattern very similar to that of synthetic N-acetyl perhydro pyrindinol-4, XI, thus proving independently the position 4 for the oxygen atom in the antibiotic.

Finally, conversion of the β,γ-unsaturated alcohol VIII into the corresponding 3,5-dinitrobenzoate causes a positive shift in the molecular rotation ($[M]_D$: -208° ⟶ -145°) while an opposite change is observed in the case of the α,β-unsaturated isomer IX and its 3,5-dinitrobenzoate ($[M]_D$: +288° ⟶ +182°), both the dinitrobenzoates having a negative Cotton effect at ca. 275 mμ. According to the benzoate rule (4) such shifts point out to an S configuration for the asymmetric centre 4 of both the unsaturated alcohols VIII and IX, and consequently abikoviromycin possesses the absolute configuration I.

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