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THE TOTAL STRUCTURE OF THE NOVEL ANTIBIOTIC MOCIMYCIN (MYC 8003)

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Recently we reported on the structures 1 and 2a of two degradation products of mocimycin (1). Further work has now led to the elucidation of the structure of the complete mocimycin molecule 5.

The previous experiments indicated that fragment 2a might be an artefact and that methylation of a hydroxylgroup might have taken place under the applied conditions (acidic methanolysis). This was confirmed by treating mocimycin with acetic acid at room temperature for several days. An apolar diene, 2b, was obtained, together with a polar compound 4a, which was acetylated with a mixture of acetic anhydride and pyridine to give 4b. The UV spectrum of 4b showed the presence of fragment 1. The structure of 4b was derived from its 220 MHz proton NMR spectrum; for data see diagram.

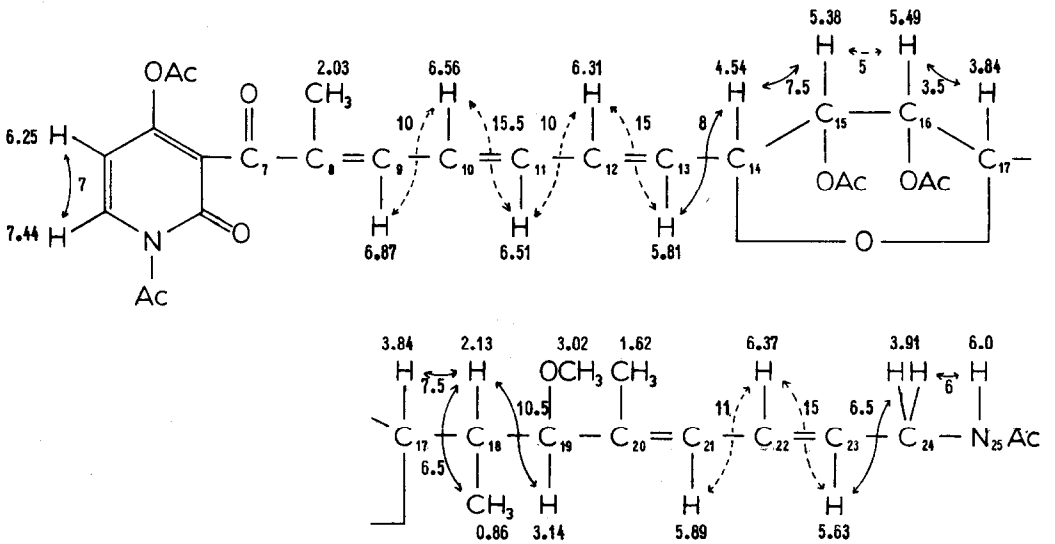
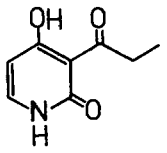
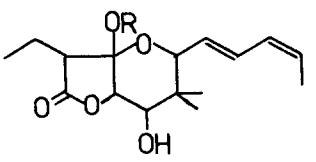


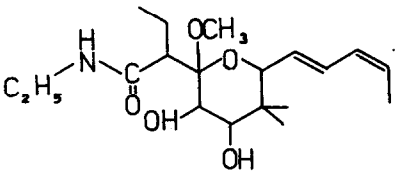
Diagram of NMR data of 4b in $CDCl_3$, where ⟷ represents couplings and ⌒ denotes couplings confirmed by spin-decoupling (values in Hz). The other figures represent δ-values for the corresponding protons.



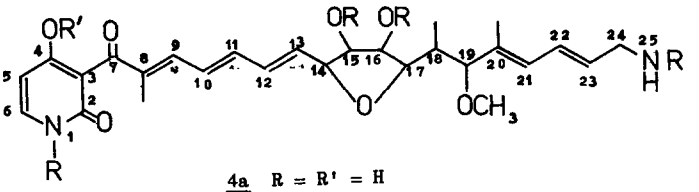
1

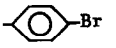


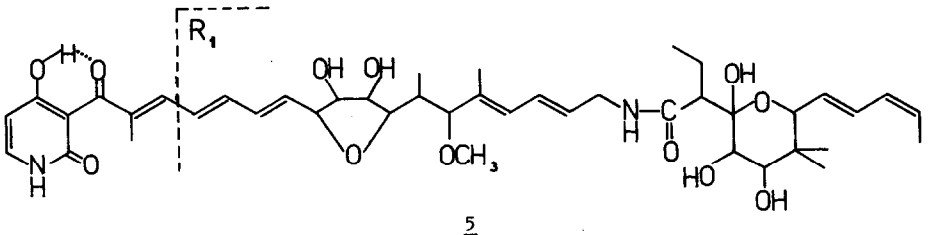
2a R = CH_3
2b R = H



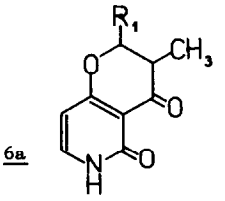
3 (ref. 1)



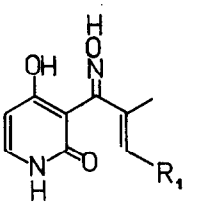
4a R = R' = H
4b R = R' = $COCH_3$
4c R = H; R' = $-CH_2$ 



5

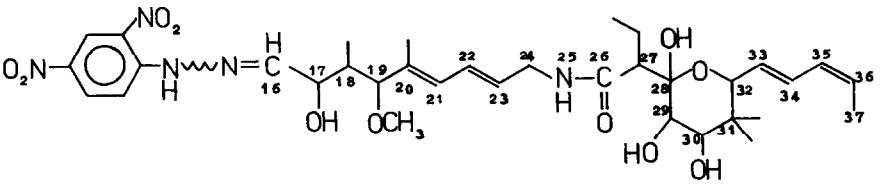


6a



6b

(R_1 stands for the right hand part of 5, as indicated by the dotted line)



7

Correspondingly, acetic acid treatment of the mono 4-bromobenzylderivative of mocimycin yielded 4c. The spectra of 4c are similar to those of 4b but indicate the presence of hydroxyl groups at C-15 and C-16 (15-H and 16-H shifted to δ^{CDCl_3} 4.30 and 4.14 respectively; no ester-carbonyl absorption present at 1735 cm^{-1}) and a free amine group (25-H shifted to δ 3.3).

In mocimycin, fragments 2b and 4a appear to be linked by an amide bond as the NMR-spectrum shows an extra amide hydrogen signal just like the compounds 3 and 4b, while the IR spectrum indicates the absence of a γ-lactone (no carbonyl absorption at 1785 cm^{-1} as present in diene 2b) and the enolic hydroxyl of the pyridone fragment fully accounts for the mono-acidic character of mocimycin. As the NMR-spectrum of mocimycin does not indicate the presence of other protons than those found in 2b and 4a, structure 5 is suggested as the two-dimensional structure of mocimycin.

Support for this structure was obtained when mocimycin was treated with sodium metaperiodate. This resulted in the formation of an aldehyde, which was purified as its 2,4-dinitrophenylhydrazone, 7. It incorporates both the diene fragment 2b and a part of 4a, as was evident from the spectral data: δ^{CDCl_3} 7.93 (d 9.5 Hz), 8.31 (dd 9.5 and 2.5 Hz), 9.10 (d 2.5 Hz), 11.13 (s, NH) (2,4-DNPH protons); 7.59 (16-H, d 4 Hz), 4.65 (17-H, dd 4 and 3 Hz), 2.12 (18-H, m), 0.79 (18-CH_3, d 7 Hz), 3.51 (19-H, d 9.5 Hz), 3.21 (19-OCH_3, s), 1.69 (20-CH_3, broadened s), 4.0 (24-H_2, m), 6.3 (25-H), 2.61 (27-H, dd 10.5 and 3.5 Hz), 1.7 (27-CH_2 CH_3, m), 0.92 (27-CH_2CH_3, t 7.5 Hz), 3.70 (29-H and 30-H, AB, J_{AB} = 3 Hz), 0.90 (31-CH_3, s), 4.20 (32-H, d 6 Hz), 1.73 (37-H_3, d 7 Hz), 5.4-6.5 (7 olefinic protons). The couplings between 16-H and 17-H, 32-H and 33-H were confirmed by spindecoupling.

The suggested structure 5 explains the occurrence of mocimycin as an equilibrium mixture of three components, as shown by two-dimensional TLC (2). Two of these components, including the main one, are acids and show a positive ferrichloride reaction, whereas the third component is a neutral, ferrichloride negative substance. This substance was isolated as yellow crystals, mp 135 - 140°C (dec.); the elemental analyses agreed with $C_{43}H_{60}N_2O_{12}$. Its spectral characteristics indicated that the enolic hydroxyl of the pyridone had reacted with the side chain to 6a: $\delta^{CDCl_3 + DMSO}$ 4.64 (9-H, dd 10.5 and 7.5 Hz), 2.6 (8-H, m), 1.10 (8-CH_3, d 6.5 Hz); $\lambda_{max}^{methanol}$ 209 sh (ε = 14,600), 234 (ε = 66,000) and 318 nm (ε = 7,800).

From the reaction of mocimycin with hydroxylamine resulted a crystalline product with the UV-spectrum: $\lambda_{max}^{methanol}$ 213 (ε = 33,000), 233 (ε = 48,000), 284 sh, 296 (ε = 37,000), 310 (ε = 51,000) and 324 nm (ε = 44,000).
The three latter absorptions resemble those of a tetraene, suggesting structure 6b. Presumably, pyridone ring and side chain are not coplanar as a result of sterical hindrance by the oxime group.
Adduct 6b does not exhibit the equilibrium phenomenon mocimycin does. The two acidic components of mocimycin may therefore represent a case of prototropy in which the ketogroup of the side chain and an enolic hydroxyl group of the pyridone ring are involved.

The configuration at the two trisubstituted double bonds (Δ^8 and Δ^{20}) is still uncertain, but in structures 4, 5 and 7 we depicted the presumably more stable transconfiguration.
In a solution of mocimycin in **acidified** aqueous acetone an acetonide is formed at C_{15} and C_{16}, suggesting a cis relation between the two hydroxyl groups. Since the vicinal coupling constants in the tetrahydrofuran ring are $J_{14,15}$ = 4 Hz, $J_{15,16}$ = 5.5 Hz and $J_{16,17}$ = 3.5 Hz for the acetonide derivative, this would indicate vicinal cis, cis, cis relations, i.e. all substituents at the same side of the ring. However, for the acetylation product 4b the vicinal coupling constants indicate a trans relation of the substituents at C_{14} and C_{15}.

The NMR-spectrum of 2b in DMSO is in fair agreement with the data published by Maehr et al. (3) for goldinono-1,4-lactone-3,7-hemiketal, which suggests that both substances are stereochemically identical also.

From the strong resemblance of the NMR-spectrum of antibiotic X-5108 (4) to that of mocimycin, it would appear that antibiotic X-5108 is the pyridone N-methylated derivative of mocimycin.

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