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STRUCTURE OF THE NEW ANTIBIOTIC MOCIMYCIN (MYC 8003): CHROMOPHORE AND FUROPYRANONE FRAGMENT

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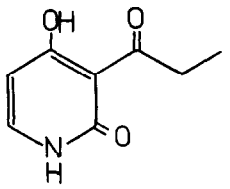
Mocimycin is an antibiotic produced by Streptomyces ramocissimus, the isolation and properties of which have recently been described (1).

In our attempts to elucidate the structure of mocimycin, in which 220 MHz - NMR spectroscopy played a major part, we had arrived at the structure of two major fragments, a substituted 4-hydroxy-2(1H)-pyridone and a substituted 2H-furo [3,2-b]pyran-2-one, when the two publications by Maehr et al. appeared (2,3) describing some structural features of a new antibiotic X-5108. The marked similarity between the structures of our fragments and those of the degradation products found by Maehr et al., plus the circumstance that the structures had been arrived at by different methods, prompt us to report our preliminary results.

Refluxing of mocimycin in 2 N NaOH afforded, besides other products, fragment 1, a colorless crystalline substance, mp. 230-231°C, $C_8H_9NO_3$ (determined by peak matching of the molecular ion m/e 167). The 220 MHz-NMR spectrum revealed signals at $\delta^{CDCl_3+\ DMSO\text{-}d_6}$ 1.08 (t, $\underline{CH_3}\text{-}CH_2\text{-}CO$, J = 7 Hz), 3.09 (q, $CH_3\text{-}\underline{CH_2}\text{-}CO$-, J = 7 Hz), 5.84 (d, H-5, $J_{5,6}$ = 7 Hz), 7.42 (d, H-6, $J_{5,6}$ = 7 Hz), 11.3 (broad, -NH-CO-), 15.7 (broadened singlet, chelated H). Together with the following UV data: $\lambda_{max}^{methanol}$ 209 (ε = 10,600), 227 (ε = 11,300), 267 (ε = 2,600) and 322 nm (ε = 9,200), this identified the substance 1 as 4-hydroxy-3-propionyl-2(1H)-pyridone. The structure of compound 1 was confirmed by synthesis from 4-hydroxy-2(1H)-pyridone and propionic acid with polyphosphoric acid as the condensating agent. Clearly, 1 is related to degradation product 3, 8-(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-pyridyl)-7-methyl-8-oxo-2,4,6-octatriene, with undetermined oxidation state of C-1 at the side chain, which is the proposed chromophore of antibiotic X-5108 (3).

Although the complete structure of the mocimycin side chain remains to be elucidated, the absence of an N-methyl in the pyridone ring system clearly distinguishes it from X-5108. Thus the NMR-spectra of antibiotic X-5108 shows an N-methyl signal at $\delta^{DMSO-d6}$ 3.1 (4), whereas mocimycin, just like its degradation product 1, gives a lactam hydrogen signal at $\delta^{DMSO-d6}$ 11.2.

When mocimycin was dissolved in methanol acidified with some hydrochloric acid, and set aside at room temperature, a diene 2a was formed, which was isolated as an oil, $C_{17}H_{26}O_5$, calcd. mol.wt. 310; found: m/e 310. The protons were identified by 220 MHz-NMR δ^{CDCl_3} 0.83, 0.95 (s, 2 gem. CH_3), 1.20 (t, $\underline{CH_3}$-CH_2, J = 7.5 Hz), 1.77 (dd, $\underline{CH_3}$-CH=CH, J = 7 Hz and 1.5 Hz), 1.9 (m, CH_3-$\underline{CH_2}$-CH), 2.57 (dd, CH_2-$\underline{CH}$, J = 7.5 Hz and 4 Hz), 3.37 (s, OCH_3), 3.62 (d, H-7, $J_{7,7a}$ = 4 Hz), 3.89 (d, H-5, J = 6.5 Hz), 4.27 (d, H-7a, J = 4 Hz), 5.5 (dq, CH_3-$\underline{CH}^{c}$=CH, J = 11 Hz and 7 Hz), 5.59 (dd, CH^{t}=$\underline{CH}$-CH, J = 15.5 Hz and 6.5 Hz), 6.00 (tq, CH_3-CH^{c}=$\underline{CH}$-CH=, J = 11 Hz and 1.5 Hz), 6.56 (dd, = CH-$\underline{CH}^{t}$=CH, J = 15.5 Hz and 11 Hz); all couplings, except those between the olefinic protons, were confirmed by spin decoupling. The presence of a carbonyl function adjacent to the methine group was indicated by the large $\delta^{CDCl_3} - \delta^{C_6D_6}$ value (0.46 ppm) found for H-3; the UV spectrum showed a λ^{MeOH}_{max} at 234 nm (ε = 21,000); the infrared spectrum revealed an absorption in the carbonyl region at 1785 cm^{-1} (γ-lactone), while the absorptions at 1125, 1100, 1080, 1028 and 985 cm^{-1} were assigned to a ketal group. It could further be shown that under mild conditions the product does not react with sodium meta-periodate. Acetylation with acetic anhydride and pyridine gave the mono acetyl derivative 2b, $C_{19}H_{28}O_6$, calcd.mol.wt. 352; found: m/e 352. While the NMR, IR and UV spectra are similar to those of 2a, they show the presence of an acetate group (δ^{CDCl_3} 2.12, ν^{CHCl_3} 1744 cm^{-1}) at C-7 (H-7 shifted to δ^{CDCl_3} 4.92). Reaction of degradation product 2a with ethylamine gave an oil, $C_{19}H_{33}NO_5$, calcd. mol.wt. 355; found: m/e 355. NMR and IR spectra indicated that the lactone ring had been opened (H-7a shifted to $\delta \sim 3.6$) with formation of an amide: δ^{CDCl_3} 1.16 (t, $\underline{CH_3}$-CH_2, J = 7 Hz), 3.30 (qd, CH_3-$\underline{CH_2}$-NH, J = 7 Hz and 6 Hz), 5.98 (t, CH_2-$\underline{NH}$-CO, J = 6 Hz), $CHCl_3$, ν 1653 cm^{-1}.



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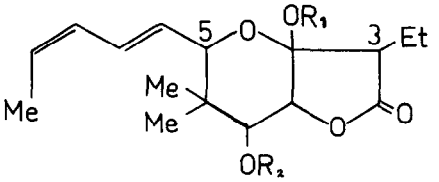


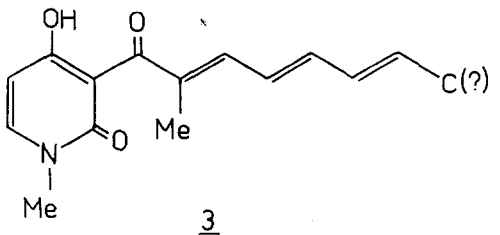
2

a: $R_1 = CH_3$, $R_2 = H$

b: $R_1 = CH_3$, $R_2 = -COCH_3$

c: $R_1 = -CH_2-CH_2-CH_3$, $R_2 = H$

d: $R_1 = R_2 = H$



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From the above data together with the results of NMR spectra of 2a after addition of tris(dipivalomethanato)europium, the following structure of compound 2a was deduced: 3-ethyl-3,3a,5,6,7,7a-hexahydro-7-hydroxy-3a-methoxy-6,6-dimethyl-5-(1(trans),3(cis)-pentadienyl)-2H-furo(3,2-b)pyran-2-one. It is probable that the methoxy group in compound 2a was introduced under the reaction conditions applied, since the corresponding propoxy compound 2c was obtained when n-propanol was used instead of methanol. Thus, 2a and 2c can be regarded as ethers of goldinono-1,4-lactone-3,7-hemiketal (2d), obtained by treating antibiotic X-5108 with acetic acid. In accordance with the evidence for antibiotic X-5108 there is no indication that a lactone ring, such as present in 2, occurs in mocimycin (no IR-absorption at 1785 cm^{-1}).

These findings, together with what has been mentioned about the occurrence of the pyridone fragment, strongly suggest that mocimycin and antibiotic X-5108 are closely related, but not identical substances.

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