Communications to the editor

THE STRUCTURE OF CANDIDOIN A COMPONENT OF THE CANDIDIN ANTIBIOTIC COMPLEX

Sir:

Candidoin, a polyene macrolide antifungal antibiotic of the nonaromatic heptaene subgroup, is one of the components of the candidin complex[1] produced by *Streptomyces viridoflavus*[2]. The structure of candidoin(**I**) established by us indicates that the compound is a derivative of candidin[1], a main component of the complex, and contains in the molecule a new deoxysugar moiety bound glycosidically at C-35 of the macrolactone ring (Fig. 1).

For our structural studies pure candidoin has been isolated from the candidin complex by counter-current distribution in the solvent system $CHCl_3$ - MeOH - borate buffer pH 8.2, 2: 2: 1 (480 transfers, K 1.81). Candidoin exhibited light absorption maxima at 347, 362, 382 ($E^{1\%}_{1cm}$ 1,100) and 406 nm in methanol.

Oxidative degradation of perhydrocandidoin yielded 2-methylheptadecanedioic acid[3]. The presence of mycosamine in the acidic hydrolysate of the antibiotic has been demonstrated by thin layer chromatography. The structure of the carbon skeleton and the positions of oxygen functions in the macrolactone ring of candidoin were established on the basis of the mass spectral data of the permethylated derivative **IIa** and its hexadeuterio analog **IIb** obtained in the following procedure: 1) *N*-acetylation of candidoin with acetic anhydride in aqueous tetrahydrofuran, 2) hydrogenation with the use of $Pd/BaSO_4$ in methanol, 3) reduction with sodium borohydride or sodium borodeuteride, 4) esterification with diazomethane, 5) reduction with lithium borohydride or lithium borodeuteride in tetrahydrofuran, 6) methanolysis, 7) methylation with methyl iodide in the presence of sodium hydride. The main diagnostic patterns of the EI spectra of **IIa** and **IIb** are shown in Fig. 2, and the molecular ions were observed at m/z 1,181 and m/z 1,187, respectively. The mass spectrum of **IIa** was identical with one obtained for an analogous product derived from nystatin A_1 of known structure[4].

Fig. 1. The structure of candidoin.

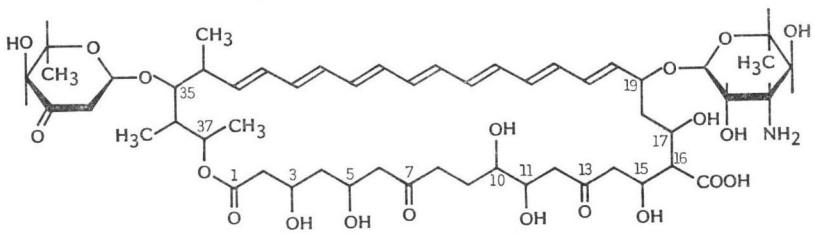

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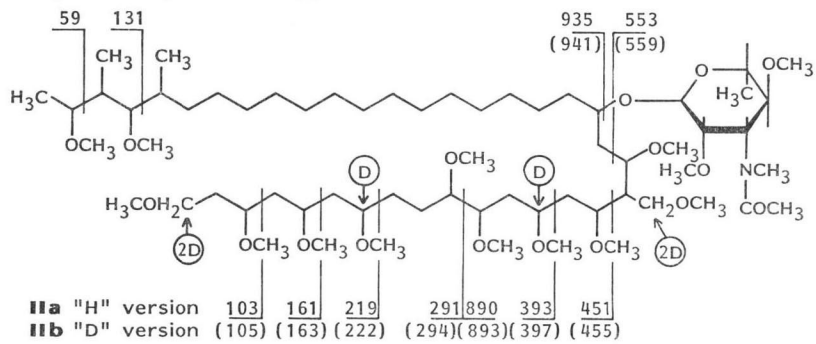
Fig. 2. The position of oxygen functions in the carbon skeleton of candidoin.



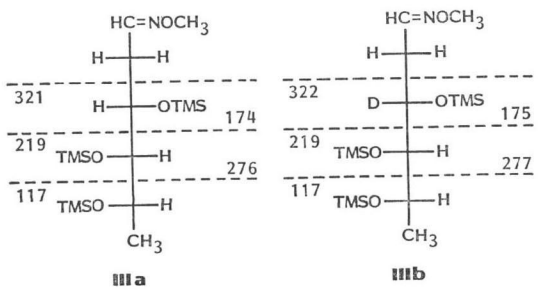
When methanolysis followed methylation (sequence of reactions 6 and 7 were reversed), the molecular ion at *m/z* 1,167 was observed in the "H" version, corresponding to the compound with one free hydroxyl group.

The structure and the place of attachment of 2,6-dideoxy-L-*erythro*-hexopyranos-3-ulose, the new naturally occurring sugar moiety, was established on the basis of mass spectral and optical rotation data. The derivative of 2-deoxy-L-rhamnose **IIIa** and its 3-deuterium analog **IIIb** was obtained in the following reaction sequence: 1) *N*-acetylation of candidoin, 2) ozonolysis, 3) reduction with sodium borohydride or sodium borodeuteride, 4) alkaline hydrolysis with barium hydroxide, 5) hydrolysis in the presence of sulfuric acid, 6) treatment with *O*-methylhydroxylamine hydrochloride, 7) silylation with *N*-trimethylsilylimidazole. The main diagnostic patterns of the EI spectra of these compounds are shown in Fig. 3.

The location of the glycosidic bond between the new sugar moiety and aglycone was determined by mass spectrometric analysis of the two diastereoisomeric glycosides obtained in the course of the reactions 1 to 4 of the above reaction sequence. One of these glycosides exhibited the same Rf value in TLC as that of L-digitoxoside obtained analogously from nystatin A_8[5,6]. The other was hydrolyzed to yield aglycone, 2,4-dimethylhexanetriol-1,3,5, identical with that isolated from nystatin A_8[5], and a sugar with the negative direction of optical rotation identical to that of 2-deoxy-L-rhamnose[7].

The place of attachment of mycosamine moiety was based on the mass spectral evidence of permethylated derivatives **IIa** and **IIb** and also on the fact that mild conditions of acid hydrolysis are sufficient to split the glycosidic bond in the antibiotic. It has been proved that the aminosugar is readily eliminated only from the allylic position in the molecule but not from the molecule with a reduced chromophore[4].

Fig. 3. The structure of silylated methoxime of 2-deoxy-L-rhamnose and of its 3-deuterio analog.



The proposed structure of the antibiotic was supported by the analysis of the FD mass spectrum of the methyl ester of *N*-acetyltetradecahydrotrimethoximecandidoin (**IV**) and EI mass spectrum of its silylated derivative (**V**). The peak of highest intensity of FD mass spectrum of **IV** was found at *m/z* 1,229 $(M+Na)^+$ confirms the presence of the lactone bond in the molecule. The location of the lactone bond at C-37 results from the position of sugar attachment at C-35. The EI spectrum of **V** was characterized by the presence of the molecular ion at *m/z* 1,854 and a fragmentation pattern consistent with the proposed location of all functionalities.

Acknowledgments

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