Tetrahedron Letters No. 17, pp 1533 - 1536. 0040-4039/79/0422-1533$02.00/0

THE STRUCTURE OF LIENOMYCIN, A NOVEL TYPE OF POLYENE MACROLIDE ANTIBIOTIC

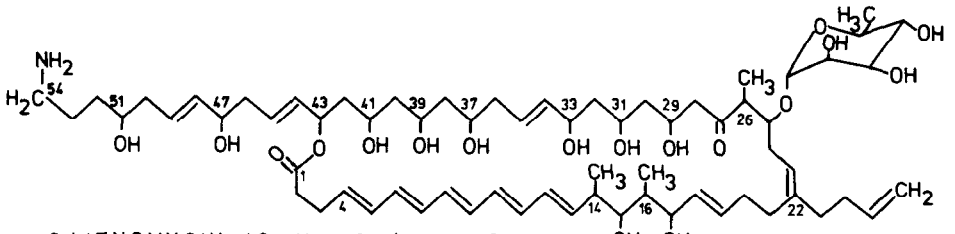
J.Pawlak, J.Zieliński, P.Kołodziejczyk, J.Golik, J.Gumieniak, E.Jereczek, E.Borowski

Department of Pharmaceutical Technology and Biochemistry,
M.K.Kudinova, M.G.Brazhnikova
Research Institute of New Antibiotics Acad. Med. Sci., Moscow, USSR

The pentaene macrolide antibiotic-lienomycin is produced by Actinomyces diastatochromogenes var. lienomycini [1].

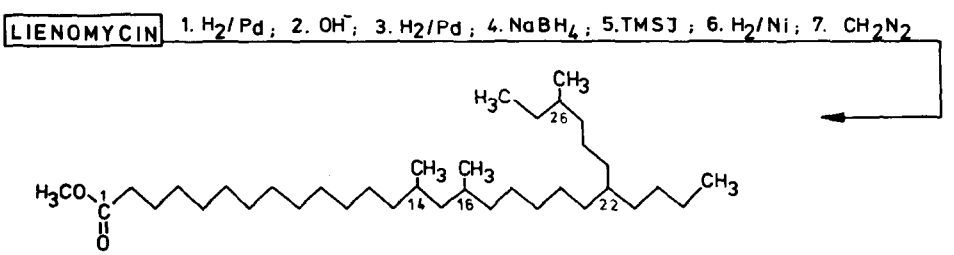
Besides antifungal activity, typical for polyene macrolides, lienomycin is characterized by antibacterial [2] and antitumor [3] activity.

Evidence on the structure of lienomycin, I, was obtained from mass spectroscopic analysis of the degradation products formed in appropriate chemical reactions.



I. LIENOMYCIN / $C_{67}H_{107}NO_{18}$ / M.W. 1213

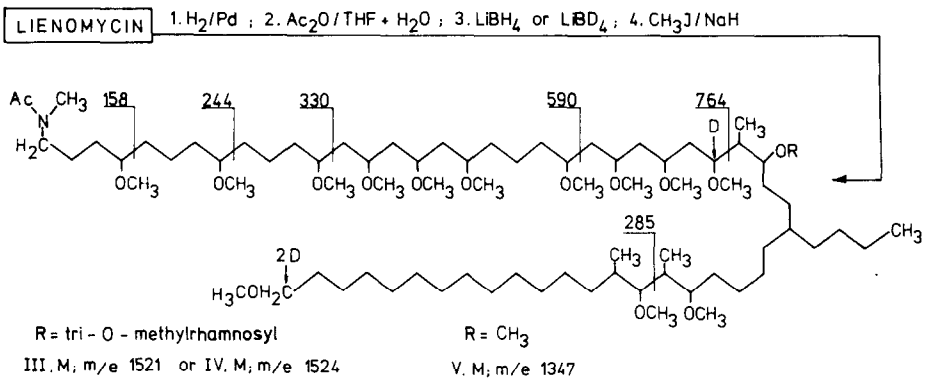
The structure of carbon skeleton between C_1 and C_{28} atoms of I was elucidated on the basis of the structure of the compound II. The sequence of reactions leading to the formation of II included at the step 2 a retroaldol cleavage of the bond between C_{28} and C_{29} of I.



II. M ; m/e 536

The evidence on the structure of II was obtained from mass spectroscopic analysis.

The structure of carbon skeleton between C_1 and C_{54} of I and the location of oxygen and nitrogen functions in this moiety were established by mass spectroscopic analysis of the compound III and of its deuterated analogue IV. The values m/e 1521 and m/e 1524 were determined for the molecular ions of III and IV, respectively.



The evidence on the location of methoxy groups and the N-methylacetamide moiety was obtained from the fragmentation patterns typical for methoxy compound and tertiary amides, observed in mass spectra of III and IV. Elementary composition of the ions m/e: 158, 244, 285, 330, 590, 764, as determined by high resolution mass spectrometry, confirmed the results obtained.

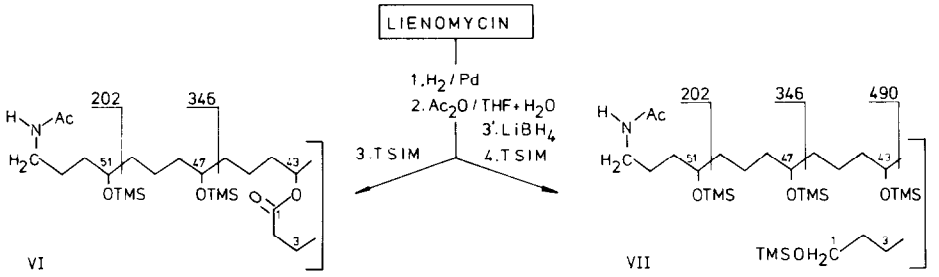
An acid hydrolysis of the compound III followed by methylation of the resulting hydroxy group led to the compound V. The evidence on the location of glycosidically bound rhamnopyranose at C_{25} in I originated from the comparison of the m/e fragmentation patterns in the mass spectra of the compounds III and IV.

Comparison of values of molecular and fragment ions observed in spectra of the compounds III and IV permitted the recognition of two deuterium atoms at C_1 and one at C_{27} in IV, respectively, and thus the presence of the carboxylic group at C_2 and the keto group at C_{27} in the lienomycin molecule was established.

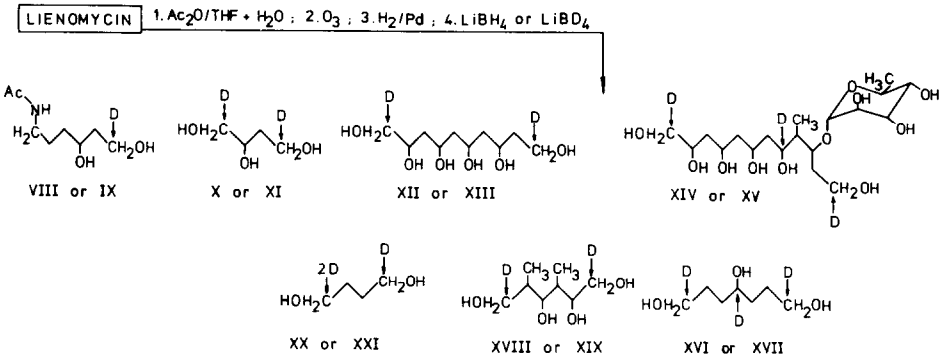
The comparison of fragment ions of cyclic and linear compounds VI and VII enabled unambigous location of a lactone bond between C_1 and C_{43} in the antibiotic molecule.

The latter evidence and the structure of the compounds II, III, IV and V allowed reconstruction of the antibiotic molecule with all double bonds reduced.

The location of isolated double bonds and of the pentaene chromophore in the lienomycin molecule is derived from the structure of the compounds VIII - XXI.



The chemical structures of the compounds VIII - XXI were established by mass spectrometric analysis of their volatile methyl or trimethylsilyl polyethers. The indicated deuterated analogues were obtained with lithium borodeuteride as a reducing agent.



The presence of deuterium atoms at terminal carbon atoms in the compounds IX, XI, XIII, XV, XVII, XIX and of one deuterium atom at C_4 in XVII resulted from the reduction of aldehyde and keto groups originating from catalytic reduction of ozonides. One deuterium atom at C_8 in XV and two deuterium atoms at C_1 in XXI resulted from the reduction of the keto group and the lactone bond existing in the native antibiotic molecule. The structures of the degradation products VIII - XXI and the structures of the compounds III and IV provided evidence for the presence of six isolated double bonds in the lienomycin molecule. The positions of isolated double bonds and of the pentaene

chromophore in the antibiotic molecule were determined from the positions of deuterium atoms, as determined by mass spectrometry, in the compounds IX, XI, XIII, XV, XVII, XIX and XXI.

The conformation of a glycosidically bound α -L-rhamnopyranose was determined on the basis of ^1H nmr analysis of the compound XIV.

Thus, the structure I was established for lienomycin, based upon all the evidence presented above.

It might be expected that a six-membered hemiketal ring structure between C_{27} and C_{31} of the lienomycin molecule can be formed, analogously to other polyene macrolides [4,5].

Lienomycin, I, exhibits novel structure features among polyene macrolides: a fourty four-membered macrolactone ring the largest of all polyenes, six isolated double bonds, a L-rhamnose moiety, and an amino group attached to the carbon skeleton of the antibiotic molecule.

ACKNOWLEDGMENTS

The authors acknowledge the financial support of these studies by the Institute of Immunology and Experimental Therapy, Polish Acad. of Sci., Wrocław, Poland.

REFERENCES

1. G.F.Gauze,T.S.Maksimova,O.L.Olhovatova,Je.S.Kudrina,G.B.Iltchenko, G.V.Kotchetkova,L.I.Volkova, Antibiotiki, 5, 387 (1971)

2. M.G.Brazhnikova,M.K.Kudinova,M.F.Lavrova,V.N.Borisova,Je.B.Kruglak, I.N.Korhavova,V.V.Proshlakova, Antibiotiki, 6, 483 (1971)

3. V.S.Bazhanov, Antibiotiki, 7, 593 (1972)

4. W.Mechliński,C.P.Schaffner,P.Gamis,G.Avitabile, Tetrahedron Letters, 3873 (1970)

5. Ramesh C. Pandey and Kenneth L.Rinehart,Jr., J.Antibiot., 10, 1035 (1976)

(Received in UK 27 February 1979)