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POLYENE ANTIFUNGAL ANTIBIOTICS : α AND β GLYCOSIDIC STRUCTURES IN LUCENSOMYCIN AND NYSTATIN

A. Boicelli*

Laboratorio dei Composti del Carbonio Contenenti Eteroatomi e Loro Applicazioni del C.N.R., Via Tolara di Sotto 89, Ozzano E. (Bologna), Italy

G. Rapi,* A. Ricci, M. Chelli and M. Ginanneschi

Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e Loro Applicazioni del C.N.R., c/o Istituto di Chimica Organica, Via G. Capponi 9, Firenze, Italy

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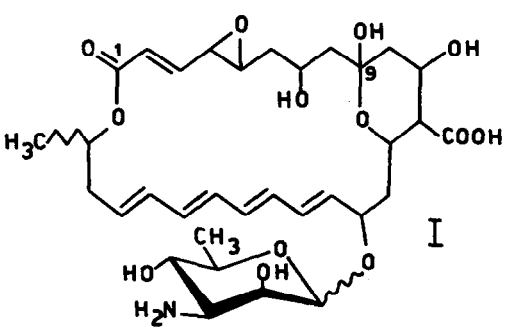
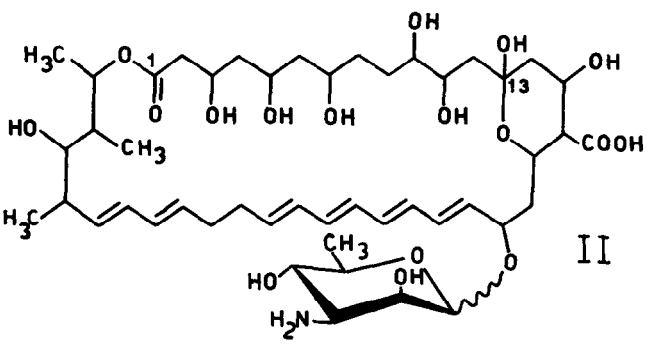
Antifungal antibiotics lucensomycin (I) and nystatin (II), present in their structures an amino sugar (mycosamine: 3-amino-3,6-dideoxy-D-mannose) glycosidically linked to the macrocyclic aglycone.[1]



I



II

The ^{13}C-NMR spectra (25.2 MHz, DMSO-d_6, t = 33 °C) show, in the region around 100 ppm from TMS, which is characteristic for hemiketal and acetal C atoms,[1,2,3] signals at 95.8, 96.2, 96.3 ppm for I,[4] and at 96.6, 97.4 ppm for II. In the fully coupled ^{13}C-NMR spectrum of I, the resonance at 96.3 ppm can be assigned to the quaternary 9-C. In turn signals at 96.2 and 95.8 can be associated with the 1'-C of the mycosamine, thus showing the existence of two types of acetal C atoms. In a similar way in II, the peak at 96.6 ppm results from the overlap of two resonances, one of them belonging to the 13-C and the other, as well as that at 97.4 ppm, can be assigned to the anomeric carbon of the mycosamine. The measured $J_{1'C-1'H}$ values show that the resonance at 96.2 ppm in I (J=165 Hz) is due to a carbon bearing an equatorial proton, while those at 95.8 in I and 96.6 in II (J=158 Hz) are due to C atoms bearing axial protons.[5] These values fit well, in fact, Bock's correlation between the

orientation of the anomeric protons and anomeric coupling constants (169-171 Hz for equatorial protons and 158-162 Hz for axial ones), which has proved to be valid [6,7] for free pyranoses and for glycopyranosides.

To ascertain the correct stereochemistry of the amino sugar, nystatin (II) has been hydrolysed and the mycosamine has been isolated as the N-carbobenzyloxy derivative (III);[8] the resulting mixture of the α and β anomers has been used as a conformational model for the mycosamine in antibiotics I and II. The ^{13}C-NMR spectrum of III shows two signals for the α and β anomeric carbons at 94.0 and 93.2 ppm and the corresponding $J_{1'C-1'H}$ values are 170 and 159 Hz respectively. Moreover ^{1}H-NMR (270 MHz, DMSO-d_6 and pyridine-d_5, t =29 °C) indicate that both the anomers of III have the same conformation; the $^{3}J_{H-H}$ (α anomer: J_{12}=2.1, J_{23}=3.0, J_{34}=11.0, J_{45}=9.4 Hz; β anomer: J_{12}=2.6, J_{23}=2.8, J_{34}=10.5, J_{45}=9.3 Hz) are in fact only compatible with a $^{4}C_{1}$ conformation but not for example with an inverted chair $^{1}C_{4}$,[9] less likely also because of steric interactions of bulky groups. The similarity of $J_{1'C-1'H}$ for III and the amino sugar glycosidically linked to the macrolides in I and II is therefore strongly suggestive of α and β configurations at the anomeric centres in these two antibiotics. Furthermore analysis of the $J_{1'C-1'H}$ values suggests that whereas the β anomer maintains the ideal chair conformation when linked to the macrolide backbone, the α is somewhat distorted.[10] The measured α / β ratios, deduced from the relative intensities of the peaks concerned, change with the nature of the aglyconic residue: the α anomer is 55% in I, but drops to 20% in II. These percentages are however only indicative because these antibiotics are natural blends of different natural active constituents [11] and the technique itself (^{13}C-NMR-FT) suffers from relatively large uncertainties in quantitative determinations.

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1) R. C. Pandey, K. L. Rinehart Jr., J. Antibiotics, 29, 1035 (1976); 2) J. B. Stothers, Carbon-13 NMR Spectroscopy, Academic Press, New York, N. Y., 1972; 3) K. Dornberg, H. Thrum, G. Engelhart, Tetrahedron Lett., 4469 (1976); 4) because of the small difference of chemical shifts (0.1 ppm) these signals are more clearly detectable in the fully coupled ^{13}C-NMR spectra; 5) the low intensity of the band at 97.4 ppm and the low solubility of II prevent to measure the related $J_{1'C-1'H}$; 6) K. Bock, I. Lundt, C. Pedersen, Tetrahedron Lett., 1037 (1973); 7) K. Bock, C. Pedersen, J. C. S. Perkin II, 293 (1974); 8) J. D. Dutcher, R. D. Walters, O. Wintersteiner, J. Org. Chem., 28, 995 (1963); 9) G. Descotes, F. Chizat, J. C. Martin, Bull. Soc. Chim. France, 2304 (1970); 10) K. Bock, C. Pedersen, Acta Chem. Scand., (B)29, 258 (1975); 11) A. H. Thomas, Analyst, 101, 321 (1976).