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Chemistry of Leucomycins. XI. Chemical Transformation of a Basic Macrolide to a Neutral Macrolide

The modification of the 16-membered macrolide antibiotics has been under study in our laboratory for several years.[1a,b] In this course of the study, the aglycone moiety[2] of leucomycin-A_3, leuconolide-A_3 5,18-hemiacetal has been succesfully isolated by applying the modified Polonovski reaction[3] to leucomycin-A_3 N-oxide. While, a new neutral macrolide was obtained from the same reaction product and it's structural determination was mainly investigated by means of proton and carbon-13 nuclear magnetic resonance (NMR) spectroscopy comparing with that of leucomycin-A_3 (I).

The oxidation of I with *m*-chloroperbenzoic acid in chloroform gave leucomycin-A_3 N-oxide (II), $[\alpha]_D^{18}$ −19.0 (c=0.5, ethanol) in a high yield (90%). Compound (II) was refluxed with acetic anhydride in chloroform for 1.5 hr and followed the hydrolysis with sodium bicarbonate in order to chemically modify the $NMe_2 \rightarrow O$ group at position-3′ on mycaminose moiety. The product was purified by silica gel column chromatography, obtaining a neutral macrolide, compound (III) as a main product (yield 35%) and aglycone moiety, leuconolide-A_3 5,18-hemiacetal (IV) (yield 10%) as shown in Chart 1. Compound (III) was crystallized from ether to give a colorless needles (mp 129—130°, $[\alpha]_D^{20}$ −104.2° (c=0.5, ethanol), UV $\lambda_{max}^{ethanol}$ nm (ε): 232 (10760), $C_{42}H_{64}O_{17}$). The acetylation of III with acetic anhydride and pyridine gave monoacetate (V) ($[\alpha]_D^{20}$ −106.4° (c=0.5, ethanol), $C_{44}H_{66}O_{18}$). The mass spectrum of V exhibited the fragmentation peak at *m/e* 451 due to the aglycone and that at *m/e* 229 due to isovaleryl mycarose moiety, suggesting that only the mycaminose moiety is subject to modification.

Concerning the structural information for III, NMR spectrometric investigation of I was carried out. The assignment of each proton on I was mainly performed by interpreting the NMR spectra of the α,β-isovaleryl mycarose, α,β-methyl-mycaminoside[4] and IV. The NMR spectrum (251 MHz) (Fig. 1) of I revealed the signals for olefinic proton at δ 5.5—6.8, β-anomeric on mycaminose at δ 4.3 ($J_{1',2'}$=7.4 Hz), α-anomeric on mycarose at δ 5.02 ($J_{1',2'}$= 2.8 Hz), and for position-2′,3′,4′ and 5′ on mycaminose at δ 2.7—3.6 region.

In the NMR spectrum (Fig. 2) of III, the signals of each proton based on aglycone and mycarose moiety unchanged comparing with those of I, but the signal of NMe_2 group observed at δ 2.56 in I disappeared, and an OAc group appeared at δ 2.1. Further, the each proton corresponding to position-1′,2′,3′, and 4′ on mycaminose disappeared in III, and the anomeric proton at position-1′ observed at δ 4.3 in I and the proton of the basis of the acetylated hydroxyl group at position-2′ appeared at δ 4.9 and δ 5.1 ($J_{1',2'}$=8.0 Hz) as a doublet, respectively, shifting to lower field. In order to assign the three protons observing at near δ 4.0, III was catalytic hydrogenated over PtO_2, forming tetrahydro compound (VI) ($[\alpha]_D^{22}$ −118.2°

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2) S. Ōmura, A. Nakagawa, K. Suzuki, T. Hata, A. Jakubowski, and M. Tishler, *J. Antibiotics*, **27**, 147 (1974).
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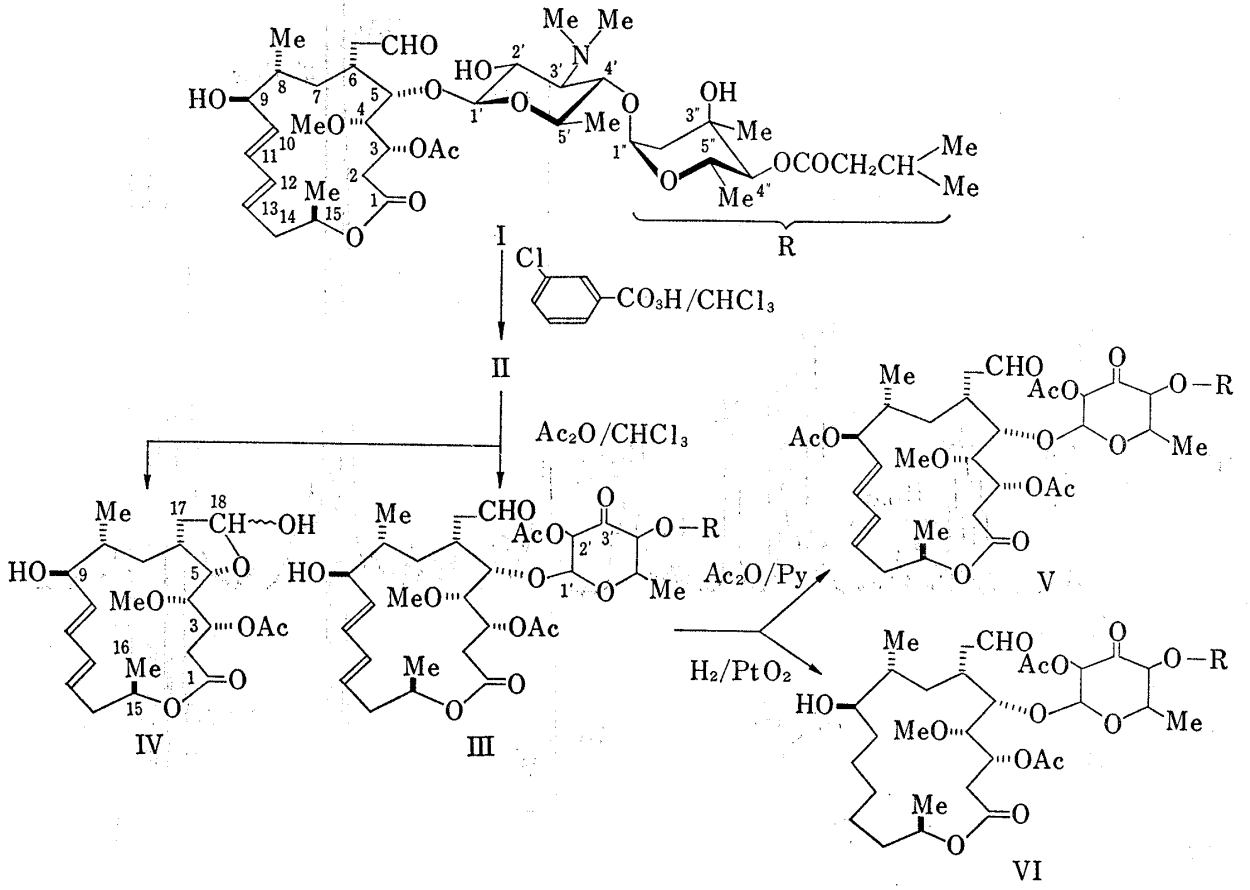

Chart 1 Py=pyridine

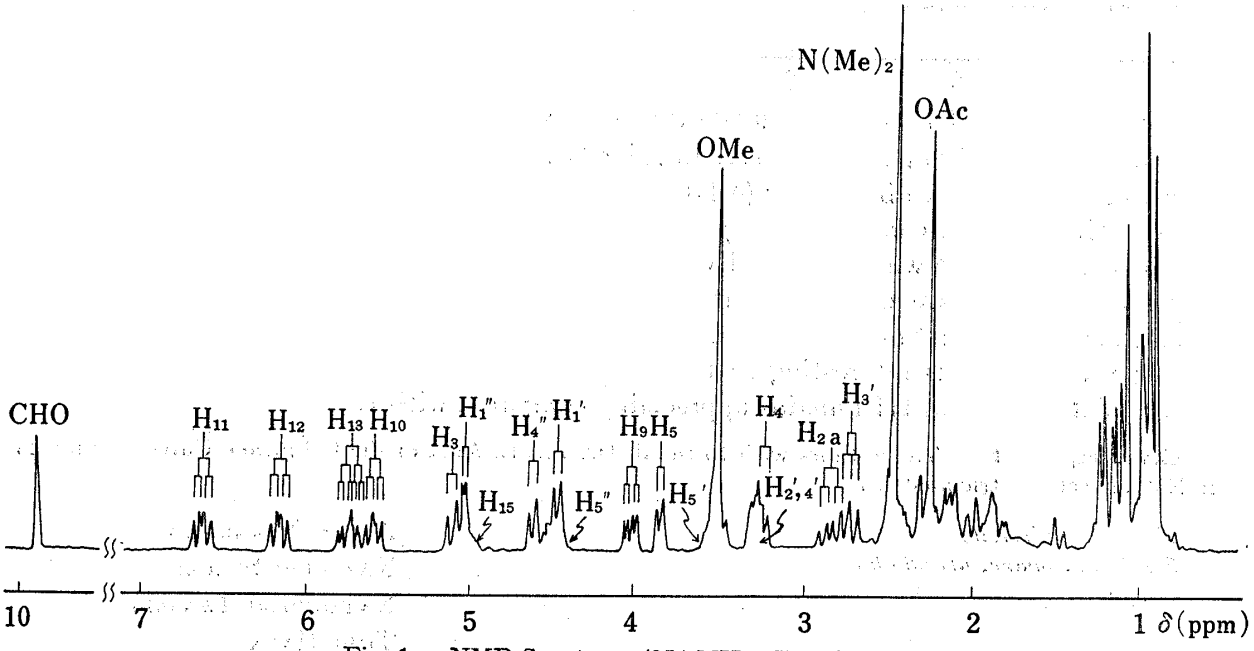

Fig. 1. NMR Spectrum (251 MHz, $CDCl_3$) of I

(c=0.5, ethanol)). In the NMR spectrum of VI, the proton of the basis of the OH group at position-9 observed at δ 4.0 as a double of doublet in I shifted to a high field region, and the remaining two protons of double of doublet at near δ 4.0 could be assigned as the protons of position-4′ on mycaminose and 5 on lactone ring, respectively. Also, from the comparison of the ^{13}C-NMR spectrum of III with that of I, two signals based on carbonyl group at δ 170

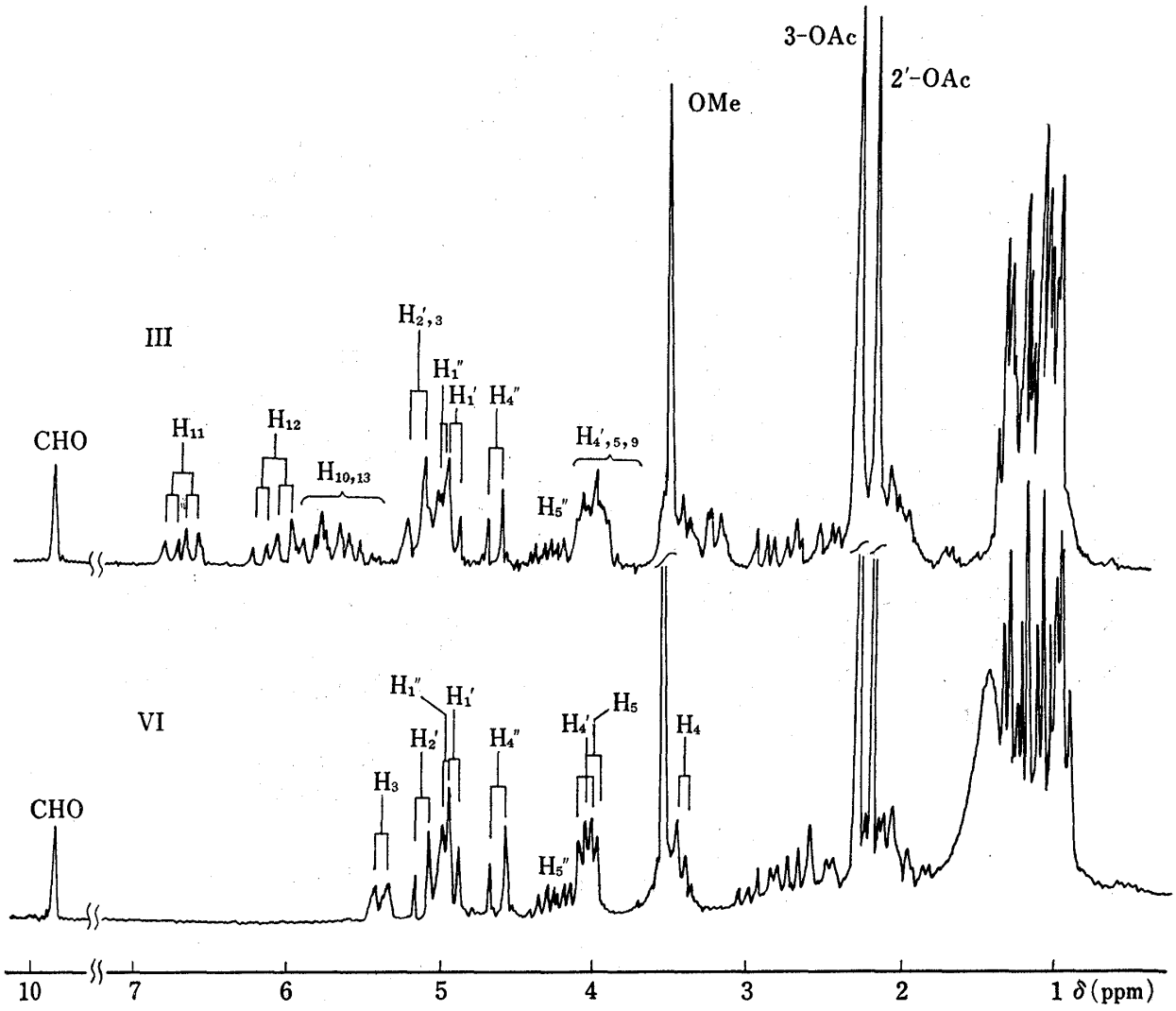

Fig. 2. NMR Spectra (100 MHz, $CDCl_3$) of III and VI

and δ 197 were freshly observed in III, and since these show singlet by a off-resonance, the both could be assigned to be a ester (δ 170) and ketone (δ 197) carbonyl carbons. From the result described above, compound (III) was confirmed to be 2'-O-acetyl 3'-desdimethylamino 3'-oxo-leucomycin-A_3 in which the >CHNMe$_2$ group at position-3' and the OH at position-2' on mycaminose in I are converted into a ketone and O-acetyl group respectively.

Thus, this is the first report on the chemical conversion of a basic 16-membered macrolide to a neutral one. It is interesting in the point of structure-activity relationship that the antimicrobial activity of III remains appreciably compared with I.

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