MYCINAMICINS, NEW MACROLIDE ANTIBIOTICS. III ISOLATION AND STRUCTURES OF MYCINAMICIN AGLYCONES, MYCINOLIDE IV AND V

Sir:

The mycinamicins are a new family of basic 16-membered macrolide antibiotics with novel skeletons[1] which have strong antibacterial activity against Gram-positive bacteria[2]. In the course of structural studies on the mycinamicins, we obtained new interesting products from mild acid treatment of these antibiotics. In this communication, we would like to describe the structures of 16-membered aglycones retaining the original lactone structures of mycinamicin IV (**1**) and V (**2**). They are named mycinolide IV (**3**) and mycinolide V (**6**), respectively.

When **1** was heated in 0.2 N hydrochloric acid (pH 2.0) at 90°C for 4 days, new products were formed. Purification by silica gel column chromatography afforded **3**, **4** and **5**, in yield 21, 3 and 24%, respectively. The physicochemical

Table 1. Physicochemical properties of **3**, **4** and **5**.

	3	**4**	**5**
Formula	$C_{21}H_{32}O_5$	$C_{29}H_{46}O_9$	$C_{29}H_{47}NO_7$
mp	242~243°	90~92°	244~245°
$[\alpha]_D^{27}$	+24.3° (*c* 0.5, MeOH)	−1.4° (*c* 0.5, MeOH)	+49.9° (*c* 0.5, DMSO)
CIMS *m/z* (isobutane)	365 (MH^+), 347	539 (MH^+), 521, 365, 349, 347, 331, 329, 175	522 (MH^+), 365, 347, 329, 176, 174, 158
UV λ_{max}^{MeOH} nm (log ε)	215, 281.5 (4.27) (4.34)	215, 281.5 (4.24) (4.27)	215, 281 (4.31) (4.33)
IR ν_{max}^{KBr} cm^{-1}	3,440, 1,700, 1,660, 1,640, 1,615, 1,580	3,460, 1,710, 1,680, 1,645, 1,630, 1,590	3,510, 3,400, 1,710, 1,670, 1,650, 1,625, 1,595
^1H NMR δ (CD_3COCD_3)	Fig. 1.	3.48 (3H, s, OCH_3) 3.54 (3H, s, OCH_3) 4.57 (1H, d, *J*=8.0 Hz, H-1″)	2.28 (6H, s, $N(CH_3)_2$) 4.29 (1H, d, *J*=7.3Hz, H-1′)

Fig. 1. ^1H NMR spectrum of **3** (in $CD_3COCD_3+D_2O$).

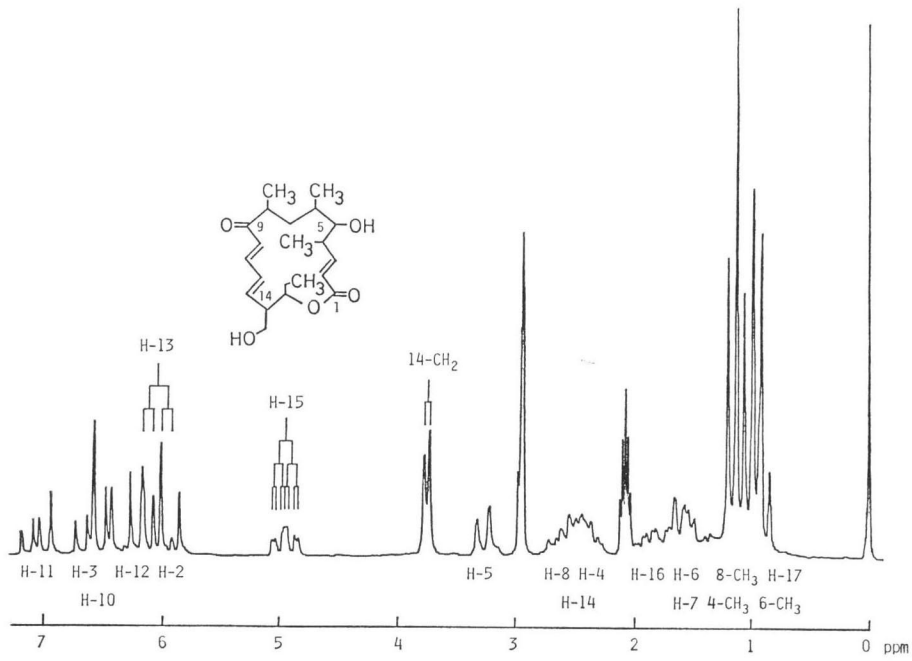
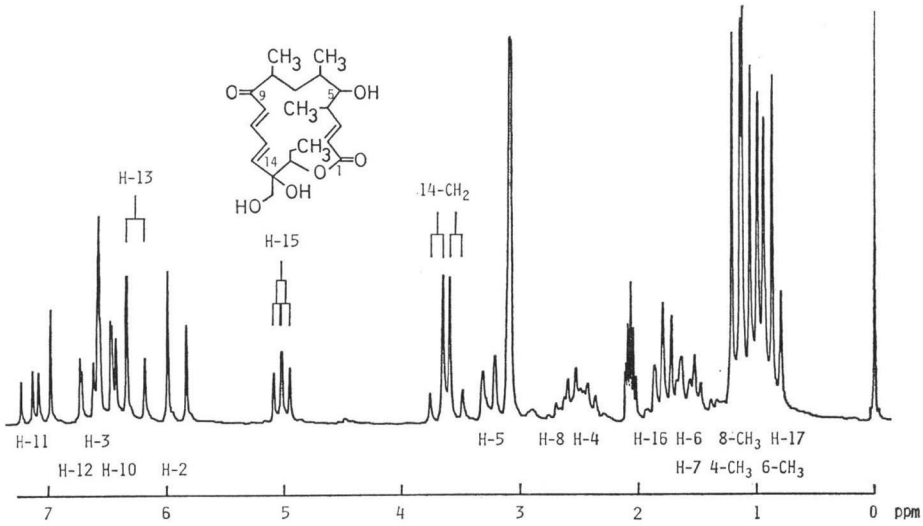


Table 2. Physicochemical properties of **6**, **7** and **8**.

	6	**7**	**8**
Formula	$C_{21}H_{32}O_6$	$C_{29}H_{46}O_{10}$	$C_{29}H_{47}NO_8$
mp	268~269°	109~112°	271~272°
$[\alpha]_D^{27}$	+36.8° (*c* 0.5, MeOH)	+14.2° (*c* 0.5, MeOH)	+58.1° (*c* 0.5, DMSO)
CIMS *m/z* (isobutane)	381 (MH^+), 363, 345	555 (MH^+), 537, 381, 365, 363, 347, 345, 175	538 (MH^+), 381, 363, 345, 176, 174, 158
UV λ_{max}^{MeOH} nm (log ε)	215, 280.5 (4.28) (4.34)	215, 281 (4.27) (4.30)	215, 280 (4.31) (4.33)
IR ν_{max}^{KBr} cm^{-1}	3,540, 3,380, 1,700, 1,665, 1,640, 1,620, 1,585	3,460, 1,705, 1,675, 1,640, 1,625, 1,590	3,420, 1,700, 1,665, 1,650, 1,620, 1,590
^1H NMR δ (CD_3COCD_3)	Fig. 2.	3.51 (3H, s, OCH_3) 3.55 (3H, s, OCH_3) 4.60 (1H, d, *J*=8.0 Hz, H-1″)	2.30 (6H, s, $N(CH_3)_2$) 4.29 (1H, d, *J*=7.1 Hz, H-1′)

Fig. 2. ^1H NMR spectrum of **6** (in $CD_3COCD_3+D_2O$).



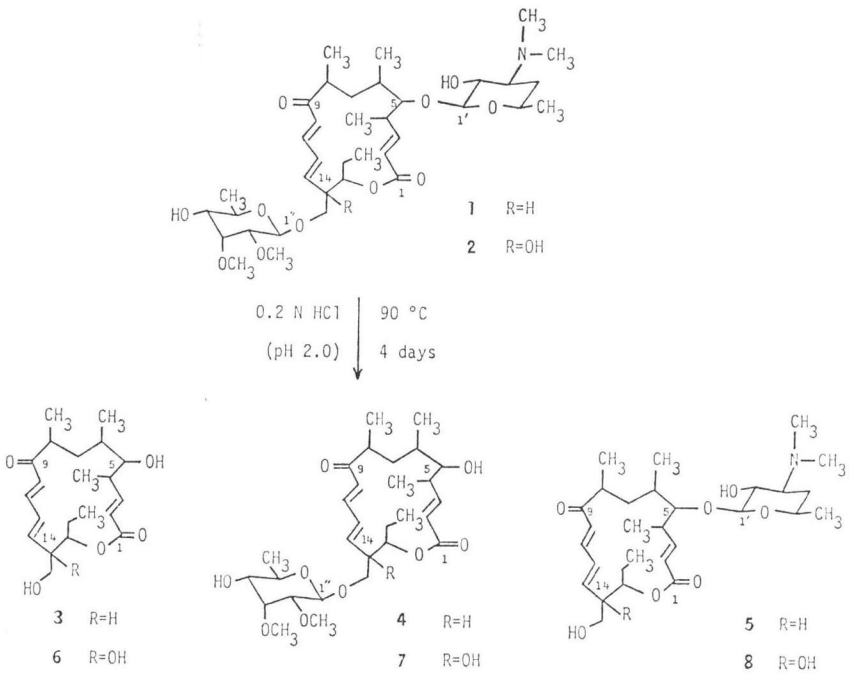
properties of these degradation products are summarized in Table 1.

The chemical ionization (CI) mass spectrum of **3** showed predominantly the protonated molecular ion (MH^+) at *m/z* 365 using isobutane as reagent gas. However, diagnostic ions (*m/z* 176, 174, 158 and 175) for desosamine and mycinose moieties could not be detected at all[8]. In addition, the characteristic signals for a $-N(CH_3)_2$, two $-OCH_3$ and two anomeric protons derived from the constituent sugars observed in the ^1H-NMR spectrum of **1** disappeared in that of **3** (Fig. 1).

These results demonstrate that **3** is the true aglycone moiety, mycinolide IV, which is formed by cleavage of the glycosidic bonds between the aglycone and sugar moieties. Acetylation of **3** with acetic anhydride and pyridine gave a diacetyl derivative, mp 152~153°, $C_{25}H_{36}O_7$, $[\alpha]_D^{27}$ +30.8° (*c* 0.5, MeOH), UV λ_{max}^{MeOH} 279 nm (log ε 4.35). In addition, structural information from the ^1H-NMR and CI mass spectra of **4** and **5** indicates that they are the partially hydrolyzed products, dedesosaminyl-mycinamicin IV (**4**) and demycinosyl-mycinamicin IV (**5**), as shown in Fig. 3, respectively.

In the same manner, **2** also gave three degradation products, **6**, **7** and **8**, in yield 22, 4 and 21%, respectively. They were characterized as in Table 2. The protonated molecular ion (*m/z* 381) in the CI mass spectrum of **6** appeared at 16 u. higher than the corresponding ion of **3**,

Fig. 3. Acid hydrolysis of mycinamicin IV and V.



suggesting that **6** had an additional oxygen atom in the molecule. A comparison of the ^{1}H-NMR spectrum of **3** (Fig. 1) with that of **6** (Fig. 2), showed that the splitting patterns of H-13 (dd), H-15 (ddd) and 14-CH_2 (d) in **3** are altered from those of H-13 (d), H-15 (dd) and 14-CH_2 (d and d) in **6**, respectively. These results suggest that **6** is a 14-hydroxylated mycinolide IV, namely mycinolide V. Furthermore, detailed analyses of diagnostic ions from the CI mass spectra and significant signals from the ^{1}H-NMR spectra of **7** and **8** show that they are dedesosaminyl-mycinamicin V (**7**) and demycinosyl-mycinamicin V (**8**), as shown in Fig. 3, respectively.

Since it is normally very difficult to obtain the intact aglycone moiety of a basic 16-membered ring macrolide antibiotic on acid hydrolysis[4~7], it is surprising that the intact aglycones, mycinolide IV (**3**) and V (**6**) together with the partial hydrolysis products, **4**, **5**, **7** and **8**, are produced in this case.

Acknowledgement

We wish to thank Miss H. OHARA of this laboratory for her technical assistances.

MITSUO HAYASHI*
MASARU OHNO
KENJI KINOSHITA
SHUZO SATOI

Research Laboratories, Toyo Jozo Co., Ltd., Ohito, Shizuoka, 410-23, Japan

MAKOTO SUZUKI
KEN-ICHI HARADA

Faculty of Pharmacy, Meijo University Tempaku-ku, Nagoya, 468, Japan

(Received November 17, 1980)

References

1) HAYASHI, M.; M. OHNO & S. SATOI: Structures of mycinamicins. J. C. S., Chem. Commun. 1980: 119~121, 1980
2) SATOI, S.; N. MUTO, M. HAYASHI, T. FUJII & M. OTANI: Mycinamicins, new macrolide antibiotics. I. Taxonomy, production, isolation, characterization and properties. J. Antibiotics 33: 364~376, 1980
3) SUZUKI, M.; K. I. HARADA, N. TAKEDA & A. TATEMATSU: Chemical ionization mass spectra of new macrolide antibiotics, M-4365 A_2 and G_2. Heterocycles 8: 199~205, 1977
4) ŌMURA, S.; A. NAKAGAWA, K. SUZUKI, T. HATA,

A. JAKUBOWSKI & M. TISHLER: Isolation and structure of leuconolide-A_8 5,8-hemiacetal and 9-dehydro-18-dihydroleuconolide-A_8. J. Antibiotics 27: 147~149, 1974

5) NAKAGAWA, A.; K. SUZUKI, K. IWASAKI, K. KAJI, S. ŌMURA, A. JAKUBOWSKI & M. TISHLER: Application of the modified POLONOVSKI reaction to leucomycin-A_8 N-oxide. Chem. Pharm. Bull. 24: 1749~1756, 1976

6) GIROTRA, N. N. & N. L. WENDLER: Leucomycin aglycones. Deglycosidation of the macrolide antibiotics leucomycin A_8. Tetrahed. Lett. 1975: 227~230, 1975

7) TATSUTA, K.; A. TANAKA, K. FUJIMOTO, M. KINOSHITA & S. UMEZAWA: Synthesis of carbomycin B. Introduction of the amino disaccharide onto the 16-membered-ring aglycone. J. Am. Chem. Soc. 99: 5826~5827, 1977