[Chem. Pharm. Bull.
18(9)1720—1723(1970)]

UDC 547.918.02.04 : 615.332.011.5

Studies on Pillaromycin A. IV.[1] The Structure of Pillaromycin A[2]

Mitsuko Asai, Eiji Mizuta, Kōmei Mizuno,
Akira Miyake and Sueo Tatsuoka

Research and Development Division, Takeda Chemical Industries, Ltd.[3]

(Received December 25, 1969)

The structure of pillaromycin A (I, PMA), $C_{28}H_{28}O_{11}$, is elucidated as I. In PMA (I) 12a hydroxyl of pillaromycinone (II, PMN), $C_{20}H_{18}O_7$, is linked glycosidicaly to the 1′-anomeric hydroxyl of pillarose (III), $C_8H_{12}O_5$.

A molecular formula, $C_{28}H_{28}O_{11}$, was given for pillaromycin A (I, PMA) from elementary[2] and X-ray[2] analyses and mass spectrometry, [1,2] and which was smaller than the sum of the molecular formulae of pillaromycinone[2,4] (II, PMN) plus pillarose (III)[1,2] by H_2O. The ultraviolet (UV) spectra[2] of I and II have similar absorption maxima and intensities each other. Four aromatic ring protons (6.74—7.44 ppm), a vinyl proton (7.08 ppm, s) and an acetyl (2.43 ppm) observed in the nuclear magnetic resonance (NMR[5]) spectrum of I (in CD_3OD) are also observed in the NMR spectrum of II[2] (in CD_3OD) at the same magnetic field (Table I). Signals assigned to phenolic OAc (two) and aliphatic OAc (three) were observed in the NMR spectrum of PMA pentaacetate (IV)[2] obtained by full acetylation of I (Table I). Thus, one acetyl conjugated with α,β-unsaturated double bond, two *sec*-hydroxyls and two chelated hydroxyls found in II are also found in I. These facts suggest that the aglycone moiety in I has derived to II without any configurational deformation. The signals of H_3 and H_4 in I shift to lower field on actylation, and their coupling constants are same as those in II. As the $J_{4,4a}$ value of 12 cps, the $J_{4a,5a}$ value of 4 cps and the $J_{4a,5b}$ value of 2 cps in I are the same as those in II, it is concluded that H_4 and H_{4a} protons in I lie in a diaxial relationship and that the conformation of C and D rings in I is as same as that in II.

In the NMR spectrum of I (in CD_3OD) the $\mathrm{Me{-}\overset{H'_5}{\underset{|}{C}}{-}O{-}}$ due to the pillarose moiety at 4.12 ppm (q) would be attributed to $\mathrm{Me{-}\overset{H'_5}{\underset{|}{C}}{-}O{-}}$ group. Field decoupling by irradiation in the region of the methyl protons at 0.52 ppm (d) shows a change in the H'_5 proton, the collapse of the quartette to a singlet. The NMR spectrum also displays signals of the H'_{3a}, H'_{3b} and H'_2 protons due to pillarose moiety, 1.59 ppm (2H, m) and 2.13 ppm (1H, m) respectively. Decoupling by irradiation at 2.1 ppm (H'_2) shows changes in the H'_1 and H'_3 protons, the collapses of the doublet (H'_1, 5.50 ppm) to a singlet and of the multiplet (H'_3, 1.59 ppm) to a broad singlet. In the NMR spectrum of IV (in $CDCl_3$) the signals due to the anomeric proton (at 5.28 ppm) and H'_5 proton (at 4.39 ppm) of pillarose moiety do not show the lowerfield shift, but the signal of two H'_{8a}, H'_{8b} protons (4.91 ppm, 2H, s) due to aliphatic methylene protons of pillarose moiety shows the lowerfield shift by the acetylation (Table I). In the NMR spectrum of I (in DMSO), the H'_8 protons are coupling with the neighbouring hydroxyl

---

[1] Part III: M. Asai, *Chem. Pharm. Bull.* (Tokyo), **18**, 1713 (1970).
[2] M. Asai, *Chem. Pharm. Bull.* (Tokyo), **18**, 1699 (1970).
[3] Location: *Juso, Higashiyodogawa-ku, Osaka.*
[4] M. Asai, *Chem. Pharm. Bull.* (Tokyo), **18**, 1706 (1970).
[5] NMR spectra were measured on a Varian HA-100 spectrometer. The chemical shifts were expressed in δ value from TMS (internal reference).

Table I. NMR Spectra of Pillaromycin A(I, PMA), PMA Mono-*m*-bromobenzoate (V) and PMA Pentaacetate (IV) (100 Mc in CD_3OD, d_5-Pyridine and $CDCl_3$)

		OH[a)]	H 8	H 6	H 7	H 1	H 9	H 1′
I (CD_3OD)	δ (ppm)		7.44 t 1H	7.41 s 1H	7.12 q 1H	7.08 s 1H	6.74 q 1H	5.50 d 1H
	J (cps)		8		8 1.5		8 1.5	2
I (d_5-Pyridine)	δ	8.6 b	7.44 t 1H	7.56 s 1H	7.08 q 1H	7.02 s 1H	6.88 q 1H	5.64 d 1H
	J		8		8 1.5		8 1.5	2
V ($CDCl_3$)	δ	13.8 s 1H						5.32 d 1H
	J							2
IV ($CDCl_3$)	δ		7.54 t 1H	7.30 s 1H	7.64 q 1H	7.26 s 1H	7.10 q 1H	5.28 d 1H
	J		7		7 1.5		7 1.5	2

		OH[a)]	H 3	H 8′	H 5′	H 4	H 5	H 4a	Ac 11
I (CD_3OD)	δ (ppm)	4.73	4.55 d 1H	4.43 s 2H	4.12 q 1H	3.4 —3.24 m 3H		2.81 m 1H	
	J		4					4,4a=12 4a,5=4 4a,5=2	
I (d_5-Pyridine)	δ		4.73 d 1H	4.80 s 2H	4.50 q 1H	3.59—3.70 m 3H		3.19 m 1H	
	J		4		7				
V ($CDCl_3$)	δ		4.48 d 2H	4.42 s 2H	4.26 q 1H	3.2 —3.4 m 3H		2.7 m 1H	2.7
	J		4		7				
IV ($CDCl_3$)	δ		6.05 d 1H	4.91 s 2H	4.39 q 1H	4.65 q 1H	3.50 m 1H	3.02 m 1H	2.43 s 3H
	J		4		7	4 12			

		Me 14	OAc	OAc	OAc	OAc	H 2′	H 3′	Me 6′
I (CD_3OD)	δ (ppm)	2.43 s 3H					2.13 m 1H	1.59 m 2H	0.52 d 3H
	J (cps)								7
I (d_5-pyridine)	δ	2.44 s 3H					2.35 m 1H	1.66 m 2H	0.79 d 3H
	J								7
V ($CDCl_3$)	δ	2.37 s 3H					2.1 m 1H	1.6 m 2H	0.68 d 1H
	J								7
IV ($CDCl_3$)	δ	2.34 s 3H	2.34 s 3H	2.23 s 3H	2.05 s 3H	1.97 s 3H	2.2 m 1H	1.63 m 2H	0.98 d 3H
	J								7

s=singlet, d=doublet, t=triplet, q=quartette, b=broad

a) substitutes with D_2O

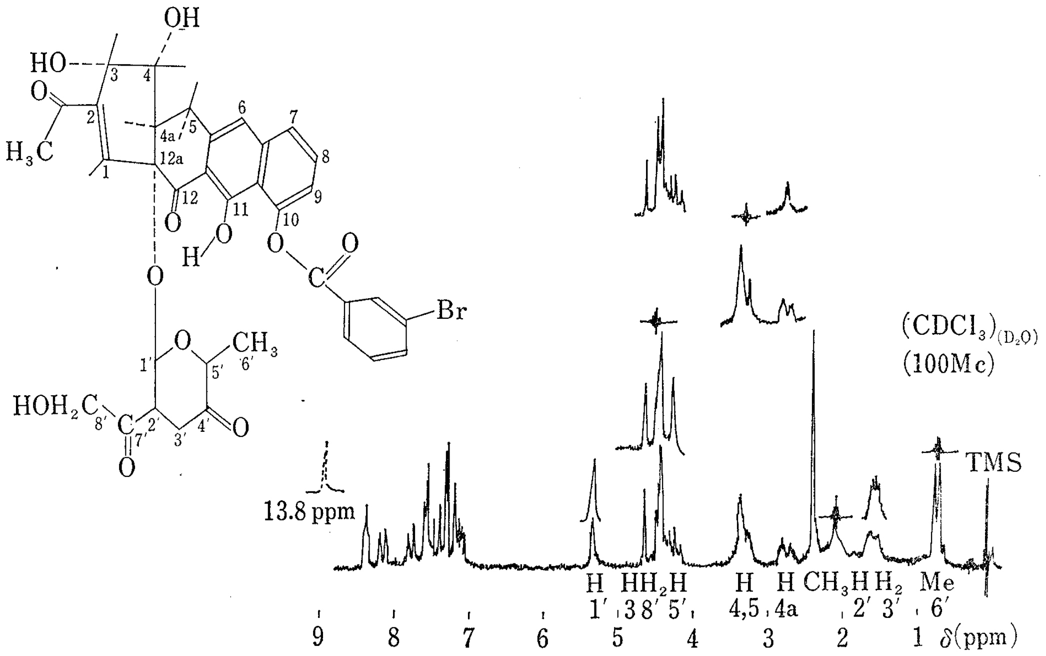
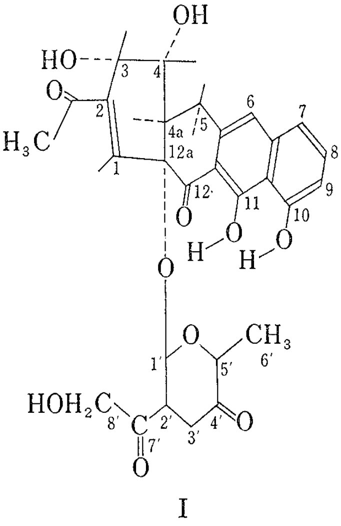


Fig. 1. NMR Spectrum of PMA Mono-*m*-bromobenzoate (V)

and decoupled by addition of D_2O. These evidence shows the presence of the residue $-\overset{H}{\underset{H}{C'_8}}-OH$ in I. Now, a new chloroform soluble derivative, PMA mono-*m*-bromobenzoate (V), useful for the NMR study of I was obtained by benzoylation at C_{10}–OH of I. In the NMR spectrum of V (in $CDCl_3$) the signal of a chelated hydroxyl[6] at near 9 ppm disappeared and a signal at 13.8 ppm was observed.



I

Chart 1

The NMR spectra of I, IV and V (Table I) and the spin decoupling of V (Fig. 1) told the relationships between the functional groups and substituents in I, II, III, IV and V. All protons observed in II plus III are similarly observed in I, so, the structures of II and III may be applied for the elucidation of the structure of I.

Next, the combination between PMN and pillarose is discussed. From the NMR spectra of PMA pentaacetate (IV), PMN tetraacetate (VI), 8-O-monoacetylpillarose (VII)[1] and PMA mono-*m*-bromobenzoate (V) two *sec*-hydroxyls, two chelated hydroxyls of II and $CH_3-\overset{H}{\underset{|}{C}}-O-$ group and the primary hydroxyl of III are omitted from the combination. So, the sole possibility of the combination remains at the *tert*-hydroxyl in II and the anomeric hydroxyl in III. Now it is concluded that pillaromycin A (PMA) must have the structural formula I. This conclusion is supported by the fact that on acid hydrolysis of IV gives VI and VII.

---

[6] These protons were observed in the NMR spectrum of isopropylidene PMN (in $CDCl_3$) in part II.

Experimental[7]

PMA Mono-*m*-bromobenzoate (V)——PMA (500 mg) in pyridine (5 ml) was benzoylated with *m*-bromobenzoyl chloride (0.6 ml) under ice cooling for 10 min. The resulting substance was purified on the preparative thin-layer chromatography.[8] Green yellowish fluorescent band (under ultraviolet light (R_f: 0.35)) was eluted with ethyl acetate, and crystallized with ethyl acetate:benzene (195 mg). mp 165—167°. *Anal.* Calcd. for $C_{35}H_{31}O_{12}Br$: C, 58.10; H, 4.32; Br, 11.04. Found: C, 57.70; H, 4.62; Br, 10.54. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ ($\varepsilon \times 10^{-3}$): 222.5 (39.40), 255 (34.05), 269 (36.29), 293 (9.04), 304 (9.90), 317 sh (4.54), 404 (7.09). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3400, 1740, 1720, 1685, 1630, 1620. NMR (100 Mc in $CDCl_3$) shows in Table I and Fig. 1.

Acknowledgement The authors are indebted to Professors K. Nakanishi, Columbia University, N. Masamune, Hokkaido University, and T. Takemoto, Tohoku University, for their valuable advices. Thanks are also due to members in charge of physicochemical measurements.

---

[7] All melting points were uncorrected.

[8] See Part I, experimental part.