Tetrahedron Letters,Vol.26,No.29,pp 3475-3478,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

THE STRUCTURES OF NEW ISOTETRACENONE ANTIBIOTICS, KERRIAMYCINS A, B AND C

Yoichi Hayakawa, Kazuo Furihata, Haruo Seto and Noboru Ōtake*
Institute of Applied Microbiology, The University of Tokyo,
Bunkyo-ku, Tokyo, Japan 113

Summary: Based on ^{1}H and ^{13}C NMR spectral analysis, the structures of kerriamycins A, B and C, new isotetracenone antibiotics, have been elucidated as shown in Fig. 1. Kerriamycin A contains a novel sugar, kerriose.

Kerriamycins A, B and C are new antitumor antibiotics produced by Streptomyces violaceolatus A32, which belong to the isotetracenone antibiotic group.[1] The kerriamycins inhibit the growth of Gram-positive bacteria and prolong the survival periods of mice bearing Ehrlich ascites carcinoma.

Hydrolysis of each kerriamycin with 2H HCl for 2 hours at room temperature gave aquayamycin[2,3] as an aglycone part, which was extracted with ethyl acetate and identified by direct comparison with an authentic sample. Aquayamycin ($C_{25}H_{26}O_{10}$), an antitumor antibiotic, contains a modified benz[a]anthraquinone chromophore which is characteristic to the isotetracenone antibiotics.

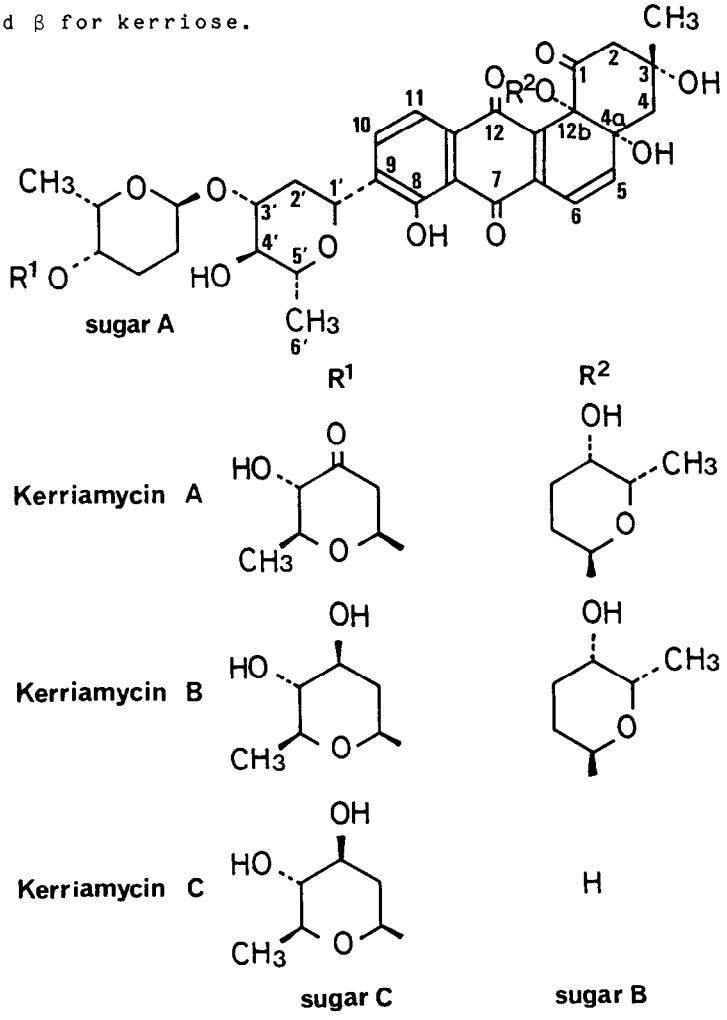
The 400 MHz ^{1}H NMR spectrum[4] of kerriamycin A (I) [$C_{43}H_{54}O_{17}$; FAB-MS, m/z 865 $(M+Na)^{+}$] in $CDCl_3$ showed the following signals; δ 12.31 (s, 8-OH), 7.91 (d, J=7.9Hz, 10-H), 7.67 (d, J=7.9, 11-H), 6.89 (d, J=9.9, 6-H), 6.41 (d, J=9.9, 5-H), 4.88 (d, J=11.0, 1'-H), 4.35 (br.s, 4'-OH), 3.72 (ddd, J=10.0, 8.2, 4.0, 3'-H), 3.50 (dq, J=8.6, 6.1, 5'-H), 3.18 (dd, J=8.6, 8.2, 4'-H), 2.78 (dd, J=12.7, 2.8, 2-Ha), 2.51 (d, J=12.7, 2-Hb), 2.46 (dd, J=13.0, 4.0, 2'-Heq), 2.17 (dd, J=14.8, 2.8, 4-Ha), 1.85 (d, J=14.8, 4-Hb), 1.43 (3H, d, J=6.1, 6'-H), 1.42 (ddd, J=13.0, 11.0, 10.0, 2'-Hax) and 1.24 (3H, s, 3-CH_3) ascribed to the aquayamycin moiety (I), δ 5.04 (br.s, 1-H), 4.13 (q, J=6.8, 5-H), 3.60 (br.s, 4-H), 2.15 (m, 2-Ha), 2.01 (m, 3-Ha), 1.99 (m, 3-Hb), 1.58 (m, 2-Hb) and 1.21 (3H, d, J=6.8, 6-H) due to sugar A (II), δ 5.39 (br.s, 1-H), 3.67 (q, J=6.8, 5-H), 3.44 (br.s, 4-H), 1.90 (2H, m, 2-H), 1.89 (m, 3-Ha), 1.72 (m, 3-Hb) and 0.58 (3H, d, J=6.8, 6-H) due to sugar B (III), 4.67 (dd, J=9.1, 2.5, 1-H), 3.81 (d, J=9.7, 4-H), 3.44 (br.s, 4-OH), 3.28 (dq, J=9.7, 5.8, 5-H), 2.92 (dd, J=14.0, 2.5, 2-Heq), 2.81 (dd, J=14.0, 9.1, 2-Hax) and 1.46 (3H, d, J=5.8,

6-H) due to sugar C (IV), which were assigned by 2-D COSY spectral analysis.

The components II and III were identified as rhodinose[5] (2,3,6-trideoxy-threo-hexopyranose) by the above spectral data. The component IV was elucidated to be a 2,6-dideoxyhexopyranose with a quaternary carbon at C-3 by ^{1}H NMR spectral analysis. The chemical shifts of 2-Hax, 2-Heq and 4-H and the ketone carbonyl carbon observed at δ 201.1 suggest that IV is a 3-ulose. In addition, the long range coupling (1.5 Hz) was observed between 2-Hax and 4-H, which are in a 1,3-diaxial-2-keto system.[5] From these analysis, the structure of IV was established to be 2,6-dideoxy-erythro-hexopyran-3-ulose. As far as we know, IV is a novel sugar found for the first time from a natural source and thus, the name kerriose was given.

Based on the coupling constants of the anomeric protons, the anomeric configurations of the sugar moieties were established to be α for each rhodinose and β for kerriose.

Fig. 1



The NOE observed between 1-H of II and 3'-H of I and between 1-H of IV and 4-H of II indicate that the glycosidic linkages between sugar A, C and the aquayamycin moiety are as shown in Fig. 1. Irradiation of H-1 (δ5.39) of sugar B caused the NOE enhancement on the carbon[7] at δ 80.2 assigned to C-12b,[9] thereby showing that the remaining rhodinose (III) is glycosidically connected to C-12b of the aquayamycin part. From these analysis, the structure of 1 was determined to be as shown in Fig. 1.

The ^{1}H and ^{13}C NMR spectra of kerriamycin B (2)[4] [$C_{43}H_{56}O_{17}$; FAB-MS, m/z 867 $(M+Na)^{+}$] in CD_3OD showed a close resemblance to those of 1 except for signals relating to sugar C. The ^{1}H NMR assignments of sugar C in 2 are as follows; δ 4.57 (dd, J=9.6, 1.8 Hz, 1-H), 3.49 (ddd, J=12.0, 8.9, 5.3, 3-H), 3.22 (dq, 9.4, 5.9, 5-H), 2.90 (dd, J=9.4, 8.9, 4-H), 2.20 (ddd, J=12.2, 5.3, 1.8, 2-Heq), 1.55 (ddd, J=12.2, 12.0, 9.6, 2-Hax) and 1.26 (3H, d, J=5.9, H-6). By these spectral data, sugar C in 2 was identified as olivose[8] (2,6-dideoxy-*arabino*-hexopyranose) with the β-configuration, indicating that kerriamycin B

Table 1. ^{13}C chemical shift assignments of kerriamycins A, B and C (ppm)

	A ($CDCl_3$)	B (CD_3OD)	C (CD_3OD)		A	B	C
				Sugar A			
				1	96.9	95.2	95.1
1	204.9	204.0	206.1	2	25.1	25.7	25.7
2	53.9	54.8	53.2	3	24.5	25.5	25.5
3	75.3	77.0	77.5*	4	76.4	77.5	77.5
$3\text{-}CH_3$	29.9	30.1	30.3	5	67.1	67.8	67.7
4	43.3	44.5	44.8	6	17.1	17.5	17.5
4a	81.6	82.6	81.9	Sugar B			
5	144.5	146.0	145.8	1	94.4	95.4	
6	116.4	117.6	117.9	2	23.1	24.3	
6a	136.9	138.2	138.7	3	25.4	26.5	
7	187.2	189.0	189.0	4	66.8	67.8	
7a	113.5	115.1	115.1	5	67.0	68.1	
8	157.4	158.2	158.2	6	16.6	17.0	
9	138.1	138.7	139.5	Sugar C			
10	133.4	134.1	134.0	1	101.6	102.6	102.6
11	119.7	120.0	119.7	2	46.9	40.7	40.7
11a	129.8	131.9	131.8	3	201.1	72.2	72.2
12	181.6	183.4	182.9	4	78.0	78.3	78.3
12a	138.5	141.1	140.0	5	72.6	73.1	73.1
12b	80.2	82.4	77.8*	6	18.8	18.5	18.5

* interchangeable

is a derivative of 1 possessing olivose in place of kerriose (Fig. 1).

The ^{1}H and ^{13}C NMR spectra of kerriamycin C (3)[4] [$C_{37}H_{46}O_{15}$: FAB-MS, m/z 753 $(M+Na)^{+}$] in CD_3OD revealed that the signals due to sugar B in 2 disappeared in 3 with the remaining part unchanged. Thus, kerriamycin C was elucidated to be the 12b-O-derhodinosyl derivative of 2 (Fig. 1).

The ^{13}C chemical shift assignments[4] of these kerriamycins were achieved by 2-D C-H correlation spectral analysis and long range selective proton decoupling experiments. The results are summarized in Table 1.

In order to establish the absolute configuration, kerriamycin B was hydrolyzed with 2N HCl at room temperature for 2 hours to give aquayamycin, rhodinose and olivose. The specific rotations of olivose ($[\alpha]_D^{21}$ +50°, c 0.26, H_2O) and 2,4-dinitrophenylhydrazone of rhodinose ($[\alpha]_D^{22}$ -19°, c 0.08, pyridine) reveal that these sugars are D-olivose (lit. +31°)[8] and L-rhodinose (lit. -14.9°)[5], respectively.

From these experimental results, the structures of kerriamycins A, B and C have been established as shown in Fig. 1.

Acknowledgements We wish to thank Dr. T. Aoyagi, Institute of Microbial Chemistry, for providing us with an authentic sample of aquayamycin. This work was supported in part by a Grant-in-Aid for Developmental Scientific Research from The Ministry of Education, Science and Culture of Japan (No. 59860012).

References and footnotes

1) Y. Hayakawa, T. Iwakiri, K. Imamura, H. Seto and N. Ōtake, J. Antibiotics, in press.

2) M. Sezaki, S. Kondo, K. Maeda, H. Umezawa and M. Ohno, Tetrahedron, 26, 5171 (1970).

3) K. Ohta, E. Mizuta, H. Okazaki and T. Kishi, Chem. Pharm. Bull., 32, 4350 (1984).

4) ^{1}H and ^{13}C NMR spectra were obtained on a JEOL GX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. Chemical shifts are given in ppm using TMS as internal standard.

5) C. L. Stevens, P. Blumbergs and D. L. Wood, J. Am. Chem. Soc., 86, 3592 (1964).

6) P. Laszlo and J. I. Musher, Bull. Soc. Chim. France, 2558 (1964).

7) N. Niccolai, C. Rossi, V. Brizzi and W. A. Gibbons, J. Am. Chem. Soc., 106, 5732 (1984).

8) Yu. A. Berlin, G. V. Borisova, S. E. Esipov, M. N. Kolosov and V. A. Krivoruchko, Chem. Abst. 71, 50409 (1969).

9) The C-H long range couplings observed between C-4a (δ81.6) and 6-H (δ6.89) and between C-3 (δ75.3) and 3-CH_3 (δ1.24) indicates that the remaining quaternary oxycarbon (δ80.2) is assignable to C-12b.

(Received in Japan 31 March 1985)