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A NEW DERIVATIVE OF ANTIBIOTIC B-58941

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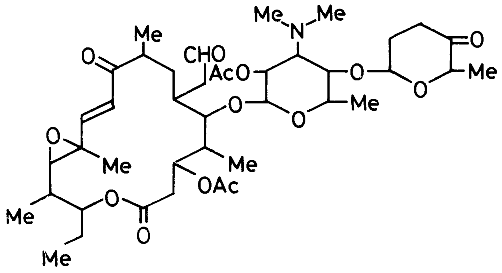
Structure of new compound derived by reaction of diacetate of antibiotic B-58941 with sodium methoxide in methanol is assumed as 2'-O-acetyl-2,3-anhydro-13-hydroxy-12-methoxy-depoxy B-58941. It is also assumed that in antibiotic B-58941, D-mycaminose and 4-ulose sugar are bound to C-5-O of the aglycone (by β-linkage) and to C-4'-O of D-mycaminose (by α-linkage), respectively.

In the previous reports, mild hydrolysis of antibiotic B-58941[1)] (I), $C_{37}H_{59}O_{12}N$ $\left[\lambda_{max}^{EtOH}\ 240\ nm\ (\varepsilon = 16200)\right]$ gave a neutral sugar[2)] (IV), $C_6H_{10}O_3$ (2,3,6-trideoxy-L-hexopyranos-4-ulose) and B-58941-B (V), $C_{31}H_{51}O_{10}N$. Treatment of depoxy B-58941-B,[3)] $C_{31}H_{51}O_9N$ with sulfonic acid-type resin in methanol gave D-mycaminose[2)] (VI), $C_8H_{17}O_4N$ and a new condensate of aglycone[3)] (VII), $C_{24}H_{38}O_6$ (3,5-dihydroxy-4,8,12,14-tetramethyl-9-oxo-6,8-(18-methoxyethano)-10,12-heptadecadien-15-olide). And formula II[1)] has been proposed as the plain structure of antibiotic B-58941 diacetate (II), $C_{41}H_{63}O_{14}N$ $\left[\lambda_{max}^{EtOH}\ 240\ nm\ (\varepsilon = 15100)\right]$. This report deals with the structure of the new compound (III) derived from II and both positions of VI and IV in I and III together with their conformations of glycosidic linkages.



II

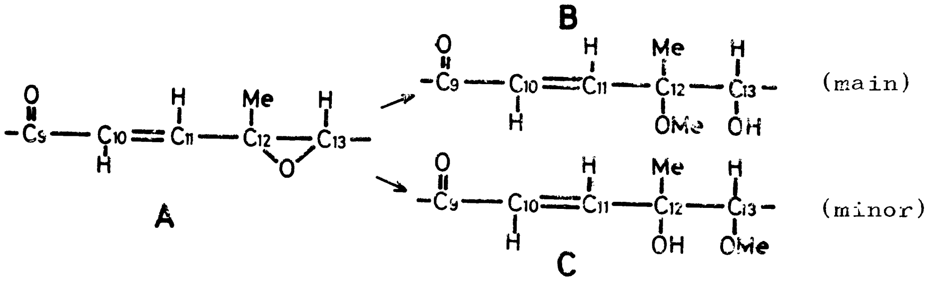
II was reacted with sodium methoxide (two moles) in absolute methanol for two hours at room temperature, followed by adjustment of the reaction mixture to pH 8.5 with acetic acid in absolute methanol and evaporation of methanol, and the mixture was separated by chromatography on silica gel column to give a new compound (III) which has one acetyl group as a main component, $C_{40}H_{63}O_{13}N$ [mp 116°C, λ_{max}^{MeOH} 215 nm (ε = 18200), ν_{max}^{KBr} 1745 (ester CO), 1730 (lactone CO, aldehyde CO), 1724 (isolated CO), 1695 (conjugated CO), 1645, 1625 cm^{-1} ($>C=C<$), NMR (Table 1), m/e 765 (M^+)] and a new compound (VIII) which has one acetyl group as a minor component, $C_{40}H_{63}O_{13}N$ [mp 106°C, λ_{max}^{MeOH} 215 nm (ε = 17200), m/e 765 (M^+)]. When III was acetylated with acetic anhydride in pyridine, its monoacetate (IX), $C_{42}H_{65}O_{14}N$ [mp 117°C, m/e 807 (M^+)] was obtained, but no further acetylation of VIII occurred.

The UV absorption maximum (ε = 18200) at 215 nm of III shows a clear change in the chromophore comparing with the maxima at 240 nm of I and II. In the IR spectrum of III, the absorptions due to an epoxy group (900, 850, 800 cm^{-1}) are extinguished and a remarkable increase of the absorption due to -CH=CH- at 1645 cm^{-1} is observed. In the NMR spectrum of III, two vinyl protons (6.80, 5.80 ppm) and one methoxy (3.30 ppm) are newly observed, but one acetyl (2.10 ppm) and one (2.1 ppm) of the methylene protons are extinguished comparing with the NMR spectrum of II. And in the NMR spectrum of IX, the signal of H-13 is shifted to a lower magnetic field. The molecular formula and the UV spectrum of

Table 1. Chemical shifts and coupling constants of the protons of III ($CDCl_3$, 100 MHz)

δ, ppm		multiplicity	J-value, Hz	functional group	δ, ppm		multiplicity	J-value, Hz	functional group
9.62	1H	t	2	$-CH_2-C\underline{H}O$	3.2	1H	m		$-CH-\overset{O-}{C}\underline{H}-CH_3$
6.80	1H	dd	15,10	$-CH=C\underline{H}-CH-$	3.2	1H	d		$-C-\overset{O-}{C}\underline{H}-CH-$
6.51	1H	d	16	$-C-C\underline{H}=CH-$	2.6	1H			$-CH-\overset{Me}{C}\underline{H}-CH-$
6.30	1H	d	16	$-C-C\underline{H}=CH-$	2.6	1H	t	9	$-CH-\overset{-N-}{C}\underline{H}-CH-$
5.80	1H	d	15	$-C-C\underline{H}=CH-$	2.40	6H	s		$-CH-N(C\underline{H}_3)_2$
5.05	1H	dd	4,6	$-O-\overset{O-}{C}\underline{H}-CH_2-$	2.05	3H	s		$-O-CO-C\underline{H}_3$
5.0	1H	t	9	$-CH-\overset{O-}{C}\underline{H}-CH-$	1.44	3H	s		$-C-C\underline{H}_3$
4.8	1H	dt	3,9	$-CH-\overset{O-}{C}\underline{H}-CH_2-$	1.25	3H	d	6	$-CH-C\underline{H}_3$
4.66	1H	q	7	$-C-\overset{O-}{C}\underline{H}-CH_3$	1.21	3H	d	7	$-CH-C\underline{H}_3$
4.28	1H	d	9	$-O-\overset{O-}{C}\underline{H}-CH-$	1.17	3H	d	7	$-CH-C\underline{H}_3$
3.58	1H	dd	10,2	$-CH-\overset{O-}{C}\underline{H}-CH-$	1.10	3H	d	7	$-CH-C\underline{H}_3$
3.30	3H	s		$-O-C\underline{H}_3$	1.06	3H	d	7	$-CH-C\underline{H}_3$
3.2	1H	t		$-CH-\overset{O-}{C}\underline{H}-CH-$	0.85	3H	t	6	$-CH_2-C\underline{H}_3$

VIII are the same as those of III, and its IR and NMR spectra are very similar to those of III. VIII may have a tertiary hydroxyl group which does not exist in III, and therefore, cleavages of epoxy bonding[4)] (partial structure (A)) in II must have taken place according to the two ways (partial structures (B) of III and (C) of VIII) as shown in the following scheme.



Furthermore, upon spin-decoupling of III, an irradiation of H-2 (5.80 ppm, d, J=15 Hz) makes H-3 (6.80 ppm, dd, J=15 and 10 Hz) a doublet (J=10 Hz) and reversely, irradiation of H-3 (6.80 ppm) makes H-2 (5.80 ppm) a singlet together with decoupling of H-4 (2.65 ppm). Thus, they (H-2, H-3) are assigned to trans vinyl protons. Irradiation of H-4 (2.65 ppm) makes H-3 (6.80 ppm) a doublet

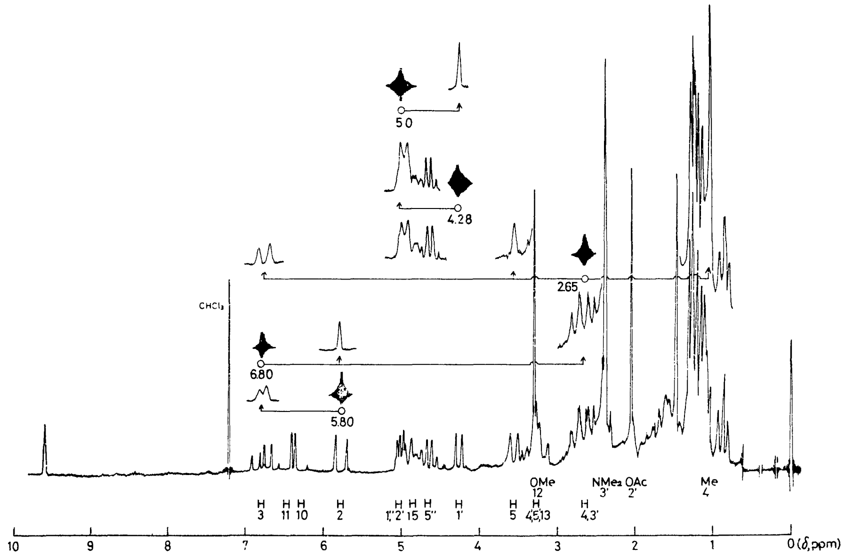
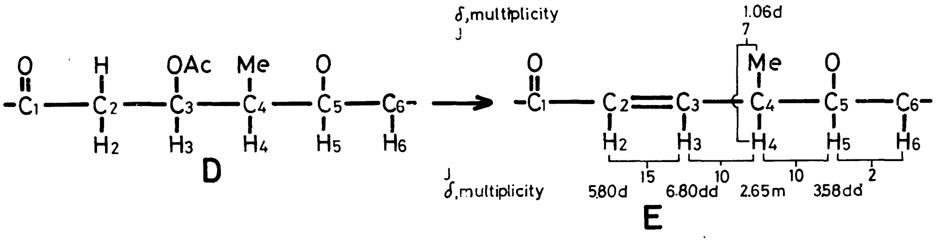


Fig. 1. NMR spectrum and spin-decoupling of III ($CDCl_3$, 100 MHz)

(J=15 Hz) and makes C-4-Me (1.06 ppm, d, J=7 Hz) a singlet together with decoupling of H-5 (3.58 ppm, dd, 10, 2 Hz ⟶ d, 2 Hz). From these data the formula

(E) may be proposed as the partial structure of III. Namely, one mole of acetic acid was lost from II by β-elimination to give a new double bond ($-C_2 = C_3-$) conjugated to the lactone carbonyl ($C_1 = O$).



On the basis of the fact that the new compound III is obtained, respective binding positions and configurations of D-mycaminose and 4-ulose moieties in I, II and III can be confirmed from the description detailed below.

At first, comparing the NMR spectrum of III with that of II, no change is observed except for the partial structures (B) and (E). Since there are two α,β-unsaturated carbonyls in the structure of III, the strong absorption ($\mathcal{E}$ = 18200) at 215 nm is observed in its UV spectrum. Thus, it is clear that the binding position of D-mycaminose in III is C-5-O.

Furthermore, the protons which are found as doublet at 4.22, 4.26 and 4.28 ppm in the NMR spectra of I, II and III, respectively, may be assigned as the anomeric protons (H-1') of D-mycaminose moieties in these compounds, in comparison with the chemical shift and multiplicity of the anomeric proton of methyl-D-mycaminoside reported in the previous paper.$^{2)}$ The protons found at 3.69 (in I), 5.0 (in II) and 5.0 ppm (in III) which are coupled with each anomeric proton (H-1') of D-mycaminose moieties may be assigned as H-2' in the respectively corresponding compounds. Thus, it may be revealed that the hydroxyl group at C-2' of D-mycaminose moiety in I is free and those in II and III are acetylated. Therefore, it is concluded that in each compound 4-ulose is bound at C-4'-O of D-mycaminose moiety.

Secondary, the anomeric protons H-1' of D-mycaminose moiety in III as well as I are coupled to H-2' with J=9 Hz. From this coupling constant, it is clear that D-mycaminose moiety is bound with β-linkage in I or III.

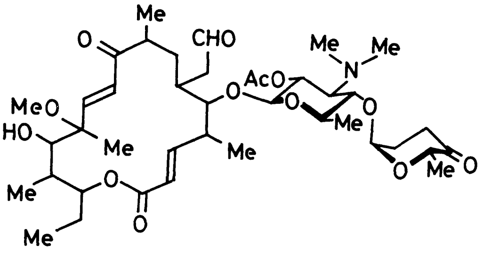
On the other hand, the anomeric protons H-1" of 4-ulose moiety in III as well as I are coupled to H-2"a with J=4 Hz and to H-2"b with J=6 Hz, and therefore it is also clear that 4-ulose moiety is bound with α-linkage in I or III.

All protons in I and III are assigned as shown in Table 2, and the total structures of III and I are shown as the formula III (2'-O-acetyl-2,3-anhydro-13-hydroxy-12-methoxy-depoxy B-58941) and formula I (5-[3',6'-dideoxy-3'-dimethylamino-4'-O-(2'',3'',6''-trideoxy-α-L-hexopyranos-4''-ulosyl)-β-D-glucopyranosyloxy]-6-formylmethyl-3-hydroxy-4,8,12,14-tetramethyl-9-oxo-12,13-epoxy-10-heptadecen-15-olide), respectively.

Table 2. NMR spectra of antibiotic B-58941 (I) and III ($CDCl_3$, 100 MHz)

		H 18	H 11	H 10	H 1''	H 15	H 5''	H 1'	H 3	H 2'	H 5	H 4',5'	OH 3,2'	OH 13	OMe 12	H 13	H 3'
I	δ (ppm)	9.70	6.54	6.34	5.10	4.83	4.47	4.22	3.84	3.69	3.56	3.3	3.3			2.78	2.6
		t	d	d	dd	dt	q	d	dt	t	dd					d	
		1H	1H	1H	1H	1H	1H	1H	1H	1H	1H	2H	2H			1H	1H
	J (Hz)	2	16	16	4 6	3 9	7	9	10 2	9	10 2					8	
III	δ (ppm)	9.62	6.51	6.30	5.05	4.8	4.66	4.28	6.80	5.0	3.58	3.2		3.3	3.30	3.2	2.6
		t	d	d	dd	dt	q	d	dd	t	dd				s	d	
		1H	1H	1H	1H	1H	1H	1H	1H	1H	1H	2H		1H	3H	1H	1H
	J (Hz)	2	16	16	4 6	3 9	7	9	15 10	9	10 2						

		NMe 3'	H 2	H 8,19	OAc 2'	H 6,7,14,16,2',3''	H 4	Me 12	Me 6'	Me 6''	Me 8	Me 14	Me 4	Me 17
I	δ (ppm)	2.52	2.5-1.9	2.6-2.4		1.9-1.5	1.5-1.3	1.40	1.26	1.24	1.18	1.11	1.09	0.85
		s						s	d	d	d	d	d	t
		6H	2H	3H		10H	1H	3H	3H	3H	3H	3H	3H	3H
	J (Hz)								6	7	7	7	7	6
III	δ (ppm)	2.40	5.80	2.8-2.4	2.05	2.0-1.6	2.6	1.44	1.25	1.21	1.17	1.10	1.06	0.85
		s	d		s			s	d	d	d	d	d	t
		6H	1H	3H	3H	10H	1H	3H	3H	3H	3H	3H	3H	3H
	J (Hz)		15						6	7	7	7	7	6



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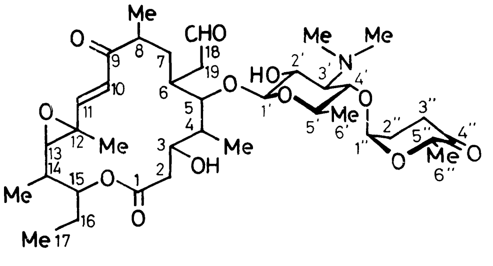

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