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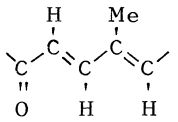
A NEW CONDENSATE OBTAINED FROM THE AGLYCONE MOIETY OF ANTIBIOTIC B-58941

Takashi SUZUKI, Eiji MIZUTA, and Norio SUGITA
Microbiological Research Laboratories, Central Research Division,
Takeda Chemical Industries, Ltd., Higashiyodogawa-ku, Osaka 532

A new condensate (macrocyclic lactone) is obtained by refluxing depoxy B-58941-B, prepared by depoxidation of antibiotic B-58941, with sulfonic acid-type resin in methanol. The structure of the condensate is assumed as 3,5-dihydroxy-4,8,12,14-tetramethyl-9-oxo-6,8-(1-methoxyethano)-10,12-heptadecadien-15-olide.

Antibiotic B-58941[1] (I), $C_{37}H_{59}O_{12}N$ dissolved in acetic acid was reacted with potassium iodide at 65°C for three hours to give a basic lipophilic substance, depoxy B-58941-B (II), $C_{31}H_{51}O_9N$ [mp 122°C, λ_{max}^{EtOH} 278 nm (ε = 19500), ν_{max}^{KBr} 1730 (lactone CO), 1710 (isolated CO), 1665 (conjugated CO), 1595 cm^{-1} (>C = C<), NMR (Table 1), m/e 581 (M^+)]. The increase of the absorption maximum (ε = 19500) at 278 nm in the UV spectrum of II and the presence of three olefinic protons and a vinyl methyl in the NMR spectrum of II indicate that a new chromophore due to $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl group was formed. In the NMR spectrum of II all protons due to D-mycaminose moiety[2,3] are observed, but no proton due to the neutral sugar moiety[3] of I is observed. And hydrolysis of II in 2 N hydrochloric acid gave about one mole of D-mycaminose, but gave no neutral sugar of I. Thus, II may be identical with depoxycirramycin A_1 which was obtained from cirramycin A_1 by Tsukiura.[4]

When methanol solution of II was refluxed with sulfonic acid-type ion exchange resin, D-mycaminose was adsorbed on the resin and a new condensate (III), $C_{24}H_{38}O_6$ [prisms, mp 190°C, $[\alpha]_D^{22}$ -46.2° ($CHCl_3$), λ_{max}^{EtOH} 276 nm (ε = 20000), ν_{max}^{KBr} 3400 (OH), 1700 (lactone CO), 1665 (conjugated CO), 1595 (>C = C<), 982 cm^{-1} (cyclopentane), NMR (Table 1, Fig. 1), m/e 422 (M^+)] was obtained from the reaction mixture. Acetylation of III with acetic anhydride in pyridine gave its diacetate (IV), $C_{28}H_{42}O_8$ [prisms, mp 204°C, λ_{max}^{EtOH} 275 nm (ε = 18000), $\nu_{max}^{CHCl_3}$ 1740 (ester CO), 1735 (lactone CO), 1245 cm^{-1} (-O-CO-CH_3), NMR ($CDCl_3$, 100 MHz) δ 2.06 (s, 3H, -CO-CH_3), 2.02 ppm (s, 3H, -CO-CH_3), m/e 506 (M^+)]. From these data of III and IV, it is suggested that III has the following groups: one $-CH_2-CH_3$, two $-\overset{|}{C}H-CH_3$, one $-\overset{|}{C}-CH_3$, one $-O-CH_3$, two $-\overset{|}{C}H-OH$ and one group of -CO-O- and that III as well as II have also a partial structure of  , because

of the strong absorption (ε = 20000) observed at 276 nm in its UV spectrum, which is very similar to that of carbomycin B,[5] of the presence of three olefinic

Table 1. NMR spectra of depoxy B-58941-B (II) and III, ($CDCl_3$, 100 MHz)

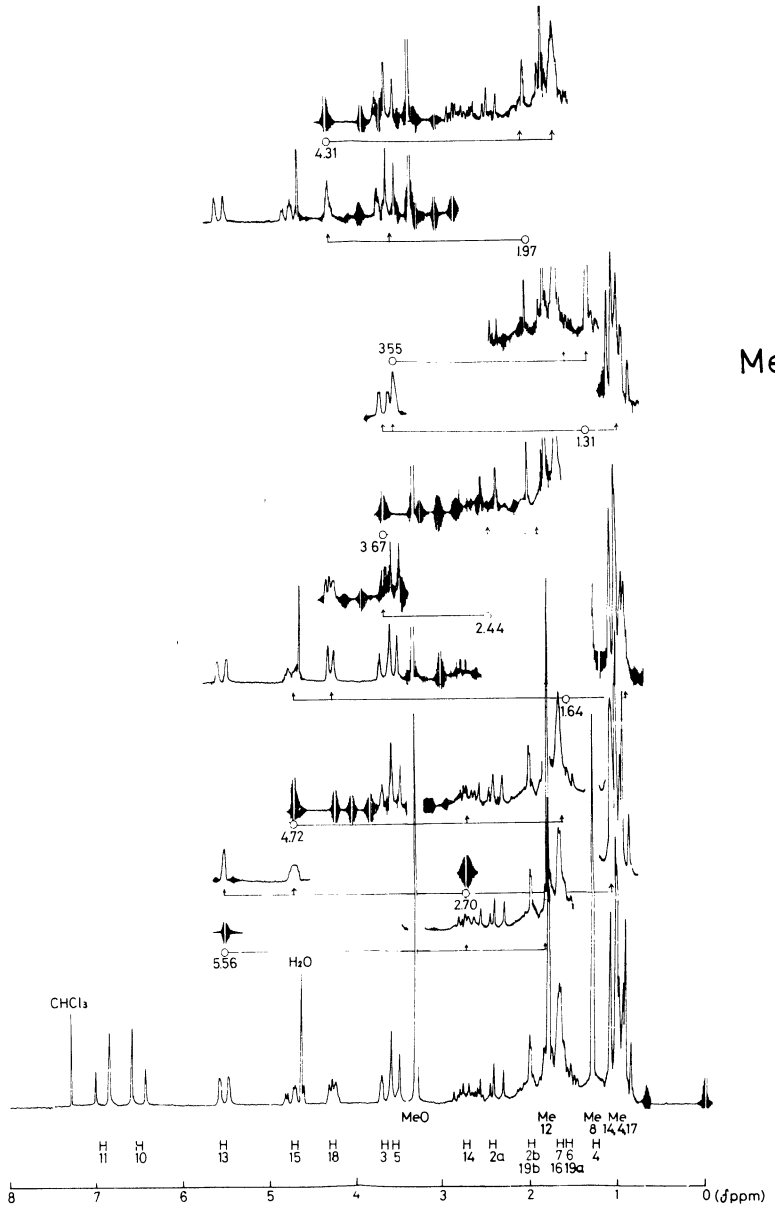
		H 18	H 11	H 10	H 13	H 15	H 1'	H 3	OH 3,5	H 5	H 2'	OMe 18	H 4',5'	OH 2',4'	H 8	H 14	H 3'
	δ(ppm)	9.67	7.25	6.24	5.63	4.71	4.23	3.82	3.1-2.7	3.69	3.43		3.3-3.0	3.1-2.7	2.8	2.8	2.6
		t	d	d	dd	dt	d	dt		dd	dd		m				m
II		1H	1H	1H	1H	1H	1H	1H	1H	1H	1H		2H	2H	1H	1H	1H
	J(Hz)	2	16	16	10	3	8	10		2	8						
					2	9		2		10	9						
	δ(ppm)	4.31	6.95	6.56	5.56	4.72		3.67	3.6	3.55		3.31				2.70	
		dd	d	d	dd	dq		dt		dd		s				m	
III		1H	1H	1H	1H	1H		1H	2H	1H		3H				1H	
	J(Hz)	6	16	16	10	8,6		11		10							
		4			2	3		2		2							

		NMe 3'	H 2a	H 19b	H 2b	Me 12	H 16	H 7	H 6	H 19a	H 4	Me 6'	Me 8	Me 14	Me 4	Me 17
	δ(ppm)	2.48	2.30	1.7-1.5	1.90	1.79	1.7-1.5	1.7-1.5	1.7-1.5	1.7-1.5	1.3	1.26	1.20	1.07	1.01	0.93
		s	dd		dd	d					m	d	d	d	d	t
II		6H	1H	1H	1H	3H	2H	2H	1H	1H	1H	3H	3H	3H	3H	3H
	J(Hz)		17		17	2						7	7	7	7	7
			9		2											
	δ(ppm)		2.44	1.97	1.92	1.79	1.64	1.6	1.54	1.54	1.31		1.29	1.06	0.98	0.92
			dd	m	dd	d	m	m	m	m	m		s	d	d	t
III			1H	1H	1H	3H	2H	2H	1H	1H	1H		3H	3H	3H	3H
	J(Hz)		15		15	2								7	7	7
			11		2											

protons and a vinyl methyl in its NMR spectrum, and of the presence of the remarkable absorption due to the conjugated carbonyl (1665 cm^{-1}) in its IR spectrum. Comparison of NMR spectrum of III with that of II shows that III loses D-mycaminose moiety, -CHO and one $-\overset{|}{C}H-CH_3$ (1.20 ppm) but has newly one $-O-CH_3$ and one $-\overset{|}{\underset{|}{C}}-CH_3$ (1.29 ppm). And unsaturation number (six) of III is equal to that (six) of the aglycone moiety of II.

There are four structures, III, IIIa, IIIb and IIIc, as the most probable ones for compound III. However, IIIa and IIIb are less probable, because III gives a diacetate and, as set forth below, methyl appearing as a singlet in III is assigned to the C-8-Me by NMR studies.

The structure of III may be clarified by means of its NMR spectrum and spin-decoupling studies as follows. At first, among the signals due to the methine protons bound to oxygen the signal at 4.72 ppm (m, 1H, J=8, 6 and 3 Hz) is assigned to the methine proton of $-COO-\underline{\overset{|}{C}H}-$ (H-15) from its chemical shift. Irradiation of H-15 (4.72 ppm) causes decoupling of the methine proton, H-14 (2.70 ppm, m) and the methylene protons, H-16 (1.64 ppm, 2H, m). Conversely, when H-14 (2.70 ppm) is irradiated, H-15 is decoupled and the vinyl proton, H-13 (5.56 ppm, dd, J=10 and 2 Hz) and C-14-Me (1.06 ppm, d, J=7 Hz) become to singlets. Irradiation of H-13 (5.56 ppm) causes decoupling of H-14 and makes the vinyl methyl, C-12-Me (1.79 ppm, d, J=2 Hz) a singlet. On the other hand, by irradiation of H-16 (1.64 ppm) C-17-Me (0.92 ppm, t, J=7 Hz) is decoupled to give a singlet. From the above facts and taking the UV spectrum of III into consideration, a partial structure at C_9-C_{15} portions is assumed to be as (A) shown



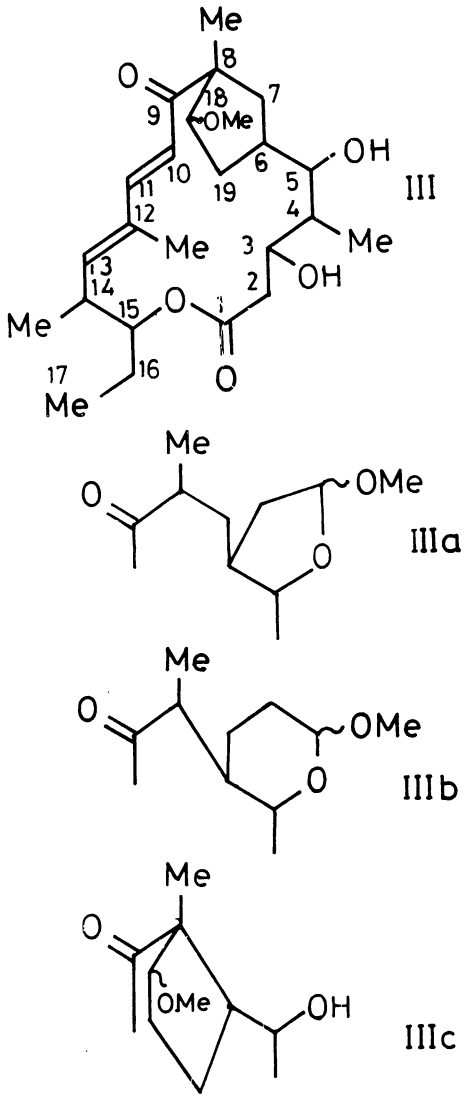
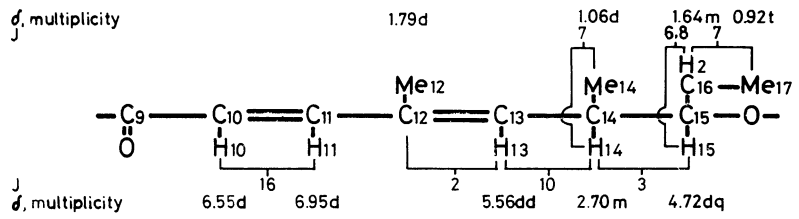


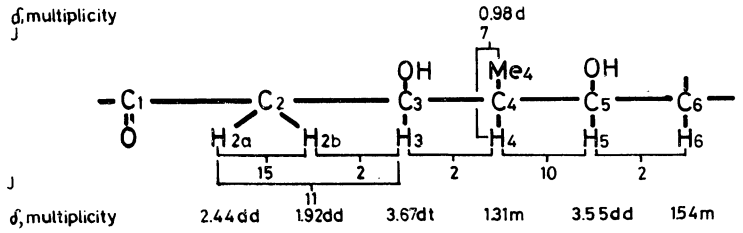
Fig. 1. NMR spectrum and spin-decoupling of III ($CDCl_3$, 100 MHz)

in the following scheme.



(A)

Irradiation of H-3 (3.67 ppm), which was shifted to a lower magnetic field by acetylation of III, makes both H-2a (2.44 ppm, dd, J=15 and 11 Hz) and H-2b (1.92 ppm, dd, J=15 and 2 Hz) doublets (AB type, J=15 Hz), which are in geminal coupling each other and are assigned to methylene protons adjacent to lactone carbonyl. Conversely, irradiation of H-2a (2.44 ppm) makes H-3 (3.67 ppm, dt, J=11 and 2 Hz) triplet (J=2 Hz). Irradiation of H-4 (1.31 ppm) makes H-3 (3.67 ppm) double doublets (J=11 and 2 Hz), makes C-4-Me (0.98 ppm, d, J=7 Hz) a singlet and makes also H-5 (3.55 ppm, dd, J=10 and 2 Hz) nearly a singlet. This proton (H-5) was shifted to a lower magnetic field by acetylation of III and hence, may be assigned to a methine proton bound to a hydroxyl group. Irradiation of H-5 (3.55 ppm) causes decouplings of H-4 (1.31 ppm) and H-6 (1.54 ppm). From the above facts, a partial structure at C_1-C_6 portions is assumed to be as (B) shown in the following scheme.



According to Tsukiura's report,[4] the aglycone moiety of cirramycin A_1 is a 16-membered lactone, but, from the spin-decoupling experiment of his compound IX as shown CH_3-CH(COOH)-CH_2-CH(CH_2COOH)-CH = C(CH_3)-CH=CH-COOH, such a further structural possibility seems to still remain in his compound as CH_3-CH(COOH)-CH(CH_2CH_2COOH)-CH = C(CH_3)-CH=CH-COOH. If his compound would have the latter structure, cirramycin A_1 should be a 15-membered lactone. Hence, it is necessary to determine whether the aglycone moiety of I is a 16-membered lactone or a 15-membered lactone (that is structure III or IIIc for the compound III).

For the elucidation of the protons at C_6-C_9 portions, 0.053 mmol of $Eu(fod)_3$/0.4 ml of $CDCl_3$ was added to III, in molecular ratio [III]:[$Eu(fod)_3$] = 1.00:0.45, to shift the proton signals to the lower magnetic field, and the NMR spin-decoupling of each proton was studied (Fig. 2). When H-6 (6.15 ppm, 1H, m) is irradiated both H-7a (5.80 ppm, t, $J_{7a, 7b}$ = 12 Hz, $J_{7a, 6}$ = 12 Hz) and H-7b (5.08 ppm, dd, $J_{7b, 7a}$ = 12 Hz, $J_{7b, 6}$ = 3 Hz) become doublets ($J_{7a, 7b}$ = 12 Hz) and both H-19a (4.66 ppm, m, $J_{19a, 19b}$ = 13 Hz, $J_{19a, 6}$ = 7 Hz, $J_{19a, 18}$ = 4 Hz) and H-19b (3.51 ppm, dt, $J_{19b, 19a}$ = 13 Hz, $J_{19b, 6}$ = 7 Hz, $J_{19b, 18}$ = 7 Hz) become double doublets (H-19a, $J_{19a, 19b}$ = 13 Hz, $J_{19a, 18}$ = 4 Hz; H-19b, $J_{19b, 19a}$ = 13 Hz, $J_{19b, 18}$ = 7 Hz). Irradiation of H-19a (4.66 ppm) makes H-19b (3.51 ppm, m) double doublets ($J_{19b, 6}$ = 7 Hz, $J_{19b, 18}$ = 7 Hz) and makes H-18 (5.63 ppm, dd, $J_{18, 19a}$ = 4 Hz, $J_{18, 19b}$ = 7 Hz) doublet ($J_{18, 19b}$ = 7 Hz). Further irradiation of H-19b (3.51 ppm) makes H-19a (4.66 ppm, dt) double doublets ($J_{19a, 6}$ = 7 Hz, $J_{19a, 18}$ = 4 Hz) and makes H-18 (5.63 ppm, dd) doublet

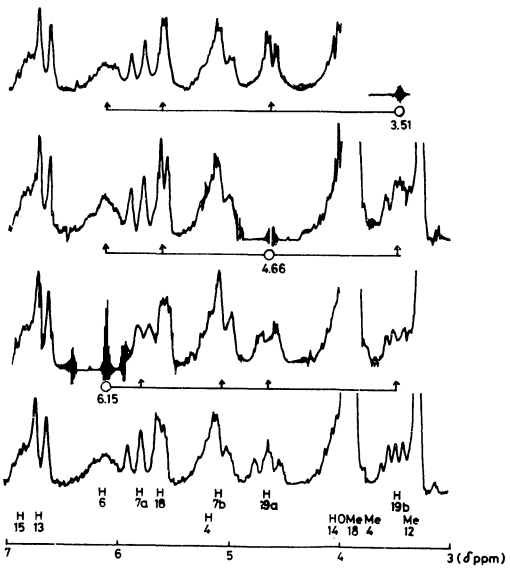
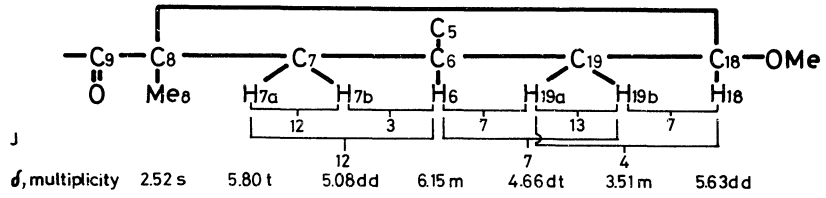


Fig. 2. NMR spectrum and spin-decoupling of III (C_6-C_9) ($CDCl_3$, 100 MHz)

Fig. 2. NMR spectrum and spin-decoupling of III (C_6-C_9) ($CDCl_3$, 100 MHz)

($J_{18,\ 19a}$ = 4 Hz). In the both cases of irradiating H-19a and H-19b, H-6 is also decoupled. As a result, it is clarified that H-19a and H-19b couple with H-18 as well as H-6. On the other hand, both H-7a and H-7b do not couple with any other protons than H-6. H-18 (4.31 ppm) did not shift to a lower magnetic field by acetylation of III, and hence was assigned to a methine proton bound to $-O-CH_3$. From the above facts, a partial structure at C_6-C_9 portions is assumed to be (C) as shown in the following scheme.



(C)

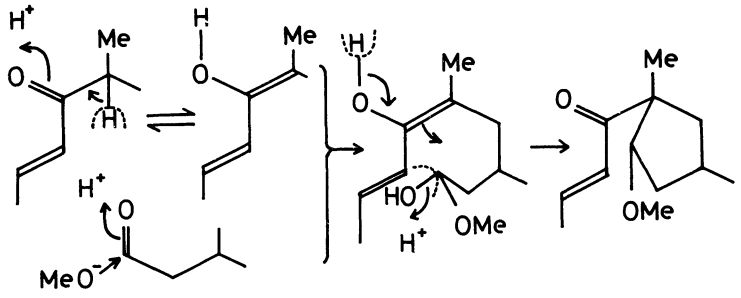
Furthermore, it is assumed that during the reaction produced III from II

H H O
\ / ||
- C - C - H in II was methylated, while 9-carbonyl was enolized and then aldol
19 18

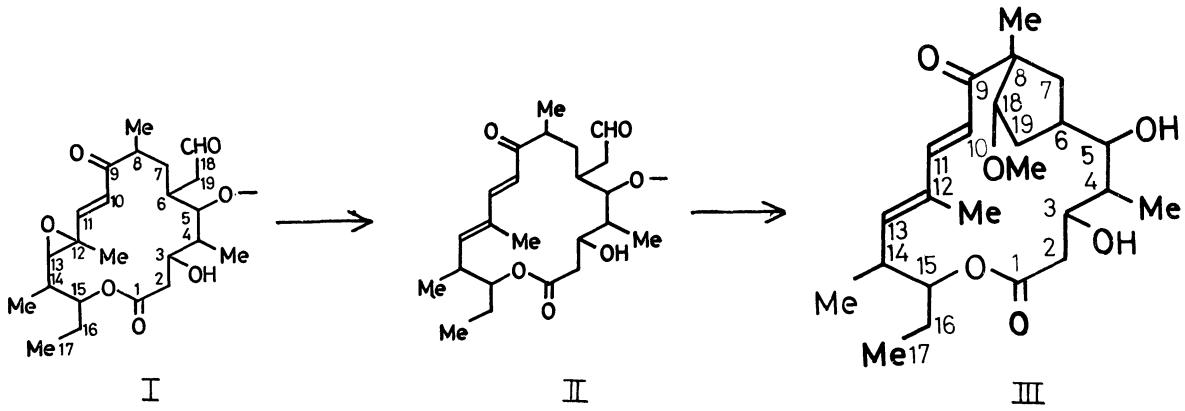
condensation took place between C-8 and C-18 in accordance with a reaction mechanism as shown below. Hence the bonding sequence of partial structures (A),

(B) and (C) may be assumed to be as $\rightarrow A(C_9\text{-}C_{15}\text{-}O) \rightarrow B(O\text{-}\overset{\overset{O}{\|}}{C}_1\text{-}C_6) \rightarrow C(C_6\text{-}C_9)$

and thus, the structure of III may be assumed as 3,5-dihydroxy-4,8,12,14-tetramethyl-9-oxo-6,8-(1-methoxyethano)-10,12-heptadecadien-15-olide.



As a result, each proton of II and III is assigned as shown in Table 1 by the NMR spectrum, and the structure of the aglycone moiety of I is identical with that of the aglycone moiety of cirramycin A_1,[4] i.e. 6-formylmethyl-3,5-dihydroxy-4,8,12,14-tetramethyl-9-oxo-12,13-epoxy-10-heptadecen-15-olide.



I II III

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