NEW POLYETHER ANTIBIOTICS, A-130B AND A-130C

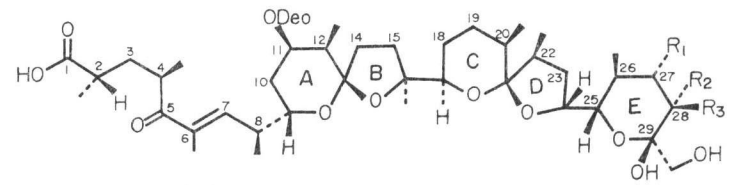
Sir:

Recently we have found two new antibacterial components A-130B (**1**) and C (**2**) in the metabolites of *Streptomyces hygroscopicus* A-130, which produces polyether antibiotic A-130A (**3**). This antibiotic was isolated and characterized as a new polyether antibiotic by KUBOTA, *et al.*[1] and later isolated also by an American group as Ro 21-6150*, which was identified with our specimen[2a].

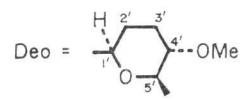
Two active minor components, **1** and **2**, found in the mother liquor of **3** were isolated by precise t.l.c. on silica gel. Like **3**, both compounds were easily assumed to be polyether antibiotics having an α,β-unsaturated ketone function from their IR (1655 cm^{-1}) and UV (λ_{max} 235 nm) spectra (Fig. 1). Up to date, two antibiotics, dianemycin[4] and **3** are known to belong to this class, but both **1** and **2** are distinguishable from these antibiotics by IR and t.l.c.

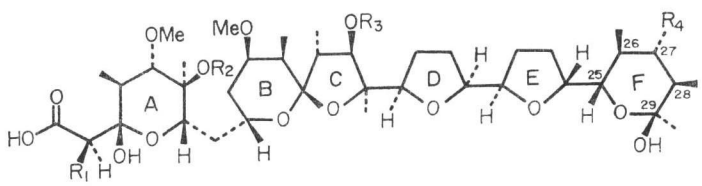
Antibiotics **1** and **2** did not give any crystals suitable for X-ray analyses, while the ^{13}C NMR spectra of their sodium salts (**1**-Na) and (**2**-Na) gave valuable information in comparison with that of **3**-Na, whose structure is established by an X-ray diffraction of **3**-Ag[2]. The ^{13}C NMR spectra were examined in C_6D_6 and $CDCl_3$, and the signals were assigned by the usual procedures including various ^1H decoupling techniques[5] and comparison with those of sodium salts of A-28695[6] (septamycin)[7] (**4**), K-41A (**5**)[8] and B (**6**)[9]; their ^{13}C NMR signals were already assigned[9,10].

As shown in Tables 1 and 2, **1** is composed of 54 carbons while **2** as well as **3** has 47 carbons. The precise comparison of the spectra led to the assumption that **1** has an additional deoxysugar (Deo) moiety $C_7H_{13}O_3$ like as **6**. The presence of two OMe signals in the ^1H NMR spectrum of **1**-Na (see Fig. 2) supports the speculation, and the ^{13}C signals due to the Deo moiety are easily pointed out as shown in Table 2. The remaining ^{13}C signals of **1**-Na essentially correspond to those of **3**-Na except 7 carbon signals. Marked and slight changes (* and ** in Table 1, respectively) in the ^{13}C chemical shifts were exhibited from **3**-Na to **1**-Na as $-\underline{C}H_2- \rightarrow -\underline{C}H-O-$ (δ_C 37.2→82.6), upfield shifts of two Me signals (17.5 and 17.9→12.9 and 14.0, respectively), downfield shifts of two $-\underline{C}H-$ signals (36.9 and 33.3→45.4 and 40.0, respectively), and slight signal shifts of $-\underline{C}H-O-$ (73.5→72.8) and $-CH\langle^{O}_{O}$ (99.1→100.3). Taking account of the structure of **3**, these spectral changes can be expected only by locating the second Deo at C-27 (in ring E). Similar changes were also observed between **4**-Na and **5**-Na (see Table 3). Further, the δ_C values for the Deo moiety at C-27 in **1**-Na are in good accordance to those of **5**-Na (see Table 2). Therefore, the second Deo of **1** should be situated just as that of **5**, and A-130B has been determined as structure **1***. (* next page)



1: R_1=ODeo, R_2=H, R_3=Me A-130B
2: R_1=H, R_2=Me, R_3=H A-130C
3: R_1=H, R_2=H, R_3=Me A-130A





4: R_1=Me, R_2=Deo, R_3=Me, R_4=H A-28695A
5: R_1=OH, R_2=Me, R_3=Me, R_4=ODeO K41-A
6: R_1=OH, R_2=Me, R_3=DeO, R_4=ODeo K41-B

* ANTEUNIS *et al.*, who studied the ^1H NMR spectra of Ro 21-6150 provided by this group, called it lenoremycin[3].

Table 1. ^{13}C Chemical shifts (δ)[a] of A-130A-Na (**3**-Na), A-130B-Na (**1**-Na) and A-130C-Na (**2**-Na).

Carbon type[b]	Assignment[c]	**3**-Na	**1**-Na	**2**-Na
C–Me (q)	2-Me[d]	20.9	20.8	20.9
	4-Me[d]	17.7	17.7	17.7
	6-Me	11.7	11.7	11.8
	8-Me[d]	14.3	14.2	14.3
	12-Me	13.9	13.9	13.9
	16-Me	27.3	27.4	27.6
	20-Me[d]	15.0	15.1	15.1
	22-Me[d]	15.3	15.2	15.3
	26-Me	17.9	14.0*	18.3**
	28-Me	17.5	12.9*	15.5*
C–CH_2– (t)	C-3	41.9	41.8	41.9
	C-10	29.8[e]	29.7[e]	29.6[e]
	C-14	36.0	36.0	36.1
	C-15	32.5	32.4	32.5
	C-18	17.7	17.7	17.7
	C-19	27.6[f]	27.4[f]	27.6[f]
	C-23	36.7	36.7	36.8
	C-27	37.2	—	36.1**
C–CH< (d)	C-2	39.8	39.8	39.8
	C-4	38.4	38.3	38.4
	C-8	41.9	41.8	41.9
	C-12	39.8	39.8	39.9
	C-20	30.4	30.3	30.4
	C-22	35.4	35.4	35.8
	C-26	33.3	40.0*	26.3*
	C-28	36.9	45.4*	36.4**
O–CH_2– (t)	C-30	64.7	64.6	65.0
O–CH< (d)	C-9	68.5	68.5	68.4
	C-11	73.5	73.5	73.7
	C-17	80.9	80.9	81.0
	C-24	79.6	79.8	79.6
	C-25	73.5	72.8**	74.2**
	C-27	—	82.6*	—
O–C< (s)	C-16	85.8	85.9	85.9
O,O>C< (s)	C-13	109.3	109.0	109.1
	C-21	111.1	111.3	111.1
	C-29	99.1	100.3**	98.0**
=CH– (d)	C-7	146.0	145.9	145.8
=C< (s)	C-6	134.5	134.5	134.8
>C=O (s)	C-1	181.3	181.6	181.9
	C-5	205.8	205.8	206.0

[a] ^{13}C FT NMR spectra were recorded on a Varian XL-100-12A spectrometer at 25.160 MHz in C_6D_6 (*ca.* 0.25 mmol·cm^{-3}) at 35°C; accuracies of δ values are $\pm$0.05 ppm.

[b] Multiplicities were obtained by ^1H single-frequency off-resonance decoupling experiments.

[c] δ values of Deo carbons are listed in Table 2.

[d] Tentative assignments.

[e,f] Assignments may be interchanged (for interchangeable signal, see Table 2).

*, ** See text.

Table 2. ^{13}C Chemical shifts (δ)[a] of the deoxysugar (Deo) moieties of A-130A-Na (**3**-Na), A-130B-Na (**1**-Na), A-130C-Na (**2**-Na), and K-41A-Na (**5**-Na).

Carbon type[b]	Assignment	Deo at C-11[c]			Deo at C-27[d]	
		3-Na	**1**-Na	**2**-Na	**1**-Na	**5**-Na
O,O>CH– (d)	C-1′	103.3	103.2	103.5	103.2	103.0
–CH_2– (t)	C-2′	28.7[f]	28.6[f]	28.8[f]	30.9	31.0
–CH_2– (t)	C-3′	26.6[e]	26.5[e]	26.7[e]	27.4	27.4
O–CH< (d)	C-4′	79.5	79.5	79.6	80.6	80.6
O–CH< (d)	C-5′	76.8	76.7	76.8	74.5	74.7
C–Me (q)	5′-Me	18.6	18.7	18.7	18.7	18.8
O–Me (q)	4′-OMe	56.3	56.3	56.4	56.2	56.2

[a] See footnote a in Table 1.

[b] See footnote b in Table 1.

[c,d] Chemical shift differences found between Deo at C-11 and that at C-27 may be attributable to the environmental difference; Deo at C-11 directly participates in the metal-ion capture in solution[11] as well as in crystal[2].

[e,f] Assignments may be interchanged (for the interchangable signal, see Table 1).

Table 3. Comparison of ^{13}C data[a] in ring E of **1**-Na, **3**-Na and in ring F of **4**-Na, and **5**-Na.

	1-Na	**3**-Na	$\Delta\delta$[b]	**5**-Na	**4**-Na	$\Delta\delta$[c]
C-25	72.8	73.5	−0.7	74.6	75.7	−0.9
C-26	40.0	33.3	+6.7	39.8	33.2	+6.6
C-27	82.6	37.2	+45.4	82.9	37.5	+45.4
C-28	45.4	36.9	+8.5	48.2	40.5	+7.7
C-29	100.3	99.1	+1.2	98.9	97.4	+1.5
26-Me	14.0	17.9	−3.9	13.8	17.5	−3.7
28-Me	12.9	17.5	−4.6	13.2	17.4	−4.2
29-CH_2OH	64.6	64.7	−0.1	—	—	—
29-Me	—	—	—	27.2	26.8	+0.4

[a] δ values in C_6D_6.

[b] Chemical-shift difference; $\Delta\delta = \delta$(**1**-Na) − δ(**3**-Na).

[c] Chemical-shift difference; $\Delta\delta = \delta$(**5**-Na) − δ(**4**-Na).

(p. 94 footnote)

* Molecular peak (1,016) for $C_{54}H_{89}O_{16}Na$ was observed in the EI-MS of **1**-Na by Mr. Occolowitz of the Lilly Research Laboratories. Details will be published by him.

As mentioned above, **2** is composed of 47 carbon atoms and the classification of the carbons, shown in Table 1, suggests that **2** should be an isomer of **3**. The comparison between the ^{13}C spectra of **2**-Na and **3**-Na revealed chemical-shift changes of 7 carbons which are assigned to those on the E-ring. The changes including a remarkable upfield shift of the C-26 signal (see * and ** in Table 1) can be explained only by the structure in which the 28-Me of **2**-Na is epimeric (α-axial conformation) to that of **3**-Na. Further, in comparison of the ^{1}H NMR spec-

Fig. 1. IR spectra of sodium salts of A-130B (a) and A-130C (b) in $CHCl_3$.

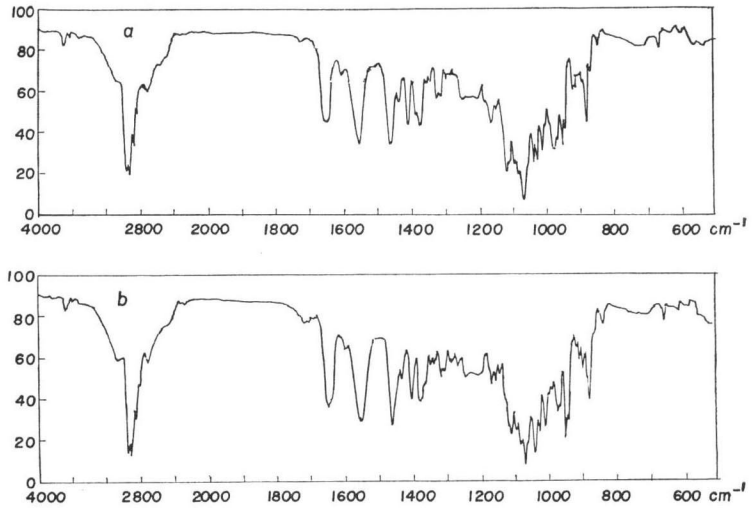
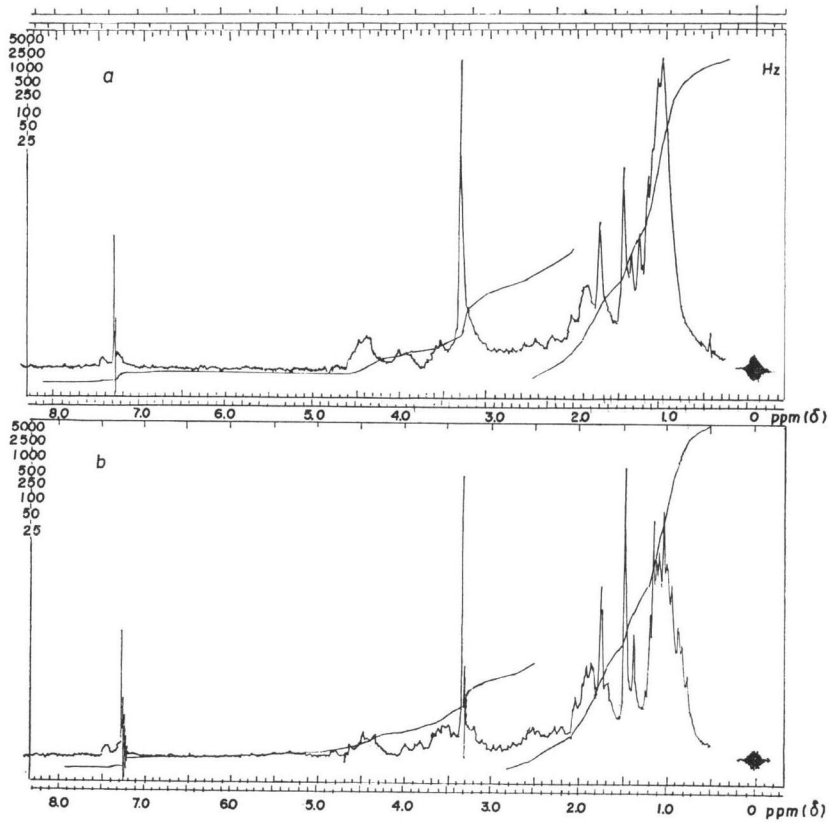


Fig. 2. ^{1}H NMR spectra of sodium salts of A-130B (a) and A-130C (b) in $CDCl_3$ (at 60 MHz).



trum (in C_6D_6) of **2**-Na to that of **3**-Na, one Me doublet moves downfield by 0.25 ppm and another Me doublet upfield by −0.06 ppm, while the other methyl signals are unchanged. This observation is in good agreement with the conclusion from ^{13}C NMR, and A-130C has been assessed to structure **2**.

A-130B is the second example of monovalent diglycoside polyether antibiotic (next to K-41B) according to WESTLEY's classification[3] and A-130C is the first example of the polyether antibiotic having an axial methyl group on the "east" terminal ring.

The details of ^1H and ^{13}C NMR studies of A-130 factors will be reported elsewhere in the near future[11].

Acknowledgments

We thank Dr. R. L. HAMILL of the Lilly Research Laboratories for providing us with the sample of **4**-Na for ^{13}C NMR measurements.

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(Received October 1, 1979)

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