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C-13 NUCLEAR MAGNETIC RESONANCE SPECTRA OF ERYTHROMYCINS

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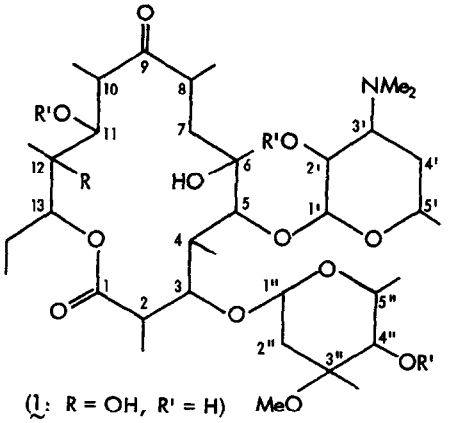
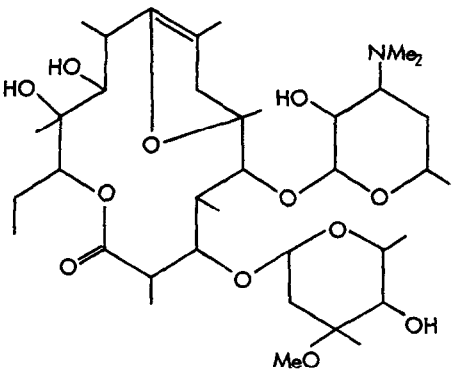
It seems worthwhile to report preliminarily here full assignments of carbon signals in ^{13}C NMR spectra of 14-membered-ring macrolide antibiotics,[1] erythromycins A and B, and some derivatives in view of explosively increased importance of ^{13}C NMR spectroscopy[2] in structure elucidation and biosynthetic studies[3] of organic natural substances. Configurations and conformations of this kind of macrolides have well been investigated by X-ray analysis, and ^{1}H NMR and CD spectroscopy.[4] The present results will also be useful for developing the chemistry of 14-membered-ring macrolides.

We have examined the natural-abundance ^{13}C FT NMR spectra of erythromycin A (1), erythromycin B (2) and its triacetate (3), 8,9-anhydroerythromycin-A-6,9-hemiketal (4),[5] anhydroerythromycin A (5)[5] and its triacetate (6), erythralosmaine (7) and its diacetate (8), α- (9) and β-methyl D-desosaminides (10), and α- (11) and β-methyl L-cladinosides (12) in $CDCl_3$ with both ^{1}H noise-decoupling and single-frequency off-resonance decoupling (SFORD)[2] techniques. The ^{13}C signals were assigned by means of SFORD techniques, where ^{1}H chemical-shift data on 1,[6] 2,[7] and 6[6] recently reported were extremely useful, by applications of known chemical-shift rules such as hydroxyl-substitution and acetylation shifts, and steric γ and δ effects,[2,8] and from comparisons of the spectra from compound to compound.

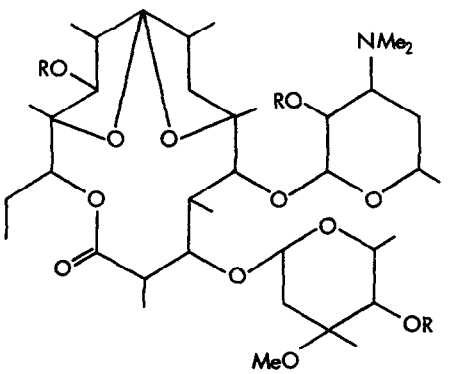
The TABLE lists the ^{13}C chemical-shift data on the four sugar glycosides 9-12; the assignments of these compounds were straightforward. Among these, 10 and 12 have the configurations naturally occurring in erythromycins.[1] Therefore, the signals due to sugar moieties were readily assigned in the spectra of 1-8. Among the signals arising from aglycone moieties, we can easily assess signals due to carbonyl carbons, olefinic carbons, quaternary carbons bearing oxygen(s), and two CH_2 (C-7 and C-13-CH_2). Differenciation between four H-$\overset{|}{\underset{|}{C}}$-O- (C-3, C-5, C-11, and C-13) signals and that between four H-$\overset{|}{\underset{|}{C}}$- (C-2, C-4, C-8, and C-10) signals were mainly based on detailed SFORD experiments. Assignments of some of



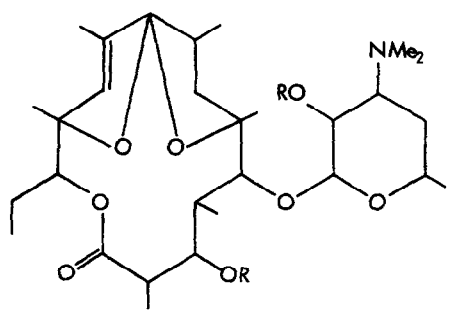
(1: R = OH, R' = H)
(2: R = R' = H)
(3: R = H, R' = Ac)



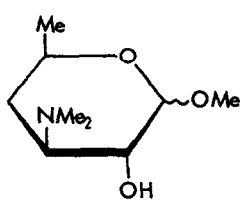
(4)



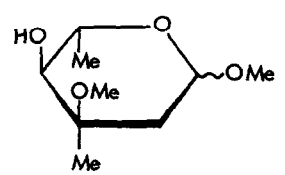
(5: R = H)
(6: R = Ac)



(7: R = H)
(8: R = Ac)



(9: α-OMe)
(10: β-OMe)



(11: α-OMe)
(12: β-OMe)

TABLE. C-13 Chemical-shift Data on Erythromycins and Their Derivatives in $CDCl_3$ (δ_C)[a]

Carbon No.	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
1	175.5	175.8	175.1	177.9	178.8	178.3	178.4	175.8				
2	44.8	44.7	44.1[b]	44.8	46.0	47.2	46.8	47.4				
3	80.0	80.2	78.0	76.8	76.3	76.8	70.1[b]	72.7[b]				
4	39.4	39.5	41.7	43.4	41.5	41.7	44.6	45.5				
5	83.6	83.5	83.3	80.3	86.2[b]	85.7	87.0	86.7				
6	74.8	74.8	74.0	85.8	81.4[c]	81.9	81.9	82.6				
7	38.5	38.1	37.7[b]	42.8	43.1	44.4	42.9	43.4				
8	44.8	44.7	43.8	101.3	41.5	41.3	39.9	40.2				
9	221.1	219.1	214.2	151.9	115.8	115.4	119.7	120.0				
10	38.2	39.0	40.7[b]	30.7	51.1	47.6	139.0	139.1				
11	68.7	69.3	72.2	71.0	86.9[b]	83.5	128.2	127.7				
12	74.8	39.8	38.0[b]	75.4	82.2[c]	81.0	88.6	88.7				
13	77.0	75.2	74.6	78.3	81.4	80.8	78.7	78.7				
2-Me	18.5[b,c]	18.5[b]	19.2[c]	16.4[b]	16.4[d]	14.9[b]	13.8	15.4				
4-Me	9.1	9.2	8.9[d]	8.8	13.8[e]	12.5[c]	12.6[c]	11.7[c]				
6-Me	26.8	27.3	24.7	26.3	28.1	29.1	29.5	29.5				
8-Me	16.2[c]	15.5[b]	13.8[c]	13.5[b]	12.3[e]	12.1	12.0[c]	12.1[c]				
10-Me	12.0	9.2	9.7[d]	11.9	14.3[d]	14.7[b,c]	13.8	13.4				
12-Me	16.0	9.2	9.3[d]	15.1	25.0	25.0	23.0	23.2				
13-CH_2	21.3	25.6	25.0	21.3	24.4	24.0	24.4	24.0				
13-Me	10.5	10.3	10.1	10.9	11.0	11.3	10.2	10.3				
1'	103.1	103.0	99.3	103.0	103.0	101.4	104.5	102.8	99.6	104.9		
2'	70.9	70.9	71.8	70.5	69.7	70.8	70.6[b]	71.1[b]	68.7	69.9		
3'	65.3	65.5	62.9	65.6	65.5	63.4	65.4	63.0	60.3	65.4		
4'	28.7	28.7	31.3	29.3	28.9	30.7	29.1	31.0	29.3	28.8		
5'	68.8	68.8	67.7	68.8	69.3	69.0	69.1	68.9	64.8	69.5		
5'-Me	21.3	21.3	21.3	21.3	21.2	21.2[d]	21.2	21.2	21.2	21.2		
NMe_2	40.3	40.2	40.7	40.3	40.5	40.5	40.3	40.7	39.9	40.3		
1"	96.2	96.5	95.2	94.8	95.0	95.9					98.8	97.5
2"	35.0	35.0	35.0	34.8	34.6	35.0					37.8	35.2
3"	72.5	72.5	72.8	73.1	72.7	73.1					74.9	73.0
4"	77.9	77.9	78.5	78.3	78.2	78.9					78.0	78.0
5"	65.4	65.6	62.9	66.0	65.0	62.5					70.8	64.5
3"-Me	21.3	21.3	21.3	21.7	21.6	21.2					21.1	21.9
5"-Me	18.3[b]	18.5	17.6	18.3	17.7	16.9					18.2	17.9
3"-OMe	49.4	49.3	48.9	49.5	49.2	49.6					48.9	49.2
OMe									55.0	56.5	56.1	55.0
OAc			20.7×2 21.3 169.5 169.7 170.0			21.0[d]×3 169.1 170.4×2		20.7 21.0 169.3 170.4				

[a] The ^{13}C FT NMR spectra were taken with a Varian NV-14 FT NMR spectrometer at 15.09 MHz in 8 mm tubes at ordinary probe temperature (30°). Samples were dissolved in $CDCl_3$ containing TMS as an internal standard (δ_C 0); concentrations were about 0.1-0.3 mmole/cm^3. FT NMR measurement conditions were typically as follows: spectral width: 3621 Hz, pulse width: 10-15 μsec, acquisition time: 0.5 sec, and number of data points: 3706. [b-e] These assignments may be interconverted in each column.

the methyl signals remain tentative, however. Thus, all the results obtained are shown in the TABLE.

An introduction of an OH group into C-12 of 2 (i.e., from erythromycin B to A) apparently causes a downfield shift of +2.8 ppm (δ-effect)[8] in the C-10-Me signal and an upfield shift of -4.3 ppm (γ-effect)[2] in the C-13-CH_2 signal; the results are in conformity with the Perun conformation for erythronolides.[4] Acetylation shifts caused by the C-11-OAc in 3 were useful for the signal assignments. Chemical-shift variations in the desosamine moiety from 2 to 3 caused by the acetylation are fairly different from those from 5 to 6 or from 7 to 8; this suggests that a minor conformational change in this moiety is caused by a change in the aglycone structure, and that an abnormal upfield shift of the C-6-Me signal (-2.6 ppm) from 2 to 3 is acceptable in view of its steric relationship to the sugar. It should be noted that an abnormal shift caused by hydroxylation (from 2 to 1) and that caused by acetylation (from 5 to 6) were observed for the C-11 signal.

Conformational changes accompanied with structural changes in the aglycone moiety often made it difficult to compare the ^{13}C chemical shift from compound to compound. However, ^{13}C NMR spectroscopy has proved extremely useful for diagnosing an aglycone-structural change (e.g., formation of a ketal, a hemiketal, or a persubstituted double-bond, or acylation) in the course of our chemical studies of erythromycins, because other methods were almost helpless against this problem.

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