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CONFORMATIONAL HOMOGENEITY IN SOLUTION OF 14-MEMBERED MACROLIDE ANTIBIOTICS AS EVIDENCED BY ^{13}C NMR SPECTROSCOPY [1].

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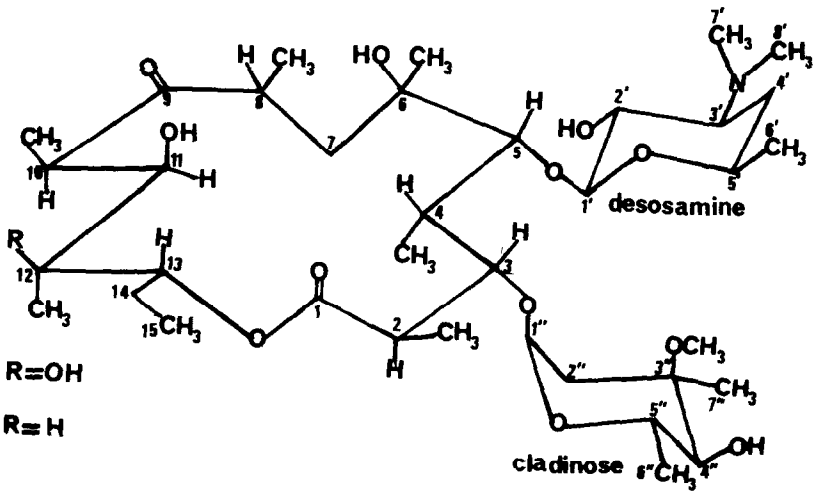
It has been shown by ^{1}H nmr that the aglycone of the erythromycin antibiotics was present in solution as a single conformation [2] of a slightly modified diamond-lattice type with the ring atoms occupying cyclohexane like positions [2],[3].The present ^{13}C nmr spectral analysis of the 14-membered macrolide antibiotics examined confirms the previous conclusions and yields evidence for the Perun-conformation for the aglycones of compounds from 1 to 5 [2],[3].

Noise,single frequency and noise off-resonance decoupled ^{13}C nmr spectra were recorded [4] for compounds from 1 to 9 and the resonance assignments are given in Table 1.The shift contrast between gitoxigenine 16-monoacetate 7 [5],oleandrine 8 and oleandrine acetate 9 yielded the signals of the α-L-oleandrose moiety of oleandomycin 3.The β-D-desosamine carbon resonances of 3 were allocated on the basis of acetylation effects observed in the spectrum of oleandomycin triacetate 4 as well as by considering the spectrum of the model 4,6-dideoxy sugar methyl β-D-chalcoside [6].The β-desosamine signal assignments were further confirmed by the presence of the resonances attributed to this hexose unit in the spectrum of all the antibiotics containing this sugar.The antibiotics studied contain three more types of hexoses.The cladinose carbons of the erythromycins 1 and 2 were easily assigned by comparison with the ^{13}C nmr spectrum of the model methyl α-L-cladinoside.The acetyl arcanose resonances of lankamycin 5 were estimated on the basis of the spectrum of methyl α-L-cladinoside while the chalcose signals of 5 were based on previous studies [6].

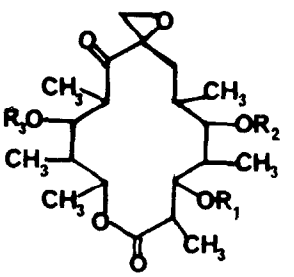
Specific assignment of the aglycone signals is based on the observed chemical shift contrast in the spectrum of the different antibiotics and on chemical shift rules [7].In most cases the differences in resonance position of the identically numbered carbons of the various aglycones can be interpreted in the light of known ^{13}C nmr shift parameters [7] generally applied in cyclohexane type compounds.This phenomenon and the data of Table 1 suggest that the 14-membered macrolide antibiotics studied with the exception of picromycin 6 have approximately the same conformation.

Inspection of the high field part of the spectra examined affords some informa-

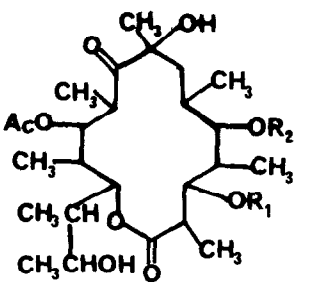


1 R=OH

2 R=H

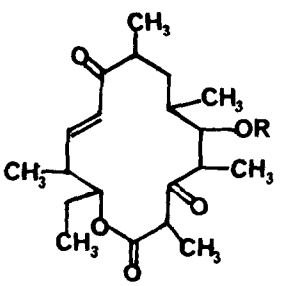


3 R_1=α-oleandrose; R_2=β-desosamine; R_3=H

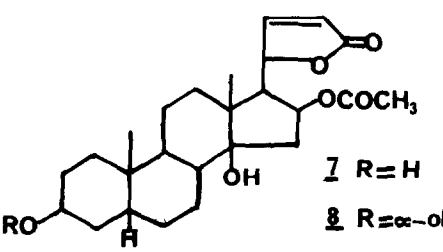


5 R_1=4''-O-ac· ; R_2=β-chalcose
α-arcanose

4 R_1=4''-O-ac. ; R_2=2'-O-ac· ; R_3=$COCH_3$
α-oleandrose β-desosamine



6 R=β-desosamine



7 R=H

8 R=α-oleandrose

9 R=4''-O-ac·
oleandrose

Table 1

	^{13}C nmr chemical shifts 1		2		3		4[e]		5[f]		6
C-1	175.7[a]		176.1		176.3		175.1		176.5		170.4
C-2	45.2		45.0		44.9		44.2		44.8		53.5
C-3	80.3[b]		80.3[a]		81.4[a]		79.0[a]		77.5		212.6[a]
C-4	38.0		39.0[a]		44.9[a]		44.2[a]		44.1		46.7
C-5	83.5		83.6		84.1		84.3[b]		84.5		83.4
C-6	75.0		75.0		30.5		33.5[b]		34.0		35.9
C-7	38.5[a]		38.1		30.5		32.2		39.1		37.6[a]
C-8	44.9		45.0		62.6		63.2		80.1		43.0
C-9	221.8[b]		219.6[a]		208.0[a]		207.4[a]		214.5[a]		203.7
C-10	39.4		39.8[a]		43.2[a]		42.6[c]		39.1[b]		129.1
C-11	69.0		69.5[a]		70.3[a]		71.7[a]		71.0[a]		145.6
C-12	74.7		39.6[a]		41.9[a]		40.0[a]		38.2[b]		75.1
C-13	77.0		75.6		69.3		69.1		73.0		81.2
C-14	21.2		25.6		14.8		13.1		42.6		22.9
C-15	10.7		10.4		-		-		75.4[c]		10.7
C-2Me	18.3		18.7		18.5[b]		18.8[d]		19.5[d]		22.9[b]
C-4Me	9.2		9.3		9.0		10.9		9.8		13.4
C-6Me	27.0		27.4		20.1 +		17.7 +		16.8		17.5[b]
C-8Me	16.2		15.6		48.9[b]		51.0[d]		27.0[d]		14.8
C-10Me	12.0		9.3		6.9[b]		10.2[d]		10.3[d]		-
C-12Me	16.2		9.3		9.6		10.2		10.3		14.8[b]
C-14Me	-		-		-		-		11.1[c]		-
C-15Me	-		-		-		-		19.0		-
C-1'	103.2		103.2		104.5		102.2[c]		102.4		105.0[c]
C-2'	71.0		70.9		70.6		71.9		74.0		70.0
C-3'	65.6	desosamine	65.6	desosamine	65.6	desosamine	63.7	chalcose	80.2	desosamine	65.8
C-4'	28.7		28.7		28.6	2'-O-ac.	30.5		37.2		28.4[c]
C-5'	69.0		69.0		69.3	desosamine	70.3		67.3		69.7
C-6'	21.4		21.4		21.3		21.5		20.9		21.3
C-7'	40.3		40.3		40.3		40.7	OCH_3	57.3		40.3
C-8'	40.3		40.3		40.3		40.7		-		40.3
C-1"	96.3		96.6		99.8		99.0		96.6		-
C-2"	34.9		35.1		34.0		34.6		30.7		-
C-3"	72.6		72.6		78.0		75.7		72.6[b]		-
C-4"	78.1	cladinose	77.9	cladinose	76.1	4"-O-ac.	76.1	4"-O-ac.	68.9		-
C-5"	65.6		65.6		68.8	oleandrose	67.1	arcanose	62.6		-
C-6"	18.7		18.7	oleandrose	17.9		17.7		14.5		-
C-7"	21.4		21.4		-		-		20.9		-
OCH_3	49.5		49.5		56.4		56.5		49.8		-

The prime symbols are applied for convenience to the desosamine and chalcose carbons and the double prime symbols are applied to the cladinose, oleandrose and arcanose carbons.

+ This signal represents an epoxy-methylene carbon.

a,b,c,d These assignments within any vertical column may be reversed.

e, acetate carbons : 170.1;170.1;170.3;21.0;21.0 and 21.0

f, acetate carbons : 170.8;170.2;20.9 and 20.9

tions having conformational implications.In the 39 - 45 ppm region of the spectrum of erythromycin B 2 five methine resonances appear.Two of them resonate at 45.0 ppm while the three others at 39.4 ± 0.4 ppm.The lower field signals must be assigned to C-2 and C-8 while the higher field three resonances represent the two methine sites C-4 and C-12 bearing axial methyl groups and C-10 whose methyl group is equatorially oriented but whose axial hydrogen interacts with the C-12Me substituent.The lowest field methyl resonance (C-6Me) of erythromycin B 2 appears at 27.4 ppm.This chemical shift satisfies only the modified alternate diamond-lattice conformation (termed Perun-conformation).In the Celmer-Dale conformation the C-6Me group would be axially oriented and would undergo a 1,3-syn-periplanar interaction with the C-4Me substituent.The C-6 Me group would be expected in this conformation to resonate quite close to the C-12 axial methyl substituent of erythromycin A 1 in contrast to what is observed (Table 1)

Two further methyl resonances appear at 18.7 and 15.6 ppm in the spectrum of 2 while three methyls resonate at very high field (9.3 ppm).Out of these five methyl signals, three appear approximately at the same position in the spectrum of 1 and two of the high field methyl signals move downfield on going from 2 to 1.This shift variation can be interpreted as the result of an additional β-effect on C-12Me in the spectrum of 1 and a syn-periplanar δ-effect [8] on C-10Me deshielding both resonances by 6.9 and 2.7 ppm respectively.The high field methyl signal whose shift is constant is attributed to the only unassigned axial methyl group at C-4 while the 18.7 and 15.6 ppm signals of 2 must represent the C-2 and C-8 methyls.

Based on the discussion presented above and on the data of Table 1 the Perun-conformation of the erythromycins is well supported by this ^{13}C nmr study.

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