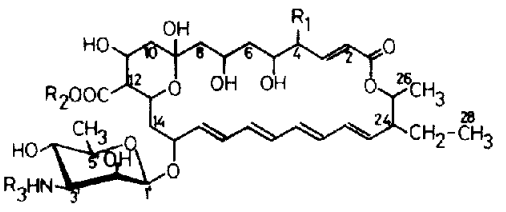
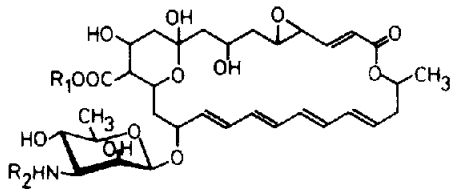


I $R_1 = R_2 = R_3 = H$
Ia $R_1 = H$, $R_2 = CH_3$, $R_3 = COCH_3$
II $R_1 = OH$, $R_2 = R_3 = H$
IIa $R_1 = OH$, $R_2 = CH_3$, $R_3 = COCH_3$



III $R_1 = R_2 = H$
IIIa $R_1 = H$, $R_2 = COCH_3$
IIIb $R_1 = CH_3$, $R_2 = COCH_3$

$(M+H)$,[1] one finds that the difference between tetramycins A and B consists in the occurrence of an additional O atom in the latter antibiotic, consequently II should have the composition C_{35} H_{53} NO_{14}.[1] In agreement with fragmentation patterns established for tetraene macrolides,[3,6] both EA and EI mass spectra of II display the following characteristic peaks:

m/z 414 ($C_{28}H_{30}O_3$, M–mycosamine–CO_2–$5H_2O$)
m/z 432 ($C_{28}H_{32}O_4$, M–mycosamine–CO_2–$4H_2O$)
m/z 450 ($C_{28}H_{34}O_5$, M–mycosamine–CO_2–$3H_2O$).

In IIa, owing to the higher resistance of the carbomethoxy group to the loss of CO_2, these are modified as:

m/z 472 ($C_{30}H_{34}O_5$, M–N-acetylmycosamine–$5H_2O$)
m/z 490 ($C_{30}H_{36}O_6$, M–N-acetylmycosamine–$4H_2O$)
m/z 508 ($C_{30}H_{38}O_7$, M–N-acetylmycosamine–$3H_2O$).

Comparison with fragmentations noted for I[1] discloses that the additional O atom must belong to the aglycone of II. Full support for this contention was provided by NMR spectra, allowing direct identification of each H and C atom and indirect determination of hetero atoms required by the above molecular formula.

NMR spectral studies. With the exception of ^{13}C spectra run on crude antibiotic complexes, all NMR measurements were performed with the N-acetyl methyl ester derivatives of the macrolides. Compared with the native antibiotics, notorious for their poor solubility and highly broadened resonances in polar solvents, these derivatives exhibited largely improved solvation and associated relaxational properties leading to narrow resonances and substantial ^{13}C–$\{^1H\}$ NOE effects in solutions with moderately polar solvents. We have found that esterification of the free carboxylic acid group gave a major contribution to these favourable properties which are only partially available with the N-acetylated derivatives employed in the NMR study of piramicin.[6] N-acetylation and subsequent esterification of the native antibiotics were carried out (with slight modifications) according to described procedures.[13,14] Although products Ia, IIa and IIIb were soluble in $CDCl_3$ in concentrations adequate for modern high-field FT NMR instruments (approx. 0.01–0.02 M), all ^1H and ^{13}C NMR spectra were made on 0.1 M solutions in $CDCl_3$–DMSO[^{12}C] (4:1) solvent mixture. This was a practical choice directed by limitations in instrument time available for the present study and the time demand of the single frequency selective ^{13}C-$\{^1H\}$ double resonance experiments run for assignment purposes (*vide infra*). In their pioneering NMR study on pimaricin, Ceder *et al.*[6] used pyridine-d_5, the only solvent in which most of the signals in the 270 MHz ^1H NMR spectrum of N-acetylpimaricin were sharp and separated. The improved solvation properties of the N-acetyl methyl ester derivatives and the increased spectral dispersion employed in the present study have rendered it unnecessary to take advantage of the generally favourable solvent effects of pyridine.[15] Instead, we have found that the $CDCl_3$–DMSO solvent mixture provided further benefits for ^1H NMR spectral analysis by allowing a clear presentation of resonances in the olefinic range and slow-exchange appearance of OH proton signals (both of which are difficult to achieve in solutions with pyridine). These particular features of spectral presentation are clearly observable in Fig. 1 displaying the 400 MHz proton spectrum of Ia run after partial D_2O exchange of NH and OH protons.

Thanks to the high spectral dispersion and Gaussian resolution enhancement of time-domain signals,[16] the analysis of the Fourier transformed proton spectra proved to be straightforward. Double resonance experiments were required in few instances only and were used primarily in order to check tentative assignments based on interproton couplings which were clearly distinguishable in the single resonance spectra, or to simplify complex multiplet patterns for more accurate evaluation of spectral parameters. The proton NMR spectral data for Ia and IIa, as obtained from first order analysis of the 400 MHz spectra, are summarized in Table 2. It includes the characterization of *all* 57 *protons* in both antibiotic derivatives and gives, in terms of chemical shifts and coupling constants, the complete assignment for all C-bonded H atoms. For the purpose of comparison with published values on pimaricin,[6] the chemical shift data of Ia are also reported for pyridine-d_5.

Summarized in Table 3 are the ^{13}C NMR data for Ia, IIa and IIIb. The assignments of resonances to individual C atoms in the molecules are based on standard ^{13}C FT NMR procedures.[17] Broad-band decoupled and a series of single frequency off-resonance decoupled ^{13}C-$\{^1H\}$ spectra were recorded to yield chemical shifts, off-resonance multiplicites, variable frequency residual ^{13}C, ^1H couplings and off-resonance band-shape information which was then matched to the known proton NMR parameters. Further distinction between ^{13}C resonances was provided by approximate T_1^C values allowing a facile separation of signals due to C atoms unaffected by slow conformational motions of the macro ring, an approach that proved particularly useful in the carbinyl carbon range (sugar vs macro ring carbon atoms) and, also, by spectral comparison based on structural differences in the three N-acetyl methyl ester derivatives, Ia, IIa and IIIb. Experimental verification of the assignments was attained through an extensive series of single frequency

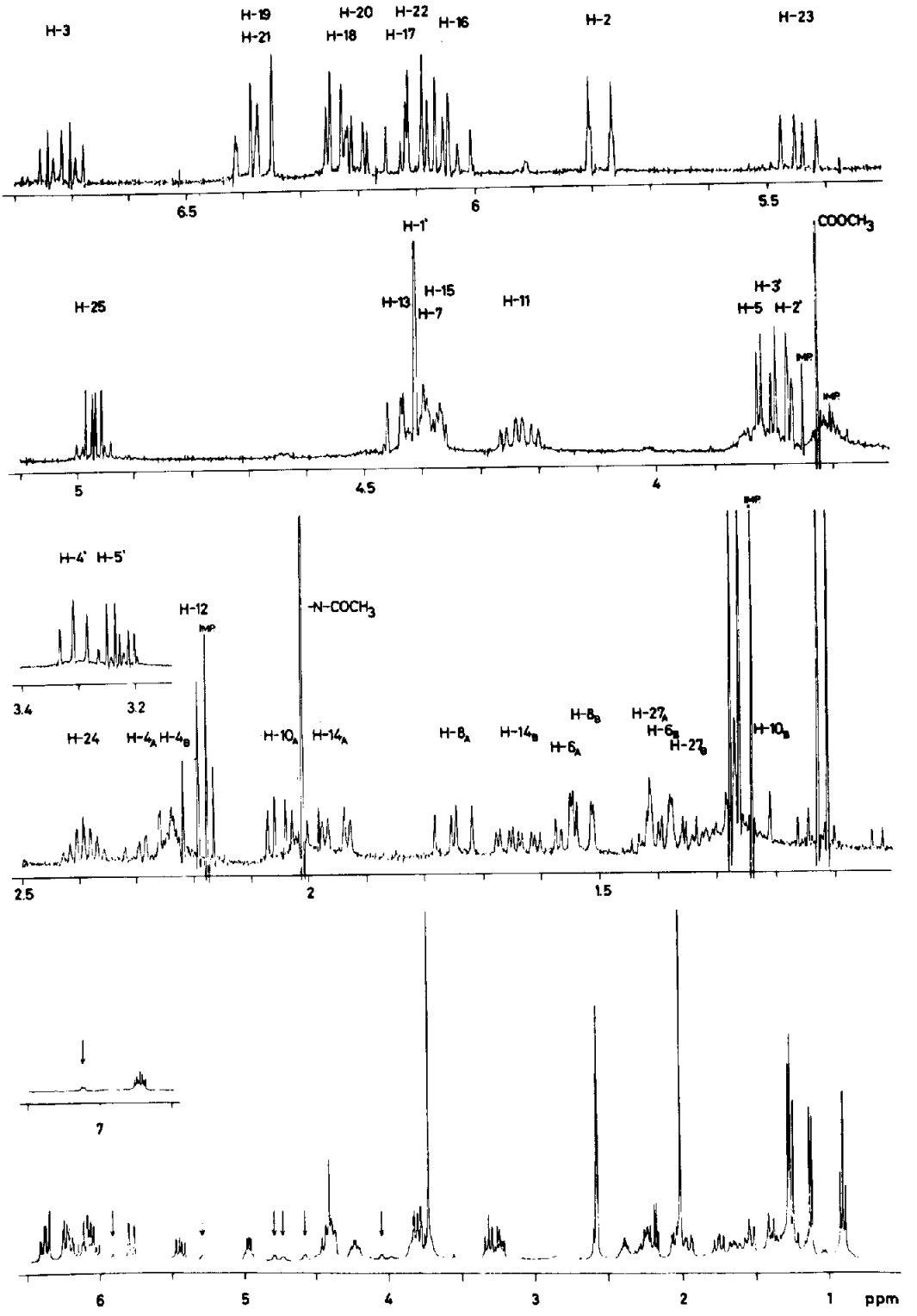


Fig. 1. 400 MHz ^{1}H NMR spectrum of N-acetyltetramycin A methyl ester (*Ia*) in $CDCl_3$-DMSO[$^2H_6$] (4:1) solvent mixture at 313 K. Bottom trace: full spectrum, upper traces: expanded parts of the resolution-enhanced spectrum. Arrows mark the position of partially ^{2}H-exchanged OH and NH proton resonances. HDO signal suppressed (at 3.1 ppm).

(low power) selective ^{13}C-{^1H} double resonance measurements. The above procedures have afforded the *complete* and consistent assignment of the ^{13}C spectra for each macrolide.

Constitution and stereochemistry of tetramycins A and B. With all protons, carbon (and hetero) atoms in I and II accounted for, the NMR results afford a detailed description of the constitution and stereochemistry of the antibiotics. Of particular relevance in this respect are the ^1H-NMR data. As the protons in these molecules are arranged in a limited number of uninterrupted, sequentially coupled spin systems extending from C-2 to C-8, C-10 to C-26, C-28 and from C-1' to C-6', Karplus type analysis of interproton coupling constants may give a fairly comprehensive portrayal of the solution form of the antibiotics.

Comparison of the ^1H-NMR data in Table 2 with those published on pimaricin[6,7] shows great similarity in the stereochemistry for most parts of the molecules which are unaffected by different substitution. The same conclusion can be inferred from the ^{13}C chemical shift values given in Table 3. The discussion below is, therefore, limited to structural details specific for the two novel antibiotics and to stereochemical characteristics of the macrolide backbone not revealed so far.

Inspection of the ^1H NMR data for Ia and IIa shows that the structural differences between the two macrolides are confined to the C-2–C-8 moiety. On going from Ia to IIa, one notes the alterations in coupling patterns and/or chemical shifts of resonances due to C-2H, C-3H, C-4H_A and C-5H accompanied by disappearance of the C-4H_B signal, and by appearance of an additional OH proton signal in the spectrum of latter molecule. These findings as well as the changes in the spectral parameters of the pertinent C atoms, of which the substantial downfield shift and the change from triplet to doublet in the off-resonance multiplicity for the C-4 signal are especially remarkable, clearly settle the structure of II as 4-hydroxytetramycin A.

A more detailed analysis of the spin systems involving all C-bonded protons between C-2 and C-8 allowed the determination of the relative configurations of OH-substituted C atoms in this moiety. A schematic presentation of the results (assuming highly preferred conformation) is given in Fig. 2. From biogenetic aspects, of particular relevance is the finding that the two OH groups at C-4 and C-5 in IIa are *cis* arranged (*vide infra*).

Both I and II were assumed to possess an Et side chain attached to C-24, a distinctive feature of tetramycins.[1] As attested by the coupling patterns of C-23H, C-24H and C-27H_AH_B and also by the spectral

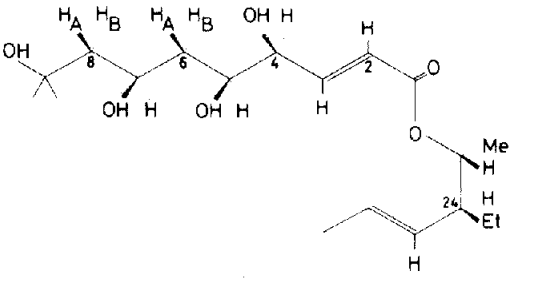


Fig. 2. Schematic view of the macrolide backbone with relative configurations of substituted carbon atoms as inferred from NMR results (see text).

parameters of pertinent C atoms in pimaricin and tetramycins, the NMR results fully support this expectation. The 4.5 Hz observed for the vicinal J(24, 25) (Table 2) indicates *gauche* relative orientation for the two protons adjacent to the vicinal alkyl groups. On the other hand, comparison of the ^{13}C chemical shift data for pimaricin and tetramycins (Table 3) shows that the C-26 Me carbon resonance undergoes substantial upfield shift upon introduction of the Et group at C-24 which is readily explained in terms of γ-*gauche* steric interaction. These two observations suggest that, in tetramycins, the alkyl substituted C atoms, C-24 an C-25, exist in the *erythro* diastereomeric form.

An important structural detail with this class of antibiotics is the occurrence of a pyranoid hemiacetal encompassing C atoms C-9 to C-13 (a partial structure readily evidenced by the appearance at approx. 97 ppm of a quaternary C signal in the ^{13}C spectrum[8]). As shown by the coupling constants of pertinent protons and the excellent agreement of chemical shift values for respective C atoms in the three macrolide derivatives (Table 3), the conformation of (and relative configurations in) the 6-membered hemiketalic ring is identical for each of these antibiotics, i.e. chair with the bulky substituents in equatorial positions.[5] Similar arguments provide corroboration for the expected β-configuration of the glycosidic bond of mycosamine, the common sugar moiety of these macrolides.[1,6]

Another important partial structure, common to these antibiotics, is the tetraene moiety. The coupling patterns of olefinic proton resonances, readily analyzable in the ^1H spectra obtained in the present study (Fig. 1 and Table 2), clearly attest to the all-*trans* configuration of the unsaturated C atoms. Coupling constants across formal single bonds (10.3 to 10.8 Hz) of the same protons, on the other hand, suggest that the tetraene moiety

Table 1. Antifungal activity of tetramycins A and B[a]

Strain	Minimal inhibitory concentration ($\mu g.cm^{-3}$)	
	I	II
Saccharomyces cerevisiae JH 1	12.5	6.25
Fusarium solani JP 20	25	12.5
Penicillium notatum JP 36	12.5	6.25
Scopulariopsis spec. JP 25	25	12.5

[a] Measured by agar dilution method.

Table 2. Proton NMR data[a]

Proton		Ia			IIa	
		$CDCl_3$/DMSO (4:1)		Pyridine-d_5	$CDCl_3$/DMSO (4:1)	
C-2H	($^3J_{2,3}$;$^4J_{2,4A}$;$^4J_{2,4B}$)	5.79	(15.4;1.0;1.5)	6.11	6.08	(15.5;2.2)
C-3H	($^3J_{3,4A}$;$^3J_{3,4B}$)	6.72	(9.2;5.4)	7.05	6.74	(3.2)
C-4H_A	($^2J_{A,B}$;$^3J_{4A,5}$)	2.29	(15.0;11.0)	2.49	4.01	(1.6)
C-4H_B	($^2J_{4B,5}$)	2.22	(2.5)	2.32		
C-5H	($^3J_{5,6A}$;$^3J_{5,6B}$)	3.82	(11.0;1.5)	4.04	3.81	(11.0;2.0)
C-6H_A	($^2J_{A,B}$;$^3J_{6A,7}$)	1.56	(14.2;10.0)	d	1.95	(14.5;10.0)
C-6H_B	($^3J_{6B,7}$)	1.40	(2.0)	1.72	1.40	(2.0)
C-7H	($^3J_{7,8A}$;$^3J_{7,8B}$)	4.40	(11.0;2.0)	4.71	4.41	(11.0;2.0)
C-8H_A	($^2J_{A,B}$)	1.75	(14.0)	1.93	1.78	(14.0)
C-8H_B		1.53		d	1.57	
C-10H_A	($^2J_{A,B}$;$^3J_{10A,11}$)	2.05	(12.5;4.8)	2.53	2.06	(12.5;4.6)
C-10H_B	($^3J_{10B,11}$)	1.26	(11.0)	1.76	1.25	(11.0)
C-11H	($^3J_{11,12}$)	4.23	(10.5)	4.98	4.23	(10.5)
C-12H	($^3J_{12,13}$)	2.19	(10.5)	2.80	2.20	(10.5)
C-13H	($^3J_{13,14A}$;$^3J_{13,14B}$)	4.43	(0.5;8.5)	5.1	4.43	(0.5;8.5)
C-14H_A	($^2J_{A,B}$;$^3J_{14A,15}$)	1.95	(15.3;4.0)	2.42	1.95	(15.3;4.5)
C-14H_B	($^3J_{14B,15}$)	1.64	(2.5)	1.97	1.65	(2.5)
C-15H	($^3J_{15,16}$)	4.38	(8.9)	4.80	4.38	(8.5)
C-16H	($^3J_{15,17}$)	6.03	(15.4)	6.3-6.5	6.03	(15.5)
C-17H	($^3J_{17,18}$)	6.11	(10.4)	6.3-6.5	6.11	(10.5)
C-18H	($^3J_{18,19}$)	6.22	(14.5)	6.21	6.22	(14.5)
C-19H	($^3J_{19,20}$)	6.39	(10.8)	6.73	6.36	(10.8)
C-20H	($^3J_{20,21}$)	6.22	(15.0)	6.3-6.5	6.21	(15.0)
C-21H	($^3J_{21,22}$)	6.39	(10.3)	6.69	6.38	(10.0)
C-22H	($^3J_{22,23}$)	6.09	(15.0)	6.3-6.5	6.06	(15.0)
C-23H	($^3J_{23,24}$)	5.45	(9.2)	5.53	5.45	(9.5)
C-24H	($^3J_{24,25}$;$^3J_{24,27A}$;$^3J_{24,27B}$)	2.39	(4.5;4.5;9.5)	2.46	2.37	(4.5;4.5;9.5)
C-25H	($^3J_{25,26}$)	4.97	(6.5)	5.1	5.00	(6.7)
C-26(Me)		1.12		1.16	1.12	
C-27H_A	($^3J_{27A,28}$;$^2J_{27A,27B}$)	1.42	(7.0;13.5)	1.28	1.42	(7.0;13.5)
C-27H_B	($^3J_{27B,28}$)	1.36	(7.0)	1.28	1.36	(7.0)
C-28(Me)		0.90		0.82	0.90	
C-1'H	($^3J_{1',2'}$)	4.41	(1.2)	4.91	4.41	(1.2)
C-2'H	($^3J_{2',3'}$)	3.77	(3.0)	4.43	3.78	(3.0)
C-3'H	($^3J_{3',4'}$)	3.81	(9.8)	4.63	3.81	(9.5)
C-4'H	($^3J_{4',5'}$)	3.30	(10.0)	4.03	3.31	(10.0)
C-5'H	($^3J_{5',6'}$)	3.22	(6.0)	3.75	3.22	(6.0)
C-6'(Me)		1.27		1.54	1.27	
COOMe		3.73		3.86	3.73	
N-CO-CH_3		2.01		2.10	2.01	
C-4(OH)[b,c]	($^3J_{OH,4}$)	-		d	4.65	(5.0)
C-5(OH)[b,c]	($^3J_{OH,5}$)	4.56	(4.6)	d	4.60	(4.2)
C-7(OH)[b,c]	($^3J_{OH,7}$)	4.75	(4.4)	d	4.80	(4.6)
C-9(OH)[b]		5.29 or 5.93		d	5.32 or 5.90	
C-11(OH)[b]		5.29 or 5.93		d	5.32 or 5.90	
C-2'(OH)[b,c]	($^3J_{OH,2'}$)	4.05	(4.2)	d	4.09	(4.2)
C-4'(OH)[b,c]	($^3J_{OH,4'}$)	4.70	(5.0)	d	4.72	(6.1)
C-3'(NH)	($^3J_{NH,3'}$).	7.12	(8.2)	d	7.12	(8.2)

[a] Obtained by first-order treatment of the 400 MHz spectra. Chemical shift (ppm) are relative to internal $SiMe_4$. Interproton couplings (Hz) are reported for one of the interacting partners only.

[b] At 343 K; temperature dependent value.

[c] Assignment is based on decoupling experiments prior to $^1H/^2H$ exchange.

[d] Not assigned.

Table 3. ^{13}C chemical shift data

Carbon	Ia	IIa	IIIb	Carbon	Ia	IIa	IIIb
C-1	164.94	165.16	164.66	C-20	132.03	131.99	131.84
C-2	124.56	122.04	124.50	C-21	132.98	132.77	132.94
C-3	145.47	148.59	144.22	C-22	134.84	135.00	135.84
C-4	41.76	73.45	54.16	C-23	131.09	131.22	128.77
C-5	71.20	73.86	58.15	C-24	42.99	42.91	33.50
C-6	43.97	40.48	40.92	C-25	71.87	71.90	66.62
C-7	65.08	65.13	65.18	C-26	18.24	18.20	20.27
C-8	46.70	46.83	46.58	C-27	23.00	23.04	-
C-9	37.65	37.61	37.43	C-28	12.30	12.27	-
C-10	37.73	37.74	37.84	COOMe	175.45	173.51	173.05
C-11	65.84	65.74	65.56	COOMe	51.39	51.84	51.57
C-12	57.36	57.25	57.38	C-1'	97.23	97.25	97.06
C-13	69.09	68.57	69.64	C-2'	69.71	69.84	69.62
C-14	44.12	44.18	44.07	C-3'	55.42	55.26	55.43
C-15	76.24	76.17	76.17	C-4'	71.20	70.83	70.81
C-16	129.37	129.22	129.09	C-5'	73.85	73.65	73.65
C-17	136.28	136.14	135.68	C-6'	17.54	17.35	17.80
C-18	131.46	131.51	131.56	N-CO-	171.45	171.32	170.38
C-19	132.98	133.01	133.29	N-CO-Me	22.97	22.90	22.90

[a] Relative to internal $SiMe_4$ in $CDCl_3$–DMSO[$^{12}C_2$,$^2H_6$] (4:1) solvent mixture.

presumably occurs in a "fully-extended" s-*trans* conformation.[18]

Related antibiotics. Besides structural similarities with pimaricin, tetramycins A and B are also related to lucensomycin[19] and differ from tetrins A and B merely in the substituent group at C-24 (Et instead of Me).[4,5] The structural similarity, most certainly, is due to a common biosynthetic pathway of these molecules. It seems therefore reasonable to assume that the difference in the oxidation state of C-4 of tetramycins A and B comes about through the intermediary formation of a C-4, C-5 epoxide (as in pimaricin or lucensomycin) which subsequently undergoes reductive or hydrolytic ring opening to yield the tetramycin congeners, much in the same way as it has been proposed for tetrins A and B.[5]

EXPERIMENTAL

M.ps were determined on a Kofler hot stage and are uncorr. IR spectra were recorded on a Perkin–Elmer 325 spectrophotometer, UV spectra on a Zeiss spectrophotometer Specord UV VIS. EI-MS were determined on a AEI MS 902 S spectrometer and EA-MS were obtained on a EA-mass spectrograph (M. v. Ardenne, Dresden). The high field NMR spectra were recorded on a Bruker WH 400E instrument operating at 400 MHz for protons and 100.6 MHz for carbons. The time-consuming selective ^{13}C-{^1H} double resonance experiments were made at 25.16 MHz using a disk-augmented Varian XL-100/15 FT NMR spectrometer.

Analytical tlc was carried out on Polygram silica gel sheets UV_{254}, (Macherey and Nagel, F.R.G.). The spots were visualized either by UV light or molybto-phosphoric acid.

Tetramycin complex. Details of fermentation and isolation have been reported elsewhere.[2]

Isolation of tetramycin A (I) *and B* (II). The two components were separated by preparative reversed phase tlc on silanized silica gel HF_{254} (Merck) plates (20 × 20 cm), thickness of layer 1 mm), using MeOH/$CHCl_3$(7:3) as the solvent system. 0.4 ml sample soln containing 10 mg of the tetramycin complex in MeOH/DMSO (9:1) was applied bandwise with CAMAG chromatocharger after Firmenich. Developing time approx. 2 hr. The bands were visualized by UV light, eluted with MeOH and the solvent evaporated to give the pure tetramycins A and B. Both tetraene antibiotics showed a single spot on tlc using MeOH/$CHCl_3$ (7:3); R_f(I) 0.88; R_f(II) 0.69.

Tetramycin B. The sample melted above 250° with decomposition; $[\alpha]_D^{20} - 45.0$ (*c* 0.2, MeOH). The UV spectrum had λ_{max}^{MeOH} ($E_{1cm}^{1\%}$) nm: 280, 292 (700), 304 (1080), 318 (960). Its IR spectrum had bands at ν_{max}^{KBr} cm^{-1}: 3430 (OH), 3020 (C=C), 2930, 2870, 1710 (lactone), 1640 (C=C), 1580 (COO^-), 1400, 1280, 1075 (C–O valency-vibration), 1010. 940 (C=C). The EI-MS did not give ions above *m/z* 460, while the FD-MS showed the highest ion at *m/z* 712 (see text). (Found: C, 56.20; H, 7.53; N, 1.70. Calc. for $C_{35}H_{53}NO_{14}$: C, 59.05; H, 7.51; N, 1.96. Calc for $C_{35}H_{53}NO_{14} \cdot H_2O \cdot CH_3OH$: C, 56.74 H, 7.81; N, 1.83%).

N-Acetyltetramycin methyl ester. A mixture of 100 mg of the tetramycin complex and 0.07 ml Ac_2O in 15 ml of abs MeOH was stirred at 0° for 2 hr. The resulting soln was concentrated and the residue was precipitated with ether to give 80 mg of N-acetyltetramycin. A soln of diazomethane in THF was added to a soln of 80 mg of N-acetyltetramycin in 10 ml of MeOH until the yellow color persisted. The mixture was left at room temp for 4 hr, excess diazomethane was decomposed with a few drops of AcOEt, the soln was concentrated *in vacuo* and the residue was precipitated with ether to give 75 mg of the product.

Isolation of N-acetyltetramycin A methyl ester and N-acetyltetramycin B methyl ester. A soln of 270 mg of N-acetyltetramycin methyl ester in 5 ml MeOH was chromatographed on a column of silica gel (27 g, Merck 60, 0.063–0.2 mm). The esters were eluted with $CDCl_3$/MeOH (8:2), and the solvent was removed to afford 96 mg of N-acetyltetramycin A methyl ester and 56 mg of N-acetyltetramycin B methyl ester. Each methyl ester derivative gave a single spot on tlc using $CHCl_3$/MeOH (8:2). Both IR spectra showed bands at ν_{max}^{KBr} cm^{-1}: 3400, 2905, 1720, 1705, 1650, 1630, 1430, 1370, 1260, 1000. The UV spectra had bands at λ_{max}^{MeOH} nm: 280, 290, 304, 318. N-acetyltetramycin A methyl ester. Fp. 155–160°; $[\alpha]_D^{20} + 60.7°$ (*c* 0.2, MeOH) R_f 0.41.

N-acetyltetramycin B methyl ester. Fp. 150–153°; $[\alpha]_D^{20}+54.1°$ (*c* 0.2, MeOH) R_f 0.34.

N-Acetylpimaricin methyl ester. This ester was prepared by the method described for N-acetyltetramycin methyl ester. Analytical tlc indicated a single component; R_f 0.42 ($CHCl_3$/MeOH, 8:2). Fp. 195–200° (dec); $[\alpha]_d^{25}+187°$ (*c* 0.26; MeOH) IR ν_{max}^{KBr} cm^{-1}: 1720 (ester) UV λ_{max}^{MeOH} nm: 280, 290, 304, 317.

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