Chemical Synthesis and Structural Study of Lincomycin Sulfoxides and a Sulfone

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Oxidation of lincomycin with dimethyldioxirane resulted in the sulfoxide-glycosides **3a** and **3b**, whose treatment with osmium tetraoxide and *N*-methylmorpholine-*N*-oxide afforded the same sulfone; **4**. According to FAB-MS and CD investigations, the absolute configuration of the sulfur atom in **3a** and **3b** is *R* and *S*, respectively. The new, unsaturated antibiotic analog (**6**) derived from clindamycin exists in the $^4C_1$ conformation. The antibiotic activities of the synthesized compounds were also studied.

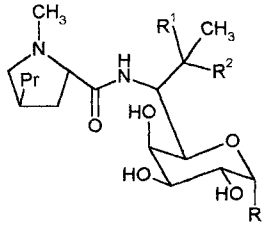
During the biosynthesis of lincomycin (**1**) ARGOUDELIS and MASON[1] found that the extended fermentation of *Streptomyces lincolnensis* var. *lincolnensis* for twelve days resulted in two biologically active products, which could be separated by counter double current distribution. Based on spectroscopic data (IR, NMR and MS), the structures of these compounds were assigned as 1-demethylthio-1-hydroxylincomycin (**2**) and the corresponding sulfoxide **3**. Later, clindamycin (**4**) could be transformed[2] into the clindamycin-sulfoxide **5** (Fig. 1) by treatment with *Streptomyces panipalus* and *Streptomyces armentosus*. However, the authors[1,2] did not mention that compound **3** is to be characterized by two different sulfoxide-glycoside structures (**3a** and **3b**) which must possess different physical data. Since thioglycosides[3~5] and the respective sulfoxides[5] have emerged as extremely useful glycosyl donors in glycoside syntheses, delineating the structures of the above derivatives (*i.e.* **3** and **5**) is desirable both from biological and chemical points of view.

The present paper describes the separation, proof of structure and biological activity of two lincomycin sulfoxides and a sulfone prepared by chemical synthesis, as well as a novel way for the chemical modification of clindamycin.

Results and Discussion

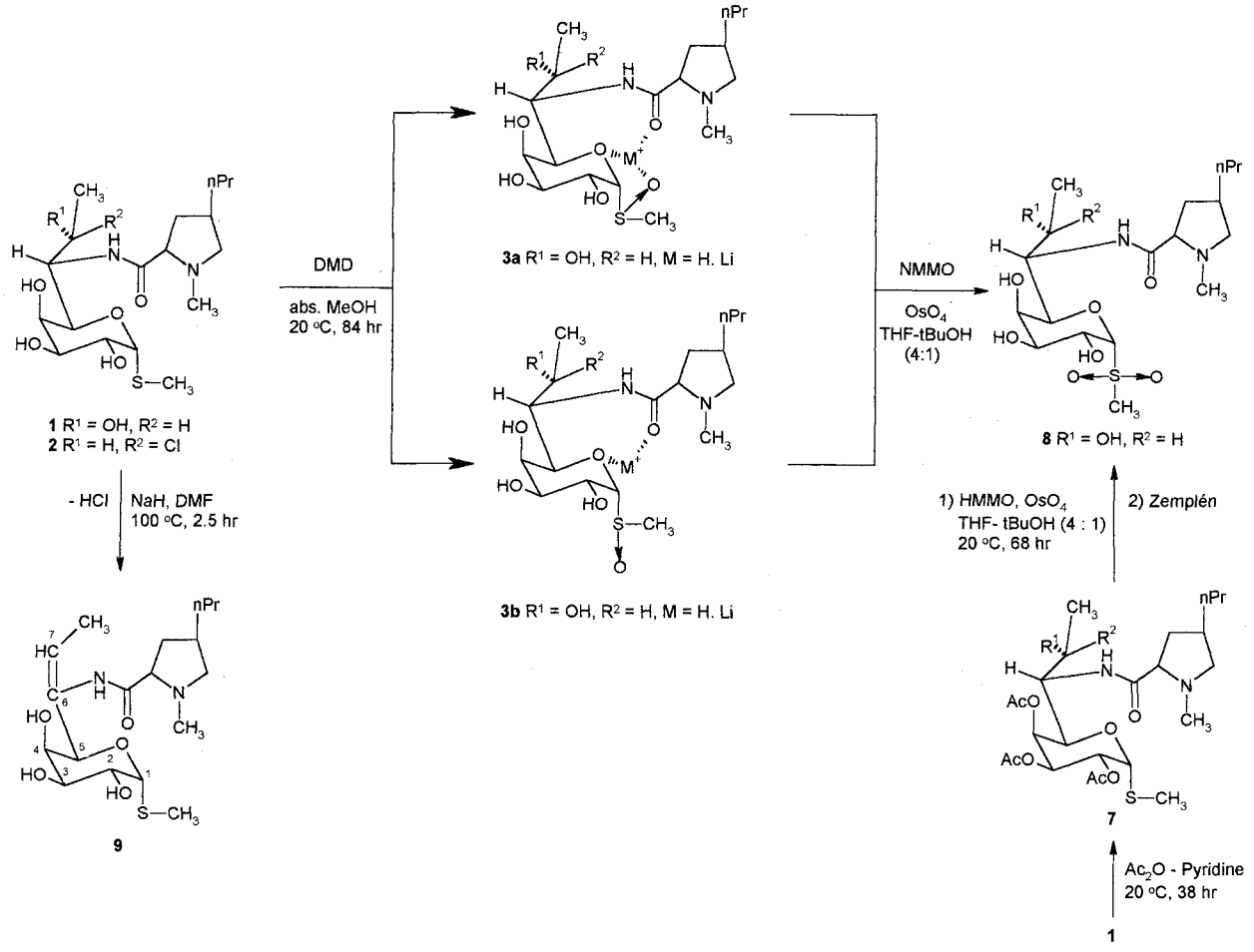
The methods most frequently employed for the preparation of sulfoxides (oxidation with peracids, $NaIO_4$ and H_2O_2, *etc.*) cannot be applied to lincomycin (**1**). At the same time, the antibiotic **1** could be chemoselectively oxidized to a 2:1 mixture of the sulfoxides **3a** and **3b** (Fig. 2) with a new electrophylic

Fig. 1. Structure of lincomycin (**1**), 1-demethylthio-1-hidroxylincomycin (**2**), clindamycin (**4**) and their sulfoxides (**3**, **5**).



1 R = S-CH_3, R^1 = OH, R^2 = H, R^3 = nPr
2 R = OH, R^1 = OH, R^2 = H, R^3 = nPr
3 R = -S-CH3, R1 = OH, R2 =H, R3 = nPr
↓ O
4 R = -S-CH_3, R^1 = H, R^2 = Cl, R^3 = nPr
5 R = -S-CH_3, R^1 = H, R^2 = Cl, R^3 = nPr
↓ O

Fig. 2. Synthetic route to lincomycin-sulfoxides and sulphone.



oxidizing agent, dimethyldioxirane (DMD)[7] under neutral conditions. The products, possessing different physico-chemical data (Table 1) were separated by column chromatography.

The full ^1H and ^{13}C NMR assignements for the sulfoxides **3a** and **3b** with the aid of the COSY, TOCSY and HETCOR methods are shown in Tables 2 and 3. The results of the ROESY off-resonance measurements proved that the pyranose ring is in the $^4C_1$ conformation in both compounds, and no significant difference is found in the spatial closeness of the hydrogen atoms in the two diastereoisomers. Qualitative evaluation of the ROESY experiments showed that the average distance of the C-7 methyl group is 3 ~ 4 Å both from the *N*-methyl and *S*-methyl substituents, and this is in good agreement with the known X-ray structure[11]. The assigned ^{13}C NMR data clearly indicate that the 7-Me and C-7 chemical shifts are the most sensitive for the change of the configuration of the sulfoxide, and of the two diastereoisomers the related chemical shift values of **3a** (Table 3) correspond to those observed for lincomycin ($\delta_{C\text{-}7\,Me} = 17.39$, $\delta_{C\text{-}7} = 66.40$ ppm). However, these data are not sufficiently enough for the determination of the configuration of the sulfoxide.

In the solid-phase IR spectra (KBr) of **3a** and **3b** the amide II and amide I bands appear with the same resonance (1526 and 1654 cm^{-1}, respectively). On the contrary, in dilute chloroform solution the amide I band of **3a** and **3b** appeared at 1648 cm^{-1} and 1642 cm^{-1}, respectively, while no difference in the amide II band-resonances was observed. The $\nu_{S\to O}$ bands caracteristic of the sulfoxides were assigned at 1012 and 1016 cm^{-1}, respectively (Table 1).

The structural difference of the two sulfoxides was also indicated by the detailed FAB mass spectrometric measurements (Table 4). Apart from the *m/z* 423 $[M+H]^+$ peak in the mass spectrum of **3a** (recorded in a glycerol-matrix), an intensive *m/z* 424 $[M+2H]^+$ ion also appeared, which is missing from the spectrum of **3b**. In addition, the *m/z* 359 $[M-CH_3SO^{\cdot}]^+$ ion in the

Table 1. Physico-chemical properties and IR spectroscopic data of lincomycin derivatives.

Compound	Yield %	mp (°C)	$[\alpha]_D^{20}$	MS (*m/z*)	IR cm^{-1}
3a	28.0	76~78	+50.97° (c=0.10, $CHCl_3$)	424[a], 377 (M+H−SCH_3) 359 (M−$SOCH_3$)	1012 1518 (amid II) 1648 (amid I)
3b	15.0	87~89	+149.57° (c=0.10, $CHCl_3$)	423, 359 (M−$SOCH_3$)	1016 1518 (amid II) 1642[c] (amid I)
3a→8	78.3	76~79	+75.59° (c=0.056, $CHCl_3$)	439[a] 359 (M−SO_2CH_3)	1148 ν_s (SO_2) 1300 ν_{as} (SO_2) 1524 (amid II) 1654 (amid I)
3b→8	64.7	76~78	+76.43° (c=0.062, $CHCl_3$)	439[a] 374 (M−SO_2) 359 (M−SO_2CH_3)	1145 ν_s (SO_2) 1294 ν_{as} (SO_2) 1524 (amid II) 1654 (amid I)
7→8	45.9	78~80	+75.21° (c=0.11, $CHCl_3$)	439[a] 374 (M−SO_2) 359 (M−SO_2CH_3)	1148 ν_{as} (SO_2) 1296 ν_{as} (SO_2) 1526 (amid II) 1655 (amid I)
7	98.8	37~40	+143.20° (c=0.1, MeOH)	575[a], 527 (M−S−CH_3)	1511 (amid II) 1684 (amid I) 1753 $\nu_{C\rightarrow O}$ (Ac)
9	36.2	42~43	+150.80 (c=0.2, $CHCl_3$)	389[a]	1498 (amid II) 1662 (amid I) 3416 ν_{OH}

[a] FAB $(M+H)^+$, [b] in $CHCl_3$.

Table 2. Assignments of signals of the ^1H NMR-spectrum of synthetic lincomycin analogues.

^1H NMR (500 MHz, $CDCl_3$) δppm			
3a	**3b**	**8**	**9**
7.928 (1H, d, NH, J=8.4 Hz)	7.86 (1H, brd, NH, J=6.6 Hz)	7.916 (1H, brd, NH, J=6.5 Hz)	8.48 (1H, brs, NH)
5.00 (1H, brs, OH)	5.10 (1H, brs, OH)	5.29 (1H, brs, OH)	5.94 (1H, dq, H-7, $^3J_{7,Me}$=6.9 Hz,
4.88 (1H, brs, OH)	4.65 (1H, d, H-1, $J_{1,2}$=6.1 Hz)	5.03 (1H, H-1, $J_{1,2}$=5.5 Hz)	$^4J_{4,7}\cong$1.6 Hz)
4.78 (1H, d, H-1, $J_{1,2}$=5.5 Hz)	4.32 (1H, dd, H-2, $J_{2,3}$=9.9 Hz)	4.70 (1H, brs, OH)	5.40 (1H, d, H-1, $^3J_{1,2}$=5.5 Hz)
4.42 (1H, dd, H-2, $J_{2,3}$=9.7 Hz)	4.28 (1H, brs, OH)	4.45 (2H, m, H-2+H-3)	4.54 (1H, br, d, H-5, $^3J_{4,5}\approx$0, $^5J_{5,7Me}$=1, 6 Hz)
4.19 (1H, dd, H-3, $J_{3,4}$=3.1 Hz)	4.00 (1H, d, H-5, $J_{5,6}$=9.2 Hz)	4.17 (1H, m, H-7)	4.30 (1H, brs, OH)
4.12 (1H, brs, OH)	3.94 (2H, m, H-6+H-7)	4.14 (1H, d, H-5, $J_{3,4}$=9.9 Hz)	4.13 (1H, dd, H-2, $^3J_{2,3}$=10.0 Hz)
4.03 (2H, m, H-6+H-7)	3.88 (1H, dd, H-3, $J_{3,4}$=3.3 Hz)	4.06 (1H, brm, H-6)	3.85 (1H, d, H-4, $^3J_{3,4}$=3.0 Hz)
3.95 (1H, d, H-4, $J_{4,5}\approx$0)	3.73 (1H, brd, H-4)	3.80 (1H, brs, H-4)	3.67 (1H, dd, H-3)
3.90 (1H, d, H-5, $J_{5,6}$=7.7 Hz)	3.14 (1H, m, H-5'a)	3.56 (1H, brs, OH)	3.23 (1H, brs, H-5'a)
3.13 (1H, brs, H-5'a)	2.94 (1H, brs, H-2')	3.23 (1H, brt, H-5'a)	3.08 (1H, brs, OH)
2.90 (1H, brs, H-2')	2.75 (3H, s, S-Me)	3.13 (3H, s, S-Me)	2.82 (1H, brs, OH)
2.81 (3H, s, S-Me)	2.30 (3H, s, N-Me)	3.01 (1H, brs, H-2')	2.45 (3H, brs, Nme)
2.30 (3H, s, N-Me)	2.00 (2H, m, H-4'+H-5'b)	2.39 (3H, S, N-Me)	2.15 (1H, m, H-4')
2.04 (1H, m, H-4')	1.87 (1H, m, H-3'a)	2.09 (2H, m, H-4'+H-5')	2.13 (1H, brs, H-5'b)
1.97 (1H, m, H-5'b)	1.79 (1H, m, H-3'b)	1.93 (1H, m, H-3'a)	2.12 (3H, s, S-Me)
1.89 (1H, m, H-3'a)	1.34 (3H, d, 7-Me, J=6.6 Hz)	1.88 (1H, m, H-3'b)	2.02 (1H, m, H-3'a)
1.75 (1H, m, H-3'b)	1.23 (4H, m, $2CH_2$-Pr)	1.36 (3H, d, 7Me, J=6.5 Hz)	1.90 (1H, m, H-3'b)
1.23 (4H, m, $2CH_2$(Pr))	0.83 (3H, m, CH_2(Pr))	1.32 (4H, m, $2CH_2$-Pr)	1.61 (1H, dd, 7-Me)
1.14 (3H, d, 7-Me, $J_{7,7Me}$=5.9 Hz)		0.91 (3H, t, Me(Pr))	1.2~1.4 (4H, m, CH_2-Pr)
0.83 (3H, m, Me(Pr))			0.91 (3H, t, Me-Pr)

spectrum of **3a** is also more pronounced than in the spectrum of **3b**.

The differences observed in the glycerol-matrix spectra became even more pronounced when a molar equivalent of an aqueous solution of lithium carbonate was added. In the case of **3a** the basic peak of the $[M+Li]^+$ ion

appeared at *m/z* 429, and for **3b** the $[M+H]^+$ ion was observed at *m/z* 423. In the two samples the $[M+H]^+$ and $[M+Li]^+$ peaks show a completely reverse ratio of intensity (Table 4), and this is explained by that in **3a** the Li^+ ion is coordinated to three oxygen atom, but—due to steric reasons—in **3b** only two oxygen atoms are involved in the coordination. Consequently, the lithium adduct of **3a** is considered more stable than that of **3b**. These observations are in good agreement with the results of the IR measurements performed in solution (Table 1). Thus, the higher amide I resonance value for **3a** can also be explained by the steric effect between the amide bond and the sufoxide-oxygen atom, which does not exist in **3b**.

At the sodium D line both sulfoxides have a positive rotation ($[\alpha]_D^{20}$ +50.9° for **3a** and +149.5° for **3b**). In an attempt to determine the absolute configuration of the sulfur chiral center, we compared the CD spectra of **3a** and **3b**. As shown in Fig. 3, the sulfoxide band near 230 nm has opposite sign in the spectra of the two compounds. (Apparently the sign of the optical rotation at the sodium D line is governed by the short-wavelength Cotton-effect which is positive in both cases.)

MISLOW *et al.*[12] have shown that there is a correlation between the absolute configuration of methyl alkyl sulfoxides and their CD band near 200 nm. In the absence of strongly perturbing groups, a negative CD band correlates with the *R* absolute configuration of the sulfur atom. OTTENHEIJM *et al.*[13] have applied this chiralitry rule for determining the absolute configuration of the sulfoxide of sparsomycin, a compound possessing antitumor and antibiotic activity. In the CD spectrum of sparsomycin a negative sulfoxide band appeared near 230 nm in acetonitrile. The CD-based *R* assignment of the absolute configuration of the sulfur atom was conformed by single-crystal X-ray structure analysis of a derivative of sparsomycin.

The sugar moieties in the lincomycin sulfoxides have no strong perturbing effect. In spite of the same chiral environment of the tertiary amide chromophore, which has an $n\pi^*$ band near 220 nm, the CD bands at *ca.* 230 nm in the spectra of **3a** and **3b** have opposite signs. (Fig. 3, the overall diastereoisomeric relationship of the two molecules is reflected only in the difference of the λ_{max} rather than in the intensity value of the bands.) This clearly shows that the optical activity of the long-wavelength CD band is dominated by the chiral contribution of the sulfoxide chromophore. Consequently, the chirality rule can also be used for determining the

Table 3. ^{13}C NMR Spectral data of synthetic compounds.

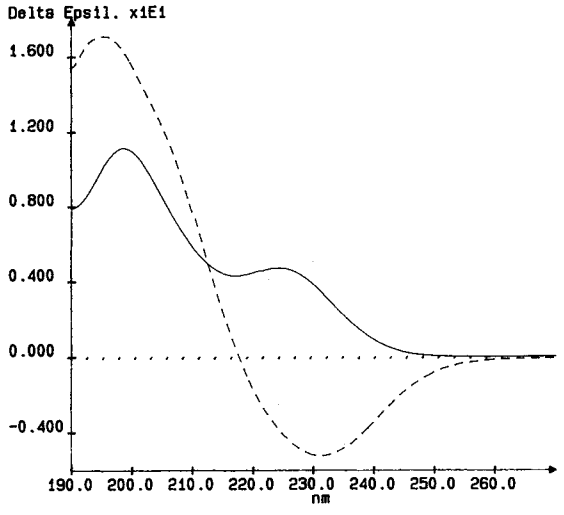
Position	^{13}C NMR (125 MHz, $CDCl_3$) δ ppm			
	3a	**3b**	**8**	**9**
C=O	176.68	176.80	177.35	175.68
C-1	93.39	93.49	90.82	87.46
C-5	75.32	75.60	76.26	71.86
C-3	70.53	71.41	68.75	71.08
C-2	70.23	68.49	68.30	69.19
C-4	68.74	68.49	68.48	69.28
C-2′	68.66	68.35	68.43	68.51
C-7	66.70	70.05 (br)	68.43	123.41
C-5′	62.78	62.62	62.66	62.77
C-6	54.41	53.38	53.46	129.28
N-Me	41.76	41.72	41.77	41.94
C-4′	37.67	37.66	37.70	37.99
C-3′	37.53	37.61	37.58	37.74
S-Me	37.11	37.78	43.41	13.48
CH_2(Pr)	35.83	35.73	35.73	35.61
CH_2(Pr)	21.51	21.48	21.47	21.54
7Me	18.85	21.08	19.35	12.44
Me(Pr)	14.24	14.21	14.22	14.19

Table 4. FAB Mass spectrometric data of lincomycin-sulfoxides **3a**, **b**.

Compound	Characteristic ions *m/z* (%)	
	in Glycerol	in Glycerol + Li_2CO_3
3a	424 (80) $[M+2H]^+$	423 (100) $[M+H]^+$
	423 (40) $[M+H]^+$	429 (100) $[M+Li]^+$
	422 (15) $M^{+\cdot}$	413 (15) $[M+Li-O^{\cdot}]^+$
	446 (100) $[M+Na]^+$	407 (20) $[M+H-O^{\cdot}]^+$
	462 (10) $[M+K]^+$	359 (80) $[M-CH_3SO^{\cdot}]^+$
	407 (10) $[M+H-O^+]^{\cdot}$	
	359 (90) $[M-CH_3SO^{\cdot}]^+$	
3b	423 (70) $[M+H]^+$	423 (100) $[M+H]^+$
	422 (12) $M^{+\cdot}$	429 (60) $[M+Li]^+$
	446 (100) $[M+Na]^+$	413 (8) $[M+Li-O^{\cdot}]^+$
	462 (10) $[M+K]^+$	407 (12) $[M+H-O^{\cdot}]^+$
	407 (6) $[M+H-O^{\cdot}]^+$	359 (60) $[M-CH_3SO^{\cdot}]^+$
	359 (60) $[M-CH_3SO^{\cdot}]^+$	

absolute configuration of the lincomycin sulfoxides. To the sulfur atom in **3a** can be assigned the *R* configuration, because the long-wavelength CD band has a negative sign in both methanol and acetonitrile. The upward orientation of the sulfoxide oxygen is possible only in **3a**, with an *R* chiral center, which is agreement with the NMR data, and the more expressed Li^+-binding ability of **3a** (Table 4).

Fig. 3. CD Spectra of **3a** (– – –), and **3b** (——) in CH_3OH.



in MeOH **3a**, $\Delta\varepsilon = -5.2$ at 231.5 nm
17.2 at 195.5 nm
3b, $\Delta\varepsilon =$ 4.7 at 224.5 nm
11.2 at 198.5 nm

in CH_3CN **3a**, $\Delta\varepsilon = -7.75$ at 235 nm
15.6 at 204 nm

UV **3a**, ε227 1.2×10^3
ε201.5 6.6×10^3
3b, ε227 sh 1.16×10^3
ε202 6.13×10^3

PRIEBE and GRYNKIEWICZ[8] have reported the selective oxidation of alkyl-thioglycosides into the corresponding sulfones with a catalytic amount of osmium tetraoxide in the presence of tertiary amine oxides. We found that this procedure is useful also for the oxidation of lincomycin (**1**). Thus, **1** was first converted into the peracetyl derivative **7** with acetic anhydride in pyridine (20°C, 38 hours), followed by oxidation with osmium tetraoxide and *N*-methylmorpholine-*N*-oxide (NMMO) in a 4:1 mixture of tetrahydrofuran and *tert*-butanol. The crude product was deacetylated[10] with sodium methoxide in methanol to obtain the lincomycin-sulfone **8** with a 46% overall yield. Oxidation of **3a** or **3b** under the same conditions also afforded the sulfone **8**, demonstrating that oxidation of the different lincomycin sulfoxides gives rise to the same sulfone (Table 1).

Depending on the acid-scavenger, nucleophylic substitution[9] of the 7(*S*) chloro atom of clindamycin is accompanied by several side-reactions. For studying related transformations, compound **2** was reacted with sodium hydride in *N*,*N*-dimethylformamide (100°C, 2.5 hours) in the absence of a nucleophile to obtain a new, unsaturated derivative **9**. Apart from the data shown in Table 1, the structure of **9** was clearly proved by the ^1H and ^{13}C NMR spectra. The theoretical and measured coupling constant values of the vicinal protons demonstrate the $^4C_1$ conformation of the galactopyranose unit (Tables 2 and 3), and the *cis*-configuration of the $C_6 = C_7$ double bond is indicated by the NOE effect (200 MHz,

Fig. 4. Proposed conformation of the unsaturated compound (**9**).

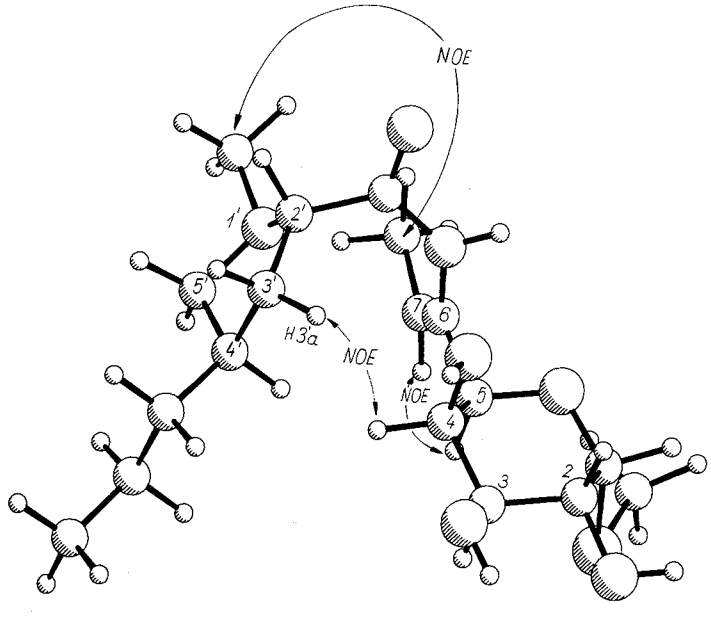


Table 5. *In vitro* antibacterial activity of **3a**, **3b**, **8** and **9** in comparison with lincomycin (**1**) clindamycin (**4**) and erythromycin.

No.	Test organism	Medium	MIC (μg/ml)						
			1	**3a**	**3b**	**8**	**9**	**4**	Erythromycin
1	*Staphylococcus aureus* KB 210 (ATCC 6538)	MHA	0.78	>100	100	50	50	<0.1	0.2
2	*Staphylococcus aureus* (MLS)[a]	MHA	N.T.	N.T.	N.T.	>100	>100	N.T.	N.T.
3	*Staphylococcus aureus* (MLS)[a]	MHA	>100	>100	>100	>100	>100	>100	>100
4	*Bacillus subtilis* KB211 (ATCC 6633)	MHA	25	>100	>100	>100	50	1.56	0.2
5	*Bacillus cereus* KB 143 (IFO 3001)	MHA	12.5	>100	>100	100	25	0.78	0.2
6	*Micrococcus luteus* KB212 (ATCC 9341)	MHA	0.39	12.5	25	3.12	12.5	0.1	<0.1
7	*Mycrobacterium smegmatis* KB42 (ATCC 607)	MHA	6.25	>100	>100	50	12.5	12.5	6.25
8	*Escherichia coli* KB213 (NIHJ)	MHA	100	>100	>100	>100	>100	25	12.5
9	*Escherichia coli* KB176 (NIHJ JC-2)	MHA	>100	>100	>100	>100	>100	>100	>100
10	*Escherichia coli* KB198 (MLS)[b]	MHA	12.5	>100	>100	>100	100	0.39	0.78
11	*Klebsiella pneumoniae* KB214 (ATCC 10031)	MHA	100	>100	>100	>100	100	50	100
12	*Poteus vulgaris* KB127 (IFO 3167)	MHA	>100	>100	>100	>100	>100	>100	>100
13	*Pseudomonas aeruginosa* KB115 (IFO 3080)	MHA	>100	>100	>100	>100	>100	>100	>100
14	*Clostridium perfringens* KB129 (ATCC 3624)	GAM	1.56	50	100	3.12	12.5	<0.1	6.25
15	*Clostridium perfringens* KB130	GAM	6.25	50	100	12.5	12.5	0.78	3.21
16	*Clostridium Kainantoi* KB 133 (IFO 3353)	GAM	1.6	50	25	6.25	12.5	0.20	0.20
17	*Bacteroidis fragilis* KB169 (ATCC 23745)	GAM	0.78	25	12.5	3.12	0.78	<0.10	0.20
18	*Fusobacterium varium* KB234 (ATCC 8501)	GAM	6.25	100	100	25	50	1.56	>100

Method: Agar dilution method. Solvents: Dist. water (**1**, **3a**, **3b**, **4**, **8**), 40~50% MeOH (**9**, Erythromycin). [a] Macrolide resistance, [b] Macrolide sensitive. MHA: Mueller Hinton Agar (Nissui) 37°C, 21 hours. GAM: GAM Agar Nissui, 37°C, 21 hours, Gas pack method (BBL).

+3% $r_{4,5}$ *ca.* 2.2~2.4 Å) between the H-7 and H-5 protons. At the same time, there is no NOE effect between H-7 and H-4, indicating that the distance is longer than 3 Å between these hydrogen atoms.

In accordance with these data the optimum geometrical values are: $\theta = 168°$, and $r_{H4,H3a} = 2.2\,Å_{(NOE)}$, and all of these data indicate the folded conformation of **6**. The $r_{H7,H5} = 2.3$ Å and $r_{H7,H4} = 4.1$ Å values are in accord with the θ dihedral angle. In this conformation the dihedral angle of the peptide bond is *ca.* 15°, indicating the *cis*-character of this bonding. Interestingly, the signal of the carbonyl-carbon is broadened in the ^{13}C NMR spectrum, which may indicate a change of the conformation, or the *cis-trans* isomerization of the peptide bond.

Antimicrobial Activity

The *in vitro* antibacterial activities of the sulfoxides **3a** and **3b**, the sulfone **8** and that of the unsaturated derivative **9** against 18 test microorganisms are shown in Table 5. Comparison of the data demonstrate an unfavourable change of the antibiotic activity either by increasing the degree of oxidation of the sulfur atom, or by introduction of the C_6–C_7 double bond. A significant difference is observed between the activities of the two lincomycin-sulfoxides (**3a** and **3b**) against the test-organisms of entries 14~18. However, the MIC values are still significantly lower than those of the parent antibiotic (**1**). The biological activity of the unsaturated compound **9** is comparable to that of **1** only against *Bacteroidis fragilis*.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. All of the new compounds possessed satisfactory elemental analytical data. ^1H and ^{13}C NMR spectra were recorded with Bruker 200 SY (200 and 50.3 MHz) and Bruker DR X 500 (500 and 125 MHz) spectrometers. Full analysis of the spectra

was achieved with the aid of COSY and inverse ^{1}H and ^{13}C NMR correlation. For conformational analysis the NOESY (500 MHz, mixing time 0.3), steady state NOE (200 MHz, 5 s) and the 1D GOESY (500 MHz) methods were applied. Fast-bombardment (FAB) mass spectra were obtained on a VG-7070MS mass spectrometer (VG Anmalytical, Ltd., Manchester, U.K.) operated at 4 kV accelerating potential with a resolving power of 1000 (10% Valley definition) and a scan rate 30 s/decade from 950 to 100. The samples were dissolved in a 1:7 (v/v) mixture of methanol and *glycerol* [W/N] on stainless steel probe tip. Operating conditions for the FAB gun (ION Tech, Teddington, U.K.) on the instrument were 8 kV at 1 mA equivalent ion current using xenon as the FAB gas. The samples and the FAB ion source were maintained at room temperature in each experiment. IR spectra (KBr disc and in methanol) were recorded with a Perkin-Elmer 16 PCFT spectrophotometer. Optical rotations were measured at room temperature with a Perkin-Elmer 141 MC polarimeter. UV/VIS and CD spectra were recorded with a Jobin-Yvon Dicrographe Mark VI instrument in cells from 0.02 cm to 0.5 cm path length, at concentrations of 1~2.5 mmol/liter in methanol and acetonitrile. Spectrograde solvents (Uvasole, Merck) were used. The $\Delta\varepsilon$ values are expressed in $cm^2\,mmol^{-1}$. TLC and column chromatography were performed on Kieselgel 60 F_{254} (Merck) and Silica Gel 60 (0.063~0.2 mesh, Merck), using (*A*) 7:3:0.1 chloroform - methanol - ammonium hydroxide, (*B*) 7:3 ethyl acetate–hexane, (*C*) 8:2 chloroform - methanol and (*D*) 9:1 chloroform - methanol mixtures. Evaporations were carried out under diminished pressure at $\leq$40°C.

Lincomycin Sulfoxides (**3a** and **3b**)

To a solution of lincomycin (2 mmol) in abs. methanol (2 ml) dimethyldioxirane (3 mmol in acetone) was added and the reaction mixture was kept at room temperature for 84 hours. It was then concentrated under diminished pressure and the residue purified by column chromatography (*A*). Following unchanged **1** (51.1%), **3b** (15.0%) and then **3a** (28.0%) were eluted, which were isolated as white amorphous materials. The physical and spectral data of these compounds are summarized in Tables 1~4.

Preparation of Lincomycin Sulfone (**8**) from **3a** and **3b**

To a mixture of **3a** or **3b** (0.12 mmol) in 4:1 abs. THF-*tert*-butanol (2 ml) a solution of NMMO (0.36 mmol) and osmium tetraoxide (0.0056 mmol) in *tert*-butanol (2 ml) was added. The mixture was stirred at room temperature for 6.5 hours, then filtered, concentrated under diminished pressure and the residue was submitted to column chromatography (*D*). The physical data (Table 1) of the samples of **8**, obtained either from **3a** (78.3%) or **3b** (64.7%) were identical with each other, as well as with those of the product prepared from **7**.

Preparation of Lincomycin Sulfone (**8**) from **1**

To a cold solution of **1** (4.51 mmol) in abs. pyridine (20 ml) acetic anhydride (20 ml) was added and the mixture was kept at room temperature for 38 hours. It was then poured onto ice, extracted with chloroform, the organic layer was washed with 10% aq. acetic acid (2 × 50 ml), water (2 × 50 ml) and aq. sodium hydrogen carbonate and dried over Na_2SO_4. Treatment of the residue with petroleum ether gave peracetyl lincomycin **7** (98.8%), as a white, amorphous powder (Table 1).

Oxidation of **7** with NMMO and osmium tetraoxide was carried out as described above for **3a** and **3b**. The crude, peracetylated lincomycin-sulfone (46.8%, mp 69~72°C) was purified by means of column chromatography (*B*). This was then dissolved in abs. methanol (5 ml) and treated with sodium methoxide in methanol (pH *ca.* 7~8) according to the ZEMPLÉN conditions[10]. The physical data (Table 1) of the product **8** (99%) was identical, in every respect, with those of the sample prepared from **3a** or **3b**.

Preparation of the Unsaturated Lincomycin Derivative **9**

To a solution of clindamycin HCl (1 mmol) in abs. *N*,*N*-dimethylformamide (5 ml) sodium hydride (2.2 mmol) was added in small portions and with cooling. The reaction mixture was stirred at 100°C for 25 hours, then filtered, and the filtrate was evaported, by the addition of toluene, onto Silica Gel 60 (4.0 g). The residue, obtained this way, was submitted to column chromatography (*A*) to elute, first unchanged **4** (12.96%) and then the product **9**, isolated as a solid foam (36.28%). The physico-chemical and NMR spectral data of **9** are summarized in Table 1 and Tables 2 and 3, respectively.

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