Amine oxides
VIII.* Preparation, infrared spectra, and antimicrobial activity of some *N*-oxides of *N*,*N*-dialkylaminoalkylesters and *N'*,*N'*-dimethylaminoalkylamides of dodecanoic acid

[a]F. DEVÍNSKY, [a]I. LACKO, [b]D. MLYNARČÍK, and [a]Ľ. KRASNEC

[a]*Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Komenský University, CS-832 32 Bratislava*

[b]*Department of Biochemistry and Microbiology, Faculty of Pharmacy, Komenský University, CS-832 32 Bratislava*

Received 12 February 1982

Paper published on the occasion of the 30th anniversary of the foundation of the Faculty of Pharmacy, Komenský University, Bratislava

Preparation, infrared spectra, and antimicrobial activity of some *N*-oxides of *N*,*N*-dialkylaminoalkylesters and *N'*,*N'*-dimethylaminoalkylamides of dodecanoic acid are described. An influence of the structure on antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* has been found.

Описано получение, ИК-спектры и антимикробиальная активность некоторых *N*-окисей, производных *N*,*N*-диалкиламиноалкиловых эфиров и *N'*,*N'*-диметиламиноалкиламидов додекановой кислоты. Обнаружено влияние структуры на антимикробиальную активность по отношению к *Staphylococcus aureus*, *Escherichia coli* и *Candida albicans*.

Amine oxides represent a large group of compounds derived from tertiary amines containing a strongly polarized N—O bond [1—3]. Great number of amine oxides occurring in nature or prepared synthetically are known as biologically active compounds (antimetabolites and chemotherapeutics, psychotropic and cancerostatic compounds, *etc.*). Though some nonaromatic amine oxides have found wide industrial utilization due to their good surface-active properties [4, 5], relatively little attention has been paid to their biological activity, contrary to aromatic amine oxides [6—8].

* For Part VII see *Collect. Czech. Chem. Commun.* 47, 1130 (1982).

Nonaromatic surface-active amine oxides represent biodegradable nonionic amphiphiles well soluble both in water and polar organic solvents [9, 10]. Besides these properties they show significant antimicrobial activity [11—14] and also lower acute toxicity when compared with the appropriate amines and structurally similar organic ammonium salts [15, 16].

In the present paper attention has been paid to such types of amine oxides which would be antimicrobially active, biodegradable, possess good surface-active properties, but simultaneously, their unwanted side effects would be suppressed. The compounds of this type belong to the so-called "soft" antimicrobially active compounds [17].

Experimental

Infrared spectra were measured in the form of film (*I—III*) or in nujol mull (*IV—XXVII*) on an IR 75 (Zeiss, Jena) spectrophotometer calibrated by polystyrene foil; the reading accuracy was ± 1 cm^{-1}. The results are presented in Tables 3 and 4.

The purity of all compounds was followed by t.l.c. (the R_f was the average value from 5 measurements) on a Silufol plates in the system acetone—1 M-HCl (1 : 1); the compounds were detected with Dragendorf reagent as modified by Munièr [18, 19].

Antimicrobial activity was determined by dilution test as minimum inhibitory concentration (MIC) [20]. The results are presented in Table 5.

Amino esters

To the solution of *N*,*N*-dialkylaminoalkyl alcohol (0.1 mol) in dry toluene (100 cm^3) dodecanoyl chloride (0.11 mol) was added at room temperature under stirring within 45 min [21]. The reaction mixture was allowed to react under reflux for 30 min. After cooling the formed ammonium chloride was dissolved in water and the product was freed with 10 % aqueous solution of NaOH under cooling. Ester was extracted with chloroform and after drying the extracts and removing the solvent by distillation, the products were redistilled. The prepared compounds are characterized in Table 1.

Amino amides

Methyl dodecanoate (1 mol) and α,ω-alkanediamine (4 mol) were refluxed for 5—7 h and the excess diamine and methanol, formed during the reaction, were distilled off under reduced pressure. Diamides as by-products were separated either by crystallization from 1-butanol [22] (in the preparation of *IV—VI*) or with the derivatives containing longer alkyl chains, where the diamide was solubilized by the monoamide, the reaction mixture was dissolved in formic acid which formed water-soluble formate with the monoamide. The insoluble diamide was filtered of and monoamides were released from the salt with 10 %

aqueous solution of NaOH. The resulting products were crystallized from the mixture of ethanol—ether (1:5) and are characterized in Table 1.

The prepared ω-aminoalkyldodecanamide (0.1 mol) was added to 98—100 % formic acid (0.7 mol) under stirring so that the temperature did not rise above 35 °C. Then 36 % solution of formaldehyde (0.5 mol) was added and the mixture was allowed to react at 40 °C under stirring until evolution of CO_2 [23, 24]. After the evolution stopped, the mixture was heated under reflux for 30 min. The excess methylation mixture was distilled off *in vacuo* and *N'*,*N'*-dimethylalkylamide of dodecanoic acid was released with 10 % aqueous solution of sodium hydroxide under stirring. The product was extracted with ether or chloroform, dried and after removal of the solvent by distillation, it was redistilled under reduced pressure in the atmosphere of inert gas. The resulting products are characterized in Table 1.

Amine oxides

All amine oxides characterized in Table 2 were prepared by the reaction of the appropriate tertiary amine (0.1 mol) dissolved in 2-propanol (30 ml) with 30 % aqueous solution of hydrogen peroxide (0.12 mol) [11, 25—27] and were recrystallized from dry acetone.

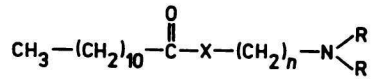
Discussion

The most important step in the whole synthesis was the preparation of ω-aminoalkyldodecanamides (Table 1). Ref. [28] described a possibility of preparing such compounds in very good yields (~80 %) by reaction of equimolar amounts of α,ω-alkanediamine and acyl chlorides. Repeated syntheses showed that it was impossible to obtain monoamides by this method, as proved also by [22], because the main products of this reaction were diamides. Therefore, we applied the method after [22] and found that the ratio of ester: α,ω-diamine could be reduced from 1:6 to 1:4 maintaining good yields. Moreover, in the case of the compounds *VII*—*X* we used a different method for separation of monoamides from diamides than described in [22].

The prepared amine oxides (Table 2) are slightly hygroscopic and soluble both in water and polar organic solvents. Amine oxides derived from esters are less soluble in water than the amide derivatives. In the i.r. spectra of amine oxides (Tables 3 and 4), contrary to the spectra of the corresponding tertiary amines, a doublet of new bands belonging to ν(N—O) occurred at 960—922 cm^{-1}. Both bands were sharp and approximately of the same medium intensity. The more intensive band was denoted as I. The position as well as the shape of these bands were in accordance with the literature data for amine oxides [29]. The positions of other bands practically did not differ from those in the spectra of the corresponding tertiary amines. However, the band belonging to ν(N—CH_3) vanished from the

Table 1

Characterization of *N*,*N*-dialkylaminoalkylesters and of *N'*,*N'*-dimethylaminoalkylamides of dodecanoic acid



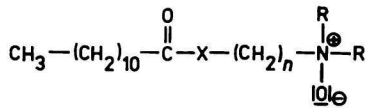
Compound	*n*	R	X	Formula M_r	Calculated/found			Yield %	B.p., °C/kPa n_D^{20}	M.p. °C	R_f
					% C	% H	% N				
I	2	CH_3	O	$C_{16}H_{33}NO_2$	70.79	12.26	5.16	63	125/0.07	—	0.68
				271.45	70.65	11.93	4.93		1.4418		
II	2	C_2H_5	O	$C_{18}H_{37}NO_2$	72.19	12.45	4.68	77	146/0.13	—	0.76
				299.50	72.40	12.21	4.71		1.4450		
III	3	CH_3	O	$C_{17}H_{35}NO_2$	71.53	12.36	4.91	72	148/0.12	—	0.67
				285.47	71.76	12.16	5.04		1.4440		
IV	2	H	NH	$C_{14}H_{30}N_2O$	69.37	12.47	11.57	53	—	87—89	0.68
				242.41	69.56	12.51	11.38				
V	3	H	NH	$C_{15}H_{32}N_2O$	70.26	12.58	10.92	74	—	98—101	0.67
				256.43	69.98	12.42	11.11				
VI	4	H	NH	$C_{16}H_{34}N_2O$	71.05	12.67	10.36	70	—	105—107	0.64
				270.47	70.89	12.81	10.26				
VII	6	H	NH	$C_{18}H_{38}N_2O$	72.41	12.83	9.38	80	—	93—96	0.63
				298.57	72.33	12.91	9.44				
VIII	8	H	NH	$C_{20}H_{42}N_2O$	73.55	12.96	8.58	79	—	85—87	0.62
				326.62	73.53	13.02	8.73				
IX	10	H	NH	$C_{22}H_{46}N_2O$	74.49	13.07	7.90	94	—	95—96	0.60
				354.72	74.52	12.91	8.06				
X	12	H	NH	$C_{24}H_{50}N_2O$	75.31	13.17	7.32	93	—	99—101	0.58
				382.77	75.40	13.03	7.26				

Table 1 (Continued)

Compound	*n*	R	X	Formula M_r	Calculated/found % C	 % H	 % N	Yield %	B.p., °C/kPa n_D^{20}	M.p. °C	R_f
XI	2	CH_3	NH	$C_{16}H_{34}N_2O$	71.05	12.67	10.36	74	210/0.13	31—33	0.65
				270.47	70.88	12.53	10.48				
XII	3	CH_3	NH	$C_{17}H_{36}N_2O$	71.77	12.75	9.85	71	162—167/0.04	26—28	0.63
				284.50	71.75	12.55	10.07				
XIII	4	CH_3	NH	$C_{18}H_{38}N_2O$	72.41	12.83	9.38	70	192—194/0.06	30—32	0.61
				298.57	72.28	13.06	9.29				
XIV	6	CH_3	NH	$C_{20}H_{42}N_2O$	73.55	12.96	8.58	71	243/0.53	36—38	0.44
				326.62	73.78	13.10	8.33				
XV	8	CH_3	NH	$C_{22}H_{46}N_2O$	74.49	13.07	7.90	89	232—234/0.15	51—53	0.31
				354.72	74.36	13.15	8.07				
XVI	10	CH_3	NH	$C_{24}H_{50}N_2O$	75.31	13.17	7.32	98	—	50—51	0.18
				382.77	75.27	13.09	7.44				
XVII	12	CH_3	NH	$C_{26}H_{54}N_2O$	76.01	13.25	6.82	90	—	53—54	0.03
				410.87	76.15	13.30	6.75				

Table 2

Characterization of *N*-oxides of *N*,*N*-dialkylaminoalkylesters and of *N'*,*N'*-dimethylaminoalkylamides of dodecanoic acid



Compound	*n*	R	X	Formula M_r	Calculated/found			Yield %	M.p. °C	R_f
					% C	% H	% N			
XVIII	2	CH_3	O	$C_{16}H_{33}NO_3$	66.86	11.57	4.87	91	36—38	0.43
				287.44	66.74	11.71	4.57			
XIX	2	C_2H_5	O	$C_{18}H_{37}NO_3$	68.53	11.82	4.44	78	28—30	0.55
				315.49	68.78	12.01	4.25			
XX	3	CH_3	O	$C_{17}H_{35}NO_3$	67.73	11.70	4.65	80	43—45	0.32
				301.47	68.02	12.81	4.32			
XXI	2	CH_3	NH	$C_{16}H_{34}N_2O_2$	67.06	11.96	9.79	73	137—140	0.54
				286.46	66.90	12.00	9.92			
XXII	3	CH_3	NH	$C_{17}H_{36}N_2O_2$	67.95	12.07	9.32	75	119—122	0.55
				300.49	68.10	11.82	9.47			
XXIII	4	CH_3	NH	$C_{18}H_{38}N_2O_2$	68.74	12.18	8.91	87	121—123	0.52
				314.52	68.56	11.84	8.73			
XXIV	6	CH_3	NH	$C_{20}H_{42}N_2O_2$	70.12	12.36	8.19	72	117—120	0.42
				342.57	70.01	12.39	8.03			
XXV	8	CH_3	NH	$C_{22}H_{46}N_2O_2$	71.28	12.51	7.56	90	123—125	0.29
				370.63	71.40	12.50	7.38			
XXVI	10	CH_3	NH	$C_{24}H_{50}N_2O_2$	72.30	12.64	7.03	86	109—111	0.15
				398.68	72.11	12.75	6.98			
XXVII	12	CH_3	NH	$C_{26}H_{54}N_2O_2$	73.18	12.77	6.56	95	105—107	0.05
				426.73	73.00	12.81	6.69			

Table 3

Infrared spectral data (cm^{-1}) of *N,N*-dialkylaminoalkylesters and of *N',N'*-dimethylaminoalkylamides of dodecanoic acid

Compound	ν(N—H)	ν(N—CH_3)	ν(C=O)	ν(C—N) + δ(C—NH)	ν_{as}(C—O—C)
I	—	2764	1733	—	1171
II	—	2761[c]	1736	—	1171
III	—	2762	1732	—	1166
XI	3293	2767	1643[a]	1550[b]	—
XII	3315	2753	1643[a]	1552[b]	—
XIII	3327	2765	1642[a]	1535[b]	—
XIV	3320	2761	1632[a]	1534[b]	—
XV	3316	2750	1638[a]	1538[b]	—
XVI	3318	2748	1636[a]	1530[b]	—
XVII	3320	2750	1634[a]	1527[b]	—

a) Amide I; *b*) amide II; *c*) N—CH_2.

Table 4

Infrared spectral data (cm^{-1}) of *N*-oxides of *N,N*-dialkylaminoalkylesters and of *N',N'*-dimethylaminoalkylamides of dodecanoic acid

Compound	ν(C=O)	ν(C—O—C)	ν(N—H)	ν(N—O) I	ν(N—O) II
XVIII	1747	1174	—	952	930
XIX	1730	1175	—	966	929
XX	1734	1164	—	963	929
XXI	1657	—	3331	954	922
XXII	1644	—	3323	960	934
XXIII	1635	—	3323	959	928[a]
XXIV	1633	—	3318	956	934[a]
XXV	1633	—	3310	959	944
XXVI	1630	—	3300	963	950
XXVII	1628	—	3292	967	933

a) More intensive band of the doublet.

spectra of *N*-oxides. This is the consequence of the change in spatial arrangement of the dimethylalkylamineoxide group in comparison with the dimethylalkylamine group [30].

The dilution test was applied to examine the antimicrobial activity of the compounds in dependence on their structures. Strains of gram-positive bacteria

(*Staphylococcus aureus*), gram-negative bacteria (*Escherichia coli*), and yeasts (*Candida albicans*) from the Czechoslovak State Collection of Typical Cultures were used for tests. The effect of the length of the joining alkyl chain in *N*-oxides of *N*,*N*-dialkylaminoalkylesters and *N'*,*N'*-dimethylaminoalkylamides of dodecanoic acid and the presence of ester and amide groups in the molecule on antimicrobial activity was investigated.

As illustrated in Table 5, only three compounds of the amide group were active against gram-negative *Escherichia coli*. Lengthening of the joining chain in *N*-oxides derived both from esters and amides positively affected their antimicrobial activity. In the amides maximum activity was achieved with the compound *XXV* (length of the joining chain C_8), further lengthening led to decrease in activity. The compound *XXV* was most active of all derivatives of dodecanoic acid.

Lengthening of the alkyl chains linked directly to nitrogen (methyl—ethyl) in esters caused a significant improvement of the effect on *S. aureus*, but a slight decrease in activity against *C. albicans* was observed (*XVIII*, *XIX*). It can be stated that *N*-oxides of esters (*XVIII*, *XXI*) are more active than *N*-oxides of amides

Table 5

Bacteriostatic and fungistatic properties of *N*-oxides of *N*,*N*-dialkylaminoalkylesters and of *N'*,*N'*-dimethylaminoalkylamides of dodecanoic acid (MIC in $\mu g\ cm^{-3}$/$mmol\ dm^{-3}$)

Compound	*S. aureus*	*E. coli*	*C. albicans*
XVIII	90	>1000	80
	0.313	> 3.48	0.276
XIX	10	>1000	100
	0.032	> 3.17	0.317
XX	50	>1000	50
	0.166	> 3.32	0.166
XXI	100	>1000	200
	0.349	> 3.49	0.698
XXII	200	>1000	300
	0.666	> 3.33	0.998
XXIII	300	>1000	200
	0.954	> 3.18	0.636
XXIV	100	600	80
	0.292	1.75	0.233
XXV	50	200	30
	0.135	0.54	0.081
XXVI	100	500	90
	0.251	1.25	0.226
XXVII	>1000	>1000	>1000
	> 1.00	> 1.00	> 1.00
Septonex	2	20	0.8
	0.005	0.05	0.002

(*XX, XXII*), however, their disadvantage is that the higher homologues are little or not soluble at all in water. The structurally similar organic ammonium salt Septonex, 2-(ethoxycarbonyl)pentadecyltrimethylammonium bromide, belonging to the so-called "hard" antimicrobially active compounds was used as standard, because at present, amine oxides are not used for disinfections in Czechoslovakia. This standard was in all cases more active than the compounds investigated.

References

1. French, H. S. and Gens, C. M., *J. Amer. Chem. Soc. 59,* 2600 (1937).
2. Culvenor, C. C. J., *Rev. Pure Appl. Chem.* (Australia) *3,* 83 (1953).
3. Linton, E. P., *J. Amer. Chem. Soc. 62,* 1945 (1940).
4. Lindner, K., *Tenside 1,* 112 (1964).
5. Nowak, G. A., *Kosmetik 43,* 951 (1970).
6. Ochiai, E., *Aromatic Amine Oxides.* Elsevier, Amsterdam, 1967.
7. Katritzky, A. R. and Lagowski, J. M., *Chemistry of the Heterocyclic N-Oxides.* Academic Press, London, 1971.
8. Bickel, M. H., *Pharmacol. Rev. 21,* 325 (1969).
9. Liras, P. and Lampen, O., *Biochim. Biophys. Acta 372,* 141 (1974).
10. Swisher, R., *J. Amer. Oil Chem. Soc. 40,* 648 (1963).
11. Šubík, J., Takácsová, G., Pšenák, M., and Devínsky, F., *Antimicrob. Ag. Chemother. 12,* 139 (1977).
12. Mlynarčík, D., Čupková, V., Devínsky, F., and Lacko, I., *Folia Microbiol.* (Prague) *23,* 493 (1978).
13. Mlynarčík, D., Devínsky, F., and Lacko, I., *Folia Microbiol.* (Prague) *24,* 188 (1979).
14. Takácsová, G. and Šubík, J., *Folia Microbiol.* (Prague) *24,* 153 (1979).
15. Dechezlepretre, S., Porter, R., and Cheymol, J., *Med. Pharmacol. Exp. 16,* 529 (1967).
16. Vrbovský, L., *Excerpta Med. Int. Cong. Ser. No. 311, 15,* 331 (1973).
17. Bodor, N., *J. Med. Chem. 23,* 469 (1980).
18. Šaršúnová, M., Schwarz, V., and Michalec, Č., *Chromatografia na tenkých vrstvách vo farmácii a klinickej biochémii.* (Thin-Layer Chromatography in Pharmacy and Clinical Biochemistry.) P. 458. Osveta, Martin, 1977.
19. Wollman, Ch., Nagel, S., and Scheibe, E., *Pharmazie 21,* 665 (1966).
20. Lacko, I., Devínsky, F., Mlynarčík, D., and Krasnec, Ľ., *Acta Fac. Pharm. Univ. Comenianae 30,* 109 (1977).
21. Vogel, A. J., *Textbook of Practical Organic Chemistry,* 4th Ed., p. 498. Longmans, London, 1978.
22. Domańska, A. and Ropuszyński, S., *Tenside Detergents 17,* 300 (1980).
23. Pècher, M. and Martin, T., *Bull. Soc. Chim. Belg. 66,* 545 (1957).
24. Baldy, J., Maurice, N., and Desnuelle, P., *Bull. Soc. Chim. Fr. 1951,* 1174.
25. Devínsky, F., Lacko, I., and Krasnec, Ľ., *Collect. Czech. Chem. Commun. 44,* 773 (1979).
26. Devínsky, F., Lacko, I., and Krasnec, Ľ., *Czech.* 201715 (1980).
27. Devínsky, F., Lacko, I., and Krasnec, Ľ., *Czech.* 201716 (1980).
28. Baldy, J. and Naudet, M., *Bull. Soc. Chim. Fr. 1954,* 1172.
29. Devínsky, F., *Thesis.* Faculty of Pharmacy, Komenský University, Bratislava, 1980 and literature cited therein.
30. Günzler, H. and Böck, H., *IR-Spektroskopie.* Verlag Chemie, Weinheim, 1975.

Translated by A. Kardošová