Amine oxides. I.
Synthesis, ^{1}H-n.m.r., and infrared spectra of 4-alkylmorpholine-*N*-oxides

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Received 18 October 1976

Paper published on the occasion of the 25th anniversary of the foundation of the Faculty of Pharmacy, Komenský University, Bratislava

The synthesis of 4-alkylmorpholine-*N*-oxides, their ^{1}H-n.m.r. and i.r. spectra are reported. The stereochemical arrangement of these substances can be deduced on the basis of spectral data. The anomalous behaviour of the title substances in some cases could be rationalized in stereochemical terms.

Описывается синтез 4-алкилморфолин-*N*-оксидов, их ^{1}H-ЯМР и ИК спектры. На основании спектральных измерений можно рассуждать о стереохимическом строении этих соединений, которое в свою очередь объясняет их аномальное поведение в некоторых случаях.

Amine oxides derived from *N*-alkyl derivatives of saturated heterocyclic amines were chosen as potential solubilizers. In contrast to ammonium salts [1], which are substantially analogous to those substances, we observed some anomalous behaviour in their physicochemical and biological properties. We found, *e.g.* a nonlinear course of the dependence of critical micellar concentration (log CMC) on the alkyl chain length [2]. Similarly, anomalies were observed also in biological properties as in antimicrobial effect [3], or acute toxicity [4]. A certain drop of linearity was always observed in substances with 10—12 carbon atoms in alkyl chain.

Since the physicochemical or biological properties of substances of this type are alkyl dependent, the stereochemical arrangement will be substantial for their behaviour. As evident, the alkyl chain can be attached to the six-membered ring either axially, or equatorially. According to *Cook et al.* [5] the equatorial orientation of the alkyl ring in 4-methyl- or 4-*tert*-butylmorpholine-*N*-oxide is favourized, *i.e.* the N—O bond is axially situated. The same result is encountered in papers by *McKenna* [6] and *Nagy et al.* [7], who ascertained that the preparation of analogous organic ammonium salts is associated with a favourable axial attack of lone electron pair of tertiary nitrogen. On the basis of ^{1}H-n.m.r. data it is, however, possible to presume the most probable orientation of the N—O bond to be axial, if the parameter $\Delta\delta(\beta)$ differs from zero [5].

Alkyl side chain with nitrogen of the N—O bond form a certain dipole as a consequence of different electric potential of σ bonds of the chain and the functional group. It is a matter of the chain length when the mutual interaction becomes effective, this being manifested as a certain deformation of the molecule. This phenomenon could be imagined as a rotation of the nonpolar moiety of the molecule (alkyl chain) around the polar moiety, in this very case around the positively charged nitrogen of the N—O bond. Although this phenomenon is a logical consequence of different electric character of both parts of the molecule, it has not been studied in more detail irrespectively of papers by *Augstein et al.* [8] and *Bovet* [9] who examined another type of compounds.

If presuming the "rotational" effect in 4-alkylmorpholine-*N*-oxides with a sufficiently long chain, then a lowering of the electron-accepting effect of nitrogen of the functional group takes place; this effect should be seen *e.g.* in ^{1}H-n.m.r. spectra on absorption of protons adjacent to nitrogen (α protons). Any lowering of this effect should evoke an upfield shift. Since the axial α proton is more influenced by the torsioning chain, the alteration of its chemical shift should be most significant. The longer is the alkyl chain, *i.e.* the higher is the measure of torsion — providing that this idea holds — and thereby also the interaction of σ electrons with nitrogen of the functional group, the greater should be the upfield shift.

This interaction should be seen in i.r. spectra: most absorption bands of the asymmetric vibrations of CH_2 and CH_3 groups should be shifted towards lower wavenumbers but only to a certain length of the alkyl chain, when the molecule occupies the most favourable steric arrangement. Further shift should not appear after the optimal length is achieved.

^{1}H-n.m.r. and i.r. spectroscopies were the tools to verify this assumption. Our attention was focused to the mutual interaction of the alkyl chain and nitrogen of the N—O group.

Experimental

The ^{1}H-n.m.r. spectra were measured at 30°C with a Tesla BS 487 A spectrometer (80 MHz) $CDCl_3$ being the solvent and tetramethylsilane the internal reference substance; reading accuracy ± 0.02 p.p.m. The spectra were analyzed as a 32 line ABCD system and evaluated by LAOCOON III programme. Results are listed in Table 2. The i.r. spectra of

Table 1

4-Alkylmorpholine-*N*-oxides

No.	R	Formula	M_r	Calculated/found % C	Calculated/found % H	Calculated/found % N	Yield %	M.p. °C
I	Methyl	$C_5H_{11}NO_2$	118.15	44.10	9.62	10.29	87	73—75*
				44.37	9.87	10.15		Capillary tube
II	Ethyl	$C_6H_{13}NO_2$	131.18	43.10	10.25	8.38	81	97.5—100**
				42.72	9.81	8.41		Capillary tube
III	Propyl	$C_7H_{15}NO_2$	145.20	57.90	10.41	9.65	88	143—146
				57.61	10.53	9.62		Capillary tube
IV	Butyl	$C_8H_{17}NO_2$	159.23	54.21	10.81	7.90	85	64—66*
				54.48	11.13	7.66		Capillary tube
V	Pentyl	$C_9H_{19}NO_2$	173.24	62.40	11.05	8.09	83	64—65
				62.48	11.16	7.93		Capillary tube
VI	Hexyl	$C_{10}H_{21}NO_2$	187.28	64.13	11.30	7.48	86	145—148
				64.30	11.60	7.25		Decomposition
VII	Heptyl	$C_{11}H_{23}NO_2$	201.30	65.63	11.52	6.96	89	139—141
				65.59	11.63	6.89		
VIII	Octyl	$C_{12}H_{25}NO_2$	215.33	66.94	11.70	6.50	92	141.5—142.5
				67.16	11.90	6.75		
IX	Nonyl	$C_{13}H_{27}NO_2$	229.37	68.08	11.86	6.12	92	144—146
				67.97	12.04	5.92		
X	Decyl	$C_{14}H_{29}NO_2$	243.40	69.09	12.01	5.75	95	143—145
				69.39	12.17	5.70		
XI	Undecyl	$C_{15}H_{31}NO_2$	257.42	69.99	12.14	5.44	86	134—135
				70.19	12.11	5.53		

Table 1 (Continued)

No.	R	Formula	M_r	Calculated/found			Yield %	M.p. °C
				% C	% H	% N		
XII	Dodecyl	$C_{16}H_{33}NO_2$	271.45	70.80	12.25	5.16	92	136—137
				70.69	12.32	5.21		
XIII	Tridecyl	$C_{17}H_{35}NO_2$	285.47	71.53	12.36	4.91	88	143—145
				71.37	12.60	4.87		
XIV	Tetradecyl	$C_{18}H_{37}NO_2$	299.50	72.19	12.45	4.68	87	139—140
				71.93	12.67	4.78		
XV	Pentadecyl	$C_{19}H_{39}NO_2$	313.53	72.79	12.54	4.47	93	130—133
				72.57	12.60	4.44		
XVI	Hexadecyl	$C_{20}H_{41}NO_2$	327.56	73.34	12.62	4.28	90	136.5—137
				73.06	12.84	4.50		
XVII	Heptadecyl	$C_{21}H_{43}NO_2$	341.59	73.84	12.69	4.10	88	75—77
				73.69	12.52	3.98		
XVIII	Octadecyl	$C_{22}H_{45}NO_2$	355.61	74.31	12.76	3.94	98	115—117
				74.18	12.75	3.82		

* Monohydrate.

** Dihydrate.

0.2 M solutions in CH_2Cl_2 were recorded with a UR-10 (Zeiss, Jena) spectrophotometer at a 12 cm^{-1}/min speed using KRS 5 (0.440 mm) cells in the 1000—850 cm^{-1} (ν(N—O)) and CaF_2 (0.023 mm) cells in the 3000—2700 cm^{-1} (ν(C—H)) range. The wavenumber was calibrated against the polystyrene foil; reading accuracy ± 1 cm^{-1}. The effective values of the molar absorption coefficient (ε^a) were calculated from absorbance measured by a compensation method.

4-Alkylmorpholine-N-oxides

4-Alkylmorpholine (0.1 mole) prepared according to [10] was dissolved in methanol (30 ml) and heated to 50—60°C; to this solution 30% aqueous hydrogen peroxide (0.12 mole) was added under stirring during 30 min. The stirring was continued for 6 h, the solution was then cooled, the excess of hydrogen peroxide decomposed with platinum black, filtered, and the solvent distilled off under reduced pressure; last traces of water were removed according to [11]. The raw product was crystallized 4 times from water-free acetone. Final products were vacuum dried over P_4O_{10} at 25°C and 13.3 Pa. Characteristic data of all synthesized white crystalline substances, which are very (*I—VI*), medium (*VII—XI*), and little (*XII—XVIII*) hygroscopic, are listed in Table 1.

Results and discussion

The ^{1}H-n.m.r. data (Table 2) allow to presume the alkyl chain to be preferentially equatorially oriented, since the parameter $\Delta\delta(\beta)$ of all investigated compounds differs from zero. As already mentioned in the introductory part, the decisive factor giving an information about the interaction of the alkyl chain with nitrogen of the N—O bond is the chemical shift of the axial α proton of the heterocyclic moiety. This chemical shift undergoes, however, a very little change in compounds *I—X* (decrease by 0.04 p.p.m., *i.e.* 3.2 Hz). The decrease is very significant in relation with the extension of the alkyl chain, the difference between compounds *X* and *XVIII* being -0.22 p.p.m. (-17.6 Hz) and between *I* and *XVIII* -0.26 p.p.m. (-20.8 Hz). Equatorial arrangement of the α proton is also associated with a certain, not as considerable chemical shift, which is almost unaltered within the *I—VIII* and *X—XVIII* groups. The position of the equatorial β proton is unchanged, whereas that of the axial β proton is upfield shifted starting with compound *XII*, the difference between *X* and *XVIII* being $+0.07$ p.p.m. (5.6 Hz). (Substances *I—X* reveal the same chemical shift.) This upfield shift is due to an enhanced electronegativity of oxygen in the heterocycle (lower electronegativity of nitrogen of the N—O bond).

Certain differences were observed also with coupling constants in relation to the alkyl chain length, the most significant being with $J_{\alpha a,\beta a}$, where the increment in compounds *I—XII* was up to $+0.91$ Hz. Further extension of the alkyl did not change the $J_{\alpha a,\beta a}$ coupling constant. A linear decrease depending on the length of the alkyl chain was observed with both interaction constants $J_{\alpha e,\beta e}$ and $J_{\alpha e,\beta a}$. The difference between compounds *I—XVIII* was found to be -0.21 and -0.76 Hz, respectively.

Basing upon these results, mainly on the change of chemical shift of the axial α proton towards higher magnetic field encountered only from compound *X* or *XII* (R = decyl or dodecyl) one is entitled to propose a mutual interaction of the alkyl chain of minimum length between 10 and 12 carbon atoms with nitrogen of the N—O bond by a probable mechanism outlined in the introduction.

The i.r. spectroscopy was chosen to verify the above-mentioned proposal as a complementary method for investigation of vibrational bands of N—O group (in the 1000—930 $\mathrm{cm^{-1}}$ range) and C—H bond (in the 3000—2700 $\mathrm{cm^{-1}}$ range). We studied the mutual relationship between the length of the alkyl chain and absorption bands ν(N—O) and also its reflexion on the energy of C—H bonds. This method of analytical utility was used for purity determination of compounds prepared. The purity criterion was the absence of $\geq$N—$\mathrm{CH_2}$ vibration characteristic of *tert*-amines, which is absent in compounds of such a type analogously as with ammonium salts [7].

Due to hygroscopicity of products, special cells KRS 5 of $\mathrm{CaF_2}$ were used. Even though the solutions were rapidly prepared, changes in spectra, ascribable to an interaction of the polar N—O group with water arising from humidity, were observed. The presence of absorption bands indicative of crystalline water (δ(H—O—H) $\sim$ 1660 $\mathrm{cm^{-1}}$, ν(O—H) $\sim$ 3400 $\mathrm{cm^{-1}}$ — measured in nujol) showed the presence of bound water.

Dichloromethane was used for dissolution, since this solvent reveals a minimum absorption in the ν(N—O) region. To suppress absorption in the ν(C$\geq$H) region a cell of minimum diameter was employed.

Infrared spectra were interpreted according to *Hummel* [12], who ascribed the most intense band of the triplet in the 1000—900 $\mathrm{cm^{-1}}$ range to stretching vibrations of the N—O group. In the afore-mentioned spectrum, this band resonated at 962 $\mathrm{cm^{-1}}$. The position of ν(N—O) of aliphatic *N*-oxides, as reported by *Nakanishi* [13], is at 970—950 $\mathrm{cm^{-1}}$. Triplet of absorption bands also found in homologic series of 4-alkylmorpholine-*N*-oxides was absent in the corresponding *tert*-amine. The absorption band I at 970 $\mathrm{cm^{-1}}$ was the most intense almost in all cases (Table 3) except for compounds with a shorter chain, *e.g.* R = ethyl (compound *II*), where the band II at 954 $\mathrm{cm^{-1}}$ was found to be the most intense. Bands I and II of compound *III* (R = propyl) are of equal intensity. The latter band is the weakest, appearing as a shoulder (beginning with *VII*) or not at all (compound *XIII*). Changes in intensity of the triplet associated with absorption bands ν(N—O) are due to crystalline water occurring in synthesized amine oxides having the alkyl chain R from ethyl to hexyl.

Table 2

^{1}H-n.m.r. spectral data of 4-alkylmorpholine-*N*-oxides

No.	Chemical shifts, p.p.m.				Coupling constants, Hz						R.m.s. error of fit	$\Delta\delta(\beta)$ Hz
	$\delta_{\alpha e}$	$\delta_{\alpha a}$	$\delta_{\beta e}$	$\delta_{\beta a}$	$J_{\alpha gem}$	$J_{\beta gem}$	$J_{\alpha e,\beta e}$	$J_{\alpha e,\beta a}$	$J_{\alpha a,\beta e}$	$J_{\alpha a,\beta a}$		
I	3.08	3.42	3.72	4.33	− 9.60	−12.36	1.68	2.56	3.09	11.03	0.107	0.61
IV	3.10	3.41	3.70	4.34	− 9.98	−12.35	1.60	2.40	3.10	11.25	0.093	0.64
VI	3.08	3.41	3.72	4.34	−10.23	−12.41	1.57	2.07	3.10	11.78	0.056	0.62
VIII	3.06	3.40	3.71	4.34	−10.09	−12.41	1.56	2.14	2.98	11.82	0.072	0.63
X	3.00	3.38	3.69	4.34	−10.07	−12.39	1.55	2.07	3.10	11.89	0.089	0.65
XII	2.97	3.27	3.67	4.36	− 9.99	−12.32	1.53	1.99	2.97	11.94	0.111	0.69
XIV	2.99	3.22	3.70	4.37	−10.01	−12.40	1.51	1.92	3.10	11.94	0.090	0.67
XVI	2.97	3.18	3.69	4.39	−10.10	−12.39	1.50	1.84	3.12	11.94	0.063	0.70
XVIII	2.98	3.16	3.70	4.41	−10.03	−12.40	1.47	1.80	3.11	11.94	0.101	0.71

a — axial, e — equatorial.

Table 3

Wavenumbers ($\tilde{\nu}$) and effective values of the molar absorption coefficients (ε^a) of the vibrations ν(N—O) and ν(C—H) in 4-alkylmorpholine-N-oxides

	ν(N—O)				ν(C—H)							
No.	Band I		Band II	Band III	$\nu_s(CH_3)$		$\nu_{as}(CH_3)$		$\nu_s(CH_2)$		$\nu_{as}(CH_2)$	
	$\tilde{\nu}$ cm^{-1}	ε^a M^{-1} cm^{-1}	$\tilde{\nu}$ cm^{-1}	$\tilde{\nu}$ cm^{-1}	$\tilde{\nu}$ cm^{-1}	ε^a M^{-1} cm^{-1}	$\tilde{\nu}$ cm^{-1}	ε^a M^{-1} cm^{-1}	$\tilde{\nu}$ cm^{-1}	ε^a M^{-1} cm^{-1}	$\tilde{\nu}$ cm^{-1}	ε^a M^{-1} cm^{-1}
II	970 sh	22	954	932	2881	73	2981	93			2953	100
III	976	58	954	935	2882	86	2980	156			2948	148
IV	970	65	954 sh	926	2879	119	2969	191			2940	148
V	973	58	951	939	2877	129	2964	196	2864	112	2935	172
VI	970	43	960 sh	946	2875	133	2960	258	2861	134	2934	252
VII	973	45	953	937 sh	2875	140	2960	269	2861	161	2934	268
VIII	969	51	950	931	2874	163	2959	289	2860	211	2932	404
IX	969	52	950 sh	943 sh	2874	163	2959	296	2859	248	2931	435
X	970	47	949	930 sh	2874	180	2958	316	2858	281	2930	503
XI	972	52	953	930 sh	2874	186	2955	289	2858	328	2930	529
XII	968	48	950	937 sh	2874 sh	194	2955 sh	322	2857	348	2930	624
XIII	969	48	947	—	2874 sh	194	2957 sh	337	2856	394	2930	669
XIV	969	48	950	936 sh	2874 sh	199	2956 sh	344	2857	424	2929	754
XV	970	47	953	936 sh	2874 sh	206	2958 sh	323	2857	440	2930	790
XVI	970	49	950	936 sh	2874 sh	217	2957 sh	323	2856	488	2929	867
XVII	971	49	950	936 sh	2874 sh	238	2958 sh	341	2856	525	2929	895
XVIII	971	48	950	936 sh	2874 sh	240	2957 sh	360	2856	565	2929	975

sh — shoulder.

Extension of the alkyl chain influences mainly the position of absorption bands ν(N—O) belonging to band I and III this being manifested by a minute lowering of the wavenumber (band I $\Delta\tilde{\nu} = -3\ \mathrm{cm}^{-1}$ and in one case $-6\ \mathrm{cm}^{-1}$) when extending the alkyl by one CH_2 group from an odd number of carbon atoms to an even one. This dependence could be observed up to R = octyl (compound *VIII*).

Effective values of the molar absorption coefficient (ε^{a}) evidence that intensities of absorption bands corresponding to stretching vibrations C—H ($\nu_s(CH_2)$, $\nu_{as}(CH_2)$) are directly proportional to the alkyl chain length (Table 3). Extension of the alkyl exerts not only a greater ε^{a}-rise of $\nu_{as}(CH_2)$ vibrations when the alkyl chain consists of an even number of carbon atoms, but also a frequency lowering of asymmetric and symmetric stretching vibrations in all structural units both in CH_3 and CH_2 groups (Table 3). This is manifested by a shift of absorption bands, where the difference in wavenumbers is as follows

$\nu_{as}(CH_2) - \Delta\tilde{\nu} = -27\ \mathrm{cm}^{-1}$ (R = ethyl—decyl, *II*—*X*)
$\nu_{as}(CH_3) - \Delta\tilde{\nu} = -26\ \mathrm{cm}^{-1}$ (R = ethyl—dodecyl, *II*—*XII*)
$\nu_{s}(CH_2) - \Delta\tilde{\nu} = -\ 7\ \mathrm{cm}^{-1}$ (R = pentyl—dodecyl, *V*—*XII*)
$\nu_{s}(CH_3) - \Delta\tilde{\nu} = -\ 7\ \mathrm{cm}^{-1}$ (R = ethyl—octyl, *II*—*VIII*)

Considering the lowering of stretching vibrations of CH_2 and CH_3 groups ($\nu_s(CH_2)$, $\nu_{as}(CH_2)$, $\nu_{as}(CH_3)$) we assume that increase of CH_2 groups in the chain attached to nitrogen atom is associated with generation of an energetically favourized formation. It looks like that the alkyl chain interacts with nitrogen of the N—O bond; as shown — similarly as with ^{1}H-n.m.r. spectra — the energetically more favourized position can be achieved by an alkyl chain of certain length corresponding to 10—12 carbon atoms.

This is in good agreement with changes in physicochemical and biological properties of this type of compounds with the alkyl length ranging from 10 to 12 carbon atoms.

Acknowledgements. We are indebted to Dr Z. Fülöp (Scientific-Research Institute, Faculty of Pharmacy, Komenský University, Bratislava) for his valuable assistance with recording the ^{1}H-n.m.r. spectra, to Dr. P. Balgavý (Department of Analytical Chemistry of the same Faculty) for the LAOCOON III programme, and to Dr V. Hartelová (Department of Inorganic and Organic Chemistry of the same Faculty) for melting point determination and elemental analyses.

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Translated by Z. Votický