

SYNTHESIS, IR SPECTRA AND ANTIMICROBIAL ACTIVITY OF 1,4-DIALKYLPIPERAZINE DIOXIDES*

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Preparation of 1-alkylpiperazines, 1-alkyl-4-methylpiperazines, 1,4-dialkylpiperazines, 1-alkyl-4-methylpiperazine dioxides, and 1,4-dialkylpiperazine dioxides is described. IR spectra of dioxides were interpreted. Antimicrobial activity of dioxides against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* was determined.

Non-aromatic amine oxides are used in many industrial products¹⁻³. Those containing in their molecule at least one aliphatic chain with ten or more carbon atoms have not only excellent surface active properties but also antimicrobial effects. Besides that, non-aromatic amine oxides exhibit substantially lower toxicity and are less irritating⁴⁻⁷ than analogous organic ammonium salts and simultaneously are biodegradable⁸⁻¹⁰ and compatible with anionic, cationic and non-ionic tensides. Little is known about synthesis, properties and effects of diamine dioxides¹¹⁻¹⁴. Some compounds of this type show both distinct surface active properties and antimicrobial activity. In all these cases, the compounds investigated were derivatives of α,ω -alkane diamines. This work is devoted to piperazine derivatives that have both N-oxide nitrogen atoms closed in a cycle. Piperazine itself is commonly used drug with antiarthritic activity, certain its alkyl derivatives exhibit anthelmintic activity^{15,16} and non-specific bacteriostatic effect¹⁶. However, with the exception of dimethyl and diethyl derivatives, 1,4-dialkylpiperazine dioxides have not yet been studied.

EXPERIMENTAL

1,4-Dialkylpiperazines (Table I, Nos 3-16)

Mixture of anhydrous piperazine (0.3 mol), anhydrous K_2CO_3 (0.2 mol) and 1-bromoalkane (0.2 mol) was heated to 100-110°C for 1.5 h and to 150°C for 1 h. After cooling to 80°C, suf-

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ficient amount of water was added to dissolve the solids. Organic layer was then separated and the aqueous one cooled to ambient temperature and extracted by chloroform. Combined extracts and the main portion were dried over anhydrous Na_2SO_4 , the solvent was removed by distillation and the crude products were either distilled (Nos 3—9) or crystallized from ethanol (Nos 9—16). 1,4-Diethylpiperazine (Table I, No 2) was prepared according to the ref.¹⁷.

1-Alkylpiperazines (Table I, Nos 17—25)

Anhydrous piperazine (0.3 mol) and 1-bromoalkane (0.15 mol) were dissolved in 99% ethanol (300 ml). The mixture was refluxed for 20 h. Ethanol was distilled off, 20% aqueous NaOH was added to the residue and the base was then extracted by chloroform. The extract was dried over anhydrous Na_2SO_4 , solvent was removed and the product was purified by distillation.

1-Alkyl-4-methylpiperazines (Table I, Nos 26—34)

1-Alkylpiperazine (0.1 mol) was slowly added to the methylation mixture consisting of 36% formaldehyde (0.36 mol) and 98% formic acid (0.5 mol) heated to 90—100°C. The reaction mixture was kept at this temperature 8 h with stirring. After cooling, an excess of hydrochloric acid was added and the volatile portions were removed *in vacuo*. Solid residue was worked up by aqueous NaOH, the amine was extracted by ether. Extracts were dried over anhydrous Na_2SO_4 , solvents were evaporated and the product was distilled. Similarly was prepared 1,4-dimethylpiperazine (Table I, No 1). In this case, 98% formic acid (2.0 mol) was added to the solution of anhydrous piperazine (0.25 mol) and 36% formaldehyde (1.1 mol) at room temperature.

1,4-Dialkylpiperazine dioxides (Table II, Nos 35—59)

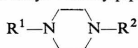
These compounds were prepared according to the ref.¹⁸ and were crystallized from the mixture acetone—ethanol 10 : 1 (Nos 35—43), 5 : 1 (Nos 44, 45), 1 : 1 (No 46), 1 : 2 (No 47), 1 : 5 (No 48) and from ethanol (Nos 49, 50) or from the mixture acetone—methanol 10 : 1 (Nos 51—59).

Measurements

IR spectra were measured in nujol mulls on a UR-20 spectrometer (Zeiss, Jena) (Nos 35—50) with NaCl windows or on an IR-75 spectrometer (Zeiss, Jena) (Nos 51—59) with KBr windows. Both instruments were calibrated using polystyrene foil, wavenumbers readout accuracy was $\pm 1 \text{ cm}^{-1}$. The results are given in Table III. The content of crystal water was determined thermogravimetrically using a Derivatograph MOM 102 (MOM, Budapest) instrument. Purity of all compounds was checked by elemental analysis and TLC on Silufol in the system according to the ref.¹⁹ (Nos 1—50) or in that described by ref.²⁰ (Nos 51—59). For the detection was employed Dragendorff reagent in Munier modification²¹. Melting points are uncorrected.

Antimicrobial activity of resulting amine oxides was determined against microorganisms *Staphylococcus aureus* Oxford Mau 1/45, *Escherichia coli* Eck 61/59 and *Candida albicans* 43/53 obtained from the Czechoslovak State Collection of Typical Cultures. The methods of dilution and diffusion tests²² were used. Table IV lists only compounds with minimal inhibition concentration (MIC) lower than $1000 \mu\text{g cm}^{-3}$.

TABLE I
Properties of 1,4-dialkyl, 1-alkyl- and 1-alkyl-4-methylpiperazines



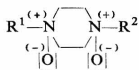
Compound	R ²	Formula (m.wt.)	B.p., °C/kPa <i>n</i> _D ²⁰	Calculated/Found			Yield, % <i>R_F</i>
				% C	% H	% N	
1	methyl	C ₆ H ₁₄ N ₂	130/101·3	63·11	12·36	24·53	66
R ¹ = R ²		(114·2)	1·4469	63·04	12·48	24·50	0·55
2	ethyl	C ₈ H ₁₈ N ₂	174—176/101	67·55	12·75	19·69	23
R ¹ = R ²		(142·3)	1·4515	67·49	12·88	19·52	0·68
3	propyl	C ₁₀ H ₂₂ N ₂	93—95/2·7	70·55	13·03	16·46	40
R ¹ = R ²		(170·2)	1·4541	70·39	13·30	16·31	0·80
4	butyl	C ₁₂ H ₂₆ N ₂	123—124/2·1	72·69	13·22	13·14	79
R ¹ = R ²		(198·3)	1·4553	72·52	14·30	14·05	0·83
5	pentyl	C ₁₄ H ₃₀ N ₂	147—149/2·1	74·29	13·36	12·38	78
R ¹ = R ²		(226·4)	1·4568	74·48	13·57	12·36	0·86
6	hexyl	C ₁₆ H ₃₄ N ₂	138—140/0·06	75·54	13·37	11·01	87
R ¹ = R ²		(254·4)	1·4588	75·59	13·62	10·92	0·88
7	heptyl	C ₁₈ H ₃₈ N ₂	142/0·07	76·40	13·56	9·92	71
R ¹ = R ²		(282·5)	1·4605	76·52	13·36	10·05	0·89
8	octyl	C ₂₀ H ₄₂ N ₂	148—150/0·07	77·35	13·63	9·02	70
R ¹ = R ²		(310·7)	1·4623	77·28	13·66	8·88	0·90
9	nonyl	C ₂₂ H ₄₆ N ₂	181—182/9·3	78·03	13·69	8·27	74
R ¹ = R ²		(338·7)	m.p. 29—31	78·10	13·65	8·05	0·91
10	decyl	C ₂₄ H ₅₀ N ₂	—	78·62	13·74	7·64	73
R ¹ = R ²		(366·7)	m.p. 34—35	78·77	13·90	7·65	0·92
11	undecyl	C ₂₄ H ₆₄ N ₂	—	79·11	13·80	7·10	76
R ¹ = R ²		(394·7)	m.p. 41—43	79·30	13·66	7·29	0·93
12	dodecyl	C ₂₈ H ₅₈ N ₂	—	79·55	13·83	6·63	89
R ¹ = R ²		(422·8)	m.p. 45—48	79·75	13·70	6·70	0·94
13	tridecyl	C ₃₀ H ₆₂ N ₂	—	79·92	13·86	6·21	74
R ¹ = R ²		(450·8)	m.p. 48—50	80·11	14·10	6·08	0·95
14	tetradecyl	C ₃₂ H ₆₆ N ₂	—	80·26	13·89	5·85	84
R ¹ = R ²		(478·9)	m.p. 53—55	80·36	13·93	5·65	0·96
15	pentadecyl	C ₃₄ H ₇₀ N ₂	—	80·56	13·91	5·52	83
R ¹ = R ²		(507·0)	m.p. 59—61	80·70	13·98	5·60	0·97
16	hexadecyl	C ₃₆ H ₇₄ N ₂	—	80·82	13·94	5·24	88
R ¹ = R ²		(535·0)	m.p. 65—67	80·96	14·09	5·33	0·98
17	octyl	C ₁₂ H ₂₆ N ₂	102—103/6·7	72·69	13·22	14·13	52
R ¹ = H		(198·4)	1·4657	72·71	13·31	14·20	0·38

TABLE I
(Continued)

Compound	R ²	Formula (m.wt.)	B.p., °C/kPa <i>n</i> _D ²⁰	Calculated/Found			Yield, % <i>R_F</i>
				% C	% H	% N	
18		C ₁₃ H ₂₈ N ₂	111–113/11	73·52	13·29	13·19	48
R ¹ = H	nonyl	(212·4)	1·4660	73·69	13·10	12·98	0·40
19		C ₁₄ H ₃₀ N ₂	137/20	74·29	13·36	12·38	48
R ¹ = H	decyl	(226·4)	1·4665	74·08	13·42	12·33	0·41
20		C ₁₅ H ₃₂ N ₂	141–143/13·3	74·49	13·42	11·65	53
R ¹ = H	undecyl	(240·4)	1·4673	74·33	13·59	11·48	0·42
21		C ₁₆ H ₃₄ N ₂	198–200/227	75·54	13·37	11·01	49
R ¹ = H	dodecyl	(254·4)	1·4671	75·71	13·22	10·96	0·44
22		C ₁₇ H ₃₆ N ₂	148–149/13·3	76·05	13·51	10·73	49
R ¹ = H	tridecyl	(268·5)	1·4701	75·86	13·41	10·39	0·46
23		C ₁₈ H ₃₈ N ₂	156–158/13·3	76·40	13·66	9·92	48
R ¹ = H	tetradecyl	(282·5)	1·4832	76·11	13·68	10·03	0·47
24		C ₁₉ H ₄₀ N ₂	207–208/333	76·70	13·60	9·45	57
R ¹ = H	pentadecyl	(296·5)	m.p. 28–29	76·60	13·64	9·41	0·49
25		C ₂₀ H ₄₂ N ₂	220–221/93·3	77·35	13·63	9·02	52
R ¹ = H	hexadecyl	(310·7)	m.p. 33–34	77·39	13·52	9·19	0·51
26		C ₁₃ H ₂₈ N ₂	124/187	73·52	13·29	13·19	93
R ¹ = CH ₃	octyl	(212·4)	1·4574	73·40	13·38	13·06	0·70
27		C ₁₄ H ₃₀ N ₂	145–146/80	74·27	13·36	12·37	72
R ¹ = CH ₃	nonyl	(226·4)	1·4580	74·18	13·27	12·40	0·72
28		C ₁₅ H ₃₂ N ₂	143/20	74·93	13·42	11·65	74
R ¹ = CH ₃	decyl	(240·4)	1·4585	74·78	13·51	11·61	0·74
29		C ₁₆ H ₃₄ N ₂	171/333·3	75·52	13·47	11·01	71
R ¹ = CH ₃	undecyl	(254·5)	1·4592	75·59	13·38	11·09	0·74
30		C ₁₇ H ₃₆ N ₂	156–158/40	76·05	13·52	10·43	93
R ¹ = CH ₃	dodecyl	(268·5)	1·4609	76·21	13·37	10·60	0·75
31		C ₁₈ H ₃₈ N ₂	164–166/160	76·53	13·56	9·92	90
R ¹ = CH ₃	tridecyl	(282·5)	1·4624	76·39	13·60	9·98	0·75
32		C ₁₉ H ₄₀ N ₂	195–196/107	76·96	13·60	9·45	88
R ¹ = CH ₃	tetradecyl	(296·5)	1·4637	77·03	13·48	9·61	0·76
33		C ₂₀ H ₄₂ N ₂	203–205/26·7	77·35	13·63	9·02	71
R ¹ = CH ₃	pentadecyl	(310·6)	1·4642	77·40	13·52	8·96	0·76
34		C ₂₁ H ₄₄ N ₂	220–221/93·3	77·71	13·66	8·63	73
R ¹ = CH ₃	hexadecyl	(324·6)	m.p. 29–32	77·65	13·73	8·70	0·77

TABLE II

Properties of 1,4-dialkylpiperazine dioxides



Compound	R ²	Formula (m.wt.)	M.p., °C	Calculated/Found			Yield, % R _F
				% C	% H	% N	
35	methyl	C ₆ H ₁₄ N ₂ O ₂ ^a (146·2)	283—284 ^b	49·29	9·65	19·16	74
R ¹ = R ²				39·63	9·90	15·52	0·0
36	ethyl	C ₈ H ₁₈ N ₂ O ₂ ^a (174·3)	208—209 ^b	55·14	10·41	16·08	75
R ¹ = R ²				45·68	10·66	13·47	0·02
37	propyl	C ₁₀ H ₂₂ N ₂ O ₂ ^a (203·3)	202—203 ^b	59·37	10·96	13·85	79
R ¹ = R ²				50·42	10·96	11·88	0·09
38	butyl	C ₁₂ H ₂₆ N ₂ O ₂ ^a (230·3)	196—197 ^b	62·58	11·38	12·16	79
R ¹ = R ²				54·50	11·29	10·42	0·14
39	pentyl	C ₁₄ H ₃₀ N ₂ O ₂ ^a (258·3)	194—195 ^b	65·10	11·71	10·84	84
R ¹ = R ²				57·57	11·82	9·60	0·20
40	hexyl	C ₁₆ H ₃₄ N ₂ O ₂ ^a (285·5)	192—194	67·26	11·99	9·80	85
R ¹ = R ²				60·13	12·01	8·79	0·26
41	heptyl	C ₁₈ H ₃₈ N ₂ O ₂ ^a (314·5)	188—189	68·74	12·18	8·91	86
R ¹ = R ²				61·70	12·05	8·15	0·30
42	octyl	C ₂₀ H ₄₂ N ₂ O ₂ ^a (342·6)	187—188	70·12	12·36	8·18	74
R ¹ = R ²				63·73	12·40	7·40	0·33
43	nonyl	C ₂₂ H ₄₆ N ₂ O ₂ ^a (370·6)	190—191	71·30	12·51	7·56	80
R ¹ = R ²				65·05	12·26	7·00	0·37
44	decyl	C ₂₄ H ₅₀ N ₂ O ₂ ^a (398·7)	180—182	72·30	12·77	7·03	88
R ¹ = R ²				66·38	12·50	6·52	0·40
45	undecyl	C ₂₆ H ₅₄ N ₂ O ₂ ^a (426·7)	183—184	73·19	12·77	6·56	75
R ¹ = R ²				67·31	12·80	6·20	0·43
46	dodecyl	C ₂₈ H ₅₈ N ₂ O ₂ ^a (454·8)	185—187	73·95	12·85	6·16	88
R ¹ = R ²				68·66	12·82	5·53	0·46
47	tridecyl	C ₃₀ H ₆₂ N ₂ O ₂ ^a (482·8)	173—175	74·63	12·94	5·80	74
R ¹ = R ²				69·59	12·80	5·30	0·49
48	tetradecyl	C ₃₂ H ₆₆ N ₂ O ₂ (510·9)	170—172	75·23	13·02	5·48	88
R ¹ = R ²				75·19	13·24	5·60	0·52
49	pentadecyl	C ₃₄ H ₇₀ N ₂ O ₂ (539·0)	166—168	75·77	13·09	5·20	72
R ¹ = R ²				75·60	12·88	5·22	0·55

TABLE II
(Continued)

Compound	R ²	Formula (m.wt.)	M.p., °C	Calculated/Found			Yield, % R _F
				% C	% H	% N	
50	R ¹ = R ² hexadecyl	C ₃₆ H ₇₄ N ₂ O ₂	153—155	76.26	13.16	4.94	86
		(567.0)		76.08	13.12	4.80	0.57
51	R ¹ = CH ₃ octyl	C ₁₃ H ₂₈ N ₂ O ₂ ^a	222 ^b	63.89	11.55	11.46	96
		(244.4)		55.70	11.46	10.06	0.75
52	R ¹ = CH ₃ nonyl	C ₁₄ H ₃₀ N ₂ O ₂ ^a	219 ^b	65.07	11.70	10.84	99
		(258.4)		57.06	11.60	10.49	0.74
53	R ¹ = CH ₃ decyl	C ₁₅ H ₃₂ N ₂ O ₂ ^a	221 ^b	66.13	11.84	10.28	99
		(272.4)		58.52	11.61	9.18	0.73
54	R ¹ = CH ₃ undecyl	C ₁₆ H ₃₄ N ₂ O ₂ ^a	216—218 ^b	67.08	11.96	9.78	99
		(286.5)		59.19	11.80	8.77	0.72
55	R ¹ = CH ₃ dodecyl	C ₁₇ H ₃₆ N ₂ O ₂	214 ^b	67.95	12.07	9.32	97
		(300.5)		67.68	11.89	9.22	0.71
56	R ¹ = CH tridecyl	C ₁₈ H ₃₈ N ₂ O ₂	212—213 ^b	68.74	12.18	8.91	98
		(314.5)		69.00	12.06	9.11	0.70
57	R ¹ = CH ₃ tetradecyl	C ₁₉ H ₄₀ N ₂ O ₂ ^a	216—217 ^b	69.46	12.27	8.53	96
		(328.5)		62.70	12.20	7.54	0.68
58	R ¹ = CH ₃ pentadecyl	C ₂₀ H ₄₂ N ₂ O ₂ ^a	221—223 ^b	70.12	12.36	8.18	99
		(342.6)		63.30	12.16	7.38	0.59
59	R ¹ = CH ₃ hexadecyl	C ₂₁ H ₄₄ N ₂ O ₂	215—216 ^b	70.73	12.44	7.86	99
		(356.6)		70.53	12.40	7.91	0.44

^a Dihydrate; ^b decomposition.

RESULTS AND DISCUSSION

The presence of anhydrous piperazine is essential for good yields in preparation of 1-alkyl- and 1,4-dialkylpiperazines. When piperazine hexahydrate was used, (e.g. as recommended in ref.²³), the yields of products markedly dropped; they were around 30 and 40% for 1-alkylpiperazines and 1,4-dialkylpiperazines, respectively. Similarly, to obtain good yields of 1-alkyl-4-methylpiperazines, it is necessary to add the amine to the methylation mixture. The modification of the reaction procedure leads to yields of 30% or more lower.

The interpretation of infrared spectra was performed according to literature^{11,18,24}. With 1,4-dialkylpiperazine dioxides, we observed two sharp bands of medium inten-

sity in the region of $980\text{--}920\text{ cm}^{-1}$ due to the N—O stretching and one band of medium intensity at $730\text{--}718\text{ cm}^{-1}$, assigned to mixed rocking vibrations $\rho(\text{CH}_2)$, characteristic for aliphatic chains containing 4 or more carbon atoms¹¹. With 1-alkyl-4-methylpiperazine dioxides we observed three intense bands in the region $970\text{--}920\text{ cm}^{-1}$ but in the compounds containing crystal water only. The middle band $\sim 940\text{ cm}^{-1}$ was absent in the spectra of anhydrous compounds (Nos 55, 56, 59). It is interesting that the band centered around 940 cm^{-1} is not present in the spectra of 1,4-dialkylpiperazine dioxides, where methyl to tridecyl derivatives (Nos 35–47) also exist as dihydrates. Mixed rocking vibrations $\rho(\text{CH}_2)$ are with 1-alkyl-4-methylpiperazine dioxides represented by a doublet of medium intensity bands whose first member is more intense.

Starting with our previous work on antimicrobial activity of amine oxides^{12,13,25}, we assumed an occurrence of similar effects in dioxides derived from piperazine. Owing to the poor solubility of 1,4-dialkylpiperazine dioxides in water, their activity could not be determined by the dilution test. Results of the diffusion assay (Table IV)

TABLE III

Infrared spectral characteristics of the prepared piperazine dioxides (wavenumbers in cm^{-1})

Compound	$\nu(\text{NO}^a)$	$\rho(\text{CH}_2)$	Compound	$\nu(\text{NO}^b)$	$\rho(\text{CH}_2^c)$
35	970; 933	—	51	965; 935; 928	744; 719
36	966; 927	—	52	967; 937; 924	750; 719
37	972; 923	—	53	960; 936; 927	748; 718
38	978; 927	—	54	962; 942; 923	752; 720
39	967; 922	—	55	961; — ; 928	738; 718
40	968; 926	725	56	965; — ; 932	743; 720
41	971; 922	725	57	963; 946; 930	745; 720
42	974; 926	722	58	962; 943; 928	751; 720
43	976; 922	722	59	962; — ; 932	741; 719
44	966; 924	722			
45	970; 925	728			
46	970; 930	729			
47	972; 924	725			
48	977; 924	720			
49	968; 921	718			
50	968; 926	730			

^a Sharp doublet; ^b sharp triplet; ^c sharp doublet, first member of the doublet was in all cases more intense.

showed that these compounds were active against *Staphylococcus aureus*; no effects against two other microorganisms (*E. coli*, *C. albicans*) were observed. It is noteworthy that the antimicrobial activity was observed in derivatives having an even number of carbon atoms in the side chain only. Maximum activity is found in butyl and hexyl derivatives, *i.e.* the compounds with relatively short alkyl chain what is in variance with all our earlier knowledge on the antimicrobial effect not only of diamine dioxides but also monoamine oxides. The activity of 1-alkyl-4-methylpiperazine dioxides which are good soluble in water so that their activity was determined both by dilution and diffusion test, increases with increasing alkyl chain length and reaches a maximum with pentadecyl derivative (No 58) and then decreases. The effect is observable starting with derivatives containing a side chain of 11 carbons. This fact is in a good agreement with the results obtained on other amine oxi-

TABLE IV
Antimicrobial activity of piperazine dioxides

Compound	<i>S. aureus</i>		<i>E. coli</i>		<i>C. albicans</i>	
	\varnothing^a	MIC ^b	\varnothing^a	MIC ^b	\varnothing^a	MIC ^b
54	—	700 (2·170)	—	1 000 (3·101)	11	500 (1·550)
55	11	600 (1·997)	—	800 (2·662)	12	300 (0·998)
56	14	400 (1·272)	—	700 (2·226)	11	200 (0·636)
57	17	100 (0·274)	—	500 (1·372)	14	50 (0·137)
58	20	30 (0·0792)	11	300 (0·792)	15	20 (0·0528)
59	17	40 (0·112)	—	400 (1·122)	12	30 (0·0841)
36	14	—	—	—	—	—
38	18	—	—	—	—	—
40	18	—	—	—	—	—
44	14	—	—	—	—	—
48	11	—	—	—	—	—

^a Diameter of the inhibition zone in mm, 1% ethanolic solution; ^b MIC minimal inhibition concentration in $\mu\text{g cm}^{-3}$ (mmol dm^{-3}).

des^{12,13,25}. However, it is interesting that despite of slightly lower activity in comparison with other diamine dioxides (derivatives of 1,6-hexanediamine)²⁵ towards *S. aureus* and *C. albicans*, the inclusion of amine oxide nitrogen atoms in the cycle has unequivocally a negative effect on the activity against *E. coli*. This fact is evidently connected with the rigid arrangement of the six-membered ring. The comparison of our compounds with dioxides derived from 1,2-ethanediamine¹³ show nearly same values of antimicrobial activity what can be explained by the equal number of carbon atoms in the bridge chain between the amine oxide nitrogen atoms both in piperazine and 1,2-ethanediamine derivatives.

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