Synthesis and properties of 1-[4-(4-alkoxyphenoxy)butyl]-1-ethylpiperidinium bromides

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The synthesis of new compounds of the type of 1-[4-(4-alkoxyphenoxy)-butyl]-1-ethylpiperidinium bromides and their u.v., i.r., and n.m.r. spectra are discussed.

Continuing the investigation into the mechanism of solubilization of the organic compounds in water [1, 2] we prepared a series of aryloxyalkylammonium salts [3] as model solubilization agents. Some of these compounds exhibited a considerable antibacterial activity [4]. This work presents another group of compounds in this series of the type of 1-[4-(alkoxyphenoxy)butyl]-1-ethylpiperidinium bromides. They are studied with respect to their solubilization properties and biological activity depending on the varying chain length of the alkoxyl group.

Experimental

The starting 4-alkoxyphenols were obtained as described previously [5, 6]. 1-Alkoxy--4-(4-bromobutoxy)benzenes, hitherto not described in the literature, were prepared by a modified method of *Marvel* [7] and are characterized in Table 1.

Table 1

Characteristic data of the prepared 1-alkoxy-4-(4-bromobutoxy)benzenes

$$R-O-C_6H_4-O-(CH_2)_4-Br$$

No.	R	Formula	M	Calculated/found		Yield [%]	M.p. [°C] (Kofler) Petroleum ether
				% C	% H		
I	Hexyl	$C_{16}H_{25}BrO_2$	329.29	58.36 58.55	7.65 7.67	56	40–41
II	Heptyl	$C_{17}H_{27}BrO_2$	343.31	59.47 59.75	7.92 8.07	50	48–49
III	Octyl	$C_{18}H_{29}BrO_2$	357.33	60.50 60.72	8.18 8.10	42	46–47
IV	Nonyl	$C_{19}H_{31}BrO_2$	371.37	61.45 61.60	8.41 8.30	50	53–54
V	Decyl	$C_{20}H_{33}BrO_2$	385.41	62.33 62.55	8.63 8.61	48	52–53

The preparation of reference compounds — 1-(4-phenoxybutyl)-1-ethylpiperidinium bromide and 1-[4-(2-methoxyphenoxy)butyl]-1-ethylpiperidinium bromide — was described in our previous work [3].

Electronic absorption spectra were measured on a recording Specord UV-VIS (Zeiss, Jena) spectrophotometer in 1×10^{-4} M ethanolic solutions by using 1-cm silica cells. The accuracy of measurements was ± 1 nm.

Infrared spectra of 0.2 M solutions of the compounds in $CHCl_3$, anal. grade, and $CDCl_3$ (99.95%) were taken in NaCl cells 0.044 mm thick on a double-beam UR-20 (Zeiss, Jena) instrument in the 4000—670 cm^{-1} region. Alcohol and moisture were removed from $CHCl_3$ before use by passing it through a column filled with blue silica gel. Polystyrene foil was used for calibration. The wavenumber reading accuracy was ± 1 cm^{-1}.

To check the effective molar absorptivities and half-band widths of the asymmetrical stretching vibration of the C—O—C bond, these values were remeasured in NaCl cells of 0.068 mm ($\varepsilon^a = 2.6\%$) and 0.052 mm ($\varepsilon^a = 4.1\%$) thickness. In one case we used $CDCl_3$, which, as compared to $CHCl_3$, shows only negligible absorption in the region of measured intensities of ν_{as}(C—O—C). The spectral data of ν_{as}(C—O—C) presented in Table 3 are the average of the values obtained from three records at stabilized current voltage 220 V. The molar absorptivity was calculated from the absorbancy measured by the method of base line.

Nuclear magnetic resonance spectra of 0.02 M solutions of the compounds in $CDCl_3$ were measured with a Tesla BS 487 A spectrometer at 80 MHz. Hexamethyldisiloxane was used as a standard.

1-[4-(4-Alkoxyphenoxy)butyl]-1-ethylpiperidinium bromides (VI—XII)

A mixture of 1-alkoxy-4-(4-bromobutoxy)benzene (0.1 mole) and 1-ethylpiperidine (0.1 mole) in dry ethanol (10 ml) was heated at 100—105°C for 24 hrs. Then the solvent was evaporated under reduced pressure and the solid residue recrystallized from dry acetone. By repeated crystallization from acetone a white crystalline product was obtained, which was dried in a vacuum desiccator over P_2O_5. The obtained products are characterized in Table 2 and the spectral data are given in Table 3.

Results and discussion

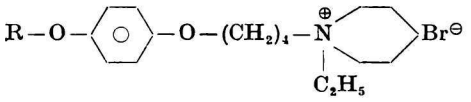
Hitherto not described 1-alkoxy-4-(4-bromobutoxy)benzenes (see Table 1) were prepared by reaction of 4-alkoxyphenols with excess 1,4-dibromobutane in aqueous NaOH medium. The method of *Marvel* [7] was modified by the way of isolation of the product from the reaction mixture. Regarding the relatively high b.p. of the compounds we applied (excepting the preparation of methoxy and butoxy derivatives) instead of fractional distillation the repeated crystallization from petroleum ether (b.p. 30—60°C).

Ammonium salts (Table 2) obtained by reaction of 1-ethylpiperidine with 1-alkoxy-4-(4-bromobutoxy)benzenes in relatively high yields, are hygroscopic compounds; this caused the difficulty in the isolation from solutions and required a long drying after the isolation.

Ultraviolet spectra of the ammonium salts (Table 3) showed two absorption maxima of different intensity. The more intense band appeared at 227—228 nm, whereas the less intense one at 292—293 nm. The unsubstituted derivative of 1-(phenoxybutyl)-1-ethylpiperidinium bromide (λ'_{max} 222 nm, λ''_{max} 282 nm) and the substitution by alko-

Table 2

Characteristic data of the prepared 1-[4-(4-alkoxyphenoxy)butyl]-1-ethylpiperidinium bromides



No.	R	Formula	M	Calculated/found			Yield [%]	M.p. [°C] (Kofler) Acetone
				% C	% H	% N		
VI	Methyl	$C_{18}H_{30}BrNO_2$	372.36	58.16	8.12	3.76	92	117
				58.58	8.02	3.64		
VII	Butyl	$C_{21}H_{36}BrNO_2$	414.44	60.86	8.76	3.38	84	116–118
				60.49	9.01	3.25		
VIII	Hexyl	$C_{23}H_{40}BrNO_2$	442.50	62.43	9.11	3.16	89	126–128
				62.86	9.28	3.12		
IX	Heptyl	$C_{24}H_{42}BrNO_2$	456.52	63.14	9.27	3.07	81	122–124
				62.83	9.50	2.90		
X	Octyl	$C_{25}H_{44}BrNO_2$	470.55	63.81	9.43	2.98	87	132–134
				63.45	9.15	3.13		
XI	Nonyl	$C_{26}H_{46}BrNO_2$	484.58	64.45	9.57	2.89	91	137–139
				63.98	9.69	3.00		
XII	Decyl	$C_{27}H_{48}BrNO_2$	498.61	65.18	9.70	2.81	83	141–143
				64.95	9.80	2.92		

Table 3

Spectral characteristics of 1-[4-(4-alkoxyphenoxy)butyl]-1-ethylpiperidinium bromides

No.	Ultraviolet spectra				Infrared spectra C–O–C		
	λ_{max} [nm]	log ε	λ'_{max} [nm]	log ε	ν [cm^{-1}]	$\Delta\tilde{\nu}\ a\frac{1}{2}$ [cm^{-1}]	ε^a [l mol^{-1} cm^{-1}]
VI	227	3.99	292	3.43	1234	19	735
					1231*	19*	746*
VII	227	3.99	292	3.38	1232	21	635
VIII	228	4.03	292	3.42	1233	21	671
IX	228	4.02	292	3.38	1232	20	653
X	228	4.02	292	3.40	1232	20	664
XI	227	4.01	292	3.38	1233	20	639
XII	228	4.03	293	3.42	1232	20	649

* Solvent $CDCl_3$, concentration 0.2 M, NaCl cells 0.044 mm thick.

xyl in *para* position causes the bathochromic shift and simultaneous increase in the intensity of absorption bands.

Infrared spectra (Table 3) of all the compounds under study exhibit a very intensive band assigned to the asymmetric stretching vibration of an ether C–O–C linkage near 1230 cm^{-1}. The band position is in line with the literature data [8]. The position

and intensity of the band corresponding to the asymmetric stretching vibration in anisoles depend on the *para* and *meta* substituents. The data may be correlated with substituent constants according to *Rao* [9]. The band intensity expressed as molar absorptivity varies from 635—735 l mol^{-1} cm^{-1} in the studied compounds. The most intensive band was observed in the case of methoxy derivative (*VI*). The presence of the methoxy group on the benzene ring increases the intensity in relation to unsubstituted compounds in the following cases: *para* derivative — $\varepsilon^a = 512 \rightarrow 735$ l mol^{-1} cm^{-1}, *ortho* derivative — $\varepsilon^a = 512 \rightarrow 643$ l mol^{-1} cm^{-1} [4]. The half-band width does not undergo a substantial change. But the band position is different: R = H $\nu = 1243$ cm^{-1}, R = = *p*-OCH$_3$ $\nu = 1234$ cm^{-1}, R = *o*-OCH$_3$ $\nu = 1253$ cm^{-1}. If the values in $CHCl_3$ and $CDCl_3$ are compared, the band intensity does not change. Only the shape of the band differs: in $CHCl_3$ a pronounced shoulder of the main band appears at 1210 cm^{-1} and in $CDCl_3$, at the same wavenumber there occurs only an inflexion point. The shoulder in all cases is not greater than the half value of absorbancy so that it does not extend the half-band width. Besides the mentioned absorption band the following bands can also be identified: at 825 cm^{-1} (ν(C—H)) confirms the *para* substituted benzene, at 1510 cm^{-1} (ν(C=C)) corresponds to the ring vibration of benzene. It is of interest that the ν(C=C) band at 1600 cm^{-1} belonging also to the aromatic ring is not present in all 1,4-disubstituted derivatives in contrast to 1,2-disubstituted and unsubstituted derivatives as a consequence of a perfect symmetry of the conjugated system [10] R—O—C_6H_4—O—R.

Methyl and methylene groups show a deformation vibration at 1466 cm^{-1} and a stretching vibration at 2870—2850 or 2970 cm^{-1}. The aromatic system exhibits the C—H stretching vibration at 3030 cm^{-1}.

The structure of the synthesized compounds was also confirmed by the interpretation of the n.m.r. spectra. The spectra of ammonium salts (*VI*—*XII*) were evaluated on the basis of a detailed analysis of the spectra of the starting compounds, *i.e.* 4-alkoxyphenols and 1-alkoxy-4-(4-bromobutoxy)benzenes (*I*—*V*). The spectrum of the butoxy derivative (*VII*; Fig. 1) is characterized by resonance signals of protons of the methyl group in alkoxyl at 1.88 δ (triplet) and of methyl group of ethyl adjacent to nitrogen cation

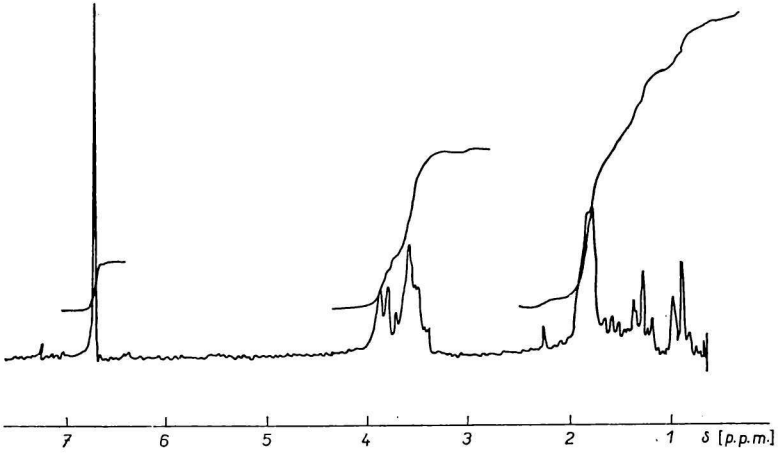


Fig. 1. Nuclear magnetic resonance spectrum of 1-[4-(4-butoxyphenoxy)butyl]-1-ethylpiperidinium bromide (*VII*) in $CDCl_3$.

of the piperidine cycle at 1.25 δ (triplet). At δ 1.88—1.3 there exist two methylene groups of tetramethylene chain and three methylene groups of the piperidine cycle (β, β', γ). Then there are the signals of methylene groups directly bonded to oxygen atoms at 3.9—3.7 δ (multiplet) and four methylene groups linked directly to quaternary nitrogen (multiplet). The singlet signal belonging to the protons of aromatic ring was observed at 6.7 δ. The increasing number of carbon atoms in alkoxyl manifests itself by the increase of the signal at 1.3 δ, whereby the signals of methylene groups of alkoxyl and methyl group of ethyl adjacent to nitrogen cation of piperidine ring overlap. The prolongation of alkoxyl can be determined quantitatively from the integral record.

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