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SYNTHESIS AND MEMBRANE ACTIVITY OF NEW DERIVATIVES OF 2,3-BENZO-18-CROWN-6

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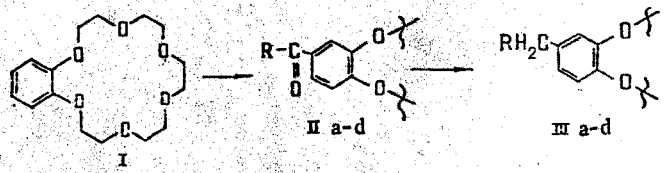
The acylation of 2,3-benzo-18-crown-6 with carboxylic acids in the presence of polyphosphoric acid has given new acyl derivatives which have been reduced to the corresponding alkyl derivatives. The ionophoric activities of the compounds have been investigated on mitochondrial membranes.

A distinguishing feature of the crown ethers is their capacity for forming complexes with ions of alkali metals and transporting them through artificial and biological membranes. An analysis of the interrelationship of structure and membrane-active properties of acyl and alkyl derivatives of cyclopolyethers performed previously [1-4] showed that the number and chemical nature of the substituents in the benzene rings largely determines the effective concentrations and cationic specificities of these synthetic ionophores. We simultaneously characterized the ionophoric properties of dialkyl derivatives of dibenzo-18-crown-6, but for the purposes of further structural-functional analysis interest is presented by information on the membrane activities of the alkyl derivatives of benzo-18-crown-6, and this is given in the present paper.

The benzo-18-crown-6 derivatives described in the literature were obtained by condensing pyrocatechol derivatives with pentaethyleneglycol dichloride [5]. The new acyl derivatives of benzo-18-crown-6 considered in the present paper were synthesized by a method we have described previously [6].

The alkyl derivatives were obtained by the Clemmensen reduction of the corresponding acyl derivatives. As for the other benzocrowns, the reaction took place with yields of 40-50%.



a $R=CH_3$; b $R=C_2H_5$; c $R=C_3H_7$; d $R=C_4H_9$

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TABLE 1. Influence of Various Concentrations of Alkyl Derivatives of Benzo-18-Crown-6 (1-4) and of Dibenzo-18-Crown-6 (5-8) on the Passive Permeability of Mitochondria for Some Uni- and Bivalent Cations

Derivative	Concentration, μM	Rate of energy-dependent swelling of the mitochondria in media, ΔE_{520}/min (×100)					
		H^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Ba^{2+}
Control	—	3,3	2,2	1,5	1,43	11,8	3,8
1. 4'-Ethyl-(IIIa)	1	3,1	2,32	1,63	1,43	11,52	3,9
	5	3,2	1,95	1,75	1,13	10,47	4,0
	10	3,3	1,92	1,8	0,95	9,84	4,0
	50	2,9	1,9	2,0	0,38	8,87	4,1
	100	2,47	1,9	2,75	0,2	7,35	3,9
2. 4'-Propyl-(IIIb)	1	3,45	2,39	1,67	1,58	11,32	3,7
	5	2,7	2,02	1,80	1,27	9,92	3,7
	10	2,2	1,57	2,04	0,99	8 32	3,57
	50	1,82	1,27	3,09	*	7,74	3,2
	100	1,7	1,07	3,77	*	7,11	3,2
3. 4'-Butyl-(IIIc)	1	3,12	1,95	1,6	1,31	12,1	4,02
	5	2,62	1,95	2,23	1,06	12,2	4,15
	10	1,74	1,07	2,9	0,43	10 5	3,15
	50	1,87	0,95	4,98	*	7,6	2,27
	100	3,87	0,95	5,5	0,31	7,4	1,9
4. 4'-Amyl-(IIId)	1	2,67	2,08	1,78	1,3	11,95	3,5
	5	2,42	1,2	2,53	0,69	11,7	3,1
	10	1,8	0,83	3,28	0,24	9,9	2,6
	50	5,05	1,95	5,97	0,31	9,2	1,6
	100	8,42	3,83	9,1	1,28	19,2	0,34
Control	—	1,8	1,6	1,42	0,9	10,6	2,8
5. 4',4"-Diethyl-	5	2,3	1,7	6,42	0,95	10,7	2,85
6. 4',4"-Dipropyl-	5	23,8	3,55	24,9	1,2	10,9	2,9
7. 4',4"-Dibutyl-	5	18,3	7,4	30,9	1,3	10,8	4,3
8. 4',4"-Diamyl-	5	24,0	3,5	63,5	1,6	10,6	2,8

*When these concentrations of the crown ethers were used, an inhibition of swelling was observed.

The compounds obtained were characterize by their IR, ^{1}H NMR, and mass spectra. The IR spectra of the acylation products each contained an absorption band at 1680 cm^{-1} corresponding to the vibrations of a carbonyl group. The ^{1}H NMR spectra of the acyl derivatives each had a triplet signal in the 2.8-2.88 ppm region that is characteristic for α-methylene protons.

In the IR spectra of the reduction products, the absorption band at 1680 cm^{-1} had disappeared, which shows the absence of carbonyl groups. In the ^{1}H NMR spectra of the alkyl derivatives, an upfield shift of the triplet of the α-methylene protons by ≈ 0.4 ppm (2.43-2.51 ppm) was observed.

The membrane-active properties of the alkyl derivatives of benzo-18-crown-6 (IIIa-d) (Table 1) were investigated on mitochondria as the test system. The methods of isolating the mitochondria (Mch) and of measuring the permeability of their membranes for various uni- and bivalent cations for the kinetics of their energy-dependent swelling have been given elsewhere [7].

An analysis of the figures given in Table 1 shows that the alkyl derivatives of benzo-18-crown-6 are characterized mainly by selectivity with respect to univalent cations, but, as compared with benzo-18-crown-6 and its acyl derivatives [3], compounds (IIIa-d) possess a higher membrane activity and pronounced K/Na selectivity in the range of concentrations studied. Among the derivatives investigated, the greatest membrane activity and cationic selectivity was possessed by compound (IIId). Thus, when this crown ether was used in a concentration of 100 μM the sequence of cationic selectivities in Mch membranes had the following form: K:H:Na:Ca:Mg:Ba = 1:0.4:0.3:0.2:0.1:0.01. The acyl-substituted analog of this compound (IId) had a K/Na selectivity three times lower, and an amyl derivative of a crown ether with a smaller ring — benzo-15-crown-5 [4] — is characterized by a K/Na selectivity of 1.7.

Thus, the greatest membrane activity is possessed by benzocrown derivatives containing five C atoms in the side chain. The presence of a second similar substituent (the diamyl derivative of dibenzo-18-crown-6) (see Table 1) increases the membrane activity approximately 100-fold. Simultaneously there is a rise in the cationic selectivity of the corresponding derivatives. Thus, the K/Na selectivity of diamyldibenzo-18-crown-6 (see Table 1) amounts to 20.5. The smaler membrane activity of the monoalkyl benzo-18-crown-6's, as compared with the dialkyl derivatives of dibenzo-18-crown-6 is due to a change in the electron distribution density on the ligand oxygen atoms of the "cavity" of the macrocycle, leading to a less stable binding of the cation.

EXPERIMENTAL

For general information on the experimental work, see [6].

Benzo-18-crown-6 (I) was obtained by Pedersen's method [8], but the product was isolated by column chromatography (with chloroform as the eluent). Yield 43.5%, mp 42-43°C. According to the literature [9]: mp 44°C.

4'-Acetylbenzo-18-crown-6 (IIa). With heating (70°C), 1.25 g of (I) was dissolved in 6 g of PPA, and 0.48 ml of acetic acid was added. The mixture was heated at this temperature with stirring for 40 min and was then decomposed with water and extracted with chloroform. The extract was washed with sodium bicarbonate solution and then with water to neutrality. The solvent was driven off, and the reaction product was purified by column chromatography in the chloroform–hexane–acetone (6:1:1) system and by crystallization from hexane. Yield 1.23 g (88%), mp 76-77°C. Molecular weight: found 354; calculated for $C_{18}H_{26}O_7$, 354.40. IR spectra (ν, cm^{-1}): 1680 (C=O), 880-820 (1,2,4-substituted benzene). ^1H NMR spectrum (δ, ppm): 7.52 (1 H, d), 7.43 (1 H, s), 6.8 (1 H, d) — ArH; 4-4.2 (4 H, m); 3.8-4.0 (4 H, m), 3.68 (8 H, s), 3.61 (4 H, s) — OCH_2; 2.48 (3 H, s, $COCH_3$). The IR and ^1H NMR spectra of the following acyl derivatives of benzo-18-crown-6 are given similarly.

Compounds (IIb-d) were obtained similarly.

(IIb), yield 80%, mp 71-72°C. Molecular weight: found 368; calculated for $C_{19}H_{28}O_7$, 368.4.

(IIc), yield 80%, mp 65-66°C. Molecular weight: found, 382; calculated for $C_{20}H_{30}O_7$, 382.45.

(IId), yield 76%, mp 67-68°C. Molecular weight: found 396; calculated for $C_{21}H_{32}O_7$, 396.47.

4'-Ethylbenzo-18-crown-6 (IIIa). A mixture of 1.06 g of (IIa), 1.4 g of amalgamated zinc covered with 2 ml of toluene, 2.1 ml of concentrated hydrochloric acid, 0.7 ml of H_2O, and 10 ml of dioxane was boiled for 40 h with the addition of 0.2-ml portions of concentrated HCl every 3 h. Then the mixture was decanted from the unchanged zinc. The solvent was evaporated off in a rotary evaporator, the residue was dissolved in chloroform, and the solution was washed with sodium bicarbonate solution and then with water to neutrality. The chloroform was driven off and the residue was purified by column chromatography in the chloroform–hexane–acetone (5:2:1) system.

The product was isolated in the pure form by crystallization from absolute hexane. Yield 0.42 g (43%), mp 41-42.5°C. Molecular weight: found 340; calculated for $C_{18}H_{28}O_6$, 340.41. ^1H NMR spectrum (δ, ppm): 4.0-4.2 (4 H, m), 3.8-4.0 (4 H, m), 3.68 (8 H, s), 3.61 (4 H, s) — OCH_2; 2.51 (2 H, q, α-CH_2); 1.14 (3 H, t, CCH_3). The spectra of the following alkyl derivatives of benzo-18-crown-6 are similar to those given.

Compounds (IIIb-d) were obtained similarly.

(IIIb), yield 43%, mp 16-17.5°C. Molecular weight: found 354; calculated for $C_{19}H_{30}O_6$, 345.44.

(IIIc), yield 40%, mp 30-32°C. Molecular weight: found 368; calculated for $C_{20}H_{32}O_6$, 368.46.

(IIId), yield 50%, mp 34-35°C. Molecular weight: found 382; calculated for $C_{21}H_{34}O_6$, 382.49.

SUMMARY

1. It has been established that the introduction of an alkyl substituent into the benzene ring of benzo-18-crown-6 leads to an increase in membrane activity and cationic selectivity as compared with the initial cyclopolyether.

2. The greatest K/Na selectivity (3.3) for mitochondrial membranes results from the presence of a hydrocarbon chain of five C atoms in the side chain of an alkyl substituent.

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