SYNTHESIS AND ANTICONVULSIVE ACTIVITY OF NEW DIBENZO-18-CROWN-6-DERIVATIVES

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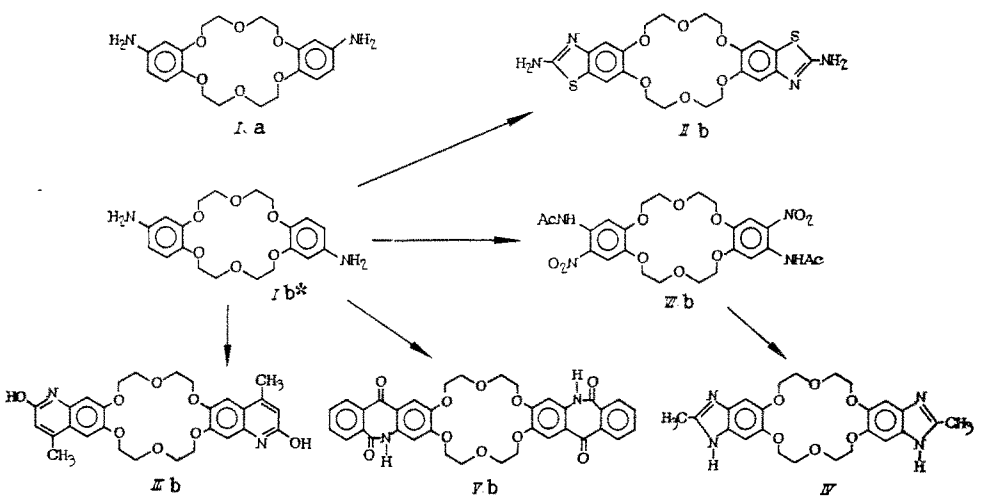
The available literature data [4, 5, 8] show that macroheterocyclic compounds containing pharmacophoric groups as structural fragments are biologically active.

With the goal of obtaining new macroheterocyclic complex-ones and physiologically active substances, we synthesized analogs of dibenzo-18-crown-6 (IIa, b, IIIa, b, IV, Va, b, and VIa, b) which incorporate nitrogen-containing heterocyclic rings such as thiazole, imidazole, pyridine, and azepine.

cis- and trans-Diaminodibenzo-18-crown-6 (Ia and Ib) were used as the starting compounds and were obtained by an established method [7]. Their reaction with dithiocyanogen in glacial AcOH (acetic acid) results in the formation of the corresponding benzothiazole derivatives IIa and b. Compounds IIIa and b were easily formed by reaction of Ia and b with acetoacetic ester in o-xylene with subsequent cyclization in conc. H_2SO_4. Acylation of the starting compounds with Ac_2O in dioxane in the presence of equimolar amounts of Et_3N with subsequent nitration with a mixture of nitric and acetic acids in chloroform yields compounds VIa and b [3]. Reduction of the isomers VIa and b by hydrozine hydrate under Raney nickel followed by cylcization with heating gives compound IV. When the starting compounds are reacted with phthalic anhydride in polyphosphoric acid, the macrocyclic azepindione derivatives Va and b are formed.

The structural formulas for compounds IIb, IIIb, Vb, and VIb obtained from trans-diaminodibenzo-18-crown-6 are shown in the diagram. The structural isomers IIa, IIIa, Va, and VIa are obtained from the cis derivative Ia.



The structures of all compounds synthesized were confirmed by IR and UV spectral data and the compositions were verified by elemental analysis. The purity was monitored by thin-layer chromatography. The molecular weights of the compounds measured by mass spectrometry correspond to the calculated values (Table 1).

It is known that among acyl derivatives of macroheterocyclic compounds there are compounds which have pronounced anticonvulsive activity but are highly toxic [2]. In this

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TABLE 1. New Heterocyclic Dibenzo-18-Crown-6 Derivatives II-V

Compound	Yield, %	mp., °C	Found, %			Empirical formula	Calc., %			M^+
			C	H	N		C	H	N	
IIa	92	169—70	52,6	5,0	10,9	$C_{22}H_{24}N_4O_6S_2$	52,4	4,8	11,1	504
IIb	90	185—6	52,3	4,9	11,0	$C_{22}H_{24}N_4O_6S_2$	52,4	4,8	11,1	504
IIIa	76	241—2	64,5	5,9	5,2	$C_{28}H_{30}N_2O_8$	64,4	5,8	5,4	522
IIIb	78	258—60	64,2	5,8	5,5	$C_{28}H_{30}N_2O_8$	64,4	5,8	5,4	522
IV	83	225	61,3	5,8	12,2	$C_{24}H_{28}N_4O_6$	61,5	6,8	12,0	468
Va	74	309—12	67,6	4,5	4,3	$C_{36}H_{30}N_2O_{10}$	67,5	4,7	4,4	640
Vb	82	332—4	67,5	4,8	4,2	$C_{36}H_{30}N_2O_{10}$	67,5	4,7	4,4	640

regard, it was of interest to search for anticonvulsive agents among our synthesized nitrogen-containing heterocyclic derivatives of dibenzo-18-crown-6.

It was shown (Table 2) that all compounds studied showed on anticonvulsive action at doses of 100-150 mg/kg and gave 15-66% protection to animals against convulsion induced by subcutaneous injection of Corazole and thiosemicarbazide and by maximal electric shock. The most effective compound tested was the macrocyclic imidazole derivative IV. The LD_{50} for this compound exceeds 400 mg/kg.

The results obtained provide grounds for continued search for anticonvulsive agents among heterocyclic derivatives of crown ethers.

EXPERIMENTAL CHEMICAL

The course of the reaction was monitored and the individuality of the substances evaluated using thin-layer chromatography on Silufol UV-254 plates in a 10:1 methanol—ammonia system. Spots were developed under UV light or with a solution of ninhydrin in ether. IR spectra were taken in a Perkin-Elmer 580B spectrophotometer (FRG) in KBr pellets. UV spectra were measured in a Specord UV VIS (GDR) in a methanol solution and mass spectra were taken in a Varian MAT CH5 (Switzerland).

2,14-Diaminodibenzothiazolo-[6,5-b;6,5-k]-18-crown-6 (IIa). To 1 g of Ia in 300 ml of anhydrous AcOH was added 1 g of potassium dithiocyanogen and 0.7 ml bromine in 40 ml of anhydrous AcOH was added dropwise with stirring over a period of 2 h. The mixture was then decanted into cold water and the pH brought up to 9 with aqueous ammonia. The precipitated crystals of IIa were cooled and filtered. UV spectrum (MeOH), λ_{max}, nm: 226, 272, 306; IR spectrum, ν_{max}, cm^{-1}: 1110 (C—O—C), 1535 (C=C and C=N), 2920 (=CH), 3260, 3280 (NH). Compound IIb was obtained under analogous conditions. UV spectrum, λ_{max}, nm: 225, 270, 305. IR spectrum, ν_{max}, cm^{-1}: 1115 (C—O—C), 1534 (C=N and C=C), 2925 (=CH), 3254, 3270 (NH).

2,14-Dimethyl-2, 16-dihydroxyquinolino[6,7-b;6,7-k]-18-crown-6 (IIIa). A mixture of 0.9 g (0.0025 mole) of Ia and 50 ml of o-xylene was heated with stirring. When the temperature of the mixture reached 100°C, 1.5 ml (0.005 mole) of freshly distilled acetoacetic ester was added dropwise and the mixture was heated for another hour. On cooling the corresponding anilide precipitated out and was recovered and dried. To 1 g (0.002 mole) of the anilide obtained were added 10 ml of conc. H_2SO_4 and the mixture was heated for 1 h at 80°C. The solution was then decanted into cold water and a white precipitate formed. After cooling the mixture was filtered and the precipitate washed with ether and air dried. Compounds IIa was obtained, UV spectrum, λ_{max}, nm: 218, 237, 341; IR spectrum, ν_{max}, cm^{-1}: 1170 (C—O—C), 1525 (C=C and C=N), 2930 (=CH), 3420 (OH). Compound IIIb was obtained under analogous conditions. UV spectrum (MeOH), λ_{max}, nm: 216, 235, 340; IR spectrum, ν_{max}, cm^{-1}: 1165 (C—O—C), 1532 (C=C and C=N), 2935 (=CH), 3425 (OH).

2,14-Dimethyldibenzimidazo[5,6-b;5,6-k]-18-crown-6 (IV). To a mixture of 2 g of VI (a or b), 300 ml of dioxane, and freshly prepared Ni/Re in a three-necked flask outfitted with a stirrer, reflux condenser, and dropping funnel, 50 ml of 85% hydrazine hydrate were added slowly drop by drop with stirring. The reaction mixture was then heated for 0.5 h. The hot solution of product in dioxane was filtered and the major portion of the solvent was boiled off. After cooling the precipitate which formed was filtered and washed with ether, yielding IV. UV spectrum, λ_{max}, nm: 210, 300; IR spectrum, ν_{max}, cm^{-1}: 1120 (C—O—C), 1545 (C=C and C=N), 2920 (=CH), 3380 (NH).

TABLE 2. Anticonvulsant Activity of Dibenzo-18-crown-6-Derivatives II-V

Compound	Dose, mg/kg	Antagonism		Maximal electroshock, %	LD_{50}, mg/kg
		with Corazole, % effect	with thiosemicarbazide, % effect		
IIa	100	50	50	16	400
IIb	100	50	33	16	400
IIIa	150	50	33	0	400
IIIb	150	33	30	0	400
IV	100	66	50	33	400
Va	100	20	16	0	450
Vb	100	16	16	0	450

5,6,16,17-Tetrahydro-5,17,22,32-tetraoxodibenzo[c]azepino[6,7-b;6,7-p]dibenzo-18-crown-6 (Va). To 20 ml of freshly prepared polyphosphoric acid, 1.95 g (0.005 mole) of Ia and 2 g (0.013 mole) of finely divided phthalic anhydride were added. The reaction mixture was stirred at 80°C for 2 h. Then it was decanted into cold water and the precipitate Va was separated by filtration. UV spectrum, λ_{max}, nm: 210, 238, 294; IR spectrum, ν_{max}, cm^{-1}: 1120 (C–O–C), 1650, 1710 (C=O), 1540 (C=C), 2935 (C=H). Compound Vb was obtained under analogous conditions. UV spectrum, λ_{max}, nm: 212, 237, 295; IR spectrum, ν_{max}, cm^{-1}: 1125 (C–O–C), 1645, 1705 (C=O), 1536 (C=C), 2930 (=CH).

EXPERIMENTAL BIOLOGICAL

The anticonvulsive activity of the synthesized compounds (II-V) was studied using white mongrel mice weighting 18-20 g. The compounds were administered ip in the form of a suspension in Tween-80 in doses of 100 and 150 mg/kg. The anticonvulsive effect was studied according to the antagonism test with subcutaneously administered corazol (120 mg/kg) and thiosemicarbazide (24 mg/kg ip) and according to prevention of convulsion invoked by maximum electroconvulsive seizure according to the method described in [1]. Acute toxicity was measured by the method of Litchfild and Wilcoxon [6].

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