7-Hydroxy-4,6-diazaheteroauxin (IIa). A mixture of 5 g (0.022 mole) of IIIa, 7 g (0.11 mole) of KCN, 60 ml of water and 15 ml of ethanol was heated at 80°C for 80 h. The solution was evaporated to dryness and the residue was treated with 20 ml of concentrated hydrochloric acid. After heating for 5 h, the solution was cooled and the resulting precipitate was filtered off to give 0.9 g of IIa.

IIb was prepared analogously.

The characteristics of the synthesized compounds are presented in Table 1.

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MACROHETEROCYCLIC COMPOUNDS.

XXIII. ANTIHYPOXIC AND ANTIAMNESTIC PROPERTIES OF AZACROWN ETHERS WITH PHARMACOPHORE GROUPS

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The ability to change the permeability of biological membranes to metal ions and certain organic molecules (amines, amino acids) is one of the most interesting of the biological properties of the crown ethers. This process modifies biomembranes so that the selective transport of ions and molecules can occur [2, 3]. In this respect, of special interest are crown ethers with pharmacophore groups, since the action of "traditional" biologically active substances can be greatly improved by increased ease of transport through hematoencephalic barriers.

In particular, it is suggested that γ-aminobutyric acid, which normally does not readily penetrate the hematoencephalic barrier, when introduced into a crown ether passes through the barrier more easily; the pharmacological activity of this amino acid (a mediator of retardation) is thereby improved.

During our search for new psychotropic agents, we have synthesized N,N'-bispyrollidonomethyl-diaza-17-crown-6 (I), N,N'-bissuccinimidomethyldiaza-18-crown-6 (II), N,N'-bis-γ-aminobutyryl-diaza-18-crown-6 (III) and studied their antihypoxic and antiamnestic properties.

CHEMICAL EXPERIMENTAL

Infrared spectra were taken on a Perkin-Elmer 580 B (USA), NMR spectra on a Tesla BS 467 spectrometer (ChSSR) with a working frequency of 60 MHz; internal standard, tetramethylsilane.

N,N'-Bis-pyrrolidonomethyl-diaza-18-crown-6 (I). A mixture of 0.31 g (0.9 moles) of N,N'-bis-methoxymethyl-diaza-18-crown-6 [1], 0.13 g (1.8 mmoles) of pyrrolidone-2, and 3 ml of dry CCl_4 were refluxed for 3 hours. The reaction mixture was filtered, and the solvent

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TABLE 1. Antihypoxic Effect of the Crown Ethers

Compound	Dose, mg/kg	Change of life-span of mice		
		hypoxic hypercapnia	hypobaric hypoxia	hemic hypoxia
Control	—	1	1	1
I	100	1,86 (1.6—2.07)	4.2 (3,6—4,8)	1,48 (1,3—1,6)
II	100	1,88 (1,4—2.18)	1.89 (1.6—2.0)	1,15 (1,09—1,21)
III	80	1,2 (1.0—1,4)	—	1,2 (0,9—1,4)

Note. Here and in Table 2, variations are given in parentheses.

TABLE 2. Antiamnestic Effect of Crown Ethers

Compound	Dose, mg/kg	Time in light chamber, seconds		Latent period of recovery of reflex after amnesia, seconds
		before training	after training and amnesia	
Control	—	25,5	55	30
I	100	(22—29) 30 (24,5—35,5)	(52,3—57,7) 114,2 (97,4—121,0)	(28,2—32,8) 104,5 (99—114)
II	100	28,5 (26—30,5)	117,8 (114,2—121,4)	85 (75,4—96,6)
III	80	22 (20—24)	118,3 (113,8—121,8)	95,8 (92,0—99,6)

evaporated to give 0.38 g (95%) of product with mp 49-50°C. NMR spectrum in $CDCl_3$ (δ, ppm): 2.07 m, 2.68 t, 3.48 m, 4.00 s.

N,N'-Bis-succinimidomethyl-diaza-18-crown-6 (II). A mixture of 1.75 g (5 mmoles) of N,N'-bis-methoxymethyl-diaza-18-crown-6 [1], 1.01 g (10 mmoles) of succinimide, and 5 ml of dry benzene was brought to boiling, and then cooled and maintained at 20°C for 1 hour. The crystals which separated were filtered off to give 2.21 g (90%) of product with mp 143-145°C. NMR spectrum in $CDCl_3$ (δ, ppm): 2.62 s, 2.82 t, 3.54 m, 4.43 s.

N,N'-Bis-γ-aminobutyryl-diaza-18-crown-6 (III). To a solution of 5.2 g (0.022 moles) of N-carbobenzoxy-γ-aminobutyric acid and 2.62 g (0.01 moles) of diaza-18-crown-6 in 40 ml of anhydrous methylene chloride cooled in ice water and vigorously mixed was added 4.5 g (0.022 moles) of dicyclohexylcarbodiimide. The reaction mixture was kept for 12 hours at 20°C, and the N,N'-dicyclohexylurea filtered off. The filtrate was successively washed with 1 N hydrochloric acid, 1 N aqueous sodium bicarbonate, and water. The solvent was evaporated in vacuum and from the residue 6.6 g (94%) of N,N'-bis-(N-carbobenzoxy-γ-aminobutyryl)-diaza-18-crown-6 was isolated by chromatography on an L 40/100 silica gel column (eluant acetone-hexane, 3:1); mp 93-95°C. Hydrogen was passed through a suspension of the catalyst (10% Pd/C) in methanol for 1 hour, after which 6.6 g (0.0094 moles) of N,N'-bis-(N-carbobenzoxy-γ-aminobutyryl)-diaza-18-crown-6 was added. The reaction mixture was stirred until no more carbon dioxide was given off. The catalyst was filtered off, washed several times with methanol, and the combined filtrates concentrated in vacuum to give 4 g (97%) of product in the form of an oil. NMR spectrum in $CDCl_3$ (δ, ppm): 3.55 m, 2.90 s, 2.75 m, 2.33 m, 1.80 m.

BIOLOGICAL EXPERIMENTAL

The pharmacological properties of the crown ethers I-III were studied on white non-pedigree male mice weighing 18-22 g. A total of 184 mice were used in the tests. The antiamnestic effect on the animals was evaluated using passive avoidance tests followed by the use of electroshock as amnestic factor. The time the mice stayed in light and dark compartments was recorded over a period of 2 minutes. The animal was then given a single shock from an electrode (0.4 mA) while in the dark compartment (training). Immediately after training, amnesia was induced by the administration of maximal electroshock (50 Hz, 0.2 seconds through corneal electrodes), which erased traces of memory. The test was repeated 24 hours after training; it was found that after electroshock the animals forgot their training, and preferred to be in the dark part of the chamber.

The antihypoxic effect was evaluated on a model of acute hypobaric hypoxia in a pressure chamber rising at 50 m/sec to a "platform" at 11,000 m, and on models of hypoxia with hypercapnia and hemic hypoxia, in which mice were injected intraperitoneally with a dose of 300 μg/kg of sodium nitrite.

The acute toxicity of the crown ethers was determined from the number of animals lost during 24 hours. The test compounds were injected into mice intraperitoneally in a physiological solution of sodium chloride in doses of 50, 80, and 100 mg/kg. The data obtained was treated statistically to give the LD_{50} [4] with $P \leqslant 0.05$.

On models of three forms of hypoxia and retrograde amnesia, it was observed that the crown ethers showed pronounced action in doses of 100 μg/kg. Moreover, compound I was found to be more effective than compounds II and III (Table 1), and increased the life-span of mice with hypoxic hypercapnia by a factor of 1.8 and of those with hypobaric hypoxia by a factor of 4.2. The effect of the compounds of hemic hypoxia was somewhat lower.

All the test compounds in doses of 80-100 mg/kg had a pronounced antiamnestic effect. The antiamnestic effect prevented the destruction of memory by electroshock, so that the time spent by the mice in the light chamber under the influence of the three compounds increased by factors of 3.4, 2.8, and 3.2 respectively in comparison with the control (Table 2). The most effective was against compound I.

It should be noted that effective doses of the test compounds were three times lower than that of piracetam, a widely used nootropic agent.

The test compounds had no sedative or myorelaxant side effects. One of the disadvantages of these crown ethers is their comparatively high toxicity, particularly in the case of compound III, for which the LD_{50} is 98 mg/kg (95-100.9 mg/kg). For compounds I and II, the LD_{50} is 490 mg/kg (437-549 mg/kg) and 450 mg/kg (400-497 mg/kg) respectively.

Thus, the tests performed show that anithypoxic and antiamnestic action was observed for derivatives of diaza-18-crown-6 with pharmacophore groups, indicating that these compounds possess nootropic properties. Compound I, which has a pyrrolidone group as pharmacophore was the most active; compound III with two γ-amino acid groups exhibited less pronounced antihypoxic and antiamnestic properties.

These compounds are of no practical use because of their high toxicity. However, the fact that derivatives of crown ethers with pharmacophore groups have nootropic properties is of theoretical value, indicating that investigation of this type of compound may yield effective psychotropic substances.

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