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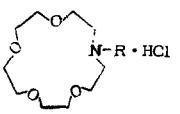
PSYCHOTROPIC PROPERTIES OF AZA-15-CROWN-5 DERIVATIVES WITH PHARMACOPHORIC GROUPS

T. A. Voronina, T. L. Karaseva,
N. Ya. Golovenko, M. G. Rokachinskaya,
S. S. Basok, S. E. Sharapova,
E. Yu. Kulygina, and N. G. Luk'yanenko

UDC 615.214:547.898].07

The pharmacological properties of diaza-18-crown-6 derivatives that contain amino acid residues as pharmacophoric groups have been previously synthesized and studied [3]. It was shown that these compounds have a broad spectrum of psychotropic activity that includes nootropic, anticonvulsant, and tranquilizing effects [3, 5]. However, their high toxicity has excluded their practical application. At the same time, with respect to their antiamnesiac and antihypoxic activity, derivatives of azacrown ethers surpassed piracetam, which is a nootropic agent that is widely used in clinical practice.

In order to search for new less toxic derivatives of azacrown ethers we synthesized aza-15-crown-5 (I), N-(β-alanyl)aza-15-crown-5 (II), N-(γ-aminobutyrylglycyl)aza-15-crown-5 (III), and N-(ε-aminohexanoyl)aza-15-crown-5 (IV) hydrochlorides and studied their psychotropic properties.



R = H (I), $CO(CH_2)_2NH_2$ (II), $COCH_2NHCO(CH_2)_3NH_2$ (III), $CO(CH_2)_3NH_2$ (IV).

EXPERIMENTAL (CHEMICAL)

The IR spectra were recorded with a Perkin–Elmer 580 B spectrometer (USA). The PMR spectra were obtained with a Tesla BS 467 spectrometer (Czechoslovakian SSR) with an operating frequency of 60 MHz with tetramethylsilane as the internal standard.

Aza-15-crown-5 Hydrochloride (I). A stream of dry HCl was passed with stirring and cooling through a solution of 2.2 g of aza-15-crown-5 [4] in absolute ether until the mixture was saturated. The resulting precipitate was removed by filtration, washed with absolute ether, and dried to give 2.4 g (94%) of I with mp 69-70°C. PMR spectrum ($CDCl_3$, δ, ppm): 2.75 t, 3.55 t, 7.1 s.

N-(β-Alanyl)aza-15-crown-5 Hydrochloride (II). A 2.25 g (0.011 mole) sample of dicyclohexylcarbodiimide was added with cooling (with ice water) and vigorous stirring to a solution of 2.5 g (0.011 mole) of N-carbobenzoxy-β-alanine and 2.2 g (0.01 mole) of aza-15-

A. V. Bogatskii Physicochemical Institute, Academy of Sciences of the Ukrainian SSR, Odessa. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 6, pp. 679-682, June, 1988. Original article submitted February 18, 1987.

 0091-150X/88/2206-0444$12.50

TABLE 1. Antiamnesiac and Antihypoxic Effects of Aza-15-crown-5 Ethers I-IV (M ± m)

Compound	Time that the animal is found in the bright compartment, sec		Latent time of reproduction of the CRPA after training and amnesia, sec	Lifetime of the mice, min
	before training	after training and amnesia		
Control	27,0±5,87	57,0±6,06	33,0±3,97	15,5±0,90
I	29,0±2,80	50,1±5,90	31,0±3,50	15,0±0,13
II	32,0±6,37	88,6±6,42*	33,0±4,64	34,1±3,53*
III	28,0±3,46	94,2±5,28*	44,0±4,37	30,0±2,65*
IV	31,0±5,87	113,6±5,74*	70,0±9,94*	24,0±0,88*

*P = 0.05.

crown-5 in 20 ml of anhydrous CH_2Cl_2, and the reaction mixture was maintained for 4 h at 20°C. The precipitated N,N'-dicyclohexylurea was then removed by filtration and washed with 30 ml of CH_2Cl_2. The filtrate was washed successively with 1 N HCl, 1 N aqueous $NaHCO_3$ solution, and water, the solvent was removed by vacuum distillation, and 3.4 g (81%) of N-(N'-carbobenzoxy-β-alanyl)aza-15-crown-5 was isolated from the residue by chromatography with a column packed with silica gel L 40/100 [elution with acetone–hexane (3:1)]. Hydrogen was passed through a suspension of 0.5 g of the catalyst (10% Pd/C) in methanol for 1 h, after which 3.4 g (0.0081 mole) of N-(N'-carbobenzoxy-β-alanyl)aza-15-crown-5 was added, and the reaction mixture was stirred until CO_2 evolution ceased. The catalyst was removed by filtration and washed several times with methanol, and the combined filtrates were concentrated in vacuo at 40°C. The resulting oily product was dried in vacuo, and 5 ml of a 10% solution of HCl in methanol was added. The solvent was evaporated to dryness, the residue was triturated in absolute ether, and the solid material was removed by filtration to give 2.45 g (97%) of II with mp 126-127°C. PMR spectrum ($CDCl_3$, δ, ppm): 2.49 m, 3.03 m, 3.50 m, 8.25 s.

N-(γ-Aminobutyrylglycyl)aza-15-crown-5 Hydrochloride (III). N-Glycyl-aza-15-crown-5 was similarly obtained from 6.9 g (0.033 mole) of carbobenzoxyglycine and 6 g (0.027 mole) of aza-15-crown-5. Workup gave 5.5 g (78%) of the product in the form of an oil. Acylation of 5.5 g (0.02 mole) of N-glycylaza-15-crown-5 by means of 5.53 g (0.022 mole) of phthalimido-γ-aminobutyryl chloride in the presence of 2.2 g (0.02 mole) of Et_3N gave 20 g (99%) of N-(phthalimido-γ-aminobutyrylglycyl)aza-15-crown-5. A 1.1-g (0.022 mole) sample of 96% hydrazine hydrate was added to a solution of the product in 200 ml of ethanol, and the mixture was refluxed for 2 h. The ethanol was evaporated to dryness, and the residue was treated with 10 ml of 2 N HCl for 0.5 h at 50°C. The reaction mixture was cooled to room temperature, the phthalylhydrazide was removed by filtration, and the filtrate was cautiously made alkaline to pH 9.0-10.0 with NaOH solution and extracted with $CHCl_3$. The chloroform extracts were dried with Na_2SO_4, the $CHCl_3$ was evaporated to dryness, the residue was dissolved in dry methanol, and 5 ml of a 10% solution of HCl in methanol was added with cooling. The solvent was evaporated to dryness, the oily product was dried in vacuo and triturated in absolute ether, and the solid material was removed by filtration to give 6.4 g (81%) of III with mp 115-116°C. PMR spectrum ($CDCl_3$, δ, ppm): 1.72 m, 2.25 m, 2.7 m, 3.6 m, 4.02 m, 6.9 s, 8.2 s.

N-(ε-Aminohexanoyl)aza-15-crown-5 Hydrochloride (IV). This compound was obtained from 2.9 g (0.011 mole) of N-carbobenzoxy-ε-aminohexanoic acid and 2.2 g (0.01 mole) of aza-15-crown-5 by a procedure similar to that used to prepare II. Workup gave 2.7 g (86%) of IV in the form of an oil. PMR spectrum ($CDCl_3$, δ, ppm): 2.02 m, 2.49 m, 3.03 m, 3.5 m, 8.25 s.

EXPERIMENTAL (BIOLOGICAL)

The experiments were carried out on white mongrel male mice with weights of 18-20 g. A total of 264 mice were used in the experiments. The antiamnesiac activity of I-IV in the animals was studied with respect to a model involving scopolamine amnesia [2]. Scopolamine, which is a blocker of m-cholinoreceptors and induces amnesia, in a dose of 2.5 mg/kg was administered intraperitoneally to the animals of the control and test groups for 15 min

TABLE 2. Anticonvulsant Activity of Aza-15-crown-5 I-IV

Compound	Dose, mg/kg	Antagonism with Corazole, %	Antagonism with thiosemicarbazide, %	Antagonism with strychnine, %
Control	—	16,6	10	10
I	100	16,6	10	10
II	50	66	30	50
III	50	33	40	30
IV	50	33	40	30

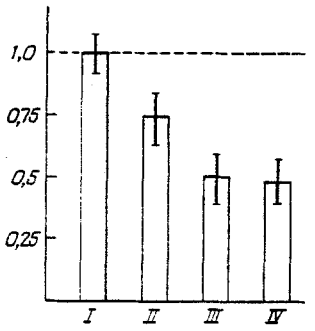


Fig. 1. Effect of acyl derivatives I-IV of aza-15-crown-5 on the motor activity of mice in an open field. The compounds are plotted along the axis of abscissas, while the degree of change in the effect with respect to the control (dash line), which was taken as unity, is plotted along the axis of ordinates.

prior to production of the conditioned reflex of passive avoidance (CRPA). The degree of retention of the skill of passive avoidance of a dark chamber in the control and test groups was carried out 24 h after training. The method of passive avoidance of electrically painful irritation was reproduced in accordance with [6]. Under the influence of scopolamine the control animals forgot their training and preferred to situate themselves in the dark part of the chamber.

To evaluate the antihypoxic activity of the compounds we investigated the effect of I-IV on the lifetime of the mice under conditions of hemic hypoxia, which was induced by the intraperitoneal administration of $NaNO_2$ in a dose of 300 mg/kg.

The anticonvulsant activity of the compounds was evaluated from the antagonism with the convulsant activity of Corazole (130 mg/kg subcutaneously), thiosemicarbazide (27 mg/kg intraperitoneally), and strychnine (2 mg/kg subcutaneously). The effect of the compounds on the motor activity was studied under "open-field" conditions, their effect on the orientational-investigative behavior was studied with respect to the test of climbing a grid, and their effect on myorelaxant manifestations was studied with respect to disruption of motor coordination in the "rotating-rod" test [1].

The investigated I-IV were administered intraperitoneally in a physiological solution for 30 min prior to the start of the experiments in doses of 50 and 100 mg/kg. The acute toxicity of the crown ethers was determined by observation of the mortality of the animals in the course of 24 h. The data obtained were treated statistically with calculation of the LD_{50} values and the mean arithmetic and square errors with P = 0.05 [7].

Using the CRPA method and scopolamine as the amnesiac factor we established that some of the investigated compounds in a dose of 50 mg/kg administered prior to the training session give rise to an antiamnesiac effect, as a result of which the index of the time spent by the mice in the bright compartment of the chamber was higher by a factor of 1.5-2 than the analogous index in the control group (Table 1). Compound IV has the most pronounced

antiamnesiac activity of all of the aza-15-crown-5 derivatives. Compounds I and II did not prevent the development of scopolamine amnesia.

With respect to the model of acute hemic hypoxia all of the aza-15-crown-5 derivatives in a dose of 50 mg/kg had pronounced antihypoxic activity. Compounds II, III, and IV increased the lifetime of the mice by factors of 2.2, 2, and 1.6, respectively; the substances that contain β-alanine (II) and aminobutyrylglycyl (III) fragments were found to be the most effective (see Table 1).

It should be noted that the diaza-18-crown-6 derivatives prevented the effects of hemic hypoxia to a lesser extent [3].

All of the investigated compounds, with the exception of I, had anticonvulsant activity. However, their effectiveness with respect to individual manifestations of the anticonvulsant activity was ambiguous (Table 2). All of the substances in a dose of 50 mg/kg provided 33-66% protection of the animals from clonic-tonic spasms and death induced by Corazole and 30-40% protection from spasms induced by thiosemicarbazide. Compound II was found to be the most active with respect to preventing the death of animals as a result of the action of strychnine.

In a study of the sedative activity of I-IV in the "open-field" test it was established that III and IV cause a 50% decrease, as compared with the control, in the overall motor activity of the mice, chiefly due to a decrease in the vertical activity (see Fig. 1). Compounds I-IV, even in doses that are close to toxic, did not give rise to disruption of the motor coordination and myorelaxation. The LD_{50} value of I is 650 (630-740) mg/kg, while the LD_{50} values of II-IV are greater than 650 mg/kg.

Thus, as a result of our investigations, we have observed that aza-15-crown-5 derivatives with pharmacophoric groups have psychotropic properties (antiamnesiac, antihypoxic, anticonvulsant, etc.).

The investigated crown ethers are considerably less toxic than diaza-18-crown-6 derivatives [3]; this is of practical value and opens up prospects for the search for new more active psychotropic preparations on the basis of similar structures.

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