In a dose of 10 mg/kg, (IIIc) on intravenous administration to cats caused a reduction in arterial pressure by on average 36 ± 2.7% (29-43). The compound reduced the volume flow rate of the cerebral blood supply by 17 ± 2.2% (11-23). The effect was noted immediately following administration of the compound, and continued for 10 min.

Intravenous administration of a dose of 10 mg/kg of (IIId) to cats reduced the arterial pressure by only 14 ± 0.4% (13-15), and the cerebral blood flow decreased by 28 ± 8.1%. The effect lasted for 10 min. For comparison, the effects of salsolidine on the arterial pressure and cerebral blood flow were examined. In a dose of 20 mg/kg intravenously, salsolidine had no marked effect on the arterial pressure and the cerebral circulation. In a dose of 50 mg/kg, salsolidine reduced the arterial pressure and decreased the cerebral blood flow to the same extent as (IIIc) at 10 mg/kg, i.e., by 36 and 12% respectively.

Thus, these compounds possess hypotensive properties, and reduce the cerebral blood supply, apparently as a result of the hypotension.

Compounds (IIIa, b) and (VI) [compound (VI) was obtained for purposes of comparison, since the imidazole residue is known to have pharmcoproperties] in doses of 5-10 mg/kg had weak hypotensive effects, and had no advantages over salsolidine.

LITERATURE CITED

1. M. Negwer, Organisch-Chemische Arzneimittel und ihre Synonyma, Berlin (1978), Vol. 1-3.
2. M. D. Mashkovskii, Drugs [in Russian], 8th edn., Moscow (1977), Vols. 1-2.
3. A. L. Mndzhoyan, L. Sh. Pirdzhanov, and M. T. Bkhiyan, Arm. Khim. Zh., No. 11, 995-999 (1971).
4. L. Sh. Pirdzhanov, A. A. Agekyan, et al., Arm. Khim, Zh., No. 8, pp. 667-674 (1973).
5. V. U. Rakhmatullina, A. A. Aduvakhabov, and Kh. A. Aslanov, Zh. Obshch. Khim., No. 3, 689 (1978).

ANALOGS OF ACETYLCHOLINE AND DIACETYLCHOLINE CONTAINING ADAMANTYL RADICALS

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Earlier it was shown [1] that when a methyl group is replaced by a highly lipophilic adamantyl radical, cholinomimetics lose their depolarizing properties and are converted to cholinolytics. This phenomenon is evidently associated with a change in the conditions of fixation of the substances on the synaptic membrane on account of hydrophobic interactions. The pattern found has been confirmed on a large series of compounds, primarily in the comparison of acetylcholine (Ia) and diacetylcholine (succinylcholine, ditilin, IIa) with their adamantyl analogs (Ib and IIb) [2]. The latter possessed the properties of cholinolytics; moreover, the adamantyl analog of diacetylcholine (IIb), called diadonium, has been approved for use in anesthesiological practice as a nonpolarizing myorelaxant [3].

We were interested in tracing the influence of different localization of the adamantyl radical on the magnitude and nature of the cholinergic activity of adamantyl derivatives of acetylcholine and diacetylcholine. Information on the role of individual fragments of the structure of curare-like substances in the mechanism, activity, and duration of their action may be useful for an approach to the understanding of the structure of the cholinoreceptors of the skeletal muscles and the mechanism of neuromuscular block, as well as for planning means of directed synthesis of myorelaxants with set properties. For this purpose we synthesized a series of analogs of I and II, in which the adamantyl radical is bounded directly to a quaternary nitrogen atom, separated from it by one or two methylene groups, or is found in the amino alcohol or acid portion of the molecule.

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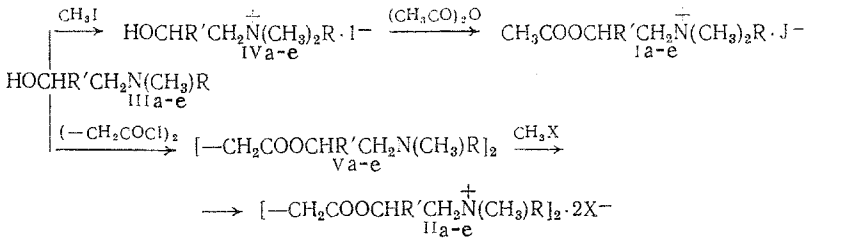
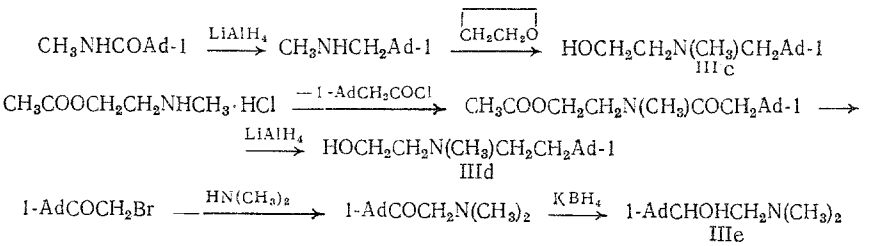


a) R = CH_3, R′ = H b) R = 1-Ad (adamantyl), R′ = H c) R = 1-AdCH_2, R′ = H
r) R = 1-AdCH_2CH_2, R′ = H e) R = CH_3, R′ = 1-Ad X = I^-, $n = CH_3C_6H_4SO_3^-$

First we produced amino alcohols IIIc-e, which were converted to the methiodides IVc-e, and then by the action of acetic anhydride to acetylcholine analogs Ic-e. Bis-esters Vc-e were produced by the reaction of the amino alcohols IIIc-e with succinyl dichloride and then converted to the bis-quaternary salts (diacetylcholine analogs) sought, IIc-e.

The methods of production of the initial aminoalcohols III are described below. The synthesis of β-[N-methyl-N-(1-adamantyl)amino]ethanol (IIIb) was described earlier [4].* For the production of β-[N-methyl-N-(1-adamantylmethyl)amino]ethanol (IIIc), the N-methylamide of 1-adamantanecarboxylic acid was reduced with lithium aluminum hydride [5], and the 1-methyl(N-methylamino)adamantane formed was treated with ethylene oxide. [N-Methyl-N-(β-acetoxyethyl)]amide of 1-adamantylacetic acid was synthesized by the action of 1-adamantylacetyl chloride on β-(N-methylamino)ethanol acetate [6]; reduction of the amide with lithium aluminum hydride led to β-[N-methyl-N-(1-adamantylethyl)amino]ethanol (IIId). α-(1-Adamantyl)- β-(dimethylamino)ethanol (IIIe) was produced from 1-(β-bromoacetyl)adamantane by the action of dimethylamine, followed by reduction of the 1-[(α-dimethylamino)acetyl]adamantane obtained with sodium borohydride.



Methiodides of β-(dimethylamino)ethyl esters of 1-adamantanecarboxylic and 1-adamantylacetic acids (If and Ig, respectively) were produced as analogs of acetylcholine containing an adamantyl residue in the acid portion of the molecule. Dimethiodides of bis(β-dimethylamino)ethyl esters of 1- and 2-adamantylmalonic acids (IIf and IIg, respectively) were synthesized as the corresponding analogs of diacetylcholine; they are more readily available than the corresponding adamantyl derivatives of succinic acid (according to the literature data [7], diacetycholine and its lower homolog malonylcholine are comparable in magnitude of the curare-like activity).

The synthesized analogs of acetylcholine and diacetylcholine were investigated in experiments on cats and pigeons. The experiments on cats were conducted under conditions of anesthesia (chloralose 60 mg/kg with urethane 400 mg/kg, intravenously). The contractions of the gastrocnemius muscle after electrical stimulation of a peripheral segment of the sciatic nerve with rectangular supramaximal stimuli (frequency one stimulus per sec, duration of stimulus 0.5 msec) were recorded in a semi-isometric system. The substances were injected intravenously against a background of stimulation of the nerve.

The nature of the paralysis arising after intravenous injection of the tested compounds was determined on intact pigeons. As is well known, depolarizing agents induce spastic paralysis, while antidepolarizing agents produce limp paralysis.

*Incidentally, we should like to correct a misprint in the article [4]: in Table 1 for AD-$(CH_3)_2N(CH_2)_4OH \cdot CH_3I$ (VII) it was printed: mp 120-122°C but should be: mp 189-190°C.

For analogs and derivatives of diacetylcholine it was shown that the introduction of the adamantyl radical into different parts of the structure of diacetylcholine is accompanied by a regular change in the mechanism of action. In contrast to the depolarizing action of diacetylcholine, its adamantyl derivatives exert an antidepolarizing effect; moreover, the N-(1-Ad) derivative (diadonium) is the most active. When the distance from the 1-Ad radical to the quaternary nitrogen atom is increased by 1-2 methylene groups (IIc, d), the curare-like activity is decreased by an order of magnitude or more. The least blocking activity among the tested diacetylcholine analogs was noted for the compound with a 1-Ad radical at the β-carbon of the aminoalcohol portion of the molecule (Ie). Thus, when the distance from the 1-Ad radical to the quaternary nitrogen atom is increased, the curare-like activity of the compounds decreases. This also finds confirmation on the example of bis-quaternary ammonium derivatives of malonic acid with 1-Ad and 2-Ad radicals at the central carbon atom (IIf, g). Both compounds possess very low activity (two orders of magnitude or more less than that of diadonium).

The introduction of adamantyl radicals into any site of the acetylcholine molecule also converts it to an antidepolarizing curare-like agent. Compounds containing an adamantyl radical in the acid portion of the molecule (If, g) are more active. The least activity was noted for the N-(1-adamantyl) derivative of acetylcholine (Ib). However, on the whole, these monoquaternary compounds are substantially less active than related bis-quaternary analogs; therefore we limited ourselves to establishing the mechanism of their blocking action.

For the properties of the synthesized compounds, see Table 1.

EXPERIMENTAL

Uncorrected values of the melting points are cited.

β-[N-Methyl-N-(1-adamantyl)amino]ethanol (IIIc). A solution of 4.4 g N-methyl-N-(1-adamantylmethyl)amine hydrochloride [5] in 100 ml of water was alkalinized with a 20% solution of sodium hydroxide; the oil that separated was extracted with ether, and the extract dried with solid potassium hydroxide. After the solvent was distilled off, 3.5 g of the base was obtained in the form of an oil, which was dissolved in 50 ml of ethanol and placed in a flask equipped with a reflux condenser, cooled with a mixture of acetone and dry ice. A solution of 8.9 g ethylene oxide in 20 ml ethanol was added dropwise with mixing. Then the temperature of the reaction mixture was gradually raised to 55°C over a period of 2 h and exposed at this temperature for 30 min. The excess ethylene oxide and methanol were distilled off under weak vacuum at a bath temperature 40°C. The residue was dissolved in ether, the ether solution filtered with charcoal, the ether distilled off, and the oil remaining redistilled under vacuum. Yield 3 g (69%) of the fraction with bp 115-116°C (2 mm), n_D^{20} 1.5130. Found, %: C 75.17; H 11.18; N 6.33. $C_{14}H_{25}NO$. Calculated, %: C 75.28; H 11.28; N 6.27.

The methiodide (IVc) was produced in acetone, mp 254-256°C (with dec.). Found, %: I 34.65. $C_{14}H_{25}NO \cdot CH_3I$. Calculated, %: I 34, 75.

N-Methyl-N-(β-acetoxyethyl)amide of 1-adamantylacetic Acid. To a suspension of 5.68 g methylaminoethanol acetate hydrochloride, cooled with ice water [6], in 60 ml of benzene, a solution of 9.38 g triethylamine in 20 ml of benzene was added with mixing, and then a benzene solution of 7.9 g adamantylacetyl chloride was added. After mixing for 2 h, the mixture was exposed for 40 min at 18-20°C, the precipitate filtered off, the benzene solution washed with water, with ammonia solution, again with water, dried with magnesium sulfate, the solvent distilled off, and the residue redistilled under a vacuum of 1 mm (bath temperature 160°C); 8 g (73.4%) of the base was obtained in the form of a colorless oil. Found, %: C 69.42; H 9.45; N 5.04. $C_{17}H_{27}NO_3$. Calculated, %: C 69.59; H 9.28; N 4.77.

β-[N-Methyl-N-(1-adamantylethyl)amino]ethanol (IIId). An ether solution of 7.5 g [N-methyl-N-(β-acetoxyethyl)]amide of 1-adamantylacetic acid was added over a period of 25 min to a suspension of 3.6 g lithium aluminum hydride in 75 ml absolute ether, maintaining boiling of the ether, and then it was mixed for 40 min at 18-20°C. To the reaction mass we successively added 3.6 ml of water, 2.7 ml of a 20% sodium hydroxide solution, and 8 ml of water with mixing. The precipitate was filtered off and washed with ether. The ether solution was dried with magnesium sulfate, the solvent distilled off, the residue redistilled, bp 132-133.5°C (1 mm). Yield 5.35 g (88.1%) of a colorless oil, n_D^{21} 1.5120. Found, % C 75.96; H 11.22; N 6.04. $C_{15}H_{27}NO$. Calculated, %: C 75.90; H 11.46; N 5.90.

TABLE 1. Cholinergic Properties of Analogs I and II, Containing Lipophilic Radicals in Various Portions of the Molecule

Compound	Structure	Block of transmission from sciatic nerve to gastrocnemius muscle in cats (dose in mg/kg, intravenously)	Ability to induce paralysis in pigeons	
			limp	spastic
Ia	$CH_3COOCH_2CH_2\overset{+}{N}(CH_3)_3 \cdot I^-$ (acetylcholine)	—		+
Ib	$CH_3COOCH_2CH_2\overset{+}{N}(CH_3)_2Ad\text{-}1 \cdot I^-_{(I)}$	25—30	+	
Ic	$CH_3COO(CH_2)_2\overset{+}{N}(CH_3)_2CH_2Ad\text{-}1 \cdot I^-$	—	+	
Id	$CH_3COOCH_2CH_2\overset{+}{N}(CH_3)_2CH_2CH_2Ad\text{-}1 \cdot I^-$	—	+	
Ie	$CH_3COOCH(Ad\text{-}1)CH_2\overset{+}{N}(CH_3)_3 \cdot I^-$	—	+	
If	$1\text{-}AdCOOCH_2CH_2\overset{+}{N}(CH_3)_3 \cdot I^-$	>15	+	
Ig	$1\text{-}AdCH_2COOCH_2CH_2\overset{+}{N}(CH_3)_3 \cdot I^-$	8—12	+	
IIa	$[-CH_2COOCH_2CH_2\overset{+}{N}(CH_3)_3]_2 2I^-$ (ditilin)	0,06—0,08		+
IIb	$[-CH_2COOCH_2CH_2\overset{+}{N}(CH_3)_2Ad\text{-}1]_2 \cdot 2CH_3C_6H_4SO_3^-$ diadonium	0,3—0,4	+	
IIc	$[-CH_2COOCH_2CH_2\overset{+}{N}(CH_3)_2CH_2Ad{=}1]_2 \times \times 2CH_3C_6H_4SO_3^-$	6—10	+	
IId	$[-CH_2COOCH_2CH_2\overset{+}{N}(CH_3)_2CH_2CH_2Ad\text{-}1]_2 \times \times 2CH_3C_6H_4SO_3^-$	12—15	+	
IIe	$[-CH_2COOCH(Ad\text{-}1)CH_2\overset{+}{N}(CH_3)_3]_2 \cdot 2I^-$	3—4	+	
IIf	$1\text{-}AdCH[COOCH_2CH_2\overset{+}{N}(CH_3)_3]_2 \cdot 2I^-$	45—50	+	
IIg	$2\text{-}AdCH[COOCH_2CH_2\overset{+}{N}(CH_3)_3]_2 \cdot 2I^-$	40—45	+	

The methiodide (IVd) was produced in acetone, mp 238.5-239°C. Found, %: I 33.52; N 5.80. $C_{15}H_{27}NO \cdot CH_3I$. Calculated, %: I 33.45; N 3.69.

1-[(α-Dimethylamino)acetyl]adamantane. To a solution of 11.2 g 1-(α-bromoacetyl)adamantane [8] in 100 ml of ethanol, 100 ml of a 10% alcohol solution of dimethylamine was added with mixing. After the reaction mixture was allowed to stand overnight, the alcohol was evaporated under vacuum, the residue dissolved in 15 ml of water, the solution saturated with potash and extracted with ether. The oil remaining after the solvent was distilled off was redistilled under vacuum. Yield 7.75 g (80.4%) of the base, bp 123-125°C (2 mm), n_D^{25} 1.5055. Found, %: C 76.04; H 10.25; N 6.21. $C_{14}H_{23}NO$. Calculated, %: C 75.97; H 10.47; N 6.33.

Hydrochloride. mp 213-215°C. Found, %: Cl 13.72; N 5.36. $C_{14}H_{23}NO \cdot HCl$. Calculated, %: Cl 13.75; N 5.43.

α-(1-Adamantyl)-β-(dimethylamino)ethanol (IIIe). To a solution of 4.25 g 1-[α-dimethylamino)acetyl]adamantane in 15 ml of methanol, 1.17 g potassium borohydride was gradually added at 15-20°C. After mixing for 1 h, 60 ml of water was added, the precipitate formed was dissolved in ether, the ether solution dried with potash, and the solvent evaporated. Yield 3.6 g (83.7%) of the crystalline base, mp 48-50°C. Found, %: C 75.47; H 11.14; N 6.29. $C_{14}H_{25}NO$. Calculated, %: C 75.28; H 11.28; N 6.27.

Hydrochloride. mp 274-275°C. Found, %: Cl 13.77; N 5.31. $C_{14}H_{25}NO \cdot HCl$. Calculated, %: Cl 13.65; N 5.39.

Methiodide (IVe). MP 248-250°C. Found, %: C 48.49; H 7.97; I 34.75. $C_{14}H_{25}NO \cdot CH_3I$. Calculated, %: C 49.32; H 7.73; I 34.74.

Acetate of α-(1-Adamantyl)-β-(dimethylamino)ethanol. A solution of 0.44 g of the amino-alcohol IIIe in 5 ml of dichloroethane was added with mixing to a solution of 0.4 g acetyl-chloride in 5 ml dichloroethane. The mixture heated up spontaneously, and a precipitate formed; after 1 h dichloroethane was distilled off under vacuum, 2 ml of water was added to the residue, it was acidified with 1 N hydrochloric acid to an acidic reaction to Congo red, extracted with ether, and the ether layer discarded. The aqueous layer was saturated with sodium bicarbonate, the oil that separated was extracted with ether and dried with magnesium sulfate. The solvent was distilled off under vacuum; yield 0.44 g (84.6%) of the base in the form of an oil. Found, %: C 72.45; H 10.22; N 5.58. $C_{16}H_{27}NO_2$. Calculated, %: C 72.41; H 10.25; N 5.28.

Hydrochloride. Mp 235-237°C. Found, %: Cl 11.73. $C_{16}H_{27}NO_2 \cdot HCl$. Calculated, %: Cl 11.76.

Methiodide (Ie). Mp 261-263°C (from an ethanol—ethyl acetate mixture). Found, % I 31.25 N 3.18. $C_{16}H_{27}NO_2 \cdot CH_3I$. Calculated, % I 31.20 N 3.44.

Methiodide of β-[N-Methyl-N-(1-adamantylethyl)amino]ethyl Ester of Acetic Acid (Id). A mixture of 0.7 g of the methiodide IVd and 3 ml acetic anhydride was boiled for 1 h. After cooling, ether was added to the reaction mass, the precipitate formed was filtered off and washed with ether. Yield 0.77 g (90%) Id, mp 143.5-144.5°C (from alcohol). Found, %: C 51.11; H 7.69; I 30.44; N 3.27; $C_{17}H_{29}NO_2 \cdot CH_3I$. Calculated, %: C 51.29; H 7.66; I 30.13; N 3.33.

Methiodide of α-(1-adamantyl)-β-(dimethylamino)ethyl ester of acetic acid (Ie) was produced analogously. Mp 260-261°C. Found, %: I 31.09. $C_{16}H_{27} \cdot NO_2 \cdot CH_3I$. Calculated, %: I 31.20. It is identical with the substance obtained from the acetate of α-(1-adamantyl)-β-dimethylamino)ethanol by the reaction with methyl iodide (see above).

Methiodide of α-[N-methyl-N-(1-adamantylmethyl)amino]ethyl ester of acetic acid (Ic) was produced analogously. Mp 167-178°C. Found, %: I 31.10. $C_{16}H_{27}NO_2 \cdot CH_3I$. Calculated, %: I 31.15.

Methiodide of β-Dimethylaminoethyl Ester of 1-adamantylacetic Acid (Ig). To a solution of 0.46 g dimethylaminoethanol in 10 ml dichloroethane we added a solution of 1.1 g 1-adamantylacetyl chloride in 10 ml of the same solvent. On the following day dichloroethane was distilled off, 1 N hydrochloric acid was added to the residue to an acid reaction to Congo red, the solution was treated with charcoal, alkalinized with ammonia, extracted with ether, dried with ammonium sulfate, and the ether was distilled off. Residue 1 g (73.5) of the base in the form of an oil, n_D^{20} 1.4902. Found, %: C 72.52; H 10.24; N 5.52. $C_{16}H_{27}NO$. Calculated, %: C 72.41; H 10.25; N 5.28.

Hydrochloride. Mp 210-212°C. Found, %: Cl 11.81. $C_{16}H_{27}NO_2 \cdot HCl$. Calculated, %: Cl 11.74.

Methiodide (Ig). Mp 216-218°C. Found, %: I 31.47. $C_{16}H_{27}NO \cdot CH_3I$. Calculated, %: I 31.15.

The base of the β-dimethylaminoethyl ester of 1-adamantylcarboxylic acid and its hydrochloride, mp 210-212°C, were produced analogously. Found, %: C 62.10; H 9.20; N 4.94; Cl 11.81. $C_{15}H_{25}NO_2 \cdot HCl$. Calculated, %: C 62.59; H 9.11; N 4.87; Cl 12.32.

Methiodide (If). Mp 224-226°C. Found, %: C 48.58; H 7.29; N 3.58; I 32.56. $C_{15}H_{25} \cdot NO_2 \cdot CH_3I$. Calculated, %: C 48.86; H 7.18; N 3.56; I 32.27.

Bis-β-[N-methyl-N-adamantylmethylamino)]ethyl Ester of Succinic Acid (Vc). To a solution of 1 g β-[N-methyl-N-(1-adamantylethyl)amino]ethanol in 20 ml of benzene at 2-5°C a solution of 0.34 g succinyl dichloride in 20 ml of benzene was gradually added. It was mixed for 1 h at 10°C, then for 2 h at 18-20°C. The solvent was distilled off under vacuum, the residue dissolved in acidified water, the solution treated with charcoal and extracted with ether. The aqueous layer was saturated with sodium bicarbonate. The oil that separated was extracted with ether, the extract dried with magnesium sulfate. The solvent was distilled off; the residue was a dense oil, 0.8 g (67.8%), n_D^{20} 1.5120. Found, %: C 72.68; H 10.22; N 5.44. $C_{32}H_{52}N_2O_4$. Calculated, %: C 72.69; H 9.91; N 5.30.

Dihydrochloride. Mp 206-208°C. Found, %: Cl 12.12. $C_{32}H_{52}N_2O_4 \cdot 2HCl$. Calculated, %: Cl 11.78.

The dimethiodide (IIc) was produced in acetone, mp 217-219°C. Found, %: I 31.57. $C_{32}H_{52}N_2O_4 \cdot 2CH_3I$. Calculated, %: I 31.23.

The Di(methyl-p-toluenesulfonate) (IIc, X = p-n-$CH_3C_6H_4SO_3^-$) was produced by fusion at 100-110°C; mp 168-170°C. Found, %: S 7.52. $C_{32}H_{52}N_2O_4 \cdot 2CH_3C_6H_4SO_3CH_3$. Calculated, %: S 7.11. The compounds Vd, Ve, and IIe were produced analogously.

The Bis{N-methyl-N-[β-(1-adamentyl)ethyl]-aminoethyl} Ester of Succinic Acid (Vd). Without isolation in individual state, this was converted to the di-(methyl-p-toluenesulfonate) (IId, X = p-$CH_3C_6H_4SO$) by fusion at 110-120°C with the methyl ester of p-toluenesulfonate. Monohydrate, mp 169-170°C (from an ethanol—ester acetate mixture). Found, %: C 63.61; H 8.23; N 3.16; H_2O 1.44. $C_{50}H_{76}N_2O_{10}S_2 \cdot H_2O$. Calculated, %: C 63.40; H 8.30; N 2.96; H_2O 1.90. Drying under vacuum 100°C yielded an anhydrous substance with mp 194-196°C.

The Bis[α-(1-adamantyl)-β-(dimethylamino)-ethyl] Ester of Succinic Acid (Ve). Yield 67%. Found, %: C 72.64; H 9.95. $C_{32}H_{52}N_2O_4$. Calculated, %: C 72.69; H 9.91.

Dimethiodide (IIe). Mp 258-260°C (with dec.). Found, %: C 50.05; H 7.43; N 3.37. $C_{32}H_{52}N_2O_4 \cdot CH_3I$. Calculated, %: C 50.25; H 7.19; N 3.45.

Bis-(β-dimethylamino)ethyl Ester of 1-Adamantylmalonic Acid. Granular metallic sodium was added to 1.2 g of dimethylaminoethanol, and after it dissolved, 1 g of the diethyl ester of 1-adamantylmalonic acid was added [9]. The mixture was heated at a residual pressure of 180 mm to 130°C in 30 min and exposed at this temperature for 1 h; after cooling it was dissolv d in ether, the small precipitate filtered off, the ether distilled off, the residue dissolved in 5% hydrochloric acid, extracted with ether, and the ether extract discarded. The base that was extracted by ether was isolated from an aqueous solution of ammonia, dried, the solvent distilled off, and the oil remaining (1.45 g) redistilled. Bp 154-156°C (2 mm), n_D^{25} 1.4893. Found, %: C 66.25; H 9.53. $C_{21}H_{36}N_2O_4$. Calculated, %: C 66.28; H 9.54.

Dimethiodide (IIf). Mp 220-222°C (from an alcohol—ethylacetate mixture). Found, %: C 41.73; H 6.51; I 38.18. $C_{21}H_{36}N_2O_4 \cdot 2CH_3I$. Calculated, %: C 41.57; H 6.37; I 38.20.

The dimethiodide of the bis-(β-dimethylamino)ethyl ester of 2-adamantylmalonic acid (IIg) was produced analogously on the basis of 2-adamantyl-malonic ester [10]. Mp 214-215°C (from an alcohol—ethyl acetate mixture). Found, %: C 41.79; H 6.42; I 38.55; $C_{21}H_{36}N_2O_4 \cdot CH_3I$. Calculated, %: C 41.58; H 6.37; I 38.20.

LITERATURE CITED

1. D. A. Kharkevich and A. P. Skoldinov, Zh. Vses. Khim. Ova. im. D. I. Mendeleeva, 15, No. 2, 145 (1970).
2. D. A. Kharkevich and A. P. Skoldinov, Dokl. Akad. Nauk SSSR, 198, No. 4, 985 (1971).
3. A. P. Arendaruk, A. P. Skoldinov, N. V. Smirnova, et al., Khim-farm. Zh., No. 8, 8 (1972).
4. A. P. Arendaruk, A. P. Skoldinov, N. V. Smirnova, et al., Khim.-farm. Zh., No. 4, 8.
5. P. E. Albrich, E. C. Hermann, W. E. Meier, et al., J. Med. Chem., 14, 540 (1971).
6. V. N. Bochenkov and V. F. Borodkin, Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol., 12, No. 8, 1110 (1969).
7. R. S. Rybolovlev, in: Ditilin and Experience in Its Clinical Use [in Russian], Erevan (1957), p. 29.
8. H. Stether and E. Rauscher, Chem. Ber., 93, 2056 (1960).
9. W. H. W. Lunn, W. D. Podmore, and S. S. Szinai, J. Chem. Soc. (C), No. 13, 1657 (1968).
10. E. K. Novitskaya, N. V. Smirnova, and A. P. Skoldinov, Zh. Org. Khim., 12, 576 (1976).