CURARE-LIKE ACTION OF MONOQUATERNARY SALTS CONTAINING AN ADAMANTYL GROUP ON THE NITROGEN ATOM

A. P. Arendaruk, A. P. Skoldinov,
N. V. Smirnova, D. A. Kharkevich,
G. I. Tsvetkova, and M. I. Shmar'yan

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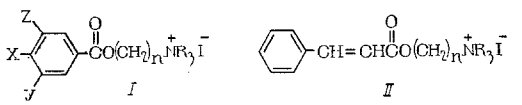
As was shown in the previous work, monoquaternary salts of alkamine esters of benzoic and cinnamic acids of the types (I) and (II) exert a distinct curare-like action [1].



I

II

In activity certain of these compounds may compare with the most effective muscle relaxants which belong to the group of bisquaternary ammonium salts. Like the majority of monoquaternary salts their action is quite short-lived. This is evidently associated to a considerable degree with the presence of hydrolyzable ester bonds in the organism. The disadvantages of compounds of the types (I) and (II) which hinder their use in anesthetic practice must be attributed to the fact that they cause a depolarized neuromuscular block. As is known, antidepolarizing muscle relaxants are of most interest for surgical use [2] and the action of these must be regulated by the use of antagonists (for example neostigmine). Furthermore, they do not disturb the distribution of the potassium ions and in this connection do not lead to the onset of a series of side effects which are characteristic of depolarizing compounds.

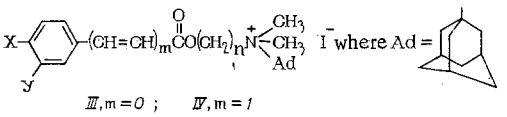
Previously, attempts have repeatedly been made to transform depolarizing muscle relaxants into the practically more valuable antidepolarizing compounds by means of various types of structural changes. The possibility of such a change has already been theoretically noted for monoquaternary muscle relaxants. Thus, it was shown for tetramethylammonium salts that the successive exchange of one of the methyl groups by an alkyl group with a constantly increasing chain length led to the situation that at a number of carbon atoms in the chain greater than 12 the substance lost the depolarizing properties and began to act as a nondepolarizing type [3]. On the basis of these data compounds were studied in which the highly lipophilic and voluminous adamantyl group was introduced at the onium center. One might expect that this would significantly change the distribution of the substance, the ease of approach of the molecule of muscle relaxant to the appropriate receptors, and the stability of the bond between them. Data are available on the fact that depolarizing and nondepolarizing curare-like substances are fixed differently in the region of the end plates of skeletal muscles [4, 5] whose lipophilic organization occupies an important place in the structure of synaptic membranes [6]. It is also known that the introduction of adamantyl groups into the structures of antidiabetic compounds [7], hormonal compounds [8], and other physiologically active substances [9] led to interesting changes in the nature of the activity of these compounds.

A series of methiodides of alkamine esters of benzoic (I) and cinnamic (IV) acids, analogous in structure to the salts I and II but containing an adamantyl group on the quaternary nitrogen atom in place of a methyl group, were synthesized.

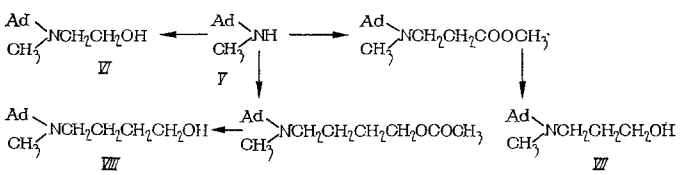
Scientific-Research Institute of Pharmacology of the Academy of Medical Sciences of the USSR, Moscow. I. M. Sechenova Moscow Medicinal Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 4, pp. 8-13, April, 1972. Original article submitted February 5, 1971.

TABLE 1. ω-[N-Methyl-N-(1-adamantyl)amino]alkanols

Compound	Overall yield (in %)	Base						Hydrochloride				Methiodide			
		found (in %)			empirical formula	calc. (in %)			mp (in deg)	Cl′		I′			
		C	H	N		C	H	N		found	calc.	mp (in deg)	found	calc.	
										%			%		
VI	80,2	74,52	11,16	7,00	$C_{13}H_{23}NO$	74,59	11,07	6,69	207—9	14,14	14,42	205—206	36,30	36,13	
		74,58	11,03	6,92						14,08			36,18		
VII	74,7	75,54	11,41	6,46	$C_{14}H_{25}NO$	75,28	11,28	6,27	189—91	13,41	13,64	193—195	35,25	37,74	
		75,55	11,36	6,63						13,34			35,24		
VIII	76,3	76,05	11,60	5,75	$C_{15}H_{27}NO$	75,89	11,46	5,89	167—9	12,63	12,94	120—122	33,14	33,37	
		76,14	11,39	5,91						12,72			32,92		



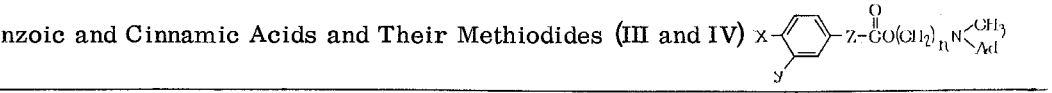
As 1-bromoadamantane does not form quaternary salts with tertiary amines under the usual conditions it was necessary to prepare a series of amino alcohols with an adamantyl group on the nitrogen atom starting from 1-(N-methylamino)adamantane (V) [10].



β-[N-Methyl-N-(1-adamantyl)amino]ethanol (VI) was synthesized by the action of ethylene oxide on V. Methyl β-[N-methyl-N-(1-adamantyl)amino]propionate was prepared by the addition of an equimolecular quantity of V to methyl acrylate and was then reduced with 2 moles of lithium aluminum hydride to γ-[N-methyl-N-(1-adamantyl)amino]propanol (VII). The reaction of 2 moles of V with δ-bromobutyl acetate gave δ-[N-methyl-N-(1-adamantyl)amino]butyl acetate which was hydrolyzed without isolation in the pure state to δ-[N-methyl-N-(1-adamantyl)amino]butanol (VIII). The amino alcohol VI was a crystalline substance; the amino alcohols VII and VIII were viscous liquids which distilled without decomposition at a high vacuum and were characterized as the hydrochlorides and methiodides (Table 1).

The conversion of the obtained amino alcohols (VI-VIII) into esters of benzoic or substituted benzoic acids was achieved by reacting them with an equimolecular quantity of the appropriate acid chloride (standard experiment A). The basic esters of the cinnamic acids were prepared by the transesterification of the methyl cinnamates with the amino alcohol in the presence of the alcoholate (standard experiment B). In both variants the separation of the formed alkamino ester from the unreacted amino alcohol was carried out by fractional basification of a solution of the reaction mixture in acid; in the majority of cases the esters which were separated in this way showed completely satisfactory analytical results without a distillation. The preparation of the methiodides was carried out by heating a solution of the reactants in acetone. The analysis results and the constants for the synthesized compounds are given in Table 2.

In the pharmacological study of compounds (III) and (IV) their curare-like action was compared with the action of the analogously constructed compounds (I) and (II). It was shown that the substitution of the N-methyl group by an adamantyl group led to a change in the mechanism of action of the substances and this related both to the derivatives of benzoic acid (I) and (III) and also to the derivatives of cinnamic acid (II) and (IV). In all cases the trimethylammonium compounds caused spasmodic paralysis in chicks typical of depolarizing substances while their adamantyl analogs evoked a limp paralysis characteristic of a nondepolarizing block (see Table 2). The change in mechanism of action of the compounds on introducing the adamantyl group into the cationic grouping is accompanied by a sudden lowering of the curare-like activity (from the data of experiments on cats by 200-300 times).

TABLE 2. Basic Esters of Benzoic and Cinnamic Acids and Their Methiodides (III and IV) 

X	Y	Z	n	Base: yield (in %)	Base: found (in %) C	Base: found (in %) H	Base: found (in %) N	Base: empirical formula	Base: calc. (in %) C	Base: calc. (in %) H	Base: calc. (in %) N	Methiodide: mp (in deg)	Methiodide: found I' %	Methiodide: calc. I' %	Methiodide: curare-like activity[a] dose (in mg/kg) intravenously	Methiodide: nature of paralysis in chicks
H	H	—	2[b]	86,2	76,42 76,38	8,42 8,55	4,51 4,58	$C_{20}H_{27}NO_2$	76,63	8,68	4,46	193—5	28,08 28,22	27,87		Limp 6—8
H	H	—	3[c]	78,1	77,24 77,31	8,95 9,10	4,35 4,55	$C_{21}H_{29}NO_2$	77,02	8,92	4,27	220—2	26,72 26,95	27,10		Limp 6—8
H	H	—	4	84,5	77,23 77,54	9,32 9,41	4,25 4,31	$C_{22}H_{31}NO_2$	77,37	9,15	4,09	203—5	26,47 26,63	26,25	10—12 (0,2—0,25)	Limp, 4—5 (sposmodic, 0,3—0,4)
CH_3O	CH_3O	—	4[d]	72,9	71,65 71,49	8,84 8,63	3,60 3,68	$C_{24}H_{35}NO_4$	71,78	8,78	3,48	158—6	23,88 23,81	23,88		Limp 5—7
NO_2	H	—	4[e]	60,1	68,30 68,23	7,76 7,81	7,34 7,29	$C_{22}H_{30}N_2O_4$	68,37	7,82	7,24	202—4	24,38 24,27	24,02	12—14 (0,05—0,06)	Limp, 4—6 (spasmodic, 0,15—0,2)
CH_3O	CH_3O	—CH=CH—	2	87,0	71,91 72,26	8,46 8,51	3,58 3,70	$C_{24}H_{33}NO_4$	72,15	8,32	3,50	207—9	23,76 23,62	23,44	8—9	Limp 5—6
CH_3O	CH_3O	—CH=CH—	3	73,6	72,40 72,56	8,66 8,77	3,60 3,72	$C_{25}H_{35}NO_4$	72,66	8,53	3,40	216—8	22,83 23,07	22,85	9—10	Limp 3—4
CH_3O	CH_3O	—CH=CH—	4[f]	61,8	72,59 72,62	8,72 8,86	3,59 3,34	$C_{26}H_{37}NO_4$	73,03	8,72	3,27	254—6	22,42 22,62	22,28	7—8 (0,03—0,05)	Limp, 3—4 (spasmodic, 0,15—0,25)

[a]Experiments in a narcotized cat (chloralose 60 mg/kg and urethane 400 mg/kg intravenously). The peripheral section of the sciatic nerve was stimulated by supramaximal square stimuli of frequency 1 stimulus/sec and duration of each stimulus 0.5 msec.

The contractions of the gastrocnemius were recorded in the semiisometric regime.

[b]Hydrochloride, mp 217-218°C, difficultly soluble in water. Found, %: Cl' 10.04, 9.99. Calculated, %: Cl' 10.10.

[c]Hydrochloride, mp 183-185°. Found, %: Cl' 9.52, 9.64. Calculated, %: Cl' 9.75.

[d]Hydrochloride, mp 92-94°. Found, %: Cl' 8.17, 8.33. Calculated, %: Cl' 8.09.

[e]Base, mp 42-43°. Hydrochloride, mp 176-178°, difficultly soluble in water. Found, %: Cl' 8.02, 8.14. Calculated, %: Cl' 8.38.

[f]Hydrochloride, mp 112-114°. Found, %: Cl' 7.44, 7.38. Calculated, %: Cl' 7.64.

Footnote. The results of the tests for the analogous compounds in which the Ad group is exchanged for a CH_3 are given in parentheses.

TABLE 3. Effect of Nitrogen Substituent on the Character of the Paralyzing Action of Monoquaternary Ammonium Compounds

Compound	Nature of paralysis in chicks and intravenous dose (in mg/kg) exerting the paralyzing action
$CH_3\overset{+}{N}(CH_3)_3I^-$ (IXa)	Spasmodic
$CH_3\overset{+}{N}(CH_3)_2(Ad)I^-$ (IXb)	Limp 30—40
$HOCH_2CH_2\overset{+}{N}(CH_3)_3I^-$ (Xa)	Spasmodic 50—60
$HOCH_2CH_2\overset{+}{N}(CH_3)_2(Ad)I^-$ (Xb)	Limp 40—60
$CH_3COOCH_2CH_2\overset{+}{N}(CH_3)_3Cl^-$ (XIa)	Spasmodic 0,10—0,15
$CH_3COOH_2CH_2\overset{+}{N}(CH_3)_2(Ad)I^-$ (XIb)	Limp 40—50

If the value of n is compared, then for the adamantyl derivatives which were tested (in contrast to the trimethylammonium derivatives), the number of methylene groups in the amino alcohol portion of the molecule does not play a significant role. When n=2, 3, or 4 the activity of the monoquaternary ammonium salts of the alkamine esters of benzoic and cinnamic acids is of the same order. The introduction of a nitro group or methoxy groups into the aromatic ring also changes the activity slightly.

In order to study more extensively the found relationship it appeared interesting to examine what effect the presence of the adamantyl group exerted on the mechanism of action of other cholinomimetics which were monoquaternary ammonium salts, and in the first place tetramethylammonium iodide (IXa), choline (Xa), and acetylcholine (XIa) were considered. The synthesis of the adamantyl analog of IXa (IXb) was reported earlier [10]. The adamantyl analog of choline (Xb) was prepared by heating VI with methyl iodide (see above); treating it with acetic anhydride led to the adamantyl analog of acetylcholine (XIb).

The results of the pharmacological tests of compounds (IX-XI) showed that in all cases substitution of a methyl group by an adamantyl group was accompanied by the transformation of the depolarizing substances into nondepolarizing substances with a simultaneous reduction of their activity (Table 3). The observable change in mechanism of action must be linked with the considerable size of the adamantyl group. However, one might rather assume that its high lipophilicity plays the main role in essentially varying both the possibility of the permeation of the substance through the hydrophilic and hydrophobic structures of the subsynaptic membrane and also the conditions of its reaction with cholinoreceptors.

EXPERIMENTAL

The yields and constants for the prepared compounds and their derivatives are given in Tables 1 and 2.*

β-[N-Methyl-N-(1-adamantyl)amino]ethanol (VI). A solution of 20 g of ethylene oxide in 30 ml of methanol was added dropwise at 20° to a solution of 15 g of V in 70 ml of methanol. The temperature of the reaction mixture rose to 40° over the first hour and to 55° over the following hour; it was maintained at this temperature for 30 min, and after this the methanol and excess of ethylene oxide were distilled off in vacuum. The crystalline residue was dissolved in 120 ml of absolute ether and filtered from carbon. After evaporation of the ether 15.1 g of crystals with mp 56-58° were obtained.

Hydrochloride. This was prepared by acidifying a solution of 2 g of VI in 10 ml of ether with an ethereal solution of hydrogen chloride until blue to congo red. The yield was 2.1 g (85.7%).

Methiodide. This was prepared by heating a solution of 2.5 g of VI and 2.2 ml of methyl iodide until the alkaline reaction of the mixture had disappeared (this required about 3 h). The yield was 3.75 g (81%).

γ-[N-Methyl-N-(1-adamantyl)amino]propanol (VII). A solution of 1.8 g of methyl acrylate in 4 ml of methanol was added dropwise to a solution of 3.52 g of V in 6 ml of methanol at a temperature not exceeding 40°; the mixture was left to stand for several days at room temperature. After evaporation of the methanol in vacuum methyl β-[N-methyl-N-(1-adamantyl)amino]propionate remained as a viscous oil. The yield was 4.86 g (92.2%). Found, %: C 71.52, 71.83; H 10.00, 10.03; N 5.61, 5.72. $C_{15}H_{25}NO_2$. Calculated, %: C 71.67; H 10.02; N 5.57.

* Uncorrected melting points and boiling points are given.

The hydrochloride had mp 151-153°. Found, %: C 62.45, 62.61; H 9.00, 8.99; Cl' 12.57, 12.61. $C_{15}H_{25}HNO_2 \cdot HCl$. Calculated, %: C 62.53; H 9.02; Cl' 12.33.

The prepared ester was dissolved in diethyl ether, 1.52 g of lithium aluminium hydride was added, and the reaction mixture was heated with boiling for 8 h. Then 3 ml of water and 9 ml of tetrahydrofuran was added with cooling, the mixture was boiled for a further 30 min, the precipitate was filtered off and after distillation of the solvent in vacuum 3.45 g (81%) of VII was obtained as a colorless oil.

δ-[N-Methyl-N-(1-adamantyl)amino]butanol (VIII). A solution of 2.65 g of δ-brombutyl acetate [11] and 4.46 g of V in 40 ml of toluene was heated with boiling and stirring for 15 h. The precipitate of hydrobromide of V which separated was filtered off, the toluene was distilled from the filtrate in vacuum, the oil which remained was dissolved in 5 ml of water, a 40% solution of hydrobromic acid was added until blue to congo red, and the mixture was heated with boiling for 3 h during which the oil had almost completely gone into solution. The solution was extracted with ether, the ether layer was discarded, and the aqueous layer after treatment with carbon was basified with 40% sodium hydroxide solution and saturated with potassium carbonate. The oil which separated was extracted with ether, the ether solution was dried and after distillation of the solvent gave the liquid base of the amino alcohol.

δ-[N-Methyl-N-(1-adamantyl)amino]butyl Benzoate (standard experiment A). To a solution of 0.5 g of VIII in 20 ml of dry dichlorethane at 0-2° was added 0.3 g of benzoyl chloride and the mixture was left to stand for 16 h at room temperature, after this the dichloroethane was distilled off and the residue dissolved in 5 ml of water. The solution was extracted with ether, the ether layer was discarded, the aqueous layer was filtered with carbon, basified with ammonia solution, and the oil which separated was extracted with ether. After drying the extract with magnesium sulfate and evaporating the ether, the base of the alkamine ester was obtained as a viscous oil. The yield was 0.6 g. The hydrochloride was prepared in ether solution and the methiodide in acetone solution.

γ-[N-Methyl-N-(1-adamantyl)amino]propyl 3,4-Dimethoxycinnamate (standard experiment B). Granules of metallic sodium were added to 2.18 g of VII and the mixture was heated gradually to 80° over 40 min while passing dry nitrogen through it. Then 1.08 g of methyl 3,4-dimethoxycinnamate was added and, while continuing to pass nitrogen, the mixture was maintained at a residual pressure of 110-115 mm for 2 h at 80-85° and 2 h at 100°. It was then treated with a 2 N solution of hydrochloric acid until violet to congo red, extracted with ether, the ether layer was discarded, and the aqueous solution saturated with bicarbonate. The oil which separated was extracted with ether, the extract was dried, and after distillation of the solvent 1.1 g (61.8%) of the amino ester was obtained as a viscous oil.

β-[N-Methyl-N-(1-adamantyl)amino]ethyl Acetate Methiodide (XIb). A mixture of 2.1 g of the methiodide of VI and 2 g of acetic anhydride was heated at 140° for 30 min. The obtained melt crystallized on cooling. It was washed with ether and recrystallized from alcohol. The yield was 1.5 g (65.2%) with mp 188-190°. Found, %: C 49.29, 49.22; H 7.35, 7.51; I' 32.60, 32.76. $C_{16}H_{28}INO_2$. Calculated, %: C 48.85; H 7.17; I' 32.27.

LITERATURE CITED

1. A. P. Arendaruk, E. L. Gracheva, A. P. Skoldinov, et al., Khim-Farmats. Zh., No. 4, 20 (1967).
2. D. A. Kharkevich, Pharmacology of Curare-like Substances [in Russian], Moscow (1969), p. 5.
3. E. Philippot and M. J. Dallemagne, Arch. Exp. Path. Pharmak., 220, 100 (1953).
4. P. G. Waser, Pflüg. Arch. Ges. Physiol., 274, 431 (1962).
5. P. G. Waser, Ann. N. G. Acad. Sci., 144, 737 (1967).
6. J. Robertson in: Molecular Biology [Russian translation], Moscow (1963), p. 102.
7. K. Gerson, E. V. Krumkalns, et al., J. Med. Chem., 6, 670 (1963).
8. R. Rapala et al., J. Med. Chem., 8, 580 (1965).
9. R. Muller and H. Auterhoff, Arch. Pharm. (Weinheim) (Mitt. Dtsch. Pharm. Ges.), 39, No. 1 (1969).
10. N. V. Klimova, A. P. Arendaruk, et al., Khim-Farmats. Zh., No. 11, p. 14 (1970).
11. L. M. Smorgonskii and Ya. L. Gol'dfarb, Zh. Obshch. Khim., 10, 1113 (1940).