ANESTHETIC PROPERTIES OF NEW AMPHIPHILIC MESIDIDES

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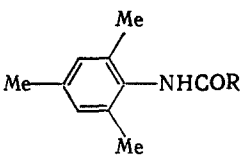
UDC 615.216.2:547.53]038

Compounds having local anesthetic action are distinguished by amphiphilicity and serve as membrane-active preparations, since the phospholipid and often the protein part of the biomembranes have in turn a pronounced amphiphilicity [2, 4, 5].

In order to broaden and extend the known concepts on the relationship between chemical structure and anesthetic activity, we synthesized a series of N-(ω-substituted aminoalkanoyl)-mesidines (Ia-e, IIa, b, IIIa-e) with various lengths of the alkane chain and different amine residues (secondary or tertiary amino group, one or two basic nitrogen atoms, etc.). These compounds can be provisionally divided into three groups.

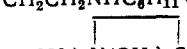
Compounds of the first group (Ia-d) contain in their structure a secondary amino group with varying lipophilicity and non-equal electronic parameters (with and without π-electrons).

Compounds of the second group (IIa, b) are characterized by the presence of a hexamethyleneimine residue and a small variation of the alkane chain length. The third group (IIIa-d) encompasses compounds differing fairly strongly from compounds of the 1-st and 2-nd groups in the electronic and structural characteristics of the nonmesidide part of the molecule.

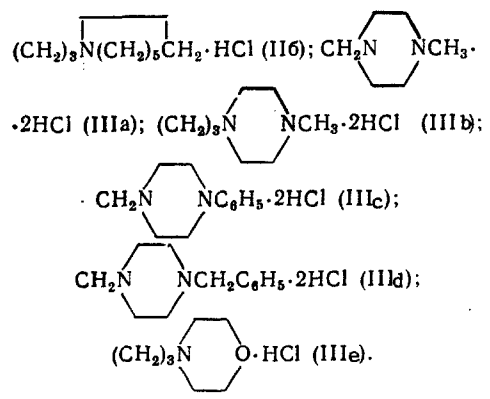


Ia-e IIa, b, IIIa-e

R = $CH_2NHCH_2CH{=}CH_2 \cdot C_4H_6O_4$ (succinate) (Ia); $CH_2CH_2NHCH_2CH{=}CH_2 \cdot HCl$ (Ib); $CH_2NHC(CH_3)_3 \cdot HCl$ (Ic); $CH_2CH_2NHC(CH_3)_3 \cdot HCl$ (Id); $CH_2CH_2NHC_6H_{11}$ cyclo-HCl (Ie);



IIa;



IIб; IIIa; IIIb; IIIc; IIId; IIIe.

TABLE 1. Physicochemical Characteristics of Synthesized Compounds I-III

Compound	Yield, %	mp, °C	Empirical formula
Ia*	79,1 †	161—3	$C_{18}H_{24}N_2O_5$
Ib	72 †	235	$C_{15}H_{23}ClN_2O$
Ic	—	222—4	$C_{15}H_{25}ClN_2O$
Base Ic	80	85—6	$C_{15}H_{24}N_2O$
Id	—	257	$C_{16}H_{27}ClN_2O$
Base Id	94,8	136—7	$C_{16}H_{26}N_2O$
Ie	—	213—5	$C_{18}H_{29}ClN_2O$
Base Ie	86,5	115—6	$C_{18}H_{28}N_2O$
IIa	—	185—7	$C_{18}H_{29}ClN_2O$
Base IIa	83,7	113—5	$C_{18}H_{28}N_2O$
IIb	—	190—2	$C_{19}H_{31}ClN_2O$
Base IIb	78	96,5—7	$C_{19}H_{30}N_2O$
IIIa	—	250—2 (dec.)	$C_{16}H_{27}Cl_2N_3O$
Base IIIa	60	111—2,5	$C_{16}H_{25}N_3O$
IIIb	—	255—6 (dec.)	$C_{18}H_{31}Cl_2N_3O$
Base IIIb	77	93—5	$C_{18}H_{29}N_3O$
IIIc	—	203—6	$C_{21}H_{29}Cl_2N_3O$
Base IIIc	60	125—6	$C_{21}H_{27}N_3O$
IIId	—	253—6	$C_{22}H_{31}Cl_2N_3O$
Base IIId	85	142—4	$C_{22}H_{29}N_3O$
IIIe	—	220—1	$C_{17}H_{27}ClN_2O_2$
Base IIIe	82,5	120—1	$C_{17}H_{26}N_2O_2$

*Succinate.

†The yield given is calculated for a base.

Note. Compounds Ia, IIIc, were recrystallized from alcohol, Ib-e, IIa, b, IIIb-e from isopropanol, bases Ic, e, IIa, b from hexane, and base Id from a mixture of hexane with benzene.

The synthesis of compounds I-III was carried out by standard methods of acylation of mesidine by ω-haloacyl chlorides, followed by the action of the appropriate amines on the intermediate ω-haloacylmesidides.

The structure of compounds I-III was confirmed by the PMR spectra on the example of compounds Ia, c, Id (base) and IIIa (base). In all cases there are signals of two equivalent aromatic protons in the ~7 ppm region, and of three methyl groups in the benzene ring in the 2 ppm region (singlets 3H + 6H). Moreover, the following characteristic signals are also detected (given are compound, solvent, group, ppm): Ia, CF_3COOH, $COCH_2N$ 4.0 (t, J = 5 Hz), and also $(CH_2)_2$ of succinic acid with intensity of 4H, 2.4; Ic, CD_3OD, $C(CH_3)_3$, 1.5, CH_2, 4.1; Id (base), $CDCl_3$, $COCH_2$ and $ArCH_2$, 3.2 and 3.5, C_6H_5, 7.4; IIIa (base), $CDCl_3$, NCH_3, 2.2; $COCH_2N$, 3.2.

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The structure of the compounds was confirmed by elemental analysis and PMR spectroscopy data. The PMR spectra were run on a "Varian T-60" spectrometer (USA), with a working frequency of 60 MHz and using HMDS as internal standard. The individual state of the compounds and the course of the reactions were monitored by TLC on Silufol UV-254 plates (CSSR) in an isopropanol—ether—ammonia, 5:3:1 system of solvents; development in UV light.

General Methods of Preparation of Bases of Aminoalkylcarboxylic Acid Mesidides (I-III).

A. A mixture of 0.014 mole of an ω-chloroalkylcarboxylic acid mesidide and 0.04 mole of allylamine or tert-butylamine is heated for 12 h at 110°C in a steel ampule and is then evaporated in a water aspirator. The residue is dissolved in 50 ml of hot water, shaken with carbon, the filtrate is made alkaline by a saturated solution of potassium carbonate, and extracted with ether. The extracts are dried over anhydrous magnesium sulfate and evaporated to yield compounds Ia-e.

B. A mixture of 0.013 mole of a ω-chloroalkylcarboxylic acid mesidide and 0.039 mole of the corresponding amine in 50 ml of absolute toluene is boiled for 10-12 h, then filtered, the filtrate is washed with water, dried over anhydrous magnesium sulfate, and evaporated to yield compounds Ie, IIa, b, IIIe.

TABLE 2. Relative Activity during Surface Anesthesia by Compounds Ia-e, IIa, b, IIIa-e, Cocaine, and Pyromecaine (M ± m)

Compound	Anesthesia[a,b]		
	time of setting in, min	depth, Regnier index	duration of action, min
Ia[c]	—	—	—
Ib	1,0±0,5	899,0±10,1	28,2±2,6
Ic	4,2±0,6	641,2±5,7	25,4±2,2
Id	1,0±0,2	1251,0±6,3	52,0±3,5
Ie	3,5±1,5	1051,9±14,3	43,5±3,3
IIa	1,0±0,4	1110,0±6,7	38,0±3,6
IIb	1,5±0,6	1213,0±9,4	45,5±4,2
IIIa[c]	—	—	—
IIIb[c]	—	—	—
IIIc[d]	...	...	...
IIId	1,0±0,2	838,0±9,8	30,0±2,5
IIIe[c]	—	—	—
Cocaine	5,0±0,5	590,0±8,7	20,2±2,6
Pyromecaine	1,0±0,5	1300,0±0,0	54,5±6,2

Note. [a]The experiments were carried out on the cornea of rabbit eyes by the Regnier method. [b]Mean data of 8 experiments with a standard error, averaged for 1% solutions. [c]The compound does not cause surface anesthesia. [d]The compound is sparingly soluble in water.

TABLE 3. Relative Activity during Conduction and Infiltration Anesthesia by Compounds Ia-e, IIa, b, IIIa-e, Novocaine, and Trimecaine (M ± m)

Compound	Anesthesia[a,b]			
	depth[b], min	k (experiment/background)	depth[b], min	k, (experiment/background)
Ia	6,3±0,5	1,3	9,1±1,2	2,0
Ib	5,2±0,3	1,3	6,3±0,7	1,4
Ic	7,7±1,4	2,0	12,7±5,4	2,8
Id	5,0±0,5	1,0	3,4±1,9	1,1
Ie	3,8±0,2	1,2	6,3±0,4	1,7
IIa	20,6±0,3	3,3	20,7±0,5	3,5
IIb	14,6±2,8	2,7	16,8±1,9	2,6
IIIa	5,1±0,2	1,1	4,4±0,6	1,1
IIIb	4,2±0,2	1,0	4,9±0,9	1,1
IIIc	5,0±0,2	1,1	6,6±0,7	1,4
IIId	3,8±0,1	1,0	4,1±0,6	1,0
IIIe	5,6±0,4	1,2	6,1±0,5	1,2
Novocaine[c]	6,2±0,3	1,2	7,2±0,8	1,3
Trimecaine	7,8±1,6	1,4	15,8±2,3	3,1

Note. [a]The experiments were carried out on white mice by the Tail-flick method. [b]Mean data of 6 experiments with a standard error averaged for 1% solutions. [c]Data for a 2% solution.

TABLE 4. Relative Activity during Conduction Anesthesia by Compounds IIa, b, Novocaine, and Trimecaine (M ± m)

Compound	Anesthesia[a,b]		
	time of setting in, min	depth[c] (change in the threshold after 30 min), %	duration of action, min
IIa	5,0±0,2	100	360,5±10,5
IIb	4,5±0,5	80	240,0±8,6
Novocaine	10,0±0,4	60	60,5±7,3
Trimecaine	5,2±0,1	100	181,0±4,2

Note. [a]The experiments were carried out on rabbits by the "pain" method. [b]Mean data of 5 experiments with a standard error averaged for 1% solutions. [c]A 1 V increase in threshold was accepted as 20%).

TABLE 5. Relative Activity during Infiltration Anesthesia by Compounds IIa, b, Novocaine, and Trimecaine (M ± m)

Compound	Anesthesia[a,b]		
	time of setting in, min (M ± m)	depth[c] (change in the threshold after 30 min), %	duration of action, min
IIa	3,5±0,5	100	270,0±15,5
IIb	5,8±0,3	60	130,0±6,4
Novocaine	7,5±1,2	60	60,0±2,4
Trimecaine	1,0±0,6	100	171,0±3,8

Note. [a]The experiments were carried out on rabbits by the "pain" method. [b]Mean data of 5 experiments with a standard error averaged for 1% solutions. [c]A 5 V increase in threshold was accepted as 20%).

C. A mixture of 3.15 g (0.0148 mole) of chloroacetic acid mesidide and 4.3 g (0.026 mole) of 4-phenylpiperazine in 50 ml of absolute toluene is boiled for 10 h, and is then filtered. The filtrate is evaporated in a water aspirator. Hexane is added to the residue, and compound IIIc is obtained. Compound IIId is obtained in a similar way.

The succinate $Ia \cdot C_4H_6O_4$ is obtained by treating an ether solution of Ia with a solution of succinic acid in isopropanol.

TABLE 6. Relative Toxicity of Compounds Ia-e, IIa, b, IIIa-e Cocaine, Pyromecaine, Novocaine, and Trimecaine

Compound	Acute toxicity*	
	LD_{50}, mg/kg (intraperitoneal admin.), (M ± m)	relative to cocaine
I a	340,0±8,4	4,2
I b	210,0±10,0	2,6
I c	153,0±5,5	1,9
I d	120,0±4,4	1,5
I e	105,0±4,4	1,3
II a	89,2±6,4	1,1
II b	93,3±5,8	1,2
III a	320,0±12,5	4,0
III b	600,0±10,2	7,5
III c	570,0±12,4	7,1
III d	250,0±8,8	3,1
III e	400,0±10,5	5,0
Cocaine	80,0±5,3	1,0
Pyromecaine	190,0±8,4	2,4
Novocaine	220,0±5,6	2,7
Trimecaine	180,0±11,5	2,2

*The experiments were carried out on mice by the Behren's method.

The hydrochlorides Ib-e·HCl, IIa,b·HCl, IIIe·HCl and dihydrochlorides IIIa-d·2HCl are obtained from the corresponding bases in ether by adding an ethereal solution of hydrogen chloride.

The yields, physical constants and results of the elemental analysis are given in Table 1.

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The general effect, acute toxicity (LD_{50}), the anesthetic and local-irritation properties of the 12 new synthesized compounds Ia-e, IIa,b, IIIa-e in the form of their hydrochlorides were examined.

The experiments were carried out on white mice weighing 18-22 g each and on rabbits weighing 2.5-3 kg each.

The activity of the compounds during surface anesthesia was studied on rabbits by the Regnier method [3] and during conduction and infiltration anesthesia, on mice using the "tail-flick" test and the "pain-producing" method in rabbits [1]. The time of setting in of anesthesia, its depth and duration were determined.

In experiments on mice, a nociceptive stimulation of the tail was applied on the "Analgesia test tail-flick, type 812, Hugo Sachs Electronic" apparatus (GFR). The compounds were administered subcutaneously to the mice in a volume of 0.05 ml from the dorsal side of the tail by means of a microinjector. The beam was successively applied to the distal and proximal parts of the tail, at intervals of 10 sec. In each case, the level of the pain reaction, expressed by the latent period of tail flicking was recorded.

Cocaine and pyromecaine were used as reference preparations in surface anesthesia, and novocaine and trimecaine in the conduction and infiltration anesthesia.

It was found that among the compounds of the first group studied, the derivatives of propionic acid containing a secondary amino group in the structure, in particular, the tert-butyl (Ia) and cyclohexyl (Ie) radicals at the nitrogen atom, and also derivatives of acetic acid with a tert-butyl radical (Ic) are of interest.

Compounds Id and Ie displayed a high activity during the surface anesthesia, and they are 1.9-2.1 times more active than cocaine (Table 2). Compound Ic is 1.4 times more active than trimecaine during conduction anesthesia (Table 3).

Compounds of the 2-nd group, derivatives of propionic and butyric acids with a tertiary amino group, the hexamethyleneimine residue (IIa and IIb), are most active in various types of anesthesia. These compounds cause a 1.8-2 times deeper surface anesthesia than cocaine and are only inappreciably (by a factor of 1.1-1.2) inferior to the pyromecaine preparation, which is highly active in this type of anesthesia (see Table 2).

With respect to the time of setting in of conduction anesthesia and the depth of the effect, compound IIa is not inferior to trimecaine. Both compounds IIa and IIb surpass novocaine with respect to these parameters by 2.5-3 times on mice, and 4-6 times on rabbits, and are active 2-2.5 and 1.3-2 times longer than trimecaine, depending on the method used (Tables 3, 4).

Compound IIa also displays a high activity in infiltration anesthesia. It causes a longer anesthesia than trimecaine (by 1.6 times) and novocaine (by 4.5 times). Compound IIb is somewhat less active in this type of anesthesia, its duration of action being twice as long as that of novocaine (Tables 3, 5).

At the same time, compounds IIa and IIb have a higher (by 2-2.5 times) toxicity than pyromecaine, trimecaine, and novocaine, and in their toxicity approach cocaine (Table 6).

The relatively low-toxic compounds of the 3-rd group with piperazine and morpholine fragments in the structure were found to be less active. None of the compounds display a local irritating action (during conjuctival application).

Thus, from the study of the relationship between the chemical structure, amphiphilicity and pharmacological activity in the series of aminoalkylcarboxylic acid mesidides, the importance for the anesthetic action of the presence of secondary and tertiary amino groups with tert-butyl and cyclohexyl radicals, and hexamethyleneimine residue in their structure has been established.

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