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Abstract

Full Text

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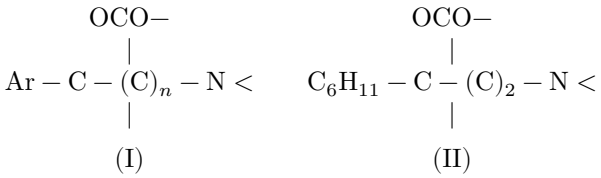
STRUCTURE AND ANESTHETIC ACTION OF AMINOCARBINOL ESTERS

As a result of a systematic investigation in the field of aliphatic-aromatic amino alcohols and their derivatives (I, II)



(I) (II)

a dependence was found of the anesthetic functions of the indicated compounds on the following structural fragments: the length of the carbon chain between oxygen and nitrogen; the position of the carbon atom bonded to the hydroxyl group (secondary and tertiary alcohols); the number of methyl substituents and their position in the chain between the first carbon atom and nitrogen; the structure of the aliphatic and cyclic radicals bonded to the first carbon atom of the chain; the nature of the nitrogen-containing residue; and the character of the acyl.

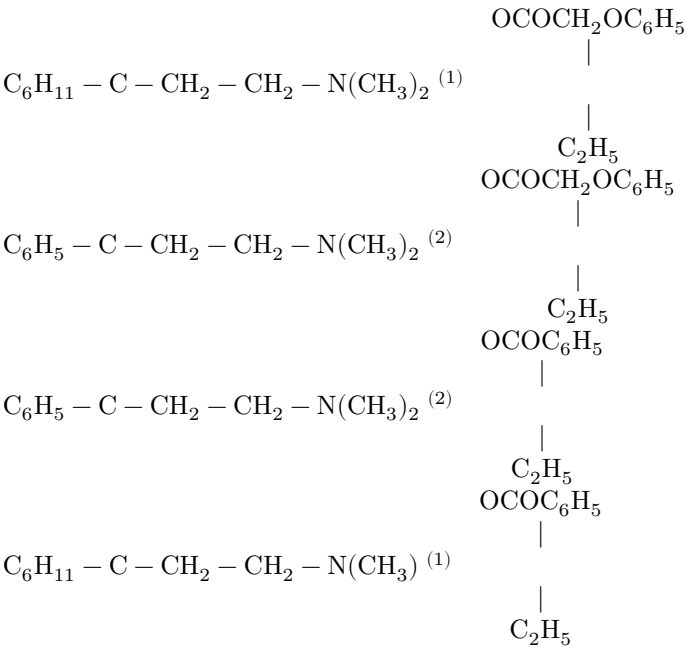
In the course of varying the initially conceived structures, considerable experimental material was accumulated, making it possible to evaluate the degree of participation of each of these fragments in the formation of the physiological activity of the indicated compounds; this made it possible to carry out a directed synthesis of effective anesthetics. Particularly active proved to be the phenoxyacetate of 1-ethyl-1-phenyl-2-methyl-3-dimethylaminopropanol, which exceeds dicaine in potency by more than 9 times (in a 0.025% solution).

From an analysis of this material it follows, first, that the most active esters are derivatives of aminopropanols. Second, these esters contain mainly aliphatic-aromatic acyls. Third, they contain, as a rule, phenyl and ethyl radicals at the first carbon atom (although the phenyl radical may, without great detriment, be replaced by cyclohexyl, provided that phenoxyacetyl is replaced by benzoyl). The fourth condition for activity is the presence in them of a dimethylamino residue. Fifth, branching of the chain between oxygen and nitrogen is very

substantial. In this case it is possible to compensate for the "deficiency" of the methyl radical at C_1 by means of the same radical introduced into position 2. The combination of two methyl radicals in the 2,2-position is very effective and, importantly, imparts to the compounds the ability to withstand sterilization while retaining activity. At the same time, introduction of a methyl group into position 3 does not enhance the anesthetic effect. Also noteworthy is the comparatively greater activity of esters of the β-forms of diastereoisomers than of the α-isomers. Further, all the material also speaks in favor of the advantages of phenoxyacetates.

All these and other facts lead to the conclusion that, within the studied series of compounds, there exist definite combinations of radicals that ensure the maximum anesthetic effect, which may be called a "combination effect." By such an effect one should understand the appearance or enhancement of a definite chemical, in particular physiological, activity in representatives of a given class of compounds as the result of an optimal combination in their molecules of certain kinds of radicals. One can

Table 1*

Formula of the compound(hydrochloride)	Surface-anesthesia index0.5% solution
	555
	1060
	135
	962

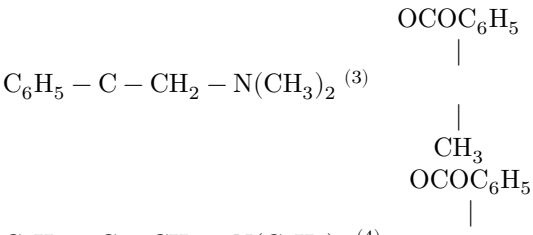
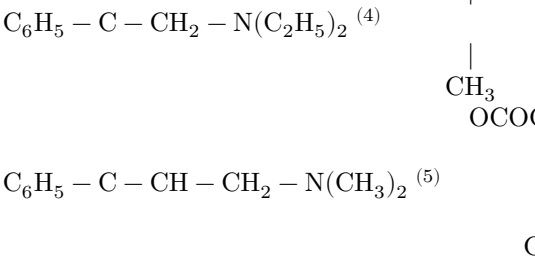
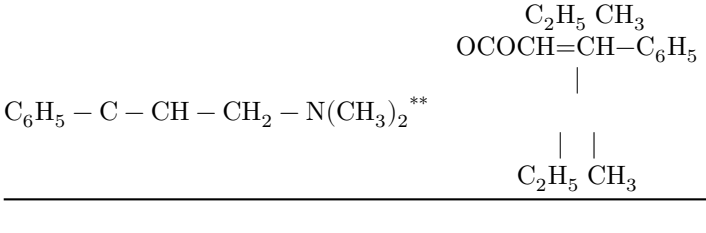
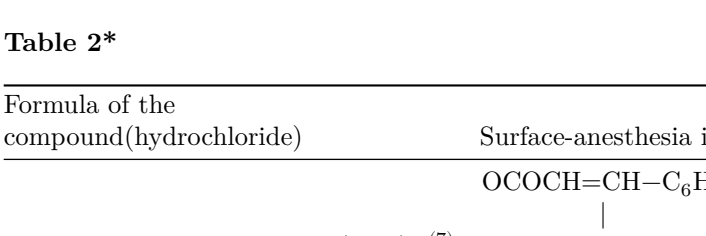
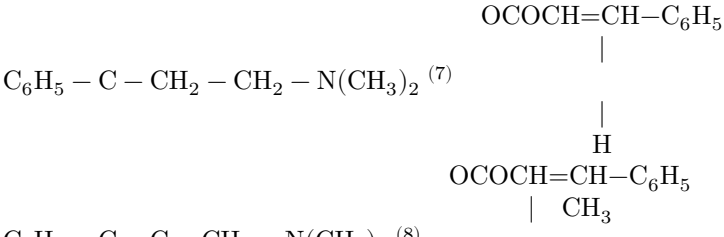
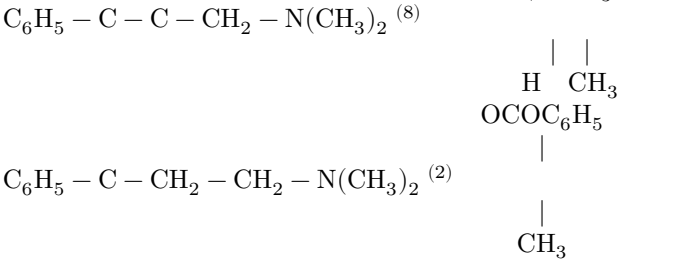
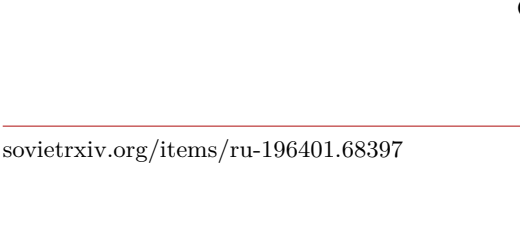
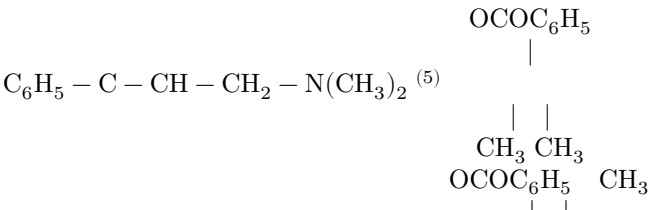
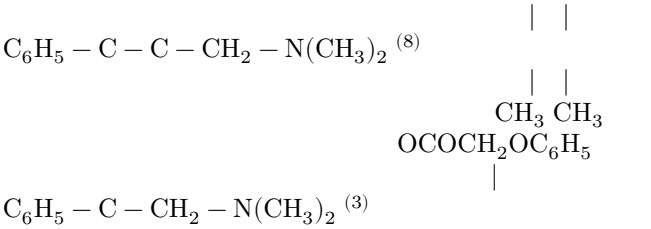
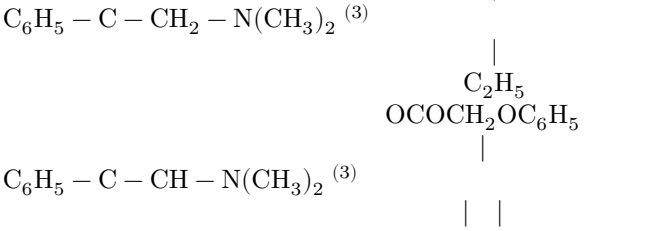
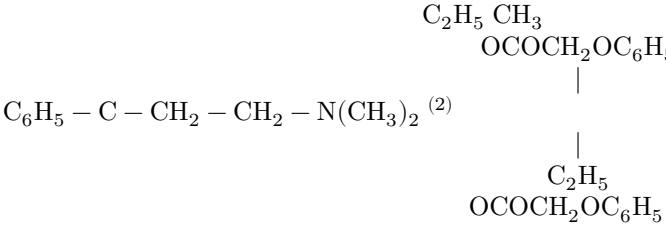
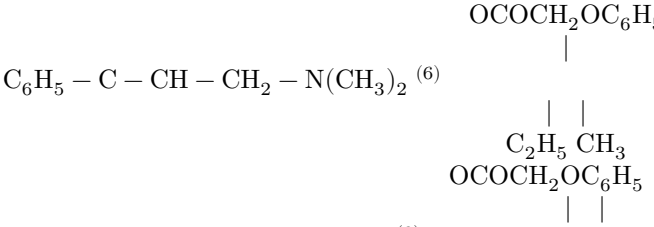
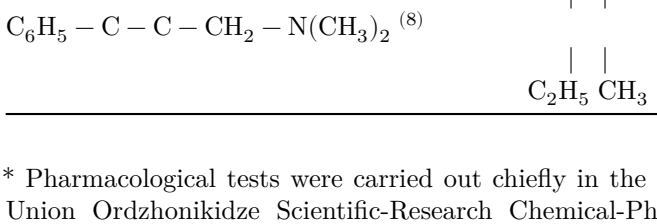
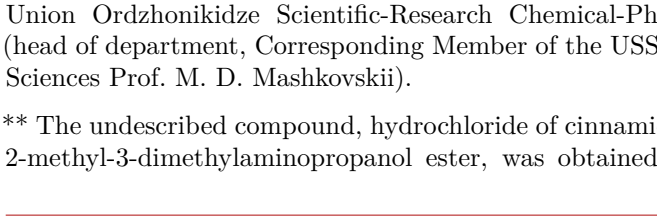
Formula of the compound(hydrochloride)	Surface-anesthesia index0.5% solution
	350
	11
	65
	796

Table 2*

Formula of the compound(hydrochloride)	Surface-anesthesia index0.5% solution
	354
	793
	132

Formula of the compound(hydrochloride)	Surface-anesthesia index0.5% solution
	185
	1216
	350
	883
	1060
	1225
	1300

* Pharmacological tests were carried out chiefly in the laboratories of the All-Union Ordzhonikidze Scientific-Research Chemical-Pharmaceutical Institute (head of department, Corresponding Member of the USSR Academy of Medical Sciences Prof. M. D. Mashkovskii).

** The undescribed compound, hydrochloride of cinnamic acid 1-ethyl-1-phenyl-2-methyl-3-dimethylaminopropanol ester, was obtained in 44% yield from 1-

ethyl-1-phenyl-2-methyl-3-dimethylaminopropanol ([6]) and cinnamoyl chloride (1 : 2) in benzene, m.p. 186–187° (from acetone).

Found, %: C 70.88, 70.96; H 7.98, 8.12; N 3.78, 3.77; Cl 8.82, 8.84.

$C_{23}H_{30}O_2NCl$. Calculated, %: C 71.22; H 7.75; N 3.61; Cl 9.17.

one should distinguish a twofold kind of combination effect: an effect of the first kind, which is achieved by replacing one radical with another analogous to it, and an effect of the second kind, arising as a result of introducing additional radicals into the molecule. The data of Table 1 may serve as an illustration of the effect of the first kind, and those of Table 2 as an illustration of the effect of the second kind.

It seems possible to us to interpret the "combination effects" from the standpoint of the multiplet theory ([9,10]). It may be supposed that local anesthesia occurs as a result of adsorption of anesthetic molecules on the sensory endings of nerve fibers or other elements of the nervous apparatus. As a consequence, they are blocked; the enzymatic cycle ensuring conduction of the nerve impulse is interrupted, owing to which painful reactions do not appear.

For such adsorption to be most effective, both structural and energetic correspondence is required between the anesthetic molecules and the protein structures of the nerve endings. The structures studied correspond to index groups superimposed on the adsorbing surface. The shape of the substituents in the anesthetic molecule should, as far as possible, closely fit the shape of the adsorbing surface alongside the index group, and a kind of surface isomorphism should occur. At the same time, the nature of these substituents should also play a most important role, since the magnitudes of the bond energies upon adsorption depend on it, both as a consequence of the induction effect and as a consequence of the superposition effect.

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Note: Figure translations are in progress. See original paper for figures.