QUATERNARY SALTS OF AMINOALKYL ESTERS OF BENZOIC ACID

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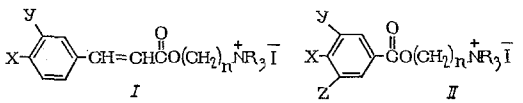
Previously conducted research has shown that monoquaternary salts of aminoalkyl esters of cinnamic acid or substituted cinnamic acids having the general formula (I) possess high curare-like activity. Those compounds prove to be most effective in which the amino-alcohol residue contains four carbon atoms (n = 4) and the substituents at the quaternary nitrogen atom are methyl groups; the activity rises upon transition to the corresponding derivatives of methoxycinnamic acids (I, X = CH_3O, Y = H or CH_3O) or of p-nitrocinnamic acids (I, X = NO_2) [1].



I II

As a result of further study of the connection between structure and action in this series, it was established that even some of the most simply structured compounds, namely, quaternary salts of aminoalkyl esters of benzoic acid (II), are also active myorelaxants. Aminoalkyl esters of aromatic acids have been widely investigated in connection with the search for local anesthetics among them, as well as for substances with atropine-like or antihistamine activity (see [2], for example). However, the curare-like action of the corresponding quaternary ammonium salts has not been discussed in the literature. For comparative tests we have synthesized a number of methiodides of ω-dimethylaminoalkyl esters (II) which differ in the length of the alkyl residue in the amino-alcohol part of the molecule. The dimethylaminoalcohols (n = 2-11), prepared by the method described in [3], were brought into reaction in dichloroethane medium with equimolecular amounts of acid chlorides of benzoic or substituted benzoic acids; the aminoalkyl ester bases were separated from the aminoalcohols which had not entered into reaction by fractional addition of ammonia, after which they were already analytically pure in most cases, even without distillation. The quaternary salts were prepared by warming a mixture of the appropriate reagents in acetone. Melting points, analytical data, and test results for the compounds synthesized are given in Table 1.

As follows from the pharmacological testing data,the curare-like activity of the (II) compounds, exactly as in the series of related derivatives of cinnamic acid (I), has a maximum at n = 4; compounds with a smaller or larger value of n are less active. It is possible that the curare-like action of the compounds under study was not detected up till now because esters with n = 2 or n = 3 were mainly studied previously. On transition to corresponding derivatives of p-substituted benzoic acids, it was noted that the introduction of electron-acceptor groups, for example, a nitro group (as for the cinnamic acid derivatives), into an aromatic ring causes a further elevation of activity, while the presence of one or several methoxy groups leads to a certain decrease in activity; compounds of type II [n = 4, X = $SO_2N(CH_3)_2$, Y = Z = H, R = CH_3] proved to be most active. In mechanism of action, all the compounds tested pertain basically to the depolarizing curare-like media. The compounds with n = 6-11 apparently exert a mixed action.

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TABLE 1. Dimethylaminoalkyl Esters of Benzoic Acids and Their Methiodides (II, R=CH_3)

X	Y	Z	n	Esters: yield (in %)	Esters: found (in %) C	Esters: found (in %) H	Esters: empirical formula	Esters: calculated (%) C	Esters: calculated (%) H	Methiodides: mp (in deg)	Methiodides: found (in %) I^-	Methiodides: calc. (%) I^-	curare-like activity (in mg/kg, intravenous dose)[a]
H	H	H	2	75,0[b]	68,52; 68,40	7,90; 7,77	$C_{11}H_{15}NO_2$	68,37	7,82	238—40	37,76; 37,90	37,87	8—9
H	H	H	3	70,0[c]	69,53; 69,78	8,19; 8,32	$C_{12}H_{17}NO_2$	69,53	8,26	186—8	36,67; 36,76	36,34	2,5—4
H	H	H	4	72,2	70,44; 70,62	8,69; 8,68	$C_{13}H_{19}NO_2$	70,64	8,65	201—3	34,59; 34,70	34,94	0,2—0,25
H	H	H	5	71,3	71,13; 71,39	9,01; 8,94	$C_{14}H_{21}NO_2$	71,40	8,99	148—50	34,10; 34,20	33,64	2—3
H	H	H	6	80,0[d]	72,00; 71,94	9,00; 8,93	$C_{15}H_{23}NO_2$	72,26	9,29	171—2	32,39; 32,46	32,43	0,7—0,8
H	H	H	7	89,0[e]	73,14; 73,02	9,60; 9,40	$C_{16}H_{25}NO_2$	72,95	9,57	172—4	31,42; 31,58	31,30	4—6
H	H	H	9	83,0	74,10; 73,90	10,01; 9,87	$C_{18}H_{29}NO_2$	74,20	10,03	179—80	29,23; 29,47	29,27	3—5
H	H	H	11	79,0	74,88; 75,14	10,20; 10,31	$C_{20}H_{33}NO_2$	75,18	10,41	167—8	27,66; 27,40	27,55	9—10
Cl	H	H	4	78,3	60,75; 60,70	7,16; 7,11	$C_{13}H_{18}ClNO_2$	61,05	7,09	199—200	32,17; 32,06	31,92	0,3—0,35
NO_2	H	H	4	71,4	58,47; 58,37	6,75; 6,85	$C_{13}H_{18}N_2O_4$	58,63	6,81	204—6	31,36; 31,47	31,09	0,05—0,06
$(CH_3)_2NSO_2$	H	H	4	77,14[f]	54,87; 55,11	7,42; 7,50	$C_{15}H_{24}N_2O_4S$	54,82	7,67	234—6	26,82; 26,85	26,98	0,04—0,05
CH_3O	H	H	4	81,2	67,01; 67,15	8,53; 8,64	$C_{14}H_{21}NO_3$	66,90	8,42	182—4	32,60; 32,71	32,27	0,4—0,45
CH_3O	CH_3O	H	4	71,4[g]	63,89; 63,98	8,36; 8,33	$C_{15}H_{23}NO_4$	64,03	8,24	184—6	30,25; 30,17	29,98	0,4—0,45
CH_3O	CH_3O	CH_3O	4	72,6	61,23; 61,45	8,10; 8,23	$C_{16}H_{25}NO_5$	61,07	8,09	146—8	28,03; 27,98	28,00	0,45—0,50

[a] The doses were determined at which the substances block transmission of a stimulus from the sciatic nerve to the calf muscle of a narcotized cat (urethane, 400 mg/kg with chloralose, 60 mg/kg, intravenously). A peripheral section of the nerve was irritated with supramaximal orthogonal stimuli at a frequency of 1 stimulus/sec and a duration of each stimulus of 0.5 μ sec. Muscle contractions were recorded under a semi-isometric regime.

[b] Lit. [4]: hydrochloride, mp 148°.

[c] Lit. [5]: bp 159-160° (20 mm).

[d] bp 144-145° (2.5 mm); n_D^{20} 1.5014. Hydrochloride; mp 88-90°. Found %: Cl^- 12.35; Calculated, %: Cl^- 12.41.

[e] bp 162-165° (2.5 mm); n_D^{20} 1.5096. Hydrochloride; mp 93-95°. Found, %: Cl^- 11.60; 11.71. Calculated, %: Cl^- 11.83.

[f] mp 93-95°. Hydrochloride: mp 176-177°. Found, %: Cl^- 9.67; 9.69. Calculated, %: Cl^- 9.71.

[g] bp 150-152° (2mm); n_D^{20} 1.5350. Hydrochloride: mp 151-153°. Found, % Cl^- 11.48; 11.65. Calculated, % Cl^- 11.15.

The compounds under examination approach the most effective curare-like compounds from the group of bis-quaternary ammonium salts in activity, but act briefly, which may be caused both by their monoquaternary structure and also by fast hydrolysis of the ester group in the organism. The reasons for their high activity, unusual for monoquaternary salts, are not too clear. It might be suggested that the carbonyl group carbon atom which carries a partial positive charge is a second positive center in the compounds under study, which intensifies their fixation in receptors. However, the presence of two positive centers separated by five atoms in the molecule usually does not lead to the appearance of curare-like activity. Moreover, in similarly structured cinnamic acid derivatives it has been shown [1] that transition to the corresponding hydrocinnamic acid derivative considerably reduces activity, although both positive centers are not involved thereupon. It is preferable to assume that the second positive center is a partial positive charge in the aromatic nucleus, created by the presence of an electron-acceptor group or by conjugation with a carbonyl group and located at a distance of 9-11 atoms from the ammonium center [4, 5]. On transition to the hydrocinnamic acid derivative, the conjugation is destroyed, because of which there can be a reduction in activity.

By the reaction of 4-dimethylamino-1-butanol methiodide with acetic anhydride the methiodide of 4-dimethylaminol-1-butyl acetate was prepared; this is a homolog of acetylcholine. In a dose of 0.35-0.45 mg/kg, this compound caused spastic paralysis in chicks. For comparative tests, we also synthesized a quaternary salt of a structure like ester II (n = 4), but containing an amide group instead of the ester group, namely, 4-dimethylaminobutylbenzamide methiodide. The curare-like activity of this substance was 3 to 4 times smaller than that of the corresponding ester.

EXPERIMENTAL

The starting α, ω-dimethylamino alkanols were prepared by the method of [3].

Preparation of Dimethylaminoalkyl Esters of Unsubstituted and Nuclearly Substituted Benzoic Acids

To a solution of 0.1 mole of the α, ω-dimethylamino alkanol in 100 ml of dichloroethane was added, at 3 to 5°, a solution of an equimolecular amount of the appropriate acid chloride in 100 ml of dichloroethane. The reaction mixture was allowed to stand overnight at room temperature; 50 ml of water was added, the dichloroethane layer was separated, and it was extracted three times (with about 25 ml) with 5% hydrochloric acid solution and once with 25 ml of water. The combined water and acid extracts were treated with charcoal, and a 25% ammonia solution was added to the filtrate to pH 9.0; the oil which separated was extracted with ether, the ether extract was dried with magnesium sulfate, and after evaporation of the ether the aminoalkyl ester remained in the form of a viscous mass. For purification, it was either distilled under vacuum or was dissolved in hydrochloric acid and again liberated with ammonia. In both cases, the substance obtained (a thick oil) showed satisfactory results on analysis (see Table 1).

The hydrochloride was prepared by the action of an ethereal hydrogen chloride solution on an ether solution of the aminoalkyl ester. The hydrochloride was purified by recrystallization from a mixture of alcohol and ethyl acetate.

Methiodides were prepared by mixing the aminoalkyl esters with excess methyl iodide in acetone solution. In some cases heating the mixture for 2 or 3 h was required to cause disappearance of the alkaline reaction. For analysis, the methiodides were recrystallized from methanol or aqueous acetone.

4-Dimethylamino-1-butyl Acetate Methiodide. A mixture of 0.01 mole of 4-dimethylaminol-1-butanol methiodide and 0.03 mole of acetic anhydride was heated in an oil bath for 20 min at 170°. The melt, which crystallized on cooling, was washed with ether and was recrystallized from a mixture of alcohol and ethyl acetate. Yield, 70.1%; mp, 145-147°. Found, %: C 36.23, 36.37; H 6.71, 6.75; I 42.3, 42.5; N 4.61, 4.65. $C_9H_{20}INO_2$. Calculated, %: C 35.88; H 6.69; I 42.14, N 4.65.

N-(4-Dimethylamino-1-butyl)benzamide. By the action of potassium cyanide, 1-bromo-3-chloropropane was converted into 4-chlorobutyronitrile [6], which was transformed into 4-dimethylaminobutyronitrile by heating with dimethylamine in a tube at 100° [7]; the latter compound was reduced with lithium aluminum hydride to give 4-dimethylamino-1-butylamine, bp 62-64° (22 mm), n_D^{20} 1.4380.

The reaction of 4-dimethylamino-1-butylamine with benzoyl chloride and isolation of the dimethylaminobutylamide were carried out under the same conditions as in the preparation of the ester bases (see

above); bp 174-175° (2 mm); yield, 68%. Found, %: N 12.85, 12.89, $C_{13}H_{20}N_2O$. Calculated, %: N 12.71. Methiodide: mp 156-158° (from aqueous acetone). Found, %: I^- 35.48, 35.50. $C_{14}H_{23}IN_2O$. Calculated, %: I^- 35,03.

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