6. M. L. Crosley, J. B. Allison, R. P. Parker, et al., Proc. Soc. Exp. Biol. Med., 83, 438 (1953).
7. I. D. Neklesova and N. V. Egorova, Dokl. Akad. Nauk SSSR, 154, 155 (1964).
8. N. P. Grechkin and L. N. Grishina, Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1898 (1974).
9. K. A. Gar, Methods of Testing Toxicity and Effectiveness of Insecticides [in Russian], Moscow (1963).
10. P. V. Popov, Khim. Selsk. Khoz., No. 10, 72 (1965).
11. M. L. Belen'kin, Elements of the Quantitative Evaluation of Pharmacological Effect [in Russian], Leningrad (1963), p. 81.
12. V. G. Malakhovskii, A. A. Berkovich, and V. G. Prozorovskii, Farmakol. Toksikol., No. 3, 336 (1963).
13. K. V. Nikonorov, I. D. Neklesova, E. A. Gurylev, et al., Zh. Obshch. Khim., 46, 560 (1976).

AMINO ACID AND PEPTIDE DERIVATIVES OF AMINES

I. SYNTHESIS AND PROPERTIES OF CHOLINE ESTERS OF α- AND ω-AMINO ACIDS

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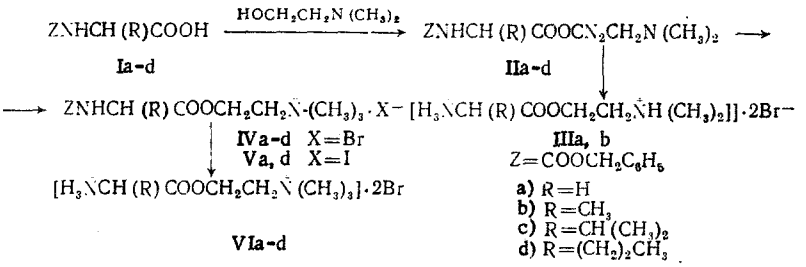
The important physiological role of acetylcholine as a nervous excitation mediator [1] has served as the basis for the synthesis of numerous analogs of this biogenic amine. Choline esters are known of various aliphatic and aromatic acids, which, as a rule, display definite biological activity [2-5].

On this plane the interest of investigators in synthesis of choline esters of natural amino acids is natural. Methods for the synthesis of these compounds have not been fully worked out, although some of them have valuable pharmacological properties [6, 7]. Various groups of researchers have prepared choline esters of glycine [8, 9], L-alanine [9], L-valine [9], L-glutamic acid [7, 9], and of some other α- and ω-amino acids [9, 10]. A number of works have been published in which the synthesis of dialkylaminoethyl esters of N-protected amino acids has been described, but only in the last of them is the synthesis of the choline ester of glycine reported [8].

The objective of the present work was the synthesis of previously undescribed amino acid derivatives of choline and the development of a reasonable method of preparing them. We have synthesized salts of the choline esters of glycine (VIa), L-alanine (VIb), L-valine (VIc), D-norvaline (VId), β-alanine (XIIa), and γ-aminobutyric (XIIb) and ε-aminocaproic (XIIc) acids by Schemes 1 and 2.

Scheme 1

Synthesis of choline esters of α-amino acids



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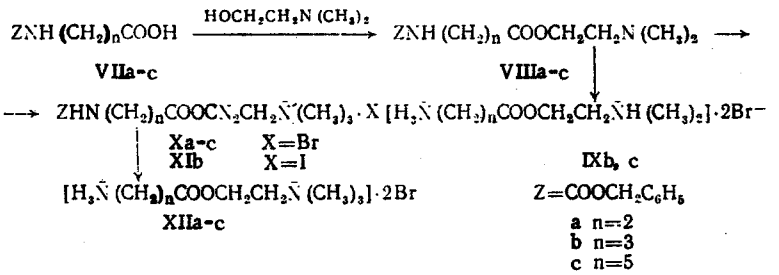
Scheme 2

Synthesis of choline esters of ω-amino acids

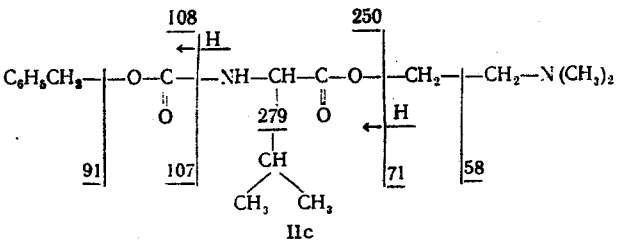


The dimethylaminoethyl esters IIa-d and VIIIa-c were prepared basically by the method of azeotropic distillation of water [12] on boiling the N-carbobenzoxy amino acids with β-dimethylaminoethanol in xylene, in yields of about 70% (Tables 1 and 2, method A). The synthesis of compounds IIa and c and VIIIc by the mixed anhydride method [11, 13] from dimethylaminoethanol and the N-carbobenzoxy amino acids (Ia and c, VIIc) with the aid of isobutyl chloroformate proved to be less effective (Table 2, method B). Upon the action of hydrogen bromide in glacial acetic acid on esters II and VIII, only the dihydrobromides of the corresponding esters of glycine (IIIa), L-alanine (IIIb), γ-aminobutyric acid (IXb) and ε-aminocaproic acid (IXc) were isolated in pure form; the analogous derivatives of the remaining amino acids proved to be very hygroscopic. The esters of the N-carbobenzoxy amino acids and choline bromide (IVa-d and Xa-c) were prepared by the reaction of methyl bromide with the esters II and VIII. It should be noted that all the methobromides except IVa proved to be extremely hygroscopic and therefore were brought into further reaction without isolation and purification. On reaction of esters II and VIII with methyl idodide in absolute alcohol or acetone, as in the method of [12], only the methiodides Va and d and XIb were isolated, due to the hygroscopicity of the remaining analogous derivatives.

By the action of hydrogen bromide in glacial acetic acid on the methobromides IV and X we synthesized the hydrobromides of esters of the unprotected amino acids and choline salts (VIa-d and XIIa-c) (Table 3).

Structures of all the compounds prepared were confirmed by data from IR, NMR, and mass spectra. In the IR spectra of the dimethylaminoethyl esters of N-carbobenzoxy-glycine (IIa), -L-alanine (IIb), -L-valine (IIc), and -ε-aminocaproic acid (VIIIc) there are absorption maxima at 1760-1740 and 1725-1695 cm^{-1}, which are assignable to the ester and amide carbonyls, respectively. It should be noted that the frequencies of the stretching vibrations of the NH of the amide group in compounds IIa and b and VIIIa are in the 3430-3410 cm^{-1} region. After removal of the N-protective groups in compounds III, VI, IX, and XII the absorption maxima in the 1725-1680 cm^{-1} region are absent but the absorption in the 1760-1740 cm^{-1} region is retained, which indicates the presence of an ester carbonyl and the absence of an amide bond in the molecule.

In the mass spectra of compounds IIa-c and VIIIb and c, peaks are observed for molecular ions whose mass numbers correspond to the proposed structures (IIa, 280; IIb, 294; IIc, 322; VIIIb, 308; VIIIc, 336). The molecular ion peaks in these esters have a very low intensity, and in some of them (IId and VIIIa) they are not observed at all, which is apparently caused by the efficiency of decomposition to form the stable fragments $CH_2 = N^+(CH_3)_2$ (m/e 58), $CH_2 = CH\text{-}N(CH_3)_2^+$ (m/e 71), $C_6H_5CH_2^+$ (m/e 91), $C_6H_5CH_2O^+$ (m/e 107), and $C_6H_5CH_2OH^+$ by the scheme



IIc

In the spectrum of IIc, moreover, due to the efficiency of charge localization upon elimination of the isopropyl group, an ion peak for $[M - CH(CH_3)_2^{\cdot}]^+$ is observed, plus ions having m/e equal to 250 and 206, caused by stepwise breakup of the molecule as shown in the scheme. It is interesting to note that the ion having m/e = 206 decomposes further with elimination of CO_2, which is accompanied by migration of the benzyl group and formation of a fragment having the mass number 162.

TABLE 1. NMR Spectra of Dimethylaminoethyl Esters of N-carbobenzoxy-α- and ω-Amino Acids

Compound	Choline fragment			Amino acid fragment			
	$N(CH_3)_3$ (singlet)	OCH_2 (multiplet)	NCH_2 (multiplet)	α-CH, CH_2	β-CH, CH_2, CH_3	γ-CH, CH_3	ε-CH_3
IIIa	2.97	4.63	3.59	4.04 (s)	—	—	—
IIIb	2,98	4.63	3,59	4.32 (qu)	1.58 (d)	—	—
Va	3,11	4,56	3.65	3,97 (s)	5,10 (s) (CH_2 in benzyl)	7,13 (s) (aromatic protons)	—
VIa	3,24	4,60	3.83	4,05 (s)	—	—	—
VIb	3,24	4,77	3,84	4,31 (qu)	1,58 (d)	—	—
VIc	3,24	4,77	3,84	4,18 (d)	—	1,05 (2×d)	—
VId	3,23	4,65	3.82	4,27 (tr)	1,92 (m)	1,44 (m)	0.92 (tr)
XIIa	3,23	4,62	3,83	2.91 (tr)	3,32 (tr) ÷	—	—
XIIb	2,98	4,45	3,53	2.61 (tr)	1,97 (m)	3,10 (tr)	—
XIIc	3,22	4,57	3,76	2.47 (tr)	1,37—1,87 (m) (β, γ, δ-CH_2)	—	3.00 (tr)

Note. s) Singlet; d) doublet; tr) triplet; qu) quartet; m) multiplet.

TABLE 2. Dimethylaminoethyl Esters of N-carbobenzoxy-α- and ω-Amino Acids

Compound	Yield, %		Found, %			Empirical formula	Calculated, %		
	A		C	H	N		C	H	N
IIa	76.4	23.8	60.4	7,21	9,71	$C_{14}H_{20}N_2O_4$	59,99	7,19	9,99
IIb	78.0	—	61.64	7,22	9,13	$C_{15}H_{22}N_2O_4$	61,22	7,53	9,52
IIc	81,3	35	63,60	8,09	8.31	$C_{17}H_{26}N_2O_4$	63,31	8,13	8,69
IId	83,0	—	63.70	7,96	8,76	$C_{17}H_{26}N_2O_4$	63,31	8,13	8,69
VIIIa	60,0	—	61.67	7,23	9,25	$C_{15}H_{22}N_2O_4$	61,22	7.53	9,52
VIIIb	70,0	—	61,72	7,76	9,18	$C_{16}H_{24}N_2O_4$	62,30	7,84	9,30
VIIIc	74.4	50	64,6	8,25	7.89	$C_{18}H_{28}N_2O_4$	64.27	8,41	8,30

TABLE 3. Dimethylaminoethyl Esters of α- and ω-Amino Acids and Their Quaternary Salts

Compound	Yield,* %	m.p.,† deg	$[\alpha]_D^{20}$, deg (c 1,0)	Found, %		Empirical formula	Calculated, %	
				Hal	N		Hal	N
IIIa	65	195—8	—	52.91	9.13	$C_6H_{14}N_2O_2 \cdot 2HBr$	51,90	9,10
IIIb	71,7	136—9	—4	49,98	8.26	$C_7H_{16}N_2O_2 \cdot 2HBr$	49,63	8,70
IVa	58,4	118—121	—	21.48	7,49	$C_{15}H_{23}BrN_2O_4$	21,38	7,46
Va	68,7	195—8	—	—	—	—	—	—
Vd	41,2	95—97	—2,3	27.63	6,20	$C_{18}H_{29}IN_2O_4$	27,40	6,05
VIa	73,0	257—9	—	50,53	8,93	$C_7H_{17}BrN_2O_2 \cdot HBr$	49,60	8,70
VIb	17,3	213—6	—3,4	48,03	8.74	$C_8H_{19}BrN_2O_2 \cdot HBr$	47,60	8,32
VIc	20	229—232	—1.2 (c, 0.5)	44.52	8,11	$C_{10}H_{23}BrN_2O_2 \cdot HBr$	44,0	7,7
VId	66	120—3	—2.0	44.08	7,73	$C_{10}H_{23}BrN_2O_2 \cdot HBr$	44,0	7,7
IXb	82,0	173,5—5	—	47,76	8.10	$C_8H_{16}N_2O_2 \cdot 2HBr$	47,60	8,32
IXc	72,0	169—172 (dec.)	—	44,36	8,02	$C_{10}H_{22}N_2O_2 \cdot 2HBr$	43,90	7,80
XIb	81.6	123—5	—	28.68	6.20	$C_{17}H_{27}IN_2O_4$	28,20	6,22
XIIa	33,2	185—7	—	47.54	8,23	$C_8H_{19}BrN_2O_2 \cdot HBr$	47,60	8,32
XIIb	65	158—160	—	46.02	8.31	$C_9H_{21}BrN_2O_2 \cdot HBr$	45,57	8,05
XIIc	70	127—130	—	41.24	6,82	$C_{11}H_{25}BrN_2O_2 \cdot HBr$	40,80	7,14

*Yields of all compounds except VIa were calculated on II or VIII; the yield of VIa was calculated on IVa.

†According to the literature, the m.p. of IIIa is 189-191° [11] or 186-187° [13]; that of Va, 110-112° [12]; of VIa, 249-251°; of VIb, 212-215°; of VIc, 210-251° [9].

Characteristic signals are observed in the NMR spectra, corresponding to the structures of compounds IIIa and b, Va, VIa-d, and XIIa-c (see Table 1).

The compounds obtained were tested for psychotropic and anticonvulsive activity by their effect on the behavior of male mice 20-22 g in weight, on the duration of chloral hydrate and hexenal sleep (60 mg/kg), and on hyperkinesis and convulsions caused by maximum electric shock (MES; 50 mA, 0.2 sec, 50 Hz). Moreover, we studied the effect of the substances on an isolated segment of the small intestine of rats, on the spontaneous contracting activity and on the effects of acetylcholine (10^{-6} mole/liter). The substances studied did not display psychotropic or cholinergic activity. In the MES test they exerted a weak anticonvulsive action. Substances VIa and VIb exerted a hypothermal action.

The authors express their gratitude to Professor A. S. Saratikov, director of the department of pharmacology of the Tomsk medical institute, for testing the compounds synthesized.

EXPERIMENTAL

The IR spectra were recorded on a UR-10 instrument in vaseline oil; the NMR spectra, on an INM-4H-100 instrument in D_2O, with tert-butyl alcohol as an internal standard (δ = 1.23 ppm); mass spectra, on an MKh-1303 instrument provided with a system for direct introduction of the sample into the source, ionizing voltage, 30 eV. The chemical purity of the compounds prepared was checked by thin-layer chromatography on plates of Silufol UV_{254} in the following systems: acetone and acetone–chloroform (1 : 8) for the dimethylaminoethyl esters of the N-carbobenzoxy amino acids (the chromatograms were developed with UV light and iodine); and benzene–butanol–aqueous ammonia (1 : 4 : 1) and isopropanol–water (7 : 3) for the esters of amino acids which were not protected on nitrogen (developed with iodine vapor). Specific rotation was determined in methanol, in an A1-SPU-M spectropolarimeter. Melting points are uncorrected; they were determined on a Kauffler block.

β-Dimethylaminoethyl Esters of N-Carbobenzoxy Amino Acids (II, VIII). A. A mixture of 0.02 mole of the acid and 0.04 mole of β-dimethylaminoethanol in 100 ml of absolute xylene was boiled under reflux with a Dean–Stark trap for 15-18 h; the mixture was cooled; the residue was washed out with 100 ml of benzene into a separatory funnel; it was washed with a 2.5% sodium bicarbonate solution (2 × 25 ml); then washed repeatedly with water to pH 7.0; it was dried and evaporated; and compounds II or VIII were obtained (see Table 2). B. To a mixture of 0.04 mole of I and 6 ml (0.04 mole) of triethylamine in 30 ml of absolute toluene at −10°, with stirring, was added dropwise a solution of 3 ml (0.04 mole) of isobutyl chloroformate in 5 ml of absolute toluene which had been cooled to −10°; the mixture was stirred for 20 min; and a solution of 4 g (0.04 mole) of β-dimethylaminoethanol in 5 ml of absolute toluene which had been chilled to −10° was added; the mixture was stirred for another 20 min at −10°; it was allowed to stand overnight at 20°; and it was worked up similarly to method A; compounds IIa and c, and VIIIc were so obtained (see Table 2).

Dihydrobromides of Dimethylaminoethyl Esters of Amino Acids (III, IX). To 0.005 mole of II or VIII was added 10 ml of a 28% solution of hydrogen bromide in glacial acetic acid; the mixture was allowed to stand at about 20° for 40 min; 100 ml of absolute ether was added, after 2 h (at about 0°) the precipitate was filtered off; it was washed with a mixture of absolute alcohol and ether (1 : 1) and then with absolute ether, and was reprecipitated from a mixture of absolute alcohol and ether; compounds III or IX were so obtained (see Table 3).

Dimethylaminoethyl N-Carbobenzoxyglycinate Methobromide (IVa). Through a solution of 0.5 g (0.003 mole) of IIa in 15 ml of absolute acetone was passed gaseous methyl bromide for 2 h; thereupon a precipitate began to fall after 30 min, the amount of it increasing with time. After 12 h at about 0°, the precipitate was filtered off; it was washed with absolute ether, and dried, and 0.4 g of IVa was obtained. From the mother liquor an additional 0.23 g of material was precipitated with absolute ether. In all, 0.63 g (58.4%) of IVa was obtained, m.p. 118-121°.

Methiodides of Dimethylaminoethyl Esters of N-Carbobenzoxy Amino Acids (V, XI). To a solution of 0.005 mole of II or VIII in 20 ml of absolute acetone was added 0.0052 mole of methyl iodide; the mixture was allowed to stand for a day at about 20°, 100 ml of absolute ether was added, after 2 h (at about 0°) the precipitate was filtered off, it was dried in a vacuum desiccator, reprecipitated from absolute alcohol and ether, and V or XI was obtained (see Table 3).

β-Dimethylaminoethyl Esters of Amino Acids, Methobromide Hydrobromides (VI, XII). A. Methyl bromide was passed through a solution of 0.05 mole of II or VIII in 25 ml of absolute acetone or alcohol at about 0° for 20 min; then the ice bath was removed and methyl bromide was passed through for 2-5 h; the mixture

was allowed to stand overnight at about 20°; 100 ml of absolute ether was added; after 2 h (at about 0°) the solvent was decanted from the oily precipitate which had separated, and it was washed by decantation with absolute ether (2 × 30 ml). To the methobromides so obtained, without further purification, was added 10 ml of a 28% solution of hydrogen bromide in glacial acetic acid; after 40 min (at about 20°) 50 ml of absolute ether was added, and the mixture was allowed to stand overnight at about 0°. The precipitate was filtered off and washed with a mixture of absolute alcohol and ether (1 : 1), then with absolute ether, and VI or XII was obtained (see Table 3). B. To 0.4 g of IVa was added 5 ml of a 28% solution of hydrogen bromide in glacial acetic acid, the mixture was allowed to stand at about 20° for 40 min with periodic shaking; 20 ml of absolute ether was added, and the mixture was cooled to about 0°. After 1 h the precipitate was filtered off; it was washed with a mixture of absolute alcohol and ether, then with absolute ether; it was dried under vacuum over calcium chloride, and 0.34 g (73%) of VI was obtained.

LITERATURE CITED

1. M. Ya. Mikhel'son and É. V. Zeimal', Acetylcholine. Molecular Mechanism of Action [in Russian], Leningrad (1970).
2. M. V. Rubtsov, E. S. Nikitskaya, and V. S. Usovskaya, Zh. Obshch. Khim., 26, 130 (1956).
3. A. L. Mndozhoyan, A. A. Sarkisyan, and N. E. Akopyan, Arm. Khim. Zh., 21, 143 (1968).
4. A. S. Lebedeva, A. M. Likhosherstov, V. C. Mitrofanov, et al., Khim. Farm. Zh., No. 1, 26 (1967).
5. O. L. Mndzhoyan and L. M. Toskunina, Arm. Khim. Zh., 21, 311 (1968).
6. I. A. Sytinskii, Gamma-Aminobutyric Acid in the Activity of the Nervous System [in Russian], Leningrad (1972).
7. British patent No. 871234; Chem. Abst., 55, 25783g (1961).
8. O. L. Mndzhoyan and S. A. Kazaryan, Arm. Khim. Zh., 26, 395 (1973).
9. M. Kanaoka and M. Kimura, J. Pharm. Soc. Jpn., 95, 231 (1975).
10. F. F. Foldes and V. M. Foldes, J. Pharmacol. Exp. Ther., 150, 220 (1965).
11. O. L. Mndzhoyan and Ts. E. Agadzhanyan, Arm. Khim. Zh., 22, 1003 (1969).
12. O. L. Mndzhoyan, Ts. E. Agadzhanyan, and N. N. Fradkina, Arm. Khim. Zh., 522 (1970).
13. A. E. Greben', V. F. Martynov, and M. I. Titov, Zh. Obshch. Khim., 38, 664 (1968).

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF N-CINNAMOYL AND β-SUBSTITUTED N-ACRYLOYL DERIVATIVES OF UREA

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The biological activity of acyl ureas as herbicides, retardants [1, 2], and pharmacological agents is known. New heterocyclic compounds may be synthesized on the basis of structural fragments of ureides [7]. Chloroacetylated derivatives of amines and ureas are able to form phosphonium salts with triphenylphosphine [8], which possess antimicrobial properties [9-11].

The aim of the present work was the investigation of the interaction of N-aryl-N'-haloacetylureas with triphenylphosphine and the synthesis of new phosphonium salts and ylides of phosphorus-containing urea fragments. The synthesis was also effected by the Wittig reaction of N-cinnamoyl- and β-substituted N-acryloyl-derivatives of urea which are accessible with difficulty by other routes. The antimicrobial activity of the synthesized compounds was studied.

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