In the rotating-rod test, test compounds were injected in doses of 100, 200, and 400 mg/kg; the greatest myorelaxant action was found for doses of 200 and 400 mg/kg, larger than in the preceding test; moreover, compound II had a bigger effect than I.

In the hot-plate test, neither compound I or II in doses of 25 and 100 mg/kg increased the duration of the latent period. Mice which received the test compounds jumped from the hot plate in the same time as the control animals.

As both I and II are hydantoin derivatives, a class of compounds known to include anticonvulsant agents (diphenine etc.), we studied the effect of I and II on the convulsant action of corazole in mice. Doses of 25 and 500 mg/kg of I and II were given one hour after an injection of corazole (125 mg/kg): neither decreased the intensity and duration of the convulsions, or the toxicity of corazole.

To determine the overall effect and the acute toxicity, suspensions of I and II in Tween 80 were injected into mice in increasingly large doses from 10 to 1000 mg/kg. Neither compound appeared to have any noticeable action on the state or behavior of the mice. Only a small decrease in the general activity of the animals was noted when they received doses of 400 mg/kg and greater.

Thus, I and II, in doses of 25-100 mg/kg (internally) do show some myorelaxant action.

In our work, we used a modification of the method described in [6], which enabled additional data on the nature of the myorelaxant action of I and II to be obtained.

Our data agrees with that reported in the literature for the myorelaxant action of these compounds when given internally and intraperitoneally to mice and rats in doses ranging from 10 to 1600 mg/kg [4].

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CHOLINE ESTERS OF N-SUBSTITUTED AMINO ACIDS: SYNTHESIS AND SOME BIOLOGICAL PROPERTIES

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The present work is a continuation of earlier studies on the synthesis and biological properties of aminoesters of amino acids [1, 2] and includes the synthesis of choline esters of α- and ω-amino acids containing various N-acyl residues (IIIa-ℓ), as well as a study of their pharmacological properties. Compounds IIIa-ℓ were synthesized by the active ester method [2].

The starting p-nitrophenyl esters of the N-substituted amino acids (IIa-ℓ) were prepared by the carbodiimide method [3]. TLC data, melting point, elemental analysis, and UV spectra of the original p-nitrophenyl esters are given in Table 1. The syntheses of the β-dimethylaminoethyl esters of the N-substituted amino acids (IIa-ℓ) were brought about by the interaction of the activated esters Ia-ℓ with β-dimethylaminoethanol (DMAE*) in

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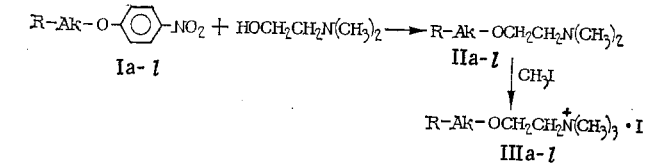
TABLE 1. p-Nitrophenyl Esters of the N-Substituted Amino Acids If-i, k, l

Compound	Yield, %	mp, °C	R_f (A)	Found, %			Empirical formula	Calculated, %			UV spectra, λ_{max} (ε)
				C	H	N		C	H	N	
If	69,8	118—9	0,48	61,70	4,80	9,06	$C_{17}H_{16}N_2O_5$	62,19	4,91	8,53	274 (4,03)
Ig	71,1	115—7	0,45	63,64	5,70	8,65	$C_{18}H_{16}N_2O_5$	63,15	5,30	8,18	278 (3,98)
Ih	56,8	87—9	0,48	63,90	5,79	7,84	$C_{19}H_{20}N_2O_5$	64,03	5,65	7,86	281 (3,87)
Ii	78,3	84—5	0,50	62,20	5,01	8,57	$C_{17}H_{16}N_2O_5$	62,19	4,91	8,53	274 (3,89)
Ik	83,2	123—4	0,43	46,06	3,93	10,31	$C_{15}H_{13}N_3O_8S$	45,47	3,31	10,63	274 (4,07)
Il	79,2	89—90	0,51	45,69	3,60	10,42	$C_{15}H_{13}N_3O_8S$	45,47	3,31	10,63	275 (4,06)

TABLE 2. β-Dimethylaminoethyl Esters of the N-Substituted Amino Acids IIa-m

Compound	Yield, %	R_f (B)	Found, %			Empirical formula	Calculated, %			Mol. wt. by MS
			C	H	N		C	H	N	
IIa	85,8	0,22	61,50	7,59	9,90	$C_{15}H_{22}N_2O_4$	61,21	7,53	9,52	...
IIb	85,3	0,20	61,40	7,63	9,80	$C_{15}H_{22}N_2O_4$	61,21	7,53	9,52	...
IIc	79,4	0,26	68,23	7,40	7,96	$C_{21}H_{26}N_2O_4$	68,09	7,07	7,56	...
IId	95,2	0,23	62,43	7,50	10,87	$C_{13}H_{18}N_2O_3$	62,38	7,24	11,19	...
IIe	95,1	0,20	63,10	7,00	10,69	$C_{14}H_{20}N_2O_3$	63,62	7,60	10,50	265
IIf	94,3	0,21	65,10	8,16	8,84	$C_{15}H_{22}N_2O_3$	64,72	7,97	10,06	278
IIg	93,7	0,21	65,40	8,40	9,99	$C_{16}H_{24}N_2O_3$	65,73	8,27	9,58	292
IIh	96,9	0,21	67,03	8,50	8,88	$C_{17}H_{26}N_2O_3$	66,64	8,55	9,14	306
IIi	94,3	0,16	64,40	8,06	10,78	$C_{15}H_{22}N_2O_3$	64,72	7,97	10,06	...
IIj	84,9	0,06	53,20	7,18	9,10	$C_{14}H_{22}N_2O_4S$	53,48	7,05	8,91	314
IIk	95,4	0,09	44,80	5,31	12,58	$C_{13}H_{19}N_3O_6S$	45,21	5,54	12,17	345
II*l*	91,6	0,10	44,60	5,58	12,43	$C_{13}H_{19}N_3O_6S$	45,21	5,54	12,17	...
IIm	96,9	0,81	60,08	7,31	9,96	$C_{14}H_{20}N_2O_4$	59,98	7,19	9,90	280

Note: All compounds were oils except for IIe (mp = 99-100°C), and IIj (mp = 110-191°C).

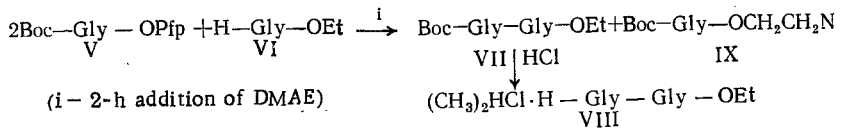


a: R = $C_6H_5CH_2OCO$; Ak = DL-Ala
b: R = $C_6H_5CH_2OCO$; Ak = β-Ala
c: R = $C_6H_5CH_2OCO$; Ak = DL-Phe
d: R = C_6H_5CO; Ak = Gly
e: R = C_6H_5CO; Ak = β-Ala
f: R = C_6H_5CO; Ak = γ-Abu
g: R = C_6H_5CO, Ak = δ-Ava
h: R = C_6H_5CO; Ak = ε-Aka
i.: R = $C_6H_5CH_2CO$; Ak = β-Ala
j: R = p·$CH_3C_6H_4SO_2$; Ak-β-Ala
k: R = o-$NO_2C_6H_4SO_2$; Ak = β-Ala
l.: R = o·$NO_2C_6H_4SO_2$; Ak = Sar

chloroform at room temperature. The results of these experiments confirm the usefulness of the p-nitrophenyl esters for the synthesis of β-dimethylaminoethyl esters of these amino acids (Table 2). However, the best results were obtained by the use of the pentafluorophenyl esters of the N-substituted amino acids. The reaction between the pentafluorophenyl ester of Z-glycine (IV) and DMAE is complete in 2 h, while the synthesis of β-dimethylaminoethyl-Z-glycine (IIm) by the use of the corresponding p-nitrophenyl ester required 40 h [2].

$$\underset{\text{IV}}{Z-Gly-OPfp} + HOCH_2CH_2N(CH_3)_2 \longrightarrow \underset{\text{IIm}}{Z-Gly-OCH_2CH_2N(CH_3)_2} \qquad (2)$$

It is now known that the use of activated esters gives an opportunity to bring about an accelerated method for the synthesis of peptides [6, 7]. Since compounds of type IIm are easily soluble in water at pH << 7, and are easily separated from the N- and C-protected peptides, the removal of the indicated excess at the end of the reaction may be accomplished by the use of DMAE according to (1). These circumstances were verified for the first preparation of Boc-glycylglycine (VII). The excess pentafluorophenyl ester of Boc-glycine (V) was removed after completion by the DMAE. The entire operation did not exceed 3.5 h for completion. The yield of compound VII under these conditions was 92%. Removal of the N-substituent from compound VII leads to the hydrochloride of ethyl glycylglycinate (VIII).



*In addition to the standard contractions recommended by the IUPAC-IUB Commission on biochemical nomenclature [4, 5], the following abbreviations are used in this work: δ-Ava) δ-aminovaleric acid; OPfp) pentafluorophenyl ester.

The structure of the compounds prepared was verified by IR and mass-spectroscopic data. The IR spectra of p-nitrophenyl esters Ia-ℓ showed maximum absorption at 1780-1765 and 1650-1720 cm^{-1} for the ester and amide carbonyls, respectively. The valence oscillation frequencies for the amide N-H groups in these materials occurred in the 3420-3375 cm^{-1} region. The IR spectra of compounds IIa-m showed ester carbonyl absorption bands at 1750-1730 cm^{-1} and at 3340-3320 for the NH-group. In addition to the above absorptions, compounds IIa-c gave peaks at 1720-1710 cm^{-1} for the urethane carbonyls, compounds,IId-m at 1660-1630 cm^{-1} for the amide carbonyls, compounds IIj-ℓ at 1170-1160 cm^{-1} and 1340-1330 cm^{-1} for the sulfonamide groups. In the mass spectra of compounds IIe-h, j, k, m molecular ion peaks were visible, in addition to peaks characteristic of cleavage of the β-dimethylaminoethyl group (cf. Table 2). The IR spectra of compounds IIIa-m gave ester carbonyl absorption bands at 1775-1750 cm^{-1}, at 3420-3350 cm^{-1} for the NH, and characteristic absorption bands for the corresponding N-substituent groups.

EXPERIMENTAL CHEMISTRY

The chemical purity of the compounds prepared was monitored by TLC on Silufol UV 254 sheets in three systems: chloroform—acetone (95:5, A); propanol—water (7:3, B); and acetic acid—ethanol—water—butanol (1:2:3:8, C). Visualization was by UV light and iodine vapor. The IR spectra were recorded on an UR-20 spectrophotometer, UV spectra on a Specord UV-VIS instrument, and mass spectra on an MX-1320 spectrometer.

β-Dimethylaminoethyl Esters of N-Substituted Amino Acids (IIa-ℓ). To a solution of 10 mmoles of p-nitrophenyl N-substituted amino acids (Ia-ℓ) [3] in 20 ml of chloroform was added 20 mmoles of DMAE, and the mixture was kept at room temperature for 40-50 h. The reaction mixture was diluted with $CHCl_3$ to 100 ml, washed with 5% potassium carbonate (3 × 20 ml), water (5 × 20 ml), and dried with sodium sulfate. After removal of the solvent, the desired products IIa-ℓ were obtained, the yields, elemental analysis data, and TLS properties of which are given in Table 2.

β-Dimethylaminoethyl Ester of N-Benzyloxycarbonylglycine (IIm). To a solution of 1.0 g (2.6 mmoles) of the pentafluorophenyl ester of Z-glycine [8] in 15 ml of chloroform was added 0.48 g (5.3 mmoles) of DMAE and the mixture was kept at room temperature for 2 h. The work-up was carried out analogously to the previous experiment to give 0.71 g (96.9%) of IIm.

Methiodides of β-Dimethylaminoethyl Esters of N-Substituted Amino Acids (IIIa-m). To a solution of 7 mmoles of IIa-m in 10 ml of anhydrous ethanol was added 10 mmoles of methyl iodide and the mixture was kept at room temperature for 24 h. Anhydrous ether (100 ml) was added to the mixture and the resulting precipitate was filtered off. The material was reprecipitated from a mixture of alcohol and ether.

For the synthesis of the choline ester of N-tosyl-β-alanine (IIIj), the mixture was heated at 60°C for 6 h. Yields and physicochemical constant for compounds IIIa-m are given in Table 3.

Ethyl N-t-Butoxycarbonylglycylglycylglycinate. To a suspension of 0.41 g (2.9 mmoles) of ethyl glycinate hydrochloride in 20 ml of tetrahydrofuran at 0°C was added 0.3 g (2.9 mmoles) of triethylamine, the mixture was stirred for 20 min, and 2 g (5.9 mmoles) of pentafluorophenyl Boc-glycinate [9] was added. The reaction mixture was kept at room temperature for 2 h, 0.78 g (8.8 mmoles) of DMAE was added, and the mixture was kept at the same temperature for 1.5 h. The solvent was distilled and to the residue was added 30 ml of water. The mixture was acidified to pH 3.0 with citric acid and extracted with ethyl acetate (3 × 20 ml). The organic layer was washed with water (3 × 10 ml), dried with sodium sulfate, and the solvent was removed under aspirator vacuum. The oily residue crystallized at room temperature after 3 h to give 0.70 g (91.7%). After recrystallization from a mixture of ethyl acetate-petroleum ether, the mp was 78-79°C. The literature [10] gives mp 80-81°C.

Ethyl Glycylglycinate Hydrochloride (VIII). To a solution of 0.6 g of compound VII in 10 ml of ethyl acetate was added ethereal hydrogen chloride. The mixture was kept at room temperature for 1 h and the solvent was removed. The residue was crystallized by treating with dry ether to give 0.35 g (77.8%) of VIII, mp 184-185°C. The literature [11] gives mp 185-186°C.

EXPERIMENTAL BIOLOGY

The cholinergic and antimicrobial properties of the above compounds were studied.

TABLE 3. Physicochemical and Biological Characteristics of Choline Esters of N-Substituted Amino Acids IIIa-m

Compound	Yield, %	R_f (B)	R_f(C)	mp, °C	Found, %			Empirical formula	Calculated, %			A_{50}, M	Maximal effectiveness or inherent activity
					C	H	I		C	H	I		
IIIa	80,8	0,75	0,57	90—3	44,39	5,90	29,54	$C_{16}H_{25}N_2O_4$	44,05	5,77	29,09	$(2,6\pm1,4)\cdot10^{-4}$	0,78
IIIb	76,8	0,64	0,54	65—8	44,25	6,03	29,37	$C_{16}H_{25}N_2O_4$	44,05	5,77	29,09	$(4,2\pm0,7)\cdot10^{-6}$	0,98
IIIc*	71,2	0,70	0,56	115—7	52,00	5,86	25,31	$C_{22}H_{29}N_2O_4$	51,57	5,70	24,77	...	...
IIId	83,4	0,71	0,50	168—70†	43,10	5,42	32,50	$C_{14}H_{21}N_2O_3$	42,90	5,39	32,35	$(5,6\pm4,2)\cdot10^{-4}$	0,82
IIIe	84,6	0,69	0,56	175—6	44,08	5,79	31,83	$C_{15}H_{23}N_2O_3$	44,34	5,70	31,24	$(2,0\pm0,05)\cdot10^{-6}$	1,00
IIIf	69,5	0,65	0,57	138—9	46,13	5,70	30,50	$C_{16}H_{25}N_2O_3$	45,72	5,99	30,19	$(8,2\pm0,1)\cdot10^{-6}$	0,86
IIIg	84,2	0,65	0,58	112—4	46,82	5,80	28,80	$C_{17}H_{27}N_2O_3$	47,01	6,27	29,22	$(4,9\pm0,05)\cdot10^{-6}$	0,94
IIIh	82,0	0,64	0,59	172—3	48,80	6,70	28,50	$C_{18}H_{29}N_2O_3$	48,22	6,52	28,30	$(4,5\pm2,45)\cdot10^{-4}$	0,95
IIIi	52,9	0,66	0,51	78—80	45,43	5,61	30,55	$C_{16}H_{25}N_2O_3$	45,72	5,99	30,19	$(5,0\pm3,25)\cdot10^{-5}$	0,91
IIIj	75,8	0,73	0,55	123—5	39,51	5,74	...	$C_{15}H_{25}N_2O_4S$	39,48	5,52	...	$(1,2\pm0,5)\cdot10^{-4}$	0,75
IIIk	88,6	0,66	0,52	149—50	35,02	4,90	...	$C_{14}H_{22}N_3O_6S$	34,50	4,55	...	$(6,0\pm0,15)\cdot10^{-6}$	0,91
IIIl	69,5	0,69	0,53	156—8	34,8	34,85	...	$C_{14}H_{22}N_3O_6S$	34,50	4,55	...	$(5,7\pm0,65)\cdot10^{-4}$	0,60
IIIm	85,1	0,73	0,57	113—4	42,50	5,14	29,90	$C_{15}H_{25}N_2O_4$	42,66	5,49	30,49	$(8,6\pm0,10)\cdot10$	0,78

*The compound is cholinolytic, $ED_{50} = 5.5\cdot10^{-5}$ M.
†Literature [12] mp = 160-164°C.

The cholinergic properties of the choline esters IIa-m were investigated on isolated animal organs. The isolated rectus muscle of frogs was used to measure the ability of the compounds to either produce muscle contractions (cholinomimetic activity) or to reverse the contraction caused by acetyl choline (cholinoblocking activity). The presence of cholinomimetic activity, defined as the concentration required to give 50% of the maximum muscle contraction (A_{50}) was also used to calculate the value of the inherent activity of the compounds [13]. The cholinoblocking activity was studied on the same test materials, but activity was defined as the concentration necessary to weaken the acetylcholine contraction by 50% (ED_{50}).

The experimental results presented in Table 3 show that, except for the choline ester IIIc, all of the compounds possess cholinomimetic properties. Their activity changes as a function of both the amino acid structure and the acyl substituent on the nitrogen atom. In addition to the dependence on the structures of the nitrogen substituent, the activity increases in passing from α-amino acids to β-alanine (cf. the value of A_{50} for compounds IIIa, b, d, e, m). A similar regularity was observed in a study of the choline esters of 1-methyl-2-ethoxycarbonyl vinyl amino acids [2]. In the case of the choline esters IIId-h, the cholinomimetic activity changes with the length of the carbon chain. After an abrupt increase in passing from IIId, where $A_{50} = 5 \cdot 10^{-4}$ M, to IIIe, where $A_{50} = 2 \cdot 10^{-6}$ M, further extension of the carbon chain does not cause sharp oscillations in activity. Some lowering can be noted for IIIf, however, with a gradual increase to IIIh (cf. the value of A_{50} for compounds IIIf-h in Table 3). A study of the influence of the acyl residue on the degree of cholinomimetic activity showed that, for the case of combination with β-alanine, it gradually increases in the series from p-toluenesulfonyl ($A_{50} = 1.2 \cdot 10^{-4}$ M) to phenylacetyl ($A_{50} = 5.5 \cdot 10^{-5}$ M), nitrophenylsulfonyl ($A_{50} = 6 \cdot 10^{-6}$ M), benzyloxycarbonyl ($A_{50} = 4.2 \cdot 10^{-6}$ M), and benzoyl ($A_{50} = 2 \cdot 10^{-6}$ M). The choline ester IIIe is not only highly active but it also is the single full agonist among the compounds studied: Its inherent activity was unity.

The choline esters IIIa-m were inactive *in vitro* against *Staphylococcus aureus* and *Bacillus dysenterii* Flexner in series dilution studies.

The chemotherapeutic properties of the o-nitrophenyl esters If-i, k, *l* also were studied on 400 randomly-bred white mice weighing 16-17 g against *Staphylococcus aureus* (strains 91 and 4-0), *Bacillus dysenterii* Flexner (strains 6858 and 114), and *Salmonella typhosa* (strain 70). The tests involved a generalized infection of the mice produced by intraperitoneal injection of the infectant [14]. The infecting dose used was sufficient to produce 100% mortality in untreated control mice 24-48 h after infection. The test compounds were introduced beforehand in a single dose of 1500 mg/kg. Reliable differences in prolongation of the life of the animals compared to the maximum possible for the control group were established by an alternative form of calculation of the response by estimation of the criterion χ^2.

Healthy animals were treated with a single oral dose of the test compounds at 2000-2500 mg/kg without visible change in their behavior and condition. It was shown that compounds If-i, k, *l* were inactive on the basis of the *Salmonella septicemia*. The p-nitrophenyl esters If-i, k, in experiments with *Staphylococcus* and *Bacillus dysenterii*, showed a prolongation of the animal's lives by 20-30% ($P < 0.001$), and *Il*, with *Dysenterii septicemia*, by 60% ($P < 0.001$). The corresponding N-substituted amino acids, as well as N-o-nitrophenylsarcosine, were inactive. The latter, in experiments with *Bacillus dysenterii*, extended the total life of mice by 20% ($P < 0.001$).

Thus, the antimicrobial activity of N-substituted amino acids is increased by transformation into the corresponding p-nitrophenyl esters.

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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF AMINOALKYL DERIVATIVES OF 5-(p-ALKOXYPHENYL)-5-METHYLHYDANTOINS

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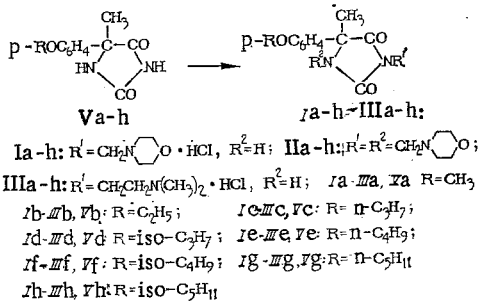
Considering the results of our research on substituted hydantoins [1, 2], as well as the literature data on the anticonsulvant activity of aminoalkyl derivatives of hydantoin [3], it seemed of interest to study the anticonvulsant effects of 3-morpholinomethyl- (Ia-h), 1,3-bis(morpholinomethyl)- (IIa-h), and 3-dimethylaminoethyl-5-(p-alkoxyphenyl)-5-methylhydantoins (IIIa-h) as compared with the effects of the known diphenylhydantoin (Diphenine) and 5-(p-butoxyphenyl)-5-methylhydantoin (IV) [1].

Compounds Ia-h and IIIa-h were obtained from 5-(p-alkoxyphenyl)-5-methylhydantoins Va-h via the scheme



Compounds Ia-h and IIa-h were synthesized via the Mannich reaction of Va-h with formaldehyde and morpholine. The reaction of equimolar amounts of the starting compounds at room temperature gave Ia-h, which were isolated in the form of the hydrochlorides (Table 1). Bis-(morpholinomethyl) derivatives IIa-h (Table 2) were obtained at a reagent ratio of 1:2:2 and a reaction temperature of 50-60°C. Hydrochlorides IIIa-h were synthesized by aminoalkylation of IVa-h with dimethylaminoethyl chloride in dimethylformamide (DMF) (Table 3) with subsequent treatment of the bases with HCl.

EXPERIMENTAL CHEMISTRY

Thin-layer chromatography (TLC) was carried out on a fixed layer of KSK silica gel—gypsum under the following conditions: a) benzene—acetic acid—water (7:3:1) as the mobile phase and development with phosphomolybdic acid; b) ether—petroleum ether (3:2) as the mobile phase and development with iodine vapors. The IR spectra were recorded with a UR-20 spectrometer. The mass spectra were obtained with an MKh-1320 mass spectrometer; the molecular-ion peaks corresponded to the molecular masses of the described compounds (the bases).

3-Morpholinomethyl-5-(p-alkoxyphenyl)-5-methylhydantoin Hydrochlorides (Ia-h) [3]. A mixture of 20 mmole of Va-h and 1.7 g (20 mmole) of morpholine was suspended in 50 ml of ethanol, and the suspension was heated at 35°C until a clear solution was obtained. The solution was treated with 2 ml of 35% formalin, and the mixture was stirred for 15 min and al-

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