CHOLINE ESTERS OF N-SUBSTITUTED AMINO ACIDS.

II. SYNTHESIS OF DIALKYLAMINOALKYL ESTERS OF N-SUBSTITUTED α,β-DEHYDROAMINO ACIDS

V. O. Topyazyan, D. A. Gerasimyan,
A. S. Édilyan, and L. O. Mndzhoyan

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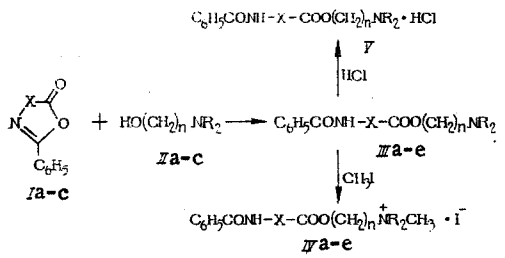
The dialkylaminoalkyl esters of a variety of acids have found application in the form of their salts (methiodides, hydrochlorides, etc.) in medicine (ditilin, fubromegan, gangleron, etc.). There are descriptions in the literature of the preparation of dialkylaminoalkyl esters of amino acids and peptides [3], but no work has been carried out on the synthesis of the dialkylaminialkyl esters of α,β-dehydroamino acids.

The object of the present investigation was to discover a method of synthesis of the dialkylaminoalkyl esters of N-substituted α,β-dehydroamino acids. We have shown previously [4] that 2-phenyl-5-oxazolone reacts with 2-(dimethylamino)ethanol to give N-benzoylglycine 2-(dimethylamino)ethyl ester. With this reaction in mind, we examined the reaction of azlactones (Ia-c) with the dialkylaminoalkanols (IIa-c). It was found that the reaction gives the required products, namely the dialkylaminoalkyl esters of the N-substituted amino acids (IIIa-e).



Ia: X = $C_6H_5CH_2CH$; Ib: X = $C_6H_5CH{=}C$; Ic: X = p-$CH_3OC_6H_4CH{=}C$; IIa: R = CH_3, $n = 2$; IIb: R = C_2H_5, $n = 2$; IIc: R = C_2H_5, $n = 3$; IIIa—IVa: X = $C_6H_5CH_2CH$, R = CH_3, $n = 2$; IIIb—IVb: X = $C_6H_5CH{=}C$, R = CH_3, $n = 2$; IIIc—IVc: X = $C_6H_5CH{=}C$, R = C_2H_5, $n = 2$; IIId—IVd: X = $C_6H_5CH{=}C$, R = C_2H_5, $n = 3$; IIIe—IVe, V: X = p-$CH_3OC_6H_4CH{=}C$, R = CH_3, $n = 2$.

The reaction of azlactones (Ia-c) with the aminoalcohols (IIa-c) was effected in chloroform or tetrahydrofuran. The presence of a tertiary amino group in the amino alcohol ($-CH_2/NR_2$), as expected, accelerated the reaction as compared with aliphatic alcohols. According to [7], the methyl ester of N-benzoylphenylalanine was obtained in 83% yield by reacting the appropriate azlactone with methanol in a ratio of 1:328 for two weeks, whereas we obtained N-benzoylphenylalanine 2-(dimethylamino)ethyl ester (IIIa) in 95% yield after 15 h, using a ratio of 2-phenyl-4-benzyl-5-oxazolone (Ia) to 2-(dimethylamino)ethanol (IIa) of 1:4. In both instances, the reaction was carried out at room temperature.

In order to determine the effect of a double bond on the reactivity of the azlactone, we examined by TLC the reaction of a mixture of azlactones (Ia) and 2-phenyl-4-benzylidene-5-oxazolone (Ib) with the amino alcohol (IIa) in chloroform (ratio of reactants 1:1:8). After seven hours, the azlactone (Ia) had disappeared completely from the reaction mixture, whereas (Ib) was still present even after 23 h. This observation indicates that the double bond in the 4-position of the azlactone retards its reaction with the amino alcohol (IIa). These results agree with literature findings [1] that saturated azlactones are more reactive than the unsaturated compounds. Reaction of the dialkylaminoalkyl esters (IIIa-e) with methyl iodide gave the methiodides (IVa-e). Also prepared was the hydrochloride of N-benzoyl-α,β-dehydro-p-methoxyphenylalanine 2-(dimethylamino)ethyl ester (V).

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The structures of these compounds were confirmed by their IR, UV, PMR, and mass spectra. The IR spectra of the dialkylaminoalkyl esters (IIIa-e) and of the salts (IVa-e) and (V) showed absorption maxima at 1665-1650 and 1730-1710 cm^{-1}, attributed to amide and ester carbonyl groups, respectively. The frequency of stretching vibrations of the amide NH group in these compounds occurred in the region 3290-3205 cm^{-1}. In the mass spectra of (IIIa-c, e) molecular ion peaks are seen (Table 1), together with peaks characteristic of the fragmentation of dialkylaminoalkyl esters. UV and PMR spectral data are given in the Experimental section.

The results of pharmacological studies (Table 2) showed that the aminoesters (IVa-e) and (v) possessed H-cholinoreceptor blocking properties.

Examination of the data presented in Table 2 and in [5] shows that choline-blocking effects are displayed by the choline esters of N-substituted phenylalanines and O-methyltyrosines.

It is known that increasing the size of the substituents on the nitrogen atom in choline esters of a number of carboxylic acids results in an increase in their choline-blocking ability [2]. For this reason, we synthesized the methiodide of N-benzoyl-α,β-dehydrophenylalanine 2-(diethylamino)ethyl ester (IVc), which has two ethyl groups in the ammonium grouping as compared with two methyl groups in (IVb). As will be seen from Table 2, (IVc) is 25 times more active as a cholinolytic than (IVb). A similar increase in activity is seen on introducing a methoxy-group into the para-position of the benzene ring (see results for (IVb) and (IVe)). However, lengthening the methylene chain between the oxygen and nitrogen in the alcohol residue results in a slight reduction in activity. The cholinolytic activity of the choline ester of the saturated N-substituted aminoacid (IIa) has greater cholinolytic activity (EC_{50} $1.7 \cdot 10^{-5}$ M) than the corresponding ester of the α,β-unsaturated acid (IVb, EC_{50} $5 \cdot 10^{-5}$ M). It will be seen from the data presented in Table 2 that the activity of the hydrochloride (V) is inferior to that of the corresponding methiodide (IVe).

EXPERIMENTAL CHEMICAL PART

The chemical purity of the compounds obtained was checked by TLC on Silufol UV-254 plates in the systems propanol—water 7:3 (A) and acetic acid—ethanol—water—butane. 1:2:3:8 (B); visualization with UV and iodine. IR spectra were obtained on a UR-20 spectrometer (East Germany), UV spectra on a Specord UV-VIS, PMR spectra on a Varian T-60 spectrometer, and mass spectra on an MX-1320 mass spectrometer.

2-(Dimethylamino)ethyl Ester of N-Benzoyl-DL-phenylalanine (IIIa). To a solution of 2 g (7.9 mmole) of 2-phenyl-4-benzyl-5-oxazolone [8] in 30 ml of dry chloroform was added 2.85 g (3.2 mmole) of 2-(dimethylamino)ethanol (IIa), and the mixture kept at room temperature for 15 h. The solution was diluted with chloroform to 100 ml, shaken with 5% potassium carbonate solution (3 × 20 ml) and water (4 × 20 ml) and dried over calcium chloride. Removal of the solvents under a water pump vacuum gave 2.6 g (95.9%) of (IIIa) as an oil. PMR spectrum (in $CDCl_3$), δ, ppm: 2.28 s 6H [$N(CH_3)_2$]; 2.60 t 2H (CH_2N); 3.26 d 1H (CHCO); 4.23 t 2H (OCH_2); 5.12 g 2H (β-CH_2); 7.00-7.80 m (aromatic protons).

2-(Dimethylamino)ethyl Ester of N-Benzoyl-α,β-dehydrophenylalanine (IIIb). To a solution of 2 g (8 mmole) of 2-phenyl-4-benzylidene-5-oxazolone [6] in 30 ml of dry chloroform was added 2.85 g (3.2 mmole) of the aminoalcohol (Ia). The mixture was boiled for 7 h on the water bath, diluted with chloroform to 100 ml, and worked up as in the preceding preparation. After removal of the solvents at room temperature, the residue crystallized. The colorless crystalline solid was triturated with dry ether (2 × 25 ml), and reprecipitated from its solution in chloroform with light petroleum. The yield, elemental analysis, TLC, and mass spectral data are given in Table 1. UV spectrum (in ethanol), λ, nm (log ε): 222 (4.36), 289 (4.16). PMR spectrum (in $CDCl_3$), δ, ppm): 2.20 s 6H [$N(CH_3)_2$]; 2.60 t 2H (CH_2N); 4.30 t 2H(OCH_2); 7.10-8.00 m 12H (NH, CH, and aromatic protons).

2-(Diethylamino)ethyl Ester of N-Benzoyl-α,β-dehydrophenylalanine (IIIc). To a solution of 3 g (1.2 mmole) of the azlactone (Ib) in 30 ml of tetrahydrofuran was added 5.62 g (4.8 mmole) of 2-(diethylamino)ethanol (IIb), and the mixture boiled on a water bath for 7 h. The solvent was removed, the residue dissolved in 100 ml of ethyl acetate, and the solution worked up as described in the preceding preparation. After removal of the solvents under reduced pressure, the (IIIc) slowly crystallized at room temperature. Reprecipitation was carried out by adding light petroleum to the chloroform solution. The yield, physicochemical and mass spectral data are given in Table 1. UV spectrum (in ethanol), λ, nm (log ε): 225 (4.24), 285 (4.24).

TABLE 1. Dialkylaminoalkyl Esters of N-Benzoylaminoacids (IIIa-e)

Compound	Yield, %	mp, °C	R_f (A)	R_f (Б)	Found, %			Empirical formula	Calculated, %			Mass spectral mol. mass
					C	H	N		C	H	N	
IIIa	95.9	oil	0.52	0.31	70.43	6.67	8.19	$C_{20}H_{24}N_2O_3$	70.56	7.11	8.23	340
IIIb	88.4	110—111	0.17	0.23	71.22	6.50	7.95	$C_{20}H_{22}N_2O_3$	70.98	6.55	8.26	338
IIIc	77.5	60—62	0.29	0.45	72.40	7.30	7.90	$C_{22}H_{26}N_2O_3$	72.11	7.15	7.64	366
IIId	67.9	51—52	0.27	0.40	72.99	7.20	7.34	$C_{23}H_{28}N_2O_3$	72.60	7.41	7.36	—
IIIe	89.2	oil	0.20	0.24	68.70	7.00	7.61	$C_{21}H_{24}N_2O_4$	68.46	6.56	7.60	268

TABLE 2. Physicochemical and Biological Properties of Salts of N-Benzoylamino Acid Dialkylaminoalkyl Esters (IVa-e) and (V)

Compound	Yield, %	mp, °C	R_f (A)	Found, %			Empirical formula	Calculated, %			EC_{50}, M
				C	H	I		C	H	I	
IVa	74.1	153—155	0.68	52.65	6.00	25.90	$C_{21}H_{27}IN_2O_3$	52.29	6.64	26.31	$1.7 \cdot 10^{-5}$
IVb	81.2	201—202	0.75	52.73	5.40	27.00	$C_{21}H_{25}IN_2O_3$	52.51	5.25	26.42	$5.0 \cdot 10^{-5}$
IVc	92.5	157—158	0.58	53.80	6.02	25.00	$C_{23}H_{29}IN_2O_3$	54.33	5.75	24.96	$2.0 \cdot 10^{-6}$
IVd	71.2	159—161	0.67	55.35	5.59	23.85	$C_{24}H_{31}IN_2O_3$	55.17	5.98	24.29	$4.0 \cdot 10^{-6}$
IVe	90.7	118—120	0.62	51.32	5.63	24.90	$C_{22}H_{27}IN_2O_3$	51.77	5.33	24.86	$4.0 \cdot 10^{-6}$
V	77.8	125—127	0.16	62.40	6.20	8.24*	$C_{21}H_{25}ClN_2O_4$	62.29	6.22	8.75*	$8.0 \cdot 10^{-6}$

*%Cl^- shown.

3-(Diethylamino)propyl Ester of N-Benzoyl-α,β-dehydrophenylalanine (IIId). This was synthesized as in the preceding preparation, from 3 g (1.2 mmole) of the azlactone (Ib) and 8.6 g (4.8 mmole) of 3-(diethylamino)propanol (IIc). Physicochemical data given in Table 1. UV spectrum (in ethanol), λ, nm (log ε): 225 (4.43), 286 (4.36).

2-(Dimethylamino)ethyl Ester of N-Benzoyl-α,β-dehydro-p-methoxyphenylalanine (IIIe). This was obtained as for (IIIb), from 4 g (1.4 mmole) of 2-phenyl-4-p-methoxybenzylidene-5-oxazolone (Ie) [9] and 5.1 g (5.7 mmole) of the amino alcohol (IIa). Its physicochemical and mass spectral data are given in Table 1. UV spectrum (in ethanol), λ, mm (log ε): 223 (4.09), 296 (4.27).

Methiodides of N-Benzoylamino acid Dialkylaminolakyl Esters (IVa-e). To a solution of 5 mmole of (IIIa-e) in 10 ml of dry ethanol was added 6 mmole of methyl iodide, and the mixture kept at room temperature for 24 h. To the mixture was then added 100 ml of dry ether, the solid of which separated and was filtered off. The yields and physicochemical constants for (IVa-e) are given in Table 2. UV spectra (in ethanol), λ, mm (log ε): (IVb) – 222 (4.44), 289 (4.42); (IVc) – 222 (4.43), 289(4.28); IVd) – 222 (4.48), 289 (4.28); (IVe) – 224 (4.42), 317 (4.37).

PMR spectra of (IVa) (in D_2O) δ, ppm: 2.93 s 9H [$N(CH_3)_3$]; 3.40 t 2H (CH_2N); 4.40 t 2H (OCH_2); 4.80 q 1H (α-CH); 6.10 s 2H (β-CH_2): 7.60 m 10H (aromatic protons).

N-Benzoyl-p-methoxy-α,β-dehydrophenylalanine 2-(Dimethylamino)ethyl Ester Hydrochloride (V). To a solution of 2 g (5.4 mmole) of the ester (IIIe) in 10 ml of methanol was added dropwise methanolic hydrogen chloride until the pH reached 1.0, and the mixture kept to room temperature for 5 h. Dry ether (100 ml) was then added, and the solid which separated was filtered off, washed with ether, and dried in a vacuum desiccator. Reprecipitation was carried out from a mixture of alcohol and ether. The physicochemical properties are given in Table 2.

Determination of the Comparative Reactivities of Azlactones (Ia) and (Ib) with 2-(Dimethylamino)ethanol. A mixture of 0.1 g (0.39 mmole) of the azlactone (Ia), 0.096 g (0.39 mmole) of azlactone (Ib), and 0.28 g (3.1 mmole) of the aminoalcohol (IIa) in 10 ml of chloroform was kept at 25°C (thermostat) for 25 h. Samples of TLC (Silufol UV-254, mobile phase chloroform–benzene 1:1, visualized in UV) were taken after 1, 2, 5, 6, 7, and 23 h. After 7 h, no spot corresponding to azlactone (I) was present (R_f 0.23). Simultaneously, a spot with R_f 0.9 appeared, attributed to the 2-(dimethylamino)ethyl ester (IIIa). Examination of the mixture by TLC after 23 h showed quite clearly a spot for the azlactone (Ib) (R_f 0.73). Note that both the ester (IIIb) and the amino alcohol (IIa) remain at the origin in this system.

EXPERIMENTAL BIOLOGICAL PART

The cholinergic properties of the methiodides (IIa-e) and the hydrochloride (V) of the N-benzoylamino acid dialkylaminoalkyl esters were examined.

The ability of the compounds to antagonize actylcholine contraction of isolated frog abdominal rectal muscle (choline-blocking activity) was assessed. Activity is expressed as the concentration which reduced acetylcholine contracted by 50% (the EC_{50}). The results are shown in Table 2.

LITERATURE CITED

1. J. Greenstein and M. Winitz, Chemistry of the Amino Acids, Wiley (1961).
2. M. Ya. Mikhelson and É. V. Zeimal', Acetylcholine [in Russian], Leningrad (1970), p. 279.
3. O. L. Mndzhoyan and V. O. Topuzyan, Usp. Khim., 50, No. 12, 2198-2211 (1981).
4. V. O. Topuzyan, G. P. Alebyan, and O. L. Mndzhoyan, Zh. Org. Khim., 19, No. 4, 827-832 (1983).
5. V. O. Topuzyan, D. A. Gerasimyan, A. S. Édilyan, et al., Khim.-farm. Zh., No. 5, 563-568 (1984).
6. M. Crawford and W. T. Little, J. Chem. Soc., 729-731 (1959).
7. M. Goodman and L. Levine, J. Am. Chem. Soc., 86, 2918-2922 (1964).
8. E. Mohr, Chem. Ber., 42, 2521-2523 (1909).
9. M. Vanghelovici and J. Moise, Bull. Chim. Pure Apl., 3A, 85-106 (1941-1942).