AMINO ACID DERIVATIVES OF PHENYLALKYLAMINES

COMMUNICATION 1. ESTERS OF N-(β-PHENYLETHYL)CARBAMOYL-α-AMINO ACIDS AND THEIR ALKALINE HYDROLYSIS PRODUCTS

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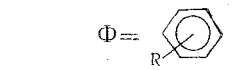
The reaction of organic isocyanates and isothiocyanates with α-amino acids is used for the synthesis of 2,4-imidazolinediones (hydantoins) and N-carbamoyl-α-amino acids [1, 2]. Another possible approach to the synthesis of these compounds is the reaction of the esters of isocyanocarboxylic acids with amines.

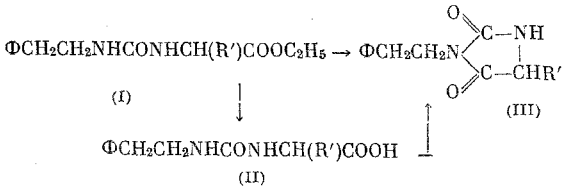
In the present paper we studied the reaction of amines of the β-phenylethylamine series with the esters of N-carbonylglycine and N-carbonyl-L- and D,L-methionine, which are easily obtained from the N-trialkylsilyl derivatives of the esters of these acids with phosgene [3], and the products of this reaction were studied. The reaction proceeds rapidly and is practically completed at the moment that the ether solutions of the reactants are mixed. The esters of β-phenylethylcarbamoyl-α-amino acids (I) are isolated here in high yield (Table 1). Most of the obtained products are crystalline compounds; (Ie) and (Ig) are viscous oils.

$$\Phi CH_2CH_2NH_2 + OCNCH(R')COOC_2H_5 \rightarrow \Phi CH_2CH_2NHCONHCH(R')COOC_2H_5 \quad (I)$$

$\Phi =$ 

R = H, R′ = H (a); R = *p*-OH, R′ = H (b); R = *p*-OCH_3, R′ = H (c); R = *p*-$OCH_2C_6H_5$, R′ = H (d); R = H, R′ = $CH_2CH_2SCH_3$ (e); R = *p*-OH, R′ = $CH_2CH_2SCH_3$ (f); R = *p*-OCH_3, R′ = $CH_2CH_2SCH_3$ (g); R = *p*-$N(CH_3)_2$, R′ = $CH_2CH_2SCH_3$ (h); R = 3,4-$(OCH_3)_2$, R′ = $CH_2CH_2SCH_3$ (k)

The alkaline hydrolysis of the (I) esters in either aqueous alcohol or aqueous dioxane medium, followed by neutralization of the hydrolyzates with hydrochloric acid, leads to the formation of the corresponding 3-phenethyl-2,4-imidazolinediones (III) instead of the expected hydantoic acids (II). The corresponding cyclic methionine derivatives were isolated in ~71-97% yields, i.e. the reaction is directed almost completely toward the formation of hydantoins (III).



Together with 3-β-phenethyl-2,4-imidazolinedione (IIIa), a substantial amount of N-β-phenethylcarbamoylglycine (IIa) was isolated in the hydrolysis of ethyl ester (Ia). The structure of the obtained compounds is confirmed by the elemental analysis data (Tables 1 and 2), and also by the data of the IR and NMR spectra.

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TABLE 1. p-R—$C_6H_4CH_2CH_2NHCONHCH(R')COOC_2H_5$

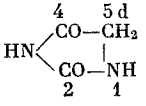
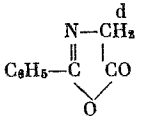
Compound	R	R'	Mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
				C	H	N	S		C	H	N	S	
(Ia)	H	H	92—94	62,33	7,28	11,07	—	$C_{13}H_{18}N_2O_3$	62,48	7,25	11,19	—	79
(Ib)	OH	H	146,5—148	58,76	6,75	10,29	—	$C_{13}H_{18}N_2O_4$	58,63	6,81	10,52	—	74
(Ic)	CH_3O	H	77—88	59,94	7,18	10,23	—	$C_{14}H_{20}N_2O_4$	59,98	7,19	10,00	—	80
(Id)	$C_6H_5CH_2O$	H	86—87	67,26	6,86	7,74	—	$C_{20}H_{24}N_2O_4$	67,40	6,79	7,86	—	90
(Ih)	$N(CH_3)_2$	$CH_2CH_2SCH_3$	91,5—92,5	58,91	7,86	11,20	8,86	$C_{18}H_{29}N_3O_3S$	58,83	7,95	11,43	8,72	96
(Ik)	3,4-$(CH_3O)_2$	$CH_2CH_2SCH_3$	97—99	55,99	7,18	7,38	8,31	$C_{18}H_{28}N_2O_5S$	56,23	7,31	7,28	8,34	85

TABLE 2. p-R$C_6H_4CH_2CH_2N$<CO—NH / CO—CHR'>

Compound	R	R'	Mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
				C	H	N	S		C	H	N	S	
(IIIa)	H	H	148—149	64,38	5,71	13,52	—	$C_{11}H_{12}N_2O_2$	64,69	5,92	13,72	—	36 *
(IIIe)	H	$CH_2CH_2SCH_3$	89,5—90,5	61,12	6,70	10,00	11,74	$C_{14}H_{18}N_2O_2S$	60,46	6,52	10,06	11,52	71
(IIIg)	CH_3O	$CH_2CH_2SCH_3$	91—92	57,94	6,47	8,94	10,86	$C_{15}H_{20}N_2O_3S$	58,42	6,54	9,08	10,40	76
(IIIh)	$N(CH_3)_2$	$CH_2CH_2SCH_3$	123—124	59,25	7,11	13,62	9,93	$C_{16}H_{23}N_3O_2S$	59,78	7,21	13,07	9,97	97
(IIIf)	HO	$CH_2CH_2SCH_3$	128,5—129	57,22	6,14	9,56	10,99	$C_{14}H_{18}N_2O_3S$	57,12	6,16	9,52	10,89	90
(IIIk)	3,4-$(CH_3O)_2$	$CH_2CH_2SCH_3$	88—89	56,71	6,51	8,17	9,60	$C_{16}H_{22}N_2O_4S$	56,88	6,55	8,28	9,47	75

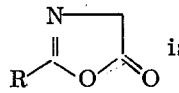
*Besides (IIIa), N-β-phenethylcarbamoylglycine was isolated in 31% yield, mp 140-141.0°.

TABLE 3

No.	Compound	δ, ppm									J, Hz	
		a	b	c	d	e	f	g	l	m	J_{BC}	$J_{fc}+J_{de}$
(Ia)	$C_6H_5\overset{a}{C}H_2\overset{b}{C}H_2\overset{c}{N}HCONH\overset{d}{C}H_2COO\overset{e}{C}H_2\overset{m}{C}H_3$	6,88	2,53	3,20	3,68	—	—	—	3,84	0,90	7	—
(Ie)	$C_6H_5\overset{a}{C}H_2\overset{b}{C}H_2\overset{c}{N}HCONH\overset{d}{C}H(\overset{e}{C}OO\overset{m}{C}H_2CH_3)\overset{e}{C}H_2\overset{f}{C}H_2\overset{g}{S}CH_3$	6,84	2,50	3,20	4,20	1,58	2,20	1,70	3,92	0,91	7	12
(IIa)	$C_6H_5\overset{a}{C}H_2\overset{b}{C}H_2\overset{c}{N}HCONH\overset{d}{C}H_2COOH$	6,88	2,51	3,20	3,72	—	—	—	—	—	—	—
(IIe)	$C_6H_5\overset{a}{C}H_2\overset{b}{C}H_2\overset{c}{N}HCONH\overset{d}{C}H(COOH)\overset{e}{C}H_2\overset{f}{C}H_2\overset{g}{S}CH_3$	6,84	2,49	3,21	4,20	1,74	2,20	1,70	—	—	7	13
(IV)		—	—	—	3,88	—	—	—	1 NH 6,71	3 NH 8,97		
(IIIe)	$C_6H_5\overset{a}{C}H_2\overset{b}{C}H_2\overset{c}{C}H_2-N\langle\begin{matrix}CO-\overset{d}{C}H(\overset{e}{C}H_2\overset{f}{C}H_2\overset{g}{S}CH_3)\\ CO-NH\end{matrix}$	6,75	2,58	3,48	3,92	1,70	2,14	1,72	6,75		—	12
(IIIa)	$C_6H_5\overset{a}{C}H_2\overset{b}{C}H_2\overset{c}{C}H_2-N\langle\begin{matrix}CO-\overset{d}{C}H_2\\ CO-NH\end{matrix}$	6,77	2,55	3,47	3,71	—	—	—	6,75	—	7	
(V)		—	—	—	4,06	—	—	—	—	—	—	

The bands of the stretching vibrations of the NH group are observed in the IR spectra of the (I) esters in the 3320-3390 cm^{-1} region. In some cases these bands are split into two bands: (Ic) 3330 and 3380 cm^{-1}; (Id) 3330 and 3390 cm^{-1}; (Ik) 3320 and 3345 cm^{-1}. All of the spectra contain a narrow intense band of $\nu_{C=O}$ (COOR) at 1740-1750 cm^{-1}. Three absorption bands are observed in the 1550-1650 cm^{-1} region, which are caused by the carbamido grouping and the aromatic ring. A broad and intense band at 1630-1640 cm^{-1} is probably complex absorption, with the main contribution made by $\nu_{C=O}$ (NHCONH), while the band in the vicinity of 1585 cm^{-1} belongs mainly to the absorption of amide II. A narrow band of medium intensity at 1520-1530 cm^{-1} can be assigned to one of the vibration types of the aromatic ring.

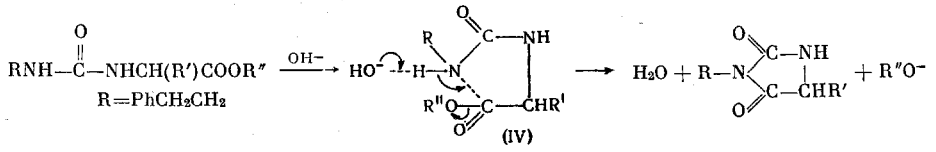
The presence of the absorption bands: 3280-3310 cm^{-1} (NH), 1745-1755 cm^{-1} (weak narrow band) and 1685-1720 cm^{-1} (broad intense band) is characteristic for the IR spectra of the imidazolinediones (III). The last two bands apparently belong to the stretching vibrations of the C = O groups of the ring, in which connection the high-frequency band is characteristic for the symmetric vibrations, while the more intense low-frequency band is characteristic for the antisymmetric stretching vibrations of the C = O bonds. Analogous absorption bands at 3280, 1762 and 1705 cm^{-1} are observed in the spectrum of the unsubstituted 2,4-imidazolinedione, namely hydantoin.

The chemical shifts and spin—spin coupling constants in the NMR spectra of some of the compounds, hydantoin (IV) and 4-phenyl-5-oxazolone (V) are given in Table 3. In all of the compounds, except (IIIe), the ethyl group attached to the phenyl ring gives a characteristic A_2B_2 spectrum, which consists of two triplets. For compound (IIIe) each component of the downfield triplet is split additionally. In compounds of the (III) type the downfield triplet is shifted toward weaker fields by 27 Hz when compared with the noncyclic compounds. This shift can be caused by a decrease in the electron density of the α-carbon atom of the phenethyl group due to the strong —I effect of the heteroring. The postulation that the (II) acids can cyclize to the isomeric (III) compounds representing oxazolone derivatives of type  is not in agreement with the obtained spectra. In this case a shift of the signal of the H^c proton upfield could be expected due to the +M effect of the N atom, not contained in the ring. In addition, a comparison of the chemical shifts of the H^d protons of the model compounds (IV) and (V) with the cyclic glycine derivatives (IIIa) shows a greater similarity of the latter with hydantoin (IV).

For the methionine derivatives (Ih) and (Ik) the rotation around the $>CH^d-CH_2^e$ bond is inhibited, which is characteristic for most amino acids [4]. Because of this the NMR signals of the $CH^d-CH_2^e-CH_2^f$ group can be assigned to the AA'BB'X type. However, a complete analysis of this portion of the spectrum is difficult, since the H^e signals are partially masked by the H^g signals of the thiomethyl group. In all cases, except (IV), the signals of the N^1H group are masked by the signals of the phenyl protons.

We were able to observe the cyclization of phenethylcarbamoylmethionine (IIe) to 3-phenethyl-5-(β-methylthioethyl)-2,4-imidazolinedione (IIIe) in an NMR ampul under the influence of CF_3COOH. A signal at 3.48 ppm of the H^d proton of compound (IIIe) appeared in the spectrum of (IIe), which after 3 h became equal in intensity to the signal of the H^d proton of acid (IIe), which had dropped to 3.21 ppm (50% conversion of the acid to the hydantoin). In a similar manner, after refluxing phenethylcarbamoylmethionine with 2 N HCl solution a product was isolated that was identical with (IIIe), which corresponds with the literature data [1, 2, 5, 6].

The formation of phenethylimidazolinediones during the alkaline hydrolysis of the esters in aqueous alcohol medium can be explained by the spontaneous cyclization of the hydantoic acids (II) when the solution is neutralized. It is known that when an organic isocyanate is reacted with an α-amino acid in aqueous alkaline solution the product that is formed when the latter is neutralized is not the hydantoic acid, but instead its cyclic anhydride — the hydantoin [7-10]. However, β-phenylethyl isocyanates react with α-amino acids under these conditions to give only the corresponding phenethylcarbamoylamino acids [11]. These compounds remain unchanged when treated with aqueous alcoholic alkali and do not cyclize, like the corresponding esters. For this reason it is possible to assume that the esters of N-carbamoyl-α-amino acids (I) are cyclized under the influence of alkali with the formation of the intermediate complex (IV), which is then converted to the hydantoin



It is interesting to mention that the 3-phenethyl-5-(β-methylthioethyl)-2,4-imidazolinediones, which are formed in the alkaline hydrolysis of the esters of N-β-phenethylcarbamoyl-L-methionine, lack optical activity.

EXPERIMENTAL METHOD

The ethyl esters of the N-carbonylamino acids were obtained by the treatment of the esters of N-trimethylsilylamino acids with $COCl_2$ [3]. The IR spectra of the samples were taken on a UR-10 spectrometer as Nujol mulls. The NMR spectra were taken on a Varian HA-100 instrument at ~32°, using CF_3COOH as the solvent and HMDS as the internal standard.

Ethyl Ester of N-β-phenethylcarbamoylglycine (Ia). To a solution of 2.58 g (20 mmoles) of N-carbonylglycine in 40 ml of ether at 0° was added in portions a solution of 2.42 g (20 mmoles) of β-phenylethylamine in 35 ml of ether in 5 min. The precipitate (Ia) was filtered, washed twice with ether, and dried. We obtained 3.95 g (79%) of (Ia), mp 92-93° (hexane—acetone). Infrared spectrum (ν, cm^{-1}): 3340, 1745, 1630, 1598. See Tables 1 and 3 for the NMR spectrum and elemental analysis.

Hydrolysis. To a solution of 2.25 g (9 mmoles) of (Ia) in 15 ml of CH_3OH was added 10.8 ml of 1 N NaOH solution and the mixture was shaken at ~20° for 2 h. The solution was neutralized with 1 N HCl solution. The obtained crystals were filtered and dried in vacuo. Based on the IR spectrum and elemental analysis the product, which had mp 127-128°, is a mixture of (IIa) and (IIIa). For the separation 1.14 g of the mixture was treated with 14 ml of 0.2825 N C_2H_5ONa solution, the alcohol was removed in vacuo, and the residue (1.28 g) was repeatedly washed on the filter with ether. From the ether solution we obtained 0.53 g (36%) of (IIIa), mp 148-149° (from aqueous alcohol). Infrared spectrum (ν, cm^{-1}): 3240 (NH), 1780 and 1704 (amide).

The crystalline product, which remained on the funnel after the ether extraction (0.87 g), was treated with 10 ml of 0.5 N HCl solution. The precipitate was separated, washed with water until the test for chloride disappeared, and dried to give 0.50 g (31% yield) of N-β-phenethylcarbamoylglycine, mp 140-141° (from water). Found: C 59.50; H 6.35; N 12.50%. $C_{11}H_{14}N_2O_3$. Calculated: C 59.45; H 6.35; N 12.60%. Infrared spectrum (ν, cm^{-1}): 3375 (NH), 1766, 1742 (amide), 1592 (COOH).

Ethyl Ester of N-p-dimethylamino-β-phenethylcarbamoylmethionine (Ih). A solution of 1.51 g (9.2 mmoles) of p-dimethylaminophenylethylamine in 10 ml of ether was added in portions to a solution of 1.87 g (9.2 mmoles) of the ethyl ester of N-carbonyl-L-methionine in 10 ml of ether. The reaction mixture warmed up slightly. The solvent was removed and the crystalline residue was washed on the filter with hexane and then with a 1:5 hexane—ether mixture. Recrystallization from a 4:1 hexane—acetone mixture gave 3.03 g (90%) of (Ih), mp 91.5-92.5°. Infrared spectrum (ν, cm^{-1}): 3230, 1765, 1725.

The other esters of methionine and glycine (Ia—k) were obtained in a similar manner (see Table 1).

3-p-Dimethylaminophenethyl-5-(β-methylthioethyl)-2,4-imidazolinedione (IIIh). A solution of 1.69 g (4.6 mmoles) of (Ih) in 20 ml of ethanol and 2.85 ml of 2.1 N NaOH solution (6 mmoles) was stirred for 2 h, after which 61 ml of 0.1 N HCl solution was added. The obtained crystals were filtered and washed with water. We obtained 1.43 g (97%) of (IIIh), mp 123-124° (from aqueous alcohol). Infrared spectrum (ν, cm^{-1}): 3275 (NH), 1765 and 1752 (amide), 1700 (CO); $[\alpha]_D^{20} \sim 0$ (1% solution of the product in alcohol).

Derivatives (IIIa—k) were obtained in a similar manner (see Table 2).

CONCLUSIONS

1. The esters of N-β-phenethylcarbamoylamino acids are obtained in high yield by the reaction of the esters of N-carbonylamino acids with β-phenylethylamine derivatives.

2. The saponification of the esters of N-β-phenethylcarbamoylamino acids by aqueous alcoholic alkali proceeds with the formation of 3-phenethyl-2,4-imidazolinediones.

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