AMINO ACID DERIVATIVES OF PHENYLALKYLAMINES

COMMUNICATION 3. ACYLATION OF β-PHENYLETHYLAMINE DERIVATIVES WITH α-AMINO ACIDS

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As a continuation of our previous research in the synthesis of the O- and N-derivatives of tyramine [1-4] we studied the conditions for obtaining the arylethylamides of α-amino acids. Some compounds of the series are described in the literature, which were obtained by the acylation of arylethylamines with α-bromoacyl chlorides and subsequent treatment with ammonia [5-6]. We used the peptide synthesis methods, the dicyclohexylcarbodiimide (DCC) method (method A) and the method of mixed anhydrides (B), to synthesize them. As the amino component we used β-phenylethylamine (PEA) and its p-hydroxy-, p-methoxy-, m-hydroxy-, and N-methyl-p-methoxy derivatives; the amino acids (AA) (glycine, L-valine, L-alanine, D,L-leucine, D,L-methionine, and L-proline) were reacted as the carbobenzoxy (Cbo) derivatives.

The condensation of the β-arylethylamines with the AA in the presence of DCC was run in a solution of THF, CH_2Cl_2, or their mixture, at either 0-5 or 20°C. The best results were obtained when the reaction was run in THF at ~20°. When excess amine is present in the reaction mixture a precipitate of the amino salt deposits, which reacts slowly with the DCC, and secondary reactions also take place, which lead to the formation of the N-acylurea [7].

The method of mixed anhydrides, using the methyl and ethyl chloroformates, proved to be more convenient. In this case the reactions proceed substantially faster and give, as a rule, higher yields of the products. Employing this method, we were able to condense some of the AA with all of the indicated amino components. The presence of a free hydroxy group in tyramine fails to lower the yield of the products: Cbo-glycyltyramine (Xa) and Cbo-leucyltyramine (XIa) were obtained in respective yields of 82.5 and 58.4%. The method of mixed anhydrides can be used to condense Cbo-leucine with O,N-bis(trimethylsilyl)tyramine. Here product (XI) was obtained in higher yield (74.5%), which is probably explained by the fact that O,N-bis(trimethylsilyl)tyramine is readily soluble in THF, whereas tyramine is practically insoluble at low temperature.

The Cbo protection was removed by hydrogenating the condensation products over Pd black at ~20°. The isolation of the products as the hydrochlorides and tartrates was made difficult due to their high hygroscopicity. The melting point of some of the compounds could not be determined for the same reason (see Table 2). Amides (XIIa) and (XIIIa) were obtained without the intermediate isolation of their Cbo derivatives.

In the IR spectra of Cbo derivatives (Ia)-(XIa) are observed aborption bands that correspond to the amide bands of the Cbo group in the 1675-1685 cm^{-1} region, the band of amide-I in the 1655-1660 cm^{-1} region, and also a band that corresponds to the total absorption of amide-II in the 1540-1575 cm^{-1} region. The bands of the stretching vibrations of the NH groups lie in the 3300-3340 cm^{-1} region. The presence of the absorption bands of amide-I and amide-II respectively at 1670-1680 and 1550-1575 cm^{-1} is characteristic for the IR spectra of the AA phenylethylamides (Ib)-(XIIIb). Bands at 3220-3225 and 3345-3355 cm^{-1} are observed in the region of the stretching vibrations of the NH groups, and also a series of bands in the

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TABLE 1

No.	Compound	Method	Yield, %	Mp, °C (solvent)	R_f	Found, %			Empirical formula	Calculated, %		
						C	H	N		C	H	N
(Ia)	Cbo-Gly phenylethylamide	A/B	45/54	106—108 (CH_3OH)	0,91	69,54	6,36	8,81	$C_{18}H_{20}N_2O_3$	69,20	6,45	8,96
(IIa)	Cbo-Ala phenylethylamide	B	32,5	123—125(benzene)	0,95	69,68	6,49	8,83	$C_{19}H_{22}N_2O_3$	69,91	6,79	8,58
(IIIa)	Cbo-Val phenylethylamide	B	56	153—154(benzene)	0,92	70,50	7,54	7,64	$C_{20}H_{26}N_2O_3$	70,14	7,57	8,20
(IVa)	Cbo-Met phenylethylamide	B	51	106—109(benzene)	0,97	65,23	6,93	7,07	$C_{21}H_{26}N_2SO_3$	65,25	6,78	7,27
(Va)	Cbo-Gly p-methoxyphenylethylamide	B	42,4	122—123(benzene)	0,94	66,19	6,41	8,14	$C_{19}H_{22}N_2O_4$	66,40	6,49	8,18
(VIa)	Cbo-Ala p-methoxyphenylethylamide	B	37,7	139—141(benzene)	0,95	67,20	6,80	7,61	$C_{20}H_{24}N_2O_4$	67,39	6,78	7,85
(VIIa)	Cbo-Val p-methoxyphenylethylamide	A/B	54,6/64,5	159—162(benzene)	0,92	68,50	7,44	7,16	$C_{22}H_{28}N_2O_4$	68,60	7,36	7,29
(VIIIa)	Cbo-Leu p-methoxyphenylethylamide	B	58	102,5—105 (aq. C_2H_5OH)	0,93	69,31	7,51	7,16	$C_{23}H_{30}N_2O_4$	69,32	7,53	7,02
(IXa)	Cbo-Pro p-methoxyphenylethylamide	B	28,8	112—113 (acetone—EtAc)	0,95	68,94	6,90	7,31	$C_{22}H_{26}N_2O_4$	69,08	6,85	7,32
(Xa)	N-Cbo-Gly tyramide	B	82,5	116—119 (ethyl acetate)	0,88	65,94	6,04	8,42	$C_{18}H_{20}N_2O_4$	65,83	6,01	8,53
(XIa)	N-Cbo-Leu tyramide	B	58,4	109—112 (ethyl acetate)	0,95	—	—	7,17	$C_{22}H_{28}N_2O_4$	—	—	7,28

TABLE 2

Compound No.	Compound	Yield, %	$[\alpha]_D^{18}$	Mp, °C	R_f	Found, %				Empirical formula	Calculated, %			
						C	H	N	Cl		C	H	N	Cl
(Ib)	H-Gly phenylethylamide hydrochloride	83		169 (softens) 208—210 *	0;52	55,65	7,12	13,00	16,58	$C_{10}H_{15}N_2ClO$	55,94	7,04	13,04	16,51
(IIb)	H-Ala phenylethylamide tartrate	70,5	+10,38	84,5—87,5	0,40	—	—	7,49 †	—	$C_{15}H_{22}N_2O_7$	52,62	6,47	7,78	—
(IIIb)	H-Val phenylethylamide tartrate	61	+7,78	150—152	0,60	52,02	7,16	7,51	—	$C_{17}H_{26}N_2O_7$	52,12	7,07	7,56	—
(IVb)	H-Met phenylethylamide tartrate	9,6		Hygroscopic	0,64	—	—	6,61	—	$C_{17}H_{26}N_2SO_7$	—	—	6,95	—
(Vb)	H-Gly p-methoxyphenyl-ethylamide tartrate	85,6		225—227	0,12	52,16	7,19	11,30	14,48	$C_{11}H_{17}N_2ClO_2$	52,10	7,15	11,04	14,48
(VIb)	H-Ala p-methoxyphenyl-ethylamide tartrate	77,5	—13,84	165,5—166,5	0,56	51,49	6,47	7,49	—	$C_{16}H_{24}N_2O_8$	51,60	6,49	7,52	—
(VIIb)	H-Val p-methoxyphenyl-ethylamide tartrate	65	+19,03	110—114	0,52	—	—	7,16	—	$C_{18}H_{28}N_2O_8$	—	—	6,99	—
(VIIIb)	H-Leu p-methoxyphenyl-ethylamide hydrochloride	64,2		179—180	0,61	60,01	8,39	—	11,92	$C_{15}H_{25}N_2ClO_2$	59,88	8,37	—	11,78
(IXb)	H-Pro p-methoxyphenyl-ethylamide tartrate	70	—43,25	Hygroscopic	0,47	—	—	6,90	—	$C_{18}H_{26}N_2O_8$	—	—	7,04	—
(Xb)	NH-Gly tyramide hydrochloride	27,5		»	0,33	—	—	—	14,12 †	$C_{10}H_{15}N_2ClO_2$	—	—	—	14,26
(Xc)	NH-Gly tyramide tartrate	73		176—177	—	—	—	8,55	—	$C_{14}H_{20}N_2O_8$	—	—	8,13	—
(XIb)	NH-Leu tyramide tartrate	71		75 (softens) 102(decompn.)	0,61	—	—	6,74	—	$C_{18}H_{28}N_2O_8$	53,98	7,04	6,99	—
(XIIb)	NH-Gly m-hydroxyphe-nylethylamide tartrate	21		Hygroscopic	0,37	—	—	8,03	—	$C_{14}H_{20}N_2O_8$	—	—	8,13	—
(XIIIb)	N-Methyl-H-Leu p-methoxyphenylethyl-amide tartrate	17,5		»	0,63	—	—	6,53	—	$C_{20}H_{32}N_2O_8$	—	—	6,23	—

* Literature data: mp 165° [6].

† The analysis was calculated for monohydrate of the product.

2600-2800 cm^{-1} region, which correspond to the stretching vibrations of the NH_3^+ group. These data confirm the structure of the obtained compounds.

EXPERIMENTAL METHOD

The IR spectra of the products were obtained on a UR-10 spectrometer as KBr pellets. For the TLC we used Silufol UV-254 plates and the system: 4:1:1 butanol–AcOH–water. The $[\alpha]_D$ values were obtained for 1% aqueous solutions on an SU-3 polarimeter.

Cbo-Gly Phenylethylamide (Ia) (method A). To a solution of 1.04 g of Cbo-Gly-OH in 20 ml of THF was added 1.03 g of DCC, and after 30 min 1.21 g of PEA in 5 ml of THF. After 24 h the mixture was filtered, the solvent was removed, and the residue was dissolved in CH_2Cl_2. The solution was washed in succession with 0.5 N HCl solution, H_2O, and 0.5 N $NaHCO_3$ solution, dried over Na_2SO_4, and the solvent was evaporated in vacuo. We obtained 0.7 g of (Ia).

Cbo-Val p-Methoxyphenylethylamide (VIIa) (method B). To a solution of 1.05 g of Cbo-Val-OH in 8 ml of THF plus 0.59 ml of TEA at −10° was added 0.43 ml of ethyl chloroformate (ECF). After 15 min a solution of 0.634 g of p-methoxyphenylethylamine in 8 ml of THF was added. The mixture was kept at −10° for 2h and then let it stand overnight. The precipitate was separated, the solvent was evaporated, and the residue was dissolved in ethyl acetate and washed in succession with 0.5 N HCl solution, 0.5 N $NaHCO_3$ solution, and water, dried over Na_2SO_4, and the solvent was evaporated in vacuo. The yield of (VIIa) was 1.03 g (64.5%). The other Cbo derivatives were synthesized in a similar manner (Table 1).

N-Cbo-Leu Tyramide (XIa). To a solution of 1.11 g of Cbo-Leu-OH in 8 ml of THF plus 0.59 ml of TEA was added 0.43 ml of ECF at −10°. After 20 min a solution of 1.18 g of O,N-bis(trimethylsilyl)tyramine in 8 ml of THF was added. The mixture was kept at −5° for 1 h and then worked up as described for (VIIa). The yield of (XIa) was 1.21 g.

H-Leu p-Methoxyphenylethylamide Hydrochloride (VIIIb). A solution of 1.16 g of (VIIIa) in 20 ml of MeOH was hydrogenated over Pd black until the CO_2 evolution ceased. The catalyst was separated, and the filtrate was evaporated to 5 ml, acidified with a solution of HCl in MeOH to pH 3, and (VIIIb) was precipitated by the addition of ether. The yield of (VIIIb) was 0.56 g (64.2%), mp 179-180° (from i-PrOH). The other amide hydrochlorides were synthesized in a similar manner (Table 2).

H-Val p-Methoxyphenylethylamide Tartrate (VIIb). A solution of 1.0 g of (VIIa) in 20 ml of MeOH was hydrogenated over Pd black, the catalyst was separated, and the solution was evaporated to 5 ml and a solution of 0.39 g of tartaric acid in 4 ml of MeOH was added. Precipitation with absolute ether gave 0.68 g of (VIIb) as a hygroscopic product that was stored over P_2O_5. The other amide tartrates were obtained in a similar manner (see Table 2).

CONCLUSIONS

Employing the peptide synthesis methods, a number of α-amino acid arylethylamides was obtained from glycine, L-alanine, L-valine, D,L-methionine, D,L-leucine, L-proline, and β-phenylethylamine, and from p-methoxyphenylethylamine, m-hydroxyphenylethylamine, N-methyl-p-methoxyphenylethylamine, and tyramine.

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