SYNTHESIS OF METHYLAMIDES OF N-ACETYL α-AMINO ACIDS AND THEIR N-METHYL DERIVATIVES

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Methylamides and dimethylamides of N-acetyl amino acids (I), (II), (V), (VI), and (IX) and their N-methyl derivatives (III), (IV), (VII), (VIII), and (X) are the simplest compounds that model fragments of peptide and protein chains constructed of aliphatic amino acid (and N-methyl amino acid) residues. To study the laws of the formation of the spatial structure of peptides and proteins, and also the influence on this structure of short-range interactions, it appeared desirable to perform a detailed investigation of this type of model peptide system with the aid of physicochemical and computing methods. The present paper describes the synthesis of the diamides (I)-(X).

Ac-L-Ala-NHMe (I), Ac-L-Ala-NMe_2 (II), Ac-L-MeAla-NHMe (III), Ac-L-MeAla-NMe_2 (IV), Ac-L-Val-NHMe (V), Ac-L-Val-NMe_2 (VI), Ac-L-MeVal-NHMe (VII), Ac-L-MeVal-NMe_2 (VIII), Ac-L-Pro-NHMe (IX), Ac-L-Pro-NMe_2 (X).

TABLE 1

Compound	mp, °C	$[\alpha]_D^{20}$, deg	c	Found, %			Formula	Calc., %		
				C	H	N		C	H	N
I[a]	175	−100	1,0	49,90	8,22	19,54	$C_6H_{12}N_2O_2$	49,98	8,39	19,43
II[b]	87—89	+25 −57	1,0 0,3 (C_2H_5OH)	53,27	8,93	18,01	$C_7H_{14}N_2O_2$	53,14	8,92	17,71
III	67—69	−280	1,0	52,90	9,22	17,80	$C_7H_{14}N_2O_2$	53,14	8,92	17,71
IV	Oil	−105	3,0	55,50	9,38	15,95	$C_8H_{16}N_2O_2$	55,79	9,36	16,27
V[c]	235	−48 −40	0,5 1,7 (H_2O)	55,52	9,19	15,92	$C_8H_{16}N_2O_2$	55,79	9,36	16,27
VI	89	+39	0,2	58,29	9,50	15,40	$C_9H_{18}N_2O_2$	58,03	9,74	15,04
VII	95	−265	1,0	57,84	9,47	14,58	$C_9H_{18}N_2O_2$	58,03	9,74	15,04
VIII	82	−210	0,2	60,32	10,35	13,80	$C_{10}H_{20}N_2O_2$	59,97	10,07	13,99
IX[d]	106	−210	1,0	56,41	8,22	16,31	$C_8H_{14}N_2O_2$	56,45	8,29	16,49
X[e]	Oil	−61	0,3	58,40	8,44	15,02	$C_9H_{16}N_2O_2$	58,67	8,75	15,21
XI[f]	Oil	−89	2,0 (H_2O)	49,80	7,55	9,72	$C_6H_{11}NO_3$	49,64	7,64	9,65
XII[g]	62	+32 −50	2,0 0,6 (H_2O)	55,74	8,85	7,94	$C_8H_{15}NO_3$	55,47	8,73	8,09
XIII		−91,5	1,0	55,82	7,61	8,02	$C_8H_{13}NO_3$	56,12	7,65	8,18
XXII		−54	5,0	62,24	7,31	11,35	$C_{13}H_{18}N_2O_3$	62,38	7,25	11,19
XXIII		−103	2,0	64,90	7,90	10,22	$C_{15}H_{22}N_2O_3$	64,72	7,97	10,07
XXIV	Oil	+8	5,0	62,27	7,19	11,39	$C_{13}H_{18}N_2O_3$	62,38	7,25	11,19
XXV		+40	2,0	64,83	7,88	10,19	$C_{15}H_{22}N_2O_3$	64,72	7,97	10,07
XXVI		−118	5,0	63,50	7,54	10,52	$C_{14}H_{20}N_2O_3$	63,61	7,63	10,60
XXVII		−65	4,0	65,61	8,22	9,76	$C_{16}H_{24}N_2O_3$	65,72	8,27	9,58
XXVIII		−30	0,0	65,32	7,42	10,22	$C_{15}H_{20}N_2O_3$	65,19	7,30	10,14

[a]Literature data: methylamide of acetyl-D-alanine, mp 175-176°C, $[\alpha]_D^{20}$ +100° (c 1; $CHCl_3$) [2]. [b]Literature data: mp 88-90°C, $[\alpha]_D^{16}$ −58.7° (c 0.3; C_2H_5OH) [3]. [c]Literature data: mp > 250°C, $[\alpha]_D^{13.6}$ −40.5° (c 1.66; H_2O [4]. [d]Literature data: mp 98° [5]. [e]The literature [6] does not give the mp and $[\alpha]_D$ for compound (X). [f]Literature data: methyl ester of acetyl-D-alanine, $[\alpha]_D^{20}$ +85° (c 2; H_2O) [1]. [g]Literature data: mp 61.5-62°C, $[\alpha]_D^{25}$ −49.3° [7].

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The methylamides of acetylalanine (I), acetylvaline (V), and acetylproline (IX) were obtained by treating with a methanolic solution of methylamine at 0°C solutions of the methyl esters of the acetylamino acids (XI)-(XIII) which, in their turn, were formed by the action of acetyl chloride on the methyl esters of the amino acids (XIV)-(XVI) in the presence of triethylamine in accordance with Scheme 1.

Scheme 1

HCl.H–X–OMe	→	Ac–X–OMe	→	Ac–X–NHMe
XIV. X=Ala,		XI. X=Ala,		I. X=Ala,
XV. X=Val,		XII. X=Val,		V. X=Val,
XVI. X=Pro,		XIII. X=Pro,		IX. X=Pro.

The aminolysis of the esters (XI)-(XIII) by the action of dimethylamine took place under considerably more severe conditions. Consequently, in order to avoid racemization, the synthesis of compounds (VI), (VII), and (X) was performed by a different method (Scheme 2); compounds (IV), (V), (VIII), and (IX) were obtained similarly. The reaction of the benzyloxycarbonylamino acids (XVII)-(XXI) with methylamine and dimethylamine by the mixed-anhydride method formed the corresponding methylamides and dimethylamides (XXII)-(XXVIII). The latter were converted by the action of HBr in glacial CH_3COOH into the hydrobromides (XXIX)-(XXXV), the treatment of which with acetyl chloride gave the acetyl derivatives (IV)-(X).

Scheme 2

$C_6H_5CH_2OCO$–X–OH	→	$C_6H_5CH_2OCO$–X–NMeR	→
XVII. X=Ala,		XXII. X=MeAla,	R=H;
XVIII. X=Val,		XXIII. X=MeVal,	R=H;
XIX. X=MeAla,		XXIV. X=Ala,	R=Me;
XX. X=MeVal,		XXV. X=Val,	R=Me;
XXI. X=PrO.		XXVI. X=MeAla,	R=Me;
		XXVII. X=MeVal,	R=Me;
		XXVIII. X=PrO,	R=Me.

→HBr·H–X–NMeR	→	Ac–X–NMeR	
XXIX. X=MeAla,	R=H;	III. X=AcAla,	R=H;
XXX. X=MeVal,	R=H;	VII. X=MeVal,	R=H;
XXXI. X=Ala,	R=Me;	II. X=Ala,	R=Me;
XXXII. X=Val,	R=Me;	VI. X=Val,	R=Me;
XXXIII. X=MeAla,	R=Me;	IV. X=MeAla,	R=Me;
XXXIV. X=MeVal,	R=Me;	VIII. X=MeVal,	R=Me;
XXXV. X=Pro,	R=Me.	X. X=Pro,	R=Me.

EXPERIMENTAL

The melting points are not corrected. The individualities of all the compounds obtained were checked by thin-layer chromatography in alumina (activity grade III) and silica gel; the $[\alpha]_D^{20}$ values were measured in chloroform. The constants and the analytical results for the compounds obtained are given in Table 1.

Methyl Esters of the Acetylamino Acids (XI)-(XIII) [1]. With stirring and cooling to −40°C, 7.5 ml of acetyl chloride and 10.1 ml of triethylamine were added simultaneously over 20 min to a solution of 0.07 mole of the hydrochloride of the methyl ester of a L-amino acid (XIV), (XV), or (XVI) and 10.1 ml of triethylamine in 100 ml of anhydrous chloroform. The reaction mixture was stirred at room temperature for 30 min, and the solvent was distilled off in vacuum. The residue was extracted with ethyl acetate (3 × 100 ml), and the combined extract was evaporated. Vacuum distillation of the residue yielded the methyl esters of the acetylamino acids (XI)-(XIII) with yields of 75-85% in the form of colorless oils with bp 80-90°C (0.2 mm).

Methylamides of the Acetylamino Acids (I)-(III). A solution of 0.05 mole of the methyl ester of an acetylamino acid (XI), (XII), or (XIII) in 10 ml of methanol was treated with 10 g of methylamine, and the mixture was left at 0°C for 12 h. Then it was evaporated in vacuum and the residue was treated with 50 ml of absolute ether. The crystals that deposited were filtered off and were recrystallized from absolute ethanol−ether. This gave the methylamides (I)-(III) with a yield of 60-80%.

Methylamides of Benzyloxycarbonylamino Acids (XXII) and (XXIII). A solution of 0.04 mole of a benzyloxycarbonyl L-amino acid (XIX) or (XX) in 10 ml of absolute tetrahydrofuran was treated with 5.6 ml of tri-

ethylamine, the mixture was cooled to 0°C, and, with stirring, 4.4 g of ethyl chloroformate was added to it over 10 min; then the reaction mixture was stirred at 0°C for another 15 min. A solution of 1.5 g of methylamine in 10 ml of chloroform was added with stirring (0°C, 10 min) to the solution of anhydride prepared in this way. The mixture was stirred at 0°C for another 3 h and was left at 20°C for 12 h. Then it was diluted with ether and was washed with 1 N HCl, with water, and with saturated $NaHCO_3$ solution and was evaporated in vacuum. This gave the methylamides of the benzyloxyamino acids (XXII) and (XXIII) in the form of colorless oils with a yield of 75-80%.

Dimethylamides of the Benzyloxycarbonylamino Acids (XXIV)-(XXVIII). Under the conditions of the preceding experiment, 0.04 mole of a benzyloxycarbonylamino acid (XVII)-(XXI) and 2.3 g of dimethylamine gave the dimethylamides (XXIV)-(XXVIII) in the form of colorless oils with a yield of 75-85%.

Methylamides and Dimethylamides of the Acetylamino and Acetylmethylamino Acids (IV)-(X). A solution of 0.03 mole of an amide of a benzyloxycarbonylamino acid (XXII)-(XXVIII) in 25 ml of a saturated solution of HBr in glacial CH_3COOH was stirred at 20°C for 20 min and was evaporated in vacuum at 40°C. The residue was treated three times with absolute ether and was dried in vacuum over P_2O_5 and KOH. The hydrobromide (XXIX)-(XXXV) obtained in this way was acetylated by the method given above for the hydrochlorides (XIV)-(XVI). The dimethylamides of acetylmethylalanine (IV) and acetylproline (X) were obtained in the form of colorless oils, while the other compounds, (IV), (V), and (VII)-(IX), readily crystallized on standing and were recrystallized from absolute ether. Yield 40-60%.

SUMMARY

A series of methylamides and dimethylamides of N-acetyl amino acids, which are the simplest models of peptides, have been synthesized by known methods of peptide chemistry.

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