AMINO ACID DERIVATIVES OF AZIRIDINE

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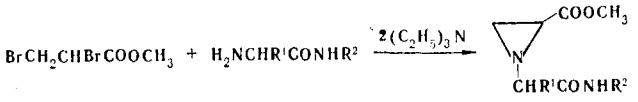
UDC 547.717'298.07:543.422

Aziridines that contain dipeptide fragments in their compositions were obtained by the reaction of esters of dipeptides with methyl 1,2-dibromopropionate. Aziridines with dipeptide fragments in the 1 and 2 positions of the ring were synthesized when activated esters of 1,2-dibromopropionic acid were used.

The possibility of the preparation of peptides containing fragments of amino acid derivatives in their compositions was investigated in [1-3]. In addition, a number of aziridines have been obtained from the methyl ester or amide of 1,2-dibromopropionic acid and amino acid esters [4]. Some of these aziridines have antibacterial properties [5]. In order to ascertain the interrelationship between the biological activity and the structure we synthesized aziridines that contain dipeptide fragments. The starting substances were esters of glycylglycine, glycylphenylalanine, glycylvaline, leucylglycine, α-alanylglycine, and methyl 1,2-dibromopropionate.

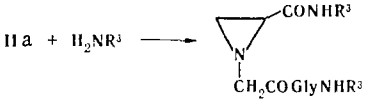
When the reaction was carried out in alcohol in the presence of triethylamine at 50°C, the yields of dipeptides II were 80-94%.



Ia-e IIa-e

I, II a $R^1=H$, $R^2=CH_2COOC_2H_5$; b $R^1=H$, $R^2=CH(COOCH_3)CH_2Ph$; c $R^1=H$, $R^2=CH(COOCH_3)CH(CH_3)_2$; d $R^1=i\text{-}C_4H_9$, $R^2=CH_2COOCH_3$; e $R^1=CH_3$, $R^2=CH_2COOCH_3$

The reaction of IIa with ammonia and hydrazine leads, respectively, to amide IIIa and hydrazine IIIb.

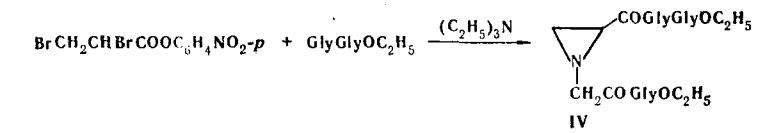


IIIa,b III a $R^3=H$; b $R=NH_2$

The structure of IIa-e and IIIa, b were confirmed by data from PMR and IR spectroscopy (Tables 1 and 2).

Thus the PMR spectrum of aziridine IIIa (Table 1) contains the ABC system that is characteristic for 1,2-substituted aziridines. The assignment of the signals of the aziridine ring was made from the spin–spin coupling constants ($J_{AB} > J_{AC} >> J_{BC}$) [6]. The protons of the N–CH_2 group resonate in the form of an AB quartet with a constant of 17.2 Hz, while the N–CH_2 fragment of glycine is represented by a singlet.

A new method for the synthesis of aziridinopeptides is the reaction of p-nitrophenyl 1,2-dibromopropionate with glycylglycine ethyl ester, which makes it possible to obtain tripeptide IV, which contains an N-substituted aziridine-2-carboxylic acid.



IV

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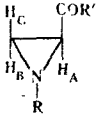
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1627-1630, December, 1982. Original article submitted February 16, 1982.

 0009-3122/82/1812-1254$07.50

TABLE 1. Parameters of the PMR Spectrum of II–IV



Compound	Solvent	δ, ppm												
		aziridine ring	N–CH	CH–CH_3	N–CH_2	CH_2–CH_3	NH–CH_2	$COOCH_3$	CH–CH_3	CH_2–CH_3	Ph	NH	CH_2–Ph	CH_2–CH
IIa	DMSO	2,60 (H_A), 1,80 (H_B), 2,09 (H_C); J_{AB}=12,2 Hz, J_{AC}=5,4 Hz			2,80, 3,18; J=21,8 Hz (AB system)	4,07 (q)	3,80 (s)	3,62 (s)		1,20 (t)		7,36 (br.s)		
IIb	$CDCl_3$	1,72—2,33 (m*)	4,85 (q)		3,09 (t)			3,64 (s)			7,23 (m)	7,42 (m)	3,00 (d)	
IIc	$CDCl_3$	1,38—2,13 (m*)	4,00 (q)	1,38—2,13 (m)	2,44, 2,92; J=15,0 Hz (two AB system)			3,30 (s)	0,78 (two d)			6,45 (br.s)		
IId	D_2O	2,02 (H_A), 2,58 (H_B), 2,29 (H_C); J_{AB}=9,4 Hz, J_{AC}=5,8 Hz, J_{BC}=2,7 Hz	2,46 (t)	1,44—1,84 (m)			4,04 (s)	3,71 (s)	0,89 (d)					1,44—1,84 (m)
IIe	$CDCl_3$	1,62—2,47 (m*)		3,91—4,22 (m)			3,91—4,22 (m)	3,76 (s)	1,31 (d)			7,36 (br.s)		
IIIa	D_2O	2,49 (H_A), 1,95 (H_B), 2,24 (H_C); J_{AB}=7,0 Hz, J_{AC}=3,4 Hz			3,07, 3,34; J=17,2 Hz (AB system)		3,97 (s)							
IIIb	D_2O	2,48 (H_A), 1,95 (H_B), 2,24 (H_C); J_{AB}=7,0 Hz, J_{AC}=3,4 Hz			3,07, 3,34; J=17,2 Hz (AB system)		3,96 (s)							
IV	D_2O	2,50 (H_A), 1,95 (H_B), 2,24 (H_C); J_{AB}=11,0 Hz, J_{AC}=5,4 Hz			3,11, 3,44; J=18,0 Hz (AB system)	4,20 (q)	4,00 (s)			1,26 (t)				

*The multiplicity of the signals of the aziridine ring in IIb, c, e is explained by the presence of a mixture of diastereomers.

TABLE 2. Characteristic Frequencies (cm^{-1}) in the IR Spectra of II-IV

Compound	νCH (aziridine ring)	δ (aziridine ring)	νCONH	νCOOMe	νNH
IIa	3080	1190	1665	1750	3365
IIb	3078	1190	1680	1745	3365
IIc	3080	1190	1685	1740	3360
IId	3080	1200	1650	1745	3300
IIe	3075	1210	1670	1750	3390
IIIa	3075	1180	1680	—	3360, 3410
IIIb	3070	1185	1685	—	3280, 3320
IV	3075	1205	1665	—	3310

TABLE 3. Physicochemical Characteristics of II-IV

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IIa	37—38	49,2	6,7	11,3	$C_{10}H_{16}N_2O_5$	49,2	6,6	11,5	94
IIb	—	60,1	6,5	8,7	$C_{16}H_{20}N_2O_5$	60,0	6,3	8,7	89
IIc	28—30	52,7	7,6	10,1	$C_{12}H_{20}N_2O_5$	52,9	7,4	10,3	86
IId	74—76	54,3	7,6	9,5	$C_{13}H_{22}N_2O_5$	54,5	7,8	9,8	80
IIe	—	49,8	6,4	11,3	$C_{10}H_{16}N_2O_5$	49,2	6,6	11,5	85
IIIa	175—176	42,2	6,1	27,8	$C_7H_{12}N_4O_3$	42,0	6,1	28,0	95
IIIb	139—140	36,7	6,1	36,4	$C_7H_{14}N_6O_3$	36,5	6,1	36,5	97
IV	105—106	48,3	6,7	14,9	$C_{15}H_{24}N_4O_7$	48,4	6,5	15,0	65

EXPERIMENTAL

The PMR spectra of 5% solutions of the compounds in $CDCl_3$, d_6-DMSO, and D_2O were obtained with a Brucker WH-90 spectrometer (90 MHz) with hexamethyldisiloxane and SDSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) as the internal standards. The IR spectra of the pure substances and suspensions in mineral oil and solutions in chloroform were obtained with a UR-20 spectrometer.

Aziridinopeptides IIa-e (Tables 1-3). A 7-ml (0.05 mole) sample of triethylamine was added dropwise with stirring at 0°C in the course of 15 min to the solution of 6.3 ml (0.05 mole) of methyl 1,2-dibromopropionate, the temperature of the reaction mixture was gradually raised to room temperature, and 14 ml (0.1 mole) of triethylamine and 0.05 mole of the dipeptide ester hydrochloride was added. The temperature of the mixture was then raised to 50°C, and the mixture was stirred for 12-14 h. At the end of the reaction [monitoring by thin-layer chromatography (TLC)] the solvent was evaporated *in vacuo*, and 200 ml of ethyl acetate was added to the residue. The triethylamine salt was removed by filtration, and the filtrate was passed through a column filled with silica gel. The ethyl acetate was evaporated, and the pure products were isolated by chromatography.

N-[(2-Carbamoylaziridino)acetyl]glycine Amide (IIIa) (Tables 1-3). A solution of 4.89 g (0.02 mole) of ester IIa in 50 ml of absolute ethanol was saturated with ammonia for 48 h. At the end of the reaction (monitoring by TLC) the solvent was evaporated, and the residue was crystallized by the addition of a small amount of absolute ether to give 3.8 g (95%) of a product with mp 175-176°C.

N-[2-[(Hydrazinocarbonyl)aziridino]acetyl]glycine Hydrazide (IIIb) (Tables 1-3). A 1.9-ml (0.06 mole) sample of anhydrous hydrazine was added dropwise with vigorous stirring at −10°C to a solution of 4.89 g (0.02 mole) of ester IIa in 25 ml of absolute ethanol. After 10 min, the temperature was raised gradually to room temperature, 200 ml of absolute ethanol was added, and stirring was continued. After 0.5-1 h, the precipitated hydrazide was removed by filtration, washed with alcohol and ether, and air dried to give 4.46 g (97%) of a product with mp 139-140°C.

[1[[N-(Ethoxycarbonylmethyl)carbamoyl]methyl]aziridine-2-carbonyl]glycylglycine Ethyl Ester (IV) (Tables 1-3). A 7-ml (0.05 mole) sample of triethylamine was added dropwise with stirring at 0°C to a solution of 17.65 g (0.05 mole) of p-nitrophenyl 1,2-dibromopropionate in 300 ml of absolute ethanol, the temperature of the mixture was gradually raised to room

temperature, and 21 ml (0.15 mole) of triethylamine and 19.65 g (0.1 mole) of glycylglycine ethyl ester hydrochloride were added. After this, the temperature was raised to 50-60°C, and the mixture was stirred for 12-15 h. At the end of the reaction (monitoring by TLC) the solvent was evaporated *in vacuo*, and the p-nitrophenol was extracted from the residue with ether. Ethyl acetate (500 ml) was added to the residue, and the triethylamine salt was removed by filtration. The filtrate was passed through a column filled with neutral aluminum oxide, the ethyl acetate was evaporated, and the resulting yellow oil crystallized in air. The yield of dipeptide IV, with mp 105-106°C, was 12.1 g (65%).

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PYRROLES FROM KETOXIMES AND ACETYLENE.

24.* ACIDIC HYDROLYSIS OF 1-VINYLPYRROLES

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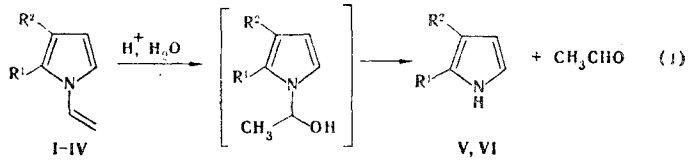
UDC 547.749'759.5.07:542.938:543.422

The hydrolysis of 2-methyl-, 2-phenyl-, and 3-methyl-2-phenyl-1-vinylpyrroles and 1-vinyl-4,5,6,7-tetrahydroindole in the presence of HCl, H_2SO_4, $NH_2OH \cdot HCl$, acetic acid, and H_2O_2 in aqueous, aqueous dioxane, and aqueous alcohol solutions leads to oligomers with complex structures and compositions, viz., products of acidic catalytic and oxidative condensation of the starting compounds and the resulting pyrroles both with one another and with the liberated acetaldehyde. 2-Phenylpyrrole was obtained in 52% yield from 1-vinyl-2-phenylpyrrole by hydrolysis in a dilute (∿0.5%) solution [water–dioxane (5:9)] with excess $NH_2OH \cdot HCl$, which ties up the acetaldehyde.

The literature contains no information regarding the transformations of 1-vinylpyrroles in aqueous acidic media, although without such information it is impossible to skillfully use these monomers and intermediates, which have now become accessible [2]. One might have assumed that 1-vinylpyrroles would be hydrolyzed in the same way as 1-vinylindole [3], 9-alkenylcarbazoles [4-7], 10-vinylphenothiazine [8], and 1-vinyllactams [9], i.e., via the scheme



I R^1=Me, R^2=H; II, V R^1—R^2=$(CH_2)_4$; III, VI R^1=Ph, R^2=H; IV R^1=Ph, R^2=Me

However, studies have shown that this scheme can be realized for 1-vinylpyrroles only in dilute solutions under the condition of tying up the liberated acetaldehyde (by means of

*See [1] for Communication 23.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1631-1639, December, 1982. Original article submitted April 28, 1982.