AMMONOLYSIS OF AZIRIDINECARBOXYLIC ACID ESTERS

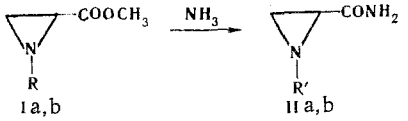
P. T. Trapentsier, I. Ya. Kalvin'sh, É. É. Liepin'sh, and É. Ya. Lukevits

UDC 547.717'783'785.5'298.1'398.1.07:543.422'51

The ammonolysis of 1-(2-methoxycarbonylvinyl)- and 1-(1,2-dimethoxycarbonylvinyl)-2-methoxycarbonylaziridines at normal pressure leads to 1-(2-methoxycarbonylvinyl)- and 1-(1,2-dicarbamoylvinyl)-2-carbamoylaziridines, respectively, whereas 1,3-diazabicyclo[3.1.0]hexan-4-one derivatives are formed under pressure.

2-Carbamoylaziridine has antitumorigenic and immunoregulating properties [1]. Functionally substituted amides of aziridinecarboxylic acids may display similar activity. We therefore studied the possibility of their preparation by ammonolysis of aziridinecarboxylic acid esters.

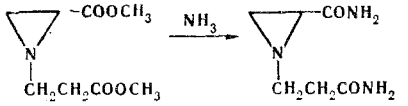
Methyl aziridine-2-carboxylate (Ia) and dimethyl aziridine-1,2-dicarboxylate (Ib) readily undergo ammonolysis in alcohol solutions at room or lower temperatures.



Ia,b IIa,b

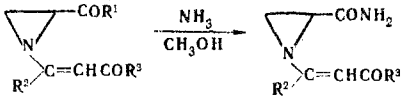
Ia R=H; b R=$COOCH_3$; IIa R'=H; b R'=$CONH_2$

Diester III did not react with ammonia under these conditions, whereas carrying out the reaction in liquid ammonia under pressure or in ammonium hydroxide led to the formation of diamide IV.



III IV

The ammonolysis of unsaturated derivatives Va,b with a saturated alcohol solution of ammonia at 0°C for 3-7 days leads to the formation of amides VIa,b. In contrast to the corresponding saturated compounds, ammonolysis does take place but only at the ester group in the 2 position of the aziridine ring. Under similar conditions the ammonolysis of Vc takes place at all of the ester groups. Addition of ammonia to the double bond is not observed in a single case.



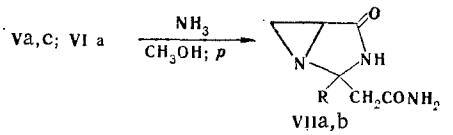
Va-c VIa-c

V a $R^1=R^3=OMe$, $R^2=H$; b $R^1=OMe$, $R^2=H$, $R^3=OEt$; c $R^1=R^3=OMe$, $R^2=COOMe$;
VI a $R^2=H$, $R^3=OMe$; b $R^2=H$, $R^3=OEt$; c $R^2=CONH_2$, $R^3=NH_2$

The direction of the reaction changes when the ammonolysis of Va,b and VIa is carried out in liquid ammonia under pressure. An analysis of the ^1H and ^{13}C NMR spectra, as well as the mass spectra, makes it possible to conclude that the products are 2-substituted 1,3-diazabicyclo[3.1.0]hexan-4-ones (VIIa,b).

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 350-352, March, 1983. Original article submitted July 14, 1982.

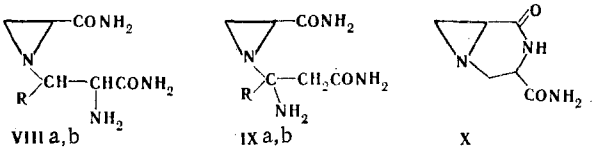
0009-3122/83/1903-0283$07.50



VIIa,b

VII a R=H; b R=$CONH_2$

Thus signals from only three nonequivalent NH protons are observed in the ^1H NMR spectrum of VIIa; this should not be the case for alternative structures VIII and IX. Possible structure X is repudiated by the absence of absorption from two nonequivalent CH protons in the spectrum of VIIb and also by the ^{13}C chemical shift of the $C_{(2)}$ atom (71.7 ppm) in VIIa.



VIII a,b IX a,b X

VIII-IX a R=H; b R=$CONH_2$

In the X structure, however, one might expect a chemical shift of the $C_{(2)}$ atom that is close to the chemical shift of the C_α atom in amino acids and peptides (~50-60 ppm [2]).

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of the compounds were recorded with Perkin-Elmer R12A (60 MHz) and Brucker WH 90/DS (90 MHz) spectrometers with hexamethyldisiloxane for ^1H and cyclohexane (δ 27.44 ppm) for ^{13}C as the internal standards. The melting points were determined with a Koefler stage. The mass spectra were recorded with an MS-50 AEI spectrometer.

2-Carbamoylaziridine (IIa). A solution of 10.1 g (0.1 mole) of 2-methoxycarbonylaziridine in 100 ml of methanol was cooled to 0°C, and a stream of dry ammonia was passed through the solution with stirring for 30 min. The solution was allowed to stand at room temperature for 8 h, after which the solvent was removed by evaporation to dryness, and the colorless ammonolysis product was crystallized from absolute ethanol to give 7.5 g (87%) of colorless amide IIa with mp 132.5-134°C (mp 116-118°C [3]). ^1H NMR spectrum (d_6-DMSO): 0.5 (1H, s, NH), 1.63 (2H, m, 3-H), 2.36 (1H, dd, 2-H), 7.2 and 7.7 ppm (2H, s, NH_2); (D_2O): 1.89 (1H, dd, J = 3.3 and 0.7 Hz, 3-H), 1.93 (1H, dd, J = 0.7 and 6.2 Hz, 3-H), and 2.67 ppm (1H, m, J = 3.3 and 6.2 Hz).

1,2-Dicarbamoylaziridine (IIb). A solution of 15.9 g (0.1 mole) of diester Ib in 50 ml of methanol was cooled to 0°C and saturated with gaseous ammonia, after which the mixture was maintained at 0°C for 48 h. The precipitated crystals were removed by filtration and crystallized from absolute ethanol to give 10.4 g (80%) of colorless crystals with mp 160-161°C. ^1H NMR spectrum (d_6-DMSO): 2.03 (1H, dd, J = 1.5 and 6.3 Hz, 3-H), 2.21 (1H, dd, J = 1.5 and 3.1 Hz, 3-H), 2.69 (1H, m, J = 3.1 and 6.3 Hz, 2-H), 6.8 (2H, s, 2-$CONH_2$), 7.1 and 7.4 ppm (1H each, s, 1-$CONH_2$).

1-(2-Carbamoylethyl)-2-carbamoylaziridine (IV). A solution of 3.8 g (20 mmole) of aziridine III in 50 ml of methanol was cooled in an autoclave to −40°C, and 30 ml of liquid ammonia was added. The mixture was heated on a water bath for 25 h, after which the solvent was removed by evaporation to dryness, and the residue was crystallized from ethanol to give 2.6 g (84%) of a colorless product with mp 132-133°C. ^1H NMR spectrum (d_6-DMSO): 1.52 (1H, dd, J = 0.9 and 6.6 Hz, 3-H), 1.76 (1H, dd, J = 0.9 and 3.1 Hz, 3-H), 1.89 (1H, dd, J = 3.1 and 6.6 Hz, 2-H), 2.1-2.5 (4H, m, CH_2CH_2), 6.83 and 6.96 (1H each, s, $CONH_2$), and 6.89 and 7.36 ppm (1H each, s, 2-$CONH_2$). Found: C 45.8; H 7.0; N 26.8%. $C_6H_{11}N_3O_2$. Calculated: C 45.9; H 7.1; N 26.7%.

1-(2-Methoxycarbonylvinyl)-2-carbamoylaziridine (VIa). A solution of 27.8 g (0.15 mole) of aziridine Va in 200 ml of methanol was saturated with ammonia at 0°C, and the mixture was allowed to stand at 0°C for 5 days. The solution was evaporated to dryness, and the resulting oil was triturated with isopropyl alcohol to give 18.7 g (73%) of colorless crystals with mp 132-133°C (from ethanol). ^1H NMR spectrum ($CDCl_3$): 2.18 [1H, dd, J = 1.4 and 6.5 Hz, 3-H (trans)], 2.38 [1H, dd, J = 1.4 and 3.2 Hz, 3-H (cis)], 2.61 (1H, m, J = 3.2 and 6.5 Hz, 2-H), 3.69 (3H, s, OCH_3), 5.47 (1H, d, J = 13.2 Hz, =CH), 6.3 (2H, s, $CONH_2$), and 7.47 ppm (1H, d, J = 13.2 Hz, NCH). Found: C 49.3; H 5.8; N 16.3%. $C_7H_{10}N_2O_3$. Calculated: C 49.5; H 5.9; N 16.5%.

1-(2-Ethoxycarbonylvinyl)-2-carbamoylaziridine (VIb). This compound was obtained by a method similar to that used for the synthesis of VIa. Workup gave 22.0 g (80%) of colorless crystals with mp 116-117°C (from ethanol). ^{1}H NMR spectrum ($CDCl_3$): 2.21 [1H, dd, J = 1.0 and 6.7 Hz, 3-H (trans)], 2.36 [1H, dd, J = 1.0 and 3.2 Hz, 3-H (cis)], 2.61 (1H, dd, J = 3.2 and 6.7 Hz, 2-H), 1.27 (3H, t, J = 6.6 Hz, CH_3), 4.12 (2H, q, J = 6.6 Hz, OCH_2), 5.43 (1H, d, J = 13.4 Hz, =CH), 5.8 (2H, s, $CONH_2$), and 7.41 ppm (1H, d, J = 13.4 Hz, NCH). Found: C 52.2; H 6.8; N 15.3%. $C_8H_{12}N_2O_3$. Calculated: C 52.2; H 6.5; N 15.2%.

1-(1,2-Dicarbamoylvinyl)-2-carbamoylaziridine (VIc). A solution of 6.58 g (27 mmole) of aziridine Vc in 50 ml of methanol was saturated with dry ammonia at 0°C, after which the mixture was allowed to stand at 0°C for 72 h. The precipitated amide VIc was removed by filtration and crystallized from ethanol to give 4.0 g (72%) of colorless crystals with mp 218-222°C (dec.). ^{1}H NMR spectrum (d_6-DMSO): 2.16 [1H, dd, J = 0.8 and 6.0 Hz, 3-H (trans)], 2.23 [1H, dd, J = 0.8 and 3.0 Hz, 3-H (cis)], 2.56 (1H, dd, J = 3.0 and 6.0 Hz, 2-H), 5.38 (1H, s, =CH), 6.9 and 8.2 (1H each, s, $CONH_2$), 7.2 and 7.4 (1H each, s, 1-$CONH_2$), and 7.3 ppm (2H, s, 2-$CONH_2$). ^{13}C NMR spectrum (d_6-DMSO): 171.2 (C=O), 167.4 (C=O), 167.1 (2-$CONH_2$), 155.5 (=CN), 109.4 (=C–), 39.1 [$C_{(2)}$], and 33.5 ppm [$C_{(3)}$]. Found: C 42.0; H 5.0; N 28.2%. $C_7H_{10}N_4O_3$. Calculated: C 42.4; H 5.1; N 28.3%.

2-Carbamoylmethyl-1,3-diazabicyclo[3.1.0]hexan-4-one (VIIa). A) A solution of 20.0 g (0.11 mole) of ester Va in 25 ml of methanol was stirred at –40°C with 50 ml of liquid ammonia, after which the mixture was maintained at 20°C in an autoclave for 10 days. The ammonia was evaporated at room temperature, and the precipitate was removed by filtration and washed with dry ether to give 10.3 g (66%) of colorless crystals with mp 204-205°C (dec., from 50% ethanol). ^{1}H NMR spectrum (d_6-DMSO): 1.68 [1H, d, J = 2.7 Hz, 6-H (cis)], 1.83 [1H, d, J = 6.0 Hz, 6-H (trans)], 2.25 and 2.37 (1H each, dd, J = 6.8 and 14.0 Hz, $COCH_2$), 2.49 (1H, dd, J = 2.7 and 6.0 Hz, 5-H), 4.89 (1H, t, J = 6.8 Hz, 2-H), and 6.94, 7.41, and 7.67 ppm (1H each, s, NH). ^{13}C NMR spectrum (d_6-DMSO): 175.1 (C=O), 171.7 [$C_{(4)}$=O], 71.7 [$C_{(2)}$], 39.9 (CH_2), 38.4 [$C_{(5)}$], and 27.7 ppm [$C_{(6)}$]. Mass spectrum: m/z 154 (M–1), 126 (M–1–$CONH_2$), 97 (M–CH_2CONH_2). Found: C 46.2; H 6.0; N 27.0%. $C_6H_9N_3O_2$. Calculated: C 46.5; H 5.9; N 27.1%.

B) Amide VIIa was similarly obtained from VIa in 45% yield and had mp 204-206°C (dec.).

2-Carbamoylmethyl-2-carbamoyl-1,2-diazabicyclo[3.1.0]hexan-4-one (VIIb). A 100-ml sample of liquid ammonia was added at –40°C to a solution of 35.0 g (0.14 mole) of ester Vc in 50 ml of methanol, and the mixture was worked up as in the preparation of amide VIIa to give 20.7 g (67%) of a colorless product with mp 193-194°C (dec., from isopropyl alcohol). ^{1}H NMR spectrum (d_6-DMSO): 1.94 [1H, d, J = 3.0 Hz, 6-H (trans)], 2.01 [1H, d, J = 6.0 Hz, 6-H (cis)], 2.63 (1H, dd, J = 3.0 and 6.0 Hz, 5-H), 2.64 (2H, s, CH_2CO), and 6.98, 7.29, 7.36, 7.45, and 8.00 ppm (1H each, s, NH). ^{13}C NMR spectrum (d_6-DMSO): 174.0 (C=O), 173.7 (C=O), 171.0 [$C_{(4)}$=O], 79.5 [$C_{(2)}$], 41.0 (CH_2), 37.9 [$C_{(5)}$], and 29.9 ppm [$C_{(6)}$]. Found: C 42.6; H 5.1; N 28.6%. $C_7H_{10}N_4O_3$. Calculated: C 42.4; H 5.1; N 28.3%.

LITERATURE CITED

1. I. Kalvins and E. B. Astapenok, Belgian Patent No. 860239; Chem. Abstr., 90, 34039 (1974).
2. K. Wüthrich, NMR in Biological Research: Peptides and Proteins, Elsevier, New York (1976), p. 177.
3. E. Kyburz, H. Els, St. Majnoni, G. Englert, C. V. Planta, and P. A. Plattner, Helv. Chim. Acta, 49, 359 (1966).