8. Y. Iwakura and A. Nabeya, J. Org. Chem., 25, 1118 (1960).
9. P. T. Black and M. L. Heffernan, Aust. J. Chem., 17, 558 (1964).
10. M. Attimonelli and O. Sciacovelli, Org. Magn. Reson., 12, 17 (1979).
11. T. Kidrič, D. Hadži, D. Kocjan, and V. Rutar, Org. Magn. Reson., 15, 280 (1981).
12. D. M. Grant and B. V. Cheney, J. Am. Chem. Soc., 89, 5315 (1967).
13. B. V. Cheney and D. M. Grant, J. Am. Chem. Soc., 89, 5319 (1967).
14. E. P. Prokof'ev and Zh. A. Krasnaya, Izv. Akad. Nauk SSSR, Ser. Khim., 15, 1011 (1980).
15. I. V. Zuika, Yu. Yu. Popelis, Z. P. Bruvers, D. E. Zaruma, Ya. É. Leeis, and M. A. Tsirule, Khim. Geterotsikl. Soedin., No. 7, 932 (1981).
16. T.-A. Su, E. Siew, E. V. Brown, and S. L. Smith, Org. Magn. Reson., 10, 122 (1977).

DERIVATIVES OF AZIRIDINE-1,2-DICARBOXYLIC ACID

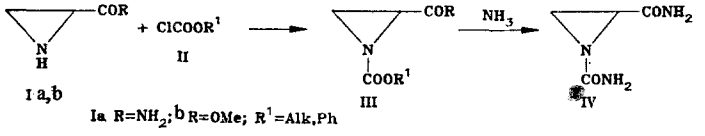
P. T. Trapentsier, I. Ya. Kalvin'sh,
É. É. Liepin'sh, É. Ya. Lukevits, and
V. Ya. Kauss

UDC 547.717'464.2'461'29'26.07

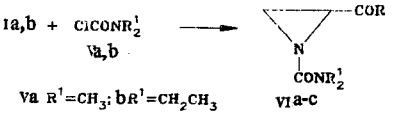
The corresponding esters and amides of aziridine-1,2-di-carboxylic acid were obtained by the reaction of esters and amides of aziridine-2-carbocylic acid with esters and amides of chlorocarbonic acid, isocyanates, and isothiocyanates. The reaction of 2-methoxycarbonylaziridine with diisocyanates and chlorides of the dicarboxylic acids leads to the formation of bisaziridines.

Derivatives of aziridinecarboxylic acids have been studied extensively as immunoregulating and carcinostatic agents [1]. It has already been observed that 2-carbamoylaziridine [2] and 1,2-dicarbamoylaziridine and 1-carbamoyl-2-cyanoaziridine [3] have antineoplastic and immunostimulating properties [3].

In order to obtain new derivatives of aziridinecarboxylic acids for biological studies we carried out reactions of esters and amides of aziridine-2-carboxylic acid with esters and amides of chlorocarbonic acid, as well as with various isocyanates and isothiocyanates. We have shown that aziridine-1,2-dicarboxylic acid esters IIIf, h or 1-alkoxycarbonyl-2-carbamoylaziridines IIIa-e (Table 1) are formed in the reaction of derivatives Ia, b with chlorocarbonic acid esters at low temperatures in the presence of triethylamine. Conclusions regarding the structure of ester IIIf were drawn on the basis of an analysis of the PMR spectra (Table 2), since this compound proved to be thermally unstable and decomposed in an attempt to purify it by vacuum distillation at 120°C (0.003 mm). Compounds IIIa-e were converted to 1,2-dicarbamoylaziridine (IV) by treatment with dry ammonia in methanol at 0-20°C.

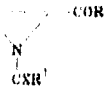


1,2-Dicarbamoylaziridines VIa, b and 1-carbamoyl-2-methoxy-carbonylaziridine (VIc) (Table 1) were obtained by the reaction of Ia,b with chloroformic acid amides Va,b. The reactions were carried out as in the case of chlorocarbonic acid esters.



Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1070-1074, August, 1985. Original article submitted October 8, 1984.

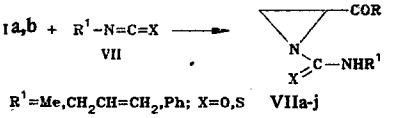
TABLE 1. Physicochemical Parameters of 1,2-Disubstituted Aziridines



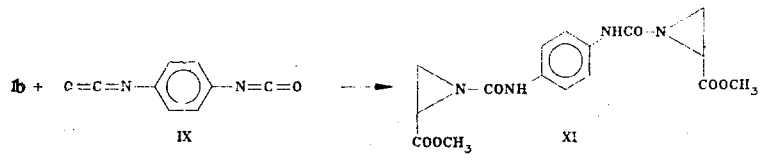
Compound	R'*	mp or bp (mm), deg C†	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
IIIa	OCH_3	116—118	41,9	5,4	19,3	$C_5H_8N_2O_3$	41,7	5,6	19,4	78
IIIb	OCH_2CH_3	125—126,5	45,4	6,1	17,5	$C_6H_{10}N_2O_3$	45,6	6,4	17,7	75
IIIc	$OCH(CH_3)_2$	103—104	48,5	6,9	16,0	$C_7H_{12}N_2O_3$	48,8	7,0	16,3	82
IIId	$OCH_2CH_2CH_2CH_3$	73—74	51,7	7,4	14,7	$C_8H_{14}N_2O_3$	51,6	7,6	15,0	70
IIIe	$OCH_2CH(CH_3)_2$	82—83	51,8	7,7	14,6	$C_8H_{14}N_2O_3$	51,6	7,6	15,0	85
IIIh	OCH_3	75 (0,004)	45,1	5,8	8,9	$C_6H_9NO_4$	45,3	5,7	8,8	98
IV	NH_2	160—161	37,3	5,8	32,2	$C_4H_7N_3O_2$	37,2	5,4	32,5	80
VIa	$N(CH_3)_2$	140—142	46,1	7,2	26,8	$C_6H_{11}N_3O_2$	45,9	7,1	26,7	36
VIb	$N(CH_2CH_3)_2$	129—130	51,7	8,3	22,9	$C_8H_{15}N_3O_2$	51,9	8,1	22,7	87
VIc	$N(CH_2CH_3)_2$	100 (0,002)	54,2	8,0	13,9	$C_9H_{16}N_2O_3$	54,0	8,2	14,0	62
VIIIa	$NHCH_3$	137—138	42,2	6,3	29,3	$C_5H_9N_3O_2$	42,4	6,4	29,1	98
VIIIb	$NHCH_3$	113—115	38,4	5,8	26,2	$C_5H_9N_3OS$	37,8	5,7	26,4	62
VIIIc	NHC_6H_5	169—171	58,1	5,2	20,2	$C_{10}H_{11}N_3O_2$	58,5	5,4	20,5	95
VIIId	NHC_6H_5	138—139	54,5	5,0	18,8	$C_{10}H_{11}N_3OS$	54,3	5,0	18,9	72
VIIIe	$NHCH_2CH{=}CH_2$	108—111	45,6	6,0	22,3	$C_7H_{11}N_3OS$	45,4	6,0	22,7	99
VIIIf	$NHCH_2CH{=}CH_2$	100 (0,003)	47,8	5,9	13,8	$C_8H_{12}N_2O_2S$	48,0	6,0	14,0	85
VIIIh	$NHCH_3$	100 (0,002)	45,8	6,4	17,9	$C_6H_{10}N_2O_3$	45,6	6,4	17,7	68
VIIIg	$NHCH_3$	90 (0,002)	41,5	5,6	16,2	$C_6H_{10}N_2O_2S$	41,8	5,9	16,3	41
VIIIi	NHC_6H_5	120 (0,003)	59,9	5,3	12,5	$C_{11}H_{12}N_2O_3$	60,0	5,5	12,7	77
VIIIj	NHC_6H_5	110 (0,003)	55,6	4,9	11,7	$C_{11}H_{12}N_2O_2S$	55,9	5,1	11,9	78

*For IIIa-e, IV, VIa, b, and VIIIa-e, R = NH_2, whereas R = OCH_3 for IIIh, VIc, and VIIIf-j; for IIIa-g, IV, VIa,c, and VIIIa,c,h,i, X = O, whereas X = S for VIIIb,d-f,g,j.
†According to the data in [6], IIIa had mp 117-120°C, and IIIb had mp 125-128°C. It was established that IIIh had n_D^{20} 1.4472 and that VIc had n_D^{20} 1.4702.

The reactions of Ia, b with alkyl, alkenyl, and aryl isocyanates and isothiocyanates VII in ether or in acetonitrile take place at room temperature with the liberation of heat. Cooling of the reaction mass is necessary in the case of isocyanates. Substituted aziridine-1,2-dicarboxylic acid amides and thioamides VIIIa-j (Table 1) were obtained.

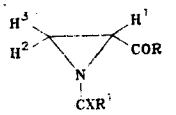


The antineoplastic activity of compounds usually increases when several aziridine rings are introduced into the molecule [4]. We therefore carried out reactions of aziridines Ia, b also with both diisocyanate IX and dicarboxylic acid halide X. The reaction of ester Ib with p-phenylene diisocyanate (IX) leads to the formation of product XI. The reaction proceeds exothermically and at a higher rate than the analogous reaction in the monosiocyanate VII series. The solubilities of the reaction products in polar solvents (water, ethanol) decrease with an increase in the number of aziridine rings.



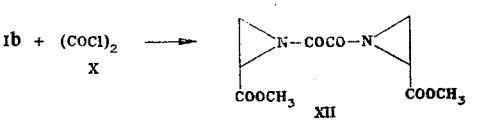
As in the case of aziridine [5], the reaction of ester Ib with oxalyl chloride (X) in the presence of triethylamine proceeds without opening of the aziridine ring and leads to disubstituted product XII.

TABLE 2. Parameters of the PMR Spectra of 1,2-Disubstituted Aziridines

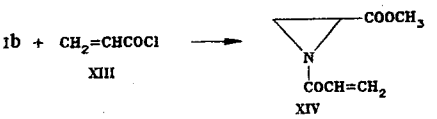


Compound	δ, ppm (DMSO)*					J, Hz		
	H¹	H²	H³	R	R¹	J_{12}	J_{13}	J_{23}
IIIa	2,96	2,24	2,32	3,54	7,9 & 7,4	3,1	5,0	1,6
IIIb	2,94	2,23	2,31	3,98 (CH_2); 1,12 (CH_3)	7,9 & 7,4	3,1	5,0	1,7
IIIc	2,93	2,23	2,28	4,69 (CH); 1,16 and 1,12 (CH_3)	7,9 & 7,4	3,1	5,0	1,6
IIId	2,95	2,23	2,30	3,93 (α-CH_2); 1,1—1,7 (β,γ-CH_2); 0,84 (CH_3)	7,9 & 7,4	3,1	5,0	1,6
IIIe	2,97	2,25	2,30	3,72 (α-CH_2); 1,81 (β-CH); 0,83 (CH_3)	7,9 & 7,4	3,1	5,0	1,7
IIIf	3,09	2,44	2,59	7,0—7,3	3,71	3,0	4,5	1,0
IIIh	3,06	2,52	2,43	3,71	3,77	2,9	4,2	1,2
IV	2,69	2,03	2,21	6,8	7,1 & 7,4	3,1	6,3	1,5
VIa	2,79	2,18	2,33	2,90 & 2,97	7,1 & 7,4	3,0	6,2	1,3
VIb	2,78	2,18	2,35	3,43 & 3,25 (CH_2); 1,13 & 1,04 (CH_3)	7,1 & 7,4	3,1	6,5	1,4
VIc	3,01	2,38	2,52	3,51 & 3,29 CH_2); 1,17 & 1,09 (CH_3)	3,76	3,5	6,6	1,7
VIIIa	2,63	2,06	2,24	7,4 (NH); 2,50 (CH_3)	7,1 & 7,4	3,4	6,2	1,2
VIIIb	2,90	2,36	2,51	9,5 (NH); 2,90 CH_3)	7,3 & 7,5	2,9	6,0	0,9
VIIIc	2,95	2,23	2,40	9,9 (NH); 7,0—7,6 (C_6H_5)	7,1 & 7,4	3,3	6,1	1,4
VIIId	3,17	2,50	2,67	10,1 (NH); 7,3—7,7 (C_6H_5)	7,5	3,0	6,0	0,8
VIIIe	2,92	2,35	2,47	9,7 (NH); 4,05 (CH_2); 5,80 (α-CH); 5,16 & 5,10 (β-CH)	7,2 & 7,4	3,2	6,0	1,2
VIIIf	3,30	2,70	2,90	8,9 (NH); 4,27 (CH_2); 5,95 (α-CH); 5,35 & 5,20 (β-CH)	3,73	3,0	6,0	1,2
VIIIh	3,01	2,25	2,45	6,7 (NH); 2,77 (CH_3)	3,75	3,2	6,2	1,4
VIIIg	3,26	2,58	2,68	8,2 (NH); 3,07 (CH_3)	3,78	3,7	6,0	1,2
VIIIi	3,17	2,40	2,56	8,8 (NH); 7,0—7,5 (C_6H_5)	3,60	3,2	6,0	1,0

*The solvent for IIIf and VIIIh was CCl_4, and the solvent for IIIh, VIc, and VIIIg, i was $CDCl_3$.



Ester Ib is acylated by acrylyl chloride (XIII) at −30°C in the presence of triethylamine to give the 1-acyl derivative (XIV) of 2-methoxycarbonylaziridine. Addition to the double bond is not observed under these conditions.



Absorption bands of an ester carbonyl group at 1710-1755 cm^{-1} and an amide carbonyl group at 1600-1695 cm^{-1}, as well as broad absorption bands of an amine at 3200-3400 cm^{-1}, are present in the IR spectra of the compounds obtained.

The parameters of the PMR spectra of the investigated compounds are presented in Table 2. It is apparent that the chemical shifts of the protons of the aziridine ring depend on the electron-withdrawing properties of both substituents, but the shielding of the 2-H

proton additionally also depends on the anisotropic effect of the substituent attached to the ring C(2) atom. The following order of increase in the acceptor properties of the substituent attached to the N atom can be formulated from the data in Table 2: $CONR_2$ < $CSNR_2$ < COOR. In agreement with this, the COOR substituent in the 2 position displays more pronounced electron-acceptor properties than the $CONH_2$ group. A similar conclusion follows from an analysis of the $^3J_{HH}$ values between the ring protons. The investigated $^3J_{HH}$ constants are smaller for substituents with more pronounced electron-acceptor properties (for example, VIIIa > VIIIb > IIIa or VIIIh > VIIIg > IIIh, as well as IIIa > IIIh, Table 2).

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil or hexachlorobutadiene or liquid films were recorded with a UR-20 spectrometer. The PMR spectra were obtained with Perkin–Elmer R-12B/60 MHz and WH 90/DS spectrometers with hexamethyldisiloxane as the internal standard. The melting points were determined with a Kofler stage.

1-Alkoxycarbonyl-2-carbamoylaziridines IIIa-e (Tables 1 and 2). A 10.1-g (0.1 mole) sample of dry triethylamine was added to a suspension of 8.6 g (0.1 mole) of 2-carbamoylaziridine (Ia) in 100 ml of dry acetonitrile, after which 0.1 mole of chlorocarbonic acid ester II was added with cooling and vigorous stirring at such a rate that the temperature of the reaction mixture did not exceed 0°C. The temperature was then raised to 25°C, and stirring was continued for another 16 h. The resulting precipitate was removed by filtration and washed with acetone. The filtrates were combined and evaporated at reduced pressure, the resulting oil was triturated with acetone, the precipitate was removed by filtration, and the filtrate was evaporated. After the addition of acetonitrile and cooling, aziridines IIIa-e crystallized out in the form of colorless crystals, which were removed by filtration and crystallized from acetone or ethanol.

1,2-Dicarbamoylaziridine (IV). A solution of 14.4 (0.1 mole) of 1-methoxycarbonyl-2-carbamoylaziridine (IIIa) in 100 ml of methanol was saturated with dry ammonia at room temperature, after which the mixture was maintained at room temperature for 24 h. It was then cooled to 0°C, and the precipitated crystals were removed by filtration and crystallized from absolute ethanol to give 10.3 g (80%) of colorless crystals of diamide IV with mp 160-161°C.

Aziridine-1,2-dicarboxylic Acid Esters IIIf, h. A 10.1-g (0.1 mole) sample of dry triethylamine in 100 ml of absolute ether was added to a solution of 10.1 g (0.1 mole) of 2-methoxycarbonylaziridine (Ib), after which 0.1 mole of chlorocarbonic acid ester was added dropwise to 0°C. The temperature was then slowly raised to room temperature, and the mixture was stirred for another 8 h. The precipitate was removed by filtration, and the solvent was evaporated to dryness. The resulting oil was distilled in a high vacuum.

1-Carbamoyl- and 1-Thiocarbamoyl-2-carbamoylaziridines VIIIa-e. A 4.3-g (0.05 mole) sample of 2-carbamoylaziridine (Ia) was suspended in 150 ml of acetonitrile, after which a solution of 0.05 mmole of the isocyanate or isothiocyanate in 20 ml of acetonitrile was added dropwise at room temperature, and the mixture was stirred at room temperature for 24 h. The precipitate was removed by filtration and washed with acetone, and the reaction product was crystallized from acetonitrile or ethanol. Additional workup of the filtrate gave another small amount of amide VIII.

1-Carbamoyl- and 1-Thiocarbamoyl-2-alkoxycarbonylaziridines VIIIf-j. A solution of 0.05 mole of isocyanate or isothiocyanate VII in 10 ml of absolute ether was added dropwise to a solution of 5.05 g (0.05 mole) of 2-methoxycarbonylaziridine (Ib) in 50 ml of absolute ether. The temperature rose to 35°C. The mixture was then stirred at room temperature for 12 h, after which the ether was evaporated to dryness, and the residue was crystallized from acetonitrile or isopropyl alcohol.

Substituted 1-Carbamoylaziridine-2-carboxylic Acid Methyl Esters or Amides VIa-c. A 10.1-g (0.1 mole) sample of dry triethylamine was added to a suspension or solution of 0.1 mole of aziridine Ia, b in 100 ml of acetonitrile, after which 0.1 mole of chloroformic acid N,N-disubstituted amide Va, b was added dropwise at 10°C, and the mixture was stirred at 80°C for 2 h. The temperature was raised to room temperature, and the mixture was stirred for another 4 h. The precipitate was removed by filtration, the filtrate was evaporated to dryness, and the residue was treated with acetone. The solvent was removed by distillation, and the product was distilled (VIc) or crystallized (VIa, b) from ethanol.

N,N-Bis(2-methoxycarbonylaziridinocarbonyl)-p-phenylene-diamine (XI). A 10.4-g (0.065 mole) sample of isocyanate IX was added with cooling and vigorous stirring to a solution of 13.1 g (0.13 mole) of ester IB in 100 ml of chloroform, and the mixture was stirred at room temperature for 2 h. The precipitate was removed by filtration and crystallized from isopropyl alcohol to give 19.7 g (84%) of colorless amide XI with mp 172-173°C. IR spectrum (mineral oil): 1670 (C=O), 1740 ($COOCH_3$), and 3340 cm^{-1} (NH). PMR spectrum (DMSO), δ: 2.34 (2H, q, 3-H), 2.53 (2H, q, 3-H), 3.13 (2H, q, 2-H), 3.69 (6H, s, OCH_3), 7.39 (4H, s, C_6H_4), and 9.9 ppm (2H, s, NH). Found: C 52.8; H 4.9; N 15.4%. $C_{16}H_{18}N_4O_6$. Calculated: C 53.0; H 5.0; N 15.5%.

Oxalylbis(2-methoxycarbonyl-1-aziridinyl) (XII). A solution of 17.2 g (0.17 mole) of ester Ib, 26.2 g (0.187 mole) of triethylamine, and 50 ml of dry benzene was cooled to 10°C, after which a solution of 10.8 (0.085 mole) of oxalyl chloride in 50 ml of dry benzene was added dropwise with stirring. The temperature was maintained at 5-15°C, after which the mixture was stirred at room temperature for 4 h. The precipitate was removed by filtration, and the solution was evaporated to dryness. The residue was washed with cold water and treated with 200 ml of acetone. The mixture was filtered to give 22.5 g (88%) of product XII with mp 170-171°C (from isopropyl alcohol). IR spectrum (mineral oil): 1690 (C=O) and 1725 cm^{-1} ($COOCH_3$). PMR spectrum (DMSO), δ: 2.49 (2H, q, 3-H), 2.66 (2H, q, 3-H), 3.56 (2H, q, 2-H), and 3.67 ppm (6H, s, OCH_3). Mass spectrum: 256 (M^+), 228 (M − CO), 225 (M − OCH_3), and 128. Found: C 46.6; H 4.4; N 11.1%. $C_{10}H_{12}N_2O_6$ Calculated: C 46.9; H 4.7; N 10.9%.

1-Acrylyl-2-methoxycarbonylaziridine (XIV). A 22.2-g (0.22 mole) sample of triethylamine was added to a solution of 20.2 g (0.2 mole) of ester Ib in 250 ml of absolute ether, after which a solution of 20.0 g (0.22 mole) of chloride XIII in 100 ml of absolute ether was added with stirring at −40°C to −30°C in the course of 1 h. Stirring was continued for another 1.5 h, and the temperature was raised slowly to 20°C. The precipitate was removed by filtration and washed with 50 ml of absolute ether. The solvents were removed, and product XIV was distilled *in vacuo* at 80°C (0.005 mm) to give 23.1 g (67%) of a product with n_D^{20} 1.4800. IR spectrum (thin layer): 1680 (C=O) and 1730 cm^{-1} ($COOCH_3$). PMR spectrum ($CDCl_3$), δ; 2.52 (1H, q, 3-H), 2.60 (1H, q, 3-H), 3.27 (1H, q, 2-H), 3.73 (3H, s, OCH_3), 5.80 (1H, dd, α-H), and 2.38 and 6.20 ppm (2H, dd, β-H). Found: C 53.9; H 5.8; N 8.7%. $C_7H_9NO_3$. Calculated: C 54.2; H 5.8; N 9.0%.

LITERATURE CITED

1. M. Von Ardenne and P. G. Reitnauer, Arzneimittel Forsch., Drug Res., 27, 1701 (1977).
2. I. Ya. Kalvin'sh and E. B. Astapenok, Belgian Patent No. 860239; Chem. Abstr., 90, 34103 (1979).
3. G. A. Luckenbach, D. Cortecampeao, M. L. Modolell, P. G. Munder, and U. Bicker, Exp. Pathol., 19, 37 (1981).
4. J. Cheymol, P. Chabrier, G. Deysson, and A. Carayon-Gentil, Biol. Med. (Paris), 56, 519 (1967).
5. C. W. Woods, A. B. Borkovec, and F. M. Hart, J. Med. Chem., 7, 371 (1964).
6. E. Bosies, R. Heerdt, R. Gall, U. Bicker, and A. E. Ziegler, West German Patent No. 2656323; Chem. Abstr., 91, 39299 (1980).