REACTIONS OF AZIRIDINE-2-CARBOXYLIC ACID DERIVATIVES WITH ESTERS AND NITRILES OF UNSATURATED ACIDS

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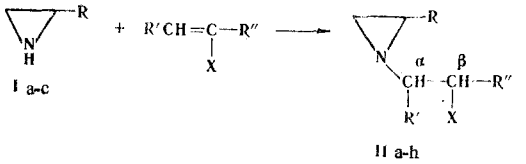
Products of addition to the multiple bond were obtained in the reaction of the methyl ester, nitrile, and amide of aziridine-2-carboxylic acid with esters or nitrides of acrylic acid and esters of maleic, acetylenemonocarboxylic, and acetylenedicarboxylic acids. The bromination of 1-(2-alkoxycarbonylethenyl)-2-methoxycarbonylaziridines under various conditions leads to the addition of bromine to the multiple bond with retention or opening of the aziridine ring.

The reactions of aziridine and some of its C-alkyl-substituted derivatives with α,β-unsaturated esters, nitriles, and ketones have been studied extensively [1, 2]. The reactions with unsubstituted aziridine in all cases proceed with retention of the aziridine ring, while the product of the reaction of trans-2-benzoyl-3-phenylaziridine with dimethyl acetylenedicarboxylate was a pyrrole derivative [3].

In order to study the effect of substituents on the reactivity of aziridine-2-carboxylic acid we investigated the reactions of aziridines I with derivatives of ethylene- and acetylenecarboxylic acids. Esters and the nitrile of acrylic acid, as well as esters of maleic, propiolic, and acetylenedicarboxylic acids, were used as the electrophilic components. The reactions were carried out in organic solvents or without solvents at 50 to 100°C.



I a R=COOMe; b R=CN; c R=$CONH_2$; II a R=R″=COOMe, R′=X=H; b R=COOMe, R′=X=H; R″=CN; c X=H, R=R′=R″=COOMe; d R=COOMe, R′=H, X=Cl, R″=CN; e R=R″=CN, R′=X=H; f R=CN, R′=X=H, R″=COOMe; h R=$CONH_2$, R′=X=H, R″=COOMe

TABLE 1. Derivatives of Aziridine-2-carboxylic Acid

Compound	bp, °C (mm)	mp, °C	n_D^{20}	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
IIa	95 (0,002)	—	1,4561	51,1	7,0	7,7	$C_8H_{13}NO_4$	51,3	7,0	7,5	86
IIb	150 (0,005)	—	1,4550	54,3	6,7	18,0	$C_7H_{10}N_2O_2$	54,5	6,5	18,2	62
IIc	150 (0,002)	—	1,4608	49,1	6,3	5,6	$C_{10}H_{15}NO_6$	49,0	6,2	6,7	58
IId	100 (0,002)	—	—	44,5	4,6	14,8	$C_7H_9ClN_2O_2$	44,6	4,8	14,9	54
IIe	100 (0,005)	—	—	59,1	5,4	34,4	$C_6H_7N_3$	59,5	5,8	34,7	67
IIf	100 (0,005)	—	1,4580	54,0	6,3	18,0	$C_7H_{10}N_2O_2$	54,5	6,5	18,2	58
IIh	—	75—76	—	48,9	7,3	16,4	$C_7H_{12}N_2O_3$	48,9	7,0	16,3	75
IVa	100 (0,002)	—	1,5022	52,4	6,1	7,4	$C_8H_{11}NO_4$	51,9	6,0	7,7	82
IVb	100 (0,002)	—	1,4954	54,0	6,4	7,0	$C_9H_{13}NO_4$	54,3	6,6	7,0	88
IVc	155 (0,002)	64—65	—	49,2	5,4	5,9	$C_{10}H_{13}NO_6$	49,4	5,4	5,8	75
IVd	—	132—133	—	49,3	5,8	16,3	$C_7H_{10}N_2O_3$	49,5	5,9	16,5	73

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TABLE 2. Parameters of the PMR Spectra of N-Ethyl-Substituted Derivatives of Aziridine-2-carboxylic Acid

Compound	R	R′	R″	X	δ, ppm (in $CDCl_3$)									J, Hz		
					2-H	3-H (*cis*)	3 H (*trans*)	H_α	H_β	R	R′	R″	X	J^{cis}_{23}	J^{trans}_{23}	J_{33}
II a	$COOCH_3$	H	$COOCH_3$	H	2,12	2,18	1,67	2,65	2,65	3,72	2,65	3,68	2,65	3,2	6,6	0,5
IIb	$COOCH_3$	H	CN	H	2,20	2,30	1,74	2,65	2,65	3,76	2,65	—	2,65	3,2	6,6	0,5
IIc	$COOCH_3$	$COOCH_3$	$COOCH_3$	H	2,49	2,23	1,84	—*	—*	3,77	3,72	3,75	—*	3,5	6,5	0
					2,23	2,34	2,01							3,4	6,3	0,2
IId †	$COOCH_3$	H	CN	Cl	2,40	2,34	1,86	2,90	4,67	3,69	2,90	—	—	3,1	6,0	0,5
IIe	CN	H	CN	H	2,18	2,32	1,83	2,62	2,62	—	2,62	—	2,62	3,0	6,1	0,2
IIf	CN	H	$COOCH_3$	H	2,03	2,22	1,72	2,59	2,59	—	2,59	3,69	2,59	3,0	6,1	0,3
IIh	$CONH_2$	H	$COOCH_3$	H	2,06	1,94	1,67	2,62	2,62	6,1; 6,4	2,62	3,73	2,62	3,1	6,2	0,5

*The protons form a complex at 2.6-3.6 ppm.
†For this compound $J_{\alpha\beta}$ = 6.5 Hz.

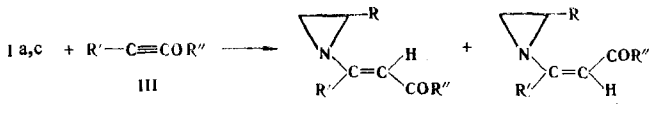
TABLE 3. Parameters of the PMR Spectra of Aziridine-2-carboxylic Acid Derivatives

Compound	Isomer	δ, ppm ($CDCl_3$)							J, Hz			
		2-H	3-H (*cis*)	3-H (*trans*)	=CH	R	R′	R″	J_{33}	J^{cis}_{23}	J^{trans}_{23}	$J_{R'N}$
IVa	E	2,72	2,52	2,21	5,43	3,79	7,46	3,79	1,7	3,2	6,1	13,6
Va	Z	2,92	2,59	2,36	5,23	3,78	6,59	3,67	1,4	3,4	5,9	9,0
IVb*	E	2,69	2,52	2,19	5,41	3,76	7,43	4,07 (CH_2); 1,25 (CH_3)	1,7	3,1	6,1	13,4
Vb*	Z	2,94	2,54	2,36	5,22	3,76	6,54	4,06 (CH_2); 1,25 (CH_3)	1,4	3,3	5,9	9,2
Vc	Z	2,88	2,55	2,34	5,40	3,74	3,84	3,65	1,1	3,2	6,1	—
IVd	E	2,61	2,38	2,18	5,47	6,3	7,47	3,69	1,4	3,2	6,5	13,2
Ve	Z	2,72	2,52	2,25	5,29	6,3	6,58	3,69	1,4	3,5	6,6	9,2

*The J_{HH} constant for the ethyl group is 6.6 Hz.

Products of addition to the double bond (IIa-h, Tables 1 and 2) were obtained. It is interesting to note that when an asymmetric center is bonded directly to the nitrogen atom (IIc), doubling of the spectral lines of the aziridine ring in the PMR spectrum is observed. This is evidently due to the mutual effect of two asymmetric centers [$C_{(2)}$ and C_α] in the diastereomeric reaction products. When both chiral centers are removed in space (for example, in IId), nonequivalence [4] of the resonances of the aziridine ring for the two diastereomers is no longer observed.

In contrast to the analogous reactions in the unsubstituted aziridine series [5, 6], the reaction of aziridines Ia,c with acetylenecarboxylic acid esters III proceeds stereospecifically. In all cases trans-addition products IV (Table 3) are primarily formed. Isomerization to

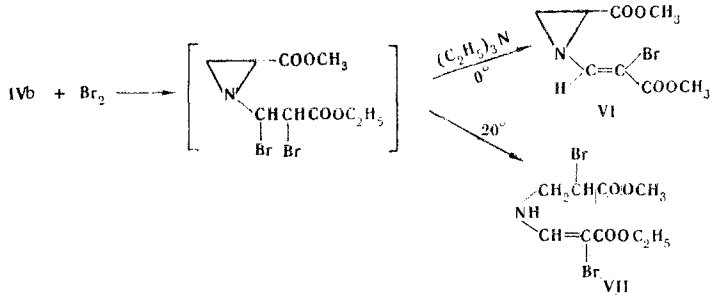


IV, V a R=COOMe, R′=H, R″=OMe; b R=COOMe, R′=H, R″=OEt; c R=R′=COOMe, R″=OMe; d R=$CONH_2$, R′=H, R″=OMe

the cis form does not occur when trans isomer IVb is heated in a sealed ampul at 60°C for 60 h.

In order to study the reactivities of the 1-(2-alkoxycarbonylethenyl)-aziridine-2-carboxylic acid esters (IVa,b) obtained we onvestigated their bromination under various conditions.

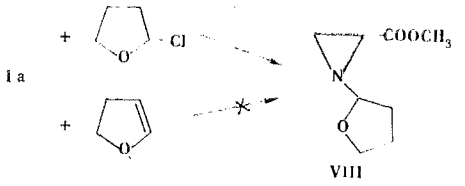
The bromination of ester IVb at 0°C in the presence of triethylamine gives a product of substitution at the multiple bond (VI). At room temperature in the absence of triethylamine bromination gives enamine VII.



It has been established [7] that in reactions with ethyleneimine the reactivities of unsaturated compounds decrease in the order

$$CH_2{=}CH{-}COOR > CH_2{=}CH{-}OCOCH_3 > CH_2{=}CH{-}OR$$

This relationship is also confirmed by our studies.



Thus we were unable to obtain 1-(2-tetrahydrofuryl)-2-methoxycarbonyl-aziridine (VIII) by the addition of ester Ia to 2,3-dihydrofuran, and no reaction occurred with ethyl vinyl ether even in the case of prolonged heating in the presence of an Na or Cu catalyst.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with Perkin-Elmer R12A (60 MHz) and Brucker WH-90/DS (90 MHz) spectrometers with hexamethyldisiloxane as the internal standard. The melting points were determined with a Kofler stage.

1-(2-Methoxycarbonylethyl)aziridine-2-carboxylic Acid Derivatives (IIa,f,h, Tables 1 and 2). A 21.5-g (0.25 mole) sample of methyl acrylate was added to 0.05 mole of methyl ester, amide, or nitrile Ia-c, and the mixture was heated at 75-80°C for 40 h. The unchanged methyl acrylate was removed by distillation, and the residue was distilled in vacuo (IIa,f) or crystallized from acetonitrile (IIh).

1-(2-Cyanoethyl)aziridine-2-carboxylic Acid Methyl Ester and Nitrile (IIb,e). A 5.3-g (0.1 mole) sample of acrylonitrile was added to 0.05 mole of methyl ester or nitrile Ia,b, and the mixture was heated at 60°C for 30-40 h. The unchanged acrylonitrile was removed by distillation, and the residue was subjected to fractional distillation.

Methyl 1-(1,2-Dimethoxycarbonylethyl)aziridine-2-carboxylate (IIc). A mixture of 5.05 g (50 mmole) of ester Ia and 10.8 g (75 mmole) of dimethyl maleate was heated at 60°C for 40 h, after which the dimethyl fumarate was removed by filtration, the unchanged dimethyl maleate was removed by distillation, and the residue was subjected to fractional distillation.

1-(2-Chloro-2-cyanoethyl)-2-methoxycarbonylaziridine (IId). A mixture of 17.2 g (0.17 mole) of ester Ia, 50 ml of carbon tetrachloride, 23.8 ml (0.17 mole) of triethylamine, and 15.0 g (0.17 mole) of α-chloroacrylonitrile was heated on a water bath at 80°C for 10 h, after which the precipitate was removed by filtration, the solvent was removed by distillation, and the residue was distilled in vacuo.

1-(2-Methoxycarbonylethenyl)-, 1-(2-Ethoxycarbonylethenyl)-, and 1-(1,2-Dimethoxycarbonylethenyl)-2-methoxycarbonylaziridine (IVa-c). A 0.1-mole sample of the alkyl acetylenecarboxylate (III) was added with stirring at room temperature in a nitrogen atmosphere to

10.1 g (0.1 mole) of ester Ia, the temperature of the reaction mixture was raised to 40-50°C, and stirring was continued at room temperature for 2 h. The reaction products were subjected to fractional distillation.

1-(2-Methoxycarbonylethenyl)-2-carbamoylaziridine (IVd). A 6.6-g (78 mmole) sample of methyl propiolate was added to 6.7 g (78 mmole) of amide Ic, and the mixture was allowed to stand at room temperature. After 20 min, the mixture was heated slowly to 60-70°C, during which the solid material dissolved, and the solution turned yellow. The reaction product crystallized at room temperature.

1-(2-Ethoxycarbonyl-2-bromoethenyl)-2-methoxycarbonylaziridine (VI). A solution of 10.1 g (51 mmole) of aziridine IVb and 7.7 ml (51 mmole) of triethylamine in 70 ml of carbon tetrachloride was cooled to 0°C, and a solution of 8.9 g (55 mmole) of bromine in 10 ml of carbon tetrachloride was added dropwise with stirring. Stirring was continued at 0°C for 1 h, after which the temperature was raised to room temperature, and the mixture was stirred for 2 h. It was then allowed to stand overnight and filtered, and the filtrate was evaporated to dryness. The residual reddish oil was distilled at 150°C (0.02 mm) to give 5.6 g (41%) of a yellow oil. PMR spectrum ($CDCl_3$): δ 1.27 (3H, t, J = 6.6 Hz, CH_3), 2.49 (1H, dd, J = 1.4 and 6.1 Hz, trans-3-H), 2.62 (1H, dd, J = 1.4 and 3.4 Hz, cis-3-H), 3.04 (1H, dd, J = 6.1 and 3.4 Hz, 2-H), 3.75 (3H, s, OCH_3), 4.20 (2H, q, J = 6.6 Hz, OCH_2), and 8.05 ppm (1H, s, CH). Found: C 38.5; H 4.2; N 4.8%. $C_9H_{12}BrNO_4$. Calculated: C 38.9; H 4.4; N 5.0%.

Methyl 2-Bromo-3-[N-(2-ethoxycarbonyl-2-bromoethenyl)amino]propionate (VII). A 4.8-g (30 mmole) sample of bromine was added dropwise at 20°C to a solution of 5.97 g (30 mmole) of aziridine IVb in 20 ml of carbon tetrachloride, after which the temperature of the mixture was maintained at 20-25°C for 24 h. The solvent was evaporated to give 9.6 g (89%) of product VII, which decomposed at 100°C upon distillation. PMR spectrum ($CDCl_3$): δ 1.28 (3H, t, J = 6.6 Hz, CH_3), 3.80 (2H, m, NCH_2), 3.82 (3H, s, OCH_3), 4.20 (2H, q, J = 6.6 Hz, OCH_2), 4.38 (1H, t, J = 6 Hz, CH), 5.4 (1H, doublet of triplets, J = 13.6 and 7.3 Hz, NH), and 7.60 ppm (1H, d, J = 13.6 and 7.3 Hz, CH=).

1-(2-Tetrahydrofuryl)-2-methoxycarbonylaziridine (VIII). A solution of 10.1 g (0.1 mole) of ester Ia and 15.4 ml (0.11 mole) of triethylamine in 50 ml of ether was cooled to 0°C, and a solution of 10.7 g (0.1 mole) of 2-chlorotetrahydrofuran in 15 ml of ether was added dropwise with stirring at 0°C to the mixture in the course of 30 min. The mixture was stirred at 0°C for 2 h, after which the temperature was raised slowly to 20°C, and the mixture was maintained at this temperature for another 4 h. The precipitate was removed by filtration, the solvent was evaporated, and the resulting oil was distilled with collection of the fraction with bp 115-118°C (12 mm) and n_D^{20} 1.4630. The yield was 12.2 g (72%). PMR spectrum ($CDCl_3$): δ 1.7-2.1 (6H, m, 3-, 3'-, and 4'-H), 2.42 (1H, dd, J = 3.0 and 5.9 Hz, 2-H), 3.65 (3H, s, OCH_3), 3.70 (2H, m, 5'-H), and 4.33 ppm (1H, m, 2'-H). Found: C 56.0; H 7.5; N 80%. $C_8H_{13}NO_3$. Calculated: C 56.1; H 7.7; N 8.2%.

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