REACTIONS OF AZIRIDINE-2-CARBOXYLIC ACID DERIVATIVES WITH ALDEHYDES AND KETONES

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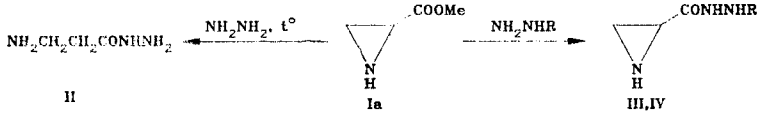
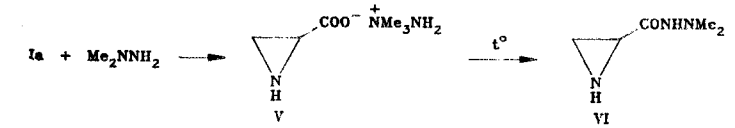
The reaction of methyl aziridine-2-carboxylate with hydrazine or alkylhydrazines gives the respective hydrazides, which with ketones form 2,2-disubstituted 1,3,4-triazabicyclo-[4.1.0]heptan-5-ones. With aldehydes they form the respective hydrazones. The reaction of the amide and methyl ester of aziridine-2-carboxylic acid with aldehydes gives a series of aziridinocarbinols.

The synthesis of functionally substituted aziridines with electron acceptor substituents has been studied quite broadly [1, 2]. Only the attempts to obtain aziridine-2-carboxylic hydrazides have been unsuccessful [3]. Methyl 1-tert-butylaziridine-2-carboxylate reacts with hydrazine to form the products of aziridine ring scission. Nevertheless the respective hydrazides are of interest in connection with the possible immunostimulant properties of aziridine derivatives [4] and as starting materials for the synthesis of new heterocyclic systems.

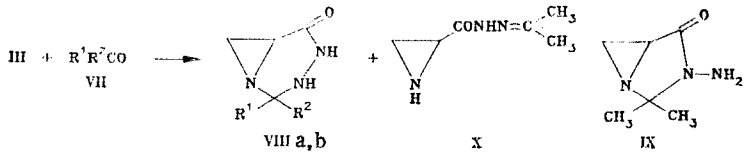
We have therefore investigated the reaction of methyl aziridine-2-carboxylate (Ia) with anhydrous hydrazine and alkylhydrazines. The reaction of Ia with anhydrous hydrazine at 60°C for 1 h forms hydrazide II, which was separated as the hydrochloride salt. At −5° to −10° in the absence of solvent the reaction proceeds with retention of the aziridine ring to give aziridine-2-carboxylic hydrazides III and IV.



In the reaction of dimethylhydrazine with Ia, the latter acts as an alkylating, but not an acylating agent, so that salt V is formed. When the latter is heated in vacuum at 120-140°, 1,2-migration of the acyl group occurs, with detachment of methyl alcohol and formation of hydrazide VI. A similar alkylation was noted in the reaction of esters of aromatic acids with dimethylhydrazine [5, 6].



Taking into account the presence in III of three "amino groups" of different reactivities we studied its reaction with carbonyl compounds. The reaction of III with ketones VII at elevated temperatures in an excess of ketone gave a new class of compounds, viz., 2,2-disubstituted 1,3,4-triazabicyclo[4.1.0]-heptan-5-ones (VIII).



VIII a $R^1=R^2=Me$; b $R^1—R^2=—(CH_2)_5—$

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TABLE 1. Properties of Aziridine-2-carboxylic Hydrazides and Arylidene Hydrazides

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
III	125—126	35,8	7,2	41,6	$C_3H_7N_3O$	35,6	6,9	41,6	90
IV	109—111	41,4	7,8	36,3	$C_4H_9N_3O$	41,7	7,9	36,5	65
VI	89	50,9	6,8	29,5	$C_5H_{11}N_3O$	51,1	7,1	29,8	12
XIIa	137—139	63,4	5,6	22,0	$C_{10}H_{11}N_3O$	63,5	5,8	22,2	64
XIIb	203—204	51,0	4,1	30,0	$C_{10}H_{10}N_4O_3$	51,3	4,3	23,9	59

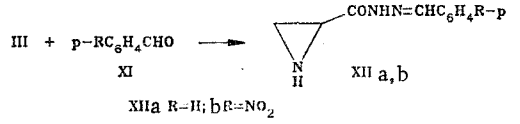
TABLE 2. ^{1}H NMR Spectra of Aziridine-2-carboxylic Hydrazides and Arylidene Hydrazides

Compound	Solvent	δ, ppm					J, Hz		
		2-H	3-H$_{trans}$	3-H$_{cis}$	1-H	other protons	J_{23} cis	J_{23} trans	J_{33}
III	DMSO-D_6	2,30	1,60	1,68	3,3	3,3 (NH_2), 9,4 (CONH)	5,0	3,1	1,9
IV*	DMSO D_6	2,29	1,62	1,62	1,1	2,42 (CH_3), 4,7 (NH), 9,5 (CONH)	—	—	—
	D_2O	2,47	1,91	1,83	—	2,52 (CH_3)	5,4	3,3	0,8
VI	D_2O	2,46	1,91	1,84	—	2,52 (CH_3)	5,9	3,5	0,7
XIIa	DMSO D_6	1,8	1,8	2,0	2,0	7,3, 7,8 (C_6H_5) 8,05, 8,25 (CH)	—	—	—
XIIb	CF_3COOH	5,10	3,4	3,4	—	7,96, 8,35 (C_6H_4), 8,30 (CH)	—	—	—

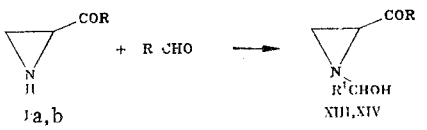
*^{13}C and ^{15}N NMR parameters given in [9].

In the ^{1}H NMR spectrum of the reaction product of III and acetone, the CH_3 proton resonance appears at δ 1.19 and 1.15 ppm; that of the aziridine protons at 2.28, 2.58, and 1.80 ppm. Moreover there are signals for the two different NH protons at 5.2 and 8.6 ppm. The anisochronicity of the methyl groups and their chemical shifts indicate the formation of a cyclic reaction product. The nonequivalence of the carbons in the two methyl groups in the ^{13}C NMR spectrum and the chemical shift of the tetrasubstituted carbon (67.6 ppm) confirm the cyclic structure of VIIIa. The presence of two NH proton signals with strongly different chemical shifts proves the formation of VIIIa, but not the alternate structure of IX; the spectrum of the latter, by analogy with other hydrazides, ought to show only one NH_2 proton signal. The easier formation of the bicyclic system of VIIIa in our case than in the case of other amines [7] is probably attributable to decreased steric hindrance between the aziridine ring and the CH_3 groups in VIIIa as compared with IX. Along with VIIIa, hydrazone X was obtained; it can be formed in parallel. The structure of X, was demonstrated by the ^{1}H NMR spectrum.

The reaction of hydrazide III with aromatic aldehydes XIa, b in methyl alcohol forms only the respective hydrazones XIIa, b.



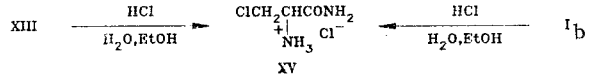
In order to try the synthesis of other heterocyclic systems we investigated the reactions of the methyl ester (Ia) and the amide (Ib) of aziridine-2-carboxylic acid with aldehydes in methanol, and demonstrated that carbinols XIII and XIV are formed.



Ia, XIV R=OMe; Ib, XIII R=NH_2; XIII R^1=CCl_3; XIV R^1=H

Since the reactions of α-aminols have been little studied until now, we studied the conversions of XIII by acid hydrolysis. Along with the ring scission at the N—$C_{(3)}$ bond that is typical of aziridine-2-carboxylic acid derivatives [8], we also found the detachment of the

aldehyde component to form the alanine derivative XV. The latter was also obtained by counter-synthesis, the hydrolysis of amide Ib. Both with XIII and Ib, aziridine ring scission takes place at the N—$C_{(3)}$ bond, in alcohol and aqueous medium alike.



EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument in mineral oil, hexachlorobutadiene, or in a liquid film; ^1H and ^{13}C NMR spectra, on Perkin Elmer R12A (60 MHz) and Bruker WH 90/DS (90 MHz) instruments. The internal standards were HMDS (for ^1H) and cyclohexane (δ 27.44 ppm) (for ^{13}C). Melting points were determined on a Kofler stage. The properties of Compounds III, IV, VI, and XII are shown in Tables 1 and 2.

3-Aminopropionohydrazide (II). A mixture of 3.03 g (0.03 mole) of Ia and 0.9 g (30 mmole) of anhydrous hydrazine was heated for 1 h on a water bath in a nitrogen atmosphere. The mixture was evaporated at 10^{-3} mm pressure and analyzed by PMR. PMR spectrum (in D_2O): δ 2.89 (2H, t, CH_2), 2.46 ppm (2H, t, CH_2). The residue was dissolved in a ethanol—ether mixture and a solution of hydrogen chloride in ether was added at 0°. The precipitate was filtered off and crystallized from ethanol. Yield, 4.4 g (83%); colorless crystals, mp 223-224°. PMR spectrum (in D_2O): δ 2.70 (2H, t, CH_2), 3.30 ppm (2H, t, CH_2). Found: C 20.5; H 5.6; N 23.8%. $C_3H_9N_3O \cdot 2HCl$. Calculated: C 20.5; H 5.7; N 23.9%.

Aziridine-2-carboxylic Hydrazide (III). To 10.1 g (0.1 mmole) of ester Ia was added 3.2 g (0.1 mole) of anhydrous hydrazine dropwise at −5° to −10° with stirring over 20 min. The mixture was stirred another hour. When the mass became viscous and began to solidify, 100 ml of ether was added. Stirring was continued for 4 h at 20°, and the precipitate was filtered off and crystallized from ethanol.

Aziridine-2-carboxylic N'-Methylhydrazide (IV). To 10.1 g (0.1 mole) of Ia was added 4.6 g (0.1 mole) of methylhydrazine in a nitrogen atmosphere at 0°, and the mixture was left in the refrigerator for 24 h. Ether, 100 ml, was added and the precipitate was filtered off and crystallized from acetonitrile.

Trimethylhydrazinium Aziridine-2-carboxylate (V). A mixture of 5.05 g (0.05 mole) of Ia and 30 ml of 1,1-dimethylhydrazine was boiled under reflux for 24 h. The colorless precipitate was filtered off, washed with ether, and crystallized from ethanol. Yield, 5.22 g (65%); colorless crystals, mp 210-212°. ^1H PMR spectrum (in DMSO-D_6): δ 1.41 (1H, q, 3-H), 1.62 (1H, q, 3-H), 2.08 (1H, q, 2-H), 2.8 (1H, s, NH_2), 3.44 (9H, s, NCH_3), 6.7 ppm (2H, s, NH_2). Found: C 44.5; H 9.1; N 26.0%. $C_6H_{15}N_3O_2$. Calculated: C 44.7; H 9.3; N 26.1%.

Aziridine-2-carboxylic Dimethylhydrazide (VI). Salt V, 0.3 g (0.019 mole) was heated at 120-140° and 0.005 mm. The fraction boiling at 65-70° (0.005 mm) was collected. After prolonged storage the viscous mass crystallized. The mixture was triturated with ether and the colorless precipitate was filtered off.

Reaction of Aziridine-2-carboxylic Hydrazide with Acetone. To 10.1 g (0.1 mole) of hydrazide III was added 23.2 g (0.4 mole) of acetone. The mixture was heated for 10-20 h at 50-60°, evaporated to dryness, and treated with chloroform. The precipitate was filtered off and crystallized from acetonitrile. Yield of aziridine-2-carboxylic isopropylidene hydrazide (X), 0.2 g (1.5%); colorless crystals, mp 121-122°. ^1H NMR spectrum (in CD_3OD); δ 2.67 (1H, d.d, J = 3.1 and 5.6 Hz, 3-H), 1.88 (1H, d.d, J = 1.1 and 3.1, Hz, 3-H_{trans}), 1.83 (1H, d.d, J = 1.1 and 5.6 Hz, 3-H_{cis}), 2.03 and 1.96 ppm (3H and 3H, s, CH_3). The chloroform solution was evaporated to dryness and the residue was crystallized from acetone. There was obtained 11.7 g (84%) of colorless crystals of 2,2-dimethyl-1,3,4-triazabicyclo-[4.1.0]-heptan-5-one (VIIIa), mp 126-127°. IR spectrum (in mineral oil): 1680 (C=O), 3180 (NH), 3270 cm^{-1} (NH). ^1H NMR spectrum (in DMSO-D_6): δ 1.15 and 1.19 (3H and 3H, s, CH_3), 1.80 (1H, d, J = 5.6 Hz, 7-H_{trans}), 2.28 (1H, d.d, J = 2.7 and 5.7 Hz, 6-H), 2.58 (1H, d, J = 2.7 Hz, 7-H_{cis}), 5.2 (1H, s, 3-H), 8.6 ppm (1H, s, 4-H). ^{13}C NMR spectrum (in DMSO-D_6): δ 169.1 (s, C=O), 67.6 (s, $C_{(2)}$), 32.8 (d, $C_{(6)}$), 24.6 (t, $C_{(7)}$), 25.2 and 25.0 ppm (q, CH_3). Found: C 50.8; H 7.7; N 29.6%. $C_6H_{11}N_3O$. Calculated: C 51.1; H 7.8; N 29.8%.

2,2-Cyclohexanespiro-1,3,4-triazabicyclo[4.1.0]-heptan-5-one (VIIIb). To 10.1 g (0.1 mole) of hydrazide III was added 39.8 g (0.4 mole) of cyclohexanone. The mixture was heated for 20-30 h at 60-80° and evaporated to dryness, and the residue was crystallized from ace-

tone. There was obtained 14.1 g (71%) of colorless crystals of VIIIb, mp 149-150°. IR spectrum (in mineral oil): 1697 (C=O), 3205 and 3287 cm^{-1} (NH). ^1H NMR spectrum (in DMSO-D_6): δ 1.50 (10H, s, protons of cyclohexanone ring), 1.78 (1H, d, J = 5.6 Hz, 7-H), 2.30 (1H, m, 6-H), 2.58 (1H, d, J = 2.8 Hz, 7-H), 4.9, (1H, s, 3-H), 8.4 ppm (1H, s, 4-H). ^{13}C NMR spectrum (in DMSO-D_6): δ 169.1 (s, C=O), 69.0 (s, $C_{(2)}$), 32.8 (d, $C_{(6)}$), 26.8 (t, $C_{(7)}$), 34.8 and 33.6 (t, $C_{(5')}$ and $C_{(7')}$), 22.9 and 22.6 (t, $C_{(4')}$ and $C_{(6')}$), 24.2 ppm (t, $C_{(5')}$). Found: C 59.3; H 8.2; N 23.0%. $C_9H_{15}N_3O$. Calculated: C 59.6; H 8.2; N 23.2%.

Aziridine-2-carboxylic Arylidene Hydrazides (XIIa,b). A mixture of 2.02 g (0.02 mole) of hydrazide III, 0.02 mole of aldehyde XIa,b, and 60 ml of methanol was heated under reflux on a water bath for 3 h. The solvent was distilled off, and the residue was triturated with ether. The yellow precipitate was filtered off and crystallized from benzene or dimethylformamide.

1-(1-Hydroxy-2,2,2-trichloroethyl)aziridine-2-carboxamide (XIII). To a suspension of 21.5 g (0.25 mole) of amide Ib in 300 ml of chloroform was added 35.0 ml (0.25 mole) of triethylamine. At room temperature a solution of 41.35 g (0.25 mole) of chloral hydrate in 300 ml of chloroform was added. The precipitate was filtered off and the filtrate was left at 20° for 24 h. A colorless precipitate of carbinol XIII formed. Yield, 48.5 g (82%); mp 68-69° (from chloroform). ^1H NMR spectrum (in DMSO-D_6): δ 1.92 (2H, d, J = 5.0 Hz, 3-H), 2.61 (1H, m, 2-H), 4.37 (1H, d, J = 6.0 Hz, CH—O), 6.78 and 7.06 (1H and 1H, s, $CONH_2$), 7.46 ppm (1H, d, J = 6.0 Hz, OH). Found: C 25.3; H 3.2; N 12.0%. $C_5H_7Cl_3N_2O_2$. Calculated: C 25.7; H 3.0; N 12.0%.

Methyl 1-(Hydroxymethyl)aziridine-2-carboxylate (XIV). Into a solution of 6.6 g (0.06 mole) of ester Ia in 100 ml of ether was passed for 15 min, a current of formaldehyde from the depolymerization of 20 g (0.6 mole) of paraformaldehyde at 130°. The mixture was stirred for 1 h at 25-30°, and was then filtered from unreacted paraformaldehyde. The filtrate was evaporated and distilled. BP 100° (0.003 mm). Yield 4.6 g (59%). ^1H NMR spectrum (in $CDCl_3$): δ 1.90 (1H, d.d, J = 1.0 and 6.3 Hz, $3\text{-}H_{trans}$), 2.11 (1H, d.d, J = 1.0 and 3.3 Hz, $3\text{-}H_{cis}$), 2.43 (1H, d.d, J = 3.3 and 6.3 Hz, 2-H), 3.73 (3H, s OCH_3), 4.12 (2H, s, NCH_2O), 4.8 ppm (1H, s, OH). Found: C 45.9; H 6.7; N 10.5%. $C_5H_9NO_3$. Calculated: C 45.8; H 6.9; N 10.7%.

2-Amino-3-chloropropionamide Hydrochloride (XV). A. Carbinol XIII, 4.67 g (0.02 mole) was dissolved in 200 ml of 5% hydrochlorid acid. The mixture was left at 20° for 48 h. The precipitate was filtered off. Yield, 2.6 g (82%); colorless crystals, mp 193-195° (with decomposition, from 1:1 ethanol—2-propanol). ^1H NMR spectrum (in D_2O): δ 4.05 (2H, d, J = 4.4 Hz, CH_2), 4.48 ppm (1H, t, J = 4.4 Hz, CH). Found: C 22.6; H 5.0; N 17.9%. $C_3H_7ClN_2O\cdot HCl$. Calculated: C 22.7; H 5.1; N 17.6%.

B. To a solution of 4.7 g (0.02 mole) of carbinol XIII in 20 ml of ethanol was added ether saturated with dry hydrogen chloride, dropwise with stirring at 0°. The mixture was left for 24 h at room temperature, and the precipitate was filtered off and recrystallized from 1:1 ethanol—isopropyl alcohol. Yield 1.9 g (60%); mp 193-194° (with decomposition). ^1H NMR spectrum (in DMSO-D_6): δ 4.2 (3H, m $CHCH_2$), 7.67 and 8.18 (1H and 1H, s, $CONH_2$), 8.5 ppm (3H, s, N^+H_3).

C. To a solution of 2.15 g (0.025 mole) of amide Ib in 30 ml of ethanol was added ether saturated with dry hydrogen chloride, dropwise with stirring at 0°. The mixture was kept at room temperature for 24 h, and the precipitate was filtered off and crystallized from 1:1 ethanol—isopropyl alcohol. Yield 3.1 g (73%); mp 193-195° (with decomposition).

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MECHANISM OF THE FISCHER REACTION. REARRANGEMENT OF CYCLOHEXANONE N-METHYLPHENYLHYDRAZONE AND N,N'-DIMETHYL-N-PHENYL-N'-(1-CYCLOHEXENYL)HYDRAZINE TO 9-METHYL-1,2,3,4-TETRAHYDROCARBAZOLE

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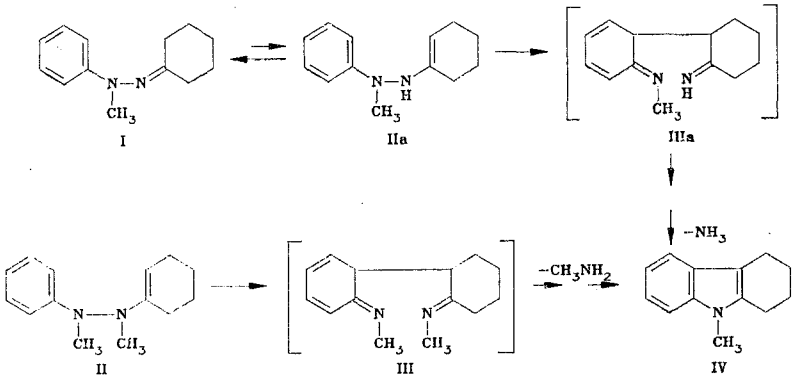
The kinetics of the thermal and acid-catalyzed Fischer reaction of cyclohexanone N-methylphenylhydrazone and N,N'-dimethyl-N-phenyl-N'-(1-cyclohexenyl)hydrazine were studied by a spectrophotometric method. Formation of the carbon–carbon bond proceeds by a [3,3]-sigmatropic shift mechanism. This conclusion was confirmed by MINDO/3 calculations of the rearrangement of a model divinylhydrazine.

We have previously reported [1, 2] that the key step in Fischer indolization (the formation of a carbon–carbon bond) goes via a [3,3]-sigmatropic rearrangement. This conclusion was based on the small effect of substituents on the proportions of isomeric N-aryltetrahydrocarbazoles that form in this reaction from unsymmetrically substituted cyclohexanone N,N-diarylhydrazones. Moreover, in a study of intramolecular Stolle cyclization of metasubstituted chloroacetyldiarylamines we established that there is a high selectivity of carbocation attack on phenyl nuclei with more-donor-like substituents [3]. In combination with the data of [1, 2], these results, in our view, indicate the unsuitability of approaching the fundamental step of the Fischer reaction as an electrophilic substitution.

For a deeper understanding of the indolization mechanism it was necessary to obtain the kinetic and thermodynamic process parameters and also to perform quantum mechanical calculations.

There are several publications [4-7] in which the cyclization rate in acid medium has been measured for various type I hydrazones substituted in the benzene and cyclohexanone rings (see Scheme 1). The kinetic results of [4-6] have been thoroughly discussed in a review [8].

Scheme 1



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