DERIVATIVES OF 1-H-AZIRIDINE-2-CARBOXYLIC ACID

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The reaction of 1,1-dimethylhydrazine with acrylic acid derivatives gave a number of 1,1-dimethyl-2-(2-substituted ethyl)hydrazines, which were quaternized by alkylating agents. The transformations of 1,1,1-trimethyl-2-(2-substituted ethyl)hydrazinium salts in the presence of sodium methoxide were investigated. 2-Cyano-, 2-carbomethoxy-, 2-carbethoxy-, and 2-carbodiethylamidoaziridines and a number of products of decomposition of the starting salts were obtained.

It has been reported [1] that the quaternized salts of some 1,1,2-trisubstituted hydrazines are converted to aziridine derivatives in the presence of sodium methoxide. Some anilides of 1-H-aziridinecarboxylic acids have been obtained by this method.

We investigated the applicability of this reaction for the synthesis of other difficult-to-obtain derivatives of aziridine-2-carboxylic acid. Quaternary salts of trisubstituted hydrazines (IV) were obtained by the addition to acrylic acid derivatives (I) of 1,1-dimethylhydrazine (II) and subsequent quaternization of the adducts (III) by alkylating agents:

$$\underset{\mathrm{I}}{CH_2{=}CH{-}R} + \underset{\mathrm{II}}{(CH_3)_2NNH_2} \longrightarrow \underset{\mathrm{III\ a{-}g}}{(CH_3)_2NNHCH_2CH_2R} \xrightarrow{CH_3X} \underset{\mathrm{IV\ a{-}h}}{X^-(CH_3)_3\overset{+}{N}NHCH_2CH_2R}$$

III a $R{=}CN$; b $R{=}CONH_2$; c $R{=}CON(CH_3)_2$; d $R{=}CON(C_2H_5)_2$; e $R{=}CON(C_4H_9)_2$; f $R{=}COOCH_3$; g $R{=}COOC_2H_5$; IV a $X{=}I$, $R{=}CN$; b $X{=}I$, $R{=}CONH_2$; c $X{=}I$, $R{=}CON(CH_3)_2$; d $X{=}I$, $R{=}CON(C_2H_5)_2$; e $X{=}I$, $R{=}CON(C_4H_9)_2$; f $X{=}I$, $R{=}COOCH_3$; g $X{=}CH_3SO_4$, $R{=}COOCH_3$; h $X{=}I$, $R{=}COOC_2H_5$

1,1,1-Trimethyl-2-(2-carboxylhydrazidoethyl)hydrazinium iodide (IVi) was obtained by hydrazinolysis of ester IVf, inasmuch as the hydrazido group also undergoes quaternization during alkylation of the corresponding trisubstituted hydrazine of the III type.

We have shown that treatment of IV with sodium methoxide in methanol leads to the formation of derivatives (V) of aziridine-2-carboxylic acid only in some cases:

TABLE 1. 1,1-Dimethyl-2-(2-substituted ethyl)hydrazines $(CH_3)_2NNHCH_2CH_2R$

Compound	R	bp, °C (mm)	n_D^{20}	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
IIIa	CN	63—64 (4) 67—71 (6)[2]	1,4349 (1,4345)[2]	$C_5H_{11}N_3$	52,9	10,0	37,6	53,0	9,8	37,1	82
IIIb	$CONH_2$	118—120 (2) 140—145 (5)[3]	1,4537	$C_5H_{13}N_3O$	46,1	10,3	31,7	45,8	10,0	32,0	92
IIIc	$CON(CH_3)_2$	74—76 (2)	1,4714	$C_7H_{17}N_3O$	53,3	10,9	27,0	53,3	10,8	26,9	98
IIId	$CON(C_2H_5)_2$	110—112 (5)	1,4740	$C_9H_{19}N_3O$	58,0	10,3	22,4	58,4	10,3	22,8	97
IIIe	$CON(C_4H_9)_2$	140—142 (5)	1,4598	$C_{13}H_{29}N_3O$	63,7	11,7	17,4	63,8	11,9	17,3	71
IIIf	$COOCH_3$	70—71 (8) 69—73 (8)[2] 62—63 (3)[5]	1,4348 (1,4350)[2] (1,4330)[5]	$C_6H_{14}N_2O_2$	50,1	9,7	19,6	50,0	9,7	19,2	88
IIIg	$COOC_2H_5$	74—75 (5) 78—80 (8)[2] 60 (0,5)[4]	1,4352 (1,4349)[2]	$C_7H_{16}N_2O_2$	52,4	9,7	17,3	52,5	9,9	17,3	83

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*Deceased.

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TABLE 2. PMR Spectra of 1,1-Dimethyl-2-(2-substituted ethyl)-hydrazines $(CH_3)_2NNHCH_2CH_2R$

Compound	R	Chemical shift, τ, ppm				
		CH_3N	CH_2N	CH_2R	NH	R
IIIa	CN	7,65	7,09	7,51	7,5	—
IIIb	$CONH_2$	7,64	7,09	7,70	7,38	2,7—3,7*
IIIc	$CON(CH_3)_2$	7,70	7,16	7,64	7,5	7,03—7,17*
III d	$CON(C_2H_5)_2$	7,77	7,20	7,70	7,7	6,78 (CH_2) 8,93—9,05 (CH_3)*
IIIe	$CON(C_4H_9)_2$	7,66	7,11	7,65	7,40	6,80 (α-CH_2) 8,4—8,9 (β- and γ-CH_2) 9,05 (CH_3)
IIIf	$COOCH_3$	7,77	7,15	7,65	7,7	6,49
IIIg	$COOC_2H_5$	7.70	7,10	7,64	7.7	5,96 (CH_2) 8,77 (CH_3)

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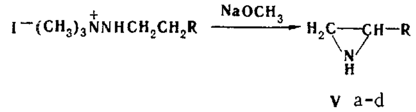
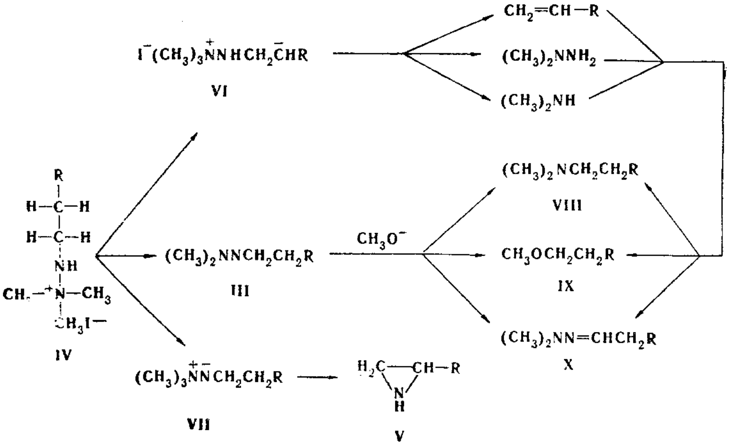
* The signals are split because of hindered rotation about the amide bond.



V a-d

V a $R=COOC_2H_5$;	b $R=COOCH_3$;	c $R=CON(C_2H_5)_2$;	d $R=CN$
Yield: 5%	30%	56%	5%

The products of decomposition of the other 1,1,1-trimethyl-2-(2-substituted ethyl)hydrazinium salts were isolated by preparative gas–liquid chromatography (GLC). Thus 1,1,1-trimethyl-2-(2-N,N-dimethylcarboxamidoethyl)hydrazinium iodide (IVc) is converted to a mixture of substances consisting of 61% 3-dimethylamino-N,N-dimethylpropionamide, 24% 3-methoxy-N,N-dimethylpropionamide, 5% 3-(2,2-dimethylhydrazono)-N,N-dimethylpropionamide, 3% 1,1-dimethyl-2-(2-N,N-dimethylcarboxamidoethyl)hydrazine, and small amounts of dimethylhydrazine. We suppose that, as in the decomposition of other quaternized hydrazinium salts [7], compounds of the VII-X type can be formed only from carbanion VI or as a result of dealkylation of IV:



When we heated 1,1-dimethyl-2-(2-N,N-dimethylcarboxamidoethyl)hydrazine with sodium methoxide in methanol we isolated 55% of the starting compound, 15% 3-(2,2-dimethylhydrazino)-N,N-dimethylpropionamide, and 26% 3-methoxy-N,N-dimethylpropionamide. Consequently, the formation of VII-X is not primarily the result of decomposition of III.

It is apparent that the intermediate in the synthesis of aziridines V may be carbanion VI or amino imine VII. Carbanion VI may be stabilized as a result of delocalization of the negative charge on the acceptor R group. Consequently, the yields of aziridine derivatives should increase as the electron-acceptor properties of substituent R increase. In this connection, we estimated the relative electron densities on the α-carbon atom by comparison of the rate constants for the deuteration of IV on treatment with deuterated sodium methoxide in deuteromethanol.*

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* The rate constants were calculated from a second-order equation by the method of least squares. A second-order reaction is confirmed by the linear dependence of the reciprocal of the concentration on the time.

TABLE 3. Quaternized Derivatives of 1,1,2-Trisubstituted Hydrazines $RNHCH_2CH_2R'$

Compound	R	R'	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
IVa	$\bar{I}(CH_3)_3\overset{+}{N}$	CN	145—146	$C_6H_{14}N_3I$	28,6	5,5	17,2	28,2	5,5	16,7	93
IVb	$\bar{I}(CH_3)_3\overset{+}{N}$	$CONH_2$	165—166 (154—155)[3]	$C_6H_{16}N_3OI$	26,8	5,9	15,7	26,4	5,9	15,4	78
IVc	$\bar{I}(CH_3)_3\overset{+}{N}$	$CON(CH_3)_2$	139—140	$C_8H_{20}N_3OI$	32,3	6,6	13,5	31,9	6,7	13,9	90
IVd	$\bar{I}(CH_3)_3\overset{+}{N}$	$CON(C_2H_5)_2$	140—141	$C_{10}H_{24}N_3OI$	32,6	6.6	11,9	32,6	6,5	11,4	92
IVe	$\bar{I}(CH_3)_3\overset{+}{N}$	$CON(C_4H_9)_2$	Undistillable oil	$C_{14}H_{32}N_3OI$	43,7	8,4	10,5	43,6	8,3	10,9	86
IVf	$\bar{I}(CH_3)_3\overset{+}{N}$	$COOCH_3$	132—133 (126,5—127,5)[3]	$C_7H_{17}N_2O_2I$	29,4	6,0	9,8	29,2	6,0	9,7	95
IVg	$CH_3S\bar{O_4}(CH_3)_3\overset{+}{N}$	$COOCH_3$	41—44	$C_8H_{20}N_2O_6S$	35,6	7,1	10,5	35,3	7,3	10,3	71
IVh	$\bar{I}(CH_3)_3\overset{+}{N}$	$COOC_2H_5$	118—119 (111,5—112,5)[2]	$C_8H_{18}N_2O_2I$	31,6	6,5	9,4	31,8	6,3	9,3	89
IVi	$\bar{I}(CH_3)_3\overset{+}{N}$	$CONHNH_2$	106—108	$C_6H_{17}N_4OI$	25,4	6,0	19,6	25,1	5,9	19,4	31
IVj	$\bar{Cl}(C_2H_5)(CH_3)_2\overset{+}{N}$	$COOCH_3$	81—82	$C_8H_{19}N_2O_2Cl$	45,3	9,1	13,0	45,6	9,0	13,3	63
IVa	$\bar{I}(CH_3)_3\overset{+}{N}$	COONa	186—188	$C_6H_{14}N_2O_2INa$	24,0	5,0	9,2	24,2	4,8	9,5	40
IVb	$CH_3S\bar{O_4}(CH_3)_3\overset{+}{N}$	COONa	184—186	$C_7H_{17}H_2O_6NaS$	29,7	6,0	9,8	30,0	6,0	10,0	30

It was found that the rates of deuterium exchange at this center are so high for IVa, f, h that they are not measurable by PMR spectroscopy. The following rate constants for deuterium exchange were obtained for other salts of the IV type [compound, K (liter · mole^{-1}/sec^{-1})]: IVb, 1.80 ± 0.02 · 10^{-1}; IVc, 3.90 ± 0.03 · 10^{-2}; IVd, 1.50 ± 0.01 · 10^{-2}; IVi, 2.60 ± 0.03 · 10^{-3}.

If VI is the intermediate in the formation of V, the highest yields of aziridines should be expected for IVa, f, h; however, this is not in agreement with the experimental data. On the other hand, the formation of an aziridine system is not observed on treatment of 1-ethyl-1,1-dimethyl-2-(2-carbomethoxyethyl)hydrazinium chloride (IVj) with sodium methoxide in methanol, despite the fact that splitting out of hydrogen chloride should be facilitated by precipitation of sodium chloride. This result is probably explained by steric factors, which hinder approach of the reagent to the secondary nitrogen atom of IVj. As a result, VII is not formed. This assumption is confirmed by the fact that the use of bulky bases of the potassium tert-butoxide type promotes decomposition of IV to VIII-X. We therefore attempted to use dilute solutions of sodium hydroxide in alcohol as the base. However, in this case the methoxy- or ethoxycarbonyl group of IVf-h is hydrolyzed without involvement of the quaternized hydrazinium grouping:

$$\text{IVf-h} \xrightarrow{NaOH} X^-(CH_3)_3\overset{+}{N}NHCH_2CH_2COONa$$

$$\text{XI a } X = I;\ \text{b } X = CH_3SO_4$$

On the basis of the above results it seems more likely that V is formed through intermediate VII rather than as a result of transformations of VI.

EXPERIMENTAL

The IR spectra of liquid films or suspensions (in mineral oil or hexachlorobutadiene) of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of the compounds (sample temperature 36°) were recorded with a Perkin–Elmer R-12B spectrometer (60 MHz).

Chromatographic analysis and isolation of the compounds were accomplished with a Pye-Unicam-105 chromatograph with a flame-ionization detector and a 6 m by 8 mm column filled with Fluoropack-80 (0.25-0.315 mm) modified with 6% E-301 or Versamide-900. The thermostat temperature was 180° or 120-220° (temperature gradient 6°/min) and the carrier gas (helium) flow rate was 300 ml/min. 1,1-Dimethyl-2-(2-substituted ethyl)hydrazines IIIa-h were obtained by the method in [5]. The synthesis of 1,1,1-trimethyl-2-(2-substituted ethyl)hydrazinium salts IVa, c-f, h and their cyclization were accomplished by the method in [1].

1,1,1-Trimethyl-2-(2-carboxamidoethyl)hydrazinium Iodide (IVb). A 20-ml (0.32 mole) sample of methyl iodide was added dropwise with stirring at 0° to 30 ml (0.21 mole) of 1,1-dimethyl-2-(2-carboxamidoethyl)hydrazine in 300 ml of acetonitrile, after which the mixture was allowed to

TABLE 4. PMR Spectra of Quaternized Derivatives of 1,1,2-Trisubstituted Hydrazines $RNHCH_2CH_2R'$

Compound	R	R′	Chemical shift, τ, ppm			
			R	CH_2N	CH_2R	R′
IVa	$\bar{I}(CH_3)_3\overset{+}{N}$	CN	6,62	6,63	7,21	—
IVb	$\bar{I}(CH_3)_3\overset{+}{N}$	$CONH_2$	6,67	6,81	7,50	—
IVc	$\bar{I}(CH_3)_3\overset{+}{N}$	$CON(CH_3)_2$	6,63	6,69	7,33	6,93—7,03*
IVd	$\bar{I}(CH_3)_3\overset{+}{N}$	$CON(C_2H_5)_2$	6,72	6,70	7,46	8,93 9,03 (CH_3)* 6,7 (CH_2)
IVe	$\bar{I}(CH_3)_3\overset{+}{N}$	$CON(C_4H_9)_2$	6,67	6,75	7,36	6,73 (α-CH_2); 8,3—9,0 (β- and γ-CH_2) 9,1 (CH_3)
IVf	$\bar{I}(CH_3)_3\overset{+}{N}$	$COOCH_3$	6,67	6,70	7,38	6,30
IVg	$CH_3S\bar{O_4}(CH_3)_3N$	$COOCH_3$	6,66 ($\overset{+}{N}(CH_3)_3$) 6,30 ($CH_3SO_4^-$)	6,70	7,39	6,30
IVh	$\bar{I}(CH_3)_3\overset{+}{N}$	$COOC_2H_5$	6,62	6,65	7,38	5,82 (CH_2) 8,74 (CH_3)
IVi	$\bar{I}(CH_3)_3\overset{+}{N}$	$CONHNH_2$	6,57	6,66	7,57	9,97
IVj	$Cl^-(C_2H_5)(CH_3)_2\overset{+}{N}$	$COOCH_3$	6,71 $\overset{+}{N}(CH_3)_2$ 6,40 (CH_2) 8,65 (CH_3)	6,75	7,37	6,29
IVa	$\bar{I}(CH_3)_3\overset{+}{N}$	COONa	6,67	6,78	7,66	—
IVb	$CH_3S\bar{O_4}(CH_3)_3\overset{+}{N}$	COONa	6,66 ($\overset{+}{N}(CH_3)_3$) 6,26 ($CH_3SO_4^-$)			—

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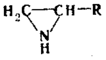
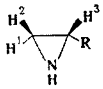
*The signals are split because of hindered rotation about the amide bond.

TABLE 5. Derivatives of Aziridine-2-carboxylic Acid



Compound	R	bp, °C (mm)	n_D^{20}	Empirical formula	Found, %			Calc., %		
					C	H	N	C	H	N
Va	CN	38—39 (0,1)	1,4748	$C_3H_4N_2$	52,8	6,3	40,0	52,9	5,9	41,2
Vb	$CON(C_2H_5)_2$	74 (2)	1,4725	$C_7H_{14}N_2O$	59,7	9,9	19,1	59,2	9,9	19,8
Vc	$COOCH_3$	68 (11) 75 (11)[6]	1,4430 (n_D^{24}=1,4405)[6]	$C_4H_7NO_2$ —	47,3	6,8	13,8	47,5	7,0	13,9
Vd	$COOC_2H_5$	51 (11) 53—54 (11)[6]	1,4391 (n_D^{24}=1,4370)[6]	$C_5H_9NO_2$	51,9	7,7	12,0	52,2	7,9	12,2

TABLE 6. PMR Spectra of Derivatives of Aziridine-2-carboxylic Acid*



Compound	R	Chemical shift, τ, ppm					$J_{H^1H^2}$, Hz	$J_{H^1H^3}$, Hz	$J_{H^2H^3}$, Hz
		H^1	H^2	H^3	R	NH			
Va	CN	8,23	8,18	7,60	—	—	1,0	3,1	5,8
Vb	$CON(C_2H_5)_2$	8,43	8,38	7,57	6,65, 6,52 CH_2 8,94, 8,78 CH_3	8,8	1,7	3,2	5,2
Vc	$COOCH_3$	8,11	8,27	7,63	6,30	8,85	1,8	3,0	5,2
Vd	$COOC_2H_5$	8,12	8,29	7,66	5,83 (CH_2) 8,70 (CH_3)	8,6	1,9	3,0	5,2

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*The spectra were obtained from 10% solutions in CCl_4 (Vb–d) and D_2O (Va).

stand at room temperature for 12 h. The resulting precipitate was removed by filtration and crystallized from ethanol.

1,1,1-Trimethyl-2-(2-carbomethoxyethyl)hydrazinium Methylsulfate (IVg). A 47.4-ml (0.5 mole) sample of dimethyl sulfate was added dropwise with stirring and cooling to 73 g (0.5 mole) of 1,1-dimethyl-2-(2-carbomethoxyethyl) hydrazine in 500 ml of absolute ether, after which the mixture was refluxed without access to moisture for 5 h. The solvent was then evaporated, and the residue was dried in vacuo (0.005 mm) over phosphorus pentoxide at 30°.

1,1,1-Trimethyl-2-(2-carboxyhydrazidoethyl)hydrazinium Iodide (IVi). A total of 32 ml of anhydrous hydrazine was added to a solution of 81.6 g (0.3 mole) of IVf in 500 ml of absolute ethanol, after which the mixture was heated on a water bath for 15 h. The solvent was then evaporated, and the residue was crystallized from ethanol–methanol.

1-Ethyl-1,1-dimethyl-2-(2-carbomethoxyethyl)hydrazinium Chloride (VIj). An 84.6-ml (1.2 mole) sample of ethyl chloride was added to a solution of 73 g (0.5 mole) of 1,1-dimethyl-2-(2-carbomethoxyethyl)hydrazine in 0.5 liter of ether, after which the mixture was allowed to stand at room temperature for 2 weeks. The resulting colorless needles were removed by filtration and crystallized from alcohol.

3-Dimethylamino-N,N-dimethylpropionamide. This compound had bp 93-95° (10 mm) and n_D^{23} 1.4585. PMR spectrum:* 6.97 (3H, s, NCH_3) and 7.12 (3H, s, NCH_3),† 7.55 (2H, t, CH_2), 7.60 (2H, t, CH_2), 7.83 (6H, s, NCH_3). IR spectrum, cm^{-1}: 2780 and 2830 (NCH_3); 1645 (C=O). The physicochemical properties of the product were identical to those of a genuine sample obtained by the method in [8].

3-Methoxy-N,N-dimethylpropionamide. This compound was identified from PMR spectral data. PMR spectrum: 6.46 (2H, t, CH_2), 6.76 (3H, s, OCH_3), 7.01 (3H, s, NCH_3), 7.16 (3H, s, NCH_3), and 7.57 (2H, t, CH_2). The product had n_D^{23} 1.4593. Found %: C 54.9; H 9.7; N 10.5. $C_6H_{13}NO_2$. Calculated %: C 55.0; H 9.9; N 10.7.

3-(2,2-Dimethylhydrazono)-N,N-dimethylpropionamide. This compound had bp 120-125° (15 mm) and n_D^{20} 1.4919. PMR spectrum: 3.47 (1H, t, J = 5.5 Hz, CH), 6.84 (2H, d, J = 5.5 Hz, CH_2), 7.00 (3H, s, NCH_3),† and 7.30 (6H, s, NCH_3). IR spectrum, cm^{-1}: 2800 and 2840 (NCH_3); 1645 (C=O). The physicochemical characteristics of the product were identical to those of a genuine sample obtained by the following method. A 44.52-g (0.28 mole) sample of 3-(2,2-dimethylhydrazino)-N,N-dimethylpropionamide was added dropwise to a suspension of 65 g (0.3 mole) of yellow mercuric oxide and 150 g of anhydrous sodium sulfate in 500 ml of dioxane, after which the mixture was refluxed for 6 h and filtered. The solid material was washed with 500 ml of hot dioxane, the filtrates were combined, the solvent was removed by distillation, and the residue was fractionated over calcium hydride to give 30.6 g (71.1%) of a fraction with bp 120-125° (15 mm). Found %: C 53.8; H 9.3; N 27.3. $C_7H_{13}N_3O$. Calculated %: C 53.5; H 9.5; N 27.4.

1,1,1-Trimethyl-2-(2-sodiocarboxylatoethyl)hydrazinium Salts XIa and XIb. A 12.5-g (0.6 mole) sample of sodium metal was added to 750 ml of 90% methanol (or ethanol), after which 0.3 mole of IVf, IVg, or IVh was added, and the mixture was refluxed for 20 h. It was then evaporated to 100 ml and cooled. The resulting white precipitate was removed by filtration and extracted with 500 ml of hot methanol. The methanol was removed by distillation, and the residue was crystallized from ethanol.

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*The chemical shifts are presented on the τ scale in parts per million. The following abbreviations are used here and subsequently: s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet.

†The absorption signal is split because of slow rotation about the amide bond.