N-ALKYLAZETIDINE-2-CARBOXYLIC ESTERS

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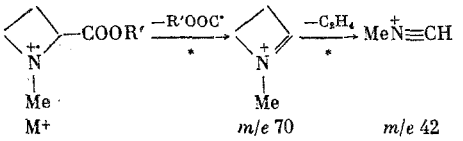
For studying the conformation of four-membered heterocycles [1] and the fragmentation of azetidines under electron impact [2] we synthesized the following N-alkylazetidine-2-carboxylic esters (Table 2).

$$RNH_2 + BrCH_2CH_2CHBrCOOR' \xrightarrow[MeCN]{Et_3N} RN(CH_2)_2CHCOOR'$$

R = Me, Et, *i*-Pr, *t*-Bu, $PhCH_2$; R′ = Me (I), Et (II), *i*-Pr (III), $PrCH_2$ (IV)

The products, which do not require additional purification, can be obtained under mild conditions, and also the N-methyl derivatives (V)-(VIII), which are not accessible under the conditions given in [3]. Compound (V) was obtained in [3] only by an indirect route, via the N-benzhydryl derivative.

A nonequivalence of the geminal protons and groups of the substituent on nitrogen is observed in all cases in the NMR spectra of the products (Table 1), which is caused by the asymmetric induction of the chiral C-2 center. Here the $\Delta\nu$ of the CH_3 groups of the isopropyl substituent increases, while that of the CH_2 protons of the ethyl and benzyl groups decreases with increase in the size of the substituent at C-2. A substantially smaller $\Delta\nu$ of the substituents in the carbalkoxyl group is observed only in the case of (XV) and (XXII). For the N-methyl-, ethyl-, and isopropylazetidinecarboxylic esters the main decomposition path under electron impact is the cleavage of the carbalkoxyl radical with the formation of the amine fragment (M—COOR), the peak of which is maximum in the spectra at 30 and 12 eV (Fig. 1).

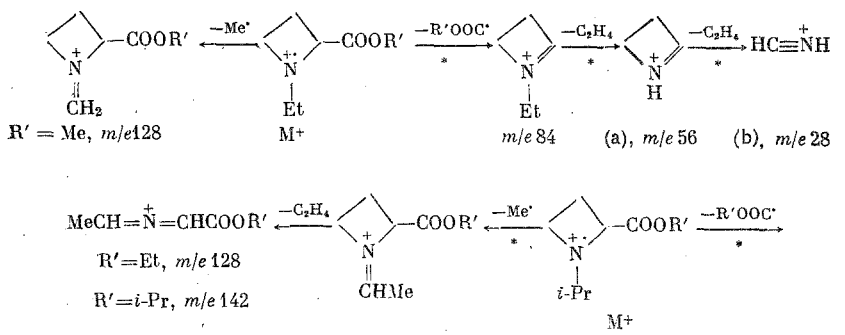


Metastable peaks with a flat top (Fig. 2), which were discussed by us in [4], are always observed for the subsequent decomposition of the amine fragment, with the ejection of C_2H_4. In the case of the N-ethyl-, isopropyl-, and tert-butyl-substituted azetidines another type of amine fragment is formed as the result of α-cleavage in the substituent on nitrogen (Fig. 3). For these derivatives the tendency

TABLE 1. Parameters of Geminal Nonequivalence of Protons and Groups (for 15% solutions in benzene)

Compound	Group	Δν, Hz	Compound	Group	Δν, Hz
(IX)	a	42,8	(XV)	b	11,0
(X)	a	41,6		c	0,2
(XI)	a	39,6	(XVI)	b	9,0
(XII)	a	44,0	(XX)	d	57,2
(XIII)	b	8,0	(XXI)	d	53,5
(XIV)	b	9,5	(XXII)	d	50,2
				c	1,5

* $MeCH_AH_BN$ (a), Me_AMe_BCHN (b), Me_AMe_BCHO (c), $PhCH_AH_BN$ (d).



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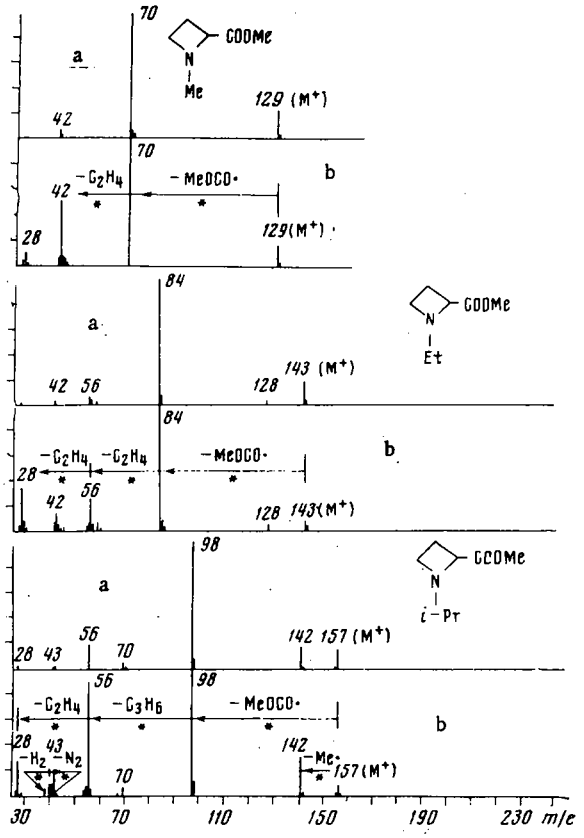
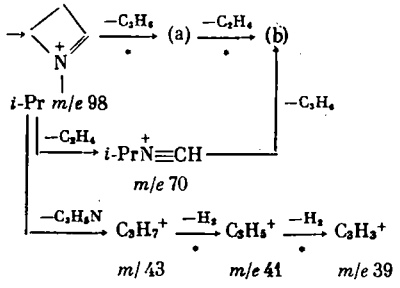


Fig. 1. Mass spectra of methyl esters of N-methyl- (V), N-ethyl- (IX), and N-isopropylazetidine-2-carboxylic acids (XIII): a) 12 eV; b) 30 eV.



for the (M—COOR) fragment to decompose with a cleavage of the substituent on nitrogen as the olefin is enhanced. Both of these processes are dominating for the N-tert-butyl derivatives. In the N-benzyl

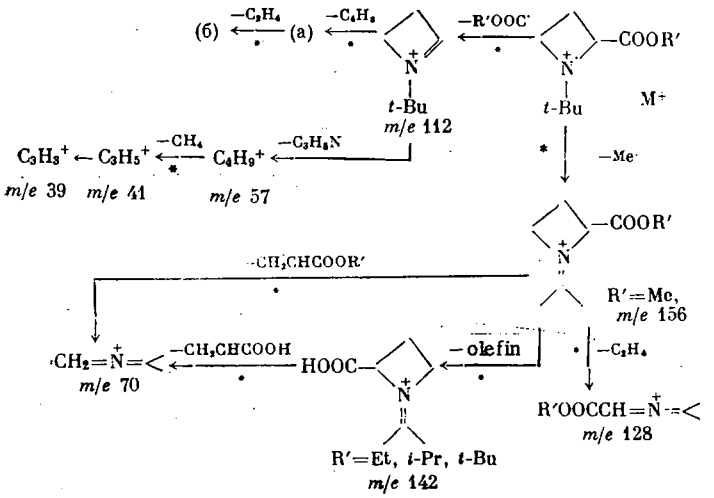


TABLE 2. Characteristics of Esters of N-Alkylazetidine-2-carboxylic Acids $RN\overline{(CH_2)_2}CHCOOR'$

Compound	R	R'	Synthesis method	Yield, %	Bp, °C (p, mm of Hg)	n_D^{20}	ν_{CO}, cm^{-1} (molecular layer)	Empirical formula	Found/calculated, %		
									C	H	N
(V)	Me	Me	A	29	55 (13)*	1,4362	1748	—	—	—	—
(VI)	Me	Et	A	30	58—59 (9)	1,4343	1746	$C_9H_{15}NO_2$	58,70 58,72	9,22 9,19	9,73 9,82
(VII)	Me	i-Pr	A	59	62(8)	1,4320	1741	$C_8H_{13}NO_2$	61,10 61,12	9,78 9,62	8,81 8,91
(VIII)	Me	$PhCH_2$	A	69	57 (0,5)	1,5196	1747	$C_{12}H_{15}NO_2$	70,24 70,22	7,35 7,37	6,73 6,82
(IX)	Et	Me	A	73	68,5—69 (12,5)	1,4389	1751	$C_9H_{15}NO_2$	58,74 58,72	9,11 9,19	9,73 9,82
(X)	Et	Et	A	64	70,5 (8)	1,4382	1748	$C_8H_{13}NO_2$	60,99 61,12	9,64 9,62	8,96 8,91
(XI)	Et	i-Pr	A	58	69—70 (10)	1,4330	1743	$C_9H_{17}NO_2$	63,19 63,13	10,09 10,01	8,36 8,18
(XII)	Et	$PhCH_2$	A	32	99,5—100,5 (0,5)	1,5168	1746	$C_{12}H_{17}NO_2$	71,25 71,21	7,81 7,81	6,46 6,39
(XIII)	i-Pr	Me	B	26	31 (2)*	1,4418	1730 1756	—	—	—	—
(XIV)	i-Pr	Et	B	60	53—54 (3)	1,4380	1743 1755	$C_9H_{17}NO_2$	63,16 63,13	10,14 10,01	8,11 8,18
(XV)	i-Pr	i-Pr	B	54	56,5 (3)	1,4362	1728 1749	$C_{10}H_{19}NO_2$	64,83 64,83	10,32 10,01	7,68 7,56
(XVI)	i-Pr	$PhCH_2$	C	64	109,5—110,5 (0,5)*	1,5100	1728 1753	—	—	—	—
(XVII)	t-Bu	Me	D	46	38,5 (1,5)*	1,4455	1728 1755	—	—	—	—
(XVIII)	t-Bu	Et	D	42	51,5—52,5 (1,5)	1,4440	1732 1757	$C_{10}H_{19}NO_2$	64,62 64,83	10,30 10,34	7,53 7,56
(XIX)	t-Bu	i-Pr	D	48,3	41—42 (1)	1,4445	1735 1760	$C_{11}H_{21}NO_2$	66,21 66,29	10,62 10,62	6,95 7,03
(XX)	$PhCH_2$	Me	E	15,6	96—97 (0,5)*	1,5071	1747	—	—	—	—
(XXI)	$PhCH_2$	Et	F	21	91—92 (0,2)	1,5100	1746	$C_{13}H_{17}NO_2$	71,28 71,21	7,77 7,81	6,54 6,39
(XXII)	$PhCH_2$	i-Pr	F	26,5	99—100 (0,5)	1,5021	1741	$C_{14}H_{19}NO_2$	71,96 72,07	8,34 8,21	6,09 6,06

*Cf. with [3].

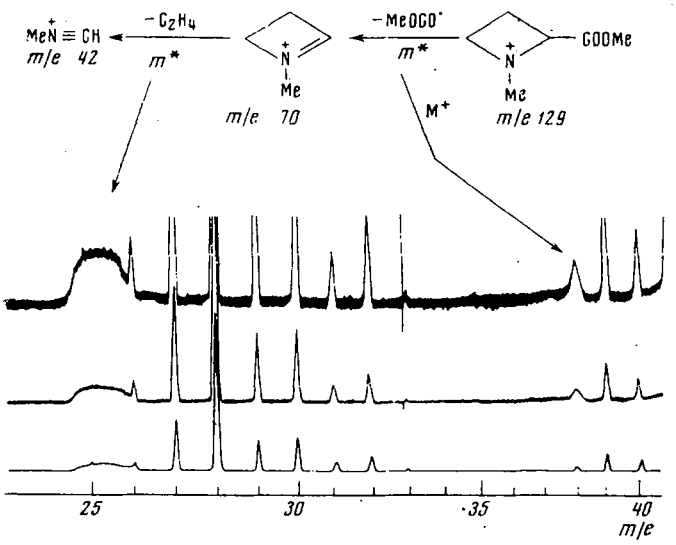
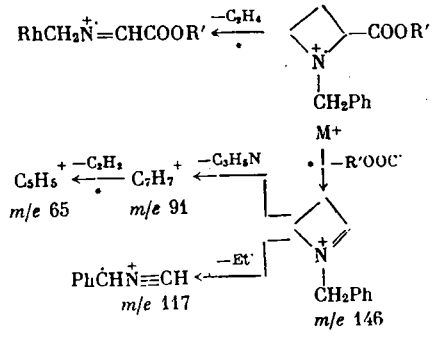


Fig. 2. Mass spectrum of (V) in region of metastable peak with a flat top, m/e 25.2 (calculated 25.2), and of metastable peak with the usual shape, m/e 38.0 (calculated 37.98), T = 0.23 eV.

derivatives the indicated main fragmentation scheme is complicated by the following competing decomposition processes.



EXPERIMENTAL METHOD

The mass spectra were measured on an MX-1303 instrument at 30 and 12 eV, the IR spectra were taken on a UR-10 spectrophotometer, and the NMR spectra were taken on a Varian-HA-100 spectrometer (100 MHz, the chemical shifts are given from HMDS).

The methyl ester of α,γ-dibromobutyric acid (I) was obtained in 81% yield as described in [5], bp 68-70° (2 mm), n_D^{20} 1.5040.

The following were obtained in a similar manner: ethyl ester of α,γ-dibromobutyric acid (II) in 73% yield, bp 81-82° (4 mm), n_D^{20} 1.4885; isopropyl ester of α,γ-dibromobutyric acid (III) in 83.5% yield, bp 96-100° (4 mm), n_D^{20} 1.4890; benzyl ester of α,γ-dibromobutyric acid (IV) in 64% yield, bp 132-134° (0.4 mm), n_D^{20} 1.5520, cf. [6].

A. Methyl Ester of 1-Methylazetidine-2-carboxylic Acid (V). A solution of 13 g (0.05 mole) of (I) and 6.2 g (0.2 mole) of methylamine in 100 ml of acetonitrile was kept at 20° for 4 days. Then the cooled mixture was filtered, the filtrate was evaporated to dryness at 20° (20 mm), and the residue was extracted with ether (2 × 100 ml). After removal of the ether the residue was distilled.

B. Methyl Ester of 1-Isopropylazetidine-2-carboxylic Acid (XIII). A mixture of 13 g (0.05 mole) of (I) and 8.85 g (0.15) mole of isopropylamine in 200 ml of CH_3CN was refluxed for 21 h and then worked up by method A.

C. Ethyl Ester of 1-Isopropylazetidine-2-carboxylic Acid (XIV). A solution of 13.7 g (0.05 mole) of (II) and 8.85 g (0.15 mole) of isopropylamine in 200 ml of CH_3CN was kept at 20° for 6 days, and then for 11 h as in the preceding experiment.

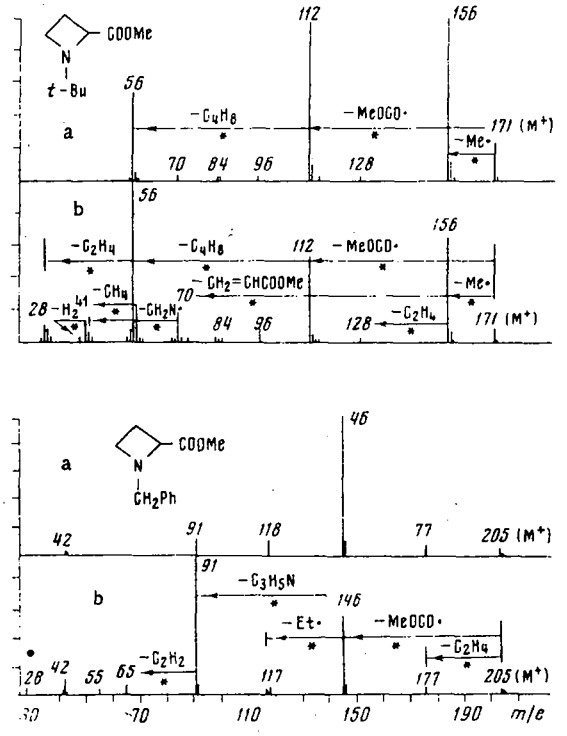


Fig. 3. Mass spectra of methyl esters of N-tert-butyl- (XVII) and N-benzylazetidine-2-carboxylic acids (XX): a) 12 eV; b) 30 eV.

D. Methyl Ester of 1-Tert-butylazetidine-2-carboxylic Acid (XVII). A mixture of 13 g (0.05 mole) of (I), 3.65 g (0.05 mole) of tert-butylamine, and 10.1 g (0.1 mole) of triethylamine in 150 ml of CH_3CN was kept at 20° for 4 days and then worked up by method A.

E. Methyl Ester of 1-Benzylazetidine-2-carboxylic Acid (XX). A solution of 13 g (0.05 mole) of (I) and 16 g (0.15 mole) of benzylamine in 200 ml of CH_3CN was kept at 20° for 10 days. After the usual work-up the ether extract was treated with 10.1 g (0.1 mole) of triethylamine, the solution was evaporated, and the product was again extracted with ether. Then the solvent was removed in vacuo and the product was distilled.

F. Ethyl Ester of 1-Benzylazetidine-2-carboxylic Acid (XXI). A mixture of 13.7 g (0.05 mole) of (II) and 16 g (0.15 mole) of benzylamine in 200 ml of CH_3CN was refluxed for 22 h and then worked up as in experiment E.

CONCLUSIONS

1. Starting with the esters of α,γ-dibromobutyric acid and primary amines, the synthesis of N-alkylazetidine-2-carboxylic esters was extended to the simple amines.

2. The geminal nonequivalence of the diastereotopic protons and groups, observed in the NMR spectra of the N-alkylazetidine-2-carboxylic esters, is greater for the substituent on nitrogen than in the carbalkoxyl group.

3. The characteristic processes for the fragmentation of N-alkylazetidine-2-carboxylic esters under electron impact are the formation of amine fragments via cleavage of the substituent at C-2 and α-cleavage in the substituent on nitrogen.

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