

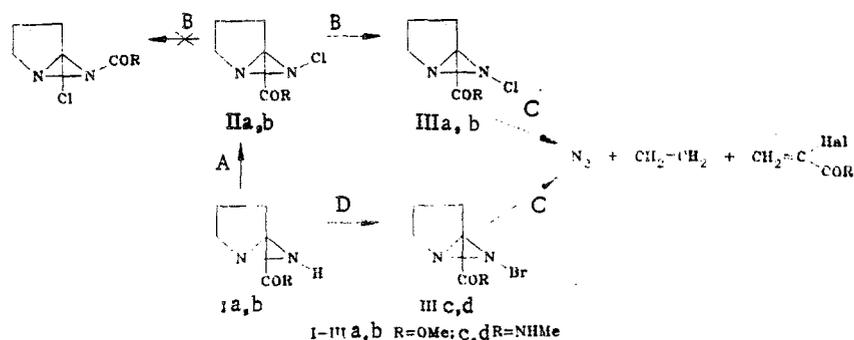
ISOMERIZATION OF 5-ACYL-6-HALO-1,6-DIAZABICYCLO[3.1.0]HEXANES,
A CASE OF INVERSION RATHER THAN 1,2-ACYL MIGRATION*

G. V. Shustov, S. N. Denisenko, I. I. Chervin,
A. B. Zolotoi, O. A. D'yachenko, S. V. Konovalikhin,
G. V. Shilov, L. O. Atovmyan, and R. G. Kostyanovskii

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X-ray diffraction structural analysis and ^{13}C and ^{15}N NMR spectroscopy were used to establish that the final product of the halogenation of 5-acyl-1,6-diazabicyclo[3.1.0]hexane is the exo-6-halo derivative. Thus, the observed transformation of the initially formed endo-N-chloro isomer is an inversion and not 1,2-acyl migration as previously proposed.

In our previous communication [2], we proposed that N-chloro derivatives IIa and IIb formed upon the chlorination of 5-acyl-1,6-diazabicyclo[3.1.0]hexanes Ia and Ib readily isomerize with retention of the diazabicyclohexane skeleton. The final reaction products, chlorides IIIa and IIIb, were assigned the structure of 6-acyl-5-chloro-1,6-diazabicyclo[3.1.0]hexanes and their formation was postulated to proceed through 1,2-acyl migration. N-Bromo derivatives IIIc and IIId were obtained in a further study of the halogenation of bicyclic diaziridines Ia and Ib. The structure of bromide IIIc as the methylamide of exo-6-bromo-1,6-diazabicyclo[3.1.0]hexane-5-carboxylic acid was established by diffraction structural analysis (Fig. 1). The unit cell of crystals of IIIc contain two independent molecules. The bicyclic fragment in both molecules has boat conformation with flexure angles relative to the central $\text{C}_{(2)}\text{N}_{(1)}\text{C}_{(5)}\text{C}_{(4)}$ plane about 30° [along the $\text{C}_{(2)}\dots\text{C}_{(4)}$ line] and 80° [along the $\text{N}_{(1)}\dots\text{C}_{(5)}$ line].



I-III a,b R=OMe; c,d R=NHMe, Reagents and conditions:

A: $t\text{-BuOCl}$, CH_2Cl_2 , -30° ; B: CH_2Cl_2 , 20° ; C: CDCl_3 , 60° , 6 h; D: $\text{PyH}^+\text{Br}_3^-$, K_2CO_3 , CH_2Cl_2 , H_2O , 20°

The final chlorination products, chlorides IIIa and IIIb and exo-bromides IIIc and IIId are identical in their ^{13}C NMR spectra (Table 1), while esters IIIa and IIIc and amide IIId identically undergo smooth decomposition into nitrogen, ethylene, and α -haloacrylate upon heating in CDCl_3 at 60°C for 6 h. This indicates a common structure for IIIa, IIIb, IIIc, and IIId as N-halo derivatives with exo orientation of the halogen atom. Then, the chlorine atom in the initially formed chlorides IIa and IIb is in the endo orientation. This assignment is indicated by analysis of the ^{13}C NMR spectra (Table 1). Previous work [3, 4] has shown that the chemical shift of $\text{C}_{(5)}$ of bicyclo[3.1.0]hexanes is a diagnostic test for the boat and chair conformation, which is determined by the orientation of the substituent at $\text{C}_{(6)}$. The boat form obtains in the case of exo orientation with characteristic upfield shift

*Communication 52 in the series "Asymmetric Nitrogen;" for Communication 51, see [1].

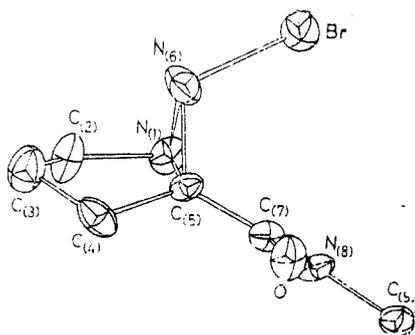


Fig. 1

Fig. 1. Bromide IIIId with 30% thermal oscillation probability ellipsoids.

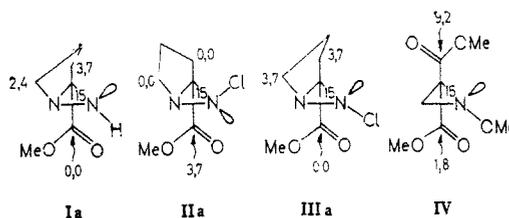


Fig. 2

Fig. 2. ${}^2J_{13C15N}$ coupling constants (Hz) for carbon atoms in Ia-IIIa and IV.

TABLE 1. Chemical Shifts (ppm) in the ${}^{13}C$ NMR Off Resonance Spectra for 5-Acyl-6-halo-1,6-diazabicyclo[3.1.0]hexanes in $CDCl_3$

Compound	$C_{(2)}(t)$	$C_{(3)}(t)$	$C_{(4)}(t)$	$C_{(5)}(s)$	Me (q)	CO (s)
IIa	55.25	28.60	27.60	74.02	53.27	167.40
IIb	54.65	28.35	26.40	75.01	25.80	166.42
IIIa	55.94	20.87	29.28	76.70	53.00	165.18
IIIb	55.56	20.94	28.54	76.73	25.30	164.43
IIIc	55.43	20.45	28.59	75.39	52.42	165.16
IIId	55.42	20.90	28.20	75.85	25.04	165.34

for $C_{(3)}$ (syn- γ -effect), while the chair form with deshielded $C_{(3)}$ is thermodynamically favored in the case of a 6-endo substituent. The similar upfield shifts for $C_{(3)}$ in chlorides IIIa and IIIb and bromides IIIc and IIId and a significantly deshielded $C_{(3)}$ in IIa and IIb indicate the identical exo orientation of the 6-halogen for IIIa-d and endo orientation for IIa and IIb. The same conclusion may be drawn from the stereospecific ${}^2J_{13C15N}$ constants, which, as shown in the case of aziridine IV and its derivatives [5], are greater for the ${}^{13}C$ nuclei in the cis position to the unshared electron pair of the ${}^{15}N$ atom (Fig. 2). Thus, chlorides IIa and IIb are endo isomers of 5-acyl-6-chloro-1,6-diazabicyclo[3.1.0]hexane and IIIa and IIIb are the corresponding exo isomers. The transformations IIa \rightarrow IIIa and IIb \rightarrow IIIb observed by ${}^{13}C$ NMR spectroscopy involve inversion and not 1,2-acyl migration. We should note 1) endo stereospecificity for the chlorination of diaziridines Ia and Ib, and 2) that the configurational stability of N-chlorodiaziridines IIa and IIb is significantly less* than would be expected on the basis of current concepts concerning the nature of inversion of the nitrogen atom [6]. The unusually high rate of inversion of N-chlorodiaziridines IIa and IIb is one of the reasons for the erroneous proposal for the structure of final chlorination products IIIa and IIIb and the nature of the transformation of IIa and IIb. We may also assume that the bromination of diaziridines Ia and Ib also proceeds stereospecifically through the formation of the corresponding endo-N-bromo isomer with subsequent inversion to exo-bromides IIIc and IIId. However, this isomer could not be detected under the conditions for observation of endo-chloride IIa, which is apparently a consequence of the still lower configurational stability of these endo-N-bromo derivatives.

EXPERIMENTAL

The PMR spectra were taken on a Jeol ICM-C-60 HL spectrometer at 60 MHz relative to HMDS. The ${}^{13}C$ NMR spectra were taken on a Bruker WM-400 spectrometer at 100.62 MHz relative to TMS. The UV spectra were taken on a Specord UV-VIS spectrometer. The mass spectra were

*N-Chlorodiaziridines IIa and IIb completely isomerize to exo isomers IIIa and IIIb over 1 h at 20°C.

TABLE 2. Atomic Coordinates in Molecules A and B ($\times 10^4$)

Atom	x	y	z	Atom	x	y	z
Br ₍₁₎	4466(2)	0789(1)	7031(3)	O ₍₁₀₎	3598(13)	1513(7)	0298(19)
O ₍₁₎	3275(9)	1440(5)	5266(15)	N ₍₁₁₎	3557(10)	0752(6)	2876(19)
N ₍₁₎	3248(9)	0718(6)	8028(18)	N ₍₁₆₎	3207(10)	0610(7)	1699(24)
N ₍₆₎	3630(10)	0568(7)	6783(24)	N ₍₁₈₎	3466(10)	1579(6)	2504(17)
C ₍₂₎	2756(14)	0401(7)	8220(23)	C ₍₁₂₎	4036(17)	0431(10)	3173(31)
C ₍₃₎	2476(15)	0314(8)	6780(28)	C ₍₁₃₎	4399*	0373(9)	1790(28)
C ₍₄₎	2569(11)	0698(9)	6043(27)	C ₍₁₄₎	4319(15)	0760(9)	1035(32)
C ₍₅₎	3160(11)	0884(6)	6609(21)	C ₍₁₅₎	3703(12)	0944(8)	1640(24)
C ₍₇₎	3299(11)	1296(7)	6431(22)	C ₍₁₇₎	3581(12)	1370(6)	1452(29)
C ₍₉₎	3511(11)	1966(6)	7333(23)	C ₍₁₉₎	3392(15)	2002(6)	2459(26)
Br ₍₁₀₎	2356(2)	0833(1)	1787(4)	N ₍₅₎	3396(10)	1546(5)	7506(17)

*Coordinate fixed.

TABLE 3. Bond Lengths (Å) and Bond Angles (deg) in Molecules A and B

Atom	Molecule A	Molecule B	Atom	Molecule A	Molecule B
Br ₍₁₎ —N ₍₆₎	1.94(2)	1.96(2)	Br ₍₁₎ —N ₍₆₎ —C ₍₁₅₎	112(2)	111(2)
O ₍₁₎ —C ₍₇₎	1.26(3)	1.25(3)	N ₍₁₎ —N ₍₆₎ —C ₍₁₅₎	61(1)	56(1)
N ₍₁₎ —N ₍₆₎	1.57(3)	1.47(3)	C ₍₇₎ —N ₍₆₎ —C ₍₁₅₎	122(2)	122(2)
N ₍₁₎ —C ₍₂₎	1.50(3)	1.51(4)	N ₍₁₎ —C ₍₂₎ —C ₍₃₎	106(2)	104(2)
N ₍₁₎ —C ₍₅₎	1.53(3)	1.42(3)	C ₍₂₎ —C ₍₃₎ —C ₍₄₎	104(2)	106(2)
N ₍₅₎ —C ₍₅₎	1.46(3)	1.54(3)	C ₍₃₎ —C ₍₄₎ —C ₍₅₎	106(2)	104(2)
N ₍₅₎ —C ₍₇₎	1.37(3)	1.28(3)	N ₍₁₎ —C ₍₅₎ —N ₍₆₎	63(1)	59(2)
N ₍₈₎ —C ₍₉₎	1.43(3)	1.42(3)	N ₍₁₎ —C ₍₅₎ —C ₍₄₎	108(2)	110(2)
C ₍₂₎ —C ₍₃₎	1.58(4)	1.59(4)	N ₍₁₎ —C ₍₅₎ —C ₍₇₎	116(2)	121(2)
C ₍₃₎ —C ₍₄₎	1.49(4)	1.50(4)	N ₍₅₎ —C ₍₅₎ —C ₍₄₎	109(2)	108(2)
C ₍₄₎ —C ₍₅₎	1.51(3)	1.57(4)	N ₍₆₎ —C ₍₅₎ —C ₍₇₎	125(2)	126(2)
C ₍₅₎ —C ₍₇₎	1.41(3)	1.45(3)	C ₍₄₎ —C ₍₅₎ —C ₍₇₎	122(2)	119(2)
N ₍₆₎ —N ₍₁₎ —C ₍₂₎	104(2)	106(2)	O ₍₁₎ —C ₍₇₎ —C ₍₅₎	118(2)	119(2)
N ₍₆₎ —N ₍₁₎ —C ₍₅₎	56(1)	64(2)	O ₍₁₎ —C ₍₇₎ —N ₍₈₎	120(2)	123(2)
C ₍₂₎ —N ₍₁₎ —C ₍₅₎	107(2)	110(2)	N ₍₆₎ —C ₍₇₎ —C ₍₅₎	121(2)	117(2)
Br ₍₁₎ —N ₍₆₎ —N ₍₁₎	105(1)	108(1)			

taken on a Finnigan 4021 spectrometer. 5-Acyl-1,6-diazabicyclo[3.1.0]hexanes Ia and Ib were described in our previous work [2, 7] and their N-chloro derivatives IIa, IIb, IIIa, and IIIb were described in our previous work [2].

Bromination of 5-acyl-1,6-diazabicyclo[3.1.0]hexanes Ia and Ib (general procedure). A solution of 5 mmoles diaziridine Ia or Ib [2, 7] in 5 ml CH_2Cl_2 was shaken in a separatory funnel with a solution of 1.62 g (5 mmoles) pyridinium bromide perbromide [8] and 0.67 g (5 mmoles) K_2CO_3 in 15 ml water. The organic layer was separated and dried over magnesium sulfate. The solvent was evaporated in vacuum and the residue was recrystallized.

exo-6-Bromo-5-carbomethoxy-1,6-diazabicyclo[3.1.0]hexane (IIIc) was obtained in 88% yield mp 47.5–48°C (from hexane). UV spectrum in heptane: λ_{max} 244 nm ($\log \epsilon$ 3.58). Found, %: C 32.9; H 4.0; N 12.7. $\text{C}_6\text{H}_9\text{BrN}_2\text{O}_2$. Calculated, %: C 32.6; H 4.1; N 12.7.

exo-6-Bromo-5-N-methylcarbomoyl-1,6-diazabicyclo[3.1.0]hexane (IIIId) was obtained in 83% yield, mp 102–103°C (from CCl_4). Found, %: C 32.6; H 4.7; N 19.0. $\text{C}_6\text{H}_{10}\text{BrN}_2\text{O}$. Calculated, %: C 32.8; H 4.6; N 19.1. The transparent white crystals of amide IIIId turned somewhat yellow-red even during the crystallization process. In daylight and, especially, in sunlight, the crystals become dark red and rapidly decompose with the release of a characteristic bromine odor. Crystals of IIIId are rectangular parallelepiped platelets extended along the C-axis and are orthorhombic in symmetry. The major crystallographic parameters are: $\text{C}_6\text{H}_{10}\text{BrN}_2\text{O}$ M = 220.106; $a = 21.310(4)$; $b = 33.306(12)$; $c = 9.990(6)$, $V = 7090.4 \text{ \AA}^3$, $Z = 32$, $d_{\text{calc}} = 1.528 \text{ g/cm}^3$, space group F2dd. A total of 961 reflections with $I \geq 3\sigma_I$ were measured on a RED-4 four-circle diffractometer using the $\theta/2\theta$ method, $\text{CuK}\alpha$ radiation, $0.056 \leq \sin \theta/\lambda \leq 0.540$. Absorption was not taken into account ($\mu_{\text{CuK}\alpha} = 66.8 \text{ cm}^{-1}$). The bromine atomic coordinates were found by the direct method. The coordinates of the other nonhydrogen atoms were found from the Fourier map. The structure was refined in the full-matrix anisotropic approximation for all atoms to $R = 0.101$ using the Roentgen-75 program [9]. The atomic coordinates

dinates are given in Table 2. The bond lengths and angles are given in Table 3. The high R factor and significant scatter in the equivalent and monotypic bond lengths is a consequence of sample decomposition during the measurement. An illustration of the molecule was obtained using the ELLIPS program [10].

Thermolysis of exo-5-Carbomethoxy-6-chloro-1,6-diazabicyclo[3.1.0]hexane (IIIa). A solution of 90 mg (0.5 mmole) chloride IIIa in 0.5 ml CDCl_3 was heated in a sealed ampule at 80°C for 10 h. Removal of the solvent gave 58 mg (95%) methyl α -chloroacrylate, which was identical in its PMR and mass spectra to an authentic sample. PMR spectrum in CDCl_3 : 3.8 (MeO), 6.0, and 6.5 ppm (JAB = 1.5 Hz). Mass spectrum at 20 eV, m/z (relative intensity), %: M^+ 122 (25), 120 (74), 119 (7), 104 (7), 102 (17), 91 (32), 89 (100), 85 (28), 63 (20), 61 (59), 59 (38), 54 (7), 41 (8).

Thermolysis of N-halo derivatives IIIb-d were carried out by the above procedure and the corresponding α -haloacrylates were identified by comparison of their PMR spectra with those of authentic samples.

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