Stereochemical Studies. Part 31.[1] Ring Closure Reaction of *cis*- and *trans*-2-(Bromomethyl)cycloalkylamines

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Cyclization of the *cis*- and *trans*-2-(bromomethyl)cycloalkylamines (7)—(12) to the fused-ring azetidines (13)—(17) was investigated. The first-order rate constants for azetidine formation as a function of the ring size are in the order: cycloheptane > cyclopentane > cyclohexane for the *cis*-isomers; and cycloheptane > cyclohexane for the *trans*-isomers. Azetidine formation could not be induced from *trans*-2-(bromomethyl)cyclopentylamine (8). A plot of the E_a values for the reactions as a function of $\Delta S^{\ddagger}$, shows an isokinetic correlation, with the exception of the point for *trans*-2-(bromomethyl)cyclohexylamine (10), where the main reaction is elimination.

THE reactivity towards ring closure of various types of bifunctional compound as a function of the ring size have been studied in great detail with many models.[2] However, the relative reactivities and types of cyclization reaction of alicyclic *cis*- and *trans*-1,2-disubstituted-1,3-difunctional compounds of various ring sizes have received little attention. As a continuation of our studies[3] on the N ⟶ O acyl migration reactions of *cis*- and *trans*-2-(aminomethyl)cycloalkanols and *cis*- and *trans*-2-(hydroxymethyl)alicyclic amines, we investigated the ring closure reactions to give azetidines of *cis*- and *trans*-2-(bromomethyl)cycloalkylamines derived from the foregoing amino-alcohols. Although there has been considerable interest recently in the chemistry of azetidines,[4] there are very few literature results on the formation of fused azetidines,[5,6] and, to our knowledge, no systematic study has been reported so far on a fused-ring homologous series. This is remarkable since the closely related fused-ring β-lactams have been examined extensively.[7]

From 2-(hydroxymethyl)cyclopentylamine, of unspecified configuration, Gassman and Heckert[5] obtained *N*-ethyl-6-azabicyclo[3.2.0]heptane, but the configuration and stereohomogeneity of the product were not examined. Moriconi and Mazzocchi[6] synthesized *cis*-7-azabicyclo[4.2.0]octane by cyclization of *N*-tosyl-*trans*-2-(tosyloxymethyl)cyclohexylamine. The *trans*-2-(aminomethyl)cyclohexanol used by Moriconi and Mazzocchi, and presumed by them to be stereohomogeneous, proved on the basis of our investigations[8] to be a mixture of the *trans*- and *cis*-isomers; this was later confirmed by Schwartz *et al.*[9]

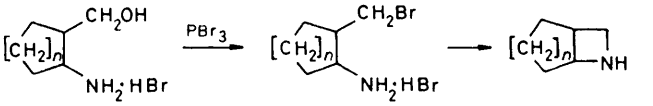
In view of these results, we studied the syntheses of the azabicyclo-octanes (14) and (15) starting from authentic *cis*- and *trans*-2-(hydroxymethyl)cyclohexylamine[8] (3) and (4), and also to prepare the homologous stereohomogeneous trimethylene- and pentamethylene-azetidine derivatives. Since a recent review[10] on four-membered cyclic compounds stresses the importance of the use of physical methods in the stereochemical and conformational analysis of these systems, we have performed a kinetic study of the azetidine ring closure reaction, and compared this reaction with the solvolysis of the (bromomethyl)cycloalkanes (18)—(20),[11] which may be regarded as model compounds.

Nucleophilic participation of the amino-group has been investigated in numerous reactions,[12] and the reactions of γ-aminoalkylamines have also been studied.[13] With the latter, depending on the conditions, ring closure to azetidine derivatives, substitution, elimination, and fragmentation may occur. In the case of our primary halogen derivative model compounds we expected that elimination and fragmentation would be relatively suppressed,[14] as the ionization-promoting neighbouring group participation of the amino-group is most marked in primary halogen derivatives.

TABLE 1

Analytical data for the *cis*- and *trans*-2-(hydroxymethyl)cycloalkylamine hydrobromides (1)—(6)

Compound	Yield (%)	M.p. (*t*/°C)	Found (%) C	H	N	Br	Formula	Required (%) C	H	N	Br
(1)	96	83	36.5	7.5	7.0	40.5	$C_6H_{14}BrNO$	36.75	7.2	7.1	40.75
(2)	87	117	36.9	7.1	7.5	40.8	$C_6H_{14}BrNO$	36.75	7.2	7.1	40.75
(3)	88	154	40.1	7.7	6.2	37.2	$C_7H_{16}BrNO$	40.0	6.7	6.7	38.1
(4)	98	160—162	39.6	7.5	6.3	37.9	$C_7H_{16}BrNO$	40.0	6.7	6.7	38.1
(5)	92	133—134	43.7	8.2	7.2	35.3	$C_8H_{18}BrNO$	42.7	8.1	6.25	35.7
(6)	87	105	42.9	8.0	6.1	35.2	$C_8H_{18}BrNO$	42.7	8.1	6.25	35.7



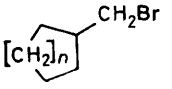
	cis	*trans*	*cis*	*trans*	*cis*	*trans*
$n = 1$	(1)	(2)	(7)	(8)	(13)	
$n = 2$	(3)	(4)	(9)	(10)	(14)	(15)
$n = 3$	(5)	(6)	(11)	(12)	(16)	(17)

SCHEME 1

The *cis*- and *trans*-2-(bromomethyl)cycloalkylamine derivatives (7)—(12) were prepared from the hydrobromides (1)—(6) of the corresponding amino-alcohols[3,8,15] (Table 1) by treatment with phosphorus

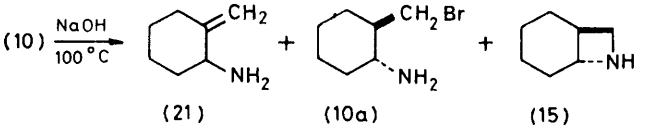
tribromide (Scheme 1). Table 2 gives m.p.s, analytical data, and yields.

In aqueous or ethanolic solutions containing 2 equiv. of sodium hydroxide, the *cis*-2-(bromomethyl)cyclopentylamine hydrobromide (7) instantaneously yields the azetidine derivative (13) almost quantitatively, even at room temperature. The *cis*-tetramethylene- (14) and *cis*- and *trans*-pentamethylene-azetidines (16) and (17)



(18) $n = 1$
(19) $n = 2$
(20) $n = 3$

can similarly be obtained without difficulty. In contrast, it was not possible to induce azetidine formation from the *trans*-cyclopentane derivative (8) even under more vigorous conditions. The *trans*-cyclohexane derivative (10) gives *trans*-7-azabicyclo[4.2.0]octane (15) in yields as low as 5—7%; 10—12% of the starting base is recovered, the main reaction being the formation of the elimination product (21) (Scheme 2). The azetidines



(21) 81—85% (10a) 10—12% (15) 5—7%

SCHEME 2

(13)—(17) were isolated in the form of their picrates. M.p.s, analytical data, and yields are given in Table 3.

Kinetic measurements were made in an ultrathermostat with aliquot portions of a 25% ethanolic stock solution (100 ml) containing the 2-(bromomethyl)-cycloalkylamine hydrobromide (mmol) and sodium hydroxide (mmol) (see Experimental section). The hydrogen bromide released was determined titrimetrically by the Volhard method after quenching the reaction by freezing. In order to establish the extent of amino-group participation, the solvolysis of the (bromomethyl)cycloalkanes (18)—(20) was also studied, under similar conditions. The k_1, E_a, and $\Delta S^{\ddagger}$ values determined are listed in Table 4.

The rate constants for the azetidine ring closure reactions of the 2-(bromomethyl)cycloalkylamine derivatives indicate a first-order reaction. For the (bromomethyl)cycloalkane model compound no reaction was observed at low temperatures (*ca.* 60 °C), while above 90—100 °C, instead of the expected second-order hydrolysis, HBr was eliminated in a first-order process. This shows that detachment of the halogen atom as an ion is promoted by the γ-amino-group *via* neighbouring group participation.

TABLE 2

Analytical data for the *cis*- and *trans*-2-(bromomethyl)cycloalkyl bromide hydrobromides (7)—(12) [a]

Compound	Yield (%)	M.p. (*t*/°C)	Found (%) C	H	N	Br	Formula	Required (%) C	H	N	Br
(7)	71	155—156	28.0	5.5	5.1	61.4	$C_6H_{13}Br_2N$	27.8	5.6	5.4	61.7
(8)	89	177—178	27.7	5.0	4.7	59.9	$C_6H_{13}Br_2N$	27.8	5.6	5.4	61.7
(9) [b]	77	160	30.6	5.6	4.9	58.1	$C_7H_{15}Br_2N$	30.8	5.5	5.1	58.5
(10) [c]	84	220—221	31.0	5.7	5.1	59.2	$C_7H_{15}Br_2N$	30.8	5.5	5.1	58.5
(11) [d]	47	205—208	34.1	6.0	4.4	55.0	$C_8H_{17}Br_2N$	33.5	6.0	4.9	55.7
(12)	52	195—196	33.3	5.7	4.7	55.7	$C_8H_{17}Br_2N$	33.5	6.0	4.9	55.7

[a] Solvent of crystallization: ethanol–ether. [b] Lit.,[17] m.p. 156—157 °C. [c] Sublimation from 175 to 190°. [d] Hygroscopic.

TABLE 3

Analytical data for the picrates (13a)—(17a) of the azetidines (13)—(17) [a]

Compound	Yield (%)	M.p. (*t*/°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
(13a)	92	166—167	44.0	4.3	16.9	$C_{12}H_{14}N_4O_7$	44.2	4.3	17.2
(14a)	83	131 [b]	46.0	5.3	15.95	$C_{13}H_{16}N_4O_7$	45.9	4.7	16.5
(15a)	86	146—147 [c]	46.1	4.5	16.0	$C_{13}H_{16}N_4O_7$	45.9	4.7	16.5
(16a)	88	135—136	47.1	5.0	15.4	$C_{14}H_{18}N_4O_7$	47.45	5.1	15.8
(17a)	92	160—162	46.9	5.3	16.1	$C_{14}H_{18}N_4O_7$	47.45	5.1	15.8

[a] Solvent of crystallization: ethanol–ether. [b] Lit.,[6] m.p. 131 °C. [c] Lit.,[6] m.p. 122 °C.

The rates of the azetidine formation reactions follow the sequence: (11) > (7) > (12) > (9) > (10). It is noteworthy that formation of the *cis*-pentamethylene-azetidine derivative (16) is the most favoured. The rate constant for the *cis*-cycloheptane derivative (11) is higher than that of the cyclopentane derivative (7) which, in turn, is higher than for the *cis*-cyclohexane derivative (9). Interestingly, the reactivity of the *trans*-cycloheptane derivative (12) is also greater than that of (9). These data indicate that in the formation of the strained azetidine ring, both *cis*- and *trans*-condensations with the flexible cycloheptane skeleton are energetically more favourable than the formation of the *cis*-tetramethyleneazetidine derivative (14).

In the reaction of (10), both end-product analysis and the parameters obtained from the kinetic results (Table 4) prove that the mechanism is different from that just described. Detachment of the halogen atom from (10) does not proceed *via* amino-group participation; the main process is elimination and the intramolecular ring

TABLE 4

Azetidine ring closure reaction of (7)—(12) and solvolysis of (18)—(20) [a]

Compound	Configuration	t/°C	$10^{-5}k_1$/s^{-1}	E_a/kcal mol^{-1} [b]	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
		2	2.5	24.6	
(7) [b]	*cis*	15	18.4	24.1	+7.8
		24	67.9	23.7	
		100	3.5	13.5	
(18)		110	7.3	13.6	−43.0
		120	8.9	13.3	
		30	7.1	18.2	
(9)	*cis*	40	18.6	17.7	−18.1
		50	45.0	18.0	
		75	4.5	20.4	
(10)	*trans*	80	6.8	21.4	−17.2
		90	15.7	21.4	
		100	25.8	21.2	
		90	2.0	20.7	
(1b)		99.8	4.2	20.3	−23.8
		118	15.4		
		1	21.4	11.3	
(11)	*cis*	9.5	40.0	10.5	−33.9
		15	57.3	11.0	
		23	12.9	16.3	
(12)	*trans*	33.5	33.4	15.4	−24.1
		43	68.0	15.4	
		99.5	32.5	12.2	
(20)		110	51.0	12.2	−42.2
		120	76.3	12.1	

[a] See Experimental section for the method used for the kinetic measurements. The k values given refer to azetidine formation in the cases of (7), (9), (11), and (12), but in the reaction of (10) the k values for the competing ring closure and elimination reactions are not separated and the k given refers to the combined loss of HBr. [b] 1 cal = 4.184 J. [c] In the attempted reaction of (8) HBr formation was not observed up to 110 °C.

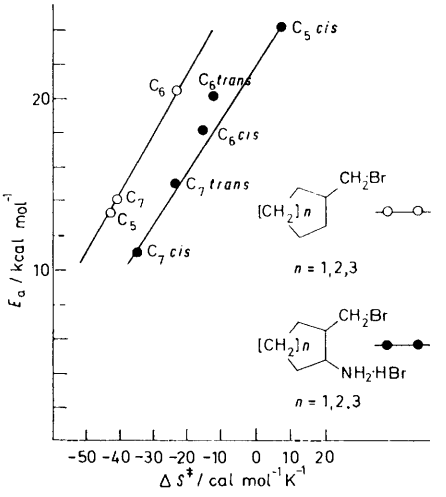
closure is only a side-reaction (Scheme 2). In contrast, elimination was not observed in the reactions of (7), (9), (11), and (12).

In the reactions in question we also examined the validity of the isokinetic correlation.[16] If this correlation holds, it indicates that the reactions of members of a homologous series have the same mechanism. This is reflected well in the formation of the *cis*-trimethylene-, *cis*-tetramethylene-, and *cis*-pentamethylene-azetidines (13), (14), and (16), respectively, where a linear isokinetic correlation is obtained. The point for the formation of the *trans*-pentamethylene-azetidine (17) likewise falls on this straight line.

It is known that large variations in the activation energies or activation entropies of the reactions of the members of a homologous series do not necessarily imply differences in reaction mechanism. In the present case, the positive activation entropy of azetidine formation from (7) differs considerably from the negative activation entropies for the conversions of the other members of the series, yet the point obtained from the reaction parameters lies on the isokinetic line of the homologous series, showing that the mechanism is the same (Figure). Similarly, the identity of the reaction mechanism does not follow from the close agreement of the E_a and $\Delta S^{\ddagger}$ values of a series. The E_a and $\Delta S^{\ddagger}$ values for the reaction of (10) fit into the series, whereas end-product analysis showed that the reaction mechanism differed from that of the other members, as confirmed by the significant deviation from the isokinetic line (Figure). The point obtained from the kinetic data for (10) does not lie on the isokinetic line for (7), (9), (11), and (12).

Moriconi and Mazzocchi [10] did not report n.m.r. data for *cis*- and *trans*-7-azabicyclo[4.2.0]octane (14) and (15). In their spectra of the 7 tosyl derivatives the protons of the carbon atoms adjacent to the nitrogen appear as a multiplet that is difficult to analyse; in the case of the *cis* isomer, a double quartet due to the AB part of the system can be observed.

The most characteristic feature of the n.m.r. spectra of the azetidines (13)—(17) is connected with the two methylene protons of the azetidine ring; as a consequence of the asymmetric structure of the ring, these are not equivalent, and they are also coupled with the angular methyne proton. However, the expected ABC multiplet is more complex because of further coupling of the angular proton, and only its AB part can be observed.



This AB spectral detail differs characteristically in the *cis*- and *trans*-isomers. In the spectra of the *cis*-isomers, all eight signals of the AB part can be distinguished, whereas in the *trans*-isomers there are only two as a result of coincidence of the chemical shifts of the CH_2Br protons. Variation of temperature or solvent did not lead to resolution of this doublet. Although the AB proton signals can be observed in all the *cis*-azetidine derivatives, they are differentiated most markedly for the *cis*-azabicycloheptane (13). The *endo*-protons have lower δ values than the *exo*-protons.

Owing to the chirality of C-1 and C-2 of the rings, the CH_2Br protons in the 2-(bromomethyl)cycloalkylamine hydrobromides (7)—(12) are not equivalent; in their spectra, as for the azetidine derivatives, the eight signals of the AB system can be differentiated. As would be expected the CH_2Br protons of the (bromomethyl)cycloalkanes (18)—(20) are equivalent.

EXPERIMENTAL

N.m.r. spectra were recorded at room temperature on a JEOL C60-HL high-resolution instrument, with tetra-

methylsilane as internal standard, except for D_2O solutions when sodium 2,2-dimethyl-2-silapentane-5-sulphonate was used.

cis- *and* trans-2-(*Bromomethyl*)*cycloalkylamine Hydrobromides* (7)—(12).—To a cooled, stirred suspension of the aminoalcohol hydrobromides (1)—(6) (0.01 mol) in benzene (20 ml) phosphorus tribromide (0.03 mol) was added in portions. The mixture was refluxed for 45 min and cooled, water (20 ml) was added in portions, and refluxing was resumed for a further 10 min. After cooling, the aqueous and benzene phases were separated, the latter was extracted with water (2 × 10 ml), and the combined aqueous solutions were washed with ether (2 × 20 ml), made alkaline (pH 8) with sodium hydroxide solution with cooling, and extracted with ether (4 × 20 ml). After drying (Na_2SO_4), the ether extracts were evaporated to dryness, and the hydrobromides (7)—(12) were immediately precipitated from the residue with ethanolic hydrogen bromide solution (Table 2).[17]

Kinetic Measurements.—The 2-(bromomethyl)cycloalkylamine hydrobromides (7)—(12) or the (bromomethyl)-cycloalkanes (18)—(20) (mmol) were dissolved in 50% aqueous ethanol (50 ml), 1M aqueous sodium hydroxide (2 ml) was added, and the solution was made up to 100 ml with distilled water. 7—8 ml Portions of these solutions were sealed in ampoules and kept in an ultrathermostat at the appropriate temperature (±0.1 °C) for the desired time. After the addition of 0.01M silver nitrate (10.0 ml), 5% iron(III) sulphate–ammonium sulphate [$Fe_2(SO_4)_3 \cdot (NH_4)_2SO_4$] indicator (2 ml), and 25% nitric acid (2 ml), an aliquot portion of the sample (5.0 ml) was titrated with 0.01M ammonium isothiocyanate solution. The first-order rate constants of the reactions were calculated from equation (1),

$$k = (2.303/t) \log[a/(a - x)] \quad (1)$$

where a is the initial concentration, and x is the quantity of material (in mol l^{-1}) converted in t s, the activation energies from equation (2), and the activation entropies

$$E_a = [4.576 \times T_1 \times T_2 \times \log (k_2/k_1)]/(T_2 - T_1) \quad (2)$$

from equation (3). The results are given in Table 4.

$$\Delta S^{\ddagger} = 4.576[\log k + E_a/(4.576T) - \log (k/h)] \quad (3)$$

Preparation of the Azetidine Derivatives (13)—(17).—The 2-(bromomethyl)cycloalkylamine hydrobromides (7)—(12) (1 mmol) were dissolved in ethanol (50 ml), 1M aqueous sodium hydroxide (2 ml) was added, and the volume was made up to 100 ml with distilled water. The solutions were sealed in a pressure tube, kept for 5—10 h at the temperature found to be optimum from the kinetic measurements, then acidified (pH 6) with ethanolic hydrochloric acid and evaporated to dryness. The residue was taken up in water (10 ml), made alkaline (pH 8) with aqueous sodium hydroxide, and extracted with ether (4 × 50 ml). After drying (Na_2SO_4), the combined ether extracts were evaporated and the resulting azetidines (13)—(17) were precipitated as their picrates (Table 3).

trans-7-Azabicyclo[4.2.0]octane (15) was prepared as just described, but the combined ether extracts were evaporated and the residue was separated by column chromatography on silica gel G with ethanol–aqueous ammonium hydroxide (9 : 1).

Samples taken from different heights of the column were developed with the Draggendorff reagent.[18] The starting material (10) gave an orange-yellow colour, the azetidine (15) a violet-purple colour, and the elimination product (21) a lemon-yellow colour. The column was cut at the pure zone boundaries: (15) and (10) were eluted with dilute hydrochloric acid, and (21) was eluted with ethanol. The solution containing the azetidine hydrochloride was made alkaline and extracted with ether; after drying (Na_2SO_4) the azetidine picrate was precipitated. The elimination product (21) was similarly identified as its picrate, 2-methylidenecyclohexylamine picrate, m.p. 170—172 °C (Found: C, 46.05; H, 4.6; N, 16.0. $C_{13}H_{16}N_4O_7$ requires C, 45.9; H, 4.7; N, 16.5%).

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