Recovery of Excess Ester from the Cycloaddition Reaction with Ethyl Maleate.—A cycloaddition reaction of 1.4 g of acridizinium bromide with 8.5 g of ethyl maleate in 8 ml of acetic acid at 100° was carried on in the usual way except that after 7.5 hr the reaction was interrupted and the excess ester fraction recovered as described in the preceding paragraph. Gas–liquid partition chromatographic analysis showed that ester recovered was essentially pure (>90%) ethyl fumarate.

Recovery of Hydrogen Bromide from an Acetic Acid Solution of Acridizinium Bromide.—Acridizinium bromide (3 g) was dissolved in 75 ml of acetic acid and the mixture heated on a steam bath for 3 hr. The flask was arranged for vacuum distillation under reduced pressure with dropwise addition of pure acetic acid to maintain the original volume. During the distillation the temperature of the solution was 88–89° under pressure used. The distillate was carefully redistilled at atmospheric pressure and was found to contain bromide ion as evidenced by formation of a pale yellow precipitate with acidified silver nitrate solution.

Reaction Rates of *p*-Substituted Styrenes with Acridizinium Chloride.—A 0.005 *M* solution of acridizinium chloride[13] was prepared by dissolving 1.168 g in enough acetic acid to make 100 ml of solution. To avoid photodimerization[14] the solution was stored in a stoppered flask made of nonactinic glass. Reactions were carried out in glass tubes maintained at a constant temperature (65°) by insertion in a methanol vapor bath.

For each run 1 ml (0.05 mmole) of the stock solution was withdrawn and placed in a 2-ml volumetric flask, 0.5 mmole of dienophile was added, and solution was made up to 20 ml by addition of dimethyl sulfoxide. The resulting mixture was placed in a reaction tube which was heated in the vapor bath. Samples of 100 μl were withdrawn by use of a syringe and diluted to 50 ml with water. The intensity of the 399-mμ peak of the acridizinium ion was used to measure the concentration.[15] Pseudo-first-order reaction rate plots were obtained for each of the styrenes. The curves shown in Figure 1 are each for a single run, but the rate constants shown are the average of three determinations.

Registry No.—1 perchlorate, 15314-07-5; 2 perchlorate, 15259-85-5; 2 bromide, 15285-87-7; 3 perchlorate, 15314-08-6; 4 perchlorate, 15350-48-8; 5 perchlorate, 15285-84-4; 6 perchlorate, 15259-86-6; 7 perchlorate, 15259-87-7; 8, 15259-88-8; 9, 15259-89-9; 10, 15285-85-5; 11, 15285-86-6; 12, 15259-90-2; 13, 15259-91-3; 14, 15259-92-4; 15, 15259-93-5; acridizinium perchlorate with tetracyanoethylene (2:1), 15281-69-3.

(13) C. K. Bradsher and J. D. Turner, *J. Org. Chem.*, **32**, 1169 (1967).

(14) C. K. Bradsher, L. E. Beavers, and J. H. Jones, *ibid.*, **22**, 1740 (1957).

(15) Earlier work in this laboratory by D. L. Kerbow [Ph.D. Dissertation, Duke University, Durham, N. C., 1966] has shown that solutions of acridizinium bromide obey Beer's law in the long-wavelength region.

Ring-Opening Alkylations of 1,1-Dialkyl-3-Substituted Azetidinium Cations. Substituent Entropy-Controlled Strained Ring–Chain Equilibria[1]

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1,1-Dialkyl-3-hydroxyazetidinium cations (1) alkylated a variety of active nucleophiles, including amines, alkoxides, mercaptides, halides, etc., reacting with ring opening. Failure to alkylate methanol indicated that the four-membered azetidinium cycle is less reactive than known aziridinium salts. The formation of 2,5-bis-(dialkylaminomethyl)dioxanes from 1 was rationalized in terms of a double alkylation *via* an azetidinium alkoxide zwitterion. Selective competitive alkylations were described. These cations (1) participate in reversible equilibria with 1-chloro-3-dialkylamino-2-propanols. Equilibrium constants in acetonitrile at 30–40° were determined directly for a series of systems and the thermodynamic quantities were calculated. The equilibria were controlled by substituent entropy, attributed to restrictive interactions between the groups in the 1 and 3 positions of the azetidinium cycle. A conformational equilibrium of the ring is also inferred.

The reactivity conferred on small cycles by ring strain and the effects of substituents on ring closure and ring scission are of current interest. The strained rings containing quaternary ammonium ring members are the three-membered aziridinium and the four-membered azetidinium ions. The studies of the former class by Leonard and his school[2a] and others[2b] have elegantly established the marked reactivity of these cations toward even weak nucleophiles. Thus nucleophilic reagents which react under SN2 conditions (alkoxides, mercaptides, cyanide, halides, amines, etc.) as well as such weak nucleophiles as methanol are alkylated under mild conditions with ring opening.

It is not clear that the lesser strain of the simpler azetidinium cycles acts to promote ring-opening alkylation. Although alkylations with bicyclic azetidinium halides have been described,[3] these cases involved bridgehead quaternary members, as did the dequaternization of certain bicyclic quinolizidinium ions.[4] There are a number of reported instances of reversal of the formation of simple azetidinium halides, *i.e.*, to give the precursor γ-halo amines,[5] but 1,1-diethylazetidinium ion has been reported not to react with cysteine under mild conditions.[6] Azetidinium ions have been advanced as intermediates to explain the formation of two isomers in reactions of substituted γ-halo amines.[7]

Our attention was directed to the 1,1-dialkyl-3-hydroxyazetidinium chlorides (1) by our interest in the spontaneous cyclization of 1-alkylamino-3-chloro-2-propanols to 1-alkyl-3-azetidinols.[8] A variety of 1 has been prepared from secondary amines and epichlorohydrin *via* 1-chloro-3-dialkylamino-2-propanols (2).[9]

(1) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(2) (a) N. J. Leonard, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **26**, 211 (1965); (b) for example, G. K. Helmkamp, R. D. Clark, and J. R. Koskinen, *J. Org. Chem.*, **30**, 666 (1965), and C. F. Hammer and S. R. Heller, Abstracts, 150th NationalMeeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, p 65S.

(3) A. Ebnöther and E. Jucker, *Helv. Chem. Acta*, **47**, 745 (1964).

(4) G. Fodor, *J. Am. Chem. Soc.*, **88**, 1040 (1966).

(5) C. F. Gibbs and C. S. Marvel, *ibid.*, **57**, 1137 (1935); C. Mannich and G. Baumgarten, *Ber.*, **70B**, 210 (1937).

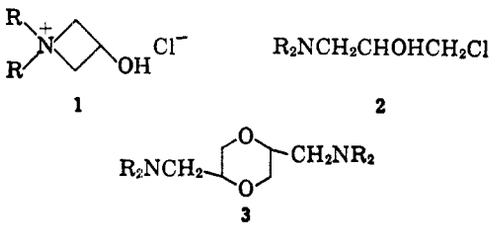
(6) M. Torigoe, *Pharm. Bull.* (Japan), **1**, 349 (1953); *Chem. Abstr.*, **49**, 11962 (1955).

(7) R. C. Elderfield and C. Ressler, *J. Am. Chem. Soc.*, **72**, 4059 (1950); W. B. Wheatley and L. C. Cheney, *ibid.*, **74**, 1359 (1952).

(8) V. R. Gaertner, *Tetrahedron Letters*, 4691 (1966); *J. Org. Chem.*, **32**, 2972 (1967).

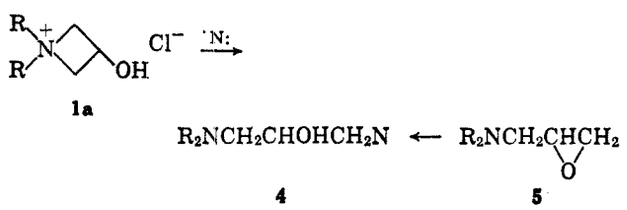
(9) (a) L. Niemilowicz, *Monatsh. Chem.*, **15**, 118 (1894); (b) R. Rothstein and K. Binovic, *Compt. Rend.*, **236**, 1050 (1953); (c) E. Schneider, German Patent 1,111,638 (1961); (d) K. Ichikawa, *Yuki Gosei Kagaku Kyokai Shi*, **22**, 546 (1964); *Chem. Abstr.*, **61**, 7008 (1964).

The structural assignment has been controversial. Only one chemical transformation of these compounds has been described—the action of aqueous alkalies to give 2,5-bis(dialkylaminomethyl)-1,4-dioxanes (**3**).[9a,b] The structure **3** has been proven beyond doubt,

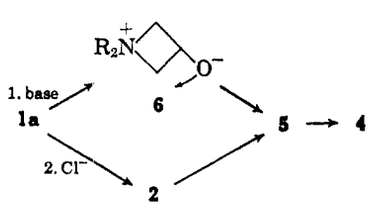


and it was suggested that **1** were merely dihydrochlorides of **3**.[10] Recent molecular weight, infrared, and pmr studies supported the original structure **1**.[11] The present paper describes chemistry which finally establishes the structure **1** and clarifies the reactivities and ring-substituent interactions in this strained system.[12]

Alkylations with 1,1-Dialkyl-3-Substituted Azetidinium Salts.—These compounds are mild alkylating agents which introduce 3-dialkylamino-2-substituted 1-propyl groups by ring scission. 1,1-Diethyl-3-hydroxyazetidinium chloride (**1a**) was used in most of the reactions. Thus diethylamine, N-methylaniline, trimethylamine, sodium *t*-butylmercaptide, potassium phenoxide, and potassium cyanide reacted with **1a** at 60–100° to give good yields of products of structure **4**. The structures (except for that of the salt from trimethylamine, which was assumed to be similar) were evident from their identity with the compounds prepared from diethyl-2,3-epoxypropylamine (**5**). Products from either source were not contaminated by isomers of **4**.

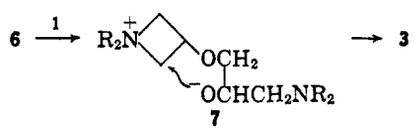


These reactions of **1a** are presumably SN2; that is, the ring is opened by direct displacement on C-1 by the nucleophile. Considered were two possible alternative pathways: (1) elimination to give **5** *via* zwitterion **6** and (2) reverse addition of chloride to give **2** and then **5** by dehydrohalogenation.



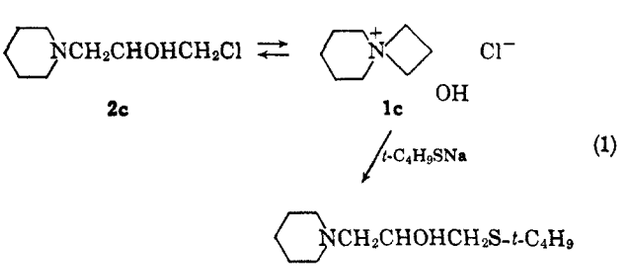
That path 2 need not be seriously considered for good nucleophiles was shown by experiments with the perchlorate, **1b**, prepared from **1a** by precipitation of silver chloride with silver perchlorate in acetonitrile (AN). Sodium methoxide converted **1b** into **4a** (N: = :OCH_3) in the same yield (74%) as **1a**. Clearly this reaction cannot involve **2**, or a comparable intermediate, since perchlorate is too weak a nucleophile to cleave small rings.[1] This fact was further demonstrated by the recovery of **1b** after heating in methanol. Even at 100° for 6 hr, only 2% of **4a** was found.

Evidence was obtained for the formation of **6**, but it did not yield **5**. Thus a higher boiling oil was obtained by the action of aqueous potassium hydroxide on **1b**. This same compound was isolated from the reactions of both **1a** and **1b** with sodium methoxide–methanol. Spectral and other data confirmed that it was 2,5-bis(diethylaminomethyl)-1,4-dioxane (**3**). Thus **2** is also not an intermediate in the formation of **3**, contrary to an earlier suggestion.[10] We suggest that these data support the existence of the zwitterion **6** in alkaline solutions of **1**. The zwitterion, as an alkoxide, is alkylated by **1**, to give zwitterion **7**, a dimeric azetidinium alkoxide. The latter is alkylated intramolecularly, forming **3**. The process thus involves two azetidinium–alkoxide alkylation steps.



Finally, alkylation of halides by **1** occurs readily in the absence of other nucleophiles. Indeed, pure **2a** may be distilled from **1a** *in vacuo* at 130–150° in at least 95% yield. The reaction is completely reversible in AN and has been studied in detail (see below). However, this reaction surely does not compete with direct alkylation of the better nucleophiles.

These alkylation reactions are general. Piperidine readily forms the crystalline salt,[9] **1c**, which alkylates the *t*-butylmercaptide anion (eq 1). The chloropropanol **2c** has been described as too rapidly isomerized



(1)

to be isolated. However, pyrolysis of **1c** *in vacuo* with collection of distillate directly in a cooled receiver gave **2c** of good purity.

It seemed likely that these mild alkylating agents would exhibit selectivity in competitive reactions. Thus **1a** reacted almost exclusively with the mercaptide in the presence of an equal excess of sodium methoxide and also with trimethylamine in a mixture containing as much triethylamine. More detailed studies will be required to establish the selectivity factors for these competitive alkylations. Presumably the more stable azetidinium salts, such as **1c**, will exhibit the greatest selectivity.

The present results clearly establish the azetidinium structures for the salts from secondary amines and epichlorohydrin. The facts that usual SN2-type reagents open the cycle and methanol does not indicate that the lesser strain in the four-membered ring leads to lesser reactivity than is found in the aziridinium salts.

(10) D. L. Heywood and B. Phillips, *J. Am. Chem. Soc.*, **80**, 1257 (1958).
(11) J. H. Ross, D. Baker, and A. T. Coscia, *J. Org. Chem.*, **29**, 824 (1964).
(12) Preliminary report: V. R. Gaertner, *Tetrahedron Letters*, 343 (1967).

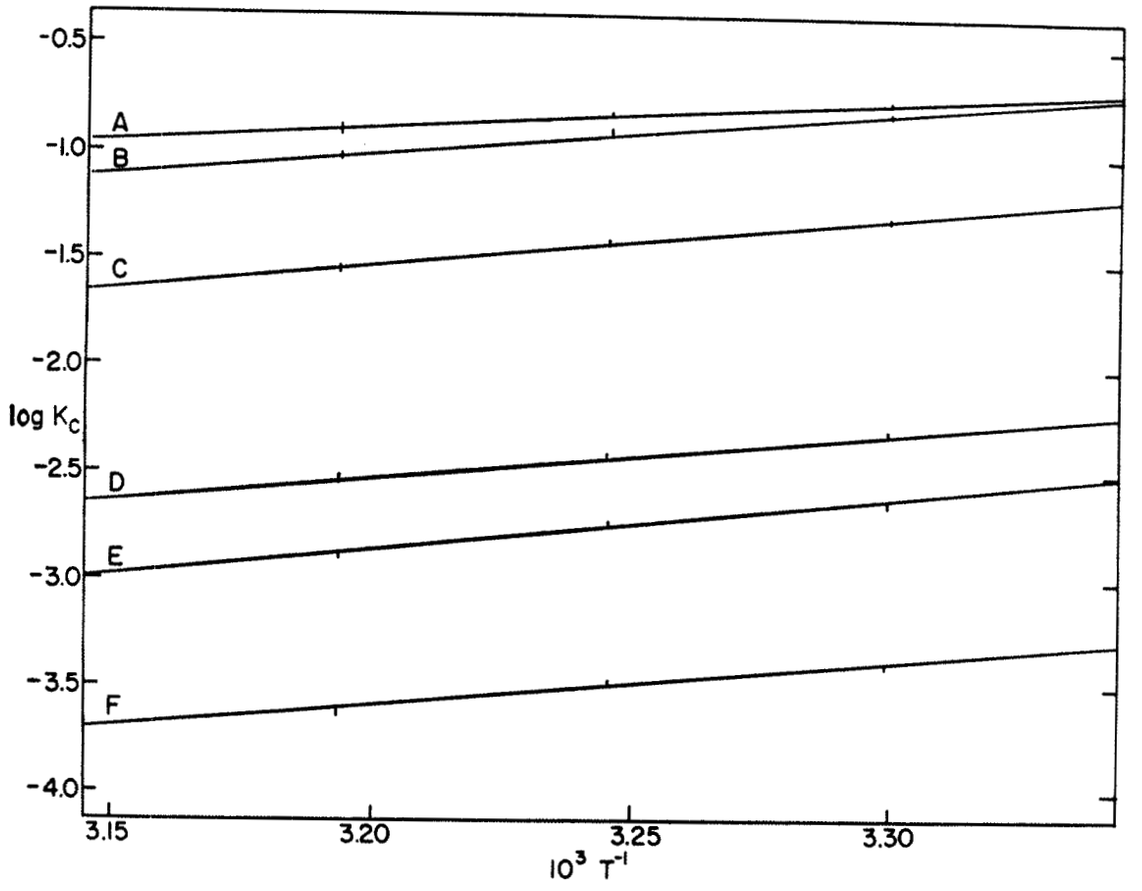


Figure 1.—Temperature dependence of cyclization constants for the equilibria listed in the text; from Table II.

More detailed studies (kinetics, etc.) will be required to quantify this conclusion.

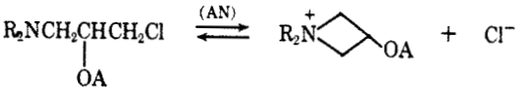
Substituent Effects on the Thermodynamics of Cyclization.—The finding that **1a** and **2a** are in equilibrium in AN solution suggested that such systems would be adaptable for a direct thermodynamic study of the effects of substituents on cyclization–scission equilibria. This approach had been suggested generally by Hammond,[13] in connection with the "*gem*-dimethyl" effect promoting cyclization. The interplay between ring size (enthalpy) and entropy or probability in the cyclization of bifunctional chains has long been understood.[14] However, the basis for the effects of substituents on ring–chain equilibria have been discussed only for unstrained rings.

Hammond[13] suggested that substituents favored chain conformations leading to the transition state for cyclization and resulted in a less negative (and more favorable) entropy of cyclization. Allinger and Zalkow[15] calculated that the "*gem*-dimethyl" effect had both entropy and enthalpy components in the formation of substituted cyclohexanes, owing to the *gauche* interactions in going from reactant to product. Similar results were obtained by Yumoto in the polymerization of substituted ϵ-caprolactams.[16] The extension of these ideas to other than six-membered rings was considered qualitatively similar but a lack of data was noted.[15] The ring closure rates for bromobutylamines were rationalized on the basis of a lower entropy of activation due to stabilization of coiled conformations by substituents.[17]

In the present work, preliminary results[8,12] pointed to the ready cyclization of **2** and related 1-alkylamino-3-chloro-2-propanols. In contrast, the corresponding acetate esters cyclized sluggishly and to markedly lesser extents.

The explanation of this discrepancy was sought in equilibration experiments involving the six systems prepared from diethylamine, di-*n*-butylamine, and piperidine with epichlorohydrin (see Table I). The acetate esters of **1** were easily prepared by direct acetylation, but the opening by chloride occurred so rapidly that only **1a** acetate was isolated and characterized completely. Experiments with this acetate

TABLE I



2 **1**

System	R_2	A
A	$-(CH_2)_5-$	H
B	$(C_2H_5)_2$	H
C	$(n\text{-}C_4H_9)_2$	H
D	$-(CH_2)_5-$	Ac
E	$(C_2H_5)_2$	Ac
F	$(n\text{-}C_4H_9)_2$	Ac

(13) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp 460–470.

(14) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison ["Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 190–192] review these effects.

(15) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).

(16) H. Yumoto, *J. Chem. Phys.*, **29**, 1234 (1958).

(17) R. F. Brown and N. M. VanGulick, *J. Org. Chem.*, **21**, 1046 (1956).

TABLE II

CYCLIZATION CONSTANTS IN ACETONITRILE

System	$10^2\ c_i$[a]	$10^2\ m_\pm$[a]	Cyclic %[b]	$10^4\ K_c$[c,d] 30.00°C	35.00°C	40.00°C
A	2.691	3.127	89.25	1788 (32)	1554 (25)	1304 (31)
B	2.771	3.104	86.71	1569 (34)	1263 (24)	976 (18)
C	3.282	2.914	68.62	492.0 (60)	383.6 (44)	299.0 (32)
D	31.03	4.676	11.86	49.56 (7)	38.72 (5)	30.88 (55)
E	30.68	3.254	8.344	23.31 (9)	18.43 (3)	13.84 (12)
F	32.40	1.426	3.478	4.065 (23)	3.194 (9)	2.333 (17)

[a] Average values of initial molarities (c_i) and autogenous ionic strengths (molalities), $m_\pm$, of duplicated runs at 30°. The **2** present in equilibrium is included as solvent in these calculations. [b] The average percentage of the system in cyclic form (**1**) at 30°. [c] The numbers in parentheses are actual error limits in the last one, or two, places, *e.g.*, K_c for system B at 30° is 0.1569 ± 0.0034 moles/l. Error limits refer only to experimental reproducibility. [d] The temperatures were maintained well within ± 0.02°.

ester indicated that the equilibrium point was approachable from either pure component.

Within the series of systems given in Table I, substituent effects shifted the degree of cyclization at 30° from 90% to as low as 3%. The equilibrium positions shifted markedly in the 25–50° range. A single rapid titration sufficed to analyze each equilibrated system completely and to give the equilibrium constant for the cyclization directly, from the chloride and initial total (c_i) concentrations (eq 2).

$$K_c = \frac{c_1{}^+\, c_{Cl}{}^-}{c_2} = \frac{c^2{}_{Cl}{}^-}{c_i - c_{Cl}{}^-} \qquad (2)$$

The K's were first determined for 0.5 — 1.0 M solutions. Even in this range, the K's for systems B and C decreased noticably with dilution. This behavior is not unexpected. The Debye–Hückel dilution law predicts that the "true" K for the ionization of a weak electrolyte is attained only at infinite dilution. Attempts to extend the present measurements below about 0.03 M gave erratic results. Therefore data obtained at similar autogeneous ionic strengths are presented in the belief that the results represent consistent trends and are not much different quantitatively from the true K's. Since we are concerned mainly with differences between thermodynamic quantities due to substituent effects, slightly, and consistently, high values for the K's do not affect the conclusions significantly.

The K's are listed for 30, 35, and 40° in Table II. These data are graphed in Figure 1, p 525, in the form log K *vs.* T^{-1}, and the plots are nearly straight lines. (Data for 45 and 50° in preliminary runs increased the curvature.) The thermodynamic quantities were calculated for 35° and appear in Table III.

TABLE III

THERMODYNAMIC QUANTITIES OF CYCLIZATION[a,b] AT 35°

System	ΔH_c	ΔF_c	ΔS_c
A	−6.0 (0.8)	+1.14	−23.0 (2.6)
B	−9.0 (0.8)	+1.27	−33.4 (2.6)
C	−9.4 (0.4)	+2.00	−37.0 (1.4)
D	−8.9 (0.4)	+3.40	−40.2 (1.4)
E	−9.8 (0.2)	+3.85	−44.4 (0.8)
F	−10.5 (0.3)	+4.93	−49.9 (0.8)

[a] Error limits in parentheses refer only to experimental reproducibility. Errors in ΔF were negligible, at the most about ±0.01 kcal. [b] Units: ΔH and ΔF, kcal/mole; ΔS, eu/mole.

These quantities exhibit consistent trends with increasingly complex substituents. As the groups on nitrogen are varied from pentamethylene to di-*n*-butyl, and on oxygen from hydrogen to acetyl, both the ΔH's and ΔS's become more negative, and the ΔF's, more positive. Thus the trend is more favorable in enthalpy for cyclization and less favorable in entropy. Since the influence of the $-T\Delta S$ term on ΔF is increasingly greater than the ΔH term, the result is a more positive and less favorable ΔF. The cyclizations are clearly entropy controlled.

The data are plotted in the form ΔH *vs.* $-T\Delta S$ in Figure 2. A roughly linear relationship between these quantities is evident.[18] The cyclic examples A and D, appear to lie on a somewhat divergent line, and the four points for the dialkyl substituents then define a good straight line, suggesting that the effect arises in a single mechanism.

The starting amines, diethylamine, piperidine, and di-*n*-butylamine, were chosen for study in order to minimize differences due to amine basicity, nucleophilicity, and solvation.[19] If we assume that these factors are of minor importance, then the data must be explained with reference to structural effects in either the chain (**2**) or ring (**1**) structures in equilibrium.

The chain conformational selectivity proposed by Hammond[13] is not applicable to the present cases. This explanation was applied to *gem*-disubstituted chain members. In the present case, the acetoxyl group should favor cyclization more than does the smaller hydroxyl by this reasoning, but in fact hydroxyl much more effectively stabilizes the cycles. There is no change in the number of *gauche* interactions in going from reactant to product, as utilized by Allinger and Zalkow,[15] in the present cases. The substituents must act by their direct influence on ring stability.

The geometry of the azetidinium cycle surely resembles closely that of cyclobutane, tetravalent ni-

(18) J. E. Leffler (*J. Org. Chem.*, **31**, 533 (1966), and references therein) discusses the interpretation of linear enthalpy–entropy relationships.

(19) Although the basicities and nucleophilicities of the amine components (**2**) are surely very similar, solvation effects are less easily assessed. However, several arguments suggest that solvation is not a decisive factor in this series. Firstly, the neat **2** and their acetates cyclize to roughly the same extents as they do in acetonitrile. This implies that solvation is unimportant or that the components themselves "solvate" each other to similar extents as does acetonitrile, an unlikely possibility. Increasing solvation of the products should be reflected in more negative ΔH's and ΔS's, as more solvent is "frozen out." This trend is observed in the series A to F, but it is difficult to see why increasingly *less* polar compounds should be solvated *more*. The opposite should be true, as should also the more hindered amines and quaternaries (dibutyl) have a lower degree of solvation than the less hindered, since the latter permit a closer approach of the polar solvent molecules to the charged centers. Acetates probably are less solvated than the corresponding alcohols, but again this reasoning contradicts the observed trends in ΔH and ΔS. We believe that these arguments suggest that the observed data are the net result of a large substituent–entropy effect and a small and opposite solvation effect. That is, the increments of both ΔH and ΔS should become less negative in passing from A to F, the opposite of the observed trend.

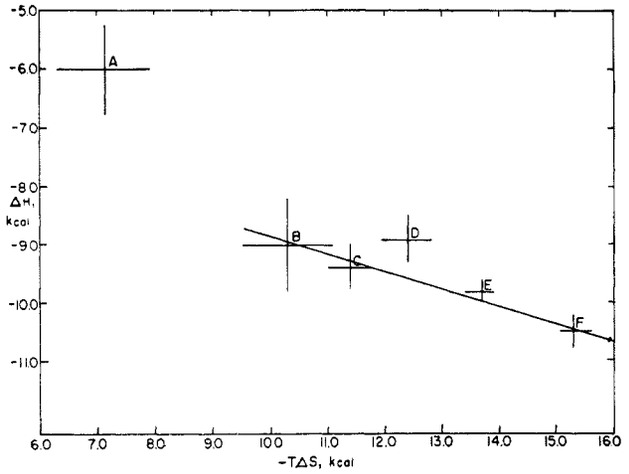


Figure 2.—Relative influences of ΔH and $-T\Delta S$ on ΔF of cyclization; data are listed in Table III.

trogen being tetrahedral. Recent studies have shown that the cyclobutane ring is puckered. Conformational equilibria of 1,1-difluoro-3-arylcyclobutanes favor the component with an equatorial (e) aryl group[20a] and *cis*-1,3-dihalocyclobutanes (e,e conformation) predominate in equilibrium with *trans* (e,a) isomers.[20b] We suggest that the entropy effect found in the present work also arises from cross-ring interactions between the substitutents in the 1 and 3 positions of the azetidinium ring.

The trends toward more negative entropies with increasing complexity and effective bulk in either substituent are consistent with this interpretation. The $\delta\Delta S$'s for acetylation (-17, -11, and -13 eu, each with respect to the corresponding hydroxyl compound) are surely too large for restriction of the acetoxyl group *per se* and must include a large contribution for the rest of the molecule, mainly the alkyl groups.

Further confirmation of this interpretation was found in the rates of cyclization of **2** and for scission of **1**, listed in Table IV. Cyclization rates were measured in fairly concentrated solutions and the appropriate K_{cyc}'s extrapolated to 25° are listed. Scission rates were calculated as usual. If the above explanation is correct, then ring opening, promoted by the steric effect, should become more rapid for the compound bearing the more complex substituents. As predicted, the scission rate for the dibutyl compound exceeded that for the diethyl cycle.

TABLE IV

RATES IN ACETONITRILE AT 25°

System	$10^5\ k_{cyc}$[a]	K_{cyc}[b]	$10^5\ k_{sci}$[c]
A	2.15 ± 0.04		
B	2.65 ± 0.03	9.89	2.68
C	1.26 ± 0.02	3.07	4.10

[a] Measured cyclization rates (sec^{-1}) at about 0.5 *M*. [b] Cyclization constants at about 0.5 *M*, extrapolated to 25°. [c] Estimated scission rates.

A conformational equilibrium may be inferred from the data and the analogy with cyclobutanes. The conformational isomers are shown in Figure 3. The conformation with the equatorial C-3 substituent is undoubtedly more stable than the axial isomer. To the extent that the latter is excluded, the entropy of mixing is lost, and ΔS is more negative. The entropy of mixing is R ln 2, or 1.4 eu/mole.

Figure 3.—Conformational equilibrium between axial and equatorial isomers.

In summary, our results support the idea that cross-ring steric interaction between the substituents in the 1 and 3 positions promotes ring opening of the strained azetidinium ring, whether in irreversible alkylations or in reversible equilibria with the aminochloropropanols.

Experimental Section[21]

Synthesis of 1,1-Dialkyl-3-Substituted Azetidinium Salts 1,1-Diethyl-3-hydroxyazetidinium Chloride (1a).[9b,11]—The best yield and purity resulted from the uncatalyzed reaction of equimolar diethylamine and epichlorohydrin. The reactants were mixed and cooled in a large cold-water bath which was allowed to warm overnight to 20–25°. The crude product cyclized and crystallized spontaneously after 2–4 days. Superior purity resulted when 20–25% by weight of acetonitrile (AN) was added after the initial condensation. The product separated as massive rhombs and was recrystallized from hot AN by the addition of acetone. The yield was 38–42%. The melting point, reported to be 154–155°,[11] is actually a decomposition temperature which varies with the rate of heating in the range 145–155°. The crystals were rapidly deliquescent. The compound did not add hydrobromic acid in acetic acid. Potentiometric titration of 1–2 *N* solutons in AN with silver perchlorate in AN indicated that fresh solutions were 100% ionic. On standing several days the solutions measured 98–99% ionic (less for more dilute solutions). The aqueous solution is 100% ionic and is not acidic to dilute alkali.

Others[11] have shown that molecular weight data indicate complete ionization in water and ion pair formation in AN and that the infrared spectrum and the nmr spectrum in dimethyl sulfoxide-d_6 support the azetidinium structure. Pmr spectra in acetonitrile-d_3 were also consistent with this conclusion: CH_3CH_2, τ 8.77 (triplet, $J = 7$ cps);[22] CH_3CH_2, 6.24, 6.45 (staggered double quartets indicating nonequivalent ethyl groups); ring C_2H, 5.1–5.8 (complex multiplet); OH, 2.71.

1,1-Diethyl-3-hydroxyazetidinium Perchlorate (1b).—The chloride **1a** (17.9 g) was dissolved in 25 ml of AN and added to a stirred solution of 20.7 g of anhydrous silver perchlorate (G. Frederick Smith Chemical Co., Columbus, Ohio) in 100 ml of AN. The instantly precipitated silver chloride was filtered and rinsed with AN; the filtrate was aspirated in a rotating vacuum evaporator below 35°, leaving a viscous mass (24.4 g) which crystallized partially. The crude product had the correct elemental contents, but recrystallization was difficult. The syrupy product was satisfactory for subsequent reactions.

Recrystallization from a mixture of ethanol and 2-propanol (refrigerated) gave colorless rhombs, mp 181–183°. They burned explosively when heated near a flame.

Anal. Calcd for $C_7H_{16}ClNO_5$: C, 36.60; H, 7.02; Cl, 15.44; N, 6.10. Found: C, 36.43; H, 6.91; Cl, 15.63; N, 6.23.

(20) (a) J. B. Lambert and J. D. Roberts, *J. Am. Chem. Soc.*, **85**, 3710 (1963); (b) K. B. Wiberg and G. M. Lampman, *ibid.*, **88**, 4427 (1966). Both effects were attributed to cross-ring interactions. In the latter case, the steric effect was evident, since the effect increased with the size of the halogen. See also, concerning the nonplanarity of cyclobutane itself, S. Meiboom and L. C. Snyder, *ibid.*, **89**, 1038 (1967).

(21) Some composite experiments are reported. Melting and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Statements of sample identity indicate that both infrared and nmr spectra were virually superimposable. The infrared spectra were usually taken on the neat liquids, and the letters indicate: i, intense, 60% absorption or more; m, medium, 30–60%; b, broad; s, shoulder. Wavelengths are in μ. The nmr spectra were determined on the Varian A-60 with internal tetramethylsilane in about 50:50 v/v chloroform-*d*; τ values are listed. Integrations were consistent with the assignments as given.

(22) All of the diethyl compounds reported in this work exhibited methyl triplets and methylene quartets (the latter often obscured by other lines) with J about 7 cps; therefore only the shifts will be reported below.

Nmr showed (in acetonitrile-d_3) CH_3CH_2 at τ 8.84, CH_3CH_2 at 6.68 (apparent pentuplet, undoubtedly overlapping quartets), and ring CH_2 and OH at 5.2–6.8 (complex multiplet).

1,1-Pentamethylene-3-hydroxyazetidinium Chloride.[9a,c] (1c).—Piperidine (40.4 g) was added dropwise during 30 min to 46.2 g of epichlorohydrin stirred and cooled in an ice bath to maintain 25–30°: (*Caution:* This reaction became violently exothermic when conducted according to the procedure for diethylamine.) After 2 hr at 25–30°, the crude aminochloropropanol was divided, 29.3 g being dissolved in an equal volume of AN and allowed to stand. After 3 days, the crystals were separated; a second crop was obtained by adding acetone and refrigerating (21.8 g, 76%), mp 146–148°. After recrystallization from AN–acetone, the colorless needles were somewhat deliquescent, mp 147–148.5° (variable).

Anal. Calcd for $C_8H_{16}ClNO$: N, 7.88; Cl, 19.96. Found: N, 7.47; Cl, 19.69.

1,1-Diethyl-3-acetoxyazetidinium Chloride.—The hydroxy chloride **1a** (17.6 g) in 10 ml of AN was treated with 11.4 g of acetic anhydride. After 18 hr at 20–25°, the solution was aspirated in the rotatory evaporator below 30° and the residual slurry was triturated with 200 ml of acetone and refrigerated, yielding 8.9 g (40%) of colorless leaflets, mp 136–137° (placed in the bath at 130°). They were deliquescent.

Anal. Calcd for $C_9H_{18}ClNO_2$: C, 52.04; H, 8.73; Cl, 17.07; N, 6.75. Found: C, 51.84; H, 8.63; Cl, 16.86; N, 6.92.

Rapid titration in AN indicated that at least 99.5% of the chlorine was initially ionic. Ring opening was evident in the pmr spectrum in AN-d_3, despite rapid scanning which gave the peaks due to 3-chloro-1-diethylamino-2-propyl acetate in addition to the following attributed to the cyclic form (saturated solution): CH_3CH_2, τ 8.82; CH_3CO, 7.97; CH_3CH_2, 6.47, 6.54 (overlapping quartets); CHOAc, 5.3–6.0 (multiplet).

Examination of the original mother liquors and the solutions of the cyclic acetate showed that 3-chloro-1-diethylamino-2-propyl acetate (below) was the only nonionic product.

Isolation and Acetylation of 1-Chloro-3-dialkylamino-2-propanols. 1-Chloro-3-diethylamino-2-propanol.[9b]—This compound could be isolated by distillation of the crude intermediate in the preparation of **1a** from a stirred pot and heating bath directly into an ice-cooled receiver: bp 43° (0.4 mm); $n^{25}D$ 1.4578; 37%, based on diethylamine.

Anal. Calcd for amine neut equiv: 166. Found: 163.

The product was identical with but less pure than the pyrolysate from **1a**; 13.5 g was heated rapidly to 140° (0.2 mm) in a similar short-path still in a metal bath. Condensate then appeared in the cooled receiver and heating was continued to 150–155° to yield 12.8 g (95%). The best sample melted at 5–7° but could not be recrystallized satisfactorily. The amine neutralization equivalent was 169. Rapid titration of a fresh sample indicated less than 0.24% ionic chlorine.

Nmr showed CH_3CH_2 at τ 8.99, CH_2N at 7.2–7.6 (eight major lines), CH_2Cl at 6.0–6.5 (multiplet, major line, 6.41), and OH at 5.69. Infrared bands were at 2.95 (m), 3.37 (i), 3.55 (m), 6.83 (ms), 6.90 (m), 7.24 (m), 7.30 (ms), 7.74 (mb), 8.0 (mb), 8.33 (m), 9.2 (ib), and 9.4 (mb) μ.

The acetate ester was prepared with acetic anhydride in ether: bp 53° (0.3 mm); $n^{25}D$ 1.4424; 88%.

Anal. Calcd for $C_9H_{18}ClNO_2$: C, 52.04; H, 8.73; Cl, 17.07; amine neut equiv, 208. Found: C, 51.86; H, 8.64; Cl, 17.26; amine neut equiv, 208.

Nmr showed CH_3CH_2 at τ 9.01, CH_3CO at 7.96, CH_2N at 7.26–7.63 (nine lines), CH_2Cl at 6.22–6.32 (three main lines), CHOAc at 4.97 (multiplet). Infrared bands were at 3.37 (i), 3.55 (i), 5.74 (i), 6.8–7.0 (m), 7.30 (i), 8.1 (ib), 8.6 (m), and 9.6 (i) μ.

3-Chloro-1-di-*n*-butylamino-2-propanol.[9b]—The condensation of di-*n*-butylamine and epichlorohydrin (1 mole of each with 3.0 g water) did not yield crystals. After 3.5 months the viscous mixture was distilled (without pyrolysis) to give a 35% yield of the chloropropanol, bp 80–81° (0.7 mm). Redistillation gave a product containing less than 0.62% ionic chlorine, $n^{25}D$ 1.4563.

Anal. Calcd for $C_{11}H_{24}ClNO$: C, 59.57; H, 10.91; Cl, 15.99; N, 6.32. Found: C, 59.61; H, 10.91; Cl, 16.16; N, 6.30.

Nmr showed *n*-$C_3H_7CH_2$ at τ 8.4–9.3, CH_2N at 7.3–7.7, CH_2Cl at 6.1–6.6 (seven lines), and OH at 6.04. Infrared bands were at 2.9 (mb), 3.37 (i), 3.47 (i), 3.52 (ms), 6.83 (m), 7.25 (i), 7.95 (mb), 9.2 (mb), and 13.27 (mb) μ.

Attempts to isolate the pure azetidinium chloride by cyclization in AN, followed by removal of the solvent and trituration with ether gave a water-soluble syrup containing at most 77% of the chlorine in ionic form.

The acetate was prepared in 73% yield: bp 95° (0.8 mm); $n^{25}D$ 1.4462.

Anal. Calcd for $C_{13}H_{26}ClNO_2$: C, 59.18; H, 9.94; Cl, 13.44; N, 5.31; amine neut equiv, 264. Found: C, 59.24; H, 10.09; Cl, 13.51; N, 5.27; amine neut equiv, 266.

Nmr showed *n*-$C_3H_7CH_2$ at τ 8.4–9.3, CH_3CO at 7.96, NCH_2 at 7.4–7.7 (six main lines), CH_2Cl at 6.23–6.34 (five lines), CHOAc at 4.7–5.2 μ (multiplet). Infrared bands were at 3.38 (i), 3.48 (i), 3.54 (ms), 5.74 (i), 6.83 (m), 7.30 (i), 8.1 (ib), 9.2 (mb), and 9.63 (mb) μ.

1-Chloro-3-piperidyl-2-propanol.—This compound has been considered too unstable to isolate,[9b] and an attempt to distil the crude adduct resulted in solidification of the pot contents below 120°. However, further heating to 160–170° (bath) at 1 mm yielded 26% of distillate at 109–120° (superheated). It solidified in the freezer, mp 10–13°. A resin remained in the still pot.

Anal. Calcd for $C_8H_{16}ClNO$: Cl, 19.96; N, 7.88; amine neut equiv, 178. Found: Cl, 19.22; N, 7.65; amine neut equiv, 186.

Infrared bands were at 2.94 (mb), 3.41 (i), 3.51 (m), 3.58 (i), 6.96 (m), 7.71 (m), 8.57 (m), 8.97 (m), 9.19 (m), 9.3 (mbs), 9.54 (mbs), 9.64 (m).

The acetate had bp 88° (2 mm) and $n^{25}D$ 1.4660.

Anal. Calcd for $C_{10}H_{18}ClNO_2$: C, 54.66; H, 8.26; Cl, 16.14; N, 6.38; amine neut equiv, 220. Found: C, 54.95; H, 8.23; Cl, 16.04; N, 6.46; amine neut equiv, 226.

Infrared bands were at 3.42 (i), 3.51 (m), 3.60 (i), 5.77 (i), 6.96 (m), 7.32 (i), 7.70 (m), 8.15 (ib), 8.65 (m), 8.95 (m), 9.17 (mb), 9.63 (ib), 10.04 (m).

Alkylations of Nucleophiles with 1,1-Dialkyl-3-hydroxyazetidinium Chlorides.—The reactions usually were conducted with 100% molar excess of the nucleophile in 50 ml of the given solvent, with 0.05 mole of the azetidinium salt, sealed in a 100-ml stainless steel bomb and heated and rotated in an oven. Aspiration of the organic solvent, basification, extraction, and distillation gave the product amines.

1,1-Diethyl-3-hydroxyazetidinium Chloride. 1. Diethylamine.—In water after 20 hr at 95°, a 95% yield of **1,3-bis(diethylamino)-2-propanol**[23] was obtained: bp 64° (0.4 mm); $n^{25}D$ 1.4447.

Anal. Calcd for $C_{11}H_{26}N_2O$: C, 65.29; H, 12.95; N, 13.85. Found: C, 65.16; H, 13.06; N, 14.10.

Nmr spectrum showed CH_3CH_2 at τ 8.99, CH_2N, at 7.24–7.67 (eight lines), CHOH at 6.1–6.5 (multiplet) and OH at 6.24 μ. Infrared bands were at 2.92 (mb), 3.40 (i), 3.58 (i), 6.90 (ib), 7.10 (m), 7.26 (i), 7.5 (ib), 7.77 (ib), 8.35 (i), 9.2–9.5 (i), 10.1 (mb), 10.3 (mb), 11.66 (mb), 12.5 (mb) and 12.8–13.1 (m) μ.

The constants and spectra were identical with those of an authentic sample prepared from diethylamine and diethylglycidylamine in 80% yield.

2. Trimethylamine.—In aqueous methanol for 18 hr at 60°, a 50% yield of **(3-diethylamino-2-hydroxy-1-propyl)trimethylammonium chloride** (mp 145–147°) was obtained from AN–acetone.

Anal. Calcd for $C_{10}H_{25}ClN_2O$: C, 53.43; H, 11.21; Cl, 15.78; N, 12.47. Found: C, 53.49; H, 11.28; Cl, 15.99; N, 12.21.

3. N-Methylaniline.—In methanol for 18 hr at 100° a 99% yield of **N-(3-diethylamino-2-hydroxy-1-propyl)-N-methylaniline** was obtained: bp 117–118° (0.2 mm); $n^{25}D$ 1.5340–1.5344.

Anal. Calcd for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.23; N, 11.86. Found: C, 70.96; H, 10.10; N, 12.10.

Nmr showed CH_3CH_2 at τ 9.07, $(CH_3CH_2)_2NCH_2$ at 7.3–7.8 (eight lines), CH_3N at 7.08, CH_2NCH_3 at 6.67–6.8 (three lines), CHOH, 5.9–6.4 (multiplet), OH at 6.28, C_6H_5 at 2.6–3.6 (multiplet). Infrared bands were at 2.94 (m), 3.394 (i), 3.57 (i), 6.27 (i), 6.69 (i), 6.83 (m), 6.92 (m), 7.32 (i), 7.47 (i), 7.60 (i), 8.08 (i), 8.3 (ib), 9.3–9.5 (i), 9.69 (m), 10.12 (i), 10.43 (m), 11.67 (mb), 13.42 (ib), and 14.49 (ib) μ.

The compound was identical with a sample prepared from N-methylaniline and diethylglycidylamine, but the latter sample contained trace impurities which gave rise to very weak absorptions in the spectra.

The acetate had bp 119–120° (0.3 mm) and $n^{25}D$ 1.5116.

(23) M. Reboul, *Compt. Rend.*, **97**, 1488 (1883).

Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.07; amine neut equiv, 208. Found: C, 69.80; H, 9.73; N, 10.46; amine neut equiv, 210.

Nmr showed CH_3CH_2 at τ 9.03, CH_3CO at 8.20, II CH_2N at 7.28–7.67 (seven lines), CH_3N at 7.13, CH_2NCH_3 at 6.48–6.60 (three lines), CHOAc at 4.84 (multiplet), and C_6H_5 at 2.6–3.5 (multiplet).

The acetate was identical with the compound obtained directly (39% yield) by alkylating N-methylaniline with a crude acetylation mixture from **1a**. Thus the acetoxyazetidinium chloride is an alkylating agent. The open acetate was isolated from the same reaction mixture in 54% yield.

4. **Sodium *t*-Butylmercaptide.**—Equimolar mercaptan and aqueous sodium hydroxide were allowed to react for 18 hr at 95° and gave an 83% yield of **3-*t*-butylmercapto-1-diethylamino-2-propanol:** bp 86° (0.3 mm); $n^{25}D$ 1.4710.

Anal. Calcd for $C_{11}H_{25}NOS$: C, 60.22; H, 11.49; N, 6.39; S, 14.61; amine neut equiv, 219. Found: C, 60.08; H, 11.56; N, 6.49; S, 14.81; amine neut equiv, 216.

Nmr showed CH_3CH_2 at τ 8.99, $(CH_3)_3CS$ at 8.69, CH_2N and CH_2S at 7.24–7.71 (14 lines), CHOH at 6.3 (multiplet), and OH at 6.19. Infrared bands were at 2.93 (m), 3.39 (i), 3.57 (is), 6.89 (i), 7.11 (m), 7.26 (m), 7.37 (i), 7.54 (m), 7.77 (m), 8.35 (i), 8.63 (i), and 9.45 (ib) μ.

An identical product was prepared similarly from diethylglycidylamine (99% yield).

5. **Potassium Cyanide.**—In water at 50° for 3 days a 74% yield of **4-diethylamino-3-hydroxybutyronitrile** was obtained: bp 70° (0.2 mm); $n^{25}D$ 1.4518.

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.94; amine neut equiv, 156. Found: C, 61.55; H, 10.60; N, 17.95; amine neut equiv, 158.

Nmr showed CH_3CH_2 at τ 8.99, CH_2 (all) at 7.2–7.7 (ten lines), CHOH at 5.9–6.4 (multiplet), and OH at 5.81. Infrared bands were at 2.90 (m), 3.37 (i), 3.55 (i), 4.45 (m), 6.8–6.9 (m), 7.09 (m), 7.23 (i), 7.44 (m), 7.73 (mb), 8.0 (ms), 8.32 (i), 8.60 (m), and 9.2–9.4 (i) μ.

The compound[24] was prepared similarly from diethylglycidylamine in 80% yield, the pH being adjusted to the phenolphthalein end point before heating at 50°.

6. **Potassium Phenoxide.**—Equimolar phenol and potassium hydroxide were allowed to react in water at 100° for 22 hr and gave a 90% yield of **1-diethylamino-3-phenoxy-2-propanol:**[25] bp 114–115° (0.2 mm); $n^{25}D$ 1.5069.

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; amine neut equiv, 223. Found: C, 70.08; H, 9.81; N, 6.36; amine neut equiv, 219.

Nmr showed CH_3CH_2 at τ 9.03, CH_2N at 7.3–7.7 (seven lines), $CHOHCH_2O$ at 5.9–6.2 and C_6H_5 at 2.6–3.3 μ. Infrared bands were at 2.93 m, 3.39 i, 3.57 m, 6.29 i, 6.72 i, 6.84–6.92 m, 7.25 (m), 7.52 (m), 7.7–7.8 (i), 8.06 (ib), 8.56 (m), 9.30 (ms), 9.52 (ib), 10.07 (m), 11.39 (m), 12.31 (m), 13.3 (ib), and 14.51 (i) μ.

The identical compound was prepared from diethylglycidylamine.

7. **Sodium Methoxide.**—In methanol for 20 hr at 60° a 75% yield of **1-diethylamino-3-methoxy-2-propanol** was[26] obtained: bp 65° (4 mm); $n^{25}D$ 1.4353.

Anal. Calcd for $C_8H_{19}NO_2$: C, 59.59; H, 11.88; N, 8.69; amine neut equiv, 161. Found: C, 59.58; H, 11.86; H, 8.89; amine neut equiv, 161.

Nmr showed CH_3CH_2 at τ 8.99, CH_2N at 7.2–7.7 (nine lines), CH_3O at 6.64, CH_2O at 6.5–6.8, OH at 6.24, CHOH at 6.1–6.5. Infrared bands were at 2.92 (i), 3.39 (i), 3.57 (i), 6.92 (m), 7.27 (m), 7.54 (mb), 7.78 (mb), 8.37 (m), 8.62 (mbs), 8.90 (ib), 9.2–9.4 (i), and 10.39 (mb) μ.

This compound was also prepared from diethylglycidylamine in 86% yield.

From the original reaction mixture, a higher boiling cut (104–105° (1 mm)) amounted to a 7% yield of 2,5-bis(diethylaminomethyl)-1,4-dioxane, identical with the product of alkaline hydrolysis of the azetidinium perchlorate.

Reactions of 1,1-Diethyl-3-hydroxyazetidinium Perchlorate (1b). 1. Alkaline Hydrolysis. 2,5-Bis(diethylaminomethyl)-1,4-dioxane.[9b,10]—The crude salt prepared from 8.3 g of **1a** and 10.4 g of silver perchlorate was isolated and treated with 11.2 g of 50% aqueous potassium hydroxide solution. The mixture was heated 1 hr at 100°. The oil was extracted with ether and distilled at 93–94° (0.2 mm, mainly) to yield 2.0 g (16%), $n^{55}D$ 1.4541–1.4563.

Anal. Calcd for $C_{14}H_{30}N_2O_2$: C, 65.07; H, 11.71; N, 10.84. Found: C, 65.06; H, 11.90; N, 11.08.

Nmr showed CH_3CH_2 at τ 9.02, CH_3CH_2 and $CHCH_2$ at 7.3–7.7 (ten lines), CH_2O and CHO at 6.0–6.8 (complex). Infrared bands were at 3.40 (i), 3.59 (i), 6.86 (m), 6.93 (m), 7.27 (m), 7.33 (ms), 7.78 (m), 8.34 (m), 9.05 (i), 9.39 (i), and 15.14 (mb) μ.

2. **Sodium Methoxide.**—The perchlorate, 12.4 g, was heated with 0.100 mole sodium methoxide in 103 ml of methanol solution at 60° for 23 hr, giving 6.2 g (74%) of 1-diethylamino-3-methoxy-2-propanol and 0.7 g (5%) of the diaminodioxane, both identical with the products described above.

3. **Methanol.**—Under the same conditions as in 2, but in 103 ml of reagent methanol, only 0.18 g (2.2%) of a residual oil was isolated. The infrared spectrum proved it to be virtually pure 1-diethylamino-3-methoxy-2-propanol.

Alkylation with N,N-Pentamethylene-3-hydroxyazetidinium Chloride.—This compound, 8.9 g, was treated with 9.0 *t*-butyl mercaptan in 30 ml of water and 12 ml of 0.437 *N* sodium methoxide in methanol, then heated in a bomb overnight at 70°. **1-*t*-Butylmercapto-3-piperidyl-2-propanol** was isolated in 78% yield: bp 119° (1.5 mm); $n^{25}D$ 1.4934.

Anal. Calcd for $C_{12}H_{25}NOS$: C, 62.28; H, 10.89; N, 6.05; S, 13.86. Found: C, 62.60; H, 11.00; N, 5.89; S, 13.97.

Nmr showed $(CH_3)_3CS$ at τ 8.71, $CH_2(CH_2)_3CH_2N$ at 8.3–8.6, 3 CH_2N and CH_2S at 7.3–7.9 (nine main lines), CHOH at 6.0–6.5 (multiplet), OH at 6.17.

Competitive Alkylations.—The chloride **1a** was treated with an aqueous solution of trimethylamine and triethylamine (fivefold excess of each), slowly warmed to 80°, and maintained at that temperature for 18 hr. The mixture was taken to dryness and analysis of the total crude salt agreed well with that calculated for exclusive reaction with trimethylamine (above).

The perchlorate **1b** was condensed with an equimolar solution of sodium methoxide and *t*-butylmercaptide obtained by adding a fivefold excess of *t*-butyl mercaptan to a tenfold excess of sodium methoxide in methanol. After 16 hr at 60° the total distilled amine was analyzed, indicating exclusive reaction with the mercaptide.

Potentiometric Titrations.—Titrations of the azetidinium chlorides in acetonitrile were accomplished with anhydrous silver perchlorate in AN using the silver and glass electrodes. The method depended on the presence of at least traces of a tertiary amine. Thus the freshly dissolved compounds gave a satisfactory deflection at the end point only when a tertiary amine was added. Triethylamine (1 drop) was effective, or a freshly titrated solution of an equilibrated salt could be added. The end points occurred at higher scale readings on a pH meter when more amine was present but were usually found in the 7 to 9 range. The titrant was standardized against lithium chloride in the presence of triethylamine. Pure 1-dialkylamino-3-chloro-2-propanols cyclized so slowly that the end point was not changed by their presence in the solutions if the analyses were completed within a few minutes, but the end points faded slowly as the chloropropanols cyclized.

Cyclization Rates for 1-Dialkylamino-3-chloro-2-propanols.—A 0.504 *M* solution of pure diethylamino-3-chloro-2-propanol in AN was quickly prepared, equilibrated in the 25.00 ± 0.01° bath, and aliquots were titrated at intervals. The data yielded a first-order rate constant of (2.65 ± 0.03) 10^{-5} sec^{-1} through more than 40% cyclization. Similarly, 3-chloro-1-di-*n*-butylamino-2-propanol gave $k_1^{25°}$ = (1.26 ± 0.02) 10^{-5} sec^{-1} in 0.787 *M* solution through at least 28% cyclization, and 3-chloro-1-piperidyl-2-propanol gave $k_1^{25°}$ = (2.15 ± 0.04) 10^{-5} sec^{-1} through 38% reaction in 0.444 *M* solution.

Equilibrations.—Preliminary experiments indicated that the identical equilibrium point resulted at the same concentration starting with either the azetidinium salt or the aminochloropropanol. However, the equilibrium constants decreased with concentration. Plots of log K_c *vs.* $\sqrt{\alpha c}$ appeared to approach a straight line at the lower concentrations. This plot derives from the Debye–Hückel limiting law behavior of weak electrolytes: log K' = log K + $2A\sqrt{\alpha c}$.[27] Extrapolation to infinite dilution

(24) H. Gilman, C. S. Sherman, C. C. Price, R. C. Elderfield, J. T. Maynard, R. H. Reitsema, L. Tolman, S. P. Massie, Jr., F. J. Marshall, and L. Goldman, *J. Am. Chem. Soc.*, **68**, 1291 (1946).

(25) F. L. Pyman, *J. Chem. Soc.*, **111**, 167 (1917).

(26) F. G. Ponomarev, *Dokl. Akad. Nauk SSSR*, **87**, 609 (1952).

(27) S. Glasstone, "Thermodynamics for Chemists," D. Van Nostrand Co., Inc., New York, N. Y., 1947, pp 421–423.

was not possible since only data of poor precision were obtained at 0.003 M.

The solutions were prepared from pure 1,1-pentamethylene (A) and 1,1-diethyl-3-hydroxyazetidinium chlorides (B), 1-di-*n*-butylamino-3-chloro-2-propanol (C), and 3-chloro-1-piperidyl- (D), 3-chloro-1-diethylamino- (E), and 3-chloro-1-di-*n*-butylamino-2-propyl acetates (F) for final measurements. Typical parallel runs are described to illustrate the procedure.

1,1-Pentamethylene-3-hydroxyazetidinium chloride (**1c**, at least two independently purified samples) was weighed into calibrated volumetric flasks (50 or 250 ml). Reagent acetonitrile (Fisher Sci. Co.) which had been distilled from phosphorus pentoxide was added. The tightly stoppered flasks were placed in the 40.00 ± 0.01° bath. At the elapsed times listed, aliquots (5 or 25 ml) were analyzed by titration with 0.104 M silver perchlorate in acetonitrile by potentiometric titration using the silver–glass electrodes. The reagent was standardized against reagent lithium chloride with addition of a drop of triethylamine; the LiCl dissolved slowly. (Pure azetidinium chlorides were convenient soluble standards.) From the chloride remaining in solution the corrected molarities of each component and the cyclization constants were calculated. The times for establishment of equilibrium at each temperature were found by one or more checks at each temperature. In the following runs only the 40° point was confirmed initially because earlier runs had shown that this system equilibrated within the allowed times.

TABLE V

TYPICAL EQUILIBRATION RUNS

Time, days	Temp, °C	K_{cyc} Run 1[a]	K_{cyc} Run 2[b]	K_{cyc} Av	K_{cyc} Av dev
0.8	40.00	0.1272	0.1308	0.1303	0.0019
			0.1335		
1.0	40.00 (to 35)		0.1322		
2.1	35.00 (to 30)	0.1578	0.1529	0.1554	0.0025
3.8	30.00 (to 40)	0.1819	0.1756	0.1788	0.0032
4.8	40.00	0.1298	0.1282	(above)	

[a] Conditions were 0.2406 g of **1c** and c_i = 0.02709 M. [b] Reaction conditions were 0.2373 g of **1c** and c_i = 0.02672.

In other cases, notably systems E and F, equilibration at 30° required up to 3 days. A number of runs at low concentrations gave erratically higher values of K_{cyc}'s and, in these cases, the final 40° value was always higher than the initial 40° value and usually drifted even higher. Apparently traces of moisture caused hydrolysis or catalyzed minor (bimolecular?) side reactions, resulting in high chloride concentrations. This effect was finally controlled by suspending the flasks by the necks in rubber stoppers fitted in holes drilled in a rigid, plastic bath cover. Confirmation of the 40° values after several days at 30 and 35° established the reversibility of the actual reaction mixtures for which values are reported.

Registry No.—1C, 15314-02-0; 1D, 15285-53-7; 1F, 15285-55-9; **1a**, 15314-03-1; **1a** acetate, 15285-56-0; **1b**, 15285-57-1; **1c**, 15285-58-2; **2a**, 15285-59-3; **2a** acetate, 15285-60-6; **2** (R = *n*-Bu), 15285-61-7; **2** (R = *n*-Bu), acetate, 15285-62-8; **2c**, 15285-63-9; **2c** acetate, 15285-64-0; 1,3-bis(diethylamino)-2-propanol, 3492-47-5; (3-diethylamino-2-hydroxy-1-propyl)trimethylammonium chloride, 15285-65-1; N-(3-diethylamino-2-hydroxy-1-propyl)-N-methylaniline, 15288-04-7; N-(3-diethylamino-2-hydroxy-1-propyl)-N-methylaniline acetate, 15288-05-8; 3-*t*-butylmercapto-1-diethylamino-2-propanol, 15288-06-9; 4-diethylamino-3-hydroxybutyronitrile, 15288-07-0; 1-diethylamino-3-phenoxy-2-propanol, 15288-08-1; 1-diethylamino-3-methoxy-2-propanol, 3141-80-8; **3** (R = Et), 15288-10-5; 1-*t*-butylmercapto-3-piperidyl-2-propanol, 15288-11-6.

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The Preparation of 9-Amino-9H-purines. II. 9-Amino-6-chloro-9H-purin-8(7H)-one[1,2]

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Reaction of benzyl 3-(5-amino-4-chloro-6-pyrimidinyl)carbazate (**11**) and 5-amino-4-chloro-6-[2-(diphenylmethyl)hydrazino]pyrimidine (**12**), respectively, with the phosgene–pyridine complex gave benzyl 6-chloro-7,8-dihydro-8-oxo-9H-purine-9-carbamate (**7**) and 6-chloro-9-(diphenylmethyl)amino-9H-purin-8(7H)-one (**8**). The blocking groups of **7** and **8** were removed with HBr in AcOH to give 9-acetamido-6-bromo-9H-purin-8(7H)-one (**1**) rather than 9-amino-6-chloro-9H-purin-8(7H)-one (**6**). Treatment of **8** with concentrated HCl, however, gave **6**. Previously, **6** was reported to result from the interaction of 5-amino-4-chloro-6-hydrazinopyrimidine (**9**) with phosgene. The product of this reaction is now identified as 8-amino-7-chloro-*s*-triazolo[4,3-*c*]pyrimidin-3(2H)-one (**13**), which is rearranged in ethanolic HCl to 8-amino-7-chloro-*s*-triazolo[1,5-*c*]pyrimidin-2(3H)-one (**15**).

The cyclization of 5-amino-4-chloro-6-hydrazinopyrimidine (**9**) has been shown to give 9-aminohypoxanthine with HCO_2H,[2] 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine with ethyl orthoformate–concentrated HCl,[3] and 8-amino-7-chloro-*s*-triazolo[4,3-*c*]-pyrimidine with diethoxymethyl acetate.[4] The interaction of **9** with phosgene was reported to give 9-amino-6-chloro-9H-purin-8(7H)-one (**6**), which was rearranged in ethanolic HCl to give an isomeric compound tentatively identified as 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazin-3(4H)-one (**3**).[5] In this paper we wish to report the unambiguous synthesis of **6** and to identify the product from the reaction of **9** and phosgene as 8-amino-7-chloro-*s*-triazolo[4,3-*c*]pyrimidin-3(2H)-one (**13**), which under acidic conditions was rearranged to the isomeric 8-amino-7-chloro-*s*-triazolo[1,5-*c*]pyrimidin-2(3H)-one (**15**). The physical properties and chemical reactions of **13** and **15** are consistent with the assigned structures.

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