Cyclopentano[*b*]pyrrole could be isolated most readily from pyrolysate produced at 600° and at an addition rate of 7.5 ml/hr. From 20 g of cyclopentano[*a*]pyrrole, there was obtained 2 g of a greenish yellow liquid: bp 67° (5 mm); 99.8% pure based on glpc; ν_{CCl_4} 3450 cm^{-1}; λ_{max}^{MeOH} 211 and 229 mμ (sh); nmr spectrum, 2.47 (multiplet, 6 H), 5.70 (triplet, 1 H) 6.34 (triplet, 1 H), and *ca.* 7.2 ppm (broad, 1 H).

Anal. Calcd for C_7H_9N: C, 78.46; H, 8.46; N, 13.08. Found: C, 78.65; H, 8.20; N, 13.27.

***cis*-Cyclopentano-2,3-pyrrolidine from Cyclopentano[*b*]pyrrole.**—Hydrogenation and work-up was the same as that described for reduction of the pyrroles above. The colorless liquid product was converted into the picrate and the picrate was recrystallized from ethanol: mp 110° (lit.[13] mp 111°).

Pyrolysis of Cyclopentano[*a*]pyrrole at 650°.—From 22.5 g of cyclopentano[*a*]pyrrole introduced at a rate of 4.5 ml/hr (nitrogen flow, 120 ml/min) there was obtained 19.8 g (87% recovery) of crude pyrolysate which was dissolved in ether and extracted with cold 5% hydrochloric acid. The ether solution was dried over magnesium sulfate and the ether was removed by distillation leaving 15.5 g of neutral components. The hydrochloric acid solution was made strongly alkaline and extracted with ether, and the ether extract was dried over sodium carbonate. Removal of the drying agent and ether left 3.5 g of basic components.

The major components of the neutral fraction were separated by fractional distillation and preparative glpc using a 10 ft × 3/8 in. 30% SE-30 column at 190°.

2- and 3-Methylpyrrole.—The glpc retention time was identical with that of 2-methylpyrrole. The infrared spectrum was essentially identical with that of 2-methylpyrrole except for a strong absorption at 1065 cm^{-1} which is characteristic of 3-methylpyrrole.[13a] The nmr spectrum was consistent for a mixture of 2- and 3-methylpyrrole and showed methyl hydrogen peaks at 2.05 and 2.15 ppm which correspond to 3- and 2-methylpyrrole, respectively.[5]

Cyclopentano[*a*]pyrrole.—Properties including glpc retention time and infrared and nmr spectra were identical with those obtained from an authentic sample.

Cyclopentano[*b*]pyrrole.—Properties were identical with those obtained in the pyrolysis at 600°.

Indole.—Obtained as a yellow liquid which solidified and was recrystallized from Skellysolve A: mp 48–49°. The infrared and nmr spectra were identical with those obtained from an authentic sample.

(13) H. Booth, F. E. King, J. Parrick, and R. L. St. D. Whitehead, *Chem. Ind.* (London), 446 (1956).

Analysis of the basic fraction by glpc using a 6 ft × 3/8 in. 20% SF-96 column at 90° showed the following four components (separated by preparative glpc): pyridine (50%), glpc retention time and infrared and nmr spectra were identical with those obtained from an authentic sample; α-picoline (8%), glpc retention time, infrared spectrum, and picrate melting point were identical with those obtained from an authentic sample; 2-ethylpyridine (21%), glpc retention time and infrared and nmr spectra were identical with those obtained from an authentic sample, picrate mp 103–105° (lit.[14] mp 107°); 2-vinylpyridine (21%), infrared spectrum identical with that obtained from an authentic sample, picrate mp 156–157° (lit.[15] mp 157–158.3°).

Anal. Calcd for $C_{13}H_{10}N_4O_7$: C, 46.72; H, 2.99; N, 16.75. Found: C, 46.56; H, 2.99; N, 16.57.

Gases formed during the 650° pyrolysis were passed into a 10-cm gas cell (after drying over Drierite and Ascarite) and the infrared spectrum was measured. The spectrum showed multiple absorbance at 1200–1400 with the main peak at 1306 cm^{-1} (lit.[16a] methane main peak at 1306 cm^{-1}) and at 800–1100 with the main peak at 950 cm^{-1} (lit.[16b] ethene main peak 949 cm^{-1}). Spectra of authentic methane and ethene accounted for all of the bands observed in the pyrolysis gas spectrum.

Cycloheptano-1,2-pyrrolidine.—Cycloheptano[*a*]pyrrole was reduced by the method described for cycloheptano[*b*]pyrrole and worked up similarly. The product was purified by preparative glpc using a 5 × 1/4 in. 20% SE-30 column at 125°. The amine, a colorless liquid, $n^{20}D$ 1.4819, was converted into the picrate, mp 217–218° (lit.[17] $n^{20}D$ 1.4822, picrate mp 214–215°).

Cyclohexano-1,2-pyrrolidine.—The reduction procedure above gave a colorless liquid, bp 152°, $n^{22}D$ 1.4685, on reduction of cyclohexano[*a*]pyrrole. The picrate of the amine melted at 228–229° [lit.[17] $n^{20}D$ 1.4711, picrate mp 233–234°, bp 66–67° (18 mm)].

Registry No.—**1a**, 13618-87-6; **1b**, 13618-88-7; **1c**, 13618-89-8; **2a**, 13618-90-1; **2b**, 13618-91-2; **2c**, 13618-92-3; cyclohexano-1,2-pyrrolidine, 13618-93-4; cycloheptano-1,2-pyrrolidine, 5715-05-9; cycloheptano-2,3-pyrrolidine, 7140-62-7.

(14) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.*, **73**, 3308 (1951).
(15) W. E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947).
(16) American Petroleum Institute Research Project, 44, Infrared Spectral Data: (a) Spectrum No. 97; (b) Spectrum No. 18.
(17) N. J. Leonard and W. E. Goode, *J. Am. Chem. Soc.*, **72**, 5404 (1950).

Cyclization of 1-Alkylamino-3-halo-2-alkanols to 1-Alkyl-3-azetidinols

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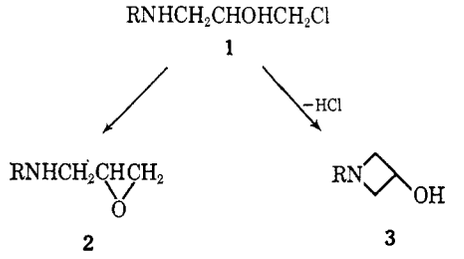
A two-step synthesis of 1-alkyl-3-azetidinols from primary alkylamines and epihalohydrins is described. 1-Alkylamino-3-chloro-2-alkanols carrying tertiary, secondary, and hindering primary N-alkyl groups cyclized spontaneously in up to 78% yields, optimally at about 50°. *n*-Alkyl or aryl groups did not provide sufficient hindrance or nucleophilicity. 1-*t*-Alkylamino-3-chloro-2-propyl acetates cyclized sluggishly and in lower yields than the propanols. The results were attributed to steric interaction of the N-alkyl and acetoxyl groups in the transition state.

Recently we described the conversion of unstable 1-alkylamino-3-chloro-2-propanols (**1**) to surprisingly stable N-alkyl-2,3-epoxypropylamines (**2**).[1] Storage of **1** resulted in diminished yields of **2** upon dehydrohalogenation. Subsequently, higher boiling oils were isolated; they have now been shown to contain new 1-alkyl-3-azetidinols (**3**).[2] This synthesis—the simplest and most direct method available for any azetidine—has been studied to determine the effects of structure



and reaction conditions. The results suggest that any primary alkylamine which is at least moderately hindered may be converted to the azetidinol in useful

(1) V. R. Gaertner, *Tetrahedron Letters*, 141 (1964); *Tetrahedron*, **23**, 2123 (1967).
(2) V. R. Gaertner, *Tetrahedron Letters*, 4691 (1966).

yield. The products are secondary alcohols, providing possible entrée to a variety of substituted azetidines, of which there has been a notable paucity.[3]

The cyclization of 1-alkylamino-3-halo-2-propanols (**1**) is a spontaneous reaction and occurs slowly even at 0°. Preparative reactions were conducted readily without isolation of the unstable **1**. The primary amines were condensed with equimolar epichlorohydrin in either methanol or dimethyl sulfoxide (DMSO) at 20–30°.[1] The aminochloropropanols were then heated *in situ* or as the neat crude **1** for 5–10 days at 50° and the 1-alkyl-3-azetidinols (**3**) were easily isolated by usual methods. The yields in favorable cases amounted to 20–34% of the theory. The simplicity of this procedure recommends it in comparison with other methods for azetidines, which usually involve multistep tedious routes.[3]

In this way were obtained the 1-*t*-butyl- (**3a**), 1-cyclohexyl- (**3b**), 1-(1,1,3,3-tetramethylbutyl)- (**3c**), 1-isopropyl- (**3d**), and 1-neopentyl-3-azetidinols (**3e**). All were low-melting solids except the last, which was a liquid. Physical and analytical data supported the structures. Spectral data and acetylation to form the acetate esters established the presence of the hydroxyl group. Finally, the nmr spectra provided conclusive proofs.

The spectrum of *t*-butylazetidinol (**3a**) was the simplest and illustrates the basic features of the other spectra. The twin triplets were clearly assignable to the pairs of methylene hydrogens *cis* and *trans* to the hydroxyl group (Figure 1), which appeared as a singlet with shift varying with concentration. The latter was converted to the acetate singlet near τ 8 by acetylation. The downfield multiplet was assigned to the proton α to the hydroxyl group. The other compounds had similar spectra, but those of **3b**, **3e**, and **3f** (below) showed symmetrical splitting of the triplet peaks in addition to the expected differences due to the alkyl groups. The pronounced coupling ($J \approx 6.5$ cps) of the ring protons resembled that in other azetidines.[4]

The cyclizations were shown to be even more facile by employing pure intermediates (**1**). Both 1-cyclohexylamino- and 1-*n*-octylamino-3-chloro-2-propanols crystallized during condensation of the amines with epichlorohydrin in hydrocarbon solvents. The *t*-butyl and *t*-octyl homologs were isolated by rapid distillation *in vacuo* of the crude compounds. Decomposition during the isolations resulted in lower over-all yields of **3**, however, than with the above *in situ* methods.

The pure aminochloropropanols carrying secondary and tertiary alkyl groups cyclized in 52–78% yields. Variations of temperature and solvent did not prove superior generally to the simple heating of the neat intermediates. Moderate steric hindrance in the alkyl group is apparently necessary to suppress intermolecular reactions, since only traces of impure products were obtained from 1-*n*-octylamino-3-chloro-2-propanol by various procedures. The primary alkyl group *per se* is not at fault, in view of the 32% yield of neopentylazetidinol obtained *in situ*. Similarly discouraging

(3) For a review, see J. A. Moore in "Heterocyclic Compounds with Three- and Four-Membered Rings," A. Weissberger, Ed., Part Two, Interscience Publishers, Inc., New York, N. Y., 1964, pp 885–977; R. A. Clasen and S. Searles, Jr. (*Chem. Commun.*, 289 (1966)) and D. H. Wadsworth and O. E. Schupp, III (*J. Heterocyclic Chem.*, **3**, 230 (1966)) recently described new azetidine syntheses.

(4) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **80**, 5203 (1958).

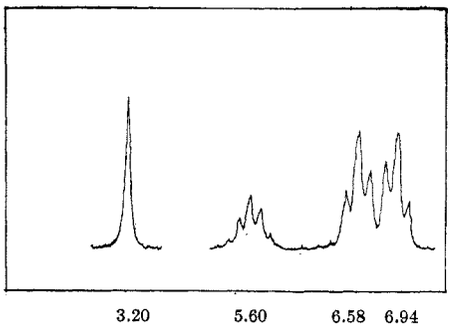
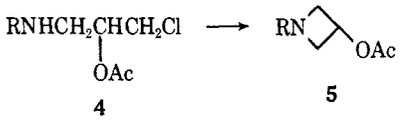


Figure 1.—Partial nmr spectrum of 1-*t*-butyl-3-azetidinol (**3a**).

results were obtained with other *n*-alkylamines. Aniline and 2,6-dimethylaniline also gave only traces of impure oils, doubtless owing to the deficient nucleophilicity of the arylamines.

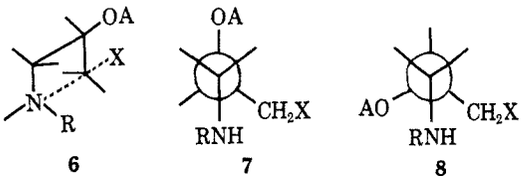
The epihalohydrin reactant was varied successfully. Epibromohydrin (*in situ*) gave fair yields of the *t*-alkylazetidinols. Added potassium iodide did not appear to catalyze the cyclizations. 3-Bromo-1,2-epoxybutane served to introduce a methyl group in the 2 position, giving 1-*t*-butyl-2-methyl-3-azetidinol (**3f**). The product, a mixture of two DL pairs, exhibited a complex nmr spectrum. However, crystals of one pair separated and showed the expected spectrum.

An interesting variation involved cyclization of the acetate esters (**4**), obtained by selective acetylation (eq 1). The acetates cyclized slowly and in lower yields



4 **5** (1)

than the free alcohols. Approximate optimization of these ring closures led to only 30 and 14% yields of the *t*-butyl- and *t*-octylazetidinyl acetates (**5**). These data contradict the generalization[5] that groups in the 2 position of γ-halo amines will hinder cyclization only if they eclipse in the transition state with substituents in the 1 and 3 positions. It is clear that the reaction involves direct displacement of halide by amino nitrogen in a planar transition state (**6**) with a linear reacting triad, N···C···X. Since the effect is more pronounced when



6 **7** **8**

R is larger, the OA and X groups alone cannot be responsible, nor are OA and X eclipsed in **6**. Instead, the explanation seems to involve the conformational isomers leading to the transition state, *i.e.*, **7**, **8**, and their diastereoisomers. As R increases in bulk, eclipsing of RNH and CH_2X becomes increasingly more difficult. If A is also enlarged, the population of **8** is reduced and the rotation of **7** to eclipse the reacting groups is buttressed by a closer approach of OA toward RNH. Thus intermolecular reactions become more likely than cyclization. This effect has been observed

(5) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, **26**, 138 (1961).

also in cyclization–scission equilibria of substituted azetidinium cations.[6]

It is interesting to note that alkylglycidylamines do not cyclize to azetidinols,[1] undoubtedly because it is impossible to achieve linearity of the triad, N···C···O, in the transition state. Rather, they dimerize and then cyclize by way of a spherical transition state in which linearity is allowed.

Experimental Section[7]

General Procedure. Cyclization (*in situ*) of 1-Alkylamino-3-halo-2-propanols (1).—Amines were condensed with equimolar epihalohydrins by methods described previously,[1] in methanol or DMSO at 20–30°. Although cyclization occurred at temperatures ranging from 8 to 100°, the optimum was in the 20–60° range for the cases studied and 50° was a good compromise. The neat crude **1** were also isolated by aspiration of methanol and cyclized.

The solutions or neat intermediates were sealed and heated in a thermostated oven. Aliquots could be titrated periodically, to follow the course of the reaction, with anhydrous hydrogen bromide in acetic acid, either with Crystal Violet indicator or, in the presence of DMSO, with Orange IV. The results indicated that the amine basicity decreased within 3–5 days at 50° to 20–30% of the initial value and stabilized at 10–20% within another 2–5 days. The reaction mixtures usually crystallized partially, but isolation was most readily accomplished by dissolution in water and ether, making strongly alkaline with sodium hydroxide, extracting repeatedly with ether, drying directly over alkali pellets, and distilling. Vacuum distillation of the crude products expedited recrystallization of the solids.

1-*t*-Butyl-3-azetidinol (3a).—The best yield from the crude intermediate was obtained by condensation of equimolar *t*-butylamine and epichlorohydrin (0.5 mole) in 200 ml of methanol at 20–25°. The mixture was divided after 3 days and half was heated and stirred at 60° for 3 days. The crude product distilled mainly at 60–66° (1 mm) and recrystallization from Skellysolve F with refrigeration gave 7.0 g (22%) of colorless deliquescent crystals with a strong amine odor, mp 44–46°.

The other half of the solution was rapidly aspirated to remove methanol below 40° in a rotating evaporator. The crude oily residue was allowed to stand at 20–25° for 2.5 months and then worked up as usual. A total of 11.1 g (34%) of the purified product resulted. A pure sample melted at 45–46°: nmr (see Figure 1), also $(CH_3)_3C$, 9.03; infrared, 3.00 m, 3.23 i, 3.41 i, 3.52 i, 3.64 m, 6.76 m, 7.19 m, 7.32 i, 7.43 i, 8.12 ib, 8.67 ib, 9.05 m, 10.16 m, 12.37 m, and 13.60 μ mb.

A sample of crude **1a** which had been refrigerated at about 8° for 2 years gave a 13% yield of **3a**. Epibromohydrin, replacing epichlorohydrin, with cyclization at 50°, gave 18% yield of **3a**. The addition of potassium iodide to methanolic **1a** gave no improvement in yields at 20–25 (18%) or at 50° (12%).

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84; mol wt, 129. Found: C, 64.79; H, 11.77; N, 11.06; mol wt, 160 (osmometric in benzene: associated); amine neut equiv, 128.

1-(1,1,3,3-Tetramethylbutyl)-3-azetidinol (3c) was prepared similarly from the *t*-octylamine, isolating the crude intermediate from methanol and heating it at 50° for 12 days. On the 0.5-mole scale, usual methods gave 46.6 g of distilled crude product, bp 92–112° (0.4 mm), which solidified. Colorless platelets, mp 51–53°, crystallized from hexane, yield 27.4 g (30%). A sample sublimed at 50° (1 mm) melted at 52–53°: nmr, $(CH_3)_3C$ 9.02, $(CH_3)_2C$ 8.99 (sh), CCH_2C 8.70, ring CH_2 6.95, 6.60 (both triplets, $J \approx 6.8$), CHOH 5.66 (multiplet, $J \approx 7$), OH, 4.11; infrared, 2.95 mb, 3.39 i, 3.43 is, 3.49 is, 6.78 m, 7.25 m, 7.35 i, 7.45 m, 8.14 i, 8.30 m, 8.57 i, 8.75 m, 9.14 m, 10.19 m, and 13.35 μ mb.

The compound was isolated (23%) from a crude neat intermediate which had been refrigerated 2.5 years; also, from epibromohydrin *in situ* neat, heated at 50° for 12 days, a 22% yield resulted.

Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56; mol wt, 185. Found: C, 71.45; H, 12.60; N, 7.70; mol wt, 210 (associated); amine neut equiv, 185.

1-Cyclohexyl-3-azetidinol (3b).—On the 0.3-mole scale, cyclohexylamine and epichlorohydrin were condensed in 30 g of DMSO at 25°. The mixture deposited crystals after 1 day and was warmed with an additional 30 g of DMSO, then heated at 40° for 6 days. Dilution with three volumes of water precipitated a gum. The decanted solution was worked up as usual. Distillation at 1 mm and recrystallization from Skellysolve F gave 9.3 g (20%) of colorless needles, mp 79–80°, not improved by vacuum sublimation: nmr, cyclohexyl 9.3–7.9, 4-ring CH_2 7.12, 6.40 (triplets with small unsymmetrical further splitting of each peak, principal $J \approx 7$), CHOH 5.59 (multiplet), OH 4.58; infrared (in KBr pellet), 3.23 ib, 3.40 i, 3.50 i, 3.60 i, 6.87 i, 7.27 i, 7.41 i, 8.36 i, 8.45 i, 8.70 m, 9.16 b, 9.69 m, 10.19 m, 11.14 m, 12.11 i, and 12.82 μ i.

The use of epibromohydrin in DMSO gave a 4% yield. The closure of pure aminochloropropanol (below) was far superior to the *in situ* methods for this compound.

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; amine neut equiv, 155. Found: C, 69.91; H, 11.16; N, 8.98; amine neut equiv, 154.

1-Isopropyl-3-azetidinol (3d).—The DMSO method (0.5 mole) was used, the solution being divided. One 0.25-mole portion heated at 40° for 4 days gave 1.0 g (3%) of impure distilled crystalline material. The other half, after 4 months at 25°, gave 2.0 g (6%). Recrystallized from Skellysolve F (refrigerated), the colorless prisms had mp 57–58°; nmr, $(CH_3)_2CH$ 9.08 (doublet, $J \approx 6.5$), $(CH_3)_2CH$ 7.74 (triplet, $J = 6.5$), ring CH_2 7.17, 6.42 (triplets, $J = 6.5$ br), CHOH 5.65 (multiplet), OH 3.53; infrared (in KBr pellet), 3.24 ib, 3.37 ib, 3.52 i, 3.79 is, 6.73 i, 7.06 ib, 7.19 i, 7.25 i, 7.44 i, 8.25 i, 8.42 is, 8.53 i, 8.82 i, 9.09 m, 9.60 m, 10.16 i, 10.50 m, 11.37 m, 11.53 m, 12.9 mb, and 13.31 μ i.

Anal. Calcd for $C_6H_{13}NO$: C, 62.57; H, 11.37; N, 12.16. Found: C, 62.66; H, 11.30; N, 12.11.

1-Neopentyl-3 azetidinol (3e).—Neopentylamine was condensed with epichlorohydrin in methanol and aspirated to obtain the crude intermediate (22.0 g) which was heated at 50° for 6 days. After preliminary distillation, the oil was refractionated giving 5.5 g (32%): bp 56° (0.3 mm), $n^{25}D$ 1.4531. It was still impure and, after being heated at 60° for 3 days, was redistilled, without change in the constants, leaving 0.5 g of gum, probably from a glycidylamine impurity: nmr, $(CH_3)_3C$ 9.14, $(CH_3)_3CCH_2$ 7.73, ring CH_2 7.07, 6.31 (triplets, with principal $J = 7$ and each peak split, $J = 2$), CHOH 5.59 (multiplet, $J = 7$), OH 4.37; infrared, 3.00 ib, 3.40 i, 3.50 is, 3.54 is, 6.80 i, 7.18 m, 7.35 i, 7.50 ms, 8.45 ib, 9.25 i, 10.22 m, and 12.50 μ m.

Anal. Calcd for $C_9H_{17}NO$: C, 67.08; H, 11.97; N, 9.78; amine neut equiv, 143. Found: C, 66.98; H, 12.03; N, 9.79; amine neut equiv, 146.

1-*t*-Butyl-2-methyl-3-azetidinol.—*t*-Butylamine (18.3 g) and 37.7 g of 3-bromo-1,2-epoxybutane[8] were condensed in 50 g of DMSO at 20–22° for 6 days. The solution was then heated at 70° for 18 hr. Preliminary vacuum distillation of the crude amine, followed by fractionation, gave a total of 9.1 g (28%, corrected for sampling): bp 65–68° (0.7 mm), $n^{25}D$ 1.4596–1.4586. The mixture had a complex nmr spectrum which was consistent with the expected azetidinol as two diasteroisomeric pairs.

Anal. Calcd for $C_8H_{17}NO$: C, 67.08; H, 11.97; N, 9.78. Found: C, 66.95; H, 12.07; N, 9.62.

The forerun bp 56–65° (0.7), crystallized partially in the refrigerator and was used to seed the main cut. The solid was recrystallized from hexane and sublimed at 50° (1 mm), mp 83–84°: nmr, $(CH_3)_3C$ 9.04, CH_3CH 8.79 (doublet, $J = 7$), ring $CHCH_3$ and CH_2 6.35–7.07 (7 br peaks), CHOH, 5.85

(6) V. R. Gaertner, *Tetrahedron Letters*, 343 (1967).

(7) Some composite experiments are reported to conserve space. Melting and boiling points are not corrected. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were determined on the Beckman IR-4 or IR-5, using neat liquids and supercooled melts of solids unless otherwise specified. The wavelengths are in microns and the letters indicate the following: i, intense; m, medium; b, broad; s, shoulder. Statements of sample identity indicate that mixture melting points were not depressed (if solids) and that infrared spectra were essentially superimposable. Nmr spectra were also identical in important cases. The nmr spectra were determined on the Varian A-60, using solutions in deuteriochloroform with internal TMS reference. τ values (J, cps) are listed; integration was employed routinely in the assignments, which are thus consistent as given. The cooperation of Research Center colleagues too numerous to name is gratefully acknowledged.

(8) Kindly supplied by Dr. D. N. VanEenam.

(multiplet), O*H* 5.44; infrared (in KBr pellet), 3.14 ib, 3.34 i, 3.44 is, 3.62 ms, 6.72 m, 7.13 ms, 7.26 ib, 7.38 ms, 7.48 i, 7.77 m, 7.89 m, 8.12 i, 8.43 m, 8.90 ib, 9.12 i, 9.28 i, 9.64 m, 9.93 ms, 10.12 i, 10.23 ms, 11.38 m, 12.38 m, 12.96–13.15 m.

Anal. Found: C, 67.37; H, 11.79; N, 10.27.

1-*t*-Butyl-3-azetidinyl Acetate.—Acetic anhydride and the azetidinol gave the acetate: bp 44° (1 mm); $n^{25}D$ 1.4364; nmr, $(CH_3)_3C$ 9.07, CH_3CO 8.01, ring CH_2 6.93, 6.53 (triplets, $J \approx 6$, with unsymmetrical finer splitting of each peak), C*H*O– 5.07 (multiplet); infrared, 3.37 i, 3.51 m, 5.75 i, 6.77 m, 7.36 i, 8.13 ib, 8.47 m, 8.82 i, 9.10 m, 9.62 m, and 10.06 μ m.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.18; amine neut equiv, 171. Found: C, 63.37; H, 10.25; N, 8.12; neut equiv, 174.

1-(1,1,3,3-Tetramethylbutyl)-3-azetidinyl acetate had bp 78° (0.7 mm); $n^{25}D$ 1.4510; nmr, $(CH_3)_2C$, $(CH_3)_3C$ 9.02, CCH_2C 8.75, CH_3CO 7.98, ring CH_2 6.92, 6.52 (basically triplets, main J = 6.5 with unsymmetrical splitting), C*H*O– 5.07 (multiplet); infrared, 3.40 i, 3.46 ms, 5.77 i, 6.80 m, 7.37 i, 8.12 ib, 8.61 m, 8.93 m, and 9.66 μ m.

Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16; amine neut equiv, 227. Found: C, 69.16; H, 11.30; N, 6.19, amine neut equiv, 224.

Isolation of Pure 1-Alkylamino-3-chloro-2-propanols.—1-Cyclohexylamino-3-chloro-2-propanol, mp 78–79°, was prepared by the method of McKelvey, *et al.*[9]

1-*n*-Octylamino-3-chloro-2-propanol.—Similarly, *n*-octylamine (0.4 mole, 51.7 g) and 74 g (0.8 mole) of epichlorohydrin were condensed in 250 ml of Skellysolve F. After 10 hr at 20–25°, the mixture was refrigerated and 10.0 g, mp 45–47°, of colorless crystals was collected. The liquors were again refrigerated overnight; after collecting second and third crops, the final liquors were kept at −20° and filtered. A total of 53.7 g (61%) was isolated. Recrystallized (refrigerated) repeatedly from the same solvent, the fine needles melted at 46.0–46.5°, but they remained slightly impure.

Anal. Calcd for $C_{11}H_{24}ClNO$: Cl, 15.99; N, 6.32; amine neut equiv, 222. Found: Cl, 15.80; N, 7.14; amine neut equiv, 209.

Cyclization of this compound and crude aminochloropropanols from other *n*-alkylamines was attempted under various conditions. Although small amounts of impure oils probably containing the alkylazetidinols were produced, no pure compounds except the *n*-alkylglycidylamines[1] could be isolated.

1-*t*-Butylamino-3-chloro-2-propanol.—The crude product[1] prepared in methanol and isolated by aspirating the solvent and unchanged reactants in a rotating evaporator below 25° was filtered to remove the crystalline hydrochloride. The filtrate was distilled rapidly in 25-g portions in a short-path still (magnetically stirred pot and bath) into an ice-cooled receiver. From 24.1 g of the crude material was obtained up to 12.7 g (53%) of distillate, bp 66° (0.3 mm), $n^{25}D$ 1.4641 (supercooled); it crystallized. Recrystallization from pentane (filtered to remove suspended hydrochloride) in the freezer gave colorless needles, mp 42–43°. The azetidinol was easily isolated from the still residue: nmr, $(CH_3)_3C$ 8.89, NCH_2 7.23–7.40 (four lines), N*H*, O*H*, 6.96, $CHCH_2Cl$, 6.0–6.6 (six major lines); infrared, 3.0 mb, 3.2 mb, 3.47 i, 6.70 mb, 6.97 mb, 7.21 m, 7.35 i, 8.32 i, 9.19 i, 9.78 mb, 13.26 mbs, and 13.47 μ mb.

Anal. Calcd for $C_7H_{16}ClNO$: C, 50.75; H, 9.74; Cl, 21.4; amine neut equiv, 166. Found: C, 50.46; H, 9.60; Cl, 21.7; amine neut equiv, 167.

3-Chloro-1-*t*-octylamino-2-propanol was isolated similarly from a preparation in pentane. Careful distillation (above) and redistillation gave 31% yield, bp 84–87° (0.3 mm); it solidified, mp 27–30°. The compound was still impure (*Anal.* Calcd for $C_{11}H_{24}ClNO$: amine neut equiv, 222. Found: amine neut equiv, 198, 200.) and could not be recrystallized satisfactorily: infrared, 2.99 i, 3.41 ib, 6.79 ib, 7.13 m, 7.32 i, 7.43 i, 8.13 ib, 8.29 m, 8.74 i, 9.14 m, 9.32 ms, 10.17 m, 13.39 mb, and 13.72 μ mb.

Selective Acetylation of 1-Alkylamino-3-chloro-2-propanols.—The acetate esters were prepared from the crude compounds in ether solution cooled at 0–5° by slow addition of a slight excess of acetic anhydride; the solution was washed with sodium carbonate solution, dried, and aspirated below 25°, and the crude product distilled under mild conditions rapidly.

(9) J. B. McKelvey, B. G. Webre, and E. Klein, *J. Org. Chem.*, **24**, 614 (1959).

1-*t*-Butylamino-3-chloro-2-propyl acetate was obtained in 52% yield: bp 49° (0.2 mm); $n^{25}D$ 1.4435; infrared, 3.39 i, 5.78 i, 6.82 ms, 7.01 i, 7.35 i, 8.2 ib, 9.10 m, 9.50 ibs, 9.7 ib, 10.10 m, 10.55 m, 13.2 mb, 13.57 mb, and 14.25 μ mb.

Anal. Calcd for $C_9H_{18}ClNO_2$: N, 6.75; Cl, 17.08; amine neut equiv, 208. Found: N, 6.72; Cl, 16.96; amine neut equiv, 206.

3-Chloro-1-(1,1,3,3-tetramethylbutylamino)-2-propyl Acetate.—The product prepared from the crude amino alcohol in 43% yield was still impure. A solid, mp 97.5–98.5°, which separated from this product was identical with authentic N-(1,1,3,3-tetramethylbutyl)acetamide. Acetylation of the distilled amino alcohol followed by extraction from the ethereal solution with 10% hydrochloric acid, basification, and distillation gave a 45% yield of the ester, bp 91–92° (0.4 mm), $n^{25}D$ 1.4558, which was still slightly impure: nmr, $(CH_3)_3C$ 9.03, $(CH_3)_2C$ 8.93, $-CH_2-$, 8.63, CH_3CO 7.98, CH_2N 7.21 (doublet, J = 6), CH_2Cl 6.21–6.31 (three lines), C*H*OAc 5.04 (multiplet); infrared, 3.04 i, 3.45 is, 5.76 i, 6.78 m, 6.83 m, 7.36 i, 8.12 ib, 8.62 m, 8.93 m, 8.58 ms, and 9.67 μ m.

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, 60.27; H, 10.21; Cl, 12.50; N, 5.01; amine neut equiv, 261.

Cyclization of Pure 1-Alkylamino-3-chloro-2-propanols. 1.—Freshly recrystallized *t*-butylaminochloropropanol (**1a**), mp 40–42°, was titrated with hydrobromic acid in acetic acid, 5.98 mequiv/g. A 7.4-g sample was sealed under nitrogen and heated at 50°. Analyses indicated a residual amine basicity of 1.18 mequiv/g after 4 days and 1.10 mequiv/g after 5 days. Usual isolation provided 3.6 g of recrystallized **3a**, or 78% yield, corrected for samples. Additional impure **3a** was present (infrared) in the mother liquors.

2.—Similarly, **1c**, mp 27–30°, 2.70 g heated neat at 50° for 5 days, then at 60° for 2 days, gave 1.54 g (68%) of **3c**.

3.—The closure of 1-chloro-3-cyclohexylamino-2-propanol (**1b**) was studied under several sets of conditions. On the 0.1-mole scale, 19.2 g of **1b** in 20 g of DMSO, heated 6 days at 40°, gave 8.6 g (55%) of recrystallized **3b**, mp 79–80°. Although higher dilution might be expected to increase the yield in such a cyclization, dropwise addition (90 min) of a solution of 5.0 g of **1b** in 30 ml DMSO to 100 ml of DMSO stirred and maintained at 100° gave only 12% yield of impure **3b**. The higher temperature alone was not detrimental, a 52% yield (crude) being obtained by heating neat **1b** at 100° for 23 hr. Closure of **1b** in acetonitrile by the action of silver perchlorate[10] gave only a 12% yield of very impure **3b**.

Cyclization of 1-Alkylamino-3-chloro-2-propyl Acetates.—The *t*-butyl homolog (**4a**, 14.8 g) in 50 ml of DMSO was heated at 50°, aliquots being titrated to the Orange IV end point; after 4 days the titer was stabilized. Addition of aqueous sodium carbonate and water gave a small aqueous DMSO layer, which was extracted repeatedly with ether. The total distillate (7.1 g, bp 43–52 (0.7)) after alkaline hydrolysis and usual isolation gave 30% yield of the crystalline azetidinol. Other runs, including neat closure at 50° for 4 days, gave similar, but not superior, results.

Neat *t*-octylaminochloropropyl acetate was cyclized at 50°. The infrared spectra of the open and cyclized acetates in the reaction mixture (as partial hydrochlorides) were very similar but spectra normalized to the 3.4-μ absorption (100) indicated that the heights at 8.9 μ (open, 16.5; cyclic, 39.4) differed sufficiently to provide a useful measure of cyclization. This band attained a maximum after 4 days. Hydrolysis in the presence of diethylenetriamine to remove the glycidylamine and isolation of the *t*-octylazetidinol gave a 13.5% yield of **3c**.

Bis(1-*t*-butyl-3-azetidinyl) Sulfite.—A solution of *t*-butylazetidinol in 25 ml of reagent pyridine was added slowly dropwise to a stirred solution of 6.0 g of purified thionyl chloride in 10 ml of pyridine cooled at −15 to −20° in a Dry Ice–acetone bath. The reaction mixture was stirred as the bath warmed overnight and was then added slowly to stirred ice–aqueous sodium carbonate mixture. Extraction with ether and distillation of the crude oil gave 1.9 g, bp 133–135° (0.2 mm), which solidified. Recrystallization from pentane and sublimation at 1 mm gave colorless crystals: mp 55.5–56.5°; nmr, $(CH_3)_3C$ 9.05, ring CH_2 6.39–6.93 (complex symmetrical multiplet), C*H*O 5.04 (pentuplet, J = 6); infrared (in KBr pellet), 2.92 mb, 3.35 i, 3.46 is, 6.72 m, 7.20 i, 7.29 i, 8.03 i, 8.23 i, 8.86 i, 8.96 is, 9.27 i,

(10) See footnote 12 of ref 6.

9.93 m, 10.07 m, 10.11 i, 11.84 m, 12.29 m, 12.29 m, 12.79 i, 13.75 i, and 14.29 μ m.

Anal. Calcd for $C_{14}H_{28}N_2O_3S$: C, 55.23; H, 9.27; N, 9.20; S, 10.53; amine neut equiv, 152. Found: C, 55.49; H, 9.29; N, 9.23; S, 10.56; amine neut equiv, 152.

In the absence of pyridine, ill-defined mixtures were obtained, probably indicating ring cleavage.

Registry No.—**3a,** 13156-04-2; **3b,** 13156-01-9; **3c,** 13156-03-1; **3d,** 13156-06-4; **3e,** 13156-07-5; 1-*t*-butyl-2-methyl-3-azitidinol, 13619-15-3; 1-*t*-butyl-3-azetidinyl acetate, 13619-16-4; 1-(1,1,3,3-tetramethylbutyl)-3-azetidinyl acetate, 13619-17-5; 1-*n*-octylamino-3-chloro-2-propanol, 13619-18-6; 1-*t*-butylamino-3-chloro-2-propanol, 13156-02-0; 3-chloro-1-*t*-octylamino-2-propanol, 13156-05-3; 1-*t*-butylamino-3-chloro-2-propyl acetate, 13619-21-1; 3-chloro-1-(1,1,3,3-tetramethylbutylamino)-2-propyl acetate, 13619-22-2; bis(1-*t*-butyl-3-azetidinyl) sulfite, 13619-23-3.

Nuclear Magnetic Resonance Spectra of Bicyclo[*n*.1.0]alkane Derivatives[1]

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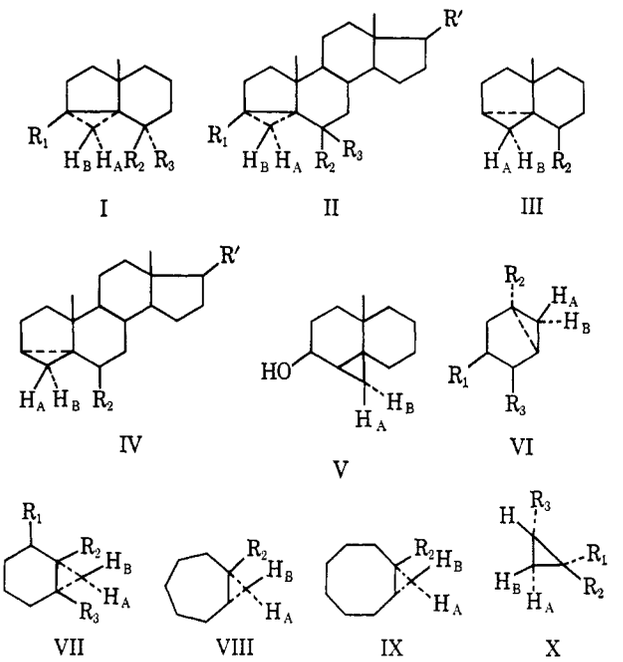
Chemical shifts and coupling constants for geminal and vicinal protons of a cyclopropane ring have been determined for 35 bicyclo[*n*.1.0]alkane derivatives. It has been found that for systems having the general structure XI (R = H or alkyl; R′ = alkyl; *n* = 3) the geminal proton with the *endo* configuration resonates at a lower field than the *exo* proton. In various bicyclo[4.1.0]heptan-2-ols, similar results are found. Possible reasons for this inversion of the expected chemical shifts, such as diamagnetic anisotropy and van der Waals interacetions, are discussed.

The utility of nmr spectroscopy as a method for identifying cyclopropane rings has been firmly established. Many studies have been made with cyclopropyl compounds having electronegative substituents on the ring,[3-9] but few studies have been made on compounds where the cyclopropane ring has no such grouping.[10-13]

In the present study, the nmr spectra of three simple alkylcyclopropanes and 35 compounds containing a fused cyclopropane ring were analyzed. The chemical shifts and coupling constants obtained are summarized in Table I. The *endo* proton is designated as H_A and the *exo* proton as H_B. The *endo* proton is always *trans* to H_X, the bridgehead proton, for all compounds (structures I–X) in Table I.

The reported parameters were derived from the experimental line positions with the aid of a computer program utilizing the equations of Bernstein, Pople, and Schneider[14] for the ABX systems and the equations of Cohen and Sheppard[15] for the ABX_2 systems. The proton, H_X, on the bridgehead of the cyclopropane ring fusion (structure XI, p 2978) could not be assigned in the most cases because of overlapping absorption by



the methylene protons of the rest of the molecule. Not being able to assign H_X did not prevent the analysis of the AB portion of the spectra in the ABX and ABX_2 cases.

In the spectra of compounds 32–36, the H_X absorptions overlap with those from H_A and H_B. From these spectra an estimate of the coupling constants and chemical shifts was made. From these parameters a theoretical spectrum was calculated using a modified Reilly–Swalen program.[16] The parameters were adjusted until a best fit was obtained between theoretical and observed spectra. The average deviation of the final calculated spectrum from the observed spectrum in all compounds analyzed was never greater than 0.4 cps and was usually less than 0.1 cps.

The assignment of the methylene protons of the cyclopropane ring was made on the basis of the *cis*

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