The crude reaction mixture was also analyzed by vpc. The analytical gas chromatography was performed on a F & M Model 5720 instrument with helium as the carrier gas on a Carbowax 20M column (20% on Chromosorb P) at 240°. Comparison of retention times and infrared spectra with those of the authentic ketone and acid established the identity of the products. The results are recorded in Table II.

Registry No.—I, 6476-12-6; II, 6372-57-2; III, 2211-61-2; IV, 2211-65-6; V, 6476-13-7; VI, 6372-58-3; VII, 6372-29-8; VIII, 6476-39-7; IX, 15830-93-0; X, 15830-81-6; XI, 15856-59-4; XII, 15830-82-7; XIII, 15856-60-7; α,β-diphenyl-4-methylacrylophenone, 15830-83-8; α-tolyl-β-phenylacrylophenone, 15830-84-9; diphenyliodonium iodide, 2217-79-0; N-1-(2-benzoyl-1-phenylethyl)cyclohexanimine, 14802-27-8.

Acknowledgment.—The authors are indebted to the U. S. Public Health Service (Grant GM 13990-01) for generous support of this research.

Small Charged Rings. XI.[1] Synthesis and Reactions of 1,1,2,2-Tetrasubstituted Azetidinium Salts[2]

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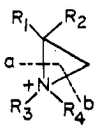
A convenient synthesis of 1,1,2,2-tetramethylazetidinium perchlorate (**2**) and 1-benzyl-1,2,2-trimethylazetidinium perchlorate (**3**) has been developed. The cyclization step in the sequence leading to these compounds involved treatment of γ-*sec*-aminoalkyl chlorides with silver perchlorate to afford the corresponding tertiary azetidine perchlorates in excellent yield. These were subsequently alkylated to give the quaternary azetidinium salts. 1,1-Dibenzyl-2,2-dimethylazetidinium perchlorate (**4**), as an intermediate, was found to undergo a facile eliminative ring opening in the presence of amines and could not be isolated. The structures of **2** and **3** have been verified by molecular weight determination and nmr spectroscopy. The tetramethyl salt **2** proved to be relatively unreactive, but the benzyltrimethyl salt **3** underwent solvolytic ring opening with alcohols to form N-(3-alkoxy-3-methylbutyl)-N-methylbenzylamine perchlorates. In the presence of sodium methoxide or upon heating in solution, both azetidinium salts exhibited a strong tendency to undergo eliminative ring opening to afford substituted 3-methyl-3-buten-1-ylamines. Azetidinium salt **3** combined with nitrones, specifically with substituted Δ¹-pyrroline-1-oxides, to afford 1:1 adducts containing the 2-oxa-1-aza-6-azoniabicyclo[5.3.0]decane ring system. This reaction is representative of a new type of ring expansion, expressed as ④⁺ + 3 → ⑦⁺, in which a four-membered charged ring combines with a 1,3-dipolar moiety to form a seven-membered charged ring. The structures of the adducts were established by cleavage of the 6,7 bond with lithium aluminum hydride, followed by cleavage of the 1,2 bond with zinc and acetic acid, accompanied by spectroscopic and chemical identification of the ultimate degradation products.

In the course of a continuing study of the reactions of 1,1,2,2-tetrasubstituted aziridinium salts (**1**), a



1

number of facile ring openings and ring expansions have been observed.[4] In general, weak nucleophiles bring about ring opening at a so that SN1-type products are obtained,[5,6] while strong nucleophiles tend to approach the ring from the less hindered side in an SN2 manner to effect bond breaking at b.[7,8] Preliminary cleavage at a is also postulated as the initial step in the expansion of the aziridinium ring with aldehydes,[8] ketones,[9] and nitriles.[10] When both the 2 and the 3 position on the aziridinium ring are unsubstituted, more vigorous conditions are necessary for reaction to occur with nitriles.[11] These ring expansion reactions of aziridinium salts are codified within the general category ③⁺ + 2 → ⑤⁺, in which a charged, three-membered cycle is increased in size to a charged, five-membered cycle. The reaction of aziridinium salts with nitrones has introduced a new category: ③⁺ + 3 → ⑥⁺.[1] As a logical extension of this study, it was of interest to determine whether suitably substituted azetidinium rings could open and expand in a manner analogous to that of the more highly strained aziridinium system. Although a variety of azetidinium salts have been known for some time,[12,13] no extensive investigations into the chemistry of these charged four-membered heterocycles have been made until recently.[14-19]

(1) For the preceding article in this series, see N. J. Leonard, D. A. Durand, and F. Uchimaru, *J. Org. Chem.*, **32**, 3607 (1967).

(2) We are pleased to acknowledge the support of the National Science Foundation by Research Grant GP 2012.

(3) Lubrizol Corp. Fellow, 1964–1965; National Science Foundation Fellow, 1965–1967.

(4) For pertinent references and a general summary of work in this area, see N. J. Leonard, *Rec. Chem. Progr.*, **26**, 211 (1965).

(5) N. J. Leonard and K. Jann, *J. Amer. Chem. Soc.*, **84**, 4806 (1962).

(6) N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963).

(7) J. V. Paukstelis, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1964.

(8) N. J. Leonard, E. F. Kiefer, and L. E. Brady, *J. Org. Chem.*, **28**, 2850 (1963).

(9) N. J. Leonard, J. V. Paukstelis, and L. E. Brady, *ibid.*, **29**, 3383 (1964).

(10) N. J. Leonard and L. E. Brady, *ibid.*, **30**, 817 (1965).

(11) E. Pfeil and U. Harder, *Angew. Chem.*, **77**, 505 (1965).

(12) S. A. Ballard and D. S. Melstrom in "Heterocyclic Compounds," Vol I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p 78.

(13) J. A. Moore in "The Chemistry of Heterocyclic Compounds," Vol. XIX, part 2, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 885.

(14) A. Ebnöther and E. Jucker, *Helv. Chim. Acta*, **47**, 745 (1964).

(15) D. H. Wadsworth and O. E. Schupp, *J. Heterocycl. Chem.*, **3**, 230 (1966).

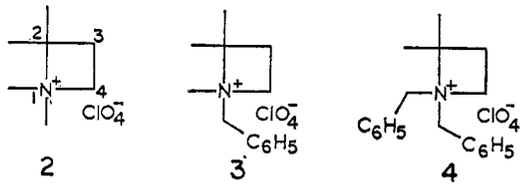
(16) G. Fodor, *J. Amer. Chem. Soc.*, **88**, 1040 (1966).

(17) (a) V. R. Gaertner, *Tetrahedron Lett.*, 343 (1967); (b) V. R. Gaertner, *J. Org. Chem.*, **32**, 2972 (1967).

(18) W. B. Wheatley and L. C. Cheney, *J. Amer. Chem. Soc.*, **74**, 1359 (1952).

(19) M. T. Wills, *Dissertation Abstr.*, **27B**, 423 (1966).

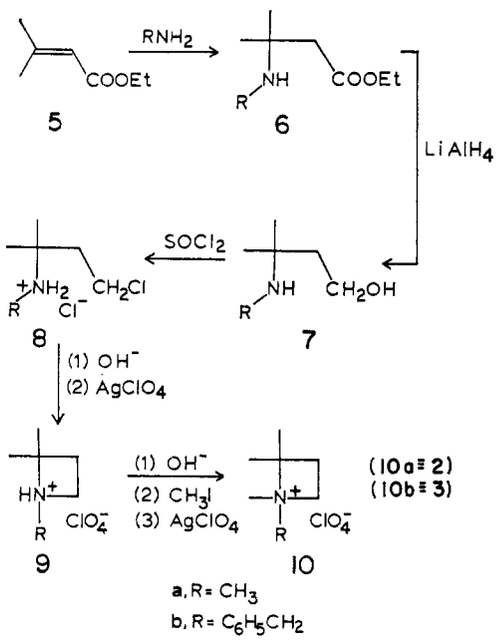
Our initial plan was to synthesize the azetidinium salts **2**–**4** and to study their reactions. It was anticipated that *gem*-dimethyl substitution at the 2 position would not only make ring formation from an acyclic precursor very efficient,[20,21] but would provide a tertiary carbon capable of carrying a developing positive charge, so that the azetidinium ring could open in an SN1 manner by cleavage of the 1,2 bond. Moreover, the selection of a series with progressively increasing benzyl substitution was directed by the finding that N-benzyl substitution greatly enhances the reactivity of aziridinium rings,[22] so much so that a 1,1-dibenzyl-2,2-dialkylaziridinium salt has not been isolated to date, and by the consideration that the series **2**–**4** would furnish a reasonably broad spectrum of reactivity.



2 **3** **4**

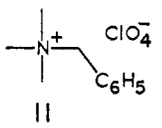
1,1,2,2-Tetramethylazetidinium perchlorate (**2**)[23] and 1-benzyl-1,2,2-trimethylazetidinium perchlorate (**3**) were synthesized conveniently and in good yield by way of the sequence shown in Scheme I. The conversion of

SCHEME I



γ-chloroalkylamine salts **8** into azetidine salts **9** is the novel feature of this sequence. Treatment of **8** with aqueous base liberated the corresponding free amino chloride, which was isolated without purification. Cyclization to **9** was then effected by means of silver perchlorate at room temperature in either acetone or acetonitrile. Although the reaction proceeded slowly (silver chloride precipitated continuously for at least one day), the yields of **9** were excellent [quantitative for 1,2,2-trimethylazetidine perchlorate (**9a**) and 85% for 1-benzyl-2,2-dimethylazetidine perchlorate (**9b**)]. Work-up was relatively simple since the perchlorates could be separated from residual silver salts by extraction with methylene chloride. This facile reaction between γ-*sec*-aminoalkyl chlorides and silver perchlorate represents a new and useful route to the azetidine ring system,[24] assisted in these examples by the presence of the *gem*-dimethyl substitution. The azetidine salts **9a** and **9b** could be converted readily into azetidinium salts **2** and **3**, respectively, by methylation of the corresponding free 1,2,2-trisubstituted azetidines.

It was desirable to demonstrate that we were in fact dealing with four-membered rings and not eight-membered dimeric structures. Therefore, the molecular weight of **3** was determined in acetone. Since the extent of dissociation of **3** varied with its concentration in solution, it was necessary to obtain apparent molecular weight data at several concentrations and to compare this dissociative behavior with that of a model compound, benzyltrimethylammonium perchlorate (**11**). The data indicated that **3** consists of a singly



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charged cation and anion, as opposed to the doubly charged cation and two singly charged anions required by the dimeric structure (See Experimental Section for details.) Further confirmation of the four-membered ring structures of **2** and **3** was obtained from the nmr spectra of these salts in trifluoroacetic acid. It had been noted previously[25] that α-methylene protons in azetidinium salts are deshielded to an unusual extent. The spectrum of the tetramethyl salt **2** exhibited a triplet at τ 5.83 ppm for the CH_2–N^+ protons. The chemical shift was in contrast to those observed for the α-methylene protons in aziridinium salts (τ 6.7–7.1)[5,6,24] and in pyrrolidinium and piperidinium salts (τ 6.4–6.6). The nmr spectrum of the benzyltrimethyl salt **3** was particularly interesting in that the chemical shifts of the nonequivalent α-methylene protons differed by approximately 1 ppm (τ 5.1–5.7 and 6.1–6.6, both multiplets) owing to the anisotropy of the aromatic ring.[26] The β-methylene protons were apparently undifferentiated by this anisotropy.

Whereas 1-benzyl-2,2-dimethylazetidine (**12**) could be methylated readily to form the azetidinium salt **3**, efforts to benzylate **12** to form 1,1-dibenzyl-2,2-di-

(20) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward [*J. Org. Chem.*, **26**, 138 (1961)] applying Grob's stereoelectronic requirements for fragmentation [C. A. Grob, *Experientia*, **13**, 126 (1957); C. A. Grob, "Kekule Symposium, Theoretical Organic Chemistry," Butterworth and Co. Ltd., London, 1959, pp 114–127] have suggested that one of the most favorable situations for effective cyclization to the azetidine system will be found in a 3-aminopropyl system in which there is *gem* disubstitution on C-3 and no substitution on C-1 and C-2.

(21) For a general discussion of the *gem*-dimethyl effect, see (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, pp 191–192; (b) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960), and references therein.

(22) P. C. Kelley, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1965.

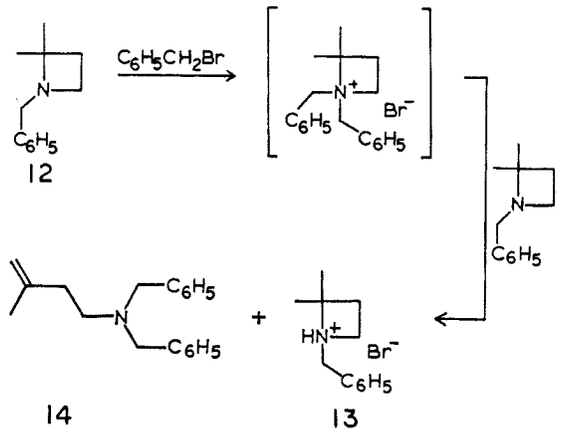
(23) 1,1,2,2-Tetramethylazetidinium reineckate has been prepared previously; see C. A. Grob, F. Ostermayer, and W. Raudenbusch, *Helv. Chim. Acta*, **45**, 1672 (1962).

(24) A similar method has been employed in the synthesis of aziridinium salts; see N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **30**, 821 (1965).

(25) O. E. Edwards, G. Fodor, and L. Marion, *Can. J. Chem.*, **44**, 13 (1966).

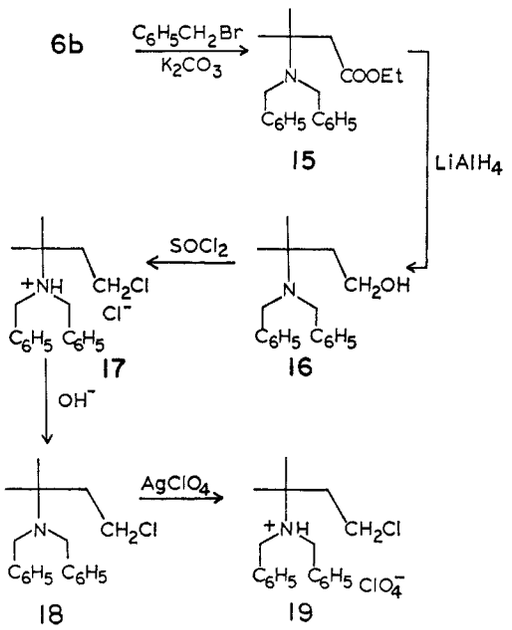
(26) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 18.

methylazetidinium perchlorate (**4**) were unsuccessful. In all attempts, following treatment of the crude benzylation product mixture with silver perchlorate, the only salt that could be isolated was 1-benzyl-2,2-dimethylazetidine perchlorate (**9b**), the conjugate acid of **12**. The fact that **9b** was always isolated in low yield led us to suspect that the desired dibenzylazetidinium salt was acting as a proton source. This was shown to be the case when the azetidine **12** was treated with benzyl bromide in the absence of solvent. Addition of ether to the crude reaction mixture caused the precipitation of 1-benzyl-2,2-dimethylazetidine hydrobromide (**13**) in 42% yield. Work-up of the resulting ethereal filtrate afforded a free amine which exhibited nmr signals in deuteriochloroform at τ 2.72 (multiplet, 10 H) and 6.45 (singlet, 4 H), indicative of a dibenzylamino group, and at 5.35 (apparent singlet, 2 H) and 8.43 (singlet, 3 H), suggesting the presence of the moiety CH_3—C=CH_2. The structure assigned to the amine was thus N-(3-methyl-3-buten-1-yl)dibenzylamine (**14**). It therefore appears that azetidine **12** is alkylated by benzyl bromide to form 1,1-dibenzyl-2,2-dimethylazetidinium bromide, but that this material is unstable under the reaction conditions and reacts with additional **12** in the manner of a base-promoted Hofmann elimination to afford a 1:1 mixture of azetidine salt **13** and amino olefin **14**. The ease with which this proton abstraction occurred is somewhat surprising and merits discussion in greater detail (see below).

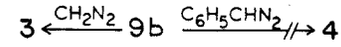


As an alternative route to the azetidinium salt **4**, we investigated the possibility of cyclizing N-(4-chloro-2-methyl-2-butyl)dibenzylamine (**18**) with silver perchlorate. The synthesis of **18** was accomplished according to the sequence shown in Scheme II. Treatment of **18** with silver perchlorate in acetone resulted in a slow precipitation of silver chloride over a 2-day period. Following the usual work-up procedure, a perchlorate salt (**19**) was isolated in very low yield. This material exhibited an nmr spectrum similar to that which would be expected for the dibenzylazetidinium salt, but the infrared spectrum showed a band for N^+–H at 3080 cm.$^{-1}$ Microanalysis indicated that **19** was merely N-(4-chloro-2-methyl-2-butyl)dibenzylamine perchlorate. Although no attempt was made in this case to detect the presence of the amino olefin **14** in the reaction mixture, the formation of **19** in low yield suggested that, as in the attempted benzylations of azetidine **12**, the azetidinium salt was formed, but quickly underwent a Hofmann elimination in the presence of excess amine. Variations in both rate and order of reagent addition were found to be ineffective in suppressing this ring-opening reaction.

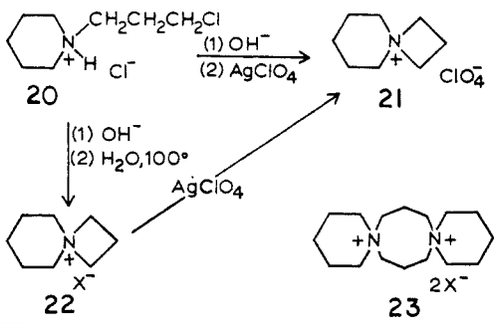
SCHEME II



In view of the apparent lability of 1,1-dibenzyl-2,2-dimethylazetidinium perchlorate (**4**) toward amines, it was concluded that further attempts to prepare and isolate this compound should avoid the presence of any basic material. One such attempt, based upon the known reaction of amine salts with diazomethane,[27-29] was the synthesis of **4** directly from 1-benzyl-2,2-dimethylazetidine perchlorate (**9b**). Treatment of **9b** in acetonitrile with diazomethane at 0° afforded 1-benzyl-1,2,2-trimethylazetidinium perchlorate (**3**), albeit in moderate yield. However, treatment of **9b** in acetonitrile with phenyldiazomethane under a variety of conditions, including the presence of boron trifluoride etherate as a catalyst, failed to yield any N,N-dibenzyl product (**4**).



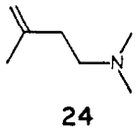
Silver perchlorate,[24] used as a cyclizing reagent in the conversion of **8** (as the base) into **9**, may also be applied to γ-*t*-aminoalkyl chlorides, so that quaternary azetidinium salts are obtained directly. For example, treatment of the γ-chloroalkylamine salt **20** with aqueous base liberated the corresponding free amine, which was cyclized with silver perchlorate in acetone to afford 4-azoniaspiro[3.5]nonane perchlorate (**21**) in 48% yield.



(27) E. Müller, H. Huber-Emden, and W. Rundel, *Ann.*, **623**, 34 (1959).
(28) T. Wieland and H. Wiegandt, *Chem. Ber.*, **93**, 1167 (1960).
(29) R. Daniels and C. G. Kormendy, *J. Org. Chem.*, **27**, 1860 (1962).

The fact that the yield was only moderate in this case is very likely due to the absence of *gem*-dialkyl groups which would facilitate the cyclization.[21] Evidence for the presence of the four-membered ring in **21** was obtained from the nmr spectrum (in deuterium oxide), which exhibited a four-proton triplet at τ 5.32 for the azetidinium CH_2–N^+ protons. Since the ring system present in **21** is identical with that of the first postulated azetidinium salt,[30] 4-azoniaspiro[3.5]nonane bromide (**22**, X = Br), an opportunity was provided to determine whether the early workers had actually synthesized an azetidinium ring, or whether the vigorous conditions that were employed favored formation of the corresponding eight-membered dimer,[31] 6,10-diazoniadispiro[5.3.5.3]octadecane dibromide (**23**, X = Br). To this end, **20** was treated with aqueous base to liberate the free amino chloride, which was subsequently heated with water at 100°. Work-up afforded the quaternary chloride as a syrup. A picrate prepared from this material had a melting point identical with that reported earlier.[30] Treatment of the syrup with silver perchlorate yielded a perchlorate salt that was identical with **21** in all respects. The quaternary chloride therefore had structure **22** (X = Cl), 4-azoniaspiro[3.5]nonane chloride, and the original claim of azetidinium salt formation was shown to be correct.

Having devised an efficient synthesis for two (**2** and **3**) of the three azetidinium salts initially desired, we proceeded to investigate the chemistry of these salts in some detail. 1,1,2,2-Tetramethylazetidinium perchlorate (**2**) proved to be completely unreactive toward reagents that have been shown to bring about facile solvolytic ring opening or ring expansion of representative aziridinium salts. For example, no detectable reaction occurred upon treatment of **2** with refluxing methanol for 35 hr, or with refluxing acetone for 5 days. The four-membered ring also failed to open under conditions of catalytic hydrogenolysis. However, **2** was found to undergo reaction with sodium methoxide in methanol. The major product exhibited nmr signals in deuteriochloroform at τ 5.28 (apparent singlet, 2 H) and 8.26 (singlet, 3 H) indicative of the CH_3—C=CH_2 grouping, thus permitting the structure to be assigned as N-(3-methyl-3-buten-1-yl)dimethylamine (**24**). No signal ascribable to the methoxy moiety could be detected, indicating that eliminative ring opening was the main reaction. It will be recalled that a similar Hofmann elimination took place during attempts to prepare 1,1-dibenzyl-2,2-dimethylazetidinium perchlorate (**4**), although the base involved in that case (*i.e.*, a free amine) was much weaker than sodium methoxide.



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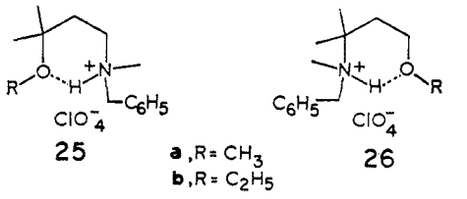
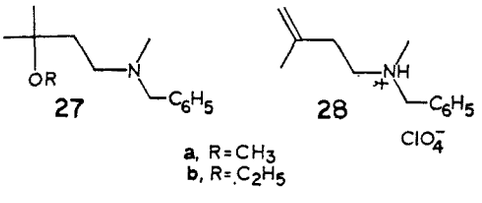
In contrast to the lack of reactivity of **2** in solvolytic ring opening, the four-membered ring in 1-benzyl-1,2,2-trimethylazetidinium perchlorate (**3**) was opened readily, reflecting the electron-withdrawing influence and, to some extent, the steric effect of the benzyl group. Upon treatment with refluxing methanol, compound **3** was converted slowly into a two-component mixture. The major product, isolated by fractional crystallization, displayed an infrared band at 3070 cm^{-1} for N^+–H and had an elemental composition satisfactory for $C_{14}H_{24}ClNO_5$, indicating that **3** had combined with methanol in a 1:1 manner. The nmr spectrum of this material in trifluoroacetic acid exhibited signals for $ArCH_2$–N^+H (τ 5.60, doublet), CH_3–N^+H (τ 6.96, doublet), and CH_3–O (τ 6.65, singlet). A clear distinction between the isomeric structures **25a** and **26a** was not offered, however, since a two-proton multiplet at τ 6.2–6.7 could be ascribed to either CH_2–N^+ (in **25a**) or CH_2O (in **26a**). The nmr spectrum (in deuteriochloroform) of the amine mixture liberated from the crude methanolysis product was more definitive. The presence of signals for CH_3–O (τ 6.93, singlet) and CH_2–N (τ 7.4–7.8, multiplet) together with the absence of any signal corresponding to CH_2–O (*i.e.*, at lower field than CH_3–O) was indicative of structure **27a**. The azetidinium ring had therefore opened in an SN1 manner to afford **25a**, N-(3-methoxy-3-methylbutyl)-N-methylbenzylamine perchlorate. Evidence for the cyclic hydrogen-bonded configuration as drawn in **25a** was provided by the nmr spectrum which displayed two signals (τ 8.65 and 8.85) for $(CH_3)_2C$–O indicating that the methyl groups were nonequivalent. In the spectrum of **27a**, where no hydrogen bonding is possible, there was only one signal (τ 8.92) for these groups. The identification of the minor product of the methanolysis as N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine perchlorate (**28**) will be discussed shortly.



25 **a**, R = CH_3; **b**, R = C_2H_5 **26**



27 **28**

a, R = CH_3; **b**, R = C_2H_5

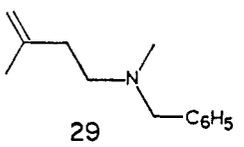
Since the methanolysis of analogous aziridinium salts is generally complete after 2 hr at reflux temperature,[5,7] it was of interest to determine the rate of opening of the azetidinium ring under similar conditions. The reaction between azetidinium salt **3** and methanol was therefore followed by means of nmr spectroscopy; pertinent details regarding the procedure are given in the Experimental Section. The data showed that the reaction is essentially complete after 8 hr and that the initial rate of formation of the amino ether **25a** is approximately three times the initial rate of formation of the amino olefin salt **28**.

In an analogous manner, azetidinium salt **3** reacted in refluxing ethanol to give a mixture of N-(3-ethoxy-3-methylbutyl)-N-methylbenzylamine perchlorate (**25b**) and the amino olefin salt **28**. The nmr spectrum of **25b** in deuteriochloroform displayed signals for $ArCH_2$–N^+H (τ 5.57, doublet), CH_3–N^+H (τ 7.01, doublet),

(30) S. Gabriel and R. Stelzner, *Ber.*, **29**, 2381 (1896).
(31) H. Hörlein and R. Kneisel, *ibid.*, **39**, 1429 (1906).

CH_2–N^+ (τ 6.4–6.9, multiplet), and CH_2–O (τ 6.61, quartet). Upon conversion of perchlorate **25b** into the corresponding free amine (**27b**), new signals appeared for $ArCH_2$–N (τ 6.51, singlet), CH_3–N (τ 7.81, singlet), CH_2–N (τ 7.3–7.7, multiplet), and CH_2–O (τ 6.67, quartet). Integration of the spectrum showed that the last signal corresponded to two protons, confirming the absence of an additional CH_2–O grouping and firmly establishing the assigned structure **27b** (and thus **25b** as well). The presence of hydrogen bonding in **25b** was demonstrated by the fact that the nmr spectrum of this salt exhibited two signals (τ 8.80 and 8.96) for $(CH_3)_2C$–O, whereas only one signal (τ 8.86) for this moiety appeared in the spectrum of **27b**. Though formation of the amino olefin salt **28** occurred to a greater extent in this case than during methanol treatment of **3**, formation of the amino ether was still the major reaction.

It was considered that treatment of the benzyltrimethylazetidinium salt **3** with sodium methoxide might open the ring in an SN2 manner, since methoxide is a much stronger nucleophile than methanol. However, the free amine that was actually obtained from this reaction proved to be N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine (**29**), as evidenced by nmr signals at τ 5.34 (apparent singlet, 2 H) and 8.32 (singlet, 3 H) for the CH_3—C=CH_2 moiety, as well as the lack of any signal attributable to CH_3—O.

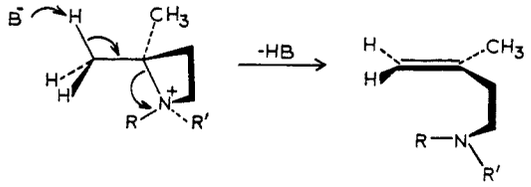


29

Attempts to effect a ④$^+$ + 2 → ⑥$^+$ ring expansion of azetidinium salt **3** by reaction with acetone or acetonitrile were likewise unsuccessful. In both instances, the only product that could be obtained was identified as **28**, the same amino olefin perchlorate that was formed as a by-product in the alcoholyses of **3**. This material was characterized by the nmr signals shown (in deuteriochloroform) at τ 5.61 (doublet, 2 H) and 7.07 (doublet, 3 H) for $ArCH_2$—N^+H and CH_3—N^+H, respectively, as well as at τ 5.20 (apparent singlet, 2 H) and 8.32 (singlet, 3 H) for the CH_3—C=CH_2 grouping. Infrared absorption at 3070 for N^+—H and at 1650 and 905 cm^{-1} for C=CH_2 supported this structural assignment.

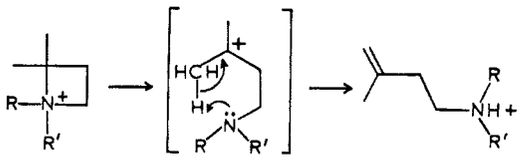
It is appropriate at this point to consider the reasons behind the relative ease with which azetidinium salts **2**, **3**, and **4** undergo eliminative ring opening. Two types of elimination have been observed for these compounds, namely based-promoted (*cf.* the attempted preparations of the dibenzyldimethyl salt **4**, and the reactions of the tetramethyl salt **2** and the benzyltrimethyl salt **3** with sodium methoxide) and "thermal" (*cf.* the alcoholyses and attempted ring expansions of **3**). In both types, the only amino olefin that could be detected was that obtained by loss of a hydrogen from one of the *gem*-dimethyl groups. It has been found that treatment of azetidinium salt **3** with sodium iodide in refluxing acetone also results in such an elimination. The facility with which the base-promoted eliminations occur can be explained relatively easily. In the normal transition state leading to Hofmann elimination, the quaternary nitrogen, the α and β carbons, and the β hydrogen all lie in a *trans* coplanar arrangement.[32] Upon examination of Dreiding models of our azetidinium salts, it can be seen that such an arrangement involving any of the six hydrogens on the *gem*-dimethyl groups is readily achieved. This property, together with the strain inherent in the four-membered ring, apparently serves to lower the free energy of activation to such an extent that elimination is the predominant if not exclusive reaction, provided that a base is present to accept the β hydrogen. The proposed mechanism for the base-promoted elimination is shown in Scheme III. It is more difficult to rationalize the ease with

SCHEME III



which the so-called "thermal" eliminations occur. A concerted mechanism is unlikely in this case since the perchlorate anion is not sufficiently basic to facilitate removal of the β hydrogen. A more plausible explanation is that the amino olefin is formed *via* the same ring-opened intermediate that gives rise to solvolysis product; this mechanism is shown in Scheme IV. There are,

SCHEME IV

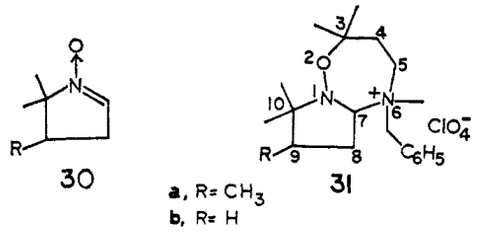


however, several discrepancies associated with this mechanism. If a carbonium intermediate such as that shown is actually formed, it would be expected that some ring-expanded product would be obtained when acetone or acetonitrile is present. In addition, some of the thermodynamically more stable olefin would very likely be formed. The products may be explained by kinetic control. Thus, alcohols, which are more nucleophilic than acetone or acetonitrile, are more effective than the latter two in attacking the intermediate before any rearrangement can take place. Moreover, rearrangement to give the less substituted olefin is kinetically favored owing to the six-membered geometry of the transition state shown in Scheme IV. The above considerations are admittedly speculative, and further study is necessary to elucidate more fully the mechanism of this "thermal" type of elimination. For example, there remains the possibility that the solvent (*i.e.*, alcohol, acetone, or acetonitrile) is acting as a proton-transfer agent in these reactions.

Although 1-benzyl-1,2,2-trimethylazetidinium perchloroate (**3**) failed to undergo ring expansion with either acetone or acetonitrile, expansion of this azetidinium ring could be effected by reaction with nitrones, in particular 4,5,5-trimethyl-Δ^1-pyrroline-1-oxide (**30a**)

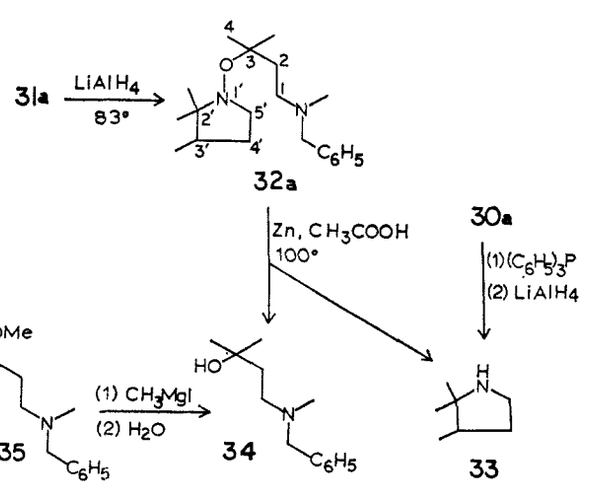
(32) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, p 484.

and 5,5-dimethyl-Δ^1-pyrroline-1-oxide (**30b**).[33] When an intimate mixture of azetidinium salt **3** and either nitrone was allowed to stand at room temperature for more than a week followed by a short period of heating at 60°, a product having the correct analysis for a 1:1 adduct was isolated in moderate yield. These adducts were tentatively assigned structure **31** by analogy



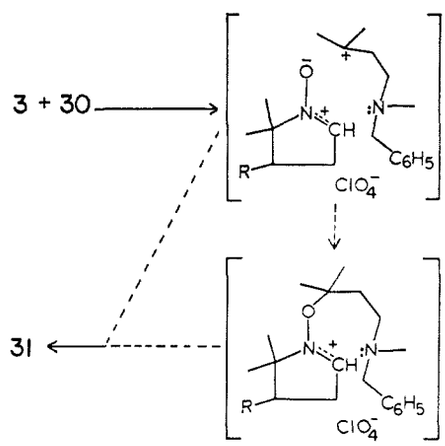
with the structures recently determined for nitrone–aziridinium salt adducts.[1] (Compound **31a** is named 6-benzyl-3,3,6,9,10,10-hexamethyl-2-oxa-1-aza-6-azoniabicyclo[5.3.0]decane perchlorate; **31b** is 6-benzyl-3,3,-6,10,10-pentamethyl-2-oxa-1-aza-6-azoniabicyclo[5.3.0]-decane perchlorate.) Formation of such a cycloadduct is representative of a new type of ring expansion, expressed generally as ④$^+$ + 3 → ⑦$^+$, in which a charged four-membered cycle combines with a 1,3-dipolar function to afford a charged seven-membered cycle. Inasmuch as infrared and nmr spectra were of no practical value in verifying structure **31**, a chemical degradative sequence was undertaken.

Upon treatment of **31a** with lithium hydride in refluxing dimethoxyethane, a free amine was obtained which showed no bands attributable to O–H or N–H in the infrared spectrum. The nmr spectrum of this material in deuteriochloroform exhibited singlets for both $ArCH_2$–N (τ 6.50) and CH_3–N (τ 7.81). The rest of the spectrum was rather complex, but upon close examination a symmetrical A_2X_2 system, which could be attributed to the C–CH_2–CH_2–N moiety, was observed at τ 7.3–7.7 and 8.1–8.5. The structure of the reduction product was thus assigned as N-methyl-N-[3-methyl-3-(2′,2′,3′-trimethylpyrrolidin-1′-oxy)butyl]-benzylamine (**32a**). This facile reduction of the C–N^+ bond in **31a** while the N–O bond remained intact is completely analogous to the mode of reduction of nitrone–aziridinium salt adducts.[1] Cleavage of the N–O bond in **32a** could be effected, however, by treatment with zinc dust and aqueous acetic acid at 100°. The products of this reduction were separated by glpc and were identified by comparison with authentic samples as 2,2,3-trimethylpyrrolidine (**33**) and 4-(N-benzyl-N-methylamino)-2-methyl-2-butanol (**34**). Authentic **33** was prepared as described earlier[1] by a two-step reduction of nitrone **30a**, while authentic **34** was synthesized from the amino ester **35** by treatment with excess methylmagnesium iodide. The symmetrical A_2X_2 pattern (τ 7.32 and 8.38) arising from the C–CH_2–CH_2–N grouping was displayed plainly in the nmr spectrum of **34** in deuteriochloroform. This double cleavage of adduct **31a** to form the pyrrolidine **33** and the amino alcohol **34** firmly established the assigned structure of the original adduct, that of compound **32a**, and that of **31b** as well.



One possible mechanism for the ④$^+$ + 3 → ⑦$^+$ reaction is shown in Scheme V. Opening of the azetidinium ring at the 1,2 bond to form the corresponding γ-*t*-aminocarbonium ion is postulated as the initial step. If this carbonium ion is indeed an intermediate, the experimental facts require that nitrone as solvent be more effective in assisting the fission of the 1,2 bond than either ketone or nitrile and, moreover, that nitrone addition proceed more rapidly than the elimination which supervenes in the other two cases. From this intermediate, pictured in Scheme V in correct orientation with respect to the 1,3-polarized nitrone, formation of the seven-membered heterocycle can proceed in either concerted or stepwise manner. The concerted process can be visualized as a "1,4-*polar*-1,3-*dipolar* cycloaddition." The question remains open as to whether the total process, **3** + **30** → **31**, can be concerted. On the basis of orbital symmetry considerations, the process would be allowed,[34] but the example is exceptional because of the polarity of the molecules involved, and the distinction from a nonconcerted process may vanish. The goal of building enough reactivity into a σ bond so that it behaves like a π bond continues to be an intriguing one.

SCHEME V



In summary, although there is a considerable decrease in reactivity in going from the aziridinium to the azetidinium ring system, solvolytic openings and expansions of 1,1,2,2-tetrasubstituted azetidinium salts may be effected provided that (a) the 1,2 bond is ac-

(33) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2094 (1959).

(34) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

tivated toward polar cleavage (*e.g.*, by N-benzyl substitution) and (b) olefin formation is suppressed kinetically. The presence of α-*gem*-dimethyl substitution in the four-membered ring series led to eliminative ring opening, probably owing to the favorable stereochemistry, whereas this competing reaction did not occur in the three-membered ring series. The new reaction of a nitrone with an azetidinium salt provides an unusual seven-membered heterocyclic ring system.

Experimental Section[35]

Ethyl 3,3-Dimethylacrylate (5).—A mixture of 200 g (2.0 mol) of 3,3-dimethylacrylic acid, 500 ml of ethanol, 60 ml of concentrated sulfuric acid, and 1.3 l. of benzene was heated under reflux with stirring for 3 days in a three-necked flask fitted with two condenser–Dean-Stark trap combinations to remove the water formed during the reaction. The mixture was subsequently cooled to room temperature and washed with 3 *M* aqueous potassium carbonate. The wash layers were then extracted with additional benzene. These extracts were combined with the original organic layer, and the resulting solution was dried over anhydrous potassium carbonate and evaporated *in vacuo*. Distillation of the residue afforded 205 g (80%) of the acrylic ester as a clear colorless liquid: bp 55–61° (21 mm) (lit.[36] mp 150°); nmr (in $CDCl_3$), with satisfactory integration, at τ 4.32 (m, C=CH), 5.86 (q, CH_3CH_2—O), 7.84 and 8.11 (d, d, J = 1.0 cps, $(CH_3)_2$-C=C), and 8.75 (t, CH_3CH_2—O).

Ethyl 3-Methyl-3-methylaminobutyrate (6a).—A solution of 111.4 g (0.87 mol) of ethyl 3,3-dimethylacrylate (5) and 34.5 g (1.11 mol) of methylamine in 1 l. of ethanol was allowed to stand at room temperature for 10 days. Removal of the solvent *in vacuo* followed by distillation of the residual oil gave the amino ester as a clear colorless liquid: bp 78–83° (17 mm); yield 107.5 g (78%); ν_{max}^{film} 3340 (N–H), 1760 cm^{-1} (C=O); nmr (in $CDCl_3$), at τ 5.87 (q, CH_3CH_2—O), 7.60 (s, CH_2C=O), 7.68 (s, CH_3—N), 8.26 (s, NH), 8.74 (partially hidden triplet, CH_3CH_2—O), 8.86 (s, $(CH_3)_2C$—N).

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.32; H, 10.64; N, 8.65.

3-Methyl-3-methylamino-1-butanol (7a).—To a stirred slurry of 19.0 g (0.5 mol) of lithium aluminum hydride in 600 ml of ether was added dropwise a solution of 47.7 g (0.3 mol) of ethyl 3-methyl-3-methylaminobutyrate (6a) in 200 ml of ether. The mixture was stirred at room temperature for 13 hr and was subsequently treated dropwise with 38 ml of water and 30 ml of 10% aqueous sodium hydroxide. The salts thus precipitated were filtered, treated with excess aqueous sodium hydroxide, and extracted with ether. The combined filtrate and extracts were dried over anhydrous potassium carbonate, filtered, and evaporated *in vacuo*. Distillation of the residual oil yielded the amino alcohol (26.5 g, 76%) as a clear colorless liquid: bp 90–91° (18 mm); ν_{max}^{film} 3300 cm^{-1} (broad, O–H and N–H); nmr (in $CDCl_3$), at τ 6.22 (t, CH_2CH_2–O), 6.44 (s, OH and NH), 7.69 (s, CH_3–N), 8.44 (t, CH_2CH_2–O), 8.88 (s, $(CH_3)_2C$–N).

Anal. Calcd for $C_6H_{15}NO$: C, 61.49; H, 12.90; N, 11.95. Found: C, 61.40; H, 12.68; N, 11.64.

N-(4-Chloro-2-methyl-2-butyl)methylamine Hydrochloride (8a).—A solution of 23.6 g (0.20 mol) of 3-methyl-3-methylamino-1-butanol (7a) in 50 ml of chloroform was added dropwise with stirring to 52.8 g (0.44 mol) of thionyl chloride cooled in an ice bath. Following the addition, the mixture was stirred at room temperature for 15 hr. At the end of this time, 30 ml of ethanol was added to destroy residual thionyl chloride. Removal of the solvent *in vacuo* afforded 32.9 g (96%) of product. An analytical sample, colorless needles from ethyl methyl ketone, had mp 137–138°; nmr (in $CDCl_3$), at τ 6.27 (t, CH_2CH_2–Cl), 7.39 (t, CH_3–N^+), 7.71 (t, CH_2CH_2–Cl), 8.52 (s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_6H_{15}Cl_2N$: C, 41.87; H, 8.79; N, 8.14. Found: C, 41.91; H, 8.75; N, 8.22.

1,2,2-Trimethylazetidine Perchlorate (9a).—Treatment of 23.6 g (0.137 mol) of N-(4-chloro-2-methyl-2-butyl)methylamine hydrochloride (8a) with 100 ml of 10% aqueous sodium hydroxide liberated the corresponding free amine, which was extracted into methylene chloride and isolated in the normal manner: yield 16.2 g (0.120 mol, 87%). This was dissolved in 400 ml of acetonitrile and added with stirring to a solution of 24.9 g (0.120 mol) of silver perchlorate in 300 ml of acetonitrile. The resulting mixture was stirred at room temperature for 27 hr. The precipitated silver chloride was then filtered and washed with additional solvent. Evaporation of the filtrate *in vacuo* yielded a solid which was treated with methylene chloride and refiltered to remove residual silver salts. Removal of the methylene chloride *in vacuo* afforded 23.8 g (quantitative from the free amino chloride) of the azetidine perchlorate. Recrystallization from ethyl acetate yielded an analytical sample as colorless needles: mp 165–166°; ν_{max}^{Nujol} 3150 cm^{-1} (N^+–H); nmr (in CF_3COOH), at τ 5.4–6.4 (m, CH_2CH_2–N^+), 7.12 (d, J = 5.5 cps, CH_3–N^+), 7.2–7.7 (m, CH_2CH_2–N^+), 8.28 and 8.31 (s,s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07; N, 7.01. Found: C, 36.00; H, 6.86; N, 6.94.

1,1,2,2-Tetramethylazetidinium Perchlorate (2).—A mixture of 20.9 g (0.105 mol) of 1,2,2-trimethylazetidine perchlorate (9a) and 80 ml of 10% aqueous sodium hydroxide was extracted with methylene chloride. The combined extracts were dried over anhydrous sodium sulfiate and filtered. Approximately 200 ml of acetone was added to the filtrate, and the methylene chloride was removed by distillation at atmospheric pressure. An additional 100 ml of acetone was then added to the clear pot residue, and the resulting solution was added with stirring to a solution of 25.1 g (0.177 mol) of methyl iodide in 200 ml of acetone. The mixture was stirred for 6 hr at room temperature and was subsequently treated with 1 l. of ether to precipitate 12.4 g (52%) of the methiodide. An analytical sample, colorless cubes from ethanol, had mp 177–178° dec.

Anal. Calcd for $C_7H_{16}IN$: C, 34.86; H, 6.69. Found: C, 35.08; H, 6.74.

The methiodide (12.4 g, 51.5 mmol) was dissolved in 600 ml of methanol and added to a solution of 10.7 g (51.5 mmol) of silver perchlorate in 400 ml of methanol. The mixture was stirred at room temperature for 5 hr, after which time the precipitated silver iodide was filtered and washed with solvent. Removal of the methanol *in vacuo* afforded 10.6 g (89% from the methiodide) of the azetidinium perchlorate. The analytical sample, colorless cubes from ethanol, had mp 172.5–173.0°; nmr (in CF_3COOH), at τ 5.83 (t, CH_2CH_2–N^+), 6.90 (s, $(CH_3)_2N^+$), 7.35 (broadened triplet, CH_2CH_2–N^+), 8.25 (s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_7H_{16}ClNO_4$: C, 39.35; H, 7.55; N, 6.56. Found: C, 39.24; H, 7.36; N, 6.29.

Ethyl 3-Benzylamino-3-methylbutyrate (6b).—A solution of 128 g (1.0 mol) of ethyl 3,3-dimethylacrylate (5) and 118 g (1.1 mol) of benzylamine in 1 l. of ethanol was heated at 50–55° for 15 days. Subsequent removal of the solvent *in vacuo* followed by fractional distillation of the residual oil afforded 121 g (52%) of the product as a clear colorless liquid: bp 115–117° (0.55 mm); ν_{max}^{film} 3350 (N–H), 1740 cm^{-1} (C=O); nmr (in $CDCl_3$), at τ 2.69 (s, C_6H_5), 5.87 (q, CH_3CH_2–O), 6.28 (s, $ArCH_2$–N), 7.51 (s, CH_2C=O), 7.87 (s, NH), 8.77 (singlet over triplet, $(CH_3)_2C$–N and CH_3CH_2–O).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.96. Found: C, 71.63; H, 9.01; N, 6.09.

3-Benzylamino-3-methyl-1-butanol (7b).—A solution of 141 g (0.6 mol) of ethyl 3-benzylamino-3-methylbutyrate (6b) in 300 ml of ether was added dropwise to a stirred slurry of 37.9 g (1.0 mol) of lithium aluminum hydride in 1 l. of ether. The mixture was stirred for 18 hr at room temperature and was then treated dropwise with 76 ml of water and 61 ml of 10% aqueous sodium hydroxide. The precipitated salts were filtered and washed with ether. The filtrate was then dried over anhydrous potassium carbonate and was subsequently evaporated *in vacuo*. Distillation of the residue yielded 97.5 g (84%) of the amino alcohol as a clear colorless liquid: bp 119–121° (0.45 mm); ν_{max}^{film} 3300 cm^{-1} (broad, O–H and N–H); nmr (in $CDCl_3$), at τ 2.72 (s, C_6H_5), 6.18 (partially hidden triplet, CH_2CH_2–O), 6.29 (s,

(35) All melting points are corrected; boiling points are uncorrected. Infrared spectra were obtained with Perkin-Elmer grating spectrophotometers, Models 521 or 337. Nmr spectra were obtained on a Varian Associates Model A-60 or A-60A spectrometer using tetramethylsilane as either an external or internal standard. Glpc analyses were carried out on an F & M Model 300 gas chromatograph using a 0.25-in. column of 20% Carbowax 20 M (1 m) on either Anakrom ABS or Chromosorb W, HMDS treated. We are indebted to Mr. J. Nemeth and his associates for the microanalyses and molecular weight determinations.

(36) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

$ArCH_2$–N), 6.53 (s, OH), 8.39 (t, CH_2CH_2–O), 8.80 (s, $(CH_3)_2$-C–N).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.56; H, 9.91; N, 7.25. Found: C, 74.44; H, 9.80; N, 7.05.

N-(4-Chloro-2-methyl-2-butyl)benzylamine Hydrochloride (8b).—A solution of 97.5 g (0.5 mol) of 3-benzylamino-3-methyl-1-butanol (**7b**) in 125 ml of chloroform was added dropwise with stirring to 131 g (1.1 mol) of thionyl chloride cooled in an ice bath. Following the addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 12 hr, during which time the product solidified. The residual thionyl chloride was decomposed by treatment with 75 ml of ethanol. Addition of excess ether to the resulting solution reprecipitated the product, which was filtered and washed with ether to yield 124.4 g (quantitative). Recrystallization from ethyl acetate afforded an analytical sample as colorless needles: mp 170–172°; nmr (in D_2O), at τ 2.03 (s, C_6H_5), 4.86 (s, $ArCH_2$–N^+), 5.78 (t, CH_2CH_2–Cl), 7.23 (t, CH_2CH_2–Cl), 8.04 (s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_{12}H_{19}Cl_2N$: C, 58.06; H, 7.71; N, 5.65. Found: C, 58.31; H, 7.77; N, 5.79.

1-Benzyl-2,2-dimethylazetidine Perchlorate (9b).—Treatment of 49.6 g (0.2 mol) of N-(4-chloro-2-methyl-2-butyl)benzylamine hydrochloride (**8b**) with 700 ml of 3% aqueous sodium hydroxide liberated the free amino chloride which was extracted into methylene chloride. Following the normal isolation procedure, this amine was dissolved in 400 ml of acetone and added with stirring to a solution of 41.5 g (0.2 mol) of silver perchlorate in 500 ml of acetone. Silver chloride began to precipitate almost immediately. After being stirred at room temperature for 40 hr, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residual oil was treated with methylene chloride and filtered in order to remove any residual silver salts. Removal of the methylene chloride *in vacuo* afforded the desired azetidine salt, which was recrystallized from isopropyl alcohol as colorless plates: mp 151.0–151.5°; yield 46.8 g (85%); ν_{max}^{Nujol} 3120 cm^{-1} (N^+–H); nmr (in CF_3COOH), at τ 2.52 (s, C_6H_5), 5.6–6.1 (m, $ArCH_2$–N^+ and CH_2CH_2–N^+), 7.1–7.9 (m, CH_2CH_2–N^+), 8.17 and 8.35 (s, s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_{12}H_{18}ClNO_4$: C, 52.27; H, 6.58; N, 5.08. Found: C, 52.30; H, 6.59; N, 4.84.

1-Benzyl-1,2,2-trimethylazetidinium Perchlorate (3) and Bromide.—Upon treatment with 600 ml of 3% aqueous sodium hydroxide, 46.8 g (0.17 mol) of 1-benzyl-2,2-dimethylazetidine perchlorate (**9b**) was converted into the corresponding free azetidine. This was isolated in the usual manner, and was subsequently dissolved in 400 ml of acetone and added dropwise with stirring to a solution of 35.5 g (0.25 mol) of methyl iodide in 400 ml of acetone. Upon heating the resulting solution in a water bath maintained at approximately 50°, the methiodide precipitated. After 4 hr of heating and stirring, the mixture was treated with excess ether and filtered to yield 50.5 g (94%) of the methiodide, mp 137–138° dec.

To a stirred solution of 50.5 g (0.16 mol) of the azetidinium iodide in 1.6 l. of methanol was added a solution of 33.2 g (0.16 mol) of silver perchlorate in 400 ml of methanol. After being stirred at room temperature for 1 hr, the mixture was filtered and the filtrate was evaporated *in vacuo*, yielding the azetidinium perchlorate in a crystalline form. A second crop of crystals was obtained by treatment of the precipitated silver iodide with hot methanol followed by filtration and removal of the solvent *in vacuo*. The total yield of product was 42.8 g (93% from the methiodide). One recrystallization from methanol afforded an analytical sample as colorless prisms: mp 142.5–143.0°; nmr (in CF_3COOH), at τ 2.45 (s, C_6H_5), 5.36 and 5.80 (AB system, J = 13.0 cps, $ArCH_2$–N^+), 5.1–5.7 and 6.1–6.6 (m, m, CH_2CH_2–N^+), 7.07 (s, CH_3–N^+), 6.9–7.5 (m, CH_2CH_2–N^+), 8.00 and 8.25 (s, s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_{13}H_{20}ClNO_4$: C, 53.88; H, 6.96; N, 4.83. Found: C, 53.86; H, 6.92; N, 4.84.

For the conversion of perchlorate into **1-benzyl-1,2,2-trimethylazetidinium bromide**, a column of 14.5 g (wet weight, 20 mequiv) of Dowex 1-X8 chloride (200–400 mesh) was washed thoroughly with water and treated with 300 ml of 10% aqueous potassium bromide. Water was then passed through the column until the eluent gave no precipitate with silver nitrate. A solution of 580 mg (2.0 mmol) of 1-benzyl-1,2,2-trimethylazetidinium perchlorate (**3**) in 175 ml of water was then passed through the column, followed by water until the eluent gave no precipitate with silver nitrate. The collected eluent was evaporated *in vacuo* and the residue was treated with ether and filtered to yield 540 mg (quantitative) of the azetidinium bromide. An analytical sample, colorless prisms from isopropyl alcohol, had mp 141–144° dec.

Anal. Calcd for $C_{13}H_{20}BrN$: C, 57.78; H, 7.46; N, 5.19. Found: C, 57.81; H, 7.40; N, 5.22.

The crystals thus obtained were judged to be suitable for X-ray analysis, and Professor L. Trefonas of Louisiana State University, New Orleans, has the compound presently under crystallographic study.

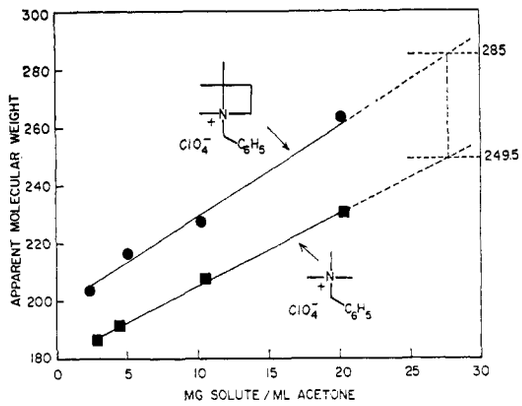


Figure 1.—The apparent molecular weights of **3** and **11** *vs.* concentration in acetone.

Determination of the Molecular Weight of Azetidinium Salt 3.—Apparent molecular weights of the azetidinium perchlorate and benzyltrimethylammonium perchlorate (**11**) were determined at various concentrations in acetone using a Mecrolab vapor pressure osmometer. The data obtained are recorded in Table I and are plotted in Figure 1.

Table I

Apparent Molecular Weights of 3 and 11 in Acetone

Compd	Concn, mg/ml of acetone	Apparent mol wt
3	2.178	204
	4.990	217
	10.13	228
	20.10	264
	(27.8)	(285)
11	2.745	187
	4.336	192
	10.45	208
	20.26	231
	(27.8)	(249.5)

By extrapolation of the roughly parallel plots to the concentration at which the apparent molecular weight of **11** is equivalent to its theoretical molecular weight (249.5), a comparable value of 285 is obtained for the molecular weight of **3** (theoretical 289.5).

Benzyltrimethylammonium Perchlorate (11).—To a stirred solution of 13.5 g (0.10 mol) of benzyldimethylamine in 20 ml of ethanol was added dropwise 19.0 g (0.13 mol) of methyl iodide. Following the addition, the mixture was heated under reflux for 45 min and was then cooled to room temperature. Upon the addition of 100 ml of ether, the methiodide precipitated and was filtered, yield 27.1 g (98%).

A solution of 8.3 g (0.03 mol) of the benzyltrimethylammonium iodide in 100 ml of methanol was added with stirring to a solution of 6.2 g (0.03 mol) of silver perchlorate in 50 ml of methanol. The mixture was stirred at room temperature for several hours and then filtered. Upon removal of the solvent *in vacuo*, 7.0 g (94% from the methiodide) of the perchlorate salt was obtained. Recrystallization from ethanol yielded an analytical sample as colorless plates: mp 129.5–131.0° (lit.[37] mp 126–127°); nmr (in CH_2Cl_2), at τ 2.50 (s, C_6H_5), 5.46 (s, $ArCH_2$–N^+), 6.89 (s, $(CH_3)_3N^+$).

Anal. Calcd for $C_{10}H_{16}ClNO_4$: C, 48.10; H, 6.46; N, 5.61. Found: C, 47.99; H, 6.37; N, 5.32.

(37) F. Schlegel, *Ber.*, **64**, 1739 (1931).

Attempted Benzylation of 1-Benzyl-2,2-dimethylazetidine (12).—A mixture of 2.76 g (10.0 mmol) of 1-benzyl-2,2-dimethylazetidine perchlorate (**9b**) and 30 ml of 3% aqueous sodium hydroxide was extracted with methylene chloride and worked up as usual to yield 1.70 g (97%) of free **1-benzyl-2,2-dimethylazetidine (12)** as a colorless liquid. This was cooled in an ice bath and treated dropwise with 3.42 g (20.0 mmol) of benzyl bromide. The ice bath was removed following the addition and the mixture was stirred at room temperature for 20 hr. Subsequent treatment with excess ether precipitated **1-benzyl-2,2-dimethylazetidine hydrobromide (13)** as a white solid which was filtered and washed with ether to yield 1.04 g (42% from the free azetidine): mp 147–149°; nmr (in D_2O), at τ 2.47 (s, C_6H_5), 5.72 (s, $ArCH_2$–N^+), 5.9–6.3 (unresolved multiplet, CH_2CH_2–N^+), 7.60 (t, CH_2CH_2–N^+), 8.32 (s, $(CH_3)_2C$–N^+).

The ethereal filtrate obtained from the above work-up procedure was concentrated *in vacuo* and extracted with 3% aqueous hydrochloric acid. These extracts were then made basic by the addition of excess 10% aqueous sodium hydroxide and the resulting mixture was extracted with methylene chloride. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* to yield a clear colorless liquid that was primarily **N-(3-methyl-3-buten-1-yl)dibenzylamine (14)**; nmr (in $CDCl_3$) absorptions appeared at τ 2.72 (m, C_6H_5), 5.35 (apparent singlet, $C{=}CH_2$), 6.45 (s, $(ArCH_2)_2N$), 7.3–8.0 (A_2B_2 system, C—CH_2CH_2—N), 8.43 (s, CH_3—$C{=}C$). A small amount of unreacted 1-benzyl-2,2-dimethylazetidine was also present, as evidenced by a singlet at τ 8.80 for $(CH_3)_2C$–N.

Ethyl 3-Dibenzylamino-3-methylbutyrate (15).—To a stirred mixture of 23.5 g (0.10 mol) of ethyl 3-benzylamino-3-methylbutyrate (**6b**) and 20.7 g (0.15 mol) of anhydrous potassium carbonate in 150 ml of ethanol was added 18.8 g (0.11 mol) of benzyl bromide. After being heated under gentle reflux with stirring for 24 hr, the mixture was brought to alkalinity with potassium hydroxide pellets and filtered. The filtrate was evaporated *in vacuo*, and the residue was combined with the previously filtered inorganic salts and treated with 10% aqueous sodium hydroxide. The resulting mixture was extracted with ether, and the combined extracts were dried over anhydrous potassium carbonate and evaporated *in vacuo*. Preliminary distillation of the residual oil through a short Vigreux column yielded 3.5 g of starting material, bp 95–100° (0.10 mm). The resulting pot residue was then distilled through a short-path head to afford the dibenzylamino ester as a clear colorless oil: bp 160–162° (0.03 mm); yield 20.6 g (63%); no N–H band in the infrared spectrum; nmr (in $CDCl_3$), at τ 2.6–3.0 (m, C_6H_5), 5.86 (q, CH_3CH_2–O), 6.25 (s, $(ArCH_2)_2N$), 7.43 (s, $CH_2C{=}O$), 8.78 (singlet over triplet, $(CH_3)_2C$–N and CH_3CH_2–O).

Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.31. Found: C, 77.43; H, 8.38; N, 4.31.

3-Dibenzylamino-3-methyl-1-butanol (16).—A solution of 19.8 g (0.061 mol) of ethyl 3-dibenzylamino-3-methylbutyrate (**15**) in 50 ml of ether was added dropwise with stirring to a slurry of 5.3 g (0.14 mol) of lithium aluminum hydride in 150 ml of ether. The resulting mixture was stirred for 6 hr at room temperature. Work-up was then effected by the dropwise addition of 100 ml of water and 50 ml of 10% aqueous sodium hydroxide. The ethereal solution was decanted from the resulting gel which was subsequently extracted with additional ether. The combined ethereal layers were dried over anhydrous potassium carbonate, filtered, and evaporated *in vacuo* to yield the crystalline product. Recrystallization from hexane afforded an analytical sample as colorless prisms: mp 86–87°; yield 14.6 g (85%); $\nu_{max}^{CHCl_3}$ 3240 cm^{-1} (broad, O–H); nmr (in $CDCl_3$), at τ 2.82 (s, C_6H_5), 5.10 (s, OH), 6.14 (partially hidden triplet, CH_2CH_2–O), 6.23 (s, $(ArCH_2)_2N$), 8.18 (t, CH_2CH_2–O), 8.88 (s, $(CH_3)_2C$–N).

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.43; H, 8.88; N, 4.89.

N-(4-Chloro-2-methyl-2-butyl)dibenzylamine Hydrochloride (17).—A solution of 14.2 g (0.05 mol) of 3-dibenzylamino-3-methyl-1-butanol (**16**) in 35 ml of chloroform was added dropwise with stirring to 11.9 g (0.10 mol) of thionyl chloride cooled in an ice bath. The ice bath was removed following the addition, and the reaction was allowed to proceed at room temperature for 6 hr. At the end of this time, 5 ml of ethanol was added to decompose any residual thionyl chloride. Evaporation of the resulting mixture *in vacuo* yielded an oil which was taken up in ethanol and treated with excess ether to precipitate 16.6 g (98%) of the desired salt. Recrystallization from ethyl methyl ketone afforded an analytical sample as a white amorphous powder: mp 156–157°; nmr (in $CDCl_3$), at 2.4–3.0 (m, C_6H_5), 5.3–6.2 (m, $(ArCH_2)_2N^+$), 6.32 (t, CH_2CH_2–Cl), 7.31 (t, CH_2CH_2–Cl), 8.23 (s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_{19}H_{25}Cl_2N$: C, 67.45; H, 7.45; N, 4.14. Found: C, 67.43; H, 7.54; N, 3.85.

Attempted Cyclization of N-(4-Chloro-2-methyl-2-butyl)dibenzylamine (18).—A mixture of 2.70 g (8.0 mmol) of N-(4-chloro-2-methyl-2-butyl)dibenzylamine hydrochloride (**17**) and 15 ml of 3% aqueous sodium hydroxide was extracted with methylene chloride. Following the normal work-up procedure, there was obtained 2.39 g (99%) of free **N-(4-chloro-2-methyl-2-butyl)dibenzylamine (18)** as colorless crystals; nmr (in $CDCl_3$) signals appeared at τ 2.79 (s, C_6H_5), 6.30 (singlet over triplet, $(ArCH_2)_2N$ and CH_2CH_2–Cl), 7.96 (t, CH_2CH_2–Cl), 8.95 (s, $(CH_3)_2C$–N).

This amino chloride was dissolved in 30 ml of acetone and added to a stirred solution of 1.65 g (7.9 mmol) of silver perchlorate in 30 ml of acetone. The resulting mixture was stirred at room temperature for 44 hr, during which time silver chloride precipitated slowly and continuously. The silver chloride was subsequently removed by filtration and the filtrate was evaporated *in vacuo* to yield a turbid oil. This was treated with methylene chloride and refiltered to remove residual silver salts. Removal of the methylene chloride *in vacuo* yielded an oil which was dissolved in hot ethyl acetate and treated with ether to precipitate 0.50 g (17%) of **N-(4-chloro-2-methyl-2-butyl)dibenzylamine perchlorate (19)**. An analytical sample, colorless prisms from ethyl acetate, had mp 161.5–162.0°; ν_{max}^{Nujol} 3080 cm^{-1} (shoulder, N^+–H); nmr (in CF_3COOH), at τ 2.5–3.0 (m, C_6H_5), 5.16 and 5.64 (AB system split into doublets, J_{AB} = 13.6 cps, J_{vic} = 3.3 cps, $J_{vic'}$ = 6.5 cps, $(ArCH_2)_2N^+H$), 6.12 (t, CH_2CH_2–Cl), 7.39 (t, CH_2CH_2–Cl), 8.25 (s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_{19}H_{25}Cl_2NO_4$: C, 56.72; H, 6.26; N, 3.48; Cl, 17.63. Found: C, 56.86; H, 6.30; N, 3.25; Cl, 17.73.

Reaction of 1-Benzyl-2,2-dimethylazetidine Perchlorate (9b) with Diazomethane.—An ethereal solution of diazomethane was added in small aliquots to a stirred solution of 1.00 g (3.63 mmol) of the azetidine perchlorate in 40 ml of acetonitrile maintained at 0–5°. As the diazomethane solution was added, decolorization occurred, and bubbles of nitrogen were evolved from the reaction mixture. When the yellow color finally persisted, the addition was terminated and the resulting solution was stirred at 0° for 30 min. A small amount of glacial acetic acid was then added to remove excess diazomethane, and the acetonitrile was removed *in vacuo*. Treatment of the residue with ethyl acetate afforded 534 mg (51%) of **1-benzyl-1,2,2-trimethylazetidinium perchlorate (3)**, mp 140–141°, identified by its infrared spectrum (Nujol).

Attempted Reaction of Azetidine Salt 9b with Phenyldiazomethane.—A solution of 1.13 g (9.6 mmol) of phenyldiazomethane, prepared according to the precedure of Farnum,[38] in 30 ml of acetonitrile was added dropwise with stirring to a solution of 2.48 g (9.0 mmol) of the azetidine perchlorate in 70 ml of acetonitrile. There was no visible evolution of nitrogen during the addition. The reaction mixture was stirred at room temperature for 5 hr and was then treated with a small amount of glacial acetic acid to decompose unreacted phenyldiazomethane. The acetonitrile was removed *in vacuo;* then the residue was treated with ethyl acetate to yield 1.81 g (73% recovery) of starting material, mp 150–151°.

N-(3-Chloropropyl)piperidine Hydrochloride (20).—A solution of 10.0 g (0.07 mol) of N-(3-hydroxypropyl)piperidine (available from the Aldrich Chemical Co., Inc.) in 20 ml of chloroform was added dropwise with stirring to 16.7 g (0.14 mol) of thionyl chloride cooled in an ice bath. Following the addition, the mixture was warmed to room temperature and was stirred for 15 hr. The product was subsequently precipitated by the addition of 100 ml of ether. Recrystallization from ethyl acetate–isopropyl alcohol afforded an analytical sample as colorless needles: mp 225–226° (lit.[31] mp 215–216°); yield 11.4 g (83%); nmr (in D_2O), at τ 5.6–6.8 (complex multiplets, CH_2–N^+–CH_2, CH_2–N^+, and CH_2–Cl), 7.0–8.2 (complex multiplets, C–CH_2–C and C–$(CH_2)_3$–C).

Anal. Calcd for $C_8H_{17}Cl_2N$: C, 48.50; H, 8.64; N, 7.07. Found: C, 48.30; H, 8.60; N, 6.91.

4-Azoniaspiro[3.5]nonane Perchlorate (21). A. From N-(3-Chloropropyl)piperidine and Silver Perchlorate.—Treatment of 8.0 g (0.04 mol) of N-(3-chloropropyl)piperidine hydrochloride

(38) D. G. Farnum, *J. Org. Chem.*, **28**, 870 (1963).

(20) with 100 ml of 4% aqueous sodium hydroxide liberated the free chloropropylpiperidine, which was extracted into methylene chloride and isolated in the usual manner. This was dissolved in 100 ml of acetone and added to a stirred solution of 8.3 g (0.04 mol) of silver perchlorate in 100 ml of acetone. Silver chloride slowly precipitated as a fine black powder. The mixture was stirred for 48 hr with intermittent heating in a warm water bath (50–60°). Subsequent filtration of the silver chloride and evaporation of the filtrate solvent *in vacuo* yielded an oily residue which solidified upon treatment with isopropyl alcohol. Recrystallization from isopropyl alcohol afforded the product as colorless needles: mp 172–173°; yield 4.3 g (48%); nmr (in D_2O), at τ 5.32 (t, azetidinium CH_2–N^+), 6.10 (m, piperidinium CH_2–N^+), 6.6–7.2 (m, C–CH_2–C), 7.5–8.1 (unresolved multiplet, C–$(CH_2)_3$–C).

Anal. Calcd for $C_8H_{16}ClNO_4$: C, 42.57; H, 7.15; N, 6.21. Found: C, 42.75; H, 7.21; N, 5.99.

B. From N-(3-Chloropropyl)piperidine at 100°.—A mixture of 2.39 g (14.8 mmol) of N-(3-chloropropyl)piperidine (liberated from 3.03 g of the hydrochloride salt **20** as described above) and 25 ml of water was heated at 100° for 5 hr. Subsequent removal of the water *in vacuo* afforded 2.65 g of **4-azoniaspiro[3.5]nonane chloride** (**22**, X = Cl) as a syrup, presumably in a hydrated form. A picrate prepared from this material crystallized from 95% ethanol as yellow needles, mp 239–240° (lit.[26] mp 239–240°).

A solution of 1.07 g of the hydrated chloride **22** in 20 ml of methanol was treated with 1.24 g (6.0 mmol) of silver perchlorate in 10 ml of methanol, precipitating silver chloride immediately. The resulting mixture was stirred for 1 hr and was then filtered. Evaporation of the filtrate *in vacuo* afforded a dark solid, which was treated with methylene chloride and refiltered to remove residual silver salts. Removal of the methylene chloride *in vacuo* yielded the desired quaternary perchlorate, which was recrystallized from isopropyl alcohol as colorless needles (1.05 g), mp 170–171°. Infrared and nmr spectra of this salt were identical with those of the product obtained by procedure A.

Attempted Methanolysis of 1,1,2,2-Tetramethylazetidinium Perchlorate (2).—A solution of 500 mg (2.34 mmol) of the azetidinium salt in 25 ml of methanol was heated under reflux for 35 hr. The solvent was then removed *in vacuo* to yield 498 mg of solid material. Recrystallization from methanol–ether afforded 253 mg (51% recovery) of starting material, mp 173–174°. The mother liquor from the recrystallization was evaporated *in vacuo* to yield 174 mg of an impure solid, mp 114–140°. The nmr spectrum of this material (in CF_3COOH) indicated that it was primarily starting material; no methanolysis product could be detected.

Reaction of Azetidinium Salt 2 with Sodium Methoxide.—A mixture of 500 mg (2.34 mmol) of the azetidinium salt and 1.10 g (20.4 mmol) of sodium methoxide in 30 ml of methanol was stirred at room temperature for 3 days. The mixture was then acidified with ethereal hydrogen chloride and evaporated *in vacuo*. Treatment of the residue with excess 6% aqueous sodium hydroxide liberated an amine which was extracted into ether. The extracts were dried over anhydrous potassium carbonate and filtered, and most of the ether was removed by slow distillation through a 6-in. Vigreux column. The residual liquid was determined (by nmr analysis) to be a mixture of ether and 176 mg (67%) of **N-(3-methyl-3-buten-1-yl)dimethylamine (24)**; nmr (in $CDCl_3$) signals appeared at τ 5.28 (apparent singlet, C=CH_2), 7.6–7.8 (partially hidden multiplet, C–CH_2CH_2–N), 7.78 (s, $(CH_3)_2N$), 8.26 (s, CH_3–C=C).

Attempted Reaction of Azetidinium Salt 2 with Acetone.—A solution of 500 mg (2.34 mmol) of the azetidinium perchlorate in 40 ml of acetone was heated under reflux for 5 days. The acetone was subsequently removed *in vacuo*. Treatment of the residue with ether afforded 495 mg (99%) of starting material, mp 172–173°.

Attempted Hydrogenolysis of Azetidinium Salt 2.—A suspension of 500 mg (2.34 mmol) of the azetidinium salt in 75 ml of ethanol was shaken under 3 atm of hydrogen for 25 hr in the presence of 250 mg of Adams catalyst. The mixture was then filtered and the catalyst was washed with acetonitrile to dissolve the crystalline material present. Removal of the solvents *in vacuo* afforded 472 mg (94% recovery) of starting material, mp 173–175°.

Methanolysis of 1-Benzyl-1,2,2-trimethylazetidinium Perchlorate (3).—A solution of 1.00 g (3.46 mmol) of the azetidinium perchlorate in 25 ml of methanol was heated under reflux for 16 hr. Removal of the solvent *in vacuo* and trituration of the residue with ether afforded 1.05 g of crude product. Two recrystallizations from ethyl acetate–ether yielded an analytical sample of **N-(3-methoxy-3-methylbutyl)-N-methylbenzylamine perchlorate (25a)** as colorless needles: mp 113.0–113.5°; ν_{max}^{Nujol} 3070 cm^{-1} (shoulder, N^+–H); nmr (in CF_3COOH), at τ 2.42 (s, C_6H_5), 5.60 (d, J = 5.5 cps, $ArCH_2$–N^+), 6.2–6.7 (unresolved multiplet, CH_2CH_2–N^+), 6.65 (s, CH_3–O), 6.96 (d, J = 5.0 cps, CH_3–N^+), 7.90 (t, CH_2CH_2–N^+), 8.65 and 8.85 (s, s, $(CH_3)_2C$–O).

Anal. Calcd for $C_{14}H_{24}ClNO_5$: C, 52.25; H, 7.52; N, 4.35. Found: C, 52.54; H, 7.70; N, 4.19.

Treatment of the crude methanolysis product with 3% aqueous sodium hydroxide liberated an amine mixture which was extracted into methylene chloride and isolated as usual. Glpc analysis (200°) and nmr spectra of the mixture indicated the presence of two components, **N-(3-methoxy-3-methylbutyl)-N-methylbenzylamine (27a)** (68%) and **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine (29)** (32%). The amino ether exhibited nmr (in $CDCl_3$) signals at τ 2.76 (s, C_6H_5), 6.58 (s, $ArCH_2$–N), 6.93 (s, CH_3–O), 7.4–7.8 (partially hidden multiplet, CH_2CH_2–N), 7.88 (s, CH_3–N), 8.40 (partially hidden triplet, CH_2CH_2–N), 8.92 (s, $(CH_3)_2C$–O); no signal ascribable to CH_2–O was detected.

Nmr Study of the Methanolysis of Azetidinium Salt 3.—A suspension of 2.00 g (6.92 mmol) of the azetidinium perchlorate in 50 ml of methanol was prepared (t = 0) and heated rapidly to reflux temperature. Aliquots (3.0 ml) were removed from the reaction mixture every 30 min for the first 3 hr, and every 60 min thereafter. Each aliquot was immediately placed in a test tube chilled in an ice bath so as to precipitate any azetidinium salt present and thus effectively quench the reaction. Following refrigeration for a short period, the methanol was removed from each aliquot *in vacuo* at room temperature. Nmr spectra (in CF_3COOH) of the resulting solids were then obtained to determine the composition of the mixtures. The spectrum of each fraction was run as soon as possible after the addition of trifluoroacetic acid because of the lability of the reaction products, N-(3-methoxy-3-methylbutyl)-N-methylbenzylamine perchlorate (**25a**) and N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine perchlorate (**28**), in that solvent. The composition of each fraction was determined as follows: (a) the singlet at τ 6.65 (CH_3–O in **25a**) provided a direct measure of **25a**; (b) the combined signals at τ 7.8–8.0 (CH_2CH_2–N^+ in **25a** and three protons of $(CH_3)_2C$–N^+ in **3** provided a measure of **25a** + **3** and therefore, by difference, a measure of **3**; (c) the singlet at τ 2.4–2.5 (C_6H_5 in **3**, **25a**, and **28**) provided a measure of all three components combined and thus, by difference, a measure of **28**. The calculated molar percentage compositions of each fraction are given in Table II,

Table II

Composition of the Reaction Mixture during the Methanolysis of Azetidinium Salt 3

Time, hr	[3], mole %	[25a], mole %	[28], mole %
0.5	92	8	0
1.0	76	21	3
1.5	62	30	8
2.0	51	38	11
2.5	41	45	14
3.0	31	52	17
4.0	21	57	22
5.0	12	64	24
6.0	15	65	20
7.0	5	68	27
8.0	2	69	29
9.0	4	73	23
10.0	2	72	26
11.0	1	74	25
12.0	0	74	26
13.0	0	76	24

and these data are plotted as a function of time in Figure 2. Certain deficiencies in the analytical procedure may be noted. Thus, zero time corresponded to the mixing of reactants at room temperature, and a finite amount of time was required to bring the system to reflux. The apparent continuing increase in the concentration of **25a** after 8 hr is probably not real since there is

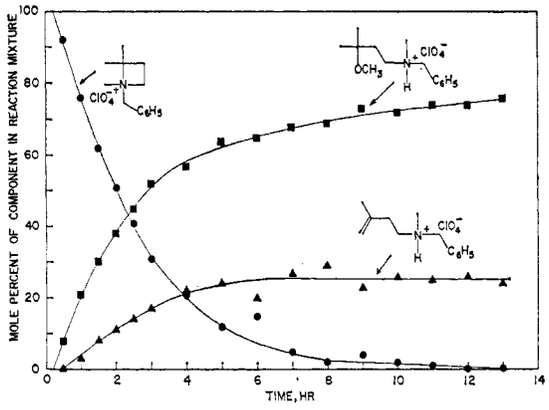


Figure 2.—Methanolysis of 1-benzyl-1,2,2-trimethylazetidinium perchlorate at reflux (~65°).

no accompanying increase or decrease in the concentration of **28** after that time. Nevertheless, it was readily determined from these data that the reaction is essentially complete after 8 hr, and that the methanolysis proceeds at a rate approximately three times that of the thermal elimination.

Ethanolysis of Azetidinium Salt 3.—A suspension of 1.00 g (3.46 mmol) of the azetidinium perchlorate in 50 ml of ethanol was heated under reflux with stirring for 28 hr. Subsequent removal of the solvent *in vacuo* yielded an oil which was taken up into ethyl acetate. Addition of ether precipitated 0.51 g of crude product. Recrystallization from ethyl acetate–ether afforded an analytical sample of **N-(3-ethoxy-3-methylbutyl)-N-methylbenzylamine perchlorate (25b)** as colorless prisms: mp 74–75°; $\nu_{max}^{CHCl_3}$ 3070 cm^{-1} (shoulder, N$^+$–H); nmr (in $CDCl_3$), at τ 2.52 (s, C_6H_5), 5.57 (d, J = 5.0 cps, $ArCH_2$–N$^+$), 6.4–6.9 (hidden multiplet, CH_2CH_2–N$^+$), 6.61 (q, CH_3CH_2–O), 7.01 (d, J = 4.5 cps, CH_3–N$^+$), 8.10 (unresolved triplet, CH_2CH_2–N$^+$), 8.80 and 8.96 (s, s, $(CH_3)_2$C–O), 8.88 (partially hidden triplet, CH_3CH_2–O).

Anal. Calcd for $C_{15}H_{26}ClNO_5$: C, 53.65; H, 7.80; N, 4.17. Found: C, 53.75; H, 7.86; N, 4.08.

The crude ethanolysis product was treated with 5% aqueous sodium hydroxide, and the amine mixture thus liberated was extracted into ether and worked up as usual. Glpc analysis (200°) and nmr spectra of this mixture demonstrated the presence of two components, **N-(3-ethoxy-3-methylbutyl)-N-methylbenzylamine (27b)** (58%) and **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine (29)** (42%). The amino ether exhibited nmr (in $CDCl_3$) signals at τ 2.71 (s, C_6H_5), 6.51 (s, $ArCH_2$–N), 6.67 (partially hidden quartet, CH_3CH_2–O), 7.3–7.7 (partially hidden multiplet, CH_2CH_2–N), 7.81 (s, CH_3–N), 8.2–8.5 (partially hidden triplet, CH_2CH_2–N), 8.86 (s, $(CH_3)_2$C–O), 8.91 (t, CH_3CH_2–O).

Reaction of Azetidinium Salt 3 with Sodium Methoxide.—A mixture of 1.00 g (3.46 mmol) of the azetidinium perchlorate and 1.60 g (29.6 mmol) of sodium methoxide in 30 ml of acetonitrile was stirred at room temperature for 18 hr. At the end of this time, the mixture was treated with aqueous sodium hydroxide and extracted with ether. Drying of the extracts over anhydrous potassium carbonate and evaporation of the solvent *in vacuo* afforded **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine (29)** as a yellow oil; nmr (in CCl_4) signals appeared at τ 2.82 (s, C_6H_5), 5.34 (apparent singlet, C=CH_2), 6.59 (s, $ArCH_2$–N), 7.4–8.0 (partially hidden multiplet, C–CH_2–CH_2–N), 7.89 (s, CH_3–N), 8.32 (s, CH_3–C=C).

Reaction of Azetidinium Salt 3 with Acetone.—A solution of 2.00 g (6.91 mmol) of the azetidinium salt in 50 ml of acetone was heated under reflux for 6 days. Subsequent removal of the solvent *in vacuo* afforded an oil which eventually crystallized after repeated treatments with ether. Chromatography on silica gel using ethyl acetate for elution yielded 0.79 g (40%) of **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine perchlorate (28)**. An analytical sample, colorless plates from ethyl acetate–ether, had mp 107–109°; $\nu_{max}^{CHCl_3}$ 3070 (shoulder, N$^+$–H), 1650, 905 cm^{-1} (C=CH_2); nmr (in $CDCl_3$), at τ 2.55 (s, C_6H_5), 5.20 (apparent singlet, C=CH_2), 5.61 (d, J = 5.5 cps, $ArCH_2$–N$^+$), 6.4–6.9 (m, C–CH_2CH_2–N$^+$), 7.07 (d, J = 4.5 cps, CH_3–N$^+$), 7.51 (t, C–CH_2–CH_2–N$^+$), 8.32 (s, CH_3–C=C).

Anal. Calcd for $C_{13}H_{20}ClNO_4$: C, 53.88; H, 6.96; N, 4.83. Found: C, 54.12; H, 7.15; N, 4.59.

Reaction of Azetidinium Salt 3 with Acetonitrile.—A solution of 500 mg (1.73 mmol) of the azetidinium perchlorate in 50 ml of acetonitrile was heated under reflux for 3 days. The acetonitrile was then removed *in vacuo*, and the residue was treated with ether and filtered to yield 483 mg (97%) of **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine perchlorate (28)**.

Reaction of Azetidinium Salt 3 with Sodium Iodide.—A mixture of 870 mg (3.0 mmol) of the azetidinium salt and 750 mg (5.0 mmol) of sodium iodide in 60 ml of acetone was heated under reflux with stirring for 22 hr. The acetone was then removed *in vacuo*, and the residual mixture was treated with 6% aqueous sodium hydroxide and extracted with ether. The combined extracts were dried over anhydrous potassium carbonate and evaporated to yield 562 mg (99%) of **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine (29)**, identified by its nmr spectrum (in $CDCl_3$).

4,5,5-Trimethyl-Δ^1-pyrroline 1-Oxide (30a) and 5,5-Dimethyl-Δ^1-pyrroline 1-Oxide (30b).—The procedure of Bonnett, *et al.*,[33] involving reductive cyclization of the corresponding γ-nitroaldehydes, was employed. These nitrones were stored at 5° under nitrogen to minimize decomposition.

General Procedure for the Formation of Nitrone–Azetidinium Salt Adducts.—1-Benzyl-1,2,2-trimethylazetidinium perchlorate (**3**) was added in portions to an excess of nitrone, and the two reactants were mixed as thoroughly as possible. There was no perceptible heat evolved during this mixing. The reaction was allowed to proceed for 9 days at room temperature with periodic shaking. At the end of this time, the azetidinium salt had dissolved completely. The mixture was then heated at 60° for 12 hr to push the reaction to completion. Treatment with excess ethyl acetate precipitated the adduct in a form sufficiently pure for most purposes.

A mixture of 2.90 g (10.0 mmol) of the azetidinium salt and 10.2 g (80.5 mmol) of 4,5,5-trimethyl-Δ^1-pyrroline-1-oxide (**30a**) yielded 2.05 g (49%) of **6-benzyl-3,3,6,9,10,10-hexamethyl-2-oxa-1-aza-6-azoniabicyclo[5.3.0]decane perchlorate (31a)**. The analytical sample, colorless needles from isopropyl alcohol, had mp 164.0–164.5°; no infrared maxima corresponding to O–H or N$^+$–H; nmr (in $CDCl_3$), at τ 2.52 (s, C_6H_5), 5.46 (s, $ArCH_2$–N$^+$), 5.62 (partially hidden unresolved multiplet, N–CH–N$^+$), 6.51 (m, CH_2CH_2–N$^+$), 6.91 (s, CH_3–N$^+$), 7.3–8.5 (several multiplets, CH_2CH_2–N$^+$ and CH_3–CH–CH_2), 8.7–9.2 (several signals, $(CH_3)_2$C–O, $(CH_3)_2$C–N, and CH_3–CH).

Anal. Calcd for $C_{20}H_{33}ClN_2O_5$: C, 57.61; H, 7.98; N, 6.72. Found: C, 57.68; H, 8.14; N, 6.87.

From 1.45 g (5.0 mmol) of the azetidinium perchlorate and 4.52 g (40.0 mmol) of 5,5-dimethyl-Δ^1-pyrroline-1-oxide (**30b**) there was obtained 0.83 g (41%) of **6-benzyl-3,3,6,10,10-pentamethyl-2-oxa-1-aza-6-azoniabicyclo[5.3.0]decane perchlorate (31b)**. An analytical sample, colorless needles from isopropyl alcohol, had mp 157–158° dec; no O–H or N$^+$–H bands in the infrared spectrum; nmr (in $CDCl_3$), at τ 2.53 (s, C_6H_5), 5.47 (s, $ArCH_2$–N$^+$), 5.61 (partially hidden unresolved multiplet, N–CH–N$^+$), 6.51 (m, CH_2CH_2–N$^+$), 6.93 (s, CH_3–N$^+$), 7.5–8.6 (several multiplets, CH_2CH_2–N$^+$ and C–CH_2CH_2–C), 8.80 and 8.93 (s, s, $(CH_3)_2$C–O and $(CH_3)_2$C–N).

Anal. Calcd for $C_{19}H_{31}ClN_2O_5$: C, 56.63; H, 7.75; N, 6.95. Found: C, 56.80; H, 7.59; N, 6.75.

Lithium Aluminum Hydride Reduction of Adduct 31a.—To a stirred slurry of 380 mg (10.0 mmol) of lithium aluminum hydride in 25 ml of 1,2-dimethoxyethane was added 1.25 g (3.0 mmol) of adduct **31a**. The mixture was heated under reflux for 26 hr and was treated subsequently with 0.76 ml of water and 0.61 ml of 10% aqueous sodium hydroxide. The salts thus precipitated were filtered and washed with hot solvent. The filtrate was then acidified with aqueous hydrochloric acid and evaporated *in vacuo*. Treatment of the residue with 25% aqueous sodium hydroxide liberated a free amine which was extracted into ether. The combined extracts were dried over anhydrous potassium carbonate and evaporated *in vacuo* to yield 926 mg (97%) of **N-methyl-N-[3-methyl-3-(2′,2′,3′-trimethylpyrrolidin-1′-oxy)butyl]benzylamine (32a)** as a yellow oil: no O–H or N–H bands in the infrared spectrum; nmr (in $CDCl_3$), at τ 2.70 (s, C_6H_5), 6.50 (s, $ArCH_2$–N), 6.7–7.3 (unresolved multiplet, CH_2–N–O), 7.3–7.7 (m, CH_2–N(CH_3)–CH_2Ar), 7.81 (s, CH_3–N), 8.1–8.6 (m, $(CH_3)_2$–C–CH_2 and CH_3–CH–CH_2), 8.85 (s, $(CH_3)_2$C–O), 8.98 and 9.20 (s, s, $(CH_3)_2$C–N), 9.12 (partially hidden doublet, J = 6.5 cps, CH_3–CH).

Zinc–Acetic Acid Reduction of 32a.—Activated zinc dust[39] (5.0 g, 77 mg-atoms) was added in portions to a solution of 913 mg (2.9 mmol) of **32a** in 30 ml of 50% aqueous acetic acid. The resulting mixture was then heated at 100° with vigorous stirring for 50 hr. At the end of this time, the residual zinc dust was filtered and washed with water. The filtrate was acidified with 3 ml of concentrated hydrochloric acid and was evaporated *in vacuo*. Upon treatment of the residue with excess 25% aqueous sodium hydroxide, an amine mixture was liberated. This was extracted into ether and the combined extracts were dried over anhydrous potassium carbonate. The ether was then removed by slow distillation through a 6-in. Vigreux column. Glpc analysis (80–200°) of the residual liquid demonstrated the presence of two major components, the retention times of which were found to be identical with those of authentic **2,2,3-trimethylpyrrolidine** (**33**) and **4-(N-benzyl-N-methylamino)-2-methyl-2-butanol** (**34**). Integration of the glpc trace indicated that the yields of the trimethylpyrrolidine and the amino alcohol were 94% and quantitative, respectively.[40] Small samples of both components were collected (70–200°). The infrared and nmr spectra of these compounds proved to be identical in all respects with those of authentic **33** and **34**.

2,2,3-Trimethylpyrrolidine (**33**) was prepared as described previously[1] by deoxygenation of nitrone **30a** with triphenylphosphine followed by lithium aluminum hydride reduction of the intermediate 4,5,5-trimethyl-Δ^1-pyrroline.

Methyl 3-(N-Benzyl-N-methylamino)propionate (**35**).—A solution of 34.4 g (0.40 mol) of methyl acrylate and 52.0 g (0.43 mol) of benzylmethylamine in 150 ml of methanol was allowed to stand at room temperature for 9 days. The methanol was then removed *in vacuo* and the residue was distilled to yield 77.2 g (93%) of the amino ester as a clear colorless liquid: bp 73–75° (0.001 mm); ν_{max}^{film} 1745 cm^{-1} (C=O); nmr (in $CDCl_3$), at τ 2.75 (s, C_6H_5), 6.40 (s, CH_3–O), 6.54 (s, $ArCH_2$–N), 7.41 (A_2B_2 system, C–CH_2CH_2–N), 7.85 (s, CH_3–N).

Anal. Calcd for $C_{12}N_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.57; H, 8.35; N, 6.90.

4-(N-Benzyl-N-methylamino)-2-methyl-2-butanol (**34**).—To 7.3 g (0.30 g-atom) of magnesium turnings under nitrogen was added a small portion of a solution of 45.5 g (0.32 mol) of methyl iodide in 150 ml of ether. As soon as a turbidity began to develop, stirring was started, and the initial vigorous reaction was moderated by cooling in an ice bath. The remainder of the methyl iodide solution was then added dropwise at a rate such that gentle reflux was maintained. The resulting solution was treated with an additional 50 ml of ether and was stirred for 1 hr at room temperature. A solution of 10.4 g (0.05 mol) of methyl 3-(N-benzyl-N-methylamino)propionate (**35**) in 100 ml of ether was then added dropwise with stirring. Following this addition, the mixture was heated under reflux for 5 hr. Work-up was effected by cooling the mixture in an ice bath and adding saturated aqueous ammonium chloride dropwise with stirring until the precipitate of magnesium salts became granular. The precipitate was filtered and washed thoroughly with ether. The filtrate was then dried over anhydrous potassium carbonate and evaporated *in vacuo*. Distillation of the residue through a 12-in. spinning-band column afforded 2.36 g (23%) of the amino alcohol as a clear colorless oil: bp 66–67° (0.025 mm); ν_{max}^{film} 3350 (broad, O–H), 1167 cm^{-1} (C–O); nmr (in $CDCl_3$), at τ 2.72 (s, C_6H_5), 4.12 (s, OH), 6.50 (s, ACH_2–N), 7.32 and 8.38 (A_2X_2 system, C–CH_2CH_2–N), 7.79 (s, CH_3–N), 8.86 (s, $(CH_3)_2$C–O).

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.20; H, 10.22; N, 6.96.

(39) Fischer reagent grade zinc dust was treated successively with 2% aqueous hydrochloric acid, water, 95% ethanol, and ether. The metal thus activated was dried and stored in a vacuum desiccator.

(40) An integrated glpc trace was also obtained for a known mixture of authentic **33** and **34** so as to correct for the difference in detector response toward the two components.

Some Reactions of Methylpyrazines with Organolithium Reagents

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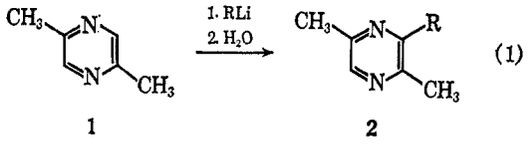
Reactions of isomeric dimethylpyrazines and trimethylpyrazine with methyllithium were studied in some detail. Evidence was found for hydropyrazine intermediates in the ring methylation of 2,5-dimethylpyrazine (**1**). Metalation of the side chain of **1** was observed, as well as ring methylation. In ether solvent vicinally dimethylated pyrazines gave products resulting exclusively from side-chain metalation. Subsequent alkylation and carbethoxylation of these metalated species gave low to moderate yields of side-chain-extended products. In hexane and benzene solvents 2,3-dimethylpyrazine underwent partial ring alkylation with ethyllithium and *n*-butyllithium to form trialkylpyrazines.

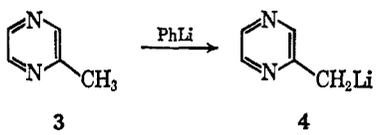
Methyl-substituted pyrazines react with organolithium reagents to form products resulting from ring alkylation (or arylation) and side-chain metalation.

Examples of ring alkylation were first reported by Spoerri[1,2] who found that 2,5-dimethylpyrazine (**1**) reacted to form 3-alkyl-2,5-dimethylpyrazines (**2**) (eq 1).



1 2 (1)

In the metalation reaction organolithium reagents attack the side chain of a methylpyrazine to form the corresponding pyrazylmethyllithium. Thus Levine[3] found that methylpyrazine (**3**) reacted with phenyllithium to produce pyrazylmethyllithium (**4**) (eq 2),



3 4 (2)

instead of products resulting from ring phenylation.

In contrast to the result obtained with **3**, no successful attempt to metalate the side chain of a dimethylpyrazine or trimethylpyrazine with an organolithium reagent has been reported. In fact it was only very recently that a monolithio derivative of tetramethylpyrazine was prepared.[4]

In the present study we investigated some reactions of dimethylpyrazines and trimethylpyrazine with organolithium reagents in order to learn more about the mechanism of ring alkylation, and also to gain further insight into factors involved in the competition between ring alkylation and side-chain metalation reactions.

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(2) B. Klein and P. E. Spoerri, *ibid.*, **73**, 2949 (1951).
(3) J. D. Behun and R. Levine, *ibid.*, **81**, 5157 (1959).
(4) S. K. Chakrabartty and R. Levine, *J. Heterocycl. Chem.*, **1**, 196 (1964).