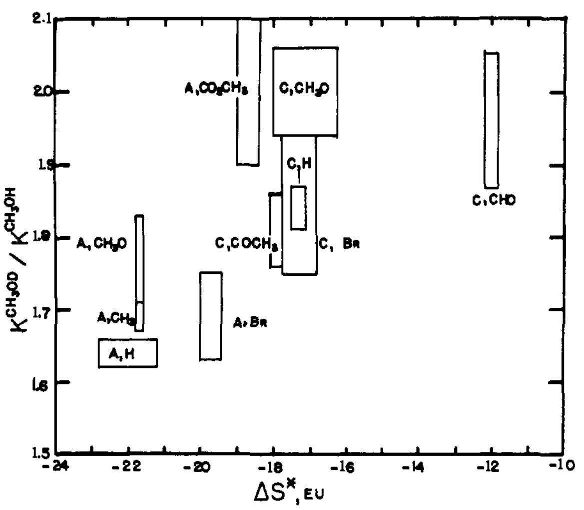

Figure 1. Solvent isotope effects *vs.* entropies of activation for the basic methanolysis of p-$XC_6H_4OCO_2CH_3$ (labeled C, X) and p-$XC_6H_4OCOCH_3$ (labeled A, X). In a general sense, the isotope effect becomes more inverse as ΔS^* becomes more positive.

cated by a decrease in entropy and by an increase in librational frequencies of solvent, thus giving an inverse solvent isotope effect. Second, such substituent effects on charge distribution in the activated complex as give rise to an increase in solvation entropy also, roughly speaking, produce a more inverse isotope effect. These effects apparently come from changes in hydrogen bonding and thus internal vibration frequencies of solvent molecules. The roughness of the second correlation may be due to the fact that, in reality, substituents act by means of both mechanisms. Another point worth noting is that, while entropy changes are (almost by definition) a good criterion of solvent-structure variations, solvent isotope effects may give less clear-cut indications about solvent structure.

Experimental Section

Materials. Esters were prepared as described previously.[1] Methanol-O-*d* was made from deuterium oxide (BioRad Laboratories), according to Streitwieser, Verbit, and Stang's procedure[14] for the acid-catalyzed hydrolysis of dimethyl carbonate. Manipulations were conducted in a glove box.

Kinetics. All measurements were made spectrophotometrically and data were reduced by a GE 625 computer as described before. Rates in CH_3OH and CH_3OD were determined successively within a 2-hr interval for each compound.

[14] A. Streitwieser, Jr., L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).

The Synthesis and Solvolysis of 4,7,7-Trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane[1,2]

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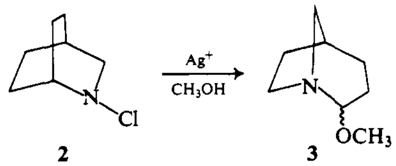
Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received November 4, 1968*

Abstract: 4,7,7-Trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane (**1**) has been prepared *via* an eight-step synthesis starting with *d*-camphor, in 43% over-all yield. In methanol at 70° **1** solvolyzed with a half-life of *ca.* 83 min. In the presence of silver perchlorate, **1** solvolyzed in methanol at room temperature with a half-life of less than 1 min demonstrating that silver ion catalysis could account for a rate acceleration of at least 2×10^3. Both the thermal and silver ion catalyzed methanolysis of **1** produced a mixture of *exo*-2-chloro-3,3,4-trimethyl-1-azabicyclo[2.2.1]heptane and *exo*-2-methoxy-3,3,4-trimethyl-1-azabicyclo[2.2.1]heptane with the chlorine-containing product being formed in 77 and 59% yields in the silver ion catalyzed and thermal reactions, respectively. The mechanism of this unprecedented silver ion catalyzed internal return of chlorine is discussed.

The facile rearrangements which occur in bicyclic molecules made these systems excellent substrates for the study of alkyl migrations to trivalent electron-deficient carbon.[4] By analogy, certain azabicyclics should serve equally well as models for alkyl migration to a divalent electron-deficient nitrogen (nitrenium ion). The usefulness of this analogy has already been demonstrated by the silver ion catalyzed rearrangement of N-chloroisoquinuclidine (**2**) to 2-methoxy-1-azabicyclo[3.2.1]octane (**3**).[5] This rearrangement provided the first unequivocal evidence for the intermediacy of a divalent electron-deficient nitrogen species. In order to expand our sphere of knowledge in this area we next chose to study the fate of



2 **3**

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[1] Paper VII in a series on the chemistry of nitrenium ions. For the previous paper in this series see P. G. Gassman and D. K. Dygos, *J. Am. Chem. Soc.*, **91**, 1543 (1969).

[2] A preliminary communication describing part of this work has appeared; P. G. Gassman and R. L. Cryberg, *ibid.*, **90**, 1355 (1968).

[3] Alfred P. Sloan Foundation Research Fellow, 1967–1969.

[4] For a review of some of the rearrangements which occur in carbocyclic systems see J. A. Berson, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 111–232.

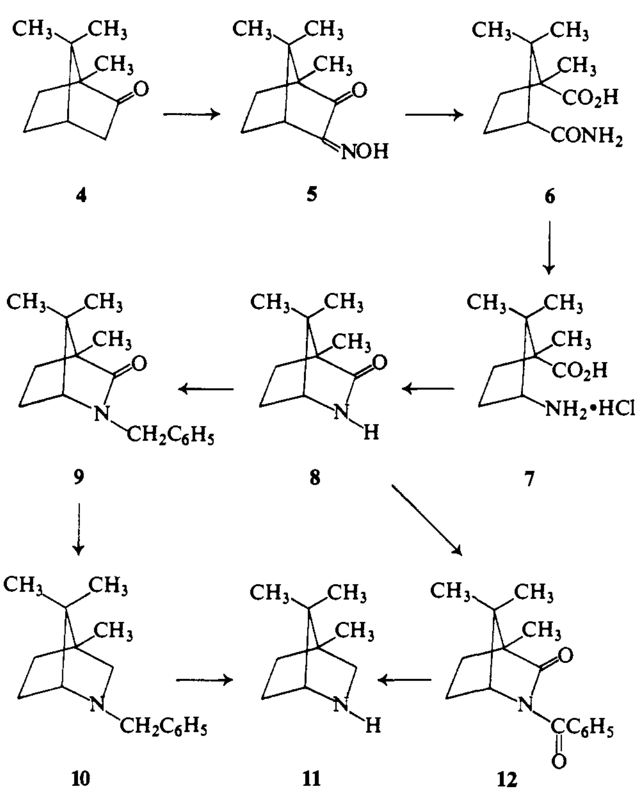
[5] P. G. Gassman and B. L. Fox, *J. Am. Chem. Soc.*, **89**, 338 (1967).

nitrenium ions generated in the 2-azabicyclo[2.2.1]heptyl ring system. This paper presents the details of our studies in this field.

Synthesis

We initially felt that the ideal ring system for obtaining a rapid alkyl migration to divalent electron-deficient nitrogen would have the 2-azabicyclo[2.2.1]heptyl structure. A perusal of the literature indicated that this desired ring system was virtually unknown.[6-8] Fortunately, the investigations of Noyes and coworkers[7] had resulted in the preparation of **8**, which appeared to be a desirable precursor for the synthesis of **11**. Thus, *d*-camphor (**4**) was treated[9] with sodium amide in liquid ammonia–ether solution to give the anion which on reaction with isoamyl nitrite produced isonitrosocamphor (**5**) in 93% yield (see Scheme I). Beckmann rearrangement[10] of **5** with concentrated hydrochloric acid gave α-camphoramidic acid (**6**) in 85% yield. Hofmann rearrangement of **6** with aqueous hypobromite gave a 90% yield of 1,2,2-trimethyl-*cis*-3-aminocyclopentanecarboxylic acid hydrochloride (**7**).[7,11] On reaction with an acetic anhydride–sodium acetate mixture **7** cyclized to give an N-acetyl lactam which on mild hydrolysis produced **8** in 80% yield from **7**.[12] Interestingly, lithium aluminum hydride reduction of **7** also produced **8** as the only detectable product, but the yield by this method was inferior to that described above.[13]

Scheme I

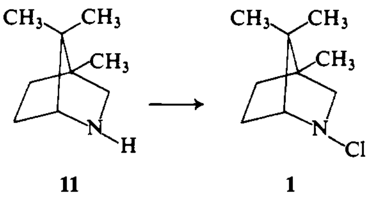


Having prepared **8** *via* modifications of the referenced literature procedures we thought that **11** would be readily accessible. However, the formation of only **8** in the lithium aluminum hydride reduction of **7** indicated that hydride reduction would not reduce **8** directly to **11**. Thus **8** was treated with sodium hydride, followed by benzyl chloride in tetrahydrofuran to give the N-benzyl lactam, **9**, in 90% yield. In contrast to the resistance of the carbonyl group of **8** to lithium aluminum hydride reduction, the carbonyl group of **9** was removed with this reagent in ether to give in 90% yield 2-benzyl-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (**10**). Hydrogenation of **10** over 5% Pd–C at 40–50 psig in ethanol followed by acidification with hydrochloric acid gave **11** as its hydrochloride, in virtually quantitative yield.

A second method for the conversion of **8** into **11** involved formation of the N-benzoyl derivative, **12**, followed by lithium aluminum hydride reduction of **12**. Unfortunately, the yields in these two steps (55 and 20%, respectively) were unsatisfactory. It should be noted that sodium borohydride reduction of **12** gave benzyl alcohol and **8** in high yield.

Solvolytic Studies

Having **11** in hand, we had only to substitute a suitable leaving group for the proton on nitrogen. This was readily accomplished by treating **11** with excess aqueous sodium hypochlorite which quantitatively produced **1** as a waxy, volatile, colorless solid. Iodometric analysis of **1** indicated that it was greater than 98% pure. In addition nmr and ir spectroscopy showed no detectable indication of **11** under conditions where less than 5% would have been very obvious.



Refluxing a solution of **1** in methanol gave *exo*-2-chloro-3,3,4-trimethyl-1-azabicyclo[2.2.1]heptane (**13**), *exo*-2-methoxy-3,3,4-trimethyl-1-azabicyclo[2.2.1]heptane (**14**), and 4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (**11**) in 59, 20, and 7% yields, respectively. When **1** was heated in methanol in a sealed tube at 70° it had a half-life of 83 min.[14] Thus, the rearrangement of **1** in refluxing methanol was reasonably slow. This behavior is in stark contrast to that observed when silver ion was added. We found that upon addition of 1.00 g of silver perchlorate to 50 ml of methanol containing 0.50 g of **1** an immediate reaction took place at room temperature with a half-life

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(6) The known derivatives of 2-azabicyclo[2.2.1]heptane are surprisingly few in number. Prior to work in our laboratory [P. G. Gassman and D. C. Heckert, *Tetrahedron*, **21**, 2725 (1965)] only three examples had been recorded in the literature.[7,8]

(7) W. A. Noyes, *J. Am. Chem. Soc.*, **16**, 500 (1894); W. A. Noyes and L. F. Nickell, *ibid.*, **36**, 118 (1914); W. A. Noyes and J. A. Cross, *ibid.*, **42**, 1280 (1920).

(8) G. Kresze and R. Albrecht, *Angew. Chem.*, **74**, 781 (1962); G. Kresze and R. Albrecht, *Ber.*, **97**, 490 (1964).

(9) F. S. Legagneur, *Ann. Chim.* (Paris), **7**, 385 (1927).

(10) L. Claissen and D. Manasse, *Ann.*, **274**, 78 (1893).

(11) G. S. Skinner, *J. Am. Chem. Soc.*, **45**, 1498 (1923).

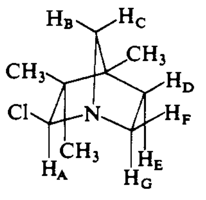
(12) W. A. Noyes and R. S. Potter, *ibid.*, **37**, 189 (1915).

(13) Ample precedent exists for the conversion of amino acids into lactams with lithium aluminium hydride: V. C. Barry, J. G. Belton, R. M. Kelley, and D. Twomey, *Nature*, **166**, 303 (1950).

(14) The half-life was determined by titrimetrically measuring the amount of unreacted N-chloramine.

of less than 1 min. This represented a rate acceleration due to the presence of silver ion of at least 2×10^3. The remarkable facet of this silver ion catalysis was that even though the reaction was drastically accelerated by the presence of silver ion the products remained the same. Even more surprising than the fact that the same three products, **13**, **14**, and **15**, were formed (in 78, 8, and 4% yields, respectively) was that the presence of silver ion increased the amount of **13** from 59 to 78%. Thus we have a reaction in which silver ion plays a dramatic part in the breaking of a nitrogen–chlorine bond but fails to form more than small amounts of silver chloride.[15] As a control reaction it was shown that freshly prepared silver chloride did not catalyze the rearrangement of **1**. Furthermore, we demonstrated that silver ion was essential by adding very small amounts of silver perchlorate to methanolic solutions of **1** at room temperature. Rapid reaction occurred until all of the silver ion was precipitated as silver chloride at which time the reaction virtually stopped. This reaction mixture still contained **1** after standing for 7 days at room temperature.

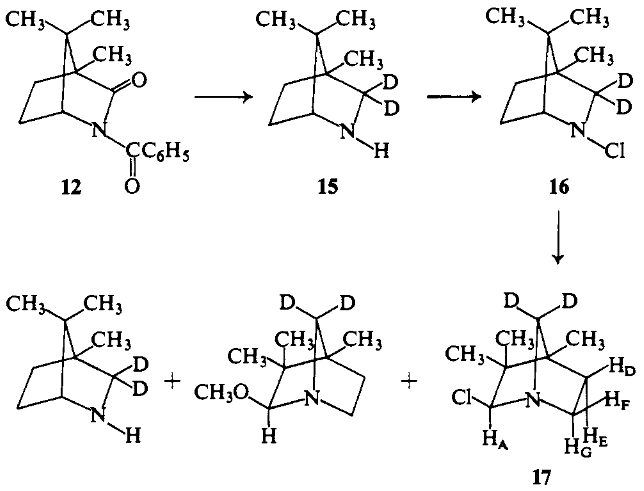
In order to determine if **14** was a primary product or if it arose from silver ion catalyzed solvolysis of **13**, pure **13** was subjected to the reaction conditions. Under the reaction conditions **13** was completely stable and no silver chloride was formed. Hence **14** must have been a primary reaction product.



13

The structure proofs for **13** and **14** rest primarily on spectroscopic data. In addition to having an elemental analysis corresponding to $C_9H_{16}NCl$, compound **13** showed no ionic or active chlorine indicating that a carbon–chlorine bond must have been formed. The crucial factor involved in the identification of the structure of **13** was its nmr spectrum (100 MHz).[16] Of particular interest in this structure proof was the one-proton doublet ($J_{AC} = 2.0$ Hz) which appeared at τ 5.42. This was assigned to the hydrogen on the chlorine-bonded carbon. The coupling constant indicated that H_A was an *endo* hydrogen[17] which was coupled to the C-7 *anti* hydrogen, H_c, which appeared at τ 7.85. Spin decoupling confirmed this assignment. The C-7 *anti* hydrogen was also coupled to the C-7 *syn* hydrogen ($J_{BC} = 10.2$ Hz) which occurred at τ 7.05. H_B was also coupled *via* long-range W-form coupling[17] to H_E and H_G ($J_{BE} = J_{BG} = 2.5$ Hz).

Formally, **13** could be derived from **1** *via* ionization of the N–Cl bond, Wagner–Meerwein rearrangement, and recapture of chloride. If this pattern of events were followed the proton initially at C-3 in **1** would end up at C-7 in **13**. These protons at C-3 of **1** originated from the lithium aluminum hydride reduction of the carbonyl group of **12**. As a result this position was readily labeled by using lithium aluminum deuteride instead of the corresponding hydride. The route *via* **12** was used instead of going through reduction of **9** in order to avoid any step involving catalytic reduction (which could give some deuterium scrambling). Thus lithium aluminum deuteride reduction gave **15** which was readily converted to **16**.



The silver ion catalyzed rearrangement of **16** gave the expected product mixture. The rearranged chloride, **17**, was isolated and purified, and its 100-MHz nmr spectrum recorded.[16] As anticipated H_A was now a sharp singlet, H_E and H_G were significantly simplified, and the signals originally due to the protons at C-7 in **13** were completely absent in **17**. This provided excellent confirmation of the structural assignment.

A comparison of the nmr spectra of **13** and **14** demonstrated that these two compounds have the same basic structure with the chloro group in **13** being replaced by the methoxyl group in **14**. The coupling of the *endo* proton at C-2 of **14** with the C-7 *anti* proton ($J = 2.0$ Hz) showed that the methoxyl function had the *exo* configuration in **14**.

Discussion

The rearrangement of **1** to give **13** and **14** represents a unique situation. In the nonsilver ion catalyzed methanolysis of **1** we can consider various mechanistic possibilities. The fact that the same products were obtained in both the nonsilver ion catalyzed reaction and in the silver ion catalyzed reaction indicated a similarity of mechanism under these two sets of conditions. The precipitation of small amounts of silver chloride in the silver ion catalyzed reaction demonstrates the formation of the chloride anion, and consequently implies the formation of a divalent electron-deficient nitrogen species.

Additional evidence for the formation of a nitrenium ion type intermediate was provided by the mere occurrence of alkyl migration from carbon to nitrogen. Since alkyl

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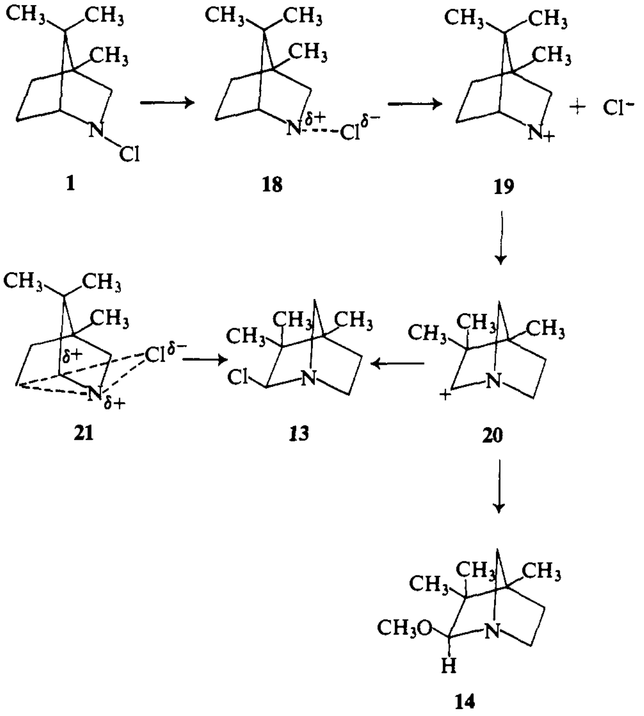
(15) To our knowledge no close analogy exists for this type of behavior. However a very unrelated case of a catalyzed rearrangement in which a migrating chlorine was never free has been reported [W. T. Miller, E. W. Fager, and P. H. Griswald, *J. Am. Chem. Soc.*, **72**, 750 (1950)]. In this case it was found that 1,1,2-trichloro-1,2,2-trifluoroethane rearranges to 1,1,1-trichloro-2,2,2-trifluoroethane with catalysis by radioactive labeled aluminum chloride, but *without incorporation of any of the labeled chlorine.*

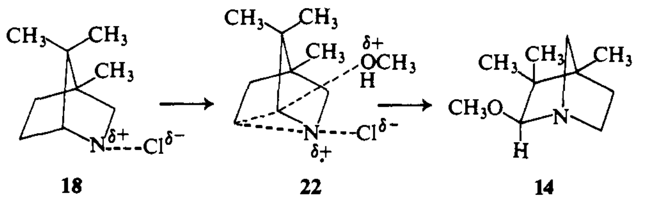
(16) For a reproduction of this spectrum see ref 2.

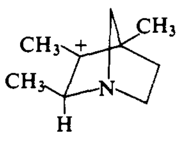
(17) Long-range W-form coupling has been previously discussed in relationship to the bicyclo[2.2.1]heptanes. In general, the coupling constants for 2-*endo* to 7-*anti* coupling vary from 2 to 4 Hz. J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *J. Am. Chem. Soc.*, **86**, 4074 (1964).

groups do not generally migrate to anionic or radical centers, the assumption that a cationic intermediate was present is a safe one. With this in mind we can view the initial stages of the nonsilver ion catalyzed reaction as involving a partial ionization of the N–Cl bond to place a partial positive charge on nitrogen and a partial negative charge on chlorine as shown in **18**. At this stage several possibilities exist: the ionization could proceed to give complete ionization of the N–Cl bond producing the nitrenium ion, **19**, and chloride anion; a concerted alkyl migration–loss of chloride ion could occur; or a concerted alkyl and chloro group migration could be envisaged as in **21**.



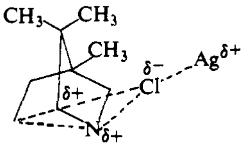
If we consider the first of these mechanisms we see that the discrete intermediacy of **19** would require subsequent rearrangement to **20**. The carbonium ion **20** could then partition itself between **13** and **14** through reaction with the chloride ion in solution or the solvent, respectively. The second possible route for **18** to follow would be direct alkyl migration–loss of chloride to produce the ion **20** without ever going through a distinct species where a unit positive charge resides on nitrogen, as in **19**. Since electronegativity arguments suggest that carbonium ions should be much more stable than nitrenium ions, this type of concerted formation of **20** is somewhat attractive. The last mechanism which calls for concerted C–N and C–Cl bond formation and C–C and N–Cl bond breakage is complicated in that it only explains the presence of **13**. Since this route can only produce **13**, an alternative mechanism would have to occur simultaneously which would account for the formation of the methyl ether, **14**. This concomitant reaction could involve either formation of **20**, which could then react with solvent to give **14**, or a pseudo S_N2′ reaction could occur in which methanol was adding as chloride ion was leaving as shown in the sequence **18** → **22** → **14**. This latter explanation might rationalize why no Nametkin type rearrangement occurs to yield what should be the very stable tertiary cation **23**.[18] However the presence of the *gem*-dimethyl groups at C-7 in **18** would make a transition state such as **22** extremely crowded from a steric point of view. Each of the mechanisms outlined has good and bad features. Unfortunately, no data are available which would justify a choice between these possibilities.





23

The most surprising feature of our studies of the solvolysis of **1** was that the silver ion catalyzed reaction gave **13**. Not only was it amazing that a reaction, in which breakage of the N–Cl bond was accelerated by a factor of 2×10^3 by the presence of silver ion, should yield a chlorine-containing product, but even more astonishing was the fact that *more chlorine-containing product was formed in the presence of silver ion than in the absence of silver ion.* We picture this silver ion catalyzed reaction as occurring *via* a transition state similar to **24**. In this case we feel that it is very likely that the migration of chlorine to carbon and of carbon to nitrogen was concerted. Clearly, if free chloride ion were formed it would have rapidly precipitated as silver chloride. By the transition state **24**, we wish to indicate that as the N–Cl bond is polarized and stretched, a partial positive charge is formed on nitrogen. At some point this charge becomes large enough that the alkyl group starts to migrate. Most of the time the chlorine which is still partially bonded to nitrogen is captured by the developing carbonium ion without ever becoming free of the skeleton. When the chlorine does become free of the molecule an ion such as **20** would be formed. In the absence of available chloride ion this species would be expected to react with methanol to give **14**.



24

The increase in chlorine retention in the silver ion catalyzed reaction in comparison to the thermal rearrange-

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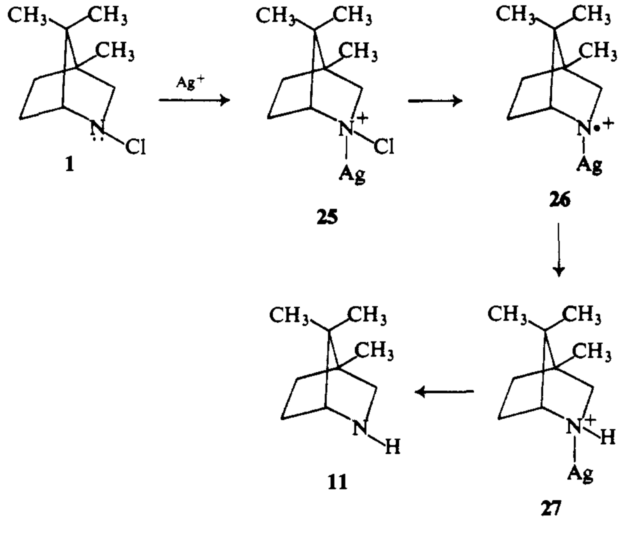
[18] Although this explanation appears reasonable, we have recently found that under very forcing conditions **13** can be converted into **14** with methanolic silver perchlorate at high temperature (R. L. Cryberg, unpublished work). Since **14** was the only product formed and since considerable positive charge must build up at C-2 (approaching or equal to that represented by **20**), the lack of methyl migration remains a dilemma.

ment merits discussion. In the absence of silver ion **1** was relatively stable. Even in refluxing polar solvent (methanol) the rearrangement was slow. This indicates to us that solvation should be extremely important in the ionization of the N–Cl bond when the solvent does not contain silver ion. In contrast the silver ion catalyzed reaction was extremely rapid even at room temperature. This implies that tight solvation of the ionizing N–Cl bond probably was not required. In a situation where extensive solvation is an important factor, such as in the nonsilver ion catalyzed solvolysis of **1**, the solvent molecules would be held in close proximity to the incipient carbonium ion which would result from the rearrangement of **1**. In contrast, the silver ion catalyzed reaction should have less solvent in a position to react with a developing carbonium ion for two reasons. First, in an extremely facile reaction over-all solvation is less important, and second, in the silver ion catalyzed reaction we have the added bulk of the silver ion shielding that side of the molecule from which methanol would have to add in order to yield **14**. Hence, the increased internal return of chlorine in the silver ion catalyzed reaction is not without a satisfactory rationale.

The last, and perhaps the least understood, aspect of the reaction which we wish to discuss is the origin of **11** in the product mixture. Although the actual amounts of **11** are small we are convinced that they are derived in some way from **1**. Several possible explanations can be offered. One might visualize a homolytic cleavage of the N–Cl bond, instead of a heterolytic cleavage, to produce a radical center on nitrogen and a chlorine radical. However since **11** was formed at least 10^3 times faster in the silver ion catalyzed reaction, silver ion necessarily would have to be involved in the transition state leading to homolysis of the N–Cl bond. Since silver ion should not pull off a chlorine radical, any interaction of the silver ion would have to be at nitrogen to yield a species such as **25**.



The very weak basicity of N-chloramines makes this type of interaction improbable; however the similarity of the electronegativities of nitrogen and chlorine make such an interaction theoretically possible. If **25** were formed it would be analogous to protonated N-chloramines which are known to undergo homolytic cleavage of the N–Cl bond to yield nitrogen radical cations analogous to **26**. These species routinely abstract hydrogens to produce quaternary ammonium salts similar to **27**, which on neutralization would give **11**. In addition to the unlikelihood of **25** being formed, there exists a second feature of this Hofmann–Löffler–Freytag type route to **11** which makes it unattractive. The Hofmann–Löffler–Freytag reaction of protonated N-chloramines (generally in concentrated trifluoroacetic acid or in 85% sulfuric acid) requires either high temperatures, peroxide decomposition, or photolysis to initiate breakage of the N–Cl bond. Our reaction requires none of these. Hence we feel that the formation of **11** *via* the route **25** → **26** → **27** is very unlikely.

Alternative mechanisms for the formation of **11** might involve (a) exchange between **1** and methanol to give **11** and methyl hypochlorite, (b) ionization of **1** to give **19** which, being an extremely reactive cation, could abstract hydride from methanol to give **11** directly, or (c) formation of **19**, of necessity in the singlet state, followed by spin inversion to give the nitrogen diradical cation which *via* double hydrogen abstraction would yield a quaternary salt. On the basis of presently available data we cannot distinguish between these three mechanisms. Studies are currently in progress which are designed to elucidate the correct mechanism of the formation of **11**.

In summary we wish to point out that the rearrangement of **1** leaves little doubt as to the existence of electron-deficient divalent positive nitrogen intermediates. In the case of the rearrangement of **1**, especially in the presence of silver ion, we have a remarkable example of internal return of chloride ion which is virtually unprecedented. We are continuing our studies in this area.

Experimental Section[19]

4,7,7-Trimethyl-2-azabicyclo[2.2.1]heptan-3-one (8). Treatment of 7[7,11] with acetic anhydride according to a slightly modified[20] literature procedure[12] gave **8** in 80% yield.

N-Benzyl-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (9). To a stirred solution of 7.5 g of sodium hydride and 33.4 g of benzyl chloride in 100 ml of dry tetrahydrofuran was added a solution of 30.0 g of **8** in 100 ml of dry tetrahydrofuran. The reaction mixture was refluxed for 6 days. At this time 50 ml of water was added dropwise, and the resulting aqueous phase was separated and washed three times with 50-ml portions of ether. The organic phases were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was distilled off. Fractional distillation of the residue gave 45.3 g (95%) of N-benzyl-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (**9**): bp 135–140° (1.1 mm); $n^{25}\mathrm{D}$ 1.5283; $[\alpha]^{25}\mathrm{D}$ −12.4° (chloroform).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.96; H, 8.77; N, 5.60.

N-Benzyl-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (10). To a stirred slurry of 10.0 g of lithium aluminum hydride in 500 ml of dry ether was added dropwise 44.6 g of **9**. The slurry was stirred at room temperature for 7 days and then hydrolyzed by dropwise addition of 40 ml of 5% sodium hydroxide solution. The salts were removed by filtration and carefully washed with ether. The organic solutions were combined and dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The ether was removed by distillation, and the residue was fractionally distilled to give 37.3 g (88%) of N-benzyl-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (**10**): bp 114–116° (1.8 mm); $n^{25}\mathrm{D}$ 1.5200; $[\alpha]^{25}\mathrm{D}$ −29.2° (chloroform).

Anal. Calcd for $C_{16}H_{23}N$: C, 83.78; H, 10.11; N, 6.11.

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(19) Melting points and boiling points are uncorrected.

(20) R. H. Schlessinger, unpublished work. We wish to thank Professor Schlessinger for providing us with the details of the modified literature procedure prior to publication.

Found: C, 83.88; H, 10.08; N, 6.03.

4,7,7-Trimethyl-2-azabicyclo[2.2.1]heptane Hydrochloride (11a). A Parr hydrogenation bottle was charged with 50.0 g of **10**, 100 ml of ethanol, and 10.0 g of 5% palladium on carbon. Hydrogenation was carried out in a Parr hydrogenation apparatus at 40 to 50 psig. After 24 hr hydrogen uptake ceased. The hydrogenated solution was acidified with concentrated hydrochloric acid and filtered, and the spent catalysts were washed thoroughly with ethanol. The ethanolic filtrate was evaporated to dryness under vacuum to give colorless, crystalline material. Recrystallization of the crude hydrogenation product from tetrahydrofuran gave 35.1 g (98%) of pure 4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane hydrochloride: mp >300° dec; $[\alpha]^{25}\mathrm{D}$ 8.15° (water).

Anal. Calcd for $C_9H_{17}N \cdot HCl$: C, 61.46; H, 10.33; N, 7.97; Cl, 20.24. Found: C, 61.27; H, 10.37; N, 7.89; Cl, 20.32.

N-Benzoyl-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (12). To 10.0 g of **8** in 100 ml of pyridine was added 15.0 g of benzoyl chloride at room temperature. The reaction mixture was heated to 100° for 1 hr, cooled, and poured onto ice. The product was extracted with two 50-ml portions of ether. The ethereal solution was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, and water. The resulting ethereal solution was dried over magnesium sulfate and filtered and the solvent distilled off to obtain an oil which consisted of **12** contaminated with benzoic anhydride. This oil was dissolved in 75 ml of ethanol and allowed to react for 24 hr at room temperature, poured into 200 ml of water, and basicified with sodium carbonate. This basic solution was extracted with two 50-ml portions of ether. The ethereal extracts were dried over anhydrous magnesium sulfate and filtered, and the ether was distilled off on a steam bath. The resulting oil was heated to 80° (5 mm) to remove any ethyl benzoate which was contaminating the product. On cooling the residue crystallized. Recrystallization from Skellysolve **B** gave 9.3 g (55%) of **12**: mp 81.5–82.0°; $[\alpha]^{25}\mathrm{D}$ +91.0° (chloroform).

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.93; H, 7.16; N, 5.25.

Lithium Aluminum Deuteride Reduction of 12. To a stirred slurry of 0.65 g of lithium aluminum deuteride in 20 ml of dry ether was added dropwise a solution of 2.57 g of **12** in 20 ml of dry ether. The reaction mixture was stirred for 5 days at room temperature and then quenched by dropwise addition of 3.0 ml of 5% sodium hydroxide. The inorganic salts were removed by filtration and washed thoroughly with ether. The combined ethereal filtrates were acidified with concentrated hydrochloric acid and evaporated to dryness under vacuum. The residue was recrystallized from tetrahydrofuran to give 0.34 g (19%) of 3,3-dideuterio-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (**15**). Nmr spectroscopy showed less than 1% proton content in the 3 position.

Anal. Calcd for $C_9H_{16}D_2NCl$: D, 11.11% excess. Found: D, 11.20% excess.

2-Chloro-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (1). A solution of 8.78 g of **11** in 10 ml of water was mixed with sufficient 10% sodium hydroxide to make the resulting solution slightly basic. Sodium hypochlorite solution (65 ml of 0.77 *M*) was added, and the reaction mixture was stirred for 30 min. The resulting N-chloramine, **1**, was extracted with ether and the ethereal extracts were dried in the usual manner. The ether was distilled off in a bath held at 50° to give **1** as an extremely volatile waxy solid which was not readily further purified. Various samples of **1** routinely titrated for 98–99% active chlorine.[21] Nmr spectroscopy showed no detectable presence of **11**.

Silver Ion Catalyzed Methanolysis of 1. The sample of **1** prepared from 8.78 g of **11** was dissolved in 100 ml of anhydrous methanol at ambient temperature and 10.4 g of anhydrous silver perchlorate was added. Silver chloride precipitation occurred immediately and was complete in less than 10 min. At this point a qualitative test for active chlorine showed the complete absence of **1**. The reaction mixture was then carefully acidified with concentrated hydrochloric acid, and the precipitated silver chloride was removed by filtration and washed with methanol. The methanolic filtrates were combined, and the methanol was removed under vacuum. The residue was made basic with 50% sodium hydroxide, and the free amines were extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and filtered, and the ether was distilled off to give a semicrystalline mass. Recrystallization from pentane gave 4.95 g (57%) of *exo*-2-chloro-3,3,4-trimethyl-1-azabicyclo[2.2.1]heptane (**13**): mp 121–122°; $[\alpha]^{25}\mathrm{D}$ +47.6° (chloroform).

Anal. Calcd for $C_9H_{16}NCl$: C, 62.24; H, 9.29; N, 8.07; Cl, 20.42. Found: C, 62.32; H, 9.33; N, 8.07; Cl, 20.43.

Removal of the solvent from the mother liquors from the above recrystallization gave an oil which was separated by preparative vpc on a 10 ft × $^3/_8$ in. 10% Carbowax 20M-KOH on Chromosorb W column at 120° to give an additional 1.0 g (12%) of **13**, a small amount of **11**, and 0.38 g (4.5%) of *exo*-2-methoxy-3,3,4-trimethyl-1-azabicyclo[2.2.1]heptane (**14**) as a colorless mobile liquid: bp 116–119° (75 mm); $n^{27}\mathrm{D}$ 1.4687; $[\alpha]^{28}\mathrm{D}$ +82.5° (chloroform).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.67; H, 11.28; N, 8.21.

Having purified samples of **11**, **13**, and **14** in hand the actual yields in the reaction could be determined by vpc using N,N-dimethylaniline as a chromatography standard. In a typical reaction the yields were determined to be 78% **13**, 8.5% **14**, and 4% **11**.

Methanolysis of 1 in the Absence of Silver Ion Catalysis. As described above 0.50 g of **11** was converted into **1** and dissolved in methanol. The reaction mixture was refluxed for 36 hr, cooled, and made basic by the addition of a solution of 3.0 g of potassium hydroxide in 15 ml of methanol. N,N-Dimethylaniline was added as an internal standard and the product mixture was analyzed by vpc. This reaction gave 59% **13**, 20% **14**, and 7% **11**.

Lithium Aluminium Hydride Reduction of 7. A solution of **7** in water was passed through a column of **IR4B** ion-exchange resin to give the free amino acid, mp >300° subl (lit.[12] >300° subl). To a stirred slurry of 1.4 g of lithium aluminum hydride in 30 ml of tetrahydrofuran was added 5.0 g of the free amino acid. The reaction mixture was refluxed for 18 hr and cooled, and 50 ml of 25% sodium hydroxide solution was added dropwise. The resulting slurry was extracted several times with ether, and the organic extracts were combined and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent was removed by distillation through a 12-in. Vigreux distillation column. When the solvent had been completely removed, the residue was allowed to cool at which time it crystallized to give 1.8 g (49%) of **8**. This material was identical in all respects with the authentic sample of **8** prepared *via* the literature method.[11]

Sodium Borohydride Cleavage of 12. To 1.5 g of **12** in 10 ml of dry tetrahydrofuran was added 1.5 g of sodium borohydride. The reaction mixture was refluxed for 7 days, cooled, and diluted with 15 ml of water. Ether (50 ml) was added, and the phases were separated. The aqueous phase was extracted twice more with 50-ml portions of ether. The organic phases were combined and dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration the solvent was distilled off through a 12-in. Vigreux distillation column. The residue (1.4 g) was separated into its two components by preparative vpc on a 10 ft × 0.25 in. 10% SE-30 on Firebrick column. These two components were shown to be benzyl alcohol and **8** by comparison with authentic samples.

Acknowledgment. We wish to thank the National Cancer Institute of the Public Health Service for Grant CA-07110 which supported this research.

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(21) Active chlorine determinations were performed by taking a methanolic solution of the N-chloramine, diluting to a measured volume with methanol, and removing an aliquot. The aliquot was diluted to *ca.* 30 ml with methanol, treated with excess solid sodium iodide, and acidified with 70% perchloric acid. The iodine in the resulting solution was titrated with standardized 0.01 *N* sodium thiosulfate solution to the disappearance of the iodine color.