PART I Derivatives of 7-Azabicyclo[2.2.1]heptane

PART II Base Catalysed Hydrogen:Deuterium Exchange of Benzyl Sulfoxides

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Thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry, the University of Ottawa, Ottawa, Canada. August 1969

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ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Dr. R.R. Fraser who was a never failing source of inspiration, expert guidance and encouragement.

The author also wishes to thank Dr. Gurudata, Dr. Schuber, and Roger Renaud, for their helpful suggestions.

Special thanks are due to Marlene who has had the almost impossible task of deciphering the author's writing and the tedious task of typing this thesis.

ABSTRACT

PART I

The synthesis of 7-azabicyclo[2.2.1]heptane (ABH) has been accomplished via two new synthetic routes both of which provide improved yields over any previous synthesis. The spectral and chemical properties of several N-substituted ABH derivatives have been studied and the rotation barriers for 7-acetyl-7-azabicyclo-[2.2.1]heptane and 7-nitroso-7-azabicyclo[2.2.1]heptane have been determined. Chlorination of the trichloroacetyl derivative of ABH and subsequent removal of the trichloroamide group gave a mono-chloro derivative whose structure was proven to be exo-2-chloro-7-azabicyclo[2.2.1]heptane. The solvolytic behavior of this derivative was briefly examined. A new reaction of trichloroacetyl chloride with triethylamine was discovered and was shown to produce a beta-acylenamine. A probable mechanism was proposed after an extensive investigation of the reaction.

PART II

The rates of hydrogen:deuterium exchange for the diastereotopic methylene protons in the benzyl group of three benzyl sulfoxides have been determined using mass spectrometry. The variation in rates with changes in structure were found to be small.

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PART I

Derivatives of 7-Azabicyclo[2.2.1]heptane

INTRODUCTION

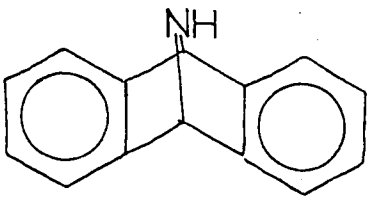
Since 1939, when Salas, Nevell, and Wilson[1] first presented a postulate about the rearrangement of camphene hydrochloride to isobornyl chloride through what has later become known as a non-classical carbonium ion, great interest has arisen in bicyclo [2.2.1] heptane systems. The existence or non-existence of a non-classical carbonium ion has been debated by Brown, Winstein, Bartlett, Schleyer and countless others for the last 25 years.[2] Although a solution to the problem is much closer today,[3] the complete answer is still not known.

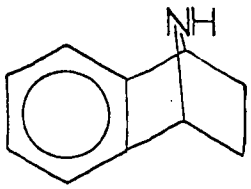
In the hope that more knowledge could be gained about the norbornane systems, researchers have attempted the synthesis of thia, oxa, and azabicyclo [2.2.1] heptane compounds. Sulfur has been placed in both the 7^4 and 2^5 positions, oxygen in the 7^6 position, and nitrogen has been placed most readily in the 2^7 position. Exotic systems involving aluminum[8] and phosphorus[9] in the 7 position have also been synthesized. The 7-azabicyclo [2.2.1] heptane system is more rare, however, and a mono-substituted derivative is virtually unknown. It was felt that if a derivative could be obtained which was analogous to the well known norbornyl compounds, for example a chloro or a tosylate derivative, then the difference in the reactivity of a compound with nitrogen in the seven position rather than carbon would give further basis for comparison of the existing postulates about these types of systems. Quite aside from the non-classical carbonium ion aspect, the system itself would be an interesting one spectroscopically, and would present a challenging synthesis.

The parent compound, 7-azabicyclo [2.2.1] heptane, has been known

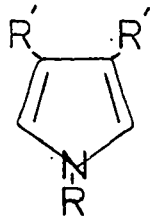
since 1930.[10] At that time, however, it was only obtained in a yield of less than 1%, but there were no further attempts made to synthesize this type of system until 1957 when Mandell and Blanchard[11] reacted N-benzyl-pyrrole and acetylenedicarboxylic acid in a Diels-Alder addition reaction. They obtained 2,3-dicarboxy-7-benzyl-7-azabicyclo[2.2.1]hepta-2,5-diene in about 9% yield. From 1957 until the present time, the Diels-Alder addition became an increasingly popular route to the 7-azabicyclo-[2.2.1]heptane system. The yields, however, were consistently low.

In 1958, Wittig and Behnisch[12] produced the compounds shown below in yields of 6%.



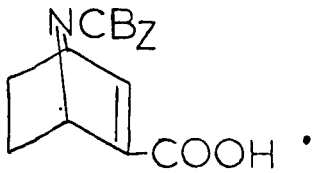


A Czechoslovakian worker, in 1961, increased the yield of the disubstituted compound, first produced by Mandell and Blanchard, to 10%.[13] Acheson and Vernon, in 1962,[14] proposed that indeed the Diels-Alder additions of acetylenes to pyrroles did form the 7-aza adduct but this adduct underwent a further addition thereby lowering the yield of the desired product. The second problem that Acheson and Vernon[15] found with the addition was that it can easily undergo a retro-Diels-Alder reaction to form the starting pyrrole, or, by loss of ethylene, the trisubstituted pyrrole where the R' groups were part of the acetylene moiety.



Kitzing[16] and co-workers, in 1968, explained the results that Mandell and Blanchard had obtained with benzyl substituted pyrroles by suggesting that if the nitrogen was substituted with an electron withdrawing substituent, the addition favored the thermodynamically-stable 7-aza derivative and made the attack of a second electrophile more difficult. By using this type of substituent, yields of between 30 and 45% of 7-azabicyclo[2.2.1]heptanes were obtained.

Although many people have proven that the Diels-Alder reaction does give 7-azabicyclo[2.2.1]heptane derivatives, the usefulness of these products in obtaining a mono-substituted derivative is open to question. It is a fact that only Shafi'ee and Hite[17] have actually achieved this goal through the use of a Diels-Alder addition reaction. The Diels-Alder reaction took place in an 18% yield. The mono-substituted derivative shown below was obtained after six steps with



an overall yield of very much less than 1%. It would appear, then, that the Diels-Alder route to the desired mono-substituted product would not be promising.

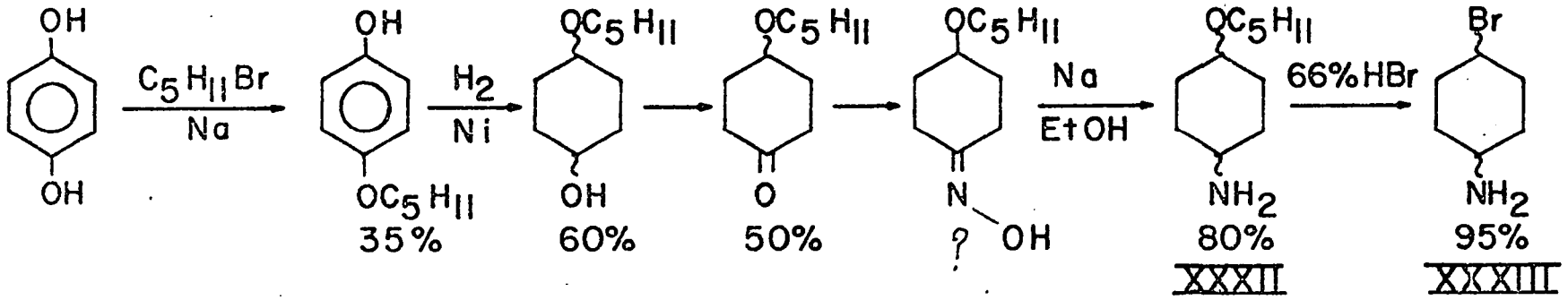
Only one other route to a mono-substituted 7-azabicyclo[2.2.1]-heptane has been reported since the original literature in 1930. Corey and Hertler,[18] in 1960, obtained the methiodide of 7-methyl-7-azabicyclo[2.2.1]heptane in some 11% yield by utilizing the Hofmann-Löffler reaction.[19] This also did not appear to be promising because if this route were used, compounds with substituents on the nitrogen (other than methyl) would not be readily available. This left the original synthesis by Braun and Schwartz[10] to consider. (Scheme I) If this synthesis were to be used, it would be necessary to plan a new route in such a way as to overcome the difficulties encountered in the original one.

The significant reaction in Braun and Schwartz's scheme is the displacement of bromine by the nitrogen in a transannular reaction of 4-bromocyclohexylamine. If one is to improve the yield of this step (15% or less) then it would be apparent that two things could be done.

The first thing to consider is that a better leaving group than bromine could be found for the reaction. For example, Veeravagrue and co-workers[20] found that the alkyl halide, n-$C_{18}H_{31}Br$, gave 85% of the eliminated product when heated with a strong base whereas n-$C_{18}H_{37}OTs$ gave 99% substitution under the same conditions. From this, then, it would appear that the use of a tosyl or a mesyl ester rather than the bromide as a leaving group would greatly favor an improved yield of the 7-azabicyclo[2.2.1]heptane.

The other thing of note is that conditions could be found to reduce the amount of the elimination product that was produced in the Braun and Schwartz synthesis. This last factor can be overcome if one

Scheme I

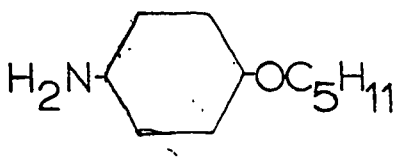


→ PICRATE OF 7-AZABICYCLO [2.2.1] HEPTANE < 15%
OVERALL YIELD ~ 1%

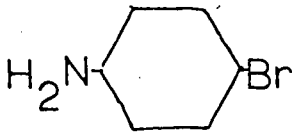
considers the following facts. Decreasing the polarity of the solvent would tend to decrease both the unimolecular neucleophilic substitution (S_N1) and the unimolecular elimination (E1) character of the transition state and allow competition only between bimolecular substitution (S_N2) and elimination (E2). A decrease in polarity would tend to increase bimolecular elimination over bimolecular substitution in the presence of strong bases at high concentrations.[21] The advantage, however, in this system over the usual systems considered, is that the substitution reaction desired is an intramolecular one while the elimination is an intermolecular reaction. Dilution should then greatly favor the cyclization reaction with the nitrogen as the nucleophile over an E2 reaction.

There is one other improvement that might be made in the final step of the synthesis. Although they did not mention the exact temperature at which the reaction was carried out, they mentioned that it was warmed. It is a known fact that although both elimination and substitution are accelerated by an increase in temperature, elimination is generally accelerated to a greater degree.[22] With this additional factor in mind, some intermediate temperature should be selected which would allow the reaction to take place but which would tend to discourage elimination.

The question that remains to be answered is how effective was the remainder of Braun and Schwartz's synthesis. One major disadvantage that is immediately apparent is that neither the amino-ether, XXXII, nor the amino-bromide, XXXIII, was separated into their respective cis and



XXXII



XXXIII

trans isomers. This meant that the amount of the elimination product was greatly increased and as the separation of 4-aminocyclohex-1-ene and 7-azabicyclo[2.2.1]heptane was exceedingly difficult (as shown by Braun's need to make the picrates before separation) the yields fell accordingly. If one is to use the amino-ether in a synthetic scheme in which improved yields are desired, it would then be necessary to do a prior separation of the isomers.

It would appear, then, that every synthetic scheme to the parent 7-azabicyclo[2.2.1]heptane system that had been attempted to date had a major flaw which made it almost useless for the purpose of synthesizing mono-substituted 7-azabicyclo[2.2.1]heptane systems. This fact made it necessary to consider alternate routes to achieve the desired goal.

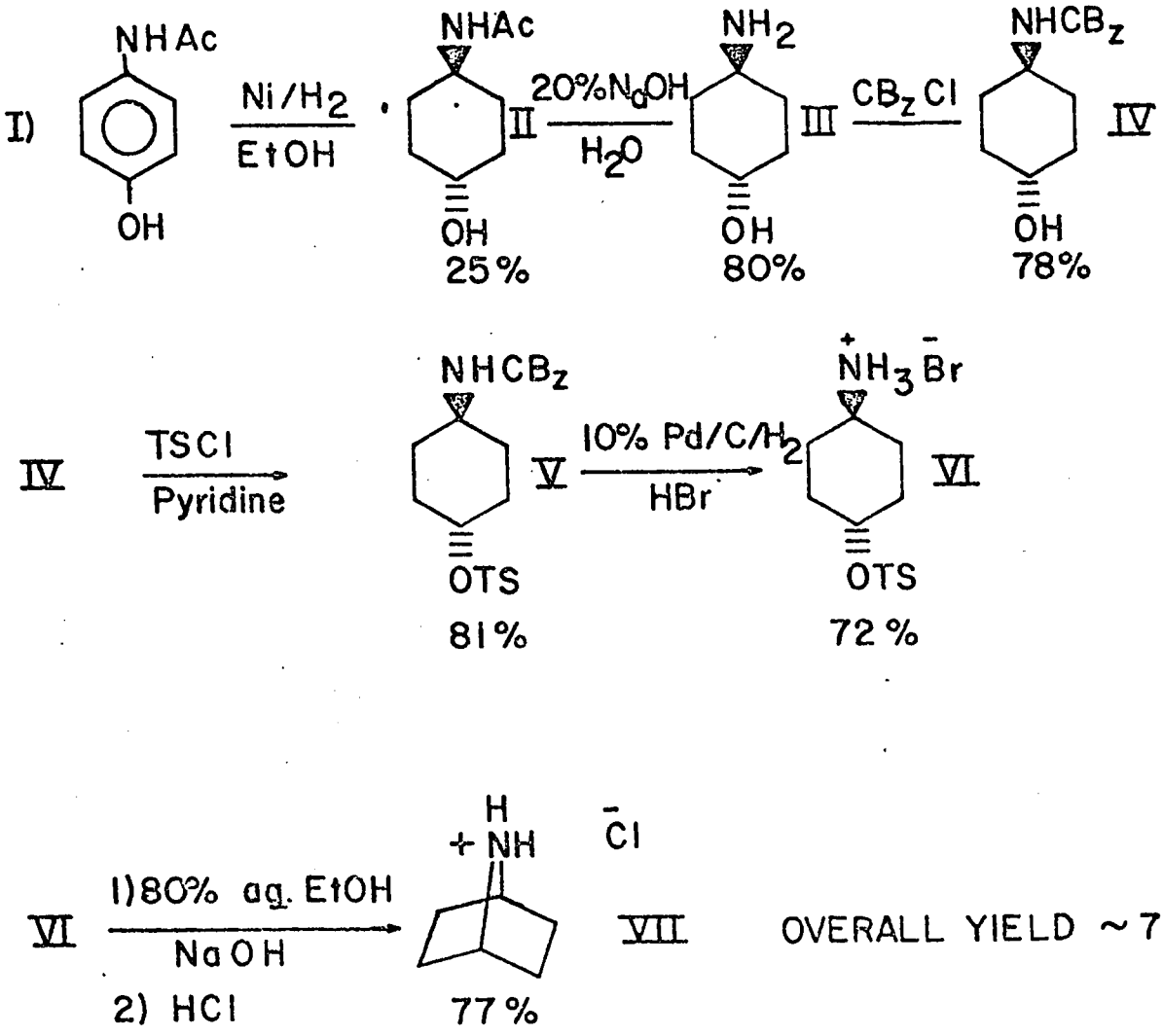
DISCUSSION AND RESULTS

I. The synthetic sequence envisaged for the preparation of 7-azabicyclo-[2.2.1]heptane is shown in Scheme II.

1. Preparation of III

The compound finally chosen for the initial point of the synthesis was 4-acetamidophenol (I). The reason for this choice was that I was commercially available and its hydrogenation had been accomplished previously.[23] It also had the advantage over 4-aminophenol in that aminophenols are exceedingly difficult to hydrogenate as they act as a poison to many catalysts.[24] When 20 g of I was hydrogenated in an aqueous medium using 2 g of platinum oxide as catalyst, Ferber and Bruckner found that they were able to obtain 16 g of trans-4-acetamidocyclohexanol and 4 g of cis-4-acetamidocyclohexanol. Since large quantities of II would be required, it seemed as if 2 g of platinum oxide for each 20 g of I hydrogenated would be excessive and a compromise was needed. The ideal quantity was found to be 0.3 g of the catalyst to twenty grams of I. This gave about 40% yield of the desired trans isomer after the isomer had been isolated by fractional recrystallization from acetone. This isomer was sparingly soluble in acetone and crystallized from it almost immediately, whereas the cis isomer was very soluble and required some three or four days at 0° to obtain crystals after most of the solvent had been removed. Although the yield of the desired isomer obtained from this hydrogenation was acceptable, I was not exceedingly soluble in water and quite often poisoned the catalyst before the reaction could be forced to completion. The size of the hydrogenation bottle also limited the scale of the reaction and as such it was felt that

Scheme II


I)
NHAc
OH
Ni/H2
EtOH
NHAc
OH
25%
II
20%NaOH
H2O
NH2
OH
80%
III
CBzCl
NHCBz
OH
78%
IV
IV
TSCl
Pyridine
NHCBz
OTS
81%
V
10% Pd/C/H2
HBr
NH3 Br
OTS
72%
VI
VI
1)80% aq. EtOH
NaOH
2) HCl
H
+NH
Cl
77%
VII
OVERALL YIELD ~7%

other conditions should be investigated.

In 1953 Billman and Bruler[25] hydrogenated I over Raney nickel in a high pressure autoclave and obtained 30 g of the trans isomer and 35 g of the cis isomer after nine fractional recrystallizations from a 95 g mixture of the two. When this procedure was followed, it was found that W_4 Raney nickel[26] gave 16 to 20 g of the trans isomer and 26 to 30 g of the cis isomer from an 80 g reaction. It was also found that three or four recrystallizations were sufficient to produce pure trans-4-acetamidocyclohexanol (II).

Della and Jefferies[27] reported that they had achieved a trans to cis ratio of 4:1 using Billman and Bruler's procedure, although they did not specify quantities. This ratio was an enviable one, but it could not be achieved under the conditions employed here. The fact that the results obtained bear a much closer resemblance to those reported by Billman and Bruler and the fact that Billman and Bruler's reported cis to trans ration has the cis isomer in the larger amount, would suggest that there is a printing error in Della and Jefferies' paper and the ratio should really be 1:4. If one considers the total yield of the trans isomer from the 80 g reaction, the ratio obtained in this case is close to 1:4 if one presumes the residue to be mainly the cis isomer.

Although the overall yield of the trans isomer was somewhat lower when Raney nickel was employed as catalyst as compared to the yield of the trans isomer when platinium oxide was used as catalyst, the advantage of the second method over the first is that solubility no longer presented a problem and therefore much more II could be prepared

in one hydrogenation. Raney nickel is also less susceptible to poison than is platinum oxide and therefore less problem was presented in getting the hydrogenation to go to completion.

The next step in Scheme II is the hydrolysis of the acetamide group to obtain 4-aminocyclohexanol (III). Ferber and Bruckner[23] accomplished this by an acid hydrolysis of II at 120°. Elimination of the hydroxyl function also occurs under acid conditions and a more convenient method for the preparation of III was proposed by Della and Jefferies[27] who hydrolyzed II in a refluxing solution of 10% aqueous potassium hydroxide. It was found, however, that a more efficient hydrolysis was achieved by the use of 20% sodium hydroxide.

The assignment of the trans configuration to the higher melting of the two isomers of III obtained in this manner was originally made by Ferber and Bruckner[23] according to the von Auwers-Skita rule.[28] Della and Jefferies[27] confirmed that the assignment was correct by converting a compound with known configuration such as trans-4-hydroxy-cyclohexanoic acid,[29] to III. The conversion of the acid to methyl ester, hydrazide, azide, ethyl urethan, and free amine are reactions which are known to proceed with retention of configuration.[30]

2. Attempted preparation of an O-Tosylate (VI) directly from III.

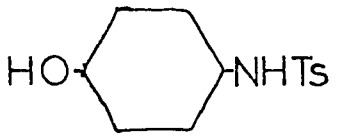
The next logical plan in the reaction sequence would have been to obtain trans-4-aminocyclohexyl toluenesulfonate (VI) directly from III. With this in mind, a series of experiments were then carried out to achieve this goal.

Amines are noted to be more basic than alcohols (as nucleophilicity is roughly in the same order as basicity[31]) and, as such, will compete more effectively for a tosyl group in a tosylation reaction than would

an alcohol. This being the case, it was felt that the best plan would be to make the oxy-anion of III and react it with tosyl chloride (thus reversing the order of basicity). The base chosen to bring about this reaction was sodium hydride.

The problem that was next encountered was in choice of solvents. Unfortunately, III was almost insoluble in most aprotic solvents; however, this, in itself, would not have presented an insurmountable obstacle, but it also happened that the anion formed from the reaction was even more insoluble than III.

Dioxane was one of the more successful solvents in that III could be dissolved to a limited extent in it. When a solution of p-toluene-sulfonyl chloride in dioxane was added to the suspended anion, the only product that could be identified from the reaction mixture was what appeared to be 4-tosylaminocyclohexanol (XVIII).



XVIII

This compound was identified from its I.R. and N.M.R. spectra. The I.R. of a solid dispersion of XVIII in potassium bromide showed a band at 3487 cm^{-1} due to dimeric (O-H) stretching and a broad band at 3300 cm^{-1}[32] due to polymeric (O-H) stretching. A single band at 3260 cm^{-1} clearly indicated that the amine retained only one hydrogen.[33] The (C-OH) deformation band was visible at 650 cm^{-1}.[32] The bands at 1155 and 1315 cm^{-1} indicated a sulfonamide.[34] An examination of the N.M.R. spectrum of XVIII showed the expected A_2B_2 pattern for a <u>para</u>-

substituted benzene, indicating that indeed tosylation had occurred. A broad doublet, centered at δ 5.33 with an area of one proton, was highly indicative of the proton on nitrogen coupled to the hydrogen on the carbon bearing the sulfonamide group. When a compound was synthesized using equimolar amounts of p-toluenesulfonyl chloride and III in pyridine, the N-tosylate that was recovered had identical melting points, mixed melting points, and spectra to those of XVIII.

Compound XVIII, from the dioxane reaction, was formed in quantities of less than 5%. 7-azabicyclo[2.2.1]heptane (ABH) which could have resulted from immediate cyclization of any O-tosylate that formed, was not isolated from the reaction nor was any of the desired product, trans-4-aminocyclohexyl p-toluenesulfonate (VI). The residue, after hydrolysis and removal of solvent, contained some unreacted III identified only by its I.R. spectrum. The remaining residue was not identified. The reaction in tetrahydrofuran gave identical results.

Dimethyl sulfoxide proved an ideal solvent as far as solubility was concerned, but the protons of the methyls were acidic enough to be removed by sodium hydride[35] and the resulting anion was quite capable of attacking the p-toluenesulfonyl chloride giving an unidentified compound which in all probability was polymer.

Two possible reasons could be presented to explain why the N-tosyl derivative was formed rather than the O-tosyl derivative.

One possibility to consider is that the anion formed was too strong a base and attacked the chlorine rather than the sulfur of the p-toluene-sulfonyl chloride. If this occurred, a hypohalite of 4-aminocyclohexanol would be formed which could decompose to the ketone and thereby allow

polymerization to take place.[37]

The second possibility to consider would be that the oxy-anion was less reactive than the nitrogen lone pair. This could have been due to a solvent effect. It was possible that in solvents such as dioxane or tetrahydrofuran, that is, solvents which are relatively non-ionizing, a tight ion pair was formed which was then enclosed by a solvent shell.[36] The nitrogen lone pair, being less polar, had fewer solvent molecules around it and therefore was more readily accessible for reaction. If this were the reason for not obtaining an O-tosylate, the reaction should occur to a much greater extent in an ionizing solvent such as ethylene-glycol-mono-methyl ether (glyme) because increased ionization should increase the relative basicity of the oxy-anion. (This solvent along with diglyme is noted for its solvation of metal alkoxide and metal alkane reactions.[38])

To check this possibility the anion was generated in glyme. The amines which formed, whether ABH or VI, were trapped after the reaction by the addition of hydrobromic acid. When the solvent was evaporated and the solids extracted with boiling ethyl acetate, it was found that a compound had been produced in about 5% yield which was spectroscopically identical to VI. (See discussion of VI.)

Attempts were immediately made to improve the yield. Since facts seemed to support the idea of increased ionization in glyme it was thought that perhaps the yield of VI was low due to intermolecular attack by the amine group of one molecule on the O-tosylate of another, resulting in dimerization or polymerization. The reaction was then repeated in such a manner so that the anion once formed could be transferred under

nitrogen pressure to a dropping funnel over a second flask containing the p-toluenesulfonyl chloride. The anion, which was partially insoluble in the glyme and therefore gave a cloudy appearance to the solution, immediately reacted. This was apparent because of the sudden clearing of the solution and the eventual formation of a sodium chloride precipitate. However, on work-up as before, only the N-tosyl derivative could be isolated. No VI was produced. Varying the temperature of the reaction and even changing the base to n-butyl lithium did not improve the yield of VI.

The question still remained as to why the reaction gave a low yield of VI under one set of conditions and gave the N-tosyl derivative under a similar set of conditions when only the order of addition had been changed. The thought that the low yield might have been caused by a lack of formation of the anion was partially answered by the fact that once, when the anion was transferred through a plastic tubing believed to be poly-vinyl acetate, a reaction occurred. Although no identification of this compound was undertaken its production would tend to suggest that, at least when glyme was the solvent, the anion was formed and was available for reaction. The cloudyness disappearing as soon as the anion reached the p-toluenesulfonyl chloride suggests that a reaction took place at this point also. As some III was identified from the residue of the reaction after the removal of solvent and the N-tosyl derivative, it would appear that at some point a proton was released and this reacted with some of the anion. One possible means of this would be for the anion to attack the chlorine of the tosyl chloride to produce the hypohalite as mentioned previously. This could

then lose hydrogen chloride in forming the ketone.[37] No proof that this type of reaction took place is available, however, as the other reaction product (p-toluenesulfinic acid) was not isolated. The production of III could also have been caused by the addition of the hydrobromic acid to unreacted anion. The only thing which perhaps supports the idea of hypohalite formation is the fact that the solution containing the anion was completely clear after its addition to the p-toluenesulfonyl chloride. If much anion was left one would not have expected the cloudyness to disappear.

A second possible explanation for the discrepancy could be that if any of the O-tosylate had formed in the reverse addition reaction, it might react with a second molecule of p-toluenesulfonyl chloride to give N-tosylaminocyclohexyl tosylate although none was isolated. With an excess of anion this would not happen.

The possibility that cyclization had occurred during the reaction was discarded when no evidence of bridgehead protons could be found in the N.M.R. spectrum of the residue. (See later discussion of the spectral properties of 7-azabicyclo[2.2.1]heptane.)

One other attempt at tosylation of the hydroxy function was made before considering protecting groups for the amine. If the lone pair of the nitrogen could be tied up as a salt, then perhaps tosylation of the oxygen could take place. With this in mind, the amine hydrochloride of III was suspended in chloroform with p-toluenesulfonyl chloride for one month. When the compounds were isolated, it was found that the main product was an N-tosylate and that some loss of the hydroxyl group to form an unsaturated product had also taken place. The explanation

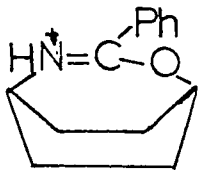
for this, of course, must lie in the acidity of the amine hydrochloride. The oxygen could have become protonated and lost as a water molecule or what is even more likely is that O-tosylation did take place and the tosylate was lost as toluenesulfonic acid. N-tosylation probably took place because of the reversibility of the amine protonation step.

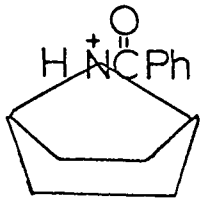
One other attempt was made to form the 7-azabicyclo[2.2.1]heptane directly from III. In 1967, Gassman and Fentiman[39] produced (5S)-1-azabicyclo[3.1.0]hexane by a two-step method starting from L-prolinol. By carefully heating the amino alcohol in the presence of sulfuric acid, the sulfate ester could be produced in some 75% yield and upon the addition of an aqueous sodium hydroxide solution they were able to form their bicyclic amine in some 54% yield. When the reaction was tried with III, however, there was some evidence that the sulfate ester had formed, (the sharp O-H stretching had disappeared in the I.R.) but the ester could not be crystallized and upon treatment with base no recognizable product resulted.

3. Preparation of 7-Azabicyclo[2.2.1]heptane

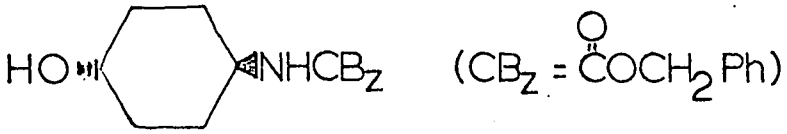
As all the attempts to produce direct tosylation of the oxygen failed, it became necessary to consider blocking the amino function prior to the tosylation reaction. This implied that the group should be one which could be removed easily without endangering the tosyl ester. One such group is the carbobenzoxy group[40] which could be removed either by hydrogenolysis[41] or by acid hydrolysis in acetic acid and aqueous hydrobromic acid.[42] (The idea of trying to displace a leaving group with the acetamide group, which was originally present, was also considered and discarded. Della and Jefferies[27] had thought

that either of the following compounds could be involved in the acetic acid-sodium acetate solvolysis of trans-4-benzamidocyclohexyl p-toluenesulfonate, but since neither were isolated as products they later rejected the possibility that the compounds formed in the reaction.)





It was found that in order to produce trans-4-carbobenzoxyaminocyclohexanol (IV) in good yield it was necessary to employ Schotten-Baumann conditions because of the solubility of III.



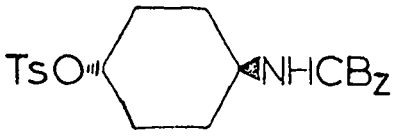
IV

The best results were obtained when the reaction mixture was shaken vigorously by hand thereby preventing the globules of IV, which were insoluble in water, from becoming large. If this did occur it was found that the carbobenzoxy chloride, which is also insoluble in water, was trapped in the center of these and did not react with the amine and consequently the yield of product was lowered. It was also necessary to keep the solution from becoming either too acidic, at which point III became protonated, or too basic which caused an increase in the rate of hydrolysis of the carbobenzoxy chloride and decomposition of the product. A pH of nine to ten is ideal for converting amino acids to their carbobenzoxy derivatives according to Boissonnas.[41] This,

however, was not quite basic enough as the pK_A of III was found by Della[27] to be 10.20 and a pH of 10.5 to 11.0 was found to be more appropriate.

The product, IV, was easily identified by its distinctive I.R. spectrum. The O-H stretching was retained at 3615 cm^{-1}[43] and the two bands of the symmetric and asymmetric NH_2 stretching were reduced to a single band at 3450 cm^{-1}.[44] The presence of the urethan carbonyl was confirmed by the band at 1720 cm^{-1}[45] and by the C-N-H group absorptions at 1515 cm^{-1}.[46]

The compound, IV, proved to be quite soluble in pyridine, and tosylation proceeded at 0° without difficulty. The product, trans-4-carbobenzoxyaminocyclohexyl p-toluenesulfonate (V), could be identified from its I.R. spectrum by the disappearance of the O-H stretching bands previously at 3615 cm^{-1} and the appearance of sulfonate ester bands at 1365 cm^{-1} and 1180 cm^{-1}.[34, 47]

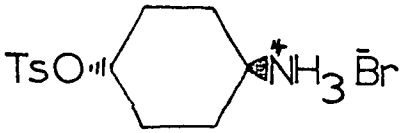


V

The urethan carbonyl and C-N-H absorptions remained at 1720 cm^{-1} and 1515 cm^{-1} respectively.

The carbobenzoxy group was now ready to be removed. This was attempted at first by using hydrobromic acid in acetic acid. It was found, however, that the cleavage was only effective for small quantities of V. The reason for this was that the solubility of V remarkably decreased as the amount of aqueous hydrobromic acid needed

for the reaction increased. If the amount of acetic acid was also increased, it was found that to remove the solvent completely, at a pressure of 0.5 mm, heat was needed and with large quantities of acid present some elimination took place and the yield of trans-4-aminocyclohexyl p-toluenesulfonate hydrobromide (VI) decreased.



VI

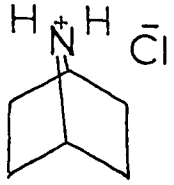
This sort of ester hydrolysis was also noted by Merrifield[48] under similar circumstances. The other method of removing a carbobenzoxy group was thus tried.[41, 49]

Hydrogenolysis of V was found to be most effective when 10% palladium-on-charcoal was used as a catalyst and ethanol was used as solvent. When acid was not present, it was found, however, that hydrogenolysis did not appear to take place to any great extent, but the addition of hydrobromic acid to the reaction allowed the hydrogenolysis to go to completion in about three to five hours. The added advantage of the acid was that the free amine formed in the reaction was trapped as its salt and could not cyclize and thereby create difficulty in separation of the two possible reaction products. (It must also be noted that partial acid hydrolysis took place as evidenced by the production of benzyl bromide. Only toluene is produced as a side product in the hydrogenolysis of a carbobenzoxy group.) The second advantage of this method was that quantities of 10 or 20 g could be hydrogenolized with yields increased some 10 to 20% over the yields obtained with the

hydrobromic acid-acetic acid hydrolysis of comparable amounts. The limitation in this case was the size of the hydrogenation bottle.

The product, VI, can be identified by the distinctive band shape of the protonated primary amine at 3000 cm^{-1}.[50] The disappearance of the urethan bands at 1720 cm^{-1} and 1515 cm^{-1} were indicative of the fact that cleavage had taken place. The SO_2 stretching bands are retained at 1365 cm^{-1} and 1180 cm^{-1}. The N.M.R. shows the loss of the five proton singlet of the benzyl aromatic protons (δ 7.33) and the loss of the benzyl CH_2's at δ 5.10.

The cyclization of VI proceeded smoothly in 70% aqueous ethanol when two equivalents of sodium hydroxide were present. A temperature study was not necessary as it was found that after 14 hours virtually all of VI had reacted to give what appeared to be only 7-azabicyclo-[2.2.1]heptane (ABH) isolated as the hydrochloride VII.



VII

(A reaction was tried at 40° and the N.M.R. examination of the crude reaction material indicated that elimination had occurred to the order of 20% of total product.) The solvent polarity, however, did appear to be quite important as a slight reduction to 80% aqueous ethanol did not allow the reaction to go to completion within the 14 hours.

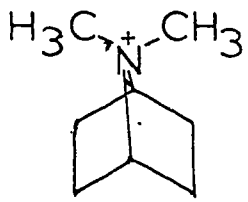
Isolation of the product was not difficult although caution was needed in handling the free base, as it proved to be extremely volatile. The solvents were removed under vacuum only after the free base had

been trapped as its hydrochloride salt (VII). Before washing the p-toluenesulfonic acid and sodium chloride from the residue it was found that the best procedure, involving the least loss of ABH, was to trap the volatile amine under a layer of ether. It was also found that the ether solution needed to be thoroughly dried with both magnesium sulfate and calcium hydride, as any moisture remaining in the ether tended to cause the hydrochloride salt to become sticky. This prevented recrystallization and, instead, caused an "oiling-out" of the product.

The picrate of ABH, which was made from an aqueous solution of picric acid and VII melted at 171-174°. This was quite surprising as the cyclization of 4-bromocyclohexylamine by Braun and Schwartz[10] gave two products isolated as picrates; one in 70% yield and the other in a 15% yield. The first product, A, formed a picrate that melted at 170-173°. The structure assigned to A by Braun and Schwartz was 4-aminocyclohexene! To the second product, which was obtained from the mother liquor, they assigned the 7-azabicyclo[2.2.1]heptane structure. The picrate of this product melted at 151-153°. Since there appeared to be a conflict as to which was the correct melting point, the picrate of 4-aminocyclohexene (see later discussion of preparation of 4-aminocyclohexene) was prepared and was found to melt at 166-168°. The possibility that compound A could have been ABH was eliminated by the fact that it was obtained in a 70% yield in spite of the fact that no attempt had been made to separate the cis and trans isomers before reacting them. The melting point obtained for the picrate of 4-aminocyclohexene would therefore confirm Braun and Schwartz's assignment of A.

It would seem likely that the second picrate obtained by Braun and

Schwartz was also not ABH although they were able to synthesize its methiodide in a subsequent reaction.



In 1960, Corey[18] photolyzed N-chloro-N-methylcyclohexylamine and from this Hofmann-Löffler reaction isolated the same methiodide. The melting points from the two reactions agreed.

This means that the only conclusion that can be reached is that Braun and Schwartz's assignment of A was correct and that they did get some ABH, but the picrate they isolated from the mother liquor of A was not the picrate of ABH but the picrate of some other amine.

The spectral evidence clearly shows that the compound VII, obtained here, is indeed 7-azabicyclo[2.2.1]heptane hydrochloride. There is a peak present at δ 4.23 with an area of two protons which could only be due to the bridgehead protons. Two sets of broad peaks which show some splitting appear at δ 2.24 and δ 1.64; each having an area consistent with four protons. This of course could be due only to the exo and endo protons of the ring. The broad peak at δ 9.5 was assigned to the protons on nitrogen.

The positions of the various chemical shifts are also in good agreement with those given by Corey and Block[4] for the 7-thiabicyclo-[2.2.1]heptane system. (Bridgehead protons δ 3.76, ring protons δ 1.63.)

The I.R. clearly shows that VII is a secondary amine with the distinctive $^{+}NH_2$ stretching bands appearing between 3000 cm^{-1} and 2700 cm^{-1} and combination bands appearing between 2700 cm^{-1} and 2550 cm^{-1}.[51] A medium-strength band at 1605 cm^{-1} shows the $^{+}NH_2$ deformation.[52] The series of bands from 1230 cm^{-1} to 1278 cm^{-1} are associated with the CH_2 wagging.[53] The 1473 cm^{-1} band is assigned to the CH_2 deformation although this usually appears near 1465 cm^{-1}.[54] The band at 1363 cm^{-1} is assigned to C-H next to the nitrogen.[55] The 1090 cm^{-1} band is probably associated with the C-N stretch.[56] The mass spectrum of VII does not show a parent molecular ion but clearly shows the $(M-HCl)^{+}$ peak at 97 m/e. (See section on mass spectra of 7-azabicyclo[2.2.1]-heptane derivatives for discussion.)

From the spectral evidence it therefore seems valid to conclude that VII is 7-azabicyclo[2.2.1]heptane hydrochloride.

The above method (see Scheme II) would appear to be an improvement over the method of Braun and Schwartz by some 6% although some doubt exists as to the ability to isolate the free amine in their synthesis. The 7% overall yield, although an improvement, was not synthetically good and it was desirable to find an alternate method to the one so far employed. Several alternate approaches were therefore investigated.

II. Alternate approaches to the ABH system.

1. Isocyanate approach to 7-azabicyclo[2.2.1]heptane

A possible route to the 7-azabicyclo[2.2.1]heptane system had been suggested indirectly by Hassner who had been interested in the addition of iodo-isocyanates to double bonds.[57] It had been demonstrated that the addition of these compounds to olefins went in a trans-diaxial manner[58] and that the beta-iodourethans derived from the addition

product could give an aziridine.[59] In the 1967 paper, Hassner stated (in one line) that there was some evidence to substantiate the idea that the addition of iodine isocyanate to 1,3-cyclohexadiene went in a 1,4 manner although no details were given. Should this be true, conversion to the iodourethan and cyclization might give ABH.

With this in mind the addition was tried. There was some evidence found in the crude reaction material to suggest that the isocyanate had been formed but attempts to form methyl carbamates, benzyl urethans, bisulfite adducts or even hydrolysis products, which were successful for the mono-enes, failed.[57]

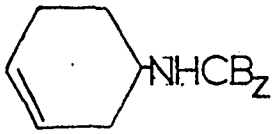
After the work had been completed a note appeared by Grimwood and Swern[60] who also had attempted to add iodine isocyanate to conjugated dienes. They found that the addition did proceed with 1,3-cyclohexadiene giving only one mole of iodine isocyanate, but attempts to get crystalline derivatives failed in all cases.

2. Attempted route to ABH via intramolecular displacement of an epoxide.

The next phase of attack was one involving the formation of the 4-substituted olefins, addition to the olefin, and eventual displacement of the added product to give the substituted 7-azabicyclo[2.2.1]heptane directly. If, for example, the trans-4-aminocyclohexene oxide could be formed it could easily be opened by an attack of the amino group on the epoxide[61,62] to give either the 2-hydroxy-7-azabicyclo[2.2.1]heptane or the 2-hydroxy-6-azabicyclo[3.1.1]heptane. The proportion of the [2.2.1] system to the [3.1.1] system should, however, be much greater as the strain in a cyclobutane ring would be larger than in a cyclopentane ring.[63]

The aspect of the problem which had to be considered most carefully was what compound should be epoxidized. The epoxidation of a free amine would in all probability fail in that the mechanisms[64] for epoxidation by peracids do not apply to the anion of the peracid which would be formed, as the amine would certainly be basic enough to abstract a proton from the acid. The second problem is that the amine itself would be oxidized by the peracid or by hydrogen peroxide if it was used. This then meant that the amine needed a blocking group. The easiest one to obtain, of course, would be the hydrochloride salt of the amine but this also appeared to be unsuitable for two reasons. The salt in all probability would not be soluble in benzene or chloroform which are the solvents of choice for peracid oxidations,[65] and even if solubility could be achieved, the proton of the amine salt could easily protonate the epoxide and cause an acid catalyzed opening of the epoxide ring.[66] The choice of blocking group, then, would be limited to those that could be removed easily and again the carbobenzoxy group was chosen. This choice was convenient in that the 4-carbobenzoxyaminocyclohexanol was already available and the carbobenzoxy group might possibly be removed under mild enough conditions so that there would be some chance of retention of the epoxide.

The 4-carbobenzoxyaminocyclohex-1-ene (XXII) was easily formed by refluxing a tetrahydrofuran solution of IV with thionyl chloride and after the chloro compound had formed, treatment with base (pyridine) caused the desired elimination.[67]

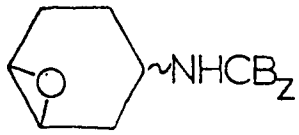


XXII

The I.R. spectrum of the product showed the expected N-H stretching at 3350 cm^{-1}[44] the urethan bands at 1690 cm^{-1}, 1550 cm^{-1}[45] and a shoulder on the 1690 cm^{-1} band at 1650 cm^{-1} due to a C=C stretch.[68]

The N.M.R. gave final confirmation of the elimination by showing a two proton signal at δ 5.60 which was assigned to the olefinic protons. (The chemical shift for the olefinic protons of cyclohexene occurs at δ 5.57.[69])

The epoxidation with perbenzoic acid also proceeded smoothly giving what was presumed to be a mixture of the cis and trans-4-carbobenzoxyaminocyclohexene oxide (XXIII) in 92% yield.



XXIII

T.L.C. of the crude product on silica gel showed only two spots. The faint spot was at the same position on the plate after elution as was the starting olefin, XXII. Solvent changes did not increase the number of spots and the sharp melting range of 77.5-79° obtained after one recrystallization would tend to suggest that the second isomer was present in very minor quantities if at all.

The next stage of the synthesis required the removal of the protecting carbobenzoxy group while still retaining the epoxide. This

unfortunately proved to be an insurmountable problem. The hydrobromic acid-acetic acid hydrolysis previously employed would not be suitable because of the opening of epoxides by acids. It was hoped, however, that the hydrogenolysis of the carbobenzoxy group could proceed without touching the epoxide, but examination of the reaction product showed that the carbobenzoxy group remained while the epoxide was replaced by a hydroxyl function.

One other possibility that could be undertaken was the reduction of the urethan with a hydride in such a manner that it would not also reduce the epoxide group. As lithium aluminum hydride alone did not open beta-diisobutene oxide[70] (although it did open cyclohexene oxide[71]) perhaps a milder hydride such as tri-tert-butoxy-lithium aluminum hydride would react first with the urethan carbonyl and, if only one equivalent were used, not at all with the epoxide. When the reaction was performed, however, neither group reacted. It was then necessary to use a stronger reducing agent to attack the urethan. When lithium aluminum hydride was used and the products separated by column on silica gel, four fractions were obtained, and of these four only the smallest fraction (9 mg) appeared to have lost the urethan group. All four contained a hydroxyl group. This being the case the epoxide approach was abandoned.

3. Attempted intramolecular photochemical addition of 4-N-nitroso-and 4-N-chloro-aminocyclohexene.

As the addition of a suitably substituted amino group to the double bond of a cyclohexene system still looked promising, other methods were sought which would be more successful. One of the ones that was considered was the photochemical addition of N-nitrosamines

to double bonds. In 1967, Chow,[72] a pioneer in this field, had shown that N-nitrosopiperidine when added to styrene gave a high yield of the corresponding alpha-piperidinoacetophenone oxime. There are two problems with this type of addition, however. The first was that when cyclohexene was added to 2-methyl-N-nitrosopiperidine the yield of alpha-(2-methylpiperidino)cyclohexanone oxime fell to 11%. This suggests that an active olefin is needed for the reaction. The second problem results from the observation that if the carbon alpha to the nitrosamine group is tertiary, photo-decomposition is usually the preferred pathway whereas if the alpha carbon is secondary, the photo addition reaction takes place readily.[73] This is not always true as it was shown that N-nitroso-2,6-dimethylpiperidine when added to styrene gave an adduct although both alpha-carbons were tertiary.[72] This fact combined with the fact that the reaction to form a 7-azabicyclo[2.2.1]-heptane system is intramolecular rather than intermolecular would hopefully speed the rate of addition over that of decomposition, making the reaction still seem plausible.

Before the addition could take place, however, it was necessary to synthesize the desired N-nitroso derivative. As 4-acetamidocyclohexanol was available, and as reduction of an amide with lithium aluminum hydride is well known, it was deemed to be an excellent starting material. Nevertheless, the elimination of water from the molecule did not prove to be as easily performed as in the case of the carbobenzoxyaminocyclohexanol. Reactions of amides with thionyl chloride are known to undergo a von Braun type cleavage to give the alkyl chloride and alkyl cyanide.[74] In spite of this Della and Jefferies[27]

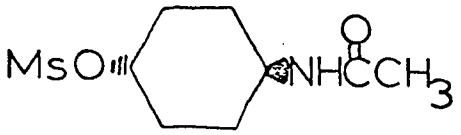
had reported that treatment of trans-4-benzamidocyclohexanol with thionyl chloride gave benzamidocyclohexene in good yield. When 4-acetamidocyclohexanol was treated with thionyl chloride the product of reaction was a black tar. A spectroscopic examination (I.R. and N.M.R.) of the residue showed it to be a mixture of olefins, nitriles and probably alkyl halides.

Other classical methods of dehydration such as treatment with sulfuric acid or phosphorous pentoxide required that the product be immediately distilled from the reaction mixture.[75] Because amides are usually non-volatile this was deemed to be somewhat difficult and was not attempted. Another possibility was to substitute the hydroxyl with an adequate leaving group and develop conditions which would favor elimination over substitution. This could be accomplished by doing the reaction in polar solvents with poor nucleophiles.[76]

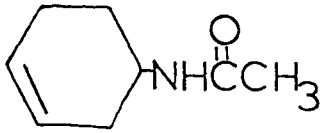
The first choice for a leaving group was the tosylate ester but the attempt at preparing the tosylate failed as the product could not be crystallized from the reaction mixture. The mesylate, on the other hand, could be prepared as a solid derivative without difficulty once the solubility problem encountered with the amide was solved. Since 4-acetamidocyclohexanol was unusually insoluble in solvents such as chloroform, methylene chloride or ethyl acetate, a mixed solvent system consisting of equal portions of pyridine and methylene chloride dissolved enough of the compound at 0° so that the reaction could take place without the problems which arise when large quantities of solvent are involved. The second problem encountered in mesylation reactions, that is the formation of a sulfene[77, 78] and its subsequent polymerization,[79]

was overcome if the reaction temperature was carefully controlled.

trans-4-Acetamidocyclohexyl methanesulfonate (XX) prepared by this method from only the trans isomer of 4-acetamidocyclohexanol could be identified from its I.R. spectrum by observing the N-H stretch at 3310 cm^{-1} [80] and the amide I and II bands at 1630 and 1550 cm^{-1} [44,81] respectively.



XX

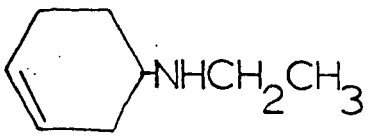


XXI

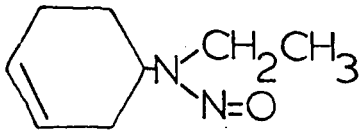
The sulfonate ester bands appeared at 1340 and 1170 cm^{-1}. [47, 80] The N.M.R. spectrum of the product clearly showed the methyl of the mesylate group at δ 3.00 and that of the acetamide group at δ 1.97.

Elimination of methanesulfonic acid from the mesylate ester (which was a mixture of cis and trans isomers) proceeded without difficulty in dimethylformamide when sodium methoxide was used as base. The product, 4-acetamidocyclohex-1-ene (XXI), showed amide bands at 3350, 1630, and 1550 cm^{-1} while mesylate bands at 1340 and 1170 cm^{-1} were completely absent. The N.M.R. spectrum of XXI showed a new peak of area equivalent to two protons at δ 5.63 indicating the presence of the olefinic protons.[69]

Refluxing XXI in a 20% sodium hydroxide solution gave 4-amino-cyclohexene previously prepared by Braun and Schwartz[10] and later by Hanack and Keberle.[82] Treatment of XXI with lithium aluminum hydride in tetrahydrofuran gave the corresponding ethyl substituted amine (XXIV) in good yield.



XXIV



XXV

Both of these compounds were isolated as hydrochloride salts for ease of handling. The N.M.R. spectrum of XXIV showed a broad triplet at δ 1.49 corresponding to the methyl protons of the ethyl group and a broad peak for the methylene protons of the ethyl group at δ 3.13. The methylene was a complex multiplet because vicinal coupling took place with the protons on nitrogen as well as on carbon.

N-nitroso-N-ethylcyclohexene (XXV), synthesized by the reaction of XXIV with an aqueous solution of sodium nitrite and hydrochloric acid had an N.M.R. spectrum which showed the methylene protons as the expected quartet at δ 3.99 with J = 7.0 Hz indicating that the extra coupling had been removed. The methyl triplet shifted to δ 1.20 (J = 7.0 Hz) and also sharpened. The N=O stretching band was apparent in the I.R. spectrum of XXV at 1430 cm^{-1} [83, 84] and the N-N stretching band appeared at 1059 cm^{-1} [84].

The nitrosamine, XXV, proved to be somewhat unstable as decomposition occurred after one week. This was shown by a marked increase in the yellow colour of the pale yellow liquid. For this reason a satisfactory analysis of XXV was not obtained.

The nitrosamine was then photolysed in methanol to which hydrochloric acid had been added. (Chow[72] had indicated that this solvent system gave the best conditions for photolytic addition.) Examination of

the crude photolysis product, isolated as its hydrochloride, showed that no bridgehead protons were present and therefore no addition had taken place. The I.R. spectrum of the neutral fraction showed bands at 1730 cm^{-1} and 1650 cm^{-1} indicative of 4-oxocyclohexene.[85] The N.M.R. spectrum of the basic fraction, appeared to have the character of the starting amine hydrochloride, XXIV, although the spectral integrals were not quite consistent with what one would have expected for pure XXIV.

The results obtained indicate that although the addition would have been intramolecular and therefore probably faster than an intermolecular one, photolytic decomposition of the nitrosamine was still the preferred pathway. This is in accordance with the original prediction for tertiary carbons, alpha to the nitroso group.[73] The products isolated are similar to the products isolated by Chow in the photolytic decomposition of N-methyl-N-nitroso-cyclohexylamine.[86] This being the case the nitrosamine route was abandoned.

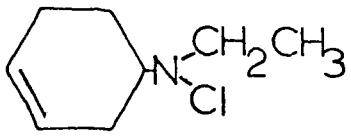
A route with equal potential to that of the nitrosamine but involving a slightly different mechanism was also considered. Neale,[87] in studying the reaction of N-chloroamines with olefins, showed that under acid conditions chloroamines photolytically added to olefins to give an alpha-chloroamine derivative. He proposed the following mechanism:

$$R_2NCl \xrightarrow{H+} R_2\overset{+}{N}HCl \xrightarrow{h\nu} R_2NH^{\cdot+} + Cl^{\cdot}$$

$$\text{olefin} + R_2\overset{+}{N}HCl \longrightarrow R_2\overset{+}{N}H\text{-}\dot{C}\text{-}\dot{C}\cdot \longrightarrow R_2NH\text{-}\dot{C}\text{-}\dot{C}\text{-}Cl + R_2NH^{\cdot+}$$

Once again, however, there was a problem. A competition was involved in

the initial decomposition of protonated N-chloroamines. The protonated chloroamine could react either by the free radical decomposition proposed above or could decompose ionically to give R_2NH and Cl^+. The evidence given for this ionic decomposition was that some of the reaction products isolated were alpha-chloroacetates rather than alpha-chloroamines when acetic acid was used as the solvent medium. Usually, however, the photochemical decomposition took precedence over the ionic decomposition and the major product of reaction was the alpha-chloroamine. With this in mind the N-chloroamine (XXVA) was prepared by the reaction of XXIV with sodium hypochlorite.



XXVA

As chloroamines are not noted for their stability,[88] XXVA was not purified further and was used immediately. The reaction was performed under the same conditions as those employed by Neale. The product showed no bicyclic characteristics (i.e. no bridgehead protons were visible in N.M.R. spectrum), but the olefin had reacted as the olefinic protons were no longer present in the spectrum. It appeared that the reaction followed the ionic decomposition pathway and addition to the olefin of positive chlorine and an acetate ion then gave what was probably a mixture of chloroacetates. The I.R. spectrum of the residue confirmed that indeed an acetate group was present, but an attempted cyclization of this product using the conditions previously employed in the preparation of AEH from 4-aminocyclohexyl p-toluenesulfonate gave no

bicyclic product.

Minisci, in 1964, and in subsequent papers,[89] had suggested an alternate method of adding N-chloroamines to double bonds which did not involve an acidic media and therefore would not involve an ionic decomposition pathway. When an N-chloroamine was treated with either cuprous or ferrous ions, Minisci proposed that it added to an olefin only by the free radical pathway.

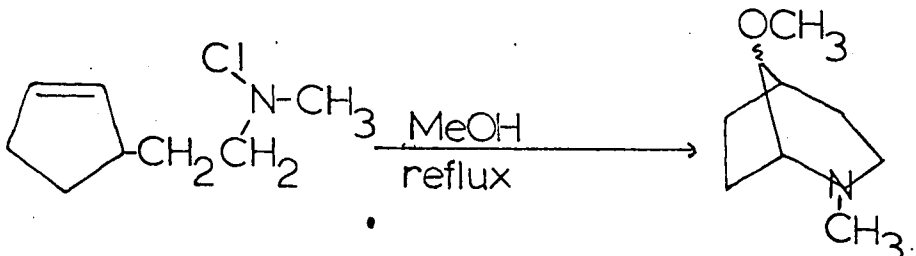
$$R_2NCl + Fe^{+2} \longrightarrow R_2\dot{N} + FeCl^{+2}\cdot$$

$$R_2\dot{N} + \dot{C}=\dot{C} \longrightarrow R_2N-\dot{C}-\dot{C}\cdot$$

$$R_2N-\dot{C}-\dot{C}\cdot + FeCl^{+2}\cdot \longrightarrow R_2N-\dot{C}-\dot{C}-Cl + Fe^{+2}$$

The solvent used for these reactions was methanol and the reaction temperature was usually -10 to 0°C. When XXVA was reacted under Minisci's conditions only 4-N-ethylaminocyclohexene XXIV could be isolated from the reaction mixture.

It was at first thought that the addition did not take place because the system lacked the necessary energy at low temperatures to overcome the barrier to a transannular addition, but a reaction in refluxing methanol did not produce any compound other than XXIV. It would appear then, that because the transition state is a strained one, provided it resembles the product to any great degree, competitive reactions involving lower energy states take precedence over the intramolecular addition. This is perhaps emphasized even more in the light of Gassman's[90] addition reaction.



In this case the system is much less strained than a bicyclo[2.2.1]-heptane system would be and the reaction does not require as much energy. Furthermore it proceeded without any catalyst.

4. Attempted cyclization of a dibromo derivative

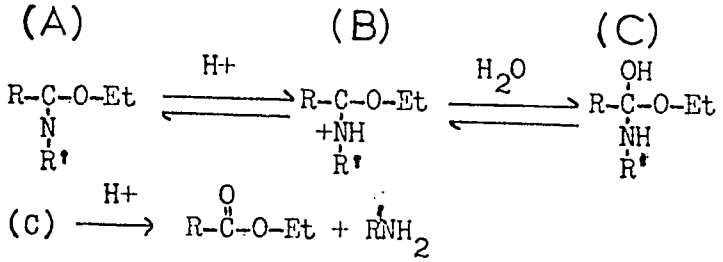
One other attempt to make use of the amino olefin was tried. Perhaps at first glance the addition of bromine or iodine to the double bond and then cyclization would appear to be a simple solution to the problem. Unfortunately, on closer examination of the situation, one sees that if the addition proceeds in a trans-diaxial manner[91] it would not give the required trans-amino halide needed to form the bicyclo[2.2.1]heptane system. Nevertheless it was hoped that a halide exchange could be accomplished by refluxing the dibromide that had formed from the reaction of bromine and 4-N-ethylaminocyclohexene with sodium iodide. This hope proved to be in vain as no bicyclic product could be found when the residue from the exchange reaction was treated with base in aqueous ethanol.

An attempt was also made to displace the bromonium ion directly with the free amine. It was felt that if the temperature was warm enough during bromination of the olefin the bromonium ion[92] that was formed could be displaced provided the molecule was in the boat configuration and provided the attack of the amine on the bromonium

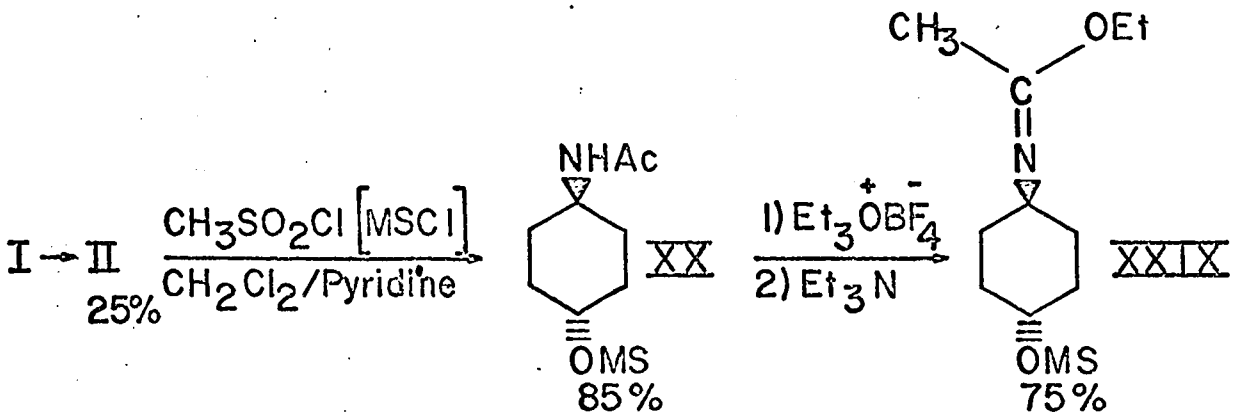
ion would be faster than the attack of the bromide ion on the bromonium ion. Unfortunately this did not prove to be the case and no bicyclic product could be isolated. The addition of hydrobromic acid across the double bond had been postulated by Braun and Schwartz[10] in their initial work as a possibility for forming the bicyclic system, but they proved this postulate to be untrue. It was then apparent that the olefinic route to the 7-azabicyclo[2.2.1]heptane system was not a profitable one.

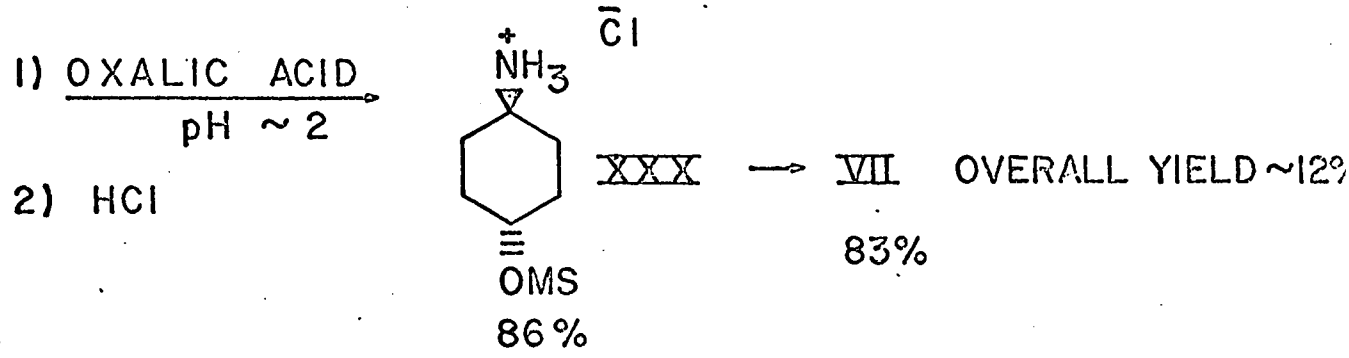
III. Treatment of XX with Meerwein's Reagent to obtain VII as shown in Scheme III

As an alternate method of synthesis could not be found, eliminating some of the less productive steps in the synthesis already at hand was considered. The worst step, and an unnecessary step as far as the structure of 7-azabicyclo[2.2.1]heptane was concerned, was the protection of the amine with some group before tosylation. The acetyl group, which had been present originally, had to be removed and a carbobenzoxy group put in its place. This, in turn, had to be removed. Since both of these steps had proceeded in only fair yields a tentative solution appeared to be the use of Meerwein's reagent,[93] triethyloxonium fluoroborate. (This reagent had been used successfully by Muxfeldt[94] to remove an N-benzamide group in high yield.) Alkylation of the amide occurs on oxygen rather than on nitrogen to give an alkyl imidate[95] and since the hydrolysis of imidate esters is acid catalyzed the resulting products are an ester and the corresponding amine.[96]



Scheme III


I → II
25%
CH3SO2Cl [MSCl]
CH2Cl2/Pyridine
NHAc
OMS
85%
XX
1) Et3OBF4
2) Et3N
CH3
OEt
C
N
OMS
75%
XXIX


1) OXALIC ACID
pH ~ 2
2) HCl
NH3
Cl
OMS
86%
XXX
VII
83%
OVERALL YIELD ~12%

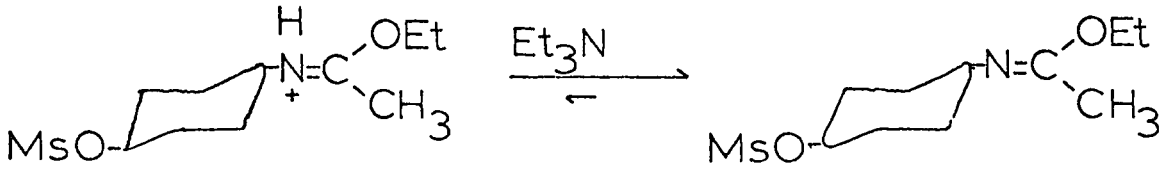
The acid can be either a mineral acid as above, or a carboxylic acid, the latter being the reagent preferred by Muxfeldt[94] and Knott.[97]

Theoretically, then, one should be able to treat the 4-acetamidocyclohexyl methanesulfonate with Meerwein's reagent and get the protonated imidate ester as its tetrafluoroborate salt. (See Scheme III) This should then hydrolyze immediately in an acidic medium to give the protonated amine and ethyl acetate. Unfortunately however, when Muxfeldt's conditions were tried or when any aqueous acidic conditions were tried the protonated imidate ester reverted to the amide. This could be seen by observing the appearance of the amide methyl peak at δ 1.97.

Theoretically it should not matter whether one starts with a protonated imidate ester and then adds acid and water or starts with the free imidate ester before the addition of acid and water, but in the case of XX it did appear to matter. The reason for this, perhaps, is that some imidate esters are much more sensitive to acid than others. Many are so reactive that even the addition of hydrogen chloride to the ester in an ether solution is enough to cause a reaction to take place.[98] If one looks at the mechanism of the hydrolysis one sees that species C can be protonated either on oxygen or on nitrogen. At a given pH the relative stability of the resulting carbonium ion will determine whether the compound loses a molecule of ethanol, in which case the carbonium ion would be stabilized by the lone pair on nitrogen, or whether the desired C-N cleavage occurs leading to the ester and the amine. The pH range in which the desired reaction could occur would therefore need to be determined for each individual compound

It is quite possible that the protonated form of the imidate ester from trans-4-acetamidocyclohexyl methanesulfonate (XX) is much more sensitive to pH than was Muxfeldt's compound. This is apparent when one takes note of the fact that Muxfeldt's reaction proceeded to product at pH's between 3 and 4.5 whereas the protonated imidate ester of XX in a medium above pH 2 and below pH 1.5 tended to return to the amide rather than proceed to product. The pH of a solution of the protonated imidate obtained directly from the Meerwein reaction tended to be outside this range and addition of external acid made the situation worse.

In conclusion, then, it was found that in order to hydrolyze the imidate ester formed in the Meerwein reaction it was necessary to isolate the unprotonated compound. This was accomplished by allowing the product from the Meerwein reaction to react with a large excess of triethylamine. Since the protonated triethylamine that is formed is virtually insoluble in methylene chloride the equilibrium between the two species is such that after a period of about 24 hours only the unprotonated form of the imidate ester is left.

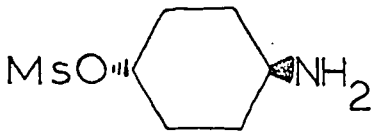


XXIX

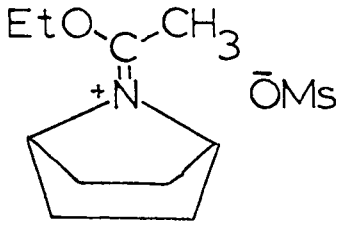
The imidate ester was then easily isolated from the reaction residue by extraction of the residue with boiling heptane.

When aqueous bases or salts of carboxylic acids were used instead

of triethylamine to isolate the free imidate ester, the yields fell remarkably and the amide was observed in the crude reaction mixture. This perhaps substantiates the previous conclusion that the protonated form of XXIX is extremely sensitive to pH and outside a very narrow range immediately collapses to amide. When the isolated imidate ester was subjected to an aqueous solution of oxalic acid at pH 1.5-2, a smooth hydrolysis in high yield was accomplished in 16 hours. The resulting trans-4-aminocyclohexyl methanesulfonate (XXX) was isolated as its hydrochloride salt.



XXX



XXXIII

One other interesting fact that was noted about the imidate ester was that if it was heated to 85 or 90° and carefully distilled under vacuum a product was obtained which had the characteristics of a bicyclic compound. The bridgehead protons were present in the N.M.R. spectrum of the compound and so was the methyl protons of an amide group. The compound produced was probably XXXIII. As the imidate ester, XXIX, also began to distill in this range of temperature and pressure, it was almost impossible to separate the two compounds. The residue in the pot (some 70% of the reacting material) no longer distilled after a short time and no longer had the characteristics of the imidate ester. This material was probably the product of an elimination and rearrangement.[99]

Cyclization of XXX was accomplished in a slightly less polar medium (80% aqueous ethanol) than was the cyclization of the corresponding

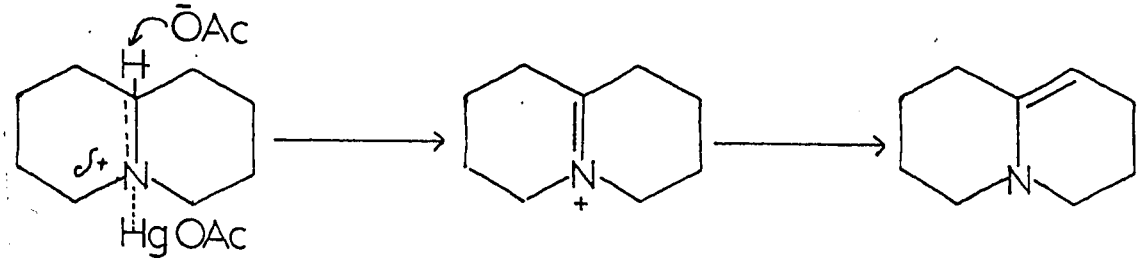
tosylate, VI. When a 70% aqueous ethanol solution was used it was noted that some elimination took place at room temperature whereas at -17° the reaction was very slow but little or no elimination was apparent. In 80% aqueous ethanol no elimination took place at room temperature but at -17° about 50% of XXX had reacted giving a ratio of 2:1 of eliminated product versus bicyclic compound. These facts appear to emphasize how much the delicate balance between temperature and polarity of the medium affect the proportion of cyclization to elimination.

What must be considered at this point is what effect has the successful hydrolysis of the imidate ester had on the overall synthetic scheme. By looking at Scheme III one can see that the overall yield of ABH was increased to about 12%. Although this is still not high enough to allow one to be satisfied with the synthetic method as a whole it was a definite improvement over the previous methods leading to the 7-azabicyclo[2.2.1]heptane system outlined in Schemes I and II and since this represented a plausible route to the system, the next synthetic problem to be solved was the one of placing a functional group on one of the carbons of the molecule.

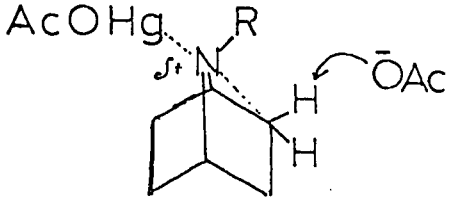
IV. Reactions of the ABH system

1. Attempted oxidations of the ABH system

It was first thought that placing a functional group on the molecule could be done with relative ease by use of a simple reaction such as the Leonard oxidation.[100] Leonard has shown that the treatment of a tertiary amine, such as quinolizidine, with mercuric acetate removes a proton from the alpha carbon and a subsequent migration of the double bond then takes place to form an enamine.



An exactly analogous situation would not be possible with the ABH system because to do so would violate Bredt's rule.[101] It was hoped, however, that perhaps a similar sort of reaction would take place at the two position because of the rigidity of the system.



Since true bonding would not be possible one might achieve substitution either by a solvent molecule or by an acetate ion at the two position. Unfortunately when the reaction was tried with either ABH or with 7-methyl-7-azabicyclo[2.2.1]heptane, prepared by the Leuckart method,[152] no reaction occurred after refluxing the mixture for long periods of time.

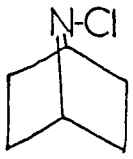
Another method was then considered. As camphane had been easily oxidized to a ketone in the two position by making use of chromium trioxide in an acetic acid and sulfuric acid medium[102] (although in only 20% yield) the attempt was made using VII. As the reaction proceeded, gas bubbles appeared to evolve from the solution. Work-up produced only about 20% of unreacted VII after five to seven hours, and as no other basic or neutral fractions were found it must be assumed that decomposition had taken place resulting in liberation of carbon dioxide and oxides of

nitrogen. A milder, although similar oxidation using chromic oxide[103] in refluxing-glacial acetic acid also failed.

2. Reactions of N-chloro-7-azabicyclo[2.2.1]heptane

Another reaction that was attempted with the ABH system arose when it was noted that Gassman and Cryberg[124] were able to rearrange 2-chloro-2-azabicyclo[2.2.1]heptane using silver perchlorate in methanol and obtained a product which had a chlorine substituted on a carbon of the ring. This appeared to be an extremely unusual reaction and it was thought that an identical reaction with 7-chloro-7-azabicyclo[2.2.1]-heptane might serve as a good test for the mechanism proposed by Gassman and Cryberg.

When the chloroamine, XII, was prepared and reacted in methanol in the presence of silver perchlorate, an almost quantitative amount of silver chloride precipitated from the reaction.



XII

The product, however, when isolated after a basic work-up, appeared to contain a mixture of which 55% was identified as VII. When a separation was done using thick-layer chromatography, a compound (3% yield) was isolated which was later identified both by spectral evidence and by an independent synthesis as 7-formyl-7-azabicyclo[2.2.1]heptane (XXXIV). The remainder of the residue, after VII had been removed, appeared from mass spectral evidence to be polymer. At first it was thought that this reaction was due to the N-chloroamine in some manner but on successive

reactions which employed no change in reaction conditions but involved only time differences in the work-up, the N.M.R. spectra of the residues were not the same. It was then discovered that when VII was placed in a methanolic solution with silver perchlorate and if hydroxide was added, both the N-formyl derivative of ABH and polymer were formed. Confirmation that it was not the N-chloroamine which reacted is provided by the fact that in a work-up of the reaction without base only the hydrochloride and hydroperchlorate salts of ABH were found.

Although no attempt was made to find a mechanism for this reaction, it was noted that when dimethylamine and silver perchlorate were placed in a methanolic solution, a reaction took place and the residue from the reaction mixture showed that some component of the mixture did have a formamide group as identified by the peak at δ 7.61.[69] The conclusion reached about the reaction is that thermolysis[125] of the chloroamine in methanol took place giving back ABH. ABH then reacted with the methanol, hydroxide, and excess silver perchlorate to give the observed products.

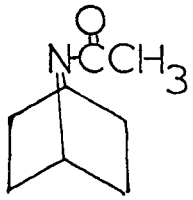
A Hofmann-Löffler[19] reaction of 7-chloro-7-azabicyclo[2.2.1]heptane also failed to take place. It was hoped that a hydrogen would be abstracted from the two position to give a radical which could then either pick up chlorine or an acetate group. The reaction yielded a mixture of at least six compounds. A separation of these using T.L.C. was attempted without much success and as such the reaction was abandoned as synthetically useless. No attempt was made to identify any of the components.

3. Attempted chlorination of the ABH system

One interesting and reasonably unusual reaction that involves

chlorination of hydrocarbons was discovered by Bartlett and workers in 1944.[104] When tert-butyl chloride is reacted with a suitable hydrocarbon in the presence of a Lewis acid such as aluminum chloride, a chlorine-hydrogen exchange occurs. Schmerling[105] in 1946, using this method, was able to successfully chlorinate norbornane in 28% yield, but when the reaction with ABH was attempted, only starting material was isolated.

The reaction was also attempted with 7-acetyl-7-azabicyclo[2.2.1]-heptane (XI) which was prepared by the treatment of VII with acetic anhydride in the presence of sodium acetate.



XI

Once again no evidence for product was found. The amide itself, however, proved to have interesting N.M.R. spectral properties as it possessed magnetically non-equivalent bridgehead protons. (Figure i) These were observed at δ 4.62 and δ 4.10. A temperature study showed that these collapsed to a single peak at δ 4.36 when the temperature was raised. (The significance of this will be discussed under the section dealing with spectral properties of ABH systems.)

4. Free radical chlorination of the ABH system

Probably the most successful method for chlorination of hydrocarbons is by the use of a suitable free radical process. As norbornane had reacted with sulfuryl chloride in the presence of benzoyl peroxide to give a 1:1 mixture of dichloro and monochloro substituted norbornanes[126]

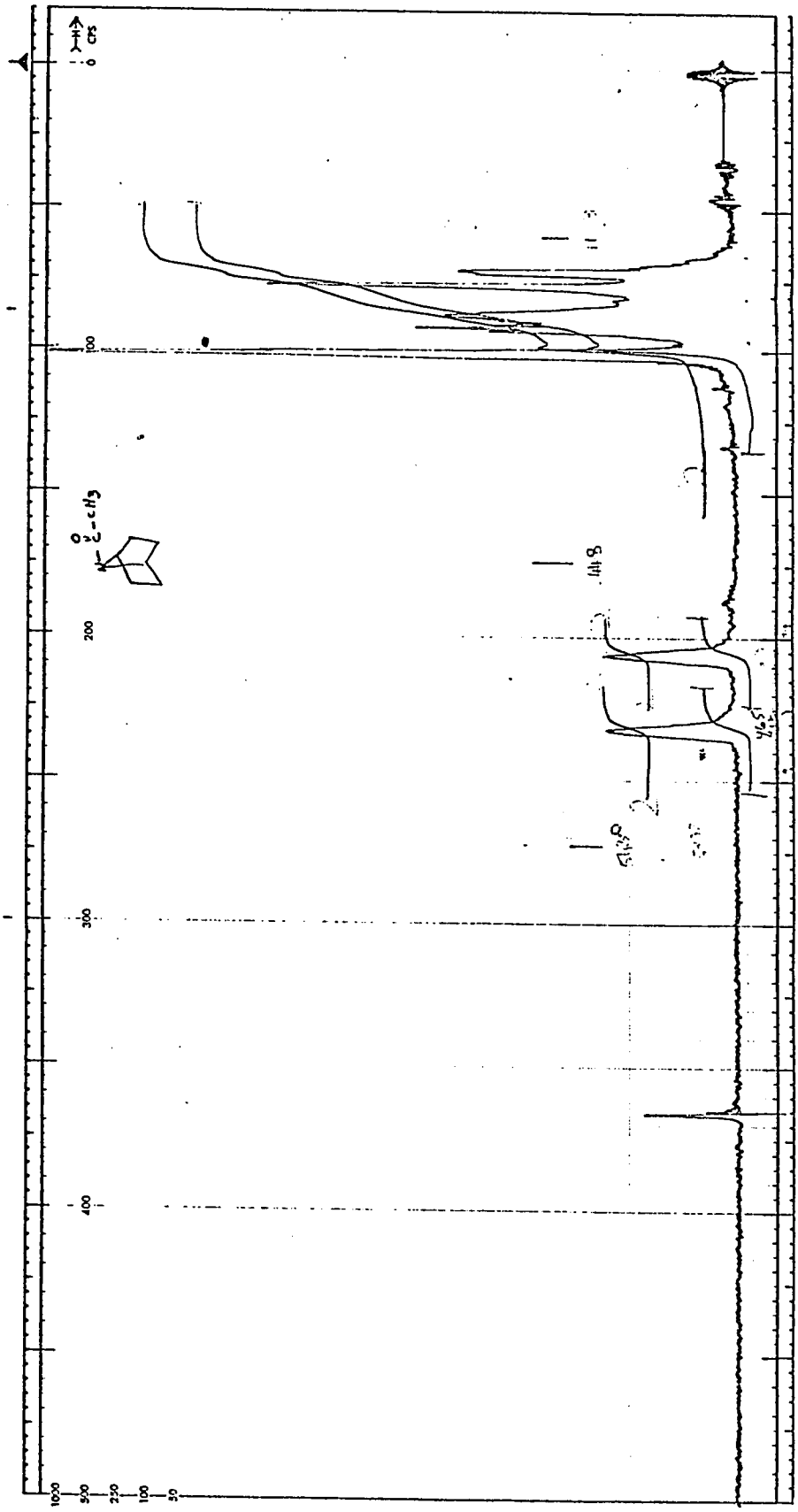
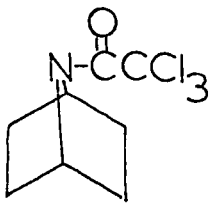


Figure 1

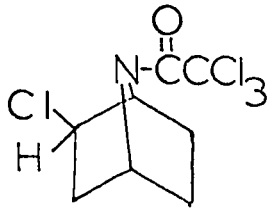
it was felt that this method might prove useful. To enable the reaction to proceed with a minimum of trouble, blocking the nitrogen of the parent compound would be essential and as the amide was probably the easiest blocking group to procure, this was the group of choice. To prevent the chance of a mixture of products the trichloroacetamide was chosen over the ordinary acetamide.

The synthesis of this amide was attempted at first by using the mixed anhydride or the acid chloride method in the presence of triethylamine. Unfortunately low yields on the order of 20 to 30% were the result and it wasn't until later that it was discovered that the triethylamine was reacting with the trichloroacetyl chloride to give a beta-acylenamine. (See discussion to follow.) A successful synthesis of the compound was only obtained when the base was changed to sodium carbonate and a two-phase Schotten-Baumann reaction was used. By dissolving the trichloroacetyl chloride and the amine in dichloromethane, the acid chloride was protected from hydrolysis long enough to react preferentially with the amine.

The free radical chlorination under the conditions employed by Roberts and co-workers[126] gave the desired product.



XIII



XIV

In order to obtain the highest yield of XIV without forming a dichlorination product, monitoring of the reaction mixture by T.L.C. was necessary. The reaction was allowed to proceed until the first traces

of the disubstituted product appeared on the plate. (This could be seen as a tail of the spot for XIV after one elution, but a second elution usually succeeded in separating the two spots.) At this point the reaction was probably close to 50% complete as shown by the recovery of about half of the amount of XIII that went into the reaction. Allowing the reaction to proceed further increased the amount of the disubstituted products which were (from N.M.R. evidence) a mixture of 2,5- and 2,6-dichloro-7-trichloroacetyl-7-azabicyclo[2.2.1]heptanes. These appeared to be inseparable by T.L.C.

The mixture of mono- and disubstituted products and starting material was adequately separated either on a column of silica gel or by using thick layer chromatography on a base of silica gel with a 15% hexane:ethyl acetate mixture employed as an eluent.

The N.M.R. spectrum of XIV (Figure ii) showed a two proton signal at δ 4.90 which was assigned to the two bridgehead protons. A triplet at δ 4.10 corresponding to one proton and a peak at δ 2.24 corresponding to two protons and coupled to the triplet were assigned to the X and AB part of the ABX spectrum respectively.

It must be noted that although the X part of the spectrum is a triplet and not the expected six lines and the AB is a doublet, the spectrum appears this way since $\nu_0 \delta_{AB}$ is very small or zero. This is essentially an A A' X spectrum and as such it is impossible to determine J_{AX} and J_{BX}. One can only determine $|J_{AX} + J_{BX}|$. (10 Hz).

Irradiation of the bridgehead protons in a decoupling experiment did not change the shape of the triplet but did clearly make the poorly resolved methylene absorption change into a doublet. Since the

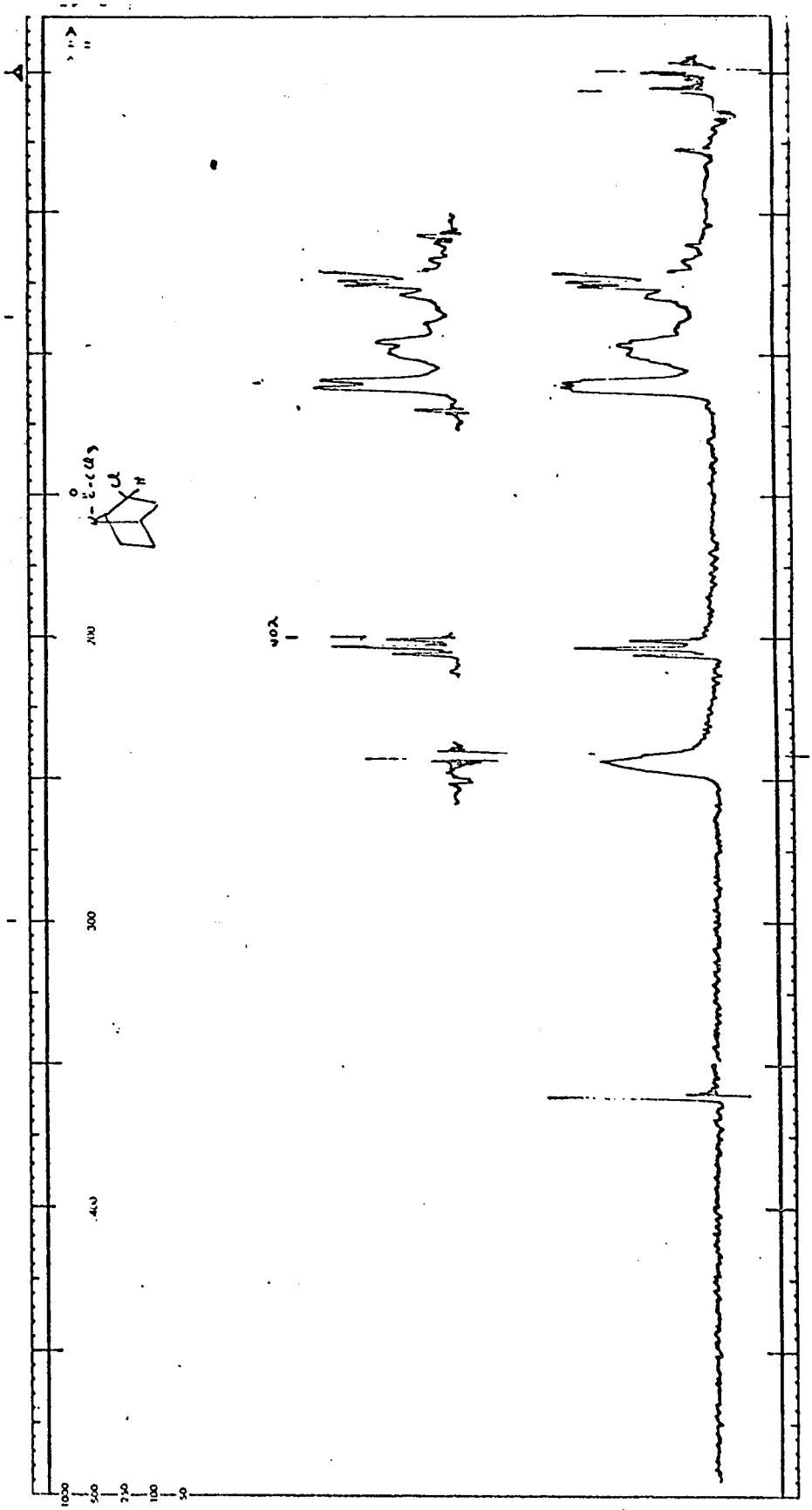


Figure ii

bridgehead protons were not coupled to the hydrogen on the carbon bearing the chlorine it can be concluded that the chlorine is in the exo position. The Karplus[173] rule states that vicinal coupling for a dihedral angle of 90° (the angle between the endo position and the bridgehead protons) is minimal.

5. Solvolysis of the chloro-substituted ABH system

Now that the goal of a monosubstituted 7-azabicyclo[2.2.1]heptane system had been achieved it was hoped that the chloride could be converted to the hydroxy function from which easy access would be available to both endo and exo derivatives. A solvolysis was undertaken at first with XIV because it was thought that solvolysis of the free amine would cause rearrangement and degradation, since a rearrangement was observed for the solvolysis of 2-chloro-7-oxabicyclo[2.2.1]heptane.[117] Under mild conditions such as refluxing 80% aqueous ethanol, a solvent system known to solvolyze endo and exo-chloronorbornanes,[138] XIV did not react. When the reaction was repeated using lithium carbonate as a base, a product (less than 10% yield) was formed which appeared (N.M.R.) to contain a double bond and the remainder of the residue appeared to be mainly XIII. Identification of the compound with the double bond was not possible. This being the case it was thought that an increase in the polarity of the solvent might benefit the reaction. When a 60% aqueous ethanol solution was used, five spots appeared on T.L.C. of the residue. The spot which did not move could quite possibly have been more than one compound.

With the hope of finding a system which would produce only solvolysis products, reactions at reflux temperatures with a variety

of solvents and bases were tried. Figure iii is a list showing the solvent system, the base, the time of reaction, and the number of spots seen on the T.L.C. of product after removing the solvent from each 10 mg reaction. (In each case there was one spot which did not move.)

From this table the following things were noted. The number of spots increased markedly when water was present. In all such systems the spots produced moved approximately the same relative distance on T.L.C. and therefore were probably the same compounds.

Perhaps the most significant point of note was that when acetone: water was used as a solvent system, eight (or more) spots were seen. This is highly suggestive of the fact that hydrolysis of the amide group was also taking place and the resulting amine was reacting with the acetone.[139] This in turn would tend to suggest that the spots which did not move or tailed on the plates were amines and those which did move were various amide derivatives.

Since solvolysis of XIV did not seem to be successful an attempt was made to dehydrohalogenate XIV rather than solvolyze it. The system chosen for this reaction was potassium tert-butoxide in tert-butanol as this system had been noted to dehydrohalogenate even difficult systems.[140]

As soon as XIV was added to the tert-butanol and base, bubbles started to evolve from the solution. The product that was isolated was still a bicyclic compound but had lost the trichloroamide group. The N.M.R. spectrum of this compound (Figure iv) clearly showed the separate bridgehead protons at δ 4.45 and δ 4.30 (one proton). The AB part was shown at δ 1.56 (two protons) and the X at δ 4.11. (The ABX pattern was much more clearly evident in this compound than in XIV.) A peak at

Figure iii

Solvent	Base	Time	# of Spots
H_2O	$BaCO_3$	16 hours	6
50% acetone/H_2O	--	16 hours	8
EtOH	$BaCO_3$	16 hours	2
EtOH/H_2O 30%	$BaCO_3$	48 hours	2 distinct & 3 faint
EtOH/H_2O 20%	$BaCO_3$	48 hours	2 distinct & 1 faint
H_2O	--	48 hours	4
50% H_2O/HCOOH	--	48 hours	4 faint
EtOH/H_2O 60%	$AgNO_3$	16 hours	5
HOAc	NaOAc	48 hours	5
HCOOH	NaOAc	48 hours	5
H_2O	$AgNO_3$	24 hours	5
HBr/H_2O	NaBr	24 hours	5
30% H_2O_2/H_2O	--	24 hours	5

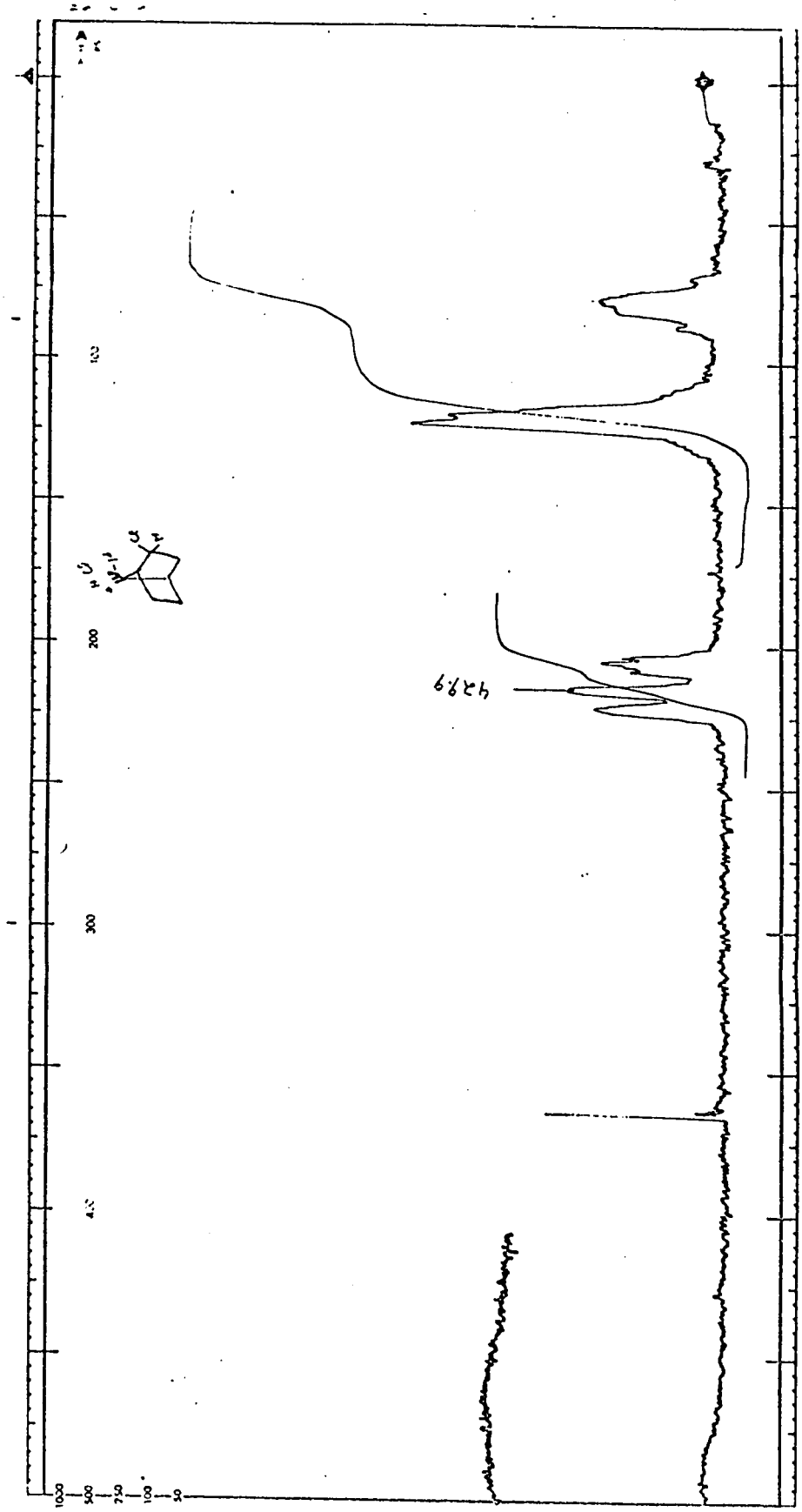
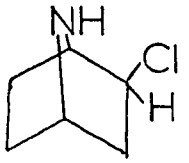


Figure iv

δ 2.20 showed the presence of four protons. No change was noticed in the remainder of the spectrum when the bridgehead protons were irradiated. The I.R. spectrum clearly indicated that the compound was a secondary amine hydrochloride. This was shown by the characteristic pattern at 3000-2550 cm^{-1} and by the 1610 cm^{-1} band.[51] The mass spectrum (discussed later) showed no molecular ion but did show an $(M-36)^+$ peak which had the characteristic ratios for a molecule containing one chlorine.[127] The compound was then assigned the structure consistent with exo-2-chloro-7-azabicyclo[2.2.1]heptane (XXXI). (XXXI had been isolated as its hydrochloride to prevent loss due to possible volatility.)



XXXI

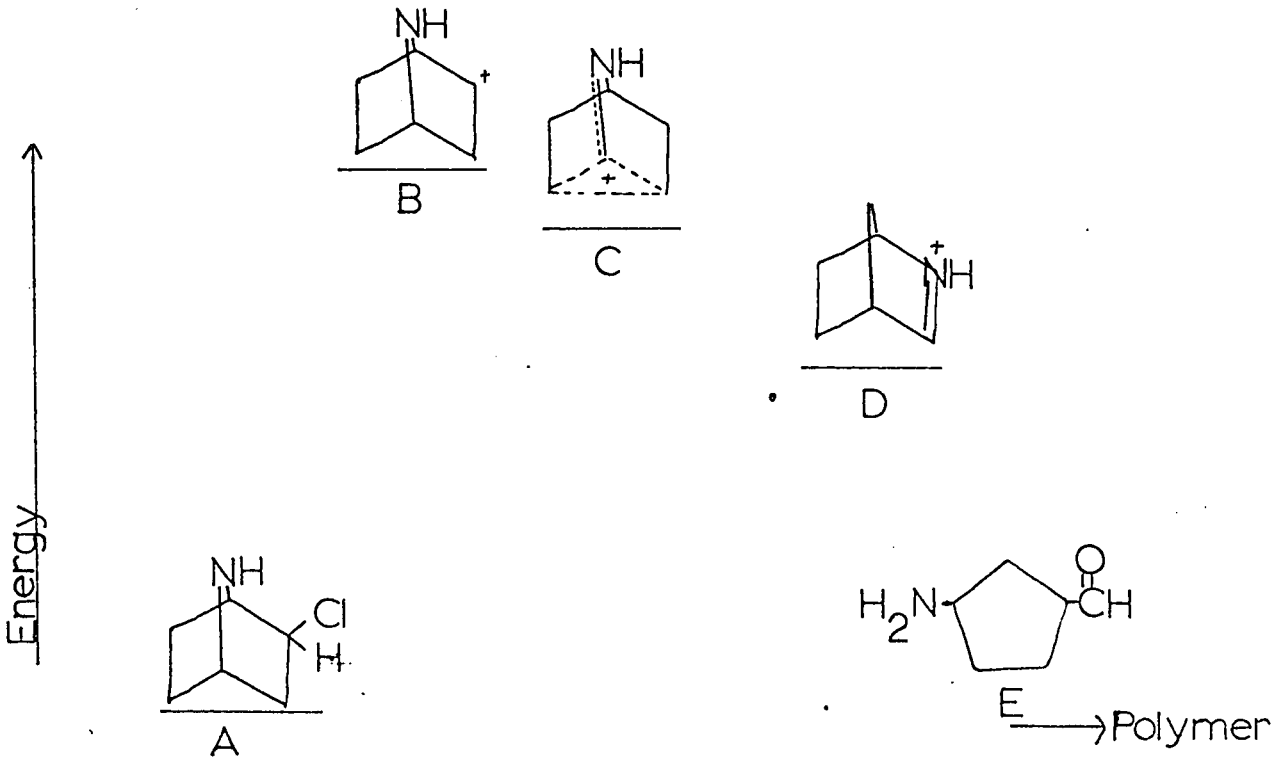
When the solvolysis of this compound was attempted in acetic acid and sodium acetate it appeared as if no reaction had taken place. When the solvent medium was changed to methanol and sodium methoxide the N.M.R. spectrum of the residue showed that one of the bridgehead protons (δ 4.45) appeared to broaden slightly. No other change could be detected. It was then thought that perhaps the partial reaction which had taken place was due to hydroxide ion present in the solid sodium methoxide as this ion is smaller than the methoxide ion and better able to attack in a sterically hindered system. (Examples of this are shown in the preferential solvolysis of norbornyl chlorides in 80% aqueous ethanol to give exclusively the hydroxy derivative and not the derivatives of ethanolysis.)[138] A 50:50 mixture of methanol and water

was prepared and XXXI was reacted in this solution in the presence of sodium hydroxide for 24 hours at 110°. The N.M.R. spectrum of the residue showed that no bicyclic compound remained.

That solvolysis failed to occur in the methanol:sodium methoxide medium might not be too strange since it must be noted that solvolysis of the 7-oxa derivative in 80% ethanol was about 10^3 slower than norbornyl chloride, reaching 100% completion after 87 hours at 85°.[117] It is therefore clear that XXXI is much less reactive than the oxa analog even with one equivalent of methoxide present.

That no solvolysis took place in an acid media is also not surprising if one considers that protonation of the amine would retard formation of a carbonium ion as two positive charges in the molecule would slow the rate of solvolysis by making the transition state less stable.

In analogy to the 7-oxa system,[117] what probably took place in the aqueous methanol reaction was the following.



A Wagner-Meerwein shift of the carbonium ion B through C would probably result in the more stable iminium ion D in exactly the same manner that the oxonium ion was formed in the solvolysis of the 7-oxa derivative. Subsequent attack of water or hydroxide ion would then hydrolyze the iminium compound to the corresponding amine and aldehyde.[141] This could then quite easily react with other molecules present in the solution. (No trace of aldehyde could be found in the spectrum of the residue.)

Very similar reactions probably took place with the trichloroacetamide XIV. The numerous compounds which resulted were due to a) solvolysis of the amide and then reaction, b) amide exchange and subsequent reaction, c) solvolysis of the chloride with subsequent reaction. However, it would appear from the solvolysis products of XXXI that perhaps a certain percentage of the amide reaction did give a desired bicyclic product but it would be highly questionable whether the yield of such a product would have been synthetically useful.

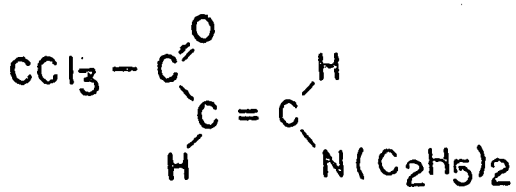
XXXI also appeared to be inert to dehydrohalogation as observed by its reaction in the presence of sodium methoxide in dimethylformamide. The N.M.R. spectrum of the crude residue showed no new peaks and only XXXI could be isolated from the reaction.

V. Reaction of trichloracetyl chloride and triethylamine

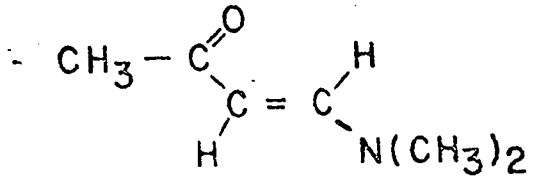
Perhaps the most interesting thing that was derived from the preparation of 7-trichloroacetyl-7-azabicyclo[2.2.1]heptane (XIII) was the discovery that triethylamine, actually reacted with trichloroacetyl chloride. The mass spectrum of the solid product XVI showed a molecular ion at m/e 243 which had an isotope ratio of the $(M)^+$, $(M+2)^+$, $(M+4)^+$ peaks which indicated that three chlorines were present.[127]

The N.M.R. spectrum of XVI (Figure v) showed peaks at τ 7.68 (doublet of spacing 12.5 Hz, area one), τ 5.46 (doublet of spacing 12.5 Hz, area one), τ 2.37 (quartet of spacing 6.8 Hz, area four), τ 1.28 (triplet of spacing 6.8 Hz, area three), and τ 1.23 (triplet of spacing 6.8 Hz, area three). The strongly coupled AX pattern for the two protons at low field is typical of two vicinal olefinic protons trans to one another on a double bond to which nitrogen is attached.[128] The high field quartet arises from two non-equivalent methylene quartets which fortuitously overlap. This assignment was substantiated by the observation that at 0° or lower the two quartets separated. The two triplets are due to methyl absorption of the two ethyl groups.

The I.R. showed carbonyl C=C bond absorptions at 1663 and 1575 cm^{-1} respectively. A tentative assignment of structure (XVI) was then made for the compound



XVI



XIX

This assignment was supported by the fact that the corresponding bands in the I.R. spectrum of 4-N,N-dimethylamino-3-buten-2-one (XIX) occur at 1673 and 1586 cm^{-1}. On the basis of this information and the fact that Dabrowska and Dabrowski[129] found a third I.R. band at 1623 cm^{-1}, attributed to the s-trans rotamer in XIX, which was absent in the

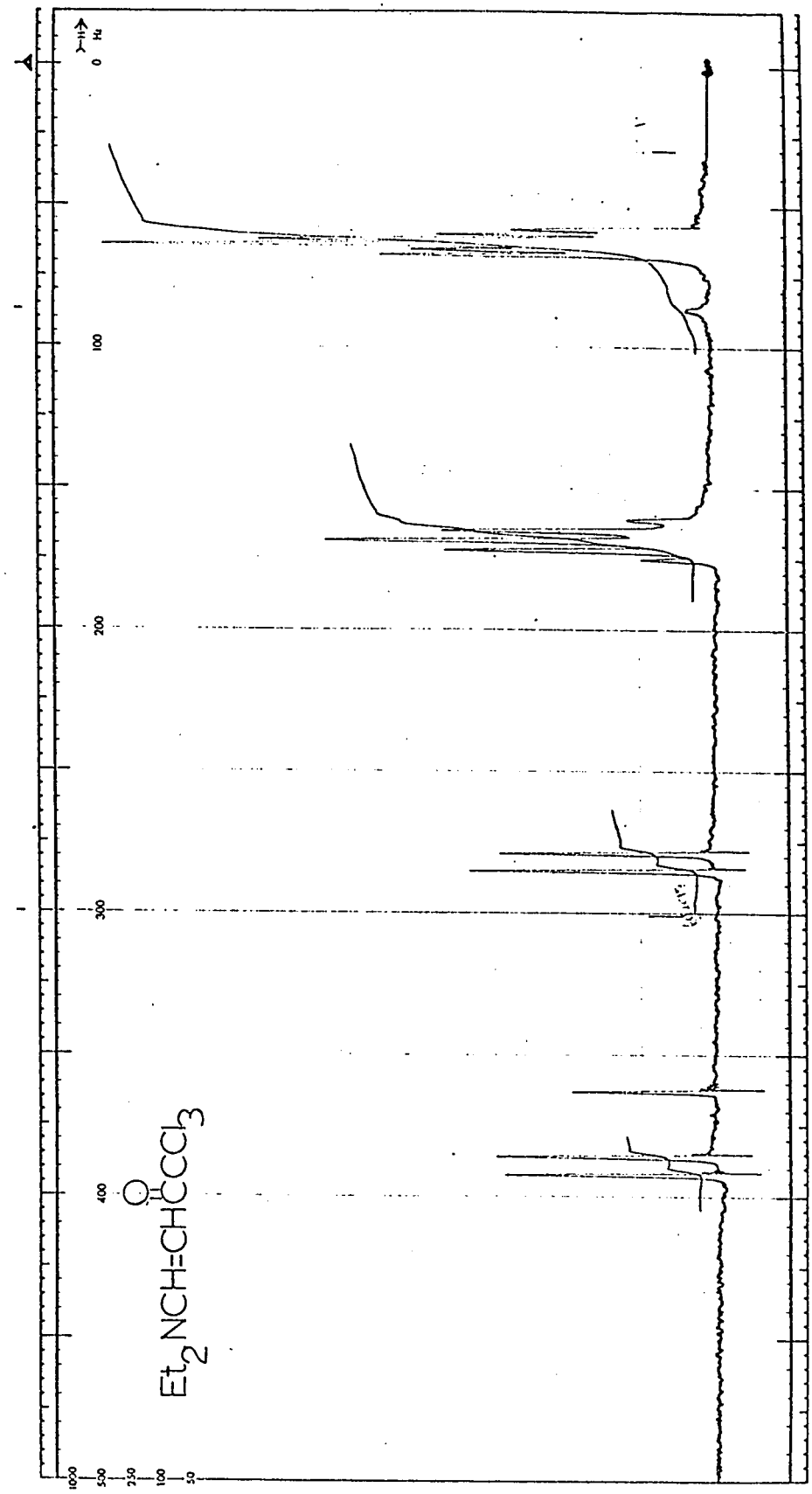


Figure V

spectrum of XVI, it could be concluded that the 1663 cm^{-1} band was due to the s-cis configuration of the molecule and therefore the final structure that was assigned the compound was that of 4-N,N-diethylamino-1,1,1-trichloro-3-buten-2-one (XVI).

When a temperature study was made of XVI no barrier to rotation could be found about the C_2-C_3 bond although one had been found for XIX.[128b] The barrier about the N-C_4 bond was found to be larger in XVI than in XIX as the coalescence was observed at +40° in XVI. An estimate of the barrier reported for XIX using the relationship $k = \frac{\pi \Delta \nu_{AB}}{\sqrt{2}}$ at Tc showed the barrier for XVI to be about 2 kcal greater that for XIX. This can perhaps be attributed to an increase in resonance energy for XVI over XIX as a result of the electronegative stabilization effect of the three chlorines.

Proof of structure was obtained by the successful synthesis of XVI by an alternate route. Diethylvinylamine was formed by the reaction of diethylamine with acetaldehyde in benzene.[130] Then in situ acylation[131] by the addition of trichloroacetyl chloride gave XVI in about 5% yield. The compound XVI could also be prepared in poor yield (5%) using trichloroacetic anhydride in place of trichloroacetyl chloride. (Reaction of trifluoracetic anhydride with triethylamine gave no evidence for the formation of any beta-acylenamines.) The mechanism of this reaction appeared to be unusual as a similar pair of reactants, dichloroacetyl chloride and triethylamine, yielded not a beta-acylenamine, but trichlorovinyldichloroacetate via acylation of an enolate anion.[132]

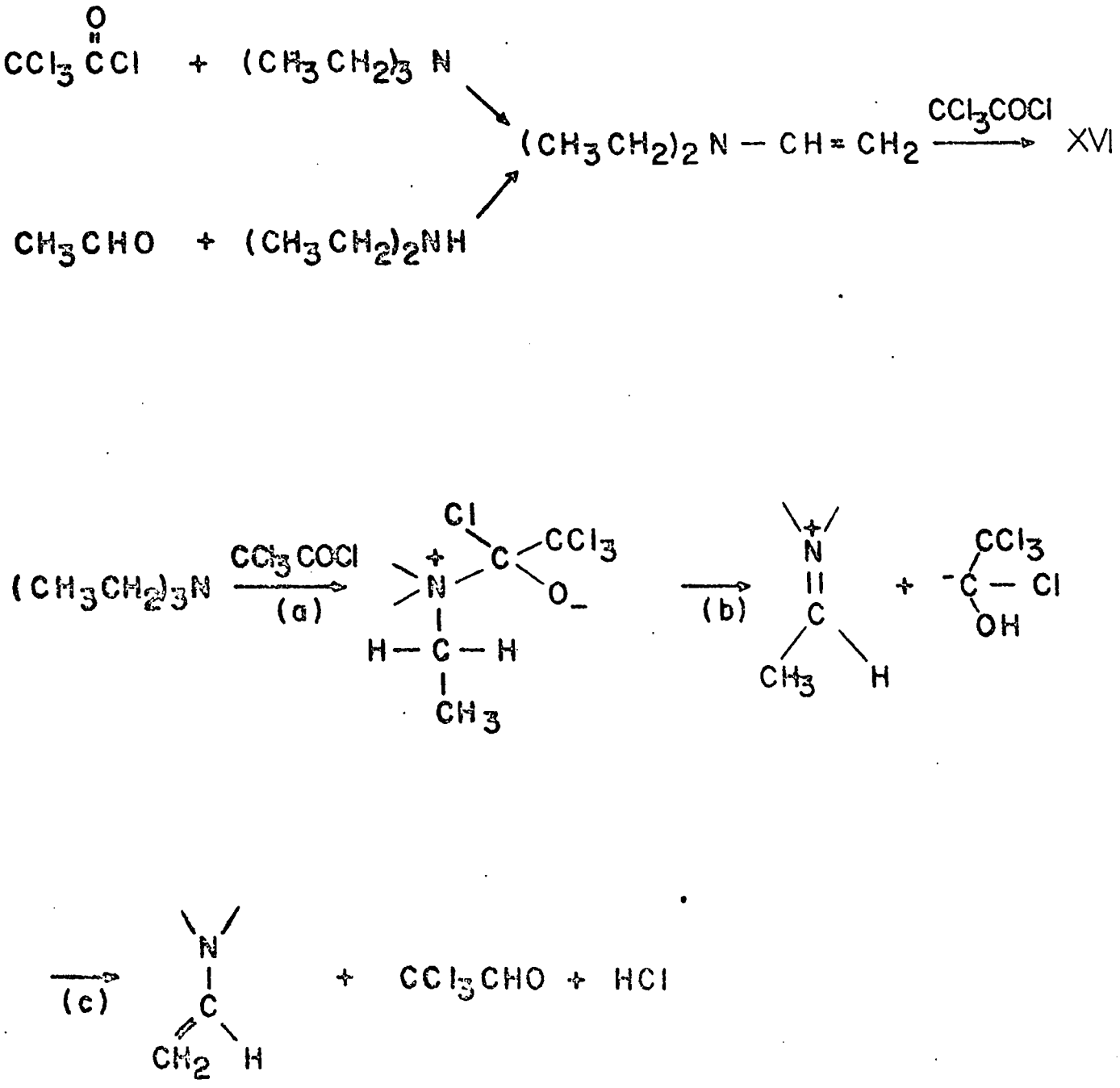
It was at first considered possible that the reaction proceeded by a free radical pathway, but as no change in reaction products or yield

occurred when the reaction was performed with scrupulously purified reactants in the dark, or in an oxygen free atmosphere, or in the presence of styrene the indications were that a free radical pathway was not involved.[133]

Evidence was then sought for some other product of reaction. The examination by mass spectrometry of the gases produced by the reaction failed to show any carbon monoxide, but the presence of trace amounts (less than 1%) of ethylene was revealed. An examination by mass spectrometry of the distillate from a crude reaction mixture also revealed trace amounts of N-N-diethyltrichloroacetamide. The N.M.R. of these distillates revealed one proton-containing product which was identified as trichloroacetaldehyde by its chemical shift (δ 9.00). The observation of a band at 1759 cm^{-1} in the I.R. spectrum of this distillate confirmed the N.M.R. evidence. (The spectra were compared to spectra of a sample of authentic trichloroacetaldehyde.) From the intensity of this band, the calculated yield of chloral in the distillate was estimated to be 25% ($\pm$ 10%). On this basis a mechanism was proposed. (See Scheme IV)

The reaction of a nucleophile with an acid halide is generally believed to form an initial addition product similar to the intermediate formed by nucleophilic attack of an ester carbonyl. Evidence for this was found in the reaction of ethoxide ion with ethyl trifluoroacetate.[134] It would be reasonable to expect that the same sort of intermediate would be formed in step a. I.R. evidence for this intermediate was sought but no change in the spectrum of trichloroacetyl chloride could be seen on the addition of triethylamine. Step b of the

Scheme IV

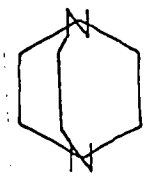

CCl3CCl
(CH3CH2)3N
CH3CHO
(CH3CH2)2NH
(CH3CH2)2N — CH = CH2
CCl3COCl
XVI
(CH3CH2)3N
CCl3COCl
(a)
(b)
(c)
CCl3CHO + HCl

proposed scheme could be a concerted cyclic process involving abstraction of the proton alpha to the nitrogen and a synchronous C-N bond cleavage. Formation of trace amounts of ethylene and N,N-diethyl trichloroacetamide could be accounted for by the attack of the oxy-anion of the intermediate on a beta hydrogen also in a concerted fashion. Loss of a proton in step c gives the enamine which is then attacked by another trichloroacetyl chloride molecule to give the product while in the other reaction product, proton migration to the carbanion and loss of chloride ion produces chloral.

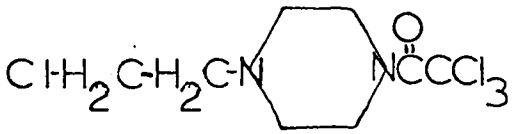
This mechanism is similar to several which have been accepted for other amine oxidations in the sense that an addition and then elimination reaction occurs. Such a sequence takes place for amine oxidations by bromine,[135] nitrous acid,[136] and mercuric acetate.[137]

The unusual aspect of the mechanism is the necessity to employ carbon as a leaving group. However, the case is justified in that the carbanion bears three electronegative substituents which could provide excellent stability as is found for the trichloromethyl carbanion.

To test the validity of the proposed mechanism an oxidation of 1,4-diazabicyclo[2.2.2]octane (DABCO, XVII) was carried out. The mechanism would predict XVII to be inert since the formation of an iminium salt at the bridgehead of a bicyclic ring is prohibited by Bredt's rule.[101] When DABCO and trichloroacetyl chloride were allowed to stand for one day it was found however that a reaction did occur. The product formed in 5% yield was not a product of an oxidation but a degradation. It was identified by structural and chemical evidence to be N-2-chloroethyl-N'-trichloroacetyl-piperazine (XXVIII).

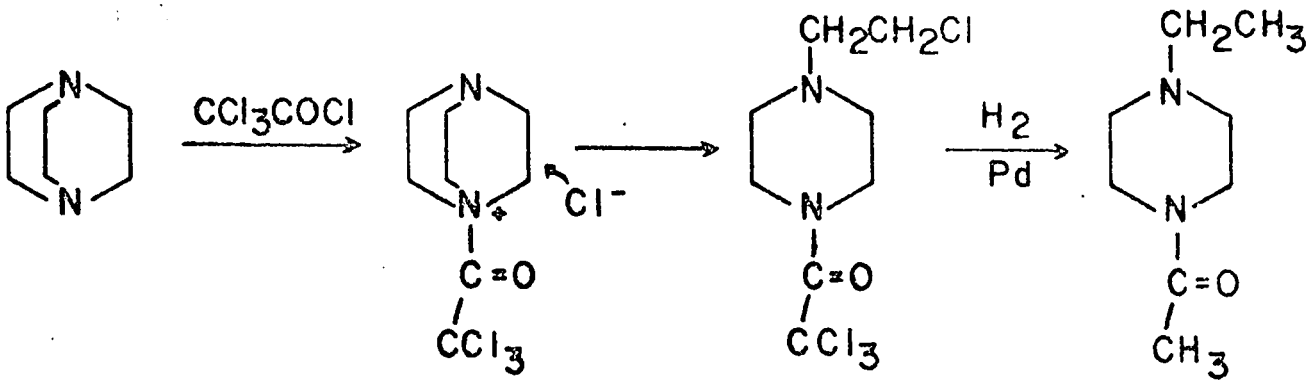


XVII (DABCO)



XXVIII

The N.M.R. showed a four proton triplet at δ 3.83, a two proton triplet at δ 3.55, a four proton triplet at δ 3.60, and a two proton triplet at δ 2.26. The I.R. showed strong carbonyl absorption at 1675 cm^{-1}. The mass spectrum showed a molecular ion at m/e 292 having $(M+2)^+$, $(M+4)^+$, $(M+6)^+$, and $(M+8)^+$ peaks in an intensity ratio typical of a tetra-chloro compound.[133] When XXVIII was reduced using a palladium catalyst a liquid resulted whose N.M.R. showed the presence of a methyl at δ 1.00 (triplet J = 6.75 Hz, three protons), a singlet at δ 1.99 (three protons), a complex multiplet at δ 2.34 (six protons), and two triplets at δ 3.40 and δ 3.56 having J = 5.0 Hz of an area equivalent to two protons each. The appearance of the methyl and ethyl group, absent in XXVIII confirmed the presence of chlorines in XXVIII as CCl_3 and CH_2-CH_2-Cl functions. A chemical proof of synthesis was not undertaken. The reaction of DABCO with trichloroacetyl chloride was then believed to be the following. Because oxidation is prohibited by the geometry of the bicyclic amine, a von Braun type[174] of degradation occurs.



The possibility that the oxidation of a tertiary amine might be a general reaction with trichloroacetyl chloride was also investigated. The reaction mixture from a reaction with N-methylpyrrolidine indicated that a beta-acylenamine had been formed but only in a very small yield (less than 5%). Since this product showed a pronounced instability, optimum conditions were not sought. The reaction mixture also contained numerous other reaction products none of which were identified.

VI Spectral properties of some ABH systems

1. N.M.R. studies of the non-equivalence of the bridgehead protons in 7-acetyl-7-azabicyclo[2.2.1]heptane

It is noted that any nucleus can undergo exchange between two sites having a different chemical shift at each site.[106] When this process is slow, two separate signals will be seen for the resonance of this nucleus. When the temperature is raised this process speeds up until a temperature is reached where only a single resonance line occurs at an

intermediate shift position. This temperature is called the coalescence temperature. The rate of exchange between the two sites at this coalescence temperature is determined by the chemical shift difference between the two sites. At the coalescence temperature, k, (which is the rate of exchange) equals $\frac{1}{2}\tau$ where τ is the mean lifetime of the nuclei at a particular site and is given by $\tau = \frac{\tau A \tau B}{\tau A + \tau B}$

At the coalescence temperature $\tau = \frac{\sqrt{2}}{2\pi(\nu A - \nu B)}$ [107]

where νA and νB are the chemical shifts of the two nuclei.

The rate for this exchange is $k = k_o e^{\frac{-\Delta F}{RT_c}}$ where ΔF is a measure of the free energy associated with the barrier to the exchange of sites, R is the gas constant and T_c is the coalescence temperature.

$k_o = \frac{BT_c}{h}$ B = Boltzman's constant and h is Planck's constant.

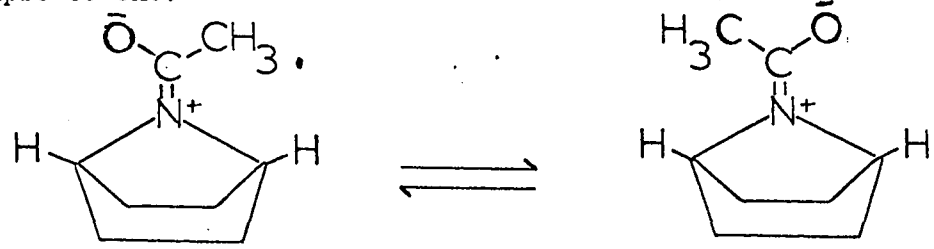
The final equation which shows the free energy associated with the transition is

$$k_o e^{\frac{-\Delta F}{RT_c}} = \frac{\pi(\nu A - \nu B)}{\sqrt{2}}$$

Although the measurement of an energy barrier by using the data gathered at only one temperature is not the ideal method[108] the error introduced by this method at the coalescence temperature is usually small.[109]

The coalescence temperature for the bridgehead protons of XI was found to be 75° which means that the free energy barrier to the exchange process is 17.1 kcal. The question then arises as to what exchange process is actually being observed. The first answer is that the process could be due to a barrier caused by hindered rotation about the C-N bond of the amide. If there is a barrier to rotation about

this bond, the two bridgehead protons are not magnetically equivalent and one sees two signals for them. When the temperature is raised the barrier is overcome and faster exchange causes the two signals to collapse to one.



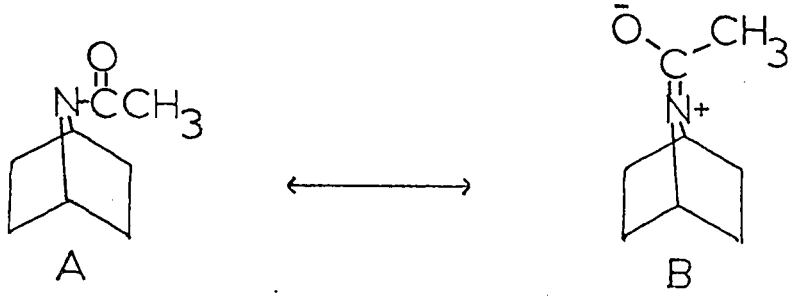
Rotational barriers have been known to exist in amides for some time and have been attributed to the partial double bond character of the amide. Rogers and Woodbrey[110] made a study of the barriers observed in some aliphatic amides and calculated, for example, that the ΔF for dimethylacetamide (D.M.A.) is 17.4 kcal at 298°C. Newman and Jonas[111] more recently placed this value at 18.6 kcal at 298°C. An entropy value for the process was given as +4.7 e.u. If one converts the ΔF_{298} value given to a corresponding ΔF at 348° (the coalescence temperature of XI) the barrier to rotation given by Newman would be 18.3 kcal. This then means that the barrier for D.M.A. is about 1 kcal higher than for XI. This implies that the energy of the ground state is greater for 7-acetyl-7-azabicyclo[2.2.1]heptane (XI) than is the energy of the ground state for D.M.A. which means that there is slightly less double bond character for XI than there is for D.M.A. One must now consider the reason for this increase in ground state energy.

The first thing to note is what affect the strain in the bicyclo[2.2.1]heptane structure has on the double bond character of the

amide. If strain is already present due to the angular requirements of the bicyclic system and if further strain would be exerted on the system by changing the hybridization of the nitrogen to sp^2, that is, increasing the double bond character, then the ground state energy of the system should be raised and the barrier lowered.

At first thought it might be supposed that this strain would be reflected in the basicity of ABH itself. When VII was titrated with sodium hydroxide in an aqueous medium, the pK_A of the amine was found to be 10.8. The pK_A of dimethylamine is 10.6[112] and that of pyrrolidine is 11.2.[113] It would appear, then, that basicity does not seem to reflect the additional strain in the system. Perhaps this is understandable in that there is no change in hybridization when the amine is protonated and therefore no change in strain.

If one takes a close look at the reasonance structures of the system one can tell more about the actual cause of the barrier observed in the system.



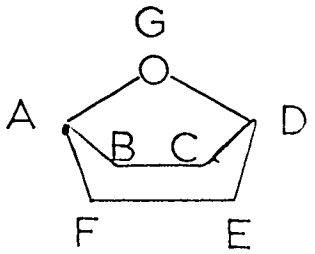
A ⟷ B

If A is the main contributor, then the nitrogen will be mainly sp^3 hybridized and any barrier observed would be due to inversion rather than rotation. If B is the main contributor to the ground state then the barrier observed would be the rotational barrier. A conflict arises in amides between the tendency for the nitrogen to be pyramidal

as in the free amine and planar as it would be when its lone pair p-electrons overlap with the π orbitals of the carbonyl carbon.[114] In formamide (ΔF = 21.7 at 298°C) and in D.M.A. the amide prefers the planar configuration and as such the barrier observed for these compounds is due to hindered rotation.[115] The formamide structure involves the least strain of any amide in the planar form and therefore has the highest free energy (21.7 kcal). When one progresses to D.M.A., the free energy drops to 18.6 kcal since this compound has slightly more strain due to the interaction of the gem-dimethyls. This strain raises the ground state energy and thereby allows less π overlap or double bond character. These two compounds both have low energy barriers to inversion.[114] When one considers a system of extreme strain such as an aziridine, one finds the barrier to inversion has risen to 10.8 kcal.[114]

If one can take 7-oxabicyclo[2.2.1]heptane as a good model for 7-azabicyclo[2.2.1]heptane (the C-O bond length does not differ much from the C-N bond length. C-O is 1.43Å and C-N is 1.47Å.[116]) calculations are available which would give some idea as to strain in the system. Bartlett and Martin[117] calculated that the 7-oxa system should have the following geometry.

C-C	1.55Å
C-O	1.44Å
Angle FAB	101°
" ABC	103°
" AGD	102° 54'
" BAG	101° 14'



The difference between the required angle of 108° 40' found by Lide[118] to be the tetrahedral angle assigned to the C-N-C bond angle in triethylamine and the angle AGD (102° 54') is probably a reasonable

indication that considerable strain exists in the ABH system. As this angle is already less than the required sp^3 angle and as the system has a fixed geometry, rehybridization of the nitrogen to an sp^2 planar system requiring angles of 120^o would involve more energy than rehybridization of the nitrogen in the D.M.A. system and therefore as the ground state would be less stable for the 7-aza system than for the D.M.A. system it should show a lower rotational barrier. The strain involved in the aziridine system with its fixed 60^o angle would be much greater and therefore rehybridized to a system requiring 120^o would be prohibitive. It is therefore not unreasonable to expect that the aziridine would not show a large barrier to rotation and indeed in comparison to the ABH system the barrier should be almost negligible.

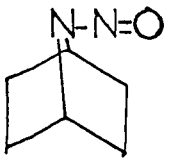
Since there is some strain involved in ABH although less than in the aziridine, it is possible that the inversion barrier is also present but diminished from that of the aziridine system. It would be difficult to assess the amount of the barrier to inversion because of the complicated N.M.R. spectrum. It is certain that a rotational barrier is observed, however, because only such a barrier could give non-equivalent bridgehead protons.

In summary, then, it can be stated that the barrier to rotation in 7-acetyl-7-azabicyclo[2.2.1]heptane is lower than that of D.M.A. Because the structure is rigid, it encounters difficulty in rehybridization thus raising the energy of the ground state.

2. N.M.R. studies of the non-equivalence of the bridgehead protons in 7-nitroso-7-azabicyclo[2.2.1]heptane

Another system was then sought which might confirm the conclusions gathered for 7-acetyl-7-azabicyclo[2.2.1]heptane. It is known that

N-nitroso compounds also exhibit rotation barriers[119] and as such N-nitroso-7-azabicyclo[2.2.1]heptane (IX) was made.



IX

The barrier when measured in this system proved to be 16.5 kcal at 52°C. Looney and co-workers[119] found the barrier for N,N-dimethylnitrosamine to be 23 kcal. It was immediately noticed that although the barrier to rotation for dimethylnitrosamine was larger than the barrier to rotation for D.M.A., the reverse was true for the bicyclic system.

One thing that is apparent if one observes the models of 7-acetyl-7-azabicyclo[2.2.1]heptane (XI) and 7-nitroso-7-azabicyclo[2.2.1]heptane (IX) is that there is a steric interaction present between the methyl hydrogens of the acetamide group and the exo protons of the ring. This interaction is not present between the exo protons and the oxygen of the nitroso group in IX. The interaction would tend to affect the transition state more than the ground state and as such would cause an increase in the barrier height. At most, however, this interaction would be slight and its effect on the barrier probably not more than 1 kcal.

Another factor which must be considered is that rehybridization of the ground state could allow the lone pair on oxygen of the acetamide and of the nitrosamine to interact with the bridgehead protons in an $A_{1,3}$[120] type interaction. This repulsive interaction would tend to raise

the energy of the ground state. Since the N-CO distance is 1.34Å[121] for D.M.F. and the N-NO distance is closer to 1.12Å[122] in nitrosamines the $A_{1,3}$ interaction would be greater in the case of IX than in the case of XI. This type of interaction has been proposed by Chow and co-workers[123] to explain the dominance of the syn configuration of N-nitrosodecahydroquinoline.

In summation, then, the factors which contribute to a lower barrier for both IX and XI relative to dimethylnitrosamine and dimethylacetamide respectively are the steric strain which is increased by a rehybridization from sp^3 to sp^2, thereby increasing the amount of ground state energy relative to the ground state energy of non-strained compounds and secondly the $A_{1,3}$ interaction which would also tend to destablize the ground state relative to the transition state. Possible reasons why the barrier for XI is lowered less than that for IX are that the amide has some steric interaction between the methyl and the exo protons in the transition state and secondly there is less $A_{1,3}$ interaction in the ground state of the amide than there is in the ground state of the nitrosamine due to the longer N-CO bond in the former.

3. Mass spectral properties of selected ABH derivatives

One very interesting aspect that arose from the work on the 7-azabicyclo[2.2.1]heptane derivatives was their mass spectral properties. If one first looks at the spectrum of VII (Figure vi) and sees the basic pattern for it, the other spectra of the substituted 7-azabicyclo[2.2.1]-heptanes appear to have at least part of this basic fragmentation pattern.

After hydrogen chloride gas is lost from VII a fragmentation of the C-C bond occurs as an alpha-cleavage of the amine.[143] This is

plausible as the system is no longer under strain when the bridge is opened. The side-chain radical which results extracts a hydrogen atom and subsequently cleaves from the ring to leave the stable ion radical m/e 68.[144] This process is clearly defined by the appearance of a metastable ion at m/e 47.6[145] A rearrangement then takes place with subsequent loss of the radical C_2H_3 to form the cyclic entity m/e 41.[146] This is also shown by the metastable ion at m/e 24.7.

A second decomposition pathway is possible for A. It can simply lose a molecule of ethylene to form the radical F. Loss of hydrogen from F again gives B. This process is shown to take place by the presence of the metastable ion at m/e 67.0. Because there is more than one pathway to B and because B would be quite stable, B then becomes the base peak. Unfortunately with this proposal for the fragmentation pattern, as with all the others, labelling would be necessary to determine if indeed the decomposition proceeded as outlined.

There is perhaps one problem in proposing B as the molecule which gives rise to the base peak. It might be asked why B does not immediately lose a positive hydrogen rather than break a carbon-carbon bond. The only answer that can be given is that perhaps some of B does lose the positive hydrogen. If it does, however, it is no longer a "visible" ion to the mass spectrometer and will be lost as a neutral fragment. Deuterium labelling on the body of B would, perhaps, show whether later fragmentation resulted from this neutral fragment or not. Loss of a hydride or even a hydrogen atom is less likely to occur from ion B as nitrogen would then be in the peculiar situation of having only three bonds but carrying a positive charge. Numerous examples are given[147]

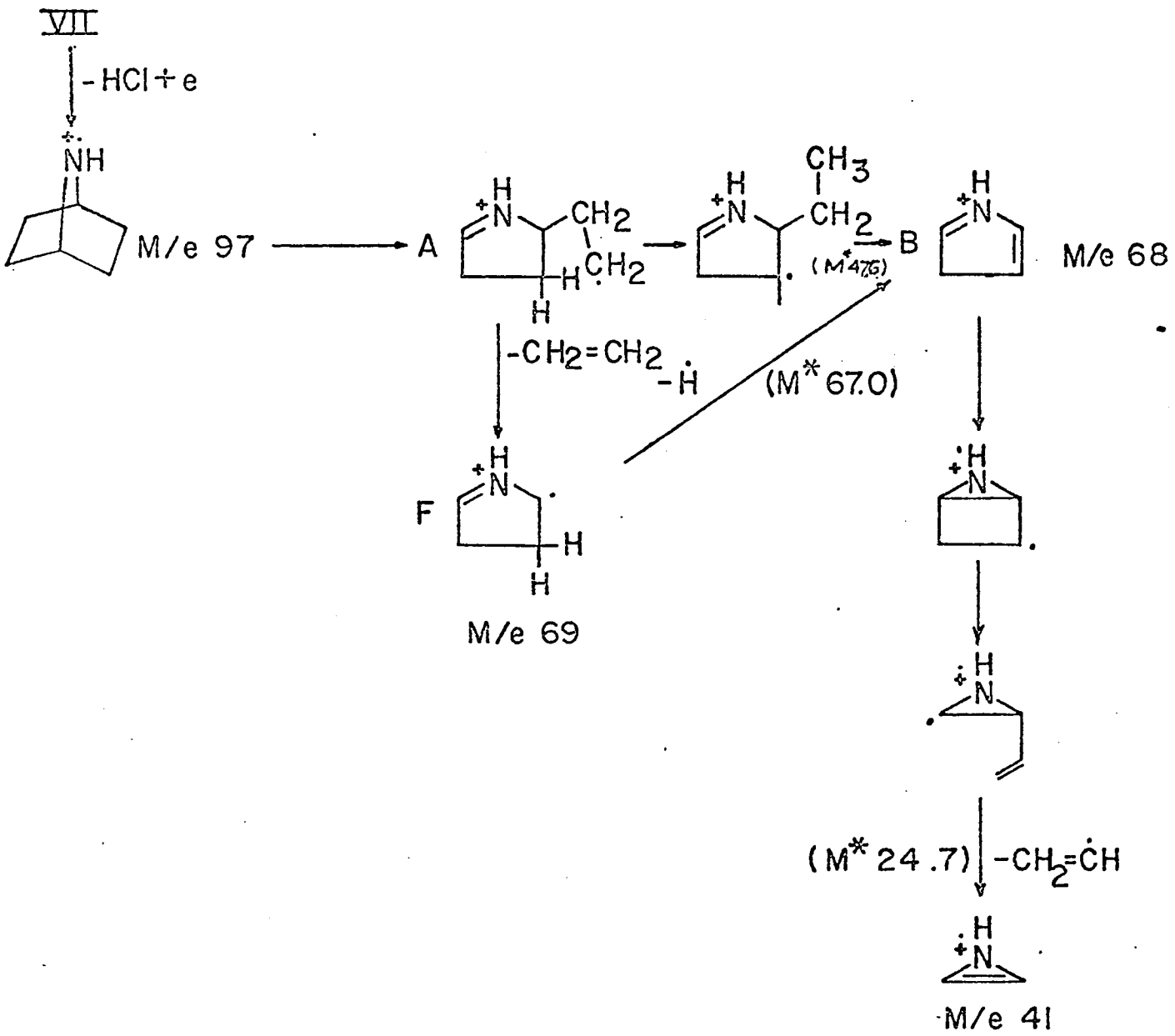

VII
-HCl + e
M/e 97
A
B
M/e 68
(M* 47.6)
-CH2=CH2
-H
(M* 67.0)
F
M/e 69
(M* 24.7)
-CH2=CH
M/e 41

Figure vi

mass spectrum of

Cl

relative stability

supporting the fact that indeed fragmentation of a carbon-carbon bond is preferable to losing the hydrogen from a positively charged nitrogen.

When XXXI was subjected to the mass spectrometer (Figure vii) it was noted that an additional fragmentation pathway became available. In this instance it was possible for the chlorine rather than the nitrogen to lose the initial electron. Subsequent loss of the chlorine atom produced an ion at m/e 96 which then lost ethylene to give the familiar ion m/e 68 (B). This loss was supported by the metastable ion at m/e 48.1. Decomposition of the ion at m/e 68 then proceeded in the same manner as before.

When the electron was removed from nitrogen, alpha-cleavage took place as before, to give G which then lost the molecule chloroethylene to give the ion at m/e 69, (F). F then lost a hydrogen atom as before to give B. This process as in the parent compound is denoted by the metastable ion at m/e 67.0. (The hydrogen which is lost is not the one on the nitrogen as the loss in the deuterium labelled compound is one unit and not two.) A second pathway involving hydrogen transfer (as in the case of ion A in the parent compound) and subsequent loss of a C_2H_4Cl radical also leads to an ion m/e 68. This process is denoted by the metastable ion at m/e 35.2.

Since there are many similar fragmentation patterns one would expect the spectra for VII and XXXI to appear alike and indeed they do. The major difference in the high end of the spectrum is in the production of an ion m/e 96 for XXXI rather than an ion at m/e 97 as is observed for VII. In both cases hydrogen transfer in ion A for

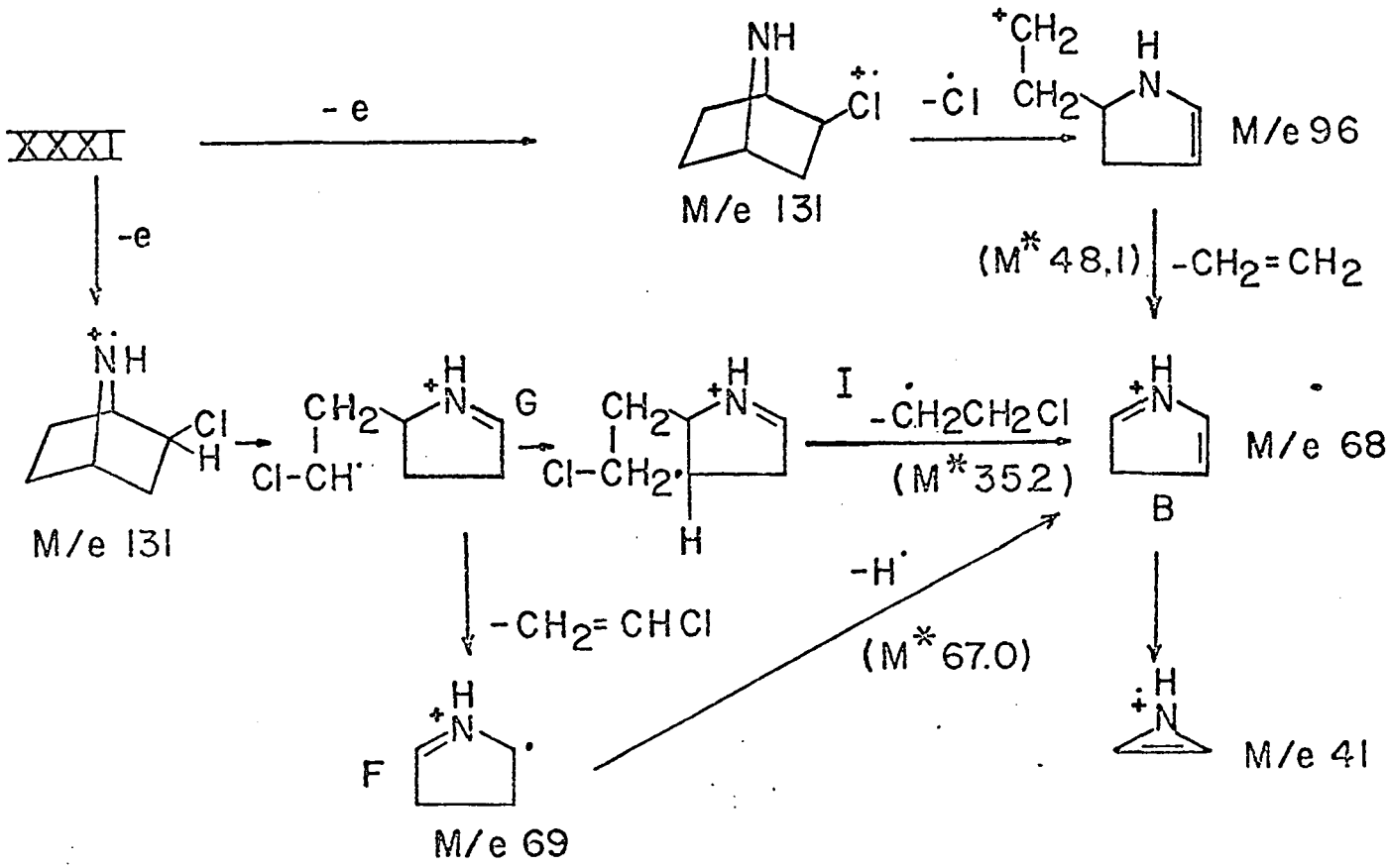
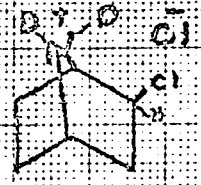

XXXI
-e
-e
M/e 131
M/e 131
M/e 96
(M* 48.1)
-CH2=CH2
G
I
-·CH2CH2Cl
(M* 352)
M/e 68
B
-CH2=CHCl
-H·
(M* 67.0)
F
M/e 69
M/e 41

Figure vii

mass spectrum of



metastable ions

49.0
36.1
35.1
25.7
24.6

Relative intensity

% 100 80 60 40 20

20 40 60 80 100 120 140 m/e

relative intensity
%
100
80
60
40
20
mass-spectrum of
m/e

molecule VII and ion I for molecule XXXI is evident. There is a very minor fragment at m/e 82 for VII and at m/e 81 for XXXI which could occur from loss of methyl from the ethyl group which had been formed. Deuterium labelling on the nitrogen of XXXI clearly shows that the primary processes leading to B or B' in the labelled case, do so without loss of deuterium. (The deuterium was placed in the molecule[148] by a hydrogen:deuterium exchange using deuterium chloride gas. This was estimated to be about 80% complete which accounts for the residual peak at m/e 68.) Scrambling of the protons of B occur as is denoted by the almost equal amounts of m/e 41 and m/e 42 in the deuterium labelled entity.

If one now looks at the 7-substituted derivatives i.e. XI (Figure viii) and XXXIV (Figure ix) one can again see the same basic pattern emerge. In the formamide compound an alpha-cleavage and subsequent abstraction of the hydrogen from the formyl group allows an easy loss of carbon monoxide. A hydrogen shift and subsequent rearrangement allows the production of B at m/e 68. This is indicated by the presence of the metastable ion at m/e 47.8. The second fragmentation pattern due to loss of ethylene before loss of the amide function is indicated by the metastable ion at m/e 73.8.

In the acetamide (XI), loss of ethylene from the parent gives the ion at m/e 110 with a metastable ion for the process at m/e 86.8. If a hydrogen transfer occurs from the acetamide to the nitrogen, ketene and an ion which then would exhibit all the characteristics of VII results. This type of transfer is quite common for acetamides.[149] It must be noted in this instance that it is the ion m/e 69 which is the

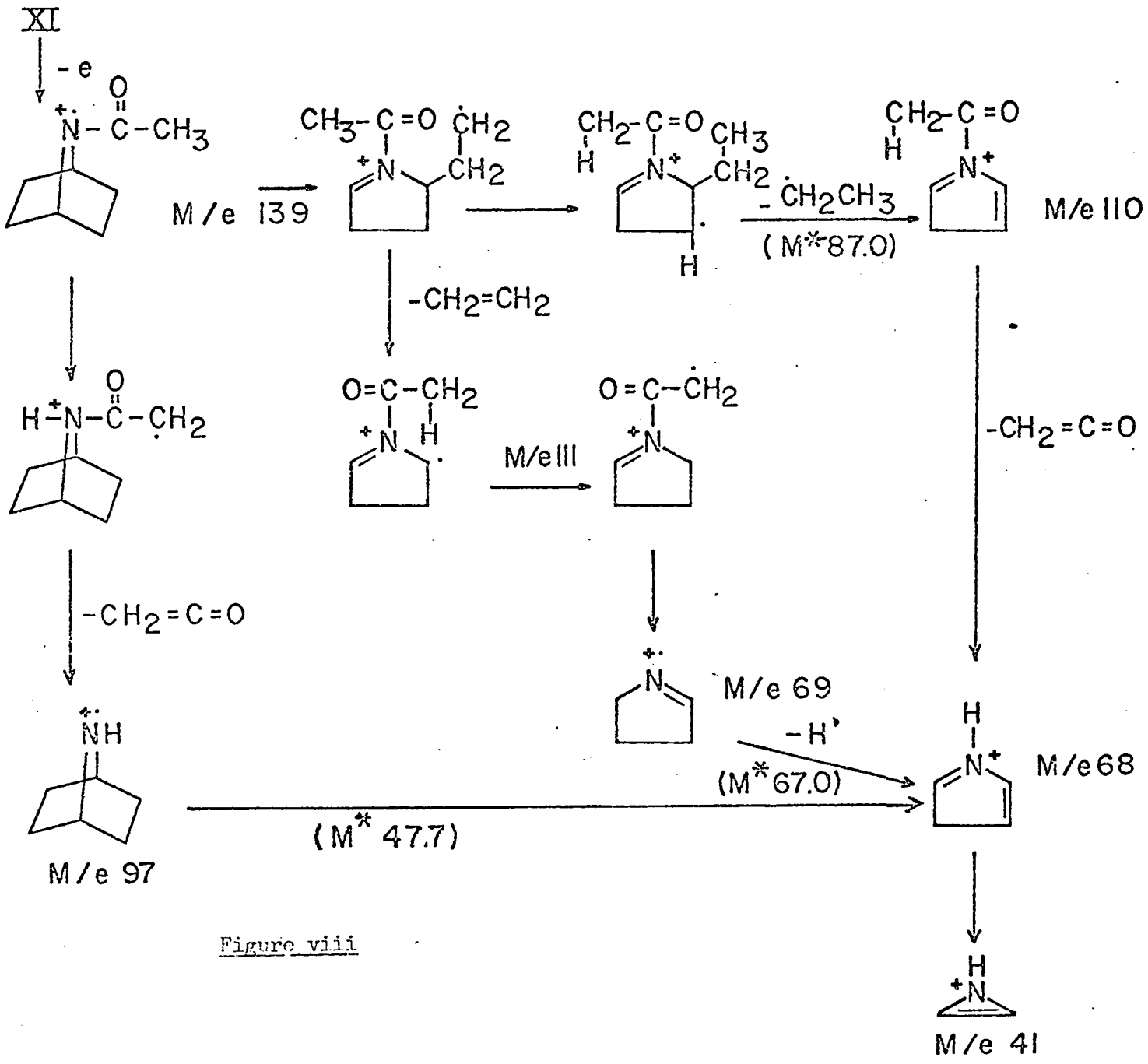

XI
- e
M/e 139
-CH2=CH2
M/e 111
- ·CH2CH3
(M* 87.0)
M/e 110
-CH2=C=O
-CH2=C=O
M/e 69
-H·
(M* 67.0)
M/e 68
(M* 47.7)
M/e 97
M/e 41

Figure viii

mass spectrum of
m/e values
relative intensity
100
80
60
40
20
molecular ions
34.4
28.0
60.1
63.4
60.2
47.8
32.3
25.0

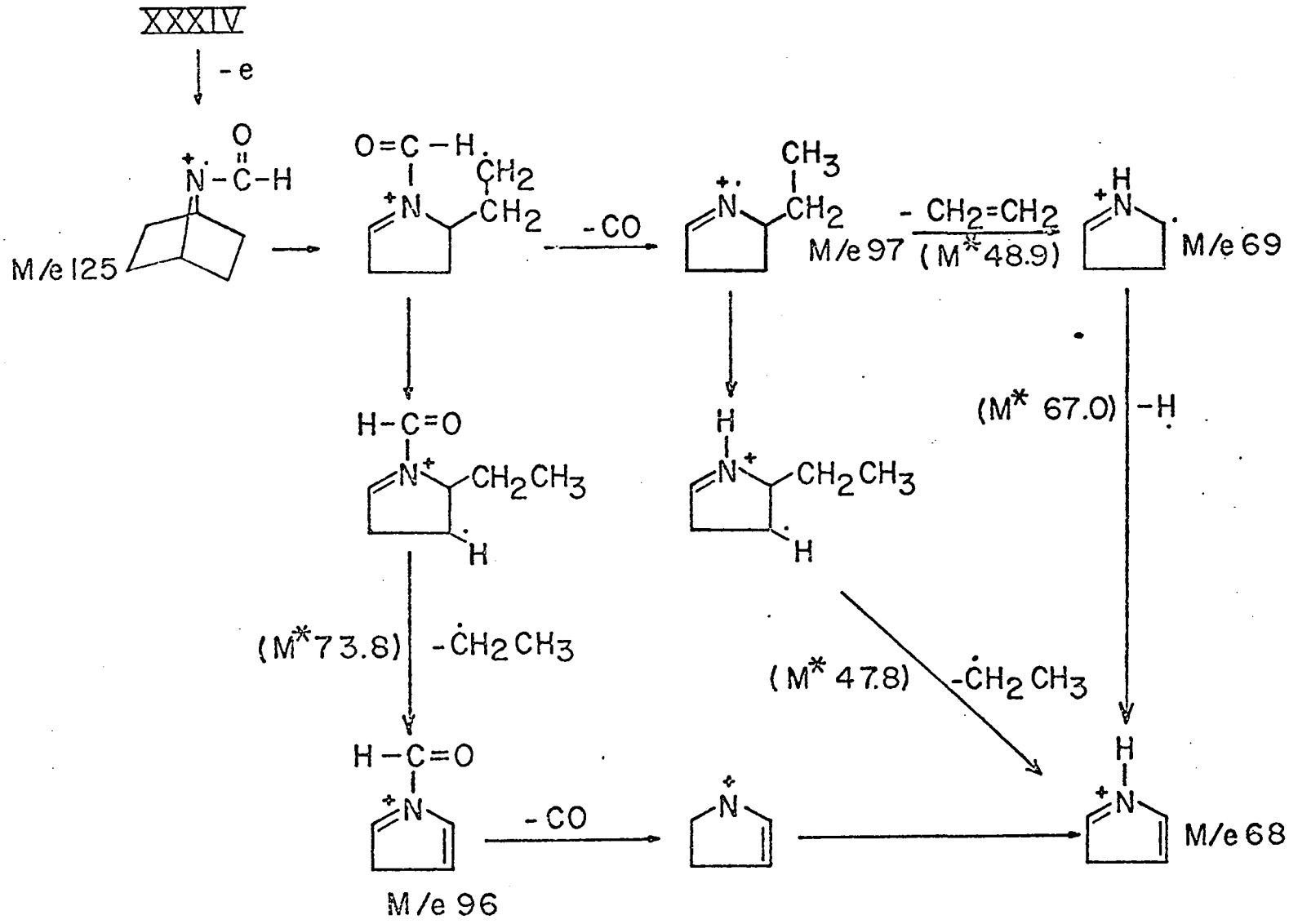
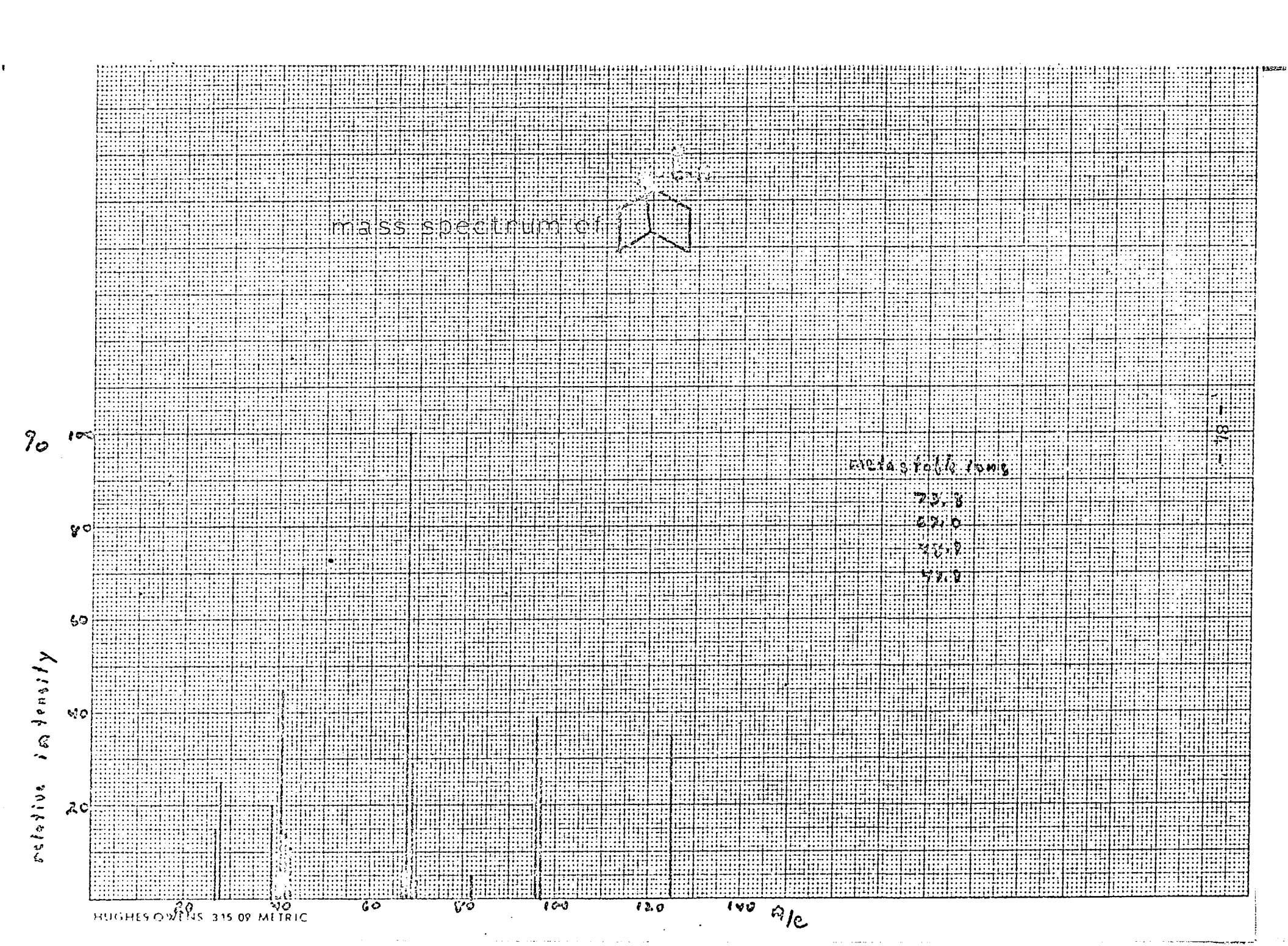

XXXIV
-e
M/e 125
-CO
M/e 97
- CH2=CH2
(M* 48.9)
M/e 69
(M* 67.0) -H
(M* 73.8) -CH2CH3
(M* 47.8) -CH2CH3
-CO
M/e 96
M/e 68

Figure ix


mass spectrum of
%
100
80
60
40
20
relative intensity
Picks for the ions
73.8
69.0
45.9
44.8
20
40
60
80
100
120
140
m/e
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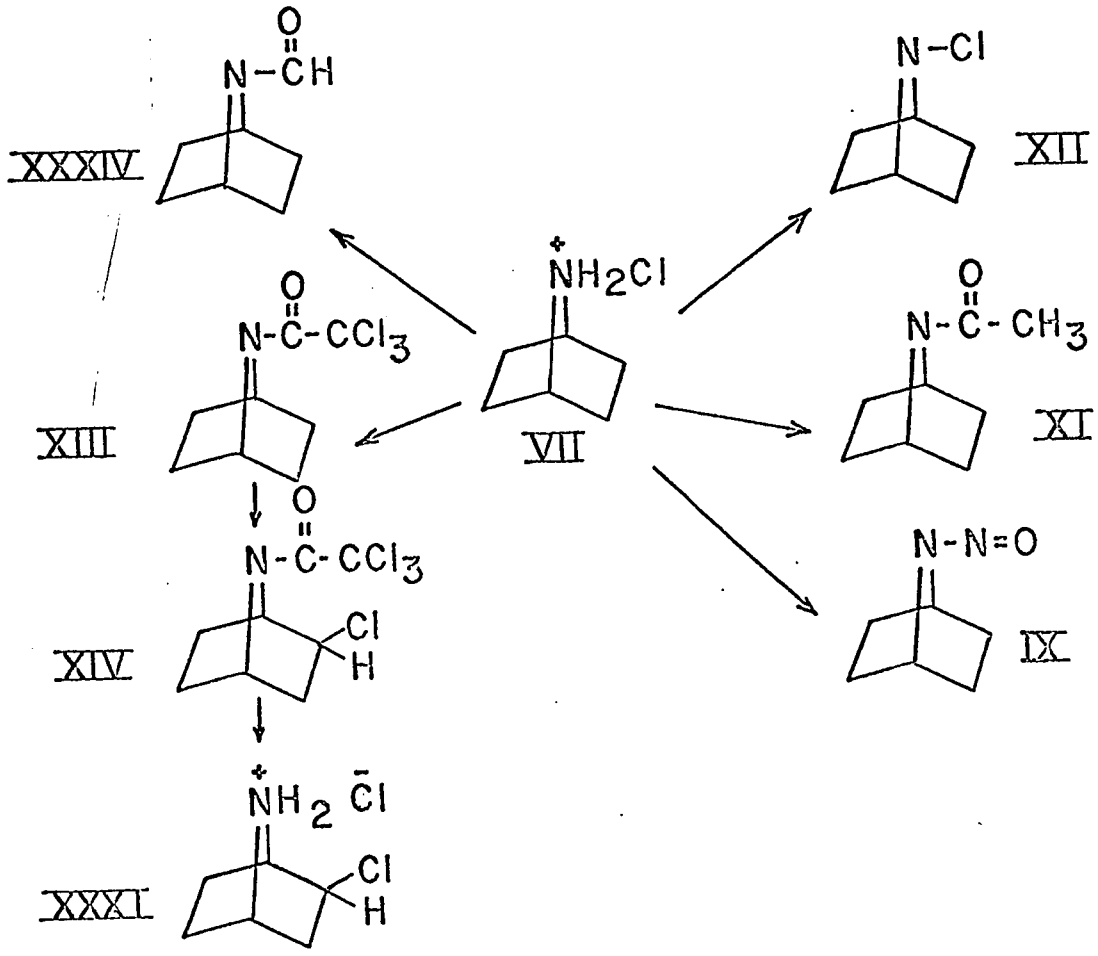
base peak rather than the fragment m/e 68. This is a reflection of the ability of the acetyl group to donate its hydrogen and depart as ketene.

CONCLUSION

In final summation of the work done on the 7-azabicyclo[2.2.1]-heptane system it can be concluded that many interesting compounds and reactions resulted from the work itself and that the original goal set out in the introduction i.e. that of achieving easy access to mono-substituted derivatives of the system was partially achieved. Scheme V shows the derivatives of 7-azabicyclo[2.2.1]heptane (VII) that were synthesized. The knowledge gained from the solvolysis of the exo-2-chloro-7-azabicyclo[2.2.1]heptane points out the fact that the system is much less reactive than the corresponding norbornyl system and even less reactive than the 7-oxa system.

Scheme V


XXXIV
N-CH
O
XII
N-Cl
VII
NH2Cl
XIII
N-C-CCl3
XI
N-C-CH3
XIV
N-C-CCl3
Cl
H
IX
N-N=O
XXXI
NH2 Cl
Cl
H

EXPERIMENTAL

All melting points are corrected. The N.M.R. spectra were recorded on a Varian HA-100 N.M.R. spectrometer, Varian T-60 N.M.R. spectrometer, or a Varian HR-60-EL N.M.R. spectrometer. The I.R. spectra were measured using either a Beckman IR-8 or IR-20 spectrometer. The mass spectral analyses were performed using an Hitachi-Perkin-Elmer RMU-6D spectrometer. The U.V. spectrum was recorded on a Perkin-Elmer 202 spectrometer. All I.R. spectra of solid compounds were taken as potassium bromide dispersions. The I.R. spectra of liquids were taken neat or in chloroform solution. The absorptions were recorded in units of cm^{-1}. All N.M.R. spectra unless otherwise noted were taken in a deuterochloroform solution. The absorptions were recorded in parts per million relative to T.M.S. The lamp used for the photochemical work was a Hanovia 679A-36, 450 watt medium pressure mercury vapor lamp.

4-Acetamidophenol (I)

4-Acetamidophenol was prepared once according to the method of Nelson and Mortimer[150] and was later purchased from Aldrich Chemical Company.

trans-4-Acetamidocyclohexanol (II)

The preparation of II by the method of Ferber and Bruckner,[23] with a slight modification, was used in the earlier stages of the work and later a second method was employed.[25]

A Parr hydrogenation pressure bottle containing 0.3 g of platinium oxide and a suspension consisting of 20 g of I in 100 ml of water was filled with hydrogen to a pressure of 60 p.s.i. The temperature was then raised to 60° and the hydrogenation was allowed

to proceed with shaking until the pressure no longer decreased. This usually required 14 to 16 hours. The catalyst was then removed by filtration and the solvent was evaporated under reduced pressure. Fractional recrystallization from acetone was used to separate the two isomers. The average yield of the trans isomer, which melted at 166-167°, was about 40%. The reported melting point was 164°.[23] The cis isomer, obtained by allowing the mother liquor to stand at 3° for two days or more, melted at 134-136° after two recrystallizations from acetone. The reported melting point was 135°.[23]

The second method used to prepare II was that of Billman and Brehler.[25]

A solution of I (80 g) in 250 ml of ethanol was placed in a high pressure autoclave. Raney nickel, W4, (5 g) was then added. The autoclave was sealed and hydrogen was introduced to a pressure of greater than 1000 p.s.i. (This pressure was maintained throughout the reaction by further introductions of hydrogen when required.) It was found that the reaction proceeded best at temperatures of 185° to 195° and went to completion within three to five hours at this temperature. After the reaction mixture had cooled sufficiently, the catalyst was removed by filtration and the solvent evaporated. The resulting syrup was then treated in an identical manner to that in the first procedure. The average quantity of the trans isomer that was obtained in this manner was from 16 to 20 g (20-25% yield).

Raney Nickel

The Raney nickel catalyst was prepared according to the method of Adkins and Billica.[26] Sodium hydroxide pellets (80 g) were added to

300 ml of distilled water and after the solution had cooled to 40°, 64 g of nickel-aluminum alloy (50:50) was added at a rate which maintained the temperature in the range of 40-50°. After the addition, the catalyst was allowed to digest for 50 minutes at 50° and then was washed by decantation with 14 l of distilled water. This was then followed by three washings with 95% ethanol (150 ml each) and three washings with absolute ethanol (150 ml each). Care was taken throughout the organic washings to keep the catalyst from contact with the atmosphere. The catalyst was then stored under absolute ethanol at 5° and appeared to have the same activity (about W4) for one week.

trans-4-Aminocyclohexanol (III)

The method of obtaining III, employed by Ferber and Bruckner,[23] proved ineffective and resulted in partial elimination of the hydroxyl group. A more convenient method was then undertaken.

A solution of II (20 g) in 500 ml of 20% aqueous sodium hydroxide was refluxed for eight hours. The aqueous solution was then placed in a continuous extractor and the mixture was extracted with chloroform for a further eight hours. III was obtained in 80% yield after recrystallization from ethyl acetate and melted at 110-111°. This was in agreement with the melting point given by Ferber and Bruckner.[23]

trans-4-Carbobenzoxyaminocyclohexanol (IV)

IV was prepared using the general method of Bergman and Zervas.[40]

A solution of III (12 g) in 100 ml of water was placed in an ice bath. The carbobenzoxy chloride (25 ml; a 3-fold excess) was added in 3 to 5 ml portions alternating with portions of 10% aqueous sodium hydroxide. Vigorous shaking by hand was maintained throughout the

reaction. After the addition, the mixture was allowed to come to room temperature and the water insoluble product was filtered off. This was then dissolved in hot ethyl acetate, and pyridine was added until the ethyl acetate no longer clouded when a drop of pyridine dissolved in it. At this point it was assumed that any excess carbobenzoxy chloride or acid had reacted. The solvent mixture was then washed three times with 25 ml portions of water, the water removed, and the ethyl acetate solution dried over magnesium sulfate while it was still warm. After filtration the solution was concentrated under vacuum until IV began to crystallize. Recrystallization of the product once more from fresh ethyl acetate yielded white needles in 78% yield melting at 159-160.5°.

Anal. Calcd for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68; N, 5.61. Found: C, 67.38; H, 7.65; N, 5.77.

I.R.: 3615, 3450, 1720, 1515.

N.M.R. (60 MHz): 7.34 (5H), 5.16 (2H), 4.58 (1H), 3.75 (2H), 2.2-1.0, broad multiplet (9H).

trans-4-Carbobenzoxyaminocyclohexyl p-toluenesulfonate (V)

To 100 ml of dry pyridine, contained in a 250 ml round bottom flask, was added 10 g of IV. The solution was cooled in an ice bath and 10 g (20% excess) of p-toluenesulfonyl chloride was added slowly. Stirring was maintained during the addition with a magnetic stirrer. The solution was kept near 0° for 12 hours after which time the pyridine was removed under vacuum. The solid residue was then dissolved in chloroform and washed three times with water, followed by a further washing with 25 ml of 1N hydrochloric acid. After drying over magnesium

sulfate, the solution was filtered, the solvent was removed and the excess toluenesulfonyl chloride was extracted with boiling (30-60°) petroleum ether. The residue which did not dissolve in the ether was recrystallized from ethanol to give V in 81% yield. The melting point of the solid obtained was 116-117°.

Anal. Calcd for $C_{21}H_{25}O_5NS$: C, 62.48; H, 6.24. Found: C, 62.29; H, 6.28.

I.R.: 3450, 1720, 1600, 1515, 1460, 1365, 1178.

N.M.R. (60 MHz): A_2 7.34, B_2 7.96, (J = 8.0), 7.33 (5H), 5.10 (2H), 4.70 doublet (1H), 4.50 (1H), 3.50 (1H), 2.45 (3H), broad multiplet 2.3-1.0 (8H).

trans-4-Aminocyclohexyl p-toluenesulfonate hydrobromide (VI)

Two methods of synthesis were employed.

A) To V (1 g), dissolved in 30 ml of glacial acetic acid was added 10 ml of a solution of 3 ml of 48% aqueous hydrobromic acid in 7 ml of acetic acid. Stirring was continued 30 minutes after the evolution of carbon dioxide had ceased. The solvent was then removed under vacuum. The residue was washed with ether and recrystallized twice from ethyl acetate to give needles melting at 135-136° in 81% yield.

Anal. Calcd for $C_{13}H_{20}BrO_3NS$: C, 44.58; H, 5.75. Found: C, 44.76; H, 5.95.

I.R.: (3200-3000), 1365, 1180.

N.M.R. (100 MHz): 8.23 (3H), $\int A_2$ 7.33, $\int B_2$ 7.87, (J = 8.0 Hz) (4H), 4.42 (1H), 3.12 (1H), 2.49 (3H), 2.3-1.9 (8H).

B) A solution of V (10 g) in 75 ml of ethanol was placed in a Parr hydrogenation bottle. 10% Palladium-on-charcoal (0.5 g) was used as

a catalyst and 5 ml of 48% aqueous hydrobromic acid was added to trap the free amine. The mixture was then shaken under hydrogen at 40 p.s.i. for six hours. At this point the hydrogenolysis was stopped and an aliquot was taken. The catalyst was then removed from the sample by filtration, and the ethanol was evaporated under vacuum. The solid residue was examined by I.R. to determine whether any carbonyl still remained. If this was the case, fresh catalyst (0.1 g) was carefully added along with 2 ml of hydrobromic acid and the mixture hydrogenolysed for a further four hours. The catalyst was removed by filtration and the solvent evaporated. The residue which remained was treated as in procedure (A) to yield 6 g of VI (72% of theoretical).

7-Azabicyclo[2.2.1]heptane hydrochloride (VII)

Into 500 ml of a 70% aqueous ethanol solution containing two equivalents of 1N sodium hydroxide (36 ml) was added 6 g of VI. The reaction was allowed to stand for 14 hours at room temperature. At the end of this time, hydrogen chloride gas was introduced into the mixture to neutralize the bases and the solvent was removed under vacuum. The residue was dissolved in 10% aqueous sodium hydroxide and the amine was extracted with ether. The ether was then dried over magnesium sulfate, filtered, and the filtrate dried further over calcium hydride. After the final filtration, dry hydrogen chloride gas was introduced into the ether and the precipitate which formed was removed by vacuum filtration. A recrystallization from a methanol:ethyl acetate mixture gave a solid melting at 261-263°. The average yield for the reaction was 72-77%.

Anal. Calcd for $C_6H_{12}NCl$: C, 53.95; H, 9.06. Found: C, 53.76; H, 9.23.

The picrate salt of this amine, formed by reacting VII with picric acid in an aqueous medium, melted at 171-173°.

I.R.: 3000-2550, 1605, 1473, 1453, 1363, 1278, 1230, 1090, 975, 908, 884.

N.M.R. (60 MHz): 4.23 (2H), 2.24, 1.64, 2 broad peaks (8H).

N.M.R. of the free amine (100 MHz): 3.63 (2H), broad multiplet with 4 main peaks at 1.32, 1.34, 1.51, 1.60 (9H).

Attempted O-tosylation of III

A) A 250 ml three-necked flask was fitted with a "Y" joint, a nitrogen inlet and outlet, a reflux condenser, a dropping funnel and a washing tube. A slurry of 0.42 g of 50% sodium hydride in oil was placed in the flask and rinsed three times with petroleum ether. The rinse was removed from the flask by applying positive nitrogen pressure forcing it out the washing tube. After the remaining ether had been swept out with nitrogen, 1 g of III, dissolved in 50 ml of dry dioxane, was added slowly and the solution was stirred rapidly with a magnetic stirrer. After one hour at room temperature, 1.5 g of p-toluenesulfonyl chloride was added in 25 ml of dioxane. A noticable precipitate of sodium chloride appeared immediately. The reaction was allowed to proceed a further two hours and then 75 ml of cold water was added to quench it. Extraction of the mixture with chloroform and ether produced only XVIII. No O-tosylate or bicyclic amine was recovered even when the solution was made basic. Evaporation of the solvent gave a solid residue which contained some III as indicated by I.R. Refluxing the sodium hydride in dioxane was also attempted with negative results.

Subsequent attempts using larger quantities of III (5 g) and

correspondingly larger quantities of the other reagents, gave white needle-like crystals of XVIII melting at 123-125° in 6% yield.

Anal. Calcd for $C_{13}H_{19}O_3NS$: C, 57.99; H, 7.11. Found: C, 58.07; H, 7.03.

B) The reaction was repeated as above with the exception that dimethyl sulfoxide was used as solvent. Two minutes after the addition of the p-toluenesulfonyl chloride the reaction turned a dark brown. Work-up by addition of water and extraction, or freeze-drying, or distillation produced only what appeared to be polymer.

C) A 500 ml flask was fitted with the above equipment and 0.6 g of sodium hydride, treated in a similar manner as in the experiment above, was dissolved in 100 ml of dry ethylene-glycol-dimethyl ether (glyme). To this solution, 1 g of III, dissolved in 50 ml of glyme, was added slowly. The reaction was kept at room temperature for three hours after which 1.4 g of p-toluenesulfonyl chloride dissolved in 50 ml of glyme was added. The reaction was stirred for a further 14 hours then water was used to clear the precipitate. After the solution was acidified with hydrobromic acid, all solvents were removed under vacuum. The residue was extracted several times with hot ethyl acetate and upon removal of this solvent 30 mg of solid remained. This appeared to be identical to VI by I.R. and N.M.R. The insoluble residue contained no recognizable product and could not be separated further.

D) In subsequent reactions the sodium salt was added to a solution of the p-toluenesulfonyl chloride in a reverse addition. This was accomplished by forcing the anion by a positive nitrogen pressure from the first flask into a dropping funnel fitted on the second flask.

In the first reaction a plastic (poly-vinyl acetate) tubing was used as a carrier. Work-up of this reaction gave a solid which upon recrystallization from ethanol melted at 52-54°. Attempts to make a picrate of this compound failed.

All-glass equipment produced a compound which again formed no picrate. This was identified by N.M.R. and I.R. as the N-tosyl derivative XVIII.

E) When 1 g of III was placed in 50 ml of glyme in the above apparatus containing 7 ml of 1.6 N n-butyl lithium, a reaction was indicated by the formation of a precipitate. After 10 minutes the material was transferred as before to the second flask containing 1.3 g of p-toluenesulfonyl chloride in 50 ml of glyme. At room temperature the precipitate disappeared almost immediately and was replaced by a clear solution. If the temperature was dropped below -20° no clearing took place.

When the products of reaction were acidified with hydrobromic acid and the solvent removed, the only picrate that was found when aqueous picric acid was added to the residue was that of unreacted III in about 10% yield. The other product appeared to be only the N-tosyl derivative.

F) The amino alcohol, III (0.5 g) was precipitated as its hydrochloride salt by the addition of hydrogen chloride gas to a solution of III in chloroform. To this suspension was added 2.5 g of p-toluenesulfonyl chloride. After four weeks the solvent was removed and the solid examined by I.R. and N.M.R. Only the N-tosyl derivative and an unsaturated product appeared to be present.

Attempted preparation of VII via the acid sulfate of III

A 5 ml aqueous solution of III (1 g) was added slowly with cooling to 0.9 g of sulfuric acid in 5 ml of water contained in a 100 ml three-necked flask which was fitted with a thermometer, and an outlet attached to a vacuum line. The solution was stirred with a magnetic stirrer. As the pressure was decreased and the temperature increased, formation of a precipitate was noticed by 100° and by 160° the material seemed to fuse in the pot giving a solid foam. Heating was discontinued at this point and the solid was analyzed by I.R. Recrystallization was attempted from many solvents but no crystals were obtained.

The solid was added to 50 ml of a 70% aqueous ethanol solution which contained 20 ml of 1N sodium hydroxide and the mixture was allowed to react for 24 hours. Upon treatment in a similar manner to that employed for the preparation of VII no product was obtained and no III was recovered.

Attempts at an alternate route

Reaction of iodine isocyanate with 1,3-cyclohexadiene

A) Following the method of Hassner,[57] iodine (25.4 g) and silver cyanate[58] (20 g) were placed in 250 ml of anhydrous ether in a three-necked flask fitted with condenser, thermometer, and mechanical stirrer. The slurry was cooled in an ice bath and 9.2 g of 60% 1,3-cyclohexadiene (estimated by N.M.R.) was added in three portions over a thirty minute period. The ice bath was then removed and the reaction was stirred at room temperature for six hours. As iodine was still present, a further 2 g of olefin was added and stirring was continued for two more hours. The reaction mixture was then filtered through Celite and the ether

removed under vacuum. The I.R. of the crude material showed the required isocyanate band at 2260 cm^{-1}.

Attempted hydrolysis of the isocyanate failed to give any recognizable product.

B) In a subsequent reaction the resulting mixture from the reaction of olefin with iodo-isocyanate was heated slowly and benzene was added to replace the evaporated ether as solvent. After filtration and removal of the benzene, hydriodic acid was added. The solution was then concentrated and the residue was placed in a round bottom flask with 80 ml of ethanol, 10 ml of water and 15 ml of 1N sodium hydroxide. Following a 12 hour reaction time the solution was worked-up in the manner used previously for VII.

Upon the addition of the hydrogen chloride gas no precipitate was noted. The N.M.R. and I.R. showed no bicyclic product after the ether had been removed.

C) The reaction was repeated as in A to the point of addition of the hydriodic acid. Neither prolonged refluxing nor reaction in the dark for 14 hours gave any VII after the usual work-up.

Tests for primary[151] and secondary amines[151] on the residue obtained from the work-up were negative. Attempts to convert the isocyanate group to a urethan by treatment of the crude iodo-isocyanate with benzyl alcohol gave no isolable product. When the iodo-isocyanate produced as in A was treated with aqueous sodium bisulfite for 20 hours, 25 mg of a solid melting at 135-140° was obtained. An examination of this solid by I.R. indicated the possibility that it might have been a bisulfite adduct. Repetition of the reaction using freshly distilled

1,3-cyclohexadiene gave a solid residue in about 15% yield which appeared to decompose at 150°. The I.R. showed the two adducts to be similar but not identical. With cyclohexene, after treatment in an identical manner, a solid was obtained which melted at 143-147°. This corresponded to the melting point of the solid adduct obtained by Hassner.[57]

Treatment of the solids obtained in the reaction of the 1,3-cyclohexadiene with sodium hydroxide in aqueous ethanol in the manner used previously for VII produced no bicyclic compound.

Ring Substitution

Leonard oxidation

Oxidation of VII with mercuric acetate was attempted using a method similar to that used by Leonard for the oxidation of quinolizidine.[100]

A solution of VII (100 mg) in 10 ml of 5% aqueous acetic acid in a round bottom flask fitted with condenser and drying tube was treated with mercuric acetate (300 mg) and heated on a steam bath for 24 hours. No precipitate was noticed. The acetic acid was removed under vacuum and the solid dissolved in 1N sodium hydroxide. The solution was extracted with ether and the ether dried over magnesium sulfate followed by further drying over calcium hydride. After the drying agent had been removed, hydrogen chloride gas was added and a solid precipitated (80 mg). The I.R. of this solid was identical to that of VII.

The reaction was repeated with the free amine of VII, which was obtained by extracting a 1N sodium hydroxide solution containing 100 mg of VII with ether, drying the ether with magnesium sulfate and calcium hydride, filtering, and finally carefully removing the ether in the cold under vacuum. The reaction vessel, after the addition of mercuric acetate,

was covered with foil and the reaction mixture allowed to reflux for three days. On work-up as before only VII was recovered.

7-Methyl-7-azabicyclo[2.2.1]heptane hydrochloride (VIII)

The general method of preparing methyl derivatives of secondary amines was employed.[152]

The amine hydrochloride, VII (500 mg), was placed in a 100 ml flask fitted with two condensers and a drying tube. Formic acid (15 ml) and 20 ml of a 37% formaldehyde solution was added and the reaction was refluxed for three hours. At this time 0.5 g of paraformaldehyde was carefully introduced and the mixture was refluxed a further 12 hours and allowed to stand at room temperature for 10 hours. 4N hydrochloric acid (10 ml) was added and the solution evaporated to dryness under vacuum. The solid residue was taken up in water and the insoluble portion removed by filtration. The water was then made basic with 1N sodium hydroxide and extracted with ether. The ether was dried over magnesium sulfate followed by calcium hydride and after removal of the drying agent, hydrogen chloride gas was introduced. The precipitate which formed was filtered and recrystallized from an ethyl acetate:methanol mixture to give a solid melting at 255.5 to 257°. The yield was 53%.

Anal. Calcd for $C_7H_{14}NCl$: C, 56.94; H, 9.56. Found: C, 56.76; H, 9.52.

I.R.: 3000-2400, 1490, 1460, 1375, 1333, 1230, 1178, 1139, 1069, 1011, 958, 880.

N.M.R. (60 MHz): 3.97 (2H), 2.79 doublet (3H), 2.67-1.49 broad multiplet (8H).

The picrate of VIII, formed from an aqueous solution of picric acid, melted at 308-309.5° with decomposition.

Anal. Calcd for $C_{13}H_{16}N_4O_7$: C, 45.87; H, 4.74. Found: C, 46.03; H, 4.83.

The methiodide of VIII had previously been made.[10,18]

Treatment of the free amine of VIII as in the Leonard oxidation of the free base of VII gave no oxidation product.

7-Nitroso-7-azabicyclo[2.2.1]heptane (IX)

A solution of VII (235 mg) in 25 ml of water was placed in a round bottom flask fitted with a condenser. Sodium nitrite (400 mg) was added in one portion along with 1.5 ml of 2N hydrochloride acid. The reaction was heated to 70-75° and stirred for three hours. The yellow nitrosamine (IX) was extracted from the cold acidic solution with ether and after the solution was dried over magnesium sulfate the ether was carefully removed under reduced pressure without heat. The resulting yellow needles were recrystallized from heptane to give 160 mg (73% yield) of a solid melting at 85-86°.

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.10; H, 7.91. Found: C, 56.92; H, 7.86.

I.R.: 1475, 1465, 1450, 1408, 1335, 1310, 1155, 1130, 990, 870, 717.

N.M.R. (100 MHz in $CDCl_3/CS_2$): multiplet 4.94 (2H), multiplet 1.70 (8H).

U.V.: cyclohexane 398 mμ (ε 64), 234 mμ (ε 10350) methanol: 370 mμ (ε 78), 234 mμ (ε 10350).

7-Acetyl-7-azabicyclo[2.2.1]heptane (XI)

This compound was prepared by three methods.

A) A three-necked flask was fitted with a gas outlet, a thermometer, a dropping funnel, and a stirrer. Triethylamine (0.4 ml) and 0.3 ml of acetic acid were added together with 0.5 ml of ethyl chloroformate in 50 ml of methylene chloride. The temperature was maintained at -20° and the reaction was stirred for one hour. The free base of VII (400 mg) was added slowly and the evolution of carbon dioxide was noted by trapping it under water. After four hours the mixture was washed with 10 ml of 1N hydrobromic acid and the solvent was dried and carefully evaporated. On bulb-to-bulb distillation of the residual liquid and subsequent recrystallization of the distillate from heptane, a solid melting at 41.0-42.5° was obtained in 40% yield.

Anal. Calcd for $C_8H_{13}ON$: C, 69.03; H, 9.41. Found: C, 68.92; H, 9.22.

I.R.: 1640, 1457, shoulder 1425, 1365, 1320, 1157, 975.

N.M.R. (100 MHz): 4.62 (1H), 4.10 (1H), 2.00 (3H), 1.62 multiplet (8H).

B) A solution of VII (500 mg) in 20 ml of acetic anhydride was added to 500 mg of sodium acetate in a 50 ml round bottom flask and was refluxed for two hours. Water was added and the excess anhydride was destroyed by warming. The solution was then made basic with 1N sodium hydroxide and extracted with chloroform. After the solvent was dried and evaporated, distillation gave 380 mg (73% yield) of XI.

C) A poor yield (less than 40%) was also obtained when the free base was treated with acetyl chloride in the presence of triethylamine with

methylene chloride as solvent.

Attempted oxidation of VII

The method of Sager and Bradley[102] used for the oxidation of camphane was attempted with VII.

An Erlenmeyer containing 2.6 g of sodium dichromate, 10 ml of water, 10 ml of sulfuric acid and 90 ml of acetic acid was cooled to 8° and 250 mg of VII was added. The solution was kept at 8° or below for five hours and was then poured onto ice and was neutralized with sodium carbonate and finally made basic with sodium hydroxide. Continuous extraction with chloroform yielded an amine which upon addition of hydrogen chloride appeared to be unreacted VII (30 mg). The reaction was repeated at room temperature and at 35° and in each case only VII was recovered.

Oxidation using chromic oxide[103]

To a round bottom flask containing 100 ml of acetic acid was added 0.5 g of chromic oxide and 100 mg of VII. The solution was refluxed for six hours and after cooling, the acid was neutralized with sodium bicarbonate and then was extracted continuously with chloroform. After the addition of hydrogen chloride gas and removal of the solvent, a total of 75 mg of VII was recovered.

Reactions with aluminum chloride[104]

A) The free base of VII (100 mg) was prepared as previously noted and was placed in a flask containing 0.1 ml of tert-butyl chloride and 25 ml of pentane. The solution was cooled to -78° in a dry ice-acetone bath and 0.2 g of resublimed aluminum chloride was added. The mixture was then gradually warmed to 0° and finally to +15°. After five hours at

this temperature the pentane was evaporated and the residue was dissolved in chloroform and washed with 25 ml of 1N hydrochloric acid. The aqueous portion was made basic and extracted with ether. The ether extract when treated as in the preparation of VII gave 30 mg of VII. No other product could be isolated.

The reaction was repeated with 340 mg of VII as its free base in 75 ml of pentane and 0.35 ml of tert-butyl chloride. In this run, less than 50 mg of aluminum chloride was added and the reaction mixture was kept at 0° for three hours and then stirred a further two hours at 20°. Throughout this reaction a dry nitrogen atmosphere was maintained. After one hour a precipitate was noticed, but upon treatment as above, 270 mg of VII was recovered.

Reaction with XI

B) In a 100 ml three-necked flask fitted with a nitrogen inlet and outlet system was placed 100 mg of XI in 50 ml of n-pentane. Then tert-butyl chloride (0.08 ml) was added along with 0.065 mg of sublimed aluminum chloride. The solution was allowed to react at 0° for one and a half hours and the pentane was then removed under vacuum. The crude solids that remained were examined by N.M.R. and showed only XI unchanged.

The reaction was repeated at room temperature and under reflux with the same result.

7-Chloro-7-azabicyclo[2.2.1]heptane (XII)

A round bottom flask fitted with a magnetic stirrer and containing 70 ml of a 5% solution of sodium hypochlorite was cooled to 0° and 200 mg of VII was added. The reaction mixture was stirred at this temperature

for four hours and was then extracted with cold chloroform. After the solvent was dried with magnesium sulfate, the solution was filtered and the chloroform removed under vacuum without heating. The crude residue was examined by N.M.R. which showed only XII and no unreacted VII. No further purification was undertaken.

N.M.R. (100 MHz): 6.40 multiplet (2H), broad multiplet 2.10 (2H), 1.76 (2H), 1.45 (4H).

Gassman reaction[124]

The chloroamine, XII, formed as above, was placed in a Carius tube containing 400 mg of silver perchlorate in 15 ml of absolute methanol. The tube was cooled with liquid nitrogen, evacuated and sealed.

Tubes prepared as above were placed in an oven at 70° for times varying from 8 to 60 hours.

A) After the tube had cooled it was opened and the silver chloride that had formed (180 mg) was recovered by filtration and the reaction mixture was dissolved in water. As nothing came from the neutral solution upon extraction with chloroform, the solution was made basic and was then extracted once again with chloroform. After drying, the chloroform solution was saturated with hydrogen chloride gas and evaporated to dryness. An N.M.R. examination of the residue showed that 50 to 60% of the crude material (147 mg) appeared to be VII.

A thin layer plate of basic alumina showed three spots when developed with a 15% mixture of ethyl acetate-hexane as eluent. Separation was then undertaken using thick layer chromatography. The band which had advanced the furthest, yielded 6 mg of compound (3% yield). This compound, when examined in the mass spectrometer,

showed a molecular ion having an m/e of 125. Comparison of the spectra (N.M.R. and mass spectra) of this compound with those of 7-formyl-7-azabicyclo[2.2.1]heptane prepared by an alternate method showed the two compounds to be identical.

B) When 50 mg of VII was placed in a solution of 100 mg of silver perchlorate in 10 ml of methanol and 10 ml of 20% sodium hydroxide, heating took place. After one hour, 25 ml of water was added and the material was extracted with chloroform. After the reaction mixture was dried with magnesium sulfate and filtered, hydrogen chloride gas was added and the solvent was removed. The N.M.R. of the residue appeared identical to that obtained from the crude product of the Gassman reaction.

C) When XII was treated as above without the base work-up only the perchlorate salt of VII and VII itself was recovered when the methanol was evaporated on a vacuum line.

D) When 200 mg of diethylamine was dissolved in 25 ml of methanol and treated with 150 mg of silver perchlorate a black precipitate formed immediately. Aqueous sodium hydroxide (20 ml) was added as before. Upon work-up as above and after the removal of the unreacted amine by an acid wash, 20 mg of a mixture was isolated. One component of the mixture had a peak at δ 7.61 of area one proton.

7-Formyl-7-azabicyclo[2.2.1]heptane (XXXIV)

In a round bottom flask was placed 1 g of 98% formic acid and 2 g of acetic anhydride. The mixture was cooled to -15° and after 20 minutes, 60 mg of VII was added. The solution was allowed to warm slowly to room temperature and after standing for 24 hours it was made basic with 20% sodium hydroxide and extracted with chloroform. After the

reaction mixture was dried and the solvent removed, distillation of the residue under vacuum at 40° gave a liquid (38 mg, 67% yield) which had an identical N.M.R. to that obtained under the Gassman reaction conditions. The liquid was distilled at 60° and 0.06 mm pressure.

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86. Found: C, 66.98; H, 8.74.

N.M.R. (100 MHz): 8.05 (1H), 4.61 (1H), 4.08 (1H), broad multiplet with four main peaks 1.82, 1.71, 1.54, 1.45 (8H).

Hofmann-Löffler reaction of XII

The chloroamine XII, prepared from 200 mg of VII, was dissolved in a solvent consisting of 14 ml of sulfuric acid and 60 ml of acetic acid. This was placed in a quartz vessel designed for photochemical reactions. Nitrogen was bubbled through the solution for ten minutes and a medium pressure mercury arc lamp was then turned on for 2.5 hours. After this time, 50 ml of water was added and the acid was neutralized with sodium carbonate. When the solution was basic, it was then extracted with chloroform and the chloroform dried over magnesium sulfate. After the solution was filtered, hydrogen chloride gas was introduced and upon evaporation of the chloroform, 180 mg of residue was left. Thin layer chromatography on plates using silica gel as the solid phase and ethyl acetate as eluent showed three spots which trailed badly. Neutralization of the hydrochloride salts gave at least six spots which also trailed badly. The N.M.R. of the crude residue showed that no VII remained.

7-Trichloroacetyl-7-azabicyclo[2.2.1]heptane (XIII)

The preparation of XIII was attempted using three methods.

A) In 50 ml of dichloromethane maintained at -15° was added 1.1 g of trichloroacetic acid, 1.3 g of triethylamine and 0.8 g of ethyl chloroformate. After the solution had been stirred for one hour, 550 mg of VII, which had been neutralized was added as a solution in 20 ml of ether. A temperature of -15° was maintained for two hours and then the mixture was warmed to room temperature where it remained for four hours. The triethylamine hydrochloride was filtered off and the solution was washed with 1N sodium hydroxide followed by 1N hydrochloric acid. The solvent was then dried and removed by vacuum to give 268 mg (26% yield) of XIII. Recrystallization of XIII from heptane gave a solid melting at 105.5-106°. The mother liquor was found to contain some 4-N,N-diethylamino-1,1,1-trichloro-3-buten-2-one (XVI).

Anal. Calcd for $C_8H_{10}NOCl_3$: C, 39.62; H, 4.15. Found: C, 3979; H, 4.21.

I.R.: 675, 1460, 1420, 1320, 1260, 1160, 985, 830, 800, 725, 650.

N.M.R. (100 MHz): 4.76 (2H), broad multiplet 2 main peaks centered at 1.94, 1.55 (8H).

B) To 25 ml of methylene chloride was added 4 ml of triethylamine and 0.3 g of VII. Trichloroacetyl chloride (0.4 ml), whose preparation will be described later, was added slowly and the reaction mixture was allowed to sit overnight. The solution was then treated as in procedure A. The residual syrup was dissolved in heptane and treated with Norite A. When XIII was recrystallized from heptane 222 mg (41% yield) was obtained. The mother liquor was also found to contain XVI.

C) A solution of VII (100 mg) in 50 ml of methylene chloride was added to 50 ml of a saturated aqueous solution of sodium carbonate. The

two phase reaction mixture was cooled and stirred vigorously while 300 mg of trichloroacetyl chloride was rapidly added. After one hour the two layers were separated and the aqueous portion extracted with more methylene chloride. The solution was dried and the solvent evaporated leaving 130 mg (70% yield) of XIII.

When aqueous sodium hydroxide was substituted for the sodium carbonate the yield fell to 47%.

Trichloroacetyl chloride

It was found that trichloroacetyl chloride prepared by the method of Carre and Libermann[153] was very difficult to separate completely from pyridine by fraction distillation. Although Gerrard and Thrush[154] observed no reaction between trichloroacetic acid and thionyl chloride at room temperature, the following procedure was found suitable.

To a flask containing 30 g of trichloroacetic acid was added 50 g of thionyl chloride. The mixture was heated under reflux for six days. The excess thionyl chloride was distilled off at atmospheric pressure through a Vigreaux column. The trichloroacetyl chloride then distilled over, b.p. 116-117°. A total of 14.5 g was obtained. The yield was 43%.

4-N,N-Diethylamino-1,1,1-trichloro-3-buten-2-one (XVI)

To a solution of 1 g of trichloroacetyl chloride in 50 ml of dichloromethane was slowly added 2 g of triethylamine. During the addition, the reaction flask was cooled in a water bath at 20°C. After standing for one hour, the contents of the flask were washed twice with 1N hydrochloric acid. The dichloromethane solution was then dried over magnesium sulfate, filtered and concentrated under reduced pressure (16 mm). The residual brown syrup was extracted several times with

heptane and the heptane extracts were treated with Norite A. Concentration of the filtrate gave 295 mg of XVI, m.p. 55.5-57°. The yield base on the stoichiometric requirement of two moles of trichloroacetyl chloride was 44%.

The same reaction has been carried out in chloroform or with neat reactants and in each case poorer yields were obtained. In addition the effect of varying the temperature from -70° to +50° was investigated. Above 50° the reaction mixture rapidly turned black, while below zero, no product was formed during an hour period. The best yield occurred at room temperature. The product XVI showed an instability to both heat and light. It began to decompose when heated above 90°. It was insoluble in dilute acid or base but soluble in concentrated hydrochloric acid. The mass spectrum of XVI showed a molecular ion at m/e 243 and M+2, M+4, and M+6 peaks in the intensity ratios typical of a compound containing three chlorine atoms.[12]

Anal. Calcd for $C_8H_{12}NOCl_3$: C, 39.39; H, 4.95. Found: C, 39.24; H, 4.86.

Oxidation with trichloroacetic anhydride

To a solution of 1 g of trichloroacetic anhydride in 50 ml of dichloromethane was added 0.65 g of triethylamine. After stirring for one hour the reaction mixture was washed with water, dilute sodium hydroxide and dilute hydrochloric acid. The organic solution was then subjected to the same work-up as above and gave 22 mg, (5.3%) of XVI, m.p. 55-57°C.

Attempted oxidation using trifluoroacetic anhydride

A solution of 1 g of trifluoroacetic anhydride in 50 ml of

dichloromethane was treated with 0.5 g of triethylamine. After one hour the solution was worked-up as above. No product could be isolated from the residue of the heptane extracts. No vinyl absorption, nor identifiable components could be seen in the N.M.R. of this crude material.

Synthesis of XVI from acetaldehyde

To a solution of 1.6 g of diethylamine in 50 ml of benzene was added 0.8 g of acetaldehyde. After the solution had turned cloudy, 2 g of trichloroacetyl chloride was added while the solution was stirred and cooled in an ice bath. After five minutes the benzene solution was washed with 1N hydrochloric acid, dried and concentrated under reduced pressure. The residue was extracted with boiling heptane. The heptane extracts were distilled under a pressure of 0.07 mm to remove all diethyl trichloroacetamide. The residue in the pot, after recrystallization from heptane amounted to 32 mg of a solid, m.p. 55.5-57°C which had I.R. and N.M.R. spectra which were identical to those of XVI.

Reaction in the presence of styrene

A mixture of 1 g of triethylamine and 0.5 g of styrene were cooled and 0.5 g of trichloroacetyl chloride was added slowly. During the addition and subsequent reaction period of one hour, the reaction flask was kept in the dark. The styrene and other volatile components were distilled off at a pressure of 0.075 mm. The residue was dissolved in chloroform and washed with 1N hydrochloric acid, followed by 1N sodium hydroxide. The chloroform solution was dried over magnesium sulfate, filtered and the filtrate concentrated under reduced pressure. The residue was extracted with boiling heptane. This extract was decolorized

with Norite A and allowed to cool whereupon crystallization yielded 140 mg (42%) of a solid having melting point and mixed melting point (55.5-57°C) identical to that of XVI.

Replacement of styrene by sulfur during the reaction produced no change in the yield of XVI.

Reaction in the dark under a nitrogen atmosphere

A total of 10 g of triethylamine was distilled under a nitrogen atmosphere into a flask fitted with a pressure-equalized dropping funnel and an outlet tube. Then 5 g of trichloroacetyl chloride was distilled into the dropping funnel, under an atmosphere of nitrogen which was maintained throughout the reaction. The freshly distilled acid chloride was then slowly added to the cooled flask which was kept in the dark throughout the reaction. The same work-up as employed in the preceding experiment gave a 41% yield of XVI.

Mass spectrometric analysis of gaseous reaction products

A pressure-equilibrated dropping funnel containing 2.5 g of trichloroacetyl chloride was fitted to a 3-neck flask containing 5 g of triethylamine. A dry-ice condenser and helium inlet were also attached to the flask. The flask was evacuated, then helium introduced, and the process was repeated several times. The pressure was finally reduced to 3 mm of mercury, and the system was closed to both the evacuation line and the helium source. The trichloroacetyl chloride was then added to the triethylamine and after ten minutes of reaction time, any gases were condensed in a bulb cooled by liquid nitrogen. The contents of this bulb were then introduced into a mass spectrometer through its gas inlet system. No carbon monoxide at m/e 28.01 could be detected,

but a noticeable peak at m/e 28.05 could be seen. In a control experiment using the same apparatus and procedure but using an amount of formic acid and sulfuric acid which would produce 7 mmole of carbon monoxide, a readily observable carbon monoxide peak (above background) could be seen.

Attempted oxidation of 1,4-diazabicyclo[2.2.2]octane (XVII)

To a solution of 5 g of XVII in 50 ml of dichloromethane was added 11 g of trichloroacetyl chloride in 25 ml of dichloromethane. The reaction was allowed to stand for 20 hours. The solid which had precipitated was filtered off and the filtrate was exaporated leaving 2.8 g of residue. The residue was washed with heptane, the heptane was then decolorized with Norite A, and after filtration, concentrated. From the concentrate 0.8 g of a solid, XXVIII, m.p. 73.5-75.5° was obtained. The mass spectrum showed a molecular ion at m/e 292 and an isotope cluster typical of a compound containing four chlorines.

Anal. Calcd for $C_8H_{12}N_2OCl_4$: C, 32.68; H, 4.12. Found: C, 32.79; H, 4.20.

Reduction of XXVIII

A solution of 300 mg of XXVIII in 50 ml methanol containing 1 g of potassium hydroxide pellets and 1 g of 10% Pd-on-charcoal in a pressure bottle was shaken at 42 p.s.i. for three hours. After filtration of the solution, the filtrate was diluted to 150 ml with water and extracted several times with chloroform. The extracts were dried over magnesium sulfate, filtered, and concentrated on a rotary evaporator. The liquid residue, 146 mg., was tentatively identified as N-acetyl-N'-ethylpiperazine. The mass spectrum of the product showed a molecular ion at m/e 156. A

satisfactory analysis of the product, which discolored on standing could not be obtained.

Attempted oxidation of N-methylpyrrolidine

A solution of 2 g of N-methylpyrrolidine in 25 ml of dichloromethane was slowly added to 1 g of trichloroacetyl chloride in 10 ml of dichloromethane. After 10 minutes, the usual work-up gave 98 mg of a syrupy residue. The N.M.R. of this material showed the presence of a compound possessing an unsplit vinyl proton at δ 7.71. Attempts at purification of the product were thwarted by its instability.

2-Chloro-7-trichloroacetyl-7-azabicyclo[2.2.1]heptane (XIV)

To a solution of XIII (300 mg) in 25 ml of methylene chloride was added 100 mg of benzoyl peroxide and 0.5 ml of sulfuryl chloride. The reaction mixture was refluxed for 24 hours under a drying tube. The solvent was then removed under vacuum and the residue was eluted from a column containing 30 g of silica gel using a 15% hexane:ethyl acetate mixture as eluent. This treatment yielded 150 mg of the crude monochloride which after sublimation melted at 70.0-71.5°. (107 mg; 31% yield) Recrystallization of the material first eluted from the column produced 110 mg of unreacted XIII. Although some disubstituted product was also obtained it was not purified. The amount of crude dichloro-compound was 45 mg.

Anal. Calcd for $C_8H_9NOCl_4$: C, 34.68; H, 3.28. Found: C, 34.52; H, 3.28.

I.R.: 1680, 1425, 1317, 870, 840, 805, 739, 610.

N.M.R. (100 MHz): 4.90 (2H), 4.10 triplet (1H), 2.24 (2H), 1.97 (2H), 1.50 multiplet (2H).

Attempted solvolysis of XIV

A variety of solvents were used in an attempt to displace the chlorine from XIV. (See table in discussion section.) Below are two sample experiments. All the other solvolytic experiments were treated in a similar manner. To a 50 ml vessel containing 75 ml of 80% aqueous ethanol was added 35 mg of XIV. The reaction was refluxed for 24 hours and the solvent was concentrated under vacuum. The residue was then extracted with chloroform and then thin layer chromatography (T.L.C.) on silica gel using a 15% hexane:ethyl acetate mixture showed a spot which moved at the same rate as XIV.

When two equivalents of lithium carbonate were used in a similar reaction, T.L.C. showed the appearance of a second spot. An examination of the N.M.R. of the crude reaction mixture indicated that some product was present which could contain a double bond. When XIV was refluxed in 40% aqueous ethanol containing lithium carbonate for one day 5 distinct spots were found after examination of the residue using T.L.C.

Attempted preparations of 4-acetamidocyclohexene (XXI)

A) A flask containing 50 ml of pyridine and 5 g of II was cooled to 0°. Thionyl chloride (2.5 ml) was added slowly while the solution was stirred with a magnetic stirrer. After 48 hours the solution was evaporated to a black tar and the tar was then dissolved in chloroform and washed with 1N sodium hydroxide. After the solution was dried and the solvent removed, the residue was examined by N.M.R. and showed less than 2% unsaturation.

B) When the solvent system was changed to tetrahydrofuran and the reaction mixture was refluxed for one hour, once again a black tar was

produced which had the same composition as that of the previous reaction.

trans-4-Acetamidocyclohexyl methanesulfonate (XX)

The acetamido alcohol II, (3 g), was finely powdered and dissolved in a solution composed of 50 ml of dichloromethane and 50 ml of pyridine at a temperature of 30°. Methanesulfonyl chloride (3.5 g) was then slowly added until about one quarter of the material had reacted and then the reaction mixture was placed in an ice bath. The remainder of the methanesulfonyl chloride was added, and the reaction mixture was stirred a further two hours. The solvent was then removed under vacuum and the residue was dissolved in chlorofrom and washed with 25 ml of 2N hydrochloric acid. The aqueous portion was then extracted 10 times with 25 ml portions of chloroform and the two organic layers were combined and dried over magnesium sulfate. After the drying agent was removed and solvent evaporated, 3.8 g (85% yield) of XX remained. The melting point of XX was 150-151° after a recrystallization from ethyl acetate.

Anal. Calcd for $C_9H_{17}NO_4S$: C, 45.93; H, 7.28. Found: C, 45.56; H, 7.07.

I.R.: 3310, 1630, 1550, 1374, 1340, 1170, 1000, 970, 945, 855.

N.M.R. (60 MHz): 5.67 (1H), 4.58 (1H), 3.77 (1H), 3.00 (1H), broad multiplet 2.37-1.20, sharp peak 1.97.

The yield was less than 25% when solvents such as pyridine, chloroform with pyridine or triethylamine, ethyl acetate or dimethylformamide were used.

4-Acetamidocyclohexene (XXI)

In a 100 ml round bottom flask containing 20 ml of dimethylformamide

was added 2 g of XX and 0.75 g of sodium methoxide. The flask was fitted with a condenser and a drying tube and the material was refluxed for four hours. The reaction mixture was cooled and allowed to stand at room temperature for a further two hours.

The solids that formed and the dimethylformamide were then dissolved in water and extracted 10 times with chloroform. After the mixture was dried over magnesium sulfate and filtered, the solvent was removed under vacuum. The residue was then placed in a bulb and distilled at 80 to 90° under a pressure of 0.05 mm. After recrystallization from ethyl acetate, a solid was obtained in 54% yield which melted at 77.5-79°.

Anal. Calcd for $C_8H_{13}NO$: C, 69.07; H, 9.35. Found: C, 68.96; H, 9.46.

I.R.: 3100, 1630, 1555, 770, 665.

N.M.R. (60 MHz): 5.81 broad (1H), 5.63 (2H), 4.05 (1H) broad, 2.4-1.6 broad peak (11H), with sharp peak 1.97.

4-Carbobenzoxyaminocyclohexene (XXII)

In 30 ml of tetrahydrofuran containing 1 g of IV was added 2.3 ml of thionyl chloride. The reaction mixture was refluxed for two hours and then 0.7 ml of pyridine was carefully added. After 20 minutes the pyridine salt was filtered from the mixture and the solvents were removed under vacuum. After the residue was dissolved in chloroform, the pyridine salts were removed by washing the solution with 1N hydrochloric acid. The material was dried over magnesium sulfate, filtered, and the solvent removed. A solid (0.8 g) was recovered which after sublimation and recrystallization from hexane melted at 60-62°. The yield was 86%.

Anal. Calcd for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41. Found: C, 72.60; H, 7.27.

I.R.: 3350, 1690, 1650 shoulder, 1550, 1310, 1275, 1240, 1150.

N.M.R. (60 MHz): 7.30 (5H), 5.60 (2H), 5.30 broad (1H), 5.05 (2H), 3.75 broad (1H), 2.5-1.2 multiplet (6H).

4-Carbobenzoxyaminocyclohexene oxide (XXIII)

To a solution of perbenzoic acid[155] (5 g in 100 ml benzene) was added 0.5 g of XXII in one portion and the mixture was stirred for one hour at 5°. The reaction mixture was then placed in a refrigerator for a further 16 hours after which it was washed with 1N sodium hydroxide. The organic layer was dried over magnesium sulfate and after filtration and evaporation of the solvent 500 mg of crude epoxide was recovered. This melted at 72-76°. A T.L.C. showed two spots, one faint and the other very distinct. The light one appeared to move at the same rate as the starting material. Recrystallization from hexane resulted in a solid melting at 78-79.5°. (92% yield)

Anal. Calcd for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93. Found: C, 67.81; H, 6.94.

I.R.: 3350, 1690, 1550, 1310, 1280, 1240, 1050.

N.M.R. (60 MHz): 5.15 broad (1H), 5.05 (2H), 3.70 broad (1H), 3.15 (2H), broad multiplet 2.2-1.2 (6H).

Attempted removal of protecting group from XXIII

A solution of XXIII (250 mg) in 150 ml of ethyl acetate was placed in a Parr hydrogenation bottle containing 0.1 g of 10% Palladium-on-charcoal. After one hour of shaking, the hydrogenolysis was discontinued, the catalyst was filtered off and the solvent was evaporated. Examination

of the residue by N.M.R. and I.R. showed the loss of the epoxide group but retention of the carbobenzoxy group.

Attempted reduction of XXIII with tri-t-butoxy-lithium aluminum hydride

In a 500 ml 3-necked flask fitted with a nitrogen inlet and outlet, a condenser, and a dropping funnel was added 150 ml of dry ether containing 0.6 g of tri-t-butoxy-lithium aluminum hydride. An ether solution of XXIII (0.5 g) was slowly added. After four hours of reaction at room temperature, ethanol was dropped into the flask to remove any unreacted hydride. The solvent was then evaporated to dryness and the residue was extracted with chloroform. The I.R. of the residue showed that the carbobenzoxy group had not been touched.

Reaction of XXIII with lithium aluminum hydride

To a 500 ml flask fitted as in the above reaction containing 100 ml of ether and 150 mg of lithium aluminum hydride was added 400 mg of XXIII dissolved in 100 ml of ether. After the solution had reacted for two hours at room temperature methanol was added slowly and the solvent was evaporated to dryness. An extraction of the residue with chloroform gave 422 mg of a material which showed four spots on T.L.C. (silica gel).

A 50 g column was made and the material was eluted from the column with ethyl acetate. The major component consisted of 348 mg of a solid which melted at 77-82°. The I.R. and N.M.R. spectra of this compound indicated that no epoxide remained. The other portions weighed 23, 31, and 9 mg respectively. All except the 9 mg sample contained the carbobenzoxy group and at least one hydroxyl function as indicated by I.R.

4-N-Ethyl-4-aminocyclohexene hydrochloride (XXIV)

In a dry three necked 100 ml flask fitted with condenser and drying tube and containing 75 ml of tetrahydrofuran was added 1.5 g of lithium aluminum hydride. A solution of XXI (2 g) in 10 ml of tetrahydrofuran was then added at a rate fast enough to maintain reflux. The reaction mixture was then refluxed a further two hours and the excess lithium aluminum hydride was destroyed with methanol and water.

After the addition of 200 ml of water containing 1N sulfuric acid to the reaction mixture the aqueous layer was extracted with chloroform to remove the tetrahydrofuran and unreacted XXI, and was then made basic with 20% sodium hydroxide and extracted with ether. The ether was dried over magnesium sulfate, filtered, redried over calcium hydride and after the final filtration hydrogen chloride gas was bubbled through the solution. The precipitate (1.8 g) was removed and recrystallized from an ethyl acetate:methanol mixture (78% yield). The product XXIV melted at 178-179°.

Anal. Calcd for $C_8H_{16}NCl$: C, 59.43; H, 9.98. Found: C, 59.27; H, 9.95.

I.R.: 3000-2250, 1435, 1420, 1370, 1110, 1030, 650.

N.M.R. (60 MHz): 5.63 (2H), 3.13 broad (3H), broad multiplet centered 2.2 (6H), triplet 1.49 (3H).

4-N-Nitroso-N-ethylaminocyclohexene (XXV)

A solution of XXIV (200 mg) in 25 ml of water was added to 2 g of sodium nitrite and 15 drops of concentrated hydrochloric acid. The reaction mixture was then maintained at 70° for two hours. After cooling, the solution was extracted with chloroform and the chloroform

dried over magnesium sulfate. The solvent was filtered and evaporated leaving 170 mg of crude XV. A molecular distillation of the compound at 55° and 0.05 mm gave a pale yellow liquid. The yield of purified XXV was 80%.

Anal. Calcd for $C_8H_{14}N_2O$: C, 62.30; H, 9.15. Found: C, 61.80; H, 9.12.

I.R.: 1430, 1378, 1363, 1320, 1245, 1160, 1059, 1041, 635.

N.M.R. (60 MHz): 5.67 (2H), 4.40 broad (1H), 3.59 quartet (2H), 1.12 (3H) triplet, J = 7 Hz, broad multiplet 2.7-1.7 (6H).

Photochemical reaction of XXV

To a solution of XXV (150 mg) in 50 ml of methanol was added 1 ml of concentrated hydrochloric acid. The photolysis apparatus was then connected and nitrogen was passed through the solution for five minutes. The source was turned on and the solution irradiated for four hours.

The solvent was then carefully removed on a vacuum line and the residue which remained was dissolved in chloroform. The chloroform was shaken with 25 ml of water to remove the acid portions. The solution was dried and the solvent evaporated leaving a residue which appeared to contain 4-oxocyclohexene. The aqueous portion was then made basic and was extracted again with chloroform and after the solvent was dried and filtered, hydrogen chloride gas was added to yield what appeared to be 4-N-ethyl-4-aminocyclohexene hydrochloride.

Photochemical reaction of 4-N-chloroaminocyclohex-1-ene (XXVA)

To XIV (200 mg) contained in a 250 ml round-bottom flask was added 75 ml of a 5% solution of sodium hypochlorite. The reaction mixture was kept at 0° for four hours after which it was extracted with chloroform.

After the solution was washed with water and dried with magnesium sulfate, the chloroform was carefully evaporated under vacuum and the residue was immediately taken up in a solution consisting of 10 ml of concentrated sulfuric acid in 70 ml of glacial acetic acid. The chloroamine was photolysed for four hours in the same apparatus as described previously. The acids were poured into 50 ml of ice water, neutralized with sodium carbonate and finally made basic with 20% sodium hydroxide. The solution was extracted with ether and the organic portion was dried with magnesium sulfate, filtered, redried with calcium hydride and after a further filtration hydrogen chloride gas was added. A solid (90 mg) precipitate was recovered after filtration of the solution. This solid was then added to a solution of 70% aqueous ethanol containing 2 equivalents of 1N sodium hydroxide. After 24 hours and work-up as in the preparation of VII, spectral examination of the residue showed no bicyclic compound.

Reaction of XXVA with ferrous sulfate

The amine hydrochloride, XXIV, was treated as before to give the chloroamine. The product was dissolved in 50 ml of methanol. Nitrogen was bubbled through the solution for ten minutes and then 1.3 equivalents of ferrous sulfate was added. The reaction mixture was kept under nitrogen for 18 hours at room temperature. The solvent was saturated with hydrogen chloride gas and removed under vacuum. The residue was extracted with chloroform and the solids removed by filtration. Only the hydrochloride of XXIV was recovered. The reaction was repeated at reflux temperature with the same result.

Bromination of 4-N-ethylaminocyclohexene

A solution of XXIV (100 mg) in 1.00 ml of chloroform was placed in a 250 ml Erlenmeyer. The solution was stirred rapidly as 200 mg of bromine was dropped in. After 25 minutes the solvent and excess bromine were removed under vacuum and the resulting syrup was placed in a flask containing 100 ml of a 70% aqueous ethanol solution and one equivalent of 1N sodium hydroxide. After 24 hours the reaction was treated in the manner used to prepare VII. Examination of the residue showed no bicyclic product.

The bromination was repeated with the free base of XXIV in refluxing carbon tetrachloride. A spectral examination of the product showed no bicyclic compound. The reaction mixture was then treated with sodium iodide under reflux in chloroform. The product of this was subjected to the aqueous ethanol treatment as above with the same result.

Meerwein reagent[93]

A 250 ml 3-necked flask fitted with a drying funnel, a condenser, a nitrogen inlet and outlet was flamed to dryness under nitrogen. Ether (50 ml) which contained 10 g of redistilled boron-trifluoride etherate complex was added and the solution was refluxed on a water bath. An ether solution containing 4.5 g of epichlorohydrin in 20 ml of ether was added slowly through the dropping funnel. The reaction mixture was allowed to stir under reflux for two hours and stand at room temperature a further 16 hours. The ether was removed under a positive nitrogen pressure and the residue was then rinsed several times with dry ether (50 ml portions) and the ether that remained was evaporated with nitrogen.

Ethyl-N-(4-mesyloxycyclohexyl)-acetimidate (XXIX)

The Meerwein reagent (1.4 g) prepared as above was added to 1 g of trans-4-acetamidocyclohexyl methanesulfonate (XX) in 50 ml of methylene chloride. The reaction mixture was allowed to stand for eight hours and then 10 ml of triethylamine was added. After standing overnight, the mixture was washed with water and dried over magnesium sulfate. The solution was filtered and the solvent was then removed under vacuum and the residue extracted with boiling heptane. The solid (0.84 g) which was recovered from the heptane melted at 80-82°. The yield for the reaction was 75%.

Anal. Calcd for $C_{11}H_{21}NSO_4$: C, 50.16; H, 8.04. Found: C, 50.15; H, 8.06.

N.M.R. (100 MHz): 4.70 broad (1H), 3.99 quartet (2H), (J = 20 Hz), 3.60 broad (1H), 3.00 (3H), broad multiplet 2.3-1.1 (11H), including singlet 1.85, triplet 1.20, (J = 7.0 Hz).

trans-4-aminocyclohexyl methanesulfonate hydrochloride (XXX)

The imidate ester, XXIX, was suspended in water and oxalic acid was added until the pH reached 1.5-2. After the mixture had been stirred for a few minutes, XXIX dissolved and was kept in the acid solution for 16 hours. Chloroform was then added and the aqueous portion was made basic with 1N sodium hydroxide. After the aqueous portions were extracted with more chloroform, the chloroform layer was dried with magnesium sulfate and hydrogen chloride gas was bubbled in. When the solvent was removed, XXX remained and was then recrystallized from a methanol:ethyl acetate mixture. The solid melted at 141-143°C. The yield varied from 70 to 86%.

Anal. Calcd for $C_7H_{16}O_3NSCl$: C, 36.59; H, 7.02. Found: C, 36.79; H, 7.20.

7-Azabicyclo[2.2.1]heptane hydrochloride VII

The hydrobromide, XXX, obtained from the previous reaction was placed in a 80% aqueous ethanol solution containing two equivalents of 1N sodium hydroxide. After 16 to 18 hours the solution was treated in the manner used to obtain VII. The reaction gave VII in yields from 70 to 83%.

2-Chloro-7-azabicyclo[2.2.1]heptane hydrochloride (XXXI)

To a solution of XIV (100 mg) in 15 ml of frozen t-butanol was added 100 mg of potassium t-butoxide. The reaction vessel was sealed and the solid allowed to melt. Fifteen minutes after the bubbles ceased to evolve the mixture was again frozen and the tube unsealed. Hydrogen chloride gas was bubbled through the solution as the solvent melted and the t-butanol was removed under vacuum. The residue was extracted with chloroform and filtered to remove the solid potassium chloride. After the chloroform was removed and the residue recrystallized from a methanol-ether mixture, 75 mg of XXXI which melted with decomposition at 242° was recovered (73% yield).

Anal. Calcd for $C_6H_{11}NCl_2$: C, 42.87; H, 6.59. Found: C, 42.68; H, 6.76.

I.R.: 3000-2450, 1610, 1581, 1450, 1435, 1369, 1354, 1320, 1050, 880, 670, 500.

N.M.R. (100 MHz): 4.45 (1H), 4.30 (1H), 4.11 (1H), 2.20 broad (4H), 1.56 broad (2H).

Attempted Solvolysis of XXXI

A) To a solution of XXXI (50 mg) in 10 ml of acetic acid was added 50 mg of sodium acetate and the solution was then sealed in a thick-walled tube. After being heated for 24 hours at 100° the tube was opened and hydrogen chloride gas was added. The solvent was removed under vacuum and the residue extracted with chloroform. The N.M.R. showed only unreacted XXXI.

B) To a solution of XXXI (50 mg) in 10 ml of methanol was added 100 mg of sodium methoxide. The solution was heated for 24 hours in a sealed tube at 110°, then opened and hydrogen chloride gas was added, and the solvent was removed. The N.M.R. of the residue showed a trace of a new peak at δ4.40, however, 40 mg of XXXI was recovered unchanged.

C) To a solution of XXXI (50 mg) in 10 ml of a 50:50 mixture of water and methanol was added 100 mg of sodium hydroxide. After 12 hours at 100° in a sealed tube the reaction mixture had turned yellow. Addition of hydrogen chloride gas and removal of solvent showed that XXXI was completely reacted. The N.M.R. of the residue (35 mg) indicated that no bicyclic product was present.

D) To a solution of XXXI (20 mg) in 5 ml of dimethylformamide was added 200 mg of sodium methoxide. The mixture was allowed to react for 24 hours in a sealed tube at 110°. After the mixture had been saturated with hydrogen chloride gas the dimethylformamide was removed under vacuum. The residue was then dissolved in water and made basic with 10% sodium hydroxide. The basic portion was extracted with ether, dried, and saturated with hydrogen chloride gas. After the solvent had been removed, the N.M.R. of the 9 mg residue showed unreacted XXXI.

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Determination of the pK_A for ABH

Samples of 7-azabicyclo[2.2.1]heptane hydrochloride (VII) weighing 35, 45, and 50 mg respectively were dissolved in 50 ml of water in a 250 ml beaker. The solution was stirred with a magnetic stirrer. Titration of VII using a solution of 0.100N sodium hydroxide (BDH volumetric reagent) was followed with a Radiometer pH meter type 24e using a glass electrode. The pH meter was standardized at pH 8, 10, and 11 before each sample determination. The pH of the solution was read after each 0.05 ml of sodium hydroxide solution was added and a plot was made of pH versus volume of sodium hydroxide added. The inflection point was determined and the pH noted at this point. This then gave the pK_A for the amine. The average value for the three determinations was 10.8.

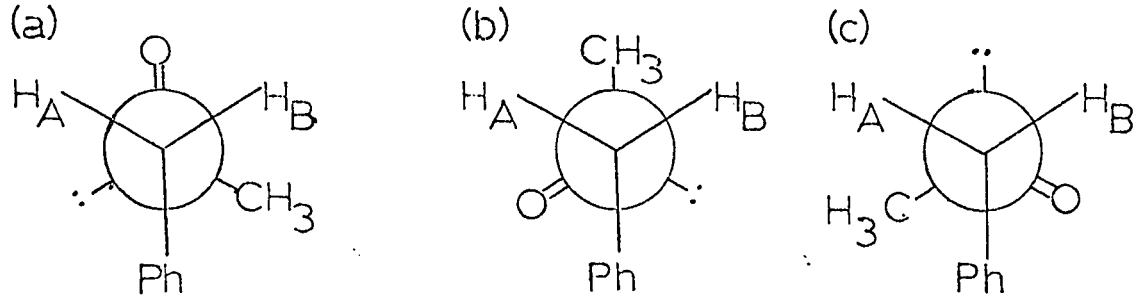
P A R T II

Base Catalysed Hydrogen:Deuterium Exchange of Benzylic Sulfoxides

INTRODUCTION

In 1966 an unusual and controversial report on a stereospecific deuterium-hydrogen exchange of benzyl methyl sulfoxide appeared in Chemical Communications.[156] Wolfe and Rauk reported the observation that the exchange of the two diastereotopic methylene protons in deuterium oxide containing sodium deuteroxide proceeded at different rates. This, of course, inferred that the molecule was giving rise to an asymmetric carbanion which contradicted the evidence previously presented by others.[157]

The problem that arose from the paper was two-fold. It was difficult to accept the conformation of the molecule which Wolfe stated to be the predominate one in solution and it was felt that Wolfe had not included all possible factors in his assessment of which configuration was dominant. On the basis of a stereospecific synthesis whose result was somewhat dubious, (the resulting compound was only 30% optically active) he stated that he had proven that H_A was preferentially exchanged from configuration a of the molecule.



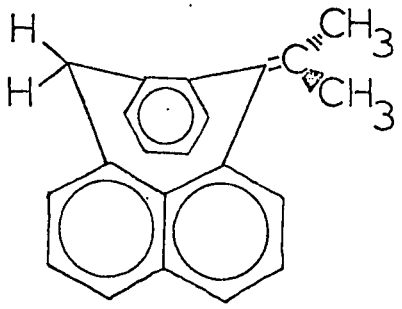
By use of dipole-moment calculations for each conformation and by comparison with the observed dipole he assigned a to be the predominate conformation. He supposedly supported this assignment by N.M.R. on the basis of two assumptions which may or may not be valid.[172] He assumed that i) the lone pair of electrons has a shielding effect

on the proton which is anticoplanar and ii) the shielding effect for the S=O bond is greater for the proton gauche than for the proton anticoplanar. This would made H_A at lower field in a and H_B at lower field in b. Since he found the lower field proton to exchange first and since he apparently had proven this to be H_A he then stated that a was the preferred conformation for the molecule. He postulated that if H_A was obtained from b then the only thing which controlled the sterochemistry of the exchange would be the repulsion between the incipient carbanion and the lone pair and since H_B of a is in the same environment there would be little or no kinetic difference between H_A and H_B.

It would appear that he neglected two possibly important factors: i) that their rates of exchange depend only on carbanion stability and not on ground state conformations[175] and ii) how much the phenyl group contributes to the differences in the rate of exchange.. It is possible that conformation b would be preferred sterically over that of a (phenyl:lone pair interaction as opposed to phenyl:methyl interaction) and that carbanion stability would be controlled not only by lone pair and developing carbanion repulsion but also by preferred overlap of the π orbitals of the benzene ring and the developing p-sp^3[158] orbital of the carbanion.

It has been proposed that the phenyl group is asymmetrically oriented with respect to the adjacent CH_2 protons in benzyl sulfoxides[159] and therefore it would exert a conformationally dependent effect on the benzylic methylenes. For example Lansbury[160] and co-workers have shown that a highly specific hydrogen-deuterium exchange occurred at the

benzylic position of 7-isoproplidene-7,12-dihydropleiadene.



To test this possibility in sulfoxides three suitable benzyl sulfoxides were prepared and a hydrogen:deuterium exchange on each was carried out.

The three sulfoxides chosen for study were the benzyl methyl sulfoxide, benzyl ethyl sulfoxide, and o-methylbenzyl methyl sulfoxide. If the phenyl group was partially responsible for the asymmetry of the benzylic methylene protons then the carbanion should develop as close to perpendicular to the plain of the phenyl ring as possible to insure maximum overlap. Substitution of an ethyl group for the methyl group or substitution of an ortho methyl for an ortho hydrogen should tend to change the ability of the phenyl group to have maximum overlap and this change in conformation should make itself felt in the rate of exchange of the protons if the theory was correct.

DISCUSSION AND RESULTS .

The compounds were prepared by standard methods of synthesis; the only new compound being the o-methylbenzyl sulfoxide. The rates of exchange were determined by an accurate analyses of the amount of deuterium incorporated in the molecule by the use of mass spectroscopy.

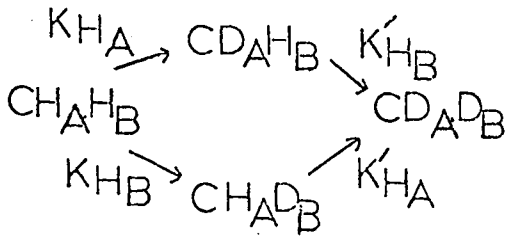
The exchange was performed on 100 mg samples in 10 ml of deuterium oxide containing a large excess of sodium deuteroxide. Aliquots of the sample were taken at intervals, the base was quenched by reaction with hydrogen chloride gas in chloroform, and the sample was purified by sublimation before submission to mass spectrometric analysis.

For each compound that was submitted, the mass spectrum of the corresponding sulfone was also determined to check whether the fragmentation pattern of the sulfone interfered with that of the sulfoxide. The reason for this check was to make certain that slight amounts of sulfone (less than 3% by I.R.) which could not be completely removed from the sulfoxide did not affect the quantitative analysis.

For each aliquot, a background was taken and its intensity subtracted from the resulting intensity of the molecular ions formed. A minimum of six determinations of the molecular ion peaks were then made. A correction for the isotopes present in natural abundance was made thus determining accurately at any given time the proportion of ions $(M)^+$, $(M+1)^+$, $(M+2)^+$, and $(M+3)^+$ in the sample. The correction was empirical rather than calculated[127] and was determined for each sulfoxide individually. This insured that machine error would be minimal.

A sample calculation is given for one aliquot of o-methylbenzyl methyl sulfoxide. The parent compound was found to have the isotopic ratio of the $(M)^+$, $(M+1)^+$, $(M+2)^+$, $(M+3)^+$ peaks as 100, 10.9, 5.3, and 0.4. This then gave the empirical correction factors for the $(M+1)^+$, $(M+2)^+$, and $(M+3)^+$ ions. One aliquot of the exchanged molecule showed the ratios of the peaks to be 91.75 $(M)^+$, 100 $(M+1)^+$, 16.98 $(M+2)^+$, 5.6 $(M+3)^+$. The correction factor using the values found for the

isotopic natural abundance for the parent compound was then applied in the following manner. The higher isotopes of the $(M)^+$ peak in the $(M+1)^+$ peak would contribute (91.75 x 10.9)% to the intensity found for the $(M+1)^+$ peak. The contribution by the higher isotopes of the $(M)^+$ peak to the intensity of the $(M+2)^+$ peak would be (91.75 x 5.3)% and to the intensity of the $(M+3)^+$ peak would be (91.75 x 0.4)%. These values were then subtracted from the intensities found for these peaks i.e. 100, 16.98, 5.6, respectively. Corrections were then made in a similar manner for the higher isotopes of the $(M+1)^+$ peak in the intensities of the $(M+2)^+$ and $(M+3)^+$ peaks and so on. From the corrected intensities then, the relative amount of undeuterated, monodeuterated, and dideuterated sulfoxide could be determined. A scheme for the exchange is envisaged as follows.



k_{H_A} is the rate constant for the disappearance of H_A and k_{H_B} is the rate constant for the disappearance of H_B. k'_{H_A} and k'_{H_B} are the rate constants for the exchange of H_A and H_B when an alpha isotope effect is present.

The kinetic equation can be considered as a pseudo-first order equation since the concentration of sodium deuteroxide remains constant throughout the exchange. The equation can be written as $\frac{-d(H_AH_B)}{dt} = k'(H_AH_B)$ where $k' = (k_{H_A} + k_{H_B})(OD^-)$ and (H_AH_B) is the concentration of

undeuterated sulfoxide at time t. The solution to this differential equation is $(H_AH_B)_t = (H_AH_B)_{t_o} e^{-k't}$. A plot of log $\frac{(H_AH_B)_t}{(H_AH_B)_{t_o}}$ versus t gives $\frac{k'}{2.303}$ which is the slope of the line. After all the parent compound has been at least monodeuterated the only remaining proton is H_B. The rate of disappearance of H_B is represented by the rate constant $k'(H_B)$ and can be determined in the same way. Subtraction of the two rate constants gives the pseudo-first order rate constant for the exchange of the first proton. A correction factor due to the secondary isotope effect should be applied to the rate constant for the disappearance of H_B from the monodeuterated species as this should show an alpha isotope effect.[161,158] These effects are usually small ranging from 0.95 to 1.4. It has been found in this laboratory that the secondary isotope effect for the deuterium hydrogen exchange for a benzylic sulfone system was 1.2.[162] This would mean that the rate of exchange of H_B should be corrected by this factor.

The rates of exchange of each diastereotopic proton in the three sulfoxides are shown in figure 1.

It must be noted from the results that although the ratio of $k_{(H_A)}$ and $k_{(H_B)}$ changed slightly, the actual rates of exchange were not appreciably different. The only positive indication that could be drawn from the exchange was that there was a small effect shown when a methyl group was substituted for the hydrogen on the ring. Unfortunately the compounds chosen still allowed free rotation about the Ph-CH_2 bond which was only slightly sterically hindered by the o-methyl group. It

Figure 1

COMPOUND	TEMP.	CONC. (OD^-)M/l	# OF POINTS	$k_{(H_A)}$	$k'_{(H_B)}$	$k_{(H_B)}$*	$k_{(H_A)}/k_{(H_B)}$
$PhCH_2\overset{O}{\overset{\|}{S}}CH_2CH_3$	24°	2.7×10^{-1}	6	2.38×10^{-3}	1.39×10^{-4}	1.67×10^{-4}	14.2:1
$PhCH_2\overset{O}{\overset{\|}{S}}CH_3$	24°	8.87×10^{-2}	9	3.00×10^{-3}	1.73×10^{-4}	2.08×10^{-4}	14.4:1
$o\text{-}CH_3PhCH_2\overset{O}{\overset{\|}{S}}CH_3$	24°	1.86×10^{-1}	10	2.73×10^{-3}	1.29×10^{-4}	1.55×10^{-4}	17.6:1

* After correction for alpha isotope effect.

would therefore appear that only a system which was locked into position, as would be the case with two methyl groups, could give more information. A study of a benzylic sulfoxide system which is completely rigid in all respects has been undertaken in this laboratory but the results are not yet completely known.[162]

Although Wolfe and his co-workers[158,163] have recently made numerous calculations to prove that indeed abstraction of the proton is from conformation a, such calculations are only as good as the various quantum mechanical parameters used to make them and furthermore do not give any information about the ground state of the molecule. Until a system is studied in which the individual protons can be identified during the exchange the question will remain open.

EXPERIMENTAL

The three compounds, benzyl methyl sulfide, benzyl ethyl sulfide, and o-methylbenzyl methyl sulfide were prepared in the same manner. The preparation of the benzyl ethyl sulfide will be given in detail.

To a solution of sodium (10 g) in 200 ml of absolute ethanol was slowly added 25 g of ethyl mercaptan. The reaction mixture was stirred a further 10 minutes, then benzyl chloride (51 g) was dropped slowly into the solution and the reaction mixture was refluxed for three hours. The mixture was then poured into ice water and extracted with ether. The extracts were dried over magnesium sulfate, filtered, and concentrated under vacuum. The product was purified by distillation at 119° and 6 mm pressure (31 g; 51% yield). The literature value for the boiling point is 222° at 759 mm.[164]

The boiling points of benzyl methyl sulfide and o-methylbenzyl-methyl sulfide were 89-91° at 12 mm (lit. 91-92° at 12 mm)[165] and 40° at 0.1 mm (lit. 61° at 0.5 mm)[166] respectively.

The sulfoxides of the three compounds were prepared according to the method of Leonard and Johnson.[167] The products were purified by sublimation followed by recrystallization from heptane. The melting points for benzyl methyl and benzyl ethyl sulfoxides were 54-55° (lit. 54°)[168] and 54-55.5° (lit. 49°).[164] The o-methylbenzyl sulfoxide was a new compound and was produced in 67% yield by this method. The melting point was 53-54.5°.

Anal. Calcd for $C_9H_{12}SO$: C, 64.29; H, 7.14. Found: C, 64.11; H, 7.00.

The sulfones were prepared by oxidation of the corresponding

sulfoxides according to the standard method[169] employing 30% hydrogen peroxide in acetic acid. The melting points were for benzyl ethyl sulfone 80-81° (lit. 84°),[164] for benzyl methyl sulfone 122-124° (lit. 125-127°), and for o-methylbenzyl methyl sulfone 76-77° (lit. 76-78°).[166]

The NaOD was prepared by dissolving a known amount of sodium in a known volume of 99% D_2O. The ideal concentration of the base for each sample was determined by trial and error so that the best plot for the results for each compound could be obtained.

The exchange was carried out by dissolving the sulfoxide (100 mg) in 10 ml of the NaOD solution which was at a temperature of 24° and the time clock was started. The solution was immediately replaced in the constant temperature bath at 24.0° and kept there throughout the exchange. At the appropriate interval, a 1 ml aliquot of the reaction mixture was pipetted out of the body of the solution into 3 ml of chloroform which had been saturated with hydrogen chloride gas. Vigorous stirring of the solution at the time of addition of the aqueous portion to the chloroform insured that the reaction would be quenched immediately and that the resulting sulfoxide would be extracted into the chloroform layer. The chloroform was then carefully pipetted away from the aqueous layer and was then dried over magnesium sulfate. After the drying agent had been removed, the chloroform solution was placed in a small-sublimation apparatus and the chloroform removed by passing a stream of air over the solution. Sublimation of the residue purified the sample sufficiently so that a good mass spectrum could be obtained. (The mass spectra of the sulfoxides showed typical fragmentation patterns[170] and will not be discussed here as only the region of the molecular ion was of interest.)

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Claims to Original Research

1) Two new synthetic routes to 7-azabicyclo[2.2.1]heptane have been devised.

2) Several N-substituted 7-azabicyclo[2.2.1]heptanes have been synthesized and their spectral and chemical properties studied.

3) A mono-substituted 7-azabicyclo[2.2.1]heptane, exo-2-chloro-7-azabicyclo[2.2.1]heptane, has been synthesized and some of its spectral and chemical properties studied.

4) The rotational barriers for 7-acetyl-7-azabicyclo[2.2.1]heptane and 7-nitroso-7-azabicyclo[2.2.1]heptane have been determined.

5) A new reaction of trichloroacetyl chloride with triethylamine was discovered and was shown to produce a beta-acylenamine.

6) A mechanism for the reaction between trichloroacetyl chloride and triethylamine has been determined.

7) The rates of hydrogen-deuterium exchange of each of the diastereotopic benzylic methylene protons in three benzylic sulfoxides have been determined by an accurate kinetic analysis. The variation in rate with structure provided evidence regarding the mechanism by which exchange occurs.

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