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REACTIONS OF SOME NORTROPANE DERIVATIVES

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INTRODUCTION

A great deal of work has been done on solvolysis in the bicyclo [2.2.1] heptane system.[1-5] This has shown that during or after ionization has taken place, several methods are available to the cation for stabilization of the positive charge. In the bicyclo [3.2.1] octane system interactions similar to those in the bicycloheptanes can be postulated for the stabilization of the incipient carbonium ion. It was desired, therefore, to study several compounds in the bicyclo[3.2.1]octane system in an effort to determine what modes of stabilization might be observable. For such an investigation the solvolysis reactions of the 3α and 3β-mesyloxynortropanes and 3α and 3β-tosyloxy-8-thiabicyclo [3.2.1] octanes were considered to be a convenient starting point. As representatives of the bicyclo[3.2.1]octane system these compounds offer two advantages: 1) they can be relatively readily prepared and 2) the presence of the hetero atom might be expected to have a significant controlling effect on their mode of solvolysis.

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1. Winstein, S. and Trifan, D., J. Am. Chem. Soc. 74, 1147, 1154 (1952).
2. Martin, J. C. and Bartlett, P. D., J. Am. Chem. Soc. 79, 2533 (1957).
3. Winstein, S., Shatavsky, M., Norton, C., and Woodward, R. B., J. Am. Chem. Soc. 77, 4183 (1955).
4. Winstein, S. and Shatavsky, M., J. Am. Chem. Soc. 78, 592 (1956).
5. Winstein, S. and Stafford, E. T., J. Am. Chem. Soc. 79, 505 (1957).

DISCUSSION

A. 2-Substituted Bicyclo [2.2.1] Heptanes

The work on solvolysis in the bicycloheptanes has shown that ionization occurs and that this is accompanied or followed by some manner of stabilization of the ion so formed. Thus with exo norbornyl-2 brosylate ionization yields a resonance stabilized carbonium ion.(1) Several valence bond structures that might contribute to this hybrid ion are A-II, A-III, and A-IV.

These forms may be summed in the representation, A-V. In any resonance hybrid it is conceivable that one of the extreme valence bond forms may have a lesser influence than the others. One such form might be the valence bond structure corresponding to the primary carbonium ion, A-IV. Since a primary carbonium ion would be less stable than a secondary carbonium ion, this might imply that the contribution of the structure, A-IV, was of smaller importance.

The results of work on the 2-chloro-1, 4-endoxocyclohexanes provide a further insight into the possible modes of stabilization of a cation.(2) Since oxygen could donate electrons to a cationic center, the structures B-VI, B-VII, and B-VIII would be possible. Therefore the interactions depicted by them would assist in the ionization process by making the hybrid more stable. Any contribution from these structures (B-VI-B-VIII) could influence the ratio of the yield of the exo isomer to that of the endo isomer. If assistance occurred through interaction of the C_1 - C_6 bond electrons with subsequent interaction of the oxygen electrons

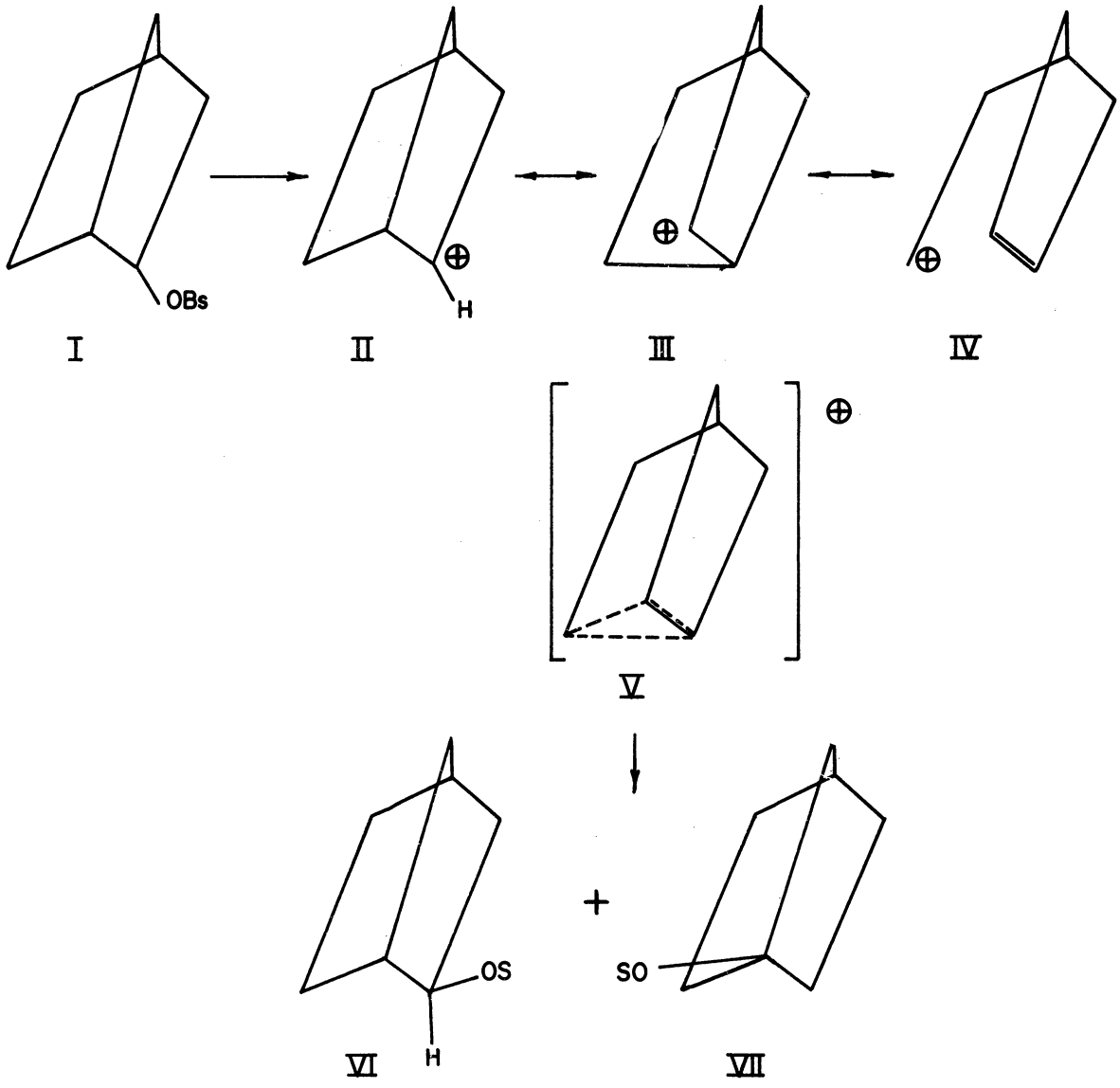


Chart A. Modes of Stabilization of the Bicyclo [2.2.1] Heptane Cation and its Solvolysis.

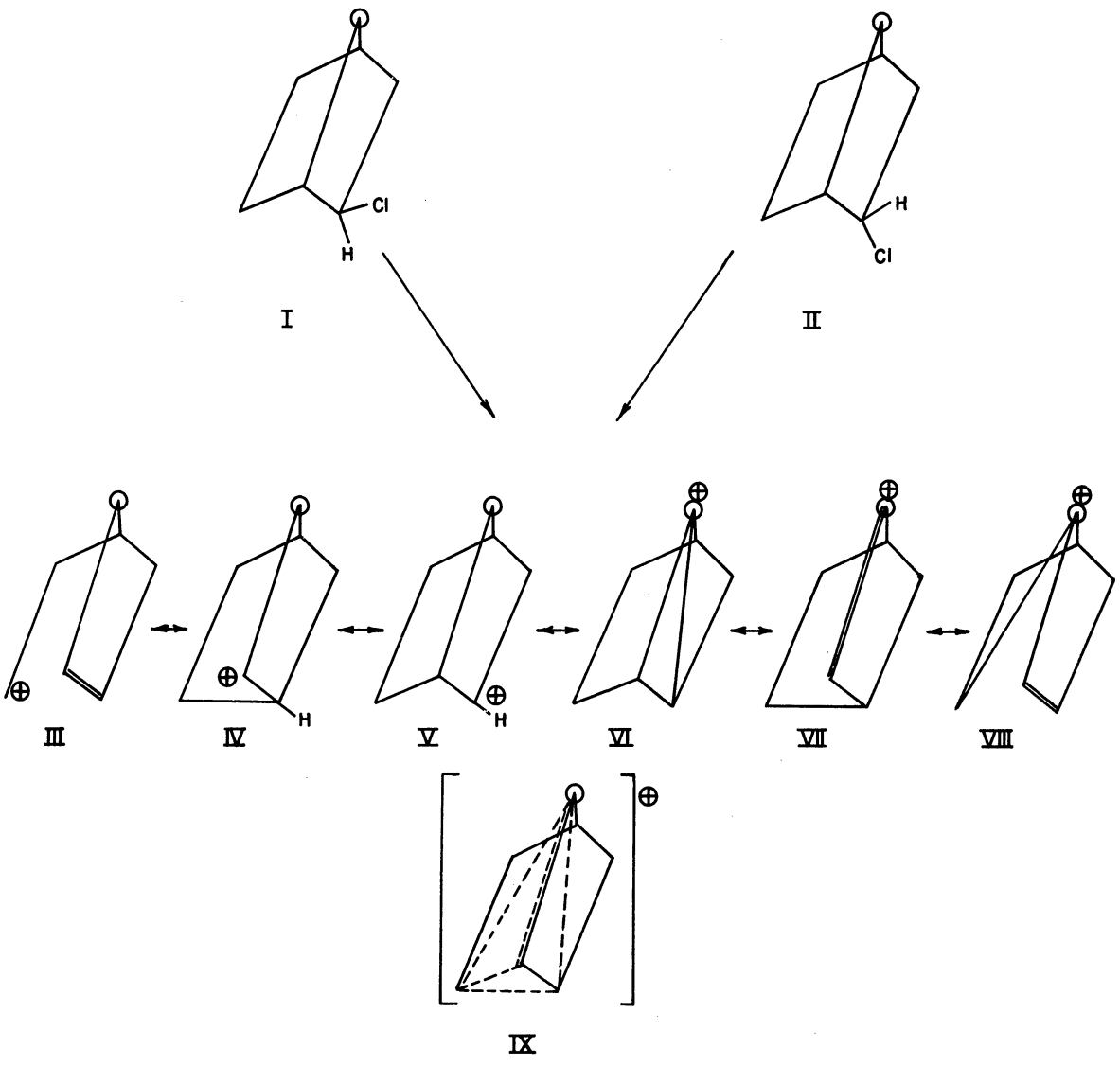


Chart B. Modes of Stabilization of the Cation from 2-Chloro-1, 4-Endoxocyclohexanes.

with the charge at C_2 the exo rate would be enhanced.(2) If it occurred by a direct interaction of the oxygen electrons the endo rate would be enhanced.(2) The results are given in Tables I and II. The rates were calculated for the endoxo compounds in 80% ethanol-water by compensating for the change in the solvent from 50% dioxane-water. This was done by assuming that the effect of this change on the 2-chloro compounds would be analogous to that observed for the 2-bromo. It can be seen from the data that in both cases the endoxo compounds solvolyze much more slowly than do the norbornanes. In addition to this the ratios of the exo to the endo rate constants for the endoxo and the carbocyclic compounds are 211 and 70 respectively at 85°C. Both of these results show that none of the modes of stabilization implying interaction of the electrons as indicated above assist appreciably in ionization. Direct interaction of the oxygen electrons is immediately excluded, since the endo isomer reacts more slowly than the exo isomer. The other pathways are excluded since the ratios for the exo to the endo rate constants are in the same order of magnitude for the endoxo and the carbocyclic compounds.

The results can be attributed to an inductive effect of the oxygen which would reduce the ability of the molecule to stabilize a positive charge.(2) This effect is enhanced by the fact that the endoxo compounds are as well as β-substituted ethers, making the ether dipole better able to interact with the carbon-chlorine bond. The same effect is observed in the pKa's of methoxyethyl amine versus ethylamine as compared

TABLE I[2]

KINETIC DATA FOR THE 2-CHLORO-1, 4-ENDOXOCYCLOHEXANES AND BICYCLO [2.2.1] HEPTANES

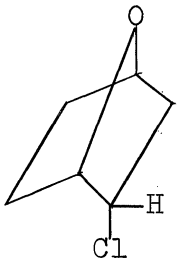
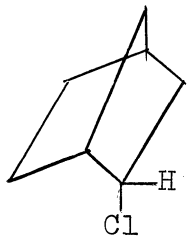
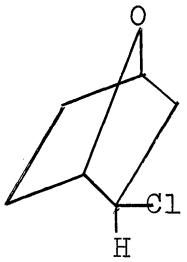
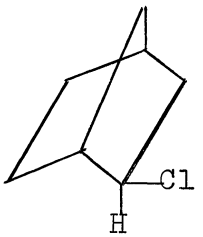
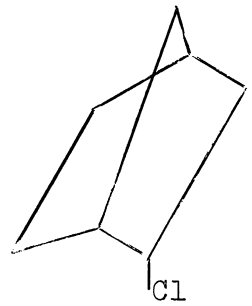
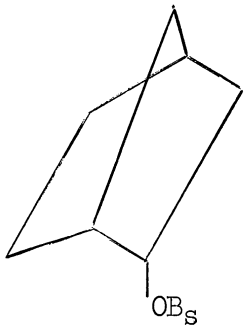
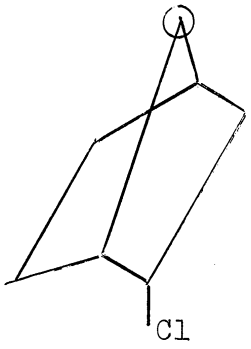
Compound				
Solvent	50% Dioxane H_2O	80% EtOH H_2O	50% Dioxane H_2O	80% EtOH H_2O
T	85°C	85°C	85°C	85°C
k	8.9×10^{-10} sec^{-1}	5.6×10^{-7} sec^{-1}	1.88×10^{-7} sec^{-1}	3.89×10^{-5} sec^{-1}
k (85°C, 80% EtOH) H_2O	9.3×10^{-11} sec^{-1}	5.6×10^{-7} sec^{-1}	1.96×10^{-7} sec^{-1}	3.89×10^{-5} sec^{-1}
$\frac{\text{k endoxo}}{\text{k carbocyclic}}$		$\frac{1}{6000}$	$\frac{1}{2000}$	

TABLE II[2]

KINETIC DATA FOR 2-SUBSTITUTED-1, 4-ENDOXOCYCLOHEXANES AND BICYCLO [2.2.1] HEPTANES

Compound	$\frac{k\ exo}{k\ endo}$	T
	70	85°C
	350	25°C
	275	85°C
	163	140°C
	211	85°C
	318	25°C

with morpholine versus piperidine (Figure 1). Thus being in a ring

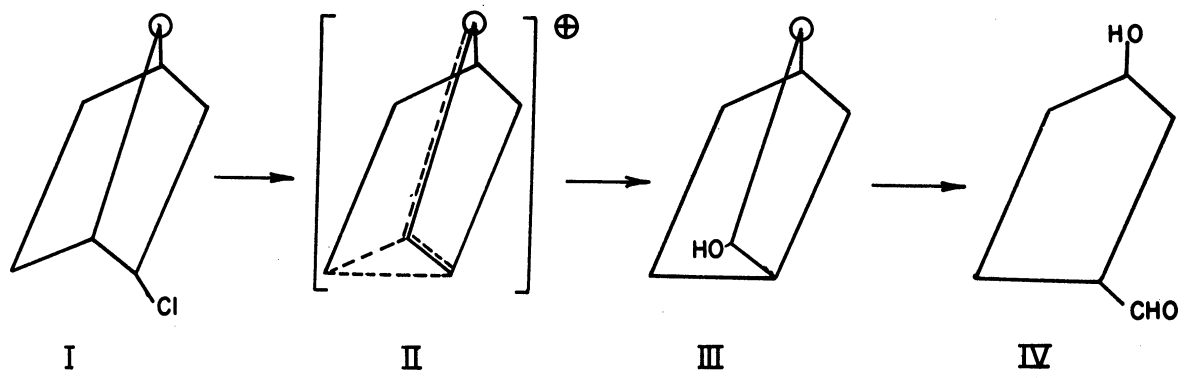
$$\frac{pK_A\ C_2H_5NH_2(10.75)}{pK_A\ CH_3O(CH_2)_2NH_2(7.90)} = 1.36 \qquad \frac{pK_A\ \text{piperidine}\ (11.20)}{pK_A\ \text{morpholine}\ (4.34)} = 2.58$$

Figure 1.[2] The Effect of Ethereal Oxygen on the pK_A's of Amines.

can multiply the inductive effect of a hetero atom by a factor of about 10^4*. In addition to this, increased hydrogen bonding of the cyclic ethers with solvent due to less steric hindrance than in the open chain analogues, can increase the positive charge on the ethereal oxygen. This would enhance the inductive effect also. This greater amount of hydrogen bonding is shown by the greater solubility of the cyclic ethers in the solvent used than their open chain analogues.[2]

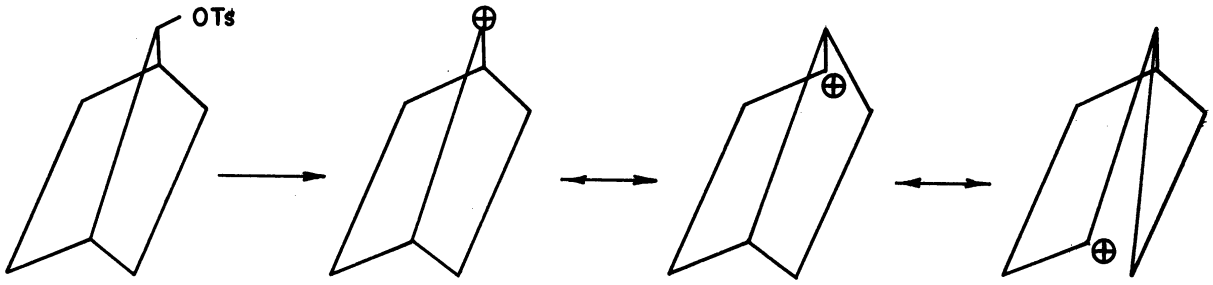
Although the data show that the nonbonded electron pairs on oxygen do not assist in the ionization step in the reaction and that the only effect of the oxygen is to retard ionization, these electrons do interact to stabilize the ion once it is formed. This is shown by the product of reaction, C-IV, which undoubtedly is produced by the path shown in Chart C. This involves an intermediate, C-III, which results from attack of the solvent exclusively on the 1 position of the hybrid ion. Therefore a portion of the charge must reside there. This would be especially true as the interaction of the nonbonded electrons on the oxygen will tend to stabilize the charge in this position.

*From ionization constants or subtraction of pK_A's.

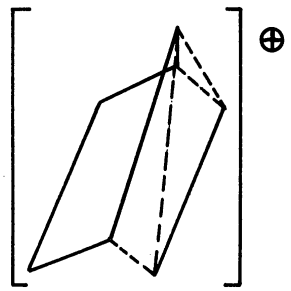


I II III IV

Chart C. Solvolysis of the 2-Chloro-1, 4-Endoxocylohexanes.



I II III IV



V

Chart D. Modes of Stabilization of Norbornyl-7 Tosylate.

B. 7-Substituted Bicyclo [2.2.1] Heptanes

If a double bond is introduced into the molecule instead of a hetero atom, there is the possibility of the interaction of the pi electrons with the incipient carbonium ion. This interaction is shown in Chart E for norbornenyl-7 tosylate, E-I and E-IV.[3-5] For comparison purposes the modes of stabilization available to the saturated ester (D-I) are shown in Chart D.

In the case of anti norbornenyl-7 tosylate interaction occurs during ionization, since the rate of solvolysis of the ester (E-I) is 10^{11} times as fast in anhydrous acetic acid as that for the saturated ester (D-I) under similar conditions. In the case of the syn isomer (E-IV) this type of interaction is impossible for steric reasons. Therefore it would not be expected to solvolyze as fast as the anti isomer. The fact that the syn isomer solvolyzes at a rate 7 powers of ten slower than that of the anti isomer in anhydrous acetic acid[5] shows that the preceding conclusion was valid. However, the syn isomer still ionizes at a rate 10^{4} times faster than the saturated ester (D-I) under the same conditions. It seems likely that this acceleration of the rate occurs during the ionization process by a rear side interaction of the C_1-C_6 bond or the C_4-C_5 bond leading to the resonance stabilized intermediate, E-VI.[5]

Thus, with the bicycloheptane system, all the possible modes of stabilization have been realized in one case or another, except those involving the primary carbonium ion.

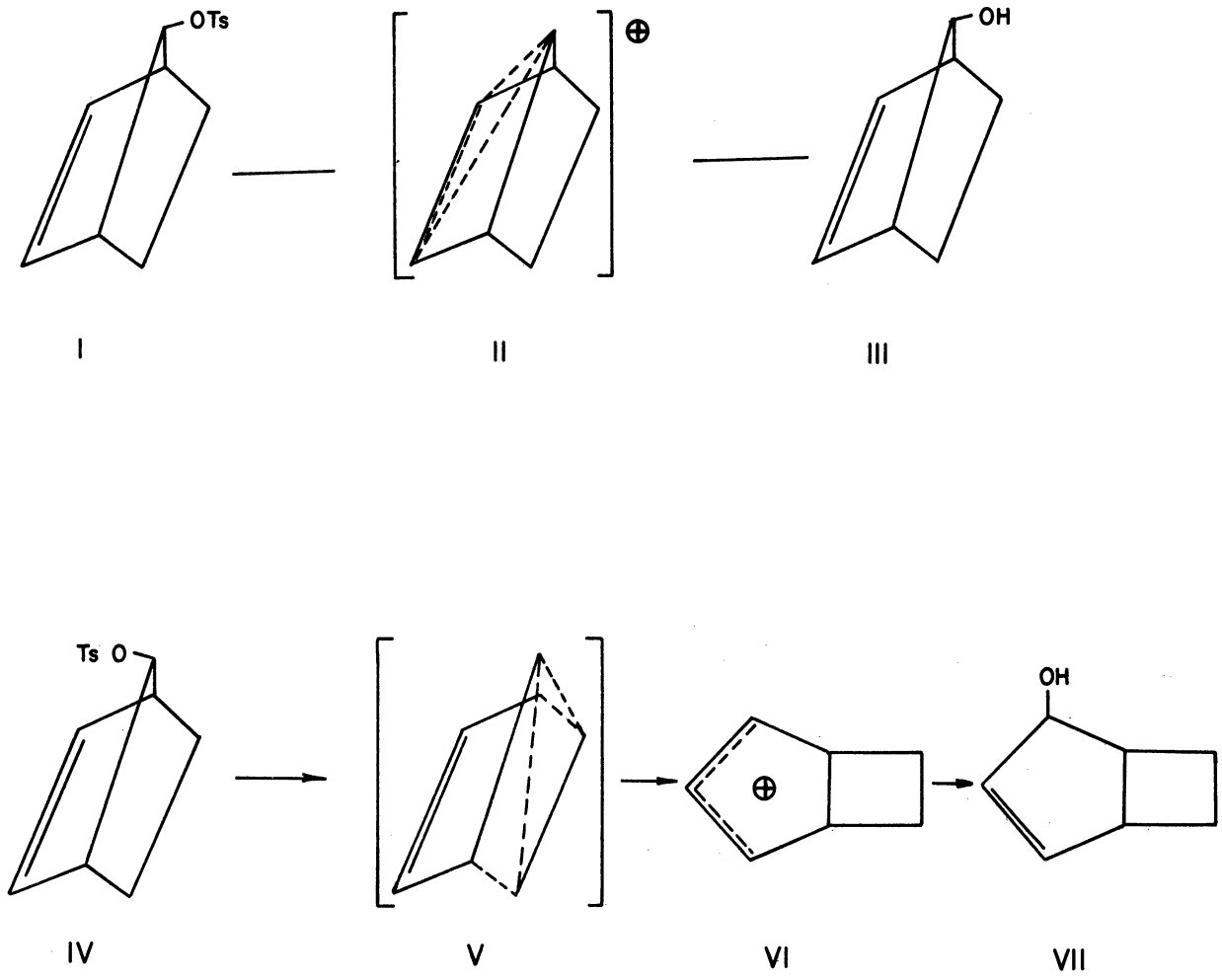


Chart E. Solvolysis of Norbornyl-7 Tosylate.

C. 3-Substituted Bicyclo [3.2.1] Octanes

The bicyclo [3.2.1] octane system can stabilize an incipient carbonium ion in a manner similar to that observed in the bicycloheptanes. Thus, as shown in Chart F, 3β-tosyloxybicyclo [3.2.1] octane (F-I) could solvolyze leading to the various resonance forms F-II-F-IV.

In addition to the valence bond structures for the 3β isomer summarized in representation, F-V, the 3α isomer has other forms, F-VIII-F-X, which are summarized in the structure, F-XI. Although no evidence is available, it is conceivable by analogy to the bicycloheptane system that the structures F-II, F-III, F-VIII, and F-IX would represent the favored modes of stabilization of the carbonium ion for this carbocyclic system.

If a hetero atom, such as nitrogen, sulfur, or oxygen, were substituted for carbon at the 8 position of 3-tosyloxybicylclo [3.2.1] octane some new resonance forms (G-V, G-X, and G-XI) might be expected to contribute to the hybrid ion. This would involve formation of an ammonium, sulfonium, or oxonium ion by interaction of the nonbonded electron pair on the hetero atom with the charge at the 1 or 3 positions.

Since the hetero atoms would probably donate an electron pair to a positive center on C_1 forming an onium ion, contributions from the resonance forms G-V and G-XI would be expected to be of some importance. Therefore the cations G-II, G-III, G-V, G-VIII, G-IX, G-X, and G-XI would probably be the most important ones for the heterocyclic compounds.

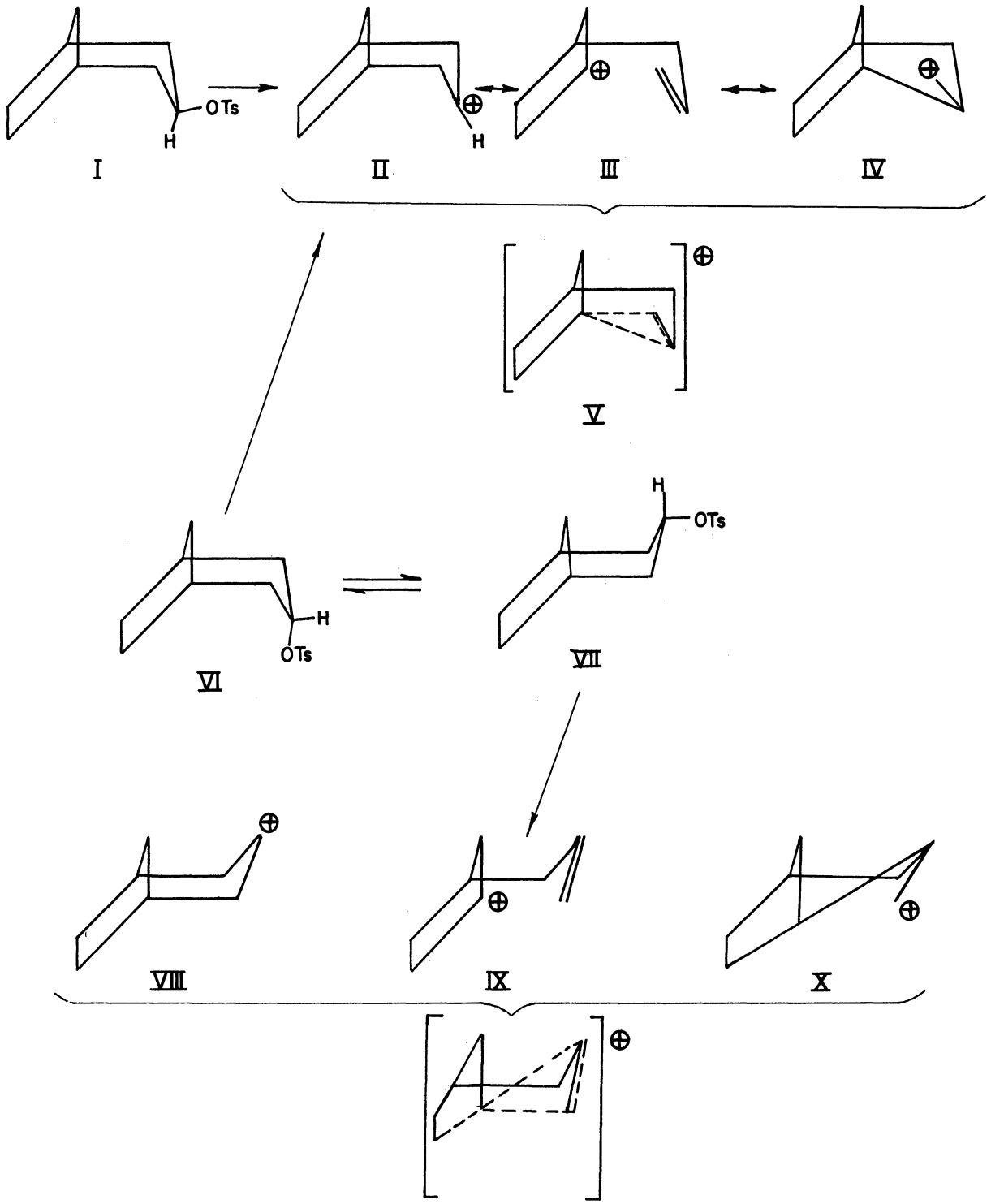


Chart F. Modes of Stabilization of the 3-Tosyloxybicyclo [3.2.1] Octanes

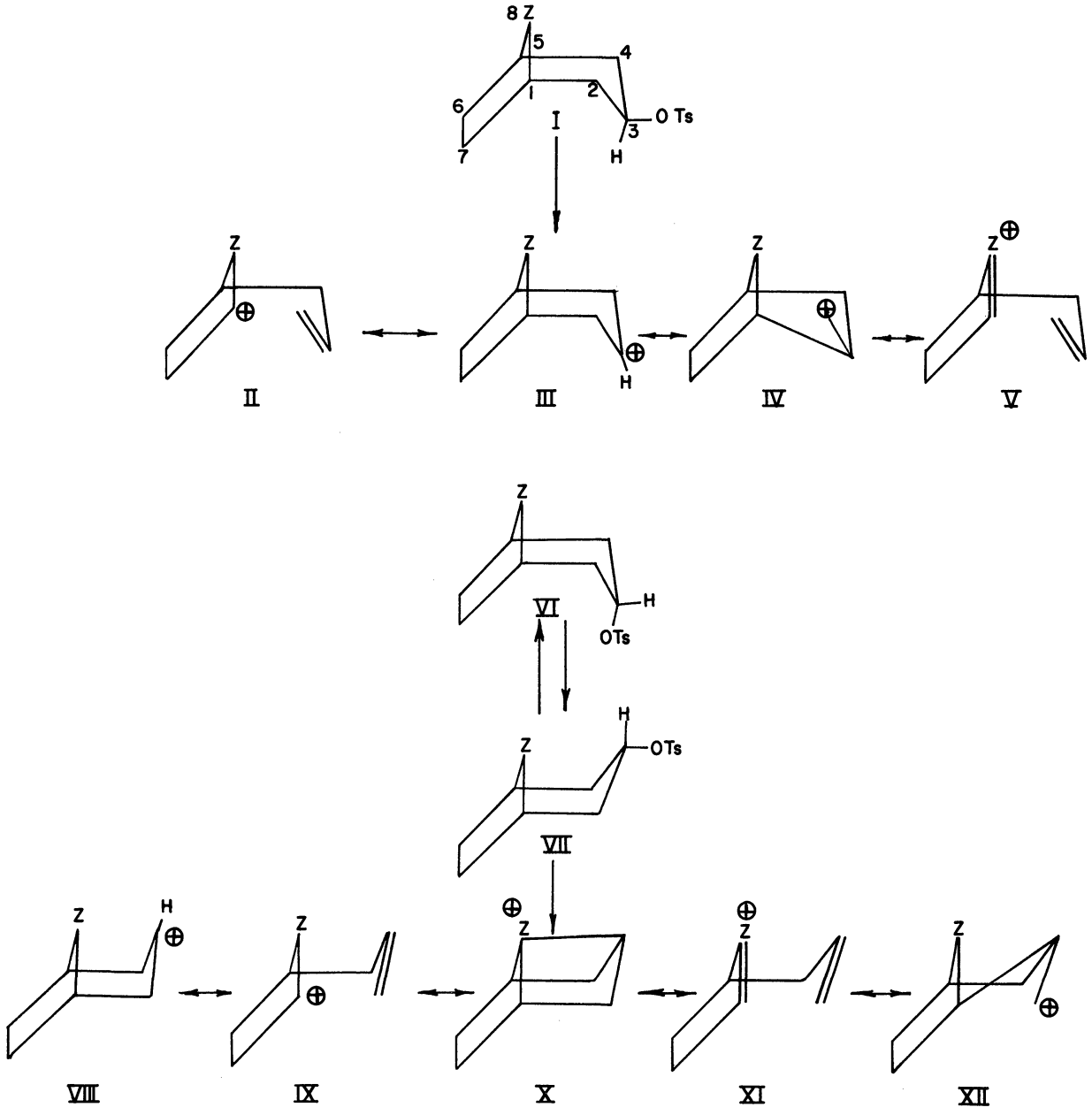


Chart G. Modes of Stabilization of 8-Hetero-3-Tosyloxybicyclo [3.2.1] Octanes.

It might be noted that stabilization occurring by interaction of the electrons of the hetero atom with the charge at C_1 left by cleavage of the C_1-C_2 bond could lead to the process known as fragmentation (Figure 2). An investigation of the reactions of 1-tropyl-2-methyl-2-chloropropane provided some information on this process.(6) It was observed that when the above compound (Chart H) was treated with silver perchlorate only tropylium perchlorate (H-II), isobutylene (H-III), and silver chloride were observed. This indicates that fragmentation occurred to the exclusion of all other processes. However, when the corresponding alcohol (H-IV) was treated with hydrochloric acid a 78% yield of nonfragmentation products (H-VI and H-VII) was obtained in addition to an 8% yield of the fragmentation product (H-VIII). According to Conrow, two mechanisms are possible. One, a concerted pathway, would lead only to fragmentation, since this process requires loss of the tropyl group in order for loss of the halogen to occur. The second mechanism is a stepwise one which passes through a carbonium ion. It is apparent that the alcohol reacts by this latter pathway in hydrochloric acid, since this is the only way that the products, H-VI and H-VII, can be explained. Thus it is possible for fragmentation to occur by either a concerted process, as in the first case, or by a stepwise process. In the latter situation fragmentation may be a minor reaction if a strong nucleophile such as chloride ion is present.

6. Conrow, K., J. Am. Chem. Soc. 81, 5461 (1959).

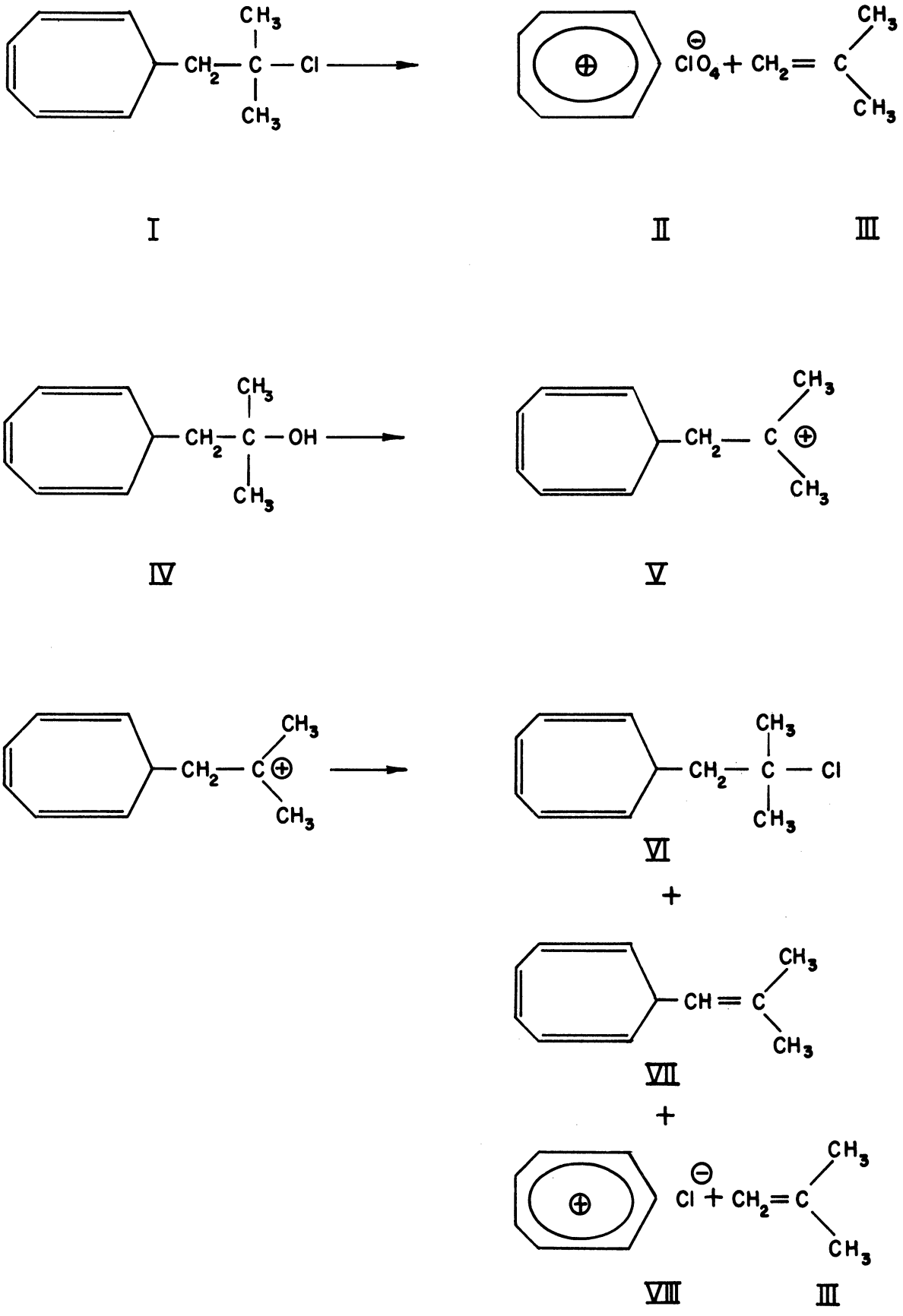


Chart H. Reactions of 1-Tropyl-2-Methyl-2-Chloropropane.

A great deal of further work has been done on this process in an effort to ascertain the requirements that a molecule must fulfill in order for fragmentation to take place. One investigation concerned the reactions of cis and trans-1-hydroxy-3β-brosyloxy or 3β-diazonium cyclohexane as well as cholestane-3β, 5α-diol 3β-tosylate, coprostane-3α, 5β-diol 3α-tosylate, and 4-substituted quinuclidines (Chart I). In the case of the quinuclidines (I-X) only would a real concerted process be expected. These studies showed that the C_1-X bond must be parallel to the C_2-C_3 bond for a so called one step fragmentation process to occur (Figure 2).[7,8] However, there was no restriction on rotation about the

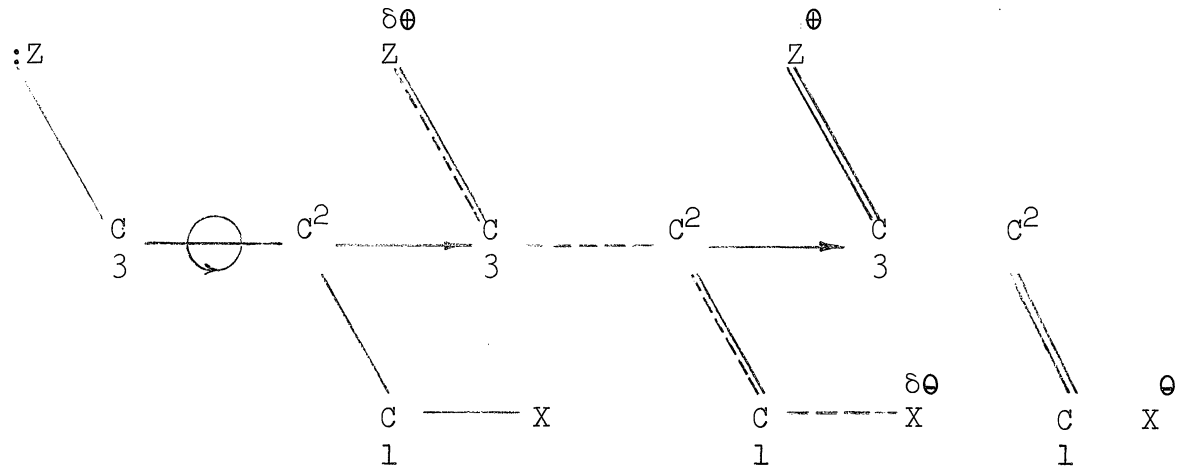


Figure 2. Stereochemistry of Concerted Fragmentation.

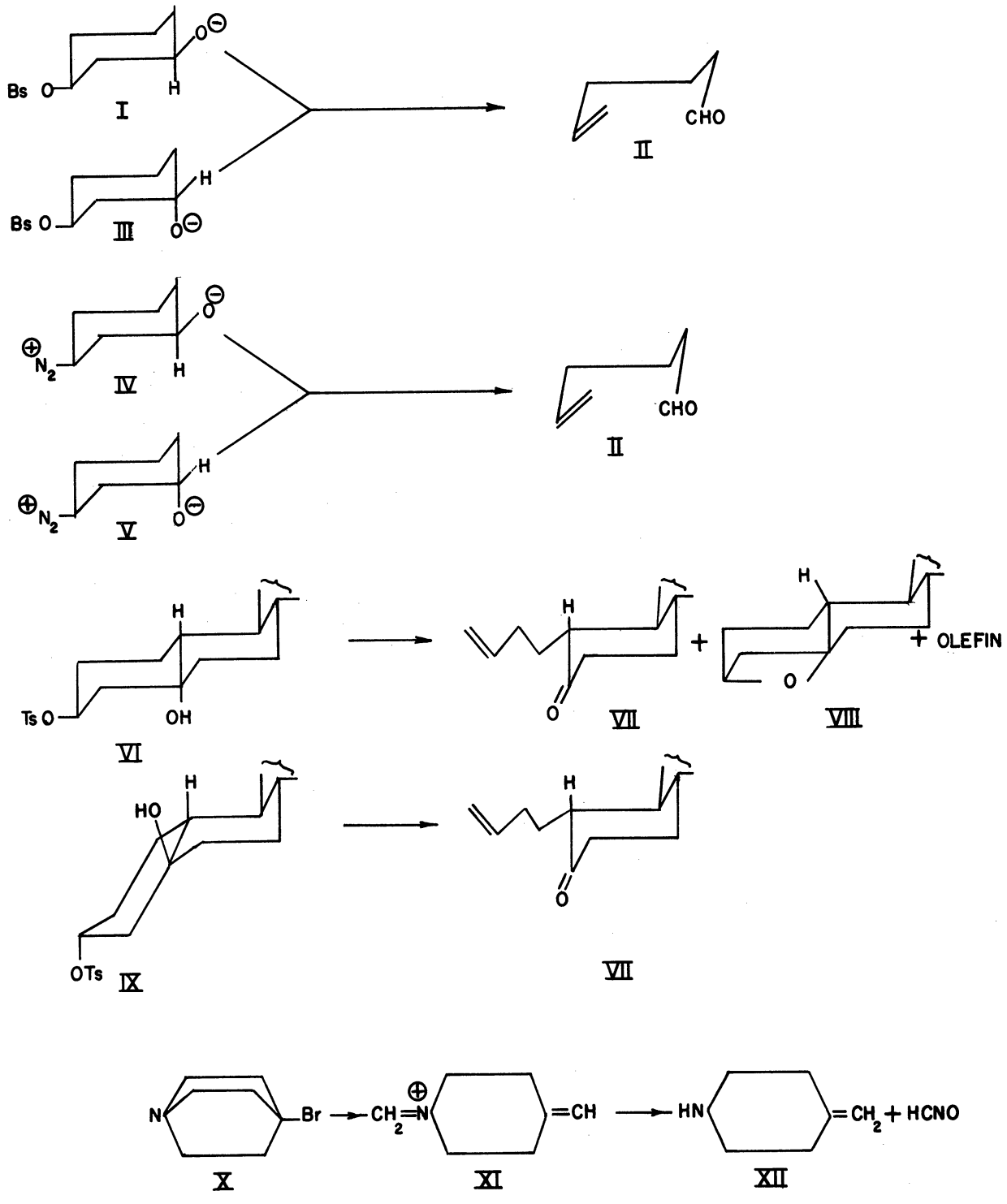


Chart I. Fragmentation Reactions.

C_2-C_3 bond as shown by the fragmentation of both the cis and trans isomers.[7,8] Where the C_1-X bond was not parallel or its probability of being parallel was low, products typical of all modes of stabilization occurred (Chart J).[10] Thus ionization must have occurred first followed by stabilization and subsequent reaction with solvent. From these results it can be seen that if the C_1-X bond is parallel to the C_2-C_3 bond (Figure 2) a concerted fragmentation process occurs, but if this requirement is not fulfilled, fragmentation can still occur as one of the modes of stabilization of the carbonium ion after ionization. However, this latter process does not seem to be as favorable as the former.[7-9]

One instance where the process of fragmentation might have been thought to be less favored, is found in the reaction of the hydrochloric acid addition products of the cinchona alkaloids, K-II, with base (Chart K).[12] The chloride, K-II, has no apparent restrictions on rotation of the C_3-C_{10} bond. Therefore it does not need to have the carbon-halogen bond parallel to the C_2-C_3 bond, as required for one step fragmentation. However, as the data in Chart K show only fragmentation products are obtained.[12] Therefore it seems possible that the rest of the molecule may have some effect on keeping the configuration of the molecule about C_{10} in the proper orientation for a concerted fragmentation process.

---

7. Clayton, R. B., Henbest, H. B., and Smith, M., J. Chem. Soc., 1982(1957).
8. van Tammelen, E. E. and Brenner, J. E., J. Am. Chem. Soc. 79, 3839(1957).
9. Bottini, A. T., Grob, C. A., Schumacher, E., Chem. & Ind., 757 (1958).
10. Grob, C. A., Angew. Chem. 69, 680 (1957).
11. Grob, C. A. and Baumann, W., Helv. Chim. Acta 38, 594 (1955).
12. Turner, R. B. and Woodward, R. B. in Manske and Holmes, "The Alkaloids", Academic Press, Inc., New York, 1953, Vol. III, p. 22.

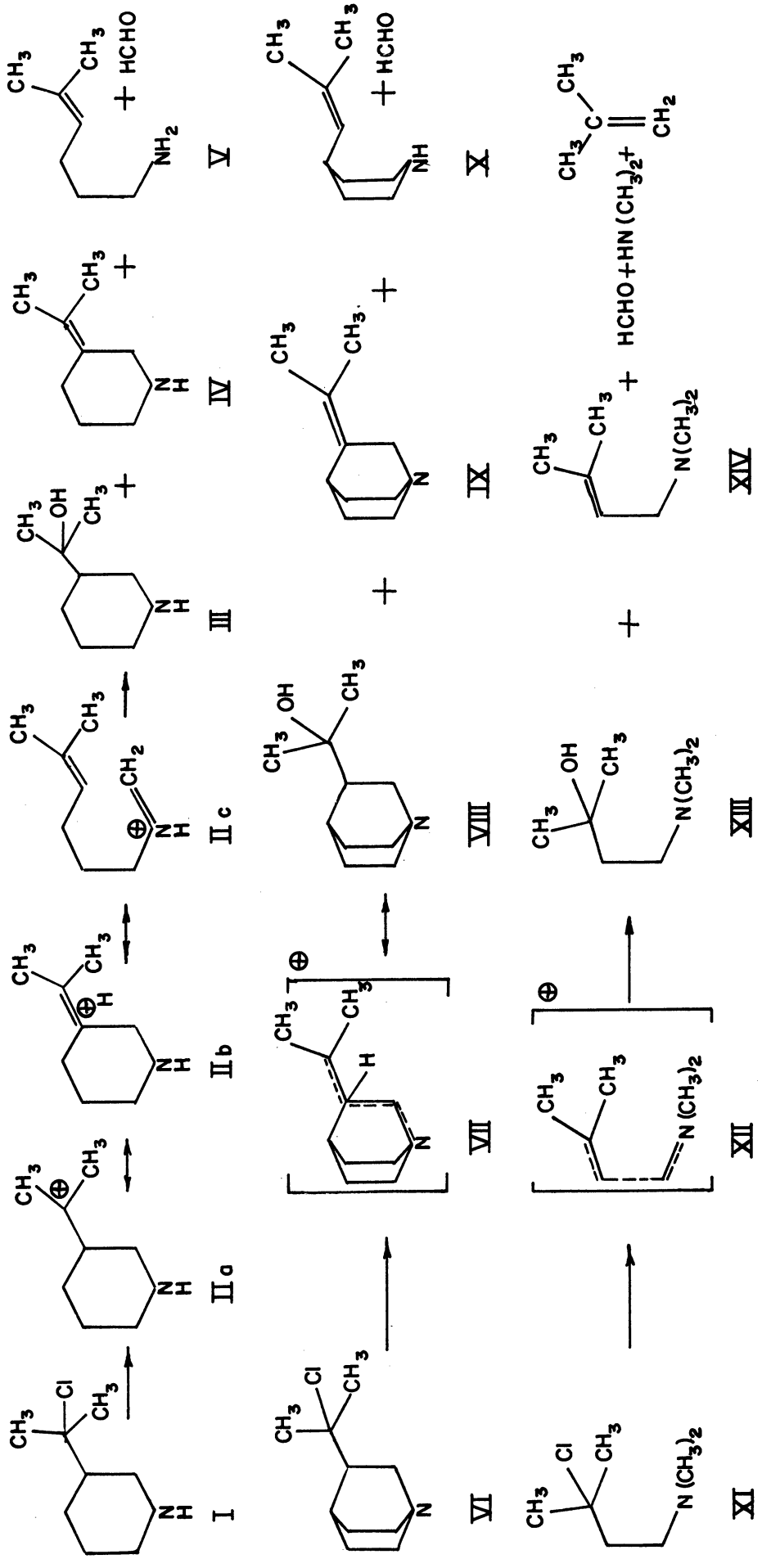


Chart J. Solvolyses without Concerted Fragmentation.

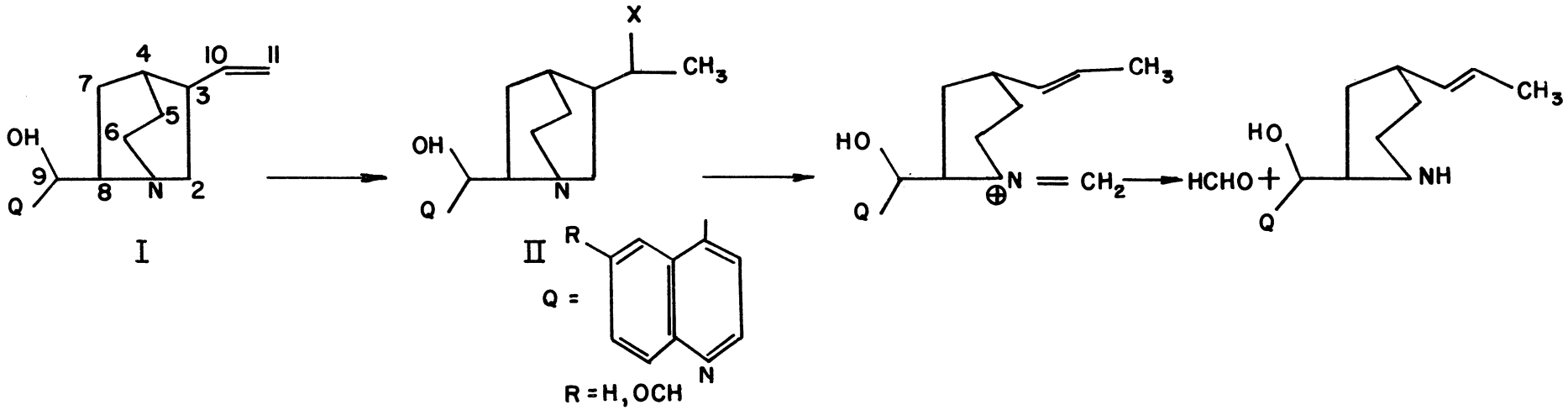


Chart K. An Unexpected Fragmentation Reaction.

Grob postulates that the orbital bearing the nonbonded electron pair on the nucleophilic center must be parallel to the C_2-C_3 bond in order that a concerted fragmentation process may occur (Figure 2).[9-11,13] Although his work on 4-substituted quinuclidines (G-IX) and on 4-halocyclohexyl zinc halides showed that the reaction does go by fragmentation where this requirement is fulfilled, he gives no evidence for any situations where it is not fulfilled. Data are available, though, which can clear up this difficulty. Epi-lupine is a molecule which for steric reasons can not have this orbital parallel to the C_2-C_3 bond (Figure 3). Therefore on tosylation and heating it would not be expected to undergo fragmentation if Grob's hypothesis is valid. Experimentally it has been found that no cleavage occurs under these conditions,[14,15] confirming Grob's ideas.

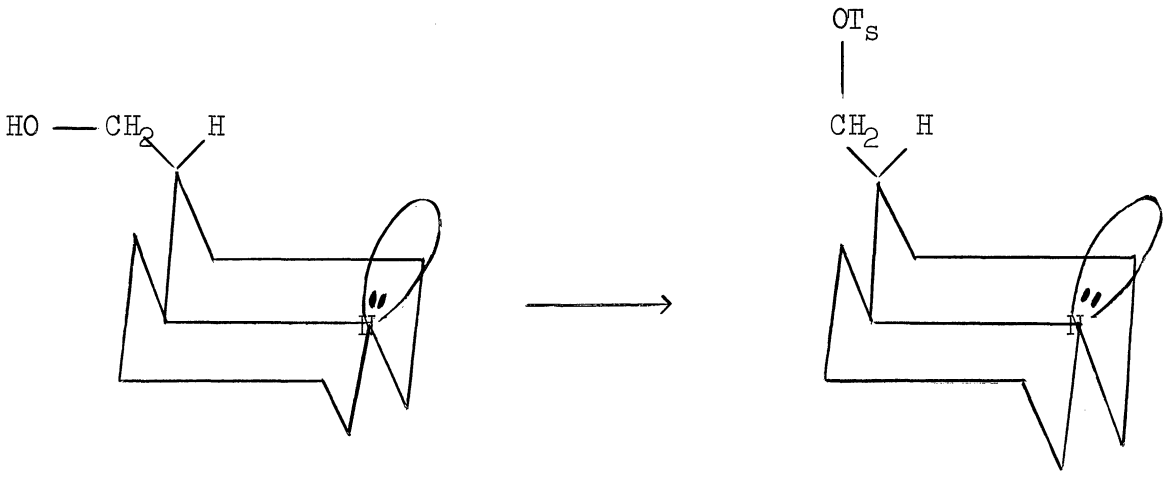


Figure 3. A Nonfragmenting Molecule.

13. Adamson, D. W., Nature 164, 500 (1949).
14. Galinovsky, F. and Nesvadba, H., Monatsh. 85, 1300 (1954).
15. Ibid., 913 (1954).

From the preceding discussion, then, it can be concluded that for fragmentation to occur during ionization, the C_1-X bond and the orbital bearing the nonbonded electron pair in the nucleophilic center must be parallel to the C_2-C_3 bond. However, fragmentation can occur as a less favorable path of reaction following ionization even if the C_1-X bond has the wrong orientation. It is noteworthy that stabilization as indicated by the valence bond structures such as G-II and G-IX could lead to products that in most cases would be similar to those from the forms G-V and G-XI. Therefore, although the structures G-II and G-V and the structures G-IX and G-XI are not identical, they can not be differentiated by means of reaction products. They can, however, be shown to contribute to the hybrid ion by this means.

If stabilization of the heterocyclic bicyclo [3.2.1] octane system could occur by the direct interaction of the electrons of the hetero atom then a participation process could be the result. This takes place by an attack of an electron pair from the atom in the 8 position on C_3. If this is to be a one step process, the six membered ring must flip up so that C_3 is opposite the 8 position. The leaving group must also be directed away from the 8 position or else it will interfere sterically with this assistance. In addition, an orbital on the atom in the 8 position must be directed toward C_3 to enable it to overlap the p orbital developing at C_3 (Figure 4). If ionization occurs first, the restrictions on the direction of the C_1-X bond are no longer required, since the leaving group would be detached and out of the way.

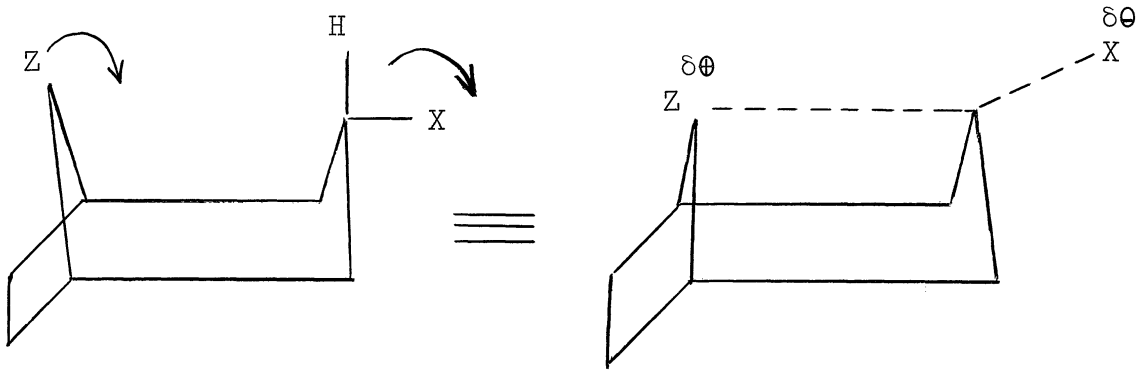


Figure 4. Stereochemistry of Participation.

Investigations on the 3α and 3β substituted tropanes sheds some light on the question of how these heterocycles actually do behave under solvolytic conditions. When they are subjected to attack by various nucleophiles such as cyanide, azide, or benzylamine, the incipient carbonium ions stabilize themselves by the modes best adapted to their stereochemistry (Chart L).[16-19] Thus the 3β compounds (which have the proper stereochemistry for fragmentation[7-13]) follow the course of reaction shown in Chart L (L-I-L-III). Therefore the intermediate, L-II, is formed which interacts with the nucleophile present to yield a 5-substituted-2-allylpyrrolidine, L-III.[16-19] This species was converted to

16. Archer, S., Lewis, T. R. and Zenitz, B., J. Am. Chem. Soc. 79, 3603 (1957).
17. Archer, S., Bell, M. R., Lewis, T. R., Schulenberg, J. W. and Unser, M. J., J. Am. Chem. Soc. 79, 6337 (1957).
18. Archer, S., Lewis, T. R. and Zenitz, B., J. Am. Chem. Soc. 80, 958 (1958).
19. Archer, S., Bell, M. R., Lewis, T. R., Schulenberg, J. W. and Unser, M. J. J. Am. Chem. Soc. 80, 4677 (1958).

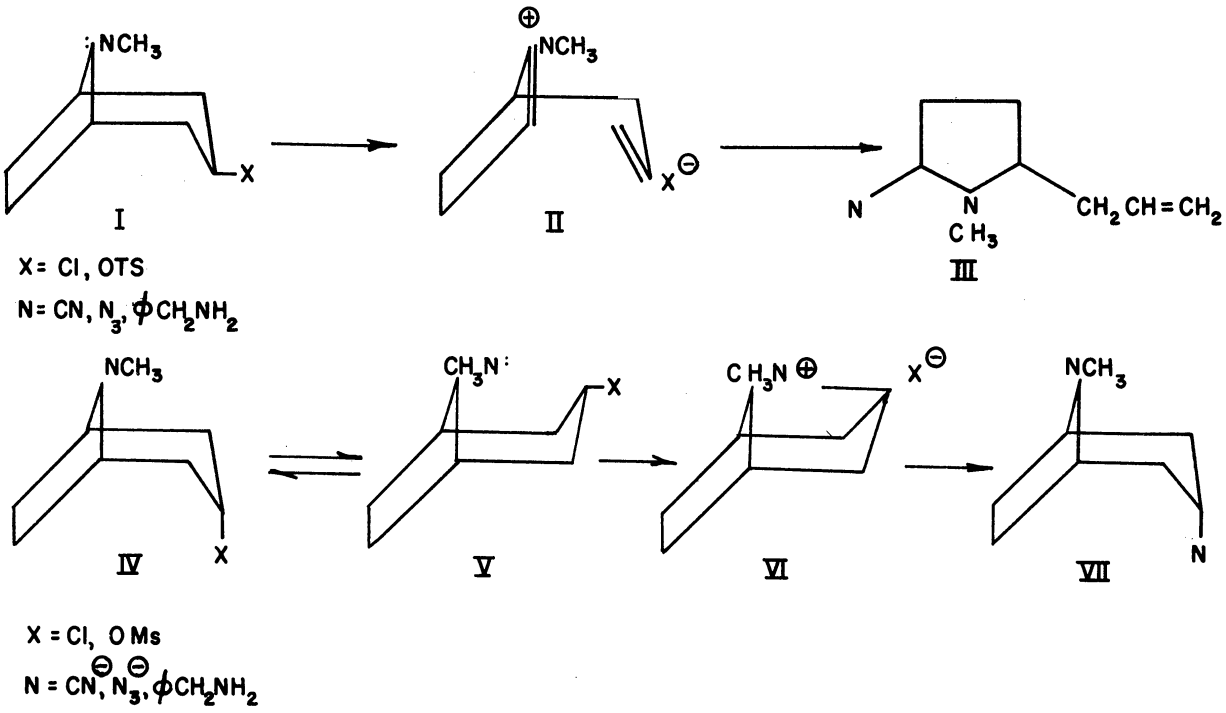


Chart L. Reactions of 3-Substituted Tropanes.

the open chain amine, M-V, in an effort to obtain a compound which could be readily synthesized by another route. The degradation involved displacement of nitrile by a phenyl group using phenyl magnesium bromide, catalytic reduction, Hoffman degradation, and catalytic reduction again (Chart M). Then the amine, M-V, was synthesized by an alternate route from γ-phenyl butyronitrile (M-VI) and n-propyl magnesium iodide (M-VII). This product proved to be identical to the amine obtained from the degradation of the pyrrolidine derivative, L-III,[16,18] and thereby the identity of this species was established.

On the other hand the 3α series, L-IV, which does not have the stereochemistry needed for fragmentation, is well adapted for stabilization through the participation process (G-X). That this is indeed the path that is followed is shown by the products of reaction, L-VIII, which have the same configuration at C_3 as does the starting material.[17,19] If stabilization had not occurred in this manner, some inversion of configuration as well as olefin formation would be expected to have occurred. Comparison of the reaction products with authentic 3α-tropanyl derivatives served to establish this stereochemical point. The benzylamine and azide derivatives were catalytically hydrogenated to the 3 amines. These proved to be identical to 3α-aminotropane[18-20] which had been described earlier. The cyano derivative was identified by equilibration in base. This resulted in a different nitrile which was stable under the conditions used. Subsequently this was subjected to alcoholysis yielding the known 3β-carbomethoxytropane.[17,19,20,21]

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20. Archer, S., Lewis, T. R. and Unser, M. J., J. Am. Chem. Soc. 79, 4194 (1957).
21. Zirkle, C. et al., "Abstracts XVI, International Congress for Pure and Applied Chemistry", Paris, July 1957, p. 153.

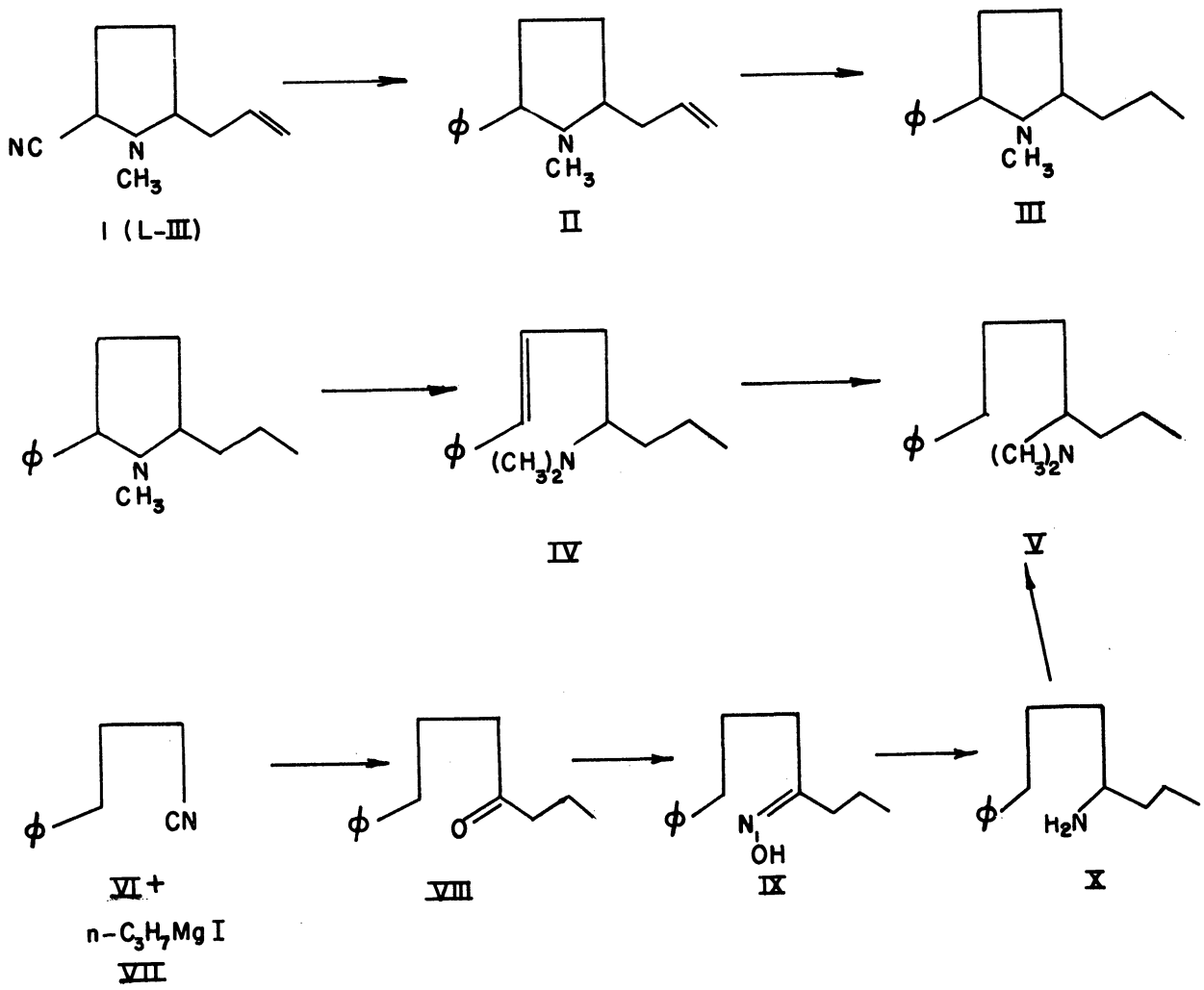


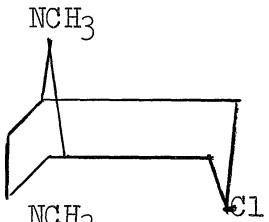
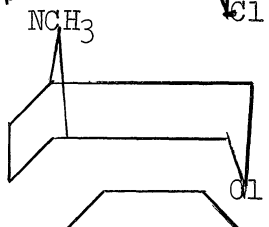
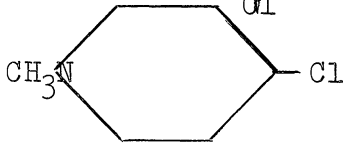
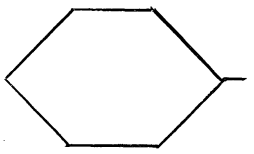
Chart M. Structure Proof of L-III

It is of interest to note that when the quaternary salts of either the 3α or 3β compounds were treated with nucleophilic agents under conditions which produced fragmentation or participation with the amines, no reaction or only displacement with inversion occurred.[17,19] This indicates that the nonbonded electron pair on the nitrogen does indeed play a major role in the stabilization of the incipient carbonium ion in the reactions of the amines.

Since only one product is observed in the preceding cases, this suggests that stabilization occurs during ionization. If this does happen rate enhancement should be observed. The kinetic work in Table III is available to answer this question.[9]

TABLE III

RATE OF SOLVOLYSIS OF THE 3-CHLOROTROPANES

Compound	k(118.2°C) (sec^{-1})	k(rel.)	ΔH# kcal/mole	ΔS# e.u.
	6.3×10^{-2}	11,500	24.1	-2.9
	4.3×10^{-3}	780	28.6	3.3
	7.7×10^{-4}	140	26.8	-4.9
	5.5×10^{-6}	1	----	----

It is readily apparent from the data that the rates are indeed enhanced over that of cyclohexyl chloride, the reference compound. Thus it appears that the stabilization by the fragmentation process for the 3β isomer and by participation for the 3α isomer must indeed occur during ionization.

It is of interest to note that even the rate of the piperidine compound is greatly enhanced.[9] This indicates that even though the stereochemistry is not fixed so as to favor some mode of stabilization as in the two preceding cases, the electron pair on the nitrogen can still interact to aid in removing the chloride group. Since no fragmentation product is observed in this reaction, it is believed that participation accounts for the rate enhancement.[9]

One other piece of evidence is available which shows that stabilization of an incipient carbonium ion by participation is very real and not just an explanation of the retention of configuration on solvolysis of the 3α compounds. This is the reaction undergone by lupine tosylate, (2) on heating (Figure 5). The product is the tricyclic quaternary salt, (3).[14,15] In addition to this, isorubijervine on tosylation forms a similar type of quaternary salt, the normal tosylate being unstable.[22]

To further investigate the modes of stabilization favored by bicyclooctanes containing a hetero atom in the 8 position, 3α and 3β-mesyloxynortropane and 3α and 3β-tosyloxy-8-thiabicyclo [3.2.1] octane were studied using trans-4-t-butylcyclohexyl tosylate as a reference compound.

22. Weisenborn, F. L. and Burn, D., J. Am. Chem. Soc. 75, 259 (1953).

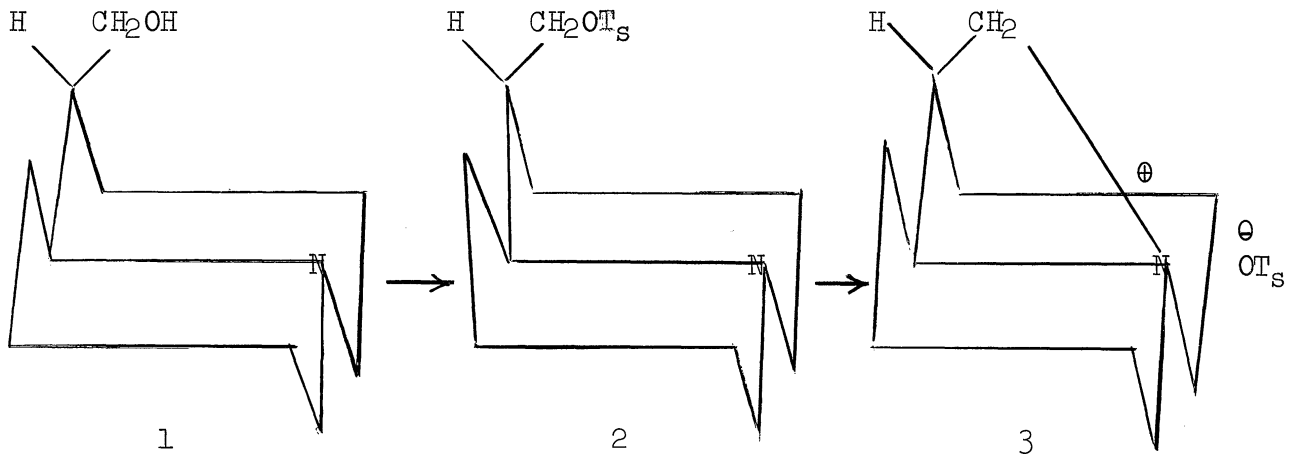


Figure 5. A Stable Participation Product.

D. Syntheses

Before this investigation could be undertaken, however, it was necessary to synthesize the needed materials. The synthesis of the 3-mesyloxynortropanes was accomplished in seven steps from tropinone hydrobromide as indicated in Chart N. Tropinone hydrobromide (N-I) was converted to tropinone in 100% yield by treatment with potassium ethoxide in ethanol. The free amine was treated with cyanogen bromide at 50-55°C to give the N-cyano derivative, N-III, in 95% yield.[23] The N-cyano ketone was reduced with sodium borohydride in aqueous solution to give a mixture of the isomeric alcohols. These were separated by chromatography on alumina giving a 64-45% yield of the 3β (N-IV) and a 30-50% yield of the 3α (N-V) alcohols.[23] Attempted reduction of the ketone with lithium aluminum hydride resulted in only recovered starting material and two oils, and

23. Fieser, L. and Nickon, A., J. Am. Chem. Soc. 74, 5566 (1952).

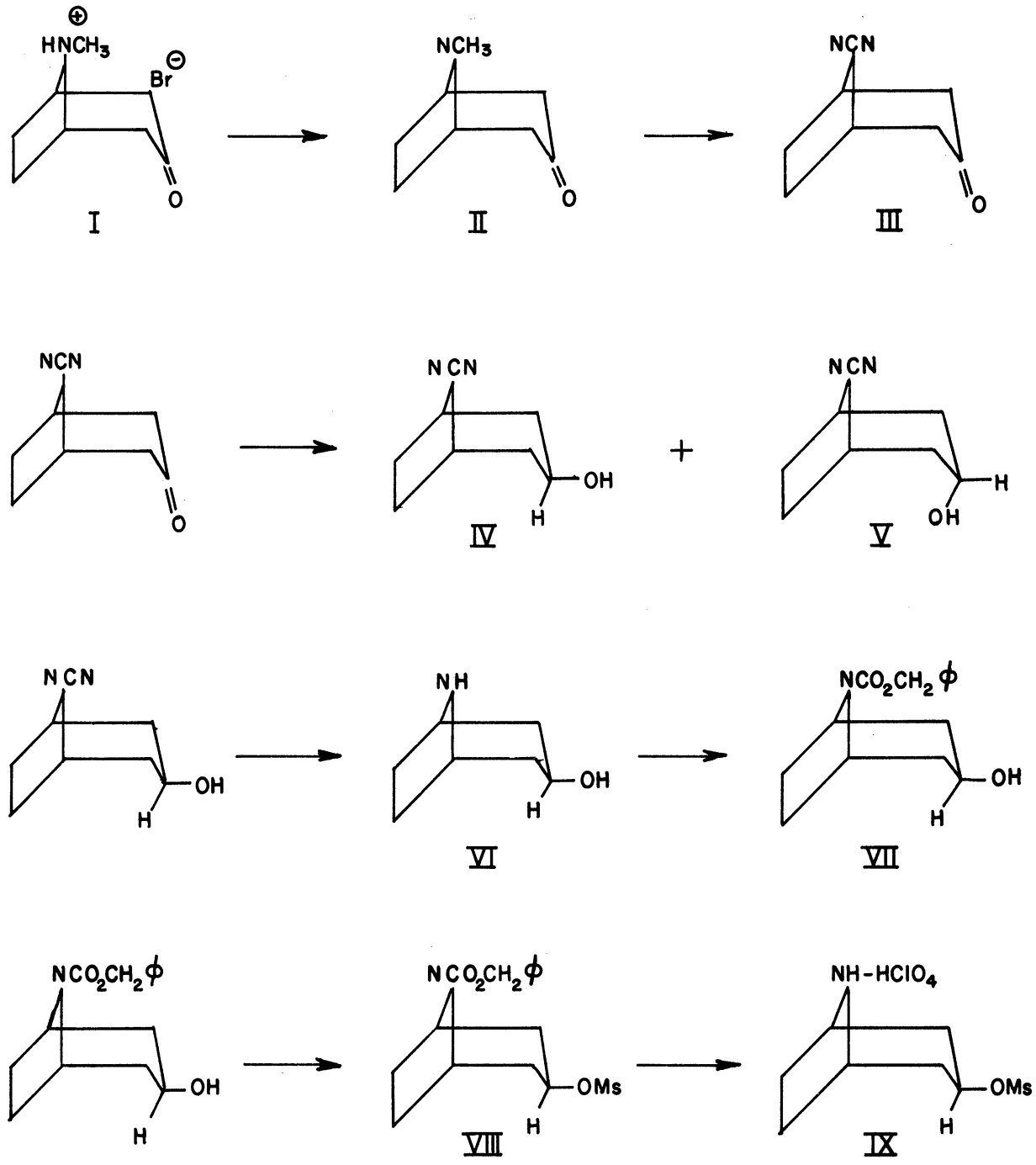


Chart N. Synthesis of the 3-Mesyloxynortropanes.

therefore was dropped. From this point each isomer was taken through the remainder of the synthesis separately. Hydrolysis of the N-cyano derivatives, N-IV and N-V, yielded the free amines (N-VI) in a 95% yield.[23] Attempts were made to esterify the amino alcohols in acidic media in which case acylation should occur on the hydroxyl group.[23-26] However, it was discovered that the presence of hydrochloric acid, which was used as the solvent, caused the methanesulfonyl chloride to decompose. Since direct esterification in this manner did not seem too promising, it was decided to block the amino group prior to esterification. This was done by treating the amino alcohols with benzyl chloroformate under Schotten-Baumann conditions[27] which would cause acylation on the amino group.[23-26] The N-carbobenzoxy derivative (N-VII), obtained in 95-98% yield, could then be esterified by treatment with methanesulfonyl chloride and pyridine in chloroform for seven days at room temperature.[22] The yield of ester, N-VIII, was 99%. When p-toluenesulfonyl chloride was used under similar conditions to that for methanesulfonyl chloride,[22] the yield was about 40%, and the product was contaminated with starting material. Therefore methanesulfonyl chloride was chosen for subsequent esterifications. To complete the synthesis, the blocking group was removed by catalytic hydrogenation using 10% palladium on carbon as the catalyst. The reaction was carried out in acetic acid with slightly more than one equivalent of perchloric acid present. This resulted in an 86% yield of the perchlorate

24. Fodor, G. and Nador, K., Nature 169, 462 (1952).
25. Fodor, G. and Kiss, J., J. Am. Chem. Soc. 72, 3495 (1950).
26. van Tammelen, E. E., J. Am. Chem. Soc. 73, 5773 (1951).
27. Org. Syntheses. 23, 13 (1943).

salts of the 3-mesyloxynortropanes, N-IX. The overall yield for the seven steps was 23-29% for the 3α isomer and 49-43% for the 3β or a total of 72%.

Several attempts were made to neutralize the products of this synthesis to the free amines. Sodium hydroxide in water, sodium hydride in dioxane, and potassium t-butoxide in t-butanol proved to be unsatisfactory for this purpose, since they resulted in no reaction or only tarry products. Potassium ethoxide in ethanol, however, did produce the desired amines, but they were contaminated with potassium salts. Although the contaminants could be removed by recrystallization from chloroform-petroleum ether, it was decided to free the amines in situ for the reactions desired.

Some alternate synthetic paths were attempted in an effort to reduce the number of operations required in the synthesis. One route was to use tropine instead of tropinone to avoid the low yield of 3α compound from the sodium borohydride reduction. However, it was discovered that only low yields, about 20%, of the desired N-cyanotropine were obtained in the von Braun cleavage reaction. Therefore this line of attack was dropped.

The other alternative was to postpone the separation of the two isomers until the amino group had been blocked by formation of the N-carbobenzoxy derivative, N-VII. Although this was successfully carried out in two attempts, the experiments were not readily reproduceable, and this procedure was given up.

The synthesis of the thia compounds analogous to the 3-mesyloxynortropanes was accomplished in four steps from tropinone (Chart O).

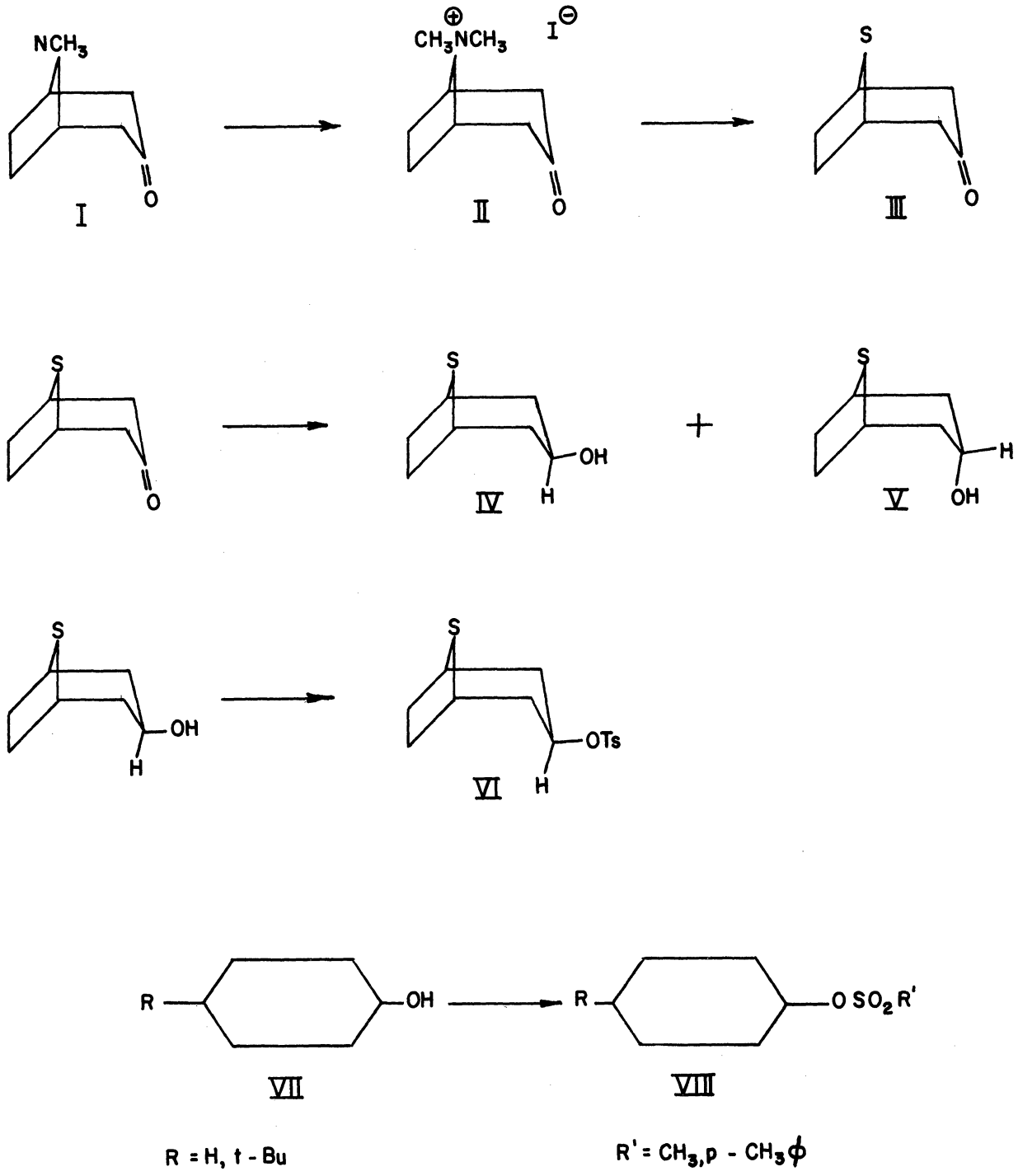


Chart O. Synthesis of the 3-Tosyloxy-8-Thiabicyclo [3.2.1] Octanes and the References Compounds.

A very ingenious method for obtaining the desired 8-thiabicyclo [3.2.1] octane system was furnished by work on the methiodides of 4-piperidones. It had been shown that treatment of these compounds with aqueous sodium sulfide solutions resulted in the replacement of the nitrogen by sulfur.[28] Thus treatment of tropinone with methyl iodide followed by treatment with 10% sodium sulfide solution resulted in a 95% yield from tropinone of the desired thia ketone, O-III. The thia ketone was reduced by sodium borohydride in aqueous solution producing a mixture of the isomeric alcohols.[23] This was separated by chromatography on Florosil resulting in a 21-29% yield of the 3α alcohol, O-V, and a 59-42% yield of the 3β isomer, O-IV.

Since the two thia alcohols had been unknown previously, it was necessary to establish their identity conclusively in order that the results of the rate and product determinations on their esters may be correctly interpretated. The configurations were assigned tentatively by analogy to the 3-hydroxynortropanes. In both cases the 3α alcohol was eluted from the chromatographic column first, followed by the 3β alcohol. In addition the yields of the two isomers from reduction of the ketone are in similar ratios, the 3β isomer being produced in about twice the yield of the 3α. This is also similar to the results of the reduction of tropinone with sodium borohydride.[29,30] Finally the bands in the infrared for the carbon-oxygen stretching frequencies are at similar

28. Horak, V., Zarada, J. and Piskala, A., Chem. & Ind., 1113 (1958).
29. Beckett, A. H., Harper, N. J., Balon, A. D. J. and Watts, T. H. E., Chem. & Ind., 663 (1957).
30. Ibid., Tetrahedron, 6, 319 (1959).

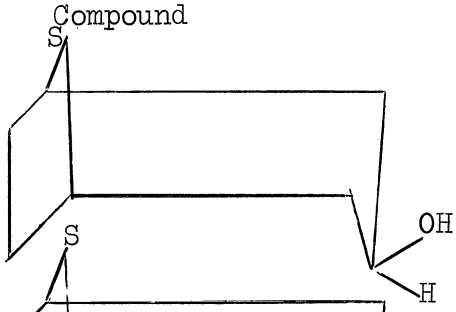
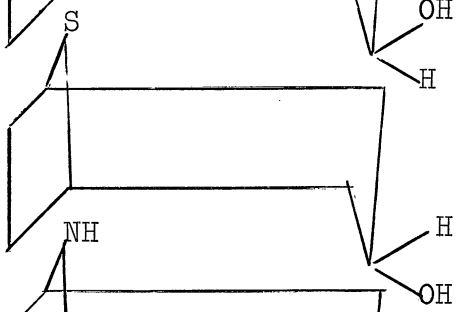
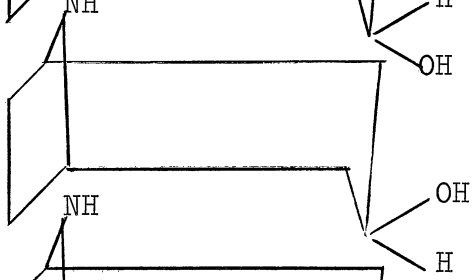
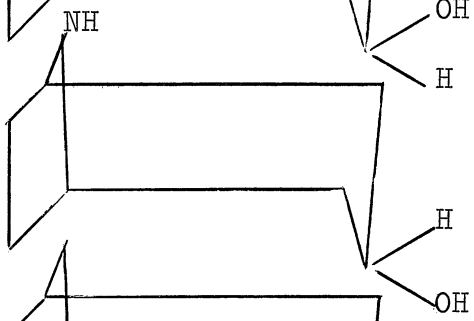
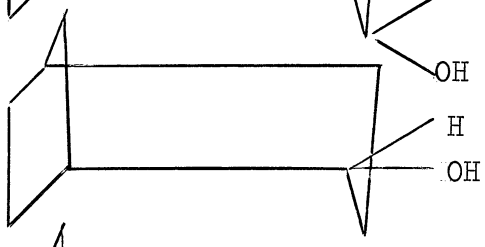
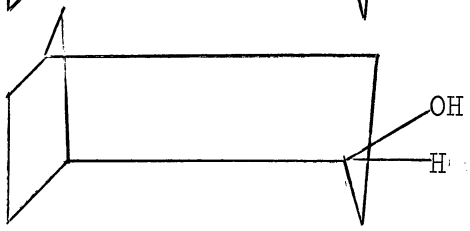
positions and are in the same relationship to each other as shown in Table IV and Plate 1. To provide conclusive proof, though, it was necessary to determine which alcohol was the most stable. This would be the 3β alcohol, since the configuration imparting the greatest stability would be the one having the hydroxyl group equatorial as in the structure O-IV. This determination was made by treating the alcohols separately with sodium amylate in refluxing n-amyl alcohol.[29,30] Such treatment will cause a reversible epimerization of the hydroxyl group. This would lead to an equilibrium mixture of the alcohols in which the more stable isomer should predominate.[29-31] The mixtures were analyzed by comparison of the sample absorptions at 840 cm^{-1}, 910 cm^{-1}, 1345 cm^{-1}, and 1455 cm^{-1} with calibration curves. These curves were made from the absorptions of solutions of known concentrations of the alcohols at these same frequencies. There was some interference with ketone absorption at 1345 cm^{-1} and 1455cm^{-1}, but in general the results at all four frequencies led to the same conclusions. The data show that the isomer that had been designated the 3β or equatorial alcohol was indeed the more stable of the two. It comprised 73±5% of the equilibrium mixtures whereas the other isomer made up 27±5% of these mixtures.

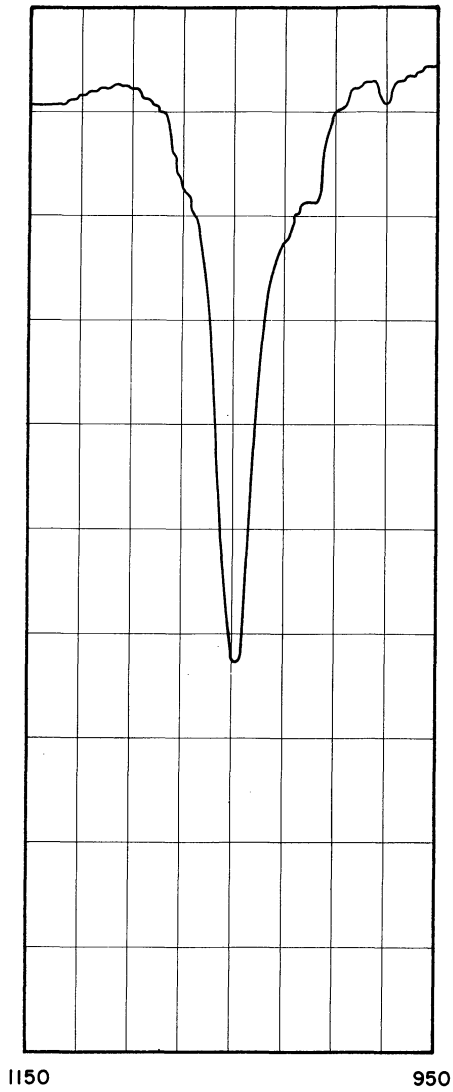
The synthesis was completed by separate esterification of the alcohols with p-toluenesulfonyl chloride in chloroform containing pyridine for ten days at room temperature.[22] The yield of the ester was 71%. This leads to an overall yield for the synthesis of 14-19% for the 3α

31. Dauben, W. G., Fonken, G. J. and Noyce, D. S., J. Am. Chem. Soc. 78, 2579 (1956).

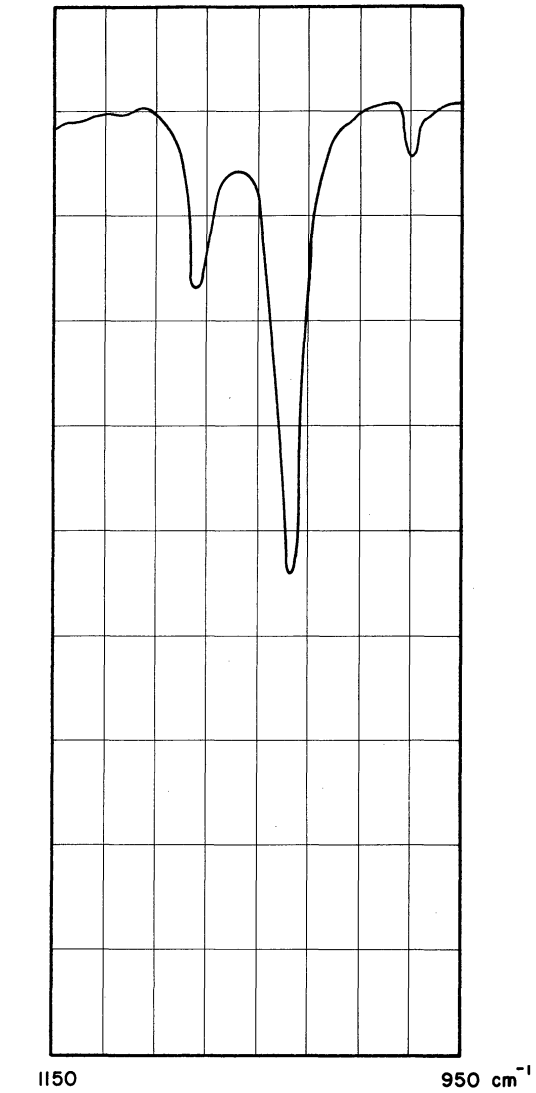
TABLE IV

CARBON-OXYGEN STRETCHING FREQUENCIES IN THE INFRARED

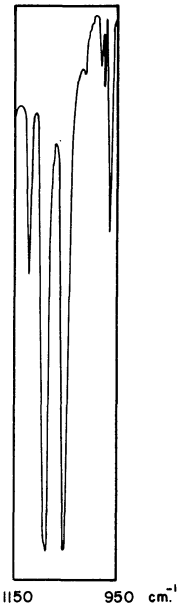
Compound	Frequency
	1048 cm^{-1}
	1034 cm^{-1}
	1055 cm^{-1}
	1045 cm^{-1}
	1065 cm^{-1} [30]
	1015 cm^{-1} [30]



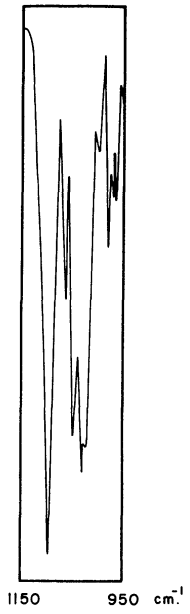
3β-Tosyloxy-8-Thiabicyclo [3.2.1] Octane



3α-Tosyloxy-8-Thiabicyclo [3.2.1] Octane



3β-Mesyloxynortropane



3α-Mesyloxynortropane

Plate 1. Infrared Spectra of the Thia and Azabicyclic Alcohols.

ester and 39-28% for the 3β ester, O-VI, or a total of 50%. Since the mesyl esters proved to be liquids and therefore harder to purify on a small scale than the solid tosylates, the tosyl esters were used for the reactions being studied.

Three reference compounds were also synthesized. Trans-4-t-butylcyclohexyl tosylate was the primary reference. This was chosen for this purpose because the parent alcohol has been accepted as having the hydroxyl group in the equatorial conformation.[32] Therefore the ester would be a conformationally pure species. The rate of solvolysis of this species, then, would be dependent on this one conformation and not on a mixture such as occurs with cyclohexyl tosylate. Cyclohexyl tosylate and mesylate were also made in an effort to determine the relative reactivities in solvolysis of the tosyl versus the mesyl groups. All three esters were made by esterification of the alcohol with the appropriate sulfonyl chloride[32,33] (Chart O). The yields were 71.5% for trans-4-t-butylcyclohexyl tosylate, 83.1% for cyclohexyl tosylate, and 89.4% for cyclohexyl mesylate.

E. Results and Meaning of the Investigation

As soon as the desired compounds were available from the synthesis, their reactions were studied. One such investigation involved the reactions of the nitrogen heterocycles with lithium aluminum hydride. It is known that lithium aluminum hydride deprotonates secondary amines.

32. Winstein, S. and Holness, N. J., J. Am. Chem. Soc. 77, 5562 (1955).
33. Winstein, S., Grunwald, E. and Ingraham, L. L., J. Am. Chem. Soc. 70, 821 (1948).

Thus it seems likely that the reacting species in this study was the anion of the amino ester under consideration.

In the case of the 3β isomer, nor-ψ-tropine mesylate, one or two products were obtained depending on the reaction conditions. When this compound was treated with lithium aluminum hydride in ether, an 86% yield of nortropane and a 10.2% yield of 2-allylpyrrolidine were obtained. The nortropane was identified by its melting point, about 60°C, its solubility in various solvents, and its characterization as a secondary amine by means of the Hinsberg test. In addition the melting points of two derivatives that of the hydrochloride, 283-285°C (dec.), and the nitrosamine, 132-134°C, agree well with the literature values of 285°C (dec.)[34,35] and 135°C[36] respectively. The nortropane undoubtedly was produced by a direct displacement of the ester group by a hydride ion.

Comparison of the saturated perchlorate salt (P-II) to an authentic sample of this derivative was used to identify the second product of the reaction, 2-allylpyrrolidine. The saturated salt, M.P. 295.0-295.2°C, was made by reduction of the 2-allylpyrrolidine over 10% palladium on carbon in acetic acid containing slightly more than one equivalent of perchloric acid. This salt was also synthesized by the reaction of three moles of n-propyl magnesium bromide with one mole of 2-pyrrolidone (Chart P).[37] Treatment of the resulting amine with perchloric acid yielded

34. Manske and Holmes, "The Alkaloids", Academic Press, Inc., New York, 1953, Vol. I, p. 341.
35. Hess, K., Chem. Ber. 51, 1014 (1918).
36. Willstätter, R. and Iglauer, F., Chem. Ber. 33, 1636 (1900).
37. Lukas, R., Sarm, F. and Arnold, Z., Collection Czechoslov. Chem. Communs. 12, 641 (1947).

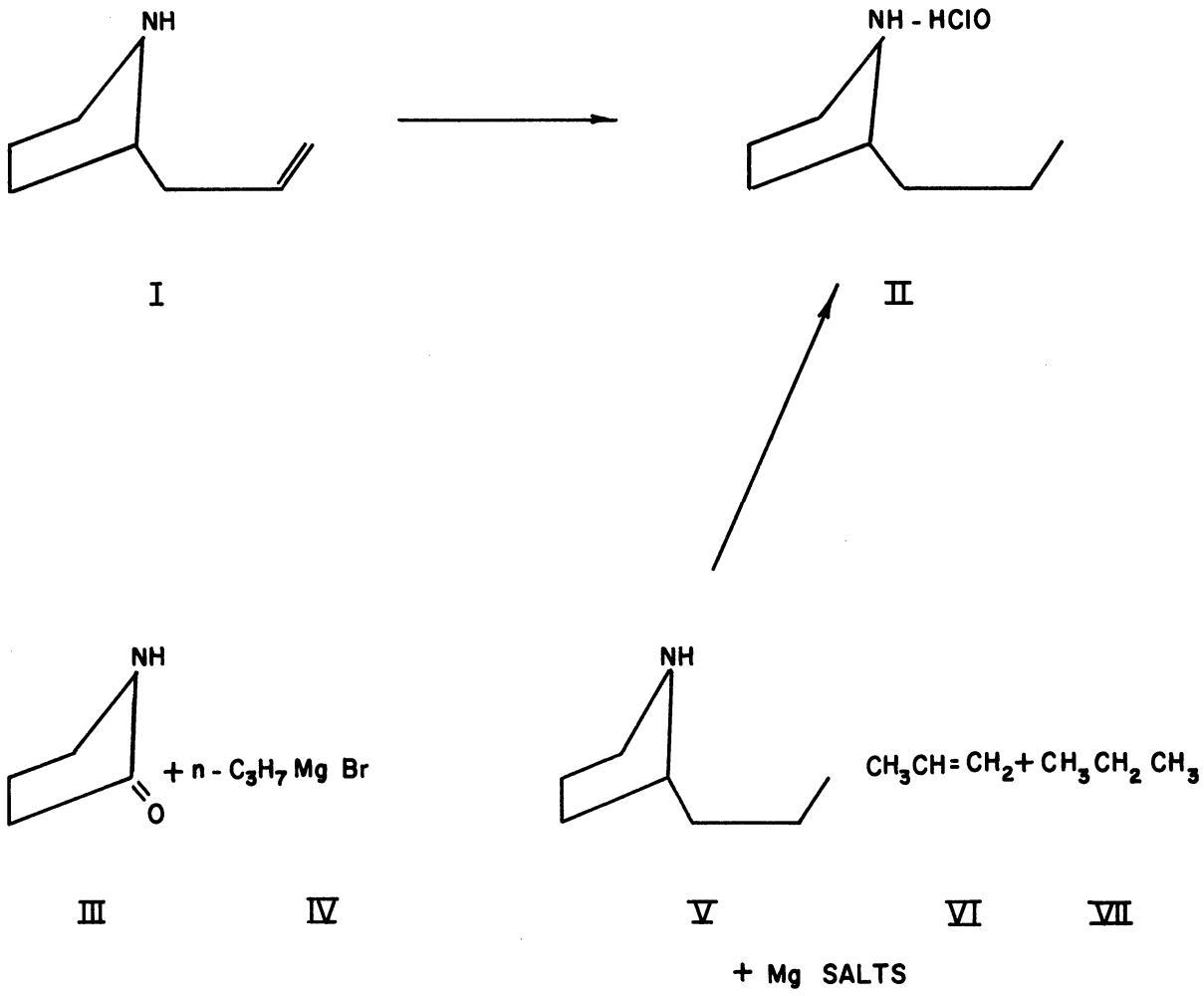


Chart P. Structure Proof of 2-Allylpyrrolidine.

the desired salt (M.P. 292-293°C), P-II. Samples of this salt prepared by the alternate routes had identical infrared spectra and their mixed melting point, M.P. 293-294°C, showed no depression.

When tetrahydrofuran was used as the solvent for the reaction of lithium aluminum hydride and 3β-mesyloxynortropane, only one product, 2-allylpyrrolidine, was obtained in a 96% yield. Apparently the hydride ion concentration was low enough to avoid direct displacement of the ester group.

In both solvents, ether and tetrahydrofuran, the only product in common was 2-allylpyrrolidine. Therefore the anion of 3β-mesyloxynortropane must preferentially react by the fragmentation process if displacement reactions are hindered. This result is to be expected, since this ion fulfills the requirements for fragmentation during ionization.

A seemingly anomalous piece of information came from a product determination in the reaction of 3α-mesyloxynortropane with lithium aluminum hydride in tetrahydrofuran. The only products isolated were 2-allylpyrrolidine in a 76% yield and a small amount of a white crystalline solid. The solid, melting at 140-141°C, is a tertiary amine as shown by a Hinsberg test. It apparently is some sort of dimeric product since a Rast molecular weight determination[38] showed that its molecular weight was at least 220. Its empirical formula as determined by analysis is $C_{28}H_{50-52}N_4O_5$. No further evidence was obtained as to the structure of the product.

38. Vogel, A. I., "Practical Organic Chemistry", Longman's, Green & Co., London, 1956, p. 1037.

The major product, 2-allylpyrrolidine, was identified by the analysis of its picrate, which showed that it must have this structure. In addition its hydrochloride was shown to be identical to that of the previously identified 2-allylpyrrolidine by infrared specta, melting points, and a mixed melting point.

Evidently fragmentation was the mode of reaction in this situation also. However, the ground state of the anion (Q-II) has the wrong stereochemistry for a concerted fragmentation process. If the piperidine ring flips up, however, the anion (Q-III) can either react by the fragmentation or participation processes during ionization. Since the orbitals are probably directed in both directions from the nitrogen, the stereochemical requirements for both processes are fulfilled. In spite of this only fragmentation occurs leading to the imine, Q-IV. Subsequent reaction of the imine with more hydride results in the observed product, Q-VI.

There is some precedence for this preference of fragmentation over participation when both are possible. In Chart I all of the compounds having the nucleophilic group cis to the leaving group (I-III, I-V, I-VI, and I-IX) can undergo both processes. Yet only in the case of cholestane-3β, 5α-diol 3β-tosylate did any participation occur.(7,8) This was shown by the production of the oxide I-VIII.(8) In all other cases fragmentation was the only process observed.

The other investigation that was undertaken was the study of the solvolytic reactions of nitrogen and sulfur heterocycles in relation to trans-4-t-butylcyclohexyl tosylate. The results of the rate determinations are shown in Tables V-VII while those for the product determinations are shown in Table VIII for both investigations.

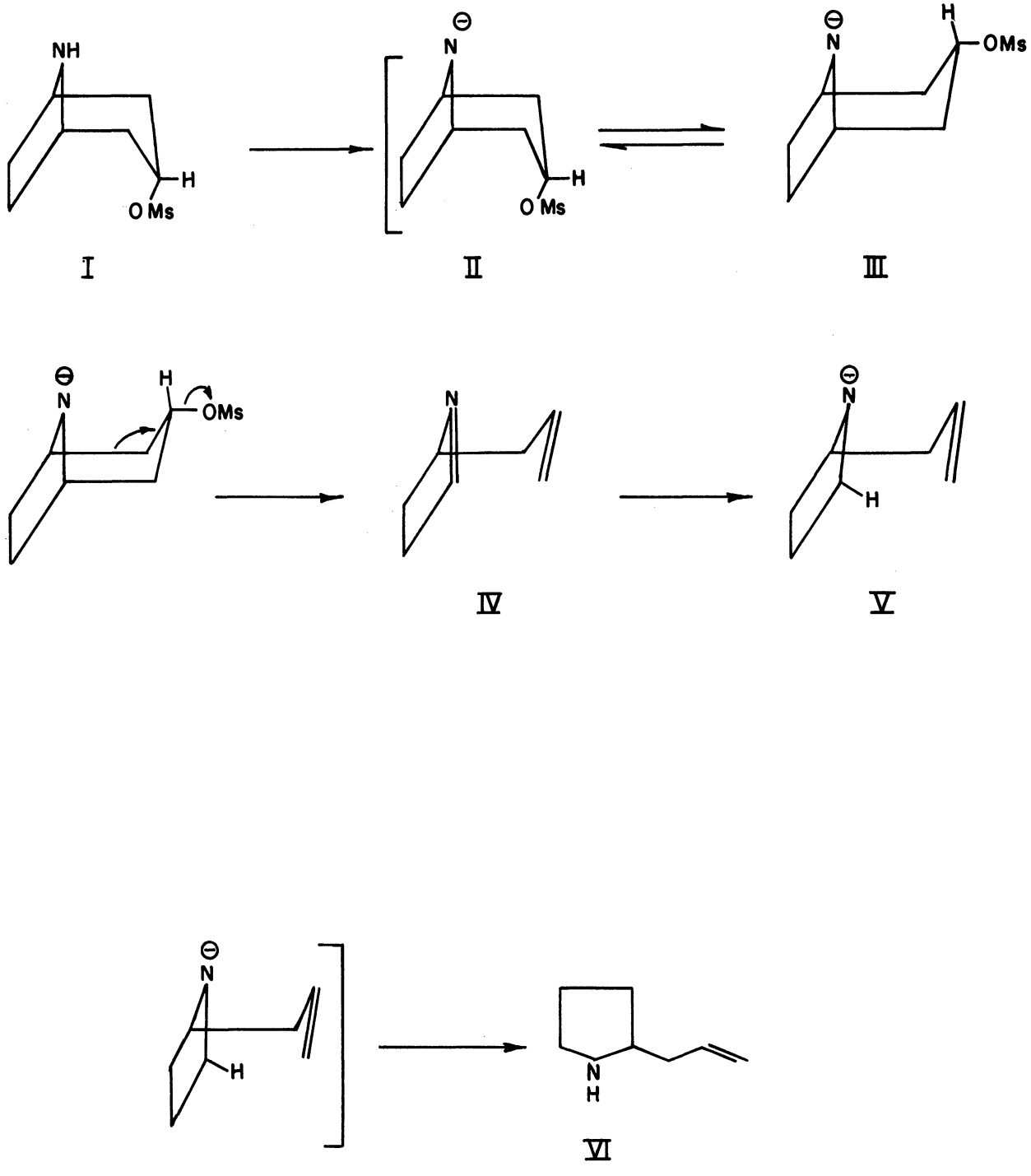


Chart Q. Reaction of 3α-Mesyloxynortropane with Lithium Aluminium Hydride.

TABLE V

RATE OF SOLVOLYSIS IN AQUEOUS ETHANOL

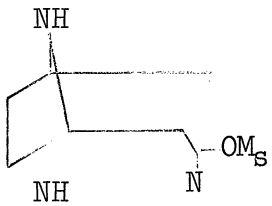
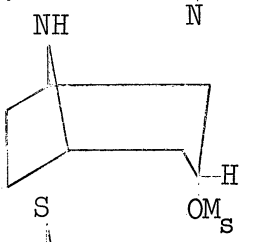
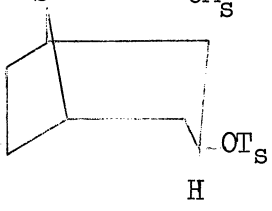
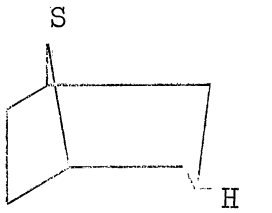
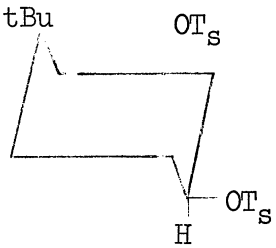
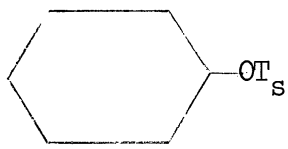
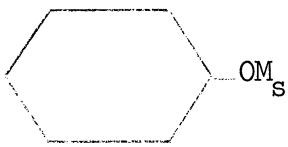
Compound	Solvent	Rate Constants (sec^{-1}) 98.5°C	77.0°C	50.8°C	36.0°C
	80% EtOH-H_2O	----	$8.06\pm.06 \times10^{-3}$	$1.31\pm.02 \times10^{-4}$	$4.39\pm.01 \times10^{-6}$
	80% EtOH-H_2O	----	$1.04\pm.01 \times10^{-3}$	$5.90\pm.05 \times10^{-5}$	$7.74\pm.01 \times10^{-6}$
	80% EtOH-H_2O	$4.12\pm.02 \times10^{-4}$	$6.40\pm.02 \times10^{-5}$	$3.66\pm.01 \times10^{-6}$	----
	80% EtOH-H_2O $NaClO_4$	----	$6.36\pm.04 \times10^{-5}$	----	----
	80% EtOH-H_2O	$3.56\pm.02 \times10^{-4}$	$1.15\pm.04 \times10^{-4}$	$1.30\pm.01 \times10^{-5}$	----
	80% EtOH-H_2O $NaClO_4$	----	$1.16\pm.01 .10^{-4}$	----	----
	80% EtOH-H_2O	$1.53\pm.03 \times10^{-3}$	$2.42\pm.04 \times10^{-4}$	$1.34\pm.01 \times10^{-5}$	----
	80% EtOH-H_2O	----	$3.05\pm.05 \times10^{-4}$	----	----
	80% EtOH-H_2O $NaClO_4$	----	$3.20\pm.05 \times10^{-4}$	----	----
	80% EtOH-H_2O	----	$2.42\pm.02 \times10^{-4}$	----	----

TABLE VI

RATE OF ACETOLYSIS

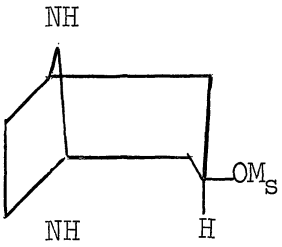
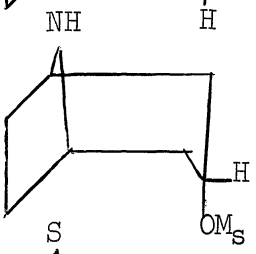
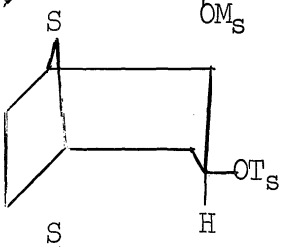
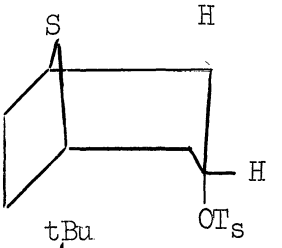
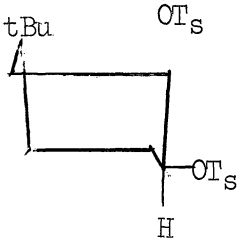
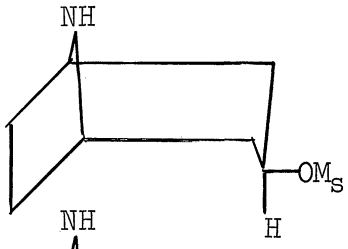
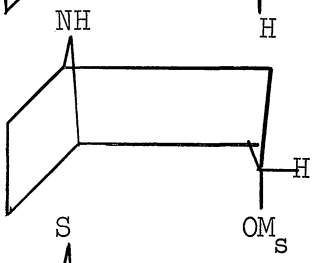
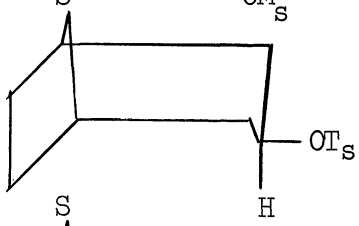
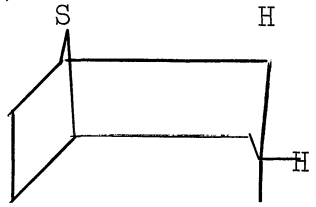
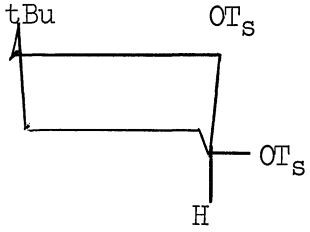
Compound	Solvent	Temperature	Rate Constants (sec^{-1})
	0.0205 M Ac_2O HOAc	77.0°C	$1.27\pm.01\times10^{-4}$
	0.0205 M Ac_2O HOAc	77.0°C	$6.04\pm.02\times10^{-5}$
	0.0205 M Ac_2O HOAc	77.0°C	$6.31\pm.01\times10^{-5}$
	0.0205 M Ac_2O HOAc	77.0°C	$1.06\pm.03\times10^{-4}$
	0.0205 M Ac_2O HOAc	77.0°C	$4.18\pm.02\times10^{-5}$

TABLE VII

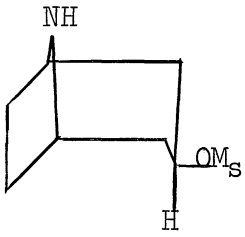
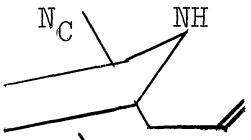
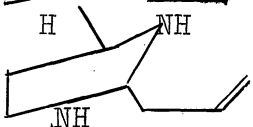
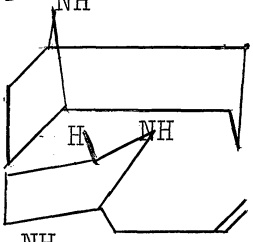
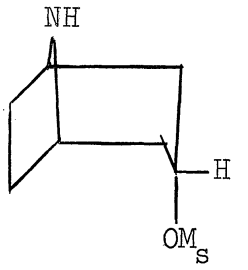
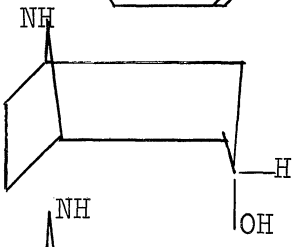
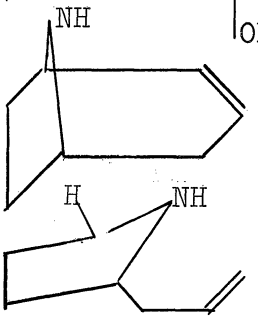
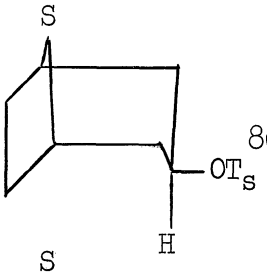
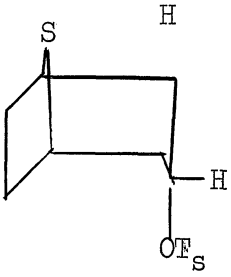
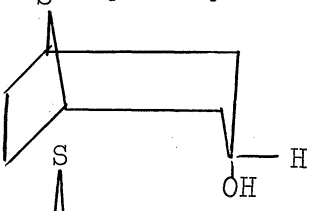
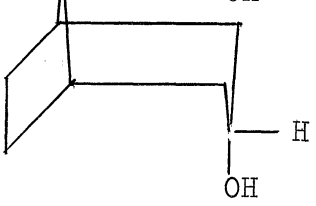
THERMODYNAMIC DATA OBTAINED FROM SOLVOLYSES IN 80% EtOH: H_2O

Compound	ΔH#(kcal/mole)*	ΔS#(e.u.)*
	37.3±0.7	36± 3
	24.8±0.2	-1.7±0.7
	23.2±0.5	-13 ±0.9
	15.9±0.5	-27.3±0.5
	23.4±0.5	-11.8±0.6

*Values obtained by least squares method and by slope intercept method.

TABLE VIII

PRODUCTS OF SOLVOLYSIS

Compound	Conditions	Products	Yield
	80% EtOH-H_2O KCN		85.5%
	THF-$LiAlH_4$		96.1%
	Ether-$LiAlH_4$		86.0%
			10.2%
	80% EtOH-H_2O		62.5%
	THF-$LiAlH_4$		25.3% 76.0%
	80% EtOH-H_2O	[Dimer]	~19%
	80% EtOH-H_2O		78.0%
			78.1%

In order to aid in the interpretation of these results, it would be necessary to know the process through which trans-4-t-butylcyclohexyl tosylate goes during solvolysis. Studies conducted on the solvolysis of this compound have shown that in addition to the cis alcohol a 70% yield of olefin was obtained.(32) Since a concerted type of elimination is stereochemically impossible for this compound, the loss of p-toluenesulfonic acid could only occur by a stepwise type of elimination. This is believed to occur by ionization leading to an intimate ion pair. Solvent may attack then leading to inversion, but the bulk of the cations tend to lose a proton resulting in olefin formation.(32) The rate determining step in this solvolysis is undoubtedly ionization. Therefore the rates of solvolysis and the enthalpy and entropy of activation for this compound may be considered as characteristic for the ionization process in the solvents used.

For cis-4-t-butylcyclohexyl tosylate ionization must also occur, since this is the only way to account for the rearranged product.(32) Thus its rate and thermodynamic data are also characteristic of the ionization process for axial leaving groups.

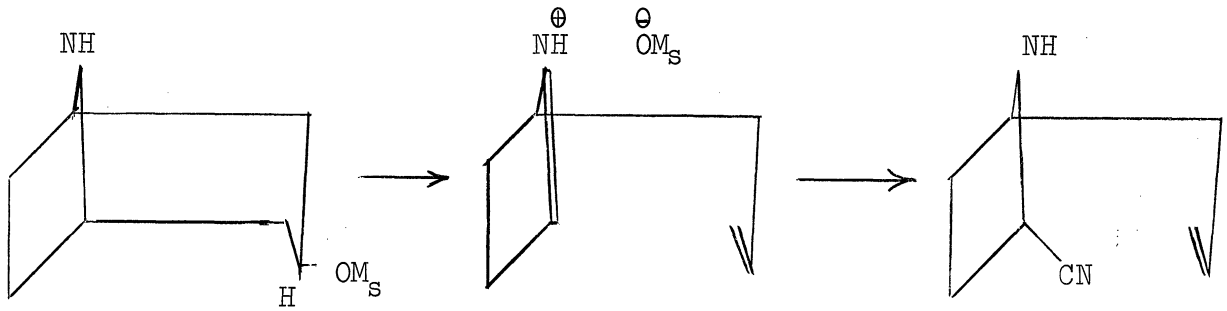
The results of the investigation of the solvolysis of the heterocycles fit in very well with the ideas previously presented on the stabilization of incipient carbonium ions. 3β-mesyloxynortropane, for instance, reacts several times faster than the reference compound, trans-4-t-butylcyclohexyl tosylate, at the temperatures studied (Table V). This accelerated rate indicates that in some way the nitrogen is aiding in the removal of the ester group. In other words stabilization is occurring during and not after ionization.

The only modes of stabilization of the cation which involve the electrons on the nitrogen are those in which these electrons interact directly, or through cleavage of the C_1-C_2 bond. Since the stereochemistry of 3β-mesyloxynortropane (N-IX) is such that the nitrogen could not enter into an attack on the carbon bearing the ester group before ionization was complete, the participation process (G-X) is impossible during ionization. However, the stereochemistry when the molecule is in the chair form (N-IX) is exactly that which is required for a fragmentation process during ionization.[7-11,13] Thus it seems plausible that this compound is interacting in such a way as to favor stabilization of the incipient carbonium ion through the interaction of the electrons by the fragmentation process.

The product of this reaction (Table VIII) further substantiates the hypothesis that this species reacts by the fragmentation process in solvolysis. Since the fragmentation product is very unstable, it was trapped by reaction with cyanide ion added to the reaction mixture. Therefore the product actually obtained from the reaction was 5-cyano-2-allylpyrrolidine instead of the immonium ion (2) shown in Figure 6. Methylation of the cyano derivative by one equivalent of methyl iodide in the cold resulted in an 85.5% yield of 5-cyano-2-allyl-1-methylpyrrolidine. The infrared spectrum of this compound, showing intense bands at 6.09μ, 10.92μ, and 3.30μ with two cyano bands at 4.25μ and 4.45μ, was identical to the reported spectrum (Plate 2).[16-17] In addition the boiling points of this product and that reported in the literature are

comparable.[16-19] The formation of 5-cyano-2-allylpyrrolidine can only be explained by fragmentation analogous to that which produced 5-cyano-2-allyl-1-methylpyrrolidine from the 3β substituted tropanes.[9,16-19]

The most probable path of reaction, then, is that depicted in Figure 6. The first step is a concerted fragmentation leading to the unsaturated immonium ion (2). This is followed by nucleophilic attack by cyanide ion on the carbon-nitrogen double bond at the carbon atom resulting in the observed products. There is a great deal of precedence for the latter reaction in addition to the observations on the 3β tropane



1 2 3

Figure 6. Solvolysis of 3β-Mesyloxynortropane.

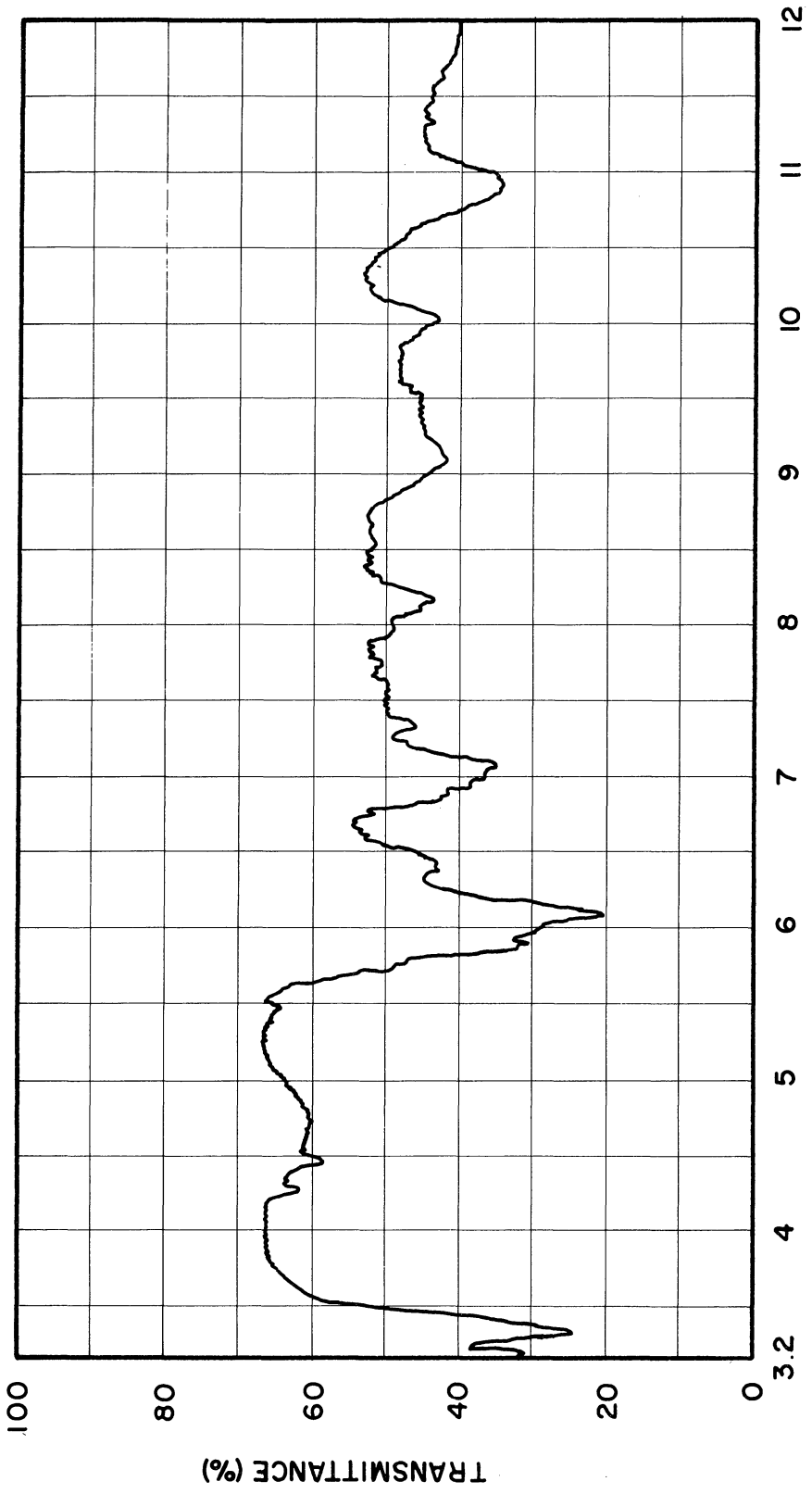


Plate 2. Infrared Spectra of N-Methyl-5-Cyano-2-Allylpyrrolidine.

system.[9,16-19] For example, $\Delta^{5(10)}$dehydroquinolizidinium perchlorate reacts readily with nucleophiles such as cyanide, hydride, and carbanions[39,30] to yield the 10-substituted quinolizidines (Chart R). Thus the 10-cyano (R-II) and 10-methylquinolizidines (R-IV) can be made by treating this perchlorate salt, R-I, with potassium cyanide or methyl magnesium iodide respectively.[39,40] Lithium aluminum hydride converts it to the parent compound, quinolizidine (R-III).[39,40] $\Delta^{4(9)}$hexahydropyrrocolinium perchlorate (R-V) also reacts readily with potassium cyanide to yield 9-cyanooctahydropyrrocoline, R-VI.[40] In addition it was observed that water can attack this position resulting in cleavage of the carbon-nitrogen bond to yield an amine and a carbonyl function or compound[12] (Chart K).

Since a definite path of reaction has been strongly suggested by the rate and product data, the thermodynamic data (Table VII) should be considered to see if they corroborate or exclude this path. The high positive entropy of activation indicates that the ground state of 3β-mesyloxynortropane is more highly restricted than the transition state. Since the transition state for stabilization of an incipient carbonium ion by the fragmentation process during ionization must be that shown in Figure 7,[7-11] then a plausible way in which the ground state could be more restricted would be if it were held in the boat form by internal hydrogen bonding (Figure 7). This would prevent

39. Leonard, N. J., Hay, A. S., Fulmer, R. W. and Gash, V. W., J. Am. Chem. Soc. 77, 439 (1955).
40. Leonard, N. J. and Hay, A. S., J. Am. Chem. Soc. 78, 1984 (1956).

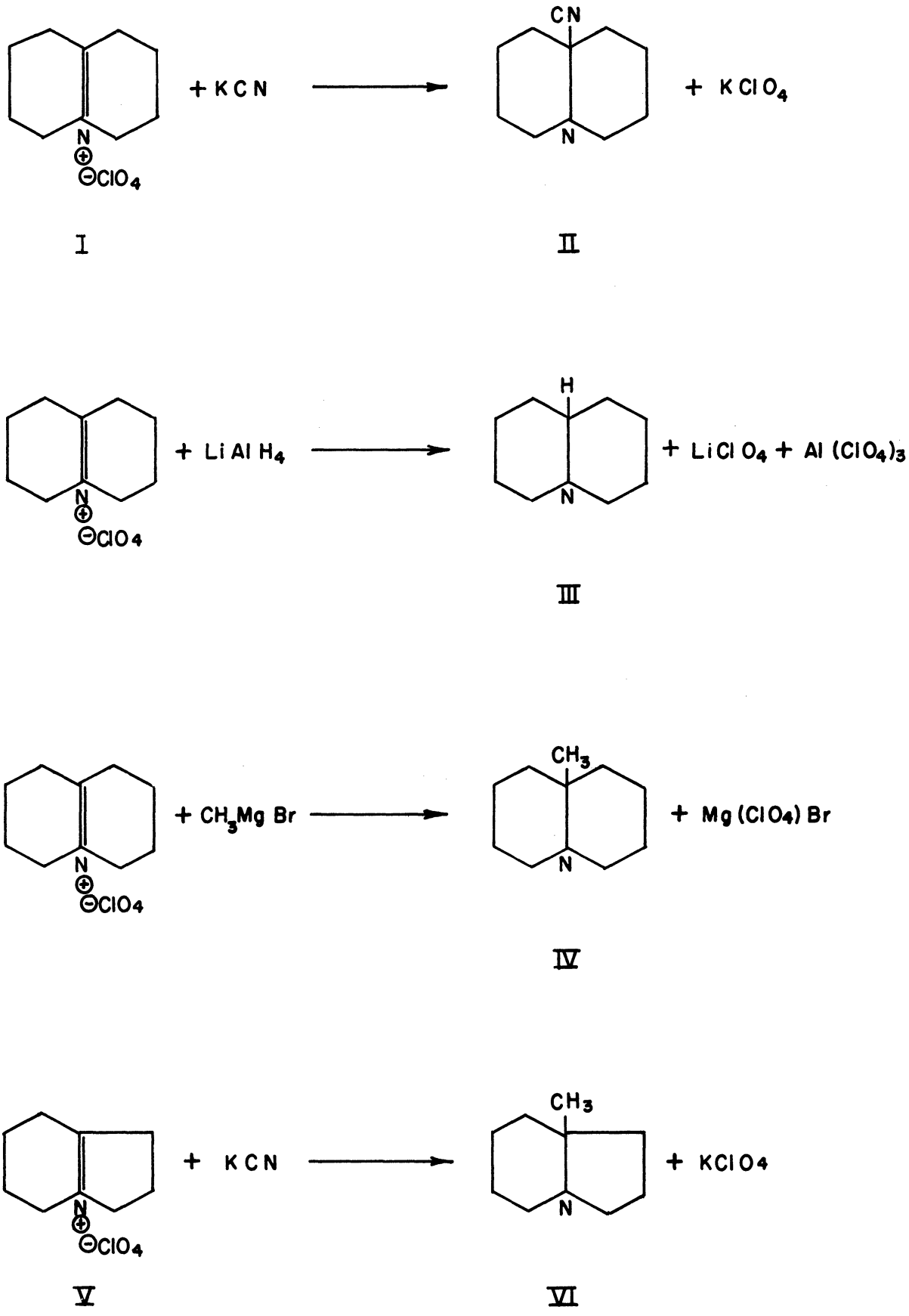
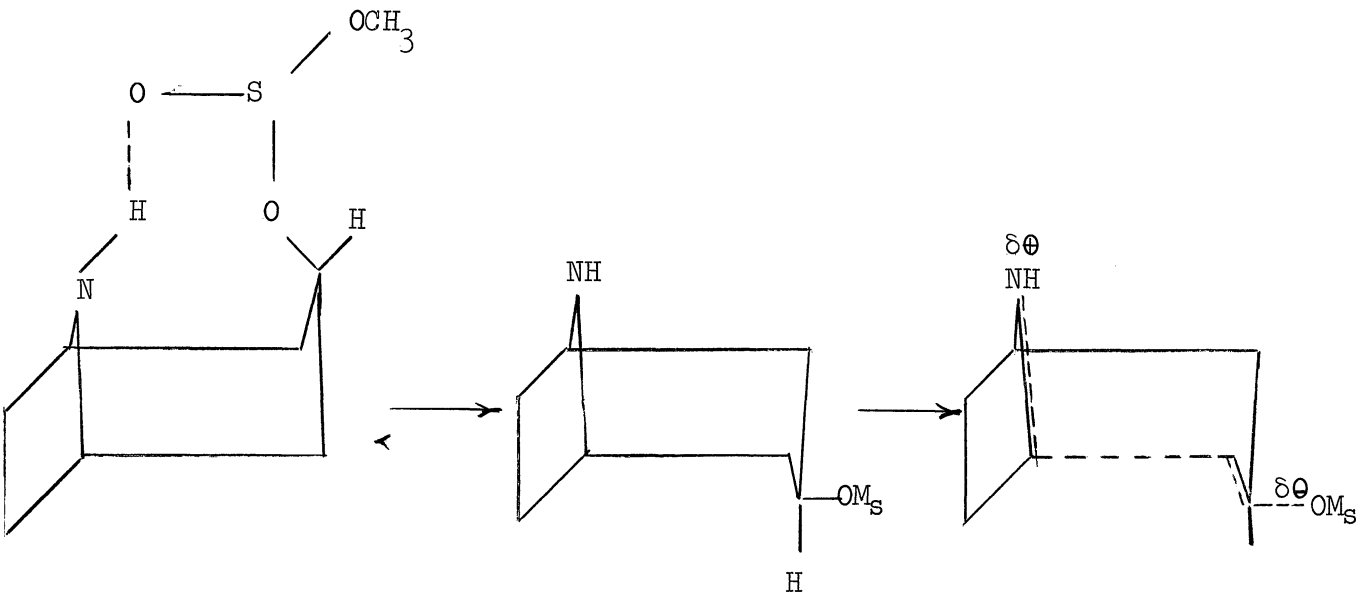


Chart R. Reactions of Imines with Nucleophiles.



Ground State

Transition State

Figure 7. Stereochemistry of Solvolysis of 3β-Mesyloxynortopane.

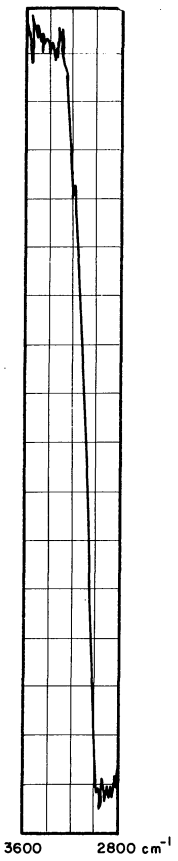
rotation of the mesyl group as well as freezing the configuration of the amino group and the rings. This highly ordered ground state, undoubtedly, would have a highly oriented solvent shell about it also. On breaking of the hydrogen bond, the ring system would flip down into the chair form disrupting the solvent shell. In this condition, no restriction is placed on the mesyl grouping which can rotate freely. Since the rotation of this group would keep the solvent stirred up in this region, there would be less orientation of the solvent about the molecule than there was in the ground state. Thus there is a change from order to disorder requiring a positive entropy change, as was observed.

It might be noted that the energy needed to break the hydrogen bond would increase the enthalpy of activation. This would explain why this compound has a rather large value for this quantity.

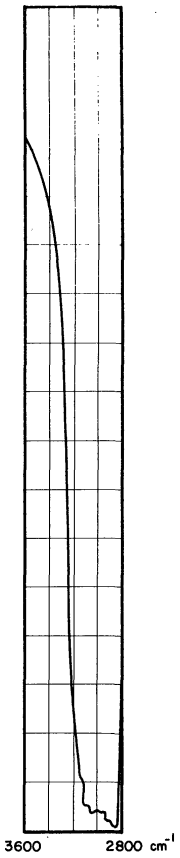
There is some evidence for the existence of the hydrogen bonded boat form shown in Figure 7 for 3β-mesyloxynortropane. The infrared spectrum for this molecule (Plate 3) shows no nitrogen-hydrogen stretching absorption between 3100-3500 cm^{-1} while that of the perchlorate salt shows only one at 3140 cm^{-1}. The 3α isomer, 3α-mesyloxynortropane, however, has a nitrogen-hydrogen stretching absorption at 3350 cm^{-1} and two for the perchlorate salt at 3050 cm^{-1} and 3160 cm^{-1} respectively. Further investigation showed that the absorption in the nitrogen-hydrogen stretching region that was missing from the 3β compounds was at 2960 cm^{-1}. Thus hydrogen bonding does seem to be present in the 3β isomers, as indicated by the shift in the nitrogen-hydrogen absorption of the amine and one absorption of its salt to lower frequencies (2960 cm^{-1}).

There is also precedence for this type of hydrogen bond formation. Spectroscopic evidence is available showing that hydrogen bonding has shifted the oxygen-hydrogen stretching absorption of 3β-hydroxytropane and that this shift is not concentration dependent.[41] This latter fact shows that the hydrogen bonding is intramolecular as was postulated for 3β-mesyloxynortropane. In addition the dipole moments for the boat and chair forms of the 3β isomer have been calculated and compared to the

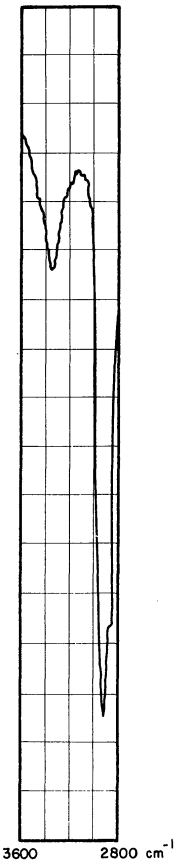
41. Zenitz, B., Martini, C. M., Priznar, M. and Nachod, F. C., J. Am. Chem. Soc. 74, 5564 (1952).



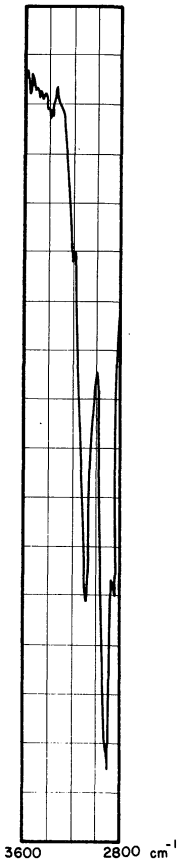
3β-Mesyloxynortropane



3β-Mesyloxynortropane
Perchlorate



3α-Mesyloxynortropane



3α-Mesyloxynortropane
Perchlorate

Plate 3. Infrared Spectra of Nitrogen-Hydrogen Stretching Region for the 3-Mesyloxynortropanes and their Perchlorates.

experimental values (Table IX).[41-43] The closer the experimental value is to one of the calculated values the more of that conformation is present. The data in both cases show that there is an appreciable amount

TABLE IX

DIPOLE MOMENTS FOR 3β-HYDROXYTROPANES

Conformation	Dipole Moment			
	Calculated		Found	
	A[41]	B[42]	A[41]	B[42]
Boat	2.5±.5	1.85	2.20	1.68
Chair	1.2±.5	2.30		

of 3β-hydroxytropane in the boat form. Undoubtedly it is held there by intramolecular hydrogen bonding. It should be noted that the two sets of calculated dipole moments are not mutually consistent. However, the results in both cases lead to the same conclusion.*

Therefore all the data for 3β-mesyloxynortropane indicate that on solvolysis it reacts by intervention of the fragmentation mode of stabilization during ionization leading to the rate enhancement, products, and thermodynamic values observed.

The data for the 3α isomer also fit in well with the ideas of stabilization of an incipient cation. This isomer also reacts more rapidly than the reference compound. Therefore here too the nonbonded electrons on the nitrogen must interact during ionization to aid in the removal of the ester group.

42. Clemo, G. R. and Jack, K. H., Chem. & Ind., 195 (1953).
43. Campbell, I. G. M., Ann. Reports Prog. Chem. 50, 165 (1953).
*Greater confidence is placed in the values in set A.

Again the three possible resonance forms showing the manner through which stabilization of the cation could occur by utilization of the nonbonded electron pair on the nitrogen are the structures similar to G-V, G-X, and G-XI. It can be seen from the configuration of this ester (S-I) that it has the wrong stereochemistry to undergo fragmentation during ionization while it is in the chair form (S-I). However, stabilization of the incipient carbonium ion could occur by the fragmentation or participation processes if the ester had the boat conformation. Although the steric requirements of the hydrogen versus the nonbonded electron pair are about the same, it seems likely that the hydrogen would favor the equatorial position with respect to the piperidine ring.[44] If such is the case, then reaction by the participation process would be favored over that by the fragmentation process, since the p orbital bearing the nonbonded electrons would be directed toward the 3 position.

The products of solvolysis in 80% ethanol-water (Table VIII) can give us an insight into which of these modes of stabilization might occur. The first, nortropidine, was obtained in 25.3% yield. It was identified by its infrared spectrum. It was also identified by its boiling point, 160°C/750 mm, which is nearly the same as the reported value, 160°C/760 mm.[34] Since 3α-mesyloxynortropane has the correct stereochemistry for a concerted trans elimination, this was probably the manner in which the nortropidine was produced.

44. Closs, G. L., J. Am. Chem. Soc. 81, 5456 (1959).

The other product, 3α-hydroxynortropane, was obtained in a 67.5% yield. It was identified by its melting point, 160-162°C, which is the same as the reported value, 160-161°C.[23] In addition its infrared was identical to that of 3α-hydroxynortropane synthesized in the preparation of the mesyl ester (Plate 1). The alcoholic product of solvolysis, then, has the same stereochemistry as the starting ester. This could only occur through the contribution of the cationic structure (G-X) to the hybrid ion, since the other modes of stabilization utilizing the nonbonded electrons on the nitrogen, G-XI, would lead to fragmentation. This result is also analogous to those obtained on solvolysis of the 3α-tropane derivatives in which participation was also postulated.[9,17,19]

The most likely path of reaction, then, is that shown in Chart S. Thus the nitrogen interacts to aid in the removal of the ester group leading to the tetracyclic ammonium salt, S-III. This on reaction with the solvent, in this case the water present, leads to the observed product, S-IV. The water reacts instead of the ethanol since it is more nucleophilic as shown by its more positive "n" value, -0.44, compared to that for ethanol, -0.53.[45]

The thermodynamic data also confirm this path of reaction. The ground state for 3α-mesyloxynortropane is undoubtedly the chair conformation depicted by structure S-I and shown in Figure 8. The boat form with thich it is probably in equilibrium is a higher energy form due to eclipsing of hydrogens on C_1 and C_2 and on C_4 and C_5. In addition to

45. Swain, C. S. and Mosely, R. B., J. Am. Chem. Soc. 77, 3727 (1955).

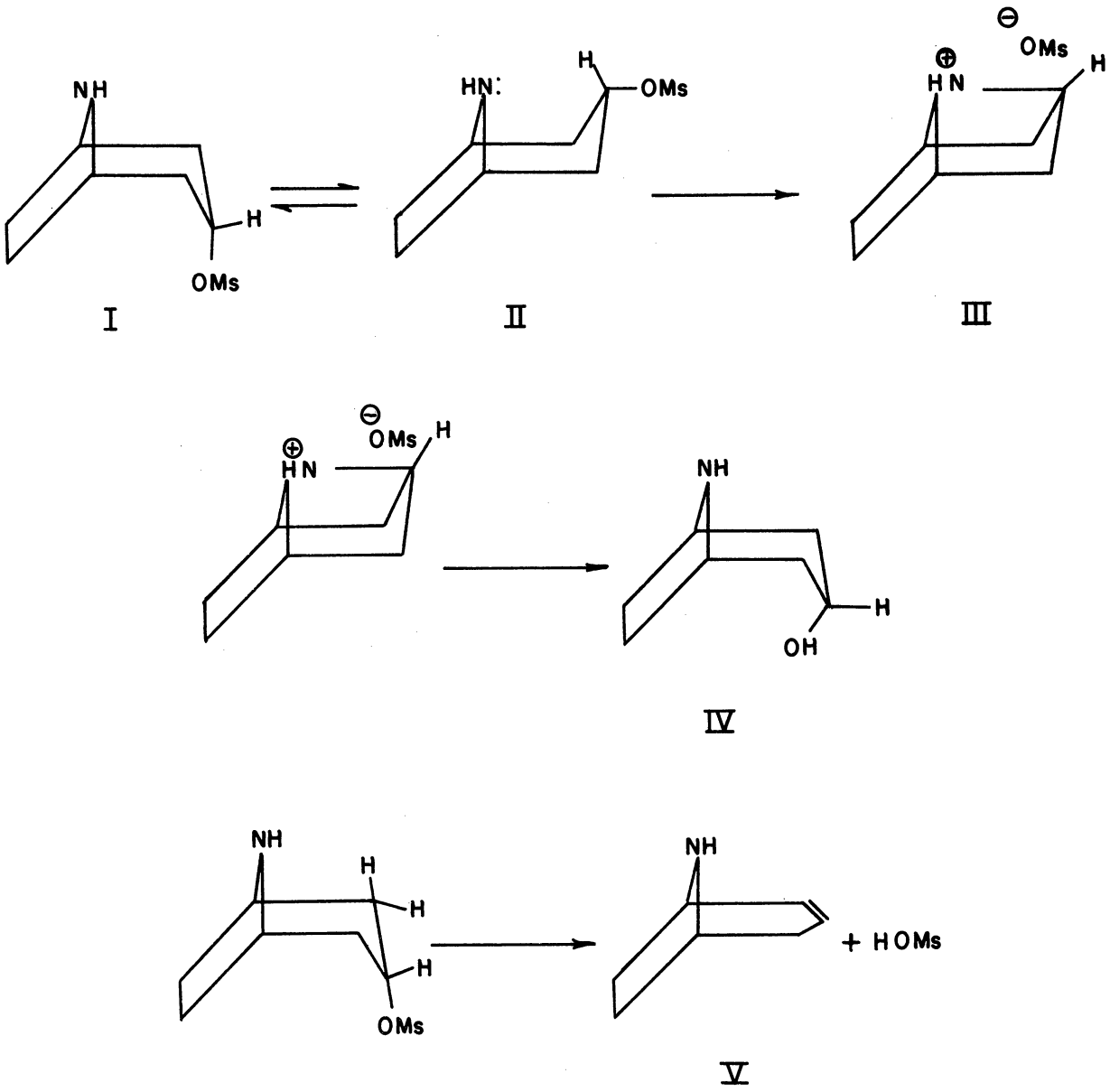
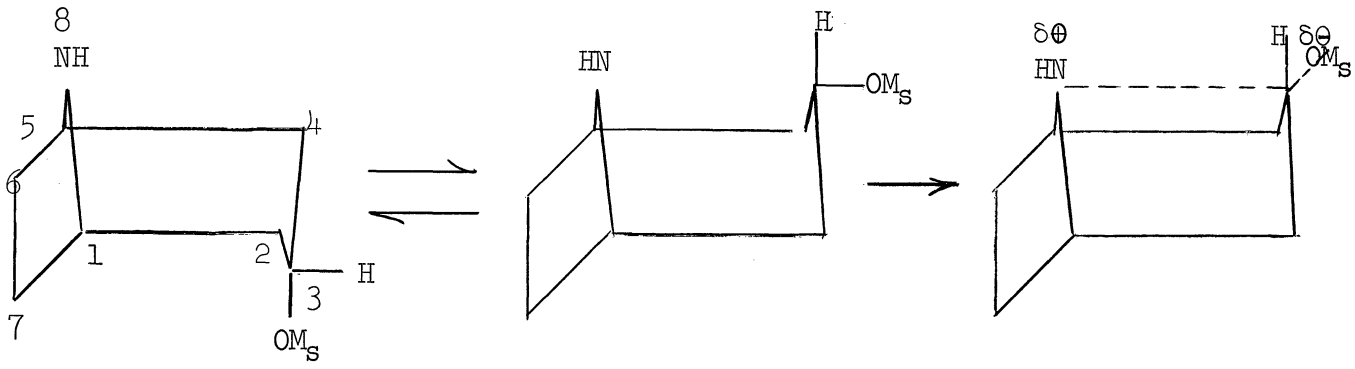


Chart S. Solvolysis of 3α-Mesyloxynortropane.

this there would be a nonbonded interaction between the nitrogen and the hydrogen on C_3. Since the molecule must be transformed to the boat form before participation can occur, this would account for the appreciable enthalpy of activation that is observed for it (Table VI). The transition state for stabilization by the participation process during ionization would be that shown in Figure 8. It is evident that this is more restricted



Ground State Transition State

Figure 8. Stereochemistry of Solvolysis of 3α-Mesyloxynortropane.

than the ground state, since it must be held in the boat form so that reaction may proceed. This increase in the restrictions on the molecule in passing from the ground state to the transition state would require a negative entropy of activation. This is indeed what is observed for this species (Table VII). Therefore the proposed reaction path is indeed consistent with the facts.

Since the nitrogen heterocycles do give evidence of nitrogen participation during the ionization process it might be expected that sulfur would exhibit this effect also. However, the evidence indicates that if this effect is present at all it is very small.

Although 3β-tosyloxy-8-thiabicyclo [3.2.1] octane had the proper stereochemistry for fragmentation to occur during ionization, it solvolyzed about four times slower than the reference compound, trans-4-t-butylcyclohexyl tosylate (Table V). This would indicate that there was no stabilization during ionization by fragmentation or by any other process. Since the absence of a rate accelerating effect would not lead to a rate retardation as was observed, this result must be due to an inductive effect of the sulfur similar to that observed with oxygen in the 2-chloro-1, 4-endoxocyclohexanes.(2)

The absence of a fragmentation reaction, is further indicated by the product of solvolysis (Table VIII). The only product observed was 3α-hydroxy-8-thiabicyclo [3.2.1] octane. It was identified by its melting point and its infrared spectrum which were identical to those for the compound designated as the 3α alcohol from the ester synthesis.

It should be noted that the configuration of this product at C_3 is inverted with respect to the starting material in the solvolysis. This inversion could have resulted by direct displacement of the leaving group by solvent or possibly by stabilization of the cation after ionization by the participation process (G-X). The thermodynamic data can aid in deciding which of these two processes is most likely. It is striking that the enthalpy of activation for this compound is almost identical to that

for the reference compound (Table VII) which also has an equatorial ester group.[32] In addition the entropies of activation are very close. The difference between them is probably due to the reduced ability of the thia compound to form a cation because of the inductive effect of the sulfur. The fact that these values are so close suggests that both compounds undergo the same rate determining step in solvolysis. From the discussion of the solvolysis of the reference compound this step has been shown to be simple ionization. Consequently the thia compound must also react in this manner in the rate determining step.

Since no olefin is formed in the solvolysis of the thia compound, it must react differently than the reference compound after ionization is complete. The thermodynamic data have shown that direct displacement prior to ionization is improbable. In addition the work on trans-4-t-butylcyclohexyl tosylate has shown that this reaction after ionization is a secondary reaction. Therefore sulfur must interact with the charge on C_2 as shown in the structure, T-IV (Chart T). Then solvent reacts with the hybrid ion leading to the observed product, T-VI, which has the inverted configuration at C_3.

The 3α isomer in contrast to the isomer just discussed appears to show some evidence for a small amount of sulfur interaction during ionization. The rate of solvolysis of this isomer was slower than that of the reference compound (Table V). On the surface, this would indicate that no stabilization of the incipient carbonium ion did occur during ionization.

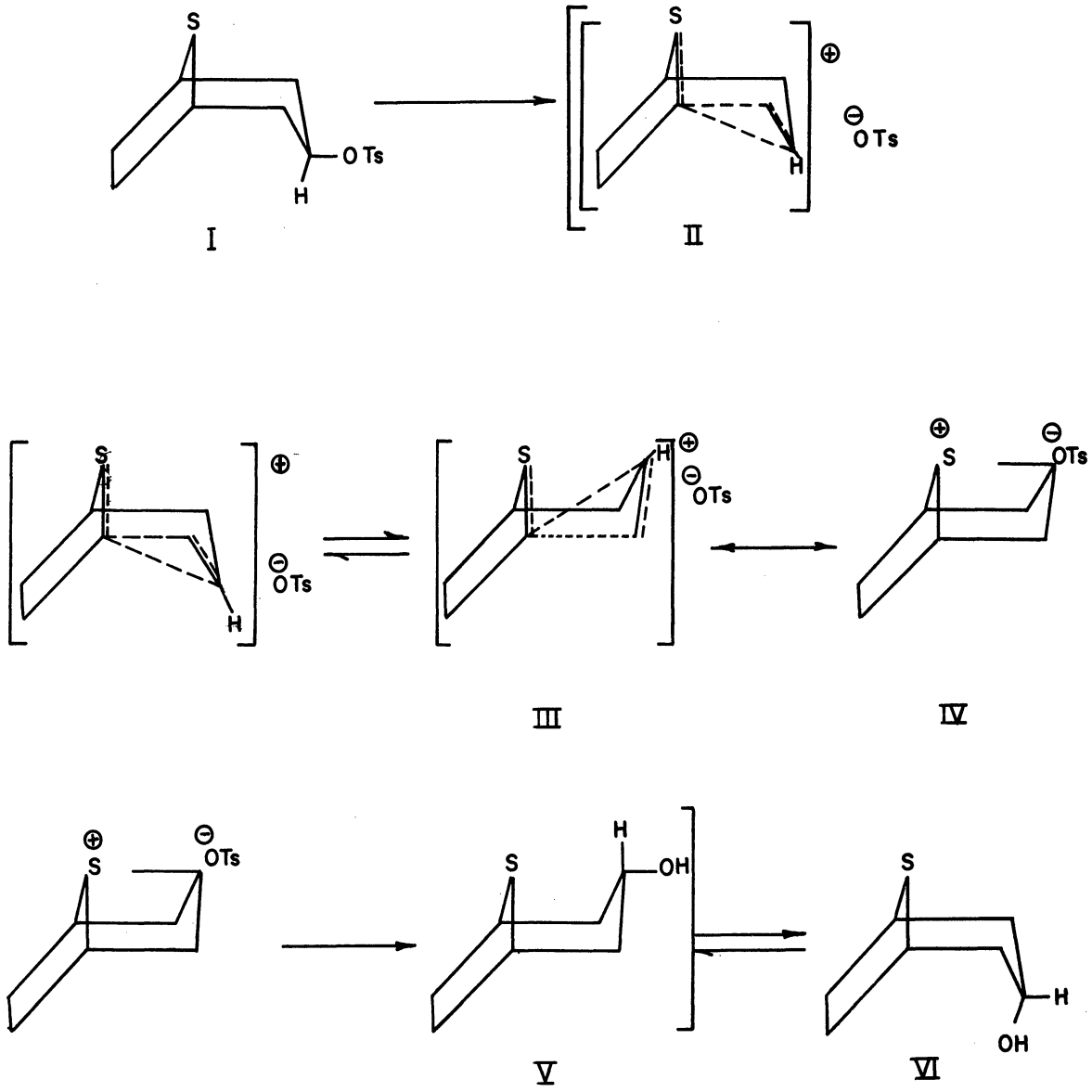
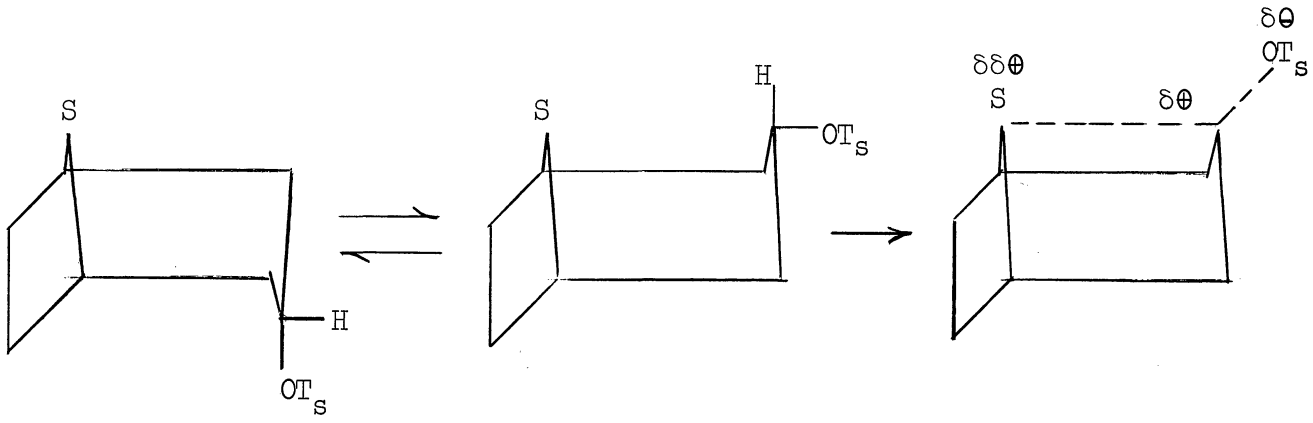


Chart T. Solvolysis of 3β-Tosyloxy-8-Thiabicyclo [3.2.1] Octane.

The product of solvolysis, 3α-hydroxy-8-thiabicyclo [3.2.1] octane, identified by its melting point and its infrared spectrum, does not alter this viewpoint much. It is true that retention of configuration, as observed here, is characteristic of the participation process in compounds having this ring system.[9,16-19] However, participation leading to this product could have occurred after ionization as it did in the solvolysis of the 3β ester.

The thermodynamic data on the other hand suggest that participation may have occurred during ionization. The 3α isomer has a very low enthalpy of activation, lower than all of the other four compounds studied. This indicates that some path of reaction with a lower energy than simple ionization is helping to reduce the activation energy. In addition the entropy of activation is very low and negative. Therefore the transition state must be more restricted than the ground state. This would be the result if the molecule passed through a boat type of transition state during ionization (Figure 9). This transition state would also be in the best configuration for participation to take place during ionization. If a small amount of participation did occur, it could make the path of reaction through the boat form a lower energy path than unassisted ionization. Thus the boat type of transition state seems very probable, and the thermodynamic data are consistent with it and with at least a small amount of participation during ionization.

In addition the work on cis and trans-4-t-butylcyclohexyl tosylates has shown that simple ionization of axial or equatorial leaving groups results in very similar entropies and enthalpies of activation.[32]



Ground State Transition State

Figure 9. Stereochemistry of Solvolysis of 3α-Tosyloxy-8-Thiabicyclo [3.2.1] Octane.

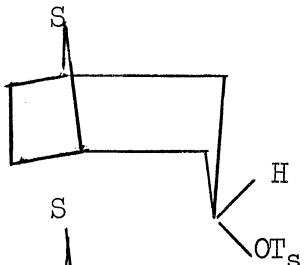
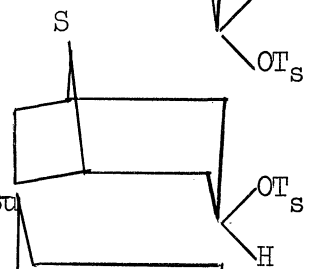
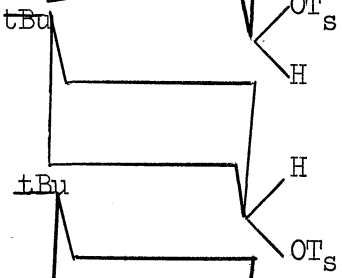
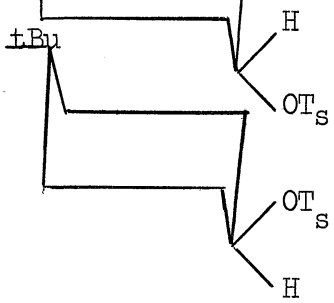
This would indicate that the thermodynamic values of the 3α and 3β thia esters should be very similar if both of these esters react by simple ionization. Since the 3β isomer undoubtedly does undergo this process, the large difference between the thermodynamic values of these esters must be due to the reaction of the 3α ester by another path.

A comparison of the rates of solvolysis of the 3α and 3β thia esters with that of the cis and trans-4-t-butylcyclohexyl tosylates leads to the same conclusion. The rate of the 3α-tosyloxy thia ester was somewhat faster than the 3β, which is also the case with the 4-t-butylcyclohexyl tosylates. If the ratio of the rates of the 3α isomer to the 3β are compared to the ratio for cis and trans-4-t-butylcyclohexyl tosylates

(Table X), however, it becomes apparent that the 3α isomer utilizes a somewhat different mode of reaction than the 3β isomer during solvolysis.

TABLE X

RATIO OF AXIAL TO EQUATORIAL RATE CONSTANTS IN ESTER SOLVOLYSIS

Compounds	Ratio		
	50.8°C	77.0°C	98.5°C
	3.7	1.8	0.87
	50°C	75°C	
	3.9	3.1	

Since the ratio of the rates for the thia compounds decreases faster with increasing temperature than does the ratio for the cyclohexanes,[32] it appears that other factors are operating in addition to the axial-equatorial effect on the rate of solvolysis. It is true that an inductive effect is operating in the thia compounds, but as it was shown with the 2-chloro-1, 4-endoxocyclohexanes,[2] this should make the rate of the axial isomer

slower than that for the equatorial isomer. This does happen at higher temperatures (Table X), but some rate enhancing effect must be present at lower temperatures to compensate for the inductive effect. The 3α thia ester has the proper stereochemistry for stabilization by either the participation or the fragmentation processes during ionization. Therefore it is possible that one or both of these contribute slightly during ionization leading to the rate enhancement observed. However, as the temperature is raised, enough energy is probably supplied by the surroundings to make this contribution less necessary for reaction and stabilization by this means gradually diminishes to nothing. This effect, which the product shows is probably participation, would not be large, but it could account for the rates and thermodynamic values observed.

It is of interest to note that this is one instance where either fragmentation or participation could take place but that participation was the dominating process in formation of the product. The only other situation where this result has been observed was that of cholestane-3β, 5α-diol 3β-tosylate which gave a higher yield of participation product, the oxide I-VIII, than of the fragmentation product, I-VII.[8] In this case olefin was also formed. This multiplicity of products suggests that stabilization must have occurred after ionization was complete, since stabilization during ionization generally results in only one product.[7,10] This might indicate that participation is favored over fragmentation as a mode of product formation after ionization. It would further indicate that very little stabilization of the incipient carbonium ion occurred

during ionization of the thia compound, since this, as has been shown previously (Chart I and Chart Q), leads to fragmentation as the dominating product producing process. Thus the major process appears to be ionization retarded by the inductive effect of sulfur with a small accelerating effect due to some participation during ionization.

To further substantiate the role that the nonbonded electron pairs on the hetero atom play in stabilization of the carbonium ion, all five compounds being investigated were allowed to react in anhydrous acetic acid. As the data in Table VI show, this had a profound effect on some of the rates. The rates of the 3β and 3α nitrogen compounds were reduced by a factor of 64 and 17 respectively at 77.0°C. The reference compound was only retarded by a factor of 6.8. This indicates that elimination of the nonbonded electron pair by quaternization as the acetate salt eliminates a large portion of the stabilization that occurred during ionization. Thus these electrons do play a major role in the solvolysis of the nitrogen heterocycles.

It should be observed that although the rates of the 3-mesyloxynortropanes were retarded, they were still faster than those of the reference compound. This is undoubtedly due to a small amount of the free amine, which can participate or fragment, in equilibrium with the salt.

In the case of the thia compounds almost no retardation was observed. Since the reference compound was retarded, the thia compounds have faster rates in this solvent. Acetic acid has been shown to be a less ionic solvent than 80% ethanol-water by the fact that its "Y" value

is -1.633 less than that of the reference solvent, 80% ethanol-water.[46] Therefore it would be expected that the thia compounds would be retarded also if they were still reacting by ionization with little or no assistence. The observed results may be due to the lower ionizing power of the solvent which would force these compounds to react by other paths that would be less energetic than ionization in this solvent. These paths could include stabilization by fragmentation or participation.

From all the data now available it is evident that the nonbonded electron pairs on the hetero atoms can interact with an incipient carbonium ion either during or after ionization. This interaction can result in a favoring of certain modes of stabilization. In the case of nitrogen, this interaction is appreciable during ionization. With sulfur it is small or nonexistent during ionization depending on the isomer concerned. However, interaction by participation is the dominating process after ionization is complete. With oxygen the interaction does not occur except after ionization as shown by previous work.[3] This correlates well with the known nucleophilic or electron donor properties of the atoms concerned.

F. Summary

Four compounds, 3α-mesyloxynortropane, 3β-mesyloxynortropane, 3α-tosyloxy-8-thiabicyclo [3.2.1] octane, and its 3β isomer were synthesized in addition to a reference compound, trans-4-t-butylcyclohexyl tosylate. Once synthesized, rate and product determinations were made in an effort to decide the course of solvolysis for each species. Through this

46. Grunwald, E. and Winstein, S., J. Am. Chem. Soc. 70, 846 (1948).

method, it was determined that 3α-mesyloxynortropane reacts mainly by a transannular nitrogen participation during ionization with some elimination. The 3β isomer undergoes fragmentation as a means of stabilizing the incipient carbonium ion. The 3β thia compound undergoes simple ionization followed by stabilization of the cation by sulfur participation in a later step. The 3α thia isomer reacts mainly by ionization with some assistance provided by participation during ionization. This is followed by further interaction of the sulfur by means of the participation process in a product determining step. The ability of the hetero atoms to aid in the removal of the leaving group and to stabilize the cation correlates well with their electron donor properties.

EXPERIMENTAL

All melting points were taken on a calibrated thermometer and are corrected. Boiling points are uncorrected. Microanalyses were done by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Infrared spectra were determined with a Perkin-Elmer Infrared Recording Spectrophotometer, Model 21, for most of the identification work and all of the analytical work. The remainder of the spectra were determined with a Perkin-Elmer "Infracord".

A. Synthesis of 3-Mesyloxynortropane Perchlorates

Tropinone:-To 100 ml of absolute ethanol in a liter three necked flask, equipped with a reflux condenser, separatory funnel, and stirrer, was added 6.27 gms (0.273 moles) of sodium in small pieces. The sodium was added at such a rate as to keep a gentle reflux. When this reaction was complete, 54.6 gms (0.248 moles) of tropinone hydrobromide (Winthrop Laboratories) in 500 ml of absolute ethanol was added slowly, with stirring, by means of the separatory funnel. The mixture was allowed to stir for twenty-four hours. Then the solution was filtered, and the solvent was removed by distillation through a 12 inch Vigreux column. The yield of tropinone was 25.9 gms (0.186 moles) or 75.0%, M.P. 38-40°C.

In a modified procedure, the sodium was allowed to react with 200 ml of anhydrous ethanol, the tropinone hydrobromide was dissolved in 400 ml of 95% ethanol, and ether was used to precipitate the inorganic salts after concentration to one-half volume. This procedure resulted in a yield of 34.6 gms. (0.248 moles) or 100% of tropinone, M.P. 39-40°C. The average yield was 100%.

Cyanogen Bromide[47]:-A solution of 234.0 gms (1.46 moles) of bromine in 175 ml of water was placed in a liter three necked flask, fitted with a stirrer, a separatory funnel, and an outlet tube leading to a weighed liter suction flask containing 46.0 gms of calcium chloride. To this a solution of 79.0 gms (1.61 moles) of sodium cyanide (Mallinckrodt) in 350 ml of warm water was added by means of the separatory funnel at such a rate as to keep the temperature below 30°C. Addition was continued until the bromine color just disappeared from the reaction mixture. The solution was stirred for three hours at room temperature. Then the cyanogen bromide was distilled into the suction filter flask. The flask was weighed, and the product was dissolved in benzene for the next reaction. The yield was 156.0 gms (1.46 moles) or 100% of cyanogen bromide, B.P. 61°C/760 mm, M.P. 52°C. The average yield was 95%.

N-Cyanonortropinone[23]:-A solution of 50.0 gms (0.359 moles) of tropinone (M.P. 40-42°C) in 300 ml of benzene was placed in a liter three necked flask fitted with a stirrer, reflux condenser, and a separatory funnel. After heating this solution to 50-55°, 65.8 gms (0.621 moles) of cyanogen bromide was added with stirring. After addition was complete, the mixture was kept at 50-55°C for one and one-half hours, with stirring, and then was allowed to react overnight at room temperature. The resulting mixture was filtered, washing the residue three times with benzene. The solvent was distilled off from the combined filtrate and washes. The residue was taken up in 500 ml of anhydrous ether and concentrated to

47. Org. Syntheses, Coll. Vol. II, 150 (1943).

precipitate the product. The yield was 54.0 gms (0.359 moles) or 100% of N-cyanonortropinone, M.P. 113-114°C. The average yield was 95%.

3α and 3β-Hydroxy-N-Cyanonortropane[23]:-To 23.3 gms (0.1550 moles) of N-cyanonortropinone (M.P. 113-114°C) in 775 ml of water, 1.96 gms (0.0517 moles) of sodium borohydride (Metal Hydrides Inc.) was slowly added. The resulting solution was allowed to stand for twenty-four hours at room temperature. The solution was shaken with six 200 ml portions of chloroform. The combined extracts were dried over magnesium sulfate, and then the solvent was removed. The residue, 22.4 gms, was taken up in benzene and chromatographed on 90.6 gms of alumina.

Chromatographic Data

Eluent	Fractions	Weight Residue	M.P.	% Yield
Benzene	3	--	--	--
50% Chloroform-benzene	10	5.00 gms	113-114°C	21.2%
100% Chloroform	1	2.10 gms	110-112°C	8.9%
	5	2.80 gms	98-100°C	11.9%
100% Ethanol	8	12.30 gms	100-101°C	52.2%

The total yield of N-cyano-3α-hydroxynortropane was 7.10 gms or 30.1% (M.P. 113-114°C), while that of N-cyano-3β-hydroxynortropane was 15.10 gms or 64.1% (M.P. 100-101°C).

The range of yields were 30-50% for the 3α isomer and 43-64% for the 3β isomer.

3α and 3β-Hydroxy-N-Cyanonortropane:-To 2.40 gms (0.0632 moles) of lithium aluminum hydride powder (Metal Hydrides Inc.) and 75 ml of sodium dried ether in a 250 ml two necked flask with stirrer and reflux condenser topped by a separatory funnel and drying tube was added 4.76 gms (0.0316 moles) of N-cyanonortropinone (M.P. 113-114°C) in 125 ml of dried ether so as to keep a gentle reflux. The mixture was stirred during addition and for one and one-half hours longer while refluxing. After the reaction time was over, 5 ml of water and 4 ml of 10% sodium hydroxide solution were added to decompose the lithium-aluminum salts, and the mixture was stirred two hours longer. The ether was decanted, and the precipitate washed with benzene. The combined supernatent liquid and wash were distilled to dryness, leaving a yellow gummy residue. This was taken up in benzene and chromatographed on Florosil. A solid melting at 99-104°C and probably starting material as well as two unidentifiable oils were obtained.

3α and 3β-Hydroxynortropane[23]:-A solution was made of 16.1 gms (0.106 moles) of N-cyano-3α-hydroxynortropane (M.P. 113-114°C) and 16.1 gms (0.402 moles) of sodium hydroxide (Baker) in 160 ml of water. This solution was placed in a 300 ml round bottom flask fitted with a reflux condenser bearing an outlet to a manometer. The system was evacuated and then put under nitrogen. Then the solution was refluxed for seven and one-half hours. After the solution cooled, 24.2 gms (0.606 moles) of sodium hydroxide (Baker) was added, and the resulting mixture was shaken six times with 150 ml portions of chloroform. The combined extracts were dried over magnesium sulfate, and the solvent was stripped

off. The yield was 13.0 gms (0.102 moles) or 96.27% of 3α-hydroxynortropane, M.P. 160-162°C. Average yield was 94.5%.

When the same reaction was done with 13.1 gms (0.0860 moles) of N-cyano-3β-hydroxynortropane with a total of 36.5 gms (0.0100 moles) of sodium hydroxide (Baker) in 145 ml of water, 10.38 gms (0.0816 moles) or 95.09% of 3β-hydroxynortropane was obtained, M.P. 137-138°C. The average yield was 95.1%.

3β-Tosyloxynortropane:-A solution of 0.50 gms (0.00393 moles) 3β-hydroxynortropane (M.P. 137.5-138.5°C) and 0.80 ml of 4.987 N HCl in dioxane was made up in 100 ml of dioxane (Eastman Organic Chemical Co.) (B.P. 100-101°C/755 mm). To this was added 1.14 gms (0.00595 moles) of tosyl chloride (M.P. 69.5-70.5°C). The system was placed under nitrogen and refluxed for five hours. After cooling, filtering, and washing the precipitate with dry ether, 0.469 gms or a 94% yield of 3β-hydroxynortropane hydrochloride was obtained (M.P. 308-312°C) indicating essentially no reaction with the acid chloride. About 97% of the tosyl chloride was obtained on distillation of the filtrate and washes.

3β-Mesyloxynortropane:-

Trial 1: When an attempt was made to mesylate 3β-hydroxynortropane under the same conditions as the tosylation was made, only 0.812 gms (0.00496 moles) or 69.7% of 3β-hydroxynortropane hydrochloride was obtained (M.P. 310-315°C), and no other products. Again no apparent reaction occurred.

Trial 2: Into 30.0 ml of methanesulfonyl chloride in a 100 ml round bottom flask was placed 2.50 gms (0.0154 moles) of 3β-hydroxynortropane hydrochloride (M.P. 308-312°C). The flask was fitted with a reflux condenser topped by an outlet tube leading to a manometer and an acid trap. The solution was refluxed for only twenty minutes under nitrogen. During this time 0.0489 equivalents of acid, or 3.18 times the theoretical amount, were collected in the acid trap. Evidently, decomposition of the acid chloride had occurred. This hypothesis was further supported by the isolation of sulfur as a precipitate from the reaction mixture.

Decomposition of Methanesulfonyl Chloride:-

Trial 1: In a 100 ml three necked flask was placed 20 ml of methanesulfonyl chloride. The system was put under nitrogen, and the liquid was refluxed thirty minutes. At the end of this time only 0.0040 equivalents of acid were caught in the acid trap.

Trial 2: The experiment was conducted in the same manner as trial one, with the exception that 0.05 gms (0.0031 moles) of 3β-hydrorynortropane hydrochloride was added. Little or no acid was collected until the solution began to reflux. Then, in thirty minutes 0.0151 equivalents of acid were collected in the acid trap. This is about four times the acid obtained without addition of the salt.

Benzyl Chloroformate[27]:-Into a 200 ml round bottom flask fitted with inlet and outlet tubes was placed 60 ml of toluene. The flask, tubes, and liquid were weighed. Then the flask was placed in an

ice bath and connected into a gas train between a phosgene tank and the remainder of the train, which included a toluene filled phosgene trap, a calcium chloride drying tube, and a scrubber. Phosgene (Matheson) was passed into the system for seven minutes, and the flask was reweighed. The difference between the initial and the final weights was 12.10 gms corresponding to 0.1223 moles of phosgene. To this solution 11.68 gms (0.108 moles) of redistilled benzyl alcohol (Eastman Organic Chemical Co.) was added by means of a dropping funnel attached to the inlet tube. During addition the solution was swirled slightly and cooled. The reaction mixture was kept in the ice bath for thirty minutes to an hour and then left overnight at room temperature. The resulting solution was concentrated to one half volume at less than 60°C at reduced pressure. Yield was assumed to be 90% as in the reported procedure. This means that 16.55 gms (0.0971 moles) of benzylchloroformate was obtained.

3α and 3β-Hydroxy-N-Carbobenzoxynortropanes[27]:-A solution of 1.00 gm (0.00785 moles) of 3β-hydroxynortropane (M.P. 137.5-138.5°C) and 0.323 gms (0.00785 moles) of sodium hydroxide in 4 ml of water was made up. To this 0.323 gms (0.00785 moles) of sodium hydroxide in 2 ml of water and 1.340 gms (0.0157 moles) benzyl chloroformate in 8.75 ml of toluene were added simultaneously with swirling over a ten minute period. Then the mixture was swirled for an additional fifty minutes. The toluene layer was separated off, and the aqueous layer was shaken with six 10 ml portions of ether. The combined toluene layer and ether extracts were dried with magnesium sulfate. On stripping off of the solvent 1.96 gms (0.00745 moles) or a 95.1% yield of

3β-hydroxy-N-carbobenzoxynortropane was obtained, M.P. 80-81°C.

Anal. Calc'd for $C_{15}H_{19}NO_3$: C, 68.97; H, 7.32; N, 5.36

Found: C, 68.62; H, 7.19; N, 5.32

The same reaction was conducted using 8.1 gms (0.0637 moles) of 3α-hydroxynortropane (M.P. 160-162°C) instead of the 3β-isomer. To it was added 2.55 gms (0.0637 moles) of sodium hydroxide in 15 ml of water and 11.95 gms (0.0701 moles) of benzylchloroformate in 23 ml of toluene. The yield after isolation was 15.33 gms (0.0625 moles) or 98.0% of 3α-hydroxy-N-carbobenzoxynortropane, M.P. 125-126°C.

Anal. Calc'd for $C_{15}H_{19}NO_3$: C, 68.97; H, 7.32; N, 5.36

Found: C, 68.62; H, 7.39; N, 5.32

3α and 3β-Mesyloxy-N-carbobenzoxynortropane:-

Modification 1[22]: To 1.30 gms (0.00530 moles) of 3α-hydroxy-N-carbobenzoxynortropane (M.P. 125.0-126.0°C) and 10 ml of reagent grade pyridine (Merck) in a 50 ml erlenmeyer flask was added 0.61 gms (0.00533 moles) of methanesulfonyl chloride (Eastman Organic Chemical Co.) in 5 ml of pyridine. The mixture was allowed to stand for seven days. Then the mixture was filtered into ice water. When the ice had melted, the mixture was basified with sodium carbonate and shaken with five 50 ml portions of ether. The extracts were dried over magnesium sulfate. The desiccant was filtered off, and the solvent was removed, leaving a resinous residue, which crystallized on treatment with ether. This resulted in a 0.99 gms (0.00306 moles) or a 57.8% yield of 3α-mesyloxy-N-carbobenzoxynortropane, M.P. 105.7-106.7°C.

Anal. Calc'd for $C_{16}H_{21}NSO_5$: C, 56.61; H, 6.24; N, 4.13; S, 9.45

Found: C, 56.64; H, 6.21; N, 4.20; S, 9.66

When the experiment was repeated using 16.93 gms (0.0690 moles) of 3β-hydroxy-N-carbobenzoxynortropane (80-81°C) and 15.82 gms (0.1380 moles) of methanesulfonyl chloride (Eastman Organic Chemical Co.) in 100 ml of reagent grade pyridine (Merck) instead of the 3α isomer, a 14.18 gms (0.0439 moles) or 63.6% yield of 3β-mesyloxy-N-carbobenzoxynortropane was obtained, M.P. 110.5-112.0°C.

Anal. Calc'd for $C_{16}H_{21}NSO_5$: C, 56.61; H, 6.24; N, 4.13; S, 9.45

Found: C, 56.59; H, 6.10; N, 4.08; S, 9.39

Modification 2: A solution of 0.750 gms (0.00306 moles) of 3α-hydroxy-N-carbobenzoxynortropane (M.P. 125-126°C) and 0.386 gms (0.00337 moles) of methanesulfonyl chloride (Eastman Organic Chemical Co.) in 3 ml of reagent grade pyridine (Merck) was cooled to 0°C and allowed to react for seven days at this temperature. The reaction mixture was poured into a mixture of ice and dilute hydrochloric acid. The resulting solution was shaken with six 50 ml portions of ether, cooling during extraction. The combined extracts were washed with cold 2% sulfuric acid solution and dried over magnesium sulfate. The mixture was filtered, and the solvent was removed yielding 0.57 gms (0.00177 moles) or 57.6% of 3α-mesyloxy-N-carbobenzoxynortropane, M.P. 100-104°C.

Modification 3: Into 3 ml of reagent chloroform 0.750 gms (0.00306 moles) of 3α-hydroxy-N-carbobenzoxynortropane (M.P. 125-126°C), 0.386 gms (0.00337 moles) of methanesulfonyl chloride (Eastman Organic Chemical Co.), and 0.267 gms (0.00337 moles) of reagent grade pyridine (Merck) were dissolved and cooled to 0°C. They were allowed to react for seven

days at 0°C and then worked up as in modification 2. A yield of 0.66 gms (0.00204 moles) or 66.7% of 3α-mesyloxy-N-carbobenzoxynortropane was obtained, M.P. 104-105°C.

Modification 4: A solution of 21.42 gms (0.0873 moles) of 3α-hydroxy-N-carbobenzoxynortropane (M.P. 125-126°C), 11.00 gms (0.0960 moles) of methanesulfonyl chloride (Eastman Organic Chemical Co.), and 7.60 gms (0.0960 moles) of reagent grade pyridine (Merck) in 85.0 ml of reagent chloroform was made up. This was allowed to react seven days at room temperature. Then it was poured into 25 ml of 5N hydrochloric acid and 10 gms of ice. The resulting mixture was shaken six times with 100 ml portions of chloroform using ice in each extraction. The extracts were washed with cold 2% sulfuric acid solution and dried over magnesium sulfate. Desiccant and solvent removal yielded 28.0 gms (0.0865 moles) or 99.2% of 3α-mesyloxy-N-carbobenzoxynortropane, M.P. 102-104°C.

3α-Tosyloxy-N-carbobenzoxynortropane[22]:-The reagents, 1.35 gms (0.00551 moles) of 3α-hydroxy-N-carbobenzoxynortropane (M.P. 125-126°C), 1.05 gms (0.00551 moles) of p-toluenesulfonyl chloride (M.P. 69.5-70.5°C), and 15 ml of reagent pyridine (Merck), were mixed in a 50 ml erlenmeyer flask and allowed to stand for seven days at room temperature. This was poured into ice water which was basified with sodium carbonate after the ice melted. The basic solution was shaken with five 50 ml portions of ether. The extracts were dried over magnesium sulfate, and the desiccant and solvent were removed. This resulted in 0.84 gms (0.0021 moles) or 38.2% of 3α-tosyloxy-N-carbobenzoxynortropane, M.P. 115-116°C.

3α and 3β-Mesyloxynortropane Perchlorate:-A mixture was made up consisting of 7.50 gms (0.0232 moles) of 3β-mesyloxy-N-carbobenzoxynortropane (M.P. 110.5-112.0°C), 0.751 gms of 10% palladium on carbon, 3.59 ml (0.0293 moles) of 70% perchloric acid (G.F. Smith Chemical Co.), and 100 ml of glacial acetic acid (du Pont). This was placed in a Paar bomb and shaker. The system was evacuated, and hydrogen admitted into it. The reaction mixture was shaken with the hydrogen for two and one-half hours. Then the shaking was stopped, and the catalyst was filtered off. The catalyst was extracted overnight with ethanol in a soxhlet extractor to remove any product that had precipitated during hydrogenation. The extract was combined with the filtrate, and the solvents were stripped off under vacuum. The residue was 6.08 gms (0.0199 moles) or an 86.0% yield of 3β-mesyloxynortropane perchlorate, M.P. 169.6-170°C.

Anal. Calc'd for $C_8H_{16}NSClO_7$: C, 31.43; H, 5.28; N, 4.58; S, 10.49; Cl, 11.60

Found: C, 31.62; H, 5.30; N, 4.49; S, 10.56; Cl, 11.66

When 7.90 gms (0.0242 moles) of 3α-mesyloxy-N-carbobenzoxynortropane, 0.79 gms of 10% palladium on carbon, and 2.18 ml (0.0254 moles) of 70% perchloric acid (G.F. Smith Chemical Co.) in 200 ml of glacial acetic acid (du Pont) were substituted for the reagents in the previous experiment, a yield of 6.90 gms (0.0225 moles) or 93.0% was obtained of 3α-mesyloxynortropane perchlorate, M.P. 168.0-168.8°C.

Anal. Calc'd. for $C_8H_{16}NSClO_7$: C, 31.43; H, 5.28; N, 4.58; S, 10.49; Cl, 11.60

Found: C, 31.39; H, 5.13; N, 4.40; S, 10.63; Cl, 11.51

3α and 3β-Mesyloxynortropane:-

Trial 1: The perchlorate salt from a hydrogenolysis was treated with a mixture of ether and a saturation solution of sodium hydroxide. The resulting mixture was shaken five times with ether. After drying of the extracts and removal of the desiccant and solvent, only a gummy residue, which was only partially soluble in ether, remained.

Trial 2: Into 30 ml of dioxane (B.P. 100-101°C) (Eastman Organic Chemical Co.) in a 200 ml round bottom flask was placed 0.200 gms (0.000654 moles) of 3α-mesyloxynortropane perchlorate (M.P. 165-167°C) and 0.079 gms (0.00328 moles) of sodium hydride. These were stirred overnight. Then the reaction mixture was filtered, washing the residue with ether. The combined filtrate and residue were dried, and the solvent was removed. Only a small amount, 0.0050 gms, of a gummy residue remained.

Trial 3: Into 1000 ml of ether in a three necked flask with a separatory funnel and a reflux condenser was placed 15.80 gms (0.404 moles) of potassium metal (Mallinckrodt) in small pieces. T-butyl alcohol (Eastman Organic Chemical Co.) was added through the separatory funnel at such a rate as to keep a gentle reflux. When the potassium had disappeared, the ether was stripped off. The solution was titrated with standard 0.100 N hydrochloric acid (Acculate) to determined the concentration of the base. This was found to be 0.839 N.

To 0.809 gms (0.00265 moles) of 3α-mesyloxynortropane perchlorate (M.P. 163-165°C) in 50 ml of t-butyl alcohol (Eastman Organic Chemical Co.) was added 3.15 ml (0.00265 moles) of the potassium t-butoxide

solution prepared above. The resulting solution was stirred for six hours, and then the precipitate was filtered off. Distillation of the solvent from the filtrate yielded only a small amount of oil. Extraction of the residue from filtration with ethanol yielded 0.1350 gms of a solid melting at 171-172°C. This could be starting material or its C_3 epimer.

Trial 4: Into 400 ml of anhydrous ether in a liter three necked flask fitted with a reflux condenser and a separatory funnel, both equipped with drying tubes, was added 6.70 gms (0.177 moles) of potassium metal (Mallinckrodt). To this system 200 ml of absolute ethanol was added at such a rate as to keep a gentle reflux. After the potassium had disappeared, the ether was stripped off, and the resulting solution was titrated with standard 0.100 N hydrochloric acid (Acculate). The base was 0.916 N.

To 2.24 gms (0.00733 moles) of 3β-mesyloxynortropane perchlorate (M.P. 169-171°C) 50 ml of absolute ethanol 8.0 ml (0.00734 moles) of 0.917 N potassium ethoxide solution was added. The mixture was allowed to stand one hour, and then it was filtered. The filtrate was concentrated, and anhydrous ether was added in order to precipitate the amino mesylate. Filtration yielded, as a residue, 1.00 gm (0.00497 moles) or 66.50% of 3β-mesyloxynortropane, M.P. 135-138°C. Recrystallization from chloroform-petroleum ether (30-60°C) gave a solid melting at 145.5-146.5°C which did not leave an ash on combustion.

When 0.440 gms (0.00144 moles) of 3α-mesyloxynortropane perchlorate (M.P. 168-169.5°C) was treated with 1.49 ml (0.00144 moles) of 0.964 N potassium ethoxide in 10 ml of absolute ethanol, and then with chloroform,

a precipitate containing only inorganic matter was formed. The filtrate was taken to dryness under vacuum. The residue was taken up in chloroform and treated with petroleum-ether (30-60°C) to precipitate the product. The yield was 0.21 gms (0.00103 moles) or 71.2% of 3α-mesyloxynortropane, M.P. 106-108°C. No inorganic matter was present, since all of it burned on combustion, and all of it sublimed. Sublimation raised the melting point to 107.4-108.6°C.

B. 3α-Hydroxy-N-Cyanonortropane[23]

A solution of 20 gms (0.1418 moles) of 3α-hydroxytropane (Aldrich Chemical Co.) in 155 ml of benzene was slowly added to 24.45 gms (0.2308 moles) of cyanogen bromide in 125 ml of benzene at 50-55°C. The reaction was conducted in a liter three necked flask equipped with a stirrer, a separatory funnel, and a reflux condenser. The solution was stirred one and one-half hours at 45-55°C, and then it was stirred overnight at room temperature. The mixture was filtered, washing with benzene. Then the solvent was stripped off from the combined filtrate and washes. The residue was taken up in 500 ml of ether. Concentration of the ether solution precipitated the product. The yield was only 4.74 gms. (0.0284 moles) or 20% of the desired N-cyano-3α-hydroxynortropane. Most of the reaction product was insoluble in ether but was soluble in ethanol. This may have been 3α-hydroxytropane, the quaternary N-cyano intermediate salt, or some other species or mixture.

C. Alternate Route from the Reduction of N-Cyanonortropinone Through the Formation of the N-Carbobenzoxy Derivative

Trial 1:-Under the same conditions as were outlined previously 33.3 gms (0.222 moles) of N-cyanonortropinone (M.P. 112-114°C) was reduced by sodium borohydride (Metal Hydrides Inc.) (94.8% yield), hydrolyzed by aqueous sodium hydroxide (84.5% yield), and acylated by benzylchloroformate (84.5% yield). The N-carbobenzoxy mixture was chromatographed on alumina, yielding 14.0 gms (0.0571 moles) or 24.2% of 3α-hydroxy-N-carbobenzoxynortropane, M.P. 123-125°C, 24.1 gms (0.0951 moles) or 39.8% of 3β-hydroxy-N-carbobenzoxynortropane, M.P 80-81°C from N-cyanonortropinone.

Trial 2:-In the same manner as trial 1, 18.00 gms (0.1200 moles) of N-cyanonortropinone (M.P. 111-113°C) was taken through the same three synthetic steps (yields were 95.8%, 85.5%, and 98.1% respectively). Chromatography yielded 7.58 gms (0.0291 moles) or 24.2% of 3α-hydroxy-N-carbobenzoxynortropane, M.P. 122-124°C, and 16.04 gms (0.0616 moles) or 51.4% of 3β-hydroxy-N-carbobenzoxynortropane, M.P. 80-81°C.

Trials 3-5:-As before 35.0 gms (0.233 moles) of N-cyanonortropinone was put through the reduction, hydrolysis, and acylation. (Yields were 97.0%, 90.0%, and 37.3%, respectively.) On chromatographing the residue from the acylation, no solid products were obtained. Later some product did crystallize or was recovered by hydrolysis to the nortropines. This resulted in 24.8 gms (0.095 moles) or 13.6% yield of 3α-hydroxy-N-carbobenzoxynortropane, 10.6 gms (0.047 moles) or 6.79% yield of 3β-hydroxy-N-carbobenzoxynortropane, and 30.9 gms (0.1185 moles) or 17.0% yield of a mixture of the two, that is mainly the 3β isomer for all three trials.

D. Synthesis of the 3-Tosyloxy-8-Thia Bicyclo [3.2.1] Octanes

Tropinone Methiodide[48]:-To 7.85 gms (0.0563 moles) of tropinone (M.P. 40-42°C) in 25 ml of absolute ethanol was added 11.39 gms (0.0802 moles) of methyl iodide (Eastman Organic Chemical Co.) slowly with stirring. The solution was allowed to stand overnight in the cold. After twenty-four hours the reaction mixture was filtered. The yield was 15.82 gms (0.0563 moles) or 100% of tropinone methiodide, M.P. 276-276.5°C.

8-Thiabicyclo [3.2.1] Octan-3-one[28]:-A solution was made of 50.5 gms (0.1795 moles) of tropinone methiodide (M.P. 276-276.5°C) in 510 ml of a 10% solution of sodium sulfide in water. The solution was allowed to stand for two hours at room temperature, and then it was filtered. The filtrate was distilled to remove water and product from the other contaminants, and the distillate was shaken three times with 200 ml portions of ether. Evaporation of the solvent from the ether solution yielded about as much product as was obtained as a residue in the initial filtration. The total yield was 24.85 gms (0.1740 moles) or 97.0% of the thia ketone, M.P. 159.8-161.0°C.

Anal. Calc'd. for $C_7H_{10}SO$: C, 59.13; H, 7.09; S, 22.59

Found: C, 59.24; H, 7.09; S, 22.39

3α and 3β-Hydroxy-8-Thiabicyclo [3.2.1] Octane[23]:-To 3.0 gms (0.021 moles) of thiaketone (M.P. 158.5-160.0°C) in 75 ml of water was added 3.8 gms (0.100 moles) of sodium borohydride (Metal Hydrides Inc.).

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After standing twenty-four hours at room temperature, the reaction mixture was shaken with chloroform. Solvent removal yielded 2.6 gms of alcohol which was taken up in benzene and chromatographed on Florosil.

Chromatographic Data

(Eluent 25% $CHCl_3$-C_6H_6)

Fraction	Weight	% Yield	M.P.
1	0.63 gms	20.8%	238-239°C
2	1.40 gms	46.3%	157-159°C
3	0.23 gms	7.6%	158-159°C
4-6	0.14 gms	4.6%	157-159°C

This resulted in a yield of 0.63 gms (0.00436 moles) or 20.8% of 3α-hydroxy-8-thiabicyclo [3.2.1] octane, M.P. 238-239°C, and 1.77 gms (0.0123 moles) or 58.5% of the 3β isomer, M.P. 158-159°C.

Anal. Calc'd. for $C_7H_{12}SO$: C, 58.30; H, 8.39; S, 22.23.

Found for 3α: C, 58.50; H, 8.33; S, 22.17.

Found for 3β: C, 58.35; H, 8.38; S, 22.27.

Equilibration of the Thia Alcohols:-

Calibration of the Infrared Machine: Standard solutions containing 0.209 gms of the respective thia alcohols in 10 ml of reagent chloroform (Merck) were made up. Chloroform compensated spectra were taken of these two solutions and mixtures of them in a 1:3, 1:1, and 3:1 ratio in a 0.1 mm cell.

Spectroscopic Data

Mole Fraction β	% Transmission						
	1455 cm^{-1}	1345 cm^{-1}	1080 cm^{-1}	1048 cm^{-1}	1034 cm^{-1}	910 cm^{-1}	840 cm^{-1}
100%	88.5	99.0	93.0	44.0	81.5	99.0	96.6
75%	91.3	98.5	88.5	38.0	61.0	97.8	97.0
50%	93.5	97.0	89.0	60.5	60.5	96.5	98.4
25%	94.0	95.0	87.0	74.0	57.5	95.0	98.5
0%	95.5	93.5	83.0	89.0	55.5	92.7	98.5

Since the thia ketone also absorbs strongly at 1345 cm^{-1}, 1048 cm^{-1}, and 1034 cm^{-1} with a weak absorption at 1455 cm^{-1}, absorptions at these frequencies could not be used if the ketone were shown to be present by its carbonyl absorption at 1715 cm^{-1}.

Equilibration of the Alcohols:-To 8 ml of reagent n-amyl alcohol (Mallinckrodt), 0.56 gms (0.0244 moles) of sodium metal (Mallinckrodt) was added. After the sodium had disappeared, 0.280 gms (0.0194 moles) of 3α-hydroxy-8-thiabicyclo [3.2.1] octane in 7 ml of reagent n-amyl alcohol was added. The solution was refluxed for twenty-four hours. Then 2.5 ml of 5N hydrochloric acid and 10 ml of water were added. After saturation of the resulting mixture with sodium chloride, it was separated, and the aqueous layer was shaken with five 20 ml portions of chloroform. The combined extracts and the alcohol layer were dried over sodium sulfate, and the solvent was removed. The residue was dried in a vacuum desiccator overnight. Then 0.209 gms were dissolved in 10 ml of reagent chloroform (Merck). The infrared spectrum was taken of this solution in a 0.1 mm

cell with chloroform compensation. Some ketone was observed in this mixture by its absorption at 1710 cm^{-1} and therefore only the absorptions at 910 cm^{-1} and 840 cm^{-1} were of value for analysis of this mixture.

The 3β alcohol was equilibrated under the same conditions using 4.00 gms (0.174 moles) of sodium metal, 40 ml of reagent n-amyl alcohol (Mallinckrodt), and 2.00 gms (0.00668 moles) of 3β alcohol for the equilibration and 0.209 gms of reaction product in 10 ml of reagent chloroform (Merck) for the spectral analysis. No ketone was observed in this reaction product.

Data from Equilibration Experiments

Frequency	From 3α Alcohol		From 3β Alcohol	
	% Transmission	Mole Fraction	% Transmission	Mole Fraction
840 cm^{-1}	97.5	29.0%	97.5	29.0%
910 cm^{-1}	97.8	26.0%	97.9	25.0%
1345 cm^{-1}	----	----	98.3	30.0%
1455 cm^{-1}	----	----	91.0	26.0%

The average percentage of the 3α isomer present in the mixture was 27.±3%. The average percentage of the 3β isomer, then, was 73.±3%.

3α and 3β-Tosyloxy-8-Thiabicyclo [3.2.1] Octane:-To 0.46 gms (0.00319 moles) of 3α-hydroxy-8-thiabicyclo [3.2.1] octane (M.P. 238-239°C) in 4.0 ml of reagent chloroform (Merck) was added 0.67 gms (0.00351 moles) of tosyl chloride (M.P. 69.5-70.5°C) and 0.28 ml of reagent pyridine (Merck). The reagents were allowed to stand seven days at room temperature. Then the reaction mixture was poured into 2.5 ml of 5N hydrochloric

acid and 1 gm ice. It was shaken with six 50 ml portions chloroform. The extracts were washed with 20 ml 2% sulfuric acid. All of the extractions and washings were done in the presence of ice. The extracts were dried over magnesium sulfate, and the solvent was removed. The residue was 0.68 gms (0.00227 moles) or a 71.3% yield of the 3α tosylate, M.P. 105-106°C.

Anal. Calc'd. for $C_{14}H_{19}S_2O_3$: C, 56.35; H, 6.08; S, 21.49.

Found: C, 56.24; H, 5.98; S, 21.38.

When 1.77 gms (0.01225 moles) of 3β-hydroxy-8-thiabicyclo [3.2.1] octane (M.P. 158-159°C), 2.57 gms (0.0135 moles) of tosyl chloride (M.P. 69.5-70.5°C), and 1.09 ml of reagent pyridine (Merck) in 10 ml of reagent chloroform (Merck) were substituted for the above reagents and the reaction carried out as before, 3.03 gms (0.01013 moles) or an 82.6% yield of the 3β tosylate was obtained, M.P. 112-114°C.

Anal. Calc'd. for $C_{14}H_{19}S_2O_3$: C, 56.35; H, 6.08; S, 21.49.

Found: C, 56.42; H, 6.05; S, 21.61.

3α and 3β-Mesyloxy-8-Thiabicyclo [3.2.1] Octanes:-A solution of 0.50 gms (0.00347 moles) of 3α-hydroxy-8-thiabicyclo [3.2.1] octane (M.P. 238-239°C), 0.44 gms (0.00382 moles) of mesyl chloride (Eastman Organic Chemical Co.), and 0.30 gms (0.00382 moles) reagent pyridine (Merck) was made up in 2 ml of reagent chloroform (Merck). The solution was allowed to stand for ten days at room temperature, and then it was poured into 1 ml of 5N hydrochloric acid and 0.3 gms of ice. The resulting mixture was shaken with six 15 ml portions chloroform. The combined

extracts were washed with 5 ml cold 2% sulfuric acid. The extracts were dried over magnesium sulfate, and then the solvent was removed. The residue was a colorless liquid.

When the 3β isomer was used under the same conditions a liquid residue was also obtained.

E. Preparation of the Reference Compounds

4-t-Butylcyclohexyl tosylate (Trans Isomer):[32]-To 1.85 gms (0.0118 moles) of trans-4-t-butylcyclohexanol (M.P. 80.8-81.4°C) in 12 ml of reagent pyridine (Merck) was added 2.26 gms (0.0119 moles) of tosyl chloride (M.P. 69.5-70.5°). The resulting solution was allowed to stand overnight at room temperature. The reaction mixture was poured into 35 ml of cold 5N hydrochloric acid and ice. The aqueous suspension was shaken with two 50 ml portions of carbon tetrachloride. The combined extracts were washed with cold 10% hydrochloric acid until neutral and then dried over potassium carbonate. After desiccant and solvent removal, 2.63 gms (0.0845 moles) or a 71.5% yield of ester was obtained, M.P. 78-83°C. Recrystallization from petroleum-ether (30-60°) with a trace of ethyl acetate yielded 1.75 gms (0.0563 moles) of ester, M.P. 89.4-90.2°C.

Cyclohexyl Tosylate:[33]-A solution of 20.0 gms (0.200 moles) of cyclohexanol (Eastman Oganic Chemical Co.) and 38.2 gms (0.200 moles) of tosyl chloride (M.P. 69.5-70.5°C) in 200 ml of reagent pyridine (Merck) was made up at 0°C and allowed to stand overnight at 0-5°C. Then the reaction mixture was poured into 400 ml of 5N hydrochloric acid and ice. The aqueous suspension was shaken twice with 500 ml portions of carbon tetrachloride. The combined extracts were washed with cold 10% hydrochloric acid until neutral and then dried over potassium carbonate. The

solvent was evaporated off from the extracts leaving 42.4 gms (0.166 moles) or an 83.1% yield of ester, M.P. 47-48°C. Recrystallization from ethyl acetate-petroleum-ether (30-60°) reduced the melting point to 44.2-45.2°C.

Cyclohexyl Mesylate:[33]-A solution was made up of 10.0 gms (0.100 moles) of cyclohexanol (Eastman Organic Chemical Co.) and 11.46 gms (0.100 moles) mesyl chloride (Eastman Organic Chemical Co.) in 100 ml of reagent pyridine (Merck) at 0°C. It was left overnight at 0-5°C. It was then poured into 200 ml of 5N hydrochloric acid and ice. The resulting mixture was shaken with three 100 ml portions carbon tetrachloride. After the combined extracts were washed with cold 10% hydrochloric acid until neutral, they were dried over potassium carbonate. Then the solvent was removed. The residue was 19.88 gms (0.0894 moles) or an 89.4% yield of ester, B.P. 79.0-80.0°C/0.1 mm.

F. Reactions of 3-Mesyloxynortropane Perchlorate with Lithium Aluminum Hydride

3β-Mesyloxynortropane in Ether:-The finely ground ester, 5.83 gms (0.01907 moles)(M.P. 169-170°C), was suspended in 300 ml of anhydrous ether (Mallinckrodt), and 45.92 ml of saturated lithium aluminum hydride solution in ether and 50 ml of ether were added. The mixture was refluxed eleven hours, and then 2.90 ml of water and 2.32 ml of 10% sodium hydroxide solution were added. The mixture was filtered. The residue yielded 1.82 gms (0.0164 moles) or 86.0% of nortropane, M.P. about 60°C. From the filtrate 0.22 gms (0.00194 moles) or a 10.2% yield of 2-allylpyrrolidine was obtained, M.P. about -17°C.

Derivatives

1. Nortropane

   a. Hydrochloride, M.P. 283-285°C (dec.)(Lit. 285°C[34,35])

   b. N-nitroso, M.P. 132-134°C (Lit. 135°C[36])

   c. N-benzene sulfonamide, M.P. 111.5-112.5°C

2. 2-allylpyrrolidine

   a. Sulfuric acid salt, M.P. 174-175°C

   b. Hydrochloride, M.P. 175-176°C

2-Propylpyrrolidine Perchlorate:-In 12 ml of glacial acetic acid (du Pont) 0.2357 gms (0.00212 moles) of 2-allylpyrrolidine was reduced with 60.59 ml of hydrogen gas over 0.0130 gms of 10% palladium on carbon (Baker Chemical Co.). In addition 0.262 ml of 70% perchloric acid (G. F. Smith Chemical Co.) was used as a catalyst in the reduction and to form a salt of the product. After ten hours the reaction was stopped, the mixture was filtered, and the solvent was removed from the filtrate. The residue was taken up in ethanol and on concentration and addition of ether, gave a white solid, 2-propylpyrrolidine perchlorate, melting at 295.0-295.2°C, 1640 cm^{-1}, (sh) 1370 cm^{-1}, 1100 cm^{-1}, 975 cm^{-1}, 760 cm^{-1}, 670 cm^{-1}, and 610 cm.

2-n-Propylpyrrolidine:[37]-Into a dry 3000 ml three necked flask with a stirrer, reflux condenser, and a separatory funnel were placed 100 gms (4.12 moles) magnesium (Fischer Scientific Co.) and 1600 ml of anhydrous ether (Mallinckrodt). To this was added 400 gms (3.25 moles) n-propyl bromide (Eastman Organic Chemical Co.) so as to keep a gentle

reflux. The mixture was refluxed until little magnesium remained. Then 1400 ml of xylene was added and the ether was distilled off. After heating to 100°C, 87.0 gms (1.022 moles) 2-pyrrolidone (Eastman Organic Chemical Co.) was added in 100 ml of xylene. Gradually the temperature was raised to reflux and was kept there for five hours. The salts were decomposed with ice and water. Then, after addition of barium hydroxide, the amines were steam distilled. The distillate was treated with 330 ml of 1N hydrochloric acid and the solvent removed under reduced pressure. The residue was taken up in concentrated potassium hydroxide solution and shaken with five 100 ml portions of ether. The ether was distilled from the extracts through a 5 inch vigreux column. Then the residue was fractionated under vacuum through a jacketed vigreux column.

Fractionation Data

Fraction	Boiling Range	Weight	%Yield
1	24.4-26.0°C/10 mm	63.7 gms	55.1%
2	26.0-30.0°C/10 mm	2.48 gms	----
3	92.0-93.0°C/10 mm	2.50 gms	----

The yield of 2-n-propylpyrrolidine was 63.7 gms (0.564 moles) or 55.1%, B.P. 24.4-26.0°C/10 mm. In addition 2.48 gms of a mixture of dipropylpyrrolidines, B.P. 26.0-30.0°C/10 mm, and 2.50 gms of tripropylpyrrolidine, B.P. 92.0-93.0°C/10 mm, was obtained. Literature values were 66-67°C/30 mm, an intermediate value not given, and 125-135°C/40 mm respectively.

Perchlorate of 2-n-Propylpyrrolidine:-To 0.24 gms (0.00212 moles) 2-n-propylpyrrolidine (B.P. 24.4-26.0°C/10 mm) in 22 ml of glacial acetic acid (du Pont) was added 0.266 gms of 70% perchloric acid (G.F. Smith Chemical Co.). The acetic acid was distilled off under a vacuum leaving a white solid, 2-n-propylpyrrolidine perchlorate, M.P. 292-293°C.

Another experiment using 3 ml of 2-n-propylpyrrolidine, 5 ml of 70% perchloric acid, and 50 ml of absolute ethanol yielded a white solid, the perchlorate salt, M.P. 294-295°C, on solvent removal. Its infrared spectrum showed absorptions at 1640 cm^{-1}, (sh) 1370 cm^{-1}, 1100 cm^{-1}, 972 cm^{-1}, 760 cm^{-1}, 665 cm^{-1}, and 610 cm^{-1}. The melting points and spectrum are in excellent agreement with the salt obtained by catalytic reduction of the product from the reaction of 3β-mesyloxynortropane and lithium aluminum hydride. A mixed melting point of the salts obtained from the two sources showed no depression.

3β-Mesyloxynortropane in Tetrahydrofuran:-Into 100 ml of purified tetrahydrofuran (du Pont) 6.00 gms (0.01961 moles) of ester (M.P. 169-170°C) and 1.12 gms (0.0295 moles) of lithium aluminum hydride (Metal Hydrides Inc.), both finely ground, were placed with stirring. After the initial reaction subsided, the mixture was refluxed thirty-six hours. Then 2.24 ml of water and 1.79 ml of 10% sodium hydroxide solution were added and the mixture filtered. The product, a liquid, was evaporatively distilled at 120°C/75 mm to purify it. This resulted in 2.10 gms (0.01885 moles) or a 96.1% yield of 2-allylpyrrolidine, M.P. -17°C, 3400 cm^{-1}, 2100 cm^{-1}, 1640 cm^{-1}, (sh) 1630 cm^{-1}, and 1450 cm^{-1}.

3α-Mesyloxynortropane in Tetrahydrofuran:-Into 65 ml of purified tetrahydrofuran (du Pont) were placed 7.40 gms (0.0242 moles) 3α-mesyloxynortropane perchlorate (M.P. 168-169°C) and 0.807 gms (0.0212 moles) of lithium aluminum hydride (Metal Hydrides Inc.), both finely ground. After the initial reaction subsided, the reaction mixture was refluxed with stirring for eighteen hours. Then 1.62 ml of water and 1.29 ml of 10% sodium hydroxide solution were cautiously added to decompose the lithium and aluminum salts. Next the mixture was filtered, and the solvent was distilled from the filtrate through a 5 inch vigreux column. The residue was fractionated. Treatment of fractions 3 and 4 with anhydrous ether

Fractionation of Crude Product

Fraction	Boiling Range	Weight	% Yield
1	Solvent	----	----
2	Water	----	----
3	89.5-95.0°C/0.7-1.0 mm	1.06 gms	39.4%
4	95.0-99.0°C/1.0-1.2 mm	0.44 gms	16.4%
5	Residue	1.01 gms	37.2%

yielded a solid, 0.12 gms, M.P. 140-141°C, and an ether soluble liquid, 1.38 gms (0.0124 moles) or a 51.2% yield of 2-allylpyrrolidine. Another 0.68 gms (0.0062 moles) or 25.0% yield was obtained from the residue in this same manner. Total yield of 2-allylpyrrolidine was 2.16 gms of 76.2%.

Properties of Liquid Product

Boiling Point	236°C/751 mm
Density	0.956 gms/ ml
Index of Refraction	1.4895
Molecular Refractivity $(R_L)_D$	33.5
Elemental Analysis	C, H, and N
Picrate	M.P. 185.5-186.0°C
Hydrochloride	M.P. 175.5-176.5°C

A mixed melting point made with the hydrochloride of this amine (M.P. 175.5-176.5°C) and with that of the previously identified 2-allylpyrrolidine (M.P. 175-176°C) gave no depression melting at 175-176°C. Since the picrate was an easily purified solid, it was used for analysis.

Anal. Calc'd. for $C_{13}H_{16}N_4O_7$: C, 45.86; H, 4.74; N, 16.38.

Found: C, 45.83; H, 4.65; N, 16.37.

M.W. Calc'd. for $C_{13}H_{16}N_4O_7$: 340.2.

Found: 337.

G. Preparation of Reagents for Kinetic Work

80% Aqueous Ethanol Solution:[49]-Anhydrous ethanol was prepared by the method of Lund and Bjerrum, namely, formation of magnesium ethoxide in a small amount of refluxing ethanol and then refluxing this with the bulk of the reagent for a few hours. The anhydrous ethanol was then

49. Fieser, L. F., Experiments in Organic Chemistry, D. C. Heath & Company, Boston, Mass., 3rd ed., p. 285, 289, 281.

distilled into a storage bottle. When desired, the 80% ethanol-water solution could be made up with distilled water by volume.

Absolute Methanolic Sodium Hydroxide Solution:-This was also made by the method of Lund and Bjerrum.[49] However, this only involved refluxing the reagent methanol with magnesium overnight. Then the dry methanol was distilled into a storage bottle. When desired, a measured amount of 50% sodium hydroxide solution could be added to the appropriate volume of methanol.

0.0205M Acetic Anhydride in Acetic Acid:-To prepare this solution it was necessary to determine the amount of water in the glacial acetic acid (du Pont) used. This was done by titrations using Karl Fischer reagent (Eberbach & Son Co.). Then the appropriate amount of reagent acetic anhydride (Merck) could be added to remove the water present and to make the solution 0.0205M in acetic anhydride.

Anhydrous Acetone:-This reagent was prepared by drying reagent acetone (Merck) over potassium carbonate.[49]

H. Method of Conducting Rate Determinations

A weighed sample of the substance being investigated was dissolved in the solvent, 80% ethanol-water or 0.0205M acetic anhydride in acetic acid, and diluted to the appropriate volume in a clean volumetric flask. In the case of the 3-mesyloxynortropanes, their perchlorate salts were neutralized in solution by the addition of one equivalent of sodium ethoxide or sodium acetate depending on the solvent being used. The solution was then pipetted into thirteen to sixteen test tubes which were

subsequently sealed. The tubes were immersed in a constant temperature bath which was held to within 0.090°C of the desired temperature. In order to allow the tubes to come to a thermal equilibrium, three minutes were allowed to elapse before the initial sample was taken. Other samples were taken at various times during the experiment. The times for taking these samples could be roughly determined from a trial determination or by estimation based on the rate of reaction at another temperature. After the time has elapsed for ten half lives of the reaction, a final sample was taken. Immediately after a sample was removed from the bath, it was quenched by immersion in an ice bath. After thirty minutes, it was removed from the ice bath and allowed to warm to room temperature for five minutes before opening the tube. Then $4.968 \pm .002$ ml was pipetted from a calibrated automatic pipette into 5 ml of reagent acetone. The resulting solution was titrated with a solution of sodium hydroxide in absolute methanol whose concentration was known exactly and was between 0.005N and 0.010N. In each case the appropriate indicator was used. Brom phenol blue was the indicator used for titration of the thia compounds and the reference compounds in 80% ethanol. All the other titrations were done with universal indicator.

I. Calculation of the Rate and Thermodynamic Data

All the rate data are averages of two or more determinations under the same conditions. The rate constants were calculated in the manner shown in Figure 10. In Equation (1) the number of moles of sulfonic acid in the total volume of solution used for the rate determination

$$[HOT_s]_{99.83} = \frac{ml_{base} \times N_{base} \times \frac{99.83ml}{4.968ml}}{1000}$$

$$= \left(\frac{N_{base} \times 20.09}{1000}\right) ml_{base} = (Z)\ ml_{base} \qquad (1)$$

$$[ROT_s]_{99.83} = (Z)\ ml^{\infty}_{base} - (Z)\ ml_{base} = (Z)(ml^{\infty}_{base} - ml_{base}) \qquad (2)$$

$$[ROT_s] = [ROT_s]_{99.83} \times \frac{1000ml}{99.83ml} = [ROT_s]_{99.83} \times 10.02$$

$$= (10.02\ Z)\ (ml^{\infty}_{base} - ml_{base}) \qquad (3)$$

$$\log \frac{[ROT_s]^{\circ}}{[ROT_s]} = \log \frac{(10.02\ Z)(ml^{\infty}_{base} - ml^{\circ}_{base})}{(10.02\ Z)(ml^{\infty}_{base} - ml_{base})}$$

$$= \log \frac{(ml^{\infty}_{base} - ml^{\circ}_{base})}{(ml^{\infty}_{base} - ml_{base})} = \frac{k}{2.303}\ T \qquad (4)$$

Figure 10. Calculation of Rate Constants.

is equal to the number of equivalents of base times a factor which is the total volume of solution divided by the volume of the aliquot used for titration. The number of moles of sulfonic ester remaining in the total volume of solution is equal to the number of moles of sulfonic acid in the final sample minus the moles of sulfonic acid in the sample under consideration (Equation (2)). This quantity is converted to moles per liter by the appropriate factor shown in Equation (3). Finally in Equation (4) the rate constant, k, can be calculated by means of the log form of the rate expression for unimolecular reactions. This was accomplished by plotting $\log \frac{ROTs^{\circ}}{ROTs}$ versus time, generally in hours, and determining the slope of the curve so determined. In all cases this was a straight line with a very good fit to the experimental data. No points or constant values were discarded in these calculations other than those points which were not determined because the contents of the tube ignited on sealing.

The thermodynamic data was calculated as shown in Figure 11. From the fundamental equation of the transition state theory, Equation (5), Equation (7) can be derived. Then $\log \frac{k}{T}$, where k is the rate constant and T the absolute temperature, was plotted against $\frac{1}{T}$. The slope of this line determined by the data at the temperatures shown in Table IV will equal the enthalpy of activation, ΔH^*, divided by 2.303R where R is the universal gas constant, 0.001986 kcal/°K mole. Equation (9) shows how ΔH^* can be calculated from this relationship. Equation (10) shows the relationship between the intercept of this same plot and the entropy of activation, ΔS^*. In this equation k' is Boltzmann's constant, 1.3805×10^{-16} erg/°K, and h is Planck's constant, 6.624×10^{-27} erg sec. Equation (11) shows how this relationship can be used to obtain ΔS^*.

$$k = \frac{k'}{h} T e^{-\frac{\Delta H^*}{RT}} e^{+\frac{\Delta S^*}{R}} \tag{5}$$

$$\frac{k}{T} = \frac{k'}{h} e^{-\frac{\Delta H^*}{RT}} e^{\frac{\Delta S^*}{R}} \tag{6}$$

$$\log \frac{k}{T} = -\frac{\Delta H^*}{2.302RT} + \frac{\Delta S^*}{2.303R} + \log \frac{k'}{h} \tag{7}$$

$$\text{Slope of } \log \frac{k}{T} \text{ versus } \frac{1}{T} = M = -\frac{\Delta H^*}{2.303R} \tag{8}$$

$$\Delta H^* = -(2.303R)M \tag{9}$$

$$\text{Intercept of } \log \frac{k}{T} \text{ versus } \frac{1}{T} = I = \frac{\Delta S^*}{2.303R} + \log \frac{k'}{h} \tag{10}$$

$$S^* = (2.303R)(I - \log \frac{k'}{h}) = 2.303R\ (I - 10.316) \tag{11}$$

Figure 11. Calculation of Thermodynamic Data by the Graphic Method.

The thermodynamic data were also calculated using the least squares method. This involved calculations to determine the summations of the rate constants, Σk, the summation of $\log \frac{k}{T}$, the summation of the rate constants squared, Σk^2, and the summation of the product of the rate constant, k, and $\log \frac{k}{T}$. Once these values had been determined the slope and the intercept of the straight line which best fits these data can be determined by Equations (12) and (13) in Figure 12. The results from this calculation can then be converted to ΔH^* and ΔS^* by use of the equations in Figure 11 (Equation (9) and (11)). The values calculated by this method agree well with those from the graphical method.

$$\text{Slope} = M = \frac{3\Sigma k(\log \frac{k}{T}) - \Sigma k \, \Sigma \log \frac{k}{T}}{3\Sigma k^2 - (\Sigma k)^2} \qquad (12)$$

$$\text{Intercept} = I = \frac{\Sigma k^2 \, \Sigma \log \frac{k}{T} - \Sigma k \, \Sigma k(\log \frac{k}{T})}{3\Sigma k^2 - (\Sigma k)^2} \qquad (13)$$

Figure 12. Calculation of Thermodynamic Data by the Least Squares Method.

J. Product Determinations

3β-Mesyloxynortropane with Potassium Cyanide in 80% Ethanol-Water:- A solution was made up of 0.26 gms (0.00396 moles) of potossium cyanide (Allied Chemical & Dye Corp.), 9.2 ml of water, 0.24 gms (0.00360 moles)

of sodium ethoxide in 37 ml of ethanol, 0.36 gms (0.00360 moles) of potassium carbonate (Baker and Adamson), and 1.10 gms (0.00360 moles) of 3β-mesyloxynortropane perchlorate (M.P. 169-170°C) in that order. The reaction mixture was refluxed for sixteen hours. Then it was cooled, saturated with potassium carbonate, and shaken with ether. The combined extracts were dried over sodium sulfate. The resulting solution was treated with 0.511 gms (0.00360 moles) of methyl iodide (Eastman Organic Chemical Co.) overnight in the cold. Then 0.24 gms (0.00360 moles) of sodium ethoxide in ethanol was added to neutralize the salt formed. The solvent was removed yielding 0.42 gms (0.00308 moles) or an 85.5% yield of 5-cyano-1-methyl-2-allylpyrrolidine, B.P. by capillary method 220-225°C/750 mm, 3.30μ, 4.25μ, 4.45μ, 6.09μ, 6.9μ, 7.1μ, 7.3μ, 8.2μ, 8.6μ, 9.0μ, 9.5μ, 10.0μ, 10.9μ, 11.8μ, and 12.3μ. The reported boiling point is 68-70°C/2 mm[18] which corresponds to about 227°C/760 mm.[50] The reported infrared spectrum shows bands at 3.27μ, two near 4.5μ, 6.08μ, 6.9μ, 7.1μ, 7.3μ, 8.2μ, 8.6μ, 8.9μ, 9.5μ, 10.1μ, 11.0μ, 11.8μ, and 12.3μ.

3α-Mesyloxynortropane in 80% Ethanol-Water:-A solution was made containing 1.00 gm (0.00327 moles) of 3α-mesyloxynortropane perchlorate (M.P. 166-167°C), 3.27 ml (0.00327 moles) of 1.00N sodium ethoxide in ethanol, and 0.82 ml of water in 20.91 ml of 80% ethanol-water. This was sealed in a tube and kept in a bath at 58°C for fifty-four hours. The tube was opened and the ethanol was distilled off. The aqueous solution remaining was basified and shaken with six 10 ml portions of chloroform. The

50. Pressure Temperature Alignment Chart, The Matheson Company Inc., East Rutherford, New Jersey.

combined extracts were dried over sodium sulfate and the solvent was removed. The residue was taken up in 25% chloroform-benzene, treated with solid sodium hydroxide to remove carbonate salts, and chromatographed on Florosil. The total yields were 0.09 gms (0.000824 moles) or 25.5%

Chromatographic Data

Eluent	Fractions	Weight Residue	M.P. or(B.P.)*	% Yield
50% Chloroform-Benzene	3	0.01 gms	(160-165°C/750 mm)	2.8%
Chloroform	2	0.08 gms	(160-165°C/750 mm)	22.5%
Chloroform	7	0.20 gms	160-162°C	42.5%
Ethanol	6	0.06 gms	159-161°C	12.7%
Water	3	0.05 gms	158-160°C	10.5%

* By capillary method

of nortropidine, B.P. 160-165°C/750 mm, and 0.31 gms (0.00215 moles) or 65.7% of 3α-hydroxynortropane, M.P. 160-162°C.

3β-Tosyloxy-8-Thiabicyclo [3.2.1] octane with Raney Nickel in 80% Ethanol-Water:-A solution of 3.00 gms (0.01003 moles) of ester (M.P. 113-114°C) in 25 ml of 80% ethanol-water was sealed in a tube and left at 77.0°C for seventy-two hours. Then the contents of the tube were added to 30 gms of Raney nickel, W-2, in 225 ml of absolute ethanol. This was contained in a 500 ml three necked flask fitted with a reflux condenser and a stirrer. The mixture was refluxed overnight with stirring. The Raney nickel was filtered off and washed with ethanol. The combined filtrate and washes were diluted with 400 ml of chloroform, and the solvent was removed. This resulted in 1.10 gms (0.00962 moles) or a 95.6% yield of cycloheptanol.

Derivatives

α-Naphthylurethan, M.P. 109-111°C

Phenylurethan, M.P. 85.0-85.5°C (Found for authentic cycloheptanol 85.0°C)

3β-Tosyloxy-8-Thiabicyclo [3.2.1] Octane in 80% Ethanol-Water:

The solvolysis was conducted under the same conditions as before. After seventy-two hours, the tube was opened, and the contents were diluted with 400 ml of chloroform. The solvent was removed, and the residue was taken up in 50 ml of reagent benzene. This solution was chromatographed on Florosil. The total yield was 1.13 gms (0.00783 moles) or 78.0% of 3α-hydroxy-8-thiabicyclo [3.2.1] octane, M.P. 234-235°C. The actual yield may have been higher as indicated by the yield in the previous experiment, but due to the volatility of this material, some of it may have been lost on solvent removal.

Chromatographic Data

Eluent	Fractions	Weight Residue	M.P. or B.P.	% Yield
Benzene	3	----	-----	----
Benzene	12	0.600 gms	234-235°C	41.4%
Chloroform	24	0.543 gms	234-235°C	37.6%
Ethanol	3	----	-----	----

3α-Tosyloxy-8-Thiabicyclo [3.2.1] Octane in 80% Ethanol-Water:-

A solution of 2.50 gms (0.00836 moles) of thia ester (M.P. 104-106°C) in 25 ml of 80% ethanol-water was left ninety-six hours at 77.0°C in a sealed tube. Then the tube was cooled, opened, and the contents diluted with 100 ml of chloroform. After washing with sodium bicarbonate and drying, the solvent was removed. The residue, 1.60 gms of oil, was taken up in 23 ml of benzene and chromatographed on Florosil. The total yield was 0.943 gms (0.00653 moles) or 78.1% of 3α-hydroxy-8-thiabicyclo [3.2.1] octane, M.P. 238-239°C.

Chromatographic Data

Eluent	Fractions	Weight Residue	Melting Point	% Yield
Benzene	4	-------	-------	-------
Benzene	16	0.713 gms	238-239°C	59.0%
Chloroform	8	0.230 gms	234-235°C	19.1%
Ethanol	2	------	-------	-------

APPENDIX I

SYNTHESIS OF AZA AND HYDRAZATERPENES

Some work was done on the synthesis of aza and hydrazaterpenes in order that these compounds might be available for the study of their reactions on solvolysis.

The first synthesis attempted was that of tetrahydroendomethylene pyridizine (Chart U). This was accomplished by a two step synthesis. The first step was a Diels-Alder reaction between cyclopentadiene (U-I) and diethyl azodicarboxylate (U-II) to give the diethyl-1, 2-dicarboxylate derivative of the desired compound (U-III).[51] An attempt was made to hydrolyze and decarboxylate the adduct by basic hydrolysis[51], but this failed to cause any reaction. Acid hydrolysis, however, did produce the carbonate salt of the desired compound (U-IV). This is to be halogenated by addition across the double bond. The compound so formed is to be investigated for the occurrence of any interaction of the nitrogen with the incipient carbonium ion formed by loss of halogen ion.

The second synthesis investigated was that of 2-keto-7-azabicyclo [2.2.1] heptane. The purpose of this synthesis was to demonstrate the interaction of the nitrogen during solvolysis as one of the steps in the synthesis as well as to provide compounds for further investigation. The synthesis (Chart V) has only been about half completed due to lack of time, but the remainder of the synthesis looks very promising. The first step was to saponify the starting material, 7-carboethoxy-1, 4-dioxaspiro [4,5] decan-8-one (V-I), and then to decarboxylate the resulting

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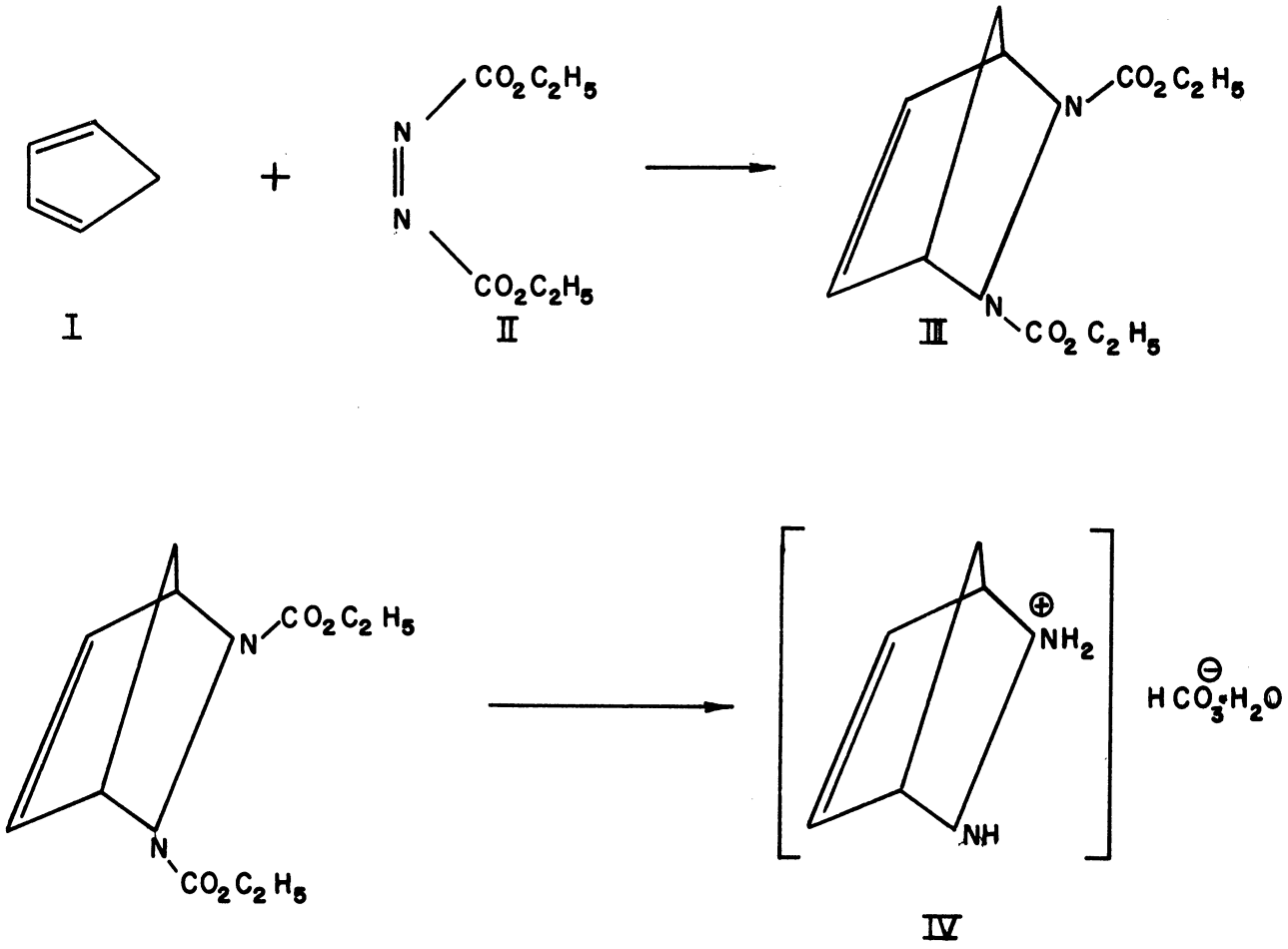
51. Diels, O., Blom, J. and Koll, W., Ann. 443, 242 (1925).



I II III IV

Chart U. Synthesis of Tetrahydroendomethylene Byridizine.

acid under very mild acidic conditions.[52] The resulting ketone (V-II) was treated with hydroxylamine hydrochloride to form the oxime, V-III.[53] This was reduced with sodium and alcohol to yield the corresponding amine (V-IV).[54] Lithium aluminum hydride was also tried for this reaction, but the isolation of products proved to be more difficult than in the previous case. The amine was treated with phthalic anhydride which blocked the amino group as the phthalimide and in addition caused the removal of the ketal grouping (V-V).[55] At this point the synthesis was stopped. However, it is believed that treatment of the phthalimido ketone with ethyl formate followed by reaction with n-butyl mercaptan would yield the thia enol ether, V-VI. This could be reduced with sodium borohydride to the hydroxy thia enol ether. On treatment with acid this would lead to the α, β unsaturated aldehyde, V-VII. The aldehyde could be reduced with sodium borohydride to the corresponding alcohol (V-VIII). The phthalimido group is removed next by means of hydrazine. Then esterification with 2,5-dichlorobenzoyl chloride would lead to the ester, V-X. It is believed that this amino ester will undergo solvolysis by interaction of the amino group with the unsaturation in such a way as to aid in the removal of the ester group. This would produce the bicyclic unsaturated amine, V-XI. Ozonolysis of the double bond would result in an amino ketone suitable for the preparation of a pair of isomeric esters whose solvolysis rates may be studied.

52. Woodward, R.B., J. Am. Chem. Soc., 74, 4223 (1952).
53. Shriner, R.L. and Fuson, R.C., The Systematic Identification of Organic Compounds, 3rd Ed., New York: John Wiley and Sons, Inc., 1948, p. 202.
54. Org. Syntheses, Col. Vol. II, p. 318 (1943).
55. Vanags, G., Acta Univ. Latviensis, Kim. Fakultat., Ser. 4, No. 8, 405 (1938) - C.A. 34, 1983 (1940).

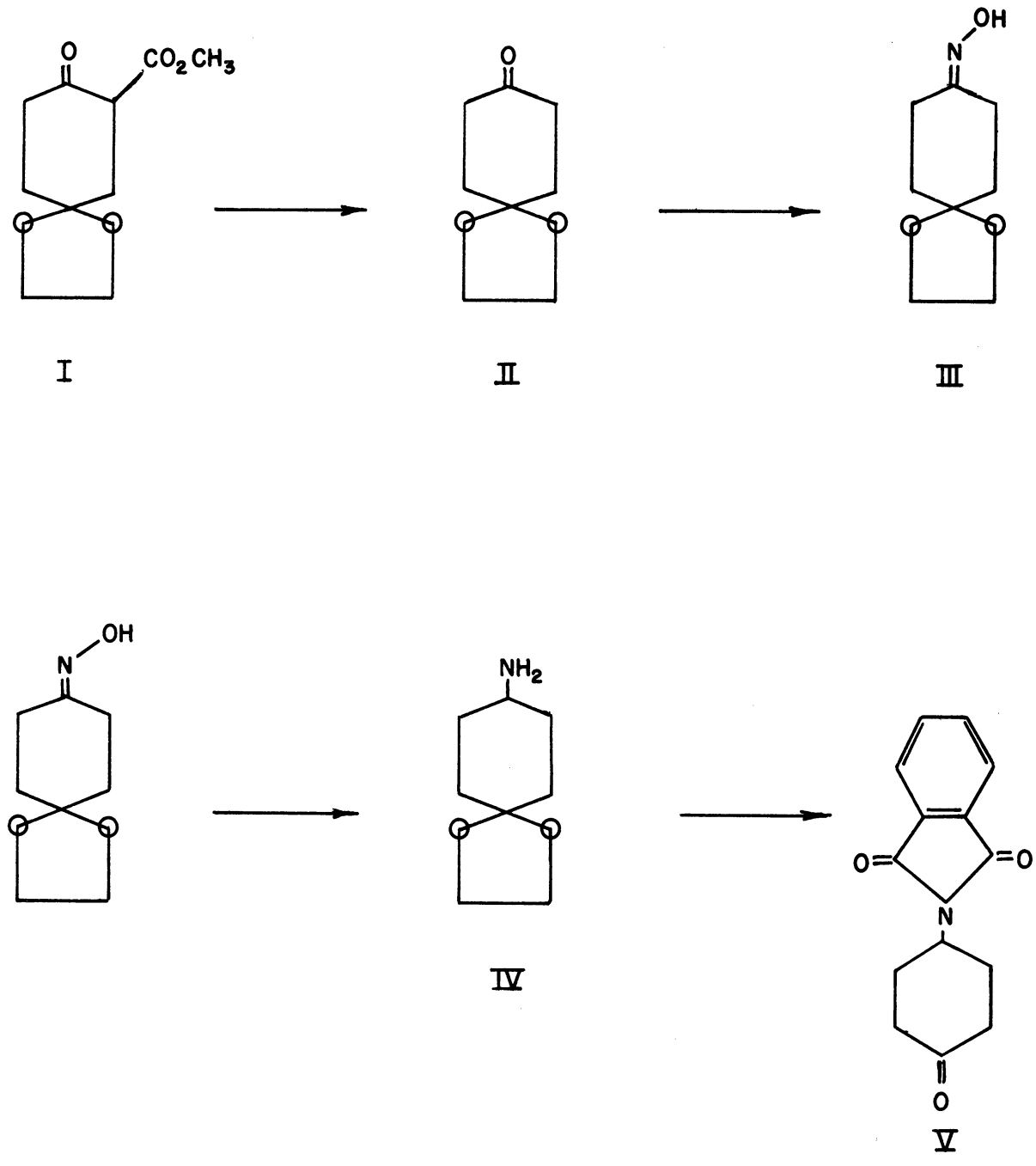
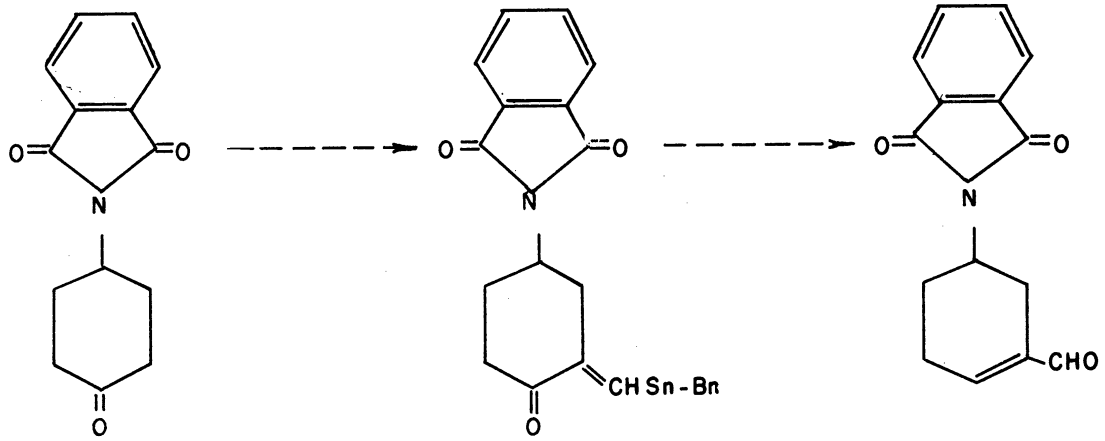
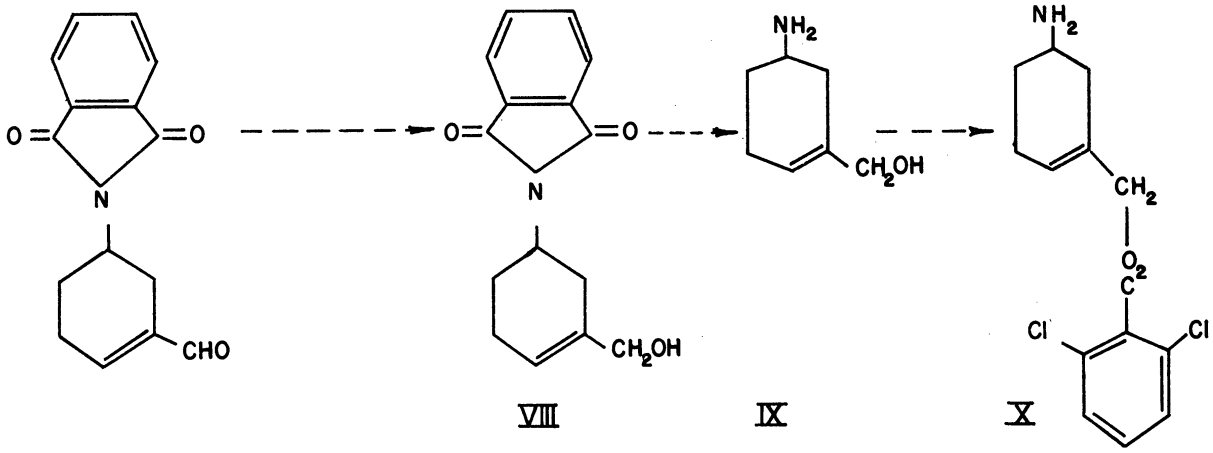


Chart V. Synthesis of 2-Keto-7-Azabicyclo [2.2.1] Heptane.

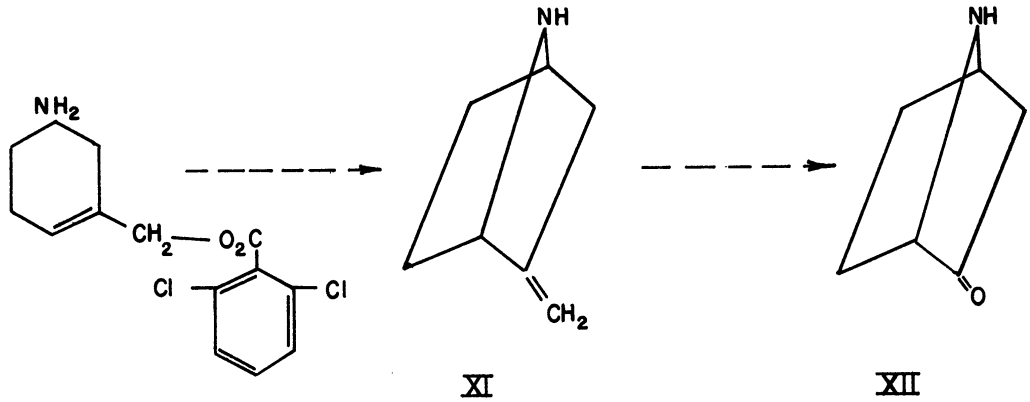
Chart V. (Cont'd)



VI VII



VIII IX X



XI XII

Experimental

A. Synthesis of Tetrahydroendomethylene Pyridizine

Dicarboethoxytetrahydroendomethylene Pyridizine:[51]-Into a 200 ml two necked flask fitted with a reflux condenser and a separatory funnel was placed 9.25 gms (0.140 moles) of freshly distilled cyclopentadiene (B.P. 42.5-48.0°C/750 mm) in 50 ml of anhydrous ether (Mallinckrodt). To this 13.85 gms (0.0796 moles) of diethyl azodicarboxylate in 50 ml of anhydrous ether was added by means of the separatory funnel at such a rate as to keep a gentle reflux. The solution was refluxed thirty minutes more at 30-40°C. Then it was allowed to stand overnight at room temperature. The ether was stripped off and the residue was distilled yielding 12.0 gms (0.0500 moles) or 62.9% dicarboethoxytetrahydroendomethylene pyridizine, B.P. 144-148°C/4 mm. (Lit. 121°C/0.5 mm, 125°C/0.8 mm, 132°C/1.2 mm, and 135°C/1.5 mm.)

Tetrahydroendomethylene Pyridizine:[51]-A solution of 12.0 gms (0.0500 moles) of the diester (B.P. 144-148°C/4 mm) and 12.6 gms (0.225 moles) of potassium hydroxide (Baker and Adamson) in 47 ml of ethanol was placed in a 200 ml round bottom flask fitted with a reflux condenser. The condenser was equipped with a tube leading to a mercury manometer. The system was put under nitrogen and refluxed for two and one-half hours. Then it was basified with potassium carbonate, concentrated, and treated with 100 ml ether. The precipitate was filtered off, and the solvent was removed from the filtrate. The residue was distilled boiling at 147-149°C/4.5 mm indicating that it was starting material. No other material was isolated.

Tetrahydroendomethylene Pyridizine:-A solution of 7.96 gms (0.0332 moles) of diester (B.P. 147-149°C/4.5 mm), 12.2 ml of concentrated hydrochloric acid (du Pont), and 50 ml of water was made up and placed in the same system that was used for the basic hydrolysis attempt. The system was placed under nitrogen and refluxed for seven hours. The resulting solution was saturated with sodium bicarbonate and shaken with ether. The combined extracts were dried with magnesium sulfate, and then the solvent was removed. The residue was 2.3 gms (0.01303 moles) or a 39.4% yield of tetrahydroendomethylene pyridizine bicarbonate monohydrate, M.P. 134.5-135.5°C.

Anal. Calc'd. for $C_6H_{12}N_2O_4$: C, 40.91; H, 6.87; N, 15.90.

Found: C, 41.02; H, 6.78; N, 16.10.

B. Synthesis of 2-Keto-7-Azabicyclo [2.2.1] Heptane

1,4-Dioxaspiro [4,5] Decan-8-one:[52]-Into a 300 ml round bottom flask were placed 56.2 gms (0.262 moles) of 7-carbethoxy-1, 4-dioxaspiro [4,5] decan-8-one (M.P. 62-64°C), 12.60 gms (0.315 moles) of sodium hydroxide (Baker), and 125 ml of water. The contents were stirred for twelve hours at room temperature. Then the pH of the solution was adjusted to a value of 6-7. The solution was stirred another hour, and then it was shaken with five 200 ml portions of chloroform. The combined extracts were dried over magnesium sulfate. Then the solvent was removed yielding 26.12 gms (0.167 moles) or a 63.7% yield of 1,4-dioxaspiro [4,5] decan-8-one, M.P. 73-74°C (Lit. 72-73°C).[56]

56. Prins, D., Helv. Chem. Acta, 40, 1621 (1957).

Oxime of 1,4-Dioxaspiro [4,5] Decan-8-one:[53]-Into 25 ml of absolute ethanol 26.12 gms (0.167 moles) of 1,4-dioxaspiro [4,5] decan-8-one (M.P. 73-74°C), 65.30 gms (0.939 moles) of hydroxylamine hydrochloride, and 260 ml of 10% sodium hydroxide solution were dissolved. The solution was heated ten minutes on a steam bath and then cooled one hour in the cold. Then it was shaken with five 200 ml portions of ether. The extracts were dried over sodium sulfate, and then the solvent was removed. The residue consisted of 22.9 gms (0.134 moles) or an 80,4% yield of the oxime, M.P. 64-66°C.

Anal. Calc'd. for $C_8H_{13}NO_3$: C 56.13; H, 7.65; N, 8.18.

Found: C, 55.93; H, 7.51; N, 8.17.

8-Amino-1,4-Dioxaspiro [4,5] Decan-8-one:[54]-Into 175 ml of absolute ethanol was dissolved 8.30 gms (0.0485 moles) of the oxime (M.P. 64-66°C). This was brought to a reflux in a 300 ml round bottom flask equipped with a reflux condenser. Then 12.10 gms (0.526 moles) of sodium metal was added in small pieces in order to maintain a gentle reflux. When addition was complete, the solution was refluxed until the sodium had disappeared and then for thirty minutes more. After solvent removal, the residue was taken up in a small amount of water and shaken with three 100 ml portions of ether. The combined extracts were dried over sodium sulfate. The solvent was removed and the residue fractionated. The total yield was 4.66 gms (0.0297 moles) or 61.1% of 8-amino-1,4-dioxaspiro [4,5] decane, B.P. 124-127°C/21 mm. Its picrate, M.P. 222.5-223.0°C, was used for analysis.

Anal. Calc'd. for $C_{14}H_{18}N_4O_4$: C, 43.53; H, 4.70; N, 14.50.

Found: C, 43.52; H, 4.78; N, 14.49.

Fractionation Data

Fraction	Boiling Range	Weight	% Yield
1	Solvent	--	--
2	26-27°C/30 mm	Solvent	--
3	124-125°C/21 mm	2.68 gms	35.2%
4	125°C/21 mm	0.36 gms	4.7%
5	125-127°C/21 mm	1.62 gms	21.2%

8-Amino-1,4-Dioxaspiro [4,5] Decan-8-one:-A solution of 1.00 gms (0.00585 moles) of the oxime (M.P. 64-66°C), 0.33 gms (0.00877 moles) of lithium aluminum hydride (Metal Hydrides Inc.), and 40 ml of anhydrous ether (Mallinckrodt) was made up adding the oxime in ether at such a rate as to give a gentle reflux. After addition was complete, the mixture was refluxed another forty-eight hours with stirring. Then 0.66 ml of water and 0.53 ml of 10% sodium hydroxide solution were added, and the mixture was stirred another hour. The solid was filtered off, and the filtrate was distilled to dryness. The residue was an oil which partially solidified. Attempted crystallization from ether was only partly successful.

Phthalimide of 8-Amino-1,4-Dioxaspiro[4,5]Decan-8-one:[55]-A solution was made containing 3.91 gms (0.0248 moles) of 8-amino-1,4-dioxaspiro [4,5] decane (B.P. 124-127°C/21 mm) and 14.5 gms (0.0980 moles) of phthalic anhydride (Eastman Organic Chemical Co.) in 50 ml of glacial acetic acid (du Pont). The resulting solution was refluxed in a 1000 ml flask fitted with an air condenser for fifty minutes. After cooling, 500 ml of water was added, and the solution was brought to reflux. Then

it was allowed to cool overnight. The precipitate was filtered off and yielded 4.60 gms (0.0189 moles) or a 76.1% yield of the phthalimide of 4-aminocyclohexanone, M.P. 145-146°C.

Anal. Calc'd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76.

Found: C, 69.13; H, 5.52; N, 5.83.

APPENDIX II

KINETIC DATA FOR SOLVOLYSIS

Solvolysis in Aqueous Ethanol

3β-Mesyloxynortropane

77.0 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.008229N)	Reaction Mixture
1	0.000	0.308	0.0214 gms
2	0.013	0.341	(6.998×10^{-5} moles)
3	0.016	0.353	Ester
4	0.017	0.356	99.83 ml
5	0.025	0.389	80% Ethanol-water
6	0.033	0.390	
7	0.050	0.392	
8	0.083	0.408	
9	0.167	--	
10	0.250	0.413	
11	0.500	0.417	
12	20.000	0.421	
13	23.500	0.422	

The rate constants for this and a duplicate experiment were 8.12×10^{-3}/sec and 8.00×10^{-3}/sec respectively.

$50.8 \pm 0.090°C$

Sample	Time (Hrs.)	ml Base (0.005241N)	Reaction Mixture
1	0.000	0.177	0.0292 gms
2	1.000	0.328	(9.550×10^{-5} moles)
3	1.250	0.360	Ester
4	1.500	0.390	199.70 ml
5	2.000	0.400	80% Ethanol-water
6	2.833	0.411	
7	4.233	0.419	
8	5.100	0.425	
9	5.681	0.428	
10	6.142	0.430	
11	7.000	0.433	
12	26.100	0.470	
13	26.100	0.470	

The rate constant for this and a duplicate experiment were 1.31×10^{-4}/sec and 1.30×10^{-4}/sec respectively.

$36.00 \pm 0.090°C$

Sample	Time (Hrs.)	ml Base (0.01486N)	Reaction Mixture
1	0.000	0.283	0.0292 gms
2	12.300	0.312	(9.550×10^{-5} moles)
3	13.500	0.320	Ester
4	15.500	0.329	199.70 ml
5	19.682	0.333	80% Ethanol-water
6	23.284	0.344	

7	40.500	0.366	
8	47.800	0.383	∞ = 20 hrs. at 100°C
9	61.000	0.395	
10	67.833	0.398	
11	83.556	0.411	
12	∞	0.445	
13	∞	0.440	

The rate constant for this and a duplicate experiment were 5.60×10^{-6}/sec and 5.65×10^{-6}/sec respectively.

3α-Mesyloxynortropane

77.00 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.008323N)	Reaction Mixture
1	0.000	0.110	0.0228 gms
2	--	--	(7.455×10^{-5}moles)
3	0.117	0.180	Ester
4	0.133	0.246	99.83 ml
5	0.150	0.264	80% Ethanol-water
6	0.183	0.271	
7	0.233	0.315	
8	0.283	0.329	
9	0.333	0.340	
10	0.417	--	
11	0.500	0.402	
12	0.667	0.430	
13	1.000	0.437	

14	1.250	0.443
15	24.033	0.447
16	24.033	0.445

The rate constants for this and a duplicate experiment were 1.04×10^{-3}/sec and 1.05×10^{-3}/sec respectively.

$50.8 \pm 0.090°C$

Sample	Time (Hrs.)	ml Base (0.005405N)	Reaction Mixture
1	0.000	--	0.0386 gms
2	0.250	--	(1.262×10^{-4} moles)
3	0.750	0.166	Ester
4	1.500	0.238	199.70 ml
5	2.500	0.301	80% Ethanol-water
6	3.500	0.332	
7	4.500	0.393	
8	6.500	0.463	
9	7.000	0.469	
10	8.000	0.511	
11	9.000	0.556	
12	10.100	0.586	
13	74.500	0.584	

The rate constants for this and a duplicate experiment were 5.85×10^{-5}/sec and 5.94×10^{-5}/sec respectively.

$36.00 \pm 0.090°C$

Sample	Time (Hrs.)	ml Base (0.01006N)	Reaction Mixture
1	0.000	0.000	0.1123 gms
2	45.067	--	(3.672×10^{-4} moles)
3	48.000	0.602	Ester
4	49.100	0.617	199.70 ml
5	50.333	0.634	80% Ethanol-water
6	56.300	0.666	
7	68.800	0.736	
8	71.000	0.753	∞ = 20 hrs. at 100°C
9	74.000	0.768	
10	77.000	0.773	
11	83.100	0.790	
12	93.475	0.820	
13	∞	0.902	
14	∞	0.910	

The rate constants for this and a duplicate experiment were 7.74×10^{-6}/sec and 7.73×10^{-6}/sec respectively.

3β-Tosyloxy-8-Thiabicyclo [3.2.1] Octane

$98.5 \pm 0.090°C$

Sample	Time (Hrs.)	ml Base (0.006451N)	Reaction Mixture
1	0.000	0.064	0.2275 gms
2	0.250	1.478	(7.624×10^{-4} moles)
3	0.750	1.991	Ester
4	1.300	2.567	199.70 ml
5	2.000	2.843	80% Ethanol-water

6	2.333	2.890
7	3.000	2.946
8	4.075	2.960
9	5.025	2.990
10	6.000	3.014
11	7.050	3.011
12	8.100	3.019
13	45.000	3.018

The rate constant for this and a duplicate experiment were 4.10×10^{-4}/sec and 4.15×10^{-4}/sec respectively.

$77.00 \pm 0.090°C$

Sample	Time (Hrs.)	ml Base (0.01181N)	Reaction Mixture
1	0.00	0.035	0.0625 gms
2	1.80	0.289	(2.095×10^{-4} moles)
3	2.32	0.376	Ester
4	2.92	0.403	99.83 ml
5	3.60	--	80% Ethanol-water
6	4.45	0.505	
7	5.25	0.558	
8	6.10	--	
9	7.00	0.663	
10	7.80	0.703	
11	8.20	--	
12	10.20	0.793	

13	13.00	0.849
14	16.00	--
15	25.50	0.869

The rate constant for this and duplicate experiments were 5.25×10^{-5}/sec, 5.24×10^{-5}/sec, and 5.20×10^{-5}/sec respectively.

$50.8 \pm 0.090°C$

Sample	Time (Hrs.)	ml Base (0.006818N)	Reaction Mixture
1	0.000	0.000	0.0678 gms
2	12.416	0.231	(2.272×10^{-4} moles)
3	13.000	0.243	Ester
4	14.000	0.253	99.83 ml
5	15.600	0.278	80% Ethanol-water
6	18.000	0.318	
7	19.000	0.320	
8	22.917	0.439	
9	35.750	0.609	
10	38.120	0.616	∞ = 20 hrs. at 100°C
11	84.500	1.101	
12	88.500	1.126	
13	93.000	1.198	
14	109.750	1.261	
15	∞	1.651	
16	∞	1.663	

The rate constants for this and a duplicate experiment were 3.66×10^{-6}/sec and 3.66^{-6}/sec respectively.

3α-Tosyloxy-8-Thiabicyclo [3.2.1] Octane

98.5 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.03749N)	Reaction Mixture
1	0.000	0.192	0.0500 gms
2	0.125	0.202	(1.676×10^{-4} moles)
3	0.375	0.228	Ester
4	0.775	0.236	99.83 ml
5	1.250	0.252	80% Ethanol-water
6	2.025	0.261	
7	2.850	0.267	
8	4.050	0.279	
9	5.000	0.281	
10	6.000	0.282	
11	7.000	0.281	
12	9.000	0.282	
13	24.000	0.282	

The rate constants for this and a duplicate experiment were 3.54×10^{-4}/sec and 3.58×10^{-4}/sec respectively.

77.00 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.006536N)	Reaction Mixture
1	0.000	--	0.0555 gms
2	0.26	0.934	(1.860×10^{-4} moles)
3	0.43	0.986	Ester
4	0.62	0.995	99.83 ml
5	0.84	1.036	80% Ethanol-water

6	1.08	1.063
7	1.33	1.086
8	1.60	1.124
9	1.83	--
10	2.10	1.173
11	2.65	--
12	3.00	1.245
13	3.75	1.303
14	6.05	1.410
15	30.00	1.415

The rate constants for this and duplicate experiments were 1.145×10^{-4}/sec, 1.145×10^{-4}/sec, and 1.188×10^{-4}/sec respectively.

50.8 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.01847N)	Reaction Mixture
1	0.000	0.000	0.0101 gms
2	17.250	0.052	(3.385×10^{-5} moles)
3	24.500	0.064	Ester
4	27.250	0.065	99.83 ml
5	40.500	0.077	80% Ethanol-water
6	43.100	0.079	
7	46.500	0.081	
8	50.417	0.086	∞ = 20 hrs. at 100°C
9	63.750	0.088	
10	66.667	0.089	

11	112.000	--
12	120.500	0.091
13	∞	0.090

The rate constants for this and a duplicate experiment were 1.31×10^{-5}/sec and 1.30×10^{-5}/sec respectively.

Trans-4-t-Butylcyclohexyl Tosylate

$98.5 \pm 0.090°C$

Sample	Time (Hrs.)	ml Base (0.003156N)	Reaction Mixture
1	0.000	1.081	0.1769 gms
2	0.100	1.376	(5.698×10^{-4}moles)
3	0.300	1.637	Ester
4	0.500	1.690	199.70 ml
5	0.700	1.701	80% Ethanol-water
6	1.250	1.716	
7	1.750	1.715	
8	2.550	1.717	
9	3.500	--	
10	5.000	1.717	
11	7.250	1.716	
12	8.500	1.717	
13	21.250	1.717	

The rate constants for this and a duplicate experiment were 1.56×10^{-3}/sec and 1.49×10^{-3}/sec respectively.

77.00 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.01253N)	Reaction Mixture
1	0.000	0.000	0.0526 gms
2	0.250	0.089	(1.654 x 10 moles)
3	0.500	0.185	Ester
4	0.783	0.288	99.83 ml
5	1.033	0.364	80% Ethanol-water
6	1.250	0.417	
7	1.550	0.482	
8	1.767	0.507	
9	2.000	0.538	
10	2.250	0.561	
11	2.500	0.580	
12	2.767	0.604	
13	3.008	0.609	
14	39.000	0.655	
15	39.000	0.660	

The rate constants for this and a duplicate experiment were 2.54×10^{-4}/sec and 2.55×10^{-4}/sec respectively.

50.8 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.008025N)	Reaction Mixture
1	0.000	0.000	0.0800 gms
2	1.225	0.027	(2.577×10^{-4}moles)
3	1.754	0.043	Ester
4	2.250	0.056	199.70 ml

5	2.750	0.081	80% Ethanol-water
6	3.632	0.105	
7	4.500	0.151	∞ = 20 hrs. at 100°C
8	5.200	0.164	
9	7.167	0.210	
10	9.000	0.264	
11	23.233	0.496	
12	--	--	
13	∞	0.756	
14	∞	0.839	

The rate constants for this and a duplicate experiment were 1.34×10^{-5}/sec and 1.34×10^{-5}/sec respectively.

Cyclohexyl Tosylate

77.00 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.006394N)	Reaction Mixture
1	0.000	0.000	0.0223 gms
2	0.250	0.126	(8.770×10^{-5}moles)
3	0.416	0.239	Ester
4	0.550	0.261	99.83 ml
5	0.784	0.330	80% Ethanol-water
6	1.000	--	
7	1.250	0.524	
8	1.550	0.556	
9	1.750	0.588	

10	2.016	0.616
11	4.765	--
12	8.000	0.668
13	14.500	0.674
14	42.000	0.684

The rate constants for this and duplicate experiments were 3.03×10^{-4}/sec, 2.99×10^{-4}/sec, 3.07×10^{-4}/sec, and 3.10×10^{-4}/sec respectively.

Cyclohexyl Mesylate

77.00 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.01119N)	Reaction Mixture
1	0.000	0.000	0.0880 gms
2	0.250	0.408	(4.939×10^{-4} moles)
3	0.500	0.811	Ester
4	0.750	0.977	99.83 ml
5	1.000	1.308	80% Ethanol-water
6	1.333	1.540	
7	1.517	1.662	
8	1.750	1.768	
9	2.000	1.829	
10	2.250	1.895	
11	2.500	1.967	
12	2.750	1.977	
13	3.000	2.010	
14	5.000	2.151	

15	45.783	2.201
16	45.783	2.192

The rate constants for this and a duplicate experiment were 2.43×10^{-4}/sec and 2.40×10^{-4}/sec respectively.

Acetolysis

3β-Mesyloxynortropane

77.00 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.002733N)	Reaction Mixture
1	0.000	0.159	0.0169 gms
2	0.250	0.172	(5.528×10^{-5}moles)
3	0.500	0.221	Ester
4	0.750	0.259	199.70 ml
5	1.000	0.285	0.0205M Acetic Anhy-
			dride in Acetic Acid
6	1.500	0.331	
7	2.000	0.383	
8	3.000	0.413	
9	3.900	0.423	
10	6.000	0.427	
11	8.000	0.430	
12	9.950	0.435	
13	86.216	0.506	

The rate constants for this and a duplicate experiment were 1.28×10^{-5}/sec and 1.26×10^{-5}/sec respectively.

3α-Mesyloxynortropane

$77.00 \pm 0.090°C$

Sample	Time (Hrs.)	ml Base (0.006231N)	Reaction Mixture
1	0.000	0.029	0.0236 gms
2	0.333	0.075	(7.718×10^{-5} moles)
3	0.674	0.112	Ester
4	1.000	0.150	99.83 ml
5	1.550	0.200	0.0205M Acetic Anhydride in Acetic Acid
6	2.000	0.220	
7	4.000	0.287	
8	5.000	0.367	
9	6.000	0.430	
10	7.008	0.493	
11	8.000	0.546	
12	10.000	0.602	
13	11.100	--	
14	72.600	0.616	
15	72.600	0.617	

The rate constants for this and a duplicate experiment were 6.06×10^{-5}/sec and 6.02×10^{-5}/sec respectively.

Trans-4-t-Butylcyclohexyl Tosylate

77.00 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.006234N)	Reaction Mixture
1	0.000	0.101	0.0282 gms
2	0.250	0.123	(9.083×10^{-5} moles)
3	0.500	0.141	Ester
4	0.750	0.176	99.83 ml
5	1.000	0.190	0.0205M Acetic Anhydride in Acetic Acid
6	1.250	0.219	
7	1.500	0.229	
8	1.750	0.240	
9	2.025	0.263	
10	2.500	0.280	
11	3.150	0.325	
12	4.025	0.392	
13	5.000	0.433	
14	51.000	0.729	
15	51.000	0.724	

The rate constants for this and a duplicate experiment were 4.16×10^{-5}/sec and 4.20×10^{-5}/sec respectively.

3β-Tosyloxy-8-Thiabicyclo [3.2.1] Octane

77.00 ± 0.090°C

Sample	Time (Hrs.)	ml Base (0.005268N)	Reaction Mixture
1	0.000	0.154	0.0320 gms
2	0.250	0.169	(1.072×10^{-4} moles)

3	0.750	0.195	Ester
4	1.250	0.239	199.70 ml
5	1.750	0.273	0.0205M Acetic Anhy-
6	2.250	0.295	dride in Acetic Acid
7	2.750	0.340	
8	3.250	0.370	
9	3.750	0.370	
10	5.000	0.372	
11	7.000	0.377	
12	9.025	0.380	
13	45.417	0.511	

The rate constants for this and a duplicate experiment were 5.29×10^{-5}/sec and 5.34×10^{-5}/sec respectively.

3α-Tosyloxy-8-Thiabicyclo [3.2.1] Octane

$77.00 \pm 0.090°C$

Sample	Time (Hrs.)	ml Base (0.003490N)	Reaction Mixture
1	0.000	0.118	0.0070 gms
2	0.550	0.155	(2.346×10^{-5}moles)
3	0.750	0.182	Ester
4	1.000	0.202	99.83 ml
5	1.250	0.219	0.0205M Acetic Anhy-
6	1.500	0.238	dride in Acetic Acid
7	2.000	0.248	
8	2.500	0.267	

9	2.900	0.269
10	3.950	0.272
11	5.000	0.285
12	6.200	0.311
13	7.000	0.316
14	47.950	0.330
15	47.950	0.340

The rate constants for this and a duplicate experiment were 1.04×10^{-4}/sec and 1.09×10^{-4}/sec respectively.