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π-ROUTE TO AZABICYCLICS II. THE SOLVOLYTIC BEHAVIOR OF 4-(N-CHLORO-N-METHYLAMINOMETHYL)CYCLOHEXENE[1]

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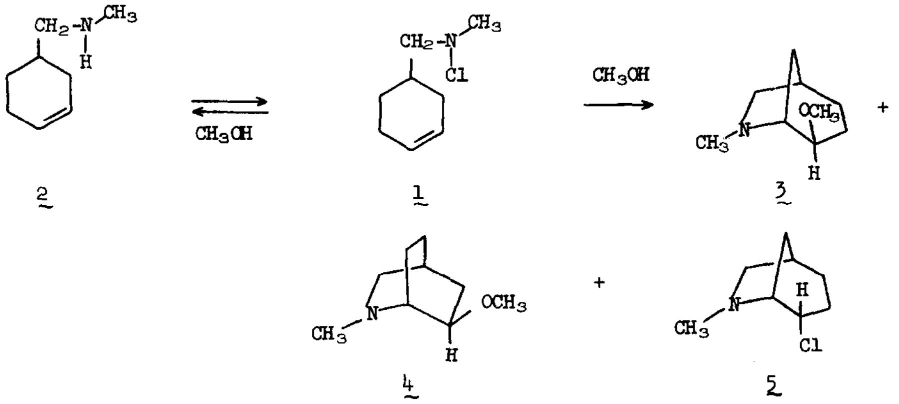
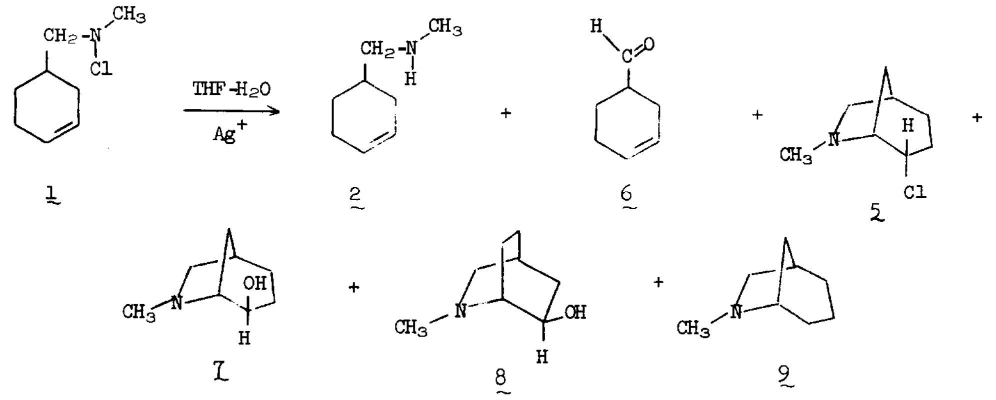
Recently we reported the first example of an intramolecular addition of a nitrenium ion to a carbon-carbon double bond.[2] As part of our investigation of the scope and mechanistic aspects of this reaction and in line with our interest in utilizing nitrenium ions in the synthesis of biologically important ring systems[3] we have investigated the solvolytic behavior of 4-(N-chloro-N-methylaminomethyl)cyclohexene (1).

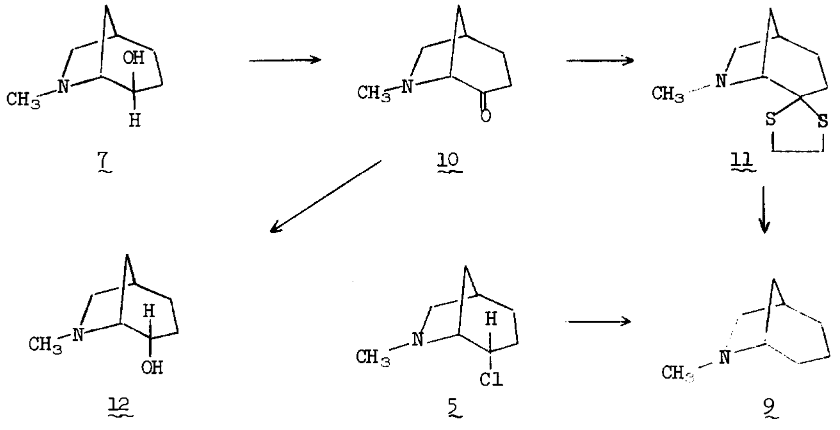
When 4-(N-methylaminomethyl)cyclohexene (2) was treated with commercial sodium hypochlorite solution the N-chloramine, 1, was obtained in essentially quantitative yield. Refluxing a methanolic solution of 1 until the solution gave a negative test for active chlorine (6 hr) resulted in the recovery of 40% of 2 and the formation of three cyclization products. These π-route products were identified as 3 (15%), 4 (23%), and 5 (13%)[4] by a combination of degradation and independent synthesis.



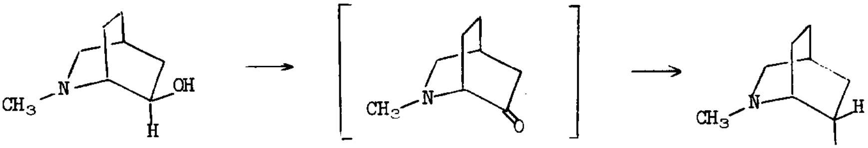
Solvolysis of 1 in tetrahydrofuran-water with silver ion catalysis gave a more complex mixture of products consisting of 2 (14-17%), 6 (13-18%), 5 (9-12%), 7 (11-14%), 8 (16-19%), and 9 (13-16%).



Compounds 3 and 7 were interrelated through conversion of 7 to the methiodide of 3 by treatment of 7 with sodium hydride followed by excess methyl iodide. In the same manner 8 could be converted to the methiodide of 4 which was synthesized independently.[5] Compounds 5, 7, and 9 were correlated as shown below. Oxidation of the hydrochloride of 7 with Jones' reagent gave 10 in 83% yield. Conversion of 10 into 11 was readily accomplished with ethanedithiol and boron trifluoride etherate. Raney nickel reduction of 11 gave 9.[6] Reduction of 5 with sodium-tetrahydrofuran-t-butyl alcohol also gave 9.



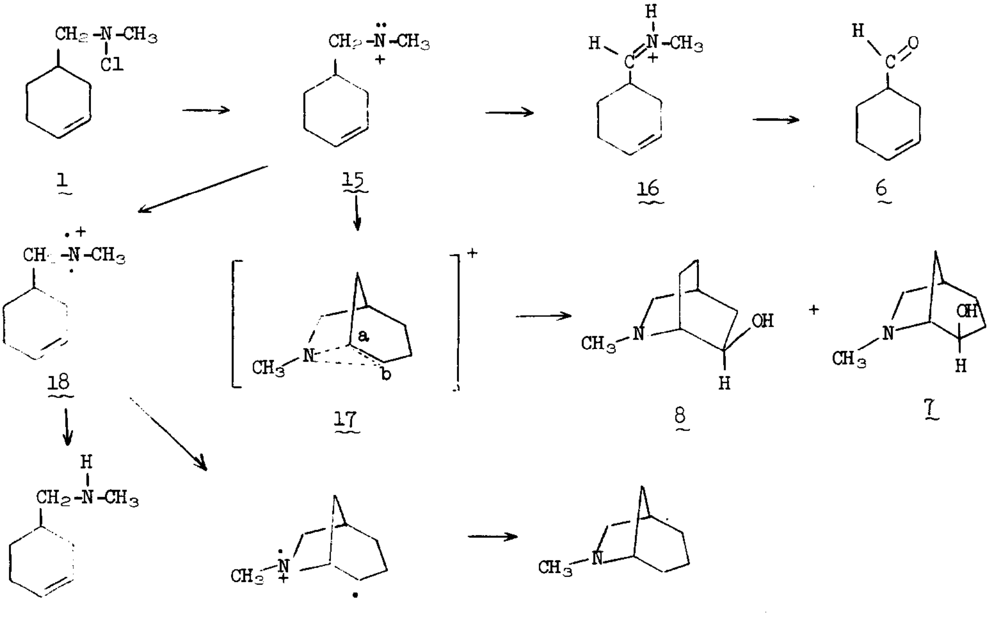
The stereochemistry of the hydroxyl functions of 7 and 8 (and hence of the methoxyl functions of 3 and 4) was established through hydrogen bonding studies. Reduction of 10 with potassium borohydride gave 12. Oxidation of the hydrochloride of 8 with Jones' reagent followed by potassium borohydride reduction gave predominately 14. Infrared studies of di-



8 13 14

lute solutions of the four alcohols 7, 8, 12, and 14 in hexane showed that the π-route products 7 and 8 had O-H stretching absorptions at 3628 cm^{-1} and 3623 cm^{-1}, respectively, indicative of a free hydroxyl and therefore requiring the <u>anti</u> stereochemistry shown. In contrast 12 and 14 gave absorptions at 3539 cm^{-1} and 3490 cm^{-1}, respectively, characteristic of a hydrogen-bonded O-H stretch. This demonstrated that the hydroxyl functions of 12 and 14 must be intramolecularly hydrogen bonded to the ring nitrogen and therefore must have the <u>syn</u> stereochemistry indicated. The stereochemistry of the chlorine atom in 5 was assigned on the basis of the similarity of the nmr spectrum of 5 with that of 12.

Mechanistically, five of the six products obtained from 1 in THF-water-Ag$^+$ are readily rationalized in terms of nitrenium ion reactions. Initial ionization of 1 would give the



1 15 16 6 18 17 8 7 2 19 9

singlet nitrenium ion 15. A 1,2-proton shift would give 16 which on hydrolysis would produce 6. Intramolecular addition of the singlet nitrenium ion to the double bond would give 17.[7] Attack of nucleophilic solvent at point a would produce 8 while a similar attack at b would yield 7. Spin inversion of 15 would result in formation of the triplet nitrenium ion 18.[8] Hydrogen abstraction from solvent would give the protonated form of 2 while intramolecular addition to the double bond could produce the 1,3-triplet diradical 19. Hydrogen abstraction by 19 would yield the protonated form of 9.[9]

It is interesting to note that 6, 7, and 8 could also be derived from 18. A 1,2-hydrogen shift would give 6 *via* 16. Spin inversion and closure of 19 could conceivably yield 17 as a discrete aziridinium salt which would eventually yield 7 and 8. The formation of 5 is best represented by a *cis* addition of the N-Cl moiety across the double bond.

This study firmly establishes that the π-route to azabicyclics *via* nitrenium ions formally involves a *trans* addition to the double bond. It also demonstrates that a variety of azabicyclics can be produced through the intramolecular π-route.

Acknowledgment. We are indebted to the National Cancer Institute of the Public Health Service for Grant CA-07110 which supported this investigation.

References

1. Paper XIII in a series on The Chemistry of Nitrenium Ions. For the previous paper in this series see P. G. Gassman and G. A. Campbell, *Chem. Commun.*, 427 (1970).

2. P. G. Gassman, F. Hoyda, and J. Dygos, *J. Am. Chem. Soc.*, 90, 2716 (1968).

3. For a review of this topic see P. G. Gassman, *Accounts Chem. Res.*, 3, 26 (1970).

4. Percentage yields were based on unrecovered 2.

5. A modification of the procedure of Huffman and coworkers was used. J. W. Huffman, C. B. S. Rao, and T. Kamiya, *J. Org. Chem.*, 32, 697, 700 (1967).

6. Compound 9 was independently synthesized from *m*-aminobenzoic acid *via* the sequence: reduction over ruthenium on carbon, thermal cyclization of the resulting *cis*-3-aminocyclohexanecarboxylic acid, N-methylation, and lithium aluminum hydride reduction.

7. The structure drawn for 17 is not meant to be rigorous. Two separate intermediates could be involved at this stage, resulting from addition of the nitrenium ion to the different ends of the double bond. It is also possible that 17 may be formed directly from 1 *via* neighboring group participation of the double bond in the ionization step.

8. For a discussion of spin inversion in nitrenium ions see P. G. Gassman and R. L. Cryberg, *J. Am. Chem. Soc.*, 91, 5176 (1969).

9. Hydride abstraction from solvent by 15 and 17 could also explain the presence of 2 and 9, respectively.