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High Resolution Mass Spectrometry
in Molecular Structure and Stereochemical Studies:
Effect of Stereochemistry on the Fragmentation
of Epimeric Derivatives of Azabicycloalkanes¹

by

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A recent study by A. L. Burlingame, H. O. House and co-workers³ involved an examination of possible correlations that might be drawn between the low resolution mass spectra and the structures and stereochemistry of a series of related azabicycloalkanes. This work concluded that the stereochemistry about the bridgehead carbon atom could be determined by examining the relative intensities of molecular ion minus a hydrogen (M-1) peaks between epimeric pairs and, in some cases, namely the secondary alcohols and ethers, the relative intensities of m/e 44 and 58.

The peak at M-1 was shown to arise from loss of a hydrogen atom from a carbon atom adjacent to nitrogen. With reference to Figure 1, it may be noted that there exists considerable 1, 3-diaxial interaction between the substituent on the bridgehead carbon and the axial hydrogens (labeled H_a) on the carbons adjacent to nitrogen. Loss of one of these axial hydrogens from a molecular ion results in relief of some of this interaction plus the formation of a stable immonium ion as illustrated. Indeed, it was found that the epimer with the larger substituent oriented toward nitrogen displayed the larger M-1 peak, and thus this fragmentation proves useful in determining stereochemistry about the bridgehead.

The fragmentations of secondary alcohols or ethers mentioned above leading to m/e 44 and 58 are more complicated processes, but also proved useful in elucidating stereochemistry. These processes are summarized in Figure 2. Cleavage of an α - β carbon bond in both epimers yields an immonium ion that can be pictured as structure A. From this molecular ion it was demonstrated that two different rearrangement processes take place dependent on the stereochemistry of the bridgehead. In the case of the β -epimer, with the hydroxyl group oriented toward nitrogen, a rearrangement that may be pictured as shown in structure B yields a fragment ion at m/e 44, with the composition C₂H₆N, while a similar rearrangement pictured in structure B' for the α -epimer yields a fragment ion at m/e 58, of composition C₃H₈N.

High resolution mass spectra of representative members of the series were determined employing a Mattauch-Herzog double focusing instrument (CEC type 21-110) with photoplate recording. Subsequent data acquisition and reduction employing our automatic plate scanning system and the computer facilities of the Lawrence Radiation Laboratory verified the compositions of the peaks discussed above in the initial paper, but, more importantly, proved invaluable in elucidating certain features of the fragmentation patterns of epimeric pairs. These epimers displayed fragmentation patterns that were quite different in many respects. For example, several peaks in the mass spectrum of one epimer were missing entirely in the spectrum of the other epimer, and there were, in certain regions of the spectra, marked intensity differences between the two epimers other than those mentioned above.

The first pair of epimers provides an illustrative example of the generalizations noted in the low resolution studies. The compound, as drawn, has a six-membered ring to the left and is a secondary alcohol. The distribution of peaks in the hydrocarbon and oxygen containing plots⁴ is quite similar for the epimers. Figure 3 represents the nitrogen and nitrogen-oxygen containing plots for the same epimers. The molecular ion has the composition C₉H₁₇NO. For the β -epimer, with OH oriented toward nitrogen, the M-1 peak C₉H₁₆NO, is larger than that of the α -epimer, with the hydrogen (less bulky than OH) oriented toward nitrogen. Also, exactly as noted before, the peak at C₂H₆H is larger than that of C₃H₈N for the β -epimer, while the intensity ratio is effectively reversed in the C/H N plot of the α -epimer. There is one more feature of this set of spectra that has significance to the following discussion, and that is the presence of relatively intense peaks in the C/H N plot of the β -epimer at C₉H₁₅N and C₉H₁₄N, representing loss of the elements of H₂O and H₃O respectively, from the molecular ion. These peaks are virtually absent in the C/H N plot of the corresponding epimer.

The next pair of epimers provides perhaps the most graphic examples of the dependence of the fragmentation pattern on stereochemistry. Again, the C/H and C/H O plots are quite similar with the exception of a much larger C_6H_5 fragment ion in the spectrum of the α -epimer, which has the phenyl group oriented toward nitrogen. This presumably arises from the 1, 3 diaxial interactions noted above; interactions that are considerably more pronounced for phenyl versus OH.

Figure 4, however, which contains the C/H N and C/H N O plots for the same pair, displays marked differences. In particular, one may note the larger M-1 peak for the α -epimer at $C_{15}H_{30}NO$, as expected; the presence of peaks in the lower C/H N O plot, at $C_9H_{15}NO$ (peak D') and C_6H_8NO (peak E') that are absent in the C/H N O plot of the β -epimer; the larger M-H₂O and M-H₃O peaks in the C/H N plot of the β -epimer at $C_{15}H_{19}N$ (peak D) and $C_{15}H_{18}N$; and finally the presence of an intense peak at $C_{12}H_{12}N$ (peak E) in the β -epimer that is entirely absent in the C/H N plot of the α -epimer. These differences can be explained quite readily if the fragmentation is assumed to proceed as shown in Figure 5. In both epimers the fragmentation proceeds either with loss of a hydrogen followed by loss of the group oriented toward nitrogen, or a single step elimination of the elements of H₂O or C₆H₆ in the β - and α -epimers respectively. In the case of the β -epimer this process yields the fragment ion D $C_{15}H_{19}N$, a much more favorable process than in the α -epimer, while in the case of the α -epimer, a peak at $C_9H_{15}NO$ (peak D') results. Elimination of a C_3H_7 radical as shown, to aromatize the system, from both of these fragments, yields $C_{12}H_{12}N$ (peak E) for the β -epimer, and C_6H_8NO (peak E') for the α -epimer. Thus this rather straightforward fragmentation scheme, dependent entirely on stereochemistry, is sufficient to account for the more obvious dissimilarities between the two spectra.

Also of interest are the fragmentation patterns of the β - and α -epimers of a compound similar to that discussed above, but with a seven-membered ring instead of six. The pairs of C/H and C/H O plots are virtually identical, but again as above, there exist several marked dissimilarities in the pairs of C/H N and C/H N O plots presented in Figure 6 (note peaks F, F', G, G', H, H'). These differences can be explained assuming a mechanism exactly as that discussed above. With reference to Figure 7, the more intense M-H₂O and M-H₃O peaks at $C_{16}H_{21}N$ and $C_{16}H_{20}N$ (peaks F) in the spectrum of the β -epimer are due to the more facile elimination of these elements from the molecular ion, $C_{16}H_{23}NO$, of the β -epimer. In the spectrum of the α -epimer, however, elimination of the elements of C₆H₆ or C₆H₇ initially from the molecular ion yields the peaks at $C_{10}H_{17}NO$ and $C_{10}H_{16}NO$ (peaks F'). In this case, both fragments F and F' can eliminate either a propyl or butyl radical to yield $C_{13}H_{14}N$ (peak G) or $C_{12}H_{12}N$ (peak H) in the β -epimer, or $C_7H_{10}NO$ (peak G') or C_6H_8NO (peak H') in the α -epimer. These peaks are unique for each compound with the exception of peak H and a very light elimination of H₂O and H₃O in the α -epimer. There exists a small peak at $C_{12}H_{12}N$ in the α -epimer's spectrum also, but the fragmentation process leading to this ion is obviously less favorable.

As the substituent on the bridgehead becomes less and less large compared to OH, the above processes become less clearly resolved. One can, however, still easily discern that these fragmentations are occurring, as may be seen in Figure 8. This epimeric pair has a methyl group on the bridgehead. The O/H and C/H O plots are again similar although there are several intensity differences. The C/H N and C/H N O plots as presented in Figure 8 again display a stereochemical influence on the fragmentation similar to those discussed above. The M-H₂O and M-H₃O peaks are more pronounced for the β -epimer. Loss of a propyl radical in this epimer as above yields a distinct difference in the intensity of the $C_7H_{10}N$ peak as compared to the α -epimer. Loss of a methyl group to yield a fragment ion with the composition $C_9H_{16}NO$ is more favorable for the α -epimer. It is important to note, however, that loss of a three carbon fragment in this spectrum in a mechanism analogous to those shown above to yield an ion of composition C_6H_8NO is neither a unique nor a dominant process. This may result from the fact that loss of a hydrogen radical from the molecular ion followed by loss of CH₃ or a single step process of loss of CH₄ is apparently not a favorable process.

The net results of this study may be summarized as follows:

1. M-1 is larger for the epimer with a larger substituent oriented toward nitrogen.
2. Fragmentation proceeds with loss of the substituent oriented toward nitrogen to yield a C/H N fragment ion in the β -epimers or a C/H N O fragmentation for the α -epimers.
3. Other differences in the C/H N and C/H N O plots may be explained by loss of an appropriate aliphatic radical from the ions in No. 2 above.

In summary, then, the techniques of high resolution mass spectrometry combined with heteroatomic plotting for data presentation have made possible elucidation of important fragmentation processes in the azabicycloalkane series studied; processes that are entirely dependent on stereochemical influences.

FOOTNOTES

- 1) This work has been supported in part by a grant from the National Aeronautics and Space Administration, NsG 101.
- 2) NASA Predoctoral Trainee, 1965-67.
- 3) W. M. Bryant, III, A. L. Burlingame, H. O. House, C. G. Pitt, and B. A. Tefertiller, J. Org. Chem., in press.
- 4) For detailed discussion of heteroatomic plotting presentation of high resolution mass spectral data, see A. L. Burlingame and D. H. Smith, Tetrahedron Letters, in press.

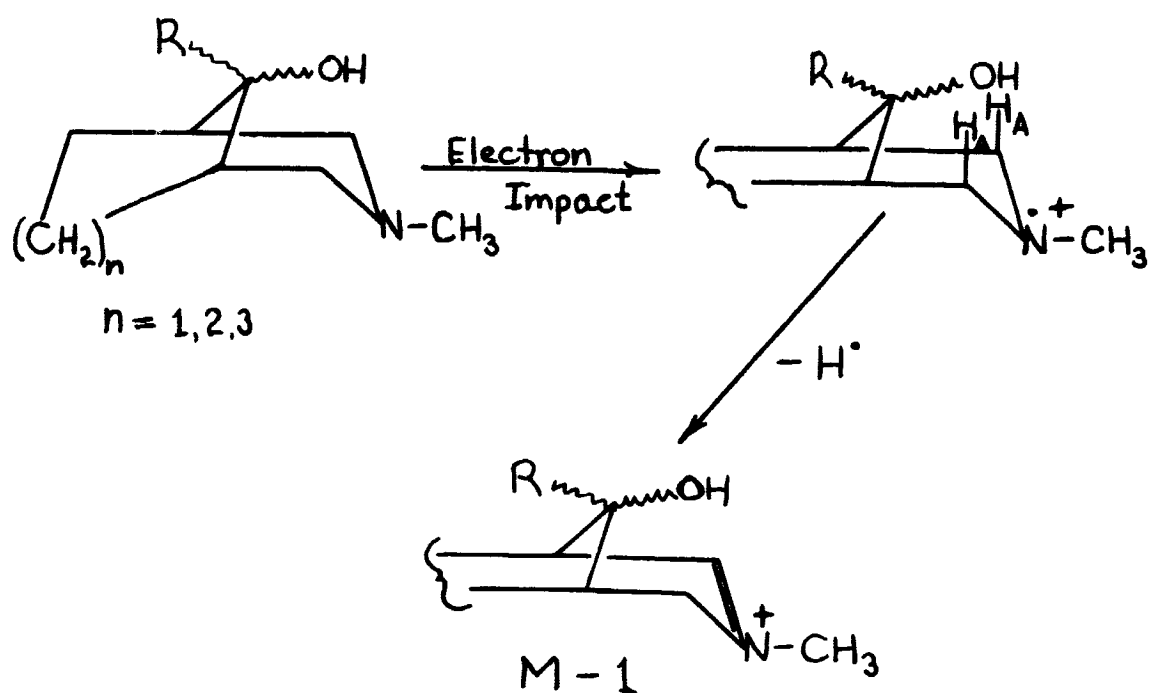


FIGURE 1

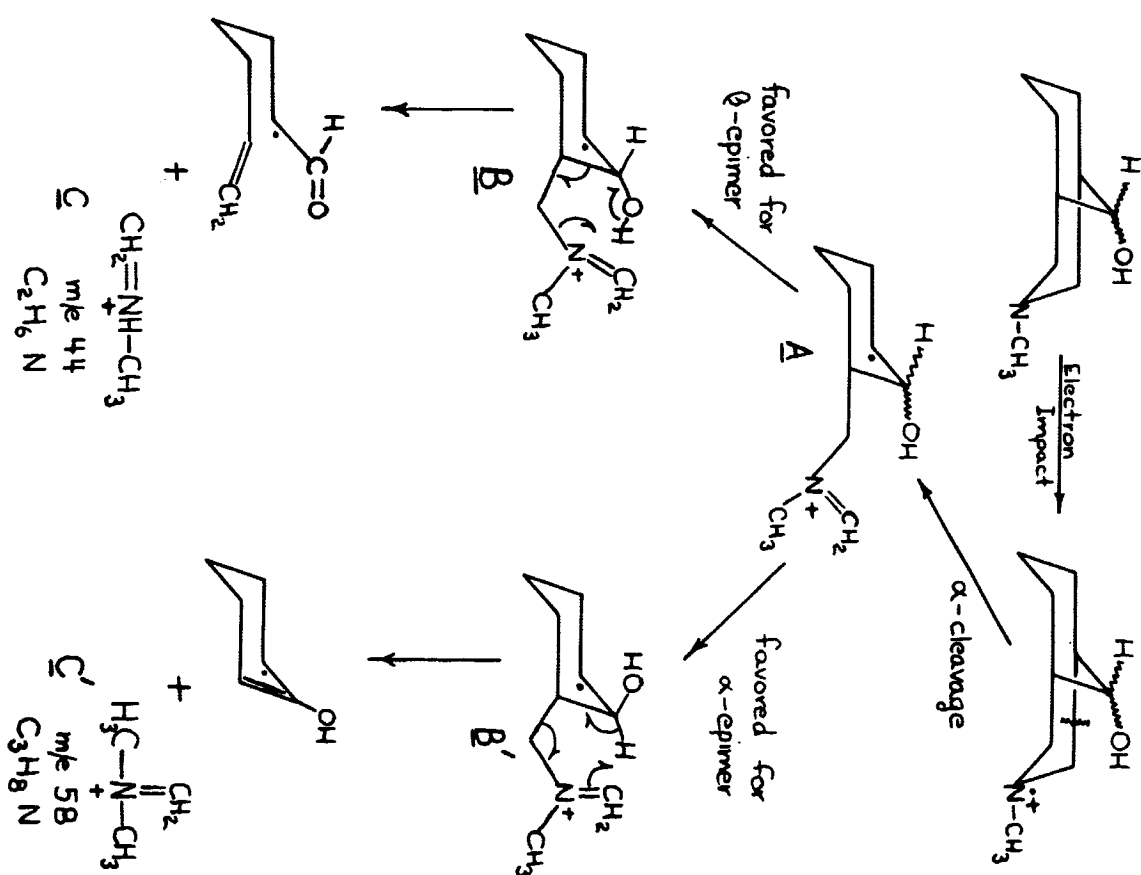


FIGURE 2

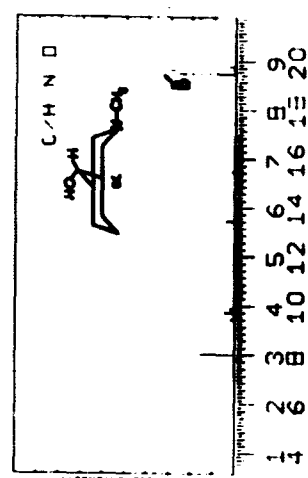
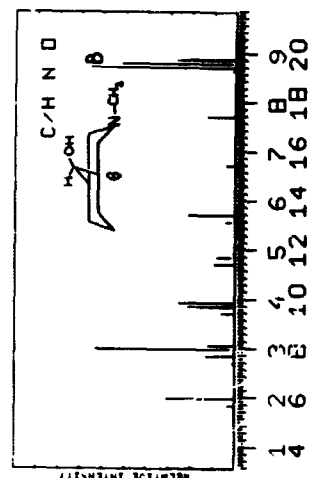
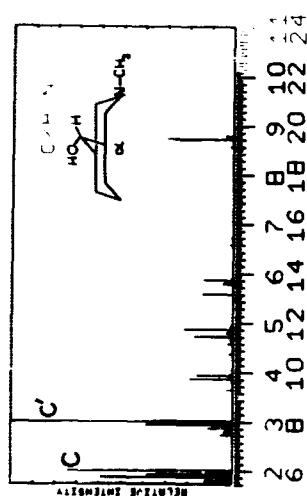
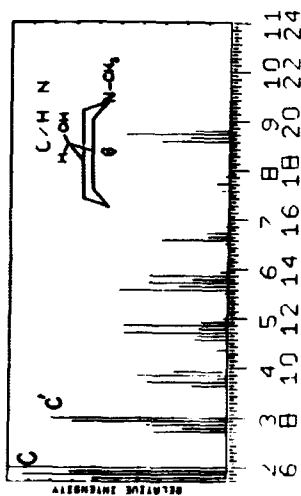


FIGURE 3

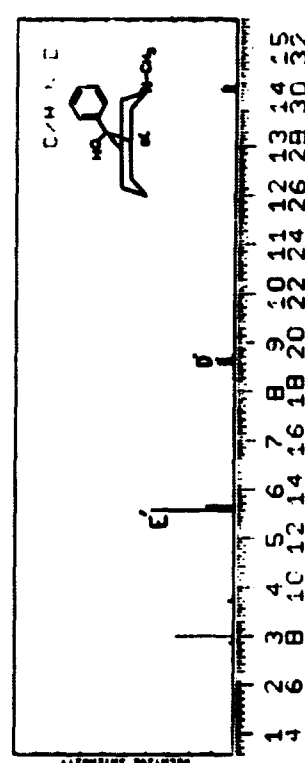
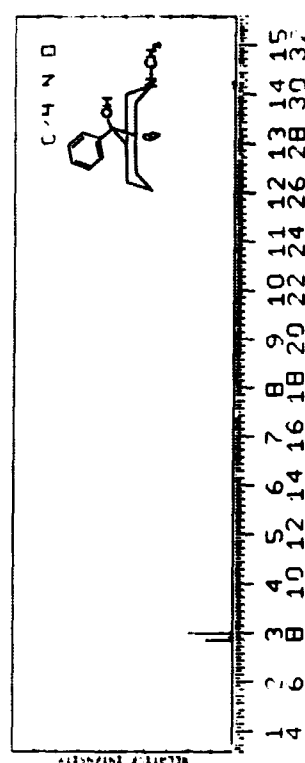
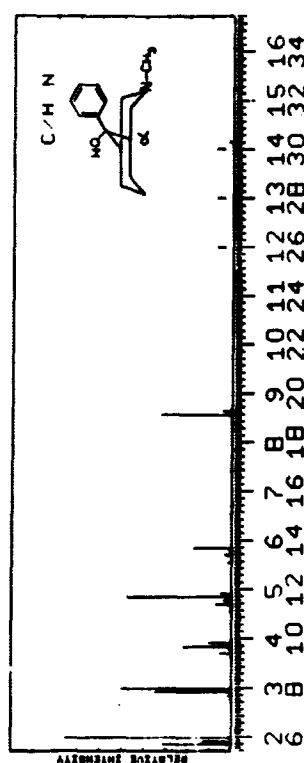
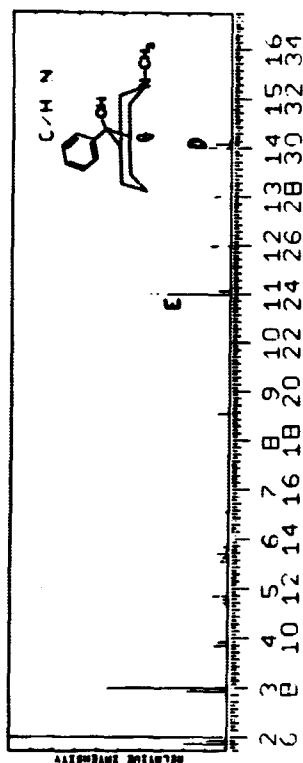


FIGURE 4

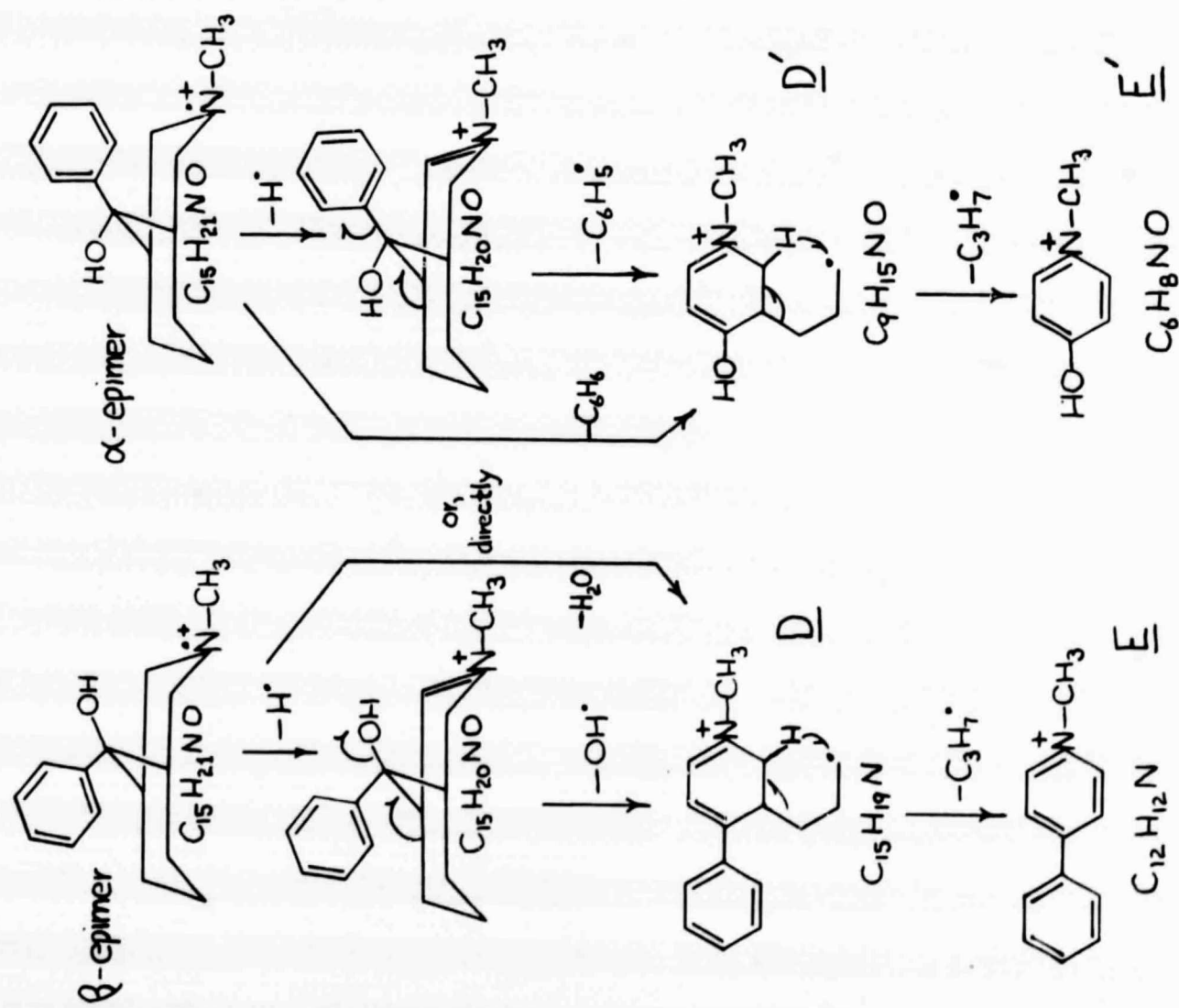


FIGURE 5

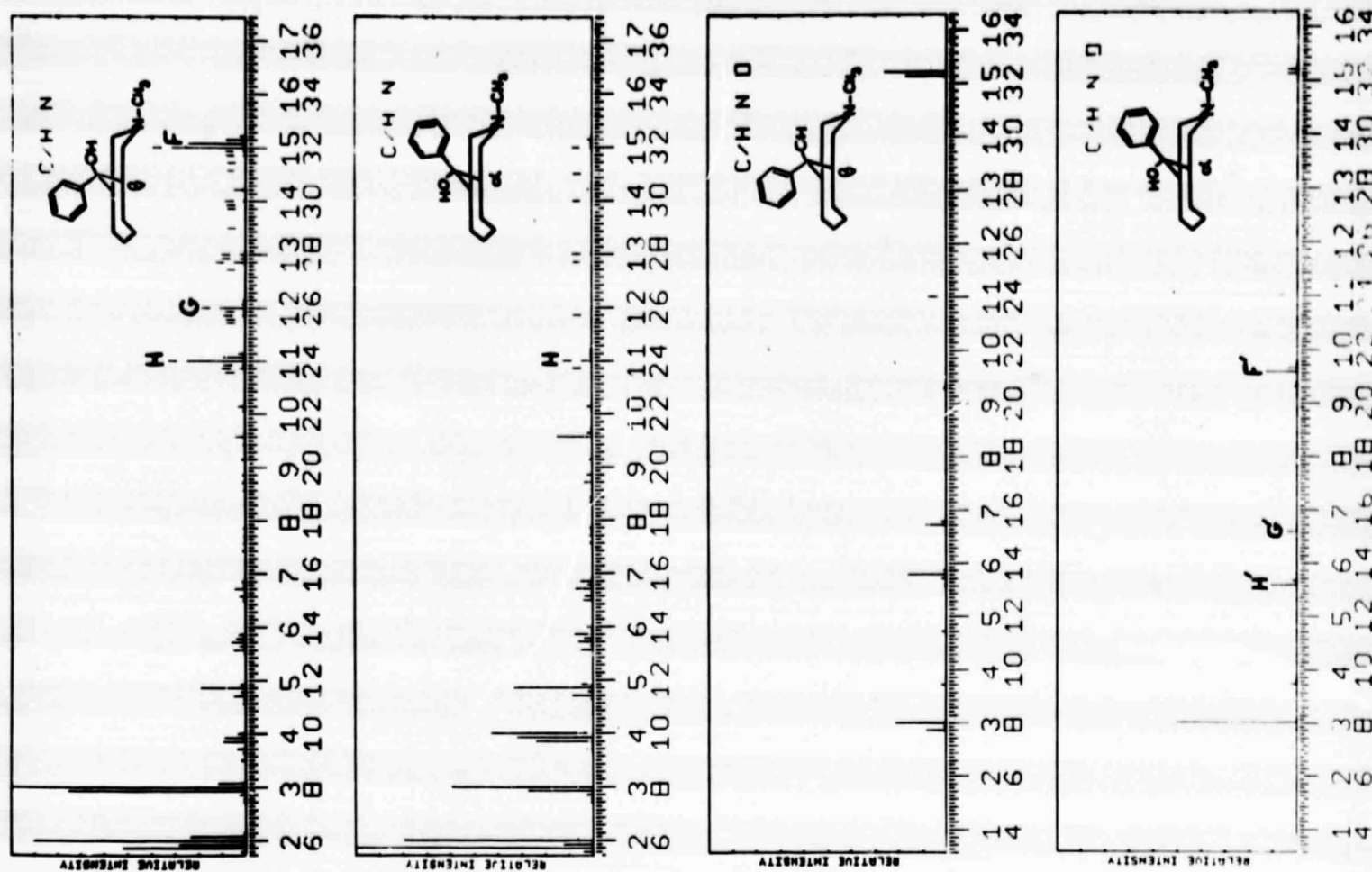


FIGURE 6

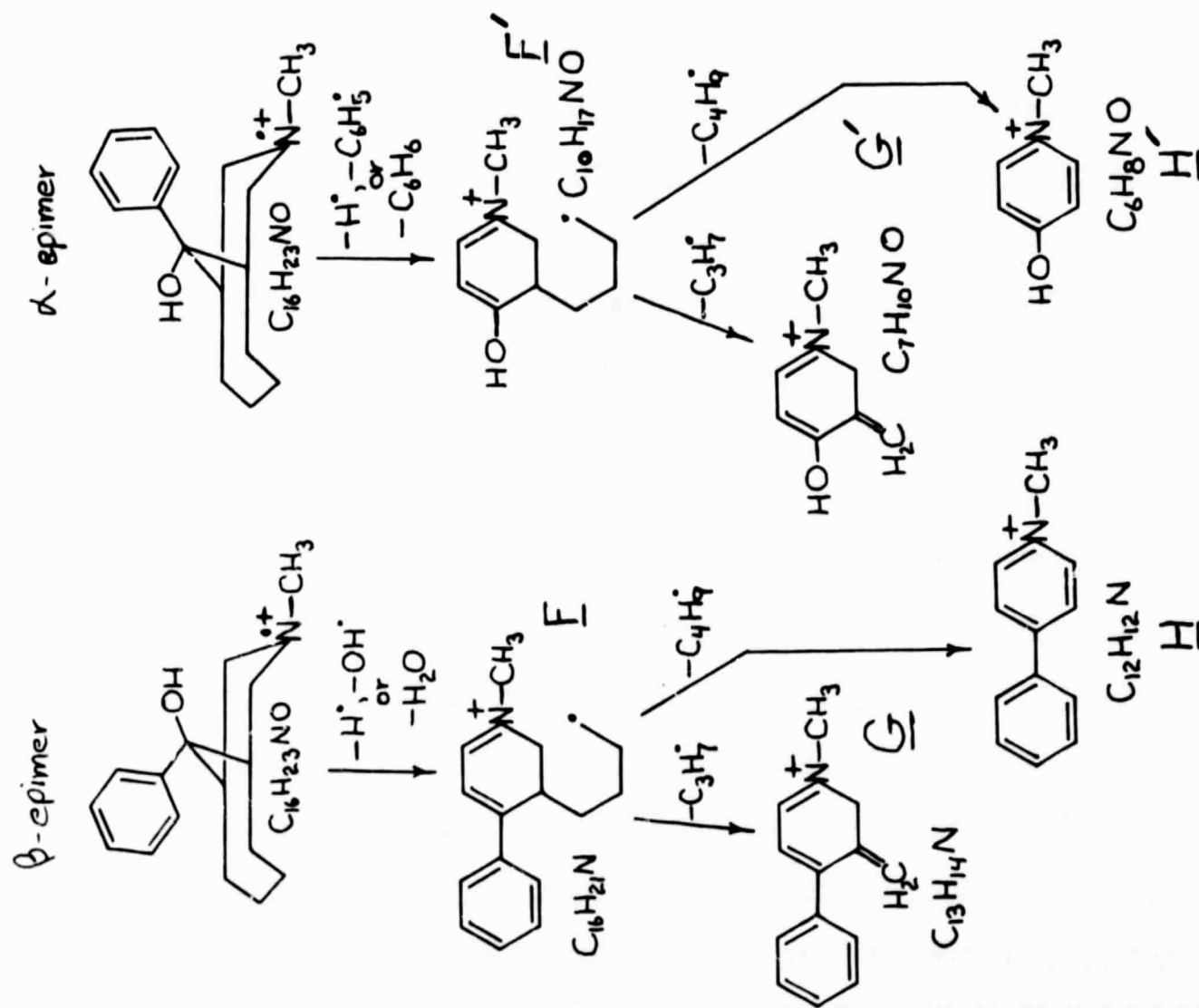


FIGURE 7

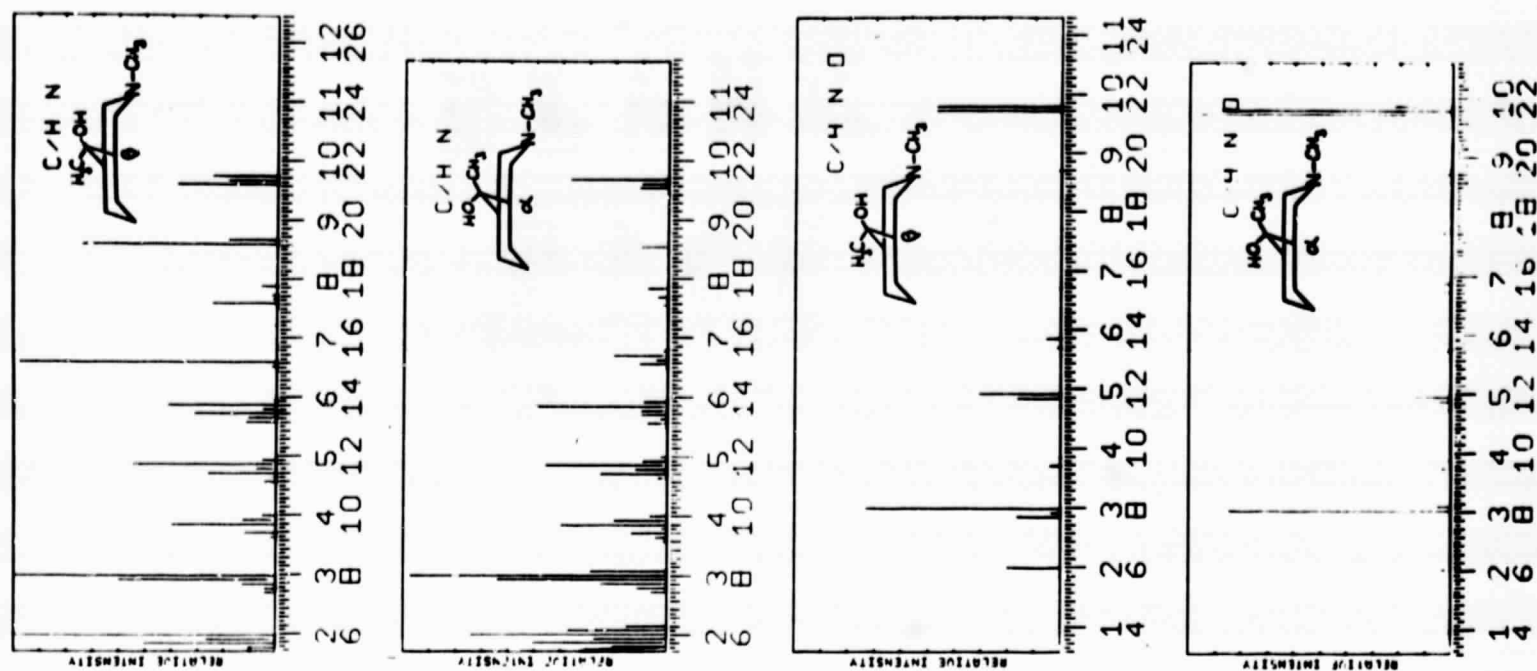


FIGURE 8