The Mass Spectra of Derivatives of 3-Azabicyclo[3.2.1]octane, 3-Azabicyclo[3.3.1]nonane, and 8-Azabicyclo[4.3.1]decane[1,2]

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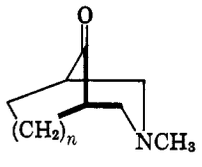
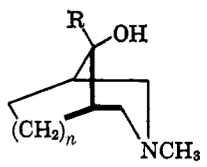
The mass spectra of the amino ketones **1–3** and amino alcohols **4–17** have been measured as well as the mass spectra of the related substances **18–26** and **33–35**. The mass spectra of stereoisomeric pairs of amino alcohols (*e.g.*, **6** and **12**) were found to differ in a systematic way which could be used to make stereochemical assignments.

The availability of a number of related azabicycloalkanes[3] (**1–19**) as well as several similar compounds (**20–26**) led us to consider what correlations might be drawn between the low-resolution[4] mass spectra of these substances and their structure and stereochemistry.[5] We were especially interested in examining whether the stereochemistry of epimeric pairs of amino alcohols (*e.g.*, **4** and **11**) could be determined from their mass spectra. The mass spectra of amines **1–19** are presented in Figures 1–9. To aid interpretation of the spectra, the deuterated ketone **27**[3b] as well as the alcohols **28** and **29** and the partially O-deuterated derivatives of alcohols **6** and **12** were also examined; these spectra are summarized in Figures 10 and 11.

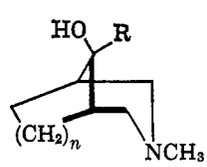


1, $n = 1$
2, $n = 2$
3, $n = 3$



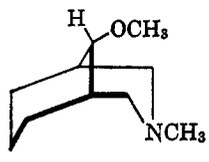
β isomers

4, $n = 1$; R = H
5, $n = 1$; R = CH_3
6, $n = 2$; R = H
7, $n = 2$; R = CH_3
8, $n = 2$; R = C_6H_5
9, $n = 3$; R = H
10, $n = 3$; R = C_6H_5



α isomers

11, $n = 1$; R = H
12, $n = 2$; R = H
13, $n = 2$; R = CH_3
14, $n = 2$; R = C_6H_5
15, $n = 3$; R = H
16, $n = 3$; R = CH_3
17, $n = 3$; R = C_6H_5



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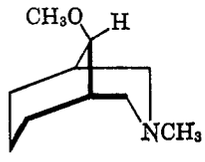

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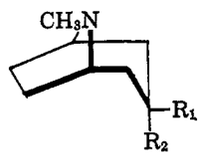
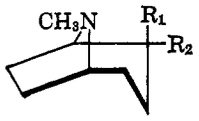
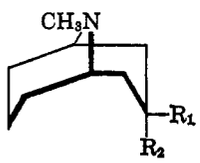


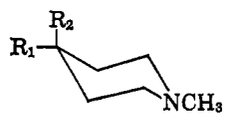
20, R_1=H; R_2=OH
21, R_1=OH; R_2=H



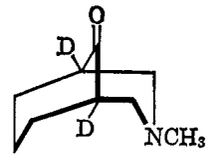
22, R_1 = H; R_2 = OH
23, R_1 = OH; R_2 = H



24, R_1 and R_2 = O
25, R_1 = H; R_2 = OH
26, R_1 = OH; R_2 = H



33, $R_1 = R_2$ = H
34, R_1 = *t*-Bu; R_2 = H
35, R_1 = *t*-Bu; R_2 = OH



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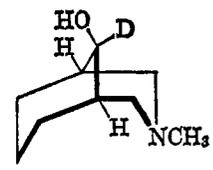

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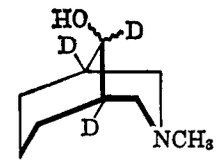
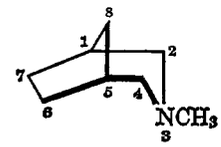


29 (mixture of stereoisomers)

The mass spectra (Figures 12–14) of the tropane derivatives **20–23**[6] and the granatanine derivatives **24–26** are included for comparison along with the spectra of the piperidine derivatives **33–35** (Figure 15). To simplify discussion of these spectra, corresponding or related fragment peaks which occur in a number of the spectra are considered together. For each of the 3-azabicyclo[3.3.1] derivatives, **2**, **6–8**, and **12–14**, the elemental compositions of the fragments were determined by accurate mass measurements; other compounds whose high-resolution mass spectra have been measured include **1**, **10**, and **17**. The numbering system employed is illustrated in formulas **30**, **31**, and **32**.



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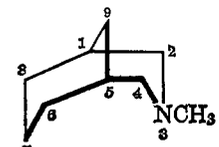

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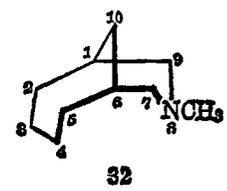

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(1) The research at the Massachusetts Institute of Technology was supported by research grants from the National Institutes of Health (Grant No. G.M.-08761) and the Petroleum Research Fund (Grant No. 594-A).

(2) The research at the University of California, Berkeley, was supported in part by National Aeronautics and Space Administration Grant NSG 101.

(3) (a) H. O. House, P. P. Wickham, and H. C. Müller, *J. Am. Chem. Soc.*, **84**, 3139 (1962); (b) H. O. House and H. C. Müller, *J. Org. Chem.*, **27**, 4436 (1962); (c) H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *ibid.*, **28**, 2407 (1963); (d) H. O. House and W. M. Bryant, *ibid.*, **30**, 3634 (1965); (e) H. O. House and C. G. Pitt, *ibid.*, **31**, 1062 (1966); (f) H. O. House, B. A. Tefertiller, and C. G. Pitt, *ibid.*, **31**, 1073 (1966).

(4) The presentation and interpretation of the high-resolution mass spectra of these compounds will be published elsewhere by A. L. Burlingame, H. K. Schnoes, and D. H. Smith.

(5) For general discussions of the mass spectra of organic compounds, see (a) J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry," Elsevier Publishing Co., New York, N. Y., 1960; (b) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; (c) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964.

(6) The mass spectra of the tropanols **20–23** have been discussed elsewhere. See (a) ref 5c, pp 92–110; (b) E. C. Blossey, H. Budzikiewicz, M. Ohashi, G. Fodor, and C. Djerassi, *Tetrahedron*, **20**, 585 (1964); (c) J. Parello, P. Longevialle, W. Vetter, and J. A. McCloskey, *Bull. Soc. Chim. France*, 2787 (1963); (d) L. W. Daasch, Abstracts 13th Annual Conference on Mass Spectrometry and Allied Topics, May 16–21, 1965, St. Louis, Mo., pp 409–414. (e) For mass spectra of the monocyclic amines, N-methylpyrrolidine, and N-methylpiperidine, see A. M. Duffield, H. Budzikiewicz, D. H. Williams, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 810 (1965) and, also, R. A. Saunders and A. E. Williams, in "Advances in Mass Spectrometry," Vol. 3, W. L. Mead, Ed., Institute of Petroleum, London, 1966, pp 681–700.

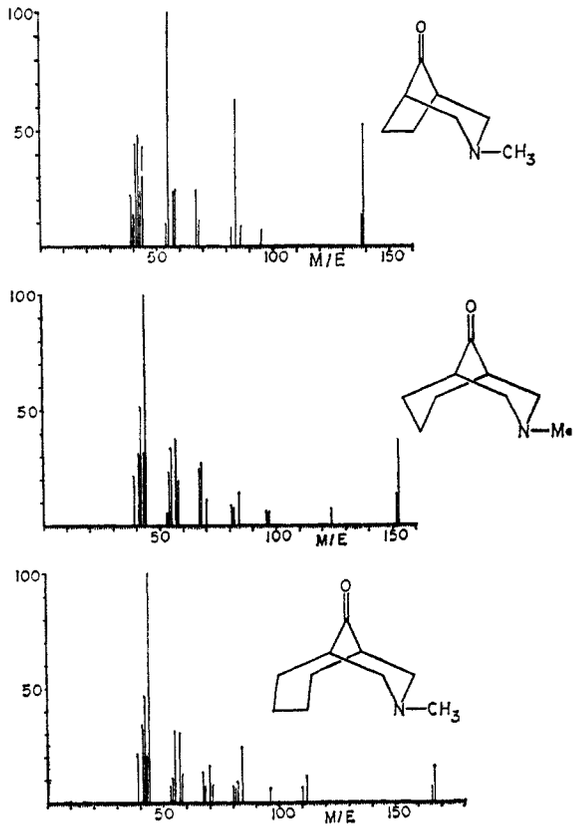


Figure 1. —Mass spectra of amino ketones **1–3.**

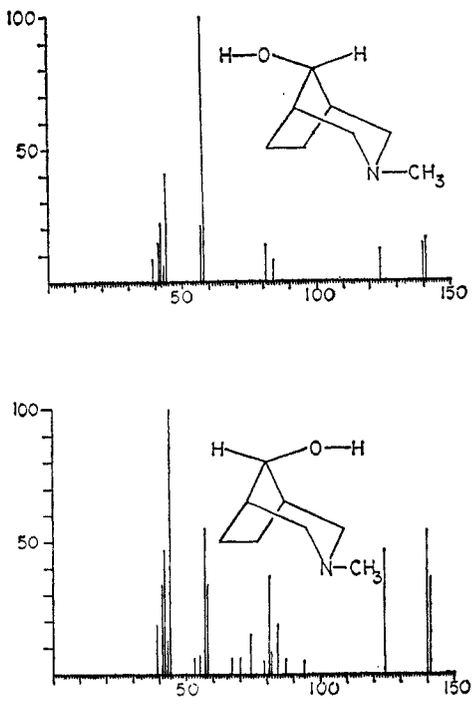


Figure 2.—Mass spectra of amino alcohols **4** and **11.**

The M − 1 Peak.—Each of the ketone and alcohol derivatives **1–19** as well as the monocyclic amines **33–35** exhibits a fragment peak of appreciable intensity corresponding to the loss of one hydrogen atom. Both analogy with the known fragmentation patterns of amines[5] and the fact that the deuterated samples **27–29** lose one mass unit (*i.e.*, hydrogen and not deuterium) strongly suggest that the hydrogen atom is being lost

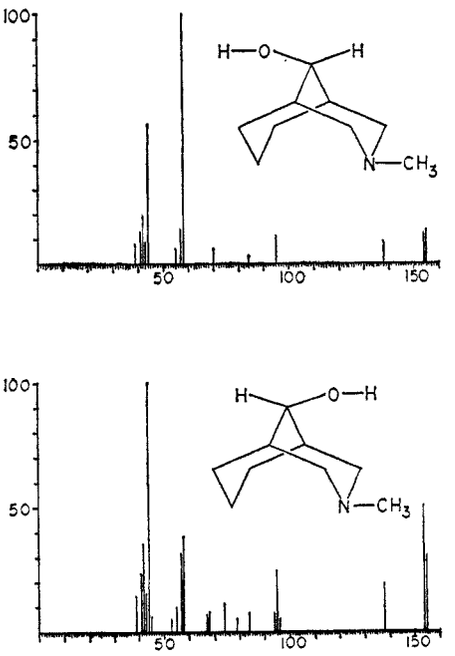
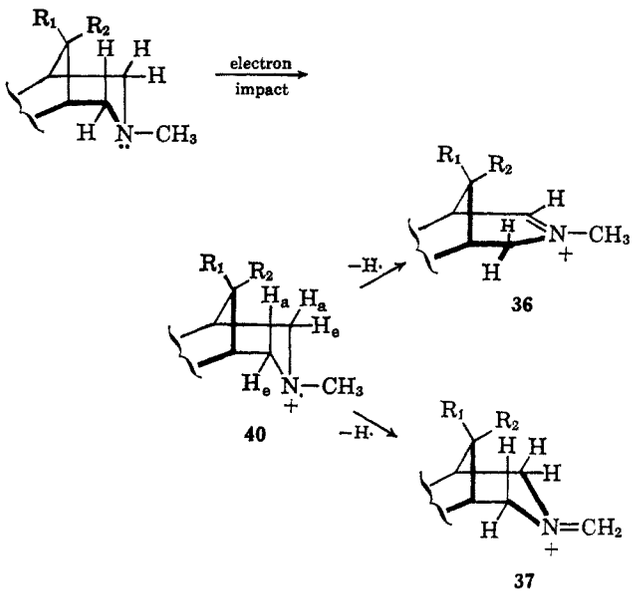
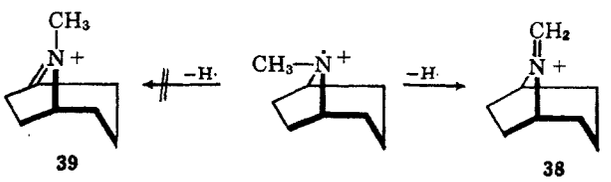


Figure 3.—Mass spectra of amino alcohols **6** and **12.**

from one of the carbon atoms α to nitrogen as in structures **36** and/or **37**. Of these two immonium ions **36** and **37**, we believe the fragmentation leading to the



more highly substituted immonium ion **36** is the more likely process. In the first place, cleavage at the α carbon of the more highly substituted alkyl group of tertiary amines is generally observed,[5] a result which presumably reflects the greater stability of the more highly substituted immonium ion. Also, neither the tropane or granatanine derivatives **20–26** exhibit appreciable M − 1 fragment peaks. The absence of this peak is readily understood if the formation of an unsubstituted immonium ion (*i.e.*, **37** or **38**) is not favorable



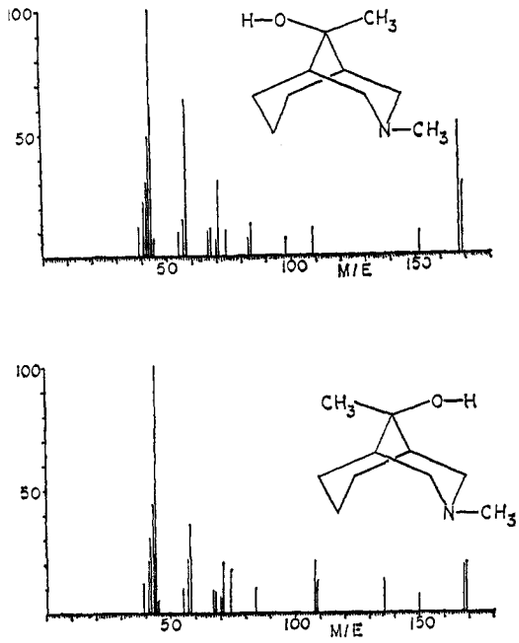


Figure 4.—Mass spectra of amino alcohols **7** and **13**.

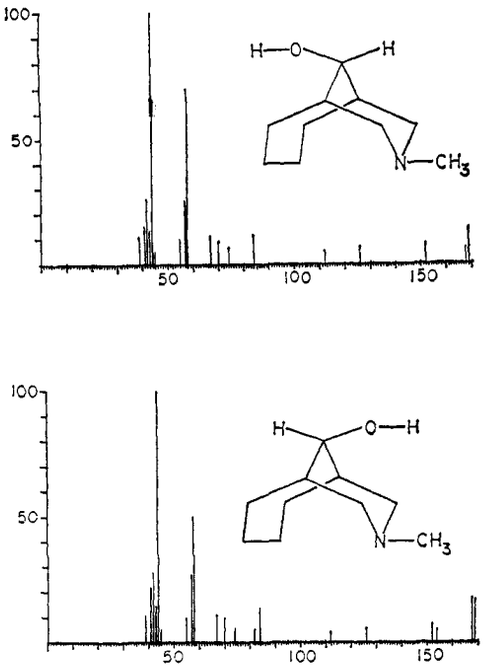


Figure 6.—Mass spectra of amino alcohols **9** and **15**.

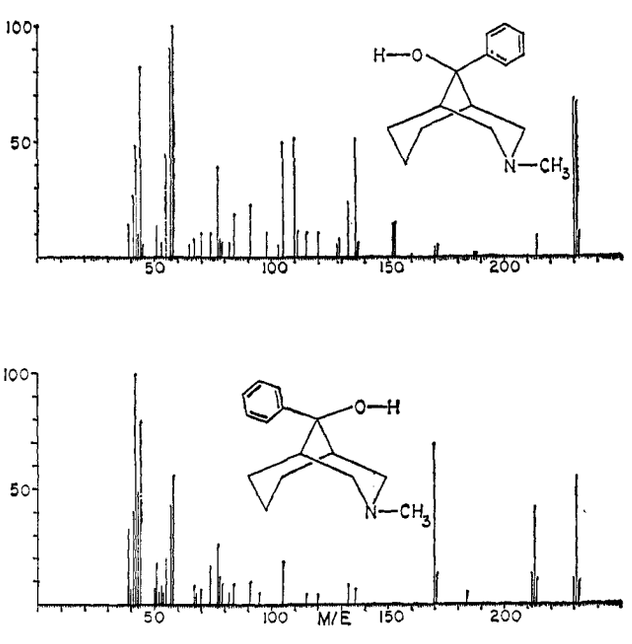


Figure 5.—Mass spectra of amino alcohols **8** and **14**.

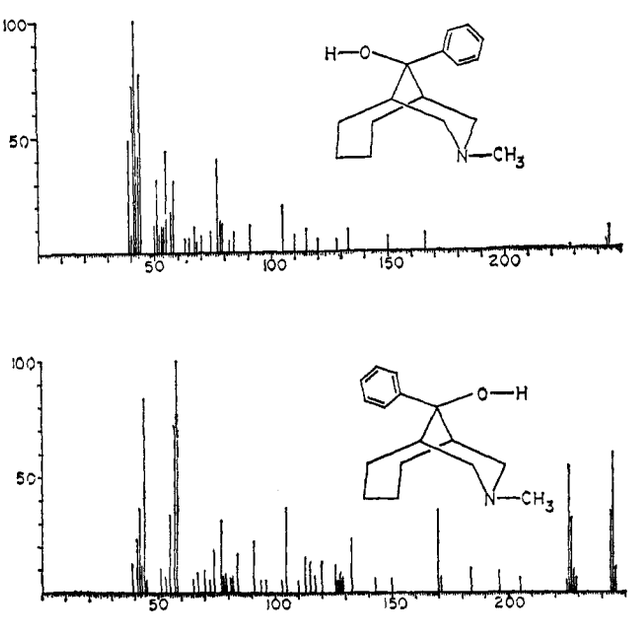


Figure 7.—Mass spectra of amino alcohols **10** and **17**.

since, unlike the ion **36**, the more highly substituted immonium ion (*e.g.*, **39**) derived from tropane or granatanine derivatives would be highly strained and, consequently, energetically unfavorable.

The relative intensities of the M − 1 peaks were found to vary with the stereochemistry of various alcohol derivatives **4**–**19**. For the various pairs of epimers studied, the M − 1 peak was more abundant for the epimer in which the larger substituent on the one carbon bridge was oriented toward nitrogen. This result can be rationalized by reference to structure **40** in which it is apparent that the substituent R_2 bears a 1,3-diaxial relationship to the hydrogen atoms designated H_a. This interaction would be relieved by loss of a hydrogen atom to form ion **36**, a result which would be expected[5b] to favor this mode of fragmentation of the molecular ion. Consequently, the fact that alcohols such as **6** (in **40**, R_1 = H, R_2 = OH) and **13** (in **40**, R_1 = OH, R_2 = CH_3) have more abundant M − 1 peaks than their epimers **12** (in **40**, R_1 = OH, R_2 = H) and **7** (in **40**, R_1 = CH_3, R_2 = OH) is understandable and offers a method for determining the stereochemistry of epimeric pairs of alcohols in the azabicyclooctane (**30**) and azabicyclononane (**31**) series. The difference between epimers diminishes in derivatives of the azabicyclodecane system **32** presumably because this system is conformationally more mobile than its lower homologs **30** and **31**.

The M − 17 Peak.—In each of the alcohols **4**–**17**, as well as the 3-tropanols **20** and **21**, the ganatanols **25** and **26**, and the deuterated alcohols **28** and **29**, M − 17 fragments are observed which are frequently comparable in abundance with the molecular ions. The relative intensities of these fragment peaks in the various amino alcohols show little, if any, difference which is

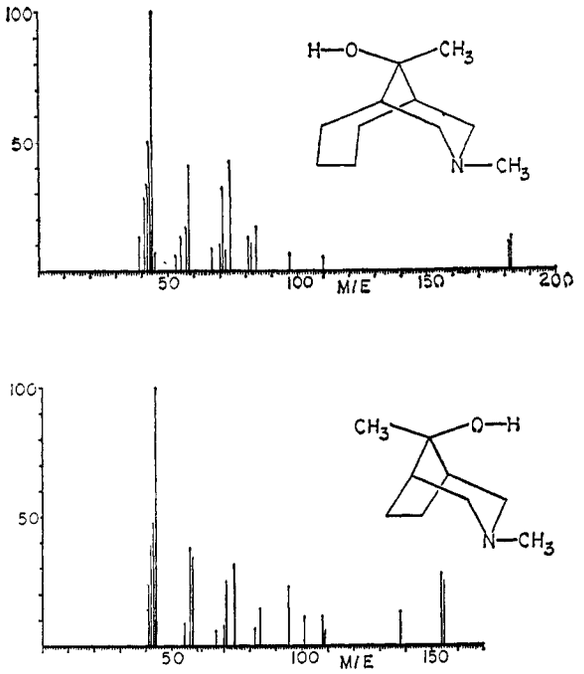


Figure 8.—Mass spectra of amino alcohols **5** and **16**.

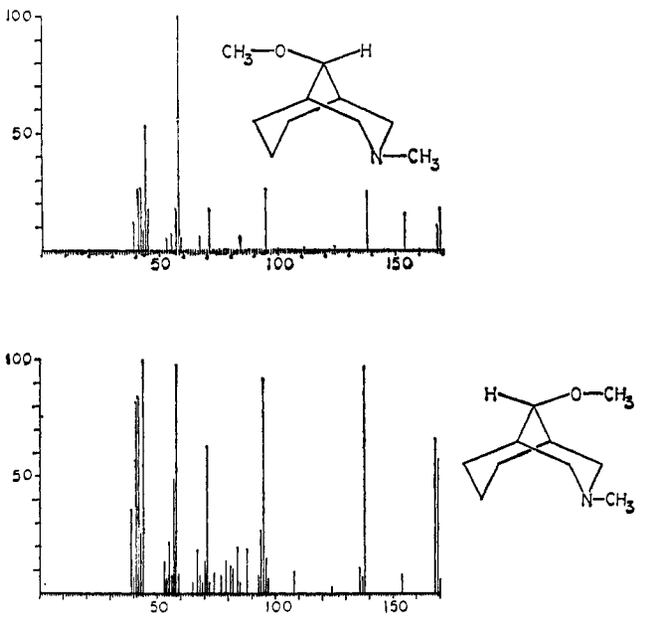


Figure 9.—Mass spectra of amino ethers **18** and **19**.

useful for assigning stereochemistry to the amino alcohols. Both the mass of the fragment lost (*i.e.*, 17) and the fact that the methoxy amines exhibit analogous peaks at M − 31 (*i.e.*, loss of CH_3O), suggest that the peak corresponds to the loss of a hydroxyl group from the molecular ion. This behavior is unusual in that alcohols normally[5] lose the elements of water (mass 18) rather than a hydroxyl group (mass 17). Two general pathways would appear plausible for this fragmentation; namely, the formation of an ammonium ion such as **41** or the fragmentation[7] illustrated in structure **42**. Although there is chemical precedent for the

(7) For reviews of this type of fragmentation in chemical reactions, see C. A. Grob in "Theoretical Organic Chemistry, Papers Presented to the Kekule Symposium," Butterworth and Co. (Publishers) Ltd., London, 1959, pp 114–126; C. A. Grob, *Bull. Soc. Chim. France*, 1360 (1960); C. A. Grob, *Gazz. Chim. Ital.*, **92**, 902 (1962).

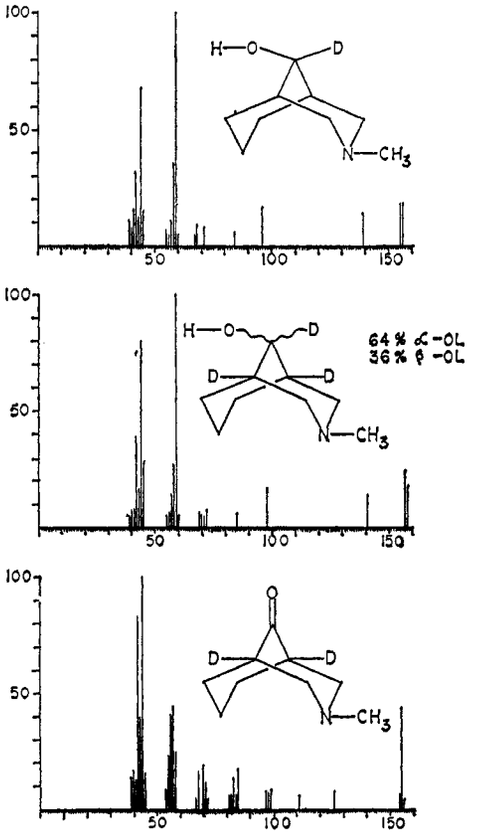


Figure 10.—Mass spectra of deuterated amines **27–29**.

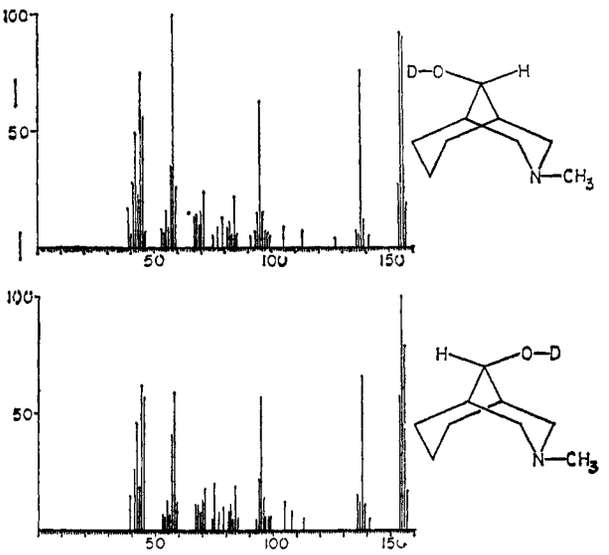
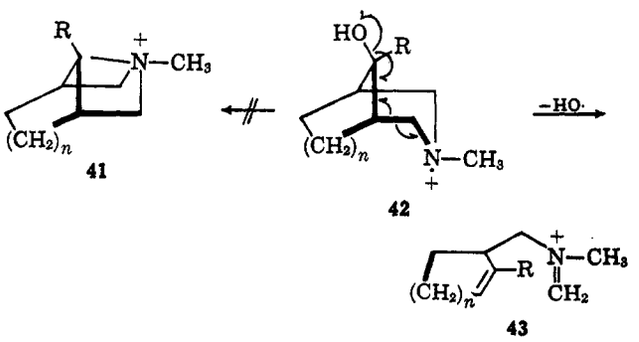


Figure 11.—Mass spectra of the O–D derivatives of amino alcohols **6** and **12** (only partial deuteration).



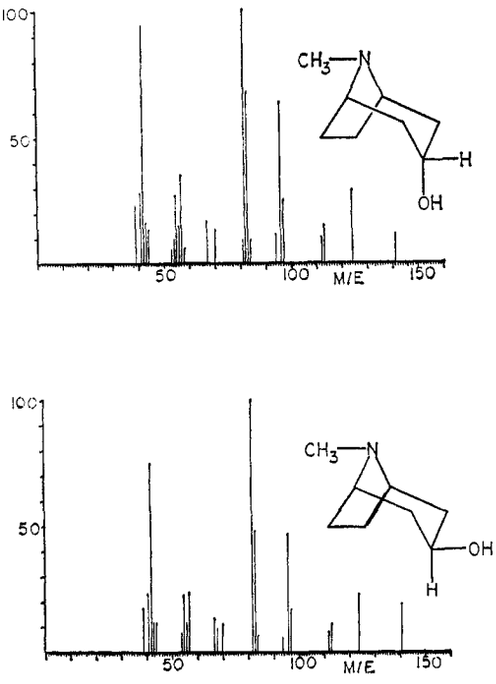


Figure 12.—Mass spectra of amino alcohols **20** and **21**.

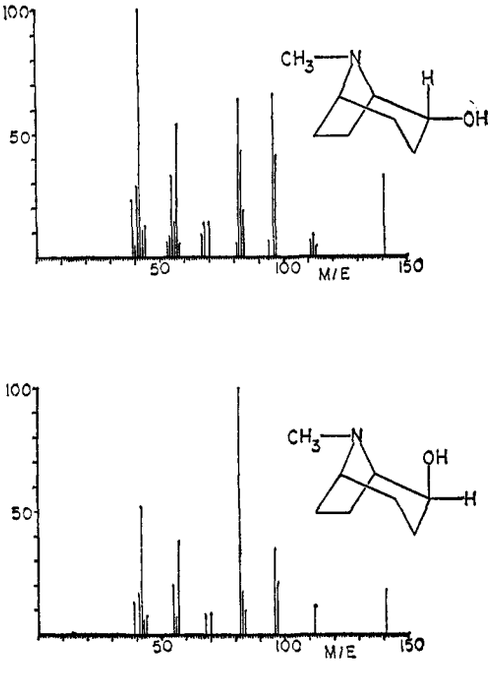


Figure 13.—Mass spectra of amino alcohols **22** and **23**.

formation of the ammonium ion **41**,[7,8] two lines of argument lead us to believe that the observed loss of a hydroxy group occurs as indicated in formula **42** (to form **43**) and not by a backside displacement by nitrogen (to form **41**). The more compelling argument is the occurrence of this fragmentation irrespective of the stereochemistry of the hydroxyl function, a result which is not consistent with a backside displacement.[7,8] In addition, neither of the 2-tropanols **22** nor **23** exhibits a significant M − 17 peak in spite of the fact that backside participation by nitrogen is known to occur[9] when the isomer **22** is treated with acetic anhydride. Further evidence favoring the fragmentation process illustrated in structure **42** to account for the M − 17 peak in the mass spectra of epimeric 1,3-amino alcohols is presented elsewhere.[10]

Peaks at *m/e* 58 and 44.—The most abundant peaks in the spectra of the bicyclic amino alcohols **4–17** and the amino ethers **18** and **19** are found at *m/e* 58 and 44, corresponding primarily to the ions $C_3H_8N^+$ and $C_2H_6N^+$. In representative cases, high-resolution mass spectral data[4] have revealed the presence of a minor component (less than 5% of the nominal intensity) in the integral mass peaks at *m/e* 44 and 58 which is due to the respective monooxygen species (*i.e.*, for O *vs.* NH_2 doublet, $\Delta M = 0.0238$). Both the monodeuterated (**28**) and the trideuterated (**29**) alcohols still exhibit the abundant *m/e* 44 peak but the second fragment appears as β, two peaks at *m/e* 59 (more abundant) and 58 (less abundant). The β secondary alcohols **44** invariably have an *m/e* 44 ion which is either comparable in intensity with or more abundant than that of *m/e* 58. However, the α secondary alcohols and ethers **45** tend to have an *m/e* 58 peak which is either comparable in in-

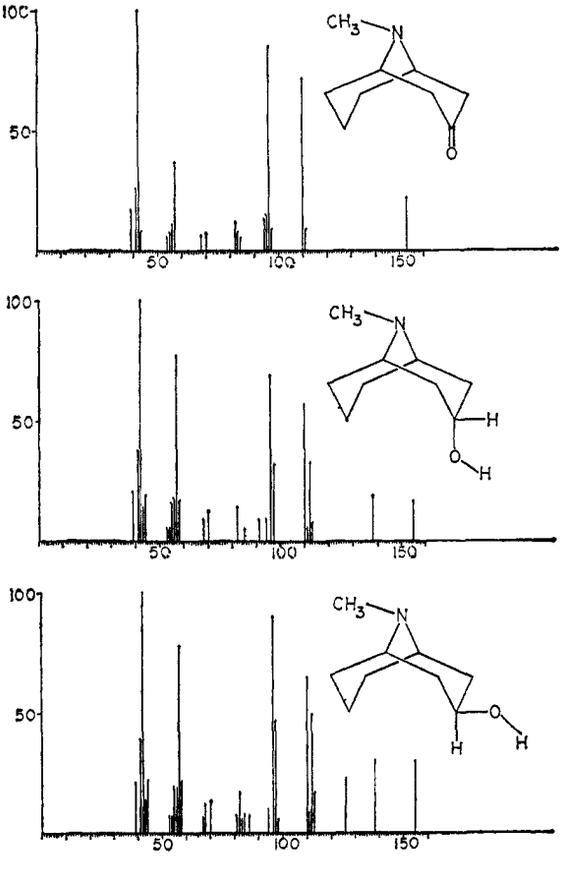
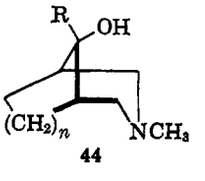


Figure 14.—Mass spectra of amines **24–26**.



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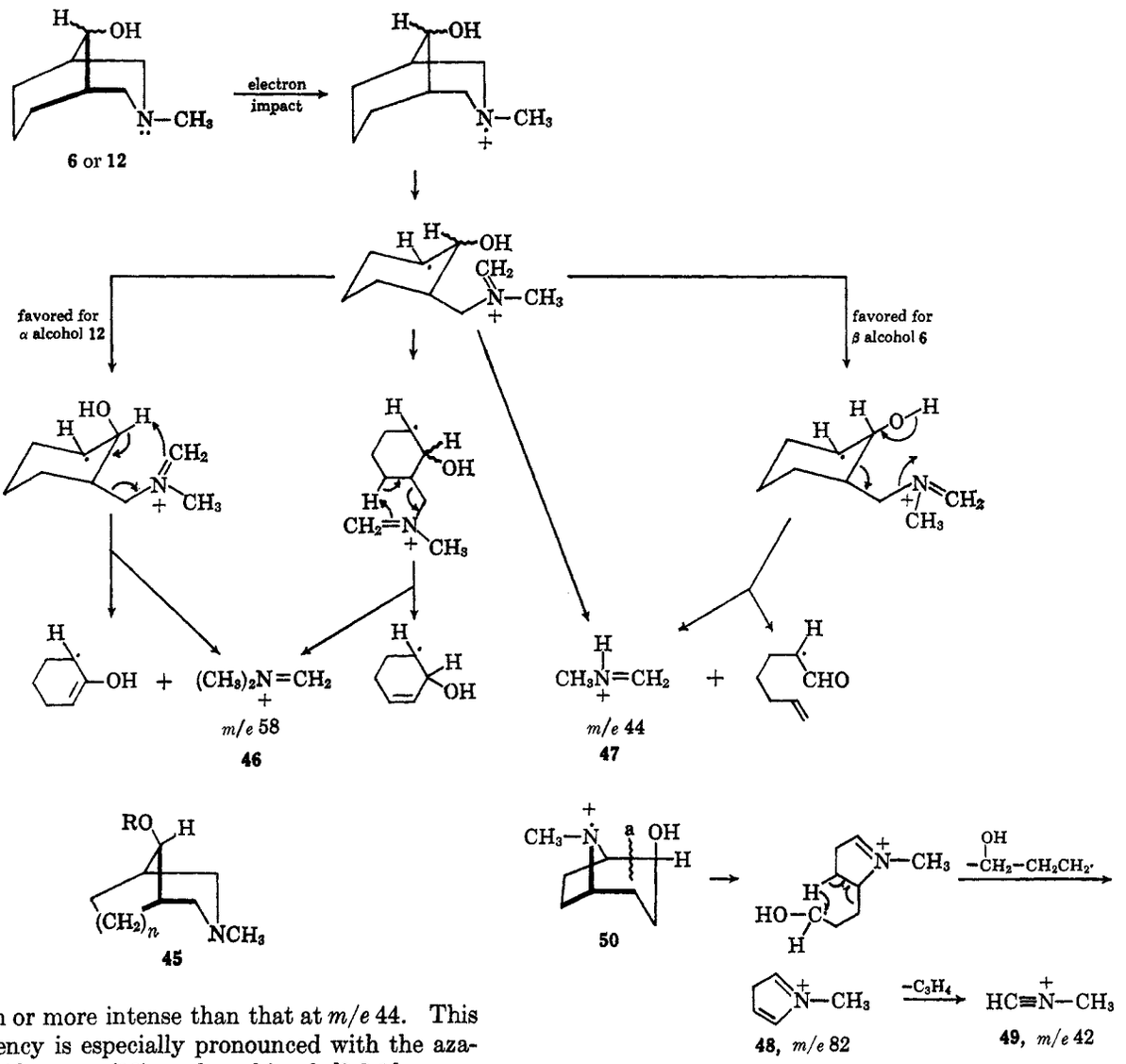
(8) S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg, and M. J. Unser, *J. Am. Chem. Soc.*, **79**, 6337 (1957); **80**, 4677 (1958).

(9) S. Archer, T. R. Lewis, M. R. Bell, and J. W. Schulenberg, *ibid.*, **83**, 2386 (1961).

(10) A. L. Burlingame, Ph.D. Dissertation, Massachusetts Institute of Technology, 1962.

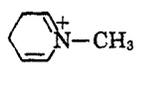
SCHEME I



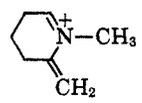
tensity with or more intense than that at *m/e* 44. This latter tendency is especially pronounced with the azabicyclo[3.2.1]octane (**30**) and azabicyclo[3.3.1]nonane (**31**) derivatives. We believe that these observations are best accounted for by assuming the predominant fragmentation scheme to be that illustrated for alcohols **6** and **12** in Scheme I in which the ions **46** and **47** are primarily responsible for the *m/e* 58 and 44 peaks. The mass spectra of O-deuterated derivatives (Figure 11) of alcohols **6** and **12** illustrate that a substantial fraction of the hydrogen atoms transferred to nitrogen to form the ion **47** (*m/e* 44) are derived from the hydroxyl function of the starting alcohol **6**. However, it is clear from these spectra that a significant fraction of the ion **47** is also derived from some other process in which hydrogen from elsewhere in the molecule is transferred to the nitrogen atom.

In the mass spectra of the tropanes **20–23**, the most abundant fragment ions are at *m/e* 82 and 42; structures **48** and **49** have been suggested[6] for these fragments. The mode of formation suggested for the ion **48**[6] is similar to the pathway suggested here for the formation of fragment **46**. The marked increase in the relative abundance of the *m/e* 82 fragment in the spectrum of 2β-tropanol (**23**) is noteworthy. Apparently, a combination of steric and electronic factors favor cleavage of the indicated C–C bond (bond a in structure **50**).

The mass spectra of the granatanols **25** and **26** exhibit the aforementioned M − 17 peak at *m/e* 138 as well as abundant fragment peaks at *m/e* 42, 57, 96, and 110. Analogy with the 3-tropanol mass spectra[6] would suggest that the *m/e* 42, 96, and 110 peaks should be attributed to the ions **49**, **51**, and **52**. However, further speculation about the fragmentation of these amino alcohols seems inappropriate until the high-resolution mass spectral data are discussed.[4]



51, *m/e* 96



52, *m/e* 110

The *m/e* 170 Peaks of the Phenylcarbinols.—Comparison of the spectra (Figures 5 and 7) of the epimeric phenylcarbinols **8** and **14** or **10** and **17** reveals that the β isomers (*e.g.*, **8**) yield an abundant *m/e* 170 fragment of composition $C_{12}H_{12}N$. The corresponding peak in the spectra of the α isomer **14** is of low intensity and has a different composition ($C_{13}H_{14}$) and the α isomer **17** displays an analogous peak at *m/e* 184 of homologous composition ($C_{14}H_{16}$). The *m/e* 170 ion from the β isomers (composition $C_{12}H_{12}N$) would appear to be best formulated as the pyridinium ion **53**. The α isomer

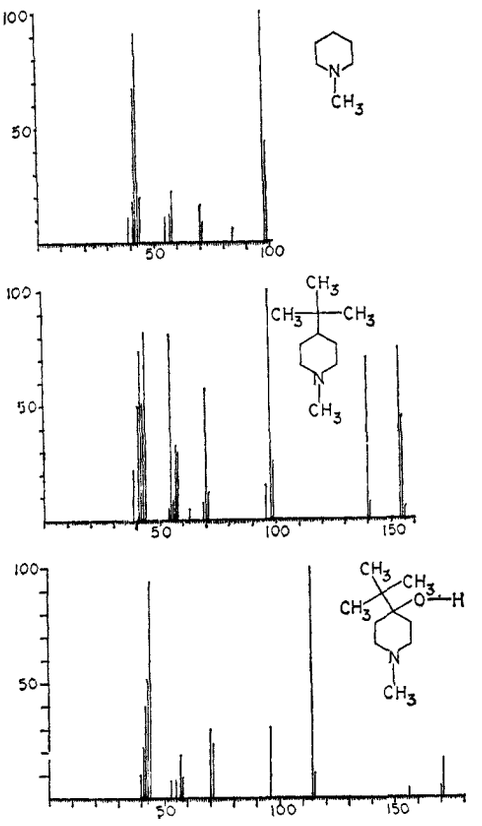
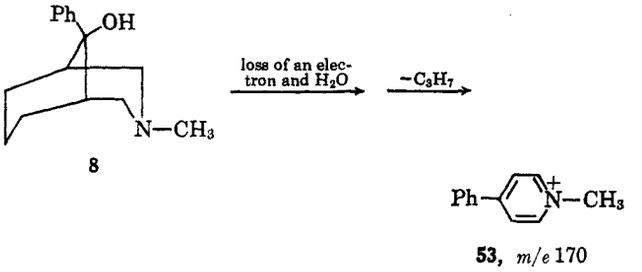


Figure 15.—Mass spectra of amines **33–35**.



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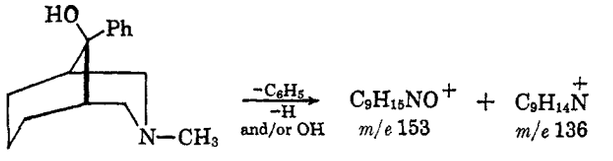
53, *m/e* 170

(*e.g.*, **14**) apparently follows a rather different fragmentation path which favors loss of the phenyl substituent early in the course of the fragmentation. In the absence of data for suitably labeled derivatives,



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it appears unwise to engage in speculation about the probable paths of these fragmentations.

Experimental Section[11]

Sources of Amino Alcohols and Ketones.—The preparations and physical constants of the amines **1–19** and **33–35** are described elsewhere.[3] Samples of the tropanols **20–23** were obtained from Dr. Malcolm R. Bell (Sterling-Winthrop Research Institute); the physical constants for these amino alcohols are summarized elsewhere.[3c] Pseudopelletierine (**24**), mp 59–60° (lit.[12a] mp 63–64°), was prepared as previously described.[12] This product has a pK^*_{mcs} value[13] of 6.45 with infrared absorption[14] at 1700 cm^{-1} (C=O) and nmr peaks[15,16] at δ 2.63 (3 H singlet, NCH_3) and 3.32 (2 H, partially resolved multiplet, bridgehead CH) with two pairs of doublets (line separation, 16 cps) having peaks located at δ 3.01, 2.73, 2.37, and 2.09 (4 H, CH_2CO) which appear to be an AB pattern with further coupling partially resolved. The spectrum also has a complex multiplet in the region δ 1.3–2.0 (6H, aliphatic C-H).

Reduction of the amino ketone **24** with sodium and ethanol as previously described[17] yielded the β stereoisomer **26** of 9-methylgranatanin-3-ol, mp 96–98° (lit.[17] mp 99–100°), yield 82%. The sample has a pK^*_{mcs} value[13] of 8.69 with infrared absorption[14] at 3595 and 3350 (broad) cm^{-1} (unassociated and associated. OH). In dilute solution (1.8×10^{-2} *M* to 1.1×10^{-3} *M*),[18] the bank at 3480 cm^{-1} (associated OH) decreased in intensity more rapidly than the band at 3610 cm^{-1} (unassociated OH) and became negligible in the most dilute solution measured. Thus, we conclude that no significant amount of intramolecular hydrogen bonding occurs in solutions of the amino alcohol **26** in carbon disulfide. The nmr spectrum[15] of the sample has a complex multiplet in the region δ 1.2–2.2 (10 H, aliphatic CH) with singlets at δ 2.48 (3 H, NCH_3) and 3.62 (1 H, OH), a broad, unresolved peak centered at δ 2.92 (2 H, bridgehead CH), and a multiplet centered at δ 4.35 (1 H, >CHO) which appears to be a five-line pattern with separations of 8 cps between each of the lines. The spectrum is similar when measured in nitrobenzene solution either at 25 or 115°.[19]

Reduction of pseudopelletierine (**24**) with lithium aluminum hydride yielded a crude basic product which was sublimed (80° at 0.05 mm) and recrystallized from petroleum ether (bp 30–60°) to separate the α isomer **25** of 9-methylgranatanin-3-ol as a white solid, mp 85–88° (lit.[17] mp 69°), yield 85%. The melting point of this sample fluctuated markedly on further recrystallizations although the infrared absorption remained unchanged. We therefore believe that this sample crystallizes as different crystalline forms which account for the melting point differences observed.

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.58; H, 11.12; N, 9.38.

The amino alcohol **25** has a pK^*_{mcs} value[13] of 8.91 with infrared absorption[14] at 3610 and 3350 (broad) cm^{-1} (unassociated and associated OH). The nmr spectrum[15] corresponds to that previously described;[19] little if any change was observed in nmr spectra[20] taken at 25 and at 122°. For reasons already noted,[19] we were unable to determine coupling constants for the A_2B_2X portion of this spectrum which we could be certain were reliable.

(11) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with a Perkin-Elmer, Model 237, infrared recording spectrophotometer fitted with a grating. The nmr spectra were determined at 60 Mc with a Varian, Model A-60, nmr spectrometer. The low-resolution mass spectra were obtained with a CEC, Model 21-130, mass spectrometer except for the phenylcarbinols **8**, **10**, **14**, and **17**, which were measured with an Hitachi (Perkin-Elmer) mass spectrometer, Model RMU-66, fitted with a glass inlet system. The mass spectra of the partially O-deuterated alcohols **6** and **12** (Figure 11) were determined with a modified CEC, Model 21-103C, mass spectrometer; the inlet system was equilibrated with deuterium oxide prior to these measurements. In the line drawings (Figures 1–15), peaks whose intensities were less than 5% of the base peak were not plotted unless they appeared to have special significance. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(12) (a) A. C. Cope, H. L. Dryden, Jr., and C. F. Howell, "Organic Syntheses," Coll. Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1963, p 816; (b) A. C. Cope, H. L. Dryden, Jr., C. G. Overberger, and A. A. D'Addieco, *J. Am. Chem. Soc.*, **73**, 3416 (1951).

(13) The values of pK^*_{mcs}, the apparent pK_a values in a mixture of 80% Methyl Cellosolve and 20% water, were determined by Dr. W. Simon; for discussion and leading references, see W. Simon, *Angew. Chim., Intern. Ed. Engl.*, **3**, 661 (1964).

(14) Determined as a solution in chloroform.

(15) Determined as a solution in deuteriochloroform.

(16) The nmr spectrum of this substance has been discussed by C.-Y. Chen and R. J. W. Le Fèvre, *Chem. Ind.* (London), 306 (1965), who have assigned coupling constants. We believe that the resolution that we (and apparently these authors) have obtained in several solvents is not adequate to permit a reliable calculation of coupling constants because the X portion of the A_2B_2X pattern is not resolved.

(17) K. Alder and H. A. Dortmann, *Chem. Ber.*, **86**, 1544 (1953).

(18) Determined in carbon disulfide solution.

(19) This spectrum can be considered as containing an A_2B_2X pattern and estimates of coupling constants can be made: C.-Y. Chen and R. J. W. Le Fèvre, *Tetrahedron Letters*, **No. 12**, 737 (1965). However, the A and B portions of the spectrum are not resolved and, hence, no rigorous way to check the validity of the estimated coupling constants exists.

(20) Determined as a solution in bromobenzene.

A solution of 183.5 mg of the *p*-toluenesulfonic acid salt of the ketone **2** in 0.5 ml of water was made basic with potassium hydroxide and the resulting free amino ketone was extracted with ether. After the ether solution (30 ml) had been dried over potassium carbonate, it was added, with stirring, to a suspension of 250 mg of lithium aluminum deuteride in 5 ml of ether. After the resulting mixture had been refluxed for 1 hr, a small quantity of water was added and the precipitated inorganic salts were extracted with methylene chloride. Concentration of the combined organic solutions and sublimation (100° at 80 mm) of the residue afforded 50 mg of a mixture of monodeuterio alcohols (**28** and its epimer), mp 63–69°, containing[21] 52.5% of the α epimer (corresponding to **12**) and 47.5% of the β isomer (corresponding to **6**). The deuterium composition, determined by mass spectrometry, was 8% d_0 and 92% d_1 species. A comparable sequence employing 63.5 mg of the *p*-toluenesulfonic acid salt of the previously known[3b] dideuterated ketone **27** produced, after sublimation, 11.5 mg of the mixture of trideuterated alcohols **29** containing 1% d_0, 5% d_1, 5% d_2, and 89% d_3 species. The mixture contained[21] 64% of the α isomer (corresponding to **12**) and 36% of the β isomer (corresponding to **6**). By use of thin layer chromatography,[22] a sample of the pure monodeuterated α isomer **28** (corresponding to **12**), mp 92–93.5°, was separated from the mixture of monodeuterated alcohols described above.

10β-Hydroxy-10α-phenyl-8-methyl-8-azabicyclo[4.3.1]decane (10).—Following the procedure previously described[3d,23] for the interconversion of phenylcarbinols **8** and **14**, a solution of 1.12 g (4.6 mmoles) of the α-hydroxyamine **17**[3d] in 28 ml of aqueous 10% hydrochloric acid was heated on a steam bath. Aliquots of the solution were removed, made basic with sodium hydroxide, and extracted with ether; the composition of the ethereal extracts was determined by thin layer chromatography.[24] After 1 hr the crude product contained an approximately equal mixture of the α (**17**, eluted more rapidly) and β (**10**, eluted more slowly) isomers and after 2 hr the β isomer (**10**) was the major component present. The crude basic product was isolated and distilled in a short-path still (120–150° at 0.15 mm) to separate 1.043 g (93%) of amino alcohol; fractional distillation in a Holtzmann column separated 671 mg of a fraction, bp 149–159° (0.13 mm), estimated from its nmr spectrum[15] to contain 95% of the β isomer **10** and 5% of the α isomer **17**. In a comparable experiment, a solution of 1.24 g (5.01 mmoles) of the α isomer **17** in 5 ml of aqueous 10% hydrochloric acid was heated to 100° for 5 hr. The resulting cold solution deposited 1.182 g (84%) of hydrochloride of the β alcohol **10** as colorless prisms, mp 217–218.5° dec. After the hydrochloride had been treated with a mixture of aqueous sodium hydroxide and ether, the ethereal extract was dried, concentrated, and distilled to separate 518 mg of the β-hydroxy amine **10** as a colorless liquid, bp 140–160° (0.1 mm), in which none of the α isomer was detected.[24] The pK^*_{mcs} value[13] for this amine is 7.59 (for the epimer **17** the pK^*_{mcs} value is 6.73).[3d] The sample has infrared absorption[14] at 3575 and 3420 cm^{-1} (unassociated and associated OH); in dilute solution (2.4×10^{-3} to 3.0×10^{-4} *M*)[18] only the unassociated band at 3600 cm^{-1} remains indicating the lack of intramolecular hydrogen bonding. The sample has a series of weak (ϵ 150–210) ultraviolet maxima[25] in the region 250–270 mμ with intense end absorption. The nmr spectrum[15] of the sample has multiplets in the regions δ 7.2–7.9 (5 H, aryl CH), 2.4–3.0 (6H, $CH_2N<$ and bridgehead CH), and 0.9–2.2 (9 H, OH and aliphatic CH) with a singlet at δ 2.30 (3 H, CH_3N). It should be noted that the N-methyl signal for the epimer **17** is found at higher field (δ 1.97)[3d] as a result of shielding by the nearby phenyl ring.

Anal. Calcd for $C_{15}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.36; H, 9.53; N, 5.87.

To a solution of 1.58 g (6.45 mmoles) of the amino alcohol **10** and 7 mg of triphenylmethane (as an indicator) in 20 ml of 1,2-dimethoxyethane was added 4.5 ml of an ethereal solution containing 7.2 mmoles of methyllithium. The resulting red solution was stirred for 30 min and then a solution of 1.20 g (6.45 mmoles) of *p*-nitrobenzoyl chloride in 15 ml of 1,2-dimethoxyethane was added and the reaction mixture was stirred for 16 hr at room temperature. After the mixture had been concentrated under reduced pressure, the residual yellow solid was partitioned between water and ether. The ethereal solution was dried and concentrated under reduced pressure to leave 2.47 g (97%) of the *p*-nitrobenzoate, mp 146–148°. Recrystallization from an ether–petroleum ether (bp 30–60°) mixture afforded the pure ***p*-nitrobenzoate of alcohol 10** as pale yellow plates, mp 149.5–150.5°. The sample has infrared absorption[14] at 1715 cm^{-1} (conjugated ester C=O) with an ultraviolet maximum[25] at 261 mμ (ϵ 11,600). The sample has an nmr[15] multiplet in the region δ 7.1–8.3 (9 H, aryl CH) with a singlet at δ 2.14 (3 H, NCH_3) and multiplets in the regions δ 3.3–3.6 (2 H), 2.4–2.8 (4 H), and 1.0–2.1 (8 H).

Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.82; H, 6.51; N, 6.90.

Our attempts to prepare this same *p*-nitrobenzoate by reaction of the alcohol **10** with *p*-nitrobenzoic anhydride (*cf.* ref 3d) were generally unsuccessful apparently because of the instability of this ester to heat and a variety of isolation procedures. In one instance after a solution of the alcohol and the anhydride in pyridine had been heated to 90° for 10 hr, we succeeded in isolating the *p*-nitrobenzoate, mp 147–149°, in 1% yield. This material was identified with the above sample by comparison of infrared spectra.

(21) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb P was employed for this analysis.

(22) The plate was coated with silicic acid adsorbent and eluted with a methanol (2 volumes)–chloroform (3 volumes) mixture containing 1% of concentrated ammonium hydroxide.

(23) Sankyo Co., Ltd., British Patent 952,137 (March 11, 1964); *Chem. Abstr.*, **61**, 5614 (1964).

(24) The thin layer plates were coated with silicic acid and eluted with a mixture of ethyl acetate (1 volume) and methanol (1 volume).

(25) Determined as a solution in 95% ethanol.