Reduction of Azabicyclic Ketones[1a]

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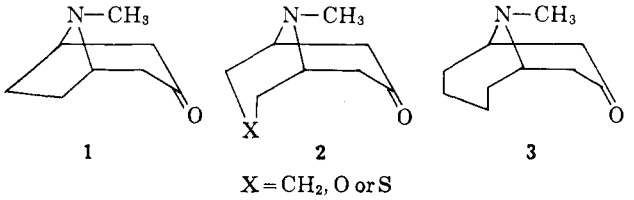
The stereochemical course of reductions of the amino ketones, 3-methyl-3-azabicyclo[3.2.1]octan-8-one (**13a**), 3-methyl-3-azabicyclo[3.3.1]nonan-9-one (**13b**), and 8-methyl-8-azabicyclo[4.3.1]decan-10-one (**13c**), with sodium and alcohol, with sodium borohydride, and with hydrogen and platinum have been studied. The metho-*p*-toluenesulfonates **14** of these amino ketones **13** also have been reduced with hydrogen and platinum. The various reductions of the azabicyclooctanones **13a** and **14a** produced primarily the β-amino alcohols **15** (hydroxyl group *syn* to the amino function) whereas the azabicyclodecanones **13c** and **14c** yielded primarily the α-amino alcohols **16**. Reductions of the azabicyclononanones **13b** and **14b** afforded mixtures of the α- and β-isomers. Reaction of the amino alcohols **15** and **16** with *p*-nitrobenzoyl chloride in chloroform proved to be an effective method, both to separate mixtures of the isomeric amino alcohols and to assign configurations to the amino alcohols. Under these conditions the β-isomers **15** afforded the *p*-nitrobenzoate esters **20**, and the α-isomers were converted to the hydrochlorides of the free amino alcohols.

Previous studies of the stereochemical outcome of reductions of the azabicyclic ketones **1**,[2a,b] **2**,[2c-e] and **3**[2f] may be summarized as in the following discussion.



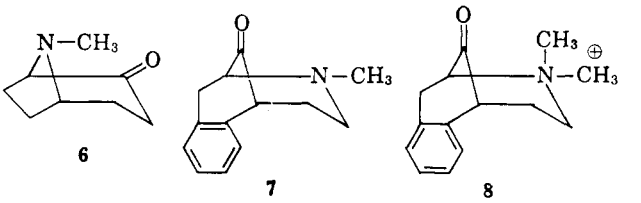
1 **2** **3**

X = CH_2, O or S

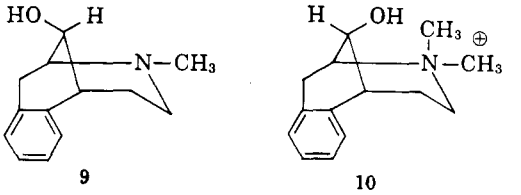
4 **5**

Catalytic hydrogenation in all cases yielded primarily the axial (or α-) isomer **4**, a result which could be attributed[3] to approach to the catalyst surface from the less hindered side. Sodium in alcohol reduction[4] gave in each case the presumably more stable equatorial (or β-) isomer **5** as the major product. Reduction with lithium aluminum hydride produced primarily the equatorial isomer **5** from **3**, primarily the axial isomer **4** from **2**, and a mixture from **1**. The results of these hydride reductions, like the hydride reductions of simpler cyclohexanones have prompted considerable discussion[2b,e,5] but no clear-cut conclusions.

An indication that the foregoing conclusions are not universally applicable to the reduction of bicyclic amino ketones was provided by the finding that reduction of the amino ketone **6** with sodium and alcohol produced the axial (or β-) isomer, whereas the other (equatorial) epimeric alcohol was the major product of a lithium aluminum hydride reduction.[6] Studies[7] of the system **7** and its quaternary salt **8** proved of special interest since the free base **7** was converted to the α-isomer **9** by either catalytic hydrogenation or hydride reduction while the β-isomer **10** was produced from the salt **8** under comparable conditions.



6 **7** **8**



9 **10**

Two factors might be considered important in determining the stereochemical course of amino ketone reductions. The results could be attributed to steric factors which either hinder approach of the catalyst or complex metal hydride (steric approach control)[5] or destabilize the transition state (product development control)[5] leading to reduction. Alternatively, certain of the results could be attributed to a prior complexing of the amine function with the catalyst surface (as in **11**) or the borane,[8] to assistance of hydride ion transfer by participation of the amine function (as in **12**),[8a] or to an electrostatic interaction in the hydride reduction.[5f,8c,d] These latter effects would not be compar-

(1) (a) This research has been supported by grants from the National Institutes of Health (RG-8761) and the McNeil Laboratories, Inc.; (b) National Institutes of Health Predoctoral Fellow, 1958–1960.

(2) (a) L. C. Keagle and W. H. Hartung, *J. Am. Chem. Soc.*, **68**, 1608 (1946); (b) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959); (c) K. Alder and H. A. Dortmann, *Chem. Ber.*, **86**, 1544 (1953); (d) W. H. Hartung and S. M. Gadekar, *J. Am. Pharm. Assoc.*, **42**, 715 (1953); *Chem. Abstr.*, **48**, 12751 (1954); (e) C. L. Zirkle, F. R. Gerns, A. M. Pavloff, and A. Burger, *J. Org. Chem.*, **26**, 395 (1961); (f) K. Alder, H. Wirtz, and H. Koppelberg, *Ann.*, **601**, 138 (1956).

(3) For example, see R. J. Wicker, *J. Chem. Soc.*, 2165 (1956).

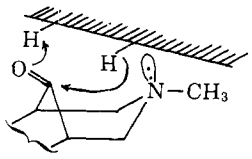
(4) S. Dev [*J. Indian Chem. Soc.*, **33**, 769 (1956)] has reported a convenient procedure for the reduction of ketones.

(5) (a) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); (b) K. D. Hardy and R. J. Wicker, *ibid.*, **80**, 640 (1958); (c) for a recent review see A. V. Kamernitskii and A. A. Akhrem, *Russ. Chem. Rev.* (English Transl.), No. **2**, 43 (1961); *Tetrahedron*, **18**, 705 (1962); (d) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962); (e) D. M. S. Wheeler and M. M. Wheeler, *ibid.*, **27**, 3796 (1962); (f) M. G. Combe and H. B. Henbest, *Tetrahedron Letters*, No. **12**, 404 (1961).

(6) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **80**, 6147 (1958).

(7) (a) E. L. May and H. Kugita, *J. Org. Chem.*, **26**, 188 (1961); (b) E. L. May, H. Kugita, and J. H. Ager, *ibid.*, **26**, 1621 (1961); (c) H. Kugita and E. L. May, *ibid.*, **26**, 1954 (1961); (d) S. Saito and E. L. May, *ibid.*, **26**, 4536 (1961); (e) S. E. Fullerton, E. L. May and E. D. Becker, *ibid.*, **27**, 2144 (1962).

(8) (a) T. Matsumoto, T. Nishida, and H. Shirahama, *ibid.*, **27**, 79 (1962); (b) J. D. Connolly and K. H. Overton, *J. Chem. Soc.*, 3366 (1961); (c) M. G. Combe and H. B. Henbest, *Tetrahedron Letters*, No. **12**, 404 (1961); (d) H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, **84**, 2833 (1962); (e) A. V. Robertson, E. Katz and B. Witkop, *J. Org. Chem.*, **27**, 2676 (1962); (f) G. Baddeley and J. W. Rasburn, *J. Chem. Soc.*, 3838 (1961); (g) the recent correction [H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **83**, 4372 (1961)] of an earlier reported catalysis of the borohydride reduction of ketones with triethylamine removes one argument (see ref. 8a) which has been offered for the probability of a process such as **12**.



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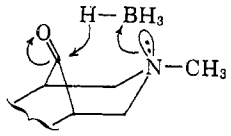


12

able with quaternary ammonium salts and could account for the differing behavior of ketones **7** and **8**. In an effort to assess the relative importance of these various factors we have studied the reduction of the amino ketones **13**, known to exist in the indicated conformations,[9] and of the corresponding quaternary salts **14** of unknown conformation.

The results of these studies are outlined in Chart I and Table I. The mixtures of quaternary salts **17** and **18** obtained by reduction of the ketones **14** were most conveniently demethylated (to form **15** and **16**) by reaction with lithium iodide in boiling decanol. This procedure, utilizing iodide ion as a nucleophile in an S_N2 reaction, offers distinct advantages over an alternative method utilizing lithium aluminum hydride as a nucleophile[10] in simplicity and duration of reaction time.

From the data in Table I, it is apparent that reduction of the azabicyclooctanone systems **13a** and **14a** produces predominantly the β-isomer **15a** in every case, whereas reduction of the azabicyclodecanone systems **13c** and **14c** affords the α-isomer **16c** as the major product. The reductions of the azabicyclononanone systems **13b** and **14b** are intermediate between these two extremes and yield mixtures of the stereoisomeric amino alcohols **15b** and **16b** whose composition is

TABLE I

REDUCTION OF AMINO KETONE DERIVATIVES **13** AND **14**

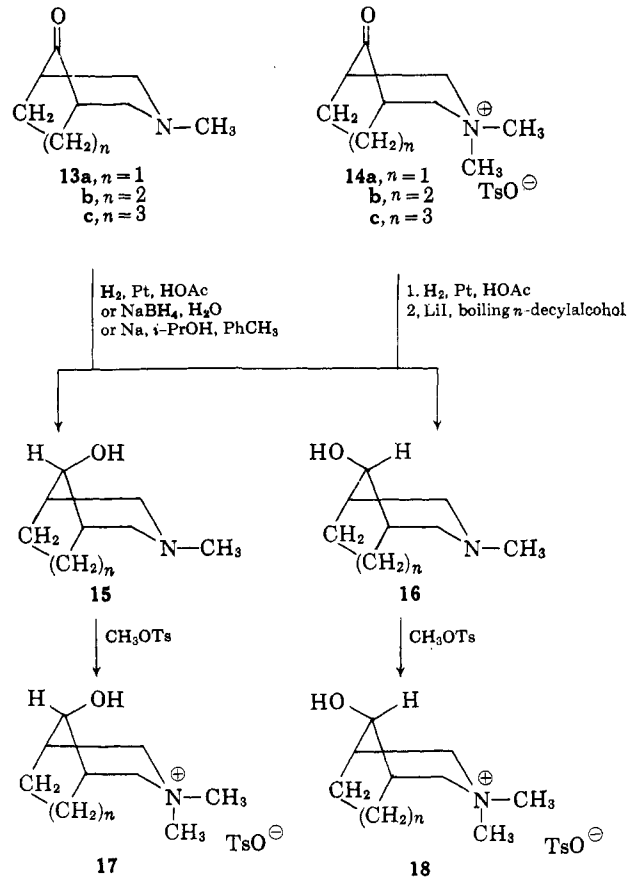
Ketone reduced	Reducing agent	Composition of the amino alcohol mixture: β-Isomer **15**, %	α-Isomer **16**, %
13a	H_2, Pt, *i*-PrOH	98	2
13a	H_2, Pt, HOAc	81	19
13a	$NaBH_4$, H_2O-MeOH	91	9
13a	Na, *i*-PrOH, $PhCH_3$	93	7
14a	H_2, Pt, HOAc[a]	85	15
13b	H_2, Pt, *i*-PrOH	38	62
13b	H_2, Pt, HOAc	4	96
13b	$NaBH_4$, H_2O-MeOH	36	64
13b	Na, *i*-PrOH, $PhCH_3$	40	60
14b	H_2, Pt, HOAc[a]	44	56
13c	H_2, Pt, *i*-PrOH	1	99
13c	H_2, Pt, HOAc	3	97
13c	$NaBH_4$, H_2O-MeOH	2	98
13c	Na, *i*-PrOH, $PhCH_3$	9	91
14c	H_2, Pt, HOAc[a]	<1	>99

[a] The mixture of quaternary ammonium salts **17** and **18** initially produced was treated with lithium iodide in boiling decanol to remove one methyl group from the quaternary nitrogen.

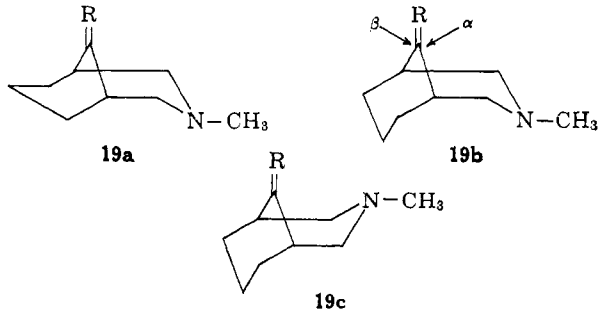
(9) (a) H. O. House, P. P. Wickham, and H. C. Müller, *J. Am. Chem. Soc.*, **84**, 3139 (1962); (b) an amino alcohol, b.p. 70–72° (0.5 mm.), which we believe to be a mixture of **15b** and **16b** has been reported by S. Rossi and W. Butta, *Ann. Chim.* (Rome), **52**, 381 (1962); *Chem. Abstr.*, **57**, 9810 (1962).

(10) (a) A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, *J. Am. Chem. Soc.*, **82**, 4651 (1962). (b) The procedure described here is comparable to the use of lithium iodide to cleave methyl esters. See F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960). There are a variety of examples of the demethylation of quaternary ammonium halides either in the dry state [*e.g.*, K. Schmid, W. von Philipsborn, H. Schmid, and P. Karrer, *ibid.*, **39**, 394 (1956)] or in a high-boiling solvent (*e.g.*, see ref. 7d).

CHART I



dependent on the nature of the reducing agent. From these results, it is clear that the major factor determining the stereochemistry of the reduction of the amino ketones **13** is the bulk and the conformation of the polymethylene chain. Our previous studies[9a] had provided evidence indicating the amino ketones **13** existed largely in conformations corresponding to **19a** and/or **19b** rather than **19c**. The relative basicities of these compounds (**13a** > **13b** > **13c**)[9a] suggested the importance of conformations corresponding to **19b** in which the methylene chain interferes with one of the groups on the protonated nitrogen atom. The data reported in this paper suggest the importance of a

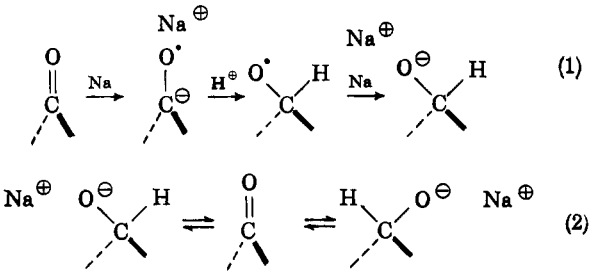


19a 19b 19c

conformation corresponding to **19a** for the azabicyclodecanone **13c**, in which the flexible methylene chain of this ketone serves to shield the carbonyl function from attack by a reducing agent in the direction labeled β in structure **19b**. With the azabicyclooctanone **13a** the same direction of attack (corresponding to the direction β in structure **19b**) is the predominate mode of reaction indicating that addition to the carbonyl function is

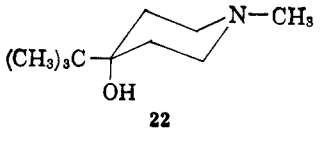
less hindered by the two carbon methylene chain than by the three-atom nitrogen-containing chain.[11] Consequently, our currently available data are most readily interpreted by assuming that the amino ketone **13b** exists largely in the conformation **19b** in which both sides of the carbonyl function are approximately equally available for attack and the amino ketone **13c** exists primarily as an equilibrating mixture of conformers corresponding to **19a** and **19b**. Although our data for reduction of the keto ammonium salts **14** are less reliable because of the possibility of unintentional fractionation of isomers during the demethylation process, the stereochemical results obtained on reduction of ketones **14** are compatible with the idea that these materials exist as a mixture of conformations corresponding to **19a** and **19c**. Molecular models suggest that a conformation corresponding to **19b** is not reasonable for the ammonium salts **14b** and **14c** because of a severe interaction between the axial N-methyl group and the polymethylene chain. The change observed (*i.e.*, an increased per cent of the β-isomer **15**) in the steric course of catalytic hydrogenation of ketones **13a** and **13b** when the solvent is changed from acetic acid to isopropyl alcohol is presumably indicative of the fact that the amino ketones are at least partially protonated on nitrogen in acetic acid. This protonation (and attendant solvation of the cation) could increase the proportion of ketone molecule existing in a conformation corresponding to **19a** and favor the production of the α-isomer **16**. Alternatively, the effect could be interpreted as evidence for an interaction between the nitrogen atom and the catalyst surface (as in **11**) in neutral media. In any case, it is clear the role of the nitrogen atom in directing the course of these reductions is of relatively minor importance.

In presenting the foregoing arguments we have implied that, in all of the reductions studied, the products are formed by kinetically controlled processes wherein the reducing agent (or proton) attacks the carbonyl carbon atom from the less hindered side. Although this implication is not at variance with other results for catalytic hydrogenation or sodium borohydride reduction, it is seemingly in disagreement with the idea that sodium–alcohol reductions usually produce the more stable secondary alcohol.[12] Since the apparent violations of the rule seem to be found with ketones [*e.g.* 6,[6] **13a**, i (ref. 11), and others[12]] which possess either strained or hindered carbonyl functions, we believe the following explanation (*cf.* ref. 11a) is applicable. The initial reaction of the ketone with a metal to form a radical ion is followed by a sterically controlled protonation in which the proton is added from the less hindered side (equation 1).



In most instances subsequent equilibration of the initially formed alkoxide *via* the ketone as illustrated in equation 2 results in formation of the more stable product. However, if the starting ketone is strained or if it is sterically hindered, then the conversion of the initially formed tetrahedral alkoxide back to the trigonal ketone as illustrated in equation 2 should be especially slow (for either steric or energetic reasons) and isolation of the initial alcohol formed in a kinetically controlled protonation process would be expected. In agreement with this idea, the epimerization of the alcohols derived from i[11a] was found to occur very slowly, if at all. The alcohols **15** and **16** were equilibrated only very slowly in the presence of benzophenone or fluorenone and the sodium alcoholate derived from the alcohol, conditions which equilibrate unstrained and/or unhindered alcohols rapidly.[13] Furthermore, the rate of equilibration was found to be slower with the system **15a** ⇌ **16a** than with the system **15c** ⇌ **16c**, in keeping with the previous hypothesis that the more highly strained is the ketone function (*i.e.*, **13a** more strained than **13c**), the more slowly will equilibration occur.

The various physical data obtained for the alcohols **15** and **16** and the corresponding quaternary ammonium salts **17** and **18** are summarized in Table II. Comparable data are included for the monocyclic amino alcohol **22** and the epimeric 2-tropanols (**23**) and 3-tropanols (**24**).



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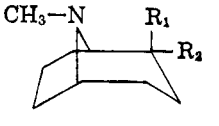
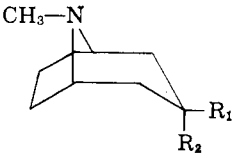


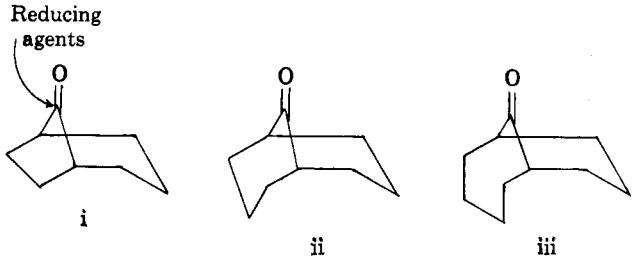
23a, R_1 = OH, R_2 = H
b, R_1 = H, R_2 = OH



24a, R_1 = OH, R_2 = H
b, R_1 = H, R_2 = OH

It will be noted that in dilute carbon disulfide solution (*ca* .5 × 10^{-3} *M*) none of amino alcohols **15a**, **15c**, **16**, **22**, **23b**, or **24** exhibit any indication of intramolecular hydrogen bonding and amino alcohol **15b** exhibits

(11) It is pertinent to consider the behavior of the carbocyclic analogs i, ii, and iii of the amino ketones **13**. Reduction of the bicyclic ketone i under conditions comparable to those reported in this study [see (a) A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Am. Chem. Soc.*, **82**, 4299 (1960); (b) C. S. Foote, Ph.D. dissertation, Harvard University, 1961] led to predominant reduction from the direction indicated in structure i. Ketone ii, being symmetrical, has an equal probability for attack from either side. To the best of our knowledge ketone iii has not been prepared and, consequently, the stereochemical course of its reduction is unknown.



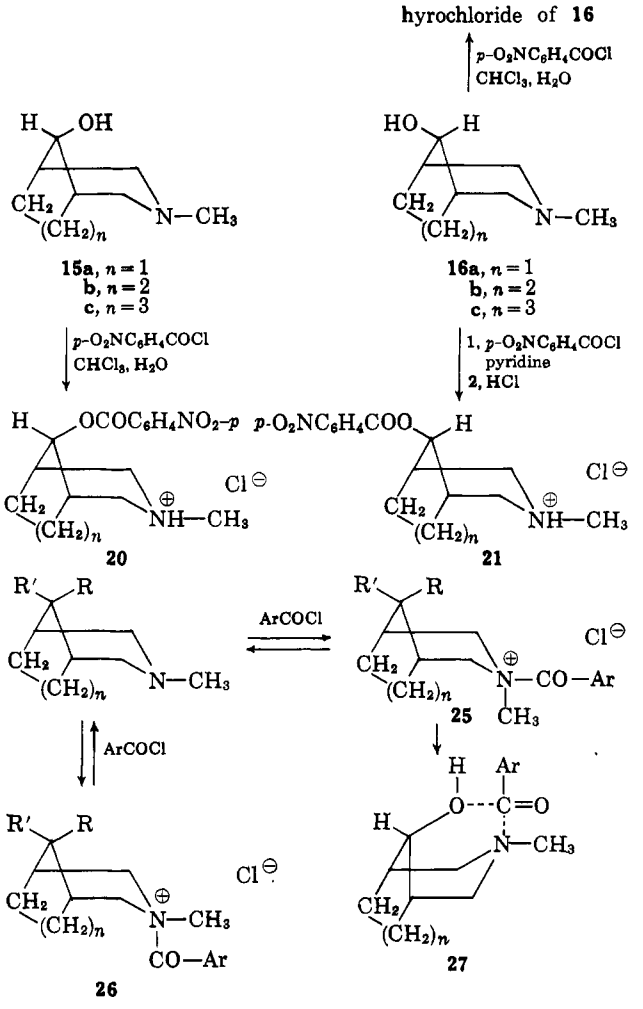
(12) (a) G. Ourisson and A. Rassat [*Tetrahedron Letters*, No. **21**, 16 (1960)] provide a number of examples where this rule is not followed; (b) for a discussion of the mechanism of dissolving metal reductions, see J. H. Brewster, *J. Am. Chem. Soc.*, **76**, 6361 (1954).

(13) (a) W. E. Doering, G. Cortes, and L. H. Knox, *ibid.*, **69**, 1700 (1947); (b) W. E. Doering and T. C. Aschner, *ibid.*, **71**, 838 (1949); (c) **75**, 393 (1953).

only a very weak peak attributable to an associated O–H function in addition to a strong peak for an unassociated hydroxyl group.[14] Of the amino alcohols studied only the 2β-tropanol exhibits absorption which is clearly attributable to an intramolecularly bonded hydroxyl function[15]; the earlier report[15g] of intramolecular hydrogen bonding in 3β-tropanol is not correct. Since molecular models indicate that intramolecular hydrogen bonding would clearly be favorable for any of the amino alcohols **15**, **22** and **24a** in a conformation corresponding to **19c**, it is clear that all of these compounds exist primarily in conformations containing the piperidine ring in the more stable chair conformation (*e.g.*, **19a** and **19b**).[16]

In general, the energy which would be gained by the formation of an intramolecular hydrogen bond is not sufficient to force a piperidine ring into a boat conformation[15b] unless the boat form is also favored because of appreciable steric repulsions which exist in the chair form.[15a,d,16a] Since the only difference in steric repulsion between the amino alcohols **15** and **16** and between **24a** and **24b** is derived from the location of the hydroxyl function,[17] we conclude that all of the amino alcohols **15**, **16**, **22**, and **24** exist very largely in conformations corresponding to **19a** and/or **19b** in which a chair piperidine ring is present. Since energy to be gained from hydrogen bond formation with the azabicyclononanol **15b** is insufficient to force the piperidine ring into a boat conformation (as in **19c**) and there is even less reason for the carbocyclic ring in this molecule to adopt a boat conformation (as in **19a**), it appears very probable that this bicyclic system (*i.e.*, **15b** and **16b**) exists very largely in the chair–chair conformation **19b**. Presumably some deformation has occurred in this conformation **19b** to relieve the interaction between the electron pair on nitrogen and axial hydrogen at C-7.

CHART II

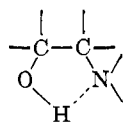


Furthermore, the presence of intense absorption in the 2600–2800-cm.$^{-1}$ region of the spectra of all of the amino alcohols **15**, **16**, and **22** indicates (ref. 9a and literature cited therein) that in each of the amino alcohols, the N-methyl group occupies primarily an equatorial position as pictured in the structural formulas.

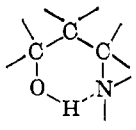
The positions of the N-methyl proton peaks in the n.m.r. spectra of the quaternary salts **17** and **18** derived from the amino alcohols **15** and **16** were instructive. Each of the ammonium sats **18b** and **18c** exhibits a single n.m.r. peak for both N-methyl groups whereas all of the ammonium salts **17** as well as **18a** have two N-methyl peaks indicating that the environments of the N-methyl groups are very similar in compounds **18b** and **18c**, but are different in compounds **17a**, **17b**, **17c**, and **18a**.[18] These offer some support for the stereochemical assignments made to **17b**, **17c**, **18b**, and **18c**. However, the data are not unequivocal because of the previously mentioned uncertainty about the preferred conformations of the ammonium salts **17** and **18**.

(14) The absorptivity of an associated N—H or O—H stretching peak is normally substantially larger than the absorptivity of the corresponding unassociated N—H or O—H stretching peak. See the published spectra in ref. 15d and R. C. Lord and T. J. Porro, *Z. Electrochem.*, **64**, 672 (1960). For this reason the weak band at 3390 cm.$^{-1}$ in the spectrum of **15b** represents a very small amount of a bonded hydroxyl function which may or may not be intramolecular.

(15) For previous examples of intramolecular hydrogen bonds in amino alcohols see (a) R. E. Lyle, *J. Org. Chem.*, **22**, 1280 (1957); (b) G. Hite, E. E. Smissman, and R. West, *J. Am. Chem. Soc.*, **82**, 1207 (1960); (c) W. A. M. Davies, J. B. Jones, and A. R. Pinder, *J. Chem. Soc.*, 3504 (1960); (d) M. Svoboda, M. Tichý, J. Fajkos, and J. Sicher, *Tetrahedron Letters*, No. **16**, 717 (1962); (e) C. H. Eugster and K. Allner, *Helv. Chim. Acta*, **45**, 1750 (1962); (f) H. H. Freedman [*J. Am. Chem. Soc.*, **83**, 2900 (1961)] suggests values of 3500 cm.$^{-1}$ and 3295 cm.$^{-1}$ for associated hydroxyl functions of the types iv and v, respectively.



iv



v

(g) B. L. Zenitz, C. M. Martini, M. Priznar, and F. C. Nachod, *ibid.*, **74**, 5564 (1952). In this study, the most dilute solution measured (*ca.* 2 × 10^{-2} *M*) was still sufficiently concentrated to exhibit some intermolecular hydrogen bonding.

(16) (a) M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962); (b) J. M. Eckert and R. J. W. LeFevre [*J. Chem. Soc.*, 3991 (1962)] have concluded that 3α-tropanol (**24b**) exists primarily in a chair conformation.

(17) The free energy difference between an axial and equatorial hydroxyl group is 0.4–0.9 kcal./mole. (E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 236.) Even if this rather small group is considered important, it is difficult to see any reason why the location of this group in an equatorial conformation with respect to the piperidine ring (as in **16**) should favor a conformation with the piperidine ring in a boat form.

(18) (a) For previous examples of this type see G. L. Closs, *J. Am. Chem. Soc.*, **81**, 5456 (1959). In this study the methiodide of tropine was found to give a single N-methyl peak whereas the methiodides of pseudotropine and tropane exhibited two N-methyl peaks. (b) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky [*J. Chem. Soc.*, 2637 (1962)] report that, for the N-methylquinolizidine derivatives, the N-methyl proton resonance in the *trans*-fused compounds (axial N–Me) is at higher field than the corresponding N-methyl resonance in the *cis*-fused compounds.

TABLE II

PROPERTIES OF THE AMINO ALCOHOLS AND THEIR DERIVATIVES

Compound	$\bar{\nu}_{OH}$, cm.$^{-1}$ ca. 10% in $CHCl_3$	$\bar{\nu}_{OH}$, cm.$^{-1}$ ca. 5×10^{-3} M in CS_2	N.m.r. spectrum in $CDCl_3$, τ: N-CH_3	N.m.r. spectrum in $CDCl_3$, τ: CH-O	pK^*_{MCS}[a]	Product with p-$O_2NC_6H_4COCl$ in $CHCl_3$	Order of elution from silica gel	Order of elution from a Carbowax 20 M g.l.c. column	Mass spectrum, m/e (% of total ionization from 25 to M[b])
15a	3600, 3400, 3180	3600	7.75 (3H)	6.08 (triplet, J = 4.5 c.p.s.)	8.44	Ester **20a**	second	second	M = 141 (5.0), M-1 (7.5), M-17 (6.5), 58 (4.8)
16a	3600, 3390	3600	7.81 (3H)	6.34 (broad)	7.87	Hydrochloride of alcohol **16a**	first	first	M = 141 (4.1), M-1 (3.7), M-17 (3.1), 58 (26.0)
17a	3310[c]	...	6.78 (3H), 6.92 (3H)	...	...	...	...	...	...
18a	3320[c]	...	6.78 (3H), 6.93 (3H)	...	...	...	...	...	...
15b	3610, 3390	3610 (s), 3390 (w)	7.65 (3H)	6.33 (triplet, J = 3 c.p.s.)	8.25	Ester **20b**	second	first	M = 155, (4.9), M-1 (8.3), M-17 (3.1), 58 (6.3)
16b	3610, 3420	3610	7.87 (3H)	6.32 (triplet, J = 3 c.p.s.)	7.50	Hydrochloride of alcohol **16b**	first	second	M = 155, (3.6), M-1 (3.2), M-17 (2.3), 58 (26.4)
17b	3380[c]	...	6.69 (3H), 6.77 (3H)	...	...	...	...	...	...
18b	3330[c]	...	6.77 (6H)	...	...	...	...	...	...
15c	3620, 3440	3620	7.78 (3H)	6.08 (broad)	7.69	Ester **20c**	second	first	M = 169 (3.2), M-1 (3.3), M-17 (1.3), 58 (9.7)
16c	3615, 3530	3615	7.87 (3H)	6.12 (broad)	7.11	Hydrochloride of alcohol **16c**	first	second	M = 169 (2.7), M-1 (1.2), M-17 (1.5), 58 (13.5)
17c	3360[c]	...	6.66 (3H), 6.83 (3H)	...	...	...	...	...	...
18c	3320[c]	...	6.83 (6H)	...	...	...	...	...	...
22	3600, 3200	...	7.72 (3H)	...	...	...	...	...	...
23a	3440	3460	7.77 (3H)	...	9.51[a]	...	...	...	M = 141 (3.4), 82 (19)
23b	3600, 3300, 3120	3600	7.77 (3H)	...	8.42[a]	...	...	...	M = 141 (4.2), 82 (8)
24a	3600, 3400	3600	7.72 (3H)	...	8.74[a]	...	...	...	M = 141 (2.8), M-17 (3.4), 82 (14.7)
24b	3600, 3360, 3160	3600	7.76 (3H)	...	9.19[a]	...	...	...	M = 141 (2.6), M-17 (3.6), 82 (12.1)

[a] See W. Simon, G. H. Lyssy, A. Mörikofer, and E. Heilbronner, "Zusammenstellung von scheinbaren Dissoziationkonstanten im Lösungsmittelsystem Methylcellosolve/Wasser," Jurluis-Verlag, Zurich, 1959. [b] M represents the molecular ion peak. [c] Determined as a Nujol mull.

The mass spectra of the epimeric pairs of amino alcohols **15** and **16**, and **23** and **24** exhibit significant differences as noted in Table II. Although we believe the interpretation of these differences, to be discussed in a future publication, will prove useful for future stereochemical assignments, we did not consider that *a priori* interpretations of these spectra offered a means for making unambiguous stereochemical assignments. The order of elution of the epimeric pairs of amino alcohols **15** and **16** from a Carbowax 20 M gas chromatography column showed no consistent pattern.[19] Each of the amino alcohols **16** was found to be eluted from silica gel more rapidly than its epimer **15** and each of the amino alcohols **15** was found to be a stronger base than its epimer **16**. Although none of these differences offered an unambiguous interpretation in terms of the stereochemistry of the amino alcohols, the relative basicities **15a** > **15b** > **15c** and **16a** > **16b** > **16c** were of interest since they parallel the relative basicities observed[9a] for the ketones (*i.e.*, **13a** > **13b** > **13c**). Like the data for the ketones, these orders of basicity for the amino alcohols **15** and **16** suggest the importance of conformations corresponding to **19b** in which the increasing bulk of the polymethylene chain in the series would offer increasing steric hindrance to the addition of a proton to the nitrogen atom (or increasing

(19) C. P. Rader, George E. Wicks, Jr., and H. S. Aaron [Abstracts of Papers, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 40M] have reported that amino alcohols which exhibit substantial *intramolecular* hydrogen bonding are eluted from a Carbowax 20 M gas chromatography column much more rapidly than their epimers which do not exhibit significant intramolecular hydrogen bonding. Since none of the amino alcohols **15** and **16** exhibit significant intramolecular hydrogen bonding, this correlation was not useful to us.

steric repulsion with either the N-CH_3 or the N-H group in the amine salt).

Although the various physical measurements discussed indicate that the amino alcohols **15** and **16** exist primarily in conformations corresponding to **19a** and/or **19b**, it was clearly necessary to obtain chemical evidence in order to learn the configurations of these compounds. The various chemical methods previously used[20] to define configurations of amino alcohols include the reversible transfer of an acyl group from the hydroxyl to the secondary amine function,[20a,b] the formation of an oxazolidine derivative from the amino alcohol and *p*-nitrobenzaldehyde,[20c] and the formation of complexes from amino alcohols and copper(II) or other metal ions.[20b] Since none of these methods is applicable to alcohols containing a tertiary amine function, we were led to explore other possible reactions which might be applied directly to the amino alcohols **15** and **16** without requiring a prior demethylation step. In the course of preparing the *p*-nitrobenzoate esters **20** and **21**, we discovered a very effective method for both separating and defining the stereochemistry of the three pairs of amino alcohols **15** and **16**. The procedure, treatment of the amino alcohols with *p*-nitrobenzoyl chloride in chloroform solution, led to the results summarized in Chart II. The very marked difference in esterification rate, which permitted clean separation of the various mixtures of amino alcohols **15** and **16**, is almost certainly attributable to the reversible formation of the acyl ammonium salts including **25** and **26** followed by intramolecular acyl transfer (*i.e.*, **27** from **25**, R = OH and R′ = H). When intramolecular acyl transfer is not possible (*e.g.*, **25**, R = H and R′ = OH), the acyl function is attacked by either chloride ion or by the ethanol or water present in the chloroform more rapidly than it is attacked intermolecularly by a second alcohol molecule.[21]

Experimental[22]

Reduction of 3-Methyl-3-azabicyclo[3.3.1]nonan-9-one (13b). A. With Sodium and Isopropyl Alcohol.[4]—To a mixture of 6.9 g. (0.30 g.-atom) of sodium and 150 ml. of boiling toluene was added rapidly a solution of 9.18 g. (0.060 mole) of the amino ketone **13b** in 45 g. (0.75 mole) of isopropyl alcohol. After the resulting mixture had been refluxed for 2.5 hr. (at which time all of the sodium had reacted), it was cooled and extracted with aqueous hydrochloric acid. The aqueous extract was made basic with sodium hydroxide, saturated with sodium chloride and extracted with pentane. After the pentane extract had been concentrated, sublimation of the residue (100° at 70 mm.) afforded 8.304 g. (89.4%) of a mixture[23] of the amino alcohols **15b** and **16b** as white needles, m.p. 65–68°. A solution of the amino alcohol mixture, 3.60 g. (23.2 mmoles) in 35 ml. of chloroform was treated with a solution of 4.75 g. (25.6 mmoles) of *p*-nitrobenzoyl chloride in 35 ml. of chloroform and the resulting yellow solution was allowed to stand at room temperature for 65 hr. and then concentrated. After the residual solid had been extracted with three 50-ml. portions of ether to remove any unchanged acid chloride, the residue was crystallized from ethanol to separate the **amino ester hydrochloride 20b** as 2.89 g. (36.5%) of white prisms, m.p. 264–265° dec. This product has infrared absorption[24] at 1715 cm.$^{-1}$ (conj. ester C=O) with no absorption in the 3-μ region attributable to a hydroxyl function and an ultraviolet maximum[25] at 259 mμ (ϵ 13,900).

Anal. Calcd. for $C_{16}H_{21}ClN_2O_4$: C, 56.38; H, 6.21; N, 8.22. Found: C, 56.31; H, 6.31; N, 8.28.

A solution of 2.00 g. (5.86 mmoles) of the amino ester hydrochloride **20b** in 20 ml. of 20% aqueous hydrochloric acid was refluxed for 8 hr. and then filtered from the liberated *p*-nitrobenzoic acid, made basic with sodium hydroxide, and extracted with chloroform. After the chloroform extract had been dried and concentrated, sublimation (100° at 50 mm.) of the residue afforded 0.845 g. (93%) of the pure[23] **amino alcohol 15b** as white needles, m.p. 94–94.1°. The product has infrared absorption[26,27] at 3610 cm.$^{-1}$ (unassoc. O-H) and at 3390 cm.$^{-1}$ (assoc. O-H) as well as bands at 2790, 2760 (sh), and 2730 cm.$^{-1}$ (two C-H bonds, adjacent, *trans* and coplanar to the unshared electron pair on nitrogen). As the solution was diluted (lowest concentration 4.4 $\times$ 10^{-3} *M*) the band at 3610 cm.$^{-1}$ (unassoc. O-H) remained whereas the relative intensity of the band at 3390 cm.$^{-1}$ (assoc. O-H) was greatly diminished. The sample has broad n.m.r. absorption[28] at 5.31 τ (1H, O-H), a triplet (J = 3 c.p.s.) at 6.33 τ (1H, >CH—O—), a broad, unresolved peak at 7.19 τ (4H, CH_2—N), and a singlet at 7.65 τ (3H, CH_3N).

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; mol. wt., 155. Found: C, 69.44; H, 11.18; N, 9.04; mol. wt., 155 (mass spectrum).

After a mixture of 310 mg. (2.0 mmoles) of the amino alcohol **15b** and 410 mg. (2.2 mmoles) of methyl *p*-toluenesulfonate had been heated to 65° for 18 hr., the crude product was washed with ether and recrystallized from a methanol–ethyl acetate mixture to separate 550 mg. (80%) of the **metho-*p*-toluenesulfonate 17b** as white needles, m.p. 149.5–150°. The material has infrared absorption[24] at 3380 cm.$^{-1}$ (assoc. O-H) with no absorption in the 6-μ region attributable to a carbonyl function, and an ultraviolet maximum[25] at 222 mμ (ϵ 10,300), as well as a series of low intensity peaks in the region 250–270 mμ. The n.m.r. spectrum[29] has two singlets at 6.69 and 6.77 τ (two N-CH_3 groups), as well as a singlet at 7.63 τ (aryl CH_3).

Anal. Calcd. for $C_{17}H_{27}NO_4S$: C, 59.81; H, 7.97; N, 4.10. Found: C, 60.03; H, 8.06; N, 4.00.

The ethanolic mother liquor remaining after separation of the amino ester hydrochloride **20b** was concentrated and diluted with acetone to separate 2.45 g. (55%) of the crude **hydrochloride of the amino alcohol 16b**, m.p. 200–210°. Recrystallization from an acetone–ethanol mixture afforded 1.9 g. (43%) of the pure **hydrochloride** as white prisms, m.p. 216–217°. An aqueous solution of 3.89 g. of this hydrochloride was made basic with sodium hydroxide, saturated with sodium chloride and extracted with ether. After the organic extract had been dried and concentrated, sublimation (100° at 80 mm.) afforded 3.013 g. (95.6%) of the pure[23] **amino alcohol 16b** as white needles, m.p. 95.5–96°. The product has infrared absorption[26,27] at 3610 (unassoc. O-H) and 3420 cm.$^{-1}$ (assoc. O-H) as well as a series of peaks at 2770, 2730 and 2690 cm.$^{-1}$ (two C-H bonds adjacent, *trans* and coplanar to the unshared electron pair on nitrogen). Dilution of the solution[27] (lowest concentration 4.4 $\times$ 10^{-3} *M*) resulted in disappearance of

(20) (a) A. Nickon and L. F. Fieser, *J. Am. Chem. Soc.*, **74**, 5566 (1952); (b) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953); (c) E. Hardegger and H. Ott, *Helv. Chim. Acta*, **36**, 1186 (1953); (d) G. Drefahl and coworkers, *Chem. Ber.*, **93**, 509, 514, 517 (1960).

(21) (a) An intermediate comparable to **25** has been suggested by B. J. Calvert and J. D. Hobson, [*Proc. Chem. Soc.*, 19 (1962)] to explain the conversion of benzoyl chloride to benzaldehyde on reaction with tropine and alkali; (b) we were able to show that our results were not attributable to an unexpected instability of the *p*-nitrobenzoate esters **21** [*cf.* H. C. Beyerman, C. H. Siegmann, F. L. J. Sixma, and J. H. Wisse, *Rec. trav. chim.*, **75**, 1445 (1956)] by preparing the esters **21** (see Chart II) and demonstrating (details to be published elsewhere) that neither ester **20b** nor **21b** was hydrolyzed rapidly by aqueous acid.

(22) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird Model B or a Perkin-Elmer Model 21 infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary Model 14 recording spectrophotometer. The n.m.r. spectra were determined at 60 Mc. with a Varian Model A-60 n.m.r. spectrometer. The mass spectra were obtained with a CEC Model 21-130 mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(23) The mixture was analyzed by thin-layer chromatography employing a silica gel coating and a mixture (by volume) of 2 parts methanol and 3 parts chloroform containing 1% of 33% aqueous ammonia as the eluent.

(24) Determined as a Nujol mull.

(25) Determined in 95% ethanol solution.

(26) Determined in chloroform solution.

(27) Determined in carbon disulfide solution.

(28) Determined as a solution in deuteriochloroform.

(29) Determined in deuterium oxide solution.

the assoc. O–H bond at 3420 cm.$^{-1}$, but not the unassoc. O–H bond at 3610 cm.$^{-1}$. The n.m.r. spectrum[28] has a triplet (J = 3 c.p.s.) at 6.32 τ (1H, >CH–O), a singlet at 7.87 (3H, N–CH_3), and a broad unresolved peak centered at 7.73 τ (4H, CH_2–N).

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; mol. wt., 155. Found: C, 69.84; H, 11.08; N, 9.14; mol. wt., 155 (mass spectrum).

Reaction of 930 mg. (6.0 mmoles) of the amino alcohol **16b** with 1.23 g. (6.6 mmoles) of methyl *p*-toluenesulfonate as previously described produced 1.51 g. (74%) of the **metho-*p*-toluenesulfonate 18b** as white prisms from a methanol–ethyl acetate mixture, m.p. 187.5–188.5°. Recrystallization raised the melting point to 189.5–190°. The material has infrared absorption[24] at 3330 cm.$^{-1}$ (assoc. O–H) with an ultraviolet maximum[25] at 222 mμ (ϵ 10,900) as well as low intensity absorption in the region 250–270 mμ and n.m.r. absorption[29] at 5.31 τ (singlet, O–H), a triplet (J = 4 c.p.s.), at 5.58 τ (1H, >CH–O), a singlet at 6.77 τ (6H, two CH_3—N), and a singlet at 7.62 τ (3H, aryl CH_3).

Anal. Calcd. for $C_{17}H_{27}NO_4S$: C, 59.81; H, 7.97; N, 4.10. Found: C, 60.07; H, 8.09; N, 4.08.

After a solution of 470 mg. (3.0 mmoles) of the amino alcohol **16b** and 612 mg. (3.3 mmoles) of *p*-nitrobenzoyl chloride in 5 ml. of pyridine had been allowed to stand at room temperature for 20 hr., the solution was diluted with ether to separate 883 mg. (86%) of the crude amino ester hydrochloride **21b**, m.p. 200–230°. Recrystallization from ethanol afforded 435 mg. (42.5%) of the pure **ester hydrochloride 21b** as white prisms, m.p. 239.5–240°, with infrared absorption[24] at 1713 cm.$^{-1}$ (conj. ester C=O) and ultraviolet absorption[25] at 258 mμ (ϵ 13,800).

Anal. Calcd. for $C_{16}H_{21}ClN_2O_4$: C, 56.38; H, 6.21; N, 8.22. Found: C, 56.25; H, 6.31; N, 8.17.

From comparable reductions of the amino ketone **13b**, the crude mixture of amino alcohols obtained (in 96 and 80% yields) was found to contain[30] 40% of the amino alcohol **15b** (first eluted) and 60% of the amino alcohol **16b** (second eluted). A portion of this mixture was chromatographed on silica gel. From the earlier fractions, eluted with ethyl acetate, the amino alcohol **16b**, m.p. 94–95°, was isolated while the later fractions, eluted with a methanol–ethyl acetate mixture, afforded the amino alcohol **15b**, m.p. 89.6–92°. Both amino alcohol samples were identified with previously described samples by comparison of infrared spectra.

To study the equilibration of the alcohols **15b** and **16b**, a reduction was run employing 465 mg. (3.04 mmoles) of the ketone **13b**, 4.5 g. (75 mmoles) of isopropyl alcohol, 345 mg. (15 mg.-atoms) of sodium and 12 ml. of toluene. Aliquots (*ca.* 0.25 ml.) were removed from the reaction mixture periodically and quenched in water (*ca.* 0.1 ml.). After the aqueous phase had been saturated with sodium chloride, the organic phase was separated and analyzed.[30] After a reaction time of 35 min. (at which time all of the sodium had reacted), 54 mg. (0.3 mmole) of fluorenone was added and refluxing was continued. After a total reaction time of 96 hr., 364 mg. (2.0 mmoles) of benzophenone was added and refluxing was continued. The composition of the alcohol mixture in the reaction mixture after various periods of time was as follows: 5 min. (ketone **13b** was still present), 40% **15b** and 60% **16b**; 35 min., 40% **15b** and 60% **16b**; 24 hr., 41% **15b** and 59% **16b**; 96 hr., 43% **15b** and 57% **16b**; 240 hr. and 360 hr., 48% **15b** and 52% **16b**.

B. With Sodium Borohydride.—A solution of 306 mg. (2.00 mmoles) of the amino ketone **13b** in 10 ml. of methanol was added to a solution of 75.6 mg. (2.00 mmoles) of sodium borohydride in 8 ml. of water and the resulting mixture was allowed to stand at room temperature for 3 hr. After the excess of borohydride had been destroyed by the addition of acetic acid, 1 ml. of hydrochloric acid was added. The mixture was concentrated, made basic with aqueous sodium hydroxide, saturated with sodium chloride, and extracted with ether. This ethereal extract was concentrated and found to contain[30] 36% of **15b** and 64% of **16b**. From a comparable reduction the amino alcohols **15b** and **16b** were collected[30] and identified by comparison of retention times and infrared spectra.

C. Catalytic Hydrogenation.—A solution of 301.2 mg. (1.97 mmoles) of the amino ketone **13b** in 22 ml. of acetic acid was hydrogenated at room temperature and atmospheric pressure over the catalyst obtained from 29.4 mg. of platinum oxide. After the hydrogen uptake (49.0 ml. or 1.02 equiv. after 1.7 hr.) ceased, the mixture was filtered, concentrated, and mixed with aqueous sodium hydroxide. The methylene chloride extract of the reaction mixture was dried and concentrated to leave 278.1 mg. (90.9%) of the crude amino alcohol **16b**, m.p. 90.3–93°. Sublimation (100° at 0.1 mm.) afforded a sample of the pure **amino alcohol 16b**, m.p. 91.7–92.7°, identified with the previously described sample by a mixture melting point determination.

For a comparable hydrogenation of 310 mg. (2.02 mmoles) of the ketone **13b** in 8 ml. of acetic acid over the catalyst from 31 mg. of platinum oxide, the hydrogen uptake (48.8 ml. or 1.01 equiv.) ceased after 35 min. The mixture was filtered and the filtrate was made basic with aqueous sodium hydroxide and then saturated with sodium chloride and extracted with ether. The concentrated ethereal extract contained[30] 96% of **16b** and 4% of **15b**.

Hydrogenation of 310 mg. (2.02 mmoles) of the ketone **13b** in 8 ml. of isopropyl alcohol over the catalyst from 31 mg. of platinum oxide at 25° and atmospheric pressure resulted in the uptake of 51.8 ml. (1.05 equiv.) of hydrogen over a period of 135 min. After filtration, the solution contained[30] 62% of **16b** and 38% of **15b**.

D. Hydrogenation of the Quaternary Salt 14b.—A solution of 5.00 g. (14.7 mmoles) of the quaternary salt **14b** in 80 ml. of acetic acid was hydrogenated for 20 hr. at 120° and 1450 p.s.i. over the catalyst obtained from 500 mg. of platinum oxide. These conditions were necessary to reduce the ketone function, preliminary experiments having established that the aromatic ring of the *p*-toluenesulfonic acid was reduced more rapidly than the ketone function. After filtration, the acetic acid solution was concentrated to leave 5.1 g. (100%) of a mixture[31] of quaternary salts, m.p. 145–165°. A solution of 810 mg. (2.35 mmoles) of this mixture of quaternary salts and 4.55 g. (34 mmoles) of lithium iodide in 4 ml. of *n*-decyl alcohol was refluxed for 1 hr. The resulting mixture was diluted with aqueous hydrochloric acid. After separation of the organic layer, the aqueous phase was extracted with ether and then made basic and again extracted with ether. The basic ethereal extract was dried and concentrated. Sublimation (100° at 80 mm.) of the residual amino alcohol mixture (270 mg. or 74%) afforded 240 mg. (66%) of the amino alcohol mixture, m.p. 66–69°, containing[23,30] the amino alcohol **16b** (56%) and the amino alcohol **15b** (44%). Reaction of a 630-mg. (4.0 mmoles) sample of this amino alcohol mixture with 742 mg. (4.0 mmoles) of *p*-nitrobenzoyl chloride in chloroform as previously described yielded 465 mg. (34%) of the **amino ester hydrochloride 20b**, m.p. 263–264°, and 300 mg. (48%) of the **amino alcohol 16b**, m.p. 94–94.5°. Both samples were identified by mixture melting point determinations.

Reduction of 3-Methyl-3-azabicyclo[3.2.1]octan-8-one(13a).

A. Catalytic Hydrogenation.—A solution of 3.07 g. (22 mmoles) of the amino ketone in 50 ml. of acetic acid was hydrogenated at room temperature and atmospheric pressure over the catalyst obtained from 570 mg. of platinum oxide. After the absorption of hydrogen (550 ml. or 1.01 equiv. in 2.5 hr.) was complete, the basic product was separated and sublimed (100° at 80 mm.) to give 1.48 g. (48%) of **amino alcohol 15a**, m.p. 80–81° (lit.[9a] m.p. 82–83°; identity established by comparison of infrared spectra), with infrared absorption[26,27] at 3600 cm.$^{-1}$ (unassoc. OH), at 3400 and 3180 cm.$^{-1}$ (assoc. O–H), and at 2795, 2740 and 2695 cm.$^{-1}$ (two C–H bonds adjacent, *trans* and coplanar to the unshared electron pair on nitrogen). The bands at 3400 and 3180 cm.$^{-1}$ (assoc. O–H) disappeared as the solution[27] was diluted (lowest concentration 5.3 $\times$ 10^{-3} M). The material has n.m.r. absorption[28] at 6.08 τ (1H, triplet with J = 4.5 c.p.s., >CH–O) with a peak at 7.50 τ (4H, CH_2N) and a singlet at 7.75 τ (3H, CH_3N). The mass spectrum of the sample indicates a molecular weight of 141.

Reaction of 141 mg. (1.0 mmole) of this amino alcohol **15a** with 205 mg. (1.1 mmoles) of methyl *p*-toluenesulfonate as previously described yielded 325 mg. (99%) of the crude **metho-*p*-toluenesulfonate 17a**, m.p. 138–148°, which crystallized from a methanol–ethyl acetate mixture as 200 mg. (61%) of white prisms, m.p. 152.5–153.5°. This product has infrared absorption[24] at 3310 cm.$^{-1}$ (assoc. O–H), an ultraviolet maximum[25] at 222 mμ (ϵ 12,400) with low intensity absorption in the region

(30) A gas chromatography column packed with 20 M Carbowax suspended on base-washed 80–100-mesh Chromsorb W was employed for this analysis.

(31) The mixture was analyzed by thin layer chromatography employing a silica gel coating and a mixture (by volume) of 6 parts methanol, 6 parts chloroform, and 1 part concentrated hydrochloric acid as the eluent.

250–270 mμ, and n.m.r. absorption[29] at 6.78 and 6.92 τ (6H, two CH_3N) and at 7.62 τ (3H, aryl CH_3).

Anal. Calcd. for $C_{16}H_{25}NO_4S$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.74; H, 7.74; N, 4.03.

After a solution of 423 mg. (3.0 mmoles) of the amino alcohol **15a** and 500 mg. (3.5 mmoles) of methyl iodide in 10 ml. of acetone had been allowed to stand at room temperature for 24 hr., the **methiodide** (625 mg. or 74%, m.p. 274–275° dec.) separated. A 430-mg. portion of this salt was recrystallized from an acetone–methanol mixture to separate 310 mg. (53% over-all) of the pure **methiodide** as white prisms, m.p. 277–277.5° dec. The product has infrared absorption[24] at 3320 cm.$^{-1}$ (assoc. O–H) with n.m.r. peaks[29] at 6.68 and 6.83 τ (6H, two CH_3N). Pyrolysis (275° at 80 mm.) of a 177-mg. sample of the methiodide followed by sublimation (100° at 80 mm.) of the crude volatile product gave 83 mg. (94%) of the **amino alcohol 15a**, m.p. 73–75°, identified by its infrared absorption.

Anal. Calcd. for $C_9H_{18}INO$: C, 38.16; H, 6.41; N, 4.95. Found: C, 37.87; H, 6.23; N, 5.04.

The crude hydrogenated product remaining after the separation of the pure amino alcohol **15a** still contained[23] primarily the same amino alcohol **15a** as well as a small amount of the isomeric amino alcohol **16a**, which moved more rapidly on thin-layer chromatography.[23] The partial separation of this mixture from the pure amino alcohol **15a** on sublimation was achieved by mechanically separating the pure crystalline amino alcohol **15a** in the sublimate from the oily mixture. A 500-mg. (3.55 mmoles) sample of this oily mixture was treated with 660 mg. (3.55 mmoles) of *p*-nitrobenzoyl chloride in chloroform as previously described to yield 698 mg. (60%) of the **amino ester hydrochloride 20a** as white prisms from ethanol, m.p. 272–273° dec. This product has infrared absorption[24] at 1725 cm.$^{-1}$ (conj. ester C=O) with an ultraviolet maximum[25] at 259 mμ (ε 14,300).

Anal. Calcd. for $C_{15}H_{19}ClN_2O_4$: C, 55.14; H, 5.86; N, 8.57. Found: C, 55.04; H, 6.04; N, 8.47.

The ethanolic mother liquor from this reaction was concentrated and then made basic with aqueous sodium hydroxide and extracted with ether. After the ethereal extract had been dried and concentrated, a short-path distillation (120° at 15 mm.) separated 22 mg. of a yellow liquid estimated to contain[23] about 80% of the second epimeric **amino alcohol 16a**, as well as a second component believed to be the O-acetyl derivative of one of the amino alcohols **15a** or **16a** which we were unable to separate with the quantities of material available. This crude sample of amino alcohol **16a** has extraneous infrared absorption[26] at 1720 cm.$^{-1}$ (medium intensity, ester C=O as impurity) as well as an extraneous peak in its mass spectrum (4% of peak at 141) at *m/e* 183 which would correspond to the molecular ion from the O-acetyl derivative of one of the amino alcohols **15a** or **16a**.

From a comparable hydrogenation employing 185 mg. (1.33 mmoles) of the ketone **13a**, 18.5 mg. of platinum oxide, 6.5 ml. of acetic acid, and a reaction time of 20 min. (hydrogen uptake 35.7 ml. or 1.10 equiv.), the crude product, isolated as previously described, contained[30] 81% of **15a** (second eluted) and 19% of **16a** (first eluted). From a similar hydrogenation employing 278 mg. (2.00 mmoles) of **13a**, 42 mg. of platinum oxide, 8 ml. of isopropyl alcohol, and a reaction time of 39 min. (hydrogen uptake. 56.4 ml. or 1.15 equiv.), the crude product contained[30] 98% of **15a** and 2% of **16a**.

B. With Sodium Borohydride.—After reduction of 51.7 mg. (0.371 mmole) of the amino ketone **13a** with 9.0 mg. (0.25 mmole) of sodium borohydride in 4 ml. of water as previously described, sublimation of the crude basic product afforded 38 mg. or 72% of the **amino alcohol 15a**, m.p. 77.3–80.6°, whose identity was determined by comparison of the infrared spectra.

For quantitative measurements the reduction was repeated using 175 mg. (1.26 mmoles) of the ketone **13a**, 47.6 mg. (1.26 mmoles) of sodium borohydride, 5 ml. of methanol, and 4 ml. of water as previously described. The crude product contained[30] 91% of **15a** and 9% of **16a**.

C. Hydrogenation of the Quaternary Salt 14a.—A solution of 1.117 g. (3.43 mmoles) of the quaternary salt in 40 ml. of acetic acid was hydrogenated for 18 hr. at 120° and 1250 p.s.i. over the catalyst obtained from 180 mg. of platinum oxide. After separation of the crude quaternary salt and reaction with 5.0 g. of lithium iodide in 5 ml. of boiling *n*-decyl alcohol as previously described, the crude product, 180 mg. (37%) of a liquid, was found to contain[23,30] primarily the amino alcohol **15a** accompanied by small amounts of the amino alcohol **16a** and the amino ketone **13a**. Reaction of a 60-mg. (0.425 mmole) sample of this product with 71 mg. (0.425 mmole) of *p*-nitrobenzoyl chloride in chloroform as previously described yielded 99 mg. (75%) of the **amino ester hydrochloride 20a**, m.p. 274–275° dec., identified by a mixture melting point determination and comparison of infrared spectra. From a comparable experiment employing 153 mg. (0.470 mmole) of the quaternary salt **14a**, 30 mg. of platinum oxide, and 7 ml. of acetic acid, the crude mixture of amino alcohols was found to contain[30] 85% of **15a** and 15% of **16a**.

D. With Sodium and Isopropyl Alcohol.[4]—The reduction was carried out in the usual way with 6.17 g. (0.0444 mole) of the ketone **13a**, 6.9 g. (0.30 g.-atom) of sodium, 50 g. (0.83 mole) of isopropyl alcohol, and 150 ml. of toluene, small aliquots (*ca.* 0.25 ml.) of the reaction mixture being removed periodically for analysis by the previously described procedure. After reaction of the sodium was complete (115 min.), 2.0 g. (0.011 mole) of benzophenone was added and refluxing was continued. After a reaction period of 136 hr., the bulk of the isopropyl alcohol was allowed to distil from the reaction mixture and was replaced with *n*-butyl alcohol to raise the reflux temperature. After 230 hr., all but 7 ml. of the reaction mixture was separated for product isolation and refluxing of the 7-ml. aliquot was continued. The composition of the amino alcohols in the reaction mixture at various times was as follows: 8 min., 93% of **15a** and 7% of **16a**; 64 min., 93% of **15a** and 7% of **16a**; 23.5 hr., 88% of **15a** and 12% of **16a**; 136 hr., 72% of **15a** and 28% of **16a**; 230 hr., 67% of **15a** and 33% of **16a**; 348 hr., 54% of **15a** and 46% of **16a**; 427 hr., 41% of **15a** and 59% of **16a**; 471 hr., 34% of **15a** and 66% of **16a**. The bulk of the reaction mixture, separated after 230 hr., was subjected to the usual isolation procedure to give 6.953 g. of a crude mixture of the amino alcohols. Reaction of this mixture with 9.15 g. (0.049 mole) of *p*-nitrobenzoyl chloride in 125 ml. of chloroform followed by the usual isolation procedure gave 8.143 g. (56.2% based on the starting ketone) of the **amino ester hydrochloride 20a**, m.p. 270° dec., and 1.639 g. (21.5% based on the starting ketone) of the **hydrochloride of the amino alcohol 16a** (white prisms from an acetone–methanol mixture, m.p. 216–217.5° dec.) This amino alcohol hydrochloride has infrared absorption[24] at 3390 cm.$^{-1}$ (assoc. O–H) and at 2610, 2490 and 2350 cm.$^{-1}$ ($\overset{+}{N}$–H) with no absorption in the 6-μ region attributable to a carbonyl function. A solution of 689 mg. of this material in 20 ml. of water was made basic with potassium hydroxide, saturated with sodium chloride and extracted with ether. After concentration of the ether extract, a short-path distillation of the residue followed by crystallization from pentane at Dry Ice temperatures separated 471 mg. (86.4%) of the **amino alcohol 16a** as a white solid, m.p. 51–53°. The product was further purified by an additional short-path distillation (95° at 10 mm.). The product has infrared absorption[26,27] at 3600 cm.$^{-1}$ (unassoc. OH), at 3390 cm.$^{-1}$ (assoc. OH), and at 2790, 2730 and 2690 cm.$^{-1}$ (two C–H bonds adjacent, *trans* and coplanar to the unshared electron pair on nitrogen) with n.m.r. peaks[28] at 6.34 τ (1H, >CH–O), at 6.93 τ (1H singlet whose position is dependent on concentration, O–H), and at 7.81 τ (3H singlet, N–CH_3). The infrared peak at 3390 cm.$^{-1}$ disappears as the solution[27] is diluted (lowest concentration 5.3×10^{-3} *M*).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92; mol. wt., 141. Found: C, 68.09; H, 10.71; N, 9.95; mol. wt., 141 (mass spectrum).

A solution of 106 mg. (0.751 mmole) of the amino alcohol **16a** and 168 mg. (0.904 mmole) of the methyl *p*-toluenesulfonate in 5 ml. of benzene was heated to 70° for 3 days. The **metho-*p*-toluenesulfonate 18a** separated as 168 mg. (68.5%) of white plates, m.p. 160.5–161.5°, whose melting point was raised to 161.5–162.5° by recrystallization from an ethyl acetate–methanol mixture. The product has infrared absorption[24] at 3320 cm.$^{-1}$ (assoc. O–H) with an ultraviolet maximum[25] at 222 mμ (ε 11,100) and n.m.r. absorption[29] at 6.78 τ (3H, N–CH_3), at 6.93 τ (3H, N–CH_3), and at 7.62 τ (3H, aryl CH_3).

Anal. Calcd. for $C_{16}H_{25}NO_4S$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.72; H, 7.72; N, 4.19.

In a comparable reduction employing 7.543 g. (0.0541 mole) of the ketone **13a**, 6.9 g. (0.30 g.-atom) of sodium, 50 g. (0.83 mole) of isopropyl alcohol, 150 ml. of toluene and a total reaction time of 2.5 hr. with no subsequent equilibration, the products isolated were 170 mg. (2.12%) of the **hydrochloride of the amino alcohol 16a**, m.p. 216.5–217.5°, and 11.342 g. (77%) of the **amino ester hydrochloride 20a**, m.p. 271° dec. An 11.30-g. sample of this ester **20a** was heated to 100° with 120 ml. of 20% aqueous hydro-

chloric acid for 18 hr. The resulting crude basic product, separated as previously described, was sublimed (100° at 80 mm.) to give 4.589 g. (93.9%) of the amino alcohol **15a**, m.p. 80.8–81.5°.

Reduction of 8-Methyl-8-azabicyclo[4.3.1]decan-10-one (13c).

A. Catalytic Hydrogenation.—A solution of 295 mg. (1.76 mmoles) of the amino ketone in 4 ml. of acetic acid was hydrogenated at room temperature and atmospheric pressure over the catalyst obtained from 30 mg. of platinum oxide. After the hydrogen uptake (44.6 ml. or 1.03 equiv. after 90 min.) ceased, use of the previously described isolation procedure followed by sublimation (100° at 50 mm.) afforded 262 mg. (88%) of the **amino alcohol 16c** as white prisms, m.p. 77–77.5°. Two additional sublimations raised the melting point to 78–78.5°.[32] The product has infrared absorption[26,27] at 3615 cm.$^{-1}$ (unassoc. O–H), at 3530 cm.$^{-1}$ (assoc. O–H), and at 2790, 2730, 2700 and 2690 cm.$^{-1}$ (two C–H bonds adjacent, *trans* and coplanar to the electron pair on nitrogen). Dilution of the solution[27] (lowest concentration 4.3 × 10^{-3} *M*) resulted in the disappearance of the assoc. O–H band at 3530 cm.$^{-1}$. The n.m.r. spectrum[28] of the material has a broad peak centered at 6.12 τ (1H, >CH–O), as well as a singlet at 7.87 τ (CH_3–N).

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28; mol wt., 169. Found: C, 70.84; H, 11.37; N, 8.24; mol. wt., 169 (mass spectrum).

Reaction of 169 mg. (1.0 mmole) of the amino alcohol **16c** with 205 mg. of methyl *p*-toluenesulfonate as previously described yielded 335 mg. (94%) of the crude **metho-*p*-toluenesulfonate 18c**, m.p. 148–165°, which crystallized from an ethyl acetate–methanol mixture as 201 mg. (56%) of white prisms, m.p. 164–165°. This material is apparently either a solvate or unstable crystalline modification since drying for 5 days at 80° and 0.1 mm. raised the melting point of the sample to 184–185°. The sample has infrared absorption[24] at 3320 cm.$^{-1}$ (assoc. O–H) with an ultraviolet maximum[25] at 222 mμ (ϵ 12,100) and n.m.r. absorption[29] at 6.83 τ (6H, two CH_3N) and at 7.62 τ (3H, aryl CH_3).

Anal. Calcd. for $C_{18}H_{29}NO_4S$: C, 60.82; H, 8.22; N, 3.94. Found: C, 60.80; H, 8.27; N, 3.94.

Reaction of 169 mg. (1.0 mmole) of the amino alcohol **16c** with 204 mg. (1.1 mmoles) of *p*-nitrobenzoyl chloride in 1.5 ml. of pyridine as previously described yielded 308 mg. (87%) of the crude **amino ester hydrochloride 21c**, m.p. 210–225° dec. Recrystallization from ethanol afforded 171 mg. (48%) of the pure hydrochloride as white prisms, m.p. 234–235° dec., with infrared absorption[24] at 1720 cm.$^{-1}$ (conj. ester C=O) and an ultraviolet maximum at 258 mμ (ϵ 12,400).

Anal. Calcd. for $C_{17}H_{23}ClN_2O_4$: C, 57.54; H, 6.53; N, 7.90. Found: C, 57.40; H, 6.73; N, 7.86.

From a comparable hydrogenation employing 250 mg. (1.50 mmoles) of the ketone **13c**, 8 ml. of acetic acid, 25 mg. of platinum oxide and a reaction time of 48 min. (hydrogen uptake 35.2 ml. or 0.98 equiv.), the product consisted[30] of 97% of **16c** (second eluted) and 3% of **15c** (first eluted). A hydrogenation employing 338 mg. (2.02 mmoles) of **13c**, 8 ml. of isopropyl alcohol, 34 mg. of platinum oxide, and a reaction time of 347 min. (hydrogen uptake 55.8 ml. or 1.13 equiv.) yielded a mixture of amino alcohols containing 99% of **16c** and 1% of **15c**.

B. With Sodium Borohydride.[32]—Reduction of 287 mg. (1.72 mmoles) of the amino ketone **13c** with a solution of 65 mg. (1.72 mmoles) of sodium borohydride in a mixture of 10 ml. of methanol and 8 ml. of water followed by the previously described isolation procedure yielded, after sublimation (100° at 50 mm.), 233 mg. (79%) of the **amino alcohol 16c**, m.p. 76–77° (identified by comparison of infrared spectra). The amino alcohol mixture from a comparable reduction employing 334 mg. (2.00 mmoles) of the ketone **13c**, 75.6 mg. (2.00 mmoles) of sodium borohydride, 10 ml. of methanol, 8 ml. of water, and a reaction time of 3 hr. contained[30] 98% of **16c** and 2% of **15c**.

C. Hydrogenation of the Quaternary Salt 14c.—A solution of 4.37 g. (12.4 mmoles) of the quaternary salt in 60 ml. of acetic acid was hydrogenated at 120° and 1500 p.s.i. for 22 hr. over the catalyst obtained from 500 mg. of platinum oxide. The previously described isolation procedure separated 4.84 g. of a crude mixture of quaternary salts, m.p. 110–134°. A 1.22-g. portion of the mixture was treated with 9.0 g. of lithium iodide in 10 ml. of boiling *n*-decyl alcohol as previously described to separate, after sublimation (100° at 50 mm.), 330 mg. (62%) of the crude amino alcohol **16c** which contained a small amount of the amino ketone **13c** as judged from thin-layer chromatography[23] and the presence of a weak infrared band[26] at 1695 cm.$^{-1}$. A 200-mg. (1.18 mmoles) sample of this mixture was treated with 220 mg. (1.18 mmoles) of *p*-nitrobenzoyl chloride in chloroform as previously described. No *p*-nitrobenzoate could be isolated. The resulting ethanol solution was concentrated, made basic with aqueous sodium hydroxide, and extracted with ether. After the ethereal solution had been dried and concentrated, sublimation of the residue afforded 154 mg. (48%) of the **amino alcohol 16c**, m.p. 75–77°, identified by a mixture melting point determination and comparison of infrared spectra.

From a subsequent hydrogenation, employing 353 mg. (1.00 mmole) of the salt **14c**, 35 mg. of platinum oxide, 15 ml. of acetic acid, a temperature of 120°, and a hydrogen pressure of 1250 p.s.i. for 18 hr., the crude salt was demethylated with 4.0 g. of lithium iodide in 4 ml. of *n*-decyl alcohol at 200 ± 10° for 30 min. The resulting solution was extracted with aqueous hydrochloric acid and the aqueous extract was made basic with aqueous sodium hydroxide and extracted with ether. Concentration and analysis[30] of the ethereal extract indicated the presence of **16c** but not **15c**.

D. With Sodium and Isopropyl Alcohol.[4]—Application of the previously described procedure to 970 mg. (5.80 mmoles) of the ketone **13c**, employing 880 mg. (38 mg.-atoms) of sodium, 20 ml. of toluene, 8.0 g. (133 mmoles) of isopropyl alcohol, and a reaction time of 1.5 hr., yielded, after sublimation (100° at 80 mm.), 878 mg. (89.5%) of a mixture of amino alcohols **15c** and **16c**, m.p. 59–72.5°.

A 9.207-g. (0.0545-mole) sample of the amino alcohol mixture from a comparable reduction was treated with 10.0 g. (0.0545 mole) of *p*-nitrobenzoyl chloride in 100 ml. of chloroform. After the mixture had been allowed to stand for 48 hr., 4 ml. of concentrated, aqueous hydrochloric acid was added and the mixture was concentrated. After extraction with two portions of boiling ether, the residue was fractionally crystallized from ethanol to separate 1.704 g. (6.0%) of a 1:1 **mixture** (apparently a molecular complex) **of *p*-nitrobenzoic acid and the amino ester hydrochloride 20c**, m.p. 226° dec. The product has an ultraviolet maximum[25] at 259 mμ (ϵ 25,600) with infrared absorption[24] at 1720 cm.$^{-1}$ (ester C=O) and 1690 cm.$^{-1}$ (carboxyl C=O) as well as a complex series of peaks in the 3-μ region at 3120, 2650, 2530 and 2430 cm.$^{-1}$. The material from two different preparations had the same properties and composition and did not appear to be altered by repeated crystallization.

Anal. Calcd. for $C_{17}H_{23}N_2O_4Cl$ + $C_7H_5NO_4$: C, 55.22; H, 5.41; N, 8.05. Found: C, 55.29; H, 5.47; N, 7.79.

A mixture of 1.335 g. of this complex and 30 ml. of 20% aqueous hydrochloric acid was heated to 100° for 24 hr. The resulting mixture was filtered to separate the *p*-nitrobenzoic acid and then made alkaline with aqueous sodium hydroxide and saturated with sodium chloride. The solid which separated was sublimed (100° at 80 mm.) to give 385 mg. (89.0%) of the **amino alcohol 15c** as white prisms, m.p. 82.5–83.5°. The product has infrared absorption[26,27] at 3620 cm.$^{-1}$ (unassoc. O–H), at 3440 cm.$^{-1}$ (assoc. O–H), and at 2780, 2760 (shoulder), 2725 and 2680 cm.$^{-1}$ (two C–H bonds adjacent, *trans* and coplanar to the electron pair on nitrogen). Dilution of the solution[27] (lowest concentration 4.3 × 10^{-3} *M*) resulted in the disappearance of the assoc. O–H bond at 3440 cm.$^{-1}$. The n.m.r. spectrum[28] has a broad peak centered at 6.08 τ (1H, >CH–O) as well as a singlet at 7.78 τ (CH_3–N).

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28; mol. wt., 169. Found: C, 70.92; H, 11.23; N, 8.27; mol. wt., 169 (mass spectrum).

After a solution of 86 mg. (0.51 mmole) of the amino alcohol **15c** and 117 mg. (0.629 mmole) of methyl *p*-toluenesulfonate in 3.1 g. of benzene had been refluxed for 4 days, the crude quaternary salt which separated was recrystallized from an ethyl acetate–methanol mixture to give 113 mg. (62.5%) of the **metho-*p*-toluenesulfonate 17c** as white plates, m.p. 203.5–204°. The material has infrared absorption[24,33] at 3360 cm.$^{-1}$ (assoc. O–H) with an ultraviolet maximum at 222 mμ (ϵ 12,300) and n.m.r. absorption at 5.84 τ (1H triplet, J = 2 c.p.s., >CH–O) as well as singlets at 6.66 τ (3H, N—CH_3), 6.83 τ (3H, N–CH_3), and 7.62 τ (3H, aryl CH_3).

Anal. Calcd. for $C_{18}H_{29}NO_4S$: C, 60.82; H, 8.22; N, 3.94. Found: C, 60.73; H, 8.25; N, 3.91.

(32) R. A. Covey [Ph.D. dissertation, University of Michigan, 1957] has reported the isolation of an amino alcohol, m.p. 78–79°, by the reduction of the amino ketone **13c** with aqueous sodium borohydride.

(33) Determined as a suspension in a potassium bromide pellet.

A subsequent reduction was carried out with 7.452 g. (0.0445 mole) of the ketone **13c**, 6.9 g. (0.30 g.-atom) of sodium, 50 g. (0.83 mole) of isopropyl alcohol, and 150 ml. of toluene, small aliquots (*ca.* 0.25 ml.) of the reaction mixture being removed periodically and analyzed as previously described. After the sodium had been consumed (128 min.), 720 mg. (3.95 mmoles) of benzophenone was added and refluxing was continued. The amino alcohol composition in the reaction mixture after various periods of time was as follows: 8 min., 9% of **15c** and 91% of **16c**; 128 min., 9% of **15c** and 91% of **16c**; 25.5 hr., 24% of **15c** and 76% of **16c**; 120 hr., 44% of **15c** and 56% of **16c**; 216 hr., 55% of **15c** and 45% of **16c**; 262 hr., 57% of **15c** and 43% of **16c**.

After a total reaction time of 262 hr., the crude mixture of amino alcohols was separated in the usual way and treated with 10.5 g. (0.056 mole) of *p*-nitrobenzoyl chloride in 120 ml. of chloroform. The resulting mixture was allowed to stand for 3 days and then worked up as previously described. The crude amino ester hydrochloride **20c**–*p*-nitrobenzoic acid mixture which crystallized from ethanol was shaken with a mixture of 100 ml. of aqueous sodium bicarbonate and 100 ml. of methylene chloride until solution was complete. The methylene chloride solution was washed with aqueous sodium bicarbonate, dried over potassium carbonate, and concentrated to leave 5.779 g. (40.7% based on the starting ketone) of the ***p*-nitrobenzoate of the amino alcohol 15c** (*i.e.*, the free base corresponding to the amine hydrochloride **20c**), m.p. 112–113°. Recrystallization from an ether–petroleum ether mixture afforded the pure amino ester as yellow plates, m.p. 114.5–115°. The material has infrared absorption[34] at 1720 cm.$^{-1}$ (conj. ester C=O) with no absorption in the 3-μ region attributable to an N–H or O–H function. The product has an ultraviolet maximum[25] at 250 mμ (ϵ 14,100) and n.m.r. absorption at 1.68 τ (aryl C–H), at 4.75 τ (broad >CH–O), and at 7.76 τ (singlet, N–CH_3).

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.08; H, 6.99; N, 8.82.

The ethanol mother liquors remaining after the separation of crude **20c** were concentrated and diluted with acetone to separate 2.535 g. (27.7%) of the crude hydrochloride of amino alcohol **16c**, m.p. 225–230°. Recrystallization from an ethanol–acetone mixture separated various fractions of the hydrochloride of **16c** contaminated with the hydrochloride of **15c**. The samples of free base liberated from these various fractions were found to contain[30] **16c** contaminated with 13 to 27% of **15c**.

4-*t*-Butyl-1-methylpiperidin-4-ol (22).—A solution of 11.7 g. (0.103 mole) of 1-methyl-4-piperidone in 20 ml. of pentane was added, dropwise and with stirring under a nitrogen atmosphere, to a solution containing 0.140 mole of *t*-butyllithium in 75 ml. of pentane.[35] After the addition was complete, the reaction mixture was stirred at room temperature for 3 hr. and then hydrolyzed with water. The pentane layer was separated and the aqueous phase was saturated with sodium chloride and extracted with ether. The combined organic solutions were dried over sodium sulfate, concentrated and fractionally distilled to separate 2.96 g. (25.1% recovery) of unchanged 1-methyl-4-piperidone, b.p. 63–65° (15 mm.), and the crude amino alcohol **22**, b.p. 110–130° (13 mm.), which solidified. Recrystallization from ligroin and subsequent sublimation (80° at 14 mm.) gave 3.684 g. (21.0%) of the **amino alcohol 22**, m.p. 79.5–80.5°. An additional crystallization from ligroin gave the pure amino alcohol as colorless plates, m.p. 80–81°. The material has infrared absorption[26] at 3600 cm.$^{-1}$ (unassoc. O–H), at 3200 cm.$^{-1}$ (broad, assoc. O–H) and at 2795, 2760, 2740 and 2680 cm.$^{-1}$ (two C–H bonds adjacent, *trans* and coplanar to the unshared electron pair on nitrogen), with n.m.r. singlets[28] at 7.72 τ (3H, N–CH_3) and 9.07 τ (9H, C–CH_3).

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18; mol. wt., 171. Found: C, 70.04; H, 12.37; N, 8.21; mol. wt., 171 (mass spectrum).

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(34) Determined in carbon tetrachloride solution.

(35) This lithium reagent was obtained from the Lithium Corporation of America.

Bicyclic Ketones. I. Reaction of Cyclopentadiene with *cis*- and *trans*-Benzalacetone and Acetylphenylacetylene[1]

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Diels–Alder addition of *cis*-benzalacetone to cyclopentadiene yielded the expected *endo-cis* adduct X. *trans*-Benzalacetone produced a mixture of the two *trans* isomers in proportions which depended on the temperature of reaction. Acetylphenylacetylene formed the expected norbornadiene derivative XV. The stereochemistry of these compounds was established by haloform degradation to the acids, followed by iodolactonization.

Our need for pure samples of isomers in the 2-acetyl-3-phenyl-5-norbornene series and their saturated analogs prompted us to investigate the Diels–Alder reactions of cyclopentadiene with the geometrical isomers of benzalacetone (I and II) and acetylphenylacetylene (III, 4-phenylbut-3-yn-2-one) as a preparative method.

It was hoped at the outset of this work that the mixtures derived from the Diels–Alder reactions could be separated by any one of the conventional methods, *i.e.*, fractional distillation, vapor phase chromatography (v.p.c.), fractional crystallization, etc.; however, this was not the case. Therefore, it was decided to analyze the mixtures by conversion of the ketones to their derived acids *via* the haloform reaction and then utilize the procedures previously reported for determination of the isomer ratios of the acids.[2–4]

Reaction of cyclopentadiene with *trans*-benzalacetone (I) at 139°, 155°, and at 155–220° yielded in each case a mixture of *endo*-2-acetyl-*exo*-3-phenyl-5-norbornene (IV) and *exo*-2-acetyl-*endo*-3-phenyl-5-norbornene (V). Treatment of IV and V under the conditions of the haloform reaction gave a mixture of *exo*-3-phenyl-5-norbornene-*endo*-2-carboxylic acid (VI) and *endo*-3-phenyl-5-norbornene-*exo*-2-carboxylic acid (VII). The procedure of Rondestvedt and Ver Nooy,[3] was used to prepare the iodolactone VIII of the *endo* acid VI,

(1) Presented at the 14th annual Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., November 1–3, 1962.

(2) K. Alder, W. Gunzl, and K. Wolff, *Ber.*, **93**, 809 (1960).

(3) C. S. Rondestvedt and C. D. Ver Nooy, *J. Am. Chem. Soc.*, **77**, 4878 (1955).

(4) G. I. Poos, J. Kleis, R. R. Wittekind, and J. D. Rosenau, *J. Org. Chem.*, **26**, 4898 (1961).