for 22 hr and was then poured into water. The mixture was acidified with HCl and the oil which separated was extracted into chloroform. The chloroform solution was evaporated under reduced pressure, leaving a glassy product which was crystallized from ethanol. The yield of XIII, mp 122–123°, $[\alpha]^{23}D$ −70° (*c* 2%, chloroform), was 0.38 g (98%). The infrared spectrum showed strong bands at 7.45 and 8.65 μ (N–Ts), whereas the band at 3.05 μ (N–H) was absent.

Anal. Calcd for $C_{19}H_{22}N_2O_4S_2$: C, 56.14; H, 5.46; N, 6.89. Found: C, 56.02; H, 5.72; N, 6.81.

Stereoselectivity in the N-Methylation of Certain Azabicyclic Systems[1]

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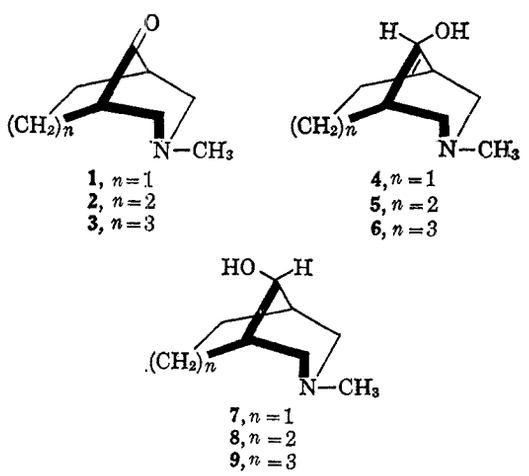
The reactions of the N-methyl azabicyclic ketones **1–3** and alcohols **4–9** with trideuteriomethyl *p*-toluenesulfonate have been examined to determine the degree of stereoselectivity with which the trideuteriomethyl group is introduced to form a quaternary ammonium salt. The predominant stereoisomer in these cases comprised from 60 to 90% of the mixture of quaternary ammonium salts; the predominant reaction path was shown to be the same for both the ketones and the alcohols. The preferred direction of attack at nitrogen is assigned as *syn* to the oxygen function.

The availability of the amino ketones **1–3** as well as the corresponding β (**4–6**) and α (**7–9**) secondary alcohols[2] prompted us to study the degree of stereospecificity which would be associated with the N-alkylation of these amines. Studies of the addition reactions of ketones **1–3**[2c,3] have demonstrated that steric hindrance at the carbonyl group from the methylene chain increased in a regular manner as the chain was lengthened from two carbon atoms (as in **1**) to three and then to four atoms (as in **3**). It was of interest to learn whether a similar steric effect might be observed for reactions at the nitrogen atom[4,5] and also whether the stereochemistry of reaction at the nitrogen atom might be influenced by the nature or steric arrangement of the oxygen function (*i.e.*, ketone, α alcohol, or β alcohol).[6]



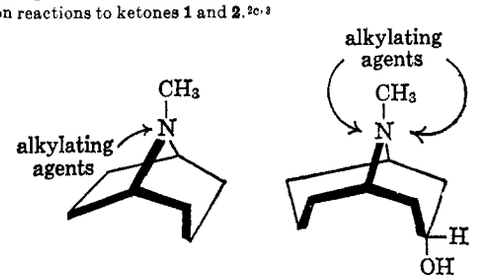
1, $n=1$ **2**, $n=2$ **3**, $n=3$

4, $n=1$ **5**, $n=2$ **6**, $n=3$

7, $n=1$ **8**, $n=2$ **9**, $n=3$

To examine these possibilities, each of the amines **1–9** was allowed to react with trideuteriomethyl *p*-toluenesulfonate in acetone solution to form trideuterio derivatives of the known[2a,2c] dimethylammonium *p*-toluenesulfonates **10–18** in which the methyl group introduced by N-alkylation was labeled with deuterium.[7,8] The stereoselectivity of the alkylation of amines **1–7** could be determined from the nmr spectra of the corresponding salts **10–16** because the nmr signals for the two N-methyl groups appeared as separate singlets.[2a,c] The proportions of isomers present in the salt **17** (in which the two N-methyl signals coincided) could be established by catalytic oxidation[9] to the corresponding keto derivative **11**.

(4) Investigations[5] of the stereochemistry of N-alkylation of tropane (i) and granatanol (ii) have led to the generalizations summarized in the accompanying formulas. These stereochemical results parallel the results of addition reactions to ketones **1** and **2**.[2c,3]



i ii

(5) For studies of the N-alkylation of tropane and granatanine derivatives, see (a) G. Fodor, J. Toth, and I. Vincze, *Helv. Chim. Acta*, **37**, 907 (1954); (b) G. Fodor, J. Toth, and I. Vincze, *J. Chem. Soc.*, 3504 (1955); (c) O. Kovacs, G. Fodor, and M. Halmos, *ibid.*, 873 (1956); (d) G. Fodor, K. Koczka, and J. Lestyan, *ibid.*, 1411 (1956); (e) G. Fodor, I. W. Vincze, and J. Toth, *ibid.*, 3219 (1961); (f) C. H. MacGillavry and G. Fodor, *ibid.*, 597 (1964); (g) G. Fodor, F. Uresch, F. Dutka, and T. Szell, *Collection Czech. Chem. Commun.*, **29**, 274 (1964); (h) G. L. Closs, *J. Am. Chem. Soc.*, **81**, 5456 (1959); (i) H. L. Holmes in "The Alkaloids," Vol. 1, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1950, pp 271–374; (j) G. Fodor, *Tetrahedron*, **1**, 86 (1957); (k) G. Fodor in "The Alkaloids," Vol. 6, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, pp 145–177.

(6) For example, the hydroxyl function in the β isomers **4–6** might be expected to solvate the leaving group during alkylation at nitrogen and, consequently, favor attack of the alkylating agent from the direction *syn* to the hydroxyl function. For a possible example of this sort of directional effect in a carbon alkylation, see F. J. McQuillin and R. B. Yeats, *J. Chem. Soc.*, 4273 (1965), and earlier papers cited.

(7) Since our earlier studies[2c] had demonstrated that even in the presence of the much better nucleophile, iodine ion, these quaternary salts did not undergo rapid reversal (by a displacement by iodide ion at an N-methyl group) at temperatures below 200°, we are confident that the *p*-toluenesulfonate salts obtained in this study are the result of kinetically controlled processes.

(8) The use of trideuteriomethyl iodide to study the stereoselectivity of alkylation of N-methylaziridine derivatives has recently been reported by A. T. Bottini and R. L. Van Etten, *J. Org. Chem.*, **30**, 575 (1965).

(9) For a recent review, see K. Heyns and H. Paulsen in "Newer Methods of Preparative Organic Chemistry," Vol. 2, W. Foerst, Ed., Academic Press Inc., New York, N. Y., 1963, p 303.

(1) This research has been supported by research grants from the McNeil Laboratories and from the National Institutes of Health (Grant No. GM-08761).

(2) (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).

(3) H. O. House and W. M. Bryant, III, *ibid.*, **30**, 3634 (1965).

This same oxidation procedure also served to relate the various salts **10–16** by means of the conversions illustrated in Chart I. However, several attempts to oxidize the alcohol **18** to the ketone **12** were unsuccessful. Since the two N-methyl signals of the salt **18** are coincident, we have no measure of the stereoselectivity of N-alkylation of amino alcohol **9**.

From the ratios of N-methyl peak areas obtained, the proportion of the major N-alkylated product in the salts **10–17** was found to range from 60 to 90%, with the majority of the salts containing approximately 70% of the predominant alkylated product. An increased stereoselectivity (89–92%) was observed with each of the stereoisomeric 3-azabicyclo[3.2.1]-octan-8-ols **13** and **16**. From the aforementioned oxidation procedure, we were able to show that among the derivatives of each ring system, the preferred direction of attack by the alkylating agent was the same. Both this fact and the lack of any obvious correlation between the degree of stereoselectivity and the nature and steric arrangement of the oxygen functions indicate that the oxygen function does not exert any significant control over the direction of these N-alkylations.[6,10]

The questions remaining are whether each of the three ring systems studied undergoes N-alkylation predominantly from the same direction and what is the preferred direction of N-alkylation. Our evidence pertaining to each of these questions is only circumstantial and, hence, our conclusions must be regarded as tentative. For the sake of clarity, each of the N-methyl groups of salts **10–18** is assigned (Chart I) the nmr peak position[11] which we believe to be correct. It will be noted that in all cases involving alcohols or the ketone hydrate **10**[12] where two N-methyl nmr signals are observed, the greater proportion of the trideuteriomethyl groups are introduced at that position which corresponds to the lower field N-methyl signal. Conversely, for the ketones **11** (related to **14** and **17**) and **12** (related to **15**), the greater proportion of the trideuteriomethyl groups are introduced at that position which corresponds to the higher field N-methyl signal. The consistency of this pattern throughout the series of compounds studied leads us to believe that the preferred direction of alkylation is the same for all of the amines **1–8**.

Several recent studies of the stereochemistry of N-alkylation[13–16] have made use of the position of the nmr N-methyl signal to define the stereochemistry of the resulting quaternary ammonium salt. These studies suggest that, in the absence of functional groups, the axial N-methyl group of a piperidinium or quinolizium salt will give an nmr signal at higher field than will the corresponding equatorial N-methyl group. However, we believe it inappropriate to apply this generalization to the salts **10–16** for two reasons. Most important is the fact that the nature of the oxygen function is obviously influencing the relative positions of the N-methyl nmr signals. For example, the N-methyl group in the alcohol **14** which is responsible for the higher field signal (at δ 3.23) is the

(10) Our studies of the N-alkylation of monocyclic piperidine derivatives also led us to the same conclusion: H. O. House, B. A. Tefertiller, and C. G. Pitt, *J. Org. Chem.*, **31**, 1073 (1966).

(11) Determined as a solution in deuterium oxide.

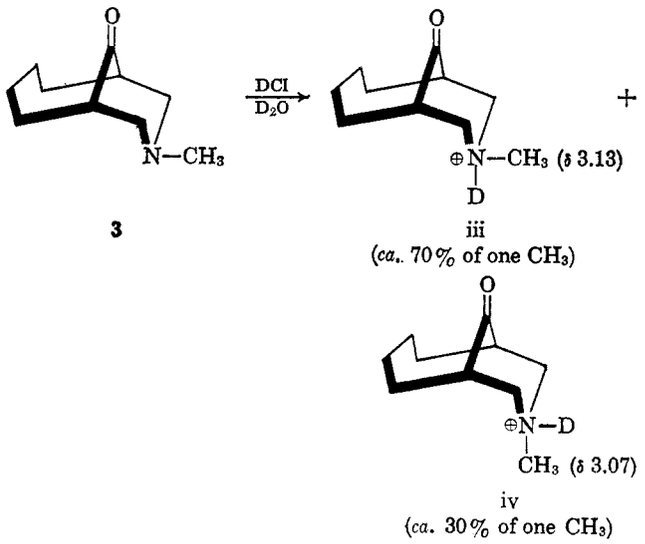
(12) Measurement of the infrared spectra of the salts **10–12** in deuterium oxide solution established that the salt **10** exists as the hydrate where salts **11** and **12** both exhibit carbonyl absorption (1703 cm^{-1} for **12** and 1712 cm^{-1} for **11**), indicating their existence in solution as the free ketones.

(13) For studies of simple quinolizidine systems, see (a) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962); (b) A. R. Katritzky, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **23**, 223 (1962); (c) K. Schofield and R. J. Wells, *Chem. Ind.* (London), 572 (1963); (d) S. F. Mason, K. Schofield, and R. J. Wells, *Proc. Chem. Soc.*, 337 (1963).

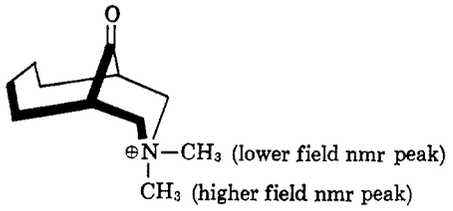
(14) For studies of more complex quinolizine derivatives including verification of an assigned stereochemistry by X-ray crystallographic studies, see (a) M. F. Bartlett, B. Korzan, R. Sklar, A. F. Smith, and W. I. Taylor, *J. Org. Chem.*, **28**, 1445 (1963); (b) M. Shamma and J. M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963); (c) S. F. Mason, K. Schofield, and R. J. Wells, *Proc. Chem. Soc.*, 337 (1963).

(15) For a study of the 4a-azaperhydroindan system, see W. L. Meyer and N. Sapianchiay, *J. Am. Chem. Soc.*, **86**, 3343 (1964).

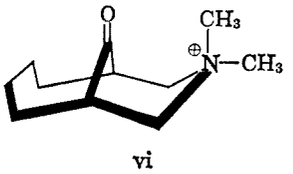
(16) For studies of pyrrolidine and piperidine derivatives, see (a) J. McKenna, J. M. McKenna, J. White, and A. Tulley, *J. Chem. Soc.*, 1711 (1965); (b) J. K. Becconsall, R. A. Y. Jones, and J. McKenna, *ibid.*, 1726 (1965); (c) J. McKenna, B. C. Hutley, and J. White, *ibid.*, 1729 (1965); (d) J. McKenna, J. M. McKenna, and J. White, *ibid.*, 1733 (1965); (e) R. Lygo, J. McKenna, and I. O. Sutherland, *Chem. Commun.* (London), **No. 15**, 356 (1965). (f) These workers have assigned N-alkyl groups to certain nmr peaks observed for quaternary ammonium salts by examining the nmr spectra of the corresponding protonated amines (the reverse of a procedure used earlier by Closs[5b]). For the amines **1–9** which we have studied, only the ketone **3** exhibits two N-methyl peaks in acid solution. If the assumption is made that the larger N-methyl peak (at δ 3.13) is attributable to the stereoisomer iii with an equatorial methyl group, then the argument used by these authors would lead to the nmr assignments indicated in structure v, which is opposite to the conclusion (structure **12**, Chart I) we have reached on other grounds. Since the nmr measurements involve different compounds (which may well have different conformations) and are made in different media, we believe that this type of correlation of small chemical shift differences involving both trialkylammonium and tetraalkylammonium salts more apt to be in error than the arguments we have used involving only tetraalkylammonium salts. For example, consideration of the data in ref 16e would suggest that trialkylammonium salt iii exists in the indicated conformation with a chair piperidine ring, whereas the tetraalkylammonium salt should be expected to exist in the conformation vi with a boat (or twist–boat) piperidine ring. If such a circumstance is true, no particular correlation should be expected between the N-methyl nmr signals of the two compounds.



3 iii (*ca.* 70% of one CH_3) iv (*ca.* 30% of one CH_3)

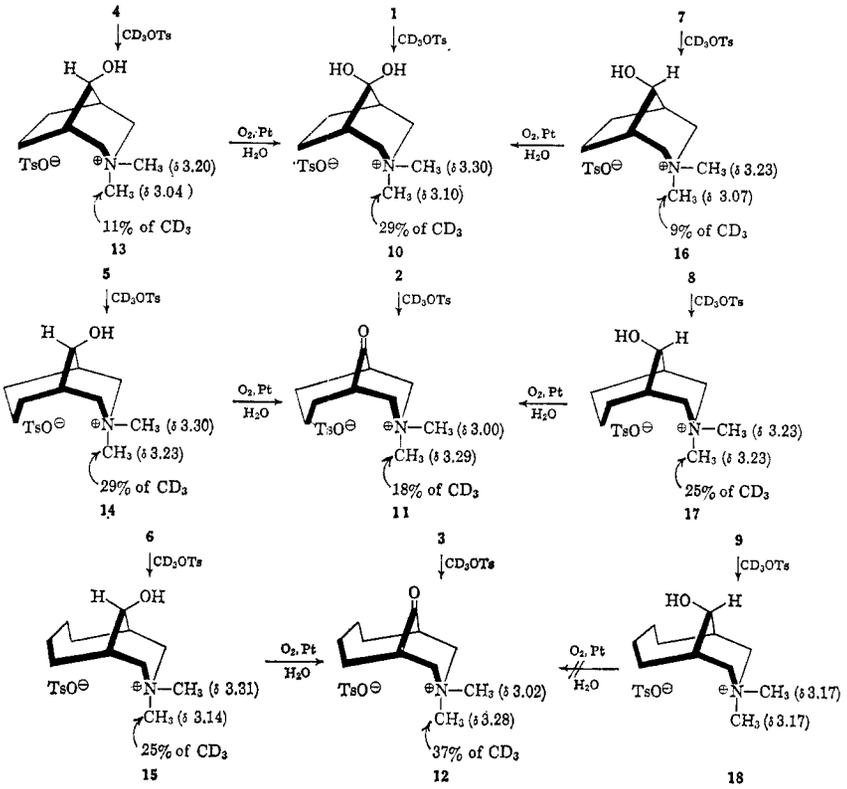


v



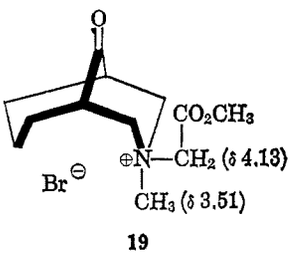
vi

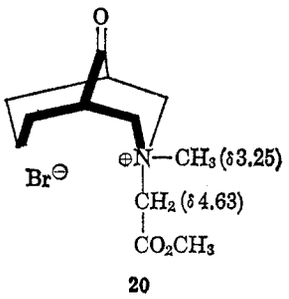
CHART I



same N-methyl group which is responsible for the lower field signal (at δ 3.29) in the corresponding ketone **11**. Although previously published information[2,17] has indicated that the free amines **1–9** have the indicated conformations with the piperidine ring in a chair conformation and the N-methyl group equatorial, we have no evidence bearing on the favored conformations of the quaternary salts **10–18**. The representations in Chart I were selected only for convenience. Consequently, even a knowledge of which N-methyl group in these salts occupies an axial position would not answer our stereochemical question.

The choice (indicated in Chart I) of having the alkylating agent (trideuteriomethyl *p*-toluenesulfonate) attack predominantly from a direction *syn* to the oxygen function was made following our subsequently described study of the reactions of amino alcohols **5** and **8** with methyl bromoacetate.[18] In this study, where proof of stereochemistry was possible, the predominant direction of attack by the methyl bromoacetate was *syn* to the oxygen function. Furthermore, the nmr assignments suggested for ketone **11** in the present study are fully compatible with the N-alkyl nmr peak positions found for the subsequently described[18] ketones **19** and **20** of known configuration. Thus, the stereochemical and nmr assignments presented in Chart I





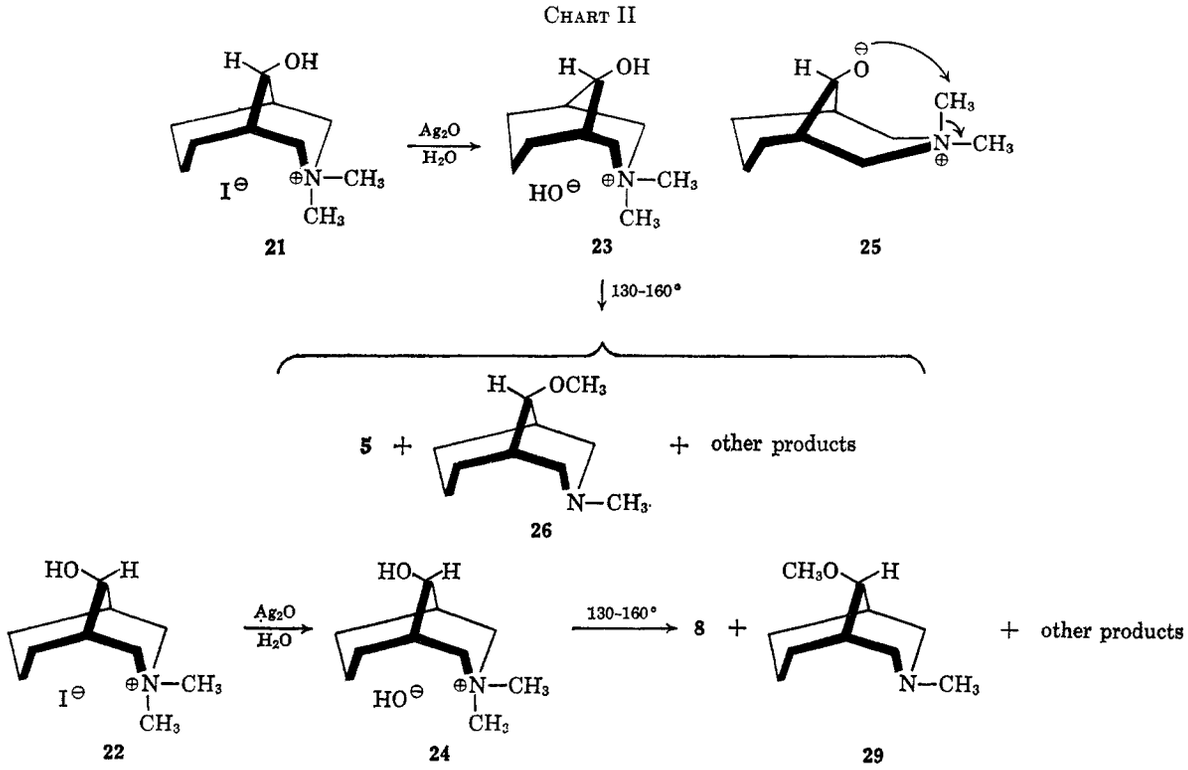
rest upon the assumptions that the preferred direction of N-alkylation is the same for each of the three ring systems studied, and that the reaction and nmr peak position correlations used for the 3-azabicyclo[3.3.1]-nonane derivatives are the same with the two different alkylating agents methyl *p*-toluenesulfonate and methyl bromoacetate.

In an effort to obtain direct evidence for the stereochemical assignments indicated in Chart I, the methiodides **21** and **22** were converted to the corresponding crude methohydroxides **23** and **24** and subjected to thermal decomposition under various conditions. (See Chart II.) It was our hope that conditions could be found which would permit the *intramolecular* transfer of a methyl group as indicated in structure **25** to form the methoxyamine **26**. The realization of such an intramolecular transfer with a methohydroxide analogous to **23** in which one of the methyl groups was labeled with deuterium would, of course, answer our stereochemical question unambiguously. In practice, thermal decomposition of the metho-

(17) (a) An X-ray crystal structure determination on the hydrobromide salt of 3-azabicyclo[3.3.1]nonane indicated that the conformation of this material in the solid state has both six-membered rings in chair conformations: M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964); see also N. W. J. Pumphrey and M. J. T. Robinson, *Chem. Ind.* (London), 1903 (1963); J. M. Eckert and R. J. W. LeFevre, *J. Chem. Soc.*, 358 (1964); C. Y. Chen and R. J. W. LeFevre, *Chem. Ind.* (London), 306 (1965); *J. Chem. Soc.*, 3473 (1965); ref 16e. (b) Similar conclusions have been reached for the analogous carbocyclic system: W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965); W. A. C. Brown, J. Martin, and G. A. Sim, *ibid.*, 1844 (1965); I. Laszlo, *Rec. Trav. Chim.*, **84**, 251 (1965); M. Eakin, J. Martin, and W. Parker, *Chem. Commun.* (London), **No. 11**, 206 (1965); R. A. Appleton and S. H. Graham, *ibid.*, **No. 14**, 297 (1965). (c) For examples of bicyclo[3.3.1]nonane derivatives where a chair–chair conformation does not appear to be preferred, see C. Y. Chen and R. J. W. LeFevre, *Tetrahedron Letters*, **No. 12**, 737 (1965); W. D. K. Macrosson, J. Martin, and W. Parker, *ibid.*, **No. 30**, 2589 (1965); ref 16e.

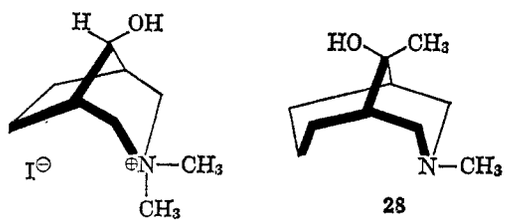
(18) H. O. House and B. A. Tefertiller, *J. Org. Chem.*, **31**, 1068 (1966).

CHART II



21 23 25 26 22 24 29

hydroxide **23** yielded the amino alcohol **5**, the methoxyamine **26**, and other unidentified products presumed to arise from Hofmann elimination. However, the conditions needed to effect this change also converted the methohydroxide **24** to the amino alcohol **8**, the methoxyamine **29**, and other unidentified products. Thus, it is clear that the methoxyamine **29** (and, at least part of the methoxyamine **26**) is being formed by an *intermolecular* transfer of a methyl group which would invalidate our plan for proof of stereochemistry. Preliminary experiments along comparable lines with the methiodide **27** were equally unrewarding. We also examined the possibility of an intramolecular transfer of a methyl group in an anion radical[19] derived from the ketone **11** and lithium in liquid ammonia to form the known[3] tertiary alcohol **28**. However, this reaction produced a mixture containing the amines **2**, **5**, and **8**, as well as other lower boiling components.



27 28

Experimental Section[20]

Preparation of Starting Materials.—Samples of the amino ketones **1–3**, the amino alcohols **4–9**, and the corresponding nondeuterated metho-*p*-toluenesulfonates were prepared by previously described procedures.[2a,c] The positions of the nmr peaks[11] for the N-methyl groups of the metho-*p*-toluenesulfonates have been reported previously[2a,c] and are restated in Chart I and Table I; for comparison of the N-methyl peak positions of the tertiary amine hydrochlorides, the nmr spectrum of a solution of each of the amines **1–9** in deuterium oxide containing 20% deuterium chloride[21] was measured. The salts of each of the amines **1**, **2**, and **4–9** exhibited a single N-methyl peak at the following position: **1**, δ 2.93; **2**, δ 2.98; **4**, δ 2.90; **5**, δ 2.90; **6**, δ 2.98; **7**, δ 2.87; **8**, δ 2.93; and **9**, δ 2.96. The corresponding solution containing the salt of the amino ketone **3** exhibited two sharp peaks at δ 3.07 (*ca.* 30% of area) and 3.13 (*ca.* 70% of area) which appear to be attributable to N-methyl peaks in different environments.[22]

A solution of 318 mg (1.0 mmole) of the *p*-nitrobenzoate of amino alcohol **6**[2c] in excess (1.0 ml) methyl *p*-toluenesulfonate was heated to 75° for 28 hr and then cooled and washed with ether. The residual solid was recrystallized from a chloroform–ethyl acetate mixture to separate 432.5 mg (86%) of the **metho-*p*-toluenesulfonate of 6** as white prisms, mp 205–207°. Drying (80° at 0.2 mm) raised the melting point to 207–208.5°. The product has infrared absorption[23] at 1730 cm^{-1} (ester C=O) with ultraviolet maxima[24] at 218 mμ (ϵ 19,000) and 258 mμ (ϵ 15,300).

Anal. Calcd for $C_{25}H_{32}N_2O_7S$: C, 59.51; H, 6.39; N, 5.55. Found: C, 59.38; H, 6.46; N, 5.47.

A solution of 259 mg (0.5 mmole) of this metho-*p*-toluenesulfonate in 5 ml of hot ethanol was added to a solution of 110 mg (0.26 mmole) of barium iodide dihydrate in 5 ml of ethanol, and the resulting solution was stirred for 5 min and then filtered. Concentration of the filtrate followed by recrystallization of the residual solid from a chloroform–ethyl acetate mixture afforded

(19) *Cf.* H. O. House, J. J. Riehl, and C. G. Pitt, *J. Org. Chem.*, **30**, 650 (1965).

(20) 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 a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The nmr spectra were determined at 60 Mc with a Varian Model A-60 nmr 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.

(21) This solution was prepared by reaction of 12.0 g (0.087 mole) of freshly distilled phosphorus trichloride with 44.0 g (2.2 moles) of deuterium oxide. The resulting solution was distilled twice to separate 42 g of the deuterium chloride solution.

(22) Since these sharp peaks are superimposed on a broad peak (total area corresponding to 5 H) attributed to the two bridgehead C–H protons, the assignment of these peaks is open to some question. Spectra of *p*-toluenesulfonic acid salt of this amino ketone **3** in deuterium oxide[2a] exhibit only a single N-methyl peak, but spectra of the hydrobromide salt resemble the spectrum of the deuteriochloride described here.

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

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

TABLE I

REACTIONS OF AMINES WITH TRIDEUTERIOMETHYL *p*-TOLUENESULFONATE

Amine, mg (mmole)	Methylating agent, mg (mmole)	Acetone, ml	Reaction time, hr (temp, °C)	Metho-*p*-toluenesulfonate, mp, °C (% yield)	N-Me nmr signal, δ (% of one CH_3 group)
1, 139 (1.00)	208 (1.10)	5.0	92 (56)[a]	**10**, 232–233 (57)	3.10 (71) 3.30 (29)
2, 76.5 (0.50)	104 (0.55)	2.5	168 (30)	**11**, 163.5–164.5 (29)	3.00 (18)[b] 3.29 (82)
3, 167 (1.00)	208 (1.10)	5.0	168 (30)	**12**, 159.5–160.5 (21)	3.02 (37) 3.28 (63)
4, 141 (1.00)	208 (1.10)	5.0	168 (30)	**13**, 153.5–154.5 (83)	3.04 (89) 3.20 (11)
5, 155 (1.00)	208 (1.10)	5.0	168 (30)	**14**, 150–150.5 (12)	3.23 (71)[c] 3.30 (29)
6, 169 (1.00)	208 (1.10)	5.0	168 (30)	**15**, 203–204 (32)	3.14 (75) 3.31 (25)
7, 128 (0.91)	189 (1.00)	5.0	168 (30)	**16**, 161.5–162.5 (52)	3.07 (91) 3.23 (9)
8, 93 (0.60)	125 (0.66)	3.0	144 (56)[a]	**17**, 190–190.5 (14)	3.23[d]
9, 169 (1.00)	208 (1.10)	5.0	168 (56)[a]	**18**, 164–164.5 (34)	3.17[d]

[a] Reaction at 25–30° for 7 days gave no isolable salt. [b] Reaction of the ketone **2** with trideuteriomethyl iodide in acetone solution at 30° afforded the corresponding methiodide of ketone **2** (65%) in which the N-methyl nmr peaks (ref 11) were at δ 3.10 (14% of one CH_3 group) and 3.38 (86% of one CH_3 group). From an experiment in which the ketone **2** was heated to 130° with an equivalent amount of perdeuteriotrimethylsulfoxonium iodide, the recovered amino ketone methiodide had nmr peaks (ref 11) at δ 3.10 (18% of one CH_3 group) and 3.38 (82% of one CH_3 group). [c] From a comparable alkylation run in refluxing acetone, the areas under the higher and lower field N-methyl peaks were 67 and 33%, respectively. The salt obtained (51% yield) by reaction of the amine **5** with the methylating agent at 70° for 18 hr in the absence of a solvent had 68% of the area under the higher field N-methyl peak and 32% of the area under the lower field peak. [d] The N-methyl peaks of this salt are not resolved from one another.

212 mg (93%) of the methiodide of 8-methyl-8-azabicyclo-[4.3.1]dec-10β-yl 4-nitrobenzoate melting with decomposition at 214°. Recrystallization gave the pure **methiodide** as yellow prisms, mp 213.5–214.5° dec, with infrared absorption[23] at 1720 cm^{-1} (ester C=O) and nmr peaks[25] at δ 8.49 (4 H, aryl C–H), 5.52 (1 H, broad, >CH–O), and 3.67 (6 H, broad, both $N-CH_3$ groups). The latter peak is superimposed on complex absorption in the region δ 1.4–4.5 (aliphatic C–H).

Anal. Calcd for $C_{18}H_{25}IN_2O_4$: C, 46.96; H, 5.47; N, 6.09. Found: C, 46.67; H, 5.52; N, 5.85.

The methiodide **27** was prepared as previously described.[2c] A solution of 1.622 g (10.6 mmoles) of the ketone **2** and 1.7 g (12 mmoles) of methyl iodide in 20 ml of acetone was allowed to stand at room temperature for 3 days. The **methiodide of ketone 2** which separated (2.694 g, 86%, mp 239–240° dec) was recrystallized from a methanol–acetone mixture to give the pure salt as white plates, mp 239–240° dec. The product has infrared absorption at 1715 and 1730 cm^{-1} (C=O, doublet believed to arise from Fermi resonance[2b]) with nmr absorption[11] in the region δ 3.5–4.5 (4 H, center two lines of an AB pattern resolved, $-CH_2-\overset{\oplus}{N}<$) with singlets at δ 3.10 (3 H, $N-CH_3$) and 3.38 (3 H, $N-CH_3$) as well as complex absorption in the region δ 1.4–3.3 (aliphatic C–H).

Anal. Calcd for $C_{10}H_{18}INO$: C, 40.69; H, 6.15; I, 43.00; N, 4.75. Found: C, 40.61; H, 6.24; I, 43.19; N, 4.80.

After a solution of 633 mg (4.08 mmoles) of the amino alcohol **5** in 5 ml of methyl iodide had been allowed to stand at room temperature for 5 days, the resulting precipitate (771 mg, 64%, mp 240° dec) was collected and washed with acetone. Recrystallization from a methanol–ethyl acetate mixture afforded the pure **methiodide 21** as white prisms, mp 240° dec, with nmr[11] singlets at δ 3.41 and 3.47 (6 H, $\overset{\oplus}{N}-CH_3$) superimposed on complex absorption in the region δ 1.3–4.4 (aliphatic C–H).

Anal. Calcd for $C_{10}H_{20}INO$: C, 40.40; H, 6.78. Found: C, 40.40; H, 6.81.

A solution of 990 mg (6.39 mmoles) of the amino alcohol **8** and 3.0 ml of methyl iodide in 10 ml of acetone was allowed to stand at room temperature for 6 days. The precipitate (1.643 g, 87%, mp 231° dec) was collected and recrystallized from a methanol–ethyl acetate mixture to separate the pure **methiodide 22** as white needles, mp 231.5° dec. The sample, which melted with decomposition at 237.5° after drying (80° at 0.2 mm), has a single N-methyl peak in the nmr[11] at δ 3.37 (6 H, both $N-CH_3$) superimposed on complex absorption in the region, δ 1.2–4.7 (aliphatic C–H).

Anal. Calcd for $C_{10}H_{20}INO$: C, 40.40; H, 6.78; N, 4.71. Found: C, 40.35; H, 6.81; N, 4.47.

A solution of 1.956 g (54.4 mmoles) of methanol-d_4[26] and 14.0 g (73.5 mmoles) of *p*-toluenesulfonyl chloride in 100 ml of anhydrous γ-collidine was stirred at 22–25° for 6 hr and then poured into an ice–water mixture. The resulting cold mixture was acidified with hydrochloric acid (100 ml) and then extracted with ether. After the ethereal extract had been washed successively with aqueous hydrochloric acid and water, it was dried over potassium carbonate and fractionally distilled.[27] The fraction collected at 92–97° (0.2 mm) was redistilled to separate 5.121 g (50%) of **perdeuteriomethyl *p*-toluenesulfonate**, bp 90–92° (0.2 mm), $n^{25}D$ 1.5155. The product contained (mass spectrometric analysis) 98% d_3 species, 1.5% d_2 species, and 0.5% d_1 and d_0 species.

Several modifications in the previously described procedure[28] for the preparation of perdeuteriomethyl iodide were found desirable. A mixture of 100 g of methyl iodide and 64 g of dimethyl sulfoxide was heated under reflux for 3 days. The crude crystalline salt (70.2 g) was collected and then recrystallized from water as quickly as practical[29] to separate 67.9 g (38.5%) of trimethylsulfoxonium iodide as white prisms, mp 172–174° dec (dependent on rate of heating). The previously described deuterium exchange procedure[28] involved prolonged refluxing of a solution of the sulfoxonium salt in deuterium oxide containing a few milligrams of potassium carbonate. We found that this procedure resulted in rapid consumption of the base and the reaction mixture invariably became acidic after a few minutes. If additional portions of potassium carbonate were added to maintain a basic reaction medium, the majority if not all of the sulfoxonium salt was destroyed (presumably from nucleophilic attack by hydroxide ion to form methanol and dimethyl sulfoxide). Thus, the previous[28] hydrogen–deuterium exchange was occurring within the first few minutes of reaction while the mixture was basic and the remaining prolonged reflux

(25) Determined as a solution in perdeuteriodimethylformamide.

(26) Available from Merck Sharp and Dohme of Canada, Ltd., Montreal, Canada.

(27) Fractional distillation was necessary to separate some unchanged *p*-toluenesulfonyl chloride, bp 80–92° (0.2 mm), present in the crude product.

(28) F. A. Cotton, J. H. Fassnacht, W. D. Horrocks, and N. A. Nelson, *J. Chem. Soc.*, 4138 (1959).

(29) Prolonged heating of this aqueous solution resulted in a marked reduction in yield presumably because of nucleophilic attack by water at one of the methyl groups of the salt to form methanol.

TABLE II

CATALYTIC OXIDATION OF THE ALCOHOLS 13–17

Alcohol, mg	PtO_2, mg	Water, ml	Reaction time, hr	Ketone, mp, °C (% yield)	N-Me nmr signals, δ (% of one CH_3 group)[a]
13, 100	100	10	58	10, 232.5–233 (47)	3.14 (92) 3.35 (8)
14, 60	60	4	48	11, 166–167 (63)	3.12 (30) 3.40 (70)
15, 60	60	10	46	12, 157–159.5 (33)	3.10 (18) 3.37 (82)
16, 102	102	9	100	10, 230.5–232 (30)	3.17 (90) 3.37 (10)
17, 26	26	2	48	11, 164.5–165 (73)	3.17 (25) 3.44 (75)

[a] The area percentages reported here are in general less reliable than those listed in Table I because smaller samples were used for the nmr determinations.

period was superfluous. Accordingly, the following exchange procedure was employed. Trimethylsulfoxonium iodide (31.5 g) and 500 mg of anhydrous potassium carbonate were dissolved in a minimum volume (100 ml) of boiling deuterium oxide. The solution was refluxed for 10 min and then cooled to 5° and allowed to stand until crystallization of the trimethylsulfoxonium salt was complete (*ca.* 2 hr). The sulfoxonium salt was collected and dried under reduced pressure. This exchange procedure was repeated two more times with the recovered sulfoxonium salt and fresh portions of deuterium oxide to give 16.0 g (49.4%) of perdeuteriotrimethylsulfoxonium iodide. The extent of deuterium incorporation in the recovered salt was followed by measuring the loss of C–H absorption in the 3-μ region of the infrared.[30] After the three exchanges described above, C–H absorption was no longer visible in the recovered salt. We also encountered difficulty in the previously described pyrolysis of the sulfoxonium salt at 200° and 25 mm pressure in that the initially collected distillate, bp 35–41°, produced a white crystalline precipitate believed to be trimethylsulfonium iodide on standing. This problem appears to arise because the dimethyl sulfoxide formed on pyrolysis remains in the hot pyrolysis flask and disproportionates to form dimethyl sulfide which is collected with the methyl iodide and reacts on standing. This problem was largely avoided by conducting the pyrolysis of the sulfoxonium salt (5.35 g) in a short-path still (180–200° at 25 mm) so that both the methyl iodide and the dimethyl sulfoxide distilled from the pyrolysis flask as formed. Redistillation of the initial pyrolysis product afforded 1.91 g (55%) of perdeuteriomethyl iodide, bp 41°, which contained 95% d_3 species, 4% d_2 species, and 1% of d_1 and d_0 species.

Reactions of the Amines 1–9 with Trideuteriomethyl *p*-Toluenesulfonate.—Employing the quantities listed in Table I, solutions of each of the amines and trideuteriomethyl *p*-toluenesulfonate in acetone were allowed to react under the conditions indicated in Table I. The resulting mixtures were concentrated under reduced pressure and the residual metho-*p*-toluenesulfonates were crystallized from mixtures of ethyl acetate with either methanol or isopropyl alcohol. The nmr spectrum[11] of each of the purified salts was measured and the areas under each of the N-methyl peaks (where two N-methyl peaks were present) was measured to give the results summarized in Table I. Since one of the N-methyl peaks was frequently superimposed on a broad peak attributable to the bridgehead C–H protons or the grouping >CH–O, the accuracy of the peak area measurements is not optimum; consequently, the peak area percentages listed in Tables I and II should be taken as approximate values.

Oxidation of the Quaternary Ammonium Salts 13–17.—Following a previously described procedure,[31] a suspension of platinum oxide catalyst in water was reduced under a hydrogen atmosphere, the hydrogen was replaced by air, and the quaternary salt was added to the suspension. Utilizing the quantities listed in Table II, the suspension was stirred at room temperature for the specified time, the reaction being followed by the uptake of oxygen. After the reaction mixtures had been filtered and the filtrates had been concentrated to dryness under reduced pressure, the residual quaternary salts were recrystallized from mixtures of ethyl acetate and either methanol or isopropyl alcohol. The nmr spectra[11] of the resulting purified salts were measured as described in the preceding section to give the results summarized in Table II. Several attempts to oxidize the alcohol **18** were unsuccessful, only the starting alcohol and by-products other than the ketone **12** being isolated after a reaction period of 105 hr.

Preparation of the 9-Methoxy-3-azabicyclo[3.3.1]nonanes 26 and 29.—A solution prepared from 33 mmoles of methyllithium, 30 mg of triphenylmethane (as an indicator), and 30 ml of 1,2-dimethoxyethane was added, dropwise and with stirring under a nitrogen atmosphere, to 465 mg (3.00 mmoles) of the amino alcohol **5** until the red color of triphenylmethyllithium persisted in the reaction vessel. Methyl iodide (1.0 ml) was then added to the *suspension* of the lithium alkoxide and the resulting mixture was stirred at room temperature for 3 hr. After the reaction mixture had been diluted with aqueous hydrochloric acid and extracted with ether, the aqueous phase was made basic with sodium hydroxide, saturated with sodium chloride, and extracted with pentane. The pentane extract was dried and concentrated to leave a semisolid residue which contained[32] the ether **26** (*ca.* 45%, first eluted) and the unchanged alcohol **5** (*ca.* 55%, eluted second). Chromatography of this mixture on silicic acid separated 93 mg of the ether **26** (eluted with benzene–ether mixtures) and 157 mg of the alcohol **5** (eluted with ether and with methanol). Sublimation (100° at 80 mm) afforded 112.5 mg of the starting alcohol **5**, mp 93–94°. Distillation in a short-path still (75–90° at 15 mm) afforded 27 mg of the pure **amino ether 26**. The product has no infrared absorption[33] in the 3- or 6-μ region attributable to O–H, N–H, or C=O functions and exhibits a molecular ion peaks in its mass spectrum at *m/e* 169 with abundant fragment peaks at *m/e* 168, 138, 95, 58, 57, 44, 42, and 41. The pK^*_{MCS} value[34] for this amine is 7.88.

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.82; H, 11.40; N, 7.85.

Following the same procedure, 465 mg (3.00 mmoles) of the amino alcohol **8** was treated with methyllithium in 1,2-dimethoxyethane until the red color of the triphenylmethyllithium indicator persisted. The *solution* of the lithium alkoxide was treated with 1 ml of methyl iodide and then stirred for 3 hr at room temperature and subjected to the previously described isolation procedure. The crude basic product (537 mg of liquid) contained[32] only the desired ether **29**. Distillation in a short-path still (85–95° at 15 mm) afforded the pure **amino ether 29**, $n^{25.5}D$ 1.4785, which has no infrared absorption[33] in the 3- or 6-μ regions attributable to O–H, N–H, or C=O functions. The mass spectrum of the sample has a molecular ion peak at *m/e* 169 with abundant peaks at *m/e* 138, 95, 58, 44, 42, and 41. The nmr spectrum[35] of the sample has singlets at δ 3.46 (O–CH_3) and 2.22 (N–CH_3) superimposed on complex absorption in the region δ 1.0–4.8 (aliphatic C–H). The pK^*_{MCS} value[34] for the amine is 7.31.

(30) Determined as a mull in perfluorokerosene.

(31) R. P. A. Sneedon and R. B. Turner, *J. Am. Chem. Soc.*, **77**, 130, 190 (1955).

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

(33) Determined as a solution in chloroform.

(34) These apparent pK_a values in a mixture of 80% Methyl Cellosolve and 20% water were determined by W. Simon [*Angew. Chem. Intern. Ed. Engl.*, **3**, 661 (1964)].

(35) Determined as a solution in deuteriochloroform.

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.76; H, 11.24; N, 7.94.

Pyrolysis of Methohydrides.—After a mixture of 258 mg of the methiodide **21** and 378 mg of freshly washed silver oxide in 7 ml of water had been stirred for 1 hr, the mixture was filtered and the filtrate was concentrated under reduced pressure. A portion of the crude methohydride **23** in methanol solution was pyrolyzed directly on a gas chromatography column[32] at 144° and the remaining crude, partially crystalline methohydride was pyrolyzed in a short-path still at 160° and 80 mm pressure. In both cases, as well as in experiments where a solution of the methohydroxide in dimethylformamide was heated, the crude pyrolysate contained[32] four components. The material from the 160° pyrolysis contained, in order of increasing retention time, unidentified component A (*ca.* 13%), the methoxy amine **26** (*ca.* 14%), unidentified component B (*ca.* 9%), and the amino alcohol **5** (*ca.* 59%).

Similarly, the crude, partially crystalline methohydroxide **24** from 300 mg of the methiodide **22**, 393 mg of silver oxide, and 6 ml of water was pyrolyzed in a short-path still at 110–130° and 70 mm pressure. The crude distillate contained,[32] in order of increasing retention time, unidentified component A (*ca.* 9%), the methoxyamine **29** (*ca.* 17%), unidentified component B (*ca.* 8%), and the amino alcohol **8** (*ca.* 67%). Attempts to minimize intermolecular reaction by pyrolysis of methanol solutions of the crude methohydroxide **24** on a gas chromatography column at temperatures in the range 140–205° yielded comparable mixtures of products which contained the methoxyamine **29**.

The Stereochemistry of the N-Alkylation of Azabicyclic Systems with Methyl Bromoacetate[1a]

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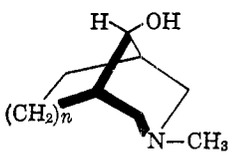
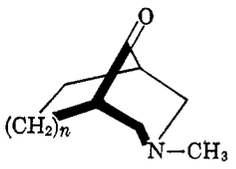
The stereochemistry of the N-alkylation of the amino alcohols **1a** and **3a** and the amino ketone **2a** has been studied. The alkylated product from the amino alcohol **1a** contained the hydroxy ester **6** (*ca.* 25%) and the lactone **12** (*ca.* 75%). Approximately equal amounts of the keto esters **8** and **9** were obtained from the amino ketone **2a**; the keto ester **9** was readily converted to the aldol condensation product **15**. Alkylation of the amino alcohol **3a** afforded the hydroxy ester **10** as the only quaternary ammonium salt isolated. Appropriate interconversions proved the stereochemistry of the various alkylated products.

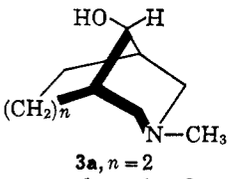
In the preceding paper[2] the reactions of the bicyclic amines **1–3** with trideuteriomethyl *p*-toluenesulfonate were found to be partially stereoselective, yielding a



1a, $n=2$
b, $n=1$ or 3



2a, $n=2$
b, $n=1$ or 3



3a, $n=2$
b, $n=1$ or 3

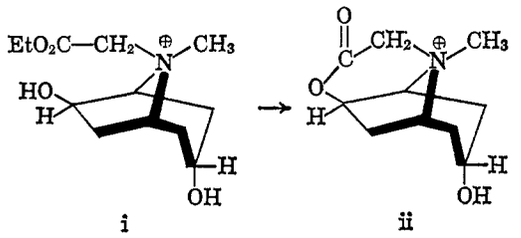
mixture of diastereoisomeric quaternary ammonium salts in which the major isomer comprised 60–90% of the mixture.[3] Within each ring system (*i.e.*, for each value of n in amines **1–3**) the preferred direction of alkylation was the same for the ketone **2** and the corresponding alcohols **1** and **3**.[3] Consideration of the positions of the N-methyl signals in the nmr spectra of these salts further suggested[2] that the preferred direction of N-alkylation was the same for the three homologous series (*i.e.*, n = 1, 2, or 3 in amines **1–3**) studied. However, these studies failed to prove which stereochemistry (*e.g.*, **4** or **5** from **2a**) was correct for the preferred isomer. To answer this stereochemical question, we have studied the N-alkylation of the amines **1a**, **2a**, and **3a** with methyl bromoacetate to form the quaternary salts **6–11**; appropriate ring closure reactions with certain of these derivatives were expected to provide rigorous chemical evidence upon which to base stereochemical assignments.[4]

(1) (a) This research has been supported by a research grant from the National Institutes of Health (Grant No. GM-08761). (b) National Institutes of Health Predoctoral Fellow, 1963–1965.

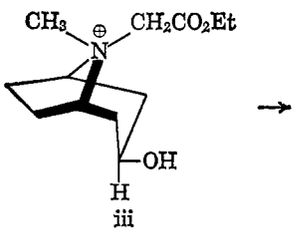
(2) H. O. House and C. G. Pitt, *J. Org. Chem.*, **31**, 1062 (1966).

(3) Experimental difficulties[2] prevented us from learning the degree of stereoselectivity in the N-alkylation of the azabicyclodecanol **3**, n = 3, and from interrelating the alkylation products of the alcohol **3**, n = 3, and the ketone **2**, n = 3.

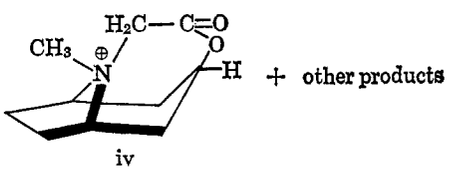
(4) This general approach was used by Fodor and co-workers to assign stereochemistry to the N-alkylated products derived from various tropane derivatives: (a) G. Fodor in "The Alkaloids," Vol. 6, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, pp 145–177. (b) The compounds included in this study differ from the previously studied tropane derivatives [*cf.* G. Fodor, K. Koczka, and J. Lestyan, *J. Chem. Soc.*, 1411 (1956)] in ease of lactone formation. For example, although the hydroxy tropane derivative i spontaneously formed the lactone ii, the pseudotropine salt iii (analogous to the salt **7**, which lactonizes spontaneously) formed the lactone iv only when heated to 200°.



i ii



iii



iv + other products