The Extent of Bond Formation in the Transition State for Alkylation at Nitrogen and at Carbon[1a]

THOMAS M. BARE,[1b] N. DAVIS HERSHEY,[1c] HERBERT O. HOUSE, AND C. GARDNER SWAIN*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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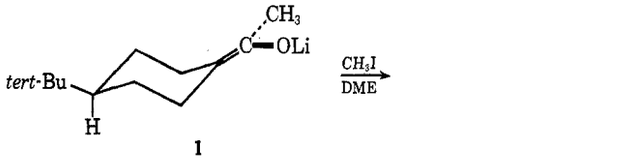
Chlorine isotope effects (k_{35}/k_{37}) in reactions of methyl chloride with 4-*tert*-butyl-1-ethylpiperidine, triethylamine, and the lithium salt of 4-*tert*-butylcyclohexanecarbonitrile in 1,2-dimethoxyethane solution at 25° are identical (1.0064) within experimental precision (0.0001) but considerably smaller than with sodium iodide (1.0086), indicating an "early" transition state for the amines and the enolate, with nearly the same small degree of bond formation at their transition states. Stereochemical differences between piperidines and enolates are therefore interpreted by consideration of relative steric strain in transition states for axial *vs.* equatorial alkylation, at relatively long but similar N–C and C–C distances.

An important aspect of stereospecific synthesis is the ability to predict (and if possible control) the stereochemical path by which an alkyl group is introduced into an organic molecule. Explorations of this problem include numerous stereochemical studies of the N-alkylation of tertiary amines[2] and, especially, of the C-alkylation of enolate anions.[3] Equations A–E illustrate a different stereochemical preference in the N-[4] and C-alkylation[5] of similarly constituted compounds: methylation of either of the enolate anions **1** or **4** produces predominantly the product **2** or **5** with an equatorial methyl group while methylation of the amines **7** and **10** yields mainly products **9** and **11** in which an axial methyl group has been introduced.[6]

With more complex piperidine derivatives which offer steric hindrance to an axial approach of the alkylating agent to the usual[7] chair conformation of the piperidine ring, this stereochemical path may not be observed.[2] For example, alkylation of the bicyclic amine **13** (and related substances) is believed to form primarily the stereoisomer **14**.[8]



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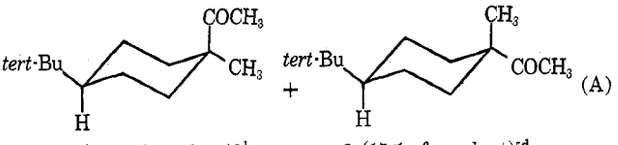
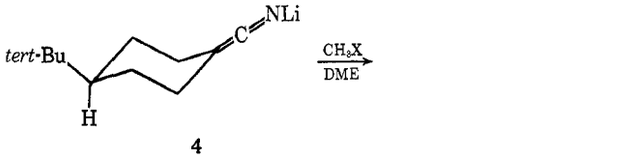


(A)

2 (85% of product)[5d] **3** (15% of product)[5d]



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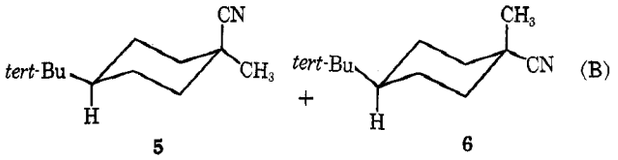

(B)

5 **6**

Methylating agent	—Product composition, %— 5	6
CH_3Cl	81	19
CH_3I	72	28
$(CH_3)_3O^+BF_4^-$	~42	~58

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(2) For recent reviews of the stereochemistry of N-alkylation, see (a) J. McKenna, *Top. Stereochem.*, **5**, 275 (1970); (b) A. T. Bottini, *Selec. Org. Transform.*, **1**, 89 (1970); (c) R. A. Y. Jones, A. R. Katritzky, and P. G. Mente, *J. Chem. Soc. B*, 1210 (1970).

(3) For recent reviews of the stereochemistry of C-alkylation, see (a) J. M. Conia, *Rec. Chem. Progr.*, **24**, 43 (1963); (b) H. O. House, *ibid.*, **28**, 99 (1967); (c) L. Velluz, J. Valls, and G. Nominé, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965); (d) L. Velluz, J. Valls, and J. Mathieu, *ibid.*, **6**, 778 (1967); (e) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., in press.

(4) (a) H. O. House, P. P. Wickham, and H. C. Müller, *J. Amer. Chem. Soc.*, **84**, 3139 (1962); (b) H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963); (c) H. O. House and C. G. Pitt, *ibid.*, **31**, 1062 (1966); (d) H. O. House and B. A. Tefertiller, *ibid.*, **31**, 1068 (1966); (e) H. O. House, B. A. Tefertiller, and C. G. Pitt, *ibid.*, **31**, 1073 (1966).

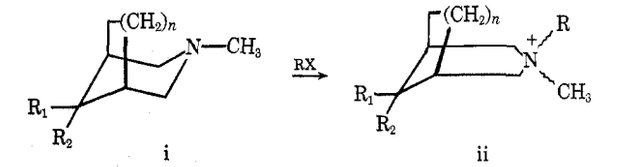
(5) (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965); H. O. House and C. J. Blankley, *ibid.*, **32**, 1741 (1967); (c) H. O. House, B. A. Tefertiller, and H. D. Olmstead, *ibid.*, **33**, 935 (1968); (d) H. O. House and T. M. Bare, *ibid.*, **33**, 943 (1968).

(6) A number of types of experimental evidence support the view that alkylation of unhindered *N*-alkylpiperidines occurs with predominant introduction of the new alkyl group from an axial direction. See ref 2 and 4c.

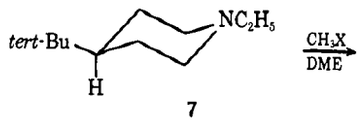
(7) F. G. Riddell, *Quart. Rev. Chem. Soc.*, **21**, 364 (1967).

(8) We have provided rigorous experimental proof for the stereochemistry of alkylation of several 3-azabicyclo[3.3.1]nonane derivatives with methyl bromoacetate and the analogous stereochemistry has been assigned to the salts **14** and **15** and the related C-9 hydroxy derivatives by an empirical correlation of nmr chemical shift data among three pairs of compounds. Although the populations in solution of the various possible conformers of these quaternary ammonium salts are not known, our experiments involving facile lactone formation and, especially, intramolecular aldol condensation required that the chair–boat conformations indicated in structures **14** and **15** are readily attained and the nmr spectrum of the methiodide of 3-methyl-3-azabicyclo[3.3.1]nonane suggests an analogous conformation for this salt. See R. Lygo, J. McKenna, and I. O. Sutherland, *Chem. Commun.*, **No. 15**, 356 (1965).

In our studies of the alkylation of other bicylic compounds of the type i (n = 1, 2, and 3, R_1 and R_2 = H and OH or = O), we noted[4c,d] that the above empirical nmr relationship suggested that all of the compounds underwent preferential alkylation in the same direction. This assignment was tentative and was predicated on the assumption that the principal solution conformations of all the quaternary ammonium salts were the same. McKenna and coworkers have subsequently argued that the 3-azabicyclo[3.2.1]nonane quaternary ammonium salts (ii, n = 1) differ in conformation from the other series (ii, n = 2 or 3) and, consequently, the stereochemical assignments should be reversed. See ref 2a and D. R. Brown, R. Lygo, J. McKenna, and B. G. Hutley, *J. Chem. Soc. B*, 1184 (1967). Until definitive experimental data (X-ray crystallographic analysis or chemical correlation) are available, we see no compelling basis for making stereochemical assignments to the salts ii (n = 1).



i ii



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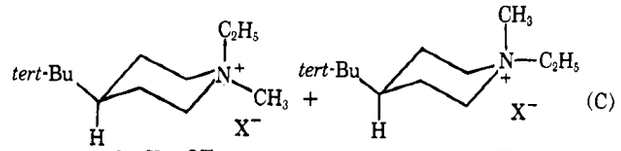
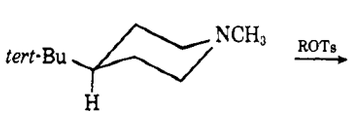


8a, X = OTs
b, X = I
c, X = Cl

9a, X = OTs
b, X = I
c, X = Cl

(C)

Methylating agent	—Product composition, %— 8	9
CH_3Cl	27	73
CH_3I	18	82
CH_3OTs	17	83



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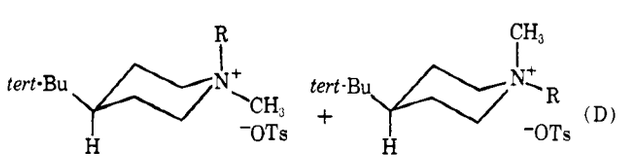
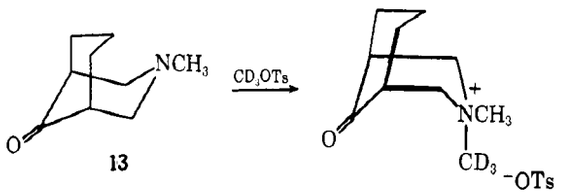


11 12

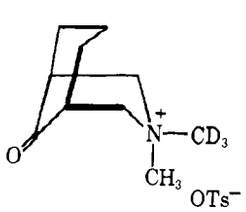
(D)

Alkylating agent	—Product composition, %— 11	12
CD_3OTs, acetone	87[4e]	13[4e]
C_2H_5OTs, DME	75	25
C_2H_5OTs, acetone	83[4e]	17[4e]



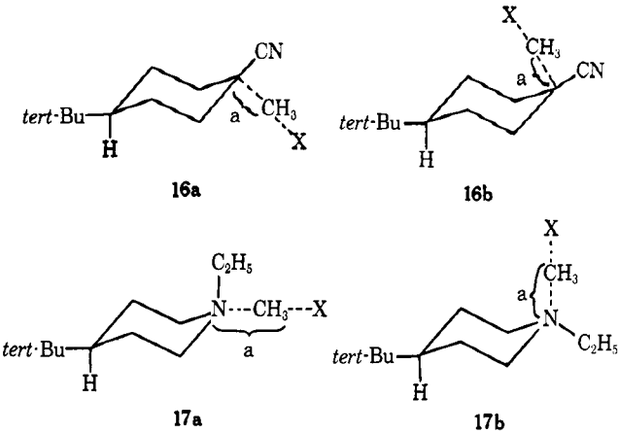
13 14 (82% of product)[4e]

(E)



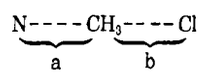
15 (18% of product)[4e]

We previously considered[5d] two general explanations for the different stereochemical results obtained from the N-alkylation of piperidine derivatives (mainly axial alkylation, eq C and D) and the C-alkylation of structurally similar enolates (mainly equatorial alkylation, eq A and B). Either the extent of bond formation between the nucleophile and the entering alkyl group (bond a in structures **16** and **17**) is very different at the transition state in the two cases[9] or the direction of attack by the entering alkyl group is different in the two cases. Since other data obtained with enolates[5] suggested a reactantlike transition state for the C-alkylation reactions, we favored the second explanation. We now wish to present experimental evidence for an early, reactantlike transition state in both the C-alkylation of the enolate **4** and the N-alkylation of the tertiary amine **5**. This evidence was obtained by measuring the heavy-atom isotope effect observed when each of several nucleophiles (N:) (see Table I) was allowed to react with excess CH_3Cl. These experiments, which measure the relative rates of reaction of CH_3–^{35}Cl and CH_3–^{37}Cl with each N:, provide a measure of the extent of C–Cl bond breaking in the transition state (structure **18**). The maximum isotope effect if the



16a 16b

17a 17b



18

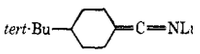
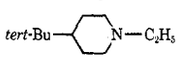
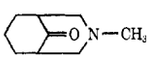
C–Cl bond were completely broken at the transition state is calculated to be $k_{35}/k_{37} = 1.017$.[10] We assume that throughout the process of nucleophilic bimolecular substitution at a methyl halide the small charge at the methyl group will not change appreciably and, consequently, the total bond order at carbon will remain approximately constant from methyl chloride through the transition state **18** to form the product. Given this assumption, if we can estimate the extent of C–Cl bond breaking in the transition state (bond b in **18**), we can also estimate the extent of formation of the new bond to the nucleophile (bond a in **18**). As previously noted, we would expect a chlorine isotope effect (k_{35}/k_{37}) of about 1.017 if the C–Cl bond were completely broken at the transition state and a value approximately one-half as large (1.009) if the bond to chlorine were only half broken (and bonding to the nucleophile were half completed). Although, in principle, the actual value could be obtained by measuring the chlorine isotope effect (k_{35}/k_{37}) in the symmetrical transition state which would be attained by displacement at methyl chloride with chloride ion composed of a third chlorine isotope, this ideal experiment is difficult to perform. However,

(9) For other uses of this argument to explain alkylation stereochemistry, see (a) A. T. Bottini, B. F. Dowden, and R. L. Van Etten, *J. Amer. Chem. Soc.*, **87**, 3250 (1965); (b) A. T. Bottini and M. K. O'Rell, *Tetrahedron Lett.*, **No. 5**, 423, 429 (1967); (c) M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, **35**, 161 (1970); M. E. Kuehne, *ibid.*, **35**, 171 (1970).

(10) Two-atom model at 298°K, CH_3 treated as a point mass of 15 amu, 3.4 mdyn/Å force constant for C–Cl bond, bending neglected.

TABLE I

CHLORINE ISOTOPE EFFECT (k_{35}/k_{37}) IN THE REACTION OF METHYL CHLORIDE WITH NUCLEOPHILES IN 1,2-DIMETHOXYETHANE SOLUTION

Nucleophile, N:	Reaction conditions	Isotope effect, k_{35}/k_{37}
 4	0.17 *M* **4**, 1.0 *M* CH_3Cl, 25°, 2.5 min	1.0063 ± 0.0002 (four runs)
 7	0.50 *M* **7**, 2.0 *M* CH_3Cl, 25°, 24 hr	1.0064 ± 0.0002 (four runs)
 13	0.50 *M* **13**, 2.0 *M* CH_3Cl, 25–30°, 60 days	1.0072 ± 0.0004 (two runs)
$(C_2H_5)_3N$ 19	0.20 *M* **19**, 2.0 *M* CH_3Cl, 25°, k_2 = 4.1 × 10^{-5} M^{-1} sec^{-1}	1.0064 ± 0.0001 (five runs)
NaI	0.20 *M* NaI, 2.0 *M* CH_3Cl, 25°	1.0086 ± 0.0001 (three runs)

a related experiment, the displacement at methyl chloride with iodide ion, was readily effected (Table I) and provides a reasonable approximation of the chlorine isotope effect (k_{35}/k_{37} = 1.0086) to be expected in a symmetrical transition state.

With this calibration point in hand we can offer at least a qualitative[11] estimate of the extent of new bond formation at the transition state between methyl chloride and the other nucleophiles studied (Table I). The most striking result for all these nucleophiles is the fact that for either carbon or nitrogen nucleophiles, bond formation at the transition state has progressed significantly less than half way. Furthermore, with the two structurally similar nucleophiles, the enolate **4** and the amine **7**, the extent of bond formation is the same within the limits of our experiment. Such results are very difficult to reconcile with any explanation for alkylation stereochemistry that requires substantially different degrees of bond formation at the transition state.

For this reason we believe that the different stereochemical results obtained by alkylating either the enolate anions such as **1** and **4** or amines such as **7** and **10** are best explained by reactantlike transition states such as **16** and **17**. An axial attack (*i.e.*, **16b**) of the alkylating agent perpendicular to the planar enolate system will clearly be impeded sterically more than an axial attack (*i.e.*, **17b**) on a tetrahedral amine system because of the differing direction of approach of the alkyl halide.

The steric environment for attack of an alkylating agent perpendicular to a planar enolate system (structures **16**) is analogous to that discussed in the hydride reduction of cyclohexylidenecyanoacetate derivatives.[13] Specifically, if the CH_3–nucleophile bond (bond a in **16**) is relatively short, steric interference will be greatest between the entering methyl group and the axial hydrogen atoms at C-2 and C-6 and transition state **16a** will be destabilized. However, when the forming bond is relatively long (*e.g.*, 2.0 Å), steric interference between the entering alkyl group and axial hydrogen atoms at C-3 and C-5 predominates and the transition state **16b** is expected to be less stable. Thus, the stereochemical results observed on alkylation of the enolates **1** and **4** (**16a** more stable than **16b**) are also in accord with an early, reactantlike transition state with a relatively long bond between the nucleophile and the entering alkyl group.

In the alkylation of the piperidine derivatives **7** and **10**, it seems most probable that in transition states **17** the nitrogen atom retains approximately the same tetrahedral geometry which is present in the starting amines and the final quaternary salt products. Further, it seems most probable that the entering pentacoordinate methyl group in these transition stages has an effective steric bulk at least as large as a fully bonded, tetrahedral methyl group. Since the stereochemical results of this alkylation require the transition state **17b** (axial alkylation) to be more stable than **17a**, these considerations also indicate that bonding of nitrogen to the entering alkyl group is relatively incomplete and the forming bond (bond a in **17**) is relatively long. If one assumes the entry of a planar CH_3 group from an axial direction to an *undeformed* chair piperidine ring, then calculation of nonbonded hydrogen–hydrogen repulsion energies[14] suggests that the forming nitrogen–methyl bond is no shorter than 2.0 Å. However, appropriate deformation of the piperidine ring will relieve the principal nonbonded hydrogen–hydrogen interaction between the entering methyl group and the axial hydrogen atoms at C-3 and C-5 so that the 2.0-Å value is not necessarily the minimum value for the forming nitrogen–methyl bond at the transition state.

The chlorine isotope effects observed (Table I) suggest that the degree of bond formation in the transition states for N- and C-methylation is not very responsive to changes in the environment of the attacking nucleophile and, consequently, generalizations about effect of reactant structure on transition-state structure[15,16] are not particularly useful for predicting the stereochemical outcome of structural changes in the nucleophile being alkylated.

Seemingly, these rules could be more useful in predictions of the stereochemical outcome of changes in the leaving group of the alkylating agent, since the rules

(11) There is no particular reason to suppose that the relationship between the isotope effect and the extent of bond breaking will be linear. In fact, measurements of sulfur isotope effects have been interpreted as not being a linear function of the extent of bond breaking.[12]

(12) A. M. Katz and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **91**, 4472 (1969).

(13) J. A. Marshall and R. D. Carroll, *J. Org. Chem.*, **30**, 2748 (1965).

(14) (a) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955); (b) H. E. Simmons and J. K. Williams, *ibid.*, **86**, 3222 (1964).

(15) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(16) (a) C. G. Swain and E. R. Thornton, *ibid.*, **84**, 817 (1962); (b) E. R. Thornton, *ibid.*, **89**, 2915 (1967).

concur in their prediction that the better the leaving group, the more reactantlike will be the transition state and, consequently, the less bonding between the nucleophile and the alkylating agent at the transition state. The very limited comparison of CH_3Cl *vs.* CH_3I or CH_3OTs made in this study would appear to support such an idea, since the use of the less reactive CH_3Cl (predicted to give increased nucleophilic bonding at the transition state) results in a more stereospecific alkylation (less axial product) of the enolate **5** and a less stereospecific alkylation (less axial product) of the amine **7**. Although use of the very reactive alkylating agent trimethyloxonium tetrafluoroborate would also seem to fit this prediction by giving very little stereospecificity in the alkylation of the enolate **4**, we have observed the opposite result in the alkylation of a different enolate with this alkylating agent.[5a] Also, the alkylation of various piperidine derivatives with triethyloxonium tetrafluoroborate was observed to be less stereospecific than alkylation with C_2H_5I,[17] a result opposite to what might be predicted. In addition, no substantial change in alkylation stereochemistry was observed when *N*-methyl-d_3-nortropine was alkylated with either CH_3Cl or CH_3I.[18] In view of such results, it clearly is desirable to obtain more compelling experimental evidence before placing reliance upon arguments concerned with the extent of bonding in the transition state to explain stereochemical changes that result when the leaving group in the alkylating agent is changed.

Experimental Section[19]

Preparation of Starting Materials.—4-*tert*-Butyl-1-ethylpiperidine [**7**, bp 72.5–74° (8 mm), $n^{27}D$ 1.4526] and 4-*tert*-butyl-1-methylpiperidine [**10**, bp 59.5–60.5° (8 mm), $n^{25}D$ 1.4504] were prepared as previously described.[4c] The preparation and characterization of the 4-*tert*-butylcyclohexanecarbonitrile (mixture of stereoisomers) and the stereoisomeric methyl derivatives **5** and **6** was described previously.[5d] To a solution of 858.4 mg (5.07 mmol) of the *N*-ethyl amine **7** in 7.5 ml of 1,2-dimethoxyethane (hereafter DME) was added 1.867 g (10.0 mmol) of methyl *p*-toluenesulfonate so that the initial concentrations after mixing were 0.5 *M* in the amine **7** and 1.0 *M* in the alkylating agent. This solution, from which the amine salt began to precipitate almost immediately, was stirred at 25° for 6 hr and then filtered. The collected mixture of amine salts (1.745 g or 97.2%, mp 190–198°) contained (nmr analysis) 83% of the axial methyl salt **9a** and 17% of the equatorial methyl salt **8a**. Fractional recrystallization from $CHCl_3$–ether mixtures separated the pure (nmr analysis) axial methyl salt **9a** as white plates, mp 207–208° (lit.[4c] mp 201–202°), with spectroscopic properties corresponding to those previously reported.[4c]

Similarly, a solution of 5.71 g (3.67 mmol) of the *N*-methyl amine **10** and 8.01 g (40 mmol) of ethyl *p*-toluenesulfonate in 40 ml of DME was stirred at room temperature for 16 hr and then concentrated under reduced pressure. Trituration of the residue with ether separated 7.186 g (55.1%) of a mixture of amine salts, mp 154–158.5°, containing (nmr analysis) 25% of the axial methyl isomer **9a** and 75% of the equatorial methyl isomer **8a**. Fractional recrystallization from an ethyl acetate–methanol mixture separated the pure (nmr analysis) equatorial methyl salt **8a** as white plates, mp 163–164° (lit.[4c] mp 158–159°), with spectroscopic properties corresponding to those previously reported.[4c]

In $CDCl_3$ solution the *N*-methyl nmr peaks for the axial methyl (**9a**) and equatorial methyl (**8a**) salts are located at δ 2.92 and 3.10, respectively. In D_2O solution,[4c] the two *N*-methyl nmr signals (δ 2.84 for the axial methyl salt **9a** and δ 2.92 for the equatorial methyl salt **8a**) are less well separated but the peak attributable to the axial methyl group remains at higher field.[20]

In order to analyze mixtures of the salts **8a** and **9a**, the nmr spectra of chloroform solutions of a series of known mixtures of the pure salts were measured to establish the validity of equating the heights of the *N*-methyl peaks at δ 2.92 (for **9a**) and 3.10 (for **8a**) to the proportions of the two isomers present.

Gaseous CH_3Cl (Matheson) was passed over $CaSO_4$ before use. Triethylamine (Eastman pure) was dried over $CaSO_4$ (Drierite), then distilled from several pellets of KOH through a 16-cm Vigreux column, bp 89.0° (766 mm) [lit.[21] bp 88.8–89.0° (760 mm)], $n^{25}D$ 1.3982 (lit.[22] $n^{20}D$ 1.40032). It was stored under dry N_2 and used within a week of distillation.

1,2-Dimethoxyethane (DME, Eastman White Label, 75 ml) was dried over $CaSO_4$ (Drierite) for several days, then filtered. About 1 g of $LiAlH_4$ (Metal Hydrides) was added and the mixture was stirred for 1 hr. The liquid was distilled through a 16-cm Vigreux column, bp 84.2° (754 mm), $n^{34}D$ 1.3730 [lit.[23] bp 84.7–84.8° (760 mm), $n^{20}D$ 1.37965]. This material was stored under dry N_2, but was always used within 2 days of distillation. Both of the common peroxide tests[24,25] were negative for the purified DME. A more sensitive test can be conducted by dissolving several large crystals of NaI in a few milliliters of DME; an orange color indicates the presence of peroxides. Freshly distilled DME gave a negative test by this method.

All inorganic materials were reagent grade used without further purification. Water was laboratory-distilled water redistilled from alkaline $KMnO_4$ in an aged Pyrex still. $CaSO_4$ was Drierite. Prepurified N_2 gas (Airco) was passed over Ascarite (NaOH on asbestos) and $CaSO_4$.

Alkylation of the *N*-Ethyl Amine 7. A. With Methyl Iodide.—To a solution of 862.5 mg (5.09 mmol) of the amine **7** in 8.4 ml of DME was added 1.392 g (9.83 mmol) of CH_3I so that the initial concentrations were 0.5 *M* in amine and 1.0 *M* in CH_3I. The resulting solution, from which a precipitate began to form almost immediately, was stirred at 25° for 6 hr and then filtered. After the residue had been washed with ether, the mixture of iodides **8b** and **9b** amounted to 1.564 g (98.3%), mp 208.5–210° dec. A sample of this mixture of salts was recrystallized from a methanol–ethyl acetate mixture to separate a mixture of salts **8b** and **9b** as white needles: mp 209–210° dec; nmr ($CDCl_3$) δ 3.42 (singlet, CH_3N of the equatorial methyl salt **8b**, *ca.* 25% of 3 H), 3.24 (singlet, CH_3N of the axial methyl salt **9b**, *ca.* 75% of 3 H), 3.5–4.2 (6 H multiplet, CH_2N), 1.1–2.2 (8 H multiplet, aliphatic CH), and 0.93 [9 H singlet, $(CH_3)_3C$]. In D_2O solution, the CH_2N nmr multiplet is shifted to the region δ 3.1–3.7 and the *N*-methyl signals are located at δ 3.01 (*ca.* 25% of 3 H) and 2.96 (*ca.* 75% of 3 H).

Anal. Calcd for $C_{12}H_{26}IN$: C, 46.30; H, 8.42; N, 4.50; I, 40.77. Found: C, 46.33; H, 8.14; N, 4.49; I, 40.60.

To determine the composition of the initially isolated mixture of iodide salts **8b** and **9b**, the mixture was converted to the corresponding *p*-toluenesulfonate salts **8a** and **9a**. To a solution of 204.8 mg (0.659 mmol) of the mixture of iodides **8b** and **9b** in 3.0 ml of acetonitrile was added a solution of 196.2 mg (0.703 mmol) of silver *p*-toluenesulfonate in 4 ml of CH_3CN. The resulting mixture, from which AgI separated immediately, was stirred for 1 hr at 25° and then filtered through Celite. The filtrate was concentrated under reduced pressure to leave 232.3 mg (99.1%) of a mixture of the *p*-toluenesulfonate salts which contained (nmr analysis) 82% of the axial methyl isomer **9a** and 18% of the equatorial methyl isomer **8a**.

(17) D. R. Brown, J. McKenna, and J. M. McKenna, *Chem. Commun.* **No. 5**, 186 (1969).

(18) (a) G. Fodor, J. D. Medina, and N. Mandava, *Chem. Commun.*, **No. 10**, 581 (1968); (b) For the latest revision in the stereochemical assignments of the tropane quaternary ammonium salts with leading references to earlier assignments, see G. Fodor, R. V. Chastain, Jr., D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *J. Amer. Chem. Soc.*, **93**, 403 (1971); P. Benci, C. H. Stam, and C. H. MacGillavry, *Tetrahedron Lett.*, **No. 3**, 243 (1971).

(19) General comments of footnote 9 of ref 5d apply.

(20) For an example where the positions of the two peaks interchange when the solvent is changed from deuteriochloroform to deuterium oxide, see ref 9b. For other examples where the relative spacing of the *N*-methyl signals changes with solvent, see ref 4a.

(21) W. Herz and E. Neukirch, *Z. Phys. Chem. (Leipzig)*, **104**, 439 (1923).

(22) J. W. Brühl, *Justus Liebigs Ann. Chem.*, **200**, 186 (1879).

(23) M. H. Palomaa and I. Honkanen, *Chem. Ber.*, **70**, 2203 (1937).

(24) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1957, p 287.

(25) A. I. Vogel, "Practical Organic Chemistry," 3rd, ed, Wiley, New York, N. Y., 1957, p 163.

To verify further the fact that the axial methyl nmr signal was located at higher field in both the iodide (**9b**) and *p*-toluenesulfonate (**9a**) salts, a warm solution of 175.8 mg (0.494 mmol) of the *p*-toluenesulfonate salts (containing *ca.* 80% of **9a** and *ca.* 20% of **8a**) in 5 ml of ethanol was added to a warm solution of 111.9 mg (0.260 mmol) of BaI_2 in 5 ml of ethanol. The resulting mixture, from which a precipitate separated immediately, was stirred for 10 min and then filtered. The filtrate was concentrated and the residual solid (157.7 mg) was taken up in $CHCl_3$, filtered, and diluted with ether. The mixture of iodides **8b** and **9b**, 136.5 mg (88.7%), mp 207.5–209° dec, which separated was identified with the previously described mixture of iodides obtained from the alkylation experiment by comparison of infrared and nmr spectra. In particular, the nmr singlets ($CDCl_3$) at δ 3.42 and 3.24 have peak heights in the ratio 1:4.

B. With Methyl Chloride.—In a flask fitted with a Dry Ice condenser were placed a solution of 1 g (20 mmol) of CH_3Cl in 8.0 ml of DME and 851.1 mg (5.02 mmol) of the amine **7** (initial concentrations 0.5 *M* in the amine **7** and 2 *M* in CH_3Cl). The resulting solution was stirred at 25° for 24 hr, during which time a mixture of the chloride salts **8c** and **9c** separated. Filtration separated 274.6 mg (24.8%) of the mixture of chlorides **8c** and **9c** as white plates, mp 261° dec. A portion of this mixture was dissolved in $CHCl_3$ and reprecipitated by the addition of ether to give the mixture of salts **8c** and **9c** as a white solid: mp 260° dec; nmr ($CDCl_3$) δ 3.5–4.2 (6 H multiplet, CH_2N), 3.47 (singlet, equatorial methyl salt **8c** CH_3N, *ca.* 30% of 3 H), 3.24 (singlet, axial methyl salt **9c**, CH_3N, *ca.* 70% of 3 H), 1.1–2.2 (8 H multiplet, aliphatic CH), and 0.93 [9 H singlet, $(CH_3)_3C$].

Anal. Calcd for $C_{12}H_{26}ClN$: C, 65.57; H, 11.92; N, 6.37; Cl, 16.13. Found: C, 65.32; H, 12.19; N, 6.14; Cl, 16.36.

A solution of 81.9 mg (0.372 mmol) of the initially separated mixture of chloride salts in 2 ml of CH_3CN was treated with a solution of 106.7 mg (0.382 mmol) of silver *p*-toluenesulfonate as previously described to yield 127.6 mg (96.8%) of a mixture of *p*-toluenesulfonate salts which contained (nmr analysis) 73% of the axial methyl isomer **9a** and 27% of the equatorial methyl isomer **8a**. In a duplicate experiment, the initially formed mixture of chloride salts, obtained in 24.1% yield, contained (nmr analysis) *ca.* 70% of the isomer **9c** and *ca.* 30% of the isomer **8c**. This material was converted in 96.8% yield to a mixture of *p*-toluenesulfonic acid salts which contained (nmr analysis) 73% of the axial methyl isomer **9a** and 27% of the equatorial methyl isomer **8a**.

To verify the fact that the axial methyl nmr signal of the chloride salt **9c** is at higher field than the methyl signal of the stereoisomeric salt **8c**, a refluxing solution of 218.9 mg (0.821 mmol) of $SrCl_2$ in 18 ml of ethanol plus sufficient water to effect complete solution was treated with a warm solution of 530.5 mg (1.49 mmol) of a mixture of *p*-toluenesulfonate salts (83% of **9a** and 17% of **8a**) in 9 ml of ethanol. The resulting mixture, from which a white precipitate separated immediately, was stirred for 10 min and then cooled and filtered. The filtrate was concentrated under reduced pressure and the residual solid was taken up in $CHCl_3$, filtered, and diluted with ether. The mixture of chlorides **8c** and **9c** separated as 326.8 mg (99.7%) of white solid, mp 238° dec, which was identified with the previous sample by comparison of infrared and nmr spectra. The nmr singlets ($CDCl_3$) at δ 3.45 and 3.23 have peak heights in the ratio 1:4.

Alkylation of the Nitrile Anion 4. A. With Methyl Iodide.—A cold (0°) solution of 1.20 mmol of methyllithium and 188 mg of biphenyl (an internal standard) in 2.8 ml of DME was treated with 87.5 mg (1.20 mmol) of diethylamine and the solution of lithium diethylamide was stirred at 0° for 5 min. The cooling bath was removed, 206.6 mg (1.25 mmol) of 4-*tert*-butylcyclohexanecarbonitrile was added, and the resulting solution was stirred for 5 min. The solution of the lithium salt **4** was added, dropwise and with vigorous stirring over a 1-min period at 25°, to a solution of 1.002 g (7.07 mmol) of CH_3I in 3.7 ml of DME (the initial concentrations after mixing were 0.17 *M* in the lithium salt **4** and 1 *M* in CH_3I). The resulting solution was stirred at 25° for 1.5 min and then quenched by the addition of dilute aqueous HCl. The ethereal extract of the reaction mixture was washed with aqueous $NaHCO_3$, dried, and concentrated by distillation of the bulk of the ether through a 40-cm Vigreux column. The residual liquid was analyzed by glpc, using LAC-728 (diethylene glycol succinate) on Chromosorb P, employing equipment that had been calibrated as decribed elsewhere.[5d] The monoalkylated product (calculated yield 91%) was composed of 28% of the axial methyl isomer **6** and 72% of the equatorial methyl isomer **5**. In a duplicate experiment, the monoalkylated product (yield 96%) contained 29% of **6** and 71% of **5**.

B. With Methyl Chloride.—A solution of the lithium salt **4** was prepared as previously described from 1.20 mmol of methyllithium, 1.22 mmol of diethylamine, 1.26 mmol of the nitrile, and 173.1 mg of biphenyl in 2.8 ml of DME. This solution was added, dropwise and with stirring at 25° over a 1-min period, to a solution of 0.36 g (7.13 mmol) of CH_3Cl in 3.7 ml of DME (the initial concentrations after mixing were 0.17 *M* in the lithium salt **4** and 1 *M* in CH_3Cl). After the resulting solution had been stirred at 25° for 1.5 min it was quenched by the addition of dilute aqueous nitric acid and then extracted with four portions of hexane. After the organic extract had been dried and concentrated, the residual liquid contained the unalkylated nitrile and the monoalkylated product (yield 92%) composed of 20% of the axial methyl isomer **6** and 80% of the equatorial methyl isomer **5**. The aqueous phase from the alkylation reaction was diluted with water to 100 ml and aliquots were titrated by the Volhard procedure. The calculated yield of chloride ion was 1.125 mmol or 102% of the amount of monoalkylated product. Three additional runs were performed at 25° utilizing as initial concentrations of reactants 0.085 *M* lithium salt **4** and 1 *M* CH_3Cl. The aqueous phases were separated as described above for analysis of the chloride ion. The calculated yields of monoalkylated products were in the range 82–96% and the compositions were 19–20% of the axial methyl isomer **6** and 80–81% of the equatorial isomer **5**.

C. With Trimethyloxonium Fluoroborate.—A solution of the lithium salt **4** from 1.20 mmol of methyllithium, 1.36 mmol of diethylamine, 1.24 mmol of the nitrile, 182.5 mg of biphenyl, and 2.8 ml of DME was added, dropwise and with stirring at 25°, to a *suspension* of 955.9 mg (7.24 mmol) of trimethyloxonium fluoroborate[26] in 3.7 ml of DME (initial concentration 0.17 *M* in the lithium salt **4**). After the mixture had been stirred at 25° for 0.75 hr, dilute aqueous HCl was added and the previously described isolation and analysis procedures were followed. The monoalkylated products (yield 24%)[27] contained 40% of the axial methyl isomer **6** and 60% of the equatorial methyl isomer **5**. In an additional run, the monoalkylated product (yield 28%) contained 45% of **6** and 55% of **5**. Collected (glpc) samples of the monoalkylated products **5** and **6** were identified with previously described samples by comparison of ir spectra and glpc retention times.

Methylation of the Amino Ketone 13.—A mixture of 533 mg (3.47 mmol) of the amino ketone **13**,[4a,28] 2 g (*ca.* 40 mmol) of CH_3Cl, and 1 ml of DME was heated to 85–90° in a sealed tube for 4.5 days. A solution of the resulting crystalline mass in methanol was concentrated to separate 618 mg (87.3%) of the crude salt as tan crystals, mp 237° dec. A methanol solution of the crude product was decolorized with charcoal and then crystallized from a methanol–ethyl acetate mixture to separate 583 mg (82.4% of the methochloride of amine 13 as hygroscopic white plates: mp 239° dec; ir (KBr pellet) 1718 and 1731 cm^{-1} (C=O split by Fermi resonance with vibrations from bridgehead C–H bonds);[29] nmr (D_2O) δ 4.08 and 3.97 (4 H, two center peaks from a partially resolved AB pattern, $-CH_2N^+$), 3.37 (3 H singlet, CH_3N^+, 3.08 (3 H singlet, CH_3N^+), 2.7–3.4 (2 H multiplet, bridgehead CH), and 1.4–2.6 (6 H multiplet, aliphatic CH).

Anal. Calcd for $C_{10}H_{18}ClNO$: C, 58.96; H, 8.90; Cl, 17.41; N, 6.88. Found: C, 58.91; H, 8.86; Cl, 17.27; N, 7.15.

In subsequent experiments, mixtures of 763–769 mg (4.98–5.02 mmol) of the amino ketone **13** and 1 g (*ca.* 20 mmol) of CH_3Cl were diluted to a total volume of 10 ml with DME and then allowed to stand at 25–30° in sealed tubes for 2 months. Filtration of the resulting solutions separated 63.1–70.9 mg (6.2–6.9%) of the quaternary salt as white plates, mp 239° dec. Two additional runs were made with 764–770 mg (4.98–5.03 mmol) of the amine **13** and 2 g (*ca.* 40 mmol) of CH_3Cl diluted to a total volume of 10 ml of DME. In these cases, the solutions were

(26) This oxonium salt was prepared by the procedure of H. Meerwein, *Org. Syn.*, **46**, 120 (1966). As noted elsewhere,[6c] it is probable that the methyl groups of this oxonium salt have equilibrated, at least in part, with the *O*-methyl groups of the solvent, DME.

(27) When these reactions were run further toward completion by use of longer reaction times, other unidentified by-products were formed in significant amounts. We, therefore, ran the reaction only to the fraction of completion described to avoid the possibility that the composition of the monoalkylated product might be altered by subsequent side reactions.

(28) H. O. House and W. M. Bryant, III, *J. Org. Chem.*, **30**, 3634 (1965).

(29) H. O. House and H. C. Muller, *ibid.*, **27**, 4436 (1962).

heated to 75–80° in sealed tubes for 7 days. The quaternary salt, isolated as usual, amounted to 533–534 mg (52%), mp 244° dec.

Measurement of Chlorine Isotope Effects.—Chlorine isotope effects for the reactions with CH_3Cl are given in Table I. All errors are standard deviations of the mean. With triethylamine (19), runs ranging from 4.2 to 10.8% reaction (amount of CH_3Cl converted to NaCl, controlled by the amount of amine present) were carried out to demonstrate that the isotope effect did not change with this variable. The insoluble product was allowed to remain in the reaction mixture for varying lengths of time to show that the isotope effect did not vary due to exchange of ionic and covalent chloride. The fact that the isotope effect showed no trend with time is evidence that such exchange does not occur. Chlorine isotope effects have been reported previously for other reactions.[30]

Reaction tubes were made from 12-mm-o.d., medium-wall Pyrex tubing 23 cm long, sealed at one end. The tubes were boiled in 70% HNO_3, rinsed, boiled, and rinsed again in distilled water, oven dried at 120° for at least 1 day, and stored over $CaSO_4$ (Drierite) in desiccators until used. A slight constriction for sealing was made about 3 cm from the open end. A file mark at the 1-ml level was made on each tube. The tube was capped with an 11-mm no-air stopper. After flushing with dry N_2 by means of needles inserted in the stopper, the tube was cooled in a Dry Ice–ethanol bath. CH_3Cl was introduced by a long needle and condensed into the tube up to the 1-ml mark (0.991 g,[31] 20 mmol). Pure DME was then added by syringe, the final total volume (after addition of amine) being 10 ml. The liquid amines were weighed into the reaction tubes by difference from syringes. The amount of amine was varied according to the desired per cent reaction (4.2–10.8%). Alternatively, NaI (Mallinckrodt reagent) sufficient for 8.6% reaction was weighed out, then quickly poured into the tube while the no-air stopper was momentarily removed; NaI is soluble in the DME. The tube was sealed at the constriction. At zero time the tube and its contents were warmed quickly to reaction temperature by immersing the tube in a stream of running tap water and shaking vigorously. The tube was then thermostatted at 25.00 ± 0.05°. After the reaction was complete, the tube was cooled in Dry Ice–ethanol, scored, and cracked open. The insoluble product was collected on a small Büchner funnel. There was no ionic chloride in the filtrate. The organic products were hygroscopic, white, crystalline solids. The product was dissolved in 5 ml of 0.4 *M* KNO_3 solution and acidified with two drops of concentrated HNO_3, and the AgCl was precipitated with 0.4 *M* $AgNO_3$–0.4 *M* KNO_3 solution, gravity filtered, and dried for 2 hr at 120°. The AgCl was cooled, crushed to a powder, and converted to CH_3Cl by the method previously described.[30] This CH_3Cl was called the product sample. CH_3Cl from the tank was used as the reactant sample.

Relative isotopic compositions of the CH_3Cl samples were determined with a Consolidated Engineering Corp. Model 21-201 isotope ratio mass spectrometer. This instrument had been modified by replacing the preamplifiers and amplifiers with two Cary 401 vibrating reed electrometers. The original voltage divider was replaced by a four-dial General Radio Co. type 1454-AH decade voltage divider. The electrometers were operated on the positive current mode using 4×10^{10} Ω input resistors (specially installed). The *m/e* 52 peak was focused on the small plate 2 (large plate 1 then collects ions of *m/e* 51–47) with amplifier 2 on the 30-V scale and amplifier 1 on the 3-V scale. The signal from amplifier 1 was switched onto the voltage divider and thus used to balance the signal from amplifier 2. When the signal on amplifier 2 was reduced nearly to zero, the recorder was used to read the residual small voltage. The damping circuit on preamplifier 2 was engaged at this point to reduce the noise level. The last dial on the voltage divider was switched from one number to the next and back again across the zero voltage line. The experimental signal ratio to six figures could then be determined from the recorder traces.[32] As the last dial of the voltage divider was switched, the voltage approached its new value exponentially. The fifth and sixth decimal figures were obtained by measuring vertical displacements on the recording relative to the zero voltage line, for the ascending and descending exponentials successively. This procedure was repeated until six values of the ratio were obtained for a sample. The average of these numbers (called a "value" for a sample) was used for subsequent calculations. The values themselves are dependent on the circuitry of the instrument and are not direct measures of the isotopic composition.

Calculation of the isotope effect[32] involves division of the signal ratio value for the reactant sample by that for the product sample. These samples were measured one after the other, so that the measurement for, say, the product (reactant) sample was bracketed by two measurements for the reactant (product) sample. If the two values for the bracketing sample were very different, no calculations were performed. If the values were close, their average was calculated and used to compute the initial ratio (reactant value over product value). The initial ratio was used to calculate the isotope effect. The calculation of R_R, the ratio of rates (k_{35}/k_{37}) corrected for % reaction, was simplified by use of the approximation

$$R_R \cong R_I\,[1 + (f/2)(R_I - 1)]$$

$$\text{where } R_R = \frac{\log (1 - R_I f)}{\log (1 - f)}$$

R_I = initial ratio (reactant value/product value)
f = fraction of CH_3Cl converted to NaCl

The R_R finally obtained from three signal ratio values was called a "measurement" of the isotope effect. Several measurements of the isotope effect were made for each product sample for a run. These measurements were averaged to give an isotope effect for that run. The observed values for 44 independent runs are recorded elsewhere,[32] with chronological run number, ratios for reactant sample, pruduct sample, and reactant sample again, each with its standard deviation, and R_I for each run.

Registry No.—**4,** 33209-52-8; **7,** 7576-03-6; **8a,** 33209-54-0; **8b,** 33209-55-1; **8c,** 33209-56-2; **9a,** 33209-57-3; **9b,** 33209-58-4; **9c,** 33209-59-5; **10,** 7576-02-5; **13,** 4146-35-4; **13** (methochloride), 33209-62-0; **19,** 121-44-8; NaI, 7681-82-5; chloromethane, 74-87-3; 1,2-dimethoxyethane, 110-71-4.

(30) R. M. Bartholomew, F. Brown, and M. Lounsbury, *Can. J. Chem.*, **32**, 979 (1955); J. W. Hill and A. Fry, *J. Amer. Chem. Soc.*, **84**, 2763 (1962); E. P. Grimsrud and J. W. Taylor, *ibid.*, **92**, 739 (1970).

(31) C. Vincent and Delachanal, *Bull. Soc. Chim. Fr.*, **31**, 12 (1879).

(32) N. D. Hershey, "Chlorine Isotope Effects as Probes for Transition-State Structure," Ph.D. Thesis in Chemistry, M. I. T., Jan 1971, pp 3, 14–62. Further details on experimental procedure may be found here and also in B. S. Magid, Ph.D. Thesis in Chemistry, M. I. T., June 1964, pp 9, 25–28, 34, and 62–67, and M. H. O'Leary, Ph.D. Thesis in Chemistry, M. I. T., May 1966, pp 53, 54, 60, 78, 79, 99, 104, and 105.