the CH_2N and CH_3N protons which are no longer accidentally equivalent at low temperatures. A chlorobenzene solution containing approximately equimolar amounts of the diamine **25** and the complex exhibited, in addition to solvent absorption and the high field singlet for the CH_3–Mg protons, two singlets (separation 5 cps) with the higher field absorption being the more intense as would be expected if the free diamine **25** were exchanging rapidly with the diamine in the complex **29**. This pattern persisted down to *ca.* −30°. Below this temperature the less intense, lower field peak broadened. However, at no point down to −63°, was there evidence for two different sets of peaks attributable to free and complexed diamine. We therefore concluded that exchange of this ligand on dimethylmagnesium is relatively rapid at or above −30°.

The diamine complex **29** was also prepared from methylmagnesium bromide by the following procedure. To 50 ml of an ethereal solution containing 0.15 mol of methylmagnesium bromide was added 15 ml (0.18 mol) of dioxane. The resulting mixture was diluted with 50 ml of ether and stirred at room temperature for 30 min after which the ether solution was separated from the insoluble dioxane complex by filtration through a filter stick. The residual solid was washed with ether and the combined ether filtrates were treated with 12 ml (*ca.* 0.1 mol) of the diamine **25**. The resulting solution was concentrated under reduced pressure and the residual white solid was sublimed (0.1–0.2 mm and 80–100°) to separate 2.4 g (21%) of the diamine complex **29**, mp 94.5–96.5° in a sealed evacuated tube (lit.[13a] mp 97–98°). This complex appears not to decompose at its melting point since the resolidified sample from the melting point determination had the same melting point as the original sample.

B. **With 1,2-Dimethoxyethane (27).**—A solution prepared from 3.2 mmol of dimethylmagnesium and 1.0 ml of 1,2-dimethoxyethane in 5.0 ml of ether was cooled in a Dry Ice–acetone bath and then allowed to warm to room temperature. Once crystallization of the complex **30** had been initiated at low temperatures, it continued at room temperature in agreement with an earlier report.[13a] The solid was separated (centrifugation followed by removal of the supernatant liquid through a cannula), washed with a 5-ml portion of ether, and then dried under reduced pressure. During this drying process partial decomposition of the complex appeared to occur. The portion of the residue which was still soluble was taken up in benzene[28] for nmr examination. Apart from absorption attributable to benzene and small amounts of ether, the sample exhibited singlets at δ 3.21 (OCH_2), 3.12 (OCH_3), and −0.90 (54 cps above TMS, CH_3–Mg). The ratio of peak areas corresponded approximately to the 1:1 complex **30**. For comparison, the nmr spectrum of a benzene solution of 1,2-dimethoxyethane has singlets at δ 3.37 (OCH_2) and 3.18 (OCH_3).

C. **With β-Methoxyethyldimethylamine (28).**—To 4.4 ml of an ether solution containing 2.8 mmol of dimethylmagnesium was added 0.55 ml (5 mmol) of the methoxyamine **28** and the resulting solution was concentrated to dryness under reduced pressure. The residual crystalline complex **31** was soluble in ether at room temperature to the extent of at least 0.5 *M* but crystallized from solution when the solution was cooled below 0°. Attempts to sublime the complex at 80–90° and 0.08 mm were not successful; the complex appeared to dissociate leaving polymeric dimethylmagnesium behind in the manner noted previously[13a] for the 1,2-dimethoxyethane complex **30**. A chlorobenzene solution of the amino ether complex **31** has nmr signals at δ 3.28 (2 H triplet, J = 5.5 cps, CH_2O), 3.21 (3 H singlet, CH_3O), 2.31 (2 H triplet, J = 5.5 cps, CH_2N), 2.12 (6 H singlet, CH_3N) and −1.25 (75 cps above TMS, 6 H singlet, CH_3Mg). For comparison, a chlorobenzene solution of the amino ether **28** has nmr peaks at δ 3.39 (2 H triplet, J = 6 cps, CH_2O), 3.22 (3 H singlet, OCH_3), 2.41 (2 H triplet, J = 6 cps, CH_2N), and 2.17 (6 H singlet, CH_3N).

Registry No.—Dimethylmagnesium, 2999-74-8; benzophenone, 119-61-9; **16**, 15476-20-7; **25**, 110-18-9; **28**, 3030-44-2; **29**, 15405-88-6; **30**, 15405-89-7; **31**, 15405-87-5.

Acknowledgments.—The authors are indebted to Dr. Francis Johnson of the Dow Chemical Co. for a generous sample of triply sublimed magnesium, to the Union Carbide Chemicals Co. for a sample of bis (N,N-dimethylaminoethyl) ether, and to Professor Stanley G. Smith for providing us with a preprint of his manuscript prior to publication.

The Chemistry of Carbanions. XV. The Stereochemistry of Alkylation of 4-*t*-Butylcyclohexanone[1a]

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Received August 4, 1967

Alkylation of the enolate anion **1** of 4-*t*-butylcyclohexanone with triethyloxonium fluoroborate yielded a mixture of O-alkylated product and a mixture of approximately equal amounts of the stereoisomeric 2-ethyl-4-*t*-butylcyclohexanones. A comparable mixture of C-alkylated products was obtained from reaction of the enolate anion with ethyl iodide for short periods of time. Quenching the enolate anion **1** in a mixture of deuterium oxide and deuterioacetic acid yielded a mixture of the axial deuterio ketone (*ca.* 70%) and the equatorial deuterio ketone (*ca.* 30%). These results are interpreted as evidence that the transition states for alkylation and protonation have geometries resembling the enolate anion **1** rather than the products.

With specific methods in hand for generating the enolate anions of simple ketones,[2] we were interested in examining the preferred direction of alkylation of an enolate anion derived from a simple cyclohexanone.[3,4] For this purpose we elected to study the alkylation and the protonation of the enolate anion **1** derived from 4-*t*-butylcyclohexanone (**2**). Solutions of this enolate anion **1** in 1,2-dimethoxyethane (DME) were obtained either by reaction of the ketone **2** with triphenylmethyllithium or by reaction of the enol acetate **3** with 2 equiv of methyllithium. The latter

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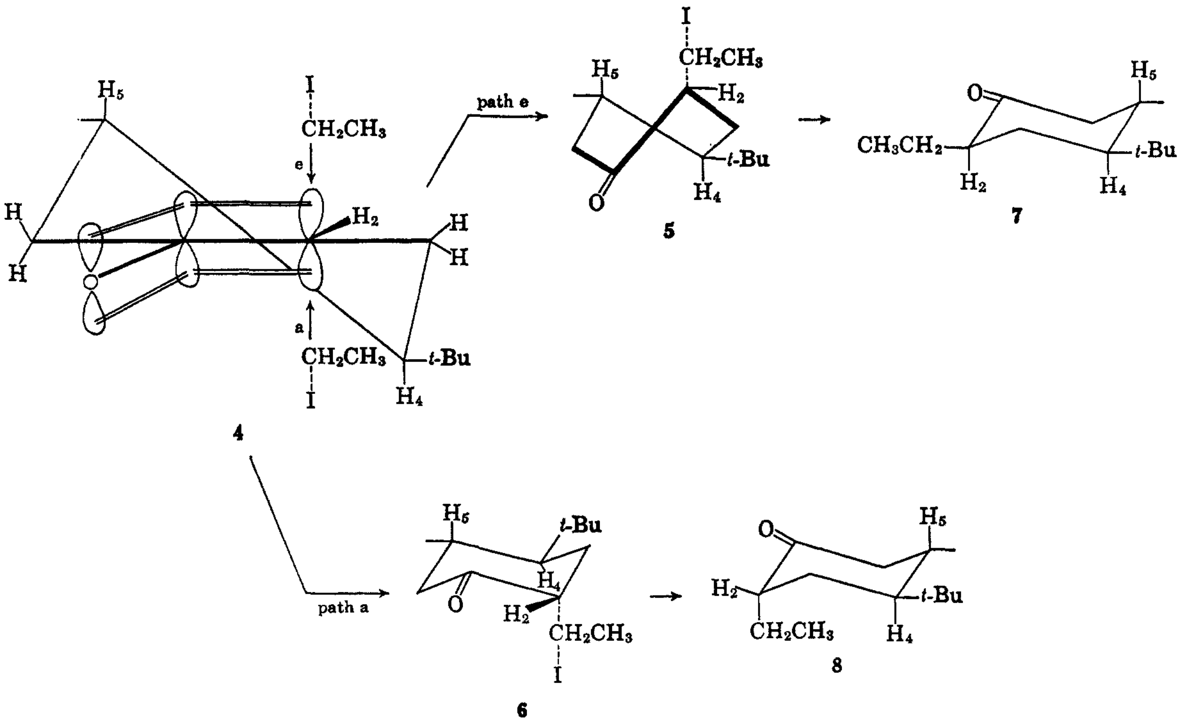
[1] (a) This research has been supported by research grants from the National Institutes of Health (Grant No. GM-08761) and the Directorate of Chemical Sciences, Air Force Office of Scientific Research (Grant No. AF-AFOSR-573); (b) National Institutes of Health Predoctoral Fellow, 1963–1965; (c) National Institutes of Health Predoctoral Fellow, 1965–1966.

[2] (a) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963); (b) H. O. House and B. M. Trost, *ibid.*, **30**, 1341, 2502 (1965).

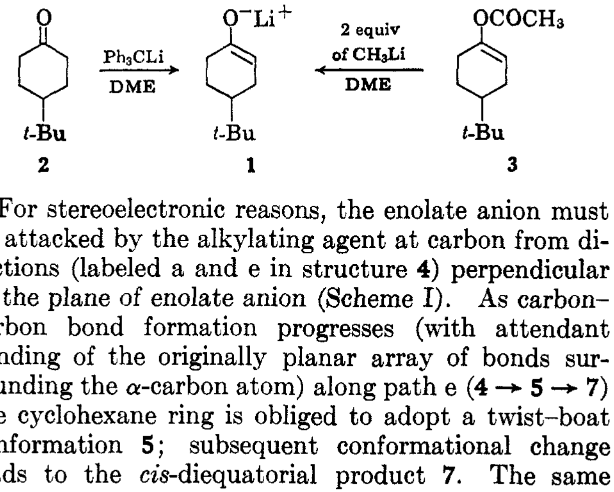
[3] For recent reviews of the stereochemistry of C alkylation, see (a) L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965); (b) J.-M. Conia, *Rec. Chem. Progr.* (Kresge-Hooker Sci. Lib.), **24**, 43 (1963).

[4] For recent studies pertinent to the stereochemistry of alkylation of simple cyclohexanone derivatives, see (a) R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 1194 (1958); (b) E. J. Eisenbraun, F. Burian, J. Osiecki, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 3476 (1960); C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *ibid.*, **83**, 4433 (1961); M. R. Cox, H. P. Koch, W. B. Whalley, M. B. Hursthouse, and D. Rogers, *Chem. Commun.*, 212 (1967); (c) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **84**, 2611 (1962); (d) J. M. Conia and P. Briet, *Bull. Soc. Chim. Fr.*, 3881, 3888 (1966).

SCHEME I



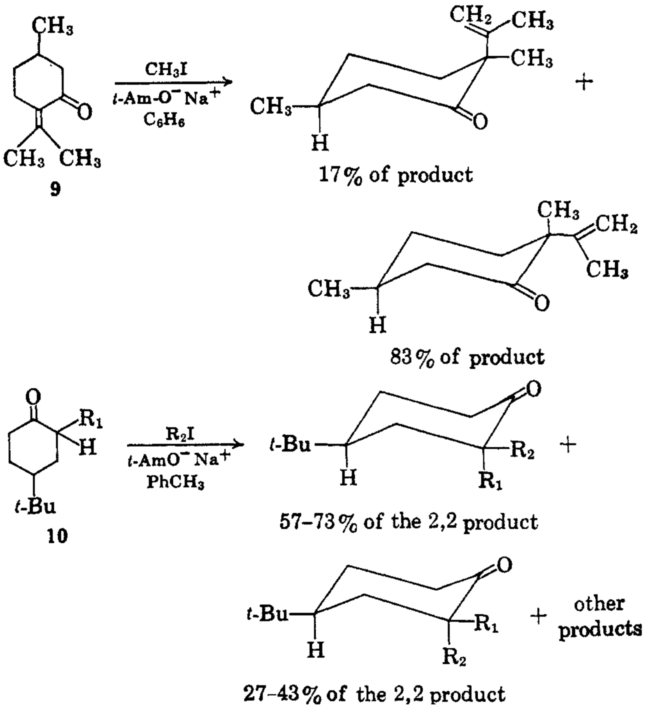
procedure[2] afforded a solution which contained equivalent amounts of the enolate anion 1 and lithium *t*-butoxide.



For stereoelectronic reasons, the enolate anion must be attacked by the alkylating agent at carbon from directions (labeled a and e in structure 4) perpendicular to the plane of enolate anion (Scheme I). As carbon–carbon bond formation progresses (with attendant bending of the originally planar array of bonds surrounding the α-carbon atom) along path e ($4 \rightarrow 5 \rightarrow 7$) the cyclohexane ring is obliged to adopt a twist–boat conformation 5; subsequent conformational change leads to the *cis*-diequatorial product 7. The same considerations applied to reaction path a ($4 \rightarrow 6 \rightarrow 8$) lead directly to a chair conformation 6 of the cyclohexane ring with the formation of the *trans*-alkylated product 8. If the assumption is made that a chairlike transition state (*e.g.*, 6) will have lower energy than the twist–boat alternative (*i.e.*, 5),[5] the aforementioned considerations have led to the general conclusion[3] that reaction *via* a chairlike transition state (*e.g.*, 6) to introduce an axial alkyl group (*e.g.*, 8) should be the favored reaction path in the absence of opposing steric and conformational interactions. The magnitude of this energy difference may be expected to depend upon the extent to which the transition states resemble the chair and boat conformations of a cyclohexanone rather than an enolate anion.

Two previous studies of simple cyclohexanone derivatives which bear on this question are the indicated methylation of pulegone (9)[4b] and related compounds and the alkylation of several 2-alkyl-4-*t*-butylcyclohexanones 10.[4d] Recent studies, correcting an earlier report, have indicated that the major alkylated product from pulegone (9) corresponds to reaction path a but the reverse stereochemical result (path e favored) is found with saturated derivatives of pulegone (9).[4b] In alkylation of the 4-*t*-butyl derivatives 10, reaction path e was favored slightly over reaction path a[4d] (Scheme II). One might argue that these latter cases are exceptional in that the expected reaction path (*i.e.*, path a *via* a transition state such as 6) is dis-

SCHEME II



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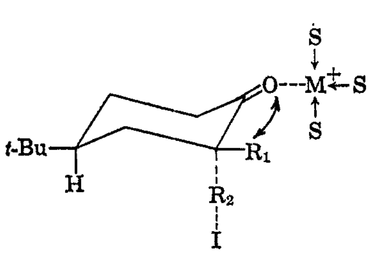
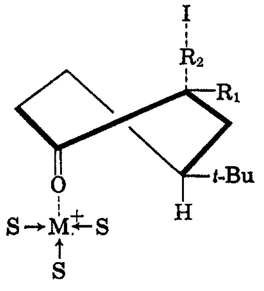
(5) *Cf.* N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *J. Amer. Chem. Soc.*, **88**, 2999 (1966).

favored by a nonbonding steric interaction in the transition state between the equatorial 2 substituent (R_1 in structure **11**) and the solvated metal-oxygen bond. This particular interaction can be lessened in a conformation approaching the geometry of a twist-boat (*i.e.*, **12**) which would lead to the observed predominant product. However, this argument loses much of its appeal when considered in light of our current finding that the alkylation of the unsubstituted 4-*t*-butylcyclohexanone enolate anion, **1**, also leads to an approximately equal mixture of *cis* and *trans* isomers **13** and **14**. In this case the interaction indicated in structure **11** (R_1 = H) certainly is not a serious deterrent to the formation of the *trans* product **14** (Scheme III).



11



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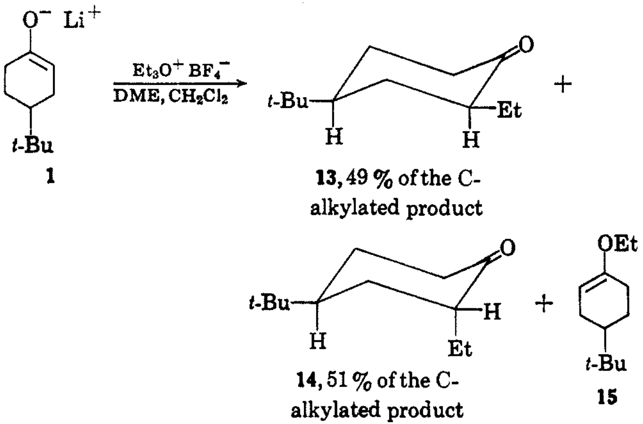
SCHEME III

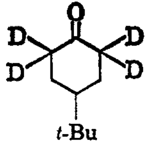


1

13, 49% of the C-alkylated product

14, 51% of the C-alkylated product

15



16

In these alkylation experiments the absence of equilibration of the products **13** and **14** was demonstrated by alkylating the enolates derived from a mixture of the ketone **2** and its tetradeuterio derivative **16** to form a mixture of ketone products **13** and **14** containing primarily d_0 and d_3 species. The formation of the O-alkylation product **15** as a by-product when the reactive alkylating agent, the triethyloxonium ion, was employed is also of interest. This side reaction, suspected earlier,[2b] has been reported elsewhere in the intervening period.[6] None of this O-alkylated product **15** was observed when the enolate anion was alkylated with the less reactive alkylating agent, ethyl iodide. Interestingly, the composition of the monoalkylated product recovered after short reaction times (54% of **14** and 46% of **13**) with ethyl iodide was not appreciably different from the composition of alkylated product obtained with triethyloxonium ion.

In view of the present stereochemical results and of results obtained on alkylation of the enolate anions from various bicyclic and polycyclic ketones,[2b,3,7] we conclude that there is no inherent factor which strongly favors the alkylation of a cyclohexanone enolate anion from that direction which will form a product with an axial alkyl substituent. Accordingly, we must also conclude that the energies of the two transition states for alkylation are approximately equal; in other words, some error exists in the previously presented argument that the transition state for path a will be of significantly lower energy than the transition state for path e. All of our presently available data are most consistent with the idea that relatively little new C–C bond formation has occurred at the transition state for the alkylation of enolate anions. For this reason, we believe that the geometries of the six-membered rings in the transition states resemble much more closely the geometry of the planar enolate ion (*e.g.*, **4**) than the geometries of chair (*e.g.*, **6**) or twist-boat (*e.g.*, **5**) cyclohexane rings.[2b,8] An examination of molecular models failed to reveal any obvious steric factors in the enolate anion **1** which would favor attack of the alkylating agent from one of the directions a or e (structure **4**). Consequently, if the geometries of the transition states for alkylation resemble the enolate ion **4** rather than structures such as **5** and **6**, the energy difference between the two transition states would be expected to be small.

Although the previously observed[2b] enhancement of the proportion of *cis*-fused product when the $\Delta^{1,9}$-enolate from 1-decalone was alkylated with trimethyloxonium ion rather than the less reactive methyl iodide is consistent with the idea that the transition state resembles the enolate anion, especially with reactive alkylating agents, other explanations are possible.[9] As noted in accompanying studies[10] of the alkylation of methyl 4-*t*-butylcyclohexyl ketone and 1-cyano-4-*t*-butylcyclohexane, the formation of *cis*-fused products

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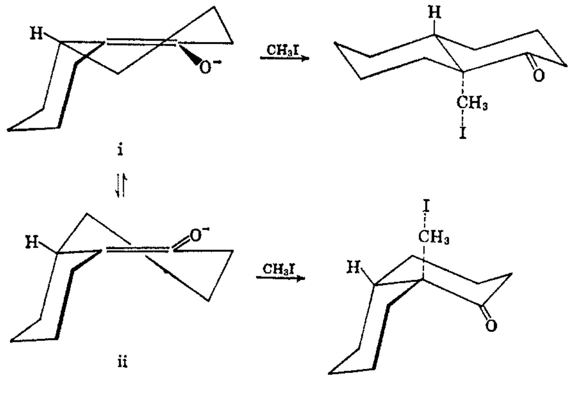
[6] G. J. Heiszwolf and H. Kloosterziel, *Chem. Commun.*, 51, 767 (1966).

[7] In the absence of opposing steric or conformational effects, both 1-ketodecalin and 1-ketoperhydroindanone systems are alkylated at the bridgehead to form predominantly *cis*-fused products. For discussion of the perhydroindanone case, see ref 3a; H. O. House and R. G. Carlson, *J. Org. Chem.*, **29**, 74 (1964); H. O. House and C. J. Blankley, *ibid.*, **32**, 1741 (1967).

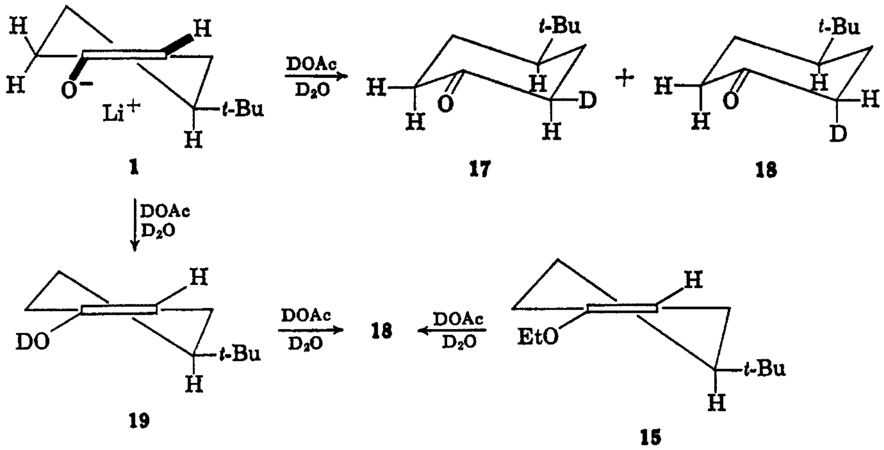
[8] W. S. Johnson, D. S. Allen, Jr., R. R. Hindersinn, G. N. Sausen, and R. Pappo, *J. Amer. Chem. Soc.*, **84**, 2181 (1962).

[9] The alkylation of 1-decalone at C-9 is ambiguous in that suitable conformations of the starting enolate anion i and ii can provide reaction paths which lead to initial products where both cyclohexane rings are in chair conformations irrespective of the stereochemistry of alkylation.

[10] H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).

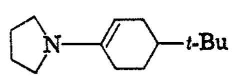


SCHEME IV



in the alkylation of 1-decalones can be regarded as an example of the preference for introduction of an equatorial alkyl group in the alkylation of a cyclohexyl ketone enolate.

In an ancillary study, we have also examined the protonation of the enolate anion **1** in a deuterium oxide–deuterioacetic acid mixture (Scheme IV). In principle, this protonation process could provide information about the stereochemistry of forming bonds to the α carbon of the enolate anion **1** in a situation where the transition state of this very rapid reaction presumably resembles the enolate anion. In practice, this goal is complicated by the fact that protonation of this strongly basic anion at either carbon (to form **17** or **18**) and at oxygen (to form **19**) are diffusion-controlled reactions[11] so that comparable amounts of the ketones **17** and **18** and the enol **19** are produced in the quenching process. Further reaction of the enol **19** with aqueous acid can also yield one or both of the ketones **17** or **18**. In an effort to learn the stereochemical course of ketonization of the enol **19**, the related enol ether **15** was subjected to the same reaction conditions to yield a ketone product calculated to contain more than 90% of the ketone **18** with axial deuterium. A comparable result was reported for the carefully controlled (see Experimental Section) acidic hydrolysis of the enamine **20**.[12] The nmr spectrum of the ketone



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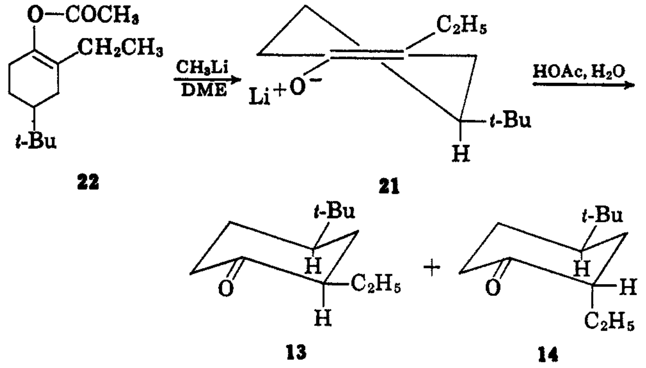
mixture obtained from quenching the enolate anion **1** in deuterated aqueous acetic acid was consistent with the presence of *ca.* 70% of the axial deuterated ketone **18** and *ca.* 30% of the equatorial isomer **17**. Supporting evidence for the validity of this result was obtained by quenching the enolate anion **21** in aqueous acetic acid to obtain a mixture of the ketone **13** (80%, axial proton) and **14** (20%, equatorial proton) (Scheme V).

Since the composition of the monodeuterated ketone mixtures obtained from the enol **19** and the enolate **1** are different, one must conclude that at least part of the enolate anion **1** reacts with a deuteron to form a C–D bond directly. Furthermore, at least 20–30% of the new C–D bonds formed by reaction of the enolate

SCHEME V



anion **1** with a deuteron occur by attack of the deuteron donor from the direction labeled e in structure **4**. If the crude assumption is made that one-half of the enolate anion is protonated on oxygen and one-half is protonated on carbon, it would then appear that protonation at carbon occurs with approximately equal ease from either side of the enolate anion **1**. The results of these protonation experiments, like the stereochemical results obtained from alkylating the enolate anion **1**, are most readily explicable if the transition state geometries for both reactions resemble the geometry of the enolate anion so that energy differences between the directions of attack on the enolate (*e.g.*, a or e in structure **4**) are small.

Experimental Section[13]

Preparation of Starting Materials.—Pure[14] 4-*t*-butylcyclohexanone (**2**), mp 47–48°, bp 110–113° (16 mm), was obtained by conversion of the crude ketone into its $NaHSO_3$ addition product which was separated and reconverted into the ketone with aqueous Na_2CO_3. A mixture of 26 g (0.17 mol) of the ketone **2** and 40 ml of D_2O containing 400 mg of Na_2CO_3 was heated to 70–80° with stirring for 24 hr and then cooled and extracted with

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[11] M. Eigen, *Angew. Chem., Intern. Ed. Engl.*, **3**, 1 (1964).

[12] J. P. Schaefer and D. S. Weinberg, *Tetrahedron Lett.*, 1801 (1965).

[13] 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; tetramethylsilane was used as the internal standard. 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. All solutions of enolate anions were prepared and transferred under a nitrogen atmosphere.

[14] A gas chromatography column packed with Carbowax 20M suspended on Chromosorb W was employed for this analysis.

ether. After the ethereal extract had been dried and concentrated, the crude recovered ketone was subjected to the same exchange procedure five additional times. In the final exchange, 5 ml of 1,2-dimethoxyethane was added to the D_2O as a cosolvent. The final crude ketone was distilled to separate 7.0 g (27%) of the tetradeuterio ketone **16**; the mass spectrum of the product indicated the presence of 6% d_3 species and 94% d_4 species.

Samples of the ketone **16**, injected on and recollected from our gas chromatography columns,[15,16] lost 5% or less of their d_4 species during this treatment. The sample also slowly lost deuterium when allowed to stand in the heated inlet system of the mass spectrometer; however, this complication was not significant when times no longer than 15 min elapsed between introduction of the sample and completion of the measurements. The infrared spectrum (CCl_4)[17] of the tetradeuterio ketone **16** has a carbonyl peak at 1710 cm^{-1} with peaks attributable to C–D stretching at 2110 (m), 2125 (m), 2180 (shoulder), and 2225 cm^{-1} (s). The infrared absorption in the finger print region differed from the spectrum of the nondeuterated ketone **2** in a number of places. The nmr spectrum ($CDCl_3$) of the nondeuterated ketone **2** has a singlet at δ 0.93 (9 H, $(CH_3)_3C$–) with a multiplet in the region 1.1–1.92 (4 H, CH_2 groups at C-3 and C-5) and two partially resolved multiplets in the regions 1.92–2.17 (*ca.* 1 H, CH at C-4) and 2.17–2.63 (*ca.* 4 H, CH_2 at C-2 and C-6). In the same solvent, the tetradeuterio ketone **16** has the multiplets in the regions 1.1–1.92 and 1.92–2.17, but lacks absorption in the lower field (2.2–2.7) region. In benzene solution,[18] the nmr spectrum of the nondeuterated ketone **2** has the *t*-butyl singlet at δ 0.75 with multiplets in the regions 0.87–1.47 (4 H, CH_2 at C-3 and C-5), 1.47–1.98 (3 H, CH at C-4 and axial[18] CH at C-2 and C-6), and 1.98–2.40 (2 H, equatorial CH at C-2 and C-6). The nmr absorption of a benzene solution of the tetradeuterio ketone **16** differs in having a multiplet in the region δ 1.47–1.98 attributable to only one proton (CH at C-4) and in lacking absorption in the region 1.98–2.40.

Ethereal solutions of methyllithium were prepared from methyl bromide in the usual way and standardized either by a double titration procedure employing 1,2-dibromoethane or by use of the chlorodimethylphenylsilane procedure.[19] Triethyloxonium fluoroborate, prepared as previously described,[20] was washed thoroughly with ether, recrystallized from a methylene chloride–ether mixtur, dried under reduced pressure, and stored under nitrogen.

1-Acetoxy-4-*t*-butylcyclohexene (3).—A solution of 25.163 g (0.163 mol) of the ketone **2** in 152 ml (1.32 mol) of isopropenyl acetate containing several milligrams of *p*-toluenesulfonic acid was refluxed for 24 hr and then cooled and partitioned between pentane and aqueous Na_2CO_3. The pentane extract was dried, concentrated, and distilled to separate 24.998 g (78.6%) of the pure[15] enol ester **3**: bp 135° (21 mm); $n^{25}D$ 1.4602 (lit.[21] bp 85–86° (2.5–3 mm); $n^{20}D$ 1.4640); ir (CCl_4), 1755 (ester C=O) and 1685 cm^{-1} (C=C); nmr ($CDCl_3$), δ 5.38 (1 H multiplet, vinyl CH), 0.88 (9 H singlet, $(CH_3)_3C$–), 2.09 (singlet, CH_3CO–), and 1.1–2.4 (multiplet, aliphatic CH); mass spectrum, molecular ion peak at *m/e* 196, abundant fragment peaks at *m/e* 154 (M − $CH_2{=}C{=}O$), 139, 97, 70, 57, 55, 43, and 41.

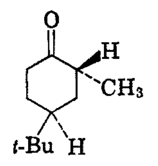
Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.48; H, 10.26.

1-Ethoxy-4-*t*-butylcyclohexene (15).—A mixture of 6.0 g of ethanol, 7.0 g (45 mmol) of the ketone **2**, 8.8 g (59 mmol) of ethyl orthoformate, and 50 mg of *p*-toluenesulfonic acid was stirred at 25° for 48 hr and made basic with sodium ethoxide and distilled. After the ethanol had been separated at atmospheric pressure, the residual liquid was distilled under reduced pressure to separate 6.5 g (57%) of 1,1-diethoxy-4-*t*-butylcyclohexane: bp 67–70° (0.1 mm); $n^{25}D$ 1.4443; ir (CCl_4), no absorption in the 6-μ region, three intense peaks at 1060, 1090, and 1120 cm^{-1} (CO of ketal); nmr ($CDCl_3$), overlapping quadruplets (J = 7 cps for each) centered at δ 3.38 and 3.48 (4 H, CH_2 of ethoxyl groups), 0.87 (9 H singlet, $(CH_3)_3C$), two overlapping triplets (J = 7 cps for each) centered at 1.14 and 1.17 (CH_3 of ethoxyl groups) superimposed on complex absorption in the region δ 1.0–2.3 (aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 228, abundant fragment peaks at *m/e* 98, 97, 70, 55, 45, 43, and 41. The ketal (6.5 g) was mixed with 0.50 g of ammonium dihydrogen phosphate and heated to 170° for 2 hr allowing the ethanol to distil from the mixture as it formed. Distillation of the residual liquid afforded 5.0 g (61%) of the enol ether **15**: bp 114–117° (11 mm); $n^{23}D$ 1.4629; ir (CCl_4), 1670 cm^{-1} (C=C); nmr ($CDCl_3$), δ 4.53 (1 H multiplet, vinyl CH), 3.64 (2 H quadruplet with J = 7 cps, CH_2 of ethoxyl group), 1.25 (triplet with J = 7 cps, CH_3 of ethoxyl group), 0.89 (9 H singlet, $(CH_3)_3C$–), 1.0–2.4 (multiplet, aliphatic CH); mass spectrum, molecular ion peak at *m/e* 182, abundant fragment peaks at *m/e* 98, 97, 70, 55, 43, and 41.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.16; H, 12.20.

The Pyrrolidine Enamine of 4-*t*-Butylcyclohexanone (20).—A solution of 12.005 g (78 mmol) of the ketone **2**, 12 g (0.17 mol) of pyrrolidine, and several milligrams of *p*-toluenesulfonic acid in 30 ml of benzene was refluxed for 6 hr with continuous separation of water. Distillation of the resulting solution separated 10.84 g (68%) of the enamine **20**: bp 110–115° (0.03 mm); ir ($CHCl_3$), 1640 (C=C) and 1705 cm^{-1} (weak, probably a small amount of the starting ketone present as an impurity); nmr ($CDCl_3$), δ 4.18 (1 H multiplet, vinyl CH), 0.86 (9 H singlet, $(CH_3)_3C$–), 2.8–3.2 (4 H multiplet, –CH_2N) and 1.0–2.4 (11 H multiplet, aliphatic CH).

Preparation of the Stereoisomeric 4-*t*-Butyl-2-methylcyclohexanones (23 and 24). A. Methylation of the Enamine.—A solution of 17.38 g (83.7 mmol) of the enamine **20** and 17.00 g (119.5 mmol) of methyl iodide in 150 ml of benzene was refluxed for 20 hr and then hydrolyzed with water and concentrated. Distillation of the crude neutral product afforded 10.657 g of colorless liquid, bp 110–113° (14 mm), $n^{25}D$ 1.4583, which contained, in order of elution on gas chromatography,[16] 21% of a mixture of dialkylated products, 9% of the *cis* isomer **24**, 25% of the *trans* isomer **23**, and 45% of the unmethylated ketone **2**.[22–24] A sample of the *trans* ketone **23**[23,24] was collected:[16] ir (liquid film), 1705 cm^{-1} (C=O); mass spectrum, molecular ion peak at *m/e* 168, abundant fragment peaks at *m/e* 112, 83, 69, 57, 55, 43, 41, and 39; nmr ($CDCl_3$), δ 1.3–2.8 (8 H multiplet, aliphatic CH), 0.95 (9 H singlet, $(CH_3)_3C$–), and 1.19 (3 H doublet with



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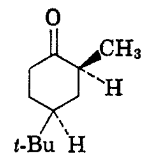

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(15) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb P was employed for this analysis.

(16) The gas chromatography column employed was packed with 1,2,3-tris(β-cyanoethoxy)propane suspended on Chromosorb W which had been neutralized and then treated with dichlorodimethylsilane prior to use.

(17) Because of the relatively low intensities of the peaks in the region 2100–2300 cm^{-1} attributable to C–D stretching vibrations, this region of the spectrum was measured both as a 10–20% solution in a 0.1-mm cell and as a 5–8% solution in a 5-mm cell.

(18) For cyclohexanone derivatives, it has been found that changing the solvent from deuteriochloroform to benzene causes an upfield shift of the axial α protons of 0.3–0.4 ppm relative to the equatorial α protons. For discussion and examples, see (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, pp 159–176; (b) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 1641, 2021 (1965); (c) D. H. Williams, *Tetrahedron Lett.*, 2305 (1965). In the present case, use of pyridine as a solvent for the ketone **2** did not lead to a useful separation of the nmr signals attributed to the axial and equatorial α protons.

(19) H. O. House and W. L. Respess, *J. Organometal. Chem.*, **4**, 95 (1965).

(20) H. Meerwein in "Methoden der organischen Chemie" (Houben–Weyl), Vol 6, Part 3, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, Germany, 1965, p 329.

(21) M. M. Rogic, *Tetrahedron*, **21**, 2823 (1965).

(22) The presence of a substantial quantity of the less stable[23,24] *trans* ketone **23** in this product mixture in spite of the fact that partial equilibration has presumably occurred during the isolation procedure reflects the stereospecificity previously observed in the alkylation and hydrolysis of the intermediate enamine. See F. Johnson and A. Whitehead, *Tetrahedron Lett.*, 3825 (1964); S. Karady, M. Lenfant, and R. E. Wolff, *Bull. Soc. Chim. Fr.*, 2472 (1965).

(23) The preparation and various spectroscopic properties of the stereoisomeric ketones **23** and **24** have been described briefly in several places (ref 5, 22, and 24). Equilibration[5,24a] of these epimers led to mixtures which contained 93–94% of the *cis* isomer **24** (equatorial methyl group) and 6–7% of the *trans* isomer **23** (axial methyl group).

(24) (a) C. Beard, C. Djerassi, J. Sicher, F. Šipoš, and M. Tichý, *Tetrahedron*, **19**, 919 (1963); (b) F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965).

J = 7 cps, CCH$_3$).[25] This material was identified with a previously described sample[22,24b] by comparison of infrared spectra.

A portion of the mixture from the enamine alkylation was stirred with aqueous sodium bisulfite for 12 hr; the unchanged ketonic material, separated from the bisulfite adduct, contained[16] 65% of dialkylated material and 35% of the monoalkylated ketones **23** and **24**. A sample of the dialkylated product was collected:[16] nmr (CDCl$_3$), δ 1.2–2.8 (*ca.* 7 H multiplet), 0.93 (*ca.* 9 H singlet, (CH$_3$)$_3$C–), and 1.04 (*ca.* 6 H, apparently a doublet with J = 7 cps, CH$_3$C); mass spectrum, molecular ion peak at *m/e* 182, abundant fragment peaks at *m/e* 126, 97, 85, 69, 57, 55, 43, and 41. These data suggest that the dialkylated product from this reaction is primarily a 2,6-dimethyl-4-*t*-butylcyclohexanone rather than the 2,2-dimethyl isomer.

B. Methylation of 2-Carboethoxy-4-*t*-butylcyclohexanone.—Following previous procedures,[5,26] the ketone **2** was converted into **2-ethoxalyl-4-*t*-butylcyclohexanone** (bp 190–195° (17 mm), yield 75%) and subsequently to **2-carboethoxy-4-*t*-butylcyclohexanone**: yield 51%; bp 160–165° (25 mm); n^{25}D 1.4747 (lit.[5] bp 128.5–129° (6 mm); n^{25}D 1.4768); ir (CHCl$_3$), 1735 (shoulder), 1715, 1655, and 1615 cm^{-1} (both enol and keto forms of β-keto ester). Methylation yielded **2-carboethoxy-2-methyl-4-*t*-butylcyclohexanone**: yield 84%; bp 120–123° (2 mm); n^{25}D 1.4614 (lit.[5] bp 105.5° (1.3 mm); n^{25}D 1.4610); ir (CHCl$_3$), 1735 (ester C=O) and 1715 cm^{-1} (ketone C=O). Hydrolysis and decarboxylation of 19.82 g (0.0826 mol) of this methylated β-keto ester with 150 ml of refluxing aqueous 4 *M* hydrochloric acid yielded a crude product (14.19 g, bp 156–159° (16 mm)) which contained[16] primarily the *cis* isomer **24** accompanied by lesser amounts of the *trans* isomer **23** and the ketone **2**. Fractional distillation with a 40-cm spinning-band column separated the *cis* ketone **24** as 4.233 g (30%) of colorless liquid: bp 158–159° (16 mm); n^{25}D 1.4595 (lit.[5] for mixture of *cis* and *trans* isomers, bp 75° (3.2 mm), n^{25}D 1.4586); this material was identified with a previously described[22,24b] sample by comparison of infrared spectra—ir (liquid film), 1710 cm^{-1} (C=O); mass spectrum, molecular ion peak at *m/e* 168, abundant fragment peaks at *m/e* 112, 97, 83, 69, 57, 55, 43, 41, and 39; nmr (CDCl$_3$), δ 1.2–2.7 (8 H multiplet), 0.96 (9 H singlet, (CH$_3$)$_3$C–), and 1.06 (3 H doublet with J = 6 cps, CCH$_3$).[25]

Alkylation of 4-*t*-Butylcyclohexanone (1). A. With Methyl Iodide.—Following previously described procedures,[2] a solution of 21 mmol of methyllithium in 30 ml of 1,2-dimethoxyethane was treated with 2.2 g (10 mmol) of the enol acetate **3**. The resulting solution of the enolate anion **1** was cooled to 0° and treated, rapidly and with stirring, with 1.9 ml (34 mmol) of methyl iodide. After the resulting mixture had been stirred for 5 min, it was diluted with aqueous hydrochloric acid and extracted with ether. The ethereal extract was dried, concentrated, and distilled to separate 1.3 g (*ca.* 70%) of fractions boiling in the ranges 110–130° (18 mm) and 90–95° (0.05 mm). The fractions contained[16] *ca.* 25% of dimethylated product, *ca.* 50% of the *cis*-monomethyl ketone **24**, and *ca.* 25% of material corresponding in retention time to the unalkylated ketone **2**. Although a small amount of the *trans* ketone **23** could be detected,[16] its gas chromatographic peak was not sufficiently well resolved to permit a reliable estimate of the amount of material. A sample of the *cis* ketone **24** was collected[16] and identified with the previously described sample by comparison of infrared and mass spectra. The polyalkylated material had infrared absorption (CCl$_4$) at 1710 cm^{-1} (C=O) with a molecular ion peak in the mass spectrum at *m/e* 182. The mass spectrum of this sample is similar to, but not identical with, the mass spectrum of the dialkylated product from the enamine **20** suggesting that the two samples contain differing proportions of 2,2 and 2,6 isomers. Because of the difficulties in analyzing mixtures of these methylated products, no further work was done to learn the composition of kinetically controlled mixtures of the monomethylated ketones **23** and **24**.

B. With Triethyloxonium Tetrafluoroborate.—For experiments in which the enolate anion **1** was generated from the enol acetate **3**, solutions of 2.8 mmol of methyllithium in 2.8–3.0 ml of 1,2-dimethoxyethane containing a few milligrams of triphenylmethane were prepared as previously described.[2] A weighed amount of durene was added as an internal standard and then the solutions were treated with the enol acetate **3** until the red color was almost discharged. Each enolate anion solution was treated, rapidly and with vigorous stirring, with a solution of excess triethyloxonium tetrafluoroborate in 3.5 ml of methylene chloride.[27] The resulting solutions were stirred for 2 min and then diluted with 30 ml of water containing 3 g of sodium acetate. After the organic products had been extracted with ether, the organic extracts were dried, concentrated, and analyzed by gas chromatography.[15] The gas chromatography equipment was calibrated with known mixtures prepared from pure samples. The retention times of the materials follow: durene, 12.3 min; enol ether **15**, 19.9 min; ketone **2**, 31.5 min; *cis* ketone **13**, 38.4 min; *trans* ketone **14**, 44.5 min. The results of these alkylations are summarized in Table I, the product yields being calculated based on the internal standard.

A sample of the enol ether **15** was collected[15] and identified with the previously described sample by comparison of infrared and mass spectra; a collected[15] sample of the ketone **2** was identified with an authentic sample by comparison of infrared spectra. The *cis* ketone **13**[28] was collected:[15] ir (CCl$_4$), 1715 cm^{-1} (C=O); nmr (pure liquid), δ 0.7–1.0 (12 H multiplet, superimposed signals for (CH$_3$)$_3$C– and CH$_3$C) and 1.0–2.5 (10 H, multiplet); mass spectrum, molecular ion peak at *m/e* 182, abundant fragment peaks at *m/e* 111, 83, 57, 55, 43, and 41. A sample of the *trans* ketone **14**[28] was collected:[15] ir (CCl$_4$), 1710 cm^{-1} (C=O); nmr (pure liquid), δ 0.7–1.0 (12 H multiplet, superimposed signals for (CH$_3$)$_3$C– and CH$_3$C) and 1.0–2.5 (10 H multiplet); mass spectrum, molecular ion peak at *m/e* 182, with abundant fragment peaks at *m/e* 111, 83, 57, 55, 43, and 41. To establish which of the epimeric ketones **13** and **14** was which, a solution of 60 mg of amixture of approximately equal amounts of the ketones in 2 ml of ethanol containing 10 mg of Na$_2$CO$_3$ was heated to 70° for 15 hr. The resulting ketone mixture contained[15] 82% of the *cis* isomer **13** and 18% of the *trans* isomer **14** in agreement with previous data.[5,28]

In an additional set of alkylation experiments, solutions of 1.4 mmol of triphenylmethyllithium in 1.3 ml of 1,2-dimethoxyethane were prepared from methyllithium and triphenylmethane.[2] Weighed samples of durene or tetralin (internal standards) were added. In certain cases 1 molar equiv of lithium *t*-butoxide was also generated in the reaction solution by reaction of methyllithium with *t*-butyl alcohol. Then these solutions were titrated with solutions of either the ketone **2** or a mixture of the ketone **2** and the tetradeuterio ketone **16** in 4–5 ml of 1,2-dimethoxyethane until the red color of the triphenylmethyl anion was just discharged. The resulting solutions of enolate anions were then treated with excess triethyloxonium tetrafluororate in 3.5 or 10 ml of methylene chloride. After the resulting mixtures had been stirred for 2 min, they were diluted with 30 ml of water containing 3 g of sodium acetate and then subject to the previously described isolation and analysis procedures. In the case of experiments employing mixtures of the d_0 ketone **2** and d_4 ketone **16**, samples of the *cis* ketone **13** were collected[16] and analyzed for deuterium content by mass spectrometry. Repassing these collected samples through the same gas chromatography column resulted in the loss of 5% or less of the various deuterated species present.

C. With Ethyl Iodide.—A solution of the enolate anion **1**, prepared in the usual way from 2.8 mmol of methyllithium in 2 ml of 1,2-dimethoxyethane containing a weighed sample of durene (internal standard) and 196 mg (1.00 mmol) of the enol acetate **3**, was added, dropwise and with stirring, to 1.190 g (7.6 mmol) of ethyl iodide. The resulting mixture was stirred for 5 min at 25° and then quenched in aqueous 1 *M* hydrochloric acid and extracted with pentane. The pentane solution was dried, concentrated, and analyzed[15] as previously described. The calculated yields of products were 48% of the unalkylated ketone **2**, 12%

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[25] As noted previously,[24b] the axial 2-methyl group of the *trans* ketone **23** occurs at *ca.* 0.13 ppm lower field than the equatorial 2-methyl group of the *cis* ketone **24** in deuteriochloroform solution.

[26] E. Arnal, G. Lamaty, C. Tapiero, P. F. Winternitz, J. Wylde, and R. Wylde, *Bull. Soc. Chim. Fr.*, 952 (1963).

[27] In preliminary experiments where the triethyloxonium fluoroborate was mixed with 1,2-dimethoxyethane prior to adding this alkylating agent to the solution of the enolate, substantial quantities of the *methylated* ketones **23** and **24** were produced. Evidently the known[20] exchange of alkyl groups between ethers and trialkyloxonium salts occurs very rapidly when 1,2-dimethoxyethane and this triethyloxonium salt are mixed. Unless otherwise noted, the formation of the methyl ketone by-products **23** and **24** was not a problem when a methylene chloride solution of the triethyloxonium salt was added to a solution of the enolate **1** in 1,2-dimethoxyethane.

[28] The 2-ethyl-4-*t*-butylcyclohexanone epimers **13** and **14** have been reported previously;[5] a mixture of the isomers boils at 88° (2.7 mm), n^{25}D 1.4592. Equilibration of these epimers in alcohol at 25° was reported to give a mixture containing 86% of the *cis* isomer **13** (equatorial ethyl group) and 14% of the *trans* isomer **14** (axial ethyl group); at 65°, the composition was 82% of **13** and 18% of **14**.

TABLE I

THE ALKYLATION OF THE LITHIUM ENOLATE ANION OF 4-*t*-BUTYLCYCLOHEXANONE WITH TRIETHYLOXONIUM TETRAFLUOROBORATE

		Product yields, %				Compn of monoalkylated product, %	
Compd (mmol)	$Et_3O^+ BF_4^-$, mmol	Enol ether **15**	Ketone **2**	*trans* ketone **14**	*cis* ketone **13**	*trans* **14**	*cis* **13**
3 (1.05)	7.5	17	0	28	30	48	52
3 (0.89)	7.7	18	4	26	28	48	52
3 (0.82)	7.5	12	12	26	26	50	50
2 (0.58)[a]	7.6	19	7	31	29	52	48
2 (0.82)	7.6	19	19	21	21	50	50
2 + **16** (1.25)[b,c]	7.4	*f*	*Ca.* 10	*Ca.* 24	*Ca.* 23[d]	51	48
2 + **16** (1.20)[b]	7.4	*f*	*Ca.* 27	*Ca.* 30	*Ca.* 28[e]	52	48

[a] This enolate anion solution also contained 1.22 mmol of added lithium *t*-butoxide. [b] An aliquot of a solution prepared from 386.3 mg of the nondeuterated ketone **2** and 438.5 mg of the tetradeuterio ketone **16** (6% d_3 and 94% d_4) was employed. [c] This enolate anion solution also contained 1.25 mmol of added lithium *t*-butoxide. [d] A collected sample[16] of this product contained 47% d_0, 1% d_1, 10% d_2, and 42% d_3 species. The calculated values in the absence of exchange are 47% d_0, 0% d_1, 3% d_2, and 50% d_3 species. [e] A collected sample[16] of this product contained 45% d_0, 1% d_1, 7% d_2, and 47% d_3 species. The calculated values in the absence of exchange are 47% d_0, 0% d_1, 3% d_2, and 50% d_3 species. [f] These analyses were obtained with a different gas chromatography column[16] and a different internal standard (tetralin) from the general procedure described in the Experimental Section. With this analytical procedure the enol ether was decomposed on the gas chromatography column and the reliability of the other analyses was lower. This gas chromatographic method[16] was used primarily to facilitate collection of the *cis* ketone **13** with a minimum of hydrogen–deuterium exchange.

of the *cis* ketone **13**, 14% of the *trans* ketone **14**, and 1% of one or more dialkylated products; no enol ether **15** was detected. These results correspond to a monoalkylated product mixture having the composition 54% of *trans* isomer **14** and 46% of *cis* isomer **13**. This experiment was repeated employing 2.8 mmol of methyllithium, 184 mg (0.942 mmol) of the enol acetate **3**, and 1.159 g (7.4 mmol) of ethyl iodide. However, the solution containing the enolate anion and ethyl iodide was stirred for 30 min at 25° in order to obtain more nearly complete reaction of the enolate anion. The calculated[15] yields of products were 19% of the unalkylated ketone **2**, 28% of the *cis* ketone **13**, 13% of the *trans* ketone **14**, and 5% of one or more dialkylated products. These latter results are almost certainly complicated by partial equilibration of the *cis*- and *trans*-monoalkylated ketones during this reaction. As in the previous experiment, none of the enol ether **15** was detected.[15] Collected[15] samples of the ketones **2**, **13**, and **14** were identified with the previously described samples of these materials by comparison of mass spectra. The mass spectrum of a collected[15] sample of the dialkylated product has a molecular ion peak at *m/e* 210 with abundant fragment peaks at *m/e* 111, 98, 83, 71, 69, 57, 55, 43, and 41.

Formation of the Monodeuterio Ketones 17 and 18. A. From the Enolate Anion 4.—Reaction of 3.9 mmol of methyllithium with 379 mg (1.9 mmol) of the enol acetate **3** in 4.0 ml of 1,2-dimethoxyethane yielded a solution of the enolate anion **1** which was added, dropwise and with vigorous stirring, to a solution of deuterioacetic acid in deuterium oxide (from 218 mg (2.1 mmol) of acetic anhydride and 20 ml of deuterium oxide). The ether extract of this reaction mixture was dried, concentrated, and distilled to separate 208 mg (70%) of the monodeuterated ketone **17** and/or **18**, mp 46.5–48.5°, which contained 6% d_0 species, 89% d_1 species, and 5% d_2 species. From two comparable reactions, the monodeuterated ketone **17** and/or **18** was obtained in yields of 71 and 69% and contained, respectively, 7% d_0, 85% d_1, and 8% d_2 species and 3% d_0, 94% d_1, and 3% d_2 species. The infrared spectra (CCl_4)[17] of the three samples exhibit no significant differences and have carbonyl absorption at 1715 cm^{-1} with the following bands attributable to C–D stretching vibrations:[29] 2215 (medium), 2190 (shoulder), 2150 (strong), 2140 (shoulder), and 2130 cm^{-1} (shoulder). The general pattern of the spectrum in the 2100–2250-cm^{-1} region is very similar to that observed[2b] for the 2-deuterio-*trans*-1-decalone obtained previously by quenching the corresponding enolate anion in a deuterium oxide–deuterioacetic acid mixture. The nmr spectrum of a benzene solution of the monodeuterated ketone was measured and the areas under the multiplets in the regions δ 1.47–1.98 and 1.98–2.40 were determined. These areas (average of three determinations) corresponded, respectively, to 2.3 protons and 1.7 protons (*cf.* the nmr spectra of ketones **2** and **16**) indicating that the monodeuterated sample contains approximately 70% of the axial deuterio ketone **18** and approximately 30% of the equatorial deuterio ketone **17**. The enolate anion **1**, prepared as previously described, was also quenched in more basic medium (pH 11) obtained from solution of 160 mg of Na_2CO_3 in 20 ml of deuterium oxide. However, the recovered ketone (75% yield) had substantial polydeuteration (17% d_0, 59% d_1, 20% d_2, and 4% d_3 species) in spite of the fact that the ketone was removed from the mixture by pentane extraction as rapidly as conventional manipulations would permit.

B. From the Enol Ether 15.—A solution of 435 mg (2.38 mmol) of the enol ether **15** in 4 ml of 1,2-dimethoxyethane was mixed with 2 ml of a mixture of equal weights of deuterioacetic acid (O–D) and deuterium oxide. The resulting solution was heated on a steam bath for 10 min and then cooled, diluted with excess aqueous $NaHCO_3$, and extracted with ether. The ethereal extract was dried, concentrated, and sublimed (80° at 10 mm) to separate 211 mg (58%) of the monodeuterio ketone **17** and/or **18**, mp 46–48.5°, which contained 13% d_0, 81% d_1, and 6% d_2 species. From a comparable run, the recovered ketone (56% yield) contained 12% d_0, 84% d_1, and 4% d_2 species. The infrared spectra (CCl_4)[17] of these samples differ from the spectra of the previous monodeuterated samples obtained from the enolate anion only in a slight difference in the intensity of a weak band at 1196 cm^{-1}. No difference is apparent among any of these spectra in the region 2100–2250 cm^{-1} where the C–D stretching bands occur.[29] The nmr absorption of a benzene solution of this monodeuterated sample was determined in the regions δ 1.47–1.98 and 1.98–2.40. The areas of these multiplets (two determinations) are equivalent (*i.e.*, 2 H each), suggesting that this monodeuterated sample is composed of more than 90% of the axial isomer **18** and less than 10% of the equatorial isomer **17**.

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(29) The stretching frequencies of axial and equatorial C–D bonds of cyclohexane derivatives were studied initially by (a) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956); (b) E. J. Corey, M. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, *ibid.*, **78**, 5036 (1956), and have been used subsequently by (c) S. K. Malhotra and H. J. Ringold, *ibid.*, **85**, 1538 (1963); **86**, 1997 (1964). The general frequency differences have been summarized by (d) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N.Y., 1962, p 217, and the possibilities of using these frequency differences for analysis were recently reviewed by (e) E. L. Eliel, *Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965). Although the generalization has been made that equatorial C–D bonds will usually have stretching frequencies at higher frequencies (2150–2180 cm^{-1}) than the stretching frequencies (2115–2155 cm^{-1}) of axial C–D bonds, the ranges of these frequencies often overlap and the positions are altered by structural changes in the molecule being studied. Furthermore, whenever the C–D bond is part of a >CHD grouping, at least two C–D stretching bands (symmetric and antisymmetric) are to be expected. Thus, the assignment of observed infrared bands to either axial or equatorial C–D stretching in the absence of other data (such as authentic samples of *both pure monodeuterated* compounds) is most hazardous. For purposes of analysis, the further problem arises that any assumption that the extinctions of equatorial and axial C–D stretching vibrations will be equal is very apt to be erroneous requiring again that *both pure monodeuterated* compounds be available if gross errors in composition estimates are to be avoided. This point is clearly illustrated by the published[29a] spectra of two stereoisomeric monodeuterio ketones and has been discussed in more general terms in ref 29e. For at least the cases studied here the infrared absorption of the axial monodeuterio ketone **18** appeared to be very insensitive to the presence of substantial amounts of equatorial isomer **17** present as an impurity. Therefore, we have concluded that the infrared data would not provide us with a reliable method for estimating the composition of mixtures of monodeuterated ketones **17** and **18**.

C. From the Enamine 20.[30]—A solution prepared from 1.25 g (8.0 mmol) of freshly distilled $POCl_3$ and 10 ml of deuterium oxide was cooled to 0°, covered with 5 ml of pentane, and then 1.03 g (5.0 mmol) of the enamine **20** was added dropwise with stirring. A precipitate formed in the aqueous layer and then redissolved over a 5-min period. After the mixture had been stirred for 20 min, the pentane layer was separated and the aqueous layer was extracted with two additional portions of pentane. Concentration of the combined pentane extracts left only 5 mg of residue which was not investigated further. The remaining aqueous phase was diluted with 300 ml of water (not deuterium oxide) and then stirred with 150 ml of pentane for 15 hr. This pentane layer was separated, combined with two additional pentane extracts of the aqueous layer, dried, and concentrated. Sublimation of the residual solid afforded 453 mg (59%) of the monodeuterated ketone **17** and/or **18**, mp 46.5–48°, which contained 3% d_0, 87% d_1, 8% d_2, and 2% d_3 species. The infrared spectrum (CCl_4)[17] of the sample closely resembles the spectra for the monodeuterated products from the enolate anion **1** and the enol ether **15** except that the band at 2215 cm^{-1} is more intense and the band at 1196 cm^{-1} is less intense. These differences could be attributable to the differing amounts of d_0 and d_2 species in these various samples. The nmr spectrum of a benzene solution of this sample has equivalent areas (*i.e.*, 2 H each) under the multiplets in the regions δ 1.47–1.98 and 1.98–2.40, suggesting that the sample is composed of more than 90% of the axial isomer **18** and less than 10% of the equatorial isomer **17**.

A variety of attempts was made to perform the hydrolysis of the enamine **20** at the level of acidity (pH < 1) originally specified.[12] However, we invariably found that the product remained in the aqueous phase (presumably as the immonium salt) even after the aqueous layer had been stirred with pentane for periods of 24 hr. A mixture prepared from 50 ml of 0.1 *M* deuterium chloride in deuterium oxide (pH ~ 1), 100 ml of pentane, and 200 mg of the enamine was stirred at 25° for 24 hr (only 5 mg of material was in the pentane after 5 min). This pentane extract was dried, concentrated, and sublimed to separate 43 mg (29%) of partially deuterated ketone, mp 46–48°, which contained 2% d_0, 76% d_1, 18% d_2, 3% d_3, and 1% d_4 species. To examine the effect of using a less acidic aqueous solution, a solution of 400 mg (1.9 mmol) of the enamine in 100 ml of pentane was shaken with a mixture of 1 ml of deuterioacetic acid (O–D) and 9 ml of deuterium oxide (pH ~ 4) for 1 min and then the organic layer was separated, dried, and concentrated. Sublimation (80° at 10 mm) afforded 232 mg (58%) of the partially deuterated ketone, mp 46–48°, which contained 8% d_0, 17% d_1, 24% d_2, 28% d_3, and 23% d_4 species. Thus, it would appear that a deuterium oxide solution buffered to a pH in the range <4 and >1 would be optimum for hydrolysis at a reasonably rapid rate with a minimum of hydrogen–deuterium exchange in the immonium salt. However, in our opinion the hydrolysis of the enol ether **15** provides a simpler preparation for the monodeuterated ketone **18**.

Preparation of the Enol Acetate 22.—A mixture of 1.823 g (10 mmol) of the ketones **13** and **14** (mixture of stereoisomers), 10.25 g (100 mmol) of acetic anhydride, 30 ml of carbon tetrachloride, and 0.05 ml of aqueous 70% perchloric acid was stirred at room temperature for 1 hr. The reaction mixture was extracted with ether, washed repeatedly with aqueous sodium carbonate, and then dried, concentrated, and distilled. The enol acetate **22** was collected as 1.831 g (82%) of colorless liquid fractions: bp 108–115° (10 mm); $n^{27}\mathrm{D}$ 1.4665–1.4678; ir (CCl_4), 1750 (enol ester C=O) and 1695 cm^{-1} (enol ester C=C); uv (EtOH), end absorption, 210 mμ (ϵ 2340); nmr (CCl_4), δ 2.02 (3 H singlet, CH_3CO), 0.87 (9 H singlet, $(CH_3)_3C$), and 0.7–2.2 (12 H multiplet, aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 224, relatively abundant fragment peaks at *m/e* 182 (M − $CH_2{=}C{=}O$), 125, 98, 82, 57, 55, 43, and 41. The sample exhibited a single gas chromatographic peak[31] accompanied in the earlier distillation fractions by 1–2% of the starting ketone **2**.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.90; H, 10.79.

Protonation of the Enolate Anion 21.—The reaction of 207.8 mg (0.928 mmol) of the enol acetate **22** with 2.0 mmol of methyllithium in 3.0 ml of 1,2-dimethoxyethane was conducted in the usual way to give a solution of the enolate anion **21** containing a slight excess of methyllithium (the red color of the triphenylmethyl carbanion was still present). The solution, which also contained a weighed amount of durene as an internal standard, was added, dropwise and with vigorous stirring, to a solution prepared from 166.5 mg of acetic anhydride (corresponding to 3.3 mmol of acetic acid) and 1.001 g (10 mmol) of sodium acetate in 10.0 ml of water. The resulting solution (pH 5–6) was stirred for 10 min and then extracted with either ether or pentane. After the organic extract had been washed with aqueous $NaHCO_3$, dried, and concentrated, it was analyzed on a gas chromatograph[15] which had been previously calibrated with known mixtures of authentic samples. The composition[15] of the recovered ketone (average value from two runs) was 78% of the *cis* isomer **13** and 22% of the *trans* isomer **14**. Corresponding experiments were performed in which 1,2-dimethoxyethane solutions of the enolate anion **21** were quenched in deuterium oxide containing acetic acid-d_1 and sodium acetate. The recovered ketone contained[15] (average of two runs) 80% of the *cis* isomer **13** and 20% of the *trans* isomer **14**. A collected[15] sample of the ketone (mixture of **13** and **14**) was analyzed for deuterium content by mass spectrometry and found to contain 16% d_0 species, 80% d_1 species, and 4% d_2 species. Control experiments indicated about 5% loss of deuterium d_3 species when trideuterated 2-ethyl-4-*t*-butylcyclohexanone was passed through the column[15] used for collection and analysis. The absence of d_3 species and substantial amounts of d_2 species in these experiments indicates the absence of extensive equilibration after the enolate anion **21** had been protonated at carbon and indicates that the composition of ketones derived from this protonation process is *ca.* 80% of the *cis* ketone **13** (axial C-2 proton) and *ca.* 20% of the *trans* ketone **14** (equatorial C-2 proton).

Registry No.—**2,** 98-53-3; **3,** 7360-39-6; **15,** 3393-97-3; **16,** 15649-46-4; **20,** 4147-00-6; **22,** 15649-48-6; **23,** 15649-49-7; **24,** 15649-50-0.

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[30] (a) The hydrolysis of the morpholine enamine (corresponding to **20**) in a medium prepared from deuterium oxide and phosphorus oxychloride has been reported previously (ref 12). We are grateful to Dr. Schaefer for providing us with their exact experimental procedures. (b) The hydrolysis of the pyrrolidine enamine of 2-methylcyclohexanone in a deuterioacetic acid–deuterium oxide mixture was found to be complete within 5 min and to give a mixture of 7% d_0, 57% d_1, 34% d_2, and 2% d_3 species: S. K. Malhotra and F. Johnson, *Tetrahedron Lett.*, 4027 (1965).

[31] A gas chromatography column packed with LAC-728 (diethylene glycol succinate) suspended on Chromosorb P was employed for this analysis.