Grignard Reagent from 2-Chlorobicyclo[2.1.1]hexane.—Sublimed magnesium (0.156 g, 6.5 mg-atoms) was placed in a dried flask with a sealed condenser and flamed out under nitrogen. To this was added 0.69 g (5.9 mmol) of 2-chlorobicyclo[2.1.1]-hexane in 4 ml of ether (distilled from lithium aluminum hydride). About 0.01 g of methyl iodide was used to initiate formation of the Grignard, and reflux was continued for 3 hr. Most of the reagent was transferred by syringe to two ampoules and an nmr tube and sealed under nitrogen, and the remaining reagent was hydrolyzed with water. Gas chromatography (column A) showed one hydrocarbon component comprising at least 99.5% of the total, which was isolated by preparative chromatography: ir (gas) 2930 (vs), 1460, 1292, 1203, 1123, 1078, 1018, 898, 829 cm^{-1}; nmr identical with reported spectra of bicyclo[2.1.1]-hexane.[9,40]

The sealed tubes were heated for 18 hr at 90°, opened, hydrolyzed, and analyzed in a similar fashion. The major component (~95%) was isolated by preparative gas chromatography: ir identical with the published spectrum[41] of 4-methylcyclopentene; nmr (CCl_4) δ 1.10 (d, 3, CH_3), 1.95 (m, 2) 2.45 (m, 3), 5.58 (s, 2, olefinic).

α-Cyclobutylethyl chloride was prepared by adding α-cyclobutylethanol (5.0 g, 0.050 mol) to a solution of preformed triphenylphosphine dichloride[42] (0.055 mol) in dry dimethylformamide (50 ml) at 35–40°. Work-up as in previous halide preparations gave a 25% yield of chloride: bp 127–128°; $n^{23}D$ 1.4408 (lit.[3] bp 122–127.5°); ir (neat) 2970 (vs), 2860 (m), 1450 (s), 1380 (m), 1252 (s,) 1050 (m), 670 cm^{-1}; nmr (neat) δ 1.34 (d, 3, J = 6.6 Hz), 3.87 (m, 1, coupling constants of 6.6 Hz to three hydrogens and 7.6 Hz to a lone hydrogen, CHCl). A small amount (*ca.* 11%) of isomeric impurity was probably responsible for a broad absorption at δ 4.24. Gas chromatography showed two components (about 12%) in addition to the major product. In a previous sysnthesis using thionyl chloride, about 56% of the product consisted of rearranged isomers with a cyclopentane ring.[3]

α-Cyclobutylethyl Bromide.—Bromine (12.95 g, 0.08 mol) was added to a stirred solution of α-cyclobutylethanol (8.0 g, 0.080 mol) and triphenylphosphine (22.0 g, 0.084 mol) in dry dimethylformamide (50 ml) at 55°. Work-up as in the case of α-cyclobutylethyl chloride gave the product bromide (5.2 g, 40%): bp 62–64° (30 mm); $n^{27}D$ 1.4730; ir (neat) 1380 (s), 1240 (s), 1181 (s), 1161 (s), 1040 (m) cm^{-1}; nmr (neat) δ 1.54 (d, 3, J = 6.7 Hz), 1.84 (m, 7), 4.00 (doublet of quartets, 1, J = 8.0, 6.7 Hz, CHBr). In addition, three broad resonances at *ca.* δ 3.50, 3.65, and 4.40 from isomeric impurities amounted to about 0.1 proton. Gas chromatography showed three minor components in addition to the major product.

Anal. Calcd for $C_6H_{11}Br$: C, 44.19; H, 6.80. Found: C, 44.17; H, 6.94.

Grignard reagents from α-cyclobutylethyl bromide and chloride were prepared in ether in a manner similar to that described for previous Grignard preparations. Immediate hydrolysis of the Grignard reagent from the chloride produced a mixture of hydrocarbons consisting of 68% ethylcyclobutane, 19% 2-hexene (almost exclusively *cis*), and 13% methylcyclopentane. After the mixture was heated, hydrolysis of the Grignard reagent yielded hydrocarbon mixtures with an equal mixture of *cis*- and *trans*-2-hexenes increasing at the expense of the ethylcyclobutane. The methylcyclopentane remained as a constant fraction of the total. Similar results were obtained from the bromide.

Registry No.—**2a**, 20826-69-1; **2b**, 20826-70-4; **3a**, 20826-71-5; **3b**, 20826-72-6; **4a**, 20826-95-3; **4b**, 20826-96-4; **5a**, 20826-97-5; **5b**, 20826-98-6; **13**, 20858-75-7; **14**, 20826-99-7; **16**, 20827-00-3; **19** (X = Cl), 20827-01-4; **19** (X = Br), 20827-02-5; **20** (X = Cl), 20858-76-8; **20** (X = Br), 20827-03-6; **22** (X = Cl), 20827-04-7; cyclobutylethyl-2-magnesium chloride, 20858-77-9; cyclobutylethyl-2-magnesium bromide, 20826-73-7; 5,5-dimethylbicyclo[2.1.1]hexane, 20826-74-8; α-cyclobutylethyl bromide, 20826-75-9.

(40) R. Srinivasan, *J. Amer. Chem. Soc.*, **83**, 4923 (1961).

(41) K. Kochloefl, V. Bazant, and F. Šorm, *Collect. Czech. Chem. Commun.*, **22**, 1895 (1957).

(42) D. G. Coe, R. S. Landauer, and H. W. Rydon, *J. Chem. Soc.*, 2281 (1954).

The Stereochemistry of Methylation of Lithium Enolates of 2-Methyl-4-*t*-butylcyclohexanone[1a]

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The reaction of the lithium enolate of 4-*t*-butylcyclohexanone and the three lithium enolates derived from *cis*- and *trans*-2-methyl-4-*t*-butylcyclohexanone with methyl iodide or methyl-d_3 iodide in 1,2-dimethoxyethane has been investigated. In all cases, mixtures of stereoisomeric methylation products were obtained. The results have been interpreted by considering that the geometry of the transition state for the alkylation reaction closely resembles the reactants.

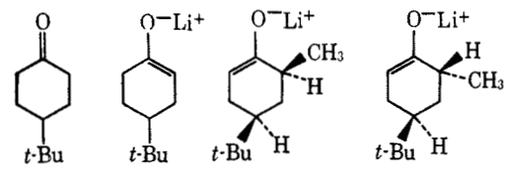
Alkylation reactions of a number of systems involving trapping of specific lithium enolates of unsymmetrical ketones have demonstrated that these species, in contrast to other alkali metal enolates, undergo slow proton-transfer reactions with derived alkylation products.[2] This unique property makes lithium enolates particularly valuable in studies on the stereochemistry of alkylation of simple enolate systems, since kinetically formed alkylation products having epimerizable centers α to the carbonyl group should be isolable under appropriate conditions.

We have studied the stereochemistry of methylation of the lithium enolate **2** derived from 4-*t*-butycyclohexanone (**1**). In addition, we have determined the stereochemistry of methylation of the enolates **3**, **4**, and **5**, derived from *cis*- and *trans*-2-methyl-4-*t*-butylcyclohexanone, **6** and **7**, respectively, by treating enolate mixtures composed largely of each of these species with methyl iodide or methyl-d_3 iodide in 1,2-dimethoxyethane (DME). Enolate **2** was formed by titration of a solution of trityl lithium in DME at room temperature with **1** until the equivalence point was reached, and then excess methyl iodide was added rapidly. Vpc

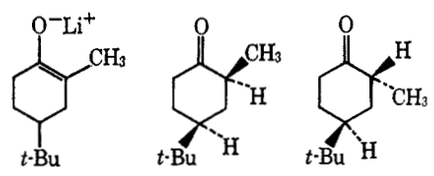
(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This work was presented in part at the Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967. (b) Abstracted in part from the Ph.D. Dissertation of B. J. L. Huff, Georgia Institute of Institute of Technology, May 1968. (c) NASA Fellow, 1965–1967. (d) NDEA Fellow, 1966–present.

(2) (a) G. Stork, P. Rosen, and N. L. Goldman, *J. Amer. Chem. Soc.*, **83**, 2965 (1961); G. Stork, P. Rosen, N. L. Goldman, R. V. Coombs, and J. Tsuji, *ibid.*, **87**, 275 (1965); (b) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965); (c) D. Caine, *ibid.*, **29**, 1868 (1964); (d) D. Caine B. J. L. Huff, *Tetrahedron Lett.*, 4695 (1966).

analysis[3] of the alkylation mixture showed that **6** and **7** were produced in a 55:45 ratio. These alkylation results are in complete agreement with those of House and coworkers,[4] who treated **2** with excess triethyloxonium tetrafluoroborate in methylene chloride and excess ethyl iodide in DME using a short reaction period. Thus, in methylations and ethylations of **2**, the C-2 alkyl group is introduced *cis* and *trans* to the *t*-butyl group with about equal facility.



1 **2** **3** **4**



5 **6** **7**

Before undertaking alkylation of the 2-methyl-4-*t*-butylcyclohexanone enolates, the composition of kinetic and equilibrium lithium enolate mixtures obtained by treating *cis*-2-methyl-4-*t*-butylcyclohexanone[5a] (**6**) and mixtures of *cis*- and *trans*-2-methyl-4-*t*-butylcyclohexanone containing largely the *trans* isomer[6] (**7**) with tritylllithium in DME at room temperature were determined by the acetic anhydride quenching method.[7] The kinetic runs involved addition of a DME solution of the ketone to excess tritylllithium in DME, while under equilibrium conditions an excess of the ketone was employed and the enolate solution was heated at reflux for 3 hr. The results are recorded in Table I. As expected, the ratios of the less to the more substituted enolates obtained by treating **6** with tritylllithium in DME were similar to those reported earlier for 2-methylcyclohexanone.[2d] For both ketones, there is a 6–7 to 1 preference for proton removal from the less substituted 6 position by tritylllithium in DME at room temperature. The exclusive conversion of **7** into **4** under kinetic conditions apparently results from the usual kinetic preference coupled with the importance of stereoelectronic control in the enolization process.[8,9]

(3) A 10 ft × 0.25 in. column containing 15% 4-methyl-4-nitropimelonitrile on 60/80 firebrick that had been acid washed and neutralized was employed for the analysis.

(4) H. O. House, B. A. Tefertiller, and H. O. Olmstead, *J. Org. Chem.*, **33**, 935 (1968).

(5) (a) Actually, the equilibrium mixture of **6** and **7**, which contains about 6% **7**, was employed.[5b] It was felt that the presence of this small amount of **7** in the mixture would not significantly influence the enolate composition and alkylation data. (b) N. L. Allinger, *et al.*, *J. Amer. Chem. Soc.*, **88**, 2999 (1966).

(6) The mixture was prepared by kinetic hydrolysis of the enamine prepared from **6** and pyrrolidine; see S. K. Malhotra and F. Johnson, *Tetrahedron Lett.*, 4027 (1965); F. Johnson and A. Whitehead, *ibid.*, 3825 (1964). We wish to thank Dr. Malhotra for making the experimental details for the hydrolysis procedure available to us.

(7) (a) H. J. Ringold and S. K. Malhotra, *J. Amer. Chem. Soc.*, **84**, 3402 (1962); (b) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

(8) Under kinetic conditions, **6** is converted into a 70:30 mixture of enolates analogous to **3** and **5** using trityl potassium in DME. This base is thus less selective than tritylllithium in forming the less substituted metal enolate. However, it was observed that tritylpotassium as well as trityl lithium converts **7** exclusively into the $\Delta^{1,6}$-enolate.

(9) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 151 ff.

TABLE I

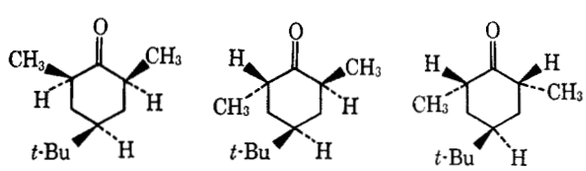
COMPOSITION OF THERMODYNAMIC AND KINETIC MIXTURES OF LITHIUM ENOLATES OF *cis*- AND *trans*-2-METHYL-4-*t*-BUTYLCYCLOHEXANONE GENERATED WITH TRITYLLITHIUM IN DME[a]

Ketone	Conditions	Enolate composition, % $\Delta^{1,6}$	$\Delta^{1,2}$
6[b]	Kinetic	86[c]	14[c]
6[b]	Thermodynamic	11[c]	89[c]
23% **6** + 77% **7**[d]	Kinetic	97 (20% **3**, 77% **4**)[e]	3

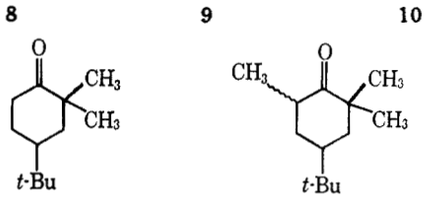
[a] The enolate compositions were determined by the acetic anhydride quenching method (ref 7); see the Experimental Section for details. [b] The presence of *ca.* 6% **7** along with **6** was neglected. [c] Percentages are averages of two or more runs. [d] Average of two runs using 25:75 and 20:80 mixtures of **6** and **7**. [e] Spectroscopic evidence indicated that ketone **7** is converted exclusively into the $\Delta^{1,6}$-enolate with tritylllithium in DME (see Experimental Section).

As with other cyclic ketones, the more substituted lithium enolate is the more stable and enolate mixtures containing mainly **5** were produced under thermodynamic conditions.[2b-d]

For the methylation runs, solutions of the kinetic and equilibrium lithium enolate mixtures derived from **6** and **7** were prepared as described for the acetic anhydride quenching experiments and then treated with excess methyl iodide at room temperature. The relative amounts of starting ketones, the four possible monoalkylation products **8**, **9**, **10**, **11**, and the dialkylation product **12**, were determined by vpc[3] and are recorded in Table II. Each of the alkylation products, with the exception of **10**, was isolated by preparative vpc[3] and exhibited nmr and mass spectral properties consistent with its structure. The structure of **10** was assigned on the basis of its behavior on vpc and by the fact that refluxing the methylation product mixture containing **10** with 10% hydrochloric acid gave the equilibrium mixture of 2,6-dimethyl-4-*t*-butylcyclohexanones (85% **8** and 15% **9** by vpc[3]) and **11** and **12** only. This 85:15 *cis*/*trans* ratio corresponds closely to that reported by Conia and Briet[10] for several 2-alkyl-6-methyl-4-*t*-butylcyclohexanones.



8 **9** **10**



11 **12**

The data in Table II allow the determination of the stereochemistry of methylation of the enolates **3** and **4**. In the methylation of **3**, the products derived from the introduction of the new group *cis* and *trans* to the *t*-butyl group, *i.e.*, **8** and **9**, respectively, were formed in a ratio of 1:1.8. Only a small amount of the dimethyla-

(10) J. M. Conia and P. Briet, *Bull. Soc. Chim. Fr.*, 3881, 3888 (1966).

TABLE II

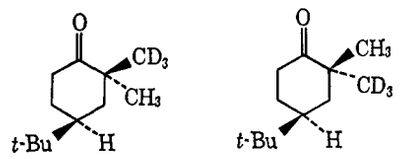
PRODUCTS OF REACTION OF LITHIUM ENOLATE MIXTURES DERIVED FROM *cis*- AND *trans*-2-METHYL-4-*t*-BUTYLCYCLOHEXANONE WITH METHYL IODIDE IN DME[a]

Enolate mixture	Composition of ketone mixtures, %[a] 6	7	8	9	10	11	12
86% 3, 14% 5	..	..	28	52	..	14	6
11% 3, 89% 5	26[b]	2[b]	5	..	..	53	13
20% 3, 77% 4, 3% 5	..	..	9	55	19	3	14

[a] See Experimental Section. [b] Excess ketone (25%) employed for equilibration of the enolates.

tion product **12** was produced in this run; thus, dialkylation did not significantly influence the **8** to **9** ratio. To establish that the ratio of **8** to **9** represented the kinetic product ratio, an experiment similar to that described by House and coworkers[4] was employed in order to demonstrate that equilibration between these ketones was insignificant during reaction and work-up. A mixture containing equal amounts of **6** and its 2,6,6-trideuterio derivative was treated under kinetic conditions with tritylllithium in DME. The mixture was alkylated with methyl iodide as described above, and then worked up in the usual way. The mass spectrum of the dialkylation products revealed the presence of d_0 and d_2 species, but no significant amount of d_1 species. Since all of the alkylation experiments reported herein were conducted under the same conditions as above, significant equilibration among kinetic alkylation products in any of the runs is unlikely. In the alkylation of **4**, after correcting for the presence of **3** (see Table II) in the enolate mixture, the ratio of **9** (new methyl group *cis* to the *t*-butyl group) to **10** (new methyl group *trans* to the *t*-butyl group) is *ca.* 2:1. The dimethylation product **12** accounted for about 14% of the alkylation mixture in this case. Ketones **8** and **9**, having axial hydrogen atoms α to the carbonyl group, should be more readily converted to their enolate anions[7b] than **10**, so that the **9** to **10** ratio may actually be slightly larger than 2:1.

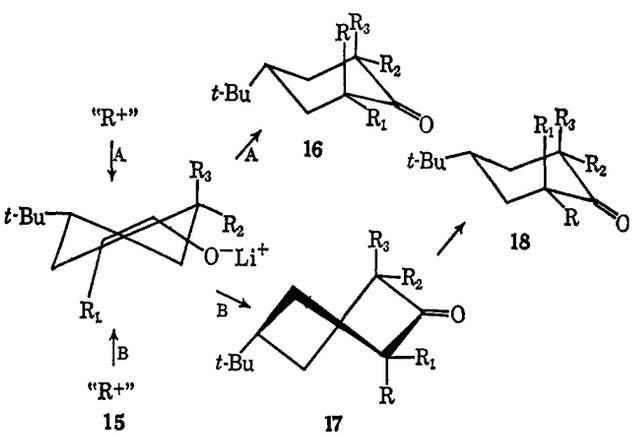
Reaction of the enolate mixture composed largely of **5** with methyl-d_3 iodide gave a mixture of 2-methyl-2-methyl-d_3-4-*t*-butylcyclohexanones, *i.e.*, **13** and **14**, which was isolated by preparative vpc.[3] Ketone **11** exhibits low ($\delta^{CCl_4}_{TMS}$ 1.13 ppm) and high field ($\delta^{CCl_4}_{TMS}$ 1.00 ppm) singlets in carbon tetrachloride solution, and these absorptions are moved upfield and downfield, respectively, when the solvent is changed to benzene.[10] This solvent shift behavior is characteristic of axial and equatorial methyl substituents.[11] The methyl absorptions of ketones **7** and **6** occur at low and high field, respectively, in deuteriochloroform[12] and carbon tetrachloride solution, and each of these absorptions show solvent shifts similar to those of **11** in benzene solution. Assuming a chair conformation for the ring in **11**, it appears that the 1.13-ppm absorption can be assigned to the axial C-2 methyl group *trans* to the *t*-butyl group and the 1.00-ppm absorption to the equatorial C-2 methyl group *cis* to the *t*-butyl group. Integration of the methyl region of the nmr spectrum of the mixture of **13** and **14** showed that the ratio of the low to high field singlets was 3:7. Thus, we have tentatively concluded that **14** is the major product of trideuteriomethylation of **5**.



13 **14**

Conia and Briet[10] have carried out alkylations of the sodium enolate analogous to **5** and related species derived from several 2-alkyl-4-*t*-butylcyclohexanones in benzene, and, on the basis of chemical evidence, originally assigned configurations to the 2-alkyl-2-methyl products which indicated that there was a slight preference for the introduction of the new group *cis* to the *t*-butyl group.[13] However, Conia has recently pointed out that the chemical evidence for the original assignments is not unequivocal and that probably the assignments should be reversed.[14]

The above results on the methylation of the lithium enolates **2**, **3**, **4**, and **5**, those of House and coworkers[4] on the ethylation of **2**, and those of Conia and Briet[10] on the alkylation of sodium enolates analogous to **5** clearly demonstrate that there is a low degree of stereoselectively involved in these reactions. Considering the half-chair conformation **15**, energetically favorable perpendicular attack by the alkylating agent can occur from either of two directions, *i.e.*, path A or path B.[15] Path A attack would lead to the chair conformation **16** having the new group axial to the ring and *trans* to the *t*-butyl group. Path B attack would lead initially to the twist-boat conformation **17** which could undergo conformational change to the chair form **18** having the new group equatorial to the ring and *cis* to the *t*-butyl group.



a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = H$; $R_3 = CH_3$
c, $R_1 = R_3 = H$; $R_2 = CH_3$
d, $R_1 = CH_3$, $R_2 = R_3 = H$

(11) M. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., Calif., 1964, p 159 ff.

(12) F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965).

(13) Apparently, the nature of the metal cation and solvent does not materially influence the alkylation stereochemistry in this system, as we obtained essentially the same ratio of products as that reported by Conia and Briet[10] on reaction of **5** with isobutyl iodide in DME.

(14) J. M. Conia, personal communication.

(15) See L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965), and references therein.

As pointed out by House and coworkers,[4] it has been generally assumed that chair-axial attack (path A) would be the more favorable reaction pathway, so that a predominance of products such as **16** would be predicted. However, such an argument requires that the formation of the new C–C bond be relatively far advanced in the transition state for the alkylation reaction.[16]

Our recent finding on the rates of alkylation of alkali metal enolates of 2,2- and 2,6-dimethylcyclohexanone appeared to be best interpreted by considering that the transition state for the enolate alkylation reaction has a geometry close to that of the reactants.[17] This interpretation has also been invoked by House and coworkers[4] and appears to provide the best explanation for the stereochemical results of the alkylation of the enolates of 4-*t*-butylcyclohexanone and derivatives as well as other systems.[4,10,18] This would mean that steric factors within the metal enolate would be the major factor controlling the stereochemistry of the alkylation reaction. The 1:1 product ratio in the alkylation of **2** suggests that the steric interactions involved for either mode of attack on the enolate **15a** (**2**) are about equal. For both **3** and **4**, attack from the side of the enolate opposite to the C-6 methyl group is favored by about 2:1. Considering enolate **15b** (**4**), the 1,3 interaction between the quasiaxial C-6 methyl group and the approaching alkylating agent that would be involved in path A attack is apparent from models. In **15c**, the quasiequatorial methyl group at C-6 does not appear to offer significant hindrance to approach of the alkylating agent from the same side of the enolate anion. However, in this species there is a sizable solvent shell–quasiequatorial methyl group interaction[19] which could be relieved to some extent if the enolate undergoes a change in conformation toward the half-boat form. Such a change would bring the C-6 methyl group into a position in which it could exert hindrance to the approach of the alkylating agent *via* path B.

The apparent slight preference for path A attack in alkylation of **15d** (**5**) as compared with **15a** (**2**) is difficult to explain. This suggests that the transition state for alkylation may have somewhat more product character in the former case. As enolate mixture composition studies on cyclohexanone derivatives show, more substituted lithium enolates are more stable than less substituted ones, and **5** should be of lower energy than **2**. Thus, a lower degree of reactivity for **5** with resultant increase in the extent of bonding in the alkylation reaction transition state might be expected. Another possibility is that the transition state for alkylation of **5**, being more sterically hindered than that for **2**, requires closer approach of the alkylating agent. In that case, steric factors within the developing product would play a more important role than in alkylation of the unsubstituted enolate.

The arguments above are probably an oversimplification, since they are not based upon knowledge of the full details of the alkylation reaction mechanism. Kinetic studies on the alkylation of **3** and **5** show that the reaction is first order in metal enolate.[20] This appears to rule out the possibility that the free enolate anion is the reactive species, but it does not establish whether monomeric ion pairs or some higher aggregates are involved in the reaction. If aggregates are involved, the actual structures of these species would be expected to have some bearing on the stereochemistry of the reaction.

Experimental Section[21]

***cis*-2-Methyl-4-*t*-butylcyclohexanone** (**6**).—This compound was prepared by the method of Conia and Briet[10] in 23% yield from 4-*t*-butylcyclohexanone. Vpc analysis[3] indicated that a mixture composed of 94% **6** and 6% **7** was obtained. The nmr spectral properties of **6** were identical with those reported.[10]

The trideuterio derivative of **6** was prepared by refluxing the ketone (3.0 g) for 10 hr with 10 ml of deuterium oxide containing 0.10 g of potassium carbonate. The exchange was repeated three times using fresh batches of deuterium oxide and potassium carbonate, and, in a final exchange, 10 ml of dioxane was added along with the deuterium oxide as a cosolvent. After cooling, the mixture was added to 10 ml of deuterium oxide and extracted with three 15-ml portions of ether. The ether solution was dried over sodium sulfate, the solvent was removed under reduced pressure, and the residue was distilled to give 2.0 g of *cis*-2-methyl-4-*t*-butylcyclohexanone-d_3: bp 60–65° (0.4 mm); mass spectrum (70 eV) *m/e* (rel intensity) 171 (77), 170 (4), 115 (100), 69 (63), 57 (93). The parent ion peak ratios showed that the sample contained 5% d_2 species and 95% d_3 species.

***trans*-2-Methyl-4-*t*-butylcyclohexanone** (**7**).—A solution of 12.0 g (0.071 mol) of **6** and 12 ml of pyrrolidine (shaken with potassium hydroxide and freshly distilled prior to use) in 60 ml of dry benzene was refluxed under nitrogen for 48 hr using a Dean–Stark water separator. After removal of the solvents under reduced pressure, the mixture was distilled and yielded 10.5 g of the enamine, N-(*trans*-2-methyl-4-*t*-butylcyclohex-6-enyl)pyrrolidine, bp 79–85° (0.1 mm). To a solution of the enamine (10.5 g) in 250 ml of diglyme (refluxed over calcium hydride and freshly distilled prior to use) under nitrogen, 10.0 g of 50% aqueous acetic acid was added dropwise with stirring over 3 min. The mixture was stirred for 10 min and poured into a mixture of 250 ml of water and 250 ml of ether. After shaking, the layers were separated and the aqueous layer was extracted with four 125-ml portions of ether. The combined ethereal extracts were washed with 125 ml of water, 125 ml of saturated aqueous sodium bicarbonate, and 100 ml of brine. The ethereal solution was dried over magnesium sulfate, the solvent was removed under reduced pressure, and the residue was distilled to give 5.6 g (71%) of a mixture of **6** and **7**, bp 60–65° (0.5 mm). Vpc analysis[3] of this mixture showed that it contained 75% **7** and 25% **6**.

Preparative vpc[3] was attempted in an effort to obtain pure **7** and a sample composed of 80% **7** and 20% **6** was obtained. Further purification of a sufficient quantity of this material for subsequent experiments appeared to be impractical and mixtures of **6** and **7** were employed. However, a small sample of **7** of greater than 95% purity was collected[3] and showed nmr (CCl_4) δ 2.7–1.2 (broad absorption, 7), 1.10 (d, 3, J = 7 Hz, C-2 axial $CHCH_3$), and 0.92 ppm [s, 9, $C(CH_3)_3$]; nmr (C_6H_6) δ 1.00 (d, 3, J = 7 Hz, C-2 axial $CHCH_3$) and 0.80 ppm [s, 9, $C(CH_3)_3$].[22]

(16) Although the free-energy differences (*ca.* 3 kcal/mol) between the boat and chair forms of α-alkyl-4-*t*-butylcyclohexanones are considerably smaller than that between the chair and boat forms of cyclohexane[6b] (and perhaps are even smaller for 2,2- and 2,6-dialkyl-4-*t*-butylcyclohexanones), products such as **16** still should be significantly favored if the transition state for the alkylation reaction closely resembled the products.

(17) D. Caine and B. J. L. Huff, *Tetrahedron Lett.*, 3399 (1967).

(18) Reference 9, p 202 ff.

(19) S. K. Malhotra and F. Johnson, *J. Amer. Chem. Soc.*, **87**, 5513 (1965).

(20) B. J. L. Huff, Ph.D. Dissertation, Georgia Institute of Technology, 1968.

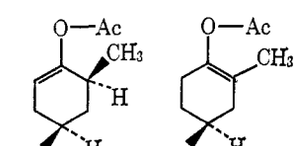
(21) Boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 137 or Model 457 infrared spectrophotometer. Nmr spectra were determined at 60 Mc with a Varian A-60 spectrometer. Mass spectra were determined using a Varian M-66 mass spectrometer. Vapor phase chromatography was performed using an Aerograph A-90-P3 with helium as the carrier gas. 1,2-Dimethoxyethane (DME) was distilled through a 6-ft column packed with glass helices and dried by reflux over lithium aluminum hydride and distillation prior to use. Methyl iodide was dried over calcium chloride and distilled prior to use. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(22) See ref 11 for the nmr spectral properties of **7** in deuteriochloroform and pyridine solution.

Determination of the Composition of Thermodynamic and Kinetic Mixtures of Lithium Enolates of *cis*- and *trans*-2-Methyl-4-*t*-butylcyclohexanone by the Acetic Anhydride Quenching Method. General Procedure.—A general procedure for preparing the lithium enolate mixtures with variations to allow for kinetic and thermodynamic control was followed. In a flame-dried apparatus, triphenylmethane was dissolved in dry DME at room temperature under nitrogen, and a solution containing approximately an equivalent amount of phenyllithium in benzene–ether was added. The red solution was stirred for 30–45 min until the disappearance of phenyllithium was indicated by a negative Gilman test.[23]

For formation of the kinetic lithium enolate mixture, 0.9 equiv of ketone (based on trityllithium) in DME was added to the solution dropwise with stirring; in all cases the red color of the trityllithium solution persisted after the addition of the ketone was complete. For the thermodynamic enolate mixture, 1.10–1.25 equiv of ketone was added dropwise with stirring and the mixture was allowed to stir for 18 hr at the ambient temperature or for 3 hr at reflux temperature to bring about enolate equilibration. The enolate solution was added dropwise with stirring under nitrogen over 15–30 min to 10 equiv of freshly distilled acetic anhydride at room temperature. The mixture was stirred for 30 min and the excess acetic anhydride was destroyed by addition of the reaction mixture to a stirred mixture of pentane and saturated aqueous sodium bicarbonate (50–75 ml of each per 0.010 mol of ketone) at 0°. The pentane solution was separated, washed with saturated aqueous sodium bicarbonate, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was distilled to yield a mixture of enol acetates.

A. *cis*-2-Methyl-4-*t*-butylcyclohexanone (6).[5] Thermodynamic Mixture.—A solution of trityllithium was prepared from 3.02 g (0.012 mol) of triphenylmethane in 50 ml of DME and 0.0080 mol of phenyllithium (2.0 *M* in 70:30 benzene–ether). After stirring for 1 hr, a solution of 1.56 g (0.0094 mol) of **6**[5] in 10 ml of DME was added dropwise with stirring and the mixture was refluxed for 3 hr. After being cooled to room temperature, the mixture was quenched with acetic anhydride as described above. Distillation gave 0.94 g of a mixture of enol acetates **19** and **20**, bp 70–75° (0.4 mm). The mixture was freed from a trace of **6** by preparative vpc.[24]

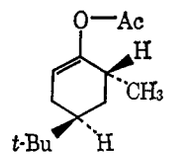


19 **20**

Although several chromatography columns were tested, we were unable to separate mixtures of isomeric enol acetates derived from **6** and **7** by vpc. However, by integration of the nmr spectrum of the above mixture, the composition was found to be *ca.* 90% **20** and *ca.* 10% **19**. An independent run gave a mixture containing 88% **20** and 12% **19**. The infrared spectrum of the mixture showed absorptions at 1750 (ester C=O) and 1710 cm^{-1} (C=C) in carbon tetrachloride. The nmr spectrum (CCl_4) of **20** was deduced from the spectrum of the mixture and was as follows: δ 2.19–1.00 (broad absorption, 7), 2.02 (s, 3, $COCH_3$), 1.47 (s, 3, C=C—CH_3), and 0.88 ppm [s, 9, $C(CH_3)_3$]. Combustion analysis of the mixture of **19** and **20** follows. *Anal.* Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.51; H, 10.70.

B. *cis*-2-Methyl-4-*t*-butylcyclohexanone (6).[5] Kinetic Mixture.—Ketone **6** [1.00 g (0.0060 mol) in 10 ml of DME] was added dropwise to a trityllithium solution derived from 2.42 g (0.0099 mol) of triphenylmethane, 50 ml of DME, and 0.0075 mol of phenyllithium (2.0 *M* in 70:30 benzene–ether). The mixture was quenched with acetic anhydride and the product was distilled to give 0.75 g (60%) of a mixture of enol acetates, bp 70–80° (0.5 mm), containing a trace of **6**. After preparative vpc,[24] nmr spectral analysis showed that the mixture contained 86% **19** and 14% **20** (average of two independent runs which agreed within 5%). The nmr spectrum (CCl_4) of **19** was deduced from the spectrum of the mixture and showed the following: δ 5.22 (m, 1, CH=C), 2.2–1.2 (broad absorption, 6), 2.01 (s, 3, $COCH_3$), 0.98 (low field peak of doublet due to $CHCH_3$), and 0.89 ppm [s, $C(CH_3)_3$ plus high field peak of doublet for $CHCH_3$].

C. Mixtures of *cis*- and *trans*-2-Methyl-4-*t*-butylcyclohexanone Containing Mainly the *trans* Isomer. Kinetic Conditions.—A solution of trityllithium was prepared from 0.484 g (0.002 mol) of triphenylmethane, 10 ml of DME, and 0.0015 mol of phenyllithium (2.0 *M* in 70:30 benzene–ether), and to this was added dropwise 0.200 g (0.0012 mol) of a mixture composed of 80% **7** and 20% **6** in 5 ml of DME. The resulting enolate mixture was quenched with acetic anhydride and after work-up the resulting enol acetate mixture was purified by preparative vpc.[24] Careful integration of the nmr spectrum of the mixture revealed that it contained no more than 3% **19** and 97% a mixture of **20** and the less substituted enol acetate of **7**, *i.e.*, **21**. A rough estimate of the percentages of **20** and **21** could be made by integration of the methyl doublet for **21** (see spectral data below) *vs.* the low-field peak of the methyl doublet for **20**, and this indicated that **21** was produced in an amount equal to the amount of **7** present in the starting ketone; *i.e.*, the mixture contained *ca.* 80% **21** and *ca.* 17% **20**. An independent run was conducted using a 25:75 mixture of **6** and **7**, and nmr spectral data indicated that a mixture of enol acetates containing 3% **19**, 22% **20**, and 75% **21** was produced. Nmr spectral studies on enol acetate mixtures resulting from other runs using ketone mixtures containing 55% **6** and 45% **7** and 40% **6** and 60% **7** also revealed that the amount of **21** formed corresponded to the amount of **7** initially present, while the sum of **19** and **20** corresponded to the amount of **6** initially present. Thus it was clear that **7** was converted essentially exclusively into **4** with trityllithium in DME under kinetic conditions.



21

The nmr spectrum (CCl_4) of **21** could be deduced from the spectrum of mixtures rich in this component and was as follows: δ 5.27 (m, 1, CH=C), 2.2–1.3 (broad absorption, 6), 2.03 (s, 3, $COCH_3$), 1.02 (d, 3, J = 6 Hz, $CHCH_3$), and 0.89 ppm [s, 9, $C(CH_3)_3$].

Methylation of the Lithium Enolate of 1 and Thermodynamic and Kinetic Mixtures of Lithium Enolates of 6 and 7. General Procedure.—The enolate solutions were prepared in a manner identical with that described above for the acetic anhydride quenching experiments. For the methylation, a sixfold excess of methyl iodide was added in one portion to the stirred enolate solution at room temperature. After stirring for 30 min, the reaction mixture was poured into a mixture of water and ether (50–75 ml of each per 0.01 mol of ketone). The ether layer was separated and the aqueous layer was saturated with sodium chloride and extracted with three 50-ml portions of ether. The combined ethereal extracts were washed with 3% hydrochloric acid (50 ml per 0.010 mol of ketone), saturated sodium bicarbonate, and brine. The ether solution was dried over sodium sulfate, the solvent was removed under reduced pressure, the residue was distilled, and the distillate was analyzed by vpc.[3]

A. Methylation of the Lithium Enolate of 1.—A solution of trityllithium was prepared as described above from 3.05 g (0.0125 mol) of triphenylmethane, 50 ml of DME, and 0.010 mol of phenyllithium (2.0 *M* in 70:30 benzene–ether). To this solution under nitrogen a solution of 1.54 g (0.010 mol) of **1** in 25 ml of DME was added with stirring. After the addition was complete, the mixture was stirred for 30 min at room temperature and 8.52 g (0.060 mol) of methyl iodide was added in one portion. After stirring for 30 min at room temperature, the reaction mixture was worked up as described above. Distillation gave 1.45 g of a mixture of ketones, bp 60–70° (1.0 mm). Vpc analysis[3] of the mixture showed that it contained 10% **1**, 41% **6**, 34% **7**, and 15% a mixture **8** and **9** (ketones **8** and **9** were identified as described below). The ratio of **6** to **7** was thus 55:45. In two other experiments performed under similar conditions, **6** to **7** ratios which agreed with this value within 5% were obtained.

(23) H. Gilman, "Organic Chemistry," Vol. I, 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1943, pp 486–500.

(24) A 5 ft × 0.25 in. column containing 20% SF-96 on Chromosorb W was employed.

B. Methylation of the Kinetic Mixture of Lithium Enolates of 6.[5]—A solution of tritylllithium was prepared from 2.73 g (0.0112 mol) of triphenylmethane, 100 ml of DME, and 0.009 mol of phenyllithium (1.8 *M* in 70:30 benzene–ether). To this solution 1.45 g (0.0080 mol) of **6**[5] in 10 ml of DME was added dropwise with stirring. After the reaction mixture was stirred for 30 min at room temperature, 8.52 g (0.060 mol) of methyl iodide was added in one portion, and the mixture was stirred for 30 min. After work-up, vpc analysis[3] of the alkylation mixture showed the following: **8** (28%), **9** (52%), **11** (14%), and **12** (6%). Distillation yielded 1.25 g of a mixture of ketones, bp 62–68° (0.4 mm), of the same composition by vpc.[3] Using this mixture, a sample of **9** was collected by vpc[3] and found to exhibit the following spectral properties: ir (CCl_4) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 2.75–1.25 (broad absorption, 7), 1.13 (d, 3, J = 7.5 Hz, axial $CHCH_3$), 0.97 (d, 3, J = 6.2 Hz, equatorial $CHCH_3$), and 0.90 ppm [s, 9, $C(CH_3)_3$]: mass spectrum (70 eV) *m/e* (rel intensity) 182 (57), 126 (77), 57 (91), and 41 (100). Exact mass calcd for $C_{12}H_{22}O$: 182.166. Found: 182.166.

The above alkylation mixture (0.80 g) was refluxed overnight with 15 ml of 10% hydrochloric acid and extracted with ether, and the ether solution was washed with aqueous sodium bicarbonate and water and dried over sodium sulfate. After removal of the solvents, the residue was analyzed by vpc[3] and found to contain 68% **8**, 12% **9**, 14% **11**, and 6% **12**.

A sample of **8** was collected from this mixture by vpc[3] and exhibited the following spectral properties: ir (CCl_4) 1715 cm^{-1} (C=O); nmr (CCl_4) δ 2.75–1.25 (broad absorption, 7), 0.96 (d, 6, J = 6 Hz, $CHCH_3$), and 0.91 ppm [s, 9, $C(CH_3)_3$]; nmr (C_6H_6) δ 2.50–1.20 (broad absorption, 7), 1.00 (d, 6, J = 6 Hz, $CHCH_3$), and 0.78 ppm [s, 9, $C(CH_3)_3$]; mass spectrum (70 eV) *m/e* (rel intensity) 182 (33), 126 (56), 57 (100), and 41 (27). Exact mass calcd for $C_{12}H_{22}O$: 182.166. Found: 182.165.

Compounds **11** and **12** were characterized as described below.

A 50:50 mixture of **6** and its 2,6,6-trideuterio derivative was converted to the kinetic lithium enolate mixture with tritylllithium, reacted with methyl iodide, and worked up in a manner identical to that described for the run with **6** alone. After distillation, a mixture of products having the same vpc[3] composition as observed above was obtained. The isomeric mixture of 2,6-dimethyl derivatives of 4-*t*-butylcyclohexanone and 4-*t*-butylcyclohexanone-d_2 was collected by vpc[3] and analyzed by mass spectrometry. Approximately equal-intensity parent-ion peaks for the d_2 and d_0 species were observed, but the presence of a significant amount of d_1 species could not be detected.

C. Methylation of the Kinetic Mixture of Lithium Enolates Derived from Mixtures of 6 and 7 Containing Mainly 7.—To a solution of tritylllithium in DME prepared from 2.73 g (0.0112 mol) of triphenylmethane, 100 ml of DME, and 0.009 mol of phenyllithium (1.8 *M* in 70:30 benzene–ether) a solution containing 1.45 g (0.008 mol) of a 25:75 mixture of **6** and **7** was added dropwise with stirring. The resulting enolate solution was stirred for 30 min, and 8.42 g (0.060 mol) of methyl iodide was added in one portion. Work-up of the reaction mixture in the usual way and distillation of the resulting ketone mixture gave 1.30 g of material, bp 60–65° (0.4 mm). Vpc analysis[3] of this mixture showed that it contained 4% **11**, 59% **9**, 11% **8**, 10% **12**, and 16% another compound having a different retention time from either of the two starting materials or any of the products. The peak for the new product appeared on the chromatogram as a well-defined shoulder on the trailing edge of the peak for **9**. When the distilled reaction mixture was refluxed overnight with 20 ml of 10% hydrochloric acid and worked up in the usual way, a mixture of products having the following composition by vpc[3] was produced: **11** (4%), **12** (10%), **8** (73%), and **9** (13%). No other volatile compounds were present. This demonstrated that the new compound was converted into the equilibrium mixture of **8** and **9**; thus it must have been the 2,6-dimethylcyclohexanone having the two methyl groups *cis* to each other and *trans* to the *t*-butyl group, *i.e.*, **10**.

A separate run was performed on one-tenth the scale used above and using a ketone mixture containing 20% **6** and 80% **7**. The ketone mixture formed in this run had the following composition by vpc:[3] 2% **11**, 7% **8**, 51% **9**, 22% **10**, and 18% **12**. The average values for these two runs are reported in Table II.

D. Methylation and Trideuteriomethylation of the Equilibrium Mixture of Lithium Enolates from 6.[5]—To a tritylllithium solution prepared from 1.52 g (0.0062 mol) of triphenylmethane, 50 ml of DME, and 0.0050 mol of phenyllithium (1.8 *M* in 70:30 benzene–ether), 0.97 g (0.0062 mol) of **6**[5] was added dropwise with stirring. After the addition, the mixture was heated at reflux for 3 hr and cooled to room temperature, and 4.2 g (0.030 mol) of methyl iodide was added in one portion. After stirring for 30 min, the mixture was worked up in the usual way and distilled to give 0.62 g of a mixture of ketones, bp 78–90° (3.5 mm), which by vpc analysis[3] showed the following composition: 26% **6**, 2% **7**, 53% **11**, 5% **8**, and 13% **12**.

Compound **11** was collected by vpc[3] and exhibited nmr spectral properties identical with those reported Conia and Briet.[10]

Compound **12** was collected and showed the following properties: nmr (CCl_4) δ 2.60–1.00 (broad absorption, *ca.* 6), 1.15 (s, 3), 1.02 (s, 3), 0.99 (d, J = 6.2 Hz, 3), and 0.91 ppm [s, 9, $C(CH_3)_3$]; mass spectrum (70 eV) *m/e* 196.

For the trideuteriomethylation, a solution of tritylllithium was prepared from 2.73 g (0.0112 mol) of triphenylmethane, 100 ml of DME, and 0.0090 mol of phenyllithium (1.8 *M* in 70:30 benzene–ether) and 1.81 g (0.010 mol) of **6**[5] was added dropwise with stirring. The solution was refluxed for 3 hr and cooled to room temperature, and 8.42 g (0.058 mol) of methyl-d_3 iodide was added in one portion. Work-up and distillation yielded 1.35 g of a mixture, bp 50–60° (0.1 mm), having the same composition by vpc[3] as that reported above. The mixture of 2-methyl-2-methyl-d_3 products **13** and **14** was collected by vpc[3] and analyzed by nmr spectroscopy. Integration of the spectrum revealed a 3:7 ratio for the singlets at δ (CCl_4) 1.13 and δ (CCl_4) 1.00 ppm. (In benzene solution the ratio of the singlets at δ (C_6H_6) 1.11 and δ (C_6H_6) 0.94 ppm was 7:3).

The mass spectrum (70 eV) of the mixture of **13** and **14** showed the following major peaks: *m/e* (rel intensity) 185 (69), 129 (88), and 57 (100).

Registry No.—**2**, 20826-82-8; **3**, 20826-60-2; **4**, 20826-61-3; **5**, 20826-83-9; **6**-d_3, 16084-13-2; methyl iodide, 74-88-4; methyl-d_3 iodide, 865-50-9; **8**, 20826-63-5; **9**, 20826-64-6; **12**, 20826-84-0; **19**, 20826-65-7; **20**, 20826-66-8; **21**, 20826-67-9.

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