Method B.—To a cold solution of 11.0 g. (0.1 mole) of I in 25.0 ml. of benzene, 14.1 g. (0.1 mole) of benzoyl chloride in 20.0 ml. of benzene was added slowly with cooling to maintain the temperature between 15° and 20°. The reaction mixture was allowed to stand at this temperature for 2 hr. and then filtered, yielding 5.8 g. of product VIII. From the filtrate, 3.8 g. of 2-pyridylmethyl benzoate was obtained by distillation (Table I).

Reaction of 2-Picoline 1-Oxide with Hydrogen Halides. Method A.—To a cold solution of 10.9 g. (0.1 mole) of 2-picoline 1-oxide (I) in 15.0 ml. of dry benzene was added 0.12 mole of hydrogen chloride in benzene. After adding 15 ml. of dry ether and cooling for 1 hr. in an ice bath, product IX was filtered (Table I). Recrystallization of this dimeric hydrochloride from ethanol yielded successively smaller amounts of material, showing progressively higher melting points, so that after three crystallizations, the product melted at 105–106° and was identical to VIII. It underwent a similar change on standing several days in a desiccator or on heating it to its melting point.

The dimeric hydrobromide, which is produced by a similar procedure with a benzene solution of hydrogen bromide, could be stored and dried at 80° without decomposing. Treatment of an ethanolic solution of all three dimeric hydrohalides with picric acid yielded the picrate of I, m.p. 125–126°.

Method B.—From a solution of 10.9 g. (0.10 mole) of 2-picoline 1-oxide (I) in 15.0 ml. of concentrated hydrochloric acid, which was taken to dryness at diminished pressure over a steam bath, the monohydrochloride (VIII) was obtained in 84.5% yield after recrystallization from acetone (Table I).

Concentrated hydrobromic acid yielded the monomeric hydrobromide (VIII) (Table I) by the same procedure.

Concentrated hydriodic acid yielded the dimeric hydriodide (IX) by this procedure (Table I). Treatment of an ethanolic solution of these hydrohalides with picric acid gave the picrate of I.

Reaction of 2-Picoline 1-Oxide with Sodium Iodide.—To (0.03 mole) of 2-picoline 1-oxide (I) in 10.0 ml. of acetone was added 4.5 g. (0.03 mole) of sodium iodide in 25.0 ml. of acetone, yielding product X (Table I). This product burned with a bright yellow flame and left a residue.

Conversion of the Monomeric Hydrochloride and Hydrobromide (VIII) to the Dimeric Hydriodide (IX).—To a solution of 0.02 mole of the monohydrohalides (VIII) in 10.0 ml. of acetone was added 0.03 mole of sodium iodide in 20.0 ml. of acetone. The solid product which separated immediately was filtered and washed with ethanol. This amounted to 1.08 g. of sodium chloride and 1.91 g. of sodium bromide. From the filtrate was obtained 3.2 g. (92.5%) of product, m.p. 145–146°, which was shown to be identical to the dimeric hydriodide (IX)—same analysis and infrared spectrum and no depression of its melting point in a mixture.

The Addition of Methyl Grignard to 4-*t*-Butylcyclohexanone

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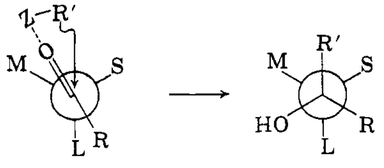
The addition of methyl Grignard to 4-*t*-butylcyclohexanone has been studied under a variety of experimental conditions. It has been found that the *cis:trans* ratio of the resultant 1-methyl-4-*t*-butylcyclohexanol is affected by the methyl halide used to form the Grignard reagent, the solvent, and the addition of magnesium halide. The magnesium source, presence of air, or cuprous halide had negligible effect on the reaction. For the reactions carried out in diethyl ether, the *cis:trans* ratios are methylmagnesium iodide—1.02, methylmagnesium bromide—1.36, dimethylmagnesium—1.40, methylmagnesium chloride—1.44, methylmagnesium bromide di(magnesium bromide)—1.84. The reaction of methylmagnesium bromide in various solvents gave anisole—1.11, diethyl ether—1.36, tetrahydrofuran—2.26. Methyllithium in diethyl ether gave a ratio of 1.86.

The addition of methyl Grignards[2] to ketones has found extensive application in the synthesis of tertiary alcohols.[3] For noncyclic ketones complexing only at the carbonyl oxygen, Cram[4] and co-workers have been able to correlate the stereochemistry of the new asymmetric center resulting from organometallic addition by use of the "open-chain" model A. Application of A has led to the prediction that the most probable mode of addition of the organometallic R′Z would be where R′ enters by the least hindered approach to give B.[5] Extension of this model to a conformationally simple cyclohexanone such as C which contains only 1,2-and 1,3-nonbonded hydrogen interactions would lead to the *a priori* prediction that the major



A B

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(1) Presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961, p. 180.

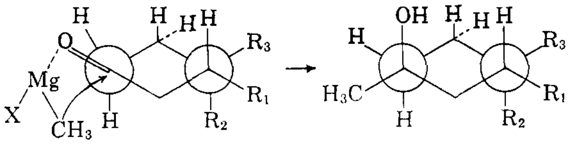
(2) The representation of the Grignard reagent as RMgX apparently is not correct, as indicated by the recent work of Dessy and Hamelin. In this paper the formula RMgX is used only for convenience or when referring to prior work where it has been applied to interpret a reaction. For recent work on the constitution of the Grignard reagent see (a) R. E. Dessy, *J. Org. Chem.*, **25**, 2260 (1960), J. H. Wotiz, R. E. Dessy, and C. A. Hollinsworth, *J. Am. Chem. Soc.*; **79**, 358 (1957); (b) A. Kirrmann and R. Hamelin, *Compt. rend.*, 2990 (1960); R. Hamelin, *Bull. soc. chim.* (France), 684, 698 (1961); and R. Hamelin and S. Hayes, *ibid.*, 692 (1961); (c) N. M. Bikales and E. I, Becker, *Chem. Ind.*, 1831 (1961); (d) M. Antenius, *J. Org. Chem.*, **26**, 4214 (1961); **27**, 596 (1962); and (e) D. O. Cowan and H. S. Mosher, *ibid.*, **27**, 1 (1962).

(3) For numerous examples see (a) "Grignard Reactions of Nonmetallic Substances," by M. S. Kharasch and O. Reinmuth, Prentice-Hall, Inc., New York, N. Y., 1954, and (b) "Handbook of Magnesium-Organic Compounds," by S. T. Yoffee and A. N. Nesmeyanov, Pergamon Press, London, 1957.

(4) For leading references see D. J. Cram and K. P. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1960).

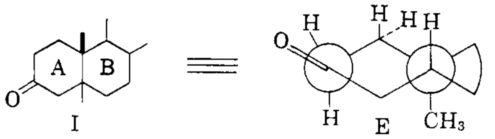
(5) For some constructive discussion on the use of this model refer to J. H. Stocker, R. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *ibid.*, **82**, 3913 (1960).

product to be expected from the reaction of C with a methyl Grignard is the axial alcohol D.

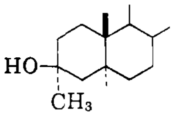


C D

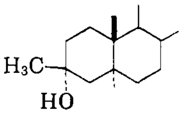
A survey of the literature disclosed that only two examples involving a cyclohexanone system of Type C and methyl Grignard have been established.[6] The first reported example is that of 3-cholestanone (I) whose simplified ring system is shown in the Newman projection. E. Barton, *et al.*,[7] have found that when I was treated with methylmagnesium iodide in diethyl ether, they obtained a 95% yield of alcohol that was found to be a 57:43 mixture of 3β-methylcholestan-3α-ol (IIa, equatorial methyl) and 3α-methylcholestan-3β-ol (IIb, axial methyl). Working independently, Beaton, *et al.*,[8] have reported that under similar conditions a quantitative yield of tertiary alcohol containing a ratio of 55.5 IIa and 45.5 IIb was obtained. During the course of this work, Cross and Whitham[9] reported that when 4-*t*-butylcyclohexanone (C; R = *t*-butyl, R_1, R_2 = H) reacted with methylmagnesium iodide in diethyl ether, a 70:30 ratio of 1-methyl-*trans*-4-*t*-butylcyclohexanol (IIIa, axial methyl) to 1-methyl-*cis*-4-*t*-butylcyclohexanol (IIIb, equatorial methyl) was formed. However, both Fevre[10] and DePuy[11] report an almost 1:1 mixture of IIIa and IIIb is formed from methylmagnesium iodide and IV.



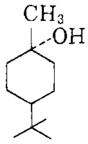
I



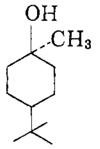
IIa



IIb



IIIa



IIIb

Since the above examples fail to agree on the isomer distribution to be expected when methylmagnesium iodide is added to an unhindered cyclohexanone of Type C, we undertook a study of the addition of various methyl Grignards to conformationally unique 4-*t*-butylcyclohexanone (IV).[12] We also have explored a variety of conditions that might affect the ratio of isomers in this reaction. The results of our findings are given below.

Results

From the reaction of 4-*t*-butylcyclohexanone with two equivalents of methylmagnesium iodide in diethyl ether, there was obtained a 97% yield of 1-methyl-4-*t*-butylcyclohexanols as a solid of m.p. 57–58°. A gas-liquid chromatograph (GLC) of this substance showed the presence of two isomers, which in order of elution amounted to 50.5% and 49.5%, respectively. Liquid chromatography on alumina afforded, in order of elution, a solid of m.p. 71° and a second solid of m.p. 97.8°. The lower melting isomer was found to correspond to the 50.5% GLC band and the higher melting substance matched the 49.5% band. The infrared spectra of the m.p. 71 and 97.8° isomers agree with those reported by Cross and Whithan[9] for the *cis* isomer IIIb and the *trans* isomer IIIa, respectively.[13]

A number of other methyl Grignard reactions were carried out on IV by varying the source of RMgX, changing solvent, and adding various inorganic salts to the reaction media. The product compositions from these reactions were determined by GLC and hydroxylamine hydrochloride analyses and are summarized in Table I.

The following general conclusions can be drawn by inspection of this table:

1. A considerable effect can be exerted on the course of methyl Grignard addition to IV as indicated by the *cis/trans* factor, which ranges from 0.95 to 2.26.
2. Comparison of experiments 2 and 3, where IV reacted with 2 and 1 molar equivalents of methylmagnesium bromide in diethyl ether, reveals that the ratio of RMgX:ketone has a slight effect on the stereochemistry.[14]
3. The replacement of X in MeMgX by chlo-

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[6] Several other reactions of methyl Grignard with a Type C system have been reported where either the yield was too low for proper interpretation or the stereochemistry was not reported. These involve (a) 4-isoprenylcyclohexanone, W. H. Perkin Jr., *J. Chem. Soc.*, **85**, 654 (1904); (b) 4-carboethoxycyclohexanone, W. H. Perkin, Jr., and F. W. Kay, *ibid.*, 372 (1907), and also R. H. Eastman and R. A. Quinn, *J. Am. Chem. Soc.*, **82**, 4249 (1960); and (c) 4-cyclopentylcyclohexanone, M. Mousseron and M. Mousseron-Canet, *Compt. rend.*, **239**, 427 (1954).

[7] D. H. R. Barton, A. da S. Campos-Naves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

[8] J. L. Beaton, T. L. Halsall, E. R. H. Jones, and P. C. Phillips, *ibid.*, 753 (1957).

[9] B. Cross and G. H. Whitham, *ibid.*, 3892 (1960).

[10] H. Fevre and D. Gravel, *Can. J. Chem.*, **39**, 1548 (1961).

[11] C. H. DePuy and R. W. King, *J. Am. Chem. Soc.*, **83**, 2743 (1961).

[12] The *t*-butyl group in IV has been shown to exist almost exclusively in the equatorial conformation and most likley is incapable of assuming an axial form. S. Winstein and N. J. Holness, *ibid.* **77**, 5562 (1955).

[13] For a more detailed discussion of the evidence for isomer assignment consult ref. 9.

[14] Several other cases have been reported where the molar ratio was found to influence the reaction. These are (a) S. J. Storfer and E. I. Becker, American Chemical Society Abstracts, 138th National Meeting, New York, N. Y., September 11–16, 1960, p. 80P, reported that when ethylmagnesium bromide reacted with phenyl cyanide only 50% of the Grignard reagent gave normal addition products; (b) H. Gilman, *J. Am. Chem. Soc.*, **62**, 1243 (1940), has also reported that two or more equivalents of phenyl Grignard are needed to complete the reaction with benzophenone and its derivatives; and (c) T. Mukai and T. Tezuka, *J. Chem. Soc. Japan*, **34**, 619 (1961), found that 2 molar equivalents of phenyl Grignard are needed (to complete the reaction) with tropone.

TABLE I

EXPERIMENTAL CONDITIONS AND PRODUCT COMPOSITION FROM THE REACTION OF 4-*t*-BUTYLCYCLOHEXANE WITH METHYL GRIGNARD REAGENTS AND METHYLLITHIUM

Experiment no.	Molarity of reactants: Organomagnesium species[a]	Molarity of reactants: Ketone	Molar ratio G/K	% Products[c]: Solvent	% Wt. yield[b]	Ketone	IIIa	IIIb	*cis/trans*
1	1.5 MeMgCl	1.88	2.0	DiEtEt	91	0.47	40.81	58.73	1.44
2	1.0 MeMgBr	1.88	2.0	DiEtEt	91	0.31	42.17	57.72	1.36
3	1.0 MeMgBr	1.88	1.0	DiEtEt	93	0.00	39.50	60.50	1.55
4	2.0 MeMgI	1.25	2.0	DiEtEt	97	0.00	49.50	50.50	1.02
5	1.0 Me_2Mg[d]	4.00	2.0	DiEtEt	91	6.80	38.77	54.43	1.40
6	1.3 MeMgBr	5.94	2.0	THF[e]	93	4.50	29.22	66.28	2.26
7	2.0 MeMgBr	4.00	2.0	Anisole[e]	98.6[f]	1.40	38.26	60.38	1.58
8	2.0 MeMgBr	5.00	2.0	Benzene[g]	92	1.42	37.66	60.92	1.62
9	1.0 MeMgI	4.00	2.0	Anisole[e]	98.0[f]	2.00	46.65	51.35	1.11
10	1.5 MeMgBr[h]	1.88	2.0	DiEtEt	93	0.15	41.94	57.91	1.38
11	1.5 MeMgBr[i]	1.88	2.0	DiEtEt	93	0.27	42.98	56.75	1.32
12	1.5 MeMgBr[j]	1.88	2.0	DiEtEt	91	0.01	34.50	65.49	1.89
13	1.5 MeMgBr[k]	1.88	2.0	DiEtEt	94	0.03	41.69	58.28	1.40
14	1.3 MeLi	4.00	2.0	DiEtEt	94	2.30	35.00	65.00	1.86

[a] The Grignard reagent was prepared from industrial magnesium turnings in an atmosphere of air unless indicated otherwise. In all experiments, except 3 and 5, 1 molar equivalent of ketone was added to 2 molar equivalents of Grignard reagent. [b] This yield was calculated with the assumption that the product contained only IIIa and IIIb. [c] The alcohols were determined by GLC, the ketone by hydroxylamine hydrochloride titration. [d] Prepared by the dioxane precipitation procedure. [e] Purified by distillation from lithium aluminum hydride. [f] Based on analysis in solution. Attempts to remove all the anisole resulted in considerable loss of products by evaporation and dehydration. [g] The reagent was prepared in diethyl ether and then the ether was displaced by an equal volume of dry benzene. [h] Sublimed magnesium obtained from Dow Chemical Co., Midland, Michigan, was used in this experiment. [i] The entire reaction was carried out in a nitrogen atmosphere. [j] The Grignard reagent was added to the ketone and 2 molar equivalents of magnesium bromide. [k] Anhydrous cuprous chloride (0.011 mole) was added to the Grignard reagent prior to the addition of ketone.

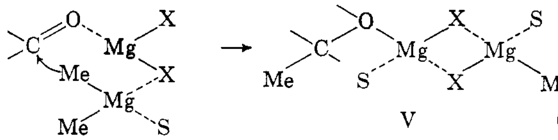
ride, bromide, and iodide (experiments 1, 2, and 4) indicate very little difference between chloride, and bromide, but a noticeable difference when iodide is used.[15] When X is methyl, experiment 5, the system behaves similarly to methylmagnesium bromide. Changing the source of magnesium used in preparing methylmagnesium bromide (experiments 2 and 10) had no effect.

4. Addition of the free radical promoter[16] cuprous chloride (experiment 13) had no effect on the stereochemistry or yield of the products. The presence or absence of air has no effect (experiments 2 and 11). The addition of magnesium bromide to methylmagnesium bromide (experiment 12) results in a change in the *cis/trans* factor.

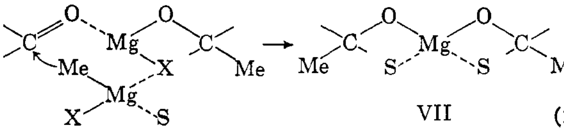
5. When the solvent is changed from diethyl ether (experiment 2) to benzene[17] (experiment 8), no noticeable effect is encountered. With tetrahydrofuran (experiment 6) a large change in the *cis/trans* factor is observed. Anisole (experiments 2 and 4 *vs.* experiments 7 and 9) appears to have little influence.

6. Methyllithium has a selectivity similar to the methylmagnesium/bromide-magnesium bromide system (experiment 14).

The extension of Cram's[4] open chain model (A and C) to the reaction of 4-*t*-butylcyclohexanone with a methyl Grignard has led to the correct isomer prediction for methylmagnesium chloride, methylmagnesium bromide, and dimethylmagnesium. The methyl iodide Grignard was an exception to Cram's rule since it gave rise to a 1:1 mixture of *cis* and *trans* isomers. In light of the present two-step Grignard addition mechanism, represented in equations 1 and 2, it is not surprising that a difference in isomer ratio was obtained when the halide component of the Grignard reagent was changed. The halogen atom undoubtedly offers a combination of inductive and steric interactions in the addition intermediates IV and VI. The direction of this effect in our system does not fit a simple pattern since the *cis:trans* ratio increased in the order I, Cl, Br, whereas the inductive effect increases I, Br, Cl, and the halogen size Cl, Br, I.



IV V (1)



VI VII (2)

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(15) That the change of X is RMgX has some influence on both the stereochemistry of addition and reduction in open-change systems has been shown by W. F. Foley, F. J. Welch, E. M. LaCombe, and H. S. Mosher, *J. Am. Chem. Soc.*, **81**, 2779 (1959), and also ref. 5.

(16) For a detailed discussion of the effect of transition metal salts on their ability to promote free radicals in the Grignard reactions see ref. 3a and M. S. Kharasch, J. W. Hancock, W. Nudenberg, and P. O. Tawney, *J. Org. Chem.*, **21**, 322 (1956).

(17) This experiment may not reflect a true "solvent effect" for benzene. Since this reagent was prepared by displacing diethyl ether with benzene after the Grignard reagent was formed, it is possible that the reagent retains tightly complexed diethyl ether molecules. The reaction of this species would then resemble the reagent found in diethyl ether alone. The results obtained (compare experiments 2, 3, and 8) strongly suggest that this is the case.

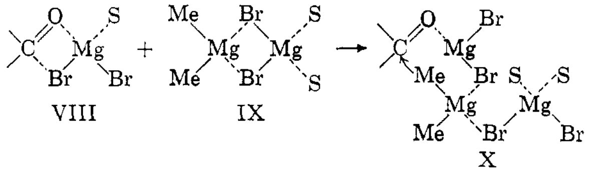
One possible explanation for this pattern may rest in the effect of solvent (S in IV and VI) participation in the addition intermediates. Depending on the strength of solvent coördination[18] with the magnesium atoms in IV and VI, the effective bulk of the incoming methyl group may be altered enough to offset a simple Cl, Br, I relation.

Evidence that the solvent[19] plays a part in determining the isomer ratio was obtained from the reaction of III and methylmagnesium bromide in three different ethers. The *cis:trans* ratio was found to increase in the order diethyl ether, anisole, tetrahydrofuran.

The change in isomer ratio produced by altering the Grignard-ketone ratio can be interperted as reflecting a change in the amount of methyl that adds by intermediate IV and VI. In the presence of excess reagent, most of the methyl probably adds by IV whereas with lower molar ratios both IV and VI determine the stereochemistry of the final products.

The isomer ratio obtained with dimethylmagnesium is interesting in that its value (1.40) is similar to those obtained from the methyl chloride (1.44) and methyl bromide (1.36) reagents. Although the dimethyl Grignard cannot form a halogen-bridged structure such as IV, it might react in a dimeric form where a methyl group serves as the bridge link[20] (IV, X = methyl). This species would have a bulk similar to the chloride and bromide reagents and account for the observed similarities in the *cis:trans* ratio.

When two equivalents of magnesium bromide were added to 4-*t*-butylcyclohexanone before it reacted with excess methylmagnesium bromide it caused a considerable increase in the stereoselectivity of the entering methyl group. Since the ketone is most likely bound in a complex like VIII the reaction with Grignard reagent (IX) may have formed an intermediate such as X. The entering methyl group from this intermediate would be expected to have a greater selectivity than that from IV since the bulk in the reaction area has been increased by a magnesium bromide molecule and one or more solvent molecules.



The reaction of methyllithium with III in diethyl ether is interesting in that this reagent has a greater selectivity (1.86) than any of the RMgX reagents (1.02–1.55). This is in contrast with the open chain ketones where it has been shown[21] that the Grignard reagent is more stereoselective than methyllithium.

Experimental[22,23]

Gas-liquid Chromatography.—All GLC analyses were carried out on a Wilkens Aerograph Model A-90 instrument equipped with a thermal conductivity detector cell and a Leeds & Northrup Speedomax Model G recorder. Helium was used as the eluent gas at a flow rate of 50 cc./min.

The columns used were (a) a 6-ft. copper tube (0.25-in. o.d.) packed with 20% by weight of sucrose acetate isobutyrate (SAIB)[24a] deposited on 60/80 mesh Chromosorb W and (b) a 6-ft. copper tube (0.25-in. o.d.) packed with 20% by weight of Hyprose[24b] deposited on 60/80 mesh Chromosorb W.

All analyses with the SAIB were carried out at 175°, those with the Hyprose column at 165°. The per cent composition of each component was calculated by the area under the peak method. Each determination was carried out in at least duplicate on different days. Agreement in all cases reported in this paper is ±2.0%.

4-*t*-Butylcyclohexanol.—A solution of commercial 4-*t*-butylphenol (75 g., 0.50 mole) and isopropyl alcohol (26 g.) was hydrogenated in the presence of dry Raney cobalt (33 g.) at *ca.* 125° and 600 p.s.i. After the hydrogen uptake had ceased (6 hr.) the catalyst was filtered off and the solvent was removed *in vacuo*. There was obtained 72 g. of solid with m.p. 62.5–64.0°. GLC analysis of this material on the SAIB column showed it to contain 24.8% *cis*-4-*t*-butylcyclohexanol (7.45 min. retention time) and 75.2% *trans*-4-*t*-butylcyclohexanol (8.65 min. retention time). The infrared spectrum of the mixture in carbon disulfide gave characteristic bands at 3.02, 7.19, 7.33, 7.48, 9.44, 10.48, and 11.17 μ.

4-*t*-Butylcyclohexanone (IV).—A stirred mixture of 4-*t*-butyl cyclohexanol (93.6 g., 0.60 mole) and water (150 ml.) was heated to *ca.* 45°. A solution of sodium dichromate (67 g., 0.25 mole), water (325 ml.), and concentrated sulfuric acid (93.6 g.) was added at such a rate that the internal temperature did not exceed 50°. The mixture was then maintained at *ca.* 50° for an additional 5 hr. The reaction mass then was steam distilled until no more organic material was carried over. The solid organic eluent was dissolved in hexane, washed with 10% sodium bicarbonate, and dried with magnesium sulfate. Removal of the solvent *in vacuo* gave 76.1 g. (81.5%) of 4-*t*-butylcyclohexanone. This material then was treated with excess semicarbazone reagent according to the procedure of Fuson and Shriner.[25] The crude semicarbazone was washed with 50% water–methanol and air dried. Simultaneous hydrolysis and steam distillation in the presence of hydrochloric acid gave 4-*t*-butylcyclohexanone, m.p. 51.8–52° (lit.,[9,10] m.p. 49–50° and 49.5–51°); carbonyl analysis by hydroxylamine hydrochloride titration[26] was 99.8%. The infrared spectrum in carbon disulfide gave characteristic bands at 5.85, 7.18, 7.33, 7.46, and 10.64 μ. GLC analyses on both SAIB and Hyprose showed only one band in both cases. An

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[18] It is assumed that the magnesium atom always has a coördination number of four.

[19] For some interesting discussion on the role of solvent in Grignard reactions see ref. 2b.

[20] Mosher (ref. 2e) has suggested recently that such a structure might account for some of his observations.

[21] D. J. Cram, F. A. Abd Elhafez, and H. L. Nyquist, *J. Am. Chem. Soc.*, **76**, 22 (1954).

[22] All melting points are uncorrected.

[23] The microanalyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

[24] (a) Obtained from Eastman Chemical Products Inc., Kingsport, Tennessee; (b) obtained from the Dow Chemical Co., Midland, Michigan.

[25] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley & Sons, Inc., New York, N. Y.

[26] Essential Oil Association of America, Scientific Section, E.O.A. No. 1, p. 3, Method I.

orange 2,4-dinitrophenylhydrazone had m.p. 152–152.5° (ethanol).

A sample of the crude semicarbazone recrystallized from ethanol had m.p. 203–205°.

Anal. Calcd. for $C_{11}H_{21}N_3O$: C, 62.52; H, 10.02; N, 19.88. Found: C, 63.09; H, 10.08; N, 19.72.

Grignard Reactions with 4-*t*-Butylcyclohexanone. A. Methyl Iodide–Diethyl Ether.—Magnesium shavings (Merck 4.85 g., 0.20 g.-atom) were added to anhydrous diethyl ether (100 ml.) and treated with methyl iodide until all the magnesium had reacted. The reagent then was cooled in an ice bath to an internal temperature of *ca.* 5°. A solution of 4-*t*-butylcyclohexanone (15.4 g., 0.10 mole) in diethyl ether (20 ml.) was added at such a rate that the internal temperature did not exceed 5°. After the addition was complete, the cooling bath was removed and the stirring was continued for an additional 2 hr.; the reaction was allowed to stand overnight at room temperature. The reaction was cooled again and treated with a saturated aqueous ammonium chloride solution until a clear separation of salts had occurred. The internal temperature was not allowed to exceed 5° during this addition. The salts were filtered off and washed with ether. The combined ether layers were dried with magnesium sulfate, filtered, and concentrated *in vacuo* on a rotatory evaporator at room temperature or lower. There was obtained 16.5 g. (97%) of 1-methyl-4-*t*-butylcyclohexanol isomers with m.p. 57–58°. A GLC analysis of this material on the SAIB column gave two bands, A (50.5%) and B (49.5%) with elution times of 5.0 and 6.2 min., respectively.

A 3.0-g. sample of the above product was dissolved in hexane and chromatographed on 150 g. of Merck chromatographic grade alumina oxide. The column was developed with hexane–benzene mixtures (100% to 100%). Elution was effected with a 50:50 benzene–ether mixture.

The first eluent was 1-methyl-*cis*-4-*t*-butylcyclohexanol (IIIb), a solid of m.p. 71°. The infrared spectrum in carbon disulfide gave characteristic bands at 2.79, 2.92, 7.19, 7.32, 9.12, 9.73, 10.10, 10.83, 11.06, and 12.13 μ. GLC analysis on the SAIB column gave one band with elution time of 5.0 min. Gas chromatography of a 50:50 mixture of this isomer and the product obtained directly from the Grignard reaction revealed that the *cis* isomer was eluted at the same time as isomer A. The literature[9,10] reports a m.p. 66–67° and 70.5–71° for the *cis* isomer.

Anal. Calcd. for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.50; H, 13.10.

The second eluent was 1-methyl-*trans*-4-*t*-butylcyclohexanol (IIIa), a solid of m.p. 97.8°. The infrared spectrum in carbon disulfide gave characteristic bands at 2.80, 3.00, 7.19, 7.33, 8.80, 9.11, 10.27, 10.98, and 11.75 μ. GLC analysis on the SAIB column gave one band with elution time of 6.2 min. Gas chromatography of a 50:50 mixture of this isomer and the product obtained directly from the Grignard reaction showed that the *trans* isomer was eluted at the same time as isomer B. The literature[8] reports a m.p. 89–90° and 97.5–98° for the *cis* isomer.

Anal. Found: C, 77.48; H, 13.11.

B. Methyl Bromide–Benzene.—The Grignard reagent was prepared from methyl bromide as indicated in procedure A. An equal volume (100 ml.) of dry benzene was added and the diethyl ether was removed by atmospheric distillation to take-off temperature of 72°. The ketone was added in a benzene solution. There was obtained a 92% yield of mixed isomers, carbonyl analysis 1.42%; GLC analysis on SAIB gave a ratio of 61.8% *cis* and 38.2% *trans.*

C. Methyl Bromide–Magnesium Bromide–Diethyl Ether.—Magnesium bromide was prepared by direct addition of bromine (24.0 g., 0.15 g.-atom) to magnesium (3.65 g., 0.15 g.-atom) in diethyl ether (200 ml.) according to the procedure of Swain.[27] The resultant two-layer mixture was cooled in an ice bath and treated with 4-*t*-butylcyclohexanone (11.55 g., 0.075 mole) in diethyl ether (50 ml.). After stirring for an additional hour the ice-cooled complex (two layers) was treated with a solution of methylmagnesium bromide (made from 3.65 g., 0.15 g.-atom magnesium) in diethyl ether (150 ml.) at such a rate that the internal temperature did not exceed 5°. One layer was obtained after completion of the Grignard addition. The reaction was worked up as in procedure A. There was obtained a 91% yield of mixed isomers, carbonyl analysis 0.01%; GLC analysis on SAIB gave a ratio of 65.5% *cis* and 35.5% *trans.*

D. Dimethylmagnesium–Diethyl Ether.—A Grignard reagent prepared by bubbling methyl bromide into diethyl ether (100 ml.) containing magnesium (4.85 g., 0.20 g.-atom) was treated with freshly purified dioxane (22.8 g., 0.26 mole) at 5°. The resultant pasty mixture was stirred for 2 hr. and then allowed to stand at room temperzture overnight. The slurry then was cooled in an ice bath to 5° and treated with 4-*t*-butylcyclohexanone (15.4 g., 0.10 mole) in diethyl ether (25 ml.). The reaction was worked up as given in procedure A. There was obtained an 81% yield of mixed isomers, carbonyl analysis 6.8%; GLC analysis on Hyprose gave a ratio of 58.4% *cis* and 41.6% *trans.*

Reaction of Methyllithium and 4-*t*-Butylcyclohexanone.—Lithium wire (2.8 g., 0.40 g.-atom; small pieces) was covered with diethyl ether (150 ml.) and treated with methyl bromide until all the lithium had reacted. The resultant slurry was cooled to 5° and with stirring was treated with 4-*t*-butylcyclohexanone (15.4 g., 0.10 mole) in diethyl ether (25 ml.). The mixture was stirred for an additional 3 hr. and then allowed to stand overnight at room temperature. The system was cooled to 5° and treated with saturated aqueous ammonium chloride until a clear ether layer was obtained. The organic layer was separated, dried with magnesium sulfate, filtered, and the ether removed *in vacuo* on a rotary evaporator at room temperature or lower. There was obtained a 94% yield of mixed 1-methyl-4-*t*-butylcyclohexanols, carbonyl analysis 2.3%; GLC analysis on SAIB gave a ratio of 65.0% *cis* and 35.0% *trans.*

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[27] C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, **73**, 870 (1951).