methoxy-2-propanone by treatment with anhydrous magnesium bromide[34]; b.p. 61–63° (0.3 mm.), $n^{20}D$ 1.5070.

(+)-1-Phenyl-1-methoxy-2-propanol.—An ether solution of 1-phenyl-1-methoxy-2-propanone, 9.8 g., $\alpha^{24}D$ −0.45° (*l* 0.5, neat), made by diluting the optically active product with the *dl*-compound, was reduced by lithium aluminum hydride to give 8.6 g. (88% yield) of colorless oil, b.p. 57–60° (0.2 mm.), $n^{20}D$ 1.5108, $\alpha^{25}D$ +4.51° (*l* 0.5, neat). The infrared spectrum showed a strong bond at 2.90 μ but no absorption at 5.7–6.0 μ.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.48. Found: C, 72.58; H, 8.57.

The Methanesulfonate of (+)-1-phenyl-1-methoxy-2-propanol.—Anhydrous pyridine (5.2 g., 0.066 mole) was added carefully to methane-sulfonyl chloride (3.8 g., 0.033 mole) at 0° and the (+)-1-phenyl-1-methoxy-2-propanol (5.5 g., 0.033 mole) from above was added with stirring at such a rate that the temperature did not exceed 0°. After being stirred at 0° for 3 hours the reaction mixture was hydrolyzed by pouring onto 15 g. of ice and 30 ml. of 10% sulfuric acid. The product was extracted with ether, washed with cold sodium bicarbonate solution, water, and dried over anhydrous sodium sulfate. The ether was evaporated under vacuum to give 8.5 g. of yellow oil. A sample of this yellow oil from a preliminary experiment was distilled from powdered calcium carbonate in an evaporative distillation apparatus at 95° to give a colorless viscous distillate, $n^{20}D$ 1.5036. The infrared spectrum showed the intense bands for the SO_3 group at 7.4 and 8.5 μ.

Anal. Calcd. for $C_{11}H_{16}O_4S$: C, 54.05; H, 6.65. Found: C, 54.28; H, 6.45.

(+)-1-Phenyl-1-methoxyethanol.—To a solution of lithium aluminum hydride (2.0 g., 0.053 mole) in anhydrous ether, 100 ml., was added an ether solution of the crude methanesulfonate, 8.5 g., from above. The mixture was refluxed for 19 hours and worked up by destroying the excess reagent with ethyl acetate, 6 ml., then water, 10 ml., and finally 20% sodium hydroxide, 100 ml. The ether layer was washed with sodium hydroxide solution, water, dried over sodium sulfate and the residue, left after the ether was removed under a column, was distilled to give 1.3 g., b.p. 105° (18 mm.), $n^{20}D$ 1.4937, and 3.1 g. of residue. The distillate was redistilled twice; b.p. 77° (17 mm.), $n^{20}D$ 1.4915, $\alpha^{26}D$ + 3.78° (*l* 0.5, neat).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.25; H, 9.71.

Gas chromatography on a Carbowax column revealed a small amount of impurity which was removed by gas chromatography to give the pure carbinol, $n^{20}D$ 1.4898, $\alpha^{25}D$ +4.41° (*l* 0.5, neat).

Methylation of (−)-Ethylphenylcarbinol.—A mixture of 5.44 g. of (−)-ethylphenylcarbinol, $\alpha^{25}D$ −0.81° (*l* 0.5, neat), from the asymmetric reduction, 5 g. of glass beads, 5 g. of anhydrous calcium sulfate, 11.6 g. of silver oxide and 25 ml. of methyl iodide was stirred and refluxed for 40 hours. The starting material was recovered unchanged.

A mixture of sodium hydride, 1.0 g., anhydrous ether, 30 ml., the (−)-ethylphenylcarbinol recovered from the previous run, and 2 g. of glass beads was stirred and refluxed for 20 hours. Methyl iodide, 2.8 ml., was added and the refluxing continued for two hours and the reaction mixture decomposed with water. The dried ether extracts were distilled to give 3.15 g. of oil, b.p. 75–78° (16 mm.), $n^{20}D$ 1.4886, $\alpha^{22}D$ −2.60° (*l* 0.5, neat). This material was homogeneous to gas partition chromatography on a Carbowax column and had a retention time identical to that of the sample prepared from (+)-mandelic acid. The infrared absorption spectra of this levo sample and the dextro sample obtained by the sequence of reaction from (+)-mandelic acid were indistinguishable.

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(34) C. L. Stevens, M. L. Weiner and C. T. Lenk, THIS JOURNAL, **76**, 2698 (1954).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Asymmetric Reductions. VIII. The Action of the Grignard Reagent from (+)-1-Chloro-2-methylbutane on Cyclohexyl Alkyl Ketones[1]

BY ELIZABETH PARKER BURROWS,[2] FRANK J. WELCH[3] AND HARRY S. MOSHER

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The extents of asymmetric reduction of a series of seven cyclohexyl alkyl ketones by the Grignard reagent from (+)-1-chloro-2-methylbutane have been determined. In this series as in the phenyl alkyl series the stereospecificity increases in the same sense with increasing length of the alkyl chain provided the α-carbon atom is not branched. Branching at the α-carbon atom in cyclohexyl isopropyl ketone greatly diminishes the stereospecificity of the reduction in contrast to the results found for phenyl isopropyl ketone. Further branching at the α-carbon atom in cyclohexyl *t*-butyl ketone, again in contrast to phenyl *t*-butyl ketone, resulted in a low degree of stereospecificity and a preponderance of the carbinol of configuration opposite to the others formed in the same series. These results are summarized in Table IV and are discussed with regard to the mechanism proposed for the reduction of carbonyl compounds by Grignard reagents and the conformation in the transition state.

Though experimental extents of asymmetric reduction of a series of *t*-butyl alkyl ketones[4,5] were in complete accord with predictions based on steric interactions in a six-membered cyclic transition state, the extents of asymmetric reduction of a series of phenyl alkyl ketones[6] were incompatible with such a simple explanation. To ascertain whether anomalies are restricted to cases involving a phenyl group, and ultimately to develop a more comprehensive and generally applicable theory of group interactions in the transition state during the Grignard reduction reaction, we have extended these investigations to a series of cyclohexyl alkyl ketones. Briegleb-Stuart[7,8] molecular models of the transition state had indicated that steric requirements of the phenyl and cyclohexyl groups should not differ widely; yet the extent of asymmetric reduction of phenyl cyclohexyl ketone was

(1) Abstracted from the theses submitted by Elizabeth Parker (Aug., 1956) and Frank Welch (Oct., 1954) to Stanford University in partial fulfillment for the requirements for the Ph.D. degree.

(2) Eli Lilly Fellowship holder, 1955–1956.

(3) Shell Fellowship holder, 1952–1953.

(4) W. M. Foley, F. J. Welch, E. M. LaCombe and H. S Mosher, THIS JOURNAL, **81**, 2779 (1959).

(5) H. S. Mosher and E. La Combe, *ibid.*, **72**, 3994 (1950).

(6) R. MacLeod, F. J. Welch and H. S. Mosher, *ibid.*, **82**, 876 (1960).

(7) G. Briegleb, *Fortschr. chem. Forsch.*, **1**, 642 (1950).

(8) H. A. Stuart, "Die Struktur des freien Molekuels," Springer, Berlin, 1952.

the largest found in the phenyl alkyl series.[6] It therefore appeared desirable to study the effect of replacing a phenyl by a cyclohexyl group on the extent of asymmetric reduction in a similar series. The results of these experiments are summarized in Table I.

TABLE I

EXTENTS OF ASYMMETRIC REDUCTION OF CYCLOHEXYL ALKYL KETONES BY THE GRIGNARD REAGENT FROM (+)-1-CHLORO-2-METHYLBUTANE

Cyclohexyl-alkyl-carbinol	Rotation observed[a] $[\alpha]^{t}_{D}$ neat	t, °C.	Rotation pure isomer $[\alpha]^{max}_{D}$, neat	t, °C.	Asymmetric reduction $[\alpha]_D/[\alpha]^{max}_D \times 100$
Methyl	+0.20	27	5.6	20[b]	3.6 ± 0.2
Ethyl	−0.07	26	8.1	30[c]	8.8 ± .1
n-Propyl	−1.39	27	10.9	29[c,d]	8.1 ± .1
Isopropyl	+0.21	27	9.9	25[d]	2.1 ± .1
n-Butyl	−1.36	28	12.9	30[c]	11.0 ± .1
Isobutyl	−2.75	28	17.1	28[d,e]	16.1 ± .6
t-Butyl	−0.64	26	25.5	26[d,e]	2.5 ± .2
Phenyl	−7.02[f]	21	28.3	22[g]	25.1 ± .5

[a] Rotations are ±0.01° of neat liquid unless otherwise designated. [b] A. Domleo and J. Kenyon, *J. Chem. Soc.*, 1841 (1926). [c] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **75**, 587 (1927). [d] See Experimental. [e] Calculated by extrapolation of data from catalytic hydrogenation of partially active phenylalkylcarbinols. [f] See ref. 6; benzene solution, *c* 7.7. [g] M. P. Balfe, G. H. Beaver and J. Kenyon, *J. Chem. Soc.*, 1857 (1950); rotation taken in benzene solvent, *c* 3.3.

The partially active cyclohexylalkylcarbinols from the Grignard reductions were isolated and purified by procedures described previously.[4-6] The carbinols were converted to the acid phthal ates. Precautions were taken to ensure that no possible concentration of one isomer occurred by preferential crystallization at the acid phthalate stage. The carbinols, regenerated from the acid phthalates, showed essentially unchanged optical activity and infrared spectra (no absorption in the carbonyl region), establishing the completeness of the separation by fractionation. The distributions of addition, enolization and reduction products, estimated by methods previously described,[4-6] are summarized in Table II.

TABLE II

YIELD OF PRODUCTS[a] FROM THE REACTION OF CYCLOHEXYL ALKYL KETONES AND THE GRIGNARD REAGENT FROM (+)-1-CHLORO-2-METHYLBUTANE

Alkyl cyclohexyl ketone	Total % recovery	Ketone, % (enolization)	Tertiary carbinol (addition), %	Secondary carbinol (reduction), %
Methyl	78	5	37	58
Ethyl	87	35	14	51
n-Propyl	94	34	9	57
Isopropyl	85	14	5	81
n-Butyl	97	28	9	63
Isobutyl	96	24	6	70
t-Butyl	70	37	13	50
Phenyl[b]	85	0	10	90

[a] Composition of crude products estimated from fractionation data, refractive indices and weights of 2,4-dinitrophenylhydrazones. Yields are based on the ketone used; Grignard reagent was in excess. [b] See ref. 6.

The resolutions of cyclohexylmethylcarbinol,[9] cyclohexylethylcarbinol,[10,11] cyclohexyl-*n*-propylcarbinol[11] and cyclohexyl-*n*-butylcarbinol[11] have been reported. Based on the literature value for the rotation of cyclohexyl-*n*-propylcarbinol ($[\alpha]^{29}D$ −10.9°) the percentage asymmetric reduction for the corresponding ketone was out of line. Therefore the resolution of this carbinol was repeated and we obtained an alcohol with appreciably greater rotation ($[\alpha]^{29}D$ +15.6°) than that reported[11] for the enantiomorph. The resolution of cyclohexylisopropylcarbinol is also described in the Experimental section of this paper. Cyclohexylisobutylcarbinol and cyclohexyl-*t*-butylcarbinol have not been resolved; the rotations of the optically pure forms necessary to determine extents of asymmetric reduction were calculated by quantitative treatment of data from catalytic hydrogenations of the corresponding partially active phenylalkylcarbinols for which the maximum rotations and configurations are known.

Phenylmethylcarbinol, $[\alpha]^{26}D$ −39.8°, has been hydrogenated to cyclohexylmethylcarbinol, $[\alpha]^{30}D$ +4.7°.[12] The specific rotations of the pure isomers, 43.2°[13] and 5.6°,[9] respectively, indicated that no racemization had taken place. Conditions have been described[14] under which there was no hydrogenolysis and the only product isolated was the desired cyclohexylalkylcarbinol. Hydrogenation of phenyl-*n*-butylcarbinol, $[\alpha]^{26}D$ −1.27°, to cyclohexyl-*n*-butylcarbinol, $[\alpha]^{22}D$ −0.85 ±0.04, was carried out to determine the configuration of the latter. From the known specific rotations of the pure isomers, −17.6°[11] and −12.9°,[11] respectively, the specific rotation of the hydrogenation product should have been −0.94 + 0.04°. The discrepancy was only slightly greater than experimental error. Had sufficient material been available for fractionation of the product, a maximum rotation of the theoretical value would probably have resulted. This experiment serves as verification of the procedure used for establishing the maximum rotations for cyclohexylisobutyl- and cyclohexyl-*t*-butylcarbinols which have not been resolved.

The specific rotations of optically pure cyclohexylisobutylcarbinol and cyclohexyl-*t*-butylcarbinol were calculated from the hydrogenation data and literature values for the specific rotations of the optically pure phenylalkylcarbinols. A linear relation was assumed between the specific rotation of a carbinol and the percentages of the optical isomers composing it. It was further assumed that any slight temperature differences would lead to insignificant corrections. Samples of phenylisobutylcarbinol, $[\alpha]^{22}D$ −2.48°, 10.2 ± 0.3% of maximum rotation,[6] and phenyl-*t*-butylcarbinol, $[\alpha]^{26.5}D$ −3.6°, 16.1 ± 0.6% of maximum rotation,[6] were hydrogenated and the resulting cyclohexylalkylcarbinols fractionated at reduced pressure.

(9) A. Domleo and J. Kenyon, *J. Chem. Soc.*, 1841 (1926).
(10) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **75**, 587 (1927).
(11) P. A. Levene and R. E. Marker, *ibid.*, **97**, 379 (1932).
(12) P. A. Levene and S. A. Harris, *ibid.*, **113**, 55 (1936).
(13) A. J. H. Houssa and J. Kenyon, *ibid.*, 2260 (1930).
(14) P. A. Levene, *J. Biol. Chem.*, **115**, 275 (1936).

The fractionations afforded cyclohexylisobutylcarbinol with a maximum rotation of $[\alpha]^{27}D$ $-1.74°$ and cyclohexyl-*t*-butylcarbinol with a maximum rotation of $[\alpha]^{30}D$ $+3.80°$. The calculated maximum rotation of optically pure cyclohexylisobutylcarbinol was therefore $17.1 \pm 0.6°$ and of optically pure cyclohexyl-*t*-butylcarbinol $25.5 \pm 1.5°$. Hence the carbinol, $[\alpha]^{28}D$ $-2.75°$, from the Grignard reduction of cyclohexyl isobutyl ketone represents an asymmetric reduction of $16.1 \pm 0.6\%$ and the carbinol, $[\alpha]^{26}D$ $-0.64 \pm 0.01°$, from the reduction of cyclohexyl *t*-butyl ketone represents an asymmetric reduction of $2.5 \pm 0.3\%$.

To establish the relative positions of groups in the preferred transition state the configuration of the preponderant enantiomorphic carbinol must be known. Cyclohexylmethylcarbinol is the only member of the cyclohexylalkyl series whose configuration has been established by direct chemical transformations.[12,15-17] The configurations of the remaining members of the cyclohexylalkyl series have been determined by catalytic hydrogenation of the corresponding optically active phenylalkylcarbinols of known[6] relative configurations. From these data, summarized in Table III, cyclohexylethylcarbinol, cyclohexyl-*n*-propylcarbinol, cyclohexyl-*n*-butylcarbinol and cyclohexylisobutylcarbinol must be assigned the same configuration as the respective phenylalkylcarbinol with the same sign of rotation. Cyclohexylisopropylcarbinol and cyclohexyl-*t*-butylcarbinol, as well as cyclohexylmethylcarbinol, are configurationally related to the respective phenylalkylcarbinols having opposite signs of rotation.

TABLE III

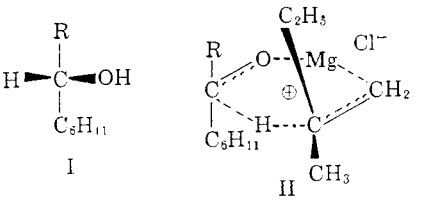
THE CATALYTIC HYDROGENATIONS OF PHENYLALKYLCARBINOLS[a]

Alkyl group	Specific rotation of phenylalkylcarbinol $[\alpha]^t_D$ neat	t, °C.	Specific rotation of cyclohexylalkylcarbinol $[\alpha]^t_D$ neat	t, °C.	Net change[c] $[\alpha]_{cyclohexyl}-[\alpha]_{phenyl}$
Methyl[d]	−39.8°	26	− 4.7°	30	+44.5°
Ethyl[e]	−25.9	23.5	−5.86	24	+20.0
Isopropyl[e]	−9.01	23.5	+2.75	23.5	+11.76
n-Propyl[f]	−7.62	25	−4.61	25	+ 3.01
n-Butyl	−1.27	26	−0.85	22	+ 0.42
Isobutyl	−2.48	22	−1.74	27	+ 0.74
t-Butyl	− 3.6	26.5[b]	+3.80	29	+ 7.4

[a] The hydrogenations were carried out in 9:1 methanol–acetic acid at 2–3 atmospheres pressure, using a platinum oxide catalyst. [b] Specific rotation in benzene at $c = 10.0$. [c] That the increments in rotation on going from a phenylalkylcarbinol to a cyclohexylalkylcarbinol of the same configuration are in each case positive is in agreement with expectation based on generalizations made by Levene and Marker, *J. Biol. Chem.*, 97, 379 (1932). [d] Levene and Stevens, *ibid.*, 89, 471 (1930). [e] Levene and Stevens, *ibid.*, 87, 375 (1930). [f] Levene, Rothen and Kuna, *ibid.*, 120, 777 (1937).

On the basis of data provided by Levene and Rothen[18] and Levene and Marker,[19] the cyclohexyl group may be placed tentatively between the hydroxymethyl and isopropyl groups in Marker's[20] configuration table. The *t*-butyl group has been assigned[21] a position between the isopropyl and methyl groups. The configurations of the cyclohexylalkylcarbinols predicted from this extension of Marker's generalization are in agreement with those found by the catalytic hydrogenation experiments.

In the asymmetric reductions of the cyclohexyl alkyl series all the preponderant enantiomorphic carbinols except cyclohexyl-*t*-butylcarbinol had configuration I. Therefore in all cases except that of cyclohexyl *t*-butyl ketone, the preferred transition state for reduction of the cyclohexyl alkyl ketone may be represented as II, where the cyclohexyl group of the ketone and the methyl group of the Grignard reagent are on the same side of the six-membered ring. In the preferred transition state for cyclohexyl *t*-butyl ketone, the *t*-butyl group rather than the cyclohexyl group is on the same side as the Grignard methyl group.



Discussion

The data so far available on asymmetric reductions of carbonyl compounds by the Grignard reagent from (+)-1-chloro-2-methylbutane are presented in Table IV. This table may be summarized as: (1) In the alkyl *t*-butyl series (second line, Table IV) as the alkyl group becomes larger, particularly as the branching on the α-carbon atom increases, the stereospecificity *decreases* (from 13% asymmetric reduction for methyl *t*-butyl ketone to 5% for isopropyl *t*-butyl ketone to 2.5% for cyclohexyl *t*-butyl ketone). Not only the extents of asymmetric reduction but also the configurations of the preponderant carbinols in each case are in accord with the postulate that the preferred conformation of the transition state is determined by the bulk of the alkyl groups of the ketone. The transition state with lower energy of activation is that one which has the larger group from the ketone on the same side of the transition ring as the smaller group from the Grignard reagent and the larger group from the Grignard reagent opposing the smaller group of the ketone on the other side of the transition ring.[4] Thus as the size of the alkyl group on the alkyl *t*-butyl ketone increases from methyl through ethyl and isopropyl, it approaches the size of the *t*-butyl group and the asymmetric bias of the reduction *decreases* accordingly.

(2) In the alkyl phenyl series (line 3, Table IV), as the bulk of the alkyl group increases from methyl through isopropyl and cyclohexyl, the stereospecificity *increases* (from 3.9 to 25%). Of great interest is the fact that the percentage asymmetric synthesis with phenyl *t*-butyl ketone is less (16%) than with phenyl isopropyl ketone (24%). Yet the known configurations of the resulting preponderant alkylphenylcarbinols are such that in the

(15) P. A. Levene and P. G. Stevens, *J. Biol. Chem.*, **89**, 471 (1930).
(16) K. Mislow, THIS JOURNAL, **73**, 3955 (1951).
(17) J. Kenyon and H. Phillips, *J. Chem. Soc.*, 1676 (1930).
(18) P. A. Levene and A. Rothen, *J. Org. Chem.*, **1**, 76 (1936).
(19) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **97**, 563 (1932).
(20) R. E. Marker, THIS JOURNAL, **58**, 976 (1936).
(21) P. G. Stevens, W. E. Higbee and R. T. Armstrong, *ibid.*, **60**, 2658 (1938).

TABLE IV

SUMMARY OF ASYMMETRIC BIAS IN THE REDUCTION OF CARBONYL COMPOUNDS BY THE GRIGNARD REAGENT FROM (+)-1-CHLORO-2-METHYLBUTANE[a]

	CH_3	C_2H_5	n-C_3H_7	n-C_4H_9	i-C_4H_9	i-C_3H_7	C_6H_{11}	t-C_4H_9	C_6H_5
C_6H_{11}	3.6	8.8	8.9	11	16	2.1	..	−2.5	−25
t-C_4H_9	13	11	11	11	6	5	2.5	...	−16
C_6H_5	3.9	5.7	5.9	7.2	9.9	24	25	16	..

[a] Signs refer to the configuration of the isomer produced in excess, not to the sign of rotation. The isomers of configuration I where R is the group at the top of the table and phenyl, cyclohexyl and t-butyl are the groups at the bottom of the projection formula I.

postulated transition state the phenyl group from the ketone and the methyl group from the Grignard reagent must be on the same side of the transition ring.[5] One is thus faced with the anomaly that as the alkyl group increases in size, the stereospecificity *increases* in direct contrast to findings in the alkyl t-butyl series.

(3) In the alkyl cyclohexyl series (line 1, Table IV), as the bulk of the alkyl group increases from methyl through isobutyl, the stereospecificity increases (from 3.6 to 16%), but drops markedly for isopropyl (2.1%); in the cases of t-butyl and phenyl the carbinol of opposite configuration is obtained. Thus the behavior from the methyl through the isobutyl case parallels that for the corresponding phenyl series while the behavior of the isopropyl and t-butyl examples corresponds to that found in the alkyl t-butyl series.

It is clearly evident that a simple steric explanation will suffice to correlate only the results in the alkyl t-butyl series and that group interactions in the transition state are far more complex than the simplified model first postulated.[5] The nature of this dilemma is emphasized by the asymmetric reductions of methyl phenyl, methyl cyclohexyl and phenyl cyclohexyl ketones. Approximately the same stereospecificity is found in the asymmetric reductions of methyl phenyl ketone (3.9%) and methyl cyclohexyl ketone (3.6%). Thus the effective bulks of the phenyl and cyclohexyl groups appear to be about the same. Accordingly one would expect that the asymmetric reduction of cyclohexyl phenyl ketone should show a very low order of stereospecificity. Actually it was one of the highest so far observed (25%) with the present Grignard reagent.

Yet the ordered variations within each series and the lack of random results offer hope that the other factors influencing the stereochemical course of this reaction will be clarified. It seems intuitively correct that the packing together of the groups in the transition state in the conformation of lowest energy would be the result of a complex interaction of all groups including the coördinated solvent. This is particularly evident when models are examined. For instance, there appears to be as much, and perhaps more, steric interference between the two groups attached to the carbonyl carbon atom of the ketone as between the groups of the ketone and Grignard reagent. This effect is particularly apparent when the groups of the ketone are large.

It should be reemphasized that this reaction offers a method of investigating the transition states of two competing reactions which differ in activation energies only by 0.15 kcal./mole.[22] It is therefore to be expected that the relative activation energies would be extremely sensitive to slight structural and electronic variations. We hope to clarify these results with further experiments using other optically active Grignard reagents and carbonyl systems.

Experimental

Preparations of the Cyclohexyl Alkyl Ketones.—Cyclohexyl methyl ketone, b.p. 97° (50 mm.), $n^{20}D$ 1.4510, was prepared by the method of Walker and Hauser in 72% yield based on the acid chloride.[23]

Cyclohexyl t-butyl ketone, b.p. 99–100° (20 mm.), $n^{20}D$ 1.4500–1.4505, was prepared by the cuprous chloride-catalyzed coupling[24] of hexahydrobenzoyl chloride with t-butylmagnesium chloride. The yield based on t-butyl chloride was 27%. The ketone has not been previously reported in the literature. Its oxime, prepared by the pyridine method, sublimed without melting at 152–153°.

Anal. Calcd. for $C_{11}H_{21}ON$: C, 72.08; H, 11.55; N, 7.64. Found: C, 71.86; H, 11.79; N, 7.70.

The five remaining ketones were each prepared in like manner: oxidation of the *dl*-carbinol which had been prepared from cyclohexylmagnesium halide and the requisite aldehyde. A typical preparation and a list of the properties of the ketones follow. Propionaldehyde, 48.8 g. (0.84 mole), was added over 1.5 hours to a cyclohexylmagnesium chloride solution, prepared from 99.5 g. (0.84 mole) of cyclohexyl chloride and 22.0 g. (0.91 mole) of magnesium in 450 ml. of ether. The mixture was kept below reflux temperature during the addition, then hydrolyzed with 10% sulfuric acid. The resulting cyclohexylethylcarbinol, distilled through a Vigreux column, b.p. 90.5–91.5° (16 mm.), weighed 76.8 g. (64.4%). Cyclohexylethylcarbinol (96.3 g., 0.68 mole) was dissolved in 20 ml. of glacial acetic acid and added dropwise over a 3-hour period, with cooling when necessary, to a rapidly stirred solution of 67.7 g. (0.23 mole) of potassium dichromate in 99.2 g. of concentrated sulfuric acid, 50 ml. of glacial acetic acid and 550 ml. of water. After being stirred 24 hours the mixture was allowed to separate into two layers, the aqueous layer was extracted with ether and the combined ether extracts and organic layer were washed first with water, then with 5% aqueous potassium hydroxide and finally twice with water. The ketone, after drying and removal of ether, was fractionated through a 19″ × $^5/_8$″ column packed with Pyrex $^3/_{32}$″ single-turn glass helices, b.p. 77° (10 mm.), $n^{21}D$ 1.4520, 65.0 g. (68.5% yield).

The following were prepared in like manner: Cyclohexyl n-propyl ketone[25] (74% yield), b.p. 107° (23 mm.), $n^{20}D$ 1.4529; cyclohexyl isopropyl ketone[26] (67% yield), b.p. 77° (9 mm.), $n^{25}D$ 1.4478; cyclohexyl isobutyl ketone[27] (87% yield), b.p. 110° (22 mm.), $n^{20}D$ 1.4528; cyclohexyl n-butyl ketone (61% yield), b.p. 119° (22 mm.), $n^{20}D$ 1.4548. This latter compound has not been reported previously.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.53; H, 12.12.

Reactions of the Cyclohexyl Alkyl Ketones with the Grignard Reagent from (+)-1-Chloro-2-methylbutane.—A

(22) See footnote 17, ref. 5.

(23) H. G. Walker and C. R. Hauser, THIS JOURNAL, **68**, 1386 (1946).

(24) N. C. Cook and W. C. Percival, *ibid.*, **71**, 4141 (1949).

(25) G. Danzens and H. Rost, *Compt. rend.*, **153**, 773 (1911).

(26) A. Favorsky, *J. prakt. Chem.*, [2] **8**, 695 (1913).

(27) P. Sabatier and A. Mailhe, *Compt. rend.*, **139**, 344 (1904).

TABLE V

ACID PHTHALATES OF ALKYLCYCLOHEXYLCARBINOLS FROM ASYMMETRIC REDUCTIONS

Alkyl-cyclohexylcarbinol			Heating	Acid phthalate			
Alkyl group	Rotation $\alpha^{26}D$ (neat)	Wt., g.	time, hr.	Yield g. (%)	Melting point[b] °C.	Rotation $[\alpha]^{t}D$ (c 20) abs. ethanol	t, °C.
Methyl	+0.10°	6.41	12	13.0 (94)	Oil	+1.10°	26
Ethyl	− .56	2.74	6	5.56 (99)	90–93	+1.10 ± 0.03	25
n-Propyl	− .60	2.32	24	3.94 (87)	99–107	−0.15 ± .05	25
Isopropyl	+ .12	2.51	6	4.69 (96)	88–90[c]	0.00 ± .05[a]	25
n-Butyl	− .60	2.95	10	4.97 (90)	47–50[d]	−0.20 ± .05	28.5
Isobutyl	−1.07	2.75	11	4.93 (96)	73–82[e]	−1.47 ± .05	28
t-Butyl[f]	−0.25	2.65	7	4.69 (94)	108–116[g]	0.00 ± .05[a]	25

[a] The observed rotations of the isopropyl- and *t*-butylcyclohexylcarbinol acid phthalates were zero within experimental error in either chloroform or ethanol. This same behavior was noted for the acid phthalate of isopropyl-*t*-butylcarbinol.[4] [b] Melting points taken on a Kofler hot-stage. [c] *Anal.* Calcd. for $C_{18}H_{24}O_2$: C, 71.03; H, 7.95. Found: C, 70.74; H, 7.95. [d] *Anal.* Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.55; H, 8.08. [e] *Anal.* Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.72; H, 8.24. [f] *Anal.* Calcd. for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.25; H, 13.15. [g] *Anal.* Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.61; H, 8.13.

representative run, using cyclohexyl ethyl ketone, will be described. The other experiments, with a single exception as noted, were done in parallel fashion; the results are summarized in Tables I and II.

To 46.0 g. (0.328 mole) of cyclohexyl ethyl ketone in 140 ml. of refluxing anhydrous ether was added 350 ml. of 1.06 *N* Grignard solution at the rate of 5 ml. per minute. The Grignard solution was prepared as previously described,[4,5] using primary active amyl chloride, $\alpha^{25}D$ +1.42° (neat) and sublimed magnesium.[28] Stirring under reflux was continued 4.5 hours after addition was complete; at the end of this time a Michler ketone test was positive. Hydrolysis was effected by pouring the reaction mixture slowly into a solution of 25 g. of ammonium chloride in 150 g. of ice-water. The ether layer was washed first with ice-cold 5% sulfuric acid, then with 2% sodium bicarbonate, and finally twice with water, and dried over magnesium sulfate. The ether was removed through a fractionating column and aliquots titrated for 2-methyl-1-butene by the bromide-bromate method.[29] The residue, on rapid distillation at reduced pressure, was separated into four fractions: b.p. 49–95° (23 mm.), b.p. 95–105° (23 mm.), b.p. 59–95° (3 mm.), b.p. 95–100° (3 mm.). A 2,4-dinitrophenylhydrazone, m.p. 151–152°, weighing 0.127 g., was prepared from a 0.159-g. aliquot of the combined second and third fractions. These combined fractions weighed 32.25 g.; the yield of enolization product calculated on this basis was 35%. The combined second and third fractions were carefully fractionated at 26 mm. through a 19" × 5/8" column packed with single-turn 3/32" Pyrex glass helices. Fractions 13–20 from this fractionation were essentially pure cyclohexylethylcarbinol; from fraction 15, b.p. 103.2°, $n^{20}D$ 1.4661 ($\alpha^{25}D$ −0.28°, *l* 0.5, neat), an acid phthalate, m.p. 90–93°, $[\alpha]^{25}D$ +1.10 ± 0.03° ($\alpha^{25}D$ +0.31 ± 0.01°, *c* 28.10, absolute ethanol) was prepared in 99% yield by the pyridine method. The phthalate was steam distilled first from water, and then from 15% aqueous sodium hydroxide to obtain the regenerated carbinol, which was then distilled, $[\alpha]^{26}D$ −0.71 ± 0.01° ($\alpha^{26}D$ −0.65°, *l* 1, neat). The yield of regenerated carbinol was 46% based on the phthalate. The extent of asymmetric reduction based on the phthalate was 8.3 ± 0.4%; that based on the regenerated carbinol was 8.8 ± 0.1%. The properties of the acid phthalates of the other six partially active cyclohexylalkylcarbinols from the Grignard reductions are summarized in Table V.

Resolution of Cyclohexylisopropylcarbinol.—The **strychnine salt** of cyclohexylisopropylcarbinol acid phthalate was prepared and subjected to systematic fractional crystallization from methanol–acetone mixtures. The less soluble diastereomer was converted by hot dilute hydrochloric acid (one part of concentrated acid to 11–12 parts water) to an acid phthalate, $[\alpha]^{23.5}D$ +2.3° (*c* 14.4, chloroform), which failed to crystallize and gave after two hours refluxing with 20% aqueous sodium hydroxide an alcohol, $[\alpha]^{26}D$ +7.08° (neat). The 3,5-dinitrobenzoate prepared from the alcohol of specific rotation of +7.08° melted at 101–102° after three recrystallizations, $[\alpha]^{23}D$ +7.6° (*c* 5.16, chloroform). The melting point–composition diagram for mixtures of the *dl*-3,5-dinitrobenzoate (m.p. 80.5°) and the (+)-3,5-dinitrobenzoate (m.p. 101–102°) was determined and indicated a eutectic mixture was formed at a concentration of 75 to 80% of the racemic ester. This provided good evidence that the resolution was at least nearly complete. To test the completeness of the resolution the acid phthalate, $[\alpha]^{23.5}D$ +2.3°, was converted to the **brucine salt** and recrystallized twice from methanol–acetone mixtures. On treatment with hot dilute hydrochloric acid the recrystallized salt gave an acid phthalate, $[\alpha]^{23.5}D$ +2.5° (*c* 14.8, chloroform), from which an alcohol, $[\alpha]^{23}D$ +7.80° (neat), was obtained on saponification. The 3,5-dinitrobenzoate, $[\alpha]^{22}D$ +7.7° (*c* 5.05, chloroform) of this alcohol melted at 102.5–103°.

Anal. Calcd. for $C_{17}H_{22}O_6N_2$: C, 58.27; H, 6.33. Found: C, 58.38; H, 6.03.

It was hydrolyzed to an alcohol having the maximum rotation obtained by the resolution, $[\alpha]^{25}D$ +9.90° (neat). The purest levorotatory alcohol, $[\alpha]^{26}D$ −8.41° (neat), was obtained from one of the more soluble strychnine salt fractions. Based on a rotation of $[\alpha]^{25}D$ +9.9° for the pure *d*-alcohol, the pure *d*-acid phthalate would have $[\alpha]^{23.5}D$ +3.2° (*c* 14, $CHCl_3$).

Resolution of Cyclohexyl-*n*-propylcarbinol.—The salt prepared from 14.1 g. (0.0461 mole) of cyclohexyl-*n*-propylcarbinol acid phthalate and 15.5 g. (0.0461 mole) of strychnine was subjected to a seven-stage systematic fractional crystallization from methanol–acetone mixtures at −10 to 0°. Solutions of the salts were unstable at higher temperatures and deposited only strychnine on standing. The phthalates obtained on treatment of the various salt fractions with hot dilute hydrochloric acid were all non-crystalline sirups; the one of maximum rotation ($[\alpha]^{26}D$ +1.54° (*c* 21.4, $CHCl_3$)), weighing 1.3 g., on saponification afforded 0.4 g. of carbinol, $[\alpha]^{29}D$ +15.6° (neat, α^{29}_4 0.900). Conversion to a crystalline 3,5-dinitrobenzoate did not proceed in sufficiently good yield to permit measurement of the rotation of the carbinol after several recrystallizations of the derivative (m.p. 103°) and then saponification. However, since the rotation of this carbinol was substantially higher than any obtained elsewhere in the resolution, (11.8–12.7°) which in turn were higher than the maximum obtained by Levene and Marker (10.9°),[11] acceptance of 15.6° as a true maximum appeared justified. On this basis, the previously reported resolution of cyclohexyl-*n*-propylcarbinol was only 63% complete.

Catalytic Hydrogenations of Partially Optically Active Phenylalkylcarbinols.—Samples of (−)-phenyl-*n*-butylcarbinol and (−)-phenylisobutylcarbinol from the Grignard reductions of the corresponding ketones[2] were purified *via* the acid phthalates. The regenerated carbinols had no infrared absorption in the carbonyl region. (−)-Phenyl-*t*-butylcarbinol from the Grignard reduction of phenyl *t*-butyl ketone was not further purified since the sample did not absorb in the carbonyl region. The hydrogenation of (−)-phenylisobutylcarbino lwill be described. The other two were carried out in exactly the same manner except there was

(28) We wish to thank the Dow Chemical Co. for a generous supply of triple-sublimed magnesium used in this investigation.

(29) H. L. Johnson and R. A. Clark, *Ind. Eng. Chem., Anal. Ed.*, **19**, 869 (1947).

insufficient (−)-phenyl-*n*-butylcarbinol available for fractionation of the product; it was simply distilled.

To 11.79 g. of phenylisobutylcarbinol, $[\alpha]^{22}D$ −2.48° (neat), dissolved in 40 ml. of 9:1 methanol–glacial acetic acid, was added 0.55 g. of freshly prepared platinum oxide catalyst.[30] The mixture was shaken 24 hours in a Parr hydrogenator. After removal of catalyst and evaporation of methanol, the residual liquid was taken up in ether and shaken with 10% aqueous potassium carbonate until evolution of carbon dioxide ceased, then dried over potasssium carbonate. The infrared spectrum of the crude product after removal of ether showed none of the absorption characteristic of the phenyl group and was identical with that of the (−)-cyclohexylisobutylcarbinol from the Grignard reduction except for a weak band in the former spectrum at 5.9 μ, probably due to acetic acid. The product was fractionated at 20 mm. through a 25″ × 3/16″ glass spiral column. The take-off was controlled automatically and the head temperature read by means of a thermocouple. The fifth and last fraction, 1.54 g., $n^{20}D$ 1.4641, had a maximum rotation: $[\alpha]^{27}D$ −1.74° (neat). Its infrared spectrum was superimposable on that of (−)-cyclohexylisobutylcarbinol; the band in the crude hydrogenation product at 5.9 μ had disappeared.

(30) Prepared from spent residues by the procedure of R. Adams, V. Voorhees and R. L. Shriner, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 463, using potassium nitrate rather than sodium nitrate in the fusion step.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Studies of Configuration. VII. The Solvolysis of 3- and 4-Methoxycyclohexyl Arenesulfonates[1,2]

BY DONALD S. NOYCE, BARBARA R. THOMAS AND BRUCE N. BASTIAN

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The ethanolysis of *cis*- and *trans*-3-methoxycyclohexyl tosylates appears to be normal. The acetolysis of *trans*-4-methoxycyclohexyl tosylate shows evidence for internally assisted acceleration of rate. The products formed, 9% *cis*-4-methoxycyclohexyl acetate, 25% *trans*-4-methoxycyclohexyl acetate and 66% 4-methoxycyclohexene, substantiate the rate acceleration. It is suggested that a large fraction of the reaction is proceeding through the symmetrical bicyclic oxonium ion II. Such an intermediate explains the large amount of net retention of configuration in the derived acetate.

Introduction

The frequent manifestation of increased reactivity due to participation by neighboring groups is well recognized. The classical work of Winstein and his co-workers[3] has provided numerous examples, including the acetoxyl group, the methoxyl group, the halogens and the aromatic ring as participating groups. More recently, the occurrence of participating interaction has been recognized in medium ring compounds.[4–7]

On the other hand, the chemical behavior of cyclohexane systems has been adequately interpreted in general by considering only the chair conformation.

Previous examples of 1,4-interaction across a six-membered ring are sparse. The reactions of a variety of 4-substituted cyclohexyl derivatives have been studied by Owen and Robins,[8] but only meager evidence of transannular participation was obtained. The monotosylate of *trans*-1,4-cyclohexanediol failed to give any 1,4-epoxycyclohexane, but *trans*-1,4-diiodocyclohexane was obtained from both *cis*- and *trans*-1,4-di-*p*-toluenesulfonyloxycyclohexane.

Bennett and Niemann[9] have suggested that 1,4-bridged cyclic halonium ions may be involved in the reactions of 4-iodocyclohexanol and 4-bromocyclohexanol. Goering and Sims[10] have recently suggested the incursion of the 1,4-bridged bromonium ion in the rearrangement of dibromocyclohexanes with ferric bromide.

Reaction through an appropriate boat conformation has been observed in some steroids[11] and sugars.[12]

We have undertaken an investigation of interaction across 6-membered rings, which may require the incursion of a boat conformation. In a previous report Noyce and Weingarten[13] have observed such interaction in the ether–acid chloride rearrangement, but failed to find evidence for participation accompanying the solvolysis of methyl 3-tosyloxycyclohexanecarboxylate.

Since the preliminary report of the results to be discussed here was presented,[2] a further example of 1,4-interaction has been presented by Heine[14] in the hydrolysis of 4-chlorocyclohexanol. Barner,

(1) Supported in part by the National Science Foundation, G-2387 and G-5921.

(2) A portion of this material has been presented in a preliminary Communication, D. S. Noyce and B. R. Thomas, THIS JOURNAL, **79**, 755 (1957).

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