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Asymmetric Reductions. VII. The Action of the Grignard Reagent from (+)-1-chloro-2-methylbutane on a Series of Alkyl Phenyl Ketones[1-3]

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Seven alkyl phenyl ketones and phenyl cyclohexyl ketone have been reduced by the optically active Grignard reagent from (+)-1-chloro-2-methylbutane to produce a series of partially active (−)-alkylphenylcarbinols. It now has been established by an independent sequence that (−)-ethylphenylcarbinol and (−)-methylphenylcarbinol are configurationally related. Application of Freudenberg's displacement rule reveals that the other (−)-alkylphenylcarbinols formed in these asymmetric reductions (*n*-propyl, isopropyl, *n*-butyl, *i*-butyl and *t*-butyl) have the same absolute configuration. Furthermore the extent of asymmetric reduction *increases* in an orderly fashion as the steric bulk of the alkyl group increases. This is in direct contrast to the findings in the completely aliphatic alkyl-*t*-butylcarbinol series. The theoretical implications of these results are discussed with regard to the cyclic mechanism for the Grignard reduction reaction and the stereochemistry of the transition state. It was necessary to resolve isobutylphenylcarbinol and additional data on the resolution of isopropyl- and *t*-butylphenylcarbinols were collected.

Studies on the asymmetric reduction reaction using the Grignard reagent from (+)-1-chloro-2-methylbutane have been extended to the alkyl phenyl ketones[6] in an attempt to uncover quantitative relationships between the nature of the interacting groups and the extent of asymmetric reduction. This series was first investigated by Vavon and Angelo[7] using the Grignard reagent from "pinene hydrochloride," but no theoretical conclusions were drawn from their work and in fact it has not been possible to fully interpret their results in terms of the mechanism which has been proposed for this reaction[8] since the relative configurations of the higher members of the alkylphenylcarbinol series have not been known with certainty until now. Although the absolute configuration of methylphenylcarbinol is known by interrelationships with lactic acid and mandelic acid,[9] that of ethylphenylcarbinol is in doubt since the application of Freudenberg's displacement rule does not give a definitive answer.

In an attempt to establish the configuration of the higher alkylphenylcarbinols, Levene and Stevens[10] came to the conclusion that (+)-methylphenylcarbinol was configurationally related to (−)-ethylphenylcarbinol, while Freudenberg,[11] Levene and Marker[12] and Leven and Rothen[13] came to the opposite conclusion. An exhaustive discussion of this problem has been presented[6] and the data upon which the arguments are based are given in Table I. The main difficulty lies in the fact that of all the (−)-alkylphenylcarbinols in Table I only (−)-methylphenylcarbinol gives a (+)-acid phthalate. If it were not for this the data would be compatible with the assumption that all of these alkylphenylcarbinols with the same sign have the same configuration.

TABLE I

MAXIMUM MOLECULAR ROTATIONS OF THE ALKYLPHENYLCARBINOLS AND DERIVATIVES[a]

Alkylphenylcarbinol alkyl group	[M]^{25}D Carbinol (neat)	Carbinol (in C_6H_6)	Acetate (neat)	Acid phthalate (in $CHCl_3$)	Acid phthalate (in C_2H_5OH)
Methyl	−53[b]		−194	+ 45	+98
Ethyl	−39[c]		−186	−100[g]	−11
n-Propyl	−44[d]	−65	−200	−130[g]	−25
Isopropyl	−37[e,f]			−133	−47[g]
Cyclohexyl	..	−54[i]	−165[j]	−178	
n-Butyl	−28	−52	−163[k]	−200[g]	−36[k]
Isobutyl	−40[f]	−54		−110	
t-Butyl	..[h]	−45[f,l]		− 86[f]	

[a] These (−)-alkylphenylcarbinols are all related and have the absolute S configuration, structure X, according to the nomenclature of R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956). [b] From E. Downer and J. Kenyon, *J. Chem. Soc.*, 1156 (1939). [c] From R. H. Pickard and J. Kenyon, *ibid.*, **99**, 45 (1911). [d] From J. Kenyon and M. S. Partridge, *ibid.*, 128 (1936), extrapolated value for supercooled liquid; see P. A. Levene, A. Rothen and M. Kuna, *J. Biol. Chem.*, **120**, 777 (1937). [e] From P. A. Levene and P. G. Stevens, *ibid.*, **87**, 375 (1930). [f] See Experimental section. [g] Approximate value based on the rotation of partially active acid phthalate. [h] The carbinol is a solid. [i] From M. P. Balfe, G. H. Beaven and J. Kenyon, *J. Chem. Soc.*, 1857 (1950). [j] In ethanol, *c* 4. [k] From P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **97**, 387 (1932). [l] See G. Vavon and B. Angelo, *Compt. rend.*, **224**, 1435 (1947).

Since no direct chemical transformation existed upon which to base a decision, we undertook to establish the configuration of ethylphenylcarbinol according to the scheme outlined in Fig. 1.[14]

Thus (+)-mandelic acid (I) has now been related to the (+)-methyl ether of ethylphenylcarbinol VII, in a process whereby the carboxyl group is replaced by the ethyl group. Since (−)-ethylphenylcarbinol from the asymmetric reduction gives the (−)-methyl ether, it follows that (−)-mandelic acid and (−)-ethylphenylcarbinol are configurationally related and that the latter is correctly represented by formula VIII which according to the Cahn, Ingold, Prelog designation would be S-ethylphenylcarbinol. Since (−)-mandelic acid and (−)-methylphenylcarbinol have been related[9,10] by a similar sequence, these two carbinols

(1) Abstracted from theses submitted by Roderick MacLeod (1953) and Frank Welch (1954) to Stanford University in partial fulfillment of the requirements for the Ph.D. degree.

(2) Previous paper in this series: W. M. Foley, F. J. Welch, E. M. LaCombe and H. S. Mosher, THIS JOURNAL, **81**, 2779 (1959).

(3) Supported in part by a grant from the Research Corporation.

(4) Shell Fellowship holder 1950–1951.

(5) Shell Fellowship holder 1952–1953.

(6) R. MacLeod, Ph.D. Thesis, Stanford University, June, 1953.

(7) G. Vavon and B. Angelo, *Compt. rend.*, **224**, 1435 (1947).

(8) See ref. 2 and previous papers in this series.

(9) K. Mislow, THIS JOURNAL, **73**, 3955 (1951).

(10) P. A. Levene and P. G. Stevens, *J. Biol. Chem.*, **89**, 471 (1930).

(11) K. Freudenberg, *Ber.*, **66**, 185 (1933).

(12) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **97**, 379 (1936).

(13) P. A. Levene and A. Rothen, *J. Org. Chem.*, **1**, 98 (1932).

(14) F. J. Welch, Ph.D. Thesis, Stanford University, Oct., 1954.

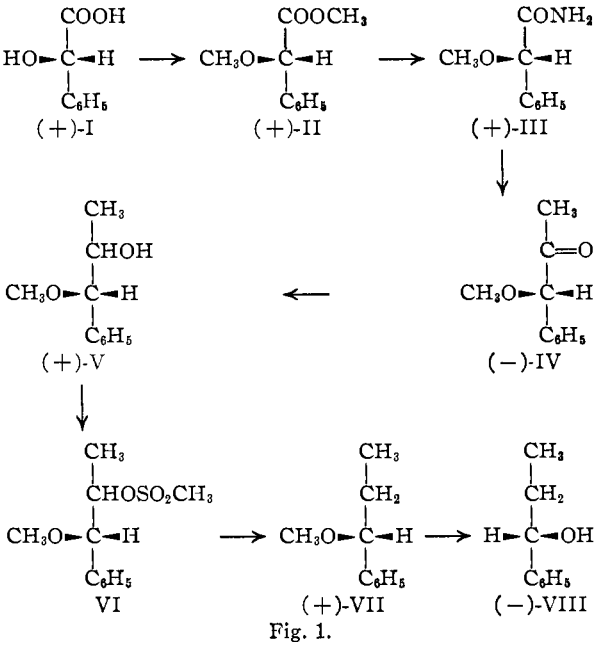


Fig. 1.

with the same sign have the same relative configurations. An alternate attempt to interrelate mandelic acid and ethylphenylcarbinol by ozonizing optically active vinylphenylcarbinol (or its acetate) to the former and reducing it to the latter failed in the ozonolysis step.

There appears to be no ambiguity concerning the application of Freudenberg's displacement rule to the higher alkylphenylcarbinols in Table I.[11,13,15] Accordingly it may be considered with a high degree of certainty that these (−)-alkylphenylcarbinols have the same configuration. Since the absolute configuration of methylphenylcarbinol and ethylphenylcarbinol are known by virtue of their relationship to lactic and mandelic acids, the absolute configuration of all members of this series can be considered established.[16]

The yield of products and the percent asymmetric reductions observed are summarized in Tables II and III, respectively. The experimental methods were those used previously.[8] Every effort has been made to obtain accurate values for the rotation of the asymmetric reduction products. The products from the reaction were fractionated through a spinning band column and the alkylphenylcarbinol fraction refractionated. Acid phthalates, purified as *oils* by extraction of non-acidic impurities and steam distillation of volatile impurities, gave regenerated carbinols which confirmed the maximum rotations of the distillation products.

These rotations have been compared to those reported in the literature or found independently

(15) In addition, hydrogenation of phenylalkylcarbinols to cyclohexylalkylcarbinols[11,18] made it possible to interrelate the phenyl and cyclohexyl series for the methyl, ethyl, *n*-propyl and isopropyl homologs. The subsequent article in this series [THIS JOURNAL, **82**, 880 (1960)] presents similar hydrogenation data for the three butyl homologs. These results, as well as the theoretical interpretation of the asymmetric reductions, are best rationalized by the conclusion that all of the (−)-alkylphenylcarbinols in Table I have the same configuration.

(16) The configurations assigned for these alkylphenylcarbinols are opposite to those predicted by Marker's generalization, *ibid.*, **58**, 976 (1936).

TABLE II

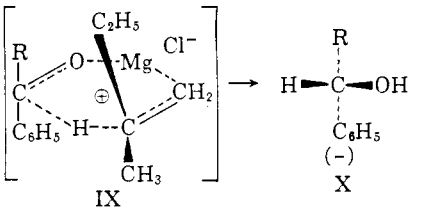
YIELD OF PRODUCTS FROM (+)-2-METHYLBUTYLMAGNESIUM CHLORIDE AND ALKYL ARYL KETONES

Alkyl phenyl ketone Alkyl group	Total recovery	Distribution of products, % Ketone (enolization)[b]	High boiling residue[a]	Secondary carbinol (reduction)	2-Methyl-1-butene (reduction)[c]
Methyl	75	34	29	37	31
Ethyl	100	30	11	59	79[c]
n-Propyl	87	27	13	60	65
Isopropyl	92	9	12	78	80
n-Butyl	83	24	15	61	74
Isobutyl	86	2	8	89	..
t-Butyl	86	0	3	97	96
	90[d]	0	2	98	..
Cyclohexyl	85	0	10	90	89

[a] The residue was measured from the Claisen flask distillation and calculated as normal addition product, b.p. above 220° (20 mm.). [b] Based on the yield of 2,4-dinitrophenylhydrazone obtained from an aliquot of crude distillation product. [c] Obtained by titration of the ether distillate for olefins.[26] By this process we have occasionally and unaccountably obtained results higher than the corresponding reduced carbinol isolated; for instance the result in the second case cannot be reliable. [d] This run was by normal addition, all others were by reverse addition.

for the completely resolved isomers. The percentage asymmetric reductions were calculated as given in the last column of Table III.

The asymmetric reduction products in this series are all levorotatory and thus have the absolute configuration represented by X. Since the absolute configuration of the Grignard reagent is known,[2] the configuration of the preferred transition state during reduction must be represented by IX in which the phenyl group from the ketone and the methyl group of the Grignard reagent are on the same side of the transition state six-membered ring.



The configuration of the product in each case is that predicted on the basis of the cyclic mechanism assuming that the phenyl group of the ketone exerts a greater steric interaction with the groups of the Grignard reagent than the alkyl group of the ketone. This is certainly the expected course of the reaction for methyl phenyl ketone but it is *not* apparent that the phenyl group should exert a greater steric interaction than the cyclohexyl or *t*-butyl groups.[17] In fact the stereospecificity of the reduction, as measured by the percentage asymmetric reduction ($[\alpha]/[\alpha]^{max}$ ×

(17) The possibility that the factor controlling the asymmetry of the transition state is some unique attraction between the methyl group of the Grignard reagent and the phenyl group of the ketone seems very remote. This would explain the results since an increase in the size of the alkyl group of the ketone would then force the phenyl and methyl groups closer together thereby increasing the degree of stereospecificity as observed. However there is no logical basis for assuming such an attraction and in fact the extent of asymmetric reduction with methyl cyclohexyl ketone where such an interaction could not exist was about the same as with methyl phenyl ketone.

TABLE III

OPTICAL ROTATION[a] AND PERCENTAGE ASYMMETRIC REDUCTION FROM THE REACTION OF ALKYL PHENYL KETONES AND THE GRIGNARD REAGENT FROM (+)-2-METHYL-1-CHLOROBUTANE

$$C_6H_5COR + CH_3CH_2\dot{C}H(CH_3)CH_2MgCl \rightarrow\rightarrow C_6H_5\dot{C}HOHCH_3 + CH_3CH_2C(CH_3)=CH_2$$

Alkylphenyl-carbinol Alkyl group	Carbinol from fractionation $\alpha^t D$	t, °C.	$n^{20}D$	Carbinol regenerated from acid phthalate $\alpha^t D$	t, °C.	$n^{20}D$	Reduction product rotation[u] $[\alpha]^t D$	t, °C.	Pure isomer rotation $[\alpha]^{max}D$	t, °C.	Asymmetric reduction, % $[\alpha]/[\alpha]^{max} \times 100$
Methyl	−1.73	21[b]	1.5283	....[c]			−1.75	21	43.5	21[d]	4.0
Ethyl	−1.69	27.5	1.5207	−1.54	22	1.5201	−1.70	27.5	29.1	27.2[d]	5.8
							−1.55	22[f]	28.1	22[d]	5.5
n-Propyl	−1.66	21.6	1.5233	−1.65	21.8	1.5127	−6.34	20[e]	108.7	20[e]	5.9
n-Butyl	−1.20	24.7	1.5092	−1.21	24.6	1.5087	−1.25	25[f]	17.6	25[g]	7.1
							−1.26	25[f]	17.6	25[g]	7.2
Isobutyl	−2.42	24.5	1.5069	−2.24	19	1.5070	−3.19	26[h]	32.3	26[h]	9.9
Isopropyl	−5.36	19.8	1.5143	−4.66	15	1.5134	−11.5	18[i]	47.7	20[i,j]	24.1
							−11.5	18[i,f]	47.7	20[i,j]	24.1
Cyclohexyl	−6.51	21.5[k]	1.5391[l]	−7.02	21.2[k]	....	−9.30	18.5[f,m]	37.6	20[a]	24.7
							−7.02	21.2[f,k]	28.3	22[o]	24.8
							−7.34	21.1[f,k,p]	28.6	22[o]	25.6
t-Butyl[t]	−3.48	28[q]	1.5121[l]	−4.18	20[q]	....[l]	−4.43	26[f,p,q]	27.3[p,q,r]		16.2
							−5.79	21.5[f,s]	36.2	20[r,s]	16.0
t-Butyl[u]	−3.5	28[q]	....	−4.24	20[q]	1.5120[l]	−4.63	20[f,p]	27.3[p,q,r]		17.0
							−6.00	21.5[f,s]	36.2	20[r,s]	16.6

[a] All optical rotations are for the neat liquid, D line of sodium, unless otherwise specified. [b] Specific rotation in ether was −5.2° (25°, *c* 7). [c] Specific rotation in ether was −4.9° (21°, *c* 11). [d] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911). [e] Acetate at 578 mμ. [f] $[\alpha]D$ based on carbinol regenerated from phthalate. [g] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **97**, 387 (1932). The value $[\alpha]D$ 17.2° at 24° was adjusted to 25° on the basis of a sample from the asymmetric reduction which gave $[\alpha]D$ −1.11° at 20° and −1.26° at 25°. [h] In heptane solvent, *c* 16.6. [i] P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **70**, 355 (1926). [j] Rotation in ether, *c* 7. [k] Specific rotation in benzene, *c* 7.7; compound is a solid. [l] Supercooled liquid. [m] Rotation in ether, *c* 10.8. [n] P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **75**, 587 (1927), rotation in ether, *c* 15.6. [o] M. Balfe, G. Beaven and J. Kenyon, *J. Chem. Soc.*, 1857 (1950), specific rotation in benzene, *c* 3.3. [p] At wavelength of 578 mμ. [q] Specific rotation in benzene, $c \cong 9$; compound is a solid. [r] G. Vavon and B. Angelo, *Compt. rend.*, **224**, 1435 (1947). [s] Specific rotation in ether, $c \cong 9$. [t] Reverse addition, 35°. [u] Normal addition at 28°. [v] These are the specific rotations of the alkylphenylcarbinols upon which the calculations of the percentage asymmetric reductions were based. In one case the rotation of the acetate was used and in several a solvent was employed to conform to the conditions for the best values of the maximum rotations reported in the literature.

100), *increases* in an orderly fashion with increasing bulk of the alkyl group: methyl, 4.0; ethyl, 5.7; *n*-propyl, 5.9; *n*-butyl, 7.2;[18] isobutyl, 9.9; isopropyl, 24; cyclohexyl, 25; *t*-butyl, 16.[19] Only *t*-butylphenyl, which one would expect to show the greatest steric bulk, is out of order. This is the reverse of the situation found in the alkyl-*t*-butyl series[2] where the stereospecificity *decreased* with increasing bulk of the alkyl group. It is apparent that the simple interpretation involving steric interactions at two points within the cyclic transition state will not suffice to explain the results. Further theoretical interpretations of these data will be considered in the subsequent paper in this series on the asymmetric reductions of the alkyl cyclohexyl ketones.[20]

The values reported by Vavon and Angelo[7] for the asymmetric reduction of the members of this series of alkyl phenyl ketones using the Grignard prepared from "pinene hydrochloride" are: methyl, 36; ethyl, 19; *n*-propyl, 46; *n*-butyl, 52; isopropyl, 55; *t*-butyl, 72. All of the carbinols have the same sign of rotation but are of opposite rotation (dextro) to the carbinols produced by the asymmetric reduction reported in our present investigation.[21] Unfortunately the rotations of the carbinols are reported in ether solvent while the known maximum rotations in the literature for the resolved carbinols are generally neat or in other solvents. It is known that solvent makes considerable difference in the rotations of these carbinols and thus precise comparison of the results from these two optically active reducing agents cannot be made. Nevertheless the over-all trend is certainly the same with stereospecificity increasing with increasing size of the alkyl group.

t-Butyl phenyl ketone has now been subjected to asymmetric reduction by the Grignard reagents from five different optically active halides to give the following extents of asymmetric reduction: pinene hydrochloride,[7] 72%; neomethyl chloride,[22]

(18) This value for *n*-butyl might be slightly high since the evidence in the literature[12] for the complete resolution of *n*-butylphenylcarbinol is not conclusive.

(19) We have confirmed the maximum rotation reported for completely resolved *t*-butylphenylcarbinol by Vavon and Angelo[7] who refer to this compound as *pseudo*-butylphenylcarbinol. Vavon and Angelo crystallized the cinchonidine salt of the acid phthalate ester and obtained (+)-*t*-butylphenylcarbinol, $[\alpha]D$ +38.4° (*c* = 0.09, ether), $[\alpha]D$ +27.3° (*c* 0.10, benzene), m.p. 55.5°. We have used successive crystallizations of the brucine salt, cinchonidine salt and acid phthalate to obtain (+)-carbinol, $[\alpha]^{27}D$ +27.8° (*c* 2.7, chloroform), $[\alpha]^{20}D$ +36.2° (*c* 9, ether), m.p. 54.0–54.5°, and the (−)-carbinol, $[\alpha]^{27}D$ −27.0° (*c* 2, chloroform) by crystallization of the strychnine salt of the acid phthalate. Therefore the figure of 16.5% asymmetric reduction is in all probability correct.

(20) E. P. Burrows, F. J. Welch and H. S. Mosher, THIS JOURNAL, **82**, 880 (1960).

(21) On the basis of (a) the known absolute configuration of the isobornyl used by Vavon and Angelo [A. Birch, *Ann. Repts.*, **47**, 190 (1950); A. Fredga and J. Milttinen, *Acta Chem. Scand.*, **1**, 371 (1947)], (b) the proposed mechanism for the asymmetric Grignard reduction reaction and (c) the assumption that there is more steric interaction in the transition state between the phenyl group of the ketone and the *gem*-dimethyl bridge of the reducing agent than between the alkyl group of the ketone and the *gem*-dimethyl bridge, it would be predicted that the carbinols would be dextrorotatory as found.

(22) M. F. Tatibouet, *Bull. soc. chim.*, [5] **18**, 867, 868 (1951).

27%; (+)-1-chloro-2-methylbutane, 16%; (+)-limonene hydrochloride,[21] 6%; and (+) 3-chloropinane,[21] 0%. With the exception of the final example, the extents of asymmetric reduction observed increase as would be expected, although the interpretation must be rather speculative since in three of the cases the halogen is attached to an asymmetric center.

Experimental

Materials.—Acetophenone, propiophenone, butyrophenone, isobutyrophenone, valerophenone and isovalerophenone were commercial materials carefully fractionated before use. *t*-Butyl phenyl ketone, b.p. 110° (20 mm.), $n^{20}D$ 1.5100, was made both by the reaction of benzoyl chloride with *t*-butylmagnesium chloride in the presence of cuprous chloride (14% yield) according to the method investigated by Cook and Percival[23] and by the action of phenylmagnesium bromide on trimethylacetonitrile (66% yield).[24] Cyclohexyl phenyl ketone, m.p. 57.0–57.5°, was prepared by the Friedel–Crafts reaction (50% yield).[25] The Grignard reagent was prepared by the method previously described in detail[2] from primary active amyl alcohol, $\alpha^{20}D$ −4.76° (neat), which was converted to the chloride, $\alpha^{20}D$ + 1.44° (neat). Two batches of 1.5 liters each of 1.2 *N* Grignard solution were prepared and stored under nitrogen.

Asymmetric Reductions.—All of the reductions were carried out by adding aliquots, 0.36 mole as measured by titration, of the stock Grignard solution to a gently refluxing solution of the ketone, 0.33 mole, in anhydrous ether, 120 ml., under a nitrogen atmosphere as previously described.[2] The reaction mixtures were hydrolyzed by an ammonium chloride solution. The ether was carefully removed through a twenty-plate helix-packed column and titrated for olefins (2-methyl-1-butene) by the method of Johnston and Clark.[26]

The yields of products reported in Table II were estimated from the data obtained by first distilling the crude reaction product from a Claisen flask up to 220° (20 mm.) and then carefully fractionating the distillate through a spinning band column (4 mm.). The fractions containing the ketone were analyzed by quantitative preparation of the 2,4-dinitrophenylhydrazone from an aliquot. The fractions containing the alkylphenylcarbinol were refractionated and a final check on the optical activity of the asymmetric reduction product was obtained by conversion to the acid phthalate, purifying the acid phthalate by extraction and steam distillation, and regenerating the carbinol by use of 20% sodium hydroxide. In the case of *t*-butyl phenyl ketone two runs were made, one as above and a second using normal addition of the ketone to the Grignard solution. The pertinent data are summarized in Tables II and III and given in complete detail in reference 7.

Resolution of Isobutylphenylcarbinol.—Isobutylphenylcarbinol, b.p. 98° (4 mm.), $n^{20}D$ 1.5071, prepared by a Meerwein–Ponndorf reduction of the ketone, was converted to the *dl*-acid phthalate, m.p. 96–98°. The brucine salt failed to crystallize, but the strychnine salt was readily prepared in methanol. It was crystallized seven times from methanol to constant rotation, $[\alpha]^{25}D$ −23° (*c* 2.8, supersaturated in methanol), m.p. 197°. The regenerated acid phthalate was an oil, $[\alpha]^{25}D$ −34.6° (*c* 4.2, chloroform). It was converted to the isobutylphenylcarbinol, which was then recrystallized from *n*-heptane; m.p. 50.0–50.5°, $[\alpha]^{26}D$ −32.3° ($\alpha^{26}D$ −2.70°, *c* 16.70, *l* 0.5, *n*-heptane). Further recrystallization of the carbinol did not raise the melting point or rotation. Several crystallizations, first from the melt, then from *n*-heptane, of the partially active isobutylphenylcarbinol obtained from the asymmetric reduction gave the pure isomer with these same properties.

Resolution of Isopropylphenylcarbinol.—Levene and Mikeska[27] report the maximum rotation of this carbinol obtained *via* the strychnine salt of the acid phthalate as $[\alpha]^{20}D$ + 47.66° (*c* 6.797, ether), but the evidence for complete resolution was not convincing. To augment these data the acid phthalate of partially active (−)-isopropylphenylcarbinol from the asymmetric reduction was converted to the acid phthalate and brucine salt which was crystallized four times from acetone; $[\alpha]^{27}D$ −4.3° ($\alpha^{27}D$ −0.47°, *c* 1.10, *l* 1, acetone), m.p. 130–135° dec. This was converted to the acid phthalate which was crystallized twice from heptane, $[\alpha]^{25}D$ + 44.5° ($\alpha^{25}D$ +3.15°, *c* 3.54, *l* = 2, chloroform), m.p. 93.5–94.0°. The melting point of the racemic acid phthalate is 133°. Melting points of mixtures of the *dl*- and *d*-acid phthalates indicate an eutectic having $[\alpha]^{23}D$ 38°, m.p. 88°. A sample of acid phthalate, $[\alpha]^{23}D$ −37.3° ($\alpha^{23}D$ −1.575, *c* 4.225, *l* 1, chloroform), m.p. 88–90°, was regenerated to the isobutylphenylcarbinol, $[\alpha]^{17.3}D$ −40.7° ($\alpha^{17.3}D$ −0.880°, *c* 4.33, *l* 0.5, ether). From these values a maximum rotation of $[\alpha]^{17.3}D$ −49 ± 2° (*c* 4.3, ether) can be calculated which is in satisfactory agreement with that reported by Levene and Mikeska.[27]

Resolution of *t*-butylphenylcarbinol.—Vavon and Angelo[7] have reported the resolution of *t*-butylphenylcarbinol (designated by them pseudobutylphenylcarbinol) *via* the cinchonidine salt of the acid phthalate. The resolved acid phthalate, $[\alpha]_{578}$ + 14.30° (*c* 5, ether), m.p. 112°, gave carbinol, $[\alpha]_{589}$ + 38.40° (*c* 0.09, ether) and $[\alpha]_{578}$ + 27.30° (*c* 0.10, benzene), m.p. 55.5°. In order to check this value the brucine salt of the acid phthalate was recrystallized four times, $[\alpha]^{27}D$ −14° ($\alpha^{27}D$ −0.74°, *c* 5.30, *l* 1, acetone), m.p. 87° dec. and converted to the acid phthalate which was crystallized from hexane, $[\alpha]^{27}D$ +27.8° ($\alpha^{27}D$ + 1.50°, *c* 2.70, *l* 2, chloroform), m.p. 112–112.5°. Conversion of this resolved acid phthalate to the strychnine salt and regeneration did not change its properties. The *t*-butylphenylcarbinol obtained by hydrolysis was sublimed, m.p. 54.0–54.5°, $[\alpha]^{22}D$ +25.9° ($\alpha^{22}D$ +1.16°, *c* 2.241, *l* 2, benzene), $[\alpha]^{27}D$ +27.8° (*c* 2.7, chloroform), $[\alpha]^{20}D$ + 36.2° (*c* 9, ether). This is slightly lower than the value reported by Vavon and Angelo, but the concentrations were not the same. The racemic acid phthalate melted at 139–140° and formed a eutectic with the *d*-form, m.p. 99°, $[\alpha]^{26}D$ 20° (*c* 4, chloroform). The racemic form of the carbinol melted at 45°.

Configuration of Ethylphenylcarbinol Relative to Mandelic Acid.—(+)-Mandelic acid,[28] 16.7 g., $[\alpha]^{23}D$ + 40° (*c* 2.5, water), was converted to the crude methyl ester[29] which was converted to the (+)-methyl O-methylmandelate (90% yield) by treating with methyl iodide and silver oxide.[30] This was in turn converted to (+)-O-methylmandelamide[31] (97% yield) by treating with liquid ammonia in methanol solution; $[\alpha]^{21}D$ +21° (*c* 4.0, acetone).

(−)-1-Phenyl-1-methoxy-2-propanone.—To a Grignard solution, 0.50 mole, from methyl iodide in 150 ml. of ether was added finely powdered O-methylmandelamide (11 g., 0.07 mole, $[\alpha]^{21}D$ +21°). The reaction mixture was refluxed 25 hours and then 90 ml. of purified 1,4-dioxane was added and the mixture refluxed for 2 more hours. The reaction mixture was hydrolyzed with ice-cold dilute sulfuric acid solution and the product isolated from the dried (sodium sulfate) ether extracts by distillation; 4.6 g., b.p. 58–60° (0.5 mm.), $n^{20}D$ 1.5062. This was dissolved in petroleum ether (35–45°), washed with 10% sodium bisulfite solution, dried and redistilled; 3.9 g. (34% yield) of yellow oil, b.p. 54–57° (0.2 mm.), $n^{20}D$ 1.5064, $\alpha^{28}D$ −2.10° (*l* 0.5, neat). From the aqueous solution of the reaction mixture was isolated by repeated methylene chloride extractions 3.5 g. of an unidentified dark oil which solidified on cooling. Treatment with Norit and crystallization from hexane gave 2.1 g. of yellow platelets, m.p. 108–113°, $\alpha^{20}D$ 0.0° (*c* 4, *l* 1, acetone).

***dl*-1-Phenyl-1-methoxy-2-propanone.**—α-Bromopropiophenone, obtained in 88% yield,[32] was treated with sodium methoxide to give a 64% yield of 1-phenyl-1-methoxy-1,2-epoxypropane[33] which was converted to the *dl*-1-phenyl-1-

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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 $C_{11}H_{10}O_4S$: 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, $\alpha^{26}D$ −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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Asymmetric Reductions. VIII. The Action of the Grignard Reagent from (+)-1-Chloro-2-methylbutane on Cyclohexyl Alkyl Ketones[1]

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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

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