Anal. Calcd. for $C_{24}H_{32}O_3$: C, 78.2; H, 8.7. Found: C, 78.0; H, 8.8.

3-*n*-Butyrylhexestrol, produced by demethylation of (IIc), crystallized from a mixture of benzene and ligroin in fine colorless needles, m. p. 134°.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.6; H, 8.2. Found: C, 77.4; H, 8.3.

The oxime of 3-*n*-butyrylhexestrol dimethyl ether formed from ethanol fine colorless needles, m. p. 135°.

Anal. Calcd. for $C_{24}H_{33}NO_3$: N, 3.6. Found: N, 3.5.

The Beckmann rearrangement readily yielded **3-*n*-butyrylaminohexestrol dimethyl ether,** crystallizing from ether in lustrous colorless leaflets, m. p. 150°.

Anal. Calcd. for $C_{24}H_{33}O_3N$: N, 3.6. Found: N, 3.4.

3-*n*-Octanoylhexestrol Dimethyl Ether (IId).—This compound (17 g., b. p. about 300° at 15 mm.) crystallized from ligroin in light colorless leaflets, m. p. 67°; its demethylation gave a greasy mass which could not be purified, but which apparently contained **3-*n*-octanoylhexestrol,** since it gave a yellow coloration with aqueous sodium hydroxide.

Anal. Calcd. for $C_{28}H_{40}O_3$: C, 79.2; H, 9.4. Found: C, 79.0; H, 9.6.

Summary

1. The Friedel–Crafts reactions of hexestrol dimethyl ether and various acid chlorides are described.

2. Several ketones and nitrogen-containing substances derived from hexestrol have been prepared for biological investigation.

PARIS, FRANCE RECEIVED FEBRUARY 13, 1950

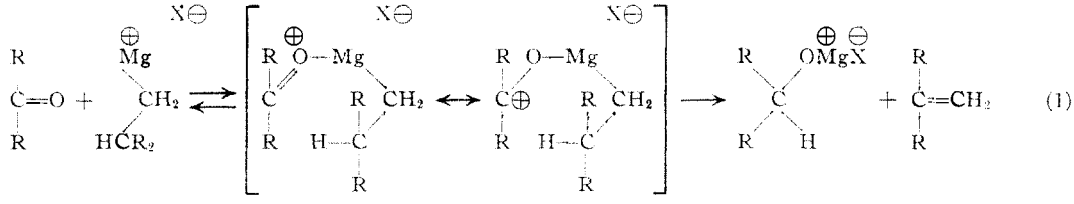
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Asymmetric Reductions. I. The Action of (+)-2-Methylbutylmagnesium Chloride on Methyl *t*-Butyl Ketone[1]

BY HARRY S. MOSHER AND EDWARD LA COMBE

Vavon and co-workers[2,3] have reported the unique action of isobornylmagnesium chloride[4] on a series of six phenyl alkyl ketones to give in each case the reduced phenylalkylcarbinol which was optically active. The optical activity of these products ranged from 19 to 72% of that reported for the pure dextro isomers. With the exception of reactions involving enzyme systems, no other case of an asymmetric reduction by an optically active reducing agent is known to the authors.[5,6]

Whitmore has proposed a common basis for the "abnormal" reactions of the Grignard reagent with carbonyl compounds[7,8] which represents the mechanism for the Grignard reduction reaction proceeding via a six-membered ring complex as formulated in equation 1.[9]



(1)

In an effort to obtain further evidence bearing on this mechanism, a study on the action of the Grignard reagent from (+)-2-methylbutyl chloride on various hindered aliphatic ketones was under-

(1) Presented before the San Francisco Meeting of the American Chemical Society, March 28, 1949. This paper was originally submitted to THIS JOURNAL on April 8, 1949, in the form of a communication.

(2) Vavon and Angelo, *Compt. rend.*, **224,** 1435–1437 (1947).

(3) Vavon, Riviere and Angelo, *ibid.*, **222,** 959 (1946).

(4) The isobornylmagnesium chloride was the Grignard solution obtained by the action of magnesium on "pinene hydrochloride." Vavon and Riviere, [*Compt. rend.*, **220,** 286 (1945); *Ann. chim.*, **1,** 157-231 (1946)] have shown by oxidation and carbonation experiments that such a solution contains a mixture of bornylmagnesium and isobornylmagnesium chlorides in approximately equal amounts, and that it was the isobornylmagnesium chloride in this solution which was primarily responsible for the reducing action. Presumably this is because of the greater hindrance existing in the isobornyl structure containing the *cis* methylene bridge.

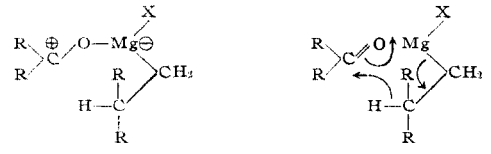
(5) The communication by Doering and Young [THIS JOURNAL, **72,** 631 (1950)], which appeared after the present paper was submitted, describes two successful experiments of this type.

(6) Baker and Linn [*ibid.*, **71,** 1399 (1949)] describe an unsuccessful attempt at the asymmetric reduction of acetophenone using the optically active aluminate from (+)-2-methyl-1-butanol.

(7) Frank C. Whitmore, paper presented before the Atlantic City Meeting of the American Chemical Society, April, 1943.

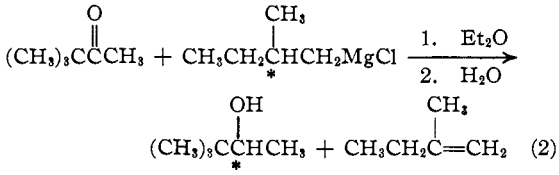
(8) For a review of this subject, prior references, and some of the experimental basis for this generalization, see the Ph.D. thesis of Richard Stanley George, The Pennsylvania State College, July, 1943, available through the University Microfilm Service, Ann Arbor, Mich. See also the reviews of the Grignard reduction by Kharasch and Weinhouse [*J. Org. Chem.*, **1,** 209 (1936-1937)] and by Runge ["Organometallverbindungen," Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1944, p. 394–404].

(9) In this and the following formulations the ether molecules which are coördinated to the magnesium have been omitted for convenience in representation. Various symbolisms may be used to delineate the postulated intermediate in this reaction. Two other representations would be

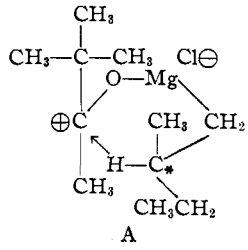


All of these are essentially equivalent. The extent of ionic character of the magnesium halogen bond in anhydrous ether is still problematical.

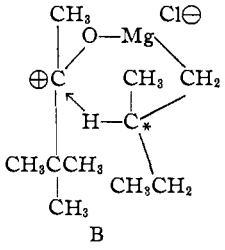
taken.[10] It was predicted on the basis of the generalization proposed by Whitmore[6] that the alcohol resulting from the reducing action of (+)-2-methylbutylmagnesium chloride[11] on an unsymmetrical hindered ketone *would contain a preponderance of one of the optical isomers.* This is indicated by equation (2) in which an asterisk labels the asymmetric carbon atoms.



This prediction was based on the assumption that there would be less steric interference occurring in the proposed ring complex of the transition state when the small methyl group from the optically pure Grignard reagent was on the same side of the ring as the large *t*-butyl group of the ketone as represented in formula A. In A the methyl



A



B

group from the ketone and the ethyl group from the Grignard reagent both lie below the plane of the ring while the *t*-butyl group from the ketone and the methyl group from the Grignard reagent both lie above the plane of the ring. The tendency for the transitory ring to form with the two larger groups, namely, the *t*-butyl group from the ketone and the ethyl group from the Grignard reagent, both on the same side of the ring as shown in formula B, should be less because of the greater apparent steric interference in the transition state. The activation energy necessary to reach the transition state represented by A should be less than that represented by B and therefore the products of the reaction resulting from A should predominate. These considerations become more apparent when the actual atomic models are compared.

If these assumptions are valid, the above mechanism for the Grignard reduction reaction predicts a partially stereochemically specific reduction when a favorably substituted ketone is treated with an optically active Grignard reagent possessing *an asymmetric center on the beta carbon atom.* This mechanism should, in fact, permit qualitative correlations of the extent of asymmetric reduction with the relative size and nature of the various groups. It should likewise allow the successful assignment of relative configurations to the alcohols formed. What is more important, this theory permits the design of experiments which will test its validity. Cases can be visualized in which the interference would result from interaction of permanent dipole forces rather than steric factors.

The partial asymmetric synthesis as represented by equation 2 has now been experimentally realized. The establishment of optical activity in the reduction product, methyl-*t*-butylcarbinol, depends upon two observations: first, upon the rotation in five different experiments of the fraction boiling at the known temperature for the boiling point of methyl-*t*-butylcarbinol and having very nearly the same refractive index[12]; second, upon the preparation of the half phthalate esters of these five fractions all of which melt at the same temperature as the known derivatives of methyl-*t*-butylcarbinol[24] and all of which are optically active. Other optically active materials are present in the reaction mixture but the fractionation data and the evidence from the half phthalate ester derivatives prove that the carbinol itself is optically active. The fractionation data of run no. 2 are representative of the five experiments and are plotted in Fig. 1. The boiling point and refractive index of the methyl-*t*-butylcarbinol fraction are constant for a series of seven cuts; the rotation is constant for the last five. The first hump in the rotation curve at approximately 100° indicates the presence of unreacted (+)-2-methylbutyl chloride. The rotations of the methyl *t*-butyl ketone fractions, which boil 5 to 6° higher, drop to zero before the temperature rises to that of the carbinol fraction. In some of the distillations, the rotation curve dips slightly near the end of the carbinol fraction which indicates the presence of a small amount of the (−)-2-methyl-1-butanol; however, in run no. 2 there is no indication of this, since the boiling point, refractive index, and rotation rise sharply. The especially sharp rise in rotation is undoubtedly caused by the presence of the coupling product, 3,6-dimethyloctane.[13] The

(10) Our original intention was to follow the reaction with a Grignard reagent labelled with deuterium in the *beta* position. It was upon the suggestion of Dr. Richard Eastman of these laboratories that the investigations were initiated with optically active reagents. This work was begun in the summer of 1947, at which time Vavon's experiments had not yet come to our attention.

(11) The term (+)-2-methylbutylmagnesium chloride is used to indicate the Grignard solution prepared from (+)-2-methylbutyl chloride. This solution is dextrorotatory and has a specific rotation of approximately $[\alpha]^{20}D$ +4.7°. That this Grignard solution may contain more or less dialkylmagnesium as well as the alkylmagnesium chloride is realized, but this would in no way alter the general theoretical conclusions arrived at from our present evidence.

(12) Whitmore and Meunier, THIS JOURNAL, **54**, 3721 (1933).

(13) The recorded rotation of this hydrocarbon [Hardin and Sikorsky, *J. chim. phys.*, **6**, 179-211 (1908)] made by the Wurtz reaction is $[\alpha]^{18}D$ +16.85. We observed a maximum rotation in run no. 2, cut 26, b. p. 156°, $\alpha^{20}D$ +20.68°. We have prepared this hydrocarbon by the Wurtz reaction and find a rotation of $[\alpha]^{20}D$ +17.4°. We feel that both this and the literature values are low since a qualitative experiment on a sample of this material showed that as much as 25% of the activity was lost on stirring in hexane solution with concentrated sulfuric acid for twenty minutes. In the Wurtz synthesis of this and other optically active hydorcarbons in the literature, purification from contaminating olefins has almost always been accomplished by shaking with concentrated sulfuric

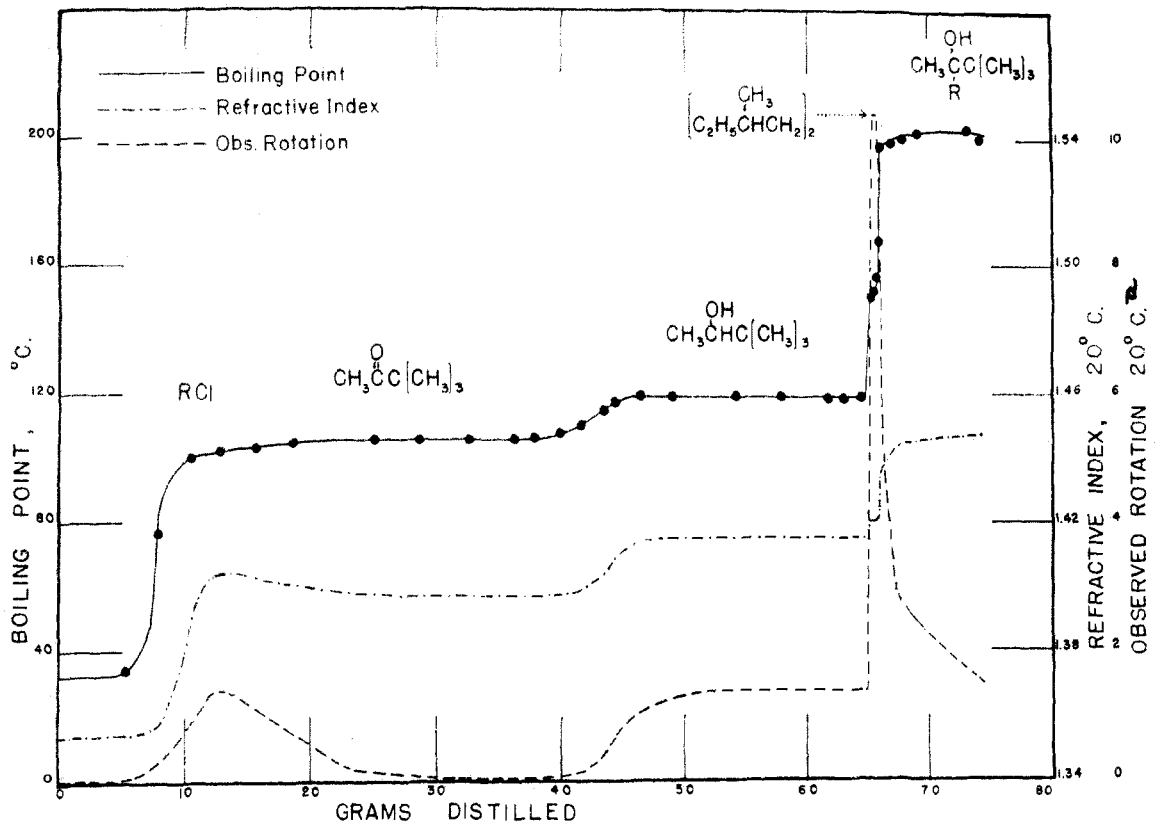


Fig. 1.—Fractionation curve run 2: [a] The observed rotations, $\alpha^{20}D$ below 2° were in a 2-dcm. tube while those above 2° were in a 0.5-dcm. tube. [b] This may also contain the condensation product of pinacolone.

amount of high-rotating coupling product found in the other four runs is much less than indicated by the sharp rise in rotation for run no. 2.

The addition and condensation products boil too high to be considered seriously as contaminants of the methyl-*t*-butylcarbinol. No attempt was made to identify the components of the high boiling material. Previous work[14,15] would indicate that it probably contains some of the condensation product, 2,2,5,6,6-pentamethyl-5-heptanol-3-one, and its dehydration product. In addition it was found that this high boiling material failed to form a derivative under conditions which successfully gave the half phthalate of methyl-*t*-butylcarbinol. Another possible contaminant, (−)-2-methyl-1-butanol, could not be converted to a crystalline half phthalate ester.

From Table I it can be seen that the rotation of the methyl-*t*-butylcarbinol fractions in the first four runs varies from 8.2 to 11.1% of the value reported[16] for the pure dextro isomer. The rotations of the half phthalate derivatives in these same four runs varies from 13.0–13.7% of the value reported for the pure dextro isomer.[24] It is felt that the lower rotations of the liquid samples is a result of contamination from the inactive methyl *t*-butyl ketone which boils 13° below the carbinol and perhaps from some of the (−)-2-methyl-1-butanol which boils 9° higher. Since the half phthalate esters were purified by crystallization, they constitute a better criterion of the optical purity of the alcohol in these respective fractions. That no concentration of the dextro derivative from the racemic derivative occurred during crystallization is shown by the experiments on the successive recrystallizations of the optically active half phthalate ester in which the specific rotation declined only very slightly after three recrystallizations. In addition the crystallization and recrystallization of a mixture of the optically active derivative and the *dl*-half phthalate ester gives a crystalline product with the rotation to be expected on the assumption that no concentration occurs. It is therefore established that approximately the same extent of *asymmetric reduction* (but not necessarily the same amount of reduction) occurs in normal addition, reverse addition, and in dilute solutions.[17] This can only mean that the

acid. The preparation of optically pure 3,6-dimethyloctane is being investigated in order to reconcile, if possible, the high rotation obtained on this fraction.

(14) Hickinbottom and Schuchterer, *Nature*, **155**, 19 (1945).

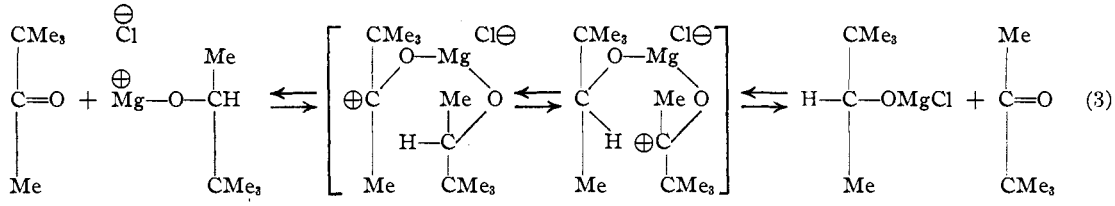
(15) Tolslapyatov and Voshilova, *J. Gen. Chem.* (*USSR*), **15**, 565 (1945).

(16) Pickard and Kenyon, *J. Chem. Soc.*, **105** 1120 (1914).

(17) If one accepts a value of 13% as the established excess of the dextro isomer in this reaction at 20°, the difference in the free energies of activation of the two transition states as represented by A and B is found to be in the order of 150 cal.

asymmetric reduction is not a matter of "association" with an optically active media. The fact that dilution has no apparent effect on the extent of asymmetric reduction means only that the same mechanism is operating at the two concentrations. This is completely compatible with the mechanism proposed since concentration should have no effect on a reaction within the complex once it is formed.

The reaction conducted at −75° gave a significantly smaller amount of the methyl-*t*-butylcarbinol. If the rotation of the crystallized half phthalate ester is taken as a measure of the extent of asymmetric reduction, it is seen that the reaction at the lower temperature is significantly more stereochemically specific, 16% as compared to 13.5%. The accuracy of this one experiment is hardly sufficient to warrant the calculation of the differences in entropy factors of the two transition states A and B. It is also possible that there is a slow racemization taking place at 15–20° and that this occurs much more slowly, if at all, at −75°. Such a racemization could possibly account for the differences in the ratio of products at these two temperatures and could proceed via a reversible reaction.



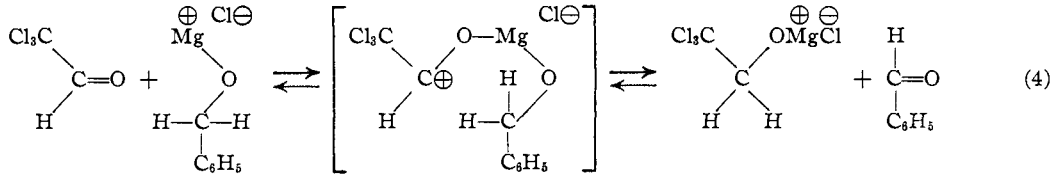
(3)

Since the stereospecificity of this reaction will not be 100%, this equilibrium will lead to racemization. This mechanism would predict that the configuration of magnesium chloro alcoholate produced would be the same as the starting alcohol. The fact that reverse addition (run no. 3), in which an excess of the ketone is always present, gave about the same extent of asymmetric reduction as normal addition (run no. 1), in which no excess of ketones was allowed to accumulate, indicates that this mechanism must play a very minor role and that racemization from this source is probably insignificant.

The partial asymmetric reduction as represented by equation 2 not only gives further experimental support to Vavon's observations but also establishes a logical explanation for the phenomenon. The example represented by equation 2 is an exceptionally simple case of asymmetric reduction. It is particularly unambiguous since the optically active reducing agent, (+)-2-methylbutylmagnesium chloride[11] is converted into 2-methyl-1-butene which no longer possesses the possibility of asymmetry. Since there is only one asymmetric center in the reducing agent, there can be no doubt as to the structure in the molecule responsible for the asymmetric reduction. It is significant that the above explanation does not call upon any elusive "asymmetric inductive force" but is based solely on the application of well-established stereochemical considerations to the transition state. This example also constitutes a simple model for stereospecific enzymatic reductions.

This evidence renders untenable the theory proposed by Blicke and Powers[18] involving the initial dissociation of the Grignard reagent into the free organic radical and magnesium subhalide. Likewise, the theory which proposes as an initial step the formation of the olefin and magnesium halohydride,[19] cannot account for the stereochemical course of the reduction.

It is quite likely, however, that the reaction proposed by Whitmore to account for the reduction products found in the Grignard reaction is not the only one possible. The small amount of reduction of chloral to trichloroethanol (1%) with benzylmagnesium chloride, reported by Gilman and Abbott,[20] cannot be accounted for by the reaction indicated in equation 1. However, it is possible that this reduction takes place essentially according to the Meerwein–Ponndorf–Verley reaction; chloromagnesium alcoholate resulting from normal addition acts as the reducing agent and is itself oxidized to the corresponding aldehyde or ketone. In the example reported by Gilman and Abbott this can be represented as follows, in which the reducing agent is chloromagnesium benzylate resulting from air-oxidation of the Grignard reagent. The reducing agent might also be the



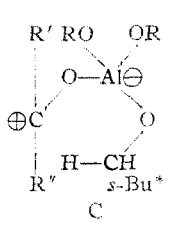
(4)

magnesium chloro alcoholate from benzyltrichloromethylcarbinol but its oxidation product, benzyl trichloromethyl ketone, was not reported as a product of the reaction. Meerwein and Schmidt[21]

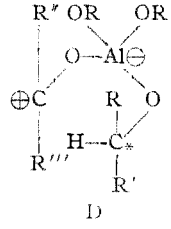
(18) Blicke and Powers, THIS JOURNAL, **51**, 3378 (1929).
(19) Hess and Rheinboldt, *Ber.*, **54**, 2043 (1921).
(20) Gilman and Abbott, *J. Org. Chem.*, **8**, 234 (1943).
(21) Meerwein and Schmidt, *Ann.*, **444**, 221 (1925).

have reported the reduction of several aldehydes to the corresponding alcohols in 60–80% yields using chloromagnesium ethylate. This reaction does not require the formation of any olefin. Since in each of our experiments the amount of olefin determined by titration approximates the percentage of reduction of the methyl *t*-butyl ketone, it is assumed that this alternate reduction plays only a minor role in the above reaction at the usual temperature.

The mechanism indicated in equation 4 to represent reduction by a chloromagnesium alcoholate is the same in its essential features as the mechanism proposed for the Grignard reduction reaction. The primary difference is the presence of two oxygen atoms instead of one in the six-membered ring transition state; instead of a carbon to carbon double bond being formed as in the Grignard reduction, a carbon to oxygen double bond results. This same mechanism has been applied recently to aluminum alcoholate reductions by Baker and Linn,[6] who represent the activated complex in the reaction of the aluminate from (−)-2-methyl-1-butanol with carbonyl compounds as shown in C.



C



D

These authors were unable to obtain demonstrable asymmetric reduction of acetophenone using the above optically active aluminate. On the basis of the stereochemistry of the six-membered ring transition state, no significant asymmetric reduction would be anticipated in a simple molecule with one asymmetric center unless that center was on the carbinol carbon atom as represented in D above.[5,22] A study of the effects of asymmetric reagents in the Meerwein–Ponndorf–Verley reaction is much more difficult than in the Grignard reduction reaction because of the reversibility of the former reaction and consequent racemization known to be catalyzed by metal alcoholates.[23]

The asymmetric carbon atom of (+)-2-methylbutylmagnesium chloride is in the *beta* position to the magnesium atom and occupies a critical location in the proposed six-membered ring transition state as shown in A and B. It would not be expected that an asymmetric center situated in the *gamma* or *delta* position of a simple non-cyclic Grignard reagent would have an appreciable effect on the stereochemical course of the reduction. This is being further investigated with the homologs of (+)-2-methylbutylmagnesium chloride.

(22) In a recent article by Mills and Jackson [*Nature*, **164**, 789 (Nov. 1949)] stereochemical evidence in the Meerwein–Ponndorf–Verley reduction of cyclohexanone derivatives is presented in support of this same mechanism.

(23) Doering and Aschner, THIS JOURNAL, **71**, 838 (1949).

The effect of dilution on the per cent. yields of the enolization, reduction, and the combined addition and condensation reactions was very interesting. Kharasch and Weinhouse[8] did not observe any large effect as a result of a tenfold concentration change on the reduction of benzophenone by *n*-butylmagnesium bromide. Our results as indicated by run no. 1 confirm this but do show a surprising increase of the amount of high boiling material assumed to be either the normal addition product or the condensation product or both, at the expense of enolization. It is planned to investigate this phenomenon further with more suitable examples. In the experiment conducted at −75°, it was found that formation of the high boiling material was greatly favored at the expense of the reduction product when compared to the reaction conducted at room temperature. This is in line with the previous observations of Rheinbolt and Roleff[24] which indicate that the reduction reaction is more temperature-dependent than is normal addition.

Experimental

(−)-2-Methyl-1-butanol[25,26,27] of 96–98% optical purity[28] was converted into (+)-2-methylbutyl chloride by treatment with thionyl chloride and pyridine[29] in a purified yield of 72–78% of optical purity 94–96%.[30] This chloride showed no change in optical activity after standing one year.

The Action of (+)-2-Methylbutylmagnesium Chloride on Methyl *t*-Butyl Ketone: Run 1.—The Grignard reagent from 84.8 g. (0.79 mole) of (+)-2-methylbutyl chloride ($\alpha^{20}D$ +1.42, $n^{20}D$ 1.4130) and 20.0 g. (0.83 mole) of magnesium was prepared in 600 ml. of dry ether under nitrogen atmosphere at 15°. To this solution was added at a temperature of approximately 20°, 75 g. (0.75 mole) of fractionated methyl *t*-butyl ketone (b. p. 106–106.5°, $n^{20}D$ 1.3970) over a one-hour period. After stirring overnight, the reaction mixture was hydrolyzed by pouring onto 600 g. of ice and 60 g. of ammonium chloride. The ether layer and three subsequent 150-ml. ether extracts of the aqueous layer were combined, dried over anhydrous magnesium sulfate, the ether removed by distillation through a twenty-plate column, and the residue distilled from a regular distilling flask. This left a residue of 6.0 g., and gave 80.7 g. of material boiling below 190°. The latter was fractionated through a thirty-plate column with the results summarized in Table I.

A sample taken from the fraction boiling at 119°, $\alpha^{20}D$ +0.70, $n^{20}D$ 1.4153, was converted into the half phthalate ester in 76% yield, m. p. 83–85°. This crude ester was recrystallized three times from hexane, m. p. 85.5–86.5°, $\alpha^{20}D$ +0.64 (l = 2, c = 3.65, chloroform) $[\alpha]^{20}D$ +8.77°.

Anal. Calcd. $C_{14}H_{16}O_4$: C, 67.18; H, 7.25. Found: C, 67.19, 67.13; H, 7.14, 7.25.

Pickard and Kenyon[16] have reported properties for the pure dextro half-phthalate ester of methyl-*t*-butylcarbinol: m. p. 85–86°, $[\alpha]^{20}D$ +63.9 (chloroform). The racemic ester is reported to melt at 84–85°. The pure dextro alcohol itself has a specific rotation $[\alpha]^{20}D$ +7.71, d^{20} 0.8199.

Run 2.—This experiment, with the exception of temperature, was essentially a duplicate of Run 1: 70 g. (0.70 mole) of pinacolone was added dropwise to 0.80 equivalent

(24) Rheinboldt and Roleff, *J. prakt. Chem.*, [2] **109**, 175 (1925).
(25) Whitmore and Olewine, THIS JOURNAL, **60**, 2570 (1938).
(26) Brauns, *J. Res. Nat. Bur. Stand.*, **18**, 315–331 (1937).
(27) Brokaw and Brode, *J. Org. Chem.*, **13**, 194 (1948).
(28) Marckwald and McKenzie, *Ber.*, **34**, 485 (1907).
(29) Brown and Groot, THIS JOURNAL, **64**, 2563 (1942).
(30) McKenzie and Clough, *J. Chem. Soc.*, **103**, 698 (1913).

TABLE I

REACTION PRODUCTS FROM (+)-2-METHYLBUTYLMAGNESIUM CHLORIDE AND METHYL *t*-BUTYL KETONE

Run	Conditions	Per cent. yield[e] Pinacolone (enol.)	Addition and/or cond.[a]	Pinacolyl alc. (reduct.)	2-Methyl 1-butene[d]	Total % recovery[b]	$\alpha^{20}D$ Pinacolyl alc.	$[\alpha]^{20}D$ half phthalate	% Excess dextro isomer[c]
1	Normal addn., 20°	39.5	12.0	25.4		76.9	+0.70	+ 8.8	13.7
2	Normal addn., 35°	32.2	8.1	25.2	22.6	66.9	+0.67	+ 8.3	13.0
3	Reverse addn., 20°	35.9	12.0	35.6	31.2	83.5	+0.52	+ 8.7	13.6
4	High diln., 20°	11.1	32.3	29.0	24.8	72.4	+0.62	+ 8.3	13.0
5	Low temp., −75°	29.7	37.9	9.0	6.2	76.6	+0.42	+10.1	16.1

[a] This is a maximum figure based on all of the material boiling above 170° and calculated as the normal addition product, 2,2,3,5-tetramethyl-3-heptanol. It undoubtedly represents both condensation product and addition product in unknown amount. [b] Based on pinacolone. [c] Based on the rotation of the recrystallized half phthalate ester prepared from the middle cut of the methyl-*t*-butylcarbinol fraction and compared to the value of $[\alpha]^{20}D$ +63.9° reported[16] for the pure dextro isomer. As indicated in the experimental section recrystallization of this derivative did not result in any concentration of the dextro isomer. [d] Not isolated but obtained by titration of the olefins in the distilled ether. [e] The yields are calculated on the pinacolone taken, since the Grignard reagent was in excess in every case. These yields include the material in the intermediate fractions; the percentage is estimated on the assumption of a two component system in the mixture between any two successive flats on the distillation curve. Estimations are based on the assumption of a linear relationship between per cent. composition and refractive index or rotation in the mixtures.

of Grignard solution in refluxing ether. Simple distillation of the ether solution from the reaction gave 81 g. of material boiling below 200° and left a residue of 1.9 g. Fractionation of the distillate through a thirty-plate column gave the results shown graphically in Fig. 1 and summarized in Table I. Titration of an aliquot of the ether removed from the reaction mixture for olefin according to the method of Johnson and Clark,[31] indicated the presence of 0.181 mole of 2-methyl-1-butene.

Run 3, Reverse Addition.—The Grignard reagent was prepared as described above using 30 g. (1.23 moles) of magnesium and 90 g. (0.84 mole) of (+)-2-methylbutyl chloride, $\alpha^{25}D$ +1.35, in approximately 1.2 liters of ether. This solution was allowed to settle and filtered by forcing with nitrogen pressure through a sintered glass filter stick. An aliquot of the resulting 1245 ml. of colorless, clear Grignard solution was titrated with standard acid showing the presence of 0.765 equivalent of Grignard reagent (90.5% yield). This solution was slowly added with stirring at 15°, over an eleven-hour period, to a solution of 70 g. (0.70 mole) of methyl *t*-butyl ketone in 500 ml. of anhydrous ether. The Gilman test showed the presence of excess Grignard reagent eight hours after addition was complete. The reaction was hydrolyzed by pouring onto 700 g. of ice and 70 g. of ammonium chloride. The residue, 100 g., obtained from concentrating the ether layer and extracts as before, was distilled from a regular distilling flask to give 94 g., distilling up to a temperature of 170° and leaving a residue of 6 g. This distillate was fractionated through the same column as used in Runs 1 and 2 with the results summarized in Table I.

Run 4, High Dilution.—A filtered solution of (+)-2-methylbutylmagnesium chloride, 2890 ml., 2.14 moles, was prepared from 73 g. of magnesium and 245 g. (2.30 moles) of (+)-2-methylbutyl chloride, $\alpha^{20}D$ +1.41, as indicated in the previous experiment, 93% yield. A solution of 47 g. (0.47 mole) of methyl *t*-butyl ketone dissolved in 3500 ml. of anhydrous ether was treated at 15° with 700 ml. (0.52 equivalent) of the above Grignard solution. The reaction was processed as indicated in Run 1 and gave 82 g. of residue, of which 63 g. boiled below 170° and 18.1 g. was left on rough distillation. The fractionation of this distillate gave results which are summarized in Table I.

Run 5, Reaction at −75°.—A three-liter, three-necked flask equipped with a condenser, dropping funnel, stirrer and nitrogen inlet tube was placed in a Dewar flask. A mixture of 40 g. (0.40 mole) of methyl *t*-butyl ketone in 100 ml. of anhydrous ether was added and cooled to −75° with Dry Ice–acetone-bath; 675 ml. (0.50 equivalent) of the Grignard solution described in Run 4 was added. The temperature of the reaction mixture was maintained at approximately −75° (−74 to −78°); after seventy-four hours the Gilman test for Grignard reagent was still positive. The residue, 53 g., obtained after concentrating the ether layer and ether extracts from the hydrolyzed reaction mixture, gave 26.2 g. of material boiling below 170° and left a residue of 20.0 g. upon simple distillation. The distillate was fractionated with the results summarized in Table I.

The half phthalate ester of the methyl-*t*-butylcarbinol fraction was prepared in each of the above runs with the results shown in Table I. That no concentration of the dextro isomer occurred in the crystallizations of this ester is shown by the experiment in which three successive recrystallizations from chloroform of the material, m. p. 83.5–84.5°, $[\alpha]^{20}D$ +8.2 ($\alpha^{20}D$ + 0.83, c = 5.015, l = 2, chloroform) gave a material m. p. 85–86°, $[\alpha]^{20}D$ +8.0 ($\alpha^{20}D$ + 0.80, c = 5.020, l = 2, chloroform). Since the precision of the polarimeter used was 0.02°, these results are within the limits of error of the experiments. In addition a sample of the optically active half phthalate ester, m. p. 85.5–86.5°, $[\alpha]^{20}D$ 8.7 was mixed with a sample of the racemic derivative, m. p. 83–84°. The rotation of the resulting solution was $[\alpha]^{20}D$ 5.2 ± 0.2 (chloroform c = 6.28). The chloroform was removed and the residue crystallized from hexane giving crystals $[\alpha]^{20}D$ +4.8 ± 0.2 (chloroform c = 7.7). These crystals were recrystallized $[\alpha]^{20}D$ +4.8 ±0.2 (chloroform c = 5.7). The mother liquors from the first crystallization gave a second crop on concentration, $[\alpha]^{20}D$ +4.9 ± 0.2 (chloroform, c = 3.56). Within the limits of error of the measurements no preferential crystallization of the dextro form occurred and thus the possibility of a chance concentration of the dextro form to about 13% excess as observed in the first four runs is eliminated.

Summary

The established partial asymmetric reduction of methyl *t*-butyl ketone to methyl-*t*-butylcarbinol by the Grignard reagent from (+)-2-methylbutyl chloride furnishes conclusive evidence for some closely associated complex in which the reduction of the ketone takes place simultaneously with the destruction of asymmetry of the Grignard reagent in a sterically specific manner. This presents convincing circumstantial evidence in favor of the postulated six-membered ring complex of the transition state proposed by Whitmore.[7]

This partial asymmetric synthesis constitutes an uniquely simple case of asymmetric reduction in a non-enzymatic system.

(31) Johnson and Clark, *Ind. Eng. Chem., Anal. Ed.*, **19**, 869 (1947).

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