acid. The crystallization took place after several days standing. The purified product melted at 178–182° (dec.) and weighed 0.44 g. (34%).

Anal. Calcd. for $C_{15}H_{14}O_4N_2$: N, 9.79. Found: N, 9.34.

5-Keto-7-julolineacetonitrile (XII).—Three-tenths gram of XI (0.001 mole) was placed in 10 ml. of acetic anhydride and heated on the steam-bath for five minutes. Carbon dioxide was evolved. The solvent was then removed under vacuum and the residue dissolved in a solution containing 15 ml. of benzene and 10 ml. of acetone. The solution was filtered and evaporated to about one-half volume. When cooled in ice, 0.1 g. of the product was recovered which melted at 194–196°. This product was not recrystallized. The yield was 50%.

Anal. Calcd. for $C_{14}H_{12}ON_2$: N, 12.50. Found: N, 12.98.

Summary

1. 7-Formyl-5-ketojuloline has been used to form a number of 5-ketojuloline derivatives with substitution in the 7 position.

2. Ethyl 7-(5-ketojuloline)-pyruvate has been prepared by the condensation of 5-keto-7-methyljuloline with diethyl oxalate and the synthesis of several compounds from the pyruvate has been described.

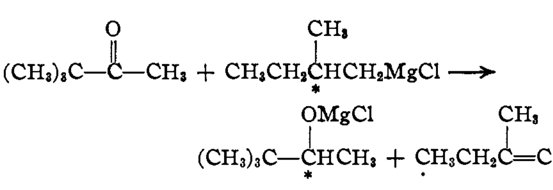
Greencastle, Indiana Received April 26, 1950

[Contribution from the Department of Chemistry, Stanford University]

Asymmetric Reductions. II. The Action of (+)-3-Methylpentylmagnesium Chloride on Methyl *t*-Butyl Ketone

By Harry S. Mosher and Edward La Combe

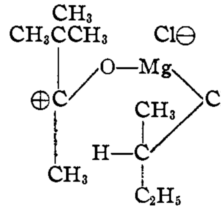
It has been demonstrated that an optically active Grignard reagent can accomplish the partial asymmetric reduction of an unsymmetrical hindered ketone.[1,2] The successful cases previously reported involved a Grignard reagent with an asymmetric carbon atom in the position *beta* to the magnesium atom; for example, the reduction of methyl *t*-butyl ketone by (+)-2-methylbutylmagnesium chloride. We have proposed that the partial asymmetric reduction is a result of the steric interference of the various alkyl groups in the postulated six-membered ring transition state[2] as represented in structure A. In addition we have predicted that significant asymmetric reduction will not occur in simple cases of this type unless the asymmetric carbon atom is a member of this postulated ring. Accordingly an optically active Grignard reagent which has an asymmetric center in the *gamma* position, such as (+)-3-methylpentylmagnesium chloride, would theoretically give a transition state represented by structure B. It can be seen that the asymmetric center is not a member of the postulated ring in B. If this mechanism is assumed and the steric factors involved are considered, a study of the various possible configurations of this transition state will lead to the conclusion that no appreciable asymmetric reduction should be expected.



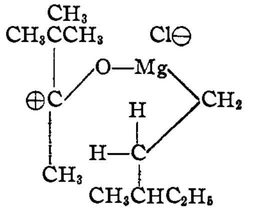
$$(CH_3)_3C-\overset{\overset{O}{\|}}{C}-CH_3 + CH_3CH_2\underset{*}{\overset{\overset{CH_3}{|}}{C}}HCH_2MgCl \longrightarrow$$

$$(CH_3)_3C-\underset{*}{\overset{\overset{OMgCl}{|}}{C}}HCH_3 + CH_3CH_2\overset{\overset{CH_3}{|}}{C}=CH_2$$

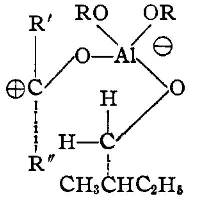
Partial



A



B



C

From a stereochemical standpoint, one would predict that the reaction would take place more readily if the transition state were as represented in either A or B, that is with the larger alkyl groups on opposite sides of the plane of the ring. But in structure B there are two hydrogen atoms on the *beta* carbon of the Grignard reagent and consequently there is an equal chance of the attack taking place on either side of the carbonyl carbon atom. The same considerations apply to the other two stereochemically less probable modes of attack in which the two larger alkyl groups are on the same side of the plane of the ring. Accordingly the formation of essentially equal amounts of the two enantiomorphic carbinols would be anticipated in a case such as B.

The reaction of (+)-3-methylpentylmagnesium chloride on methyl *t*-butyl ketone has now been studied. The amount of reduction to methyl-*t*-butylcarbinol was very small (0.2%) but there was no doubt that the carbinol formed was without significant optical activity. The success of

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

(2) Mosher and La Combe, This Journal, **72**, 3994 (1950).

the six-membered ring mechanism[3] in predicting the absence of asymmetric reduction in the above case adds additional convincing evidence in favor of the validity of this theory.

It is interesting to note the similarity in structure B and structure C. The latter is a representation of the transition state in the Meerwein–Ponndorf–Verley reduction of an unsymmetrical ketone by the aluminate of (+)-2-methylbutanol. Structure C differs from B primarily in that aluminum and oxygen atoms replace the magnesium and methylene groups in the respective rings of the transition state. The reaction represented by C has been studied by Baker and Linn[4] who failed to find optical activity in the reduction products. In contrast to this, the successful asymmetric reductions in the Meerwein–Ponndorf–Verley reaction recently reported by Doering and Young[5] gives a transition state comparable to structure A. The similarity between the Grignard reduction reaction and the Meerwein–Ponndorf–Verley reduction is therefore definitely indicated.

Experimental

(+)-3-Methyl-1-pentanol.[6]—(+)-2-Methylbutyl chloride, 207 g. (1.93 moles, $\alpha^{20}\mathrm{D}$ +1.26°, $n^{20}\mathrm{D}$ 1.4122), was added to 48.6 g. (2.0 moles) of magnesium in 1500 ml. of dry ether under a dry nitrogen atmosphere at 15°. Paraformaldehyde, 80 g. (2.67 moles), was depolymerized over a ten-hour period and the resulting formaldehyde was swept into the Grignard solution *via* a 15-mm. glass tube by means of a stream of dry nitrogen. The complex was hydrolyzed by pouring onto a mixture of 600 g. of ice and 500 g. of ammonium chloride and the product steam distilled. The ether layer was separated, dried, and distilled, first from a Claisen flask and finally through a glass helix-packed column rated at thirty theoretical plates. The weight of (+)-3-methyl-1-pentanol in cuts 6–11, b. p. 151.2–152°, $n^{20}\mathrm{D}$ 1.4182–1.4195, $\alpha^{20}\mathrm{D}$ +5.24–6.94°, was 101.9 g. or 52% yield based on the chloride taken.

(+)-3-Methylpentyl Chloride.[6]—To 100.0 g. (0.97 mole) of (+)-3-methyl-1-pentanol in 71.0 g. (0.90 mole) of dry pyridine was added 149 g. (1.25 moles) of thionyl chloride over a period of one hour at 0–5°. After heating for five hours on a steam-bath, the excess thionyl chloride was hydrolyzed with ice, the upper layer separated, washed with dilute sodium carbonate solution and water, dried over calcium chloride, and distilled. This distillate was carefully fractionated to give 90.4 g. (77.0% yield) of (+)-3-methylpentyl chloride, b. p. 128.0–129.4°, $n^{20}\mathrm{D}$ 1.4215–1.4217, $\alpha^{20}\mathrm{D}$ +16.26–16.73°.

The Action of (+)-3-Methylpentylmagnesium Chloride and Methyl *t*-Butyl Ketone.—The Grignard reagent from 87.2 g. (0.72 mole) of (+)-3-methylpentyl chloride ($\alpha^{20}\mathrm{D}$ +16.73°, $n^{20}\mathrm{D}$ 1.4217) and 18 g. (0.75 mole) of magnesium was prepared in 1300 ml. of anhydrous ether under a nitrogen atmosphere at 15°. The reagent was filtered by applied nitrogen pressure through a sintered glass filter stick to give a clear solution. Titration of an aliquot indicated 0.606 mole (86% yield) of Grignard reagent. This solution was added to 55.0 g. (0.55 mole) of pinacolone ($n^{20}\mathrm{D}$ 1.3978) at room temperature over a period of four hours and the reaction mixture stirred for two hours. The complex was hydrolyzed with a mixture of 800 g. of ice and 75 g. of ammonium chloride. The ether layer and the extracts were dried, the ether removed by careful fractionation and the residue distilled giving 75.5 g. of distillate, b. p. 36–145° (760 mm. pressure), $\alpha^{20}\mathrm{D}$ +2.28°; and 14.5 g., b. p. (25–30 mm.) 110–130° with $\alpha^{20}\mathrm{D}$ +2.14–3.30°. The distillate boiling from 36–145° was carefully fractionated through a thirty-plate column. These distillation data are represented graphically in Fig. 1.

The carbinol in cut 21–25 was converted to the half-phthalate ester, m. p. 79–81°, crude yield 0.17 g. (0.0007 mole). A portion of the crude ester on recrystallization from *n*-hexane gave m. p. 83–84°, and a reading of $\alpha^{20}\mathrm{D}$ +0.005° (l = 0.5, c = 3.0, chloroform, readings taken on Rudolph and Sons precision polarimeter no. 80) for an average of twenty readings. Chloroform alone, from an average of twenty readings gave $\alpha^{20}\mathrm{D}$ −0.001°. The mean deviation of the total forty readings was 0.010°. The determination of the melting point of a mixture of the half-phthalate ester with an authentic sample of the racemic derivative gave a m. p. 83.5–85°.

An amount of 3-methyl-1-pentene equivalent to the ketone reduced, should have been formed from the (+)-3-methyl-1-pentylmagnesium chloride. Cuts 3–12 were combined and the olefin determination, made according to the method of Johnson and Clarke,[7] indicated 0.0009 mole of 3-methyl-1-pentene.

Discussion

The results of a careful fractionation of the products from the reaction of methyl *t*-butyl ketone and (+)-3-methylpentylmagnesium chloride are represented in Fig. 1. The constant boiling material at 63° is the saturated hydrocarbon, 3-methylpentane.[8] This hydrocarbon is formed from the Grignard reagent as a result of enolization of the methyl *t*-butyl ketone. The constant boiling material at 105.2° represents a 53% yield of methyl *t*-butyl ketone. The lag in the rise of the boiling point curve between 105 and 126° indicates the presence of a small amount of the reduction product, methyl-*t*-butylcarbinol which boils at 119°. Further indication of the carbinol can be seen in the refractive index curve which shows a hump at the appropriate point and the optical activity shown by the material boiling at about 60°. This can only be adequately explained by assuming the presence of optically active 3-methyl-1-pentene which would result from the Grignard reagent by reduction. Titration of an aliquot of this material indicated the presence of approximately 0.0009 mole of the olefin. To our knowledge this hydrocarbon has not been reported in an optically active form. The literature gives the following constants for the racemic olefin: b. p. 53.6°, $n^{20}\mathrm{D}$ 1.3855.[9]

The amount of reduction is obviously very small and separation of the methyl-*t*-butylcarbinol was therefore accomplished by conversion to the half-phthalate ester. The weight of the half-phthalate ester isolated was that which we found in parallel experiments to be obtained from approximately 0.001 mole of the methyl-*t*-butylcarbinol. This is in good agreement with the amount of olefin determined by titration. The

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(3) Frank C. Whitmore, paper presented before the September, 1941, Atlantic City meeting of the American Chemical Society.

(4) Baker and Linn, THIS JOURNAL, 71, 1399 (1949).

(5) Doering and Young, *ibid.*, 72, 631 (1950).

(6) Levene and Marker, *J. Biol. Chem.*, 77 (1931).

(7) Johnson and Clarke, *Ind. Eng. Chem., Anal. Ed.*, 19, 869 (1947).

(8) Bruun, Hicks-Bruun and Faulconer, THIS JOURNAL, 59, 2355 (1937).

(9) Schmitt and Boord, *ibid.*, 54, 751 (1932).

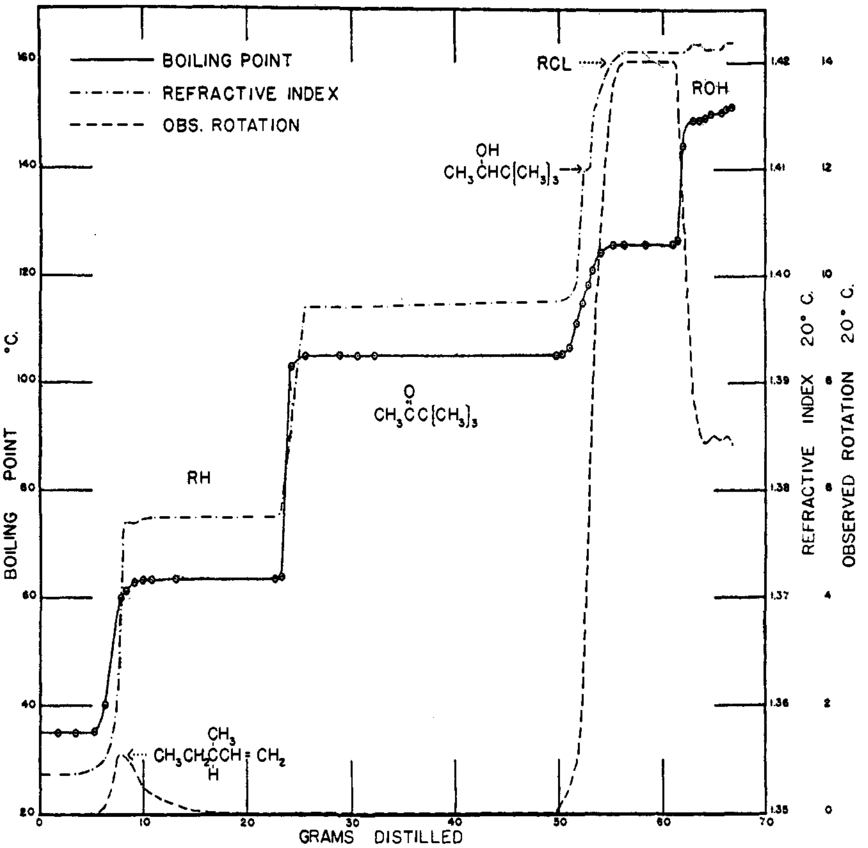

Fig. 1.—Fractionation of the products from the reaction of methyl *t*-butyl ketone and (+)-3-methylpentylmagnesium chloride.

observed rotation of this half-phthalate ester (+0.006°, $l = 0.5$, chloroform, $c = 3$) was less than the mean deviation (0.01°) of the readings. Since it already has been demonstrated[2] that repeated crystallizations of the half-phthalate ester of (+)-methyl-*t*-butylcarbinol from hexane do not result in any significant change in concentration of the isomer mixture, activity if present would not be lost by crystallization. On the basis of the known rotation for this half-phthalate ester[10] the maximum possible asymmetric reduction would be 0.01%. This is beyond the accuracy of the experiment and it accordingly can be safely stated that *no appreciable asymmetric reduction occurred in this reaction.* From a theoretical standpoint the fact that the total amount of reduction was very low (approximately 0.2%) in no way alters the significance of this evidence as it pertains to the mechanism of the Grignard reduction reaction. As further evidence for the inactivity of the methyl-*t*-butylcarbinol, the rotation curve approaches a vertical rise from zero rotation of the methyl *t*-butyl ketone to 14.04°, the observed rotation for that of the (+)-3-methylpentyl chloride, with no evidence of any additive effect which would be the case if either optical isomer of the carbinol were present in excess.

The material boiling at 126° represents unreacted (+)-3-methylpentyl chloride. The material boiling irregularly at about 152° is considered to be (+)-3-methyl-1-pentanol obtained as a result of oxidation of the Grignard reagent. The residue and higher boiling material are presumably addition and/or condensation products in about 20% yield. The yields of enolization, reduction, addition and/or condensation represent a total 73% recovery based on methyl *t*-butyl ketone.

Both (+)-3-methylpentyl chloride and the corresponding alcohol are reported in the literature.[6] Levene and Marker used malonic ester and *s*-butyl bromide to prepare the corresponding acid which they partially resolved as the quinine salt. The optically active acid was esterified and the ester reduced to the (+)-3-methyl-1-pentanol having $[\alpha]^{27}\text{D}$ + 3.62°. Upon treatment of the alcohol with thionyl chloride they obtained (+)-3-methylpentyl chloride having $[\alpha]^{27}\text{D}$ + 7.46°.

Our method of preparing this (+)-3-methylpentyl chloride started with 74% optically pure (+)-2-methylbutyl chloride which was converted to the Grignard reagent and treated with formaldehyde to obtain (+)-3-methyl-1-pentanol having $[\alpha]^{20}\text{D}$ + 8.4°. This alcohol upon treatment with thionyl chloride gave the (+)-3-methylpentyl chloride having $[\alpha]^{20}\text{D}$ + 18.7°. Assuming this alcohol and chloride to be as pure optically as the (+)-2-methylbutyl chloride from which they were prepared, the pure (+)-alcohol by calculation should have $[\alpha]^{20}\text{D}$ + 11.4° and the chloride $[\alpha]^{20}\text{D}$ + 25.3°.

Acknowledgment.—We wish to thank the Research Corporation for a grant which made this work possible.

Summary

It has been shown that essentially no asymmetric reduction (less than 0.01%) of methyl *t*-butyl ketone occurs when the asymmetric center of the aliphatic Grignard reagent is at the *gamma* position as exemplified by the action of (+)-3-methylpentylmagnesium chloride on

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[10] Pickard and Kenyon, *J. Chem. Soc.*, **105**, 1120 (1914), report a value of $[\alpha]^{20}\text{D}$ ×63.9° for the pure dextro isomer.

methyl *t*-butyl ketone. These results can best be explained by use of the six-membered ring transitory state proposed as a common basis for the "abnormal reactions" of the Grignard reagent with carbonyl compounds.[3]

STANFORD, CALIFORNIA RECEIVED APRIL 24, 1950

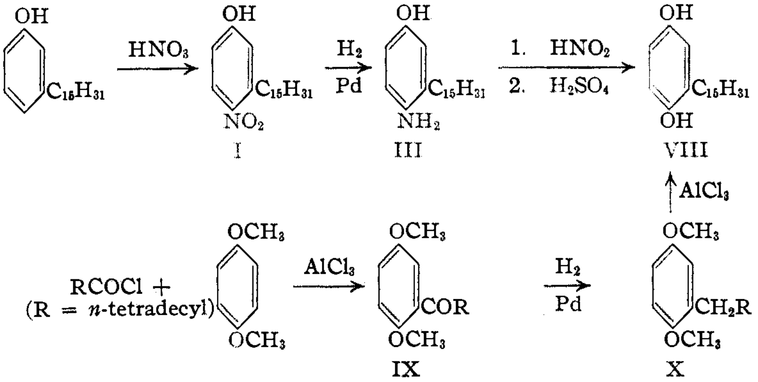
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Cashew Nut Shell Liquid. VIII. A Proof of Structure of the Mono-nitro and Mono-amino Derivatives of 3-Pentadecylphenol (Hydrocardanol)[1]

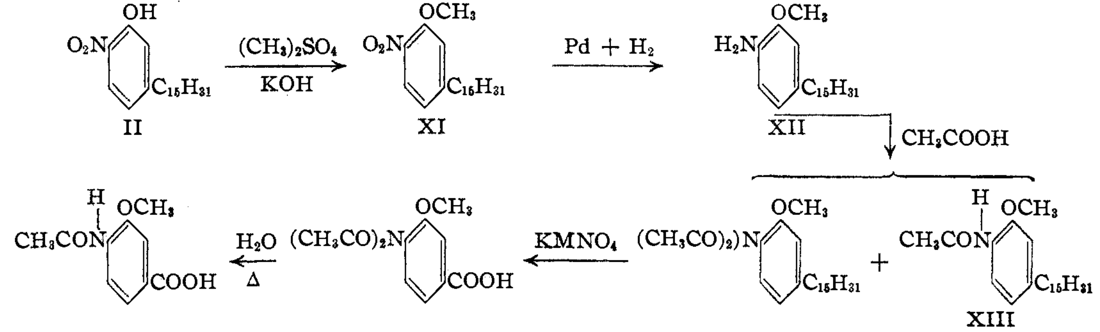
BY DAVID WASSERMAN[2] AND CHARLES R. DAWSON

During the past few years an increasing amount of work on cashew nut shell liquid and the products derived from it has appeared in the literature.[3,4,5,6,7] The main product of the decarboxylation and vacuum distillation of cashew nut shell liquid is a 3-alkenylphenol (cardanol) which upon catalytic hydrogenation and vacuum fractionation yields 3-pentadecylphenol (hydrocardanol). This unique alkyl phenol is produced commercially in a high state of purity.[8]

A: Proof of structure of 4-nitro-3-pentadecylphenol.



B: Proof of structure of 6-nitro-3-pentadecylphenol.



The 4-amino-3-pentadecylphenol is particularly well suited for use as a gasoline gum inhibitor because of its insolubility in aqueous alkali, its solubility in gasoline, and its strong anti-oxidant activity. This amine and its isomer, 6-amino-3-pentadecylphenol, were first obtained from 3-pentadecylphenol by direct nitration, separation of the isomeric nitro compounds, and then catalytic reduction. The structures of the two isomeric amines (and the corresponding nitro compounds) were established by the synthetic procedures indicated below. An alternative method of synthesizing 4-amino-3-pentadecylphenol, which involved the coupling of sodium 3-pentadecylphenolate with diazotized aniline or sulfanilic acid and subsequent reduction of the azo compound with sodium hydrosulfite, resulted in a pure compound, uncontaminated by the 6-amino isomer, in excellent yields.

The 4 position of the nitro group in the higher melting mononitro isomer (I) of 3-pentadecylphenol was established by converting it into 2-pentadecylhydroquinone (VIII) and comparing this product by mixed melting point with that obtained by the unequivocal route of synthesis outlined in Chart IA.

The reactions outlined in Chart IB were used to establish the 6 position of the nitro group in the lower melting mono-nitro isomer (II) by converting it into 3-methoxy-4-acetaminobenzoic acid.

(1) For the seventh article in this series, see Izzo and Dawson, *J. Org. Chem.*, **15**, 707 (1950).

(2) Chemical Products Division, Irvington Varnish and Insulator Co., Irvington, N. J.

(3) Wasserman and Dawson, THIS JOURNAL, **70**, 3675 (1949).

(4) Sletzinger and Dawson, *ibid.*, **68**, 345 (1946).

(5) Wasserman and Dawson, *Ind. Eng. Chem.*, **37**, 396 (1945).

(6) Backer and Haack, *Rec. Trav. Chem.*, **60**, 661 (1941).

(7) Harvey and Caplan, *Ind. Eng. Chem.*, **32**, 1306 (1940).

(8) Produced by the Chemical Products Division of the Irvington Varnish and Insulator Co., Irvington, N. J.