[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

STRUCTURE OF THE GRIGNARD REAGENT FROM 6-CHLORO-2,2,6-TRIMETHYLCYCLOHEXANONE

K. R. BHARUCHA, H. L. COHEN, AND GEORGE F. WRIGHT

Received November 17, 1953

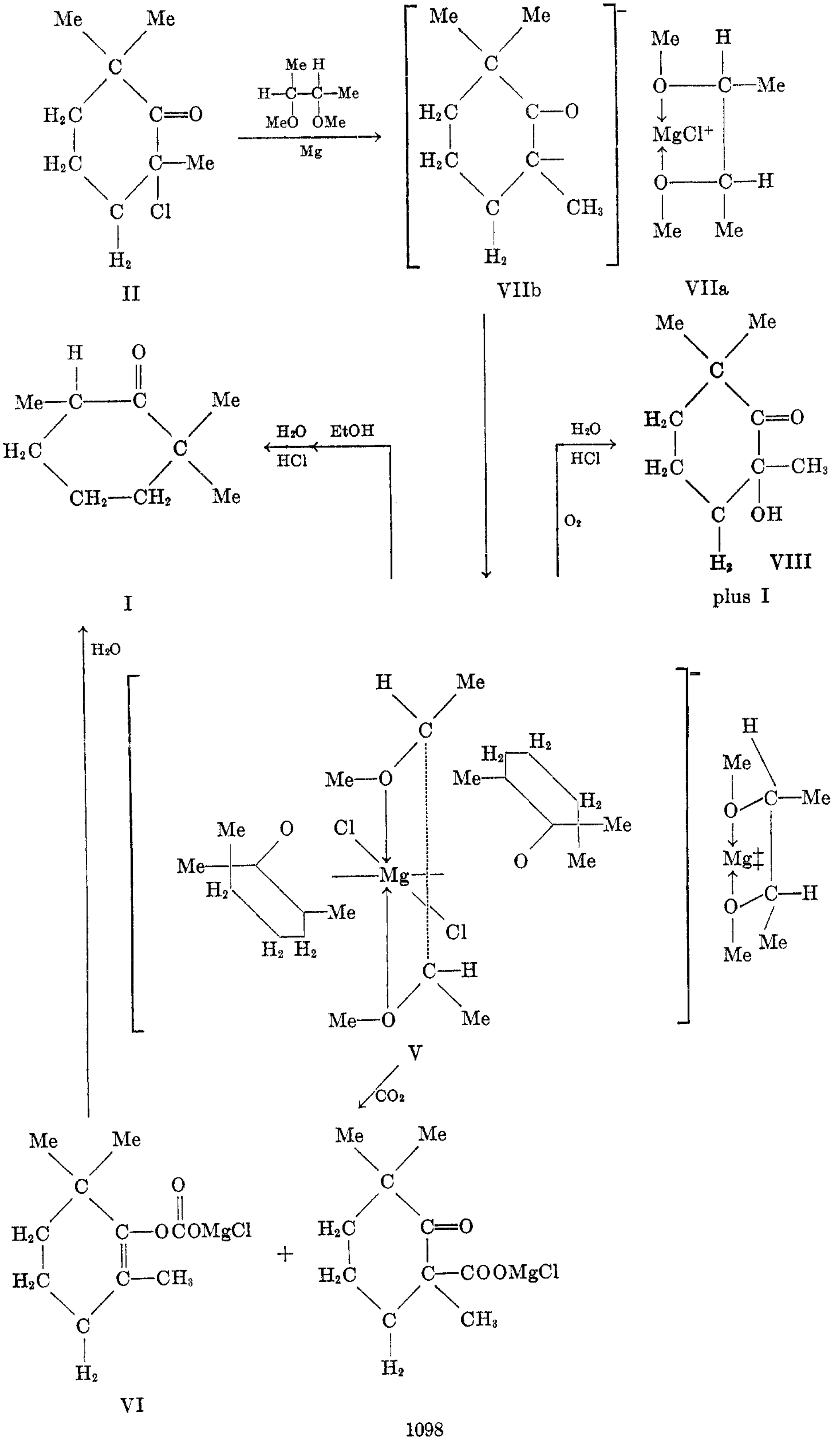
The preparation of a Grignard reagent from the highly-hindered 6-chloro-2,2,6-trimethylcyclohexanone has been reported (1) with the expressed opinion that this reagent was ionic in nature. It seemed worthwhile to test this hypothesis by use of the optically active 2,3-dimethoxybutane. This coördinating solvent has been found to confer optical activity to adducts of Grignard reagents that have been prepared in the enantiomeric medium (2). If the postulated ionic structure were prevalent then the products arising from adducts ought to be optically inactive, because the nucleophilic ether would be expected to coördinate with the metallic cation (VIIa) but not the organic anion (VIIb). Therefore we have examined the hydrolysis, carbonation, and oxidation products which have been prepared from the hindered Grignard reagent.

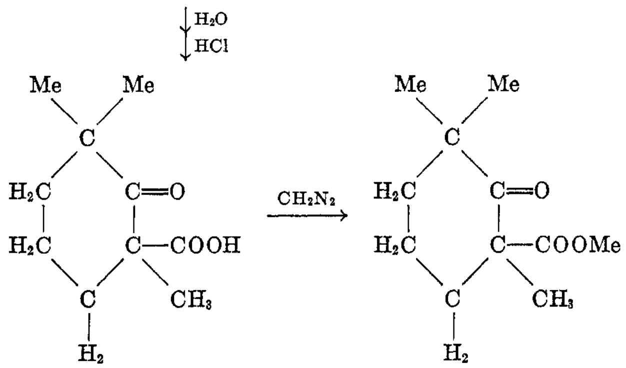
In order to evaluate any observed optical activity of the hydrolysis product, trimethylcyclohexanone (I), we have resolved this ketone by use of 3-[1-phenylethyl]semicarbazide hydrochloride of specific rotation +67.1° (23°). One of the diastereomers, of constant melting point, has been isolated by fractional crystallization and then decomposed with hot aqueous oxalic acid. No claim is made that the 2,2,6-trimethylcyclohexanone, +12.42° ± 0.05°, is enantiomerically pure.

When the Grignard reagent from 6-chloro-2,2,6-trimethylcyclohexanone (II) in benzene-dimethoxybutane is solvolyzed by ethanol, the resulting trimethylcyclohexanone (purified through its inactive semicarbazone) is optically active to the extent of +0.31° ± 0.02°. The authenticity of this activity was confirmed qualitatively by conversion of the ketone to its oxime, $[\alpha]_D^{23}$ +0.32° ± 0.03°.

If the resolved trimethylcyclohexanone is converted to its semicarbazone and then is regenerated from this (inactive) product by hot aqueous phthalic acid, the optical activity, $[\alpha]_D^{23}$ +12.36° ± 0.04°, is essentially unchanged. Since there is no racemization upon regeneration the optical activity of the trimethylcyclohexanone obtained from the Grignard reagent corresponds to not more than 2.5% of possible asymmetric synthesis. Indeed it may be less if the resolution *via* phenylethylsemicarbazide is not complete. Nevertheless an activity exists which is not in accord with the ionic structure previously postulated (1).

Treatment of the Grignard reagent in benzene-*dextro*-dimethoxybutane with carbon dioxide also produces an optically active product. This optical activity is evidently lost if one allows the β-keto acid, 6-carboxy-2,2,6-trimethylcyclohexanone (III), to be decarboxylated to trimethylcyclohexanone (I), but is retained when this acid is converted to its methyl ester (IV) by diazomethane. In addition to this 6-carbomethoxy-2,2,6-trimethylcyclohexanone, $[\alpha]_D^{22}$ +5.83 ±


II
MeO OMe
Mg
VIIb
VIIa
I
H₂O EtOH
HCl
H₂O
HCl
O₂
VIII
plus I
H₂O
V
CO₂
VI



III IV

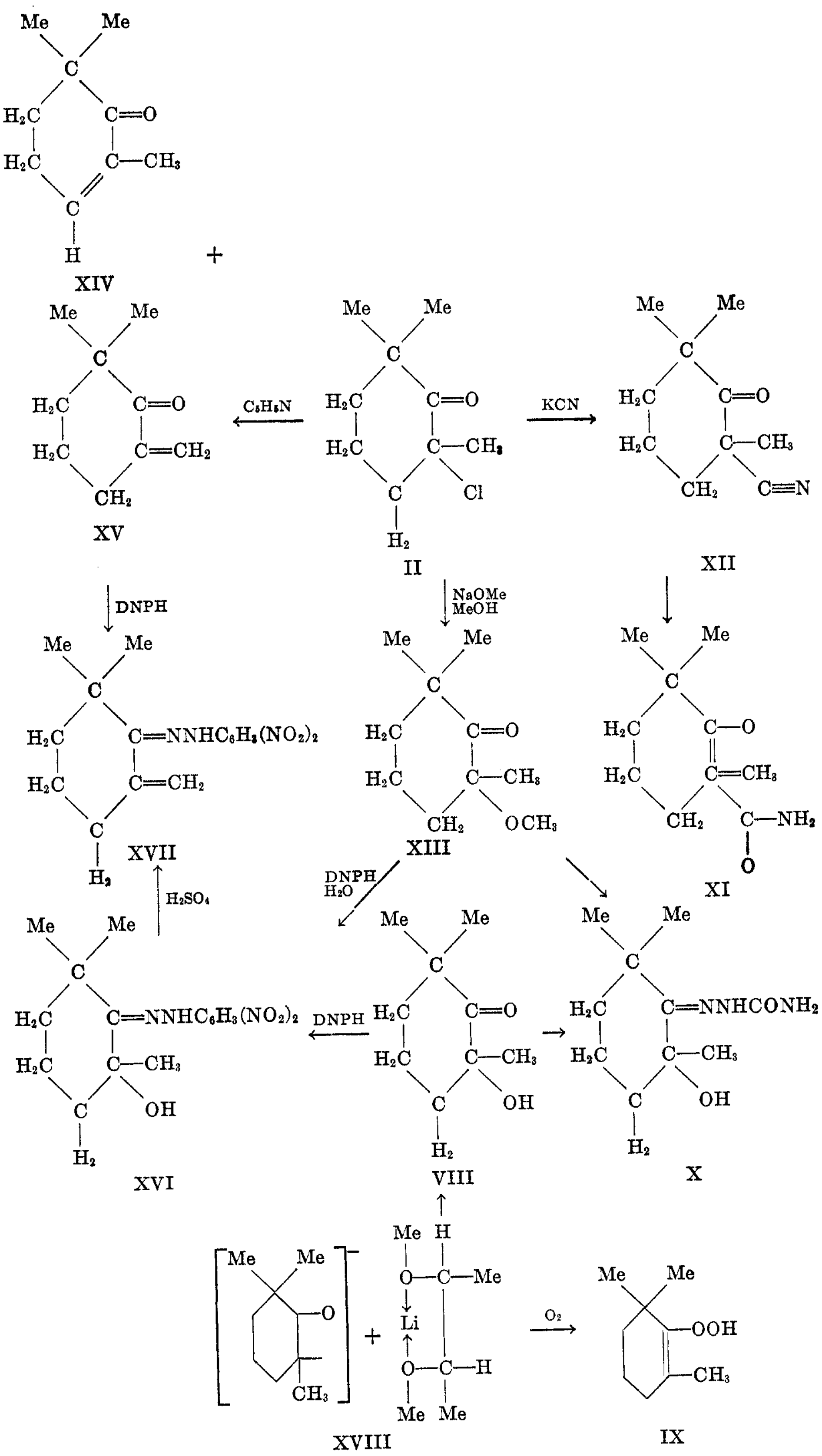
0.01°, an appreciable yield of trimethylcyclohexanone is obtained. Since the presence of this product, which might arise from the bicarbonate of its tautomer (VI), is significant to the postulation of the ionic Grignard reagent, its optical activity was examined. However difficulties involved in separation from a chlorine-containing impurity made a polarimetric determination of doubtful value.

Therefore we turned to Grignard reagent oxidation in the hope of isolating the expected by-product (I) of the ionic species. It was first necessary to ascertain means of separating trimethylcyclohexanone from the oxidation product, 6-hydroxy-2,2,6-trimethylcyclohexanone (VIII), and to characterize the latter compound. A synthesis *via* 6-chloro-2,2,6-trimethylcyclohexanone (II) was not satisfactory, although this halide reacts well in non-aqueous solution. Thus potassium cyanide in acetone converts it to 6-cyano-2,2,6-trimethylcyclohexanone (XII), characterized by conversion to the acetamide (XI). Likewise sodium methoxide converts the halide to 6-methoxy-2,2,6-trimethylcyclohexanone (XIII).

When this α-methoxyketone is treated with acidic 2,4-dinitrophenylhydrazine or with neutral aqueous semicarbazide, the derivatives (XVI and X) are those of 6-hydroxy-2,2,6-trimethylcyclohexanone (VIII).

The 2,4-dinitrophenylhydrazone (XVI) may be converted by concentrated sulfuric acid to the analogous derivative (XVII) of 6-methylene-2,2-dimethylcyclohexanone (XV). The latter compound has been prepared by dehydrohalogenation of 6-chloro-2,2,6-trimethylcyclohexanone in pyridine, and identified by the formaldehyde produced upon ozonization. As might be expected it seems to be contaminated with some 2,2,6-trimethyl-Δ^5-cyclohexenone (XIV). All of these reactions show that the cyclohexanone ring is not expanded or contracted during these nucleophilic displacements. The reactions also establish identities among those compounds which are difficult to purify for analysis because of contamination with chlorine-containing substances.

Although these reactions do not furnish 6-hydroxy-2,2,6-trimethylcyclohexanone except in the form of derivatives, they provide information sufficient for processing of the oxidation products of the Grignard reagent. After slow treatment with oxygen at 0° these products are separated either by fractional


XIV
+
C₅H₅N
KCN
XV
II
XII
DNPH
NaOMe
MeOH
XVII
XIII
XI
H₂SO₄
DNPH
H₂O
DNPH
XVI
VIII
X
XVIII
O₂
IX

distillation or by utilizing the more rapid (but not always reproducible) reaction rate of trimethylcyclohexanone compared with that of hydroxytrimethylcyclohexanone toward semicarbazide. In either case the hydroxyketone (VIII) is optically active, but it is difficult to evaluate the maximum activity of the product. Unlike the enantiomeric semicarbazone of trimethylcyclohexanone, which is not lost during purification, the enantiomeric semicarbazone of 6-hydroxy-2,2,6-trimethylcyclohexanone either is racemized (which seems extremely unlikely) or else is lost among the impurities during crystallization.

In contrast to the asymmetric synthesis of the hydroxyketone the other product, trimethylcyclohexanone, is entirely inactive. This inactivity illustrates firstly that the hindered ketone (I) is not produced by simple solvolysis of the Grignard reagent, since such a product would be *dextro*-rotatory when prepared in *dextro*-dimethoxybutane. Secondly the inactivity can be thought to arise from the configurational loss in 2,2,6-trimethylcyclohexenyl hydroperoxide (IX) as a primary oxidation product which reverts to trimethylcyclohexanone during hydrolysis of the oxidized Grignard reagent.

The isolation of trimethylcyclohexanone from each of these three Grignard reactions, and the demonstration in one case that this product is optically inactive when the solvent has conferred activity on the other product, present an apparent contradiction. The evidence that reaction occurs at either oxygen or carbon is remindful of reactions such as the Claisen, Perkin, Knoevenagel, and Aldol condensations which undoubtedly proceed *via* a hybrid anion. On the other hand such an anion should not coördinate with the optically active ether. The coördinative solvent may, instead, be expected to associate itself with the metallic cation (VIIa) rather than with the organic anion (VIIb), but it is the latter in which stereochemical preference must occur during asymmetric synthesis.

Of course it is possible that the organometallic compound exists as ion pairs rather than as free cations and anions. The 2-octyllithium of Letsinger (3), which is enantiomerically stable at −80° in petroleum ether-diethyl ether (but not at 0°), may be considered as such an ion pair at the low temperature. We find evidence at 0° for such an ion pair when we carbonate 2-butyllithium in petroleum ether containing one equivalent of *dextro*-dimethoxybutane. The product, 2-methylbutanoic acid, is optically active, $[\alpha]_D^{23}$ $-0.16° \pm 0.02°$. This result is not unexpected since carbonation of the vicinally-linked stilbene-dilithium adduct in *dextro*-dimethoxybutane has been found to produce optically active diphenylsuccinic acid (4). In these instances the metal must be bonded closely to the asymmetric carbon atom. It should be noted that in the stilbene adduct lithium halide is absent, so that effective coördination of the ether must occur with the lithium that is bound to carbon rather than to halogen.

In the aforementioned examples the organolithium compounds in media containing *dextro*-dimethoxybutane give optically active products. On the other hand both the 6-hydroxy-2,2,6-trimethylcyclohexanone (VIII) and the 2,2,6-trimethylcyclohexanone (I), prepared by oxidation of the organolithium compound (XVIII) from 6-chloro-2,2,6-trimethylcyclohexanone in benzene-dimethoxybutane, are optically inactive. Likewise this organolithium reagent in benzene-dimethoxybutane is solvolyzed by ethanol to optically inactive trimethylcyclohexanone, whereas the product from the organomagnesium derivative is *dextro*-rotatory. Therefore it would appear that this trimethylcyclohexanonyl lithium differs from the covalent or ion-paired types described above. Indeed the multiplicity of products (VIII and I) is remindful of reactions involving alkali salts of tautomers which seem to be free-ionic in coördinating media.

It is not so simple to state, conversely, whether the organomagnesium derivative of chlorotrimethylcyclohexanone is covalently or electrovalently bonded. Firstly this and other Grignard reagents may be wholly or partly colloidal in nature, in which case an argument based on the chemistry of homogeneous systems is of doubtful utility. Secondly the ever-present magnesium halide may combine with the anion VIIb to give a hexa-covalent anion such as is shown as V, together with a metallic cation. Both of these ions would be solvated with 2,3-dimethoxybutane which might thus exert its influence toward asymmetric synthesis.

The concept of the complex ion V is not new. Evans and Pearson, from their observation of transport of magnesium to the anode during electrolysis of Grignard reagents (5), have considered a complex anion. A similar postulation has been made by Décombe and Duval (6) on the basis of electrolysis of the organometallic reagent prepared from zinc-magnesium alloy. These workers, and also Terent'ev (7), have suggested hexa-covalent and tetra-covalent magnesium in ion pairs, under conditions (cryoscopic molecular weight determinations in benzene) which would depress the ionization.

The postulation of the hexa-covalent anion is an attractive one in the instance of the trimethylcyclohexanonyl-magnesium derivatives because it accounts for the enolic and ketonic products in terms of a free-ionic species in which asymmetric synthesis can occur. The asymmetric synthesis observed during reaction of organolithium compounds (where, so far as has been shown, the metal is not involved in a complex anion) shows that the asymmetric synthesis may be explained adequately in simpler cases (as with butyllithium) in terms of ion pairs. Yet there are several phenomena in the chemistry of organomagnesium compounds that can best be explained on the basis of the complex anion. Thus the effect of magnesium halide in alteration of the addition-reduction-enolization ratios in reactions of Grignard reagents with ketones may be explained in terms of the complex ion (8). Likewise the tendency of two moles of phenylmagnesium bromide to partake in addition to benzophenone (9) may be explained in terms of the transformation of a dibromodiphenyl-magnesium anion coördinated with ether to one coördinated with ether and benzophenone. The complex ion concept may also be utilized to explain the observation that less asymmetric synthesis in *dextro*-dimethoxybutane is observed when the reagent contains combined bromine rather than combined chlorine. Thus one may assume that the tetracovalent dibromodiorganomagnesium anion is more stable than its hexa-covalent dietherate, whereas the opposite obtains for the dichlorodiorganomagnesium anion. Of course it should not be inferred from these speculations that the tetra- or hexa-covalent anion entirely represents Grignard reagents in general. These reagents will vary from free ionic systems through ion pairs and polymeric multiples of ion pairs to systems which are largely covalent in bonding.

We are grateful to the Tennessee Eastman Company for some financial aid, for generous supplies of trimethylcyclohexanone, and for some of the microanalyses. We wish to thank the National Research Council of Canada for adequate supplies of *levo*-2,3-butanediol from which the enantiomeric ether is prepared.

EXPERIMENTAL

All melting points have been corrected against reliable standards. X-ray diffraction data are recorded as relative intensities $[I/I_1]$ at spacings in Å, using Cu K_α radiation, nickel-filtered. Magnesium used for Grignard reactions was the sublimed variety which was activated by prior treatment with bromobenzene in ether and subsequent etching with dilute hydrochloric acid.

Resolution of 2,2,6-trimethylcyclohexanone (I). The *l*-phenylethylsemicarbazide hydrochloride, prepared by the method of Hopper and Wilson (10), melted at 185–188°, $[\alpha]^{23}_D$ +67.1°.

A solution of 2.3 g. (0.0165 mole) of 2,2,6-trimethylcyclohexanone in 25 ml. of ethanol was treated with a concentrated aqueous solution of 3.6 g. (0.0168 mole) of the optically active semicarbazide hydrochloride and 2.3 g. (0.0165 mole) of sodium acetate trihydrate. This system was boiled under reflux for four hours, and chilled to 4° for 12 hours. The precipitate (2.7 g.) was crystallized from 10 ml. of ethanol to give 1.21 g., m.p. 114–117°, $[\alpha]^{23}_D$ −118° (5% solution in chloroform). A second crystallization from 4 ml. of ethanol yielded 0.95 g., m.p. 118–119.5°, $[\alpha]^{23}_D$ −127° (chloroform). A third crystallization from 4 ml. of ethanol gave 0.861 g. with the same melting point and specific rotation.

The resolved phenylethylsemicarbazone was decomposed by boiling in a solution of 10 g. of oxalic acid in 50 ml. of water for 15 minutes. An extract of the cooled mixture in 20 ml. of petroleum ether was washed, dried and distilled. This 2,2,6-trimethylcyclohexanone, 0.4 g. (98% from the semicarbazone), boiled at 181–183°, $[\alpha]^{23}_D$ +12.42° ± 0.05° (45% solution in ethanol).

This distillate was converted by sodium acetate and semicarbazide hydrochloride to the semicarbazone, m.p. 208–210°, with no detectable activity. This derivative was steam-distilled with 10 g. of phthalic acid and 50 ml. of water until no more oil came over (20 ml.). The oil was taken up in petroleum ether and distilled as recovered trimethylcyclohexanone, b.p. 181–183°, $[\alpha]^{23}_D$ +12.36° ± 0.04°.

Trimethylcyclohexanone oxime. A solution of hydroxylamine acetate (0.03 mole) was prepared by grinding 2 g. of hydroxylamine hydrochloride and 2.3 g. of anhydrous sodium acetate in 10 ml. of methanol. This filtered solution plus an additional 20 ml. of methanol and 0.92 g. (0.0065 mole) of the enantiometic trimethylcyclohexanone was refluxed for four hours. After removal of the solvent in an air stream, the residue was crystallized from 4 ml. of 1:1 methanol-water to give a 50% yield, m.p. 102–103°, $[\alpha]^{23}_D$ +12.56° ± 0.08° (ethanol).

6-Methoxy-2,2,6-trimethylcyclohexanone (XIII). A solution of 0.46 g. (0.02 atom) of sodium in 10 ml. of absolute methanol was refluxed for three hours with 1.7 g. (0.01 mole) of 6-chloro-2,2,6-trimethylcyclohexanone. After vacuum-evaporation of the methanol, the residue was treated with water, and the oil was collected in ethyl ether. The etherous solution, dried with calcium chloride, was distilled, finally at 9 mm. This crude product, b.p. 65–77°, 0.88 g. (51%), n^{20}_D 1.4500, was redistilled (b.p. 76–78° at 14 mm.), and then fractionated to separate the 6-methoxy-2,2,6-trimethylcyclohexanone, b.p. 185–186° at 755 mm., from an impurity containing chlorine. This product, n^{20}_D 1.4448, d^{20}_4 0.935, still gave a positive test for combined chlorine.

Anal. Calc'd for $C_{10}H_{18}O_2$: C, 70.6; H, 10.6; OCH_3, 18.2.
Found: C, 70.4; H, 10.4; OCH_3, 18.7.

6-Hydroxy-2,2,6-trimethylcyclohexanone semicarbazone (X). A solution of 0.21 g. (9.24 ×

10^{-3} mole) of 6-methoxy-2,2,6-trimethylcyclohexanone, 0.22 g. (2×10^{-3} mole) of semicarbazide hydrochloride, and 0.16 g. (2×10^{-3} mole) of sodium acetate in 1 ml. of methanol, was diluted to turbidity with water after 30 minutes. After 12 hours the semicarbazone (60%) was filtered off, m.p. 177–178°. After crystallization from methanol, this melted at 179.5°.

Anal. Calc'd for $C_{10}H_{19}N_3O_2$: C, 56.3; H, 8.99; N, 19.7.
Found: C, 55.8; H, 8.68; N, 19.6.

6-Hydroxy-2,2,6-trimethylcyclohexanone dinitrophenylhydrazone (XVI). When 0.08 g. of 6-methoxy-2,2,6-trimethylcyclohexanone was heated with 0.05 g. of 2,4-dinitrophenylhydrazine, 4 ml. of ethanol, and 0.2 ml. of concentrated hydrochloric acid, 0.07 g. of the dinitrophenylhydrazone of VII precipitated, m.p. 215–216°. Three crystallizations from 95% ethanol raised this melting point to 224–225°.

Anal. Calc'd for $C_{15}H_{20}N_4O_5$: C, 53.5; H, 5.98.
Found: C, 54.0; H, 5.89.

Relative intensities of the x-ray powder diffraction spacings are: [10] 10.04; [9] 6.23, 4.45; [8] 3.87; [7] 3.56; [5] 4.95; [3] 3.02, 2.84; [2] 4.16, 2.70; [1] 12.44, 4.64, 3.78, 3.23.

6-Methoxy-2,2,6-trimethylcyclohexanone dinitrophenylhydrazone. A suspension of 6-hydroxy-2,2,6-trimethylcyclohexanone dinitrophenylhydrazone (0.05 g.) in 1 ml. of absolute methanol containing 0.05 ml. of conc'd sulfuric acid, was refluxed for three hours, then cooled and carefully diluted with water. The crystals, m.p. 126–128°, gave an x-ray diffraction powder pattern identical with that previously found for the methoxy derivative (1).

6-Methylene-2,2-dimethylcyclohexanone (XV). A solution of 8.70 g. (0.05 mole) of 6-chloro-2,2,6-trimethylcyclohexanone in 25 ml. of anhydrous pyridine was refluxed for two hours, then chilled, acidified, and the oil taken up in ethyl ether and washed with aqueous sodium bicarbonate. After drying with magnesium sulfate, the solution was distilled, finally at 17 mm., to yield crude XV, b.p. 74–75°, n_D^{20} 1.4734, d_4^{20} 0.934, 5.0 g. (73%), then a fraction (1.41 g.) containing XV, and a substance containing combined chlorine, b.p. 75–83°, n_D^{20} 1.4725, d_4^{20} 0.951. The crude XV was redistilled, b.p. 63–65° (10 mm.), n_D^{20} 1.47215, d_4^{20} 0.950, b.p. 186–187° (755 mm.). This product tends to polymerize when distilled at 750 mm.

Anal. Calc'd for $C_9H_{14}O$: C, 78.3; H, 10.2.
Found: C, 77.7; H, 10.4.

*6-Methylene-*2,2*-dimethylcyclohexanone, dinitrophenylhydrazone* (XVII). This derivative (0.085 g., m.p. 150°) was prepared by heating 0.1 g. of XV with 0.075 g. of 2,4-dinitrophenylhydrazine in 3 ml. of ethanol and 0.1 ml. of conc'd hydrochloric acid. The derivative was purified by crystallization from 10 ml. of ethanol, m.p. 155.0–155.5°.

Anal. Calc'd for $C_{15}H_{18}N_4O_4$: C, 56.5; H, 5.72; N, 17.6.
Found: C, 56.5; H, 5.92; N, 17.4.

Relative intensities of the x-ray diffraction spacings are: [10] 3.41; [8] 4.75, 4.13; [7] 3.13; [6] 6.12; [4] 7.93; [3] 14.36, 3.82; [2] 2.88, 2.60, 1.95; [1] 3.34, 2.47, 2.37, 2.24, 1.70; [0.5] 5.80, 5.35, 5.14, 4.01. The similarity of this powder diagram showed that the dinitrophenylhydrazone of XV was formed also when 6-hydroxy-2,2,6-trimethylcyclohexanone dinitrophenylhydrazone was warmed to 50° in concentrated sulfuric acid (0.001 g. per 0.5 ml.), and then diluted with water. A mixture melting point was not lowered. On the other hand, two hours' reflux of 0.05 g. of the dinitrophenylhydrazone of the hydroxyketone with 0.1 ml. of acetic anhydride and 1 ml. of acetic acid yielded a dinitrophenylhydrazone with similar elemental analysis (C, 56.0; H, 5.67), but which must be isomeric; its melting point is 161° (crystallized from ethanol, mixture melting point with the derivative of XV depressed), and its diffraction pattern is dissimilar: [10] 8.26; [9] 3.52, 3.15; [7] 7.10, 6.96; [5] 5.90, 5.82; [3] 4.92, 3.22; [2] 5.32, 5.23, 3.37, 3.10, 3.05; [1] 6.86, 6.51, 6.41, 6.17, 4.47, 4.06, 3.83, 3.67, 2.62, 2.03. This derivative is probably that of 2,2,6-trimethyl-Δ^5-cyclohexenone (XIV).

Ozonization of 6-methylene-2,2-dimethylcyclohexanone (XV). After ozonization of 0.69 g. of XV in 10 ml. of pre-ozonized carbon tetrachloride, the system was reductively hydrolyzed with zinc and acetic acid. The aqueous layer, upon treatment with dimedone, gave 0.05 g., m.p. 165°, which was crystallized from ethanol, m.p. 189–190°. A mixture melting point with the formaldehyde-dimedone derivative was not lowered. The water-washed carbon tetrachloride solution, evaporated (0.52 g.), was heated with dinitrophenylhydrazine, ethanol, and concentrated hydrochloric acid. The precipitate was purified by crystallization from dioxane-petroleum ether, from benzene, and from ethanol. This dinitrophenylhydrazone, m.p. 142°, may be that of the lactol of 4,4-dimethylheptanoic-5,6-dionoic acid, since it dissolves in aqueous sodium bicarbonate and is re-precipitated by acids. It has not been investigated further but it probably occurs as the ozonization product of contaminant XIV

Anal. Calc'd for $C_{15}H_{18}N_4O_7$: C, 49.1; H, 4.97; N, 15.3.

Found: C, 48.9; H, 5.30; N, 15.8.

2,2-Dimethylglutaric acid. A suspension of 6-methylene-2,2,6-trimethylcyclohexanone (XV, 0.69 g., 0.005 mole) in 25 ml. of ice-water was stirred and chilled while 2.61 g. (0.0165 mole) of potassium permanganate was added during three minutes. After three hours the stirred solution was reduced with methanol. The precipitate was filtered off and dissolved in saturated aqueous sodium bisulfite. This solution, acidified with strong hydrochloric acid, was exhaustively extracted with ethyl ether. The residue from evaporation of the etherous extract washed with the minimum of cold water, weighed 0.59 g., m.p. 70–73°. This crude acid was repeatedly dissolved in 3 ml. benzene per gram, was allowed to crystallize slowly by addition of 4.5 ml. of petroleum ether (b.p. 60–70°) per gram. The dimethylglutaric acid finally melted at 83–84°.

Anal. Calc'd for $C_7H_{12}O_4$: C, 52.5; H, 7.55.

Found: C, 52.7; H, 7.84.

The acid was characterized by converting it to its dimethyl ester by etherous diazomethane; this solution was then treated with concentrated ammonia. Evaporation left a residue which was washed with water, m.p. 171–173°. This 2,2-dimethylglutaramide was crystallized from methanol, m.p. 185–187°.

Anal. Calc'd for $C_7H_{14}N_2O_2$: C, 53.2; H, 8.90; N, 17.7.

Found: C, 53.0; H, 8.70; N, 17.6.

6-Cyano-2,2,6-trimethylcyclohexanone (XII). A solution of 6-chloro-2,2,6-trimethylcyclohexanone (2.8 g., 0.016 mole) in 10 ml. of acetone was heated under reflux for 12 hours with potassium cyanide (1.1 g., 0.017 mole). After removal of the solvent, the residue was treated with ether and water. The etherous layer was separated, dried (Na_2SO_4), and distilled to give 1.8 g. (68%) of a colorless liquid, b.p. 207–212° (*ca.* 750 mm.), n_D^{20} 1.4565. Careful refractionation at 12 mm. gave the following three fractions: (i) 0.4 g. with b.p. 97–99°, n_D^{20} 1.4575; (ii) 0.8 g. with b.p. 99–101°, n_D^{20} 1.4563; and (iii) 0.3 g. with b.p. 101–103°, n_D^{20} 1.4571. An analytical sample boiled at 98° (13 mm.), n_D^{20} 1.4561, m.p. 7–8°.

Anal. Calc'd for $C_{10}H_{15}NO$: C, 72.7; H, 9.15; N, 8.45.

Found: C, 72.5; H, 9.34; N, 8.14.

6-Acetamido-2,2,6-trimethylcyclohexanone (XI). A solution of 0.14 g. (0.006 atom) of sodium in 5 ml. of methanol was boiled under reflux for 15 hours with 0.50 g. (0.003 mole) of cyano-trimethylcyclohexanone. Then 1.5 ml. of water was added, while reflux was continued for eight hours. Finally 4 ml. of 40% aqueous alkali was added, and the solution was refluxed for 18 hours longer. The mixture was cooled and extracted with ether. The dried ether solution, upon evaporation, yielded 0.31 g. of semisolid, from which 0.18 g., m.p. 144–145°, was obtained by crystallization from petroleum ether (b.p. 60–70°).

Anal. Calc'd for $C_{10}H_{17}NO_2$: C, 65.6; H, 9.35; N, 7.65.

Found: C, 66.1; H, 9.13; N, 7.83.

The aqueous alkaline phase was acidified and extracted with chloroform. Evaporation did not yield an acidic substance, which might have been expected if a Dieckmann scission had occurred.

The Grignard reagent from 6-chloro-2,2,6-trimethylcyclohexanone (II) *in dextro-dimethoxybutane.* When a solution of 0.5 g. of 6-chloro-2,2,6-trimethylcyclohexanone in 5.0 g. (0.04 mole) of *dextro*-2,3-dimethoxybutane under nitrogen was stirred with 0.7 g. (0.03 atom) of sublimed magnesium, evolution of heat within five minutes indicated initiation of reaction. After a solution of 4.3 g. (total 0.028 mole) of the chloroketone in 30 ml. of benzene had been added to the warmed, stirred solution during one hour, the system was stirred 30 minutes longer. Although titration of the homogeneous system indicated a 90% yield of Grignard reagent, a Gilman test was negative. The successful preparation of this reagent is dependent on complete elimination of water from the system.

A. Reaction with ethanol. The dropwise addition of 2.3 g. (0.05 mole) of ethanol in 10 ml. of benzene to 0.027 mole of the reagent gave a gelatinous precipitate which redissolved after the mixture had been stirred for 20 minutes. The system was made slightly acidic with acetic acid, and the benzene layer was extracted twice with 10-ml. portions of water and once with aqueous sodium bicarbonate. After drying with magnesium sulfate, the solution was distilled, to yield 2.7 g., b.p. 140–190°, with a specific rotation of +3.07° ± 0.03°. This crude product was mixed with 27 ml. of ethanol, 3 g. of semicarbazide hydrochloride, 4 g. of sodium acetate trihydrate, and 27 ml. of water; this system was refluxed for 8 hours. Dilution and chilling yielded a precipitate which was crystallized from 20 ml. of ethanol. The 2,2,6-trimethylcyclohexanone semicarbazone produced in this manner weighed 1.2 g. (20%), m.p. 207–209°.

A solution of this semicarbazone in pyridine showed no optical activity, but the trimethylcyclohexanone, which was regenerated from it with phthalic acid as described above, b.p. 181–183°, showed a specific rotation of $[\alpha]_D^{23}$ +0.31° ± 0.02°. The oxime, which was prepared from it as described above, had a specific rotation of +0.32° ± 0.03° (ethanol).

B. Reaction with carbon dioxide. A Grignard reagent containing 0.027 equiv. of basic magnesium in a mixture of 2,3-dimethoxybutane (7 ml.), benzene (15 ml.), and toluene (20 ml.) was chilled in a Dry Ice bath while gaseous carbon dioxide (dried through calcium chloride) was passed through for four hours. After gradual warming during ten hours to room temperature the resulting pale yellow solution was evaporated under reduced pressure. The residue was treated with ice-cold aqueous ammonium chloride and then twice extracted cold with diethyl ether. Evaporation of the dried (Na_2SO_4) etherous solution left a residue which was distilled (*ca.* 750 mm.) at 181–183°, n_D^{20} 1.4532. This 2,2,6-trimethylcyclohexanone (0.61 g., 16%) was contaminated with a chloro-compound. The semicarbazone, after two recrystallizations from abs. ethanol, melted at 205–206°; the mixture melting point was not lowered.

The ether-extracted ammoniacal solution was cooled in ice, acidified to *p*H 3–4 and quickly extracted six times with diethyl ether. The combined extract, containing 6-carboxy-2,2,6-trimethylcyclohexanone, was chilled to −70°, and treated immediately with an etherous solution of diazomethane until an excess was indicated by a yellow color. After gradual warming to room temperature and drying with sodium sulfate, the solution was distilled, finally at 10 mm. The distillate was 6-carbomethoxy-2,2,6-trimethylcyclohexanone (2.18 g., 41%), b.p. 108–109°, m.p. 19.5–20.5°, n_D^{20} 1.4591, d_4^{20} 1.025, $[\alpha]_D^{22}$ +5.83 ± 0.01°. In a second carbonation run, the crude 6-carboxy-2,2,6-trimethylcyclohexanone obtained upon removal of solvent was allowed to decarboxylate at room temperature and subsequently distilled to give 2,2,6-trimethylcyclohexanone (27%), b.p. 182–183°, n_D^{20} 1.4464. A solution (47%) of the latter in ethanol showed no rotation. The ketone was identified as its *semicarbazone*, m.p. and m.m.p. 206–208° (decomp.).

C. Reaction with oxygen. A Grignard reagent containing 0.024 equiv. in 7 ml. of dimethoxybutane and 25 ml. of benzene was cooled in ice-water while oxygen (purified through sulfuric acid and sodium hydroxide) was bubbled through during eight hours. The color changed from orange-red to yellow. Next day the solvents were removed under reduced pressure. The residue was treated with 35 ml. of 8% hydrochloric acid and then thoroughly extracted with benzene. The extract, washed thrice with water to remove acid, was dried with sodium sulfate and distilled (16–17 mm.) to yield a first fraction comprising 2,2,6-trimethylcyclohexanone (b.p. 75–77°, 0.488 g., 14%). This was redistilled (*ca.* 750 mm., b.p. 180–181°, $[\alpha]_D^{22}$ in 41% ethanolic solution was less than experimental error). This inactive compound was identified as its semicarbazone, m.p. and mixture m.p. 206–208° (decomp.).

The second fraction at 16–17 mm. boiled at 87–97° (2.234 g., n_D^{20} 1.4614, 60%). This 6-hydroxy-2,2,6-trimethylcyclohexanone was converted to its semicarbazone by treatment with 2.1 g. (0.018 mole) of semicarbazide hydrochloride in 4 ml. of water and 2.6 g. (0.019 mole) of sodium acetate trihydrate in 4 ml. of methanol. The product (1.3 g., 43%, m.p. 168–171°) was crystallized from 4 ml. of ethanol, 0.91 g., m.p. 178–179° (dec.), $[\alpha]_{4}^{20}$ +0.57° ± 0.04°, in 21.3% pyridine solution. The hydroxyketone was regenerated (70% yield) by steam-distillation with phthalic acid, b.p. 86–87° (14 mm.), n_{D}^{20} 1.4622, d_{4}^{20} 0.992. Optical rotation was zero within experimental error.

Anal. Calc'd for $C_9H_{16}O_2$: C, 69.2; H, 10.3.

Found: C, 68.7; H, 10.3.

The semicarbazone (m.p. 179–179.5°) which was reformed from the hydroxyketone in almost quantitative yield was inactive (pyridine solution). A mixture melting point with the sample of the hydroxy derivative prepared from 6-methoxy-2,2,6-trimethylcyclohexanone was not depressed.

A repetition of this oxidation gave a combined crude yield of 45% of the two products, b.p. 180–205° (*ca.* 750 mm.). A solution of 2.1 g. with 2.1 g. of semicarbazide hydrochloride and 2.6 g. of sodium acetate trihydrate in 20 ml. of methanol was boiled under reflux for 30 minutes, then cooled and filtered to yield 0.1 g. (1%) of 2,2,6-trimethylcyclohexanone semicarbazone, m.p. 207–210°, identified by mixture melting point. In this instance, inexplicably, the hydroxyketone did not react noticeably during the period of time with semicarbazide. The filtrate, evaporated to remove methanol, was extracted with 50 ml. of hot petroleum ether (b.p. 60–70°). The dried non-aqueous phase was distilled, to yield 1.5 g. of crude hydroxyketone, b.p. 200–205° (*ca.* 750 mm.), $[\alpha]_{D}^{23}$ −2.24° ± 0.04°, contaminated with a chloro-compound. The product was converted to the semicarbazone (m.p. 173–175°, 74%) which, crystallized from ethanol in 50% recovery, melted 178–179°, $[\alpha]_{D}^{21}$ +0.50° ± 0.09° (22% pyridine solution) and was identified by a mixture melting point.

The organolithium reagent from 6-chloro-2,2,6-trimethylcyclohexanone. When 10.8 g. (0.09 mole) of *dextro*-2,3-dimethoxybutane, 10 ml. of benzene, and 1.0 g. of 6-chloro-2,2,6-trimethylcyclohexanone under nitrogen were stirred for five minutes with 0.9 g. (0.12 atom) of shredded lithium, the system became warm. While it was stirred and water-cooled, a solution of 3.8 g. (total, 0.028 mole) of the chloroketone in 30 ml. of benzene was added dropwise. After 12 hours of additional stirring, a yield of 0.027 mole (95%) of organometallic compound was indicated by titration, although a Gilman test was negative. The solution was decanted and washed from unchanged lithium and precipitated lithium chloride.

A. Reaction with ethanol. The reagent described above was treated slowly with 2.0 g. (0.04 mole) of absolute ethanol in 10 ml. of benzene. Processing by the procedure described for the similar reaction with Grignard reagent yielded 2.2 g. (58%), b.p. 178–182°, $[\alpha]_{D}^{23}$ −0.16° ± 0.02°. Purification through the semicarbazone, followed by regeneration with phthalic acid, gave 1.1 g. (29%) of 2,2,6-trimethylcyclohexanone, b.p. 181–183°, which was optically inactive.

B. Reaction with oxygen. The identical reagent used in procedure A was treated with sulfuric acid-dried oxygen until heat no longer was evolved. The system was processed identically with that used for the reaction of oxygen with the Grignard reagent (second experiment). The yield of 2,2,6-trimethylcyclohexanone semicarbazone was 0.12 g. (2.2%). The yield of 6-hydroxy-2,2,6-trimethylcyclohexanone, b.p. 200–205°, was 1.0 g. (23%). A solution of this product in benzene was optically inactive.

2-Butyllithium in dextro-dimethoxybutane with carbon dioxide. The reagent was prepared from 2-chlorobutane and shredded lithium in petroleum ether containing one molar equivalent of *dextro*-2,3-dimethoxybutane, ($[\alpha]_{D}^{23}$ +3.72°, n_{D}^{20} 1.3908, m.p. −84.2° to −84.5°) of purity identical with that used for other organometallic reagents described in this report. The preparation, carbonation, and subsequent processing were similar to the operations for the 2-chlorobutane Grignard reagent previously described (2). The specific rotation of the 2-methylbutanoic acid was $[\alpha]_{D}^{23}$ −0.16 ± 0.02°.

SUMMARY

1. The Grignard reagent from 6-chloro-2,2,6-trimethylcyclohexanone in *dextro*-2,3-dimethoxybutane-benzene medium reacts with ethanol, carbon

dioxide, or oxygen to give the normal products from these reagents in slightly optically active form. Trimethylcyclohexanone is also obtained in low yield from the carbonation and oxidation reactions; in the latter instance examination shows it to be optically inactive.

2. Identical reaction with the organolithium compound gives optically inactive products. This inactivity is interpreted in terms of free-ionic species of which the organic anion is not coördinated with the optically active reaction medium.

3. The Grignard reactions, which give optically active products, cannot be free-ionic in the same sense and yet give products characteristic of α-ketomethylene compounds which react in a free-ionic manner. This behavior has been interpreted in terms of a free-ionic reaction involving a hexa-covalent anion comprising dihalogenodiorganomagnesium dietherate.

Toronto 5, Canada

REFERENCES

(1) Bell, Strickland, and Wright, *J. Org. Chem.*, **16**, 1742 (1951).
(2) Cohen and Wright, *J. Org. Chem.*, **18**, 432 (1953).
(3) Letsinger, *J. Am. Chem. Soc.*, **72**, 4842 (1950).
(4) Brook, Cohen, and Wright, *J. Org. Chem.*, **18**, 447 (1953).
(5) Evans and Pearson, *J. Am. Chem. Soc.*, **64**, 2865 (1942).
(6) Décombe and Duval, *Compt. rend.*, **206**, 1024 (1938).
(7) Terent'ev, *Z. anorg. Chem.*, **156**, 73 (1926).
(8) Swain, *J. Am. Chem. Soc.*, **73**, 870 (1951).
(9) Gilman and Jones, *J. Am. Chem. Soc.*, **62**, 1243 (1940).
(10) Hopper and Wilson, *J. Chem. Soc.*, 2483 (1928).