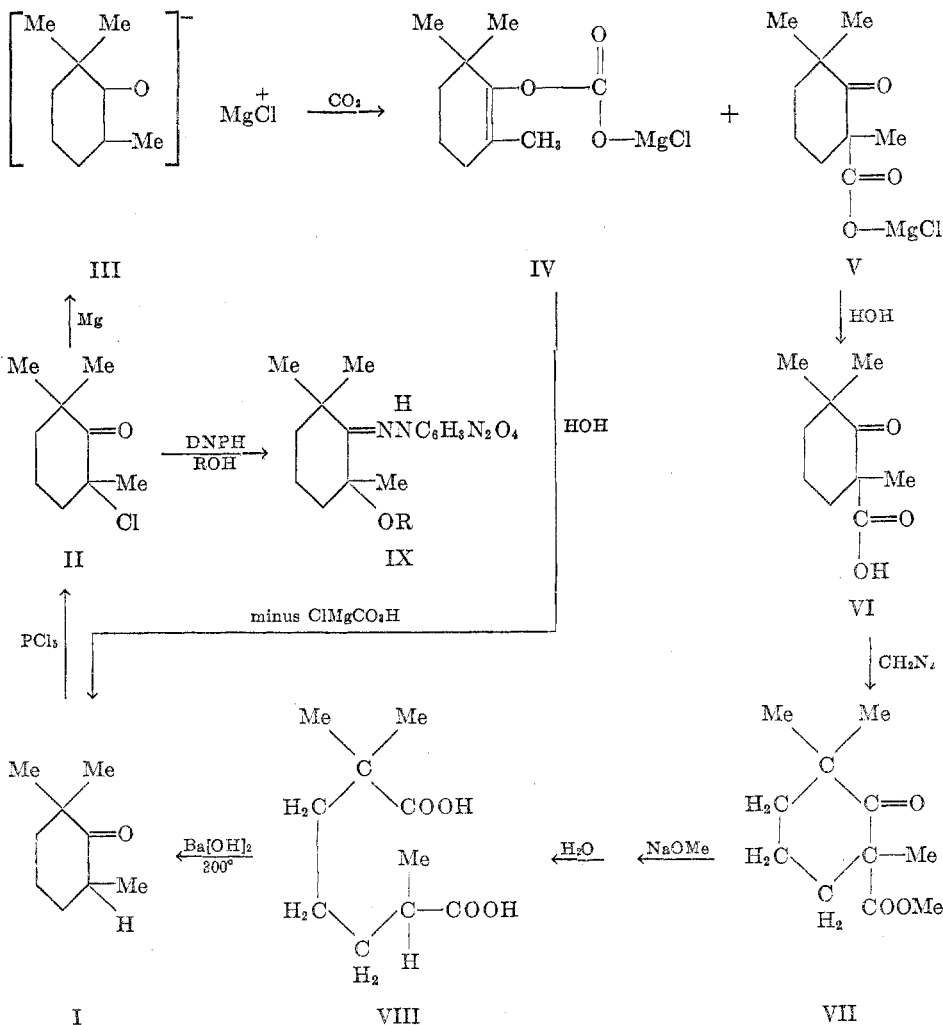


PREPARATION OF A GRIGNARD REAGENT CONTAINING
A CARBONYL GROUP

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Received July 23, 1951

Considerable steric hindrance has been noted in respect of the 1-position in 2,2,6-trimethylcyclohexyl derivatives (1). An extreme instance of this hindrance has now been found in 2,2,6-trimethylcyclohexanone, I. Thus, although 2-methylcyclohexanone yields (among other chlorinated products) 1,1-dichloro-2-methylcyclohexane when it is treated with phosphorus pentachloride (2), the carbonyl group remains intact after similar treatment of 2,2,6-trimethylcyclohexanone.



Instead, *alpha*-chlorination occurs to give a 90 per cent yield of 6-chloro-2,2,6-trimethylcyclohexanone, II.

The behavior of this compound with acidic 2,4-dinitrophenylhydrazine indicates that steric restriction is operative. The reaction occurs smoothly in methanol to replace chlorine as well as oxygen, and this yields 6-methoxy-2,2,6-trimethylcyclohexanone dinitrophenylhydrazone (IX, R = CH₃). On the other hand the comparable reaction in ethanol gives only a trace of the ethoxy analogue (IX, R = C₂H₅).

The steric shielding of this carbonyl group has made it possible to convert II into several organometallic compounds. Although no reaction can be effected with magnesium in diethyl ether under a variety of conditions, the more active lithium dissolves readily to form a suspension which reacts slowly with Michler's ketone to give a positive Gilman test.

It has been found in these laboratories that 1,2-dimethoxyethane is effective in the preparation of organometallic compounds which cannot be formed in diethyl ether. The value of the alternative solvent is diminished by the fact that coupling in the Wurtz sense is also usually accentuated. It seemed therefore anomalous that the reaction of II with magnesium (or calcium) in 1,2-dimethoxyethane occurred smoothly at 50–60° to give a Grignard reagent, but such was the case.

None of these organometallic compounds are very reactive. The Gilman test is difficult to obtain, and no reaction can be detected with phenyl isocyanate, ethyl orthoformate, or ethoxymethylaniline. They resemble in this respect those reagents previously obtained by Fuson, *et al.* (3) by the action of normal Grignard reagents on hindered ketones. However, reaction of III with carbon dioxide occurs smoothly to form the metallic salt of the β -keto acid, V.

We believe it to be significant that the reaction of II with magnesium or calcium in 1,2-dimethoxyethane does not yield an appreciable amount of coupling product. Furthermore, the hydrolysis of the carbonated reagent always results in one-third conversion to carbon dioxide and 2,2,6-trimethylcyclohexanone, despite the care used in this hydrolysis. We interpret these facts to mean that the organometallic compounds derived from 6-chloro-2,2,6-trimethylcyclohexanone show no tendency toward homopolar dissociation into free radicals, but, instead, are ionic in character as exemplified by the magnesium salt, III. Carbonation of III might be expected to yield the chloromagnesium salt of 6-carboxy-2,2,6-trimethylcyclohexanone, V, as well as chloromagnesium 2,2,6-trimethylcyclohexenyl bicarbonate, IV. The latter might be expected to hydrolyze in neutral solution to form chloromagnesium bicarbonate and trimethylcyclohexanone, I.

This seems to be the case. Hydrolysis of the carbonated organolithium compound with water or the organomagnesium and calcium compounds with aqueous ammonium chloride yields trimethylcyclohexanone in 30% yield. Subsequent acidification of the ether-extracted solution to pH 2 causes evolution of carbon dioxide indicative of a bicarbonate, and the appearance of an oily acid. This 6-carboxy-2,2,6-trimethylcyclohexanone acid decarboxylates slowly; but it is sufficiently stable to collect in ether and convert with diazomethane to the corresponding methyl ester, VII.

When this ester is subjected to ketonic scission by sodium methoxide in methanol to which water is slowly added, an acid which should be 2,2,6-trimethylpimelic acid, VIII, is obtained in good yield. While the analysis and neutralization equivalent conform with this empirical formula, the melting point (79°) is quite different from that reported by Colonge and Dumont for the acid which they obtained by oxidation of the compound they specified as 2,2,6-trimethylcycloheptanone. Since they reported that the barium salt of their acid was convertible to trimethylcyclohexanone by pyrolysis, we pyrolyzed our acid with 5 weight-per-cent of barium hydroxide at 300° and found that the same 2,2,6-trimethylcyclohexanone was formed.

Since 1,2-rearrangements are not uncommon at these temperatures of pyrolysis, the formation of a product such as trimethylcyclohexanone may not be definitive as a proof of structure. Indeed, we found that the pyrolysis of our acid yielded an isomer which was isolated as the dinitrophenylhydrazone. Since this isomer could be oxidized by hydrogen peroxide, we suspect it to be 1,2,2-trimethyl-1-formylcyclopentane.

Despite the discrepancy between the melting point of our trimethylpimelic acid and that described by Colonge and Dumont we consider that the structure and metallization of 6-chloro-2,2,6-trimethylcyclohexanone has been demonstrated satisfactorily. We depend on our relatively simple reaction series, in contrast to that of Colonge and Dumont which permits of at least two alternative explanations.

We are grateful for the analytical work carried out in Mr. D. C. Siever's laboratory.

EXPERIMENTAL¹

6-Chloro-2,2,6-trimethylcyclohexanone, II. A mixture of 35 g. (0.25 mole) of 2,2,6-trimethylcyclohexanone, I, (4, 5) and 62.5 g. (0.30 mole) of phosphorus pentachloride was maintained for one hour while the temperature was gradually raised from 60° to 100°. After a subsequent hour at 100° the gas evolution had ceased. The whole was poured into ice and neutralized cold with 30% aqueous potassium hydroxide. The oil was taken up in ether, washed with sodium bicarbonate solution until neutral, dried with magnesium sulfate, and distilled *in toto* at 77–80° (11 mm.). The crude yield of 42 g. was redistilled at 755 mm. to yield 2 g. boiling up to 203°, and the remainder (39 g.) from 203–204.5°. This 90 per cent yield could be redistilled, b.p. 82° (12 mm.); d_4^{20} 1.039; n_D^{20} 1.46826; MR_D calc'd 46.4, found 46.6; m.p. 12.5–13.5°.

Anal. Calc'd for C₉H₁₅ClO: C, 61.9; H, 8.65; Cl, 20.3.

Found: C, 62.1; H, 8.85; Cl, 21.0.

6-Methoxy-2,2,6-trimethylcyclohexanone 2,4-dinitrophenylhydrazone. The chloro ketone was treated with a methanolic hydrogen chloride solution of 2,4-dinitrophenylhydrazine. The solution soon deposited orange needles which were recrystallized from methanol, m.p. 126–127.5° (micro).

Anal. Calc'd for C₁₆H₂₂N₄O₅: C, 54.9; H, 6.34; N, 16.0; OCH₃, 8.8.

Found: C, 54.8; H, 6.35; N, 15.8; OCH₃, 9.0.

The X-ray diffraction pattern (Cu, K_α) was determined. Decreasing relative intensities (I/I₀) at d spacing in Å are: [10], 3.72, 6.75; [9], 10.16; 8, 4.75; [7], 3.04; [3], 8.07, 5.68, 3.37; [2], 5.12, 2.56, 1.97; [1], 6.43, 5.01, 4.59, 4.37, 3.49, 2.97, 2.45, 2.18, 1.73.

¹ All melting points are corrected against reliable standards.

6-Ethoxy-2,2,6-trimethylcyclohexanone 2,4-dinitrophenylhydrazone. When a solution of the chloro ketone in an ethanolic hydrogen chloride solution of 2,4-dinitrophenylhydrazine was cooled, the latter compound crystallized out. Evaporation of the filtrate yielded a few crystals which melted at 118–123° (micro) after crystallization from methanol. A mixed melting point with the methoxy analog was strongly depressed. Dilution of the ethanolic filtrate yielded the unchanged chloro ketone.

Anal. Calc'd for $C_{17}H_{24}N_4O_5$: C, 56.0; H, 6.6; N, 15.4.

Found: C, 55.5; H, 6.7; N, 15.0.

6-Chloro-2,2,6-trimethylcyclohexanone, II with metals. When a diethyl ether solution of II was treated with distilled magnesium under dry oxygen-free nitrogen, no reaction occurred after many hours, even when activated magnesium was also added. On the other hand, when 1 ml. of the solution of 1.58 g. (0.01 mole) of II in 10 ml. of 1,2-dimethoxyethane (distilled from sodium benzophenone) was added under nitrogen to 0.12 g. (0.05 atom) of magnesium a reaction commenced after about five minutes; the temperature increased to 45–50°. This temperature maintained itself over the fifteen minute addition period and subsequently was held at 50° for an equal time. Either during this period or subsequently during thirty minutes' spontaneous cooling, a heavy gray precipitate appeared. A portion of this suspension gave a yellow precipitate with Michler's ketone which, when heated, hydrolyzed and oxidized with iodine, gave a faint positive Gilman test. Hydrolysis of the reaction mixture yielded 0.80 g. of trimethylcyclohexanone, I, which was identified by boiling point, 58–60°, 11 mm., n_D^{20} 1.4490, d_4^{20} 0.905, and by treatment with a methanolic solution of 2 N hydrogen chloride containing 4% of 2,4-dinitrophenylhydrazone, to yield trimethylcyclohexanone dinitrophenylhydrazone, m.p. 126.2° or 143.5–145.5 (micro) after crystallization from ethanol.

The X-ray powder diagram of the higher melting form using $CuK\alpha$ radiation gave the following decreasing relative intensities I/I_0 at d spacings in Å: [10], 7.87, 3.81; [8], 11.6, 8.25, 6.20, 5.80, 4.65, 4.13, 3.11; [6], 7.37, 5.58, 5.18, 3.56, 3.44, 2.96; [4], 6.58, 3.24, 2.78; [2], 3.68, 2.83; [1], 2.66, 2.58, 2.47, 2.38, 2.26, 2.16, 2.11, 2.00. These spacings differ from those of the lower-melting form which are reported later. The compound evidently exists in two polymorphic forms, since the melting point of a mixture is that at the higher temperature.

Anal. Calc'd for $C_{15}H_{20}N_4O_4$: C, 56.3; H, 6.31; N, 17.5.

Found: C, 56.3; H, 6.48; N, 17.4.

The reaction with distilled calcium in 1,2-dimethoxyethane was identical except that it started more easily than with magnesium. Reaction of II with lithium in diethyl ether occurred after several minutes and was complete in about a half hour. The yield of trimethylcyclohexanone was about the same with all three metals.

6-Carboxy-2,2,6-trimethylcyclohexanone. The reagent prepared with magnesium or lithium from 0.03 mole of II at 50–68° was poured into solid carbon dioxide. When 1,2-dimethoxyethane was used, it was removed under reduced pressure and the residue treated with iced ammonium chloride solution and ether in that order. When solution was complete after fifteen minutes shaking, the ether layer was separated and evaporated to leave 1.74 g. of trimethylcyclohexanone, I, n_D^{20} 1.4514, slightly contaminated with a chloro compound. Molar yield of I is about 35% in every experiment.

The ether-extracted ammoniacal solution was iced, acidified to pH 2 and quickly extracted thrice with ether, which was dried quickly with magnesium sulfate. An aliquot withdrawn and evaporated *in vacuo* showed that the yield of carboxytrimethylcyclohexanone, VI, was 1.86 g. (30 mole %) n_D^{20} 1.4562. It decarboxylated spontaneously even in aqueous alkali to yield trimethylcyclohexanone. It would not react with ω -diazoacetophenone in ether.

6-Carbomethoxy-2,2,6-trimethylcyclohexanone, VII. The ether solution of carboxytrimethylcyclohexanone (volume 50 ml.) was chilled to –30° and treated with 0.03 mole of diazomethane in ether. When reaction was complete the solvent was evaporated and the residue (1.79 g., n_D^{20} 1.4531) was distilled under 13 mm. to yield a slight first fraction and then 1.54 g. at 109–110° (87 mole %), n_D^{20} 1.4583, d_4^{20} 0.98.

Anal. Calc'd for $C_{11}H_{18}O_4$: C, 66.4; H, 9.18.

Found: C, 66.2; H, 9.32.

2,2,6-Trimethylpimelic acid. When 0.59 g. (0.003 mole) of the methyl ester, VII, was refluxed with a solution of 0.14 g. (0.006 atom) of sodium in 5 ml. of absolute methanol for one day a solid was precipitated which dissolved after 1.5 ml. of water was added during eight hours more reflux. Then, 7 ml. of 30% aqueous sodium hydroxide was added and reflux continued for one day. Ether extraction of the cooled solution gave negligible residue after evaporation. The aqueous phase was acidified and the precipitate was air dried and extracted with chloroform. Evaporation of this solvent left 0.45 g. which was crystallized from 0.5 ml. of hot petroleum ether (b.p. 60-70°). The crystals (m.p. 78.9-79.7°) weighed 0.395 g., (65%).

Anal. Calc'd for $C_{10}H_{18}O_4$: C, 59.4; H, 8.98, neut. eq. 101.

Found: C, 59.4; H, 9.11, neut. eq. 102.

The X-ray powder diagram using Cu, K_{α} radiation gave decreasing relative intensities (I/I_0) at d spacings in Å as follows: [10], 4.70, 4.42; [7], 7.46; [6], 4.12; [4], 5.03; [3], 5.92, 5.17, 3.94, 3.36, 2.82, 2.72, 2.62; [2], 4.90, 3.53, 2.54, 2.52, 2.48, 2.32; [1], 2.93, 2.40, 2.17.

Cyclization of 2,2,6-trimethylpimelic acid. The temperature of a finely ground mixture of 0.39 g. (0.002 mole) of trimethylpimelic acid and 0.02 g. of barium hydroxide was raised from 150 to 370° over two hours. The distillate weighed 0.17 g. or 60% yield if it were trimethylcyclohexanone.

The presence of two products in this distillate was shown by treatment of 50 mg. with 50 mg. of dinitrophenylhydrazine ethanolic hydrochloric acid. The product, m.p. 90-130° weighed 40 mg. It was separated by fractional crystallization from hot ethanol into a red and yellow compound. The red compound, m.p. 199.8°, has not been identified. Decreasing relative intensities (I/I_0) at d spacings in Å are: [10], 13.69; [7], 7.76; [6], 4.62; [4], 5.20; [3], 3.60, 3.27; [2], 4.15, 3.89; [1], 3.73.

Anal. Calc'd for $C_{15}H_{20}N_4O_4$: C, 56.4; H, 6.32; N, 17.5.

Found: C, 56.1; H, 6.13; N, 17.8.

The yellow compound was freed from the less-soluble red compound by extraction with hot petroleum ether (b.p. 60-70°). The solution was evaporated, the process repeated, and the residue after evaporation was crystallized from 95% ethanol. The crystals melted at 126-128°. Complete identification as 2,2,6-trimethylcyclohexanone dinitrophenylhydrazone was effected by mixed melting point and by comparison of X-ray diffraction powder diagrams using Cu, K_{α} radiation. Decreasing relative intensities (I/I_0) at d spacings in Å are: [10], 14.48, 3.53; [9], 3.28; [8], 7.02; [6], 7.56; [5], 6.48, 4.92; [4], 5.24, 3.42; [3], 4.46; [2], 4.63, 4.15; [1], 5.5, 4.32, 3.90, 3.06, 2.92, 2.84.

The remainder of the distillate was dissolved in ether, washed with saturated aqueous sodium bisulfite, then treated for thirty minutes with 0.25 ml. of 20% hydrogen peroxide and finally washed with alkali. The oil remaining after evaporation was treated with 70 mg. of semicarbazide hydrochloride, 0.5 ml. of ethanol and then adjusted to pH 7 with alkali and acetic acid. After twelve hours 30 mg. of 2,2,6-trimethylcyclohexanone semicarbazone, m.p. 190-197° was obtained. After crystallization from 95% ethanol (30 ml. per g.) this product melted at 200-203.5°. The substance was fully identified by mixed melting point and comparison with the X-ray diffraction powder pattern (Cu, K_{α} radiation) from an authentic sample. Decreasing relative intensities (I/I_0) at d spacings in Å are: [10], 4.74; [8], 3.63; [3], 6.75, 2.74; [1], 5.68, 4.44, 4.09; 0.5, 8.24, 3.28, 1.85.

SUMMARY

1. The action of phosphorus pentachloride on 2,2,6-trimethylcyclohexanone gives 6-chloro-2,2,6-trimethylcyclohexanone in good yield.
2. This chloro derivative reacts with magnesium, calcium, and lithium to give organometallic compounds.

3. Treatment of these reagents with carbon dioxide and then with water, yields trimethylcyclohexanone and 6-carboxy-2,2,6-trimethylcyclohexanone. This β -keto acid decarboxylates slowly, but can be converted by diazomethane to its stable methyl ester.

4. The structure of this β -ketoester was demonstrated by scission with sodium methoxide to give 2,2,6-trimethylpimelic acid, which, in turn, was cyclized to 2,2,6-trimethylcyclohexanone.

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