[CONTRIBUTION OF THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Factors Influencing the Course and Mechanism of Grignard Reactions. XV. The Reaction of β,β-Dimethylphenethyl Chloride with Phenylmagnesium Bromide in the Presence of Cobaltous Chloride

BY W. H. URRY AND M. S. KHARASCH

The use of metallic halides as catalysts in Grignard reactions has brought about two general results. First, it has increased the usefulness and versatility of the Grignard reagent as a preparative tool; second, it has provided a convenient way to generate free radicals in solution.

In this Laboratory, a large number of free radicals have been generated in ether solution, and their reactions have been studied. In general, it has been found that, when alkylmagnesium halides react with alkyl halides of low molecular weight in the presence of cobaltous chloride, the free alkyl radicals thus produced disproportionate.[1] On the other hand, free radicals derived from weakly electronegative radicals such as benzyl and benzohydryl are thus produced, they dimerize. Free hydrocarbon radicals derived from radicals of intermediate electronegativity, such as cyclohexyl and bornyl, undergo both dimerization and disproportionation.[2] Since the free phenethyl radical in ether solution yields ethylbenzene and styrene in equivalent quantities (17% of each), together with 1,4-diphenylbutane (49%),[3] it appeared desirable to study the reactions of the neophyl (β,β-dimethylphenethyl) radical in ether solution. This free radical has no hydrogen atom attached to the carbon atom adjacent to the trivalent carbon atom, and hence cannot disproportionate. One of the usual reactions of a free radical derived from a weakly electronegative radical is thus blocked. It was of importance to determine whether the free radical would dimerize exclusively or would react in some other manner.

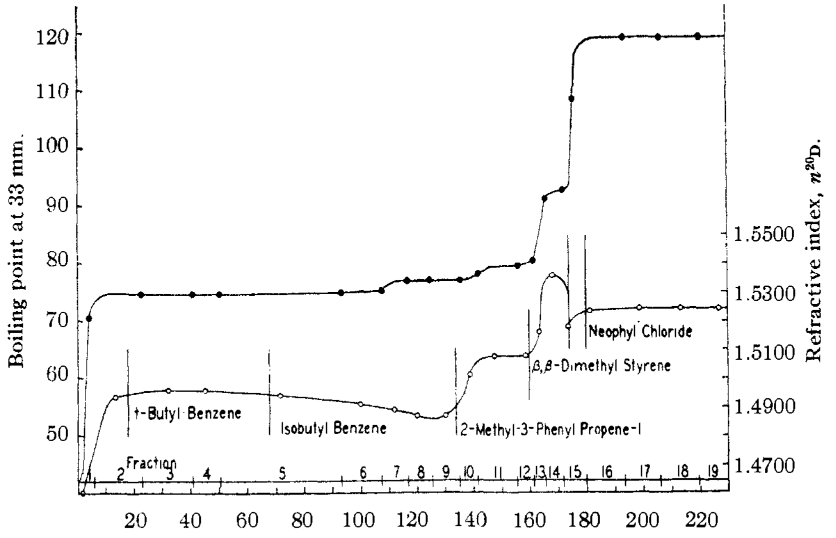


Fig. 1.—Fractional distillation and index of refraction curves: ●, boiling point; O, refractive index.

Discussion

Neophyl chloride ($C_{10}H_{13}Cl$) does not react with phenylmagnesium bromide (or butylmagnesium chloride) even on prolonged heating in ether solution. However, in the presence of a small quantity of cobaltous chloride, a reaction readily takes place, and about 90% of the neophyl chloride is consumed. The reaction mixture, when carefully worked up, gave the following products: (1) *t*-butylbenzene (27%), (2) isobutylbenzene (15%), (3) 2-methyl-3-phenylpropene-1 (9%), (4) β,β-dimethylstyrene (4%), (5) a mixture of dimers of mol. wt. 266 $(C_{10}H_{13})_2$ (41%), (6) biphenyl. The products (1 to 5) account for 96% of the neophyl chloride consumed (Fig. 1); the yield of biphenyl, on the basis of the Grignard reagent consumed, is almost quantitative (96%).

Products (1) to (4) were carefully identified. The *t*-butylbenzene (1) was identified by its boiling point, index of refraction and ultraviolet absorption spectrum (Fig. 2), as well as by the melting point of its *p*-acetamido derivative. The latter compound did not depress the melting point of an authentic sample of *p*-acetamido-*t*-butylbenzene. The isobutylbenzene (2) was similarly identified. The two unsaturated compounds (3 and 4) were identified by their boiling points, indices of refraction and ultraviolet absorption spectra (Fig. 2). They were converted by hydrogenation to isobutylbenzene. The melting points of the *p*-acetamido derivatives of all the isobutylbenzene fractions thus prepared were identical; they did not depress the melting points of one another.

---

(1) Kharasch, Lewis and Reynolds, THIS JOURNAL, **65**, 493 (1943).

(2) Kharasch, Engelmann and Urry, *ibid.*, **66**, 365 (1944).

(3) Kharasch and Sayles, unpublished work.

The formation of the products (1 to 6) may be explained by assuming the series of intermediate reactions

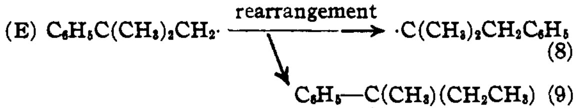
(A) $C_6H_5MgBr + CoCl_2 \longrightarrow C_6H_5CoCl + MgBrCl$

(B) $2C_6H_5CoCl \longrightarrow C_6H_5C_6H_5 + 2CoCl\cdot$

(C) $C_6H_5C(CH_3)_2CH_2Cl + CoCl\cdot \longrightarrow \underset{(7)}{C_6H_5C(CH_3)_2CH_2\cdot} + CoCl_2$

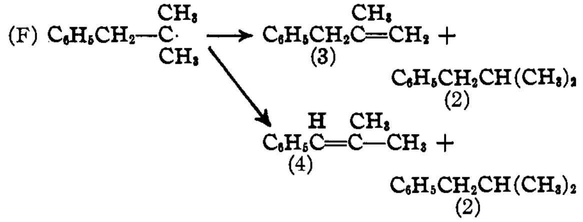
The free neophyl radical (7) appears to undergo the reactions

(D) $C_6H_5C(CH_3)_2CH_2\cdot \xrightarrow{\text{ether}} C_6H_5C(CH_3)_2CH_3$



(E) $C_6H_5C(CH_3)_2CH_2\cdot \xrightarrow{\text{rearrangement}} \underset{(8)}{\cdot C(CH_3)_2CH_2C_6H_5}$; $\searrow$ $C_6H_5{-}\dot{C}(CH_3)(CH_2CH_3)$ (9)

The product formed in reaction (E) depends upon whether the migrating group is phenyl or methyl. The α,α-dimethylphenethyl free radical (8) then undergoes the following reactions:



(F) $C_6H_5CH_2{-}\overset{CH_3}{\underset{CH_3}{C}}\cdot \longrightarrow \underset{(3)}{C_6H_5CH_2\overset{CH_3}{C}{=}CH_2} + \underset{(2)}{C_6H_5CH_2CH(CH_3)_2}$; $\searrow$ $\underset{(4)}{C_6H_5\overset{H}{C}{=}\overset{CH_3}{C}{-}CH_3} + \underset{(2)}{C_6H_5CH_2CH(CH_3)_2}$

The unsaturated compounds (3) and (4) were both isolated. Additional support for the suggested mechanism is the fact that the quantity of isobutylbenzene (2) isolated is roughly equivalent to the sum of the quantities of the two unsaturated compounds (3) and (4).

As yet there is no evidence for the rearrangement of the free neophyl radical into the α-methyl-α-ethylbenzyl free radical (9), although the reaction mixture was carefully examined for the products of disproportionation of this free radical. However, of all the possible free radicals (7, 8 and 9) which might be formed in the reaction, (9) is the one most likely to dimerize.[3] The total amount of dimer isolated was equivalent to 41% of the amount of neophyl chloride consumed. One crystalline substance (m. p. 129°) was isolated from this mixture; the oily residue resisted all efforts to separate the components. Since six different dimers may be formed by the union of radicals (7), (8) and (9), further attempts to isolate the components of the dimer mixture were abandoned.

One other point is worthy of comment. Of the two unsaturated compounds (3) and (4) formed by disproportionation of (8), compound (4) has the lower energy content since it is stabilized by resonance; nevertheless it is formed in smaller amount.

The rearrangement of the free neophyl radical is the first unambiguous demonstration of the rearrangement of a free radical in solution. In this instance, there is a rearrangement of the carbon skeleton of the molecule.[4] Another rearrangement involving the shift of a hydrogen atom in a free radical has been observed in this laboratory; it will be reported in a future publication.[5]

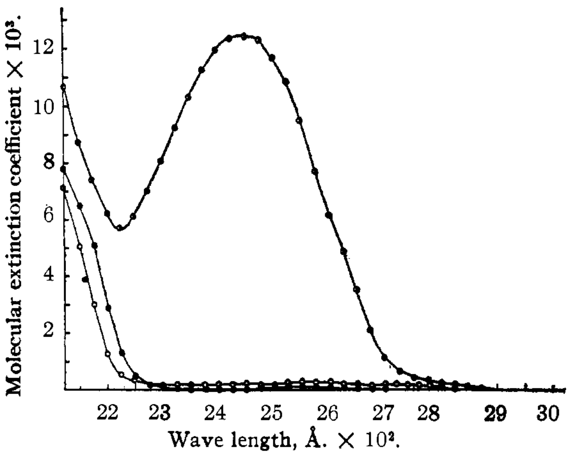


Fig. 2.—Absorption spectra in isooctane: ○, *t*-butylbenzene; ●, 2-methyl-3-phenyl-1-propene, ⊙, β,β-dimethylstyrene.

Experimental Details

Reagents.—The phenylmagnesium bromide solution was prepared according to the procedure of Kharasch and Fields.[6] The solution was titrated acidimetrically for content of Grignard reagent; by the Volhard method for content of halide ion. Anhydrous cobaltous chloride was prepared from c. p. cobaltous chloride hexahydrate (Mallinckrodt) by heating the hexahydrate at 150° in a stream of hydrogen chloride.

The neophyl chloride used in this work (b. p. 53° (1 mm.), $n^{20}D$ 1.5248) had been carefully fractionated through a thirty-plate column packed with single-turn glass helices. When a quantity of this material was distilled through a 100-plate column, the index of refraction remained unchanged.

Reaction of Neophyl Chloride with Phenylmagnesium Bromide in the Presence of Cobaltous Chloride.—Phenylmagnesium bromide (3 moles) in 2 liters of ether was placed in a 3-liter, 3-necked flask with ground glass joints. A condenser, a dropping funnel, and a mercury-sealed stirrer were attached, and anhydrous cobaltous chloride (7 g.) was added slowly while the mixture was stirred. Then, over a period of three hours, neophyl chloride (2.7 moles) dissolved in 500 cc. of anhydrous ether, was added. After half of the neophyl chloride solution had been added, two grams of anhydrous cobaltous chloride was added with each additional 100 cc. of solution. The total amount of cobaltous chloride used was thus 12 g. = 0.09 mole. After all of the neophyl chloride solution had been added, the reaction mixture was refluxed for three hours.

Excess Grignard reagent in the reaction mixture was decomposed, and the precipitated salts were dissolved by the addition of dilute acetic acid solution. The ether solution was washed with dilute sodium carbonate solution and with water, and was dried over anhydrous sodium sulfate. The aqueous extracts were collected, and diluted to an exact known volume. A Volhard halogen determination of an aliquot of this aqueous solution indicated that the reaction had been 90% complete.

The ether was distilled from the ether solution, and the lower-boiling substances were stripped from the reaction

---

[4] *Cf.* Whitmore, Weisgerber and Shabica, THIS JOURNAL, **65**, 1469 (1943).

[5] Kharasch and Lambert, unpublished work.

[6] Kharasch and Fields, THIS JOURNAL, **63**, 2316 (1941).

product by rapid distillation at low pressure. When all products boiling below 104° at 8 mm. had been collected, the high-boiling residue was fractionated at 33 mm. through a 100-plate Podbielniak HeliGrid column. The results obtained are given in Fig. 1.

Analysis of the distillation curve (Fig. 1) indicates the following products: fractions (3) and (4), *t*-butylbenzene (88 g. = 0.66 mole), $n^{20}\mathrm{D}$ 1.4968, b. p. 74.8° (35 mm.); fractions (8) and (9), isobutylbenzene (45 g. = 0.34 mole), $n^{20}\mathrm{D}$ 1.4880, b. p. 77.5° (33 mm.); fraction (11), 2-methyl-3-phenylpropene-1 (27 g. = 0.204 mole), $n^{20}\mathrm{D}$ 1.5080, b. p. 78.5–79.5° (33 mm.); fraction (14), β,β-dimethylstyrene (8 g. = 0.065 mole), $n^{20}\mathrm{D}$ 1.5367, b. p. 92–93° (33 mm.); fraction (16) to (19), recovered neophyl chloride (56 g. = 0.33 mole), $n^{20}\mathrm{D}$ 1.5250, b. p. 119.4° (33 mm.).

The high-boiling residue was steam distilled to remove the biphenyl (223 g., 1.45 mole, m. p. 69–70°). The residual oil (130 g.) was subjected to molecular distillation. The analysis and molecular weight (262) of the distillate indicate that this material consists of dimers (calcd. mol. wt. 266) of two neophyl radicals; it is not a single substance, but a mixture. From this mixture one solid dimer (m. p. 128–129°) was isolated. The residual oil could not be crystallized.

Identification of the Reaction Products.—The *t*-butylbenzene was identified by the melting point (169–170°, uncor.) of its *p*-acetamido derivative.[7] The melting point of a mixture with an authentic sample of *p*-acetamido-*t*-butylbenzene showed no depression.

The structures of 2-methyl-2-phenylpropene-1 and of β,β-dimethylstyrene have recently been proven by ozonolysis.[4] The physical constants of the 2-methyl-3-phenylpropene-1 (Fraction 11) here obtained are identical with those found by Whitmore. The refractive index here observed for β,β-dimethylstyrene (fraction 14) is a little lower than his figure; but this fraction is small and probably slightly impure. As corroborative evidence for the identity of these compounds, their molecular weights were determined by bromide–bromate titration[8]: 2-methyl-3-phenylpropene-1: calcd. mol. wt., 132; found, 127. β,β-Dimethylstyrene: calcd. mol. wt., 132; found, 131. The absorption spectra of these two substances and that of *t*-butylbenzene (Fig. 2) were determined on a Beckman photoelectric quartz spectrophotometer. Isooctane was used as solvent. The spectrum of β,β-dimethylstyrene is similar to that of styrene, with an absorption maximum at 2450 Å. On the other hand, Fraction (3) has an absorption spectrum corresponding closely to that of *t*-butylbenzene, as would be expected if the fraction is 2-methyl-3-phenylpropene-1.

To prove the identity of the carbon skeleton in the compounds composing fractions (9), (11), and (14), the latter two fractions were hydrogenated at 2000 pounds pressure and at 80°; ether was used as the solvent and Raney nickel as the catalyst. The two hydrogenation products and the isobutylbenzene (fraction 9) were converted to the *p*-acetamido derivatives. The melting points are listed in Table I.

TABLE I

MELTING POINTS (UNCOR.) OF SOME *p*-ACETAMIDO DERIVATIVES OF BENZENE

	Hydrocarbon	M. p. of *p*-acetamido derivative, °C.	M. p. of *p*-acetamido isobutylbenzene, °C.	M. p. of mixture, °C.
1	Fraction 9	129–130	129–130	129–130
2	Fraction 11 (hydrogenated)	129–130	129–130	129–130
3	Fraction 14	129–130	129–130	129–130
4	*s*-Butylbenzene	123–124	129–130	110–112

These results are compatible with the previous assumption that fraction (9) is isobutylbenzene; fraction (11) is 2-methyl-3-phenylpropene-1; fraction (14) is β,β-dimethylstyrene.

Summary

1. Neophyl chloride does not react with pure phenylmagnesium bromide, but, in the presence of cobaltous chloride, it reacts vigorously to give *t*-butylbenzene, isobutylbenzene, 2-methyl-3-phenylpropene-1, β,β-dimethylstyrene, a mixture of dimers and biphenyl.

2. A free-radical mechanism, involving rearrangement of the neophyl free radical to the β,β-dimethylphenethyl free radical is shown to be consistent with the products isolated.

CHICAGO, ILLINOIS RECEIVED APRIL 7, 1944

---

[7] Ipatieff and Schmerling, THIS JOURNAL, **59**, 1056 (1937).

[8] "Scott's Standard Methods of Chemical Analysis," Vol. II, p. 2253. Van Nostrand and Company, New York, N. Y.

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

Identification of Some Barbiturates

BY RAYMOND N. CASTLE AND CHARLES F. POE

The investigation reported in this communication was undertaken with the object of studying the possibilities of differentiating among some of the more recent barbituric acid derivatives placed on the market.

The numerous color tests[1,2,3,4,5] for barbiturates reported in the literature are usually not sufficiently specific. It was therefore decided to seek a more reliable identification among derivatives prepared by use of certain reagents. A search of the literature revealed that substituted benzyl halides have already proved their worth in such identifications.[6,7,8,9,10] We have, therefore undertaken the preparation and study of the substituted benzyl derivatives of four new barbituric acids[11] recently introduced into medicine, namely,

---

[1] Zwikker, *Pharm. Weekblad*, **68**, 975 (1931).

[2] Koppanyi, Dille, Murphy and Krop, *J. Am. Pharm. Assocn.*, **23**, 1074 (1934).

[3] Dille and Koppanyi, *ibid.*, **23**, 1079 (1934).

[4] Pesez, *J. pharm. chim.*, **25**, 508 (1937).

[5] Pesez, *ibid.*, **28**, 379 (1938).

[6] Lyons and Dox, THIS JOURNAL, **51**, 288 (1929).

[7] Hargreaves and Nixon, *J. Am. Pharm. Assocn.*, **22**, 1250 (1933).

[8] Hultquist and Poe, *Ind. Eng. Chem., Anal. Ed.*, **7**, 398 (1935).

[9] Jespersen and Larsen, *Arch. Pharm.*, **275**, 28 (1937).

[10] Hultquist, Poe and Witt, *Ind. Eng. Chem., Anal. Ed.*, **14**, 219 (1942).

[11] The authors wish to express appreciation to Eli Lilly and Company, Riedel de Haen, Inc., Sharpe and Dohme, and the Upjohn Company for furnishing, respectively, the samples of seconal, sigmodal, delvinal, and cyclopal.