TABLE I

HYDROLYSIS OF CALCIUM PHOSPHOCITRATE IN 0.1 *N* H_2SO_4, 100°

Each aliquot contains 1.09 μmoles esterified P

Time, min.	Inorg. P released, μM	Hydrolysis, %	Citric acid released
0	0	0	0
20	0.32	29	0.29
40	.63	58	.47
60	.80	73	.66
90	.98	90	.81
105	1.09	100	.90

tallized when left at 3° overnight. After collection by centrifugation, the material became completely solidified by stirring with acetone. Two additional crops of 135 and 65 mg. were obtained from the mother liquor by the addition of more acetone. The three dry fractions were pooled, dissolved in 0.5 ml. of water and acetone added until a faint cloudiness developed (approximately 5 ml. required). Within 15 min. at room temperature a heavy precipitate of broad double pointed needles developed which were collected and dried over P_2O_5 *in vacuo*. The yield was 155 mg. or 43%. Additional crystals obtained from the mother liquor were contaminated with a yellow amorphous solid and were discarded. The pure material is the tricyclohexylammonium salt of citric acid phosphate. The melting point of the substance may best be determined by microscopic observation of individual crystals placed on a block preheated to approximately 130°. Under these conditions the compound is seen to melt at 138–140°.

Anal. Calcd. for $C_{24}H_{60}O_{10}PN_3$: C, 50.4; P, 5.4; N, 7.3. Found: C, 50.2; P, 5.4; N, 7.2.

Acid Hydrolysis of Calcium Phosphocitrate.—The phosphate group of citric acid phosphate is moderately labile as shown in Table I. After approximately 35 minutes, 50% of the phosphate was split in 0.1 *N* sulfuric acid at 100°.

A parallel formation of free citric acid was found by analysis.[10] Milder conditions may produce a 1:1 correlation between the appearance of free citrate and inorganic phosphate. This fact offers a means for the analytical determination of citric acid phosphate. The compound *per se* gives no color in the standard citric acid analytical procedure. The difference between citrate values before and after hydrolysis is a measure of the phosphocitrate present.

Partial Saponification of Triethyl Phosphocitrate.—If alkaline hydrolysis of triethylphosphocitrate is effected in the absence of calcium ion and with only a slight excess of alkali present, partial saponification occurs producing a compound whose calcium salt is remarkably soluble in water. For example, 28.5 mmoles (10.2 g.) of triethyl phosphocitrate was dissolved in 100 ml. of water, the free phosphate group neutralized and 90 meq. of alkali added. This is 5% in excess over that required for complete saponification. After standing overnight at room temperature, 53 meq. of alkali (62% of theory) had been consumed. This indicates that approximately one ester group was intact. When treated on an ion exchange column as previously described, the substance gave the appearance of being a single compound. The purified calcium salt gave a P:C ratio of 1:7.9 indicating the presence of an ethyl group in keeping with the titration data. The P:Ca ratio was 1:1.9 which is approximately the same as for the fully saponified product. However, while the latter compound is soluble in distilled water only to the extent of about 113 mg. %, the former is soluble in excess of 25 g. %. A concentrated solution of the soluble form apparently enters into some sort of reversible polymerization since on standing at room temperature for some hours it may develop a heavy precipitate which is easily redissolved with the aid of acid and remains in solution when the *p*H is adjusted back to 8.5. Critical investigation of these factors was beyond the scope of the present work and is mentioned here to indicate that the physical properties of citric acid phosphate and its derivatives might merit detailed study.

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(10) S. Natelson, J. E. Lugovoy and J. B. Pincus, *J. Biol. Chem.*, **170**, 597 (1947).

NEW ORLEANS, LA.

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Carbonyl Addition Condensations of Diphenylmethane Involving Methylene Hydrogen by Alkali Amides. Synthesis of Certain Benzhydryl Type Carbinols[1,2]

BY PHILLIP J. HAMRICK, JR.,[3,2] AND CHARLES R. HAUSER

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Sodium and potassium diphenylmethides prepared from diphenylmethane and sodium and potassium amides in liquid ammonia undergo a reversible addition reaction with benzophenone and certain aromatic aldehydes to form the alkali salts of the corresponding carbinols. Instantaneous acidification of the reaction mixtures produced good yields of the carbinols, whereas gradual neutralization regenerated the starting materials. Replacement of the liquid ammonia with ether precipitated the sodium salt of 1,1,2,2-tetraphenylethanol but not the potassium salt of this carbinol which underwent reversion. Convenient methods of synthesis of several benzhydryl type carbinols are described.

It has previously been shown that diphenylmethane can be metalated at a methylene hydrogen with sodium amide or potassium amide in liquid ammonia and that the resulting alkali diphenylmethide can enter into several types of carbon–carbon condensations. For example, this hydrocarbon has been benzylated almost quantitatively through its sodium derivative in liquid ammonia (equation 1).[4]

$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. } NH_3]{NaNH_2} \underset{\text{(red)}}{(C_6H_5)_2CHNa} \xrightarrow{C_6H_5CH_2Cl} (C_6H_5)_2CHCH_2C_6H_5 \quad (1)$$

Other types of condensations that have been realized with diphenylmethane through its sodium or potassium derivative in liquid ammonia or ether include carbonation,[5] carbethoxylation,[5] benzoylation[5] and conjugate addition.[6]

It has now been found that diphenylmethane can enter into an addition condensation through its

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(2) Preliminary report given at the 132nd Meeting of the American Chemical Society at New York, N. Y., Sept., 8–13, 1957.

(3) Department of Chemistry, Wake Forest College, Winston-Salem, N. C.

(4) C. R. Hauser and P. J. Hamrick, Jr., THIS JOURNAL, **79**, 3142 (1957).

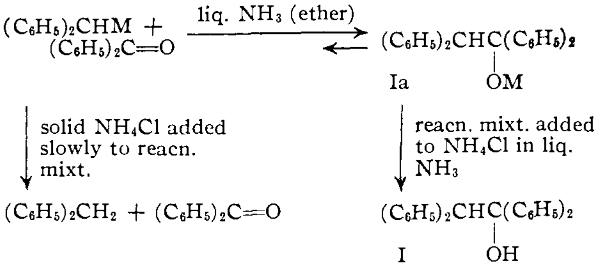
(5) R. S. Yost and C. R. Hauser, *ibid.*, **69**, 2325 (1947).

(6) M. T. Tetenbaum and C. R. Hauser, *J. Org. Chem.*, **23**, 229 (1958).

sodium and potassium derivatives with the carbonyl group of benzophenone and certain aromatic aldehydes to form the alkali salt of the corresponding carbinols. In contrast to the irreversible alkylation represented in equation 1, this addition reaction is so reversible in the liquid ammonia–ether medium employed that good yields of the carbinols are obtained on acidification only under certain conditions. Thus, in the reaction with benzophenone, yields of 78–86% (in three runs) of 1,1,2,2-tetraphenylethanol (I) were realized when the reaction mixture was poured into a solution of excess ammonium chloride in liquid ammonia, whereas only diphenylmethane and benzophenone were recovered (in two runs) when solid ammonium chloride was added slowly to the reaction mixture (Scheme A).[7]

SCHEME A

RAPIDLY EQUILIBRATING SYSTEM (M = Na OR K)



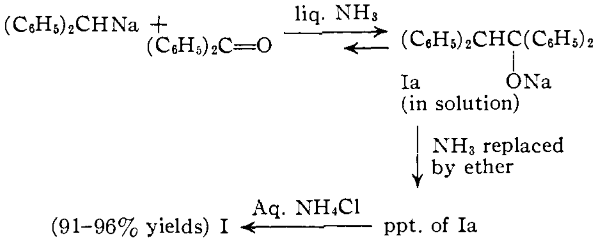
As can be seen from Scheme A, the equilibrium of the addition reaction is considered to be far on the side of the alkali salt of the carbinol Ia. Evidence for this is the observation that the characteristic red color of the diphenylmethide ion is discharged by a molecular equivalent of the ketone. Moreover, this explains the high yields of the carbinol I obtained when the reaction mixture is poured into excess ammonium chloride, under which conditions the neutralization may be regarded as instantaneous. The fact that the addition reaction reverses to regenerate starting materials when the neutralization is effected gradually may be accounted for by the preferential reaction of the acid with the diphenylmethide ion, which is presumably present in the equilibrium in very low concentration.

Although a rapidly equilibrating system is evidently set up in liquid ammonia (Scheme A), the equilibrium may be effectively frozen far on the side of the sodio salt of the carbinol Ia (M = Na) by replacing the ammonia with ether, from which the sodio salt precipitates. Thus, when the liquid ammonia was evaporated as ether was introduced and aqueous ammonium chloride then added, carbinol I was obtained in yields of 91–96% (Scheme B).

However, in contrast to the sodio salt of the carbinol, the potassio salt does not precipitate on replacing the ammonia from the rapidly equilibrating system by ether. Instead, there precipitates the potassium amide–benzophenone adduct II. This apparently arises through the reversal of the metalation of diphenylmethane (ammonolysis) by which the potassium diphenylmethide was prepared from potassium amide and diphenylmethane. The regenerated potassium amide then adds to the regenerated ketone as indicated in Scheme C.

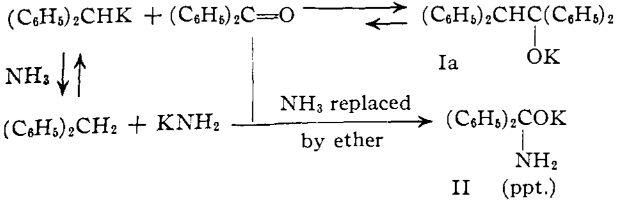
SCHEME B

RAPIDLY EQUILIBRATING SYSTEM



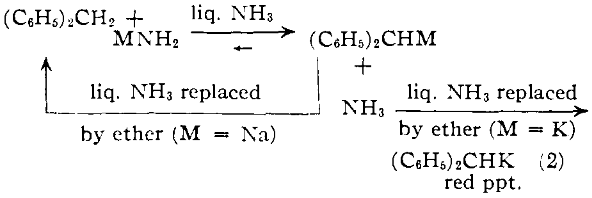
SCHEME C

RAPIDLY EQUILIBRATING SYSTEM



Adduct II was identified by hydrolysis to benzophenone and ammonia and by cleavage in refluxing benzene to form benzamide. This type of cleavage is well known.[8]

The reverse metalation of potassium diphenylmethide that evidently accompanied the precipitation of adduct II shown in Scheme C was not anticipated, since this does *not* occur on similarly replacing the liquid ammonia by ether from potassium diphenylmethide itself[9] in the absence of benzophenone. In fact the latter procedure furnishes a convenient method for the preparation of potassium diphenyl methide in ether, which is a useful reagent for certain condensations.[9] On the other hand, such a reverse metalation of sodium diphenylmethide on replacing the ammonia by ether from the equilibrium system of this reagent and benzophenone would not have been surprising, because this reagent itself undergoes reversion on exchanging these solvents. The two reagents are compared in equation 2.



(2)

The fact that the sodium salt of the carbinol precipitates on replacing the liquid ammonia by ether from the equilibrium system of sodium diphenylmethide and benzophenone (Scheme B) may be ascribed to the relative insolubility of the sodium salt of the carbinol in ether.

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[7] Low to fair yields (up to 40%) of carbinol I were obtained when the ammonium chloride was added rapidly to the reaction mixture. Variations in the proportions of the liquid ammonia and ether employed appeared to influence the yields under these conditions.

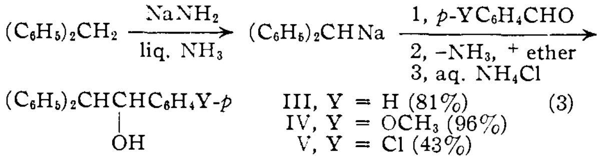
[8] See A. Haller and E. Bauer, *Ann. chim. phys.*, [8] **16**, 146 (1909).

[9] See C. R. Hauser, D. S. Hoffenberg, W. H. Puterbaugh and F. C. Frostick, Jr., *J. Org. Chem.*, **20**, 1531 (1955).

Although the potassium salt of the carbinol underwent reversion under the conditions indicated in Scheme C, this salt was stable when it was produced by adding benzophenone to the red ethereal suspension of potassium diphenylmethide prepared as indicated in equation 2. Thus, when the resulting reaction mixture was added to glacial acetic acid in ether, an 88% yield of carbinol I was obtained. However, when the reaction mixture was neutralized with aqueous ammonium chloride, only a 13% yield of carbinol I was isolated. Apparently the potassium salt of the carbinol underwent predominant reversion under the latter conditions.

Synthesis of Benzhydryl Type Carbinols.—In spite of its tendency to reverse, the addition reaction of the alkali diphenylmethides with benzophenone furnishes a useful method for the synthesis of 1,1,2,2-tetraphenylethanol (I). The recommended procedure is that indicated in Scheme B in which the liquid ammonia is replaced by ether before acidification. The 91–96% yields of the carbinol I obtained in several runs were based on the diphenylmethane used to prepare the sodium diphenylmethide or on the ketone.

Similarly diphenylmethane was condensed through its sodio derivative with benzaldehyde, anisaldehyde and *p*-chlorobenzaldehyde to form carbinols III, IV and V in yields of 81, 96 and 43%, respectively (equation 3).



$$(C_6H_5)_2CH_2 \xrightarrow[\text{liq. NH}_3]{\text{NaNH}_2} (C_6H_5)_2CHNa \xrightarrow[\text{2, -NH}_3,\ ^+\text{ether; 3, aq. NH}_4\text{Cl}]{\text{1, }p\text{-YC}_6\text{H}_4\text{CHO}} (C_6H_5)_2CH\underset{\displaystyle OH}{\underset{|}{C}}HC_6H_4Y\text{-}p \quad \begin{array}{l}\text{III, Y = H (81\%)}\\ \text{IV, Y = OCH}_3\text{ (96\%)}\\ \text{V, Y = Cl (43\%)}\end{array} \quad (3)$$

The *p*-chloro carbinol V was obtained in somewhat better yield (57%) when the reaction mixture in liquid ammonia was poured into excess ammonium chloride in this solvent. The yield was 52% even when ammonium chloride was added rapidly to the reaction mixture in liquid ammonia.

One or more of these procedures would probably be suitable also with certain other aromatic ketones and aldehydes, but the method illustrated by equation 3 failed with acetophenone and diethyl ketone. At least with acetophenone, the α-hydrogen was evidently ionized by the sodium diphenylmethide, since the ketone was recovered.

The present method is considered more convenient than that of Schlenk and Bergmann[10] who prepared sodium diphenylmethide by the cleavage of benzhydrylmethyl ether by means of sodium in ethyl ether. This reagent was reported to react with benzophenone and benzaldehyde to form carbinols I and III in quantitative yield and 39% yield, respectively. This method may be illustrated for carbinol I (equation 4).

$$(C_6H_5)_2CHOCH_3 \xrightarrow[\text{ether}]{\text{Na}} (C_6H_5)_2CHNa \xrightarrow[\text{2, acid}]{\text{1, }(C_6H_5)_2C=O} \text{I} \quad (4)$$

Whereas diphenylmethane is readily metalated with sodium amide in liquid ammonia in our method, this cleavage of the benzhydrylmethyl ether was indicated to be somewhat tedious.[10,11] Moreover, the diphenylmethane is generally more available than this ether.

The present method would presumably also be superior to the use of benzhydrylmagnesium bromide, the usual preparation of which is known to be accompanied by extensive coupling.[12]

Indirect methods have apparently not been satisfactory. Thus, the reaction of phenylmagnesium bromide with benzhydryl phenyl ketone[13] and with desyl bromide[14] have produced carbinol I in yields of only 27 and 1%, respectively. The reduction of α-bromo-α,α-diphenylmethyl phenyl ketone with zinc and acetic acid has given carbinol III in poor yield.[15]

Experimental[16]

Addition Reactions of Sodium Diphenylmethide with Benzophenone. **(A) Neutralization in Liquid Ammonia.**—To a stirred suspension of 0.1 mole of sodium amide in 300 ml. of liquid ammonia[17] there was added a solution of 16.8 g. (0.1 mole) of diphenylmethane in 50 ml. of dry ether. The red color of sodium diphenylmethide appeared immediately.[4] After 10 minutes, a solution of 18.2 g. (0.1 mole) of benzophenone in 50 ml. of dry ether was added. The red color was discharged as the last few drops of the ketone solution was added. The resulting solution was neutralized with ammonium chloride under the two sets of conditions indicated in Scheme A.

In one of these procedures, the reaction mixture was added with stirring to a solution of 12 g. of ammonium chloride in 200 ml. of liquid ammonia. The liquid ammonia was then evaporated, and the residue shaken with ether. The resulting ethereal suspension was cooled and shaken with 100 ml. of water. The solid was collected on a funnel, washed with ether, and recrystallized from methylene chloride to give 30 g. (86%) of 1,1,2,2-tetraphenylethanol (I), m.p. 243–244°; reported m.p. 236°[18] and 244°.[19] Evaporation of the ethereal layer of the filtrate left only a small amount of a liquid.

In the second procedure of neutralization, 12 g. of solid ammonium chloride was added gradually to the reaction mixture. The liquid ammonia was evaporated (steam-bath) as 200 ml. of ether was added. When the ether began to reflux, the mixture was cooled and shaken with 100 ml. of water. The two homogeneous layers were separated. The ethereal layer was dried over Drierite, and the solvent removed. The liquid residue was treated with 2,4-dinitrophenylhydrazine reagent to precipitate (after 1 hr.) the 2,4-dinitrophenylhydrazone of benzophenone, which was collected on a funnel and washed with water. There was obtained 34.4 g. (98%) of this derivative, m.p. and mixed m.p. 238–239°. The filtrate from this treatment was concentrated (hot-plate) to about 100 ml., and extracted with ether. The ethereal solution was dried over Drierite, and the solvent removed. The residue was fractionally distilled to give 12.6 g. (75%) of diphenylmethane, b.p. 118–120° at 10 mm. A sample of this hydrocarbon was oxidized

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[10] W. Schlenk and E. Bergmann, *Ann.* **464**, 20 (1928).

[11] E. Bergmann, *J. Chem. Soc.*, 413 (1936).

[12] Even when the Grignard reagent was prepared from benzhydryl bromide and magnesium in a high dilution cyclic reactor and then carbonated, only a 25% yield of diphenylacetic acid was obtained; D. C. Rowlands, K. W. Greenlee and C. E. Boord, Abstracts of Papers of 117th Meeting of the American Chemical Society at Philadelphia, Pa., April 9–13, 1950, p. 8L.

[13] A. McKenzie and J. S. W. Boyle, *J. Chem. Soc.*, **119**, 1131 (1921).

[14] R. Roger and A. McGregor, *ibid.*, 7850 (1934).

[15] A. Gardeur, *Chem. Zentr.*, **68**, II, 661 (1897).

[16] Melting points were taken on a Fisher–Johns melting point apparatus. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

[17] See C. R. Hauser, F. W. Swamer and J. T. Adams, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 122.

[18] W. Schlenk and E. Bergmann, *Ann.*, **464**, 20 (1928).

[19] A. Banchetti, *Gazz. chim. ital.*, **72**, 74 (1942).

with hot chromic acid to give benzophenone which was isolated as its 2,4-dinitrophenylhydrazone, m.p. 238–239°.

(B) Replacement of Ammonia with Ether and Neutralization. Synthesis of Carbinol I (Scheme B).—A solution of diphenylmethane in ether was added to a stirred suspension of an equivalent of sodium amide in liquid ammonia, followed by an equivalent of benzophenone in ether as described above. The liquid ammonia was evaporated on the steam-bath as an equal volume of ether was added The resulting ethereal suspension was treated cautiously with stirring with an aqueous solution of excess ammonium chloride. The precipitate was removed by filtration, washed with water, and dried. Recrystallization from methylene chloride gave 1,1,2,2-tetraphenylethanol (I), m p. 244–245°. Yields of 91–96% were obtained employing 0.1–0.5 mole of each of the reactants.

Addition Reaction of Potassium Diphenylmethide with Benzophenone. (A) Neutralization in Liquid Ammonia.—To a stirred solution of 0.1 mole of potassium amide in 300 ml. of liquid ammonia,[20] was added 16.8 g. (0.1 mole) of diphenylmethane in 50 ml. of ether to give the red solution of potassium diphenylmethide. After 10 minutes, 18.2 g. (0.1 mole) of benzophenone in 50 ml. of ether was added, the red color being discharged. The resulting reaction mixture was neutralized with ammonium chloride under the two sets of conditions as described above for the corresponding reaction with sodium diphenylmethide and summarized in Scheme A.

Under one of these conditions, the reaction mixture was added with stirring to a solution of 12 g. of ammonium chloride in 200 ml. of liquid ammonia to give a 76% yield of 1,1,2,2-tetraphenylethanol (I), m.p. 244°.

Under the other condition, 12 g. of ammonium chloride was added gradually to the reaction mixture to give benzophenone (96%) and diphenylmethane (79%). None of the carbinol I was found.

(B) Reversion of Addition Reaction On Replacing Ammonia by Ether.—A solution of diphenylmethane in ether was added to a stirred solution of an equivalent of potassium amide in liquid ammonia, followed by an equivalent of benzophenone in ether. The ammonia was evaporated on the steam-bath to leave an ethereal suspension. The solid was removed by filtration and decomposed with water, ammonia being evolved. The resulting oil was taken up in ether and the solution dried over magnesium sulfate. The ether was removed, and the residue distilled *in vacuo* to give 16 g. (89%) of benzophenone, b.p. 166–167° at 8 mm. The 2,4-dinitrophenylhydrazone melted at 238–239°.

In another experiment, 0.06 mole of potassium amide in 150 ml. of liquid ammonia was treated with 0.06 mole of diphenylmethane in 100 ml. of ether, followed by 0.06 mole of benzophenone in 100 ml. of ether. The red color of the intermediate potassium diphenylmethide was discharged and a precipitate formed. The ammonia was evaporated as 100 ml. of ether was added, followed by 100 ml. of thiophene-free benzene. The ether was distilled until the temperature of the vapors reached 80°. The resulting benzene solution (green) was refluxed for 8 hr. to produce a precipitate (red). After cooling, 50 ml. of water was added, and the two layers were separated. The benzene layer was dried, the solvent removed, and the oily residue triturated with petroleum ether to precipitate 4 g. of benzamide, m.p. 128°, after recrystallization from water. The original aqueous layer was acidified to give 2.5 g. of benzoic acid, m.p. 121°. The combined weights of the benzamide and benzoic acid corresponded to 88% cleavage of the potassium amide–benzophenone adduct II.

Addition Reaction of Potassium Diphenylmethide with Benzophenone in Ether.—Diphenylmethane was added to an equivalent of potassium amide in liquid ammonia, and the ammonia then replaced by ether. To the resulting red ethereal suspension of potassium diphenylmethide was added an equivalent of benzophenone, the color being discharged. The ethereal reaction mixture was then added to excess glacial acetic acid in ether to give an 88% yield of 1,1,2,2-tetraphenylethanol (I).

In another experiment, the reaction mixture obtained on treating the red ethereal suspension of potassium diphenylmethide with benzophenone was neutralized with aqueous ammonium chloride to give only a 13% yield of carbinol I.

Addition Reaction of Sodium Diphenylmethide with Aromatic Aldehydes. Synthesis of Carbinols III, IV and V.—To a stirred suspension of 0.06 mole of sodium amide in 100 ml. of liquid ammonia was added 0.06 mole of diphenylmethane in 100 ml. of ether, followed by 0.06 mole of the appropriate aldehyde in 100 ml. of ether. The ammonia was removed on the steam-bath, and the resulting ethereal suspension was neutralized with aqueous ammonium chloride.

The reaction with freshly distilled benzaldehyde gave 13.3 g. (81%) of crude 1,1,2-triphenylethanol (III). Recrystallization from ethanol gave white crystals, m.p. 87–88°, reported[11] m.p. 88–89°.

The reaction with anisaldehyde produced 17.7 g. (96%) of 1,1-diphenyl-2-*p*-methoxyphenylethanol (IV), m.p. 163° (recrystallized from ethanol–acetone).

Anal. Calcd. for $C_{21}H_{20}O_2$: C, 82.58; H, 6.93. Found: C, 82.41; H, 7.08.

The reaction with *p*-chlorobenzaldehyde gave 8 g. (43%) of 1,1-diphenyl-2-*p*-chlorophenylethanol (V), m.p. 153–154° (recrystallized from ethanol).

Anal. Calcd. for $C_{20}H_{17}OCl$: C, 77.80; H, 5.56; Cl, 14.33. Found: C, 77.99; H, 5.57; Cl, 14.40.

In another experiment in which the reaction mixture was added to ammonium chloride in liquid ammonia, the yield of carbinol V was 57%. In still another experiment in which ammonium chloride was added rapidly to the reaction mixture, the yield of carbinol V was 52%.

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[20] See C. R. Hauser and T. M. Harris, THIS JOURNAL, **80**, 6360 (1958).