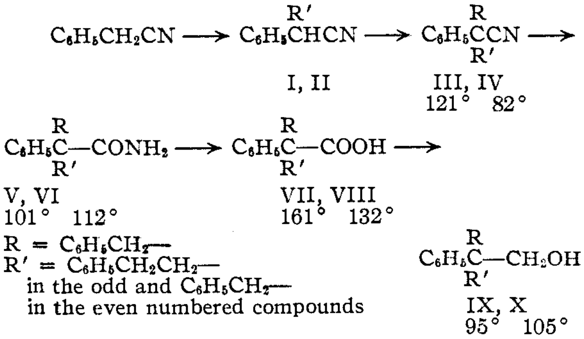
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

A Side Reaction in the Williamson Synthesis

BY ROBERT H. BAKER

In the preparation of benzyl 2-phenethyl ether for hydrogenation studies[1] an interesting by-product was encountered and its identity can now be reported. The ether was prepared by the reaction of benzyl chloride with sodium 2-phenylethoxide suspended in toluene, and the by-product remained in the distillation flask after removing the ether *in vacuo*. When an attempt was made to wash out the residue with petroleum ether it crystallized in large rhombs and was easily crystallized from ethanol to give small rhombs, m. p. 104–105.5°. It was readily shown to be an alcohol by direct esterification and by conversion to its phenyl carbamate. Analysis of neither the alcohol nor its derivatives allowed a decision between the formulas $C_{23}H_{24}O$ and $C_{22}H_{22}O$. Attempted hydrogenation by methods particularly applicable to cleaving benzyl–oxygen bonds failed and thus showed that the hydroxyl function was at least two carbons removed from the nearest aryl group.[1] Exhaustive oxidation produced only benzoic acid, and limited quantities of a variety of oxidizing agents failed to produce any water insoluble acid.[2]

These facts pointed to a phenethyl alcohol substituted on the β-carbon by either a benzyl and phenethyl group or two benzyl groups. It was reasoned that the first of these might result from the benzylation at the *t*-carbon of a Guerbet[3] product, 2,4-diphenylbutanol. The second would involve a dibenzylation of phenethyl alcohol. After many fruitless efforts to synthesize the first of these, IX, from known compounds closely related to it[4] the synthesis was accomplished as shown only to find that it was not identical with the by-product. The lower homolog, X, was then made and was found by m. p., mixed m. p., and m. p. of the two crystalline forms of the acetate ester to be identical with the by-product. Since IX and its precursors are racemic no regularity in m. p. comparisons can be expected.



$$C_6H_5CH_2CN \longrightarrow C_6H_5\overset{R'}{C}HCN \longrightarrow C_6H_5\overset{R}{\underset{R'}{C}}CN \longrightarrow$$

I, II

III, IV
121° 82°

$$C_6H_5\overset{R}{\underset{R'}{C}}\text{—}CONH_2 \longrightarrow C_6H_5\overset{R}{\underset{R'}{C}}\text{—}COOH \longrightarrow$$

V, VI
101° 112°

VII, VIII
161° 132°

$R = C_6H_5CH_2\text{—}$
$R' = C_6H_5CH_2CH_2\text{—}$
in the odd and $C_6H_5CH_2\text{—}$
in the even numbered compounds

$$C_6H_5\overset{R}{\underset{R'}{C}}\text{—}CH_2OH$$

IX, X
95° 105°

The alkylations were carried out in benzene solution using lithium amide.[5] Although this may not produce as high yields as sodium or potassium amide its greater ease of handling warrants its use. Hydrolysis of the nitriles could not be effected by sodium hydroxide in boiling ethylene glycol but their almost quantitative conversion to the amides in acetic acid containing 70% sulfuric acid[6] was effected in one hundred hours. Diazotization of the amides was necessary to produce the acids which were in turn reduced by lithium aluminum hydride in boiling butyl ether.[7]

Although a number of possible reaction sequences leading to the formation of the by-product present themselves, none of them have been previously described and further work is planned to establish the correct one. For the present it appears that the minimum requirement for reagents is according to the equation, $C_6H_5CH_2CH_2OH + 2C_6H_5CH_2Cl + 3Na \longrightarrow C_{22}H_{21}ONa + 2NaCl$. The complexity of the reaction system is demonstrated by two comparable runs. When one-half mole of each reagent was used the yield of the by-product was 10.5%, but when the amounts of sodium and benzylchloride was doubled the yield was not increased.

Experimental[8]

Benzyl Phenethyl Ether.—To 11.5 g. (0.5 atom) of powdered sodium under 200 ml. of toluene there was added dropwise with stirring 61 g. (0.5 mole) of phenethyl alcohol. When about one-half of the alcohol had been added it was necessary to heat the mixture to boiling in order to continue stirring. Within forty-five minutes the evolution of hydrogen had practically ceased and then there was added to the refluxing suspension 63 g. (0.5 mole) of benzyl chloride. The separation of blue particles indicated that not all of the sodium had been used. The suspension was heated for an hour and was allowed to stand overnight. The mixture was decomposed by water and the toluene layer after washing was distilled at 13 mm. into eight fractions, b. p. 87–200°. Three of these fractions, b. p. 175–182°; $n^{20}D$ 1.5545–1.5549, were combined to give 37.9 g., 30% of the ether. Another run employing double quantities of sodium and benzyl chloride gave 34.2% of ether, b. p. 112–113° (0.2 mm.); d^{20}_4 0.964; $n^{20}D$ 1.5544–1.5550.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.40; H, 7.73.

Isolation of 2-Benzyl-2,3-diphenylpropanol, X.—The residue left after distillation of all the ether as previously described was treated with petroleum ether, b. p. 30–60°, which caused crystals to separate, 5.5 g., m. p. 100–101°.

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[1] Baker, Cornell and Cron, THIS JOURNAL, **70**, 1490 (1948).

[2] Mosher and Whitmore, *ibid.*, **70**, 2544 (1948), describe the anomalous behavior of other alcohols toward oxidizing agents.

[3] For a discussion of the Guerbet reaction see Weizmann and Garrard, *J. Chem. Soc.*, **117**, 324 (1920). The reaction has not been applied to phenethyl alcohol.

[4] L. Maria Bohm, M.S. Thesis, Northwestern University, 1947.

[5] Kindly supplied by Metalloy Corp., Rand Tower, Minneapolis, Minn.

[6] Compare Newman, THIS JOURNAL, **62**, 870 (1940).

[7] Although Nystrom and Brown, *ibid.*, **69**, 2548 (1947). state that triphenylacetic acid is not reduced at 25°, Dr. Brown reported in an address before the Chicago Section of the American Chemical Society that reduction could be effected at higher temperatures.

[8] Microanalyses by Margaret Ledyard, Virginia Hobbs and Margaret Hines.

This sample was crystallized from dilute ethanol to give 3.6 g. of massive rhombs, m. p. 103–105°, and a second crop, 1.1 g., m. p. 101–104°. Another crystallization from ethanol gave m. p. 104.5–105°.

Anal. Calcd. for $C_{22}H_{22}O$: C, 87.37; H, 7.33; mol. wt., 302; active H, 1.00. Found: C, 86.57; H, 7.10; mol. wt. (Rast), 318; active H, 0.95.

Acetate Ester of X.—The alcohol, 50 mg., was treated with 1 ml. of acetic anhydride and refluxed for one-half hour. After standing overnight, 2 ml. of water was added to precipitate a solid and oil. This mixture was heated on the steam-bath and treated with ethanol until homogeneous. On cooling to room temperature and scratching short white needles were deposited, wt. 23 mg. Either these crystals or those produced from cold dilute ethanol melt first at 88–89° and when the temperature of the bath is slowly raised the melt resolidifies at about 92° and remelts at 101–101.5°. In one experiment it was possible to produce the high melting form by inducing crystallization in hot dilute ethanol. Rapid cooling of the pure melt, from 101°, produces the high, and slow cooling the low-melting form. An analytical sample dried at 30 mm. and 70° melted at 101–101.5° and mixed with an equal weight of the starting alcohol melted at 81°.

The acetate was also prepared by direct esterification. When 250 mg. of the alcohol, X, in 4 ml. of glacial acetic acid containing two drops of concd. sulfuric acid was treated with 35 mg. of 5% palladium-on-charcoal and shaken with hydrogen for three hours only 0.6 ml. of hydrogen was absorbed. Filtration and dilution with water produced an oil which on standing under the mother liquor for a month began to produce needles. After another month the needles were removed and crystallized from hot dilute ethanol to produce 40 mg., m. p. 103–104°, which showed no depression with the analytical sample above.

Anal. Calcd. for $C_{24}H_{24}O_2$: C, 83.68; H, 7.02. Found: C, 84.10; H, 6.99.

Phenylcarbamate of X.—The alcohol, 250 mg., and phenyl isocyanate, 0.12 ml., were heated at 100° for fifteen minutes. Four crystallizations from 30–40° petroleum ether were required to give pure needles, m. p. 154–155°.

Anal. Calcd. for $C_{29}H_{27}NO_2$: C, 82.48; H, 6.46; N, 3.3. Found: C, 82.20; H, 6.17; N, 3.2.

2,4-Diphenylbutanonitrile, I.—Part of this was prepared by Mr. Martin Knell using Newman's excellent method.[6] Some was prepared, though in poorer yield, by substituting lithium amide for sodium amide, b. p. 147–151° (1.0 mm.), n^{23}D 1.5622.

2-Benzyl-2,4-diphenylbutanonitrile, III.—A refluxing solution of 7.7 g. (0.035 mole) of the nitrile, I, in 100 ml. of dry thiophene-free benzene was treated with 1 g. (0.04 mole) of lithium amide. The mixture was stirred under reflux for five hours at the end of which time it had practically ceased to liberate ammonia. While still boiling the red solution was treated with 5 g. (0.04 mole) of benzyl chloride. This was heated and stirred for an hour and was allowed to stand overnight. The mixture was poured into water and the benzene layer, after washing, was evaporated almost to dryness. The addition of petroleum ether (30–60°) caused the separation of crystals in two crops, 6 g., 60%, m. p. 112–114°. An additional crystallization from benzene–petroleum ether and three more from equal parts of methanol and ethanol were performed practically without loss of material, m. p. 119–121°.

Anal. Calcd. for $C_{21}H_{21}N$: N, 4.5. Found: N, 4.7.

2-Benzyl-2,4-diphenylbutanoamide, V.—A solution of 1.0 g. of the nitrile, III, in 10 ml. of acetic acid containing 1 ml. of 70% sulfuric acid was refluxed one hundred hours, filtered and the filtrate diluted with water to produce a gum which was dissolved in benzene. This solution, after washing with 5% sodium hydroxide solution was decolorized with Norit and diluted with petroleum ether (30–40°) to produce rosettes of crystals, 1.0 g., m. p. 98–100°. The analytical sample, m. p. 98–101°, was obtained by three additional crystallizations from benzene–petroleum ether (30–60°).

Anal. Calcd. for $C_{23}H_{23}NO$: N, 4.2. Found: N, 3.5.

2-Benzyl-2,4-diphenylbutanoic Acid, VII.—This was first obtained from the purified amide but better over-all yields are obtained by avoiding this isolation step. The hydrolysis mixture resulting from refluxing for one hundred sixteen hours a solution of 3.3 g. of the nitrile, III, 30 ml. of acetic acid and 3 ml. of 70% sulfuric acid was cooled to 0° and treated dropwise with a solution of 2 g. of sodium nitrite in 3 ml. of water. The acid was precipitated immediately. The suspension was allowed to come to room temperature, then was heated to 50° and diluted with 70 ml. of water. Cooling slowly to 0° produced 3.3 g., 94% of acid, m. p. 157–163°. Recrystallized from 20 ml. of 95% ethanol, this gave 2.35 g., m. p. 161–162°, and by dilution 0.8 g. of a second crop, m. p. 155–158°. The acid melts with sublimation and its sodium salt is difficultly soluble in water.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.59; H, 6.71. Found: C, 83.35; H, 6.89.

2-Benzyl-2,4-diphenylbutanol, IX.—To a suspension of 1 g. of lithium aluminum hydride in 20 ml. of butyl ether there was added 1.0 g. of the acid, VII. The acid was washed through the condenser with 5 ml. more of the ether. The suspension was heated slowly to reflux temperature and after thirty minutes it was decomposed with 6 *N* hydrochloric acid. Ethyl ether was added and the emulsion broken with ethanol. Sodium hydroxide may also be used to decompose the reaction mixture but the emulsion is just as difficult to break. The ether layer was separated, washed with 10% sodium hydroxide, then water and after drying was evaporated *in vacuo*. The oil which remained crystallized as needles when covered with low boiling petroleum ether, 0.88 g., m. p. 82–87°. Crystallized from petroleum ether (40–60°) the yield was 0.6 g., m. p. 94–95.5°. The compound is very soluble in methanol and ethanol and its m. p. is not raised by repeated crystallization.

Anal. Calcd. for $C_{23}H_{24}O$: C, 87.30; H, 7.64. Found: C, 87.31; H, 7.75.

The alcohol gives a poor yield of the phenyl carbamate, m. p. 144–145°, but all attempts to produce a crystalline acetate have failed.

2-Benzyl-2,3-diphenylpropanonitrile, IV.—Benzyl cyanide was dibenzylated in two stages using lithium amide as metallating agent in boiling benzene. Instead of distilling the product it was crystallized from benzene–petroleum ether (40–60°) to give a 60% yield, m. p. 80–82°; lit.,[9] 83°.

2-Benzyl-2,3-diphenylpropanoamide, VI.—The hydrolysis of 10 g. of IV was carried out in a manner similar to that of III to give 7.6 g. of crude amide which, recrystallized from benzene–petroleum ether, gave 5 g., m. p. 111–112°. For analysis 1 g. was crystallized from glacial acetic acid, yield 0.75 g., m. p. 110–112°.

Anal. Calcd. for $C_{22}H_{21}NO$: C, 83.77; H, 6.73; N, 4.4. Found: C, 83.70; H, 6.63; N, 3.7.

2-Benzyl-2,3-diphenylpropanoic Acid, VIII.—A solution of 3.8 g. of VI in 20 ml. of acetic acid, 7 ml. of concd. sulfuric acid and 3 ml. of water was cooled to 0° and treated dropwise with a solution of 1 g. of sodium nitrite in 2 ml. of water. No solid separated during 30 minutes in the cold nor on coming to room temperature. Heating on the steam-bath caused the separation of an oil which partially solidified on cooling. This gummy material was washed with water by decantation then was taken up in benzene and extracted with 10% potassium hydroxide. The alkaline solution was washed with benzene then the gummy acid was precipitated with acetic acid. The crude acid was crystallized from hot acetic acid by adding water to a cloudy point and scratching. The yield of 1.7 g., m. p. 130–131°, was reduced to 1.4 g. by an additional crystallization from 10 ml. of acetic acid, m. p. 131–132°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.50; H, 6.73. Found: C, 83.14; H, 6.33.

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(9) Jullien, *Bull. soc. chim.*, **6**, 1252 (1939).

2-Benzyl-2,3-diphenylpropanol, X.—A butyl ether solution of 1 g. of VIII was reduced by the method previously described for VII. Evaporation of the ether left 0.68 g. of massive crystals, m. p. 99–101°. Crystallization from dilute ethanol gave 0.45 g., m. p. 101–103°. A mixture of this and the alcohol isolated from the ether preparation was fused, allowed to solidify and remelted at 103–105°.

The mother liquor from the ethanol crystallization gave a second crop, 0.10 g., m. p. 101–102°. This was converted into the **acetate** by the anhydride method, yield 0.06 g., m. p. 85–87° and 101–102°.

Summary

2-Benzyl-2,3-diphenylpropanol has been shown to be a by-product in the production of benzyl phenethyl ether *via* sodium phenethyl oxide and benzyl chloride.

Two series of compounds have been carried from 2-benzyl-2,4-diphenylbutanonitrile and 2-benzyl-2,3-diphenylpropanonitrile through their amides and acids to the corresponding alcohols.

The reduction of highly hindered acids to alcohols by lithium aluminum hydride in boiling butyl ether has been described.

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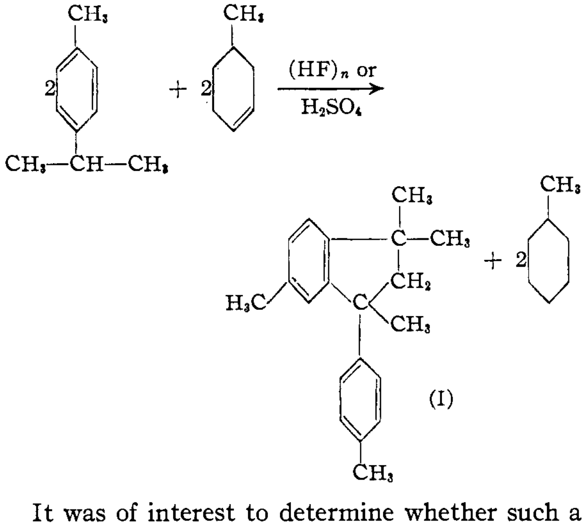
Hydrogen Transfer. II. Reaction of Diisopropyltoluene and Isopropylcyclohexyltoluene with Methylcyclohexene[1]

BY HERMAN PINES, ANNA WEIZMANN[1a] AND V. N. IPATIEFF

In the previous paper of this series[2] it was shown that an abnormal reaction occurs when *p*-cymene (*p*-isopropyltoluene) is contacted, in the presence of sulfuric acid or hydrogen fluoride, with branched chain olefins, such as trimethylethylene or with a substituted cyclohexene such as methylcyclohexene. Instead of only the expected alkylation and cycloalkylation, a hydrogen transfer was the main reaction causing the formation of the corresponding saturated hydrocarbons and 1,3,3,6-tetramethyl-1-*p*-tolylindan (I). The olefinic hydrocarbons acted as hydrogen acceptors while the *p*-cymene acted as a hydrogen donor. The reaction proceeded as follows



It was of interest to determine whether such a reaction would proceed also with a substituted *p*-cymene. For that reason 2,4-diisopropyltoluene and 4-isopropyl-2-cyclohexyltoluene have now been prepared by the reaction of *p*-cymene with propene and cyclohexene, respectively, in the presence of sulfuric acid. The structrue of the diisopropyltoluene was determined by comparing the infrared absorption spectra of this hydrocarbon with that of the hydrocarbon synthesized from 2-bromo-4-isopropyltoluene and acetone *via* the Grignard reaction. Both spectra were identical. The 2,4-dinitrophenylhydrazones of the acetyl compounds prepared from the two samples of diisopropyltoluene were identical.

The structure of cyclohexyl-*p*-cymene was not determined directly but, by comparison with diisopropyltoluene, it is fair to assume that this hydrocarbon is 2-cyclohexyl-4-isopropyltoluene. This was further substantiated by the fact that the tetranitrocompounds of the indans produced from the 2,4-diisopropyl- and 2-cyclohexyl-4-isopropyltoluene were identical.

The diisopropyltoluene and the cyclohexylisopropyltoluene were treated separately with methylcyclohexene in the presence of hydrogen fluoride at 0°. Hydrogen transfer occurred in each case; the products consisted of methylcyclohexane and 1,3,3,6-tetramethyl-5-isopropyl-1-(4-methyl-3-isopropylphenyl)-indan (II) and 1,3,3,6-tetramethyl-5-cyclohexyl-1-(4-methyl-3-cyclohexylphenyl)-indan (III). The hydrogen transfer was the primary reaction and amounted to about 60–70% of the total reaction. Part of the substituted *p*-cymene seemed also to react with methylcyclohexene to form the addition product.

The hydrogen transfer reaction proceeded according to the equation shown.

Compound II melted at 79.5° and analyzed as $C_{26}H_{36}$. On nitration under controlled conditions it yielded a dinitroderivative melting at 115–116° and corresponding to 1,3,3,6-tetramethyl-5-nitro-

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[1] This work was made possible in part by the financial assistance of Universal Oil Products Company.

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[2] V. N. Ipatieff, H. Pines and R. C. Olberg, THIS JOURNAL, **70**, 2123 (1948).