[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

A Side Reaction in the Williamson Synthesis. II[1]

ROBERT H. BAKER AND WILLIAM B. MARTIN

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The alkylation of sodium 2-phenylethoxide with benzyl chloride produces, in addition to the expected ether, 2-benzyl-2,3 diphenylpropanol. This abnormal reaction results from the presence of aldehydes or other phenylacetaldehyde precursors. Thus, the course of the reaction probably involves a sequence of oxidation-reduction steps and the successive alkylations of aldehyde enolates. In one experiment, with 3-phenylpropanol, the intermediate 2,2-dibenzyl-3-phenylpropanal was isolated. The abnormal alkylation has been accomplished also with 2-phenylethanol and allyl chloride and with 4-phenylbutanol and benzyl chloride. The products demonstrate that dialkylation is the rule and that only the β carbon atom is involved.

Some years ago it was shown that the reaction of sodium 2-phenylethoxide with benzyl chloride in toluene produced not only the ether but also a surprising quantity of the carbon-alkylation product, 2-benzyl-2,3-diphenylpropanol.[2] Subsequently, it was shown that this result could not be due to the presence of a carbanion which would be tautomeric with the phenylethoxide ion.[3] It was also demonstrated that freshly prepared alcohols such as 2,3-diphenylbutanol and 2,3-diphenylpropanol gave only the *O*-benzyl derivatives, and further that benzyl 2-phenylethyl ether, under the conditions of abnormal benzylation, gave none of the unusual alcohol.[4]

The fact that we were unable to perform the second stage of benzylation on the latter two alcohols, and indeed that we could not alkylate any but aged samples of 2-phenylethanol itself led to the investigation of aldehydes as possible promoters of the abnormal alkylation. With phenylacetaldehyde, up to 5 mole %, it was not possible to produce the C-alkylation product in high yield; but with benzaldehyde or ketones which cannot themselves be destroyed through aldol condensation, excellent yields were obtained as shown in Table I. For each of the promoters there was an optimum concentration at about 7.6 mole % (based on the alcohol) and best results were encountered when the aldehyde or ketone was added slowly as a solution in the alkylating agent.

It appears most reasonable that the reaction sequence involves the production of phenylacetaldehyde followed by the alkylation of its enolate ion; subsequent proton removal, a second alkylation, and finally, reduction completes the chain of events with regeneration of the promoter (or its equivalent). The minimum number of equations required to express the processes occurring prior to hydrolysis is six as represented in the reaction scheme.

TABLE I

EFFECTIVENESS OF VARIOUS CARBONYL COMPOUNDS ON YIELD OF 2-BENZYL-2,3-DIPHENYLPROPANOL

Aldehyde or Ketone	Equivalent, %[a]	Yield, %[b]
Phenylacetaldehyde	5.0	4.5
Benzaldehyde	3.8	11.6
Benzaldehyde	7.6	19.2
Benzaldehyde	7.6	12.3
Benzaldehyde	7.6	38.4[c]
Benzaldehyde	11.4	37.5
Benzaldehyde	15.2	34.6
Benzophenone	7.6	26.7
Fluorenone	7.6	23.6
Cyclohexanone	7.6	0.5

[a] Equivalent % is the moles per 100 moles of 2-phenylethanol. [b] The yield is based on the alcohol. [c] Twice the usual amount of benzyl chloride was used.

$$C_6H_5CH_2CH_2O^- + R_2CO \rightleftharpoons C_6H_5CH_2CHO + R_2CHO^- \quad (1)$$

$$C_6H_5CH_2CHO + C_6H_5CH_2CH_2O^- \rightleftharpoons C_6H_5{}^-CHCHO + C_6H_5CH_2CH_2OH \quad (2)$$

$$C_6H_5{}^-CHCHO + C_6H_5CH_2Cl \longrightarrow C_6H_5CH(CH_2C_6H_5)CHO + Cl^- \quad (3)$$

$$C_6H_5CH(CH_2C_6H_5)CHO + C_6H_5CH_2CH_2O^- \rightleftharpoons C_6H_5{}^-C(CH_2C_6H_5)CHO + C_6H_5CH_2CH_2OH \quad (4)$$

$$C_6H_5C^-(CH_2C_6H_5)CHO + C_6H_5CH_2Cl \longrightarrow C_6H_5C(CH_2C_6H_5)_2CHO + Cl^- \quad (5)$$

$$C_6H_5C(CH_2C_6H_5)_2CHO + C_6H_5CH_2CH_2O^- \rightleftharpoons C_6H_5C(CH_2C_6H_5)_2CH_2O^- + C_6H_5CH_2CHO \quad (6)$$

Such a lengthy path is not to be lightly accepted, particularly as in some of the experiments each molecule of aldehyde added must account for as many as five molecules of final product and that the enolate ions, though of necessity in low relative concentration, must compete with alkoxide ions for the alkylating agent. Further, this course of the reaction would account for a number of other byproducts that have not been found. Among these would be the monoalkylated alcohol, its benzyl ether, and the intermediate aldehydes. The final products certainly do not consist wholly of ether and dialkylated alcohol, but characterization of the other products has not been possible except that when 3-phenylpropanol was used the dialkylated

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[1] This work was supported by a grant from the Abbott Fund of Northwestern University.

[2] R. H. Baker, *J. Am. Chem. Soc.*, **70**, 3857 (1948).

[3] R. H. Baker and S. H. Jenkins, Jr., *J. Am. Chem. Soc.*, **71**, 3969 (1949).

[4] Maryann Compton, M. S. thesis, Northwestern University, 1949.

aldehyde was isolated. These difficulties in isolating other by-products calls attention to the fortunate circumstances attending the original isolation of 2-benzyl-2,3-diphenylpropanol which, because of its ease of crystallization, was readily separated from other reaction products.

Before accepting the oxidation-alkylation-reduction path, efforts were made to ensure that the reaction did not proceed by some simpler though possibly more obscure manner. That the source of the benzyl groups was wholly from the benzyl chloride and not from the solvent, toluene, was proved in two ways. First, benzene instead of toluene was used, and although the yield was reduced to 9% the result left little doubt that the explanation invoked merely the lower reflux temperature. Secondly, the benzyl chloride was replaced by allyl chloride whereupon a diallylphenethyl aldohol was obtained. With butyl bromide no C-alkylation product could be isolated and it is probable that only quite rapidly acting alkylating agents would be successful.

The phenyl group in the alcohol is without doubt of value in the success of the reaction sequence through its stabilizing effect on the enolate ions as seen in Equations 2 and 4. It did seem important, however, to determine not only if it were necessary but also, in homologues of phenethyl alcohol, if it rather than the potential aldehyde group might govern the position of alkylation. To this end 3-phenylpropanol and 4-phenylbutanol were subjected to the benzylation reaction and both were found to be alkylated in the 2-position. The yields in the latter two reactions were so low as to make isolation of the products difficult. This again points to the efficacy of the phenyl group, when properly placed, in promoting the side reaction.

EXPERIMENTAL[5]

2-Benzyl-2,3-diphenylpropanol. To 5.8 g. (0.25 mole) of powdered sodium under 150 ml. of toluene there was added dropwise with stirring 30.5 g. (0.25 mole) of 2-phenylethanol. Toward the end of the addition it was necessary to bring the suspension to reflux in order to continue stirring. When the evolution of hydrogen had ceased, there was added during 5 to 25 min. a solution of 31.5 g. (0.25 mole) of benzyl chloride containing 0.02 mole of benzaldehyde or other promoter as listed in Table I. After approximately 1 hr. of reflux and stirring, the mixture was cooled; water was added and the organic layer was separated and distilled. Toluene and then benzyl 2-phenylethyl ether were distilled up to 150° at 0.6 mm. The latter was not always isolated but generally occurred in about 40% yield. Treatment of the residue with petroleum ether (b p. 30–60°) gave the product, m.p., 101–103°.

Benzylation of 3-phenylpropanol. The reaction was carried out using the molar quantities and conditions described above, and using benzophenone as the promoter. Distillation of the hydrolyzed product gave three fractions, b.p. 200–217° at 2 mm. which partially solidified after several days. The material, 3.5 g., could not be purified by crystallization and was chromatographed over alumina. Benzene elution produced crystals of m.p. 118–120°, recrystallized from methanol-water, m.p. 122–124°, which proved to be an aldehyde. Methanol-benzene elution then produced the alcohol, m.p. 80°. The high melting substance showed the infrared absorption of an aldehyde and it yielded a 2,4-dinitrophenylhydrazone, crude m.p. 175–176°. The aldehyde, 0.4 g. was reduced by 0.1 g. of lithium aluminum hydride in ethyl ether to 2,2-dibenzyl-3-phenylpropanol, m.p. 80° (from methanol-benzene), which was identical with that synthesized below.

2,2-Dibenzyl-3-phenylpropanol. Tribenzylacetonitrile was prepared by the method of Bergstrom and Agostinho[6] except that three equivalents of benzyl chloride was used, and the solid product, after washing with alcohol, was crystallized from benzene; yield 59%, m.p. 223°. Hydrolysis of the nitrile was by Newman's method and like similar compounds, it gave the amide.[2] Diazotization of the amide[2] produced the crude tribenzylacetic acid, m.p. 111–113°; neut. equiv. 328, calcd., 330. The acid was reduced by lithium aluminum hydride in hot butyl ether.[2] After hydrolysis the product was washed with potassium hydroxide solution and was distilled, b.p. 200–205° at 0.05 mm. On standing the alcohol solidified, m.p. 80–81°. Its infrared spectrum was identical with that of the product described above.

Anal., Calcd. for $C_{23}H_{24}O$: C, 87.30; H, 7.65. Found: C, 87.9; H, 7.6.

Benzylation of 4-phenylbutanol. This alcohol as produced by hydrogenation of the ester[7] was difficult to purify and thus was treated with lithium aluminum hydride to produce the pure material, b.p. 92–93° at 0.3 mm., n_D^{25} 1.5170.

The alkylation was carried out as previously described, using benzophenone, and two equivalents of benzyl chloride. Distillation produced seven fractions; the first six, b.p. 124–138° at 0.3 mm., were fractionated in a 50-plate Podbielniak Heli-Grid column giving a 25% yield of *benzyl 4-phenylbutyl ether*, b.p. 133–134° at 1.1 mm.,; n_D^{25} 1.5369.

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found: C, 84.6, H, 8.6.

The last fraction from the preliminary distillation, b.p. 200–210° at 0.3 mm. weighed 6.7 g.; 8% crude yield. It could not be crystallized but was converted into *2,2-dibenzyl-4-phenylbutyl 3,5-dinitrobenzoate*, m.p. 174–175°, from methanol, which was identical with that from synthetic material.

Anal. Calcd. for $C_{31}H_{28}N_2O_6$: C, 70.99; H, 5.38; N, 5.34. Found: C, 71.1; H, 5.3; N, 5.5 (Dumas).

Synthesis of 2,2-dibenzyl-4-phenylbutanol. The benzylation of 4-phenylbutanonitrile, 0.5 mole, in liquid ammonia-sodamide followed the Bergstrom and Agostinho method[6] as modified above. The pasty mass obtained upon evaporation of ammonia was washed with methanol, then with water and was crystallized from methanol-benzene to give *2,2-dibenzyl-4-phenylbutanonitrile*, 50% yield, m.p. 131–133°. Two crystallizations from ethanol raised the melting point to 132–133°.

Anal. Calcd. for $C_{24}H_{23}N$: N, 4.30. Found: N, 4.5.

The nitrile, 30 g. (0.093 mole) was refluxed for 122 hr. in a solution containing 400 ml. of acetic acid, 50 ml. of sulfuric acid and 15 ml. of water.[2] Upon cooling to 5° there was added dropwise a solution of 6.4 g. of sodium nitrite in 30 ml. of water, then after 0.5 hr. the nitrosation was repeated and the solution deposited crystals. The solid was dissolved in aqueous potassium hydroxide and was filtered from a small amount of neutral material. Acidification produced 26 g., 82%, of *2,2-dibenzyl-4-phenylbutanoic acid;* m.p. 120–121°, after crystallization from methanol-water; neut. equiv., calcd. for $C_{24}H_{24}O_2$, 344, found, 340.

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(5) Microanalyses were performed by Misses J. Sorensen, C. White and H. Beck. All melting points were observed on the hot stage of a polarizing microscope and are corrected.

(6) F. W. Bergstrom and R. Agostinho, *J. Am. Chem. Soc.*, **67**, 2152 (1945).

(7) H. Adkins, B. Wojcik, and L. W. Covert, *J. Am. Chem. Soc.*, **55**, 1669 (1933).

This acid, 8 g. (0.023 mole) was reduced by refluxing for 4 hr. with 1.5 g. (0.04 mole) of lithium aluminum hydride in ethyl ether. After hydrolysis the alcohol was distilled at 0.3 mm.; after some weeks it solidified: m.p. 76°. A small sample was converted into 2,2-dibenzyl-4-phenylbutyl 3,5-dinitrobenzoate, m.p. 174–175°, from methanol, whose infrared spectrum was identical with that of the analytical sample previously described.

Allylation of 2-phenylethanol. The alkoxide, 0.25 mole, was made and treated as previously described, but using benzaldehyde as promoter and allyl chloride, 0.028 mole, as alkylating agent. The product, after hydrolysis, was distilled at 5 mm. into eight fractions. Approximately 50% of the 2-phenylethanol was recovered. The last fraction, b.p. 135–137° at 5.5 mm., n_{D}^{25} 1.5416 was redistilled into three fractions, most of the material, *2,2-diallyl-2-phenylethanol* distilling at 98–99° at 0.6 mm., n_{D}^{25} 1.5406. With palladium-charcoal in acetic acid it absorbed 97% of the hydrogen required for two double bonds, and a Zerewitinoff determination showed 1.1 equivalents of active hydrogen.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.9; H, 8.9.

EVANSTON, ILL.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Conjugate Bimolecular Reduction of Hindered Ketones Involving Replacement of Methoxyl Groups. IV. Mesityl 2-Methoxy-1-naphthyl Ketone[1]

REYNOLD C. FUSON AND DAVID E. FRANKHOUSER[2]

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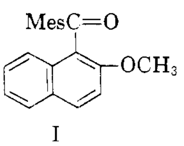
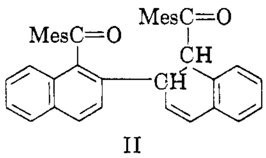
Reduction of mesityl 2-methoxy-1-naphthyl ketone with the binary mixture, magnesium–magnesium iodide, gave 1,2-dihydro-1,1′-dimesitoyl-2,2′-binaphthyl and 1,1′-dimesitoyl-2,2′-binaphthyl. The dihydro diketone underwent cleavage with chloranil to give a monoketone, 1-mesitoyl-2,2′-binaphthyl, and mesitoic acid. The monoketone, synthesized independently, was cyclized with polyphosphoric acid. Conversion of the dihydro diketone to the aromatic diketone was effected with palladium-on-charcoal.

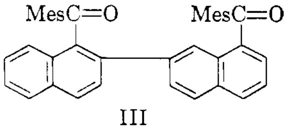
It has been shown that hindered *o*-methoxyphenyl ketones undergo reductive coupling and cyclization to yield the corresponding 9,10-diarylphenanthrenes.[3] The analogous behavior of mesityl 2-methoxy-1-naphthyl ketone (I) would afford a new entry into the picene family. A greater tendency for coupling might be expected in the naphthalene series as the methoxy ketone, because of the greater double bond quality of the 1,2-linkage, would be expected to behave more like an ester than does the benzene analog. Under reaction conditions very similar to those employed previously, the naphthyl ketone gave coupling products in comparatively high yields. The transformation stopped, however, at the diketone stage. The principal product II proved to be the dihydro derivative of the completely aromatized diketone III. The latter was obtained also but in much smaller amounts.



I

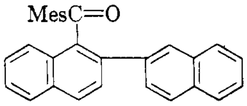


II

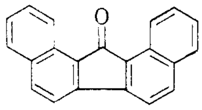


III

Of special interest was the transformation realized when the dihydroaromatic diketone II was treated with chloranil in anisole. The products were a monoketone, 1-mesitoyl-2,2′-binaphthyl (IV), and mesitoic acid. This result is unusual; the treatment with chloranil was expected to give the aromatized diketone. Aromatization was accomplished, however, by heating with palladium-on-charcoal.



IV



V

The monoketone IV was synthesized independently by displacement of the methoxyl group of the methoxy ketone I by the action of the 2-naphthyl Grignard reagent. Ring closure of the monoketone was effected with polyphosphoric acid, the product being the known 13H-dibenzo[a,i]fluoren-13-one (V).

The aromatic diketone presumably was produced by dimerization of the ketyl formed by the interaction of the methoxy ketone and the binary mixture, magnesium–magnesium iodide.[4] The dihydro diketone could conceivably be the intramolecular reduction product of the aromatic diketone, if ring closure were prevented by steric factors. Further reduction of the diketone pre-

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(1) This investigation was supported in part by a grant from the Office of Ordnance Research, U. S. Army (Contract No. DA-11-022-ORD-874).

(2) American Cyanamid Company Fellow, 1958–1959.

(3) R. C. Fuson and R. O. Kerr, *J. Org. Chem.*, 19, 373 (1954).

(4) M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, 49, 236 (1927).