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

The Catalytic Reduction of Bromobenzene to Biphenyl[1,2]

BY FRANK R. MAYO[3] AND MELVIN D. HURWITZ[4]

Busch and co-workers[5] have shown that bromobenzene and some other aromatic halides could be reduced in the presence of a palladium catalyst to yield both benzene and biphenyl. The latter reaction was unique in that only partial reduction of the carbon–halogen bond occurred, and a new carbon–carbon bond was formed. The object of the present work was to determine the effect of experimental conditions on the yield of biphenyl in the hope that it would extend knowledge of the mechanism of catalytic reduction, and might also make possible new applications of semi-reduction methods in organic synthesis.

Standard Experiment.—A set of experimental conditions was chosen as a standard of comparison for reagents and for the effect of varied conditions. Methanol served as both solvent and reducing agent.

In a 200-cc., 3-necked, round-bottomed flask, equipped with an oil-sealed stirrer and reflux condenser, 7.85 g., 0.05 m., of bromobenzene, 3 g. of 1% palladium-on-calcium carbonate (Pd–$CaCO_3$) catalyst, 10 cc. of 10 *N* aqueous potassium hydroxide, and 90 cc. of methanol were mixed and refluxed until the catalyst was completely black or reduced. The catalyst was then separated by filtration, and the filtrate evaporated on a steam-bath to a volume of 25 cc. Water was then added to precipitate the biphenyl which was collected on a filter, dried in a vacuum desiccator, and weighed. The filtrate was made up to 500 cc., and an aliquot was titrated for bromide by the Volhard method to determine the extent to which bromobenzene had been reduced.

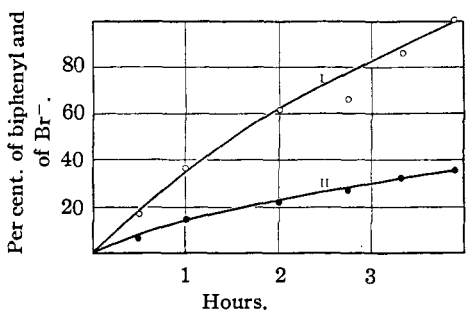

Fig. 1.—Reduction of bromobenzene to biphenyl and to Br^- as a function of time: I, biphenyl; II, Br^-.

The two reactions occurring may be represented by the equations

$$C_6H_5Br + KOH + CH_3OH \longrightarrow C_6H_6 + KBr + H_2O + CH_2O \quad (1)$$

$$2C_6H_5Br + 2KOH + CH_3OH \longrightarrow (C_6H_5)_2 + 2KBr + 2H_2O + CH_2O \quad (2)$$

End-Point of Reduction.—The light brown palladium oxide catalyst was reduced to black palladium during the course of the reaction.

Six batches of 1% Pd–$CaCO_3$ catalyst, designated A to F, were prepared according to a modification of Busch's[5a] procedure by adding an aqueous solution of palladium chloride to the calculated amount of C. P. calcium carbonate in a water suspension and heating to complete the precipitation of palladium oxide. The product was then washed with water until free of chloride, and dried *in vacuo* over concentrated sulfuric acid.

Since the bromobenzene protected the metal oxide from reduction, the color change indicating complete reduction of the catalyst was sharp and indicated complete reduction of the bromobenzene. Catalyst B, which required 2.75 hours for complete reduction in a standard reaction mixture, was reduced in four minutes when the bromobenzene was omitted. Results of standard experiments with fresh portions of catalyst C are summarized in Fig. 1, which shows the correlation of yield of biphenyl and reduction of the bromobenzene with time.

As already indicated, the time for completion of a standard experiment, recorded in Table I, varied with the batch of catalyst. Although the reduction times varied over a wide range, the yields of biphenyl were constant within experimental error.

TABLE I

TIME FOR COMPLETE REDUCTION OF VARIOUS CATALYST BATCHES

Catalyst	Reduction time, hr.	Found, % Br^-	Found, % $(C_6H_5)_2$
A	0.50	96.4	34.0
B	2.75	98.8	35.6
C	3.91	100.6	35.3
D	1.00	99.0	35.3
E	2.00	100.5	35.0
F	6.50	99.8	34.0

Properties of the Reduced Catalyst.—The reduced catalyst was more active for reducing the halide, but less active for biphenyl production than the unreduced catalyst. This enhanced activity decreased with re-use, with the activity for biphenyl formation dropping off more sharply. A catalyst reduced originally in the absence of bromobenzene exhibited the same characteristics.

In a series of standard experiments Catalyst C was reused in seven successive runs. The time was held constant at 1.33 hours, since after the first run there was no indicator to give the end-point of the reduction. The fresh Catalyst C required 3.91 hours for complete reduction (see Fig. 1). In the second run 88.6% of the halide was

(1) Presented at the meeting of the American Chemical Society in New York City, September, 1947.

(2) From the Master's Thesis of M.D. Hurwitz, 1942.

(3) Present address, General Laboratories, U. S. Rubber Co., Passaic, New Jersey.

(4) Present address, Resinous Products and Chemical Co., Philadelphia, Pennsylvania.

(5) (a) Busch and Stove, *Ber.*, **49**, 1063 (1916); (b) Busch, *Z. angew. Chem.*, 232 (1918); (c) Busch, *ibid.*, **38**, 519 (1926); **47**, 536 (1934); (d) Busch and Schultz, *Ber.*, **62**, 1458 (1929); (e) Busch and Schmidt, *ibid.*, **62**, 2612 (1929); (f) Busch and Weber, *J. prakt. Chem.*, **146**, 1 (1936).

reduced in 1.33 hours. This state of reduction would have taken about 3.5 hours with fresh catalyst, and indicated that the reduced catalyst was about 2.6 times more active. The activity of the reduced catalyst fell off, so that in the eighth run only 67.4% of the halide was reduced in 1.33 hours—or only 2.1 times as fast as with the unreduced catalyst. The yield of biphenyl decreased more rapidly, from 20.2% in the second to 11.4% in the eighth.

Effect of Water.—Water up to a concentration of 50% by volume increased the yield of biphenyl. Above 50%, where the reaction liquids separated into two phases, the biphenyl yield fell off rapidly.

TABLE II

EFFECT OF WATER ON BIPHENYL YIELD[a]

% H_2O by vol.[b]	Reduction time, hr.	Found, % Br^-	Found, % $(C_6H_5)_2$
0.0	5.0	101.0	27.0
9.0[c]	2.75	98.8	35.6
16.0	2.0	87.8	40.3
25.0	2.0	100.9	42.7
50.0	2.0	98.8	50.4
68.0	2.0	98.0	20.8

[a] Catalyst B. [b] In alcohol-water-KOH reaction mixture. [c] Standard experiment.

Effect of Bases.—To obtain the maximum yield of biphenyl, at least one equivalent of potassium hydroxide was required per mole of bromobenzene. The effect of additional alkali on the yield was small, but the rate of reduction was accelerated. Potassium carbonate, pyridine, aniline, and sodium methoxide were substituted for potassium hydroxide in the standard experiment. The reduction with potassium carbonate required about six times as long as with potassium hydroxide and only about half the usual yield was obtained. There was no reduction of the halide in the presence of pyridine or aniline unless potassium hydroxide was present, in which case they greatly retarded the rate of reduction and decreased the yield of biphenyl. With sodium methoxide there was no reduction in twenty hours of refluxing. Biphenyl and benzene were the only reduction products formed. These results are summarized in Table III.

TABLE III

EFFECT OF BASES ON REDUCTION[a]

Ratio moles base/C_6H_5Br	Reduction time, hr.	Found, % Br^-	Found, % $(C_6H_5)_2$
0.0 KOH	5.0[b]	Trace	0.0
0.8 KOH	5.0	76.0	26.5
1.0 KOH	4.5	94.4	36.4
2.0 KOH[c]	2.5	100.5	35.0
4.0 KOH	2.0	99.6	34.8
1.7 K_2CO_3	25.0	100.8	18.2
1.0 C_5H_5N	24.0[b]	0.0	0.0
2.0 KOH 1.0 C_5H_5N	24.0	98.4	26.5
2.1 $C_6H_5NH_2$	6.0[b]	0.0	0.0
2.0 KOH 2.1 $C_6H_5NH_2$	6.0	58.4	21.8
1.0 MeONa	20.0[b]	0.0	0.0

[a] Catalyst B. [b] Catalyst not fully reduced. [c] Standard Experiment.

Effect of Hydrogen Gas.—In runs where hydrogen gas was bubbled through a standard reaction mixture, at reflux, the reduction of the halide was accelerated but the yield of biphenyl was decreased.

Catalyst F, requiring 6.5 hours for complete reduction in the absence of hydrogen, required only an hour in its presence; the biphenyl yield dropped to less than 2%. Re-use of the reduced catalyst gave the same results as the fresh catalyst.

Effect of Solvent.—Three other solvents, ethanol, isopropyl alcohol, and dioxane, were substituted for methanol in the standard experiment. Reduction was negligible; no biphenyl was isolated, and tars were formed.

Other Catalysts.—Metals other than palladium were tried as catalysts to check Busch's[5f] conclusion that palladium was truly specific for biphenyl formation. Nickel and copper catalyst, prepared like the standard Pd-$CaCO_3$ catalyst were found to be totally inert with or without hydrogen. Platinum oxide catalyst was inert in the absence of hydrogen and very sluggish with hydrogen in the standard aqueous-alcohol reaction mixture or in alcohol alone. No trace of biphenyl was found in any of the experiments described above. Raney nickel catalyst was active in reducing the halide in the presence of hydrogen only, but again there was no trace of biphenyl formed.

A colloidal palladium-on-polyvinyl alcohol catalyst (Pd-PVA), prepared according to the directions of Rampino and Nord,[6] was completely inert in the Standard Experiment, but very active in reducing the halide in the presence of hydrogen, yielding no biphenyl.

The reductions with the Pd-PVA catalyst with hydrogen were carried out in a conventional low pressure hydrogenator, at a hydrogen pressure of about 2 atmospheres. While this catalyst was not reduced readily if the bromobenzene was added before its reduction in the presence of hydrogen, the rate of the reduction of the bromobenzene was not affected.

Vapor Phase Experiments.—No biphenyl was produced in any of the vapor phase experiments using palladium catalysts, with or without hydrogen. The essentially quantitative recovery of the bromobenzene in all runs indicated little reaction.

Catalysts were prepared in the following manner: (a) Potassium hydroxide, 3.0 g., was powdered by grinding under ether and mixed there with 1.5 g. of the Pd-$CaCO_3$ catalyst. The powder left after evaporation of the ether was dispersed in glass wool which filled the 1.4 × 20 cm. U-tube reaction vessel. Each filling of the reaction vessel contained 0.05 g. of palladium metal. (b) Solutions of palladium chloride, with and without potassium hydroxide, were dried on clay chips and on asbestos fibers, used as catalyst carriers.

The reaction vessel was immersed in an oil-bath held at 195–200°, 50 cc. of methanol solution containing 0.05 m. of bromobenzene was dropped in from a separatory funnel at such a rate that complete addition took two

(6) Rampino and Nord, THIS JOURNAL, 63, 2745, 3268 (1941).

hours. The solution volatilized on reaching the hot portion of the tube, and the gases that passed through the tube were condensed and collected at the other end.

Effect of Catalyst Poisons.—Catalytic amounts of nickel and copper salts had no significant effect on the rate of reduction of the bromobenzene in the standard experiment, but the biphenyl yield dropped to less than 5%. The stronger hydrogenation catalyst poisons, arsenic trioxide, and sulfides, completely inhibited all reaction.

Miscellaneous Experiments.—Analyses of the reduction products of each group of experiments showed only biphenyl, less than 1% of higher polyphenyls, and benzene. The biphenyl fractions of all runs were combined, and subjected to a sodium fusion. Only a trace of halide was found.

Benzene and biphenyl were added to standard runs without affecting either the expected yield of biphenyl, the rate of reaction, or the products. In runs using a standard reaction mixture with added biphenyl, but without bromobenzene, the recovery of biphenyl was the same as in a control run without catalyst after four hours of refluxing. Only biphenyl was recovered.

In a standard run using *p*-bromobiphenyl in place of bromobenzene, the reaction rate approximated that of the reaction with bromobenzene. The yield of quaterphenyl was 30.8%, biphenyl 61.0%.

Discussion

In view of the fact that detailed mechanisms have not yet been formulated for common catalytic reductions, it would be surprising if the present work could present a detailed mechanism for a very unusual type of catalytic reduction, the formation of biphenyl from bromobenzene. This work, however, has produced evidence that this unusual reaction required a palladium catalyst in a fairly specific state, a reducing agent with specific properties, and experimental conditions favorable to the adsorption of bromobenzene on the catalyst.

Repeated recovery and re-use of a catalyst sample led to a gradual diminishing rate of reduction, but the rate of formation of the biphenyl decreased faster than the rate of formation of benzene. These effects suggest that the two reductions are at least partially independent, the biphenyl formation being more sensitive to poisons or the state of the catalyst. This conclusion is further indicated in that copper and nickel salts suppress the formation of biphenyl but do not affect the reduction to benzene. The fact that no biphenyl could be obtained with nickel, platinum, or even colloidal palladium indicated that biphenyl formation is a reaction probably highly specific for certain palladium surfaces.

A highly specific reducing agent also seems to be required for biphenyl formation. The only successful reducing agent employed in the present work was methanol in the presence of strong base, at least equivalent to the amount of bromobenzene used. If insufficient alkali was used in the standard experiment, the solution approached neutrality and the reduction stopped. These proportions suggest but do not prove, that methylate ion was the reducing agent. Ethanol and isopropyl alcohol were found to be ineffective reducing agents. Busch suggested that the differences between these alcohols were related to their dielectric constants, but the latter differ little. A more probable explanation depends on the relative ease of dehydrogenation of the alcohols and the effect of aldehyde or ketone condensation products on the catalyst. Hydrogen gas, by accelerating the formation of benzene, inhibited the formation of biphenyl. These observations suggested that the bromobenzene was reduced by the alcohol or alcoholate ion to phenyl radicals on the active centers on the surface of the catalyst. If further reduction did not occur too easily, the phenyl radicals combined to give biphenyl. In the presence of hydrogen, even at atmospheric pressure, practically all were reduced to benzene.

The effect of water and amines in the standard experiment can be explained on the basis of the probable effect of these factors on the ease of adsorption of the halobenzene on the catalyst. Increasing the proportion of water in the alcohol solution increased the yield of biphenyl, presumably by decreasing the solubility of the bromobenzene and increasing its adsorption on the catalyst. Addition of pyridine or aniline decreased the rate of reduction without greatly affecting the proportions of products formed by being preferentially adsorbed on the catalyst.

Failure of added benzene to increase the yield of biphenyl from bromobenzene or of biphenyl to yield terphenyl, showed that biphenyl and benzene were not intermediates in terphenyl and biphenyl formation, respectively. The fact that *p*-bromobiphenyl gave considerable quaterphenyl on reduction, and that only traces of quaterphenyl were formed from bromobenzene, showed that bromobiphenyls are probably not intermediates in the formation of biphenyl. All the evidence seems consistent with the view that the reduction of bromobenzene to biphenyl is a surface reaction probably proceeding through adsorbed phenyl radicals.

Summary

The reduction of bromobenzene was studied using methanol as solvent and reducing agent, and palladium on calcium carbonate as catalyst. In the presence of strong base, up to 50% yield of biphenyl was obtained, benzene being the other reduction product. The effects of solvents, quantity and kind of base, other catalysts, hydrogen, metal salts, and end-products on the rate of reduction and on the benzene–biphenyl ratio were determined. Most changes in procedure reduced or eliminated the formation of biphenyl, often

without appreciably affecting the rate of formation of benzene. Biphenyl seems to be formed by coupling of adsorbed phenyl radicals on a specific surface in the absence of a more adequate source of hydrogen.

PHILADELPHIA, PA. RECEIVED SEPTEMBER 13, 1948

[CONTRIBUTION FROM THE LABORATORY OF EXPERIMENTAL THERAPEUTICS, U. S. PUBLIC HEALTH SERVICE, AND JOHNS HOPKINS SCHOOL OF HYGIENE AND PUBLIC HEALTH]

Arsenoso Derivatives of Phenyl-substituted Fatty Acids[1]

BY LEON D. FREEDMAN[2] AND G. O. DOAK[3]

The substitution of an acidic group in arsenosobenzene or its derivatives generally inhibits the activity and decreases the potential therapeutic utility of this class of compound.[4] An exception has been found in γ-(*p*-arsenosophenyl)-butyric acid which possesses marked trypanocidal activity and has undergone extensive therapeutic trial.[5] This unusual activity is not shown by the homologous *p*-arsenosophenylacetic and β-(*p*-arsenosophenyl)-propionic acids.

The present paper describes the preparation and properties of two higher homologs, one isomer and one derivative of γ-(*p*-arsenosophenyl)-butyric acid, as well as two other acid-substituted derivatives of arsenosobenzene.

For the preparation of several of these compounds, the *p*-nitro- and *p*-aminophenyl derivatives of the corresponding fatty acids were required as intermediates. The method of Van der Scheer[6] was previously used in this Laboratory for the preparation of γ-(*p*-nitrophenyl)- and γ-*p*-aminophenyl)-butyric acids, necessary for the synthesis of γ-(*p*-arsenosophenyl)-butyric acid.[7] The nitration procedure gave poor yields, probably due to oxidation of the side chain at the temperature employed. In an attempt to improve the yield, γ-phenylbutyric acid was nitrated under a variety of conditions. The most satisfactory yield was obtained by a procedure described in the Experimental Part. This procedure was also used for the nitration of δ-phenylvaleric acid. An improved method for the reduction of these nitro compounds to the desired amino compounds is also described.

For the preparation of *m*-arsonocinnamic acid the Scheller reaction was used.[8] The remaining arsonic acids were synthesized by the method of Palmer and Adams.[9] Since *p*-arsonomandelic acid was obtained as a sirup, which could not be crystallized, it was converted to the disodium salt which was readily crystallized from alcohol.

The arsenoso compounds were prepared by reduction of the corresponding arsonic acids with sulfur dioxide and hydriodic acid in the presence of hydrochloric acid, followed by hydrolysis of the resulting dichloroarsines with sodium bicarbonate. We were unable to isolate *p*-arsenosomandelic and γ-(2-amino-4-arsenosophenyl)-butyric acids because of their solubility in water. Therefore these two compounds were isolated as the dichloroarsines and neutralized in solution just prior to therapeutic testing.

The chemotherapeutic activity of these compounds has been reported previously.[5,10] δ-(*p*-Arsenosophenyl)-valeric acid was one-half as active against *T. equiperdum* as γ-(*p*-arsenosophenyl)-butyric acid, while none of the remaining compounds possessed any appreciable activity.

Experimental Part

δ-Phenylvaleric Acid.—This compound has previously been described by Ali, *et al.*,[11] but no yield was reported. Using a somewhat similar procedure[12] we reduced γ-benzoylbutyric acid to the desired compound, which was purified by distillation under reduced pressure. The yield was 63%; b. p. 164–168° (5 mm.); m. p. 51–53° (cor.).

ε-Phenylcaproic Acid.—The method used for the preparation of this compound differed from that previously described by Grateau[13] in that δ-benzoylvaleric acid, rather than the corresponding ethyl ester, was reduced by the Clemmensen method.[12] The yield was 86%; b. p. 165° (1 mm.); f. p. 10–11°.

Nitration of γ-Phenylbutyric Acid.—γ-Phenylbutyric acid (140 g.) was added in small portions to 250 ml. of fuming nitric acid (d. 1.50) which was maintained at a temperature between −20 and −30° by means of an alcohol–Dry Ice-bath. The time of addition was two to three hours and the mixture was stirred mechanically throughout this period. A further 10 ml. of acid was then used to wash down the sides of the reaction vessel and the temperature was kept at −10° for a further one-half hour. The clear solution was poured into a four-liter beaker filled with cracked ice. The oil which precipitated solidified on standing for fifteen minutes. The mixture was allowed to stand in the ice-box overnight after which the solid was removed by filtration and washed with cold water.

(1) Paper X in the series entitled "The Preparation of Phenylarsenoxides"; previous paper, THIS JOURNAL, **67**, 719 (1945).

(2) Present address: Department of Chemistry, Johns Hopkins University, Baltimore, Maryland.

(3) Present address: School of Public Health, Chapel Hill, North Carolina.

(4) Gough and King, *J. Chem. Soc.*, 669 (1930); Eagle, Hogan, Doak and Steinman, *J. Pharmacol.*, **70**, 221 (1940).

(5) Eagle, Hogan, Doak and Steinman, *Pub. Health Rep.*, **59**, 765 (1944); Eagle, *ibid.*, **61**, 1019 (1946).

(6) Van der Scheer, THIS JOURNAL, **56**, 744 (1939).

(7) Doak, Steinman and Eagle, *ibid.*, **62**, 3012 (1940).

(8) Doak, *ibid.*, **62**, 167 (1940).

(9) Palmer and Adams, *ibid.*, **44**, 1356 (1922).

(10) Eagle, *J. Pharmacol.*, **85**, 265 (1945).

(11) Ali, Desai, Hunter and Muhammad, *J. Chem. Soc.*, 1013 (1937).

(12) Martin, Clemmensen method III in "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., p. 166.

(13) Grateau, *Compt. rend.*, **191**, 947 (1930).