

Observations on the Reduction of Aryl Nitro Groups with Palladium-Sodium Borohydride

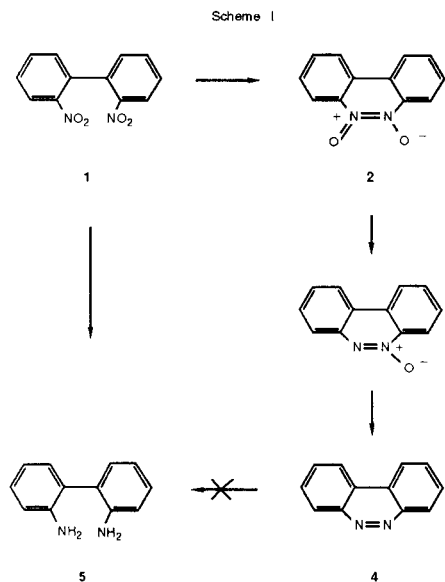
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The reduction of aryl nitro groups by the palladium-sodium borohydride system can be controlled in some instances to give products differing from those of catalytic hydrogenation. With six equivalents of borohydride added to the catalyst 2,2'-dinitrobiphenyl formed only 2,2'-diaminobiphenyl. With added sodium hydroxide and varying amounts of borohydride and catalyst, the reduction can be controlled to give benzo[c]cinnoline, benzo[c]cinnoline 5-oxide or benzo[c]cinnoline 5,6-dioxide. In a closed system, the reagents reduce both the nitro and olefin functional groups in 6-nitro-5,8-dimethoxy-1,4-dihydro-1,4-ethanonaphthalene. In an open flask flushed with argon, the reduction is confined to the nitro group. Reduction of 2-chloro and 4-chloronitrobenzene with palladium-borohydride gives substantial yields of the appropriate chloroanilines. In contrast, hydrogen and palladium give aniline as the major product from each of these. These results suggest that the addition of sodium borohydride to palladium on carbon produces a reductive entity differing from that of catalytic hydrogenation.

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In anticipation of projected research needs, a method for the reduction of a series of substituted 2,2'-dinitrobiphenyls to the corresponding diamines was required. The reduction of such compounds has been the subject of a review [1], and it has been established that a multiplicity of products may be produced depending on the reduction conditions. As applied to 2,2'-dinitrobiphenyl, these possibilities are shown in Scheme I. Catalytic hydrogenation of various 2,2'-dinitrobiphenyls over palladium on carbon or with a Raney nickel catalyst has been reported to give either the corresponding diaminobiphenyls or benzo[c]cinnolines [1]. Using aged Raney nickels of low activity Kempter and Castle [2] have reported conditions for the reduction of a series of dinitrobiphenyls to form benzo[c]cinnolines as well as their 5-monoxides and 5,6-dioxides.



More recently, Cornforth, Sierakowski and Wallace [3] have reported the transfer hydrogenation of a series of substituted 2',2''-dinitro-*m*-quaterphenyls to their diamines using Raney nickel and hydrazine. These reductions required a period of heating, and the formation of small amounts of benzo[c]cinnolines was reported.

In a brief note in 1962, Neilson, Wood and Wylie [4] reported that the reductive properties of sodium borohydride could be modified by adding it to a mixture of palladium on carbon in water or methanol while flushing the system with an inert gas. Satisfactory yields were obtained for the reduction of a number of aromatic nitro compounds to the corresponding amines. In the one detailed example, *o*-nitrophenol in dilute sodium hydroxide was added to the sodium borohydride-palladium mixture in water while flushing with nitrogen. The yield of *o*-aminophenol was 79%, and the reaction required 5 minutes at room temperature. They entered into no speculations on the mechanism of the reduction beyond the observation that azobenzene was not a likely intermediate in the reduction of nitrobenzene to aniline since its reduction under the same conditions stopped at hydrazobenzene. Only two further examples of the application of this interesting combination of reagents have been found in the literature [5]. Both involve the reduction of nitroaryl ethers, and no comment was made on the mechanism of the reduction. The palladium-sodium borohydride reagent offered a potential solution to our synthetic problem, and a study of the utility of the system is reported herein.

Results and Discussion.

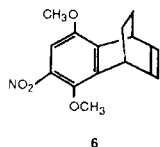
The catalyst of Neilson, Wood and Wylie was prepared by adding aqueous sodium borohydride (six equivalents) to 5% palladium on carbon slurried in methanol while

flushing with argon. The addition of 2,2'-dinitrophenyl in methanol produced a mildly exothermic reaction which was over in one hour producing the diaminobiphenyl (**5**) in 94% isolated yield.

In their original description [4], it was unclear whether the conduct of the reduction required the presence of added base. While the above result answers the implied question in the negative, a series of experiments were carried out to determine the effects of added base, inverse addition of the nitro compound and borohydride, and the amount of added hydride. The results of this study showed that in the presence of added sodium hydroxide benzo[*c*]cinnoline (**4**) as well as its 5-oxide **3** could be produced during the reduction. Consequently conditions were sought where these additional products might be formed in favorable amounts.

Decreasing the borohydride ratio from six mole equivalents to two in the presence of added sodium hydroxide produced a 95% yield of benzo[*c*]cinnoline (**4**) plus a small amount of the diamine **5**. With one molar equivalent of borohydride, the major product (83-85%) became benzo[*c*]cinnoline 5-oxide (**3**). When limited to a molar equivalency of 0.5 in sodium borohydride, the product was the 5,6-dioxide **2** in 85% yield. The latter result depends on running the reaction in a limited amount of solvent so the product precipitates as formed. When too much methanol was used, the reduction produced a complex mixture of **2**, **3**, and **4**. In the presence of added base, benzo[*c*]cinnoline was not reduced to the diamine.

The totality of information suggests that the addition of sodium borohydride to palladium on carbon produces a reagent (or reagents) differing in properties from chemisorbed hydrogen on palladium. The point has been explored by application of this system to molecules containing more than one type of functional group. The bicyclic molecule **6** contains an aryl nitro group plus an olefinic



double bond. When reacted with the palladium-sodium borohydride reagent in a closed system, reduction of both functional groups occurred. However, under the conditions employed by Neilson, Wool and Wylie [5] reduction occurred only at the nitro group giving the unsaturated bicyclic amine 97% yield.

The catalytic hydrogenation of 2-chloro and 4-chloronitrobenzene over palladium was accompanied by a substantial amount of hydrogenolysis forming aniline (48% and 76% respectively). In contrast, premixing the hydride and palladium under an argon atmosphere resulted in the

formation of the appropriate chloroanilines in 86% and 87% yields respectively.

It has been known for many years that sodium borohydride was capable of reducing palladium salts to metallic palladium and that the latter catalyzes a slow release of hydrogen from the borohydride [6]. The hydrogen-palladium system so produced has been used for nitro group reductions [6b]. However, the combination of palladium with sodium borohydride under the conditions described by Neilson, Woods and Wylie [5] clearly produces a reducing reagent with properties different from those of catalytic hydrogenation. While the structure of this reagent remains unknown, its utility has been demonstrated.

EXPERIMENTAL

The nmr spectra were obtained on Varian XL-300 or EM-390 instruments. In most cases product composition was ascertained by proton nmr at 300 MHz with integration (a 45° pulse width was used with a 60s pulse delay). When overlapping lines presented a problem, the relative intensities of appropriately identified lines in the ¹³C spectrum were used. This method is quite satisfactory as long as the relaxation times of these carbons are comparable *i.e.* with the same degree of protonation in molecules of roughly the same size and rotational motion. For these spectra a 45° pulse width was used with a 1s pulse delay. Checks between proton and ¹³C results indicated about 1-5% difference in product composition, an insignificant amount for this study. All spectra were taken in deuteriochloroform. Chemical shifts are given in ppm with respect to internal tetramethylsilane as a standard. Carbon assignments, where given, were made with the aid of standard substituent additivity values. Homonuclear correlation spectra for protons were determined in the phase sensitive mode using 512 increments and a 1024 x 1024 data matrix. Heteronuclear correlation spectra were obtained with 256 increments and a 1024 x 1024 data matrix. Melting points were taken on a Kofler Heizbank apparatus. Gas Chromatography was carried out on a Perkin-Elmer Sigma 3 instrument equipped with an 1/8 inch glass column with an OV-17 packing and hydrogen-flame ionization detector. The method (a) of Cornforth, Sierakowski and Wallace [3] was used to prepare 2,2'-dinitrophenyl from 2-nitroiodobenzene. The preparation of 6-nitro-5,8-dimethoxy-1,4-dihydro-1,4-ethanonaphthalene has been given previously [7]. Palladium catalyst (5% on charcoal) was from Matheson Coleman & Bell.

Reductions of 2,2'-Dinitrophenyl. a. With No Added Base.

A slurry of 0.18 g of palladium catalyst was stirred in 25 ml of methanol while bubbling argon through the mixture. A solution of 0.36 g (9.6 mmoles) of sodium borohydride in 10 ml of water was added, and the purging continued. Over the next five minutes, 0.38 g (1.6 mmoles) of 2,2'-dinitrophenyl in 30 ml of methanol was added in three portions. The mixture was stirred at room temperature for one hour, filtered under suction through a pad of Celite filter aid and taken to dryness by rotary evaporation at 80°. The residue was extracted with methylene chloride (50 ml) and ether (50 ml). The combined extracts were taken to dryness by rotary evaporation yielding 0.27 g (94%) of nmr pure 2,2'-diaminobiphenyl. A portion of this material was crystallized from hexane yielding buff colored crystals, mp 79-80° (lit [8] 81°). The ¹³C nmr consisted of six lines 124.6 (C-1), 144.1 (C-2), 115.6 (C-3), 131.0 (C-4), 119.4 (C-5) and 128.6 (C-6). The proton nmr spectrum consisted of two complex multiplets of equal intensity. Assignments were made with the aid of a 2D-heteronuclear correlation experiment: 6.78 (H-3), 7.12 (H-4), 6.83 (H-5) and 7.18 (H-6).

For convenience, the nmr parameters for 2,2'-dinitrophenyl are given here; ¹H nmr: 7.31 (dd, 2H, J = 2.3, 7.1 Hz), 7.59 (m, 2H), 7.69 (m,

2H), 8.22 (dd, 2H, $J = 1.5, 8.5$); ^{13}C nmr: 134.2 (C-1), 147.2 (C-2), 124.8 (C-3), 129.1 and 130.9 (C-4/6), 133.4 (C-5).

b. With Added Base. (1).

Four concurrent experiments were conducted as follows: a. 2,2'-Dinitrobiphenyl (0.24 g, 1 mmole) was dissolved in 30 ml of methanol in each of four 125 ml flasks. b. To each was added 4.0 ml of 2 *N* sodium hydroxide with stirring. c. To each was added 0.20 g of palladium catalyst. d. Sodium borohydride (0.5 *M* in 2 *N* sodium hydroxide) was added as follows: 1. 2 ml; 2. 4 ml; 3. 6 ml; 4. 12 ml. Each flask was stirred at room temperature for thirty to thirty-five minutes and then worked up as described above. The crude yields were 0.16 to 0.17 g for the four. Each extract was analyzed by proton and ^{13}C nmr. The characterization of benzo[c]cinnoline and its 5-oxide will be detailed below. The product distributions in percents for these experiments may be summarized as follows:

Flask	1	2	3	4
Sodium borohydride (mmoles)	1	2	3	6
2,2-Diamine	13	13	34	52
Benzo[c]cinnoline	10	48	51	48
5-Oxide	77	39	15	0

(2). Preparation of Benzo[c]cinnoline.

To a solution of 0.24 g (1 mmole) of 2,2'-dinitrobiphenyl in 30 ml of methanol was added 4.0 ml of 2 *N* sodium hydroxide and 0.05 g of palladium catalyst. The mixture was stirred, and argon bubbled through the solution. A 0.5 *M* solution (4.0 ml) of sodium borohydride in 2 *N* sodium hydroxide was added in one portion. The argon purge was stopped after twenty minutes though the reaction was not worked up for two hours. The solution was filtered as above, and the methanol removed by rotary evaporation. The slurry of products and water was extracted as above, and rotary evaporation was employed to isolate the crude products, yield 0.18 g. The proton and ^{13}C analysis indicated a composition of 95% benzo[c]cinnoline and 5% 2,2'-diaminobiphenyl. The crude reaction product was crystallized twice from hexane yielding 0.07 g of benzo[c]cinnoline, mp 155-156° (lit [9] 156°). The proton nmr consisted of three complex multiplets as follows: 7.88 (4H), 8.53 (2H) and 8.73 (2H). The ^{13}C nmr showed six carbons assigned as follows: 120.9 (C-1), 145.3 (C-2), 121.4 (C-3), 131.2 and 131.6 (C-4/6) and 129.2 (C-5).

In a related experiment 0.13 g (0.72 mmole) of benzo[c]cinnoline in 30 ml of methanol and 4 ml of 2 *N* sodium hydroxide was stirred at room temperature with 0.20 g of palladium catalyst. A solution of 0.19 g (5 mmoles) of sodium borohydride in 10 ml of 2 *N* sodium hydroxide was added in one portion, and the mixture was stirred for one hour. The mixture was filtered and worked up as described above yielding a quantitative recovery of unreacted starting material.

(3). Preparation of Benzo[c]cinnoline 5-Oxide.

The reduction and workup were carried out as with the benzo[c]cinnoline above except that only 2.0 ml of the 0.5 *M* sodium borohydride solution in 2 *N* sodium hydroxide was added. The yield of crude material was 0.16 g. The nmr analysis indicated 83-85% benzo[c]cinnoline 5-oxide. The balance of the product was not identified, but there were isolated lines in both the proton and ^{13}C nmr spectra on which the above analysis was based. Crystallization from ethanol-water gave 0.05 g of pure benzo[c]cinnoline 5-oxide, mp 140-142° (lit [9] 139-140°). The mass spectrum was acquired on a Finnigan model 1020 instrument which gave *m/e* 196 (M^+ 100) and 180 ($M-16, 4$). The proton nmr was resolved into two systems of four spins each by use of the 2D-homonuclear correlation (COSY) experiment. Proton and carbon chemical shifts were correlated by a 2D-heteronuclear correlation experiment and may be summarized as follows with the carbon chemical shifts in parentheses: 7.66 (128.9), 7.72 (130.5), 7.96 (126.3), 8.32 (121.2) and 7.77 (129.9), 7.90 (132.6), 8.45 (122.4), 8.84 (122.3). Quaternary carbons were found at 118.3, 119.3, 137.1 and 142.3.

(4). Preparation of Benzo[c]cinnoline 5,6-Dioxide.

A solution of 0.24 g (1 mmole) of 2,2'-dinitrobiphenyl was prepared in 20 ml of methanol. To this was added 4 ml of 2 *N* sodium hydroxide. If a precipitate formed at this point, the solution was gently warmed to bring all back into solution. To this was added 0.05 g of palladium catalyst. As the mixture was stirred, 1 ml of 0.5 *M* sodium borohydride in 2 *N* sodium hydroxide was added. Stirring was continued for one hour, and the mixture was filtered as above. The filter cake was washed with ether which was combined with the initial reaction solution. The ether and methanol were removed by rotary evaporation. The yield of crude material was 0.18 g (86%), and the proton ^{13}C nmr showed pure benzo[c]cinnoline 5,6-dioxide which was crystallized from either methanol-water or acetone-water, mp 246-248° (two preparations) or 262-264° (one preparation) (lit [2,10] 240, 249-250, 234-236°).

The nmr spectra from these three preparations were identical. The proton nmr spectrum closely resembled that of benzo[c]cinnoline except that the chemical shifts were altered. The 2D-heteronuclear correlation spectrum allowed the following correlations of proton and ^{13}C chemical shifts: 7.80 (4H, 130.1 and 131.0), 8.43 (2H, 122.5) and 8.52 (2H, 119.4) with quaternary carbons at 120.8 and 136.4.

Reductions of 6-Nitro-5,8-dimethoxy-1,4-dihydro-1,4-ethanonaphthalene. (a). Preparation of 6-Amino-5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-ethanonaphthalene.

The reduction was conducted in a 100 ml three-necked flask connected to a dropping funnel and a gas burette filled with brine. The reaction vessel was swept with argon. A solution of 0.24 g (1 mmole) of the nitroolefin in 25 ml of methanol was stirred with 0.06 g of palladium catalyst and 3 ml of water containing 0.07 g of sodium borohydride was added over a five minute period. Gas was given off at first (to 55 ml) and then slowly reabsorbed (final volume 16 ml). After one hour the reaction was worked up by filtering through a Celite pad and rotary evaporation to dryness. Extraction of the organic material from the residue with methylene chloride (two 50 ml portions) gave 0.22 g (95%) of residue which both proton and ^{13}C nmr showed to be pure saturated amine. A portion of this material was crystallized from hexane, 0.04 g, mp 98-100°; ^1H nmr: 1.36 and 1.73 (m, 4H each, 4 CH_2s), 3.32 (broad s, 2H, bridge CH), 3.72 and 3.76 (singlets with broad base, 8H, CH_3Os and NH_2), 6.22 (s, 1H, ArH); ^{13}C nmr: 25.4 and 27.4 (C-1 and 4), 25.8 and 26.0 (4 CH_2), 55.9 and 61.0 (CH_3Os), 97.0 (C-7), and quaternary carbons at 122.5, 136.6, 137.2, 137.8 and 150.5 ppm.

Anal. Calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_2$: C, 72.0; H, 8.2; N, 6.00. Found: C, 71.8; H, 8.2; N, 5.8.

(b). Preparation of 6-Amino-5,8-dimethoxy-1,4-dihydro-1,4-ethanonaphthalene.

A solution of 0.19 g (5 mmoles) of sodium borohydride in 5 ml of water was added to a slurry of 0.05 g of palladium catalyst in 20 ml of methanol. Argon gas was bubbled through the liquid, and 0.49 g (2 mmoles) of nitroolefin in 10 ml of methanol was added in one portion. The reaction was allowed to stir at room temperature for ninety minutes. It was then filtered and worked up as above. The crude extract (0.45 g, 97%) was pure 6-amino-5,8-dimethoxy-1,4-dihydro-1,4-ethanonaphthalene by both proton and ^{13}C nmr. The residue was crystallized from hexane yielding 0.22 g of white, fine crystals mp 109-110°; ^1H nmr: 1.45 (m, 4H, CH_2s), 3.67 (broad s, 2H, NH_2), 3.75 (s, 6H, CH_3s), 6.10 (s, 1H, ArH), 6.44 and 6.52 (t, 2H, $J = 6.6$ Hz).

Anal. Calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: C, 72.7; H, 7.4; N, 6.1. Found: C, 72.7; H, 7.5; N, 6.0.

Reductions of the Chloronitrobenzenes. a. 2-Chloronitrobenzene with Palladium/Sodium Borohydride.

A slurry of 0.05 g of palladium catalyst in 30 ml of methanol was stirred while argon was bubbled through the mixture. To this was added 0.38 g (10 mmoles) of sodium borohydride dissolved in 10 ml of 1:1 methanol-water containing 0.2 g of sodium hydroxide. The argon purge was continued throughout. After two or three minutes, a solution of 1.58 g (10 mmoles) of 2-chloronitrobenzene in 25 ml of methanol was added in portions over five minutes. A vigorous evolution of gas was noted, and the

solution became warm. After stirring for fifteen minutes the reaction mixture was filtered under vacuum through a Celite pad. The methanol was distilled off slowly. The residue was taken up in ether and washed with a small portion of brine. Rotary evaporation of the ether gave 1.2 g of residue which was analyzed by gas chromatography as 8% aniline, 86% 2-chloroaniline and 6% starting material. Comparisons were made with known mixtures of these compounds.

b. 4-Chloronitrobenzene with Palladium/Sodium Borohydride.

The reduction and workup of 4-chloronitrobenzene was carried out in the same procedure as above except that the reaction stood for one hour before workup. The crude yield was 1.3 g of material analyzing as 13% aniline and 87% 4-chloroaniline.

c. The Reduction of 2-Chloronitrobenzene with Palladium and Hydrogen.

A solution of 0.80 g (5 mmoles) of 2-chloroaniline in 30 ml of methanol was stirred with 0.05 g of palladium catalyst. The flask was flushed with argon and then attached to a gas burette filled with hydrogen. Over ninety minutes approximately 750 ml (ca. 15.6 mmoles) of hydrogen was taken up. The reaction mixture was filtered to remove the catalyst, and the methanol solution of products was injected directly onto the gc column to ascertain the composition. Comparison with known mixtures of potential products indicated that the reduction product consisted of 48% aniline and 52% 2-chloroaniline.

d. The Reduction of 4-Chloronitrobenzene with Palladium and Hydrogen.

4-Chloronitrobenzene was reduced exactly as above. The gc analysis of

the methanol solution showed the composition of the products to consist of 76% aniline and 24% 4-chloroaniline.

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REFERENCES AND NOTES

- [1] B. E. Buntrock and E. C. Taylor, *Chem. Rev.*, **68**, 209 (1968).
- [2] F. E. Kempter and R. N. Castle, *J. Heterocyclic Chem.*, **6**, 523 (1969).
- [3] Sir John Cornforth, A. F. Sierakowski and T. W. Wallace, *J. Chem. Soc., Perkin Trans. I*, 2299 (1982).
- [4] T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).
- [5a] R. L. Edwards and N. Kale, *ibid.*, 4084 (1964); [b] J. P. Marsh and L. Goodman, *J. Org. Chem.*, **30** 2491 (1965).
- [6a] H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.*, **84**, 1493 (1962); [b] H. C. Brown and K. Sivasankaran, *ibid.*, **84**, 2828 (1962).
- [7] W. B. Smith, L. Stock, and Sir John Cornforth, *Tetrahedron*, **39**, 1379 (1983).
- [8] E. Tauber, *Ber.*, **24**, 197 (1891).
- [9] F. Ullman, and P. Dieterle, *ibid.*, **37**, 23 (1904).
- [10a] E. Tauber, *ibid.*, **24**, 3083 (1891); [b] A. Bellart, *Tetrahedron*, **1**, 3285 (1965).