

Further studies on the reduction of benzylic alcohols by hypophosphorous acid/iodine

Paul E. Gordon, Albert J. Fry*, and Latorya D. Hicks

Chemistry Department, Wesleyan University, Middletown, CT 06459, U. S. A.

E-mail: afry@wesleyan.edu

This paper is dedicated to Prof. Eusebio Juaristi in honor of his many contributions to organic stereochemistry and the advancement of science in Mexico

(received 17 Jun 05; accepted 15 Aug 05; published on the web 23 Aug 05)

Abstract

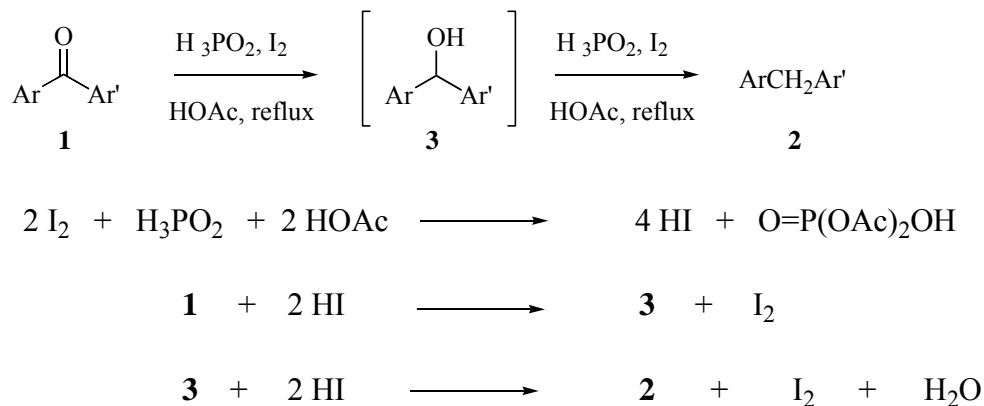
Hydrogen iodide, generated (and regenerated) *in situ* by the action of iodine upon hypophosphorous acid, was found to reduce a variety of aryl carbinols to the corresponding diphenylmethanes under mild conditions. The generality of the reaction was explored by extension to several diols, heterocyclic alcohols, and allylic alcohols. Several lines of evidence, including occasional isolation of alkyl iodides, dependence of the rate of reduction upon substituent effects, and isolation of ethers and esters in the early stages of reduction, reveal that the first step in the reduction process is conversion of the alcohol to a carbocation. Isolation of dimers from cinnamyl alcohol and 1-phenyl-2-propen-1-ol demonstrates the intermediacy of radical intermediates in at least some reductions.

Keywords: Reduction, hydrogen iodide, hypophosphorous acid, benzylic alcohols, allylic alcohols

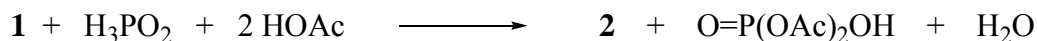
Introduction

We have reported that hydrogen iodide can be generated efficiently by the reaction between hypophosphorous acid and iodine in acetic acid. When generated in this fashion it is an efficient reagent for the reduction of substituted benzophenones (**1**) to the corresponding diarylmethanes (**2**).¹ Reduction of the organic substrate regenerates iodine, which is again reduced by hypophosphorous acid according to Scheme 1. Thus, iodine is required in only small amounts since the actual reducing equivalents are supplied by hypophosphorous acid. The double bond in a variety of diaryl alkenes² and α,β -unsaturated ketones³ was also found to be reduced by the same combination of reagents. More recently, we found that substituted benzhydrols (**3**), the presumed intermediates in the reduction of **1** to **2**, are indeed reduced to **2** under rather mild

conditions by this reagent system.⁴ We now wish to report further studies on the reduction of substituted benzhydrols and the results of subjecting a wider variety of benzylic alcohols to the hypophosphorous acid-iodine-acetic acid reagent system.

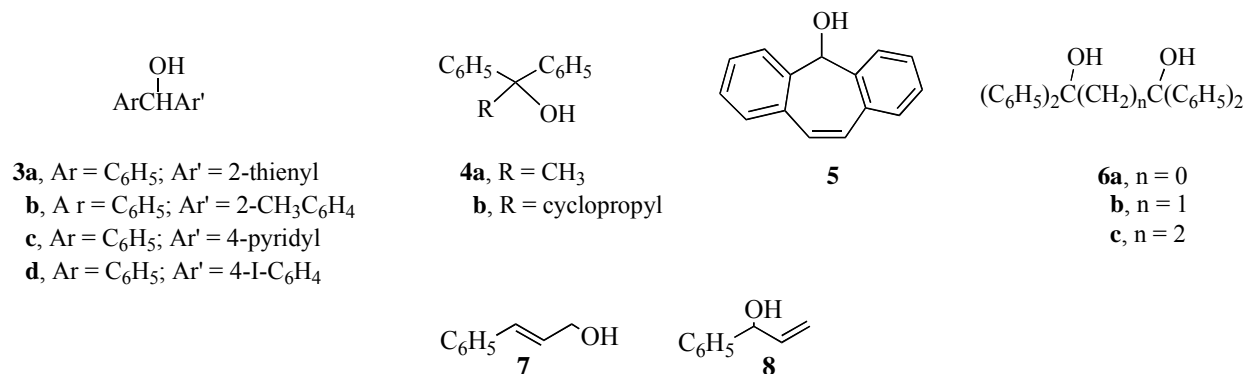


Net reaction:



Scheme 1

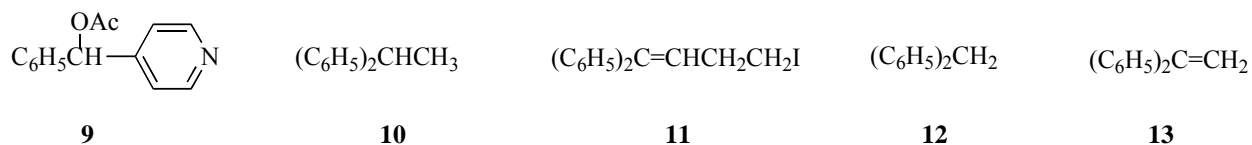
We previously reported that 17 benzhydrols (**3**) were converted to the corresponding diphenylmethanes **2** in 100% purity (75-85% isolated yields) in acetic acid containing iodine and aqueous hypophosphorous acid in 1:1:5 molar ratio at 60 °C.⁴ Compounds **3-8**, all of which are known compounds, were allowed to react under the same conditions.



Results and Discussion

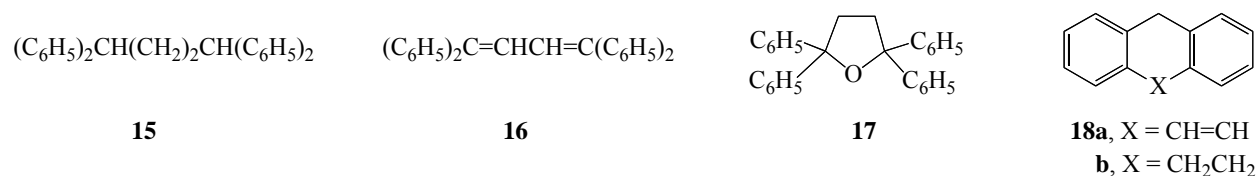
Benzhydrols (3a-d). Phenyl-2-thienylcarbinol (**3a**) and 2-methylbenzhydrol (**3b**) were reduced cleanly to the corresponding diarylmethanes, identified by their mass spectra and the

correspondence of their ^1H NMR spectra with those of the known substances.⁵⁻⁷ On the other hand, 4-azabenzhydrol (**3c**) was converted slowly to a 99:1 mixture of the corresponding acetate (**9**)⁸ and the corresponding diphenylmethane (**2c**).⁹ 4-Iodobenzhydrol (**3d**) afforded a 95:5 mixture of 4-iododiphenylmethane and diphenylmethane.

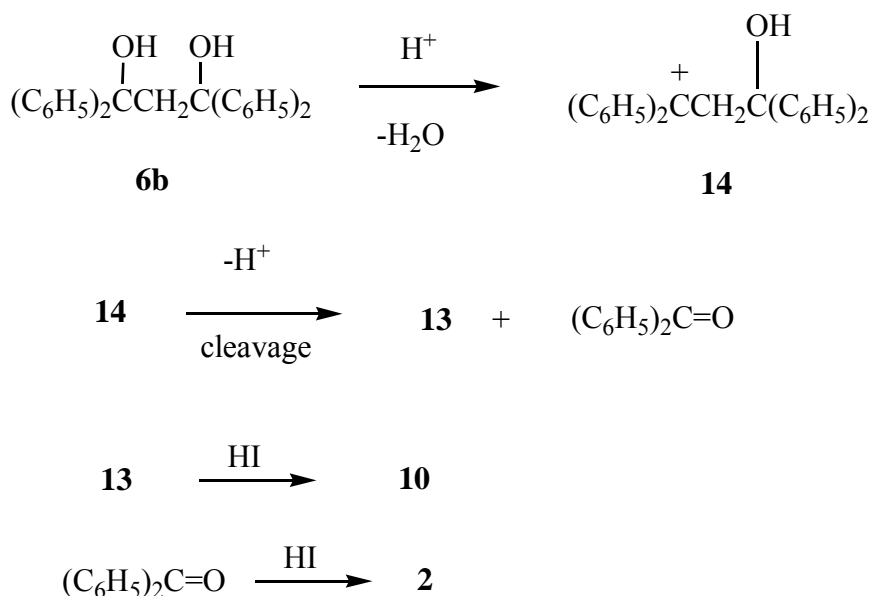


Tertiary diphenylcarbinols (4). 1,1-Diphenylethanol (**4a**) was reduced rapidly and cleanly to 1,1-diphenylethane (**10**), identified by comparison with an authentic sample. On the other hand, 1,1-diphenylcyclopropylcarbinol (**4b**) was converted in high yield into a single substance, identified as 1,1-diphenyl-4-iodo-1-butene (**11**) by its mass spectrum and comparison of its ^1H NMR spectrum with the literature values.¹⁰

Tertiary diols. 1,1,2,2-Tetraphenylpropane-1,2-diol (benzpinacol) (**6a**) was converted cleanly to benzpinacolone, identical in mass and ^1H NMR spectroscopic properties with an authentic commercial sample. 1,1,3,3-Tetraphenylpropane-1,3-diol (**6b**) was converted to a mixture consisting of 1,1-diphenylethane (**10**) (95%), benzophenone (74%), and diphenylmethane (**2**) (8%), together with small amounts (0.5–3% each) of 1,1-diphenylethylene (**12**), 1,1,3,3-tetraphenylpropane, and 1,1,3,3-tetraphenylpropene. These products can be accounted for in terms of an intermediate carbocation **13** (Scheme 2). We have previously reported that **12** is reduced to **10** under these conditions.² The primary product from reduction of 1,1,4,4-tetraphenylpropane-1,4-diol (**6c**) was 1,1,4,4-tetraphenylbutane (**15**) (59%), together with 1,1,4,4-tetraphenylbutadiene (**16**)¹¹ (31%), and 2,2,5,5-tetraphenyltetrahydrofuran (**17**)¹² (10%). **16** and **17** are reported products of heating **6c** in acetic acid.¹³



Dibenzosuberanol (5). Dibenzosuberanol (**5**) was converted into a mixture of dibenzosuberene (**18a**) (87%) and dibenzosuberane (**18b**) (13%). We reported earlier that the ketone dibenzosuberone is converted into a 64:36 mixture of **18a** and **18b** in the same solvent system in 24 hr at reflux.¹



Scheme 2

Cinnamyl alcohol (7) and 1-phenyl-2-propen-1-ol (8). These compounds afforded an identical mixture of products, consisting of 1-phenyl-3-iodopropane (**19**) (21%),¹⁴ an authentic sample of which was prepared by overnight reaction of the corresponding bromide with sodium iodide in acetone, together with a complex mixture of dimeric products whose mass spectra indicate that they are all possible products of coupling of the intermediate 1-phenylallyl radical at either the benzylic and terminal positions. The major dimer was 3,6-diphenyl-1-hexene (**20**) (18%), identified by its mass spectral fragmentation pattern. Allylbenzene (1%) and propylbenzene (2%) were also produced in these reductions.

Solvent effects. Reductions carried out in chloroform and benzene were slower than in acetic acid and not as clean. In methanol at reflux, benzhydrol was converted quickly into benzhydryl methyl ether (**21a**) and then slowly into diphenylmethane.

Likewise, reduction in ethanol resulted in rapid conversion to benzhydryl ethyl ether (**21b**), followed by further conversion to diphenylmethane. Surprisingly, examination of reaction mixtures for reduction of benzhydrol in acetic acid demonstrated that **21b** and benzhydryl acetate (**21c**) are produced in substantial quantities in the first 15-30 minutes and are then slowly converted to diphenylmethane. The source of the ethyl group is not acetic acid, because reduction in propionic acid for 30 minutes afforded benzhydryl propionate (46%) and **21b** (35%), together with diphenylmethane (7%) and unreacted benzhydrol (6%). Benzhydryl propyl ether was not detected. The presumption that acetic acid is not reduced by hydrogen iodide at these temperatures was confirmed by attempted reduction of heptanoic acid in triethylene glycol dimethyl ether at 70 °C. The only products were ethyl heptanoate (22%), methyl heptanoate (4%) and unreacted heptanoic acid (74%). We are forced to the conclusion that our commercial

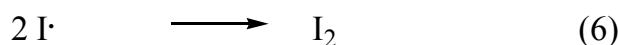
samples of hypophosphorous acid contained ethanol in substantial proportion. The supplier (Aldrich Chem. Co.) was unable to provide any information on this point.

Competitive reductions. A 1:1 mixture of 4-bromobenzhydrol and 4-methylbenzhydrol was examined after 2 hr at 40°C. About 5% more 4-methyldiphenylmethane had been produced than 4-bromodiphenylmethane. Under the same conditions, a 1:1 mixture of 4,4'-dichloro- and 4,4'-dimethoxybenzhydrol afforded a mixture corresponding to 85% reduction of the dimethoxy compound but only 15% reduction of the dichloro alcohol. Reduction of a 1:1 mixture of 3,3'-*bis*[trifluoromethyl]benzhydrol and 4,4'-dimethylbenzhydrol resulted in complete reduction of the dimethylbenzhydrol but only 2% formation of 3,3'-*bis*[trifluoromethyl]diphenylmethane. We had reported earlier that 3,3'-*bis*[trifluoromethyl]benzhydrol is reduced exceptionally slowly under our standard reaction conditions.⁴

As others have noted,^{15,16} mechanistic analyses of reductions by hydrogen iodide in acid are often necessarily speculative. It is further clear that this reagent system can effect reduction by a number of mechanisms. Some of these mechanisms, e.g., reduction of sulfoxides [attack by iodide on an intermediate S-iodo sulfoxide],¹⁷⁻¹⁹ deiodination of iodophenyl phenyl ethers¹⁶ and iodophenols²⁰ [electrophilic aromatic substitution], deiodination of α -iodo carbonyl compounds²¹ and reduction of α -hydroxy ketones²² [acid-catalyzed enolization], cannot be operative in the reductions of benzhydrols discussed here. There is excellent evidence that the first step in the reductions reported herein is conversion of the alcohols to the corresponding carbocations and that the ease of reduction correlates with carbocation stability. Thus triphenylmethanol is reduced much easier than benzhydrol,⁴ and the competitive reductions we have carried out show a preference for reduction of the alcohol that would form the more stable carbocation. The very slow reduction of several *bis*-trifluoromethylbenzhydrols⁴ may also be ascribed to the slow formation of the corresponding carbocation. Likewise, the failure of the pyridyl alcohol **3c** to reduce can be ascribed to protonation on nitrogen and thus conversion of the pyridyl group to a strongly electron-withdrawing substituent. The comparatively facile reduction of 4,4'-*bis*[dimethylamino]benzhydrol⁴ might seem inconsistent with this, but its pK_{R+} is in fact quite high (5.61) compared to benzhydrol (-13.3),²³ reflecting the high stability of the carbocation. The subsequent course of transformation of these carbocations into product is not clear. We outline a likely mechanism in Scheme 3. Examination of the reduction of benzhydrol at short times in acetic acid demonstrates the initial formation of **21b** and **21c**, products of nucleophilic trapping of the benzhydryl cation formed in the first step (Eq 1). The route to the eventual product, diphenylmethane, is believed to involve re-ionization of these substances to the benzhydryl cation. On the other hand, several such reactions have been found to afford significant amounts of alkyl iodides, e.g., reduction of **4b**, **7**, and **8** as well as formation of α -iodobibenzyl during the early stages of reductive conversion of stilbene to bibenzyl² and of cyclooctyl iodide as the only product of reduction of cyclooctene.² It is entirely possible that iodides are formed reversibly in the other reductions. For example, benzhydryl iodide might re-ionize back to the benzhydryl cation faster than do the corresponding alcohol, ether, or acetate and hence never build up in measurable quantities in solution. On the other hand, of the two

iodides actually isolated from these reactions, **11** is likely to re-ionize relatively slowly compared to the starting α -cyclopropylbenzhydryl alcohol, and competitive reduction of the carbon-carbon double bond of cinnamyl iodide² would afford the observed product **19**. Isolation of propylbenzene from the reduction of **7** or **8** is consistent with this hypothesis. Unconjugated double bonds are not reduced by this reagent system,² explaining the isolation of allylbenzene and **20** from **7** or **8**. Reduction of the intermediate carbocation by electron transfer from iodide ion would form a radical, which could then be reduced by another equivalent of iodide (Eqs 3 and 4). We are inclined to discount the possibility of direct conversion of alkyl iodides (RI) to alkanes (RH). We consider it more likely that iodides, though quite likely formed reversibly as intermediates in many of these reactions (Eq 8), are probably not on the reaction path to the alkane products, although equations 8 and 9 do represent one possible route. Hydrogen iodide is a good hydrogen atom donor because of its low H-I homolytic bond strength. However, it should be fully ionized in the highly polar aqueous acetic acid system used for reduction of these alcohols. Molecular hydrogen iodide (which can effect reductions by hydrogen atom or hydride in non-ionizing media)^{22,24,25} should be present at negligibly low concentrations in our reaction medium. Hydride transfer from HI to the initial carbocation is unlikely for the same reason.

A final comment is in order on the somewhat surprising contrast in behavior which we found earlier⁴ between 4-methoxybenzhydrol and 4,4'-dimethoxybenzhydrol. The monomethoxy compound is 100% demethylated (and the resulting phenol slowly acetylated) under our standard reduction conditions, whereas the dimethoxy compound is reduced to the corresponding diphenylmethane without demethylation.⁴ The pK_{R^+} of 4,4'-dimethoxybenzhydrol is -5.71 ²⁶ and that of 4,4'-bis[dimethylamino]benzhydrol is similar (-5.61).²³ As we have noted, these substances are reduced readily. However, the pK_{R^+} of 4-methoxybenzhydrol is -7.9 ,²³ so the concentration of the corresponding benzhydryl carbocation should be lower by a factor of more than 100 than that of the dimethoxy compound under our conditions. This would afford a greater opportunity for protonation on the methoxy oxygen atom, leading to demethylation by iodide ion by an S_N2 mechanism.



Overall Reaction:



Scheme 3

Experimental Section

General Procedures. Commercially available ketones were reduced to the corresponding alcohols by lithium aluminum hydride in tetrahydrofuran. The general procedure used for reduction of alcohols has been reported previously.⁴ Products were identified by mass and ¹H NMR spectra and comparison with literature values. ¹H NMR spectra were measured on a Varian 300 MHz spectrometer equipped with pulse gradient probe. Mass spectra were measured on a Hewlett-Packard model 5850 gas chromatograph-mass spectrometer.

General procedure for reduction of alcohols

Iodine (1.00 g, 4 mmol) and the alcohol (4.0 mmol) were dissolved in 25 mL of acetic acid and the system was flushed with nitrogen. Hypophosphorous acid (50% aq., 2 mL, 19.3 mmol) was added and the mixture was heated to 60 °C. After 24 hr, the mixture was diluted with water

and extracted with hexane. The hexane extracts were washed once with saturated NaHSO₃, dried over MgSO₄, and evaporated to afford the product in generally high yields.

Acknowledgments

Financial support from the National Science Foundation under grants CHE-0100727 and CHE-0411699 is gratefully acknowledged.

References

1. Hicks, L. D.; Han, J. K.; Fry, A. J. *Tetrahedron Lett.* **2000**, *41*, 7817.
2. Fry, A. J.; Allukian, M.; Williams, A. D. *Tetrahedron* **2002**, *58*, 4411.
3. Allukian, M.; Gordon, P. E.; Han, G. S.; Hicks, L. D.; Fry, A. J. *ARKIVOC* **2002**, 76.
4. Gordon, P.; Fry, A. J. *Tetrahedron Lett.* **2001**, *42*, 831.
5. Bowie, J. H.; Cooks, R. G.; Lawesson, S.-O.; Nolde, C. J. *Chem. Soc. B* **1967**, 616.
6. Montaudo, G.; Caccamese, S.; Finocchiaro, P. *J. Am. Chem. Soc.* **1971**, *93*, 4202.
7. Meyerson, S.; Drews, H.; Fields, E. K. *J. Am. Chem. Soc.* **1964**, *86*, 4964.
8. Mase, T. *Tetrahedron Lett.* **1999**, *40*, 8823.
9. Hatano, B.; Tagaya, H. *Tetrahedron Lett.* **2003**, *44*, 6331.
10. Saicic, R. N.; Cekovic, Z. *Tetrahedron* **1990**, *46*, 3627.
11. Sisenwine, S.; Day, A. J. *J. Org. Chem.* **1967**, *32*, 1770.
12. Richard, D.; Scilly, N. *J. Chem. Soc. C* **1969**, 2661.
13. Valeur, A. *Compt. rend.* **1903**, *136*, 694.
14. F. W. McLafferty, *Anal. Chem.* **1962**, *34*, 2.
15. Stoner, E. J.; Cothron, D. A.; Balmer, M. K.; Roden, B. A. *Tetrahedron* **1995**, *51*, 11043.
16. Jorgensen, E. C.; Reid, J. A. W. *J. Org. Chem.* **1964**, *29*, 3396.
17. Montanari, F.; Hogeveen, H.; Maccagnani, G. *Tetrahedron Lett.* **1964**, *5*, 2691.
18. Johnsson, H.; Allenmark, S. *Chem. Script.* **1975**, *8*, 223.
19. Strecker, R. A. *Diss. Abstr. B* **1967**, *28*, 602.
20. Gold, V.; Whittaker, M. *J. Chem. Soc.* **1951**, 1184.
21. Ichikawa, K.; Miura, E. *Nippon Kagaku Zasshi* **1953**, *74*, 798.
22. Ho, T.-L. *Synth. Commun.* **1979**, *9*, 665.
23. Freedman, H. H. In *Carbonium Ions*; Olah, G.; Schleyer, P. v. R., Eds; Wiley: New York, 1973; Vol. 4, p 1533.
24. Meyers, C. Y.; Hou, Y.; Lutfi, H. G.; Saft, H. L. *J. Org. Chem.* **1999**, *64*, 9444.
25. Hou, Y.; Meyers, C. Y. *J. Org. Chem.* **2004**, *69*, 1186.
26. Deno, N.; Jaruzelski, J.; Schriesheim, A. *J. Am. Chem. Soc.* **1955**, *77*, 3044.