

# MODERN SYNTHETIC REACTIONS

H. O. HOUSE



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**HERBERT O. HOUSE** MASSACHUSETTS INSTITUTE OF TECHNOLOGY

W. A. BENJAMIN, INC.   ▪   New York, Amsterdam

**1965**

## **MODERN SYNTHETIC REACTIONS**

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**Library of Congress Catalog Card Number 64-25245  
Manufactured in the United States of America**

*The final manuscript was put into production on March 19, 1964  
This volume was published on January 28, 1965*

**W. A. BENJAMIN, INC., New York, New York 10016**

## ■ EDITOR'S FOREWORD

AS THE SCIENCE of organic chemistry continues to expand, a need has become apparent for teaching materials which can supplement the usual undergraduate organic chemistry textbook. A good undergraduate will want to go beyond his textbook by independent reading in areas of interest to him, and many teachers find that they personally want to give more emphasis to certain aspects of organic chemistry than is done in an otherwise excellent text. In order to help satisfy this need we have initiated a series of short monographs, usually in paperback form, which examine important topics in organic chemistry in more depth than is possible in comprehensive textbooks. These books are intended to supplement, not supplant, the ordinary introductory text, and they will also be useful in intermediate level courses. If they have any general characteristic, it is their tendency to concentrate on established facts rather than shaky generalizations, bringing the student to current research frontiers and pointing out gaps in our knowledge.

The first volume of this series, *Modern Synthetic Reactions* by Professor Herbert O. House, is in many ways typical. The usual undergraduate textbook presents synthetic reactions with very little real indication of the advantages and limitations of each method. The interested student will want to know more about which oxidation method is really best for a particular purpose, for instance, and in this monograph Professor House presents the

needed critical discussion of a variety of important synthetic procedures together with literature references as a further guide for the student. However, this particular book is also ideally suited for use as the textbook in an advanced course on synthetic methods, and it will probably be widely employed by practicing synthetic chemists. For these latter reasons, and because the present monograph is longer than typical members of the series will be, it has been published only in a hardcover edition.

The editor hopes that these books will serve the important teaching purpose for which they are designed. We welcome all suggestions which will help us to provide a truly useful series.

RONALD BRESLOW

*New York, New York*  
*October 1964*

## ■ PREFACE\*

THIS BOOK was written for advanced undergraduate and beginning graduate students of organic chemistry as a survey of certain reactions that currently enjoy widespread application to the synthesis of organic compounds in the laboratory. It was not my intention either to survey all of the important synthetic methods or to offer an exhaustive survey of those reactions which have been included. The Diels-Alder reaction, reactions of organometallic compounds, acylations at oxygen and nitrogen atoms, and elimination reactions leading to the formation of double and triple bonds are examples of important synthetic reactions which have received little, if any, mention. Nevertheless, I believe students will find that the assortment of reactions included have wide applicability to the practical solution of synthetic problems, and I can only hope that someone else, engaged in the training of students, will be sufficiently indignant about my omission of certain reactions to write a second volume which includes them.

The chapters have been written to survey reactions as they are currently used in the organic laboratory; accordingly, many of the references included refer to recent detailed descriptions of the applications of these reactions. In many cases examples have been taken from *Organic Syntheses* because of the detailed

\* Written in collaboration with Joseph Ciabattini, Theodore W. Craig, David B. Ledlie, George M. Rubottom, and Barry M. Trost.

descriptions of experimental procedure which these preparations offer. In general, I have chosen not to trace the historical development of reactions and experimental procedures. However, these references may usually be found in the articles cited. Also, students of organic chemistry today are already burdened with the necessity to assimilate an immense body of factual knowledge, and I believe they should not also be required to concern themselves with which chemist should be allotted priority for discovering a particular reaction or procedure.

Discussions of the mechanisms of the various reactions included have been limited for the most part to statements and expressions of opinion, with leading references. Except for discussions of the stereochemical consequences of the various reactions, I have not reviewed the evidence that has led to the reaction mechanisms proposed since this is not the purpose of this book. In reading the mechanisms suggested, the student will do well to bear in mind that the evidence on which these proposals have been made is often tenuous and the mechanisms proposed may be shown to be partially or totally incorrect as additional evidence is accumulated.

Since the task of citing references to all of the synthetically important modifications of a reaction is impossible for one person to accomplish, I have asked a number of people in this country to offer suggestions of other material that might be included. I am indebted to Drs. W. G. Dauben, C. H. DePuy, E. L. Eliel, D. S. Heywood, K. B. Wiberg, and Mr. P. Starcher for offering suggestions relevant to certain portions of the manuscript, and I am particularly grateful to Drs. A. W. Burgstahler, R. K. Hill, R. E. Ireland, W. S. Johnson, G. Poos, and Mr. G. Mitchell for reading the entire manuscript and offering many helpful suggestions. The burden of preparing the manuscript and index as well as locating references, checking references, and proofreading the manuscript in various stages of preparation was lightened considerably by my five collaborators: Messrs. Joseph Ciabattini, Theodore W. Craig, David B. Ledlie, George M. Rubottom, and Barry M. Trost, all of whom are currently graduate students at the Massachusetts Institute of Technology. Finally, I am most grateful to Miss G. C. Martin, who typed the entire manuscript.

HERBERT O. HOUSE

*Cambridge, Massachusetts*  
*February 24, 1964*

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## • CATALYTIC HYDROGENATION

OF THE MANY REACTIONS AVAILABLE for the reduction of organic compounds, catalytic hydrogenation—the reaction of a compound with hydrogen in the presence of a catalyst—offers the advantages of widespread applicability and experimental simplicity to a unique degree.<sup>1</sup> Catalytic hydrogenation is usually effected in the laboratory by stirring or shaking a solution of the compound to be reduced with a heterogeneous catalyst under an atmosphere of hydrogen gas. The progress of the reduction may be followed readily by measuring the uptake of hydrogen, and the crude reduction product is usually isolated simply by filtration of the catalyst followed by evaporation of the solvent.

- (1) (a) H. Adkins and R. L. Shriner in H. Gilman (ed.), *Organic Chemistry, An Advanced Treatise*, Vol. 1, 2d ed., Wiley, New York, 1943, pp. 779–832; (b) G. Schiller in E. Müller (ed.), *Methoden der organischen Chemie (Houben-Weyl)*, Vol. 4, Part 2, Georg Thieme Verlag, Stuttgart, Germany, 1955, pp. 283–332; (c) K. Wimmer, *ibid.*, pp. 163–192; (d) V. I. Komarewsky, C. H. Riesz, and F. L. Morritz in A. Weissberger (ed.), *Technique of Organic Chemistry*, Vol. 2, 2d ed., Wiley-Interscience, New York, 1956, pp. 94–164; (e) F. J. McQuillin in A. Weissberger (ed.), *Technique of Organic Chemistry*, Vol. II, Wiley-Interscience, New York, 1963, pp. 497–580.

### Catalysts, Solvents, and Equipment

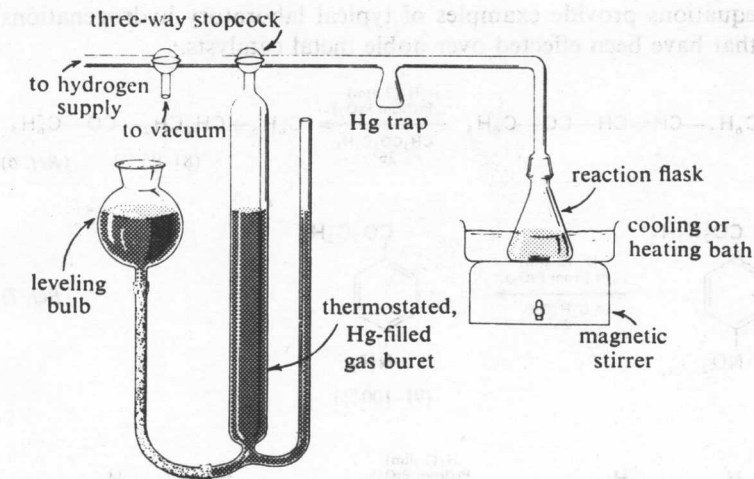
The selection of the solvent, reaction temperature, and hydrogen pressure for a given hydrogenation is dependent on the catalyst chosen. It is convenient to divide the common hydrogenation catalysts into the group of certain noble metal catalysts as well as active grades of Raney nickel, which are generally used with low (1 to 4 atm or 0 to 60 psi) hydrogen pressures and at relatively low (0 to 100°) temperatures; and the group of less active catalysts, which are normally used at higher (100 to 300 atm or 1500 to 4500 psi) hydrogen pressures and may require higher (25 to 300°) reaction temperatures.

The noble metal catalysts frequently used for low-pressure hydrogenations contain platinum, palladium, or rhodium. Whereas reductions over platinum frequently employ finely divided metallic platinum obtained by the reduction of platinum oxide ( $\text{PtO}_2$ )<sup>2</sup> in the hydrogenation apparatus, the palladium<sup>3</sup> and rhodium<sup>4</sup> catalysts are usually deposits of the metal on the surface of an inert support such as carbon, alumina, barium sulfate, calcium carbonate, or strontium carbonate. The activity of a catalyst on an inert support is normally diminished as the support is changed from carbon to barium sulfate to calcium or strontium carbonate. Also, the activity of a given catalyst is generally increased by changing from a neutral, nonpolar solvent to a polar, acidic solvent. Solvents frequently employed for low-pressure hydrogenation include ethyl acetate, ethanol, water, acetic acid, and acetic acid plus perchloric acid. Obviously, the acidic solvents cannot be employed with catalysts that are supported on metal carbonates. Diagrams of typical laboratory equipment used for low-pressure catalytic hydrogenations are provided in Figure 1-1a and b. The apparatus illustrated in Figure 1-1a utilizes a hydrogen pressure of 1 atm, and the hydrogen uptake is measured as the change in volume of the hydrogen gas in the system. Some workers prefer a modification of this apparatus in which the suspension of the catalyst in the reaction solution is shaken rather than stirred.

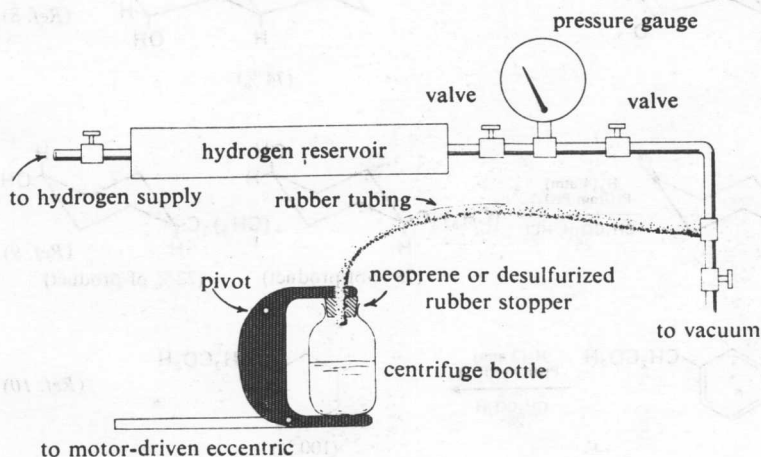
(2) R. Adams, V. Voorhees, and R. L. Shriner, *Org. Syn., Coll. Vol. 1*, 463 (1944).

(3) (a) E. R. Alexander and A. C. Cope, *Org. Syn., Coll. Vol. 3*, 385 (1955); (b) R. Mozingo, *ibid.*, 685 (1955).

(4) Palladium, platinum, rhodium, and ruthenium catalysts are commercially available from Engelhard Industries, Inc., Chemical Division, 113 Astor St., Newark 14, New Jersey.



(a)



(b)

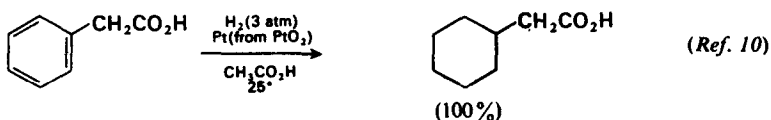
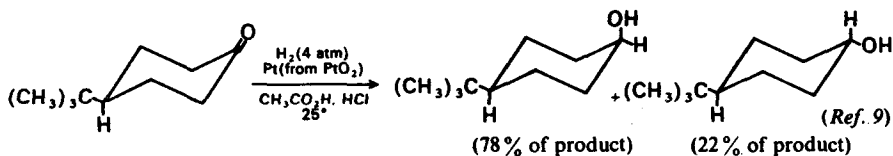
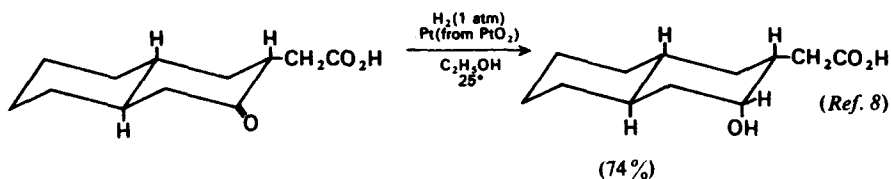
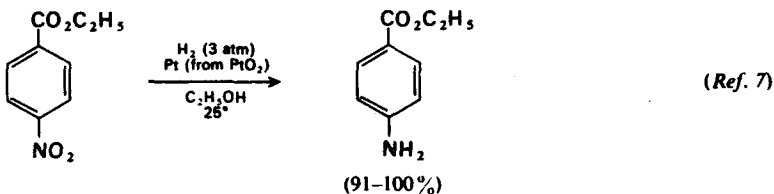
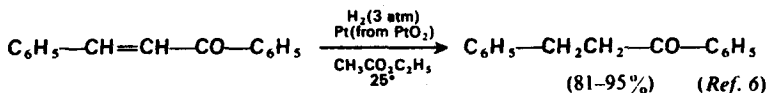
FIGURE 1-1.

*Apparatus for low-pressure catalytic hydrogenation.*

Apparatus of this type is often used to obtain a quantitative measure of the number of reducible functions in a compound of unknown structure. Figure 1-1b represents apparatus<sup>5</sup> usually used with 2 to 4 atm hydrogen pressure, the hydrogen uptake being measured by observing the pressure change within the system. The following

(5) R. Adams and V. Voorhees, *Org. Syn., Coll. Vol. 1*, 61 (1944).

equations provide examples of typical laboratory hydrogenations that have been effected over noble metal catalysts.



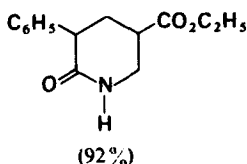
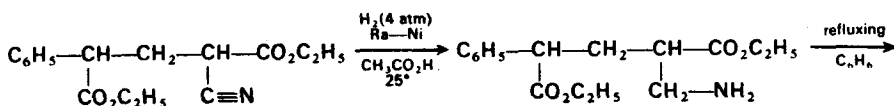
(6) (a) R. Adams, J. W. Kern, and R. L. Shriner, *Org. Syn., Coll. Vol. 1*, 101 (1944); see also (b) E. C. Horning, J. Koo, M. S. Fish, and G. N. Walker, *Org. Syn., Coll. Vol. 4*, 408 (1963).

(7) R. Adams and F. L. Cohen, *Org. Syn., Coll. Vol. 1*, 240 (1944).

(8) W. S. Johnson and co-workers, *J. Am. Chem. Soc.*, **83**, 606 (1961).

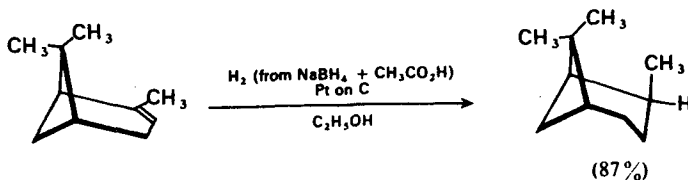
(9) (a) E. L. Eliel and R. S. Ro, *ibid.*, **79**, 5992 (1957); see also (b) R. J. Wicker, *J. Chem. Soc.*, **1956**, 2165; (c) for a discussion of reaction conditions useful in the reduction of ketones, see E. Breitner, E. Roginski, and P. N. Rylander, *J. Org. Chem.*, **24**, 1855 (1959).

(10) R. Adams and J. R. Marshall, *J. Am. Chem. Soc.*, **50**, 1970 (1928).



(Ref. 11)

A recent modification of the usual low-pressure catalytic hydrogenation technique utilizes the reaction of various metal salts with either sodium borohydride or a trialkyl- or triarylsilane to generate the hydrogenation catalyst.<sup>12</sup> Salts of rhodium, platinum, and palladium are reduced to the finely divided free metals, which may be used directly as catalysts or, preferably, adsorbed on carbon prior to use.<sup>12a</sup> Reaction of excess sodium borohydride with an acid added to the reaction mixture provides a source of hydrogen,



(Ref. 12a)

- (11) (a) R. K. Hill, C. E. Glassick, and L. J. Fliedner, *ibid.*, **81**, 737 (1959); see also (b) H. J. Dauben, Jr., H. J. Ringold, R. H. Wade, and A. G. Anderson, Jr., *ibid.*, **73**, 2359 (1951).
- (12) (a) H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.*, **84**, 1493-1495, 2827, 2829 (1962); (b) H. C. Brown and K. Sivasankaran, *ibid.*, **84**, 2828 (1962); (c) H. C. Brown, K. Sivasankaran, and C. A. Brown, *J. Org. Chem.*, **28**, 214 (1963); (d) R. W. Bott, C. Eaborn, E. R. A. Peeling, and D. E. Webster, *Proc. Chem. Soc.*, **1962**, 337; (e) R. Paul, P. Buisson, and N. Joseph, *Ind. Eng. Chem.*, **44**, 1006 (1952); (f) H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.*, **85**, 1003, 1005 (1963).

permitting the direct hydrogenation of easily reducible functions (nitro groups and unhindered olefins). This procedure, illustrated in the preceding equations, offers the advantage of simplicity. However, it suffers from the fact that the final hydrogenated product must be separated into a number of components in the reaction mixture and that any functional groups present which are reduced by sodium borohydride (see Chapter 2) will also be altered by the reduction procedure. A hydrogenation catalyst, thought to be nickel boride,<sup>12e,12f</sup> has similarly been prepared by the reduction of various nickel salts with sodium or potassium borohydride. This catalyst is reported<sup>12e,12f</sup> to be more reactive than commercially available Raney nickel.

For hydrogenations at relatively high hydrogen pressures (100 to 300 atm), the common catalysts are Raney nickel, copper chromite, and ruthenium<sup>4</sup> supported on carbon or alumina. Raney nickel (abbreviated Ra-Ni)<sup>13</sup> is a porous form of metallic nickel, obtained by reaction of a nickel-aluminum alloy with aqueous sodium hydroxide.<sup>14</sup> Copper chromite (abbreviated CuCr<sub>2</sub>O<sub>4</sub>)<sup>15</sup> is a mixture of copper and chromium oxides. Depending on the physical properties of the compound to be reduced, the

- (13) (a) R. Schröter in *Newer Methods of Preparative Organic Chemistry*, Wiley-Interscience, New York, 1948, pp. 61-101; (b) Raney nickel catalyst of ordinary activity, designated W-2, can be purchased or prepared as described by R. Mozingo, *Org. Syn., Coll. Vol. 3*, 181 (1955); more active grades of Raney nickel, designated W-3 to W-7, which are effective at lower hydrogen pressures, may also be prepared: see (c) H. R. Billica and H. Adkins, *ibid.*, 176 (1955), and (d) X. A. Dominguez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, **26**, 1625 (1961); (e) nickel catalysts are commercially available from the Raney Catalyst Co., Inc., Chattanooga, Tennessee, and from Girdler Catalysts, Chemical Products Division, Chemetron Corp., Louisville, Kentucky.
- (14) The reduction of organic compounds by reaction with the Raney alloy and aqueous alkali has also been used: for examples, see (a) D. Papa, E. Schwenk, and B. Whitman, *J. Org. Chem.*, **7**, 587 (1942); (b) D. Papa, E. Schwenk, and H. F. Ginsberg, *ibid.*, **16**, 253 (1951); (c) E. Schwenk, D. Papa, H. Hankin, and H. Ginsberg, *Org. Syn., Coll. Vol. 3*, 742 (1955). This procedure may involve, at least in part, a low-pressure catalytic hydrogenation in which the hydrogen liberated from reaction of the aluminum with the aqueous alkali is adsorbed on the surface of the newly formed Raney nickel catalyst; however, certain of the reductions performed by this procedure resemble more closely the subsequently discussed dissolving metal reductions (see Chapter 3).
- (15) (a) C. Grundman in *Newer Methods of Preparative Organic Chemistry*, Wiley-Interscience, New York, 1948, pp. 103-123; (b) W. A. Lazier and H. R. Arnold, *Org. Syn., Coll. Vol. 2*, 142 (1943); (c) commercially available from Girdler Catalysts, Chemical Products Division, Chemetron Corp., Louisville, Kentucky.

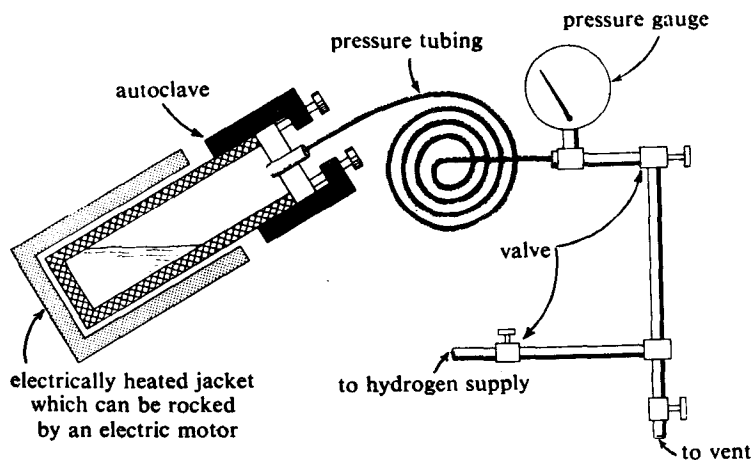
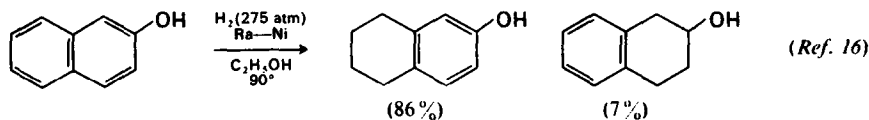


FIGURE 1-2.

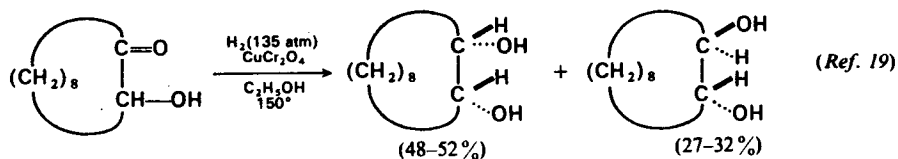
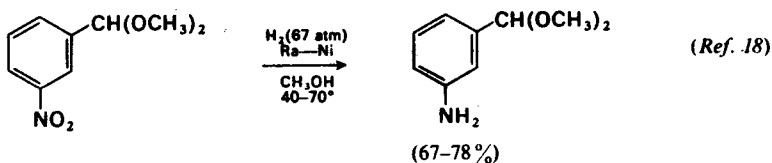
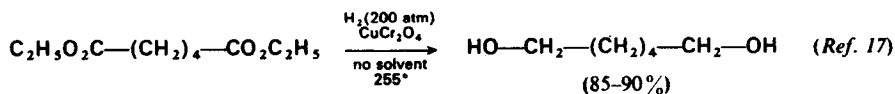
*Apparatus for high-pressure catalytic hydrogenation.*

high-pressure hydrogenations may be performed with or without a solvent. The solvents usually employed with these catalysts are ethanol, water, cyclohexane, or methylcyclohexane. Strongly acidic solvents or reactants cannot be used with nickel or copper chromite because these catalysts will dissolve. Figure 1-2 illustrates a typical autoclave used in the laboratory for high-pressure hydrogenations. The uptake of hydrogen in this apparatus is followed by observing the change in pressure. The total volume of liquid placed in such an apparatus should never exceed one-half the total volume of the autoclave, in order to allow room for the liquid to expand as it is heated. Typical examples of high-pressure laboratory hydrogenations are described by the following equations.



- (16) H. Adkins and G. Krsek, *J. Am. Chem. Soc.*, **70**, 412 (1948). If the reaction mixture is alkaline during the hydrogenation, the alcohol rather than the phenol becomes the major product [G. Stork, *ibid.*, **69**, 576 (1947)].





The rate of a given hydrogenation may be increased by increasing the hydrogen pressure,<sup>20</sup> by increasing the amount of catalyst employed,<sup>6a</sup> or by increasing the temperature. However, many compounds can be reduced either by low-pressure or by high-pressure hydrogenation. The selection of the reaction conditions in such cases is usually determined by the quantity of material to be reduced. The type of low-pressure hydrogenation apparatus illustrated in Figure 1-1a is normally useful for reduction of quantities ranging from 10 mg to 25 g, whereas the apparatus shown in Figure 1-1b is most often used with 10- to 100-g quantities. The high-pressure equipment (Figure 1-2) available in most organic laboratories permits the reduction of 10- to 1000-g quantities.

### Reduction of Functional Groups

From the equations previously used to illustrate reaction conditions, it is apparent that a variety of functional groups can be

- (17) (a) W. A. Lazier, J. W. Hill, and W. J. Amend, *Org. Syn., Coll. Vol. 2*, 325 (1943);  
(b) for a discussion and review of this reaction, see H. Adkins, *Org. Reactions*, **8**, 1 (1954).
- (18) R. N. Icke, C. E. Redemann, B. B. Wisegarver, and G. A. Alles, *Org. Syn., Coll. Vol. 3*, 59 (1955).
- (19) A. T. Blomquist and A. Goldstein, *Org. Syn., Coll. Vol. 4*, 216 (1963).
- (20) For example, see C. F. H. Allen and J. VanAllan, *Org. Syn., Coll. Vol. 3*, 63 (1955).