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ORGANIC FUNCTIONAL GROUP PREPARATIONS

Volume 1

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PREFACE

This work is an outgrowth of an attempt by us to ease the burden of those in our laboratory engaged in organic syntheses. Since suitable directions for the preparation of a functional group attached to an invariant carbon chain are scattered throughout the literature, we undertook to compile procedures which we believe to be reliable as to yield and certainty of the structures produced. Some attention was paid to the problem of presenting specific laboratory directions for the many name reactions which are often presented only as a set of equations in textbooks. Thus, it is the purpose of this book to provide in a single volume a convenient source of modern procedures for the preparation of functional groups.

The unique feature of this work is that each chapter deals with the preparation of a given functional group by various reaction types (condensation, elimination, oxidation, reduction) and a variety of starting materials and reagents. Detailed laboratory directions are given which are also representative of a general class of procedures. To a limited extent indications of the scope of the reactions are presented.

Since the primary synthetic object in most cases is to convert one functional group to another, the book serves as a guide to effect these changes. This work is not intended to be encyclopedic in nature nor to mention every available procedure ever published up to the date of this printing. Rather, it is a brief critical review; and because of the limitations of space, it was necessary to be selective in the choice of procedures cited.

The procedures, for inclusion in this text, had to meet the following requirements: (1) The procedures should be generally used for a wide range of organic structures. (2) The yield of product should be high. (3) The preparation should be relatively uncomplicated and should be able to be carried out in most laboratories. (4) The laboratory operations should be safe and free from the danger of explosion.

Most of the preparations were taken from the recent literature; however, since several well-known classic reactions are included, the older literature in some cases was deemed satisfactory in light of recent developments. No attempt was made to include preparations with a 1966–1967 date just for the sake of having an up-to-date bibliography. The preparations were chosen solely for their ability to meet the four criteria mentioned above. The recent

literature is cited; and, where possible, methods showing wide applicability have been included. Otherwise, they are briefly mentioned as being worthy of further scrutiny.

While information on the safety of various procedures is not always available, an effort was made to point out hazards, particularly toxicity and explosion hazards, of many of the reactions discussed. Unfortunately, we are not in a position to state that where no hazards are mentioned in connection with a given reaction, none exist. The literature abounds with examples of reactions that have been used for many years which, for reasons frequently not at all clear, suddenly lead to violent explosions. Also, the toxicity hazards of many reactants which have been used with impunity for years have only recently come to light. The extent to which this may be true of other materials cannot be stated at this time.

In several cases the preparations have been repeated in our laboratory and supplementary information is given. In some cases unpublished information is cited where insufficient data is available in the literature.

It should be emphasized that where possible chromatography should be used to check the purity and isomeric nature of the product. In some cases minor variations of a procedure will cause changes in the above factors.

This book is also written with the hope that it will stimulate interest in the reader to reinvestigate several of the methods cited to either improve them or to aid in further extending their general applicability.

We should like to take this opportunity to thank Dr. Samuel Loshaek, Director of Research and Development of The Borden Chemical Company, for his encouragement in the preparation of this work. We should also like to thank The Borden Company for permission to publish this work. We express our gratitude to our wives and our families for their patience, understanding, and encouragement at all stages of the preparation of the manuscript.

July, 1968

STANLEY R. SANDLER
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CONTENTS

CHAPTER 1 / HYDROCARBONS (PARAFFINIC AND AROMATIC)

1. INTRODUCTION

Hydrocarbons are conveniently prepared in the laboratory by reduction, condensation, elimination, or hydrolysis reactions. Isomerization, oxidation, and photochemical reactions are less common on a preparative scale.

The reduction methods depend on converting a given functional group to a methylene group. For example, olefins, aromatic rings, alcohols, aldehydes, ketones, and halides give hydrocarbons on reduction. These methods allow the preparation of hydrocarbons of known structure. The Clemmensen (zinc amalgam and hydrochloric acid) and Wolff–Kishner (hydrazine and base) methods can be used to reduce aldehydes and ketones. Catalytic hydrogenation methods can be used to reduce olefins and aromatic compounds. The catalytic hydrogenation method can also be used for ketones, provided that a high-pressure apparatus is available. Nickel and platinum are the most commonly used catalysts.

Recently, the use of sodium borohydride and palladium chloride has been described for the reduction of olefins in excellent yields. The method is quite reliable and it has been applied as an analytical technique for the quantitative estimation of the degree of unsaturation of a compound or of a mixture.

$$RCH{=}CH_2 + NaBH_4 \xrightarrow[H^+]{PdCl_2} RCH_2{-}CH_3 \qquad (1)$$

Condensation reactions are used to synthesize a hydrocarbon from two or more compounds which may or may not be the same as described in Eq. (2)

$$R{-}Y + RX \longrightarrow R{-}R + XY \qquad (2)$$

where X or Y may be a hydrogen, halogen, diazo, or organometallic group. The Friedel–Crafts, the Wurtz, the Wurtz–Fittig, organometallic coupling, Ullmann, and Pschorr syntheses are some representative condensation reactions. The Friedel–Crafts reaction and the coupling of organometallics with halides are the most useful laboratory syntheses of hydrocarbons, especially branched-chain hydrocarbons such as neohexane.

The hydrolysis of the Grignard reagent is a useful method of preparing hydrocarbons from halides.

$$ROH \xrightarrow{HX} RX \xrightarrow{Mg} RMgX \xrightarrow{H_2O} RH \qquad (3)$$

The yields by this method are usually excellent and pure hydrocarbons are obtained. The chloromethylation reaction can thus be used as a step in the addition of a methyl group to an aromatic nucleus.

Carboxylic acids eliminate carbon dioxide when heated with soda lime or electrolyzed to produce paraffins (Kolbe reaction). The former is a more useful method in the laboratory.

Aldehyde, diazo, and sulfuric acid groups are a few of the other groups which can be eliminated and replaced by hydrogen to give hydrocarbons.

Cyclodehydration of aromatic alcohols and ketones give tetralins, anthracenes, phenanthrenes, and other ring systems.

The Jacobsen reaction involves the isomerization by sulfuric acid of an aromatic system containing several alkyl halo groups to give vicinal derivatives.

More recent procedures such as photochemical, oxidative, electrochemical, and other methods will be mentioned only briefly unless they have been shown to be of general synthetic applicability in the laboratory. (Several of the methods in the earlier literature are mentioned where appropriate since they are of a classical nature.) However, one should be cautious of reactions prior to the 1950's since vapor chromatography (VPC) and nuclear magnetic resonance (NMR) techniques were not available for the determination of the purity and structure of the products. Several research problems today are based on re-examining earlier reported research findings by VPC.

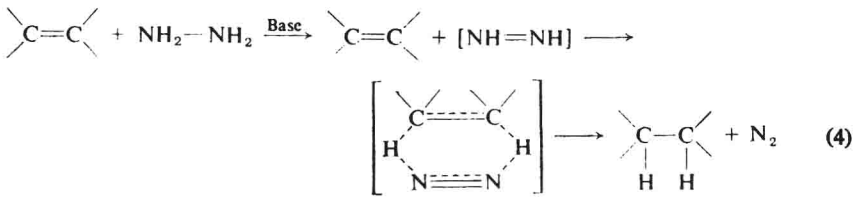
2. REDUCTION REACTIONS

A. Reduction of Unsaturated Compounds (Olefins)

Olefins can be reduced by one of the following methods: Adkins catalytic hydrogenation [1], sodium borohydride and palladium chloride [2], triphenylsilane [3], triphenyltin hydride [4], and rhodium on alumina in the presence of hydrogen for halogenated olefins [5].

The platinum oxide catalyst is useful for hydrogenations of olefins at room temperature and low pressure [6]. On the other hand, Raney nickel requires high-pressure equipment [7].

Diimide [8–12] has also been used as a reducing agent for activated double bonds. The diimide is unstable and is therefore produced *in situ* by first oxidizing hydrazine or its derivatives in the presence of olefins.



(4)

Olefins can also be hydroborated to organoboranes which are then converted to the hydrocarbon by refluxing with propionic acid [13]. This procedure is a convenient noncatalytic laboratory method for the hydrogenation of olefins.

$$3\ RCH{=}CH_2 + NaBH_4 + BF_3 \longrightarrow (RCH_2CH_2)_3B \xrightarrow{C_2H_5COOH} 3\ RCH_2CH_3 \quad (5)$$

Terminal olefins are readily hydroborated but internal olefins require additional reaction time and heating prior to refluxing with propionic acid. Substituents such as active sulfur, chlorine, and nitrogen are not affected by this hydrogenation procedure.

2-1a. Conversion of 1-Hexene to n*-Hexane by Hydroboration Method* [13]

$$3\ CH_3(CH_2)_3{-}CH{=}CH_2 + NaBH_4 + BF_3 \longrightarrow [CH_3(CH_2)_3CH_2CH_2]B \longrightarrow CH_3(CH_2)_4CH_3 \quad (6)$$

To a three-necked flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser with attached drying tube is added 16.8 gm (0.20 mole) of 1-hexene and 2.0 gm of sodium borohydride (0.055 mole) in 55 ml of diglyme. While stirring under nitrogen 10.0 gm (0.075 mole) of boron trifluoride etherate in 25 ml of diglyme is added during a period of 1.5 hr. Then 222 gm (0.3 mole) of propionic acid is added and the mixture is refluxed for 2 hr while ether and the product distill over. The product is washed with sodium bicarbonate solution, then water, dried, and fractionally distilled to yield 15.6 gm (91%) of *n*-hexane, b.p. 68°–69°C (738 mm), n_D^{20} 1.3747.

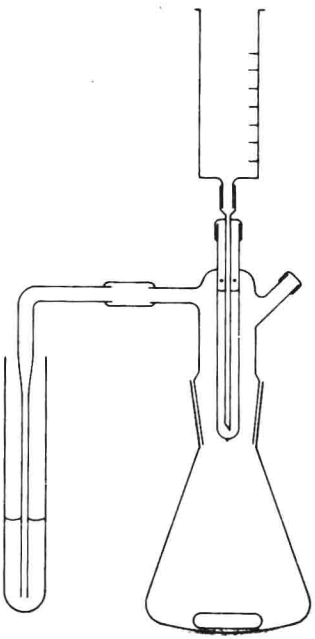


FIG. 1. Hydrogenation apparatus with automatic valve. [Reprinted from C. A. Brown and H. C. Brown, *J. Am. Chem. Soc.* **84**, 2829 (1962). Copyright 1962 by the American Chemical Society. Reprinted by permission of the copyright owner.]

Another reduction technique utilizing sodium borohydride is the *in situ* preparation of platinum black while hydrogen is evolved from the borohydride [14, 14a]. An active nickel catalyst [15] in the latter procedure has been found to be a very selective hydrogenation catalyst for the conversion of acetylenes to yield cis olefins [16]. In addition there has been developed a simple, pressure-activated device for controlling the rate of addition of the borohydride solution (Fig. 1). In this device a syringe barrel, or a buret fitted to a hypodermic needle, is inserted through a rubber serum cap into a mercury well to a depth adequate to support the column of borohydride solution. As hydrogen is utilized in the hydrogenation flask, the pressure drops 10 to 20 mm below atmospheric, drawing a small quantity of the borohydride solution through the mercury seal where it rises to the top of the mercury and runs into the flask through the small vent holes located just above the mercury interface. The acidic solution in the flask hydrolyzes the borohydride and the resulting increase in pressure seals the valve. The addition proceeds smoothly to the completion of the hydrogenation, with the amount of the borohydride solution corresponding quantitatively to the amount of unsaturated compound contained in the flask.

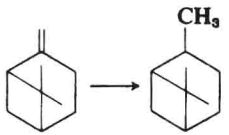
2-1b. Hydrogenation of Diethyl Maleate to Diethyl Succinate [14a]

$$\begin{matrix} HC{-}COOC_2H_5 \\ \| \\ HC{-}COOC_2H_5 \end{matrix} + NaBH_4 + \text{Chloroplatinic acid} \longrightarrow \begin{matrix} H_2C{-}COOC_2H_5 \\ | \\ H_2C{-}COOC_2H_5 \end{matrix} \qquad (7)$$

The following procedure involving the hydrogenation of diethyl maleate is representative. In a 500 ml Erlenmeyer flask is placed 5 gm of Darco K-B carbon, 100 ml of anhydrous ethanol, and 5.0 ml of 0.20 *M* chloroplatinic acid solution. The system is assembled (Fig. 1) and the solution stirred vigorously by a magnetic stirrer as 20 ml of 1.0 *M* solution of sodium borohydride in ethanol is injected to reduce the catalyst. This is followed in approximately 1 min by 25 ml of concentrated hydrochloric acid to decompose the borohydride and provide a hydrogen atmosphere. The reaction is initiated by injecting 81 cc, 86.0 gm of diethyl maleate. The reaction is complete in 60 to 70 min. The reaction solution is filtered to remove catalyst, treated with 5% sodium bicarbonate, and extracted with methylene chloride. Distillation of the extract yields 77.6 gm (90% yield), of diethyl succinate, b.p. 103°–104.5°C (15 mm), n_D^{20} 1.4201.

In some cases the presence of a strong acid, such as hydrochloric acid, may be undesirable. In such cases, acetic acid may be utilized. Moreover, by maintaining essentially anhydrous conditions in the hydrogenation flask, one can minimize solubility problems, encountered with higher hydrocarbons, terpenes, and steroids. This procedure is illustrated by the hydrogenation of β-pinene.

2-1c. *Hydrogenation of* β-*Pinene* [14a]

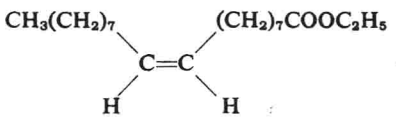


(8)

In the 250 ml flask is placed 5 gm of Darco K-B carbon, 100 ml of anhydrous ethanol, and 5.0 ml of a 0.20 *M* solution of chloroplatinic acid in ethanol. After addition of 20 ml of 1.0 *M* sodium borohydride in ethanol to reduce the catalyst, 10.0 ml of acetic acid is added. The hydrogenation is initiated by the addition of 78.5 ml, 68 gm, of (—)-β-pinene. There is isolated 60.0 gm (87%) of pinane, b.p. 164°–165.5°C (740 mm), n_D^{20} 1.4618, $[\alpha]_D^{25}$ — 21.3°.

In some cases it might be desirable to generate hydrogen in one flask as the hydrogen is being absorbed in the hydrogenation flask. For large-scale hydrogenations this has the advantage of reducing the amounts of solvent which must be handled. The following procedure is representative.

2-1d. *Hydrogenation of Ethyl Oleate to Ethyl Stearate* [14a]



$$\longrightarrow CH_3(CH_2)_{16}COOC_2H_5 \qquad (9)$$

Hydrogen is generated by adding a 2.5 *M* solution of sodium borohydride in water to aqueous acetic acid in a generator fitted with the valve previously described. In the hydrogenation flask, a 500 ml Erlenmeyer with a stirrer, is placed 5 gm of carbon, 100 ml of ethanol, 5.0 ml of 0.20 *M* chloroplatinic acid in ethanol, and 20 ml of 1.0 *M* sodium borohydride in ethanol. Ethyl oleate, 179 ml (155 gm), is added, and the flask connected to the generator. The system is flushed with hydrogen from the generator, acetic acid (10.0 ml) is injected into the hydrogenation flask, and the hydrogenation allowed to proceed. The reaction is complete in 2 hr. The solution is filtered, and added slowly to ice water to recover ethyl stearate, m.p. 32°–33°C, in 91% yield.

The procedure has been applied successfully to the hydrogenation of 500 gm of ethyl oleate, using a 1 liter flask with a larger quantity of catalyst [14a].

The controlled generation of hydrogen should be very helpful even in cases where it is desired to follow literature procedures for hydrogenations. For example, the hydrogenation of cholesterol is a capricious reaction. However, Hershberg *et al.* reported that the erratic tendencies of this reaction could be overcome by performing the hydrogenation with platinic oxide in ethyl

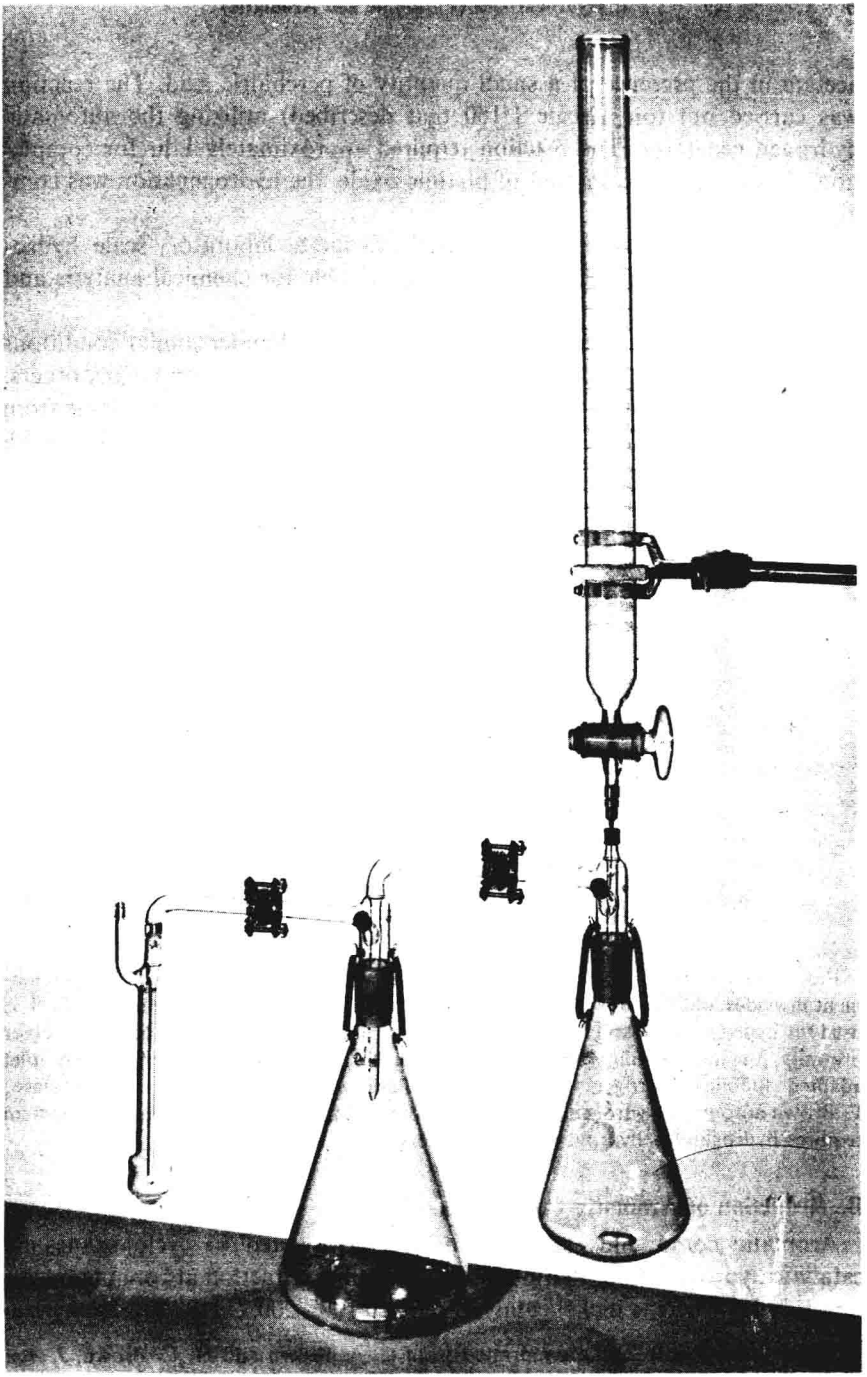


FIG. 2. Commercial form of the H. C. Brown hydrogenator. (Reproduced by permission of the Delmar Scientific Laboratories, Inc., Maywood, Illinois.)