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TO MY WIFE VICKY

*WHO FOR SO MANY YEARS HAS EDITED AND
TYPED THOUSANDS OF PAGES OF MY WRITINGS*

INTRODUCTION TO THE THIRD EDITION

Significant changes have taken place in our industry during the last two decades. Modern instrumentation has given us a better understanding of natural products by making feasible the isolation and identification of hundreds of compounds found in trace amounts in essential oils and foods. The discovery and synthesis of methyl jasmonate and related compounds in jasmine, and undecatriene and pyrazines in galbanum, to cite a few examples, have widened the horizon of the creative perfumer. Advances have been even more exciting for the flavorist. A whole range of pyrazines, thiazoles, furanones, and other heterocyclic compounds, have made his task immensely challenging and rewarding.

The perfumer's and flavorist's palette in the 1980's is much more extensive than it was in the 1960's, and today's compounds are far superior in quality, thanks to the availability of a range of powerful new materials. It can be anticipated that in the near future, new discoveries will make possible the duplication of natural fragrances and flavors with a yet higher degree of fidelity.

We are on the threshold of manufacturing aroma chemicals not only by traditional chemical methods but also by the application of microbiological techniques. Spectacular developments are occurring in agricultural areas as well. By cloning procedures, we may be able to increase the yields of essential oils manyfold, thus making the use of natural products more economical. Discoveries that lie ahead may be beyond our boldest imagination.

The appearance of the third revised edition is due in part to the many requests from the industry (the earlier edition published in 1967 has long been out of print) and in part to the author's desire to bring to the reader's attention some of the advances which have taken place during the last two decades.

The format of the second edition has been maintained, but changes have been made where pertinent or necessary. Several new chapters have been incorporated on materials such as menthol, nitriles, heterocyclic compounds, alkadienals and alkenals, and single-page chapters have been added to cover a number of compounds which have become important to the industry.

In the light of increasing governmental regulations with respect to the use of flavor and fragrance substances, it was considered advisable to mention wherever possible their present FEMA and RIFM status.

As in the former editions, the present volume gives the history of most of the aroma chemicals used in our industry, be they entirely synthetic or duplications of naturally occurring materials, and deals at some length with their chemistry, properties, applications, and commercial methods of manufacture. An effort has been made to indicate the total consumption of these chemicals in the United States.

It is hoped that this book will continue to be useful to the perfumer, flavorist, and chemist engaged in our industry or related fields.

INTRODUCTION TO THE SECOND EDITION

The last two paragraphs of the introduction to the first edition indicated the need of probing more deeply into the constitution of essential oils and flavors with a view to identifying these minute amounts of materials which give natural products their highly desirable characteristics.

Tremendous progress has been made in this area since 1950. The application of infra red and ultra violet spectroscopy, gas-liquid and thin-layer chromatography, X-ray and N.M.R. spectrometry, mass spectroscopy, and optical rotatory dispersion have made possible the detection and identification of even trace amounts of most of the components of such complex materials as essential oils. As a result of instrumental analysis, we are on the verge of duplicating nature's fragrances with hitherto undreamed of faithfulness, and it is to be expected that before long, the laboratory rather than nature will supply us with a major portion of our essential oils.

The improvement in methods of manufacturing terpenes synthetically has been commensurate with our better understanding of the composition of essential oils. The discoveries of Cope (1948) and Kimel (1958) that the Carroll reaction could be applied to dehydrolinalool to produce pseudoionone led to the large-scale application of acetylene chemistry to the production of linalool, ionones, and a host of related materials. This development came about because of the demand of Vitamin A manufacturers for a stable source of citral or beta ionone.

Perhaps even more far-reaching effects in our industry were achieved by developments in pinene chemistry. The researches of Bain and co-workers in the past two decades have made available a wide range of terpene materials from pinene, such as linalool, geraniol, citronellol and citral. In addition, derivatives such as ionones, hydroxycitronellal and menthol can be made, as well as numerous other materials to be used as such for the reconstitution of synthetic essential oils.

The use of synthetic aromatics has increased three-fold in the past fifteen years and the pace is accelerating. The exciting discoveries which lie ahead will offer many challenges to the organic chemist.

PREFACE

Since the publication of the first edition of this book in 1951, the perfume and flavor industries have expanded greatly and significant changes have been made in manufacturing methods and materials. No comprehensive publication has appeared, however, to bring these advances to the reader's attention.

It was found necessary to rewrite all the chapters and add new ones. Certain sections were eliminated and others condensed in order to keep the size of the book within reasonable limits and permit a discussion of important developments. Thus, almost all the literature data on the occurrence of natural products were omitted, as was the analytical section. These omissions, however, were considered necessary to emphasize the subject dealt with in this book. The former data are adequately covered in other works (Guenther; Gildemeister and Hoffmann, 4th ed.), and analytical procedures including instrumentation are now beyond the scope of this volume.

The present edition gives the history of the principal perfumery synthetics (naturally occurring, derived from natural sources, or entirely laboratory produced), their chemistry, application, physical and chemical properties, manufacture, uses, and other pertinent information. The several hundred compounds discussed comprise most of the materials used by the industry.

It is hoped that this book will be useful to chemists engaged in the field of essential oils, perfumes, flavors, soaps and cosmetics. Chemists in other fields may also find it of interest since many unusual reactions, seldom used in other organic chemical industries, are employed in the synthesis of a number of perfumery materials.

Hastings-on-Hudson, N.Y.
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P. Z. BEDOUKIAN

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Thanks are due to the Essential Oil Association of U.S.A. for permission to include in this volume the E.O.A. Specifications and Standards. The flash points quoted in the text were all taken from the Givaudan Index, Second Edition, with the kind permission of Givaudan-Delawanna Inc.

Finally, this book could not have been written without the encouragement and help given by my wife, Victoria, who did much of the editing and all the typing. The dedication of this book to her is well deserved.

P. Z. B.

INTRODUCTION TO THE FIRST EDITION

The synthetic perfumery industry may be considered a junior member of the family of industries which have developed in the past century as a result of research in organic chemistry. It has benefited from the general broadening of our knowledge in this branch of chemical science and in turn has made modest but not insignificant contributions to the advancement of organic chemistry.

The development of the perfume industry has proceeded along several channels. As could be expected, many desirable compounds have been isolated from essential oils for use in perfumery. For example, the important terpene alcohol, geraniol, which has a rose odor, is obtained from citronella oil which in itself is not valued to the same extent because of the presence of other ingredients. Similarly, linalool is obtained from rosewood oils and after thorough purification is used in many compositions. Numerous other instances may be cited illustrating our dependence on natural sources for the production of certain perfumery isolates.

Another phase of development involves the production of naturally occurring perfumery materials which cannot be separated from the oil economically either because only small quantities are present in the oil or because of the high cost of the natural oil in which they occur. Many of these chemicals have been synthesized from a naturally occurring raw material or from completely synthetic sources. Thus, phenyl ethyl alcohol which is present in the expensive oil of rose flowers is synthesized from coal tar products, whereas terpineol is synthesized from the naturally occurring hydrocarbon, pinene.

A third source of perfumery materials are certain odorous compounds which have not been found in nature. Some of these have been discovered accidentally, as in the case of artificial nitro musks, or have been found as the result of painstaking research in quest of odorous synthetics, as in the case of amyl cinnamic aldehyde. Quite often such discoveries are made by chemists working in other fields who are not familiar with the perfume industry, and a compound possessing many desirable odor characteristics is thus reported in the literature without any comment on its odor. This was true of amyl salicylate which remained unnoticed for decades until a perfumer "discovered" it and developed several famous perfumes based on this compound. There is no doubt that, of the hundreds of thousands of organic chemicals which have been synthesized, many pleasant smelling compounds which are as yet unknown to perfumers will eventually be found and put to practical advantage.

A study of the development of perfumery compounds reveals the names of many prominent chemists who have made important contributions to the perfume industry and to organic chemistry in general.

From the earliest days of organic chemistry, the constitution of naturally occurring perfumery materials has attracted the attention of chemists. Looking at their efforts in chronological order, we find the interdependence of the discovery of many perfume compounds and advances made in organic chemistry.

In 1833, Dumas carried out interesting experiments with a number of terpene compounds and reported empirical formulas for camphor, anethole, borneol, and others. At the same time he studied the formation of addition products of some terpenes with the purpose of characterizing them.

A year later, Mitscherlich prepared nitrobenzene which was used as a very cheap synthetic odorant in certain industrial products.

In 1837, Liebig and Wöhler made a study of the hydrolysis of amygdalin, the glucoside found in the seeds of bitter almonds and obtained benzaldehyde, hydrocyanic acid and sugar. Their work included a study of the benzoyl radical and gave us our first knowledge of glucosides, a valuable contribution to organic chemistry.

In 1844, Cahours noted that methyl salicylate was the chief ingredient of winter-green oil. This compound was later prepared synthetically in large quantities and used as a flavoring agent.

A number of esters of aliphatic acids were synthesized in 1850 and eventually proved useful as synthetic flavoring agents.

In 1853 Bertagnini noted the powerful odors of aliphatic aldehydes and their possible use as perfumery materials. In the same year he discovered a method of purifying aldehydes by forming their bisulfite addition compounds.

Also in 1853, Piria discovered the now classical method of preparing aldehydes by distilling a mixture of calcium salts of acids with calcium formate. Another important reaction was carried out by Cannizzaro who treated benzaldehyde with alkali and obtained benzyl alcohol and sodium benzoate. This reaction is known by his name to this day.

In 1856, Chiozza condensed benzaldehyde with acetaldehyde in the presence of alkalies and obtained cinnamic aldehyde, a valuable flavoring product which Dumas and Peligot had isolated from cinnamon oil in 1834.

The year 1856 was notable also for Perkin's discovery of the condensation of benzaldehyde with acetic anhydride in the presence of sodium acetate to give cinnamic acid. This reaction was subsequently studied in detail by many chemists.

In 1860 Kolbe found that on treatment of sodium phenolate in the presence of carbon dioxide, salicylic acid is obtained in good yields. This reaction led to the large-scale manufacture of many salicylates, some of which are important in perfumery.

In 1868, Cahours found a way of preparing benzaldehyde by treating benzal chloride with water in the presence of alkali.

Possibly the most eventful year in the history of the synthetic perfume industry was 1875. In that year Perkin applied his reaction to salicylic aldehyde and obtained coumarin, a very important perfumery and flavoring ingredient. At about the same time, Tiemann and Reimer synthesized vanillin from guaiacol by treatment

with chloroform and alkali. The reaction is general for the preparation of aromatic aldehydes and is commonly known as the Tiemann-Reimer synthesis. The discovery of a practical method for the manufacture of vanillin and coumarin served as a basis for the establishment of the synthetic perfume industry.

The year 1875 was also important in the history of the chemistry of terpene compounds. Until then very little was known of these naturally occurring compounds and it was difficult to work with them. In 1865 Tilden discovered that pinene and other terpene hydrocarbons could be identified by preparing the nitrosochloride derivative. It is true that some earlier work had been done by Berthelot in 1862, Barbier in 1872, and Kekule in 1873, but no real progress could be made until a method could be found to definitely identify these products. Although Bouchardat in 1875 polymerized isoprene and obtained dipentene, thus indicating a relationship between the two compounds, the significance of this observation could not yet be understood. As early as 1876, however, the art of distillation and a practical knowledge of the constituents of essential oils were sufficiently advanced so that terpeneless oils could be prepared for the flavoring and perfumery industries.

In 1877 Tiemann and Herzberg produced anisic aldehyde from *p*-hydroxy benzaldehyde, a by-product of the manufacture of coumarin.

In 1878 heliotripin was manufactured by the oxidation of piperic acid. The process, an extremely expensive one, was in use until 1890 when Eykmann discovered the relationship between safrol and heliotropin. It was in 1878 that Tilden found the true structure of terpin hydrate, and this valuable compound was placed on the market some twelve years later.

One of the milestones in the development of purely synthetic perfumery ingredients was the discovery of nitro musks by Baur in 1888. This led to the rapid development of several nitrated benzene derivatives which are used extensively to this day.

The year 1888 marked the interest of Wallach in terpenes. In this year he established the identity of *dl*-limonene and dipentene. From then on, Wallach continued his painstaking studies of the many problems related to terpenes. His work was important not only to terpene chemistry but to organic chemistry in general.

While Wallach was mainly interested in the analysis of terpenes and the clarification of their structures, Tiemann took greater interest in the synthesis of such products. As a result of his studies in connection with the constitution of irone, he stumbled upon the synthesis of ionone in 1893 and thus opened another brilliant chapter in the development of synthetic perfumes. Tiemann's discovery of ionone ranks in practical importance with the discovery of nitro musks and the manufacture of vanillin. Nor was Tiemann's discovery of ionone without its influence on the development of organic chemistry. In 1929 when Karrer was studying the degradation products of carotenes, he noted the characteristic violet odor of ionone at one stage of his oxidation experiments. This led to the correct interpretation of the structure of end groups in vitamin A.

In 1895 Tiemann and Semmler established the true structure of terpineol. The

structure of alpha pinene was established in the preceding year by Wagner. The last decade of the nineteenth century was the period of the greatest progress in the chemistry of terpenes. It was largely during this period that geraniol, linalool, anethole, etc., were produced on a commercial scale from naturally occurring essential oils. Credit for much of the work leading to the elucidation of the structure of many of these compounds must go to many other chemists, especially to Perkin in England and Bouveault in France.

Before the end of the past century a number of other perfumery products had appeared on the market. Most of these were obtained from natural sources and involved either a careful fractional distillation or a simple chemical treatment for the separation of these compounds in a relatively pure state. For example, menthol, santalol, borneol, citronellal, and cinnamic alcohol were manufactured and sold in substantial quantities. Aside from these, cinnamic aldehyde was produced by the condensation of benzaldehyde with acetaldehyde. A number of other synthetics—namely, benzyl alcohol and benzyl acetate, methyl salicylate and amyl salicylate, phenylacetaldehyde, etc., were manufactured and used in many perfumes, especially for soap compositions.

Just before the turn of the century, Grignard discovered the reaction of alkyl halides with magnesium and thus provided the organic chemist with a most useful tool. It is noteworthy that the discovery of the Grignard reaction took place in connection with attempts to synthesize new perfumery compounds.

The first decade of the present century marked a further advance in the development of perfumery synthetics. In 1904 Bouveault and Blanc carried out their famous sodium reduction reaction which was applied to the synthesis of perfumery chemicals. The first commercial application of this reaction was in the production of phenyl ethyl alcohol which had just been found in rose oil. Likewise, the discovery of indole and methyl anthranilate in flower oils brought about their synthesis in this period.

In 1903 Moureu carried out his studies on acetylenic acids and their preparation. As a result of his studies, methyl heptene carbonate and its homologs were introduced to the perfume industry.

Also in this decade hydroxycitronellal was discovered. This valuable product which has not yet been found in nature was first marketed in 1905.

The second decade of the present century was not as fruitful because World War I stopped chemical research in perfumery. A most notable development, however, was the discovery of cyclamen aldehyde by Blanc, a product which has become important and well established as a perfumery synthetic. Other products developed during this period include phenyl propyl aldehyde, phenyl propyl alcohol, and a number of fatty alcohols which have found wide acceptance.

Important contributions to organic chemistry have been made by chemists working with perfumery materials. For example, in 1925 Meerwein and Ponnordorf and also Verley discovered a method of reducing carbonyl compounds by means of aluminium alcoholates. This serves as an elegant method for the reduction of alpha

beta unsaturated aldehydes to produce the corresponding unsaturated alcohol without attacking the double bond.

In the early 1920's Ruzicka synthesized nerolidol and farnesol and began a series of investigations into the structure of sesquiterpenes. This work has led to an extension of our knowledge of terpene chemistry.

During this period also, Ruzicka began his investigations on the structure of natural musk compounds. The existence of large membered ring compounds was shown and a new chapter was opened in organic chemistry. Theories of ring structure and ring strain had to be revised and placed on a new basis. As a result of the studies on macrocyclic compounds, a number of large ring lactones and ketones have been placed on the market and are widely used in fine perfumes.

The constituents of violet flower and violet leaf oil were investigated by Ruzicka and the presence of the highly odorous aldehyde and alcohol—namely, nonadienal and nonadienol—shown in violet leaf oil.

The third decade of the century saw numerous improvements in the manufacturing processes of perfumery materials, especially in the United States where the great increase in the consumption of cosmetics was matched by an increase in the production of aromatic chemicals.

It was in this decade that Carothers carried out his brilliant researches on polyesters which led to the development of nylon. As a result of his studies on the depolymerization of polyesters, he discovered a new practical method of preparing macrocyclic esters possessing musk odors.

The structure of jasmone was proven by Treff and Werner but in view of the difficulty of its manufacture, this valuable ketone is not yet in general use.

The fourth decade of the century was largely barren as a result of the devastating effects of World War II which stopped research in most countries except Switzerland. It was in 1948 that the problem of the structure of irone was brought to a successful conclusion. Tiemann's work in 1893, which led to the discovery of ionones, was taken up by Ruzicka in 1919 and continued until its culmination in 1948. Credit for the final solution goes to both Ruzicka and Naves.

Much work remains to be done in the synthetic perfume industry. Very little is known of the odor ingredients of many flowers, and a fascinating field of research is open to the investigator. Although considerable quantities of flower oils are used in the perfume industry, efforts to duplicate them synthetically have met with only limited success. The determination of the constituents of minute amounts of unknown compounds in flower oils which contribute to the aroma of the natural oil will be of inestimable value to the perfume industry.

Another closely related field which is almost untouched involves the study of the constitution of the odorous ingredients of fruits. Only a few rudimentary studies have been reported in the literature and further knowledge along these lines will undoubtedly be of great importance to the food industry. The solutions of these and many other problems will tax the ingenuity of the organic chemist.

ABBREVIATIONS USED

B.p.	Boiling point
°C	Degree centigrade
<i>d</i>	Specific gravity
E.O.A.	Essential Oil Association of U.S.A.
°F	Degree Fahrenheit
g	Gram or grams
GLC	Gas-liquid chromatography
GRAS	Generally Recognized As Safe by a committee of experts of the Flavoring Extract Manufacturers' Association of America
IR	Infrared spectroscopy
M.p.	Melting point
<i>n_D</i>	Refractive index
Spec. grav.	Specific gravity
T or t	Temperature
TCC	Tag Closed Cup method
FEMA	Flavor Extract Manufacturers Association
RIFM	Research Institute for Fragrance Materials
	Irritation and sensitization results as reported by RIFM

Trade names of products are shown in parentheses.

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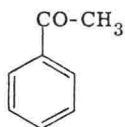
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ACETOPHENONE AND HOMOLOGS

Acetophenone

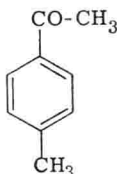
Methyl phenyl ketone

C_8H_8O Mol.Wt. 120.14



p-Methyl acetophenone

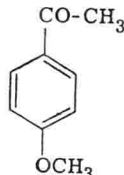
$C_9H_{10}O$ Mol.Wt. 134.17



p-Methoxy acetophenone

Acetanisole

$C_9H_{10}O_2$ Mol.Wt. 150.17



Related materials:

- 2,4-Dimethyl acetophenone
- 3-Isopropyl-6-methyl acetophenone
- 4-Isopropyl acetophenone

Although the quantities of acetophenone and its homologs used in the perfume industry are limited, these compounds are important because of their olfactory properties and because they serve as raw materials in the manufacture of other useful perfumery synthetics.

Acetophenone itself has a rather harsh hawthorn odor and must be used sparingly. The odor of methyl acetophenone is milder and lends itself to greater flexibility in its application. The methoxy acetophenone is somewhat different as it actually has an odor resembling cyclamen as well as hawthorn. The odor of *p*-isopropyl acetophenone is further removed from the hawthorn family. This compound has a floral cuminic odor useful in imparting leafy notes to certain types of compositions.

The GRAS list published in 1965 includes acetophenone, methyl acetophenone and acetanisole indicating their usage in various flavors.

All these ketones are stable and very desirable in fragrances for soaps and cosmetics. Because of their powerful odor, small portions are sufficient in most formulations.

In soaps acetophenone is a bright, coarsely odorous aroma chemical useful especially in hawthorn and apple blossom blends. Traces may be used to enliven a lilac or neroli. *p*-Methyl acetophenone has a strong, rather exotic odor effect in florals, spice blends and in some orientals. Both acetophenones are non-discoloring in soaps and detergents.

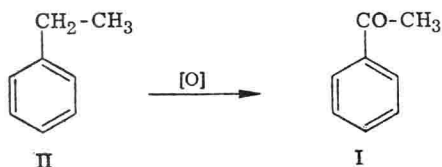
Acetophenone is inexpensive and serves admirably as a raw material for the preparation of the so-called strawberry aldehyde (C-16) which is chemically ethyl methyl phenylglycidate. From the latter, phenyl propyl aldehyde, another important odor-

ant can be prepared. Reduction of acetophenone gives phenyl methyl carbinol (see Carbinols) which, together with its acetate, is used in the perfume industry.

Occurrence. – The presence of acetophenone, generally on the order of several per cent, has been reported in about fifteen natural sources. It is found in cistus and labdanum oils and is the main constituent of *Stirlingia latifolia*. It is interesting to note its presence in castoreum, an animal product. The heavy fractions of coal tar distillate have been shown to contain small quantities of this ketone. Methyl acetophenone has been found in linaloe oil. The occurrence of *p*-methoxy or *p*-isopropyl acetophenone in natural sources has not been reported.

Preparation. – Numerous methods of synthesizing acetophenone have been published. Its first preparation was described in 1857 by Friedel¹ who obtained acetophenone by the distillation of calcium benzoate and calcium acetate.

Attempts have been made to prepare it by oxidizing ethyl benzene, although in some cases the yields were rather poor. Oxidation with chromyl chloride was reported to give acetophenone (I) along with benzaldehyde and other oxidation products². Somewhat similar results were obtained by oxidizing ethyl benzene (II) with chromic

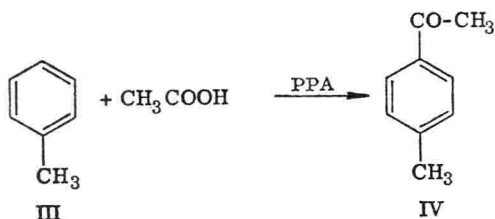


acid in a solution of acetic acid³. The same workers prepared acetophenone by treating bromostyrene with water at 180° C. Commercially, air oxidation of ethyl benzene yields a mixture of acetophenone, styrene and methyl phenyl carbinol. The products are then purified by fractional distillation.

Ketones are easily produced from acetylenic compounds. For example, phenyl acetylene on treatment with water and sulfuric acid yields acetophenone⁴.

Acetophenone has also been prepared by reacting benzaldehyde with an equimolar portion of methyl magnesium bromide⁵. In another synthesis, interaction of acetaldehyde with phenyl magnesium bromide gave acetophenone⁶.

An interesting acetylation reaction for many benzenoid compounds is conducted in the presence of polyphosphoric acid. Thus, toluene (III) and acetic acid in the presence of polyphosphoric acid give good yields of methyl acetophenone (IV)⁷. The method is applicable to a wide range of benzenes with higher aliphatic acids.



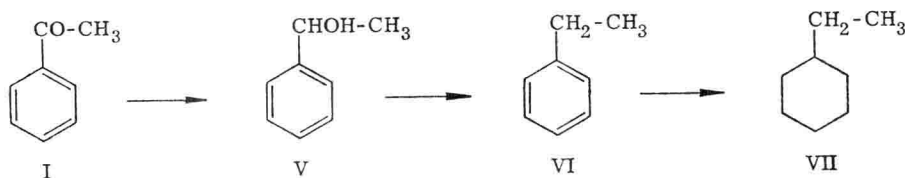
Ketene has been used successfully to acetylate toluene, *p*-isopropylbenzene and other substituted benzenes to *p*-acetophenones⁸.

Anisole and other compounds can be acetylated with acetic anhydride by using catalytic amounts of perchloric acid⁹.

Many other interesting syntheses of acetophenone and its homologs have been reported in the literature. In effect, almost any synthesis of an aromatic methyl ketone is applicable to the preparation of acetophenone and its homologs.

Commercially, methyl acetophenone and related compounds are prepared by the Friedel-Crafts method and also oxidation of substituted benzenes. These will be described later.

Chemical Properties. – Acetophenone exhibits the characteristic reactions of aromatic ketones. On oxidation with potassium dichromate and sulfuric acid, the ketonic group is cleaved resulting in benzoic acid and carbon dioxide¹⁰. This can also be accomplished with potassium permanganate oxidation.



The carbonyl group is easily reduced in the usual manner. Thus, methyl phenyl carbinol (V) is obtained by reduction with sodium in an alcoholic solution¹¹ or by electrolytic reduction¹². Similar results are obtained by catalytic hydrogenation with platinum black and the reduction can be extended to make ethyl benzene (VI) and the fully hydrogenated product—namely, ethyl cyclohexane (VII)¹³. Clemmensen reduction with zinc and hydrochloric acid gives ethyl benzene¹⁴.

As a methyl ketone, acetophenone undergoes aldol condensation with aldehydes. In the presence of sodium methylate in methyl alcohol solution, it condenses with benzaldehyde to give benzalacetophenone¹⁵.

The acetal of acetophenone is obtained by treating it with orthoformic ester in the presence of acids¹⁶.

The homologs of acetophenone, namely, methyl acetophenone and *p*-methoxy acetophenone, undergo the same typical reactions.

One of the most important reactions, from the perfumer's point of view, is the application of Darzens' synthesis to produce ethyl methyl phenylglycidate (C-16) from acetophenone. This reaction is discussed in the chapter on Phenylacetaldehyde.

Physical Constants. – Acetophenone and its two homologs have the following physical constants: