

# THE OZONIZATION REACTION

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## I. HISTORICAL INTRODUCTION

The addition of ozone to the ethylenic<sup>o</sup> double bond, followed by ozonolysis, the decomposition of the resulting ozonides, has been described recently (47) as the most general and reliable procedure for oxidative cleavage with simultaneous location of the double bond. Although ozone was discovered as early as 1785, its usefulness has been realized only within the last thirty-five years.

The reaction of ozone with organic compounds was first described by Schönbein in 1855 (134). When he bubbled ethylene through water into ozonized air, the bubbles exploded at the surface of the water, and a mixture of carbonic acid, formaldehyde, and formic acid was obtained. Many investigators attempted to apply the method during the next fifty years, but few favorable results were reported. Of the numerous papers which appeared during this fifty-year period, only those of Houzeau and Dieckhoff were important contributions. Houzeau (79) was the first observer to describe the isolation of an ozonide. He obtained, from the treatment of benzene with ozone, a white amorphous product which exploded very readily, yielding a relatively large amount of acetic acid. Dieckhoff (32) carried these experiments a step further by isolating a crystalline product which exploded at 50°C.

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Harries (52) continued this work, and from 1901 to 1916 published ninety-six papers (53) concerning ozone and its reaction with organic substances. These researches covered the entire field of ozonolysis in a comprehensive manner, and resulted in establishing the reaction on a useful basis.

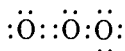
Further investigation has added new knowledge of the mechanism of the reaction, but its complete elucidation still remains for future solution. In 1925, Staudinger (142) made an important contribution to the theory of ozonization, which has been added to in the work of Rieche (126), Pummerer (122), F. G. Fischer (42), and Briner (18). Other advances have been made by F. G. Fischer (40) and Whitmore (152) in the methods of decomposing ozonides. Quantitative studies of rates of ozonization have been undertaken in recent years (23, 115), and, in addition, Briner and his collaborators have made numerous measurements of the physical properties of ozonides, such as the Raman spectra (16), dielectric constant (17), and heat of ozonization (20).

## II. THE THEORY OF OZONIZATION

The theoretical treatment of ozonization has received the attention of many investigators, but still remains an unsolved problem. The reaction has, nevertheless, been applied successfully to many questions of structure. The slow development of the theory of ozonization is easily understood when the unstable and explosive nature of the intermediates, the so-called ozonides, is considered. In addition, the course of the reaction is very sensitive to numerous factors, such as the ozone concentration, the duration of ozonization, the temperature of the reaction, the solvent, the concentration of the solution, and, of most importance, the method of decomposition.

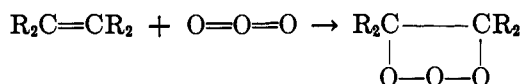
In formulating a theory of ozonization, consideration must first be given to the structure of the ozone molecule. Many arrangements of the oxygen atoms have been presented (136), of which the two most commonly con-

sidered have been the cyclic structure  $\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{O} \text{---} \text{O} \end{array}$ , in which the three oxygen atoms are bivalent, and the chain formula of Harries,  $\text{O}=\text{O}=\text{O}$ , adopted by analogy to that of sulfur dioxide,  $\text{O}=\text{S}=\text{O}$ . The pronounced reactivity of one of the three oxygen atoms in the ozone molecule is not accounted for by either of these structures, and a third formula (104, 105), in which only two of the oxygen atoms are linked by a double bond, is currently accepted.



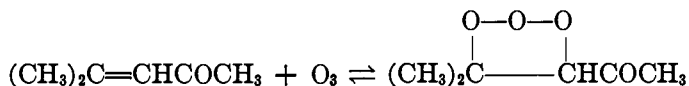
There is in ozone, accordingly, one oxygen atom held by a coordinate valence, which should account for the abnormal reactivity of the molecule. This atom would be repelled easily, would exhibit a tendency to complete its octet, and would facilitate the addition of the molecule to the carbon-to-carbon double bond.

Harries (54) visualized an addition compound as the initial substance arising from the action of ozone on a double bond, analogous to other products of addition to an unsaturated linkage,

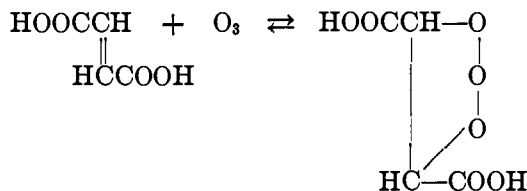


but his experimental evidence was relatively meager.

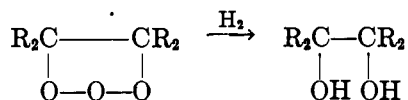
His proof rested chiefly on two observations: firstly, that mesityl oxide forms an ozonide which, on heating, spontaneously regenerates mesityl oxide (54),



and that fumaric acid adds ozone loosely and loses it on standing (54).

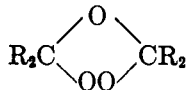


Pummerer (122) and Briner (15) have recently repeated these experiments and have been unable to duplicate Harries' observations. Harries had found, however, that these ozonides, on reduction using all of the methods then known, did not yield either the starting materials or the 1,2-glycols which would be expected according to his formula.

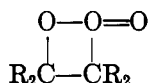


Pummerer (122) and F. G. Fischer (42) have repeated Harries' reduction of mesityl oxide ozonide, employing the gentlest methods of reduction in the cold, such as the use of hydroquinone, hydrazobenzene, aluminum amalgam, zinc dust plus silver nitrate and hydroquinone as catalysts, and catalytic hydrogenation at 0°C., and have been unable to detect the presence of the glycol in any experiment.

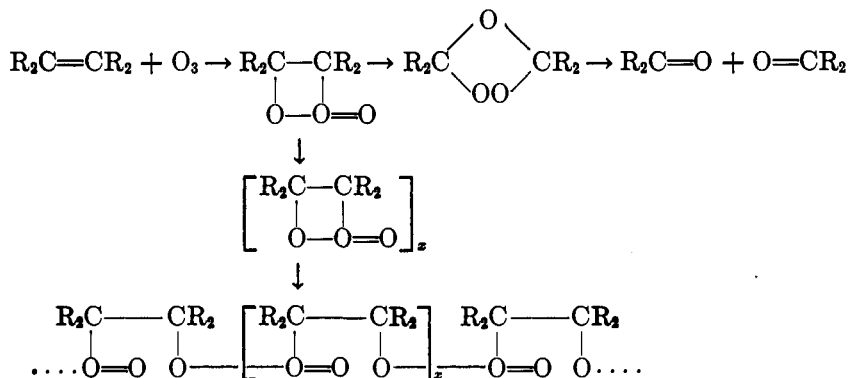
Staudinger (142), in 1925, had stressed the importance of these fundamental objections, and considered his isozonide formula,



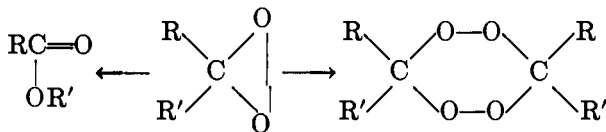
to be correct for most ozonides. Here the carbon chain is already broken, so that only the usual decomposition products would be expected on reduction, and not glycols with intact carbon chains. As primary products of ozonization he assumed the formation of molozonides, to which he assigned the formula,



which could become stabilized either through rearrangement into isozonides or through polymerization to higher molecular forms. He arrived at this hypothesis because, firstly, both monomeric and polymeric ozonides can be obtained from the same substance by using different solvents, and, secondly, the monomeric ozonide once formed cannot be polymerized. On this account, it appeared necessary to assume that these are secondary products, and that, initially, a primary ozonide, a so-called molozonide, is formed, which can either polymerize or undergo rearrangement into the stable monomeric form, the so-called isozonide. The lability of the molozonide is a logical consequence of its four-atom ring structure. The frequent explosions encountered in the action of ozone on unsaturated organic compounds can be attributed to the decomposition of such an unstable product. Harries (67) states, for example, that, in the ozonization of amylenes in a concentrated hexane solution, the liquid suddenly inflames, whereas the pure amylenes ozonide can be heated to 60°C. without exploding. In the latter case, the molozonide is assumed to have been converted through rearrangement into the more stable five-atom ring isozonide. Staudinger represents these assumptions as follows:



This formulation is analogous to the formation of an unstable monomeric peroxide, a so-called moloxide (37), which can then either rearrange or polymerize.

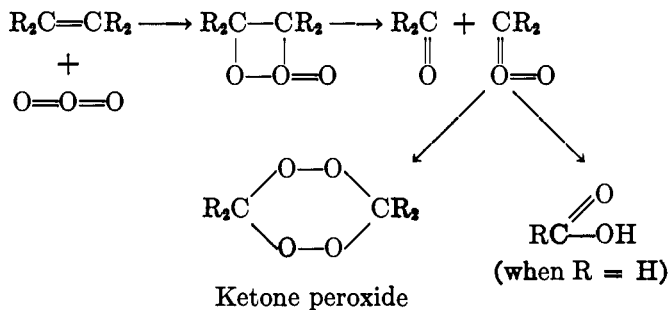


The less labile five-atom ring configuration of the isozonide favors its formation by rearrangement, and is the formula assigned to all stable monomeric ozonides, which include those of all aliphatic ethylenic derivatives, the monomeric form of cyclopentadiene, dicyclopentadiene, oleic acid and also the ozonide of rubber. The fact that the products of reduction are aldehydes and ketones or the corresponding alcohol, and the fact that glycol derivatives have never been obtained, are favorable indications of the validity of the isozonide formula.

In connection with the polymeric ozonides, it is interesting to note, in support of this hypothesis, that such products have always been observed where they would be expected: namely, where the rearrangement would be difficult, particularly where the double bond is in a ring. These cases include cyclopentene, cyclohexene, cycloheptene, dicyclopentadiene, dihydrodicyclopentadiene, and ozonides of aromatic compounds.

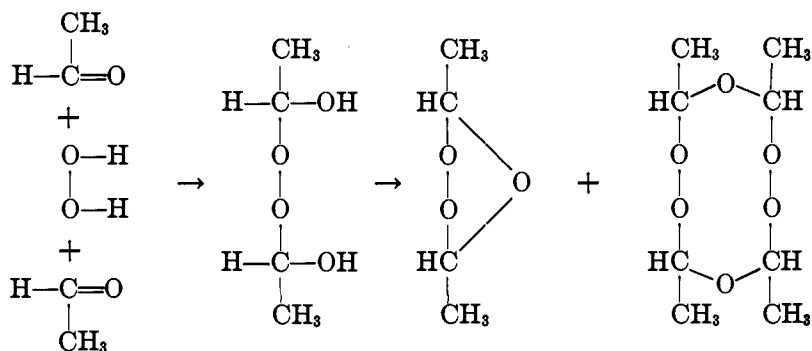
The effect of the solvent is also important. In acetic acid, where association of molecules does not readily take place because of its polar character, monomeric ozonides are almost invariably obtained. On the other hand, in carbon tetrachloride, which is non-polar and favors association, the polymeric form is the rule.

Staudinger visualizes a third reaction of a molozonide, to satisfy those cases where no stable ozonide can be isolated, in which an immediate breakdown of the molecule takes place, yielding a ketone and a ketone peroxide.

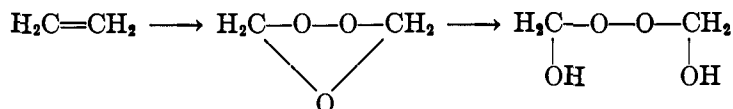


Staudinger considered his theory an important new conception of the constitution of ozonides; it has been partially substantiated, though not completely proved. He considered its analogy to the action of oxygen to form peroxides a strong factor in its favor.

Since the publication of this paper (142), the constitution of the monomeric butylene isozonides has been partially proved synthetically. Rieche (127), in 1932, reported the synthesis of a substance which he stated to be identical with the ozonide obtained by ozonization of butylene. By the addition of 2 moles of acetaldehyde to a 3 per cent ethereal solution of hydrogen peroxide, a solution of dihydroxy ethyl peroxide was obtained, which yielded, on removal of the ether *in vacuo* and subsequent dehydration *in vacuo* in the cold, a small amount of the monomeric butylene isozonide together with a larger quantity of its dimer, as follows:

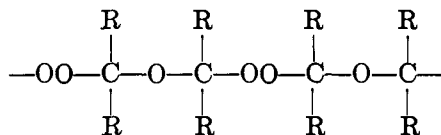


The isozonide theory also offers a simple interpretation of the formation of a peroxide by hydration of the ozonide of ethylene, reported by Briner and Schnorf (21).



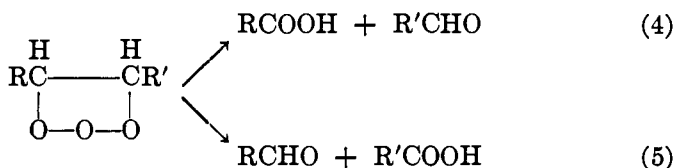
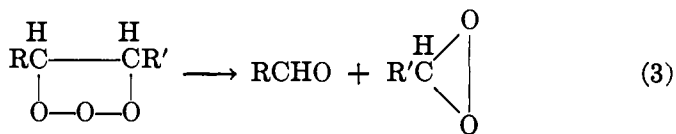
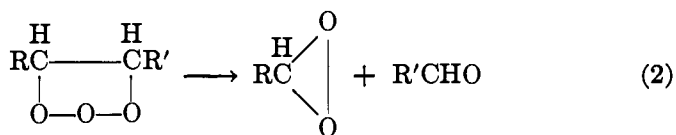
Other evidence in favor of Staudinger's formula was obtained by Rieche (126) from a consideration of the physical properties of ethylene and butylene ozonides. A comparison of the molecular refraction, the parachors, and the ultraviolet absorption spectra of these substances with those for monohydroxy dimethyl peroxide, dimethyl peroxide, and monohydroxy ethyl methyl peroxide, indicated the presence of a similar group in both types of compounds. As a result, Rieche concluded that two of the oxygen atoms in an ozonide form a peroxide linkage, and that the third oxygen forms an ether bridge.

Rieche has suggested an alternate formula for polymeric ozonides to that proposed by Staudinger: namely,—

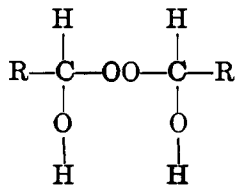


It is based on the alternation of ether and peroxide linkages, and consequently finds some support from the ultraviolet absorption spectra of these compounds.

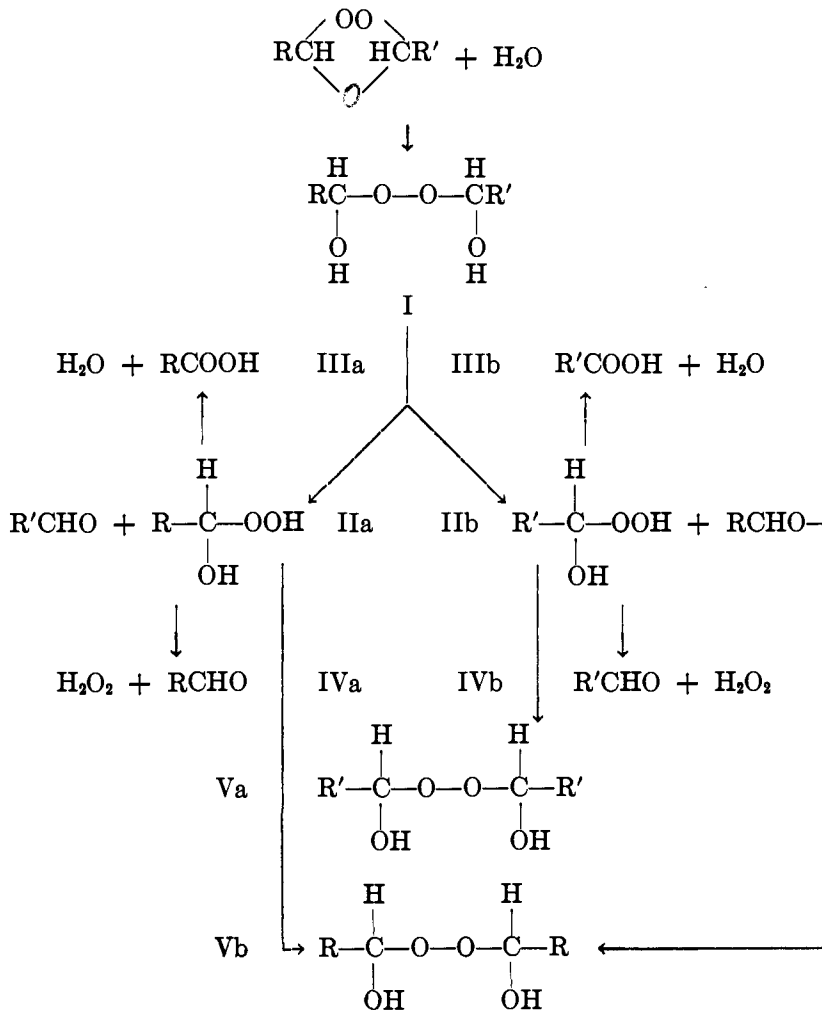
Harries presented his ozonide formula on the basis of investigations of the products of decomposition of ozonides, which he found to include acids, aldehydes (or ketones), and frequently peroxides. Harries conceived the following scheme of decomposition (54):



Rieche maintained this decomposition mechanism to be improbable for three reasons: (1) The indubitable rôle of water becomes thereby inconsiderable. (2) The peroxide bridges of the ozonide are broken. This contradicts his experience with alkyl peroxides. (3) The peroxides resulting from decomposition, which show stability, have a different constitution than Harries assumed. Molecular weight determinations indicate a double value, and the peroxides should be formulated thus:



Rieche (126), in 1931, developed a new scheme (see below) of decomposition, based on much experimental work, which apparently accounted for all the known facts.

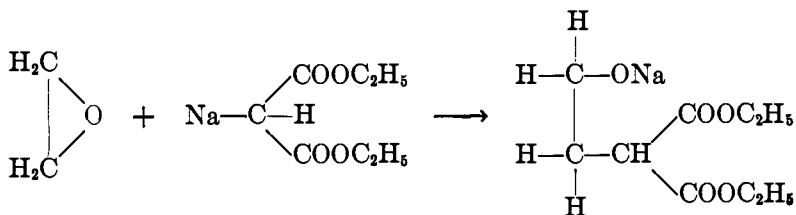


The sequence and probability of the various steps in the decomposition was supported by Rieche by analogy to similar processes occurring with alkyl peroxides.

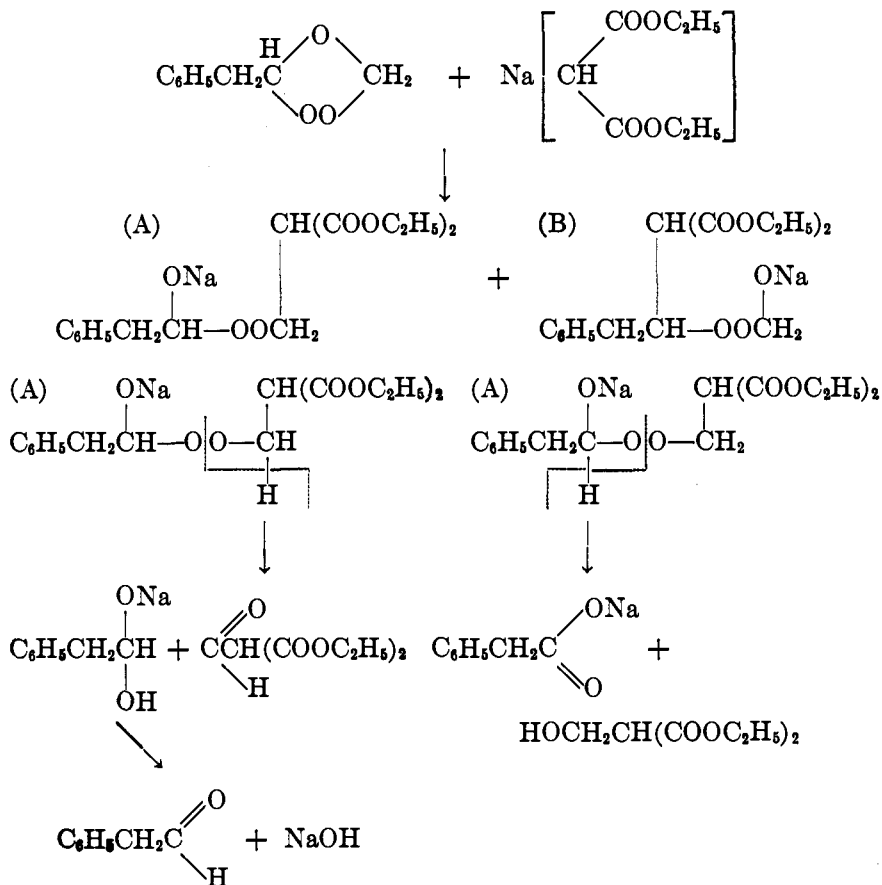
An interesting substantiation of Rieche's ozonide formula and of his ozonide decomposition mechanism has been obtained recently by W. Lehmann (102). Allylbenzene ozonide was treated with sodium malonic ester,



and the resulting product decomposed with water. This reaction was attempted because W. Traube and E. Lehmann (148) had reported that sodium malonic ester and ethylene oxide react vigorously in the following manner:



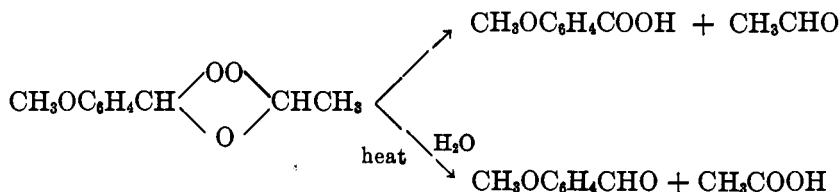
Since a like grouping is assumed to be present in ozonides, a similar reaction should occur. The reaction was assumed to follow the course outlined below.





Equation 7, the so-called "acid rearrangement", was observed to take place as a secondary reaction to the hydrogenation. The yield of acid was found to vary proportionately with the temperature of hydrogenation.

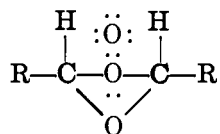
In 1938, Briner (18) tentatively suggested an alternate ozonide formula in order to account for certain properties of ozonides which had been observed in his laboratory. His experiments indicated that certain ozonides can decompose in two ways. For example, anethole ozonide yielded, in the absence of water, chiefly anisic acid and acetaldehyde, whereas hot water, with acceleration of the reaction, gave anisaldehyde and acetic acid.



It was also found, by treatment of the ozonide with potassium iodide, that an amount of active oxygen was present corresponding to that required for the addition of 1 mole of ozone per mole of anethole. It was concluded, therefore, that a characteristic property of the ozonide molecule is the retention of the peroxide activity possessed by the mole of ozone added. The Staudinger formula was found to account for the first observation with respect to the two methods of decomposition of the anethole ozonide, but it was held to be an inadequate representation of the peroxide character of the compound.

The contention was that the oxygen atom endowed with peroxide properties does not occupy a special position in the formula. The only oxygen atom which has a special position is known to function like the oxygen of an anhydride on the basis of the hydration of ozonides and dehydration of peroxides previously referred to. The peroxide oxygen atom is therefore one of the two others, and it is in connection with this formulation that a question has been raised. A similar problem exists in the case of the peroxides.

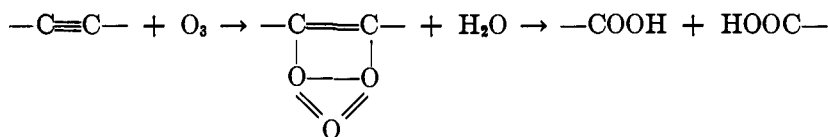
One method of separately identifying one of the atoms is to use a coordinately bound oxygen atom.



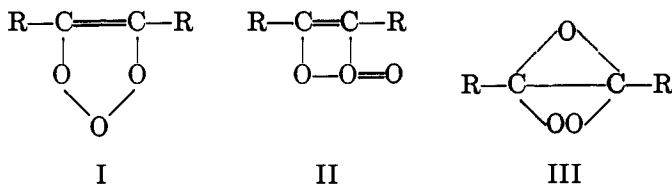
This type of formula has been suggested for hydrogen peroxide (111) and other peroxides (143) by many authors, but it has inspired much opposition because the expected products of decomposition have not been observed

(8, 157). For these reasons, Rieche placed the two oxygen atoms adjacent to each other without a bond, thereby admitting implicitly that the oxygen bridge —OO— determines the peroxide action. On the basis of recent work with Raman spectra (11), certain Russian authors have reconsidered a coordinately bound oxygen atom in peroxides. Without discussing it further, Briner has indicated the possibility of renewing the consideration of peroxide and ozonide formulas.

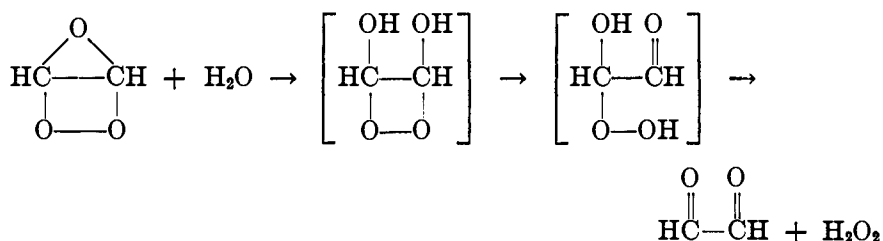
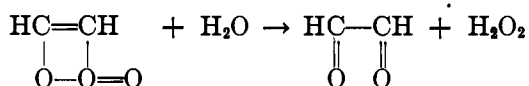
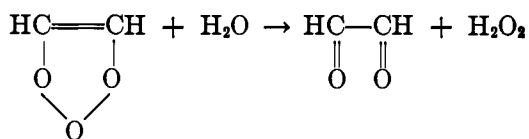
The theory of the ozonization of acetylenes has been developed to a lesser extent than for olefins. Harries (55, 56) was the first to attempt the addition of ozone to a triple bond. Practically quantitative yields of the acids anticipated from scission of the triple bond were obtained from the ozonization of stearolic acid and phenylpropionic acid. Consequently, Harries formulated the reaction in an analogous manner to that for olefins, with the substitution of acids for aldehydes, or ketones, as the reaction products.



In 1929, Briner and Wunenberger (22) improved the work of Wohl and Braunig (162) by isolating glyoxal in 81 per cent yield from the ozonization of acetylene. This was an exception to the previously observed phenomena, in that it represented the only instance wherein the —C—C— bond had not been broken by the decomposition of an ozonide. More recently Hurd and Christ (83) have discussed the course of the ozonization of acetylenes. By analogy to the olefinic structures, three possible formulas were suggested. Formula I is a modification of Harries' structure, whereas formulas II and III correspond to Staudinger's molozonide



and isozonide representations. All of the various formulas satisfactorily interpret the evidence of hydrolysis, giving rise to acids, *via*  $\alpha$ -diketones (or glyoxals) and hydrogen peroxide. In the case of glyoxal formation from acetylene ozonide, the reactions would be:



In all cases, the subsequent reaction is



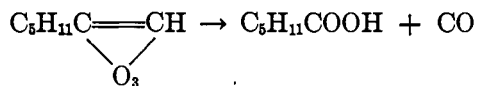
By analogy to the olefins, the authors favored structure II, in preference to I, for the initial addition product.

Shortly thereafter, Jacobs (84) reported the isolation of 1,2-diketones from the ozonization of diphenylacetylene and benzylphenylacetylene, evidence which offered strong support for the formation of such compounds as intermediates in the ozonization of acetylenic substances. The amorphous character of the unstable product of ozonization at low temperatures indicated that it was polymeric, whereas Hurd and Christ assumed the formation of only monomeric species. Another example of a similar nature has been reported currently for the ozonization of benzoylmesitylacetylene (45) to mesityl phenyl diketone. Although mesityl phenyl triketone would be expected as the primary product of the action of ozone, it is known (46) that the diketone is a decomposition product of the triketone.



Another theoretical interpretation (118) of the decomposition of acetylene ozonides has been suggested recently, prompted by the observed decomposition of 1-heptyne ozonide into caproic acid and formic acid but with an abnormally low yield of the latter. This low yield could be

accounted for by a spontaneous decomposition of the ozonide into caproic acid and carbon monoxide.



As a mechanism, the authors suggested that the unstable ozonide rapidly rearranges into the mixed anhydride of caproic and formic acids,  $\text{C}_5\text{H}_{11}\text{COOOCH}$ , which would decompose into caproic acid and carbon monoxide, as observed by Behal (10) for the mixed anhydride of acetic and formic acids. This suggestion of Paillard and Wieland appears to be substantiated by very little experimental evidence. The work of Jacobs and Fuson, in which 1,2-diketones were isolated, indicating that the original carbon-to-carbon bond was unbroken, presents facts of a definitely contradictory nature, of which Paillard and Wieland were not cognizant.

### III. THE METHODS OF OZONIZATION

Although ozonolysis has been referred to frequently as the most suitable method for the location of an unsaturated carbon-to-carbon linkage, its application in many laboratories has been curtailed by the lack of a suitable ozonizer. In the papers of Smith (139) and Henne (75), a simple, efficient, inexpensive apparatus is described which has been designed to generate ozone of high concentration.

The vessel in which the ozonization takes place has apparently received less attention from experimenters than almost any other phase of the reaction. Its construction, however, materially affects the use of the method, and is a subject which deserves more consideration. The problem is chiefly one of contact between a gas and a liquid, and is met usually by merely inserting a gas inlet tube (78) in a test tube. Vollmann and coworkers (150) advocated the use of a tube with a fritted-glass bottom, a decided improvement over the usual method. An isolated instance of an interesting modification of the ozonization reaction vessel has been described in the application of a countercurrent flow of ozone and the solution to be ozonized through a tower packed with small glass rings (122).

It has been found necessary to vary the concentration of ozone in the ozonized oxygen bubbled through the solution to be ozonized, in accordance with the nature of the compound being tested. A high concentration, 14 or 15 per cent, facilitates addition of the reagent to aromatic compounds and substances with conjugated double bonds (78, 103), whereas a low concentration, 1 to 5 per cent, is essential for the isolation of certain aldehydes which are sensitive to oxidation. To reduce the concentration of ozone, the gas stream is passed through a solution of sodium hydroxide before entering the ozonization vessel. In the ozonization of ergosterol

(123), an abnormally high oxygen concentration was found in the ozonide isolated when 8 to 10 per cent ozone was used. By reducing it to about 2 per cent, the normal ozonide was obtained, which led to the elucidation of the side-chain structure. In almost every instance, excessive ozonization must be avoided, because of the oxidative effect of the ozonized oxygen on the reaction products. When complete absorption of ozone does not occur, this factor becomes one of the most difficult problems in the reaction.

A number of solvents have been found useful by various workers, and no very general rules can be given. Although substances which are attacked by ozone would seem to be inapplicable, this is not necessarily the case, for methyl alcohol (15), chloroform, and other liquids known to be sensitive to ozone have been used successfully. In special cases, as in the ozonization of maleic acid (15, 57), water also has been found to be suitable. Dry pure ethyl acetate was stated by F. G. Fischer (42) to be the best solvent for a number of alicyclic and straight-chain unsaturated compounds. Acetic acid (with and without the addition of acetic anhydride), hexane, petroleum ether, carbon tetrachloride, and methyl and ethyl chlorides have been used frequently and successfully.

The concentration of the solution may be varied widely, but for most olefins dilute solutions and low temperatures are preferable (42). For aromatic substances, in cases where the material is a liquid, no solvent is necessary, as exemplified by Harries' classical ozonization of benzene (73). However, the danger of explosion is here greatly magnified.

The effect of structure on the relative stability of the ozonides of different compounds has been noted in a few instances. The ozonolysis of aromatic compounds has frequently led to substances of an explosive nature (53). In a study of the ozonization of the dehydration products of the alcohols  $R_3COH$ ,  $R'R_2COH$ , and  $R'R''R'''COH$  containing normal alkyl groups from methyl to *n*-amyl, it has been reported recently (30) that, though most of the ozonides showed little explosibility, those of the highly branched and heavier olefins were the most unstable to light and heat.

#### IV. THE METHODS OF DECOMPOSITION

The significance of the ozonization method for the proof of structure and preparative purposes is diminished greatly because of the often unsatisfactory decomposition of the ozonide. Little exact work has been done on these methods.

In general, the ozonides of the higher aliphatic, simple, unsaturated hydrocarbons are very stable, like those of hydroaromatic substances. On the other hand, the ozonides of the doubly unsaturated, aliphatic hydrocarbons decompose readily. Aliphatic ozonides containing oxygen in other parts of the molecule react readily, in almost every case, with ice

water. Similarly, decomposition of ozonides of benzal compounds and their oxygen derivatives takes place very quickly. Of the different ring systems, the ozonides of six- and seven-membered ring compounds are stable in comparison with those of five-membered ring compounds. Ozonides of compounds of very high molecular weight, like rubber, resinify when heated with water, owing to intramolecular oxidation.

Because of the explosibility of the ozonides of the keto chlorides of unsaturated ketones and aldehydes, Straus (146) developed a useful application of the decomposition with water. By drawing a stream of moist air through the ozonized solution, and thereafter adding water and heating, it was found possible to decompose gently these extremely unstable compounds, and to isolate products which could be used to prove the structures of the keto chlorides of benzalacetophenone,  $C_6H_5CCl=CHCHClC_6H_5$ , cinnamylideneacetophenone,  $C_6H_5CCl=CHCH=CHCHClC_6H_5$ , dibenzalacetone,  $C_6H_5CH=CHCCl=CHCHClC_6H_5$ , and cinnamal chloride,  $C_6H_5CH=CHCHCl_2$ .

Methods of oxidative cleavage of ozonides lead to acids as the products of ozonization, and have found relatively few applications. Düll (35) has made a comprehensive investigation of a number of different oxidants, including chromic acid, alkaline and acid potassium permanganate, alkaline hydrogen peroxide, Caro's acid, nitric acid, iodine in alkaline solution (160), and catalytic oxidation with manganous hydroxide, manganous acetate, and palladium as catalysts. Decomposition with alkaline permanganate or with hydrogen peroxide in alkaline solution proved to be the most useful methods.

The important isolation of geronic acid and isogeronic acid from the ozonization of  $\alpha$ -carotene in glacial acetic acid was accomplished by Karrer (91) by decomposition of the ozonide with water and a small amount of hydrogen peroxide.

Since, in many cases, it is essential to isolate certain aldehydes or ketones, instead of acids, as products of decomposition of ozonides, methods of reductive decomposition have been investigated extensively. Treatment of the ozonide with the reducing reagent without delay after the ozonization has been found essential for the avoidance of acid decomposition products in many cases. In Pummerer and Richtzenhain's (122) apparatus for countercurrent flow of ozone and the solution of the substance to be ozonized, the decomposition is accomplished without any delay, as the ozonized solution flows directly into the flask containing the reducing agent. Aluminum amalgam and water was found to be a good reducing agent for mesityl oxide ozonide, as well as a mixture of water, zinc dust, silver nitrate, hydroquinone, and dioxane. For the decomposition of the very stable ozonide of dihydrodicyclopentadiene, it was

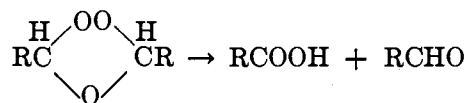


necessary to resort to zinc dust, glacial acetic acid, and heat. 3,6-endo-Methylenehexahydrohomophthalic dialdehyde was isolated in fair yield. Potassium ferrocyanide was found by Harries (58) to serve well for the preparation of particularly sensitive aldehydes and ketones, since the formation of tarry products was retarded.

Whitmore and coworkers (30, 152) have made a thorough study of various methods of decomposing ozonides, including the use of zinc and acetic acid (66, 114), of potassium ferrocyanide (58), of sodium bisulfite (21), of catalytic hydrogenation (40, 42), and of other new methods involving the action of acetic anhydride, propionic anhydride, liquid ammonia, and hydrazine hydrate solution. The olefins employed in this study of ozonolysis were obtained by dehydration of some twenty-two tertiary alcohols containing various combinations of normal alkyl groups, from methyl to amyl. The best method for decomposing the ozonides was by treatment with water and zinc in the presence of traces of silver and hydroquinone. The effectiveness of these catalysts was indicated by the following yields of carbonyl products isolated: acetaldehyde, 38 per cent; propionaldehyde, 18 per cent; butyraldehyde, 27 per cent; valeraldehyde, 38 per cent; diethyl ketone, 57 per cent; and di-*n*-amyl ketone, 63 per cent. Although this method proved to be most successful in the hands of Whitmore and coworkers, it has not had a wide acceptance. It involves several disadvantages: the isolation of a pure ozonide is often impossible, owing to the instability of the compound; the apparatus is complicated, and when destroyed by explosions, which can readily occur, is difficult to replace. As a result, the method of catalytic hydrogenation, discovered by F. G. Fischer (40), has received a more widespread acceptance, and appears to be the best method of reductive decomposition.

Düll (35) made a series of experiments to determine the utility of ozonolysis as a preparative method for aldehydes. The use of potassium ferrocyanide, sodium sulfite, sodium bisulfite, and catalytic hydrogenation was tested with oleic acid; the highest yield of aldehydes was obtained with the last method.

Certain precautions have been found to increase the yields of aldehydes and ketones (42): e.g., ozonization in dilute solutions and at low temperatures, careful avoidance of an excess ozonization, and hydrogenation at low temperatures. The hydrogenation usually proceeds very quickly and with much evolution of heat. The resultant secondary reaction, an "acid-rearrangement" of the ozonide, increases with the temperature, and was found to be the main cause of low yields. The formation of acid becomes



negligible, however, if warming is prevented during the hydrogenation. By consideration of these precautions, yields of 50 to 90 per cent of the theoretically possible quantity of aldehydes or ketones were obtained. Some sensitive dialdehydes,—glutaraldehyde, adipaldehyde, and pimelaldehyde,—were isolated in 50 to 75 per cent yields. These results may be compared with a 5 per cent yield of glutaraldehyde from cyclopentene ozonide by water decomposition, according to Harries (71), and a 20 per cent yield of glutaraldehyde and adipaldehyde obtained from cyclopentene and cyclohexene ozonides, respectively, by reduction with titanous chloride, reported by R. Robinson (110).

The hydrogenation of highly polymerized ozonides,—for example, solid cyclohexene ozonide,—did not proceed at room temperature, but was accomplished by warming in an autoclave with hydrogen under pressure. Decomposition of the resulting aldehyde was retarded by the use of methanol or ethanol as the solvent, whereby unreactive acetals were formed. A 60 per cent yield of adipaldehyde was thus obtained.

It was found preferable, however, to ozonize in a solvent in which highly polymerized insoluble ozonides did not form. Ethyl acetate was found particularly useful; cyclohexene ozonide prepared in this solvent remained completely in solution. Ethyl acetate was not appreciably attacked by ozone, as long as olefin was still present in solution (41), and had the added advantage that hydrogenation could be accomplished in the same solvent. Halogenated solvents, such as ethyl chloride, chloroform, or carbon tetrachloride, had to be distilled before reduction. The hydrogenation flask was cooled with ice water during the shaking process; 0.5 g. of catalyst,—palladium on calcium carbonate (24), with 5 per cent palladium content,—was used for each reduction.

An interesting application of the catalytic hydrogenation method has been made by Pummerer (121). By hydrogenation of carotene ozonide in glacial acetic acid with a platinum-charcoal catalyst, glyoxal was isolated in 3 per cent yield, giving additional evidence of a conjugated double bond structure. Another important characterization of a natural product was accomplished in the location of the double bond in the side chain of ergosterol (123) by catalytic hydrogenation of the ozonide of ergosterol acetate. The hydrogenation was carried out in a 1:1 ether-glacial acetic acid mixture as solvent with platonic oxide as the catalyst. The isolation of methylisopropylacetaldehyde was an unexpected result on the basis of the previous work on ergosterol, and rectified the former conception of the side chain.

#### V. RATES OF OZONIZATION

The relative rates of ozonization of different compounds have been little studied. In 1910, Harries (54) observed that compounds containing

two conjugated double bonds add the first mole of ozone more rapidly than the second. Brus and Peyresblanques (23), in 1930, presented curves for the ozonization of pinene, limonene, and oleic acid, in which the unabsorbed ozone was plotted against liters of oxygen used. The results indicated that, for an aliphatic double bond, ozone was absorbed quantitatively until the double bond was saturated. Thereafter, the amount of unabsorbed ozone increased very rapidly for a time, and finally gradually approached the original ozone concentration. These observations were interpreted as indicating that perozone was formed by over-ozonization, after the completion of the formation of the normal ozonide. Harries (59) had postulated the simultaneous formation of ozonides and perozone, owing to the presence of oxozone in the ozonized oxygen. Brus and Peyresblanques doubted the hypothesis of Harries, and agreed with Kailan (87) and Riesenfeld (128) that the existence of oxozone is improbable. In a second paper (23), also in 1930, curves were given for the ozonization of styrene, phenylcyclohexene, benzene, and heptyne. With the concentrations of ozone used, 9 to 10 per cent, benzene added ozone extremely slowly and heptyne moderately so, while the other compounds added 1 mole of ozone very rapidly.

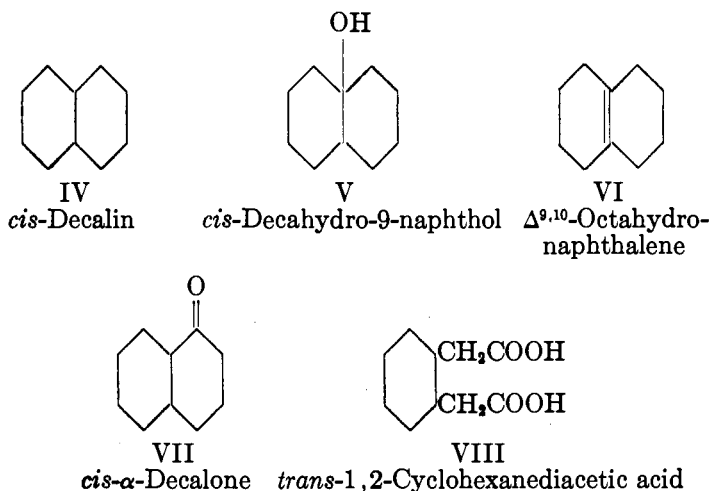
In 1936, Noller (115) and coworkers extended the procedure of Brus and Peyresblanques to the rates of ozonization of a number of other compounds. Curves were shown in which an "adjusted" per cent of unabsorbed ozone was plotted against the equivalents of ozone entering the solution. From the ozonization curves for some twenty-one compounds of varied structure, it was possible to draw certain interesting conclusions. Whereas a double bond, unaffected by the presence of other groups, was found to add ozone extremely rapidly, the rate was markedly decreased when the double bond was conjugated with carbonyl groups. Three or more phenyl groups or two chlorine atoms attached to the doubly bound carbon atoms also decreased the rate of addition. Where two or three double bonds were conjugated with each other, one bond added ozone rapidly while the others added it only slowly. In the case of *cis-trans* isomers, where the rate of addition was decreased by other groups, the *trans*-isomer was found to add ozone more rapidly than the *cis*-form. The latter fact has recently been corroborated by Briner (15).

#### VI. OZONE AS AN OXIDANT

The oxidation of saturated hydrocarbons and other saturated compounds with ozone has received the attention of but few investigators. This may be ascribed to the importance of the ozone reaction with unsaturated compounds, and to the complexity of the reaction mixtures obtained in the oxidation reaction. Harries (53) observed that aliphatic hydrocarbons such as hexane, petroleum ether, and ligroin were slowly

attacked by ozone. Mixtures of different compounds were found, including ozonides, peroxides, and fatty acids. Hexane yielded valeraldehyde and adipic acid in addition to other unidentified substances. Recently, a quantitative study of the oxygen consumption of various aliphatic hydrocarbons in the presence of both oxygen and ozone in the gaseous state has indicated (14) that a chain mechanism best explains the results. The compounds studied included all the lower members of the homologous series through normal octane, and two isoöctanes. In every case, a catalytic effect of ozone was found. For the straight-chain hydrocarbons, the catalytic effect occurred at lower temperatures than for the higher members. The branched-chain hydrocarbons exhibited a marked resistance to the oxidative effect of ozone. As the dilution of ozone increased, its catalytic action also increased, a fact consistent with a chain mechanism.

In an extended, but qualitative, investigation of the products of ozonization of technical decalin, Koetschau (95) identified  $\alpha$ -decahydronaphthol amongst other substances which were considered to include peroxides and acids. Currently, Adkins (36) has investigated the problem further and, in connection with other work, has reported some interesting results for the action of ozone on cyclohexane, decalin, and certain hydrophenanthrenes. A variety of compounds were obtained, including saturated alcohols, ketones, acids, and unsaturated ketones and hydrocarbons. The yields, in several cases, were from 20 to 35 per cent of the theoretical. Among the saturated compounds, cyclohexane was the most resistant toward ozone, the products identified being cyclohexanone, formic acid, and adipic acid. *cis*-Decalin (IV) gave *cis*-decahydro-9-naphthol (V) and  $\Delta^{9,10}$ -octahydronaphthalene (VI) in good yields, and small amounts of *cis*- $\alpha$ -decalone (VII). A large quantity of a mixture of unidentified acids was also obtained.



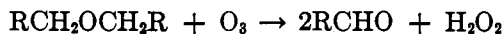
*trans*-Decalin gave *trans*-decahydro-9-naphthol (V) and *trans*- $\alpha$ -decalone (VII) in 28 per cent yield, but unless special precautions were taken the chief product was the octalin (VI) in 21 per cent yield. A mixture of acids similar in amount to that from the *cis*-isomer was obtained. Among these was identified *trans*-1,2-cyclohexanediacetic acid (VIII). Similar results were reported for the ozonization of various hydrophenanthrenes.

The authors considered the course of the oxidation of the saturated hydrocarbons to have involved primarily a reaction of ozone at the tertiary carbon atoms, forming an hydroxyl group. Oxidation subsequently took place at secondary carbon atoms to give hydroxyketones. The dehydration of these alcohols gave unsaturated hydrocarbons or unsaturated ketones. Further oxidation gave acids.

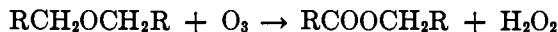
The reactivity of ethers toward oxygen and ozone forms a striking characteristic of these unreactive compounds. For instance, ozone strongly oxidizes ethyl ether. This was one of the earliest observations (135) of the action of ozone on organic compounds. Among the products of oxidation, von Babo (5) later identified hydrogen peroxide, acetaldehyde, and acetic acid. Berthelot (12), by distillation of ozonized ethyl ether, obtained "ethyl peroxide", an explosive syrupy liquid, but was unable to prove its identity. It has since been shown by Harries (52) that this product was not homogeneous, but its explosibility deterred further investigation.

In two papers, published in 1929 and 1931, F. G. Fischer (41, 43) and coworkers reported the isolation and identification of the principal products resulting from the reaction of ozone with ethers, alcohols, and aldehydes, and were able to present a theoretical explanation of their formation. The oxidation of isoamyl ether was first carefully studied, and it was shown later that other ethers react similarly, including methyl ether, ethyl ether, butyl ether, isoamyl ethyl ether, and benzyl ether.

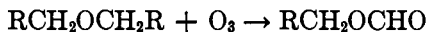
The first reaction was assumed to be the oxidation of the ether to an aldehyde and hydrogen peroxide, which would then interact to form a dihydroxy alkyl peroxide (156).



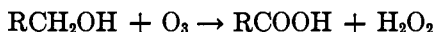
A further reaction was the formation of an ester and hydrogen peroxide. In the case of isoamyl ether, the isoamyl ester of isovaleric acid was isolated in 70 to 80 per cent yield.



Fractionation of the products from the distillation of the butyl and isoamyl ether ozonizations gave fractions identified as the formic acid ester of the corresponding alcohols.



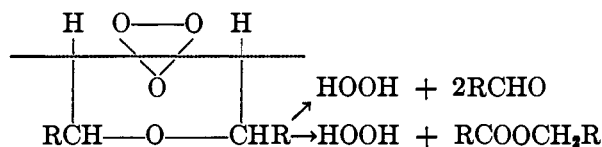
Methyl alcohol, ethyl alcohol, and isoamyl alcohol were ozonized also. The primary reaction was the formation of acids,



accompanying which were found aldehydes to the extent of about one-fifth to one-third of the quantity of acid.

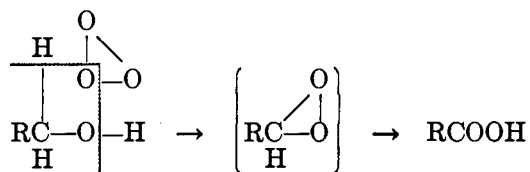


As an explanation of these reactions, Fischer has assumed the formation of an addition product as an intermediate, which would be very unstable and decompose rapidly. For the ethers, this would be



In this intermediate, the bridge oxygen becomes quadrivalent. This mechanism is analogous to certain peroxide rearrangements observed by von Baeyer (6), Harries (60), and others.

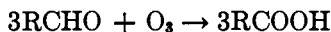
The formation of acids from primary alcohols may be written in a similar manner:



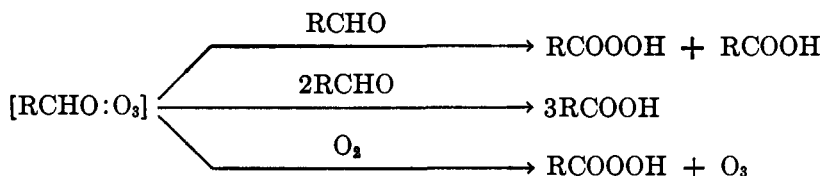
Fischer found that aldehydes formed mostly acids and per acids when subjected to the action of ozonized oxygen. Per acids were isolated and characterized from isobutyraldehyde, isovaleraldehyde, heptaldehyde, and benzaldehyde.



To explain a lower yield of per acids than would be expected from the above equation, he assumed a second reaction to be



These reactions explained satisfactorily the reaction of the pure aldehydes with ozone, and accounted quantitatively for the ozone consumed. In solution, however, the amount of acids and per acids formed was larger than could be accounted for by the ozone consumption, indicating that oxygen had also taken part in the reaction. This was clarified by the assumption that the aldehyde added 1 mole of ozone to form a primary addition product, which then reacted with another mole of aldehyde to give per acids and acids; with 2 other moles of aldehydes to yield acids; or with oxygen to form per acids and ozone.



The oxidation of ketones by ozone has not been as carefully investigated, but peroxide formation has been noted. The carbonyl group of aldehydes and ketones yields a peroxide relatively easily, whereas that of acids reacts with ozone only in the case of long-chain acids containing one or more double bonds.

Amines are, in general, not attacked by ozone, nor are amino acids and acid amides (69). Aromatic amines, on the other hand, undergo deep-seated decomposition in some unknown manner. Harries has also oxidized dulcitol (69) and mannitol (69) by ozone and has isolated galactose, glucose, and fructose.

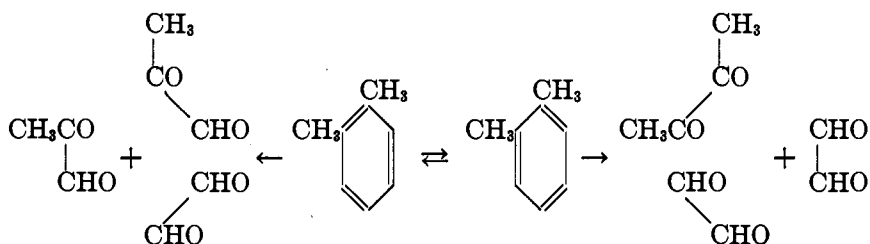
A knowledge of the oxidizing action of ozone is of importance in its reaction with a double bond, as an avoidance of this effect may account to a large extent for a reasonable yield of the desired products.

#### VII. THE OZONIZATION OF AROMATIC COMPOUNDS

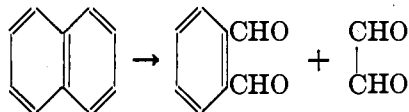
The quantitative investigation of the ozonization of aromatic hydrocarbons was one of Harries' (52, 73) most noteworthy contributions. Houzeau (79), in 1873, and Renard (125), in 1895, had previously studied the ozonization of benzene. After overcoming many difficulties due to the explosibility of the substance, Harries was able to analyze quantitatively the reaction product of ozone and benzene. It proved to be a triozonide, as had been anticipated from the structure of benzene postulated by Kekulé. In addition, 2 moles of glyoxal were isolated per mole of ozonide on decomposition with water, a further corroboration of the Kekulé structure. Working with the pure substances, increasing difficulties were encountered in the ozonization of toluene and xylene. These ozonides could be formed only at very low temperatures, and were so

explosive that it was found impossible to continue the experiments. On the other hand, it was possible to isolate the ozonide of mesitylene in a moist condition, and, on decomposition with water, to isolate methylglyoxal as the disemicarbazone. Since this was the only product that could be identified, it offered another confirmation of the Kekulé structure.

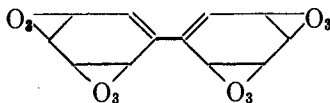
In 1932, Levine and Cole (103) demonstrated the existence of isomeric ortho-disubstitution products of benzene, by the ozonization of *o*-xylene in solution. Three products were identified after decomposition of the ozonide: namely, glyoxal, methylglyoxal, and diacetyl. Since neither form of xylene could have yielded all three oxidation products, the hydrocarbon must have consisted of an equilibrium mixture of the two Kekulé forms.



Polynuclear aromatic compounds add less ozone than the number of double bonds in the molecule should require. Naphthalene (52) was found to add only 2 moles to form a diozonide, from which *o*-phthalaldehyde and glyoxal were obtained by decomposition.



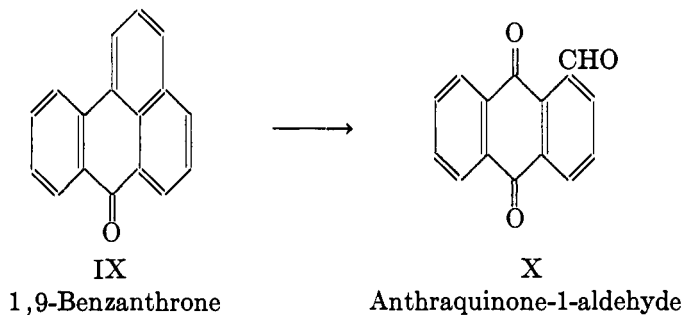
Phenanthrene behaved similarly; an analysis of the ozonization product proved the formation of a diozonide, but no products of decomposition could be identified. The insolubility of anthracene prevented its ozonization by Harries' methods, but it was possible to establish the formation of a diphenyl tetraozonide by analysis.



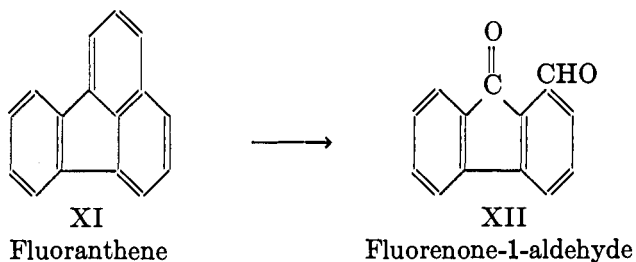
Recently, modern methods have overcome the obstacles encountered by Harries in the ozonization of anthracene. Vollman (150) and coworkers have reported several interesting ozonizations of polynuclear aromatic hydrocarbons. On the basis of results obtained with 1,9-benzanthrone



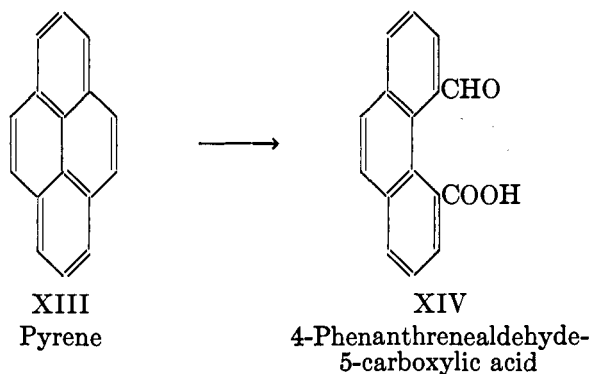
and fluoranthene, it was possible to achieve an ozonization of pyrene suspended in glacial acetic acid. From 1,9-benzanthrone (IX) had been obtained the difficultly accessible anthraquinone-1-aldehyde (X) in 20 per cent yield,



together with a large amount of anthraquinone-1-carboxylic acid; and fluoranthene (XI) had been ozonized in about 30 per cent yield to a mixture of fluorenone-1-aldehyde (XII) and fluorenone-1-carboxylic acid.



When pyrene (XIII) was treated with 0.5 per cent ozone and subsequently decomposed with water and sodium hydroxide, an excellent yield of 4-phenanthrenealdehyde-5-carboxylic acid (XIV) was obtained.



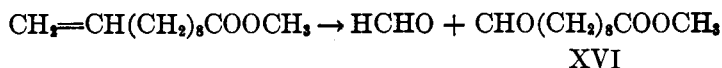
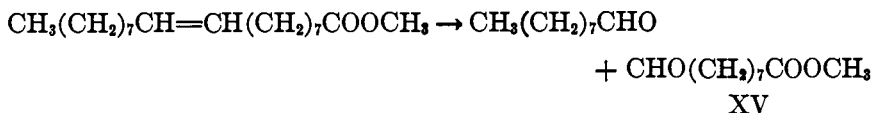
The ozonides of the hydroaromatic compounds are different from those of either aliphatic or aromatic substances in their very unusual stability. It is difficult, and sometimes impossible, to decompose these ozonides with water.

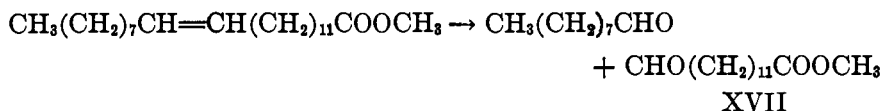
An interesting study of the rate of absorption of ozone by aromatic compounds was made by Brus and Peyresblanques (23). The curves for benzene indicated a different phenomenon than that observed for compounds with an aliphatic double bond. In the latter case, no unabsorbed ozone was found until the double bond was saturated. Thereafter, this quantity increased rapidly, finally approaching the original ozone concentration. For benzene and naphthalene complete absorption was never observed, even with low concentrations of ozone and a large excess of the aromatic hydrocarbon.

#### VIII. OZONIZATION AS A SYNTHETIC METHOD

The earliest descriptions of the use of ozonization as a preparative method were made by Otto (117) and Trillat (149), who reported the commercial production of vanillin from isoeugenol and of piperonal from isosafrole. An improved method of decomposition of the ozonide was developed by Harries (66) in 1915, whereby a 70 per cent yield of vanillin was obtained. By the further application of the new method of decomposition, using zinc dust and acetic acid, several phenolic aldehydes (65) were prepared which had been hitherto unknown, including homovanillin, methylhomovanillin, homopiperonal, and homoanisaldehyde. More recently Briner (19) has made an extensive investigation of optimum conditions of the reaction and has found, in the case of vanillin, that the best yields were obtained using a low temperature and a relatively high concentration of ozone.

Noller and Adams (114), in 1926, reported an investigation of the ozone reaction for the specific purpose of its utilization as a method of preparation. The aldehyde esters methyl  $\eta$ -aldehydoöctanoate (XV), methyl  $\theta$ -aldehydononanoate (XVI), and methyl  $\lambda$ -aldehydododecanoate (XVII) were synthesized from methyl oleate, methyl undecylenate, and methyl erucate by ozonization. These substances should offer valuable starting materials, especially for the synthesis of acids of high molecular weight.



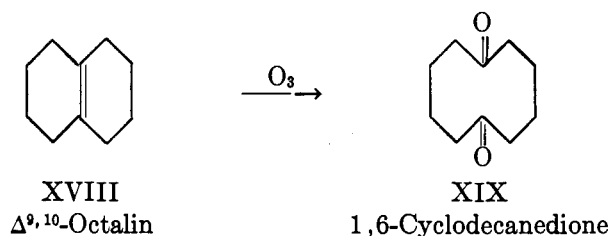


No difficulty was encountered in the isolation of over 55 per cent of the calculated amount of aldehyde ester boiling over a range of 5°C. In addition, pelargonaldehyde in yields of 60 to 70 per cent was obtained from methyl oleate and methyl erucate. The use of the aldehyde esters in synthesizing hydroxy acids and unsubstituted acids was illustrated by the conversion of methyl  $\eta$ -aldehydoöctanoate by means of butylmagnesium bromide into methyl  $\theta$ -hydroxytridecanoate and, finally, conversion of this latter compound through the bromide and olefinic acid to tridecanoic acid.

The significance of ozonization for preparative purposes has been diminished frequently because of inadequate methods of decomposition. Acids and other undesirable secondary products are isolated instead of the anticipated aldehydes. F. G. Fischer and coworkers (42) have obviated these discouraging results to a large extent by the application of the method of catalytic hydrogenation to the ozonide decomposition. The sensitive dialdehydes glutaraldehyde, adipaldehyde, and pimelaldehyde were obtained in 50 to 75 per cent yield by ozonizing cyclopentene, cyclohexene, and cycloheptene, respectively.

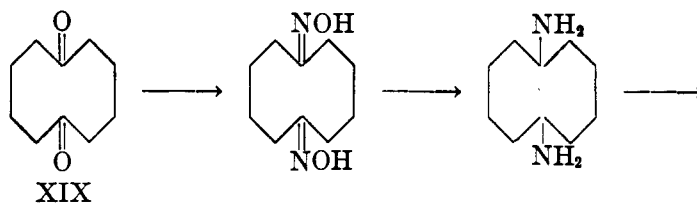
Within the past few years several unusual instances of ozonolysis have been reported, which have interesting preparative applications. In particular, the formation of aldehydes in reasonable amounts by the ozonization of polynuclear aromatic hydrocarbons like 1,9-benzanthrene, fluoranthene, and pyrene, as previously described, should open new synthetic possibilities in this important field.

Of equal interest has been the use of ozone for the preparation of such an unusual compound as 1,6-cyclodecanedione (XIX) by W. Hüchel (80). The latter was obtained from  $\Delta^{9,10}$ -octalin (XVIII) by ozonization. The diketone has been the starting point for significant syntheses in three directions.

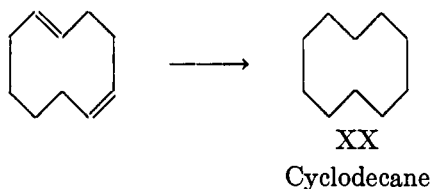


By reduction of the dioxime of XIX, exhaustive methylation, and catalytic hydrogenation, W. Hüchel (81) has synthesized cyclodecane

(XX), a compound which it has not been possible to prepare directly by the usual methods of closing an open chain or widening a ring with fewer carbon atoms (131).

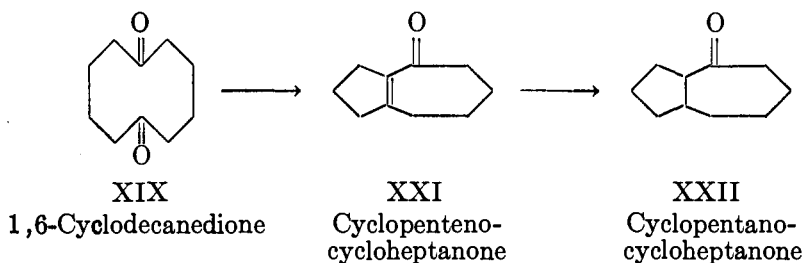


XIX  
1,6-Cyclodecanedione



XX  
Cyclodecane

The diketone (XIX), when treated with either acids or alkalis, formed cyclopentenocycloheptanone (82) (XXI) by an inner-molecular aldol condensation followed by dehydration. This  $\alpha,\beta$ -unsaturated ketone, on catalytic hydrogenation, gave a mixture of *cis*- and *trans*-cyclopentano-cycloheptanones (XXII), interesting compounds from the point of view of the stereochemistry of bicyclic ring systems.

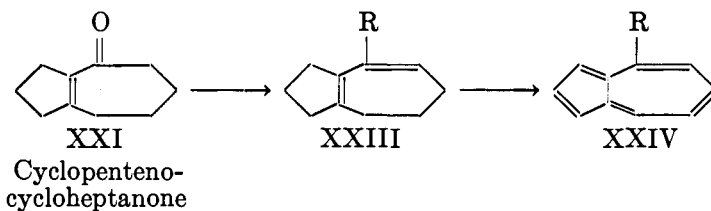


XIX  
1,6-Cyclodecanedione

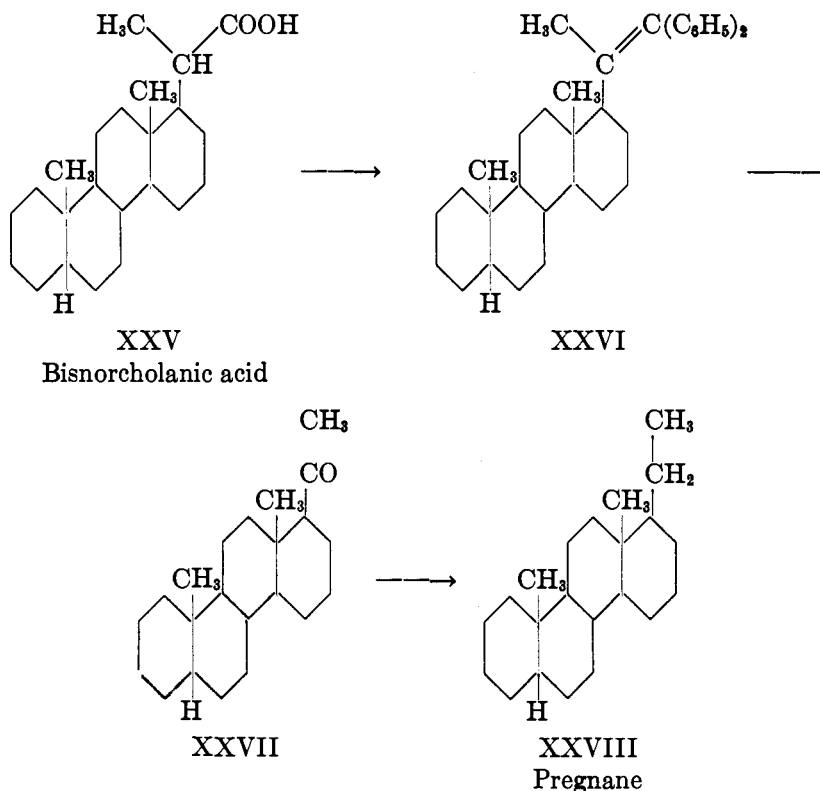
XXI  
Cyclopenteno-  
cycloheptanone

XXII  
Cyclopentano-  
cycloheptanone

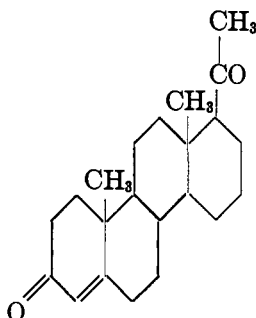
In a third, and equally important, application, cyclopentenocycloheptanone (XXI) has been used as the starting material for the only synthesis of an azulene thus far described (147). By treatment of the ketone XXI with either methyl-, ethyl-, or phenyl-magnesium halide there was obtained a hydrocarbon with two double bonds (XXIII), which was dehydrogenated with sulfur, or catalytically with nickel, to yield the desired azulene (XXIV).



In the important and related fields of sex hormones and adrenal cortex hormones, the use of ozone as a preparative method has been applied in several instances. In 1931, Butenandt proved the structure of pregnanediol (25),—the interesting but oestrogenically inactive substance isolated from human pregnancy urine by Marrian (106),—by relating pregnane (XXVIII), the corresponding saturated hydrocarbon, to bisnorcholanic acid (XXV) in three steps. These involved a Wieland-Barbier degradation of the latter acid (XXV), ozonization of the resulting unsaturated hydrocarbon (XXVI) to yield the saturated ketone (XXVII), and finally reduction of the ketone by the Clemmensen method to give 17-ethyletiocholane (XXVIII), identical with pregnane.



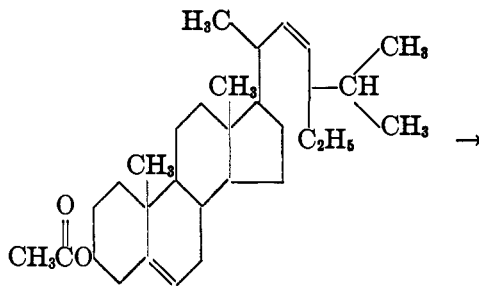
The isolation of acetoxybisanorcholeonic acid from the ozonization of stigmasterol by Fernholz in 1933 (38) proved of value in the preparation of progesterone (XXIX), the corpus luteum hormone discovered by Corner



XXIX

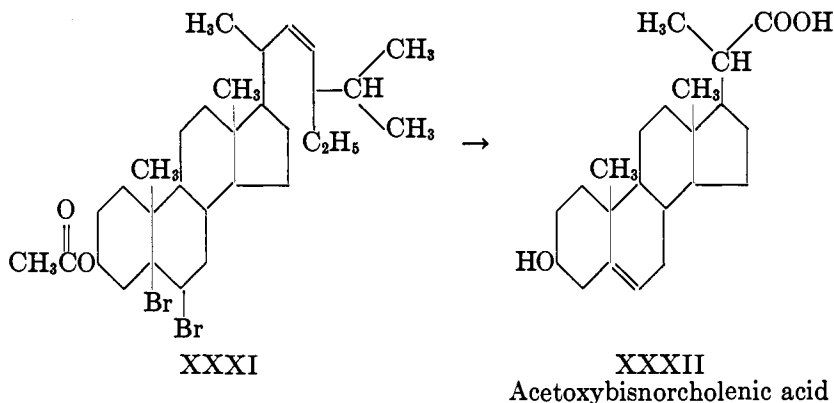
Progesterone

and Allen in 1928 (31). The latter compound was prepared synthetically from stigmasterol at practically the same time by both Butenandt (26, 27, 28) and Fernholz (39), independently. The work of Fernholz involving the ozonization of stigmasteryl acetate dibromide also gave the first proof of the long-suspected relationship of stigmasterol to cholesterol, and completely established the carbon framework of the sterol. In the preparation of acetoxybisanorcholeonic acid (XXXII), stigmasteryl acetate (XXX) was converted into the 5,6-dibromide (XXXI) by using just 1 mole of bromine. Ozone oxidation followed by dehalogenation with zinc, accompanied by simultaneous decomposition of the ozonide, gave the desired unsaturated acid (XXXII).

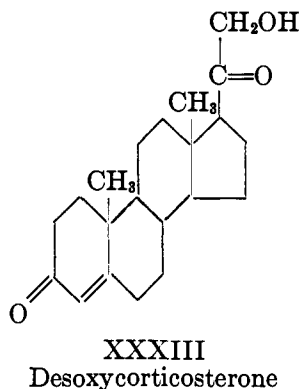


XXX

Stigmasteryl acetate



Later, in 1937, acetoxybisorcholenic acid again proved useful in the synthetic preparation of desoxycorticosterone (XXXIII) by Reichstein (144). This compound has proved to be one of the most potent androgenic hormones isolated from the adrenal cortex.



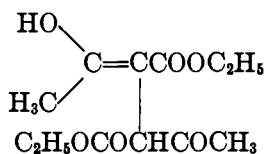
#### IX. THE PROOF OF STRUCTURE BY OZONIZATION

The most important application of ozone in organic chemistry is in the solution of structural problems by cleavage of unsaturated compounds, since the identification of the decomposition products presents the possibility of determining the position of the double bond. In most other reactions, only an addition to the double bond occurs, and its position cannot be inferred from the addition products.

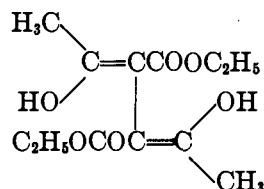
An unusual application of the reaction has been its assistance in the determination of the constitution of enols, by ozonization of the enolic form of an enolizable substance (132). Few chemical methods were available for this determination at low temperatures without displacing

the equilibrium. The formation and decomposition of the ozonide was carried out at low temperatures, under conditions which excluded rearrangement.  $\beta$ -Dibenzoylacetylmethane, for instance, does not add ozone, whereas its enolic tautomer readily forms an ozonide. Scheiber and Herold applied the method to numerous enolic compounds, including acetoacetic ester, ethyl oxalate, acetylacetone, benzoylacetone, and others. Abderhalden and Schwab (1) later applied the method to dihydroxypiperazines, dipeptides, and similar compounds.

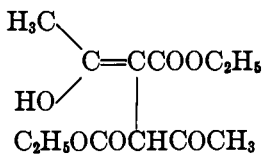
Kaufmann and Wolff (93, 94) combined ozonization with K. H. Meyer's bromine titration and ferric chloride colorimetric methods and were able to determine the three enolic forms of ethyl diacetylsuccinate. Bromine titration established the amount of the  $\alpha_1, \beta$ -ester (XXXIV) present, a ferric chloride colorimetric titration the sum of the  $\alpha$ -ester (XXXV) and the  $\alpha_2, \beta$ -ester (XXXVI), and ozonization the total enolic content. The combination of the three determinations made possible a quantitative estimation of the relative amounts of the three enols.



XXXIV

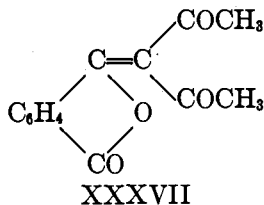


XXXV

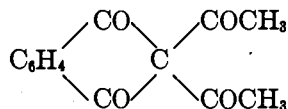


XXXVI

The problem of which structural isomer best represented the constitution of phthalylmalonic ester and similar compounds was solved by Scheiber and Hopfer (133) by the use of ozone. In the case of phthalylacetylacetone, structure XXXIX was shown to be correct, rather than XXXVII or XXXVIII, by the isolation of phthalic acid, methylglyoxal, and acetic acid as products from the decomposition of the ozonide.

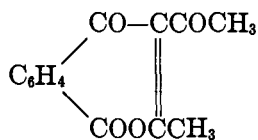


XXXVII



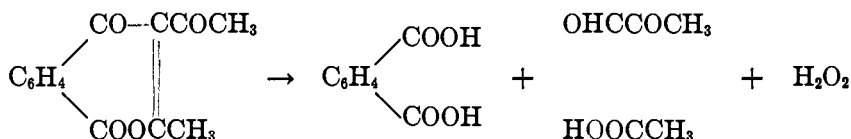
XXXVIII





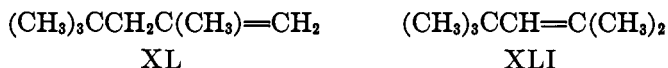
XXXIX

Phthalylacetylacetone



An interesting use of ozone was in the clarification of the constitution of the keto chlorides by Straus (146) in 1912. By the application of this reagent it was possible to prove the structure of a whole series of these compounds. Cinnamyl chloride, one of the simplest examples, reacted with ozone and yielded benzaldehyde, benzoic acid, dichloroacetaldehyde, and dichloroacetic acid, after decomposition with water. As a result its constitution was proved to be  $\text{C}_6\text{H}_5\text{CH}=\text{CHCHCl}_2$ .

A more recent example of ozonolysis has been the proof of the structure of the two isomeric diisobutylenes discovered by Butlerow. McCubbin and Adkins (107) established definitely the presence of the two isomeric octylenes, 2,4,4-trimethyl-1-pentene (XL) and 2,4,4-trimethyl-2-pentene (XLI), by the isolation of methylneopentyl ketone,  $(\text{CH}_3)_3\text{CCH}_2\text{COOCH}_3$ , and trimethylacetaldehyde.

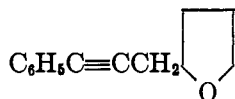


Their experiments indicated XL and XLI to be present in a ratio of approximately 4:1. Whitmore and Church (152) separated the low-boiling isomer from the higher boiling isomer by fractional distillation, and identified the low-boiling isomer with XL and the high-boiling component with XLI by the separate ozonization of each.

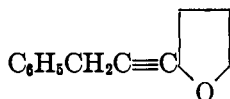
Ozonolysis as an indirect method of analysis has been exemplified in a series of papers published by Whitmore (30, 153, 154) in 1933 and 1934, dealing with the ozonization of purely aliphatic olefins. A variety of tertiary alcohols composed of different combinations of alkyl groups from methyl to *n*-amyl, and also 2,2-dimethyl-1-hexanol, containing a neo carbon atom, were converted into the chlorides, and hydrogen chloride was removed. The resultant olefins were then ozonized. The results were markedly successful, in that the decomposition products were isolated in good yields and served to indicate unequivocally the direction of the dehydration.

In the aromatic series, the importance of the structural proof offered by the use of ozone has been out of proportion to the few experiments reported. Harries' (73) ozonization of benzene and mesitylene offered proof for the Kekulé structure with three alternating double bonds, and Levine's (103) results with *o*-xylene strengthened the early evidence. In the case of the polynuclear aromatic compounds, the isolation of phthalaldehyde from the ozonide of naphthalene (52) located the position of two double bonds, and Vollman's (150) recent experiments with pyrene have established the position of one double bond of this high-molecular-weight hydrocarbon and confirmed the bond structure previously assigned to it.

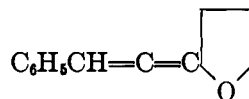
The use of ozone for the elucidation of acetylenic structure has been even less extensive than its application to aromatic compounds, and the available examples are of recent date. By the isolation of phenylacetic acid as a product of the ozonolysis of Carlina-oxide (an oil obtained from the roots of *Carlina acaulis*), Gilman (48) was able to rule out formulas XLII and XLIV, leaving XLIII, benzyl-2-furylacetylene, as the structure of the compound.



XLII

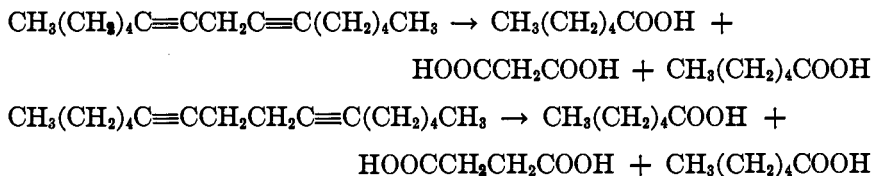


XLIII



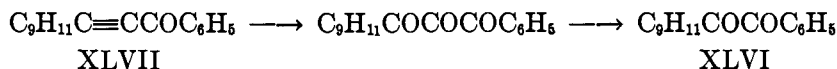
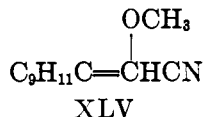
XLIV

Lai (100) has synthesized a series of  $\beta$ - and  $\gamma$ -diacetylenic compounds, and by ozonization has proved their structure. In the case of the  $\beta$ -diacetylenic compounds, diheptynymethane was ozonized and malonic and caproic acids were isolated as decomposition products, whereas succinic and caproic acids were isolated from the decomposition of the ozonide of diheptynylethane, a  $\gamma$ -acetylenic compound.



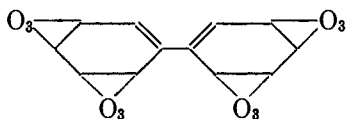
It was by ozonization of the unknown compound obtained by treating the enol methyl ether (XLV) of 2,4,6-trimethylbenzoylacetone (45) with phenylmagnesium bromide that the first insight into its correct structure was obtained. The isolation of isodurylic acid, benzoic acid, and a small amount of mesityl phenyl diketone (XLVI) suggested that the unknown ketone might be benzoylmesitylacetylene (XLVII), which was later proved by synthesis to be correct. Mesityl phenyl triketone would be

expected as a product of the action of ozone, and the diketone was known to be a product of the decomposition of the triketone (46).

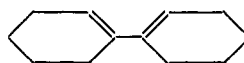


The solution of the problem of the stereochemical configuration of various compounds has been aided by ozonolysis in certain cases. The geometric isomerism of oleic and elaidic acids was proven by Harries (72) by the quantitative identity of the products obtained on ozonization. In the same way, the stereoisomerism of erucic and brassidic acids, fumaric and maleic acids (61), and crotonic and isocrotonic acids (52) was shown to be correct.

Although benzene had been observed to form a triozone, in accordance with the Kekulé formula, biphenyl formed only a tetraozonide. Harries (52) suggested that the tetraozonide had formula XLVIII and that the non-addition of ozone to the double bonds in the 1- and 1'-positions was due to steric hindrance.



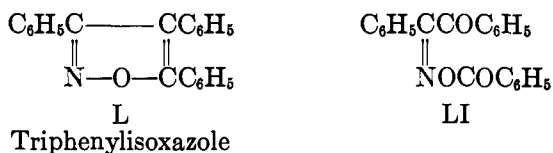
XLVIII

XLIX  
1,1'-Bicyclohexenyl

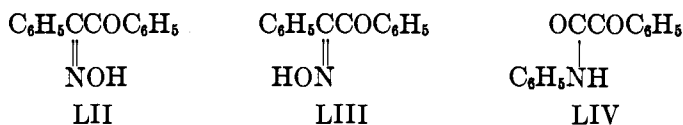
Because of the difficulty of preparing the ozonide, the products formed on decomposition with water have not been identified. Noller (116) suggested that it should be possible to determine whether steric hindrance plays a rôle by studying compounds such as 1-phenyl-1-cyclohexene and 1,1'-bicyclohexenyl (XLIX) in which non-benzenoid double bonds occur in positions similar to those which are supposed to be sterically hindered in biphenyl. On ozonization, it was found that 1-phenyl-1-cyclohexene added 1 mole of ozone to the double bond in the cyclohexene ring and that 1,1'-bicyclohexenyl added ozone to both double bonds. This indicated that steric hindrance in the 1- and 1'-positions was not the factor involved in the failure of biphenyl to form a hexaozonide.

Until the discovery in 1921 of a method of determining the configuration of ketoximes which was entirely independent of the Beckmann rearrangement, the erroneous mechanism of Hantzsch (51) had been almost uni-

versally accepted. In a study of triphenylisoxazole (L) Meisenheimer (108) found that this compound furnished on ozonization the benzoate of a benzil monoxime. An examination of the formulas will show that if no shift in configuration has taken place after ring opening, this benzoate should have the configuration represented by formula LI. Two benzil monoximes were known, a high-melting or  $\alpha$ -oxime and a low-melting or

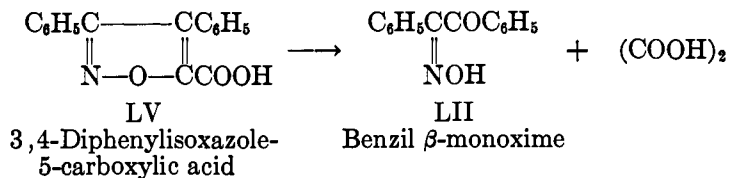


$\beta$ -oxime. Beckmann (9), from an examination of the products which these two oximes furnished on rearrangement, and assuming a *cis*-shift to have taken place on rearranging, had assigned to the  $\alpha$ -oxime the configuration LII and to the  $\beta$ -oxime the configuration LIII.



It is obvious from a comparison of formulas LI and LII that Meisenheimer's product from the ozonization of triphenylisoxazole should be the benzoate of the  $\alpha$ -monoxime. Actually, that product proved to be the benzoate of the  $\beta$ -monoxime. It followed therefore that the rearrangement involved not a *cis*- but a *trans*-shift.

The ozonization of 3,4-diphenylisoxazole-5-carboxylic acid (LV) by Kohler (96) was of particular importance, for the reaction did not furnish a derivative of a benzil monoxime, but yielded directly the  $\beta$ -monoxime of benzil (LII).

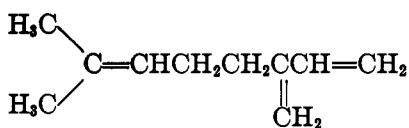


By confirming the configuration LII assigned to the  $\beta$ -monoxime of benzil by Meisenheimer, this work strengthened the conclusion that the rearrangement of this  $\beta$ -monoxime involved a *trans*-shift. A final confirmation of configuration LII for the  $\beta$ -monoxime of benzil was afforded by the ozonization of 3,4-diphenyl-5-*p*-bromophenylisoxazole, which furnished the *p*-bromobenzoate of  $\beta$ -benzil monoxime (97).

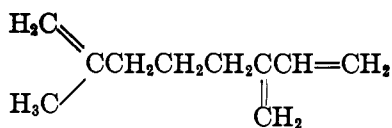
One of the earliest and most successful applications of the ozone method was the partial elucidation of the structure of rubber. Harries and his students (62) clarified its general structure by isolating levulinialdehyde and levulinic acid as the principal products of ozonization. This established the recurrence of an isoprene unit in the molecule and the position of the double bond adjacent to the methyl group. Since no other products were identified, Harries favored a ring structure made up of recurrent isoprene units and discounted Weber's open-chain formula, as such a compound would have to yield other additional decomposition products. In 1931, Pummerer (120) repeated Harries' ozonization experiments on a quantitative basis and isolated levulinic products in an amount equal to 90 per cent of the theoretical. In addition, by more refined methods, it was possible to detect acetic acid in an amount equivalent to at least 2 per cent of the carbon skeleton. A small amount of pyruvic acid was also detected. As a result, although the ends of a chain cannot be identified, a chain structure cannot be excluded from among the possible formulas.

Probably the most numerous examples of the use of ozone for structural proof may be found in the field of terpene chemistry. One of the most obvious points of attack of these complicated substances is the carbon-to-carbon double bond, when present, and its location, as well as the constitution of adjoining structures in many cases, has been demonstrated clearly by the isolation and identification of the ozonide decomposition products. All of the investigators in this field, including Harries, Semmler, Wallach, Ruzicka, Simonsen, and many others, have utilized the reaction in various instances, of which only a few examples will be considered here.

A correlation of the results of several investigators led Semmler (137), in 1901, to suggest that myrcene, one of the simpler terpene hydrocarbons, was represented by either formula LVI or LVII.



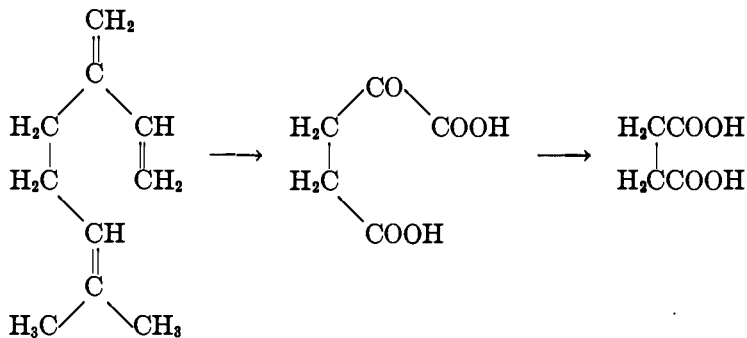
LVI  
Myrcene



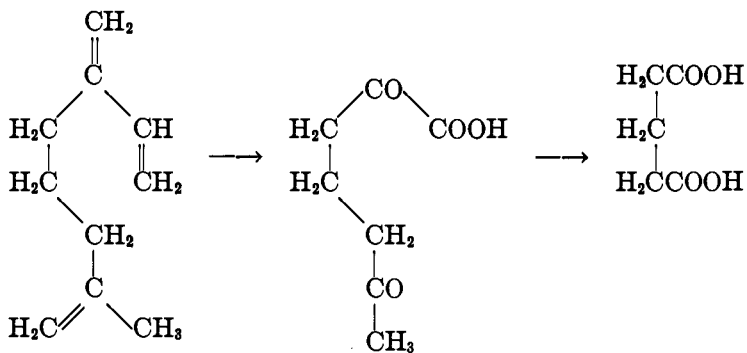
LVII

Recently Ruzicka and Stoll (130) showed conclusively that formula LVI correctly represents myrcene. The hydrocarbon was subjected to oxidation with ozone, and, after decomposition of the ozonide, followed by treatment with chromic acid and sodium hypobromite, succinic acid was obtained as the sole product of the reactions. If the hydrocarbon had

formula LVII, the formation of glutaric acid would have been anticipated, as indicated in the schematic representation given below:

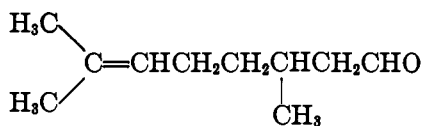


LVI

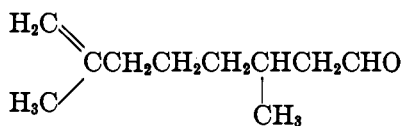


LVII

An interesting case of ozonization was the elaborate application of the reaction to the proof of structure of citronellal by Harries and his collaborators (63). Earlier work had indicated that this compound was a mixture of the aldehydes represented by formulas LVIII and LIX.



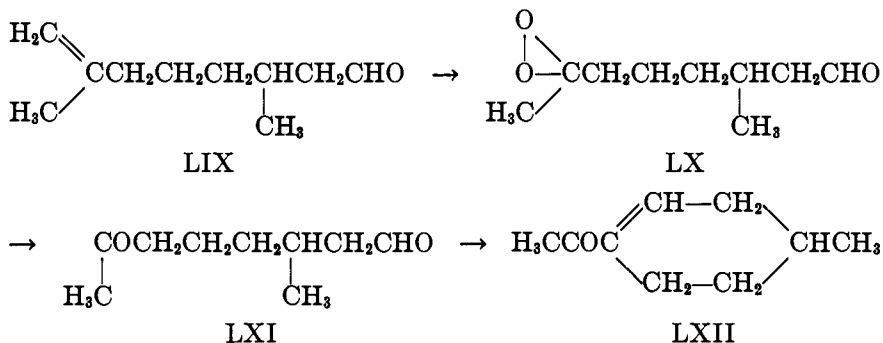
LVIII



LIX

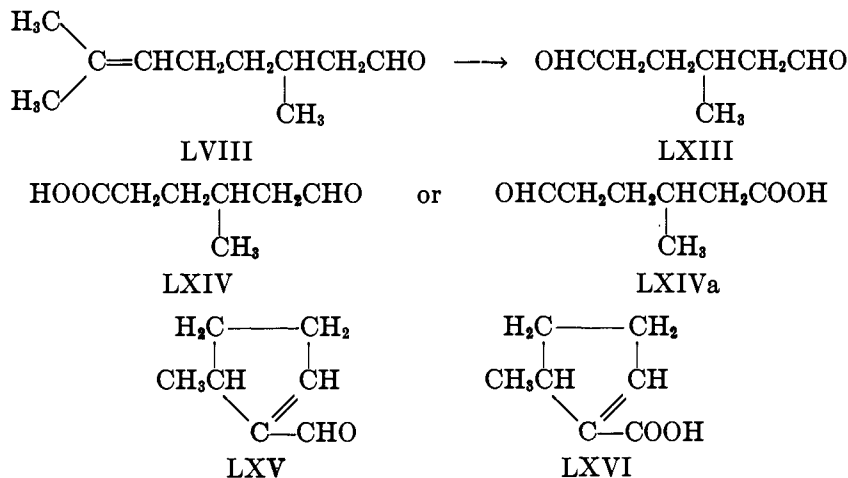
Harries, in collaboration with Wagner and Comberg, completely confirmed the view that citronellal was a mixture. From citronellal dimethyl acetal were obtained formic acid, acetone, the peroxide of methylactonal (LX), the cyclic ketone LXII, the semialdehyde of  $\beta$ -methyladipic acid

(LXIV or LXIVa), 5-methyl- $\Delta^1$ -cyclopentene-1-al (LXV), and 5-methyl- $\Delta^1$ -cyclopentene-1-carboxylic acid (LXVI). The separation of the per-

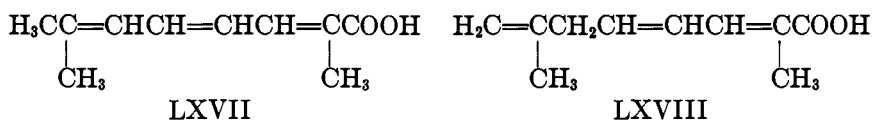


oxide LX established the presence of the aldehyde of formula LIX in the mixture. When this was decomposed by alkali the primary product, LXI, could not be isolated, since it passed immediately into the cyclic ketone LXII, a substance which had been described previously by Wallach and Evans (151).

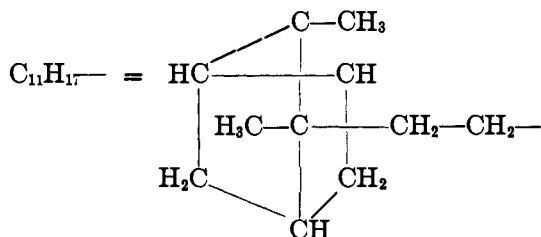
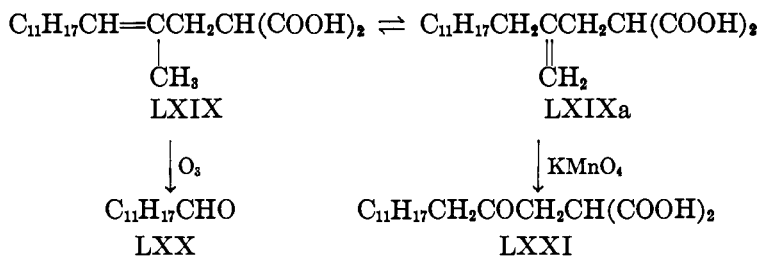
The other oxidation products were derived from the aldehyde of formula LVIII. The cyclopentenaldehyde (LXV) and acid (LXVI) were formed by the internal condensation of the primary oxidation product LXIII, the aldehyde LXV having been oxidized to the acid LXVI, while the di-aldehyde LXIII also formed the half-aldehyde of  $\beta$ -methyladipic acid (LXIV or LXIVa). The yields of the various oxidation products showed the aldehyde to consist approximately of 60 per cent of LVIII and 40 per cent of LIX.



Since the completion of these experiments, there has been much discussion as to the correct formulation of simple terpene derivatives like geraniol, citral, etc.: namely, as to whether an isopropenyl or an isopropylidene group should be placed at the end of the chain. The majority of these substances have been oils, and it has been generally held that inseparable mixtures of substances containing these two groups were present. R. Kuhn and Roth (99), in 1932, estimated quantitatively on a micro scale the acetone formed in the ozonization of a number of substances containing the isopropylidene group, and found it to vary from 60 to 90 per cent of the theoretical value. In particular, the crystalline acid dehydrogeranic acid (LXVII or LXVIII) was studied, and here, in agreement with earlier observations (29), both acetone and formaldehyde were obtained, the yield of acetone amounting to 60 per cent of the theoretical value.



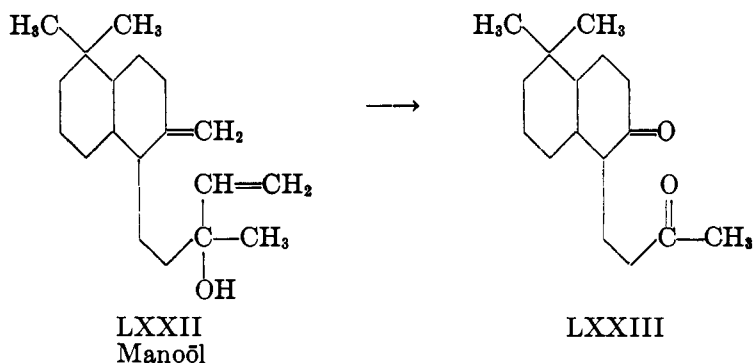
On the basis of comparisons of absorption spectra, Kuhn and Roth concluded that the acid was homogeneous and was represented by formula LXVII, but that the ozonization proceeded abnormally. According to Simonsen (138), a more satisfactory explanation has been provided by recent observations on the oxidation of  $\alpha$ -santalylmalonic acid. When this acid, which is crystalline and readily purified, was ozonized, it yielded practically quantitatively tricycloekasantalal (LXX) or the corresponding acid. On the other hand, in alkaline solution, oxidation with potassium permanganate yielded the keto acid LXXI. To explain these results it was assumed that  $\alpha$ -santalylmalonic acid exists in the tautomeric forms LXIX and LXIXa.



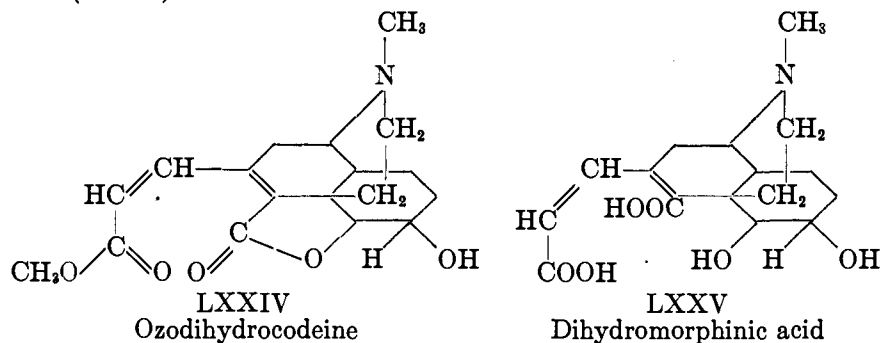


These represent the isopropenyl and isopropylidene forms of the acid, and tautomerism of this nature can provide an adequate explanation of Kuhn and Roth's results with dehydrogeranic acid. Simonsen considered it very probable that a similar tautomerism occurs also in the cases of geraniol, citral, etc.

Of the recent work with terpenes, the ozonization (77) of manoöl (LXXII) may be mentioned briefly. This is a diterpene alcohol excreted from the wood of *Dacrydium biforme*. Its structure was elucidated through characterization of the 1,5-diketone (LXXIII), isolated in about 50 per cent yield from decomposition of the diozonide.

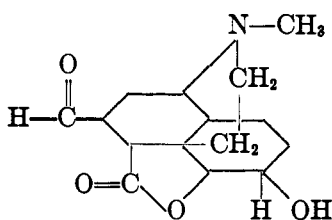


In the last fifteen years the application of the ozone degradation to various alkaloids has been improved, and in certain instances has yielded important results. By treatment of dihydrocodeine in formic acid solution with ozone, Speyer and Popp (140) obtained ozodihydrocodeine, which apparently resulted from scission of the 3,4-double linkage of the aromatic nucleus of dihydrocodeine. Ozodihydrocodeine contained two oxygen atoms more than the starting material, had neither aldehyde nor ketone properties, and was not phenolic. On the theory that the aromatic nucleus had been attacked, the substance was given formula LXXIV, which accounted well for its chemical behavior. By saponification, ozodihydrocodeine was converted to a dibasic acid, dihydromorphinic acid (LXXV).



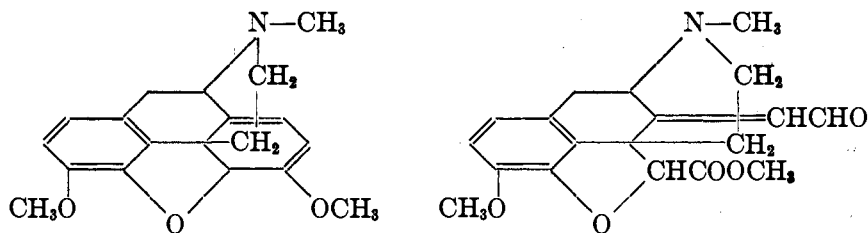
Additional evidence for the opening of the aromatic nucleus in this ozonization was found in the products from the treatment of dihydroethylmorphine with ozone; a homolog of ozodihydrocodeine, ozodihydroethylmorphine, was obtained (formula LXXIV, with  $\text{COOC}_2\text{H}_5$  in place of  $\text{COOCH}_3$ ), which yielded the same dihydromorphinic acid (LXXV) on saponification. This degradation differed from previous reactions in that the original position of the nitrogen ring was undisturbed.

In a later paper, Speyer (141) showed that ozonolysis of the lactone-ester LXXIV removed three carbon atoms as glyoxylic acid ester to form codinal (LXXVI), which was identical with the end product obtained in the ozonization of morphine.



LXXVI  
Codinal

In the case of thebaine, Wieland and Small (155) have brought to a successful conclusion the ozonolysis experiments begun by Pschorr and Einbeck in 1907 (119), to show that ozonization of thebaine results in the rupture of the 6,7-double bond, yielding the methyl ester of an acid containing an aldehyde group.

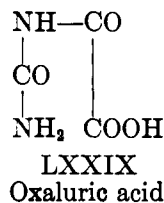
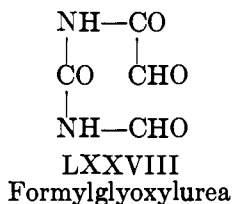
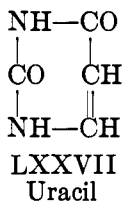


Thebaine

$\alpha$ -Thebaizone

In 1931, Johnson and Flint (85), for the first time, investigated the behavior of pyrimidines toward ozone. It was found that uracil (LXXVII) and ozone interacted in glacial acetic acid at ordinary temperature to

form chiefly formylglyoxylurea (LXXVIII) and oxaluric acid (LXXIX). In addition, part of the uracil molecule was completely broken down with formation of urea, oxalic acid, and formic acid. Formylglyoxylurea was the first member of its type to be described.



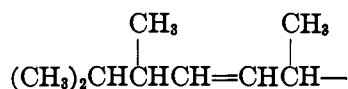
In a second paper (86), the behavior of derivatives of uracil, including the 4-methyl-, 4-phenyl-5-bromo-, 5-nitro-, and 1,3-dimethyl-5-bromo-uracils and thymine, toward ozone was investigated with similar results. The authors stated: "The application of ozonization makes possible an improved technique for determining the structure of uracil compounds. The advantages gained experimentally become apparent when one is called upon to separate and identify the products of ozonization."

In the field of the azulenes, the blue substances which are constituents of certain essential oils, frequent applications of ozonolysis (4, 13, 109, 129) have been reported in attempts to prove the structure of these compounds. Experiments with the original substances and with partially hydrogenated compounds have been conducted. The products isolated and identified included formaldehyde, acetone, formic, acetic, oxalic, isobutyric, and  $\alpha$ -methylglutaric acids. From these results it became evident (147) that further investigation of azulenes by oxidative degradation was unpromising, since only small fragments would be obtained, from which inferences could not be drawn concerning the original compounds. It is of interest that in this instance, as previously described, ozone proved to be of great value in synthesis, but of little use in degradation.

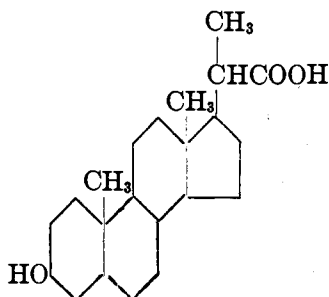
In the chemistry of the sterols, the early usage of ozone was fraught with difficulties, and led only to anomalous results. A number of papers were published (33, 34, 59) reporting the formation of an ozonide of cholesterol with a composition corresponding to the addition of about 2 moles of ozone, but no product could be identified on decomposition. The second mole of ozone added appears to have been due to a dehydration of the molecule during the initial action of ozone on the double bond, followed by addition of ozone to the bond so formed. The method was therefore abandoned in this connection. Recently, however, several important

discoveries have been made by the ozonolysis of ergosterol and related compounds.

In 1932, Reindel and Kipphan (123) identified the aldehyde previously obtained (124) from the ozonide of ergosterol as methylisopropylacetaldehyde, a previously unexpected development, and the same aldehyde was also obtained from ergosterols B<sub>1</sub> and B<sub>2</sub>, lumisterol, calciferol, and suprasterols I and II (50). All of these compounds therefore contained the same side chain,—



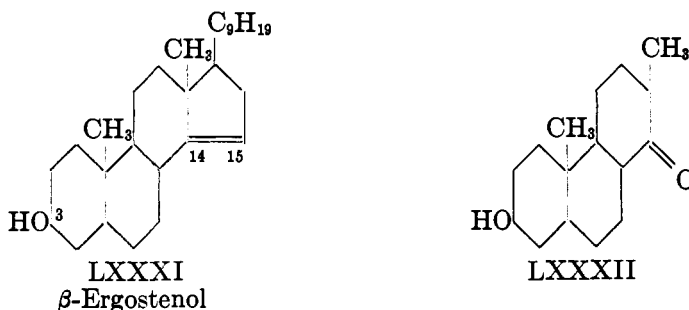
This was also found to be present in the maleic anhydride addition products of ergosterol, dihydroergosterol, and tachysterol, showing that the conjugated double bonds in these compounds were independent of the double bond between C<sub>22</sub> and C<sub>23</sub> in the side chain. Stigmasterol was later found to give ethylisopropylacetaldehyde on ozonization, in agreement with the formula C<sub>29</sub>H<sub>46</sub>O assigned to it (49). In further work on stigmasterol, Fernholz (38) found that bromine could be added to the double bond situated in the nucleus, without affecting the one in the side chain. By ozonolysis of the acetate of this dibromide, a portion of the side chain was removed, and the product after debromination was reduced. Finally, hydrolysis yielded 3-hydroxybisanorallocholic acid (LXXX), which on removal of the hydroxyl group gave bisnorallocholic acid, a known compound. This sequence of operations proved that stigmasterol contained the same ring system as cholesterol and ergosterol.



LXXX

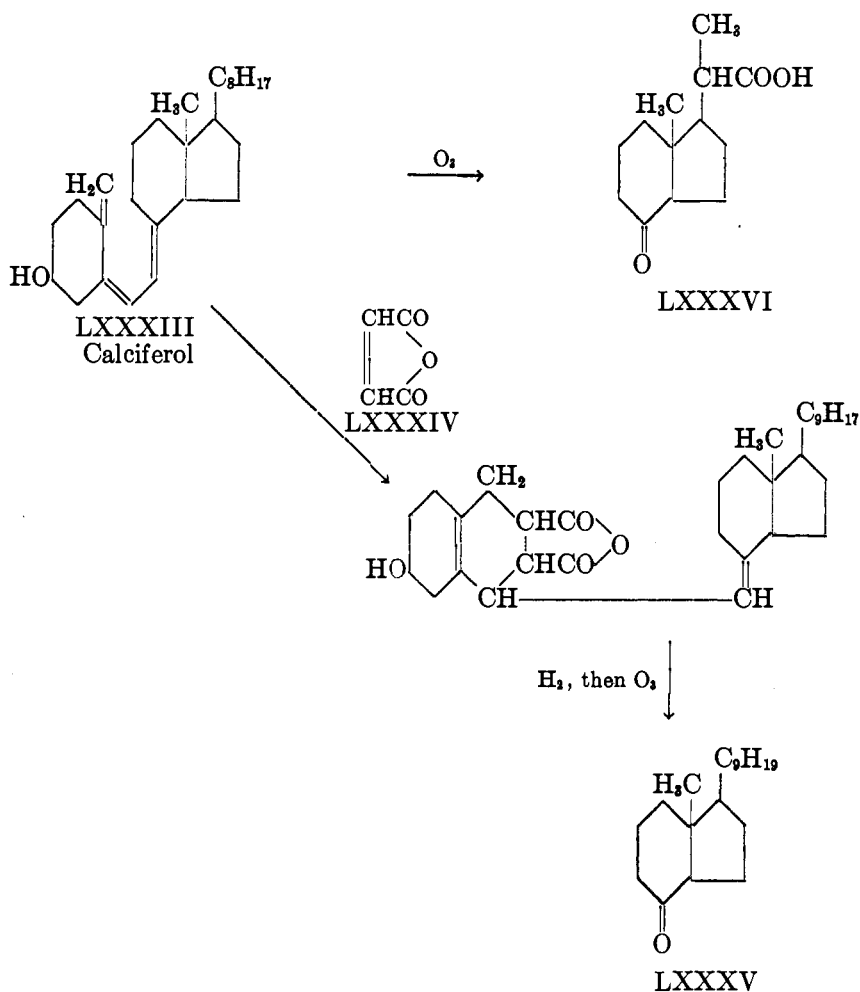
3-Hydroxybisanorallocholic acid

The exact position of the double bond in the nucleus of  $\beta$ -ergosterol (LXXXI) was proved by the use of ozone. Achtermann (2) ozonized the acetate, submitted the ozonide to reductive fission, followed by pyrolysis, and obtained a keto alcohol of the formula  $C_{16}H_{26}O_2$  (LXXXII). This substance was fully characterized in 1935 by Laucht (101), who converted it by dehydrogenation with selenium into 2-methylphenanthrene. The other fragment of the pyrolysis, an  $\alpha$ -unsaturated aldehyde,  $C_{12}H_{22}O$ , was isolated as the semicarbazone. These products could arise only from an initial ozonolysis between positions 14 and 15.



In connection with the important antirachitic substance, vitamin  $D_2$  or calciferol (LXXXIII), ozonolysis has also recently been of value. Windaus and Thiele (161) located the position of the double bonds in a series of experiments concerning the addition product of calciferol with maleic anhydride (LXXXIV). On ozonization of the dihydro derivative of the addition product there was obtained a saturated ketone which, from its composition ( $C_{19}H_{34}O$ , bicyclic), must have the structure shown in formula LXXXV. This observation established the presence of a double bond in the 7,8-position.

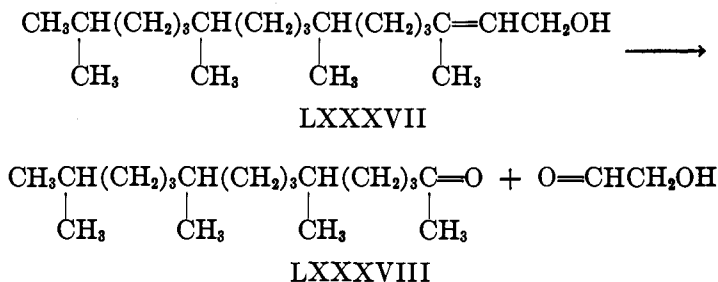
Further, Heilbron and his collaborators (74) ozonized vitamin  $D_2$  and isolated as one product a keto acid,  $C_{13}H_{20}O_3$  (LXXXVI), which must have resulted from the fission of the molecule at the  $C_7, C_8$ - and the  $C_{22}, C_{23}$ -ethylenic linkages.



As a second product of ozonolysis, formaldehyde was isolated and characterized as the dimedon derivative. This established the presence of an exocyclic methylene group, as postulated by Windaus and Thiele (161), and removed any uncertainty in the evidence adduced by these investigators arising from the possibility of a rearrangement in the course of the Diels-Alder condensation. Windaus and Grundmann (159) confirmed these observations, and also obtained about 30 per cent of the calculated amount of formaldehyde, using ozone. Since ergosterol under similar conditions gave a few per cent of formic acid and a trace of formaldehyde,

even though it contains no methylene group, Windaus regarded the isolation of the other oxidation products as providing the most reliable indication of the structure.

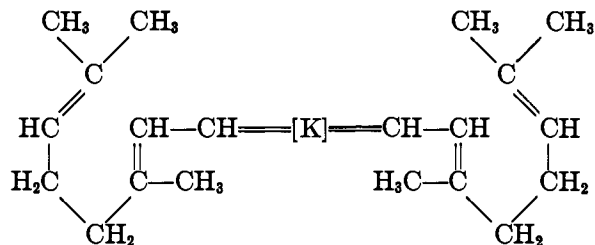
By the application of the ozone method Fischer and Löwenberg were able to deduce the structure of phytol, the alcoholic component of chlorophyll, and later proved the structure by synthesis. Willstätter and coworkers in 1911 (158) had obtained by oxidation of phytol a ketone which was considered to be  $C_{17}H_{34}O$ . Fischer and Löwenberg (40) reduced the ozonide of phytol, a  $C_{20}$  compound, using hydrogen and palladium-calcium carbonate as catalyst, and obtained glycolaldehyde and this same ketone, which must therefore be  $C_{18}H_{36}O$ . It was next assumed that phytol was built up of reduced isoprene units, and that its constitution might be 3,7,11,15-tetramethyl- $\Delta^2$ -hexadecen-1-ol (LXXXVII). This would give on hydrolysis of the ozonide a ketone, 6,10,14-trimethylpentadecan-2-one (LXXXVIII). The latter substance was synthesized from farnesol, and was found to be identical with the ketone derived from phytol. The constitution of phytol thus established was later confirmed by synthesis (44).



The presence of the large number of double bonds characteristic of the carotenoids renders the latter open to attack by ozone at all these points, and decomposition of the ozonides so formed has resulted in a great variety of products. The determination of terminal groups has been the chief service of ozonolysis in this field.

Karrer and Bachmann (88) reported that ozonization of lycopene produced a large amount of acetaldehyde and acetic acid, and further the particularly important product, acetone. The isolation of the latter substance in an amount equal to 80 per cent of that calculated for two isopropylidene groups indicated that both ends of the molecule consisted of these groups, since neither geronic or isogeronic acid could be found. In addition, Strain (145) confirmed the earlier qualitative observation of

Karrer, by isolating from 0.90 to 1.32 moles of levulinic acid per mole of lycopene ozonized. These results substantiated the formula (LXXXIX) suggested for lycopene by Karrer and Bachmann.



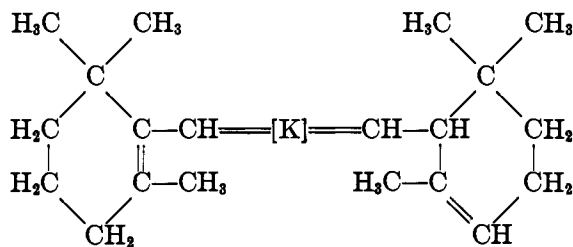
LXXXIX

Lycopene

([K] = chain of four isoprene units)

Thus, lycopene is entirely acyclic,  $\gamma$ -carotene is acyclic at only one end, and  $\alpha$ - and  $\beta$ -carotenes are cyclic at both ends.

The constitution of  $\alpha$ -carotene was proved conclusively in 1933 by the ozonolysis experiments of Karrer and coworkers (92), who isolated geronic acid and isogeronic acid by ozonization of pure  $\alpha$ -carotene. Therefore the correct formula must be



XC

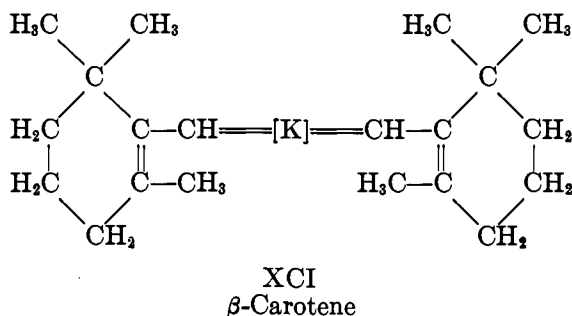
 $\alpha$ -Carotene

This proof of the structure of  $\alpha$ -carotene was of fundamental importance, since the simultaneous appearance of geronic and isogeronic acids as decomposition products proved the presence of two ionone carbon-ring systems in the carotenoids.

The ozonolysis of  $\beta$ -carotene (89) yielded much the same larger cleavage fragments as  $\beta$ -ionone. The observation that one molecule of  $\beta$ -carotene yielded two of geronic acid, whereas  $\beta$ -ionone gave only one (121), showed that  $\beta$ -carotene must contain two such ionone cycles. In addition, the



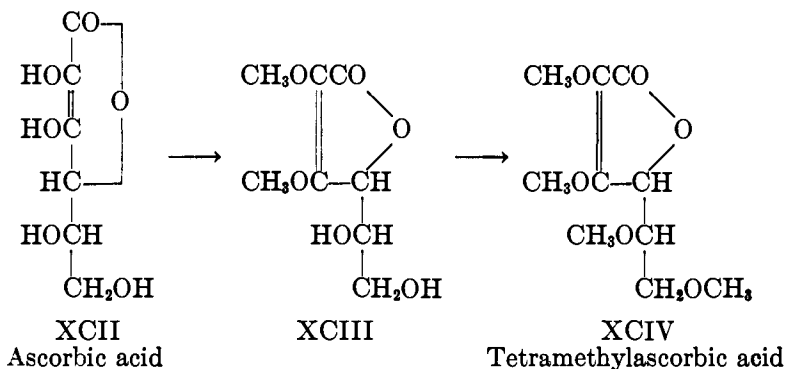
isolation of glyoxal strengthened the evidence in support of Karrer's formula (XCI).

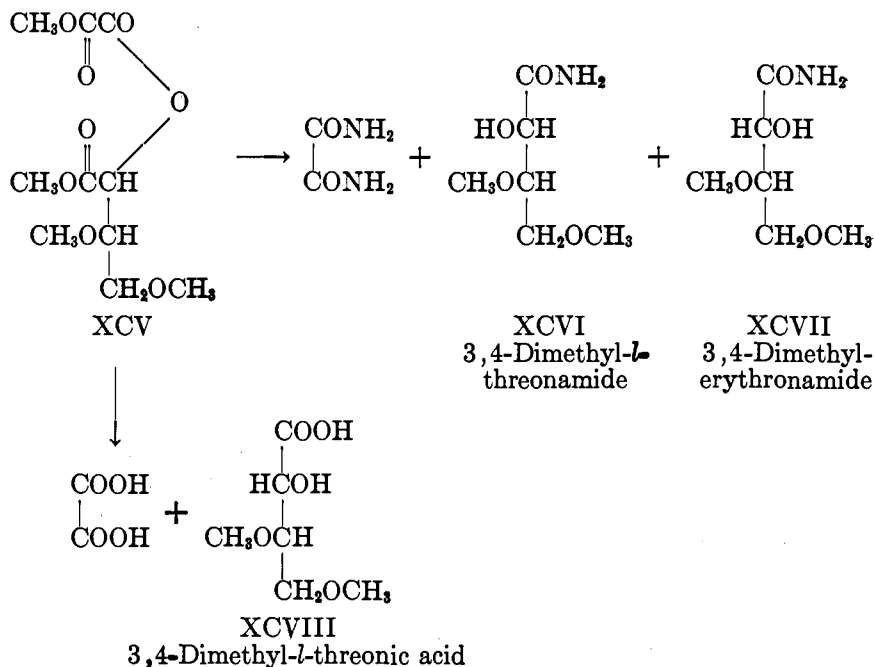


Another important result of ozonolysis in this field was its application to vitamin A. The first light on the structure of this substance was the formation of geronic acid from it on ozonization (90), which indicated that it contained an unsubstituted  $\beta$ -ionone cycle.

The rapid solution of the ascorbic acid (vitamin C) problem has been one of the major achievements in the field of sugar chemistry, and in it ozonolysis has played its part by contributing a direct proof of the ring structure of the compound.

By the action of diazomethane on ascorbic acid (XCII), a dimethyl derivative (XCIII) was readily obtained (92, 112). Hirst and collaborators (76) found that both the methoxyl groups so introduced were enolic in origin. In addition, there were two other hydroxyl groups which could be methylated by Purdie's reagents, silver oxide and methyl iodide, giving tetramethylascorbic acid (XCIV). This substance reacted easily with ozone (76), two atoms

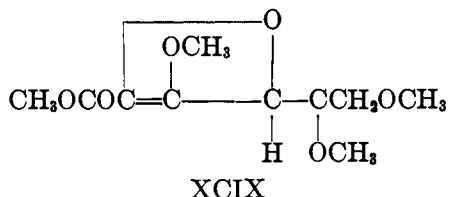




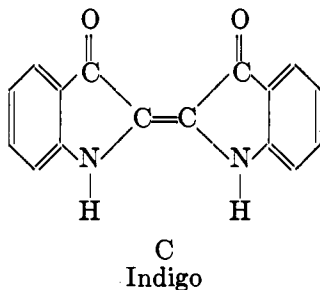
of oxygen being added with formation of a neutral product, XCV, which was identified as methyl-3,4-dimethyl-*l*-threonate substituted in position 2 by a methyl oxalate residue. This reaction proceeded similarly to the ozonization of di-(*p*-nitrobenzoyl)dimethylascorbic acid studied by Micheel and Kraft (112). On treatment with methyl alcoholic ammonia the neutral ester XCV gave immediately oxamide and 3,4-dimethyl-*l*-threonamide (XCVI), together with a small quantity of the epimeric 3,4-dimethylerythronamide (XCVII). Hydrolysis of XCV with barium hydroxide gave barium oxalate and the barium salt of 3,4-dimethyl-*l*-threonic acid (XCVIII), again admixed with a small amount of 3,4-dimethyl-*l*-erythronic acid.

The reaction between tetramethylascorbic acid (XCIV) and ozone involved the addition of two oxygen atoms with formation of a neutral ester (XCV), and the breaking of the bond between the two carbon atoms which were united by a double linkage, but did not result in the formation of a substance containing a smaller number of carbon atoms. It followed, therefore, that a ring system was present in tetramethylascorbic acid and the nature of the reaction left open only two possibilities for the structure of XCIV, for which the alternative was as shown in formula XCIX, which contains a propylene oxide ring. The latter was inherently improbable,

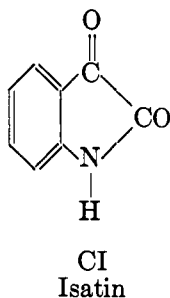
owing to the strained nature of the ring and the properties of dimethyl-ascorbic acid.



Although indigo is one of the oldest known and most widely used organic compounds, the problem of its structure is still being investigated. The ozonization of indigo (C) reported in 1938 by van Alphen (3) gave, for the first time, a direct proof of von Baeyer's formula (7), advanced in 1883, which assumed that the two indole halves of the molecule are connected



by a double bond between two carbon atoms. Previously, no direct evidence for this double bond had been found. The common reagents, including bromine, chlorine, and hydrogen, are not added by it and, although two geometrical isomers should exist, only one form of indigo is known. The isolation of isatin (CI) on decomposition of the ozonide of



indigo with water has finally established the presence of an aliphatic double bond in the indigo structure.

#### X. THE LIMITS OF THE OZONE REACTION

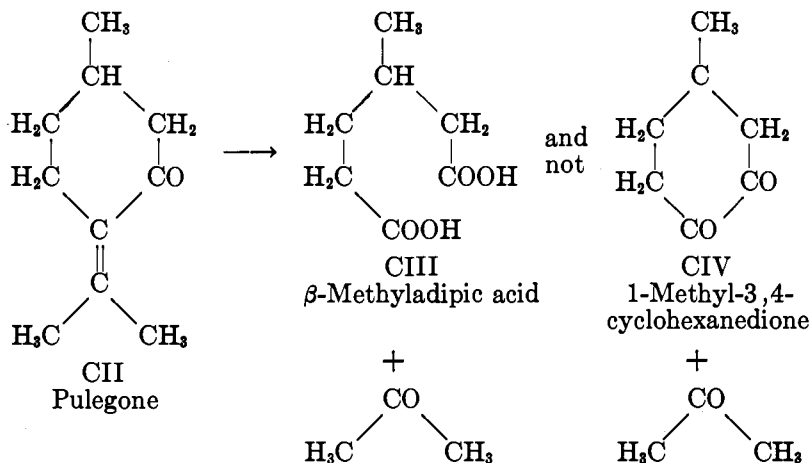
In the application of the ozonization method, there are certain limitations, based on past experience, which can be followed to advantage. Probably the most obvious disadvantage is the explosibility of certain ozonides, which may lead to the failure of an experiment. In almost every case, however, it is possible to avoid explosions either by exercising special precautions, such as working at low temperatures, or by carrying out the decomposition of the ozonide in solution.

There are, also, various structural configurations which have a marked effect on the course of the reaction. Ozone reacts more rapidly with isolated open-chain ethylenic linkages than with two or more conjugated double bonds or those present in aromatic ring systems, and it reacts more readily with a carbon-to-carbon than with a carbon-to-nitrogen double bond. Thus the ethylenic linkages in the side chain are attacked on ozonization of phenylated ethylenes, and the ozonization of triphenylisoxazole furnishes the benzoate of benzil monoxime. In general, however, the presence of a carbon-to-nitrogen double bond leads to complications which may render the results of ozonolysis inconclusive.

As regards the ozonization phase of the reaction, as distinguished from the decomposition of the ozonide, no general rules may be stated, since small changes in the structure of a molecule may require important modifications of procedure. In any case, nevertheless, over-ozonization is to be avoided. Ozone itself has seldom been observed to change the structure of a molecule, although, in one instance, Harries (70) reported the dehydration of a terpene alcohol with concentrated ozone, thereby obtaining a triozone instead of the expected diozone. The normal reaction ensued when weaker ozone was used.

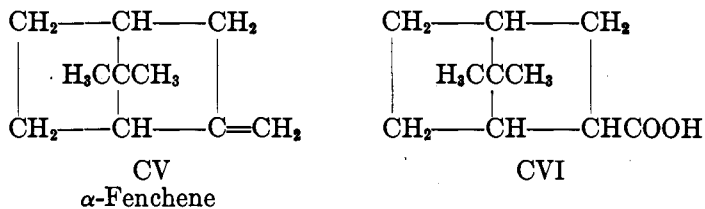
Difficulties in the interpretation of the reaction may arise, owing to interaction, oxidation, or further decomposition of the primary decomposition products. An example may be cited in the case of the azulenes, previously described, where the small size of the products identified made it impossible to deduce the original structure.

Unstable aldehydes may either polymerize or decompose at the temperature necessary for the decomposition. On this account, the half-aldehyde of malonic acid could not be identified by Harries and Fonrobert (68), but instead acetaldehyde and carbon dioxide were found. Similarly, in the ozonization of pulegone (113) (CII) it was not possible to identify 1-methyl-3,4-cyclohexanedione (CIV), since  $\beta$ -methyladipic acid (CIII) was formed immediately.



Fortunately it is often possible to prove the structure of the original compound from an identification of the secondary products formed, by a knowledge of the behavior of the primary products under similar experimental conditions.

One other unusual decomposition of an ozonide may be cited. Komppa and Roschier (98), in the ozonization of  $\alpha$ -fenchene (CV), obtained a monobasic saturated acid CVI of which the structure was proved by synthesis.



This represents the only case recorded in which the addition of ozone to a double bond has not resulted in fission of the molecule at this point.

Despite its limitations, the method has the decided advantage that it permits isolation of the primary cleavage products, for the excess oxidant, ozone, can be removed before the ozonide is cleaved. In oxidation with potassium permanganate and chromic acid the cleavage products are exposed to the action of the oxidant. In addition, no displacement of a double bond through addition of ozone and subsequent decomposition of the ozonide has ever been observed.

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