THE EFFECTS OF OZONE UPON A LIGNIN-RELATED MODEL COMPOUND CONTAINING A β-ARYL ETHER LINKAGE

A thesis submitted by

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SUMMARY

The ozonation of the lignin model compound, 1-(3,4-dimethoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propan-1-ol, in aqueous acetone at 25°C was investigated to determine the initial sites of attack. Mild conditions were employed to minimize the occurrence of secondary reactions that might otherwise hinder the identification of these initial sites of attack. The ozonation stoichiometry (moles of ozone consumed to moles of starting material consumed) was determined, and an extensive product analysis was conducted.

Prior to analysis, the ozonation products were usually separated into neutral-phenolic and acidic fractions and subsequently converted to the corresponding silyl derivatives. The consumption of ozone was determined via titrimetric methods while the amount of starting material consumed was determined via gas chromatography. Quantitative product analysis was conducted via gas chromatography and thermogravimetric analysis. Positive identification of the ozonation products was accomplished via gas chromatography-mass spectrometry and nuclear magnetic resonance spectrometry. The major products detected by gas chromatography were identified, and they accounted for about one-fourth of the starting material consumed. The product analysis indicated that there were at least four types of initial reactions occurring during the ozonation of the model compound.

Two of these initial reactions involved the ozone-induced cleavage of the β-aryl ether linkage and accounted for at least 20% of the starting material consumed. The identification of 2-methoxy-4-methylphenol as an ozonation product provided evidence for cleavage initiated on the aliphatic side of the β-aryl ether linkage while identification of 1-(3,4-dimethoxyphenyl)propan-1,2-diol provided evidence for cleavage initiated on the aryl side of the ether linkage. This is the first study to demonstrate ozone-induced cleavage of the β-aryl ether linkage.

The other two initial reactions involved ozonolysis (oxidative opening) of the two aromatic rings of the starting material. The identification of 4-carbomethoxymethylene-5,6-dihydroxy-2-heptenoic 1,5-lactone and 2,3-dihydroxybutyric acid as ozonation products provided evidence for ozonolysis of the 3,4-dimethoxyphenyl ring, initiated between the adjacent ring carbons bearing the methoxyl substituents. The identification of 1-(3,4-dimethoxyphenyl)-2-methyloxaloxypropan-1-ol provided evidence for ozonolysis of the 2-methoxy-4-methylphenoxy ring initiated at a site other than between the adjacent ring carbons bearing the alkoxyl substituents.

In addition to the major reaction products mentioned, many minor constituents, present in amounts too small to allow identification, were detected by gas chromatography. In all, the products detected by gas chromatography accounted for about 40% of the starting material consumed. Thermogravimetric analysis indicated the presence of nonvolatile reaction products equivalent to an additional 30-60% of the starting material consumed. Although these nonvolatile products were not identified, they are thought to be comprised of the higher molecular weight initial ozonation products and condensation products formed from both initial and secondary ozonation products. This conclusion was supported by the ozonation stoichiometry and a comparison of the ultraviolet spectra of ozonized and unozonized reaction solutions.

INTRODUCTION

Ozone was first proposed as a bleaching agent for wood in 1871 (1). However, the possible benefits of utilizing ozone in the pulp and paper industry have just begun to surface. Prompted by environmental factors, investigations into the use of ozone as a pulping and bleaching agent in the production of wood pulps have intensified (2-6) and have now reached pilot-plant proportions (7). In addition, recent reports indicate that ozone can be employed to improve the strength of mechanical pulps (8-13). However, the underlying chemistry involved with the ozonation of wood pulps is not yet fully understood.

Inasmuch as the pulping and subsequent bleaching of wood entails removal and/or modification of the wood lignin, the investigation of ozone-lignin reactions could provide information useful in deducing the chemistry connected with the ozone treatment of wood pulps. While the complex chemical composition of lignin renders such an investigation rather difficult, some insight into the possible mechanisms associated with the ozonation of lignin may be gained from model compound studies. Thus this thesis was undertaken to investigate the fundamental chemistry involved during the ozonation of a lignin-related model compound containing a β-aryl ether linkage.

GENERAL CONSIDERATIONS

Ozone is a nonlinear triatomic molecule possessing two interoxygen bonds of equal length (1.278 A) and an average bond angle of 116°49' (14,15). Ozone can be depicted as a resonance hybrid of structures I-IV (Fig. 1). Structures III and IV allow ozone to be classified as a 1,3-dipolar compound (15,16) and, as a result, ozone is capable of following reaction routes characteristic of 1,3-dipolar compounds, a phenomenon that has been incorporated into proposed ozonation mechanisms (17-21).

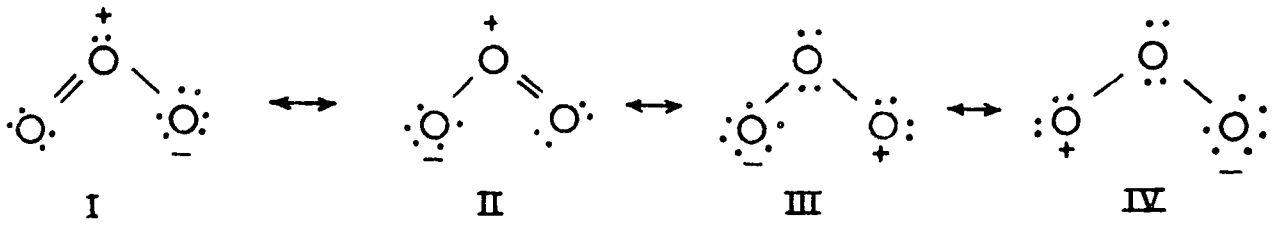


Figure 1. Resonance Structures of Ozone (15,16)

Ozone is among the most powerful oxidizing agents known and is capable of reacting with most organic compounds (16). Thus ozone will react with most of the commonly used organic solvents (16,22). Greenwood (22) studied the reaction between ozone and various common solvents and found ethyl chloride and acetic acid to be the most resistant to ozone attack, while methanol and ethanol demonstrated the least resistance (Table I). Ozone can decompose in water *via* a free radical mechanism thought to involve the formation of the hydroxyl radical as an unstable intermediate (16). This aqueous decomposition can be fairly rapid in alkaline solutions but is substantially slower under acidic conditions (16), and is virtually nonexistent in distilled water (Table I).

TABLE I

THE REACTIVITY OF VARIOUS PURE SOLVENTS TO OZONE (22)

Solvent	% Unreacted Ozone Passing Through Solvent
CH_2Cl_2	96
$CHCl_3$	96
CCl_4	95
C_2H_5Cl	100
$n\text{-}C_5H_{12}$	71
CH_3COOH	98
$CH_3COOC_2H_5$	85
CH_3OH	27
C_2H_5OH	38
H_2O	99

OZONE REACTIONS WITH SIMPLE ORGANIC COMPOUNDS

OZONE REACTIONS WITH OLEFINS

Oxidative cleavage of carbon-carbon double bonds (ozonolysis) is an important ozone reaction and may be of significance during the course of ozone-lignin reactions (16-20). Some form of the syn-anti zwitterion mechanism (18,23) — which is actually a modification of the Criegee mechanism (17) to account for the stereoselectivity displayed during ozonolysis — is the most widely accepted explanation for the ozonolysis of olefins (24).

According to this mechanism (Fig. 2), ozone reacts with a carbon-carbon double bond via a 1,3-dipolar cycloaddition to form the 1,2,3-trioxolane intermediate, V. Next, decomposition of V via a 1,3-dipolar cycloreversion yields the syn and anti isomers of zwitterion, VI, and a carbonyl compound, VII. [Recent reports indicate that the syn and anti isomers of VI may be in equilibrium, thereby providing an additional factor influencing the stereochemistry of olefin ozonolysis (24,25).] One of three routes may then be followed depending upon the reaction conditions:

Route 1 — A "final" ozonide, VIII, can be produced by another 1,3-dipolar cycloaddition in which VI and VII recombine. Although this step has previously been assumed to be concerted, a recent study suggests that under certain conditions formation of VIII may be nonconcerted (26).

Route 2 — Zwitterion, VI, may react with a "participating solvent" to form a hydroperoxide intermediate, IX. This appears to be the dominant route when employing protic solvents (16,27).

Route 3 — Dimerization and polymerization of VI may occur to form diperoxides, X, and polymeric peroxides. This pathway is most probable in nonprotic solvents when VII is a ketone.

Intermediates VIII-X may subsequently decompose to form more stable oxidation products such as acids, esters, aldehydes, and ketones.

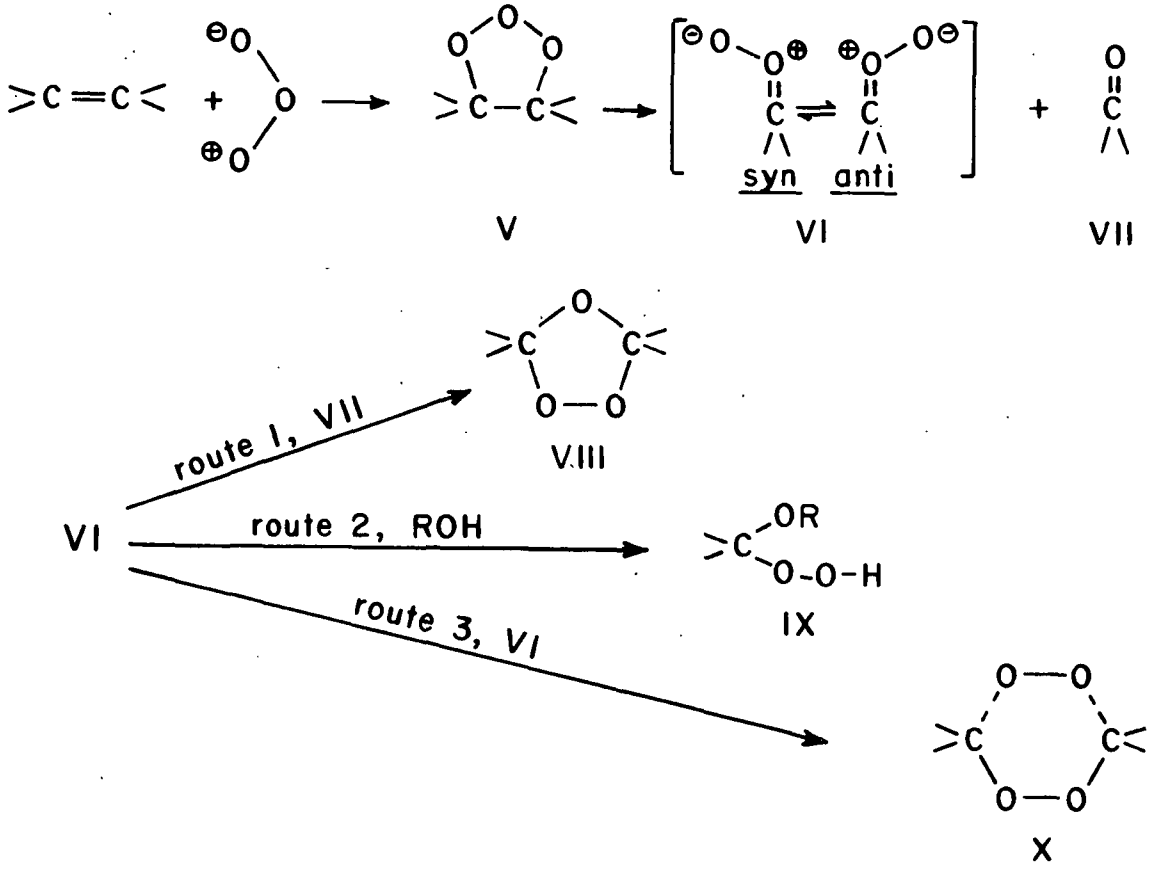


Figure 2. Probable Mechanism for Olefin Ozonolysis (18,23,27)

OZONE REACTIONS WITH SIMPLE AROMATIC SUBSTRATES

Ozone will also cleave the carbon-carbon bonds of aromatic rings but usually at a slower rate than observed for olefinic substrates (20,28), and although less is known about such reactions, the current consensus is that aromatic ozonolysis proceeds via a 1,3-dipolar cycloaddition mechanism (Fig. 3) similar to that proposed for olefinic ozonolysis (16,20,28).

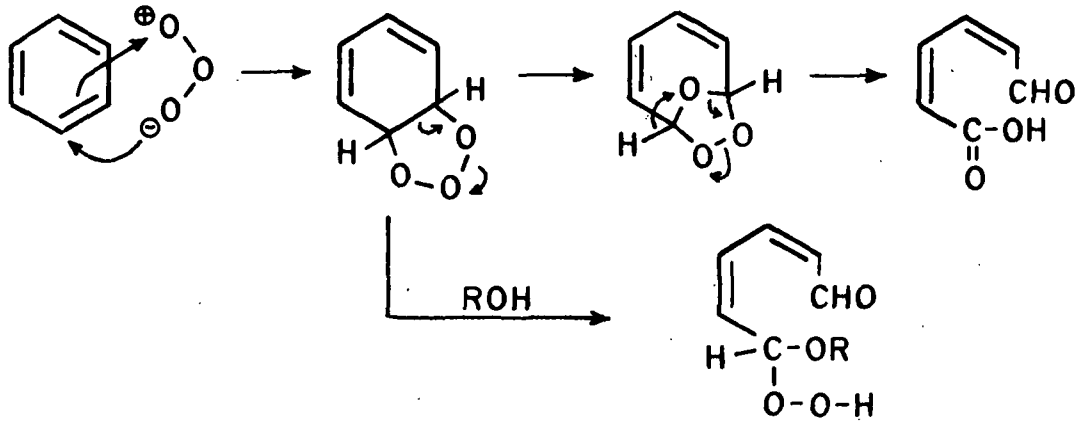


Figure 3. Probable Mechanism for Aromatic Ozonolysis (20,28)

Studies indicate that electron releasing substituents tend to promote aromatic ozonolysis, while the converse is true for electron — withdrawing groups (16,28). Thus it is not surprising that phenolic substrates have been observed to be significantly more susceptible to ozone attack than benzene or many other aromatic compounds (29,30), and this fact may be of importance in understanding lignin ozonation.

In addition to ozonolysis, ozone may attack aromatic nuclei via electrophilic substitution, although the extent of such reactions is currently unknown (16,28). Ring hydroxylation and quinone formation are likely results of this mode of attack, and thus ozonation of benzene produced a small amount of phenol (31) while phenol yielded catechol, XI, and o-quinone as intermediate products upon ozonation (32,33). A possible mechanism is depicted in Fig. 4, based upon the discussion of these findings by Eckert and Singh (16).

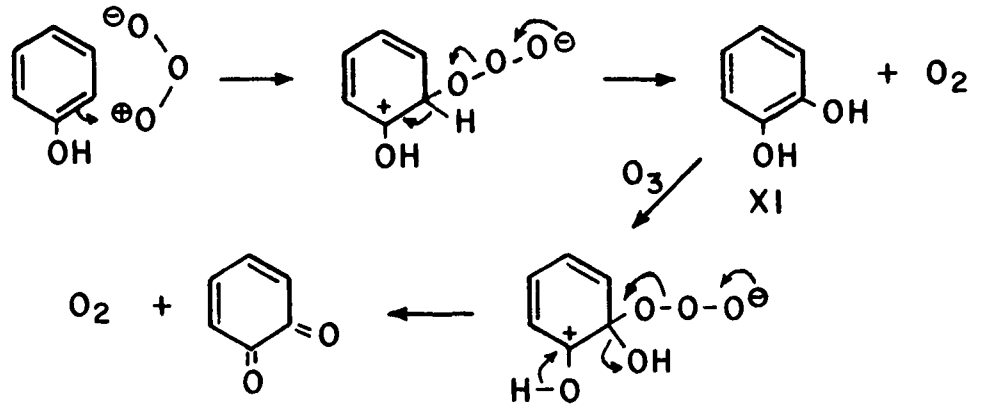


Figure 4. Ozone Attack of Phenol Via Electrophilic Substitution (16)

OZONE REACTIONS WITH SIMPLE ETHER LINKAGES

Ozone attack of ether linkages may provide a significant mode of degradation during ozonation of lignin since as many as 65% of the "intermonomer" linkages in lignin are estimated to be of the α- and β-aryl ether type (34). The current consensus is that such reactions proceed via a mechanism involving a hydrotrioxide intermediate, XIV (16,21,35,36). This intermediate could arise as depicted in Fig. 5.

Accordingly (Fig. 5, Route 4) ozone can attack a carbon-hydrogen bond adjacent (i.e., α) to the ether oxygen via a 1,3-dipolar insertion to form hydrotrioxide, XIV. The transition state, XII, predicts that insertion at a given carbon-hydrogen bond becomes more favorable as the acidity of the hydrogen decreases. Thus, tertiary α hydrogens have been shown to be significantly more reactive than secondary α hydrogens during the ozonation of propyl isopropyl ether (21).

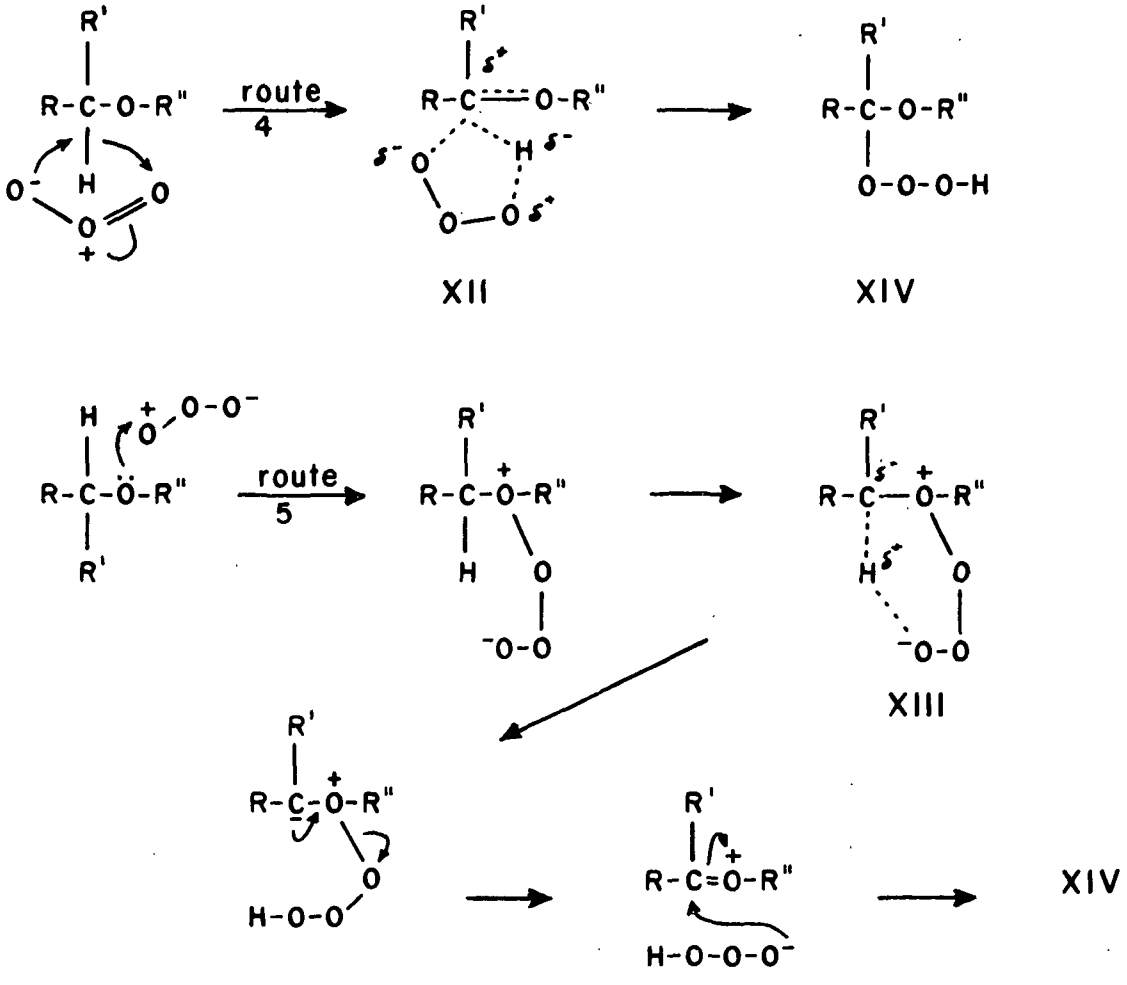
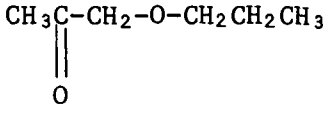


Figure 5. Possible Mechanisms for Formation of the Hydrotrioxide Intermediate During the Ozonation of Ethers (21,35,36)

Alternatively, Bailey and Lerdal (21) have recently proposed that the hydrotrioxide intermediate may arise via an internal oxidation mechanism under certain conditions (Fig. 5, Route 5). This mechanism involves initial ozone attack on the ether oxygen followed by abstraction of an α proton and subsequent rearrangement to yield hydrotrioxide, XIV. This pathway would be favored for ozonation of ethers in which transition state XIII would be more stable than transition state XII and would favor attack (i.e., proton abstraction) at the α carbon bearing the more acidic hydrogen. Thus, the ozonation of ether XV, which involved preferential attack at the more acidic α methylene group, was proposed to proceed primarily via Route 5 (21). In this case, the carbonyl group of XV

could help stabilize the developing negative charge (on the carbon adjacent to the ether oxygen) in the transition state, XIII, thereby facilitating ozonation *via* Route 5.



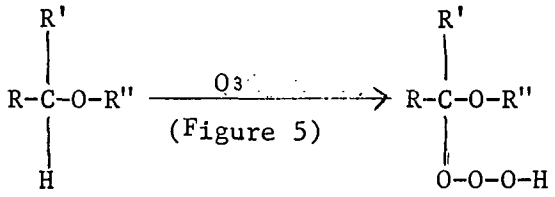
XV

Once formed, the hydrotrioxide, XIV, apparently decomposes *via* both ionic (Fig. 6, Routes 6 and 7) and free radical (Fig. 6, Routes 8 and 9) pathways to yield oxidation products such as aldehydes, ketones, and esters. The importance of each route varies with the reaction conditions and the nature of the ether under investigation (21,35).

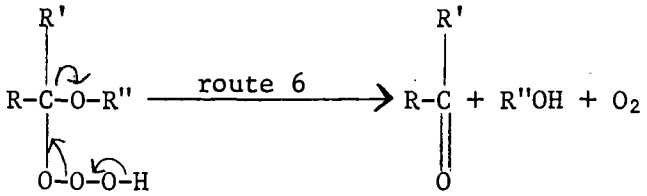
OZONE REACTIONS WITH LIGNIN AND LIGNIN-RELATED MODEL COMPOUNDS

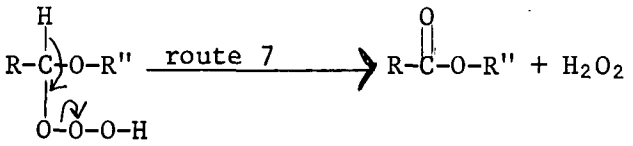
OZONE REACTIONS WITH LIGNIN-RELATED MODEL COMPOUNDS

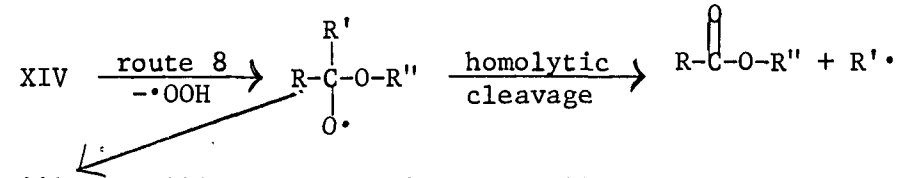
Several studies (37,39,41,42) have been conducted employing lignin-related model compounds to elicit possible reaction routes of importance during ozonation of lignin. Tanahashi, *et al.* (37) found ozone to preferentially cleave the aliphatic double bond of a phenylcoumarone, XVI, during mild ozonation (Fig. 7). This suggests that the olefinic bonds of lignin would be more susceptible to ozonolysis than the aromatic analogs, as would be expected based upon studies of simple alkenes and aromatic compounds (16,28). These workers also observed that ease of ozonation of "monomer" model compounds followed the order: 2,6-dimethoxyphenol > guaiacol > phenol, which corroborates an earlier report that ozonolysis of phenols was enhanced by electron releasing substituents (38).



XIV







$R'''O\bullet + R'''H \longrightarrow R'''OH + R'''\bullet$

$R'''\bullet + O_2 \longrightarrow R'''O_2\bullet$

$R'''O_2\bullet + R'''H \longrightarrow R'''\bullet + R'''O_2H$

$R'''\bullet + O_3\bullet \longrightarrow R'''O_3\bullet$

$R'''O_3\bullet + R'''H \longrightarrow R'''\bullet + R'''O_3H$

$R'''O_3\bullet \longrightarrow R'''O\bullet + O_2$

$2R'''O\bullet \longrightarrow R'''OOR'''$

Other Termination Reactions

Figure 6. Possible Mechanism for the Ozonation of Simple Ether Linkages (21,35)

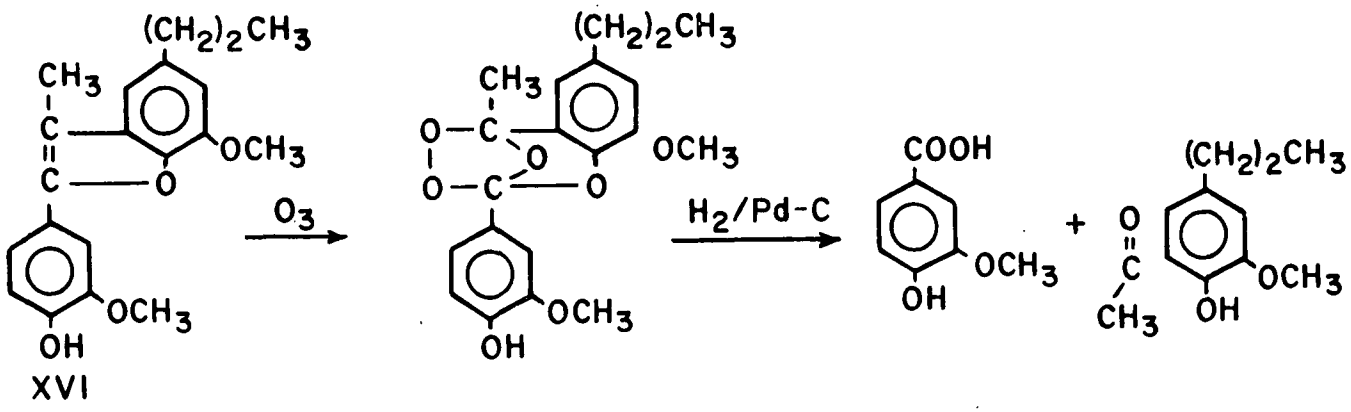


Figure 7. Ozonation of a Phenylcoumarone Under Mild Conditions (37)

Hatakeyama, et al. (39) ozonized vanillyl and veratryl alcohol, XVII and XVIII, under acidic and basic conditions. The δ-lactone, XIX, was identified as the major reaction product from both substrates and indicates preferential cleavage between the ring carbons bearing the hydroxyl and methoxyl substituents. This preferential cleavage has also been observed during the ozonation of catechol (40) and catechol ethers (20). In addition, the formation of XIX indicates that the methyl group of XVII and XVIII was retained upon oxidative ring opening, which is consistent with a 1,3-dipolar cycloaddition mechanism. Based upon these findings, the mechanism shown in Fig. 8 was proposed to explain the reaction products arising from the ozonation of XVII and XVIII (16,39).

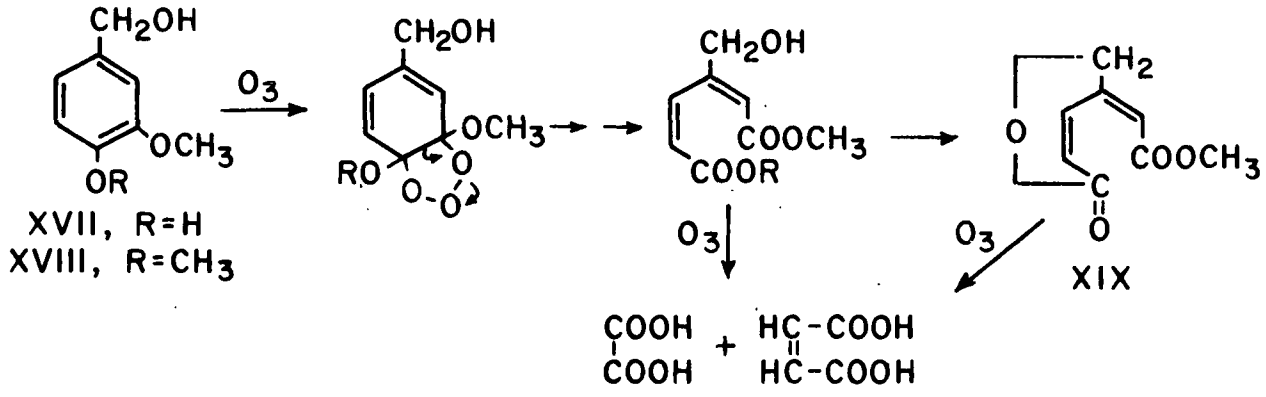


Figure 8. Possible Mode of Attack on a Lignin-related Monomer Unit (16,39)

Hatakeyama, et al. (39) also identified minor products such as XX and XXI arising from ozone attack of the aromatic ring substituents of XVII and XVIII. These products were more numerous under basic conditions and, as suggested by Eckert and Singh (16), may be the result of ozone-induced electrophilic substitution and 1,3-dipolar insertion mechanisms (Fig. 9).

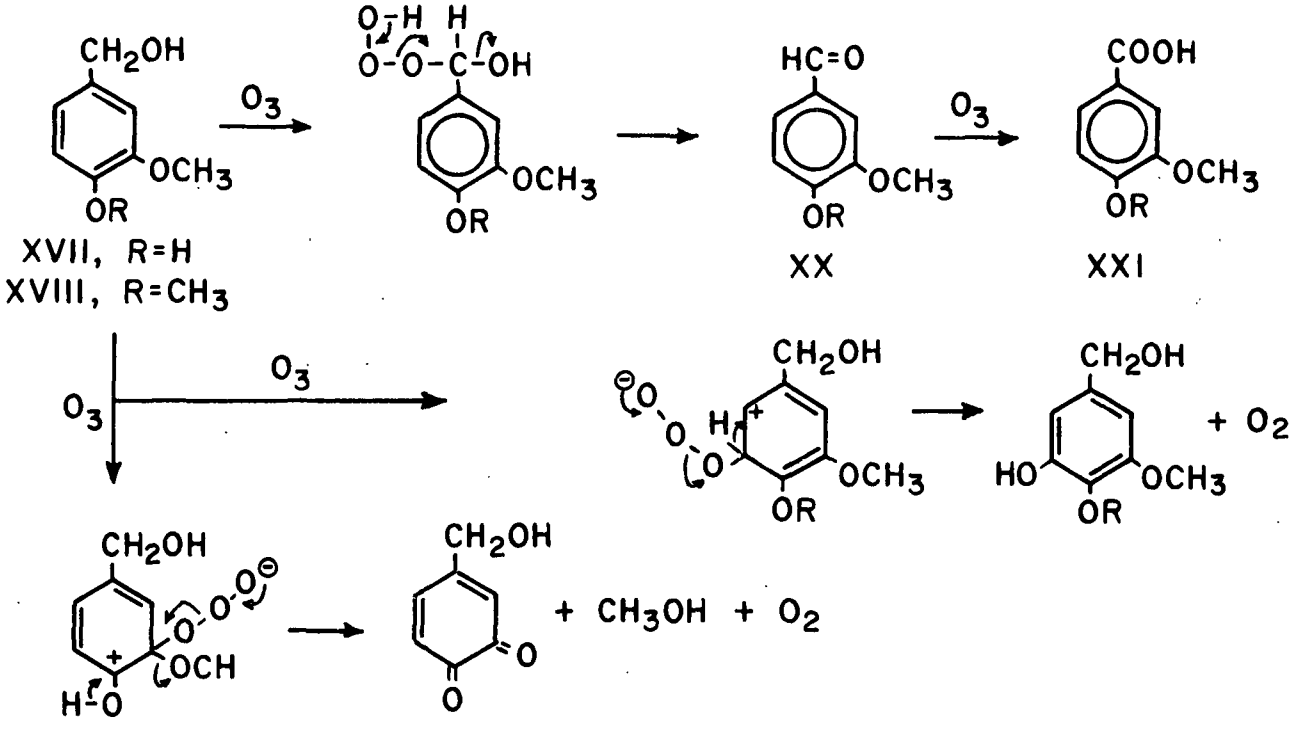


Figure 9. Possible Minor Reaction Routes During the Ozonation of XVII and XVIII (16)

On the other hand, Kratzl, et al. (41) studied the ozonation of various substituted veratrols and concluded that, although cleavage between the methoxyl bearing ring carbons was important (Fig. 10, Route 10), aromatic ring opening may also be initiated at other sites on the ring (Fig. 10, Route 11), especially when R is an electron-withdrawing group. The occurrence of ring cleavage via Route 10 was indicated by the identification of the muconic acid dimethyl ester, XXII, as a reaction product while the prevalence of cleavage via Route

11 was determined by the yield of dimethyl oxalate, XXIII, produced. Again, retention of the methyl groups in these products suggests that the ozonolysis of the veratrols proceeded *via* a 1,3-dipolar cycloaddition mechanism, and this was further substantiated by the reported identification of ozonides as unstable reaction products.

In the most recent model compound study, conducted by Kojima, *et al.* (42), the effects of ozone upon several softwood lignin model compounds, including some complex "dimeric" model compounds, were investigated. As in previous model compound studies (39,41), ozonolysis of the aromatic ring was implicated as a major mode of degradation. Ozonolysis of the aromatic ring of various 4-substituted 2-methoxy phenols was found to be enhanced when this substituent was electron-releasing and suppressed when it was electron-withdrawing, thereby corroborating earlier reports that the nature of the ring substituent has an effect upon the rate of aromatic ring ozonolysis (16,28).

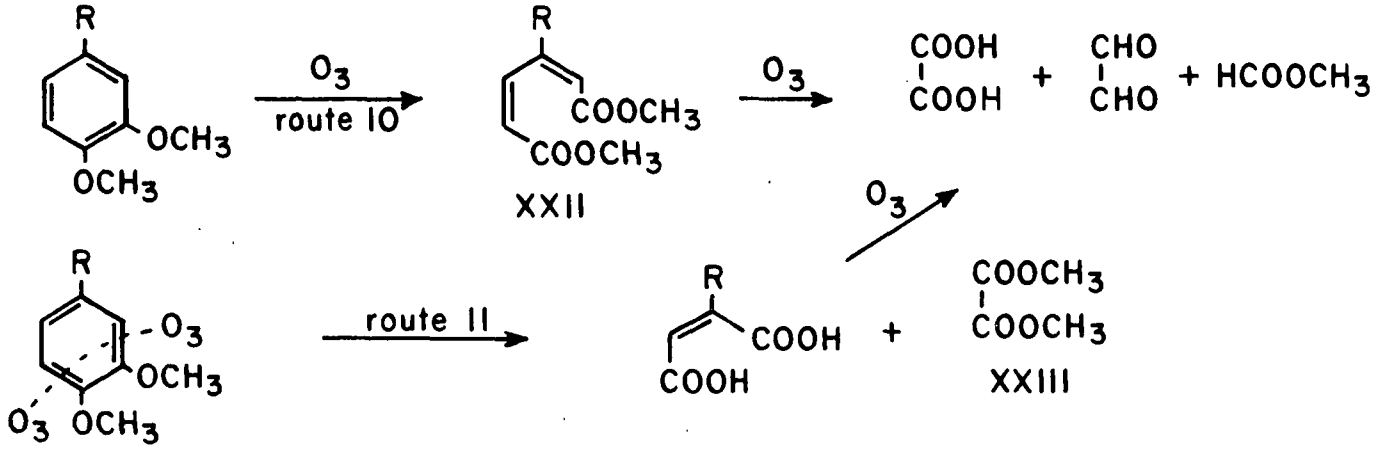
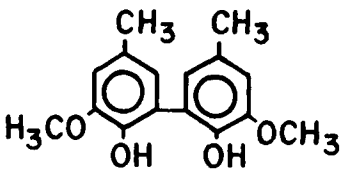
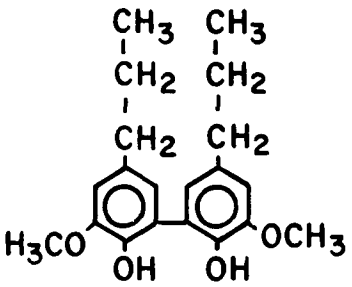


Figure 10. Possible Ozonation Pathway of Substituted Veratrols Proposed by Kratzl, *et al.* (41); R = $COCH_3$,Cl,H,CH_3,t-butyl,$N(CH_3)_2$

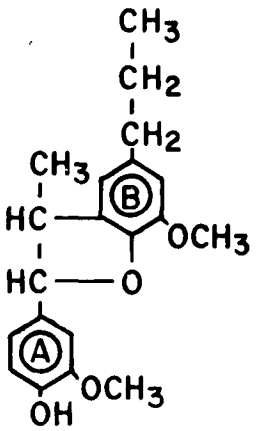
Ozonolysis of the dimeric model compounds demonstrated the following order of reactivity: XXIV, XXV (two tetrasubstituted rings) > XXVI (one tetra- and one trisubstituted ring) > XXVII (one tri- and one disubstituted ring). Moreover,



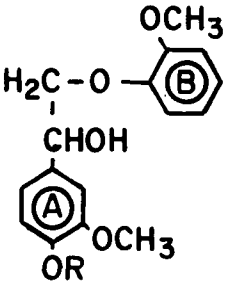
XXIV



XXV



XXVI



XXVII

XXVIII and all of the other identified ozonation products of XXVI were found to arise via ozonolysis of Ring B, the more substituted ring of XXVI; likewise, XXIX and all of the other identified ozonation products of XXVII were found to arise via ozonolysis of Ring A, the more substituted ring of XXVII (Fig. 11). Based upon these findings, it was concluded that the reactivity of a lignin-related model compound toward aromatic ring ozonolysis is not only dependent upon the nature but also the number of ring substituents (i.e., as the number of ring substituents increases so does the rate of ozonolysis).

In addition to aromatic ring ozonolysis, Kojima, et al., obtained evidence for the occurrence of other ozonation mechanisms. Specifically, along with ozonolysis products, compounds XXXI and XXXII were identified as ozonation products of XXX, as indicated in Fig. 12. The formation of XXXI provided evidence for ozone-induced side-chain oxidation and thus corroborates the earlier findings of Hatakeyama, et al. (39). The formation of XXXII was proposed to result from oxidative radical coupling involving the phenoxy radical and thus for the first time provides evidence for the condensation of phenolic compounds during the ozonation of lignin-related model compounds.

OZONE REACTIONS WITH WOOD AND MODIFIED LIGNINS

In addition to model compounds, the ozonation of modified lignins (43-47) and even wood pulps (10,19) has been investigated to ascertain possible reaction routes of importance during the ozonation of lignin. Hatakeyama, et al. (43) reported that the ozonation of calcium lignosulfonate led to a significant increase in carboxyl and carbonyl group content, and that 90% of the newly formed carboxyl groups arose from oxidative cleavage of aromatic nuclei.

Subsequently, Soteland (19) subjected extracted western hemlock groundwood to ozonation in acetone-water. In addition to an observed decrease in aromatic character and an increase in the carbonyl and carboxyl group content, analysis of the isolated lignin after ozonation indicated the formation of methyl esters. Also, evidence for the presence of active oxygen groups (i.e., peroxides and ozonides), arising from the ozonation, was obtained. These results are consistent with the model compound studies previously discussed and led the author to postulate that oxidative opening of the aromatic rings is an important mode of degradation during the ozonation of lignin. It was further postulated that this degradation probably proceeds via a 1,3-dipolar cycloaddition mechanism similar to those proposed for ozonation of lignin-related model compounds (Fig. 8-11).

The results of Katuscak, et al. (44-47), obtained from the ozonation of methanol lignin and HCl-lignin, corroborated the findings of Soteland (19). Of particular interest in this study was the observation that carbon-14 was incorporated into the lignin macromolecule when employing carbon-14 labelled methanol as the ozonation solvent (47). This was interpreted as evidence that a methoxyhydroperoxy derivative was formed during the ozonation of lignin in

the protic solvent, methanol. Reaction (1) was proposed to explain this phenomenon and is consistent with the generally accepted mechanism for the ozonolysis of olefins in protic solvents (Fig. 2, Route 2):

$$\text{Lig} - \text{C}^{+} - \text{OO}^{-} + \text{C}^{14}\text{H}_3\text{OH} \rightarrow \text{Lig}\begin{cases}\text{OC}^{14}\text{H}_3 \\ \text{OOH}\end{cases} \qquad (1)$$

Katuscak, et al., also obtained evidence that free radical mechanisms may be of importance during the ozonation of lignin. The presence of ozone-induced free radicals was demonstrated by the fact that ozonized lignin initiated homopolymerization of styrene and graft copolymerization of styrene with lignin (44,47). In addition, analysis via electron spin resonance spectrometry indicated that ozonation increased the concentration of paramagnetic centers in both methanol lignin and HCl-lignin (46). The authors speculated that hydroperoxides, as formed via Reaction (1), may serve as a source of such radicals and that ozone may act as an initiator for the autoxidation of lignin [Reactions (2)-(5)]:

$$\text{Lig-H} + \text{O}_3 \longrightarrow \text{Lig-O}\cdot + \cdot\text{OOH} \qquad (2)$$

$$\text{Lig-O}\cdot + \text{Lig-H} \longrightarrow \text{Lig-OH} + \text{Lig}\cdot \qquad (3)$$

$$\text{Lig}\cdot + \text{O}_2 \longrightarrow \text{Lig-OO}\cdot \qquad (4)$$

$$\text{Lig-OO}\cdot + \text{Lig-H} \longrightarrow \text{Lig-OOH} + \text{Lig}\cdot \qquad (5)$$

THESIS OBJECTIVE AND EXPERIMENTAL APPROACH

OBJECTIVE

Previous studies of ozone-lignin reactions have focused upon attack and subsequent degradation of the aromatic ring structure. Investigations into the ozonation of lignin-related model compounds, isolated lignins, and wood pulps have revealed a close correlation between ozonolysis of aromatic nuclei and ozone-induced lignin degradation. However, the possible importance of other modes of ozone attack during the ozonation of lignin has not been adequately considered. For example, the β-aryl ether bond is thought to be the most common intermonomer linkage in lignin (48,49), and inasmuch as ozone is known to readily induce cleavage of alkyl ether linkages (21,35), it would seem logical that ozone could likewise cleave the β-aryl ether linkages found in lignin. This cleavage would result in a rapid decrease in the degree of polymerization of the lignin and thus could be of importance in ozone delignification.

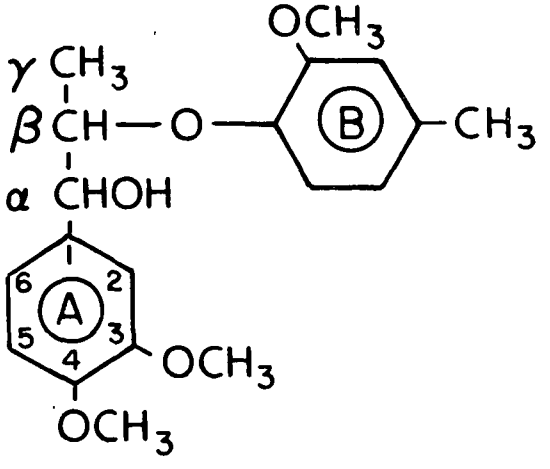
For this reason, the primary objective of this thesis was to investigate the effects of ozone upon a lignin-related model compound containing a β-aryl ether linkage. In this respect, the emphasis was directed toward identification of the initial sites of ozone attack, in an effort to ascertain the important mechanisms involved during the ozonation of the model compound.

APPROACH

SUBSTRATE SELECTION

The model compound employed as the substrate in this study is depicted in Fig. 13. Subsequent discussions will employ the numbering and lettering systems shown in this figure when referring to the various sites on the model compound. Model compound XXXIII was selected to serve as the substrate in this

study because it possesses many of the basic structural features of a typical lignin moiety containing a β-aryl ether linkage (49). In addition, the methyl group at position 4 of Ring B serves as an excellent label for distinguishing between ozonation products arising from Rings A and B. Finally, the synthesis of XXXIII can be accomplished via a proven synthetic route (50).



XXXIII

Figure 13. Structure of the Model Compound Employed in This Study

GENERAL REACTION CONDITIONS

Studies indicate that the products arising from initial ozone attack of lignin and related model compounds are quite susceptible to further degradation via ozone (16,19,39,47). Therefore, to facilitate identification of the initial sites of ozone attack upon XXXIII, it was necessary to limit the exposure of the products to ozone. Essentially, this meant applying ozone in an amount significantly less than that of the XXXIII employed for a given experiment.

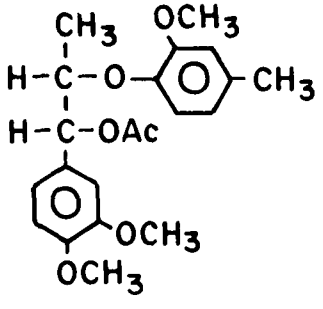
Furthermore, as previously discussed, the nature of the solvent can influence the structure of the initial ozonation intermediates. During the ozonolysis of olefinic and aromatic substrates, including lignin (47), hydroxylic

solvents such as water tend to favor formation of hydroperoxide intermediates, while aprotic solvents favor ozonide formation. Consequently, since in all probability ozone processes in the paper industry would be conducted in the presence of water, the ozonations in this study were performed in aqueous media. Because XXXIII is insoluble in water, it was necessary to employ an aqueous organic solvent as the reaction solvent to effect solution of the substrate. Thus, aqueous acetone was employed as the reaction solvent in this study, although some preliminary experiments were conducted in aqueous acetic acid as well. Further discussion of the use of aqueous acetone as an ozonation solvent is presented in Appendix I.

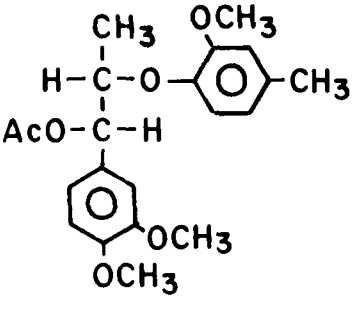
RESULTS AND DISCUSSION

PREPARATION OF SUBSTRATE

As already discussed, the lignin model compound XXXIII was employed as the substrate in this study. The compound was prepared *via* the four step synthetic route of Lawrence (50) depicted in Fig. 14. Lawrence reported that, as a result of the sodium borohydride reduction employed in Step 4 of this synthesis, a mixture of the *erythro* (XXXIIIa) and *threo* (XXXIIIb) configurational isomers of XXXIII was obtained. Subsequently, an acetylated sample of the XXXIII was analyzed *via* nuclear magnetic resonance (NMR) spectrometry and, based upon the relative size of the acetoxy proton signals of isomers XXXIVa and XXXIVb, Lawrence determined that the mixture was comprised of 94% *erythro* and 6% *threo* isomer. Similarly, the XXXIII prepared for use in the current study was found to be an isomeric mixture composed of 92% *erythro* and 8% *threo* XXXIII.



XXXIVa



XXXIVb

EXTENT OF OZONATION

As previously alluded to, mild ozonation conditions were employed in this study to minimize the occurrence of secondary reactions and thereby facilitate the identification of the initial sites of ozone attack upon model compound XXXIII. In a typical ozonation experiment, a known amount of XXXIII was

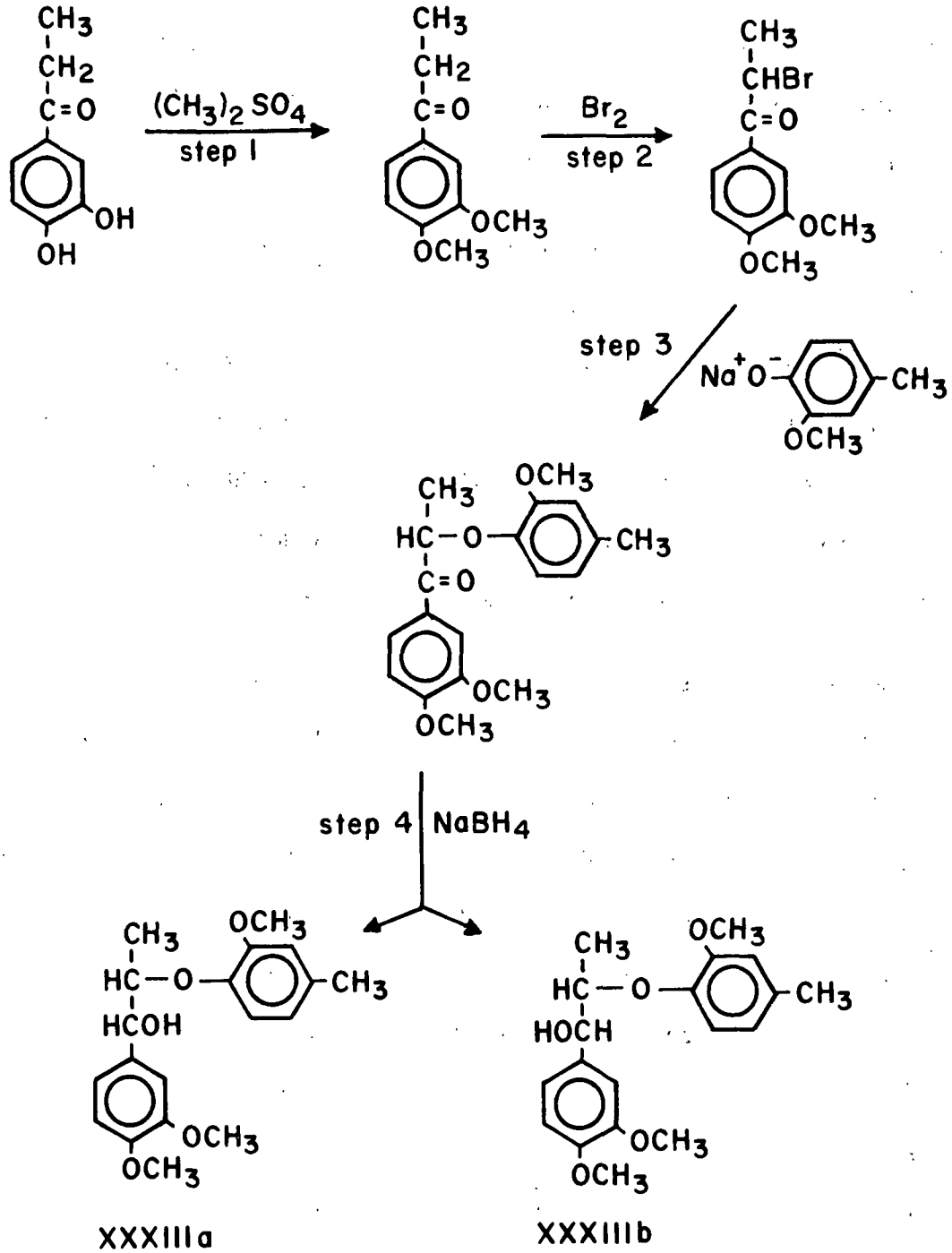


Figure 14. Synthetic Route for Preparation of Compound XXXIII (50)

dissolved in 80% aqueous acetone in the reaction vessel. An ozone-oxygen stream was then bubbled through the reaction solution at a constant flow rate for a given period of time. Subsequently, the solution was purged with nitrogen to remove any unreacted ozone. Reaction solution samples were taken before and after ozonation and analyzed *via* gas chromatography (GC) to determine the amount of starting material, XXXIII, that was consumed.

The amount of ozone offered to the reaction solution was determined *via* the standard iodometric titration method (51), and the amount of ozone consumed was determined *via* a new acid-base titration method devised for this study. The new method for ozone analysis was required to circumvent analytical difficulties associated with the standard iodometric titration method when employing acetone as the ozonation solvent. Appendix II provides a detailed discussion of the development and validity of this new analytical procedure.

The results of the starting material and ozone analyses are summarized in Table II. These results indicate that about 30% of the starting material employed for the ozonation was consumed while 99% of the ozone employed was consumed. Inasmuch as the ozone was in contact with the starting material for only a brief time, this finding indicates that the ozone reacts quite rapidly with XXXIII. Furthermore, the ozonation stoichiometry indicates that 1.33 moles of ozone was consumed for each mole of XXXIII consumed, implying that about 25% of the ozone consumption during the ozonation was the result of secondary reactions. This suggests that at least 75% of the XXXIII consumed during an ozonation took the form of initial products which were not degraded further by ozone; thus it appears that minimization of ozone-induced secondary reactions was successful.

TABLE II

INFORMATION CONCERNING THE EXTENT OF OZONATION
OF MODEL COMPOUND XXXIII IN AQUEOUS ACETONE

XXXIII Offered (mmoles)	XXXIII Consumed (mmoles)[a]	O_3 Offered (mmoles)	O_3 Consumed (mmoles)[a]	Stoichiometry[b]
8.9738	2.5844(28.8)	3.4640	3.4356(99.2)	1.33

[a]The value in parentheses indicates percent consumption.
[b]Moles of ozone consumed/mole of XXXIII consumed.

OZONATION PRODUCTS IDENTIFIED

Aliquots of the ozonized reaction solutions of XXXIII were subjected to various work-up procedures and then analyzed qualitatively and quantitatively *via* GC, usually after silylation of the samples, to determine the identities and the respective amounts of the various products formed from the ozonation of XXXIII. Mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectrometry were also employed as major modes of qualitative product analysis. Table III lists the compounds positively identified as ozonation products of XXXIII, the amount of each detected, and the modes of analysis employed for the identification. The structures of these products are shown in Fig. 15. A detailed discussion of the experimental evidence employed to identify these products is presented in a subsequent section of this thesis.

It might be suggested that products XXXV and XXXVI could arise by means other than ozonation of XXXIII (e.g., hydrolysis). To disprove this hypothesis, an experiment was conducted to test the stability of XXXIII, in the absence of ozone, to the usual reaction conditions and analytical procedures employed in this study. Essentially, this involved treating an aqueous acetone solution of XXXIII with an oxygen stream, rather than an ozone-oxygen stream, under otherwise

typical reaction conditions. Aliquots of the treated solution were then prepared and analyzed for starting material (XXXIII) consumption and the presence of degradation products *via* the usual starting material and product analysis procedures.

TABLE III

SUMMARY OF IDENTIFIED OZONATION PRODUCTS OF XXXIII

Product	% of XXXIII Accounted For[a]	Mode of Analysis[b]
XXXV (creosol)	8.0 ± 1.0	1,2,4
XXXVIa (diol)	8.7 ± 1.2	1,2,4
XXXVIb (diol)	2.1 ± 0.3	2
XXXVII	1.5 ± 0.1	3,5
XXXVIII	0.2	3,5
XXXIX	1.6	1,2

[a] Expressed as a percentage of the millimoles of XXXIII consumed during the ozonation.

[b] The modes of analysis were:
1. GC retention time comparison with an authentic sample
2. Mass spectral comparison with an authentic sample
3. Mass spectrum — no authentic sample available
4. NMR spectral comparison with an authentic sample
5. NMR spectrum — no authentic sample available

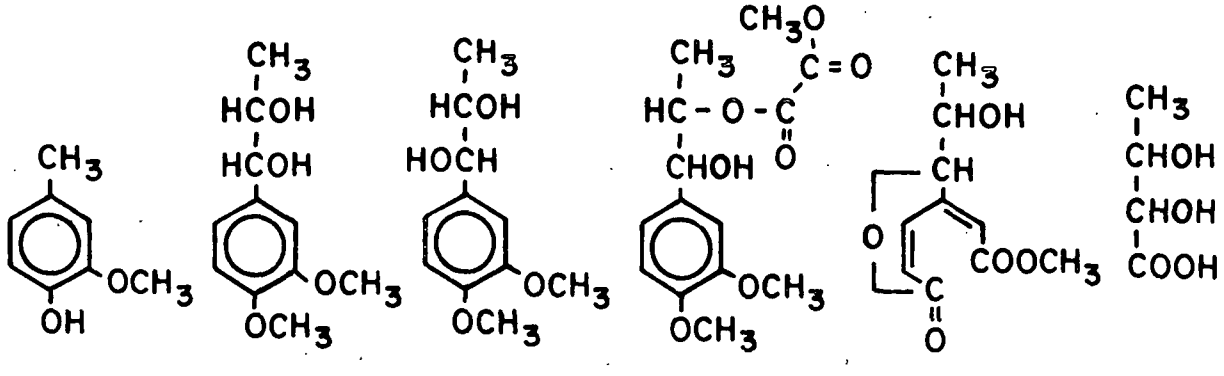


Figure 15. Identified Ozonation Products of Model Compound XXXIII

The results of this experiment (summarized in Table IV) indicate that about 95% of the starting material treated was recovered. Moreover, the GC chromatogram obtained by analyzing a large aliquot of the treated solution *via* the usual product analysis procedures demonstrated virtually a complete absence of any substances other than XXXIII, internal standard, and silylation artifacts. Thus it is concluded that XXXIII is stable to the reaction conditions and analytical procedures that were employed in this study and that the compounds detected in the ozonized reaction solutions of XXXIII arose solely as a result of ozone-induced degradation of XXXIII.

TABLE IV

EXTENT OF DEGRADATION OF XXXIII IN THE ABSENCE OF OZONE

XXXIII Offered (mmoles)	% of XXXIII Recovered	Detected Degradation Products of XXXIII
2.9518	94.6	None

MECHANISTIC IMPLICATIONS

INITIAL SITES OF ATTACK

Based upon the results listed in Table III, a reaction scheme indicating the initial sites of attack during the ozonation of model compound XXXIII has been devised and is depicted in Fig. 16. Accordingly, there are four general pathways by which XXXIII is attacked and subsequently degraded by ozone. Pathways A and B provide two general routes whereby initial ozone attack of XXXIII leads directly to cleavage of the β-aryl ether linkage. Pathway C involves ozonolysis of Ring B of XXXIII, initiated at a site other than between the adjacent ring carbons bearing the alkoxyl substituents. And Pathway D involves both ozonolysis of Ring A of XXXIII, initiated between the methoxyl-bearing

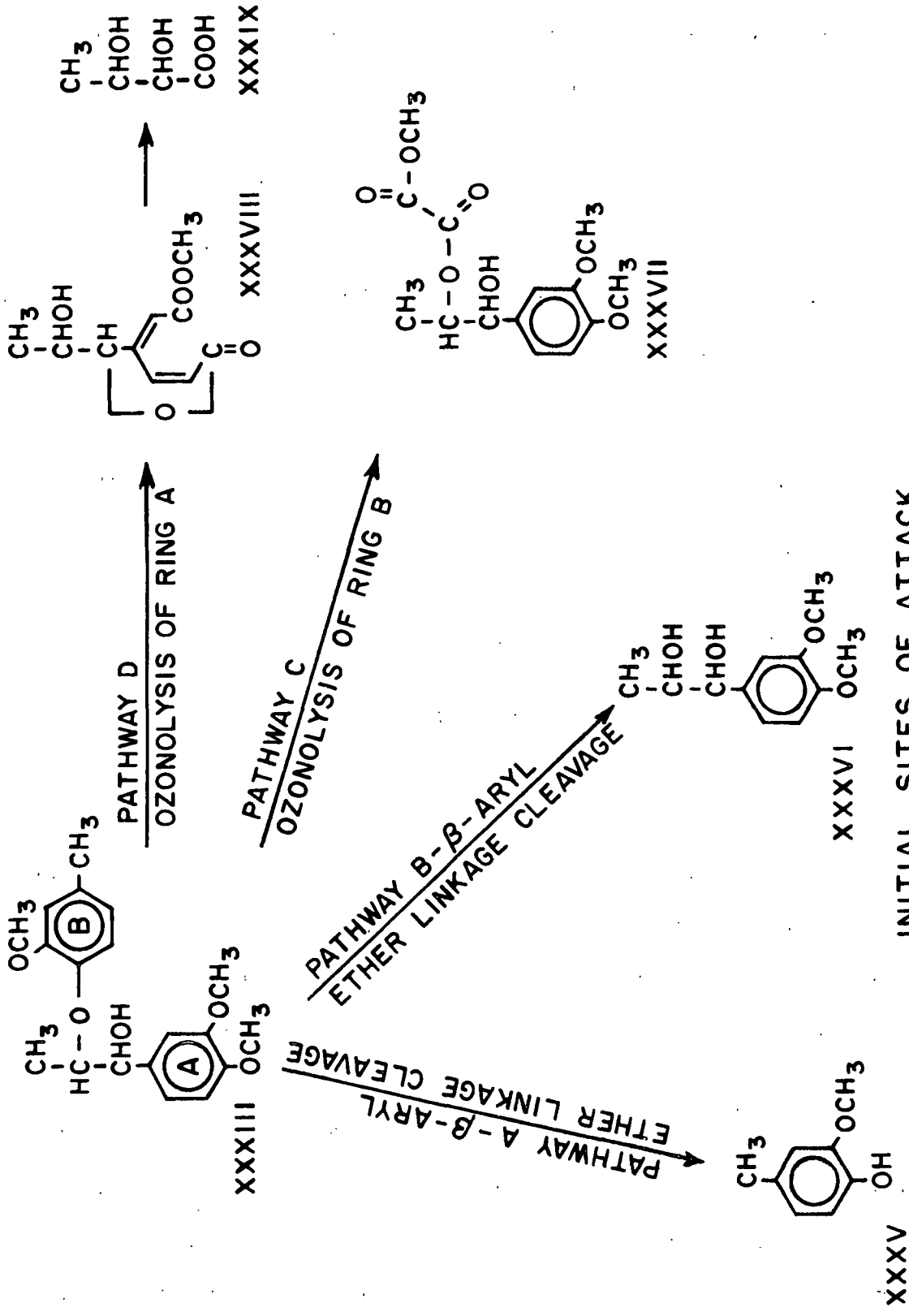


Figure 16. Major Degradation Pathways for Ozonation of Compound XXXIII

ring carbons, and cleavage of the β-aryl ether linkage. A detailed discussion of each of these pathways will now be presented.

Attack at the β-Aryl Ether Linkage (Pathways A and B)

As indicated by Pathways A and B of Fig. 16, the formation of creosol (XXXV) and the diol, XXXVI, provides strong evidence that the β-aryl ether linkage is an initial site of attack during the ozonation of XXXIII.

Creosol could arise as a result of ozone-induced cleavage of the β-aryl ether linkage initiated at the alkyl end of the linkage (Fig. 17). Accordingly, ozone would attack the carbon-hydrogen bond via a 1,3-dipolar insertion to form the hydrotrioxide intermediate, XL. At 25°C, intermediate XL would then rapidly decompose ionically to yield creosol and the ketol, XLI (Route 12), or via a free radical process to yield XXXV· and the ketol (Route 13), XLII (Route 14), and XLIII (Route 15). Compounds XLII and XLIII could then undergo ester hydrolysis to form creosol, XLIV and acetic acid.

As discussed in a previous section, a similar mechanism (cf. Fig. 5 and 6) appears to provide the principal pathway during the ozonation of alkyl ethers such as ethyl isopropyl ether (21). In the case of compound XXXIII, attack of the carbon-hydrogen bond of the β carbon via 1,3-dipolar insertion would involve development of a positive charge on the β carbon in the transition state, XLVI, leading to the formation of hydrotrioxide, XL. This developing positive charge would be stabilized via electron donation from both the ether oxygen and the methyl group attached to the β carbon, and thus the β carbon of XXXIII should provide an excellent site for ozone attack via a 1,3-dipolar insertion mechanism (21).

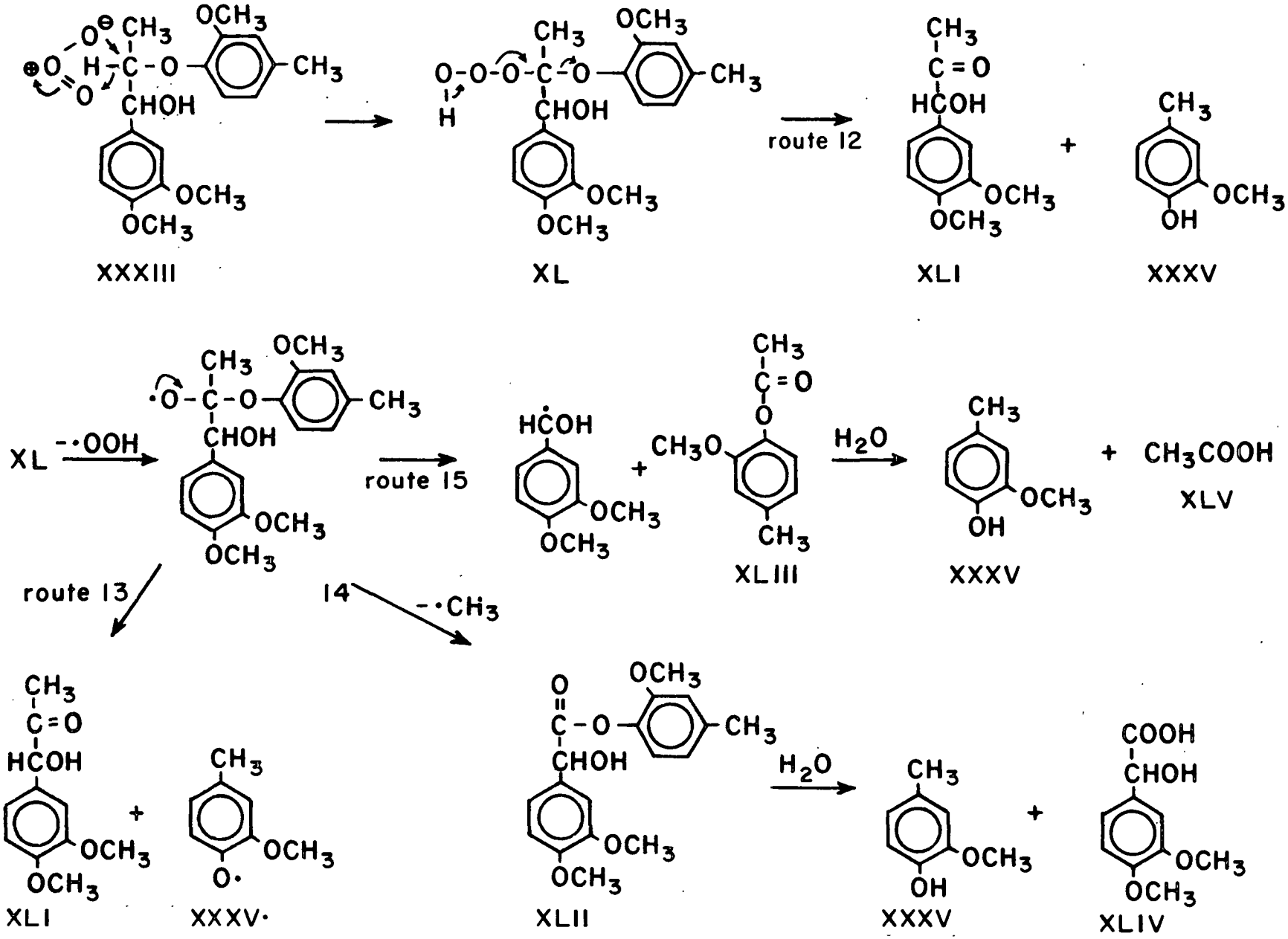
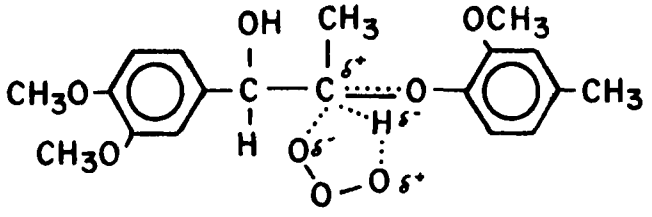
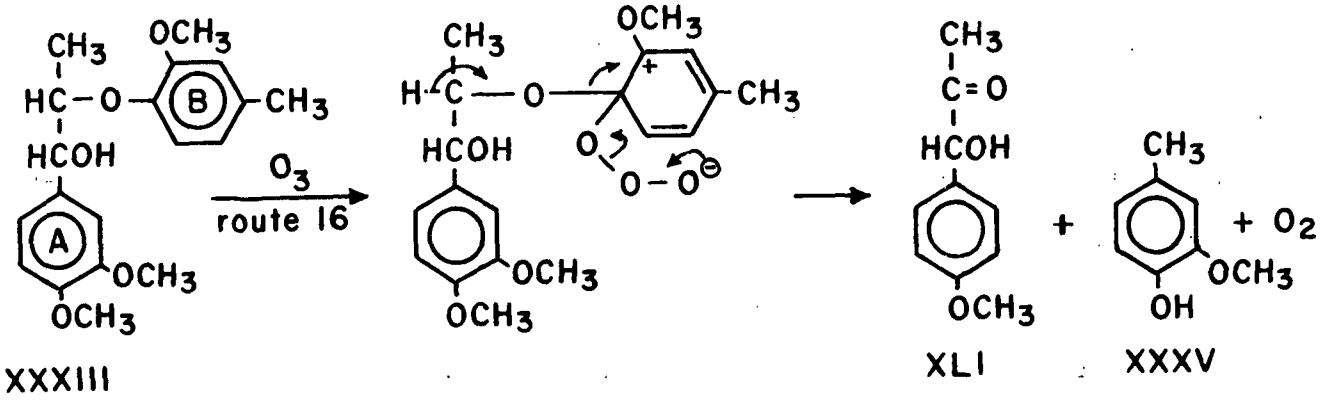


Figure 17. Proposed Reaction Routes for Formation of Product XXXV From Ozonation of XXXIII



XLVI

Alternatively, creosol could arise via ozone-induced cleavage of the β-aryl ether linkage of XXXIII initiated at the aryl end of the linkage. As depicted in Fig. 18, the initial step of this mechanism (Route 16) involves electrophilic attack by ozone upon Ring B of XXXIII. Subsequent loss of the proton on the β carbon of the side chain yields creosol and the ketol, XLI. As already alluded to, ozone has been shown to attack various aromatic substrates via electrophilic substitution (16,28) and, in fact, the propoxyl-bearing carbon atom of Ring B should provide a prime site for electrophilic attack due to the presence of electron-releasing substituents located ortho and para to this position (52). In addition, a similar mechanism has been proposed to explain the formation of creosol and the ketol, XLI, via peroxyacetic acid oxidation of XXXIII (50).



XXXIII XLI XXXV

Figure 18. Possible Mechanism for Formation of XXXV Initiated on the Aryl End of the β-Aryl Ether Linkage of XXXIII

However, ketol XLI was not identified as an ozonation product of XXXIII. Moreover, since a competition reaction between substrate XXXIII and ketol XLI indicated that XXXIII is three times as reactive toward ozone as is XLI, it appears that the absence of XLI as an ozonation product was not due to subsequent degradation during the ozonation of XXXIII but rather reflects a lack of formation of XLI, thereby strongly suggesting that formation of creosol *via* Route 16 (Fig. 18) was not a principal pathway during the ozonation of XXXIII. Consequently, it would appear that a significant portion of creosol was formed *via* cleavage of the β-aryl ether linkage initiated at the alkyl end of the linkage (e.g., Routes 12-15 of Fig. 17). Furthermore, the absence of significant quantities of the ketol also suggests that Routes 12 and 13 (Fig. 17) were not principal pathways, while the absence of XLIV minimizes the possible importance of Route 14. Thus, Route 15 (Fig. 17) could be postulated to be the principal pathway for the formation of creosol during the ozonation of XXXIII, with possible minor contributions arising from Routes 12-14 and 16.

The diol, XXXVI, most likely arises as a result of ozone-induced cleavage of the β-aryl ether linkage of XXXIII initiated on the aromatic end of the linkage. The results from Table III indicate that the diol possesses an isomer ratio of 81% *erythro* (XXXVIa) to 19% *threo* (XXXVIb), which is somewhat different than the *erythro* to *threo* isomeric ratio of 92 to 8% observed for the XXXIII employed as the substrate in this study. This difference in isomeric ratio could be due to a difference in the reactivity to ozone of the *erythro* and *threo* isomers of XXXIII. An equally likely explanation, which merits further consideration, is that the difference in isomeric ratio arose because at least one mechanism producing the diol during the ozonation of XXXIII involved inversion of configuration. As suggested in Fig. 19, there are at least four routes by which the diol could be formed during the ozonation of XXXIII, and although

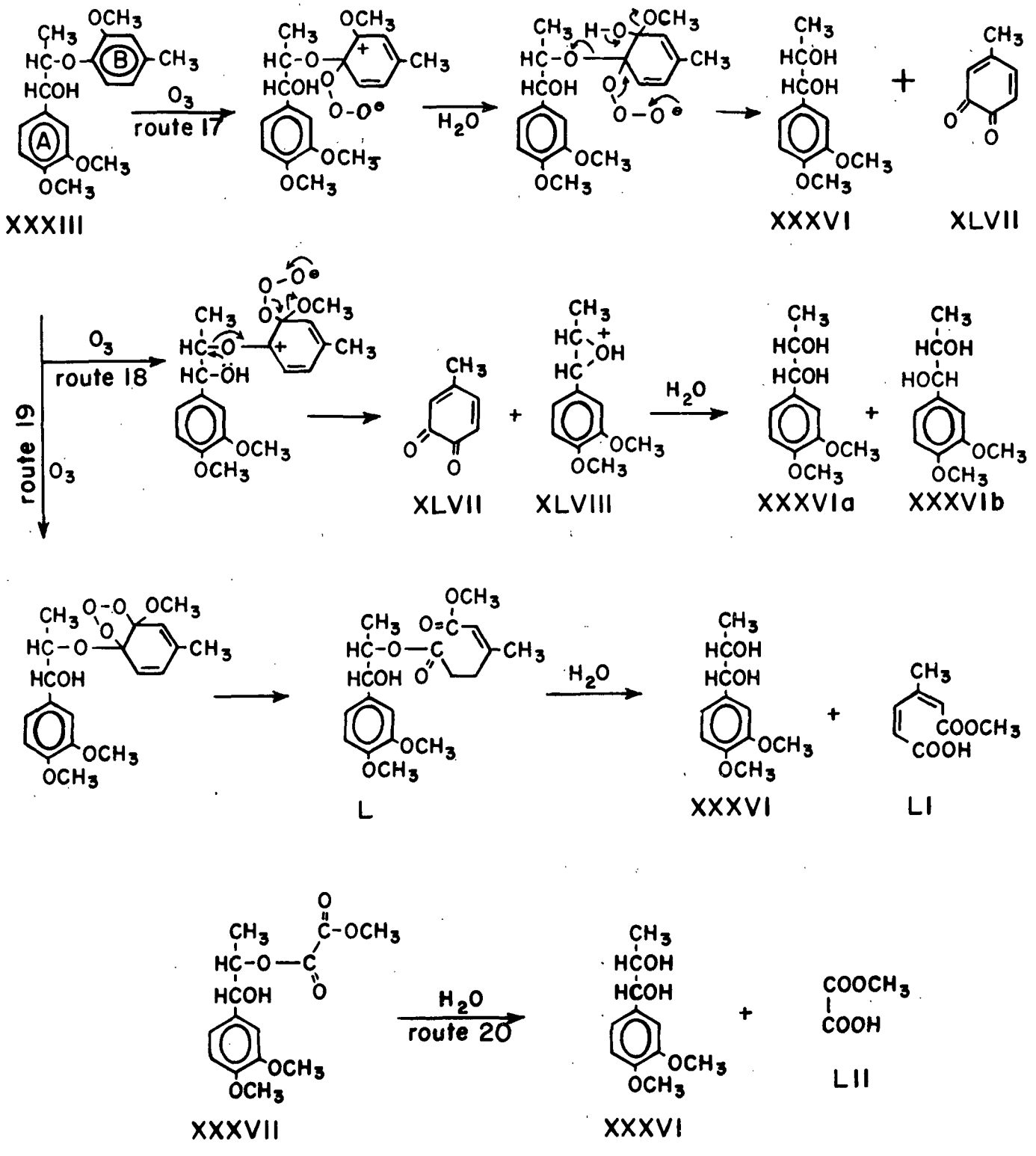


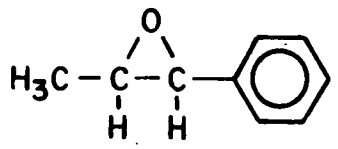
Figure 19. Proposed Reaction Routes for Formation of Product XXXVI from Ozonation of XXXIII

Routes 17, 19 and 20 would be expected to proceed with complete retention of configuration, Route 18 provides a means by which partial inversion of configuration can be realized:

Route 17 — Initial electrophilic attack by ozone upon XXXIII occurs at the propoxyl-bearing carbon atom of Ring B followed by an interaction between water and the newly formed carbonium ion. Subsequently, the β-aryl ether linkage is cleaved to yield the diol (XXXVI) and an ortho quinone, XLVII. As already discussed, the propoxyl-bearing carbon atom of Ring B provides an excellent site for electrophilic attack, and a preference for cleavage via Route 17, to yield the diol, may be the reason why cleavage via Route 16 (Fig. 18) does not appear to be a major pathway. Quinone XLVII was not identified as an ozonation product; however, it could have been degraded to acidic products by subsequent ozonation or formed large nonvolatile condensation/polymerization products (e.g., via Diels-Alder reaction) not amenable to GC analysis, thereby providing an explanation for this apparent absence. A detailed discussion of the possible condensation/polymerization reactions that could occur during the ozonation of XXXIII is presented in Appendix III.

Route 18 — Initial electrophilic attack by ozone occurs at the methoxyl-bearing carbon atom of Ring B. Cleavage of the β-aryl ether linkage is then facilitated by neighboring-group assistance (53) from the benzylic hydroxyl group of XXXIII to yield the protonated epoxide, XLVIII, and quinone, XLVII. Hydrolysis of XLVIII then proceeds with partial inversion of configuration to yield the erythro and threo isomers of the diol. The stereochemistry suggested for this last step is based upon the fact that the

structurally similar epoxide, XLIX, demonstrates partial inversion of configuration upon acid hydrolysis (54). As a result, this route provides a means whereby the diol can arise from ozonation of XXXIII without complete retention of configuration.



XLIX

Route 19 — Ring B of XXXIII is cleaved between the adjacent alkoxyl bearing ring carbons via a typical 1,3-dipolar cycloaddition mechanism (16) to yield a muconic acid ester, L, which subsequently undergoes ester hydrolysis to yield the diol and a muconic acid derivative, LI. Compounds L and LI were not identified as ozonation products, but failure to detect these compounds may also be due to further degradation and/or formation of large nonvolatile condensation/polymerization products, as suggested for XLVII.

Route 20 — Compound XXXVII, which has been positively identified as an ozonation product of XXXIII, could undergo ester hydrolysis to yield the diol and LII. However, failure to identify LII in the reaction solution of XXXIII suggests that this route may be only a minor pathway for the formation of XXXVI.

Since compounds XLVII, XLVIII, and L-LII were not identified as ozonation products of XXXIII, the relative importance of Routes 17-20 in the formation of the diol could not be accurately assessed, although the stereochemical evidence

suggests that a mechanism such as Route 18 may be involved. It is quite possible that all four reaction routes are operating to some extent during the ozonation of XXXIII. Under such circumstances, compounds XLVII, and L-LII would be produced in small amounts which, along with the possibility of subsequent degradation and/or formation of condensation/polymerization products, could hinder attempts to detect these compounds.

In summary, the identification of creosol and diol (XXXVI) as ozonation products provides conclusive evidence that ozone-induced cleavage of the β-aryl ether linkage is a fundamental route of degradation during the ozonation of XXXIII. The pathways proposed (i.e., Routes 12-20) provide feasible explanations for the origins of creosol and the diol, although the data do not allow an accurate assessment of their importance relative to one another.

Aromatic Ring Attack (Pathways C and D)

The formation of compounds XXXVII-XXXIX during the ozonation of XXXIII indicates that both aromatic rings of XXXIII provide initial sites for ozone attack. Product XXXVII could arise from extensive degradation of Ring B of XXXIII, as depicted in Fig. 20 (Route 21). Accordingly, oxidative ring opening proceeds via a typical 1,3-dipolar cycloaddition mechanism in which the intermediate would probably be a hydroperoxide such as LIII, rather than an ozonide, because of the protic nature of the reaction solvent (16,47). The hydroperoxide, LIII, then decomposes to yield the muconic acid derivative, LIV, which undergoes further ozonolysis to yield product XXXVII. The structure of XXXVII indicates that neither the β-aryl ether linkage nor the bond between the alkoxyl bearing carbon atoms of Ring B were cleaved. Thus, identification of XXXVII as an ozonation product provides conclusive evidence that an initial site of attack during the ozonation of XXXIII is on Ring B at some point other than the bond between the adjacent ring carbons bearing the alkoxyl substituents.

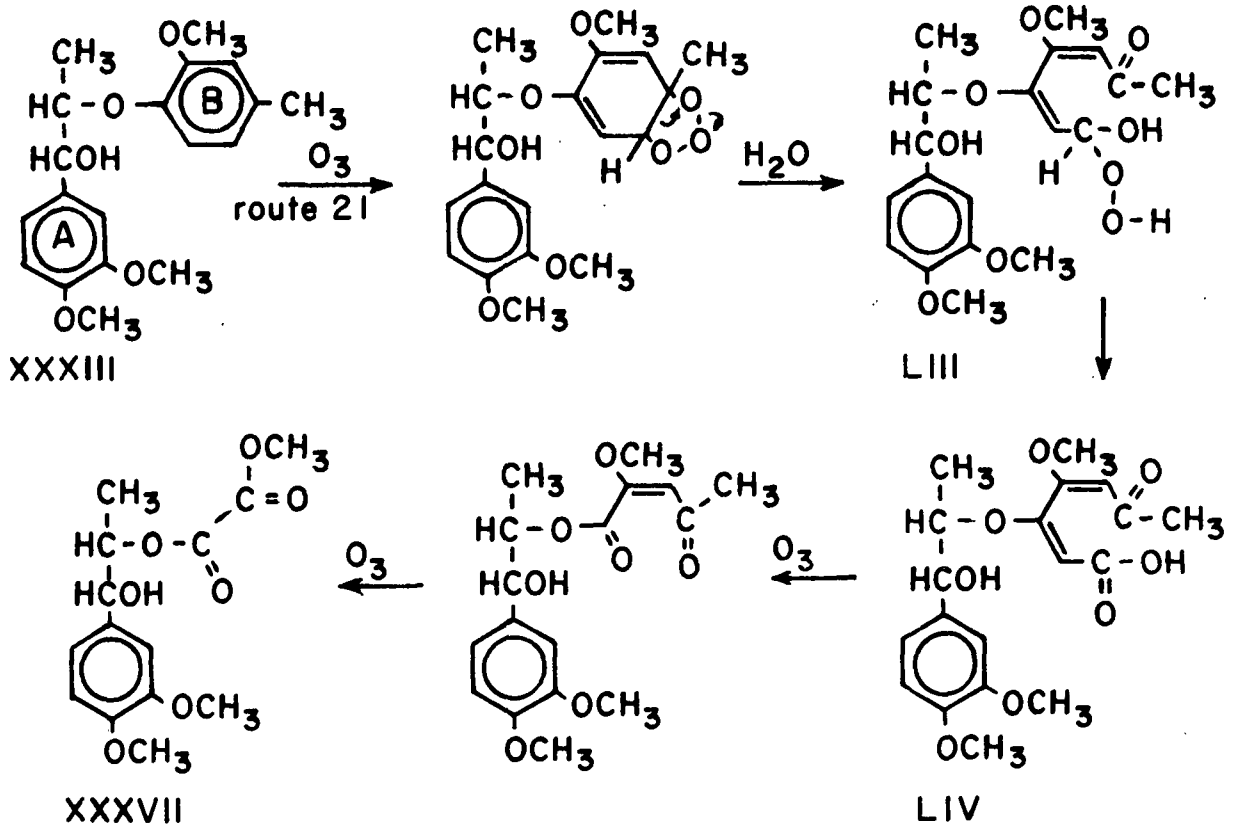


Figure 20. Possible Reaction Route for Formation of Product XXXVII from Ozonation of XXXIII

Conversely, the formation of product XXXVIII involves ozonolysis of Ring A of XXXIII, initiated between positions 3 and 4, followed by lactonization of the resultant muconic acid derivative to yield δ-lactone LV (Route 22 in Fig. 21). A similar mechanism has been proposed as a major pathway during the ozonations of XVIII (Fig. 8) and XXVII (Fig. 11), both of which yielded muconic acid δ-lactones as reaction products. Subsequent cleavage of the β-aryl ether linkage of LV *via* ozone attack at the aryl end of the linkage (cf. Routes 17-20 of Fig. 19) yields product XXXVIII.

Product XXXIX then can arise *via* degradation of product XXXVIII (Route 23 in Fig. 21). Accordingly, ozonolysis of the two carbon-carbon double bonds of XXXVIII yields LVI. Compound LVI then undergoes decarboxylation followed by oxidation *via* a 1,3-dipolar ozone insertion mechanism (16) to yield product XXXIX.

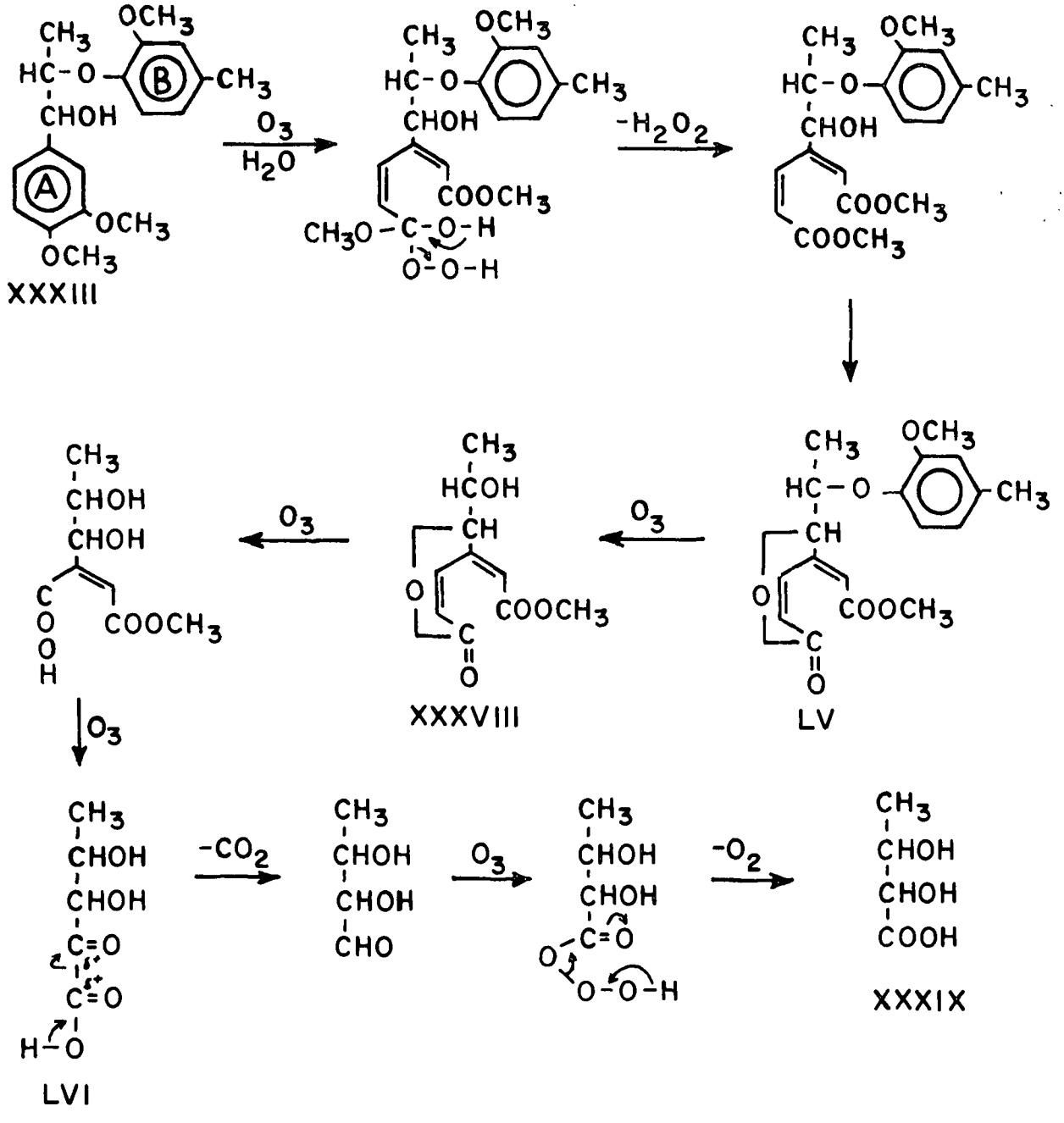


Figure 21. Proposed Reaction Routes for Formation of Products XXXVIII and XXXIX from Ozonation of XXXIII

Alternatively, cleavage of the β-aryl ether linkage of XXXIII could precede ozonolysis of Ring A in the formation of products XXXVIII and XXXIX. However, in either case, the identification of XXXVIII and XXXIX as ozonation products provides evidence for extensive degradation of Ring A (initiated via scission

between the methoxyl bearing ring carbons) as well as additional evidence for cleavage of the β-aryl ether linkage as fundamental modes of attack during the ozonation of XXXIII.

The fact that formation of XXXVIII suggests ozone induced aromatic ring scission between adjacent ring carbons bearing alkoxyl substituents while formation of XXXVII suggests the converse corroborates the similar findings of Kratzl, et al. (41) during the ozonation of various substituted veratrols (Fig. 10). Thus, although others have observed preferential cleavage between adjacent ring carbons bearing hydroxyl and methoxyl substituents during the ozonation of various aromatic substrates (16,39,42), the aforementioned findings provide conclusive evidence that this cleavage is not exclusive.

QUANTITATIVE ANALYSIS RESULTS

The general work-up procedure employed for sample preparation prior to the quantitative and qualitative product analysis via GC divided the ozonized reaction solution samples into a "chloroform-soluble (neutral and phenolic) products" fraction and a "water-soluble products" fraction. Another sample work-up procedure was also employed in which a large sample of ozonized reaction solution was subjected to column chromatography, and the resultant fractions were then analyzed via GC. An approximate accounting of the XXXIII consumed during an ozonation is presented, on a weight basis, in Table V. These data are based upon the results of the quantitative GC analysis of the "neutral and phenolic products" fraction obtained via the general sample work-up procedure and the fractions obtained via column chromatography (no measurable amount of material was found via GC analysis of the "water-soluble products" fraction). A representative GC chromatogram of the neutral and phenolic products fraction obtained from the ozonation of XXXIII is shown in Fig. 22. The compounds corresponding

to all of the major peaks in Zone B of this chromatogram have been positively identified (the nature of products LXII and LXIII is discussed in a later section) and, as indicated in Table V, represent about 11% (weight basis) of the XXXIII consumed during an ozonation. Assuming that the remainder of the peak area in Zone B of the chromatogram corresponds to numerous initial and secondary ozonation products present in amounts too small to allow identification, an additional 26% of the XXXIII consumed can be attributed to detected, but unidentified, ozonation products (assuming a response factor of 1.00). Still another 3% of the XXXIII consumed corresponds to volatile material lost during the sample work-up procedure prior to analysis.

TABLE V

ACCOUNTING FOR XXXIII CONSUMED DURING AN OZONATION (WEIGHT BASIS)

Item	% of XXXIII Accounted For[a]
Identified ozonation products	10.5-11.5
Detected unidentified ozonation products[b]	25.3-27.8
Volatile products[c]	3.2
TOTAL VOLATILE AND DETECTED PRODUCTS	39.0-42.5
Undetected ozonation products	57.5-61.0[d]

[a] Expressed as a weight percent of the theoretical yield of reaction products produced from the ozonation of XXXIII, employing the data of Table II.

[b] The material corresponding to the peak area of Zone B of the GC chromatogram in Fig. 22 less the area arising from the internal standard and identified ozonation products.

[c] The material lost due to volatility prior to GC analysis.

[d] This value was arrived at by subtracting the total percentage of volatile and detected products from 100.

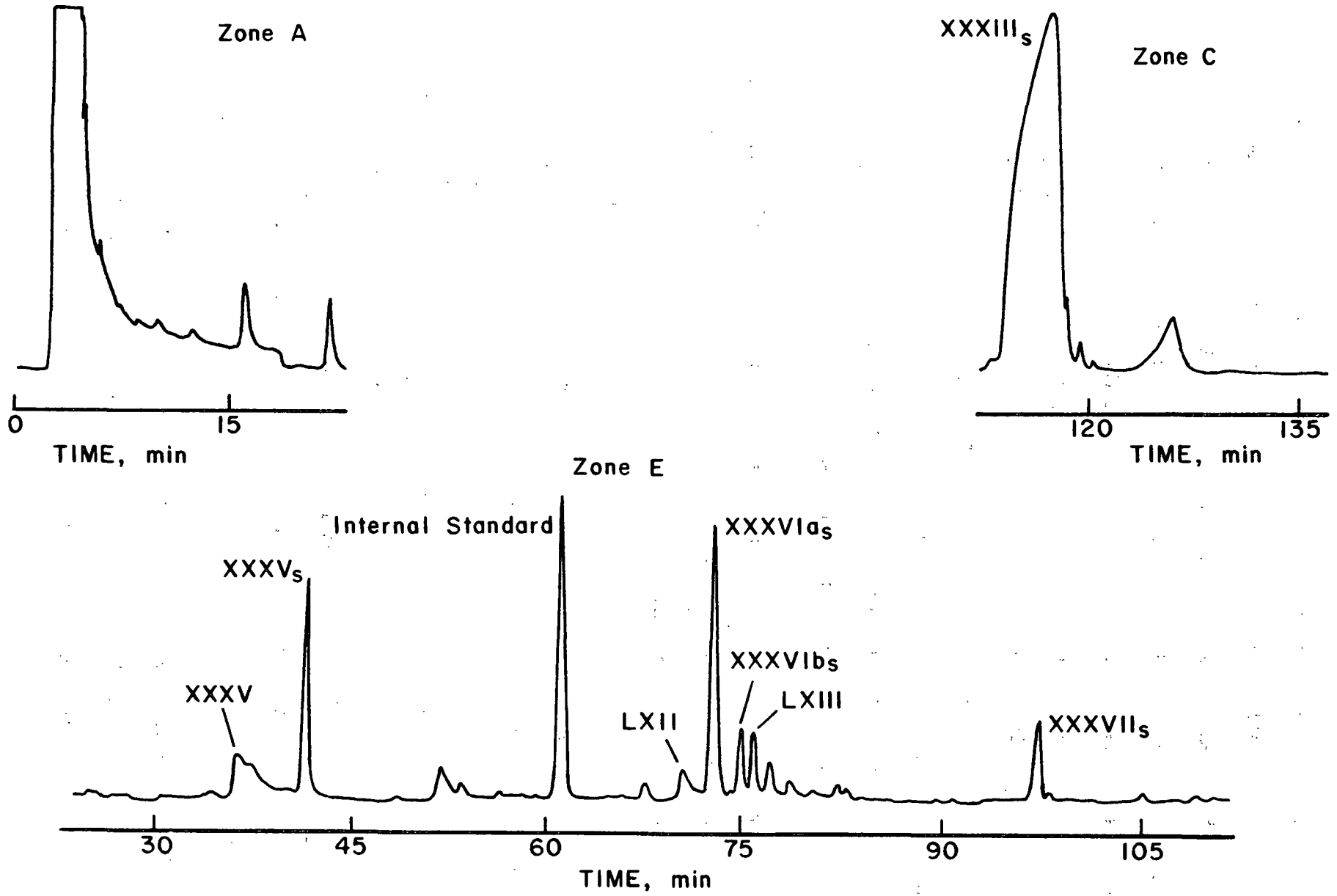


Figure 22. Representative GC Chromatogram of the Neutral and Phenolic Products Fraction Obtained from Ozonation of XXXIII (s Subscripts on the Roman Numerals in the Figure Denote Silyl Derivatives)

Since the peak area in Zone A of the GC chromatogram (Fig. 22) corresponds primarily to silylating reagents and solvents and the peak area in Zone C corresponds to the unreacted XXXIII and other material of comparable GC retention time, Zone B represents almost all of the GC peak area due to the ozonation products with GC retention times shorter than XXXIII and consequently provides a reasonably accurate quantitative measure of these products. In other words, the GC product analysis results indicate, with reasonable certainty, that about 40% of the XXXIII consumed during the ozonation was present as reaction products possessing GC retention times shorter than XXXIII. The remaining 60% of the ozonation products must therefore have been present as compounds possessing GC retention times equal to or greater than that of XXXIII.

This proposed presence of a significant amount (60%) of ozonation products possessing GC retention times equal to or greater than that of XXXIII (and therefore possessing volatilities less than or equal to that of XXXIII) was further substantiated by thermogravimetric analysis (TGA). In TGA, a sample is heated at a given rate on a balance, and the consequent change in weight is measured as a function of temperature (55). Accordingly, when a sample of an ozonized solution of XXXIII is subjected to TGA, any weight remaining after complete vaporization of XXXIII should represent the amount of material formed during the ozonation of XXXIII which is less volatile than XXXIII. In other words, TGA provides a method of measuring the amount of ozonation products of XXXIII which are less volatile than XXXIII (and therefore could not be detected *via* the GC analysis employed in this study).

TGA was conducted upon silylated samples of an unozonized and an ozonized solution containing similar concentrations of XXXIII, employing operating conditions which approximate those employed for the usual GC product analysis.

The results of these analyses were recorded as plots of weight (expressed as a percentage of the original sample weight) vs. temperature and are depicted by the three curves in Fig. 23. The curve obtained for the unozonized sample indicates that XXXIII (silylated) is completely vaporized at about 250°C, which is consistent with the detection of unreacted XXXIII (silylated) at about 240°C via the GC product analysis. Conversely, the curves (representing duplicate runs) obtained from the ozonized sample indicate (points A and B) that between 10 and 20% of the total sample weight is still present at the temperature at which XXXIII (silylated) should be completely vaporized. Subsequently, as the temperature continues to rise, the material slowly dissipates but is not completely vaporized until a temperature of about 400°C is attained.

These results strongly suggest that between 10 and 20% of the total ozonized sample consists of material of less volatility than XXXIII (silylated). Moreover, since the ozonation of XXXIII was only taken to about 30% completion, this 10 to 20% of the total sample weight actually represents about 31 to 66% of the total ozonation products formed from the ozonation of XXXIII. Thus, comparison of the TGA curves of an ozonized and an unozonized solution of XXXIII (silylated) provides conclusive evidence that 31 to 66% of the XXXIII consumed during the ozonation assumed the form of products possessing volatilities lower than XXXIII (silylated). Consequently, if the additional 31 to 66% of the reaction products detected via TGA is combined with the 40% detected via GC analysis (Table V), between 71 and 106% of the XXXIII consumed during the ozonation is accounted for in terms of detected material.

To determine more about the nature of these nonvolatile ozonation products an approximate accounting of the XXXIII consumed during an ozonation is presented on a molar basis in Table VI, based upon the reaction stoichiometry (i.e.,

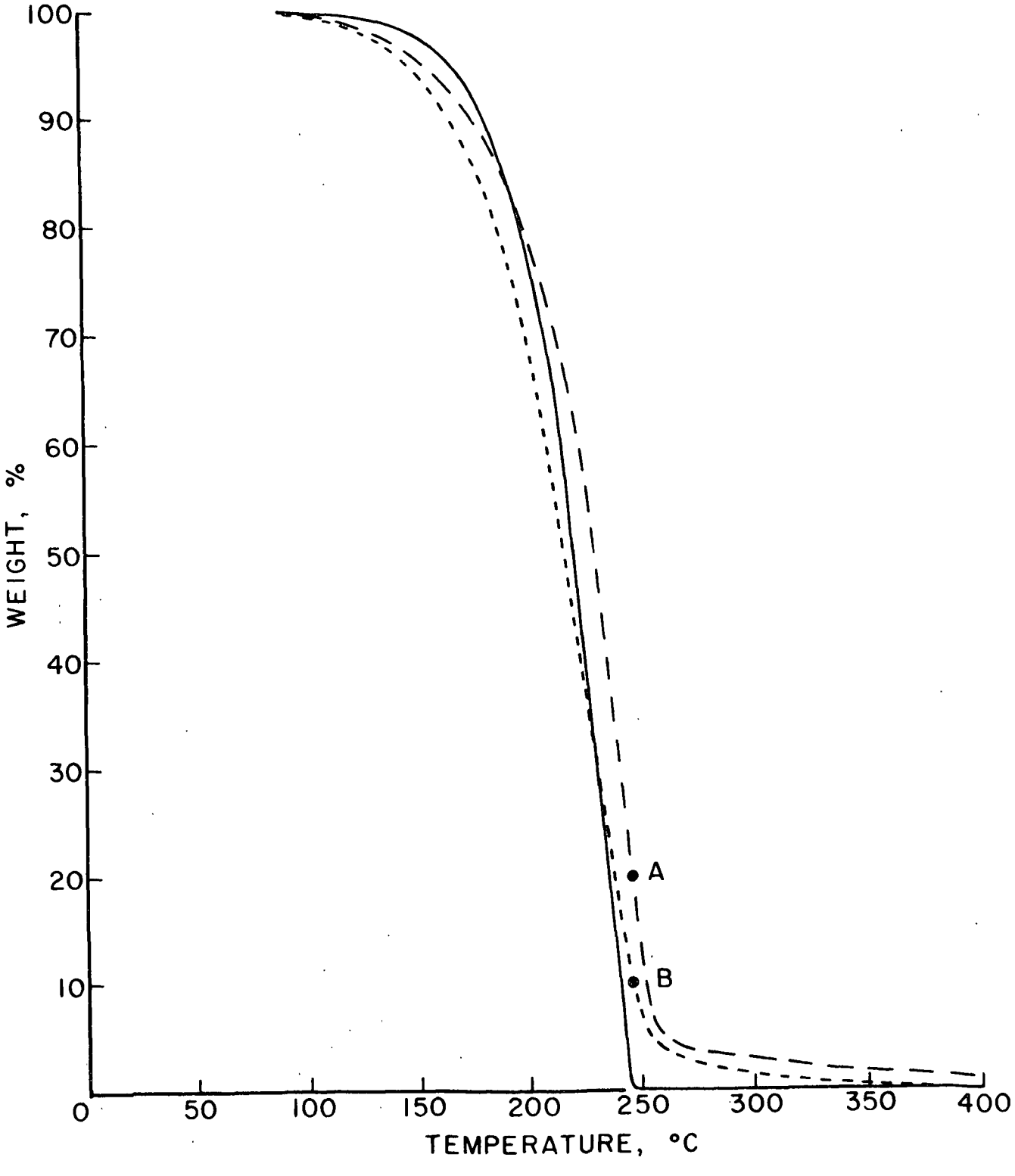
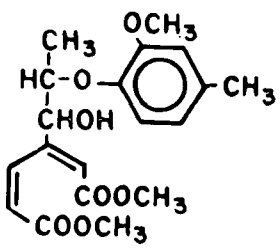


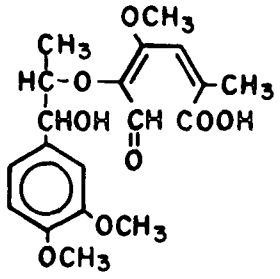
Figure 23. TGA Curves for Ozonized and Unozonized Solution of XXXIII

moles of ozone consumed/mole of XXXIII consumed) and the quantitative results listed in Table III. As discussed in a previous section, the reaction stoichiometry implies that at least 75% of the initial ozonation products of XXXIII were not degraded further by ozone under the mild reaction conditions employed in this study. Moreover, the identification of the secondary reaction products, XXXVII-XXXIX, which require from one to four additional moles of ozone for a given mole of XXXIII to be produced, indicates that in fact at least 79% of the initial ozonation products were not subject to further ozonation. Thus it appears that at least 79% of the XXXIII consumed during the ozonation is present in the form of initial ozonation products while not more than 21% is present in the form of secondary products arising from ozonation of the initial products. Furthermore, the quantitative results listed in Table III indicate that 19% of the ozonized XXXIII can be accounted for by identified initial ozonation products (i.e., products XXXV and XXXVI) and 3% by identified secondary products (i.e., products XXXVII-XXXIX); thus, as indicated in Table VI, 60% of the XXXIII consumed could be present as unidentified initial ozonation products, while 18% is present as unidentified secondary ozonation products.

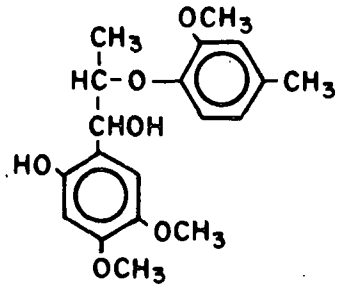
Inasmuch as the information in Table VI suggests that over 75% of the unidentified ozonation products of XXXIII are initial reaction products, it therefore follows that a significant portion of the "undetected" products referred to in Table V (and detected <u>via</u> TGA) is comprised of these unidentified initial ozonation products. Reasonable structures for such initial ozonation products would include compounds LVII-LX:



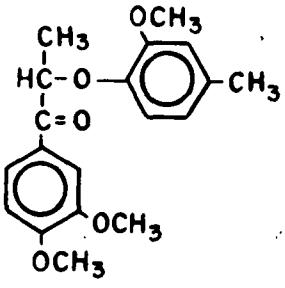
LVII



LVIII



LIX



LX

TABLE VI

ACCOUNTING FOR XXXIII CONSUMED DURING AN OZONATION (MOLAR BASIS)

Item	% of XXXIII Accounted For[a]
1. Total initial ozonation products	79
a. identified initial ozonation products	19[b]
b. unidentified initial ozonation products	60[c]
2. Total secondary ozonation products	21
a. identified secondary ozonation products	3[b]
b. unidentified secondary ozonation products	18[c]
3. Total unidentified ozonation products	78

[a]Expressed as a percentage of the millimoles of XXXIII consumed during the ozonation.
[b]Taken from Table III.
[c]This value represents the difference between the total and identified initial (or secondary) ozonation products

As discussed in a previous section, ozonolysis can be initiated between any two adjacent carbon atoms of the aromatic rings of XXXIII. Thus compounds LVII and LVIII represent only two of a possible fourteen initial ozonation products arising from ozonolysis of the aromatic rings of XXXIII. On the other hand, compounds such as LIX and LX could arise *via* electrophilic attack upon the aromatic rings and the 3-carbon side chain of XXXIII. Lawrence (50) obtained evidence for ring hydroxylation and identified LX as a reaction product during peroxyacetic acid oxidation of XXXIII, and as discussed in a previous section, electrophilic attack has led to ring hydroxylation and oxidation of

benzyl groups during the ozonation of various simple aromatic substrates (16,31-33,39) suggesting that similar reactions could occur during the ozonation of XXXIII.

Based upon chemical structure, compounds such as LVII-LX would be expected to have GC retention times greater than that of XXXIII. As a result, such products would probably not be detectable via the GC methods employed due to low volatility. Therefore, it is proposed that much of the nonvolatile "undetected" ozonation products listed in Table V is comprised of initial ozonation products such as compounds LVII-LX. The remainder of the undetected material, then, is most likely composed of high molecular weight compounds arising from the condensation/polymerization of initial and secondary ozonation products of XXXIII. As discussed in Appendix III, these condensation/polymerization reactions could proceed via a number of pathways and thus provide a means by which almost every conceivable ozonation product of XXXIII could have combined to form larger nonvolatile compounds not amenable to GC analysis as employed in this study.

This proposal was further substantiated by ultraviolet (UV) spectrometry. Pew (56) found that the UV spectra of most simple lignin model compounds display an absorption maximum at 280 nm followed by a sharp decrease to zero by 300 nm, and an absorption minimum at 250 nm followed by a significant increase in absorption at shorter wavelengths forming a large "trough" between 230 and 280 nm. On the other hand, a significant decrease in the size of this trough along with an increase in absorption in the 300-320 nm region were characteristics observed in the UV spectra of lignin and biphenyl condensation products such as XXV (p. 15).

In comparison, the UV spectrum of an unozonized sample of XXXIII (Fig. 24), with maxima at 230 and 280 nm and a minimum at 250 nm, was consistent with

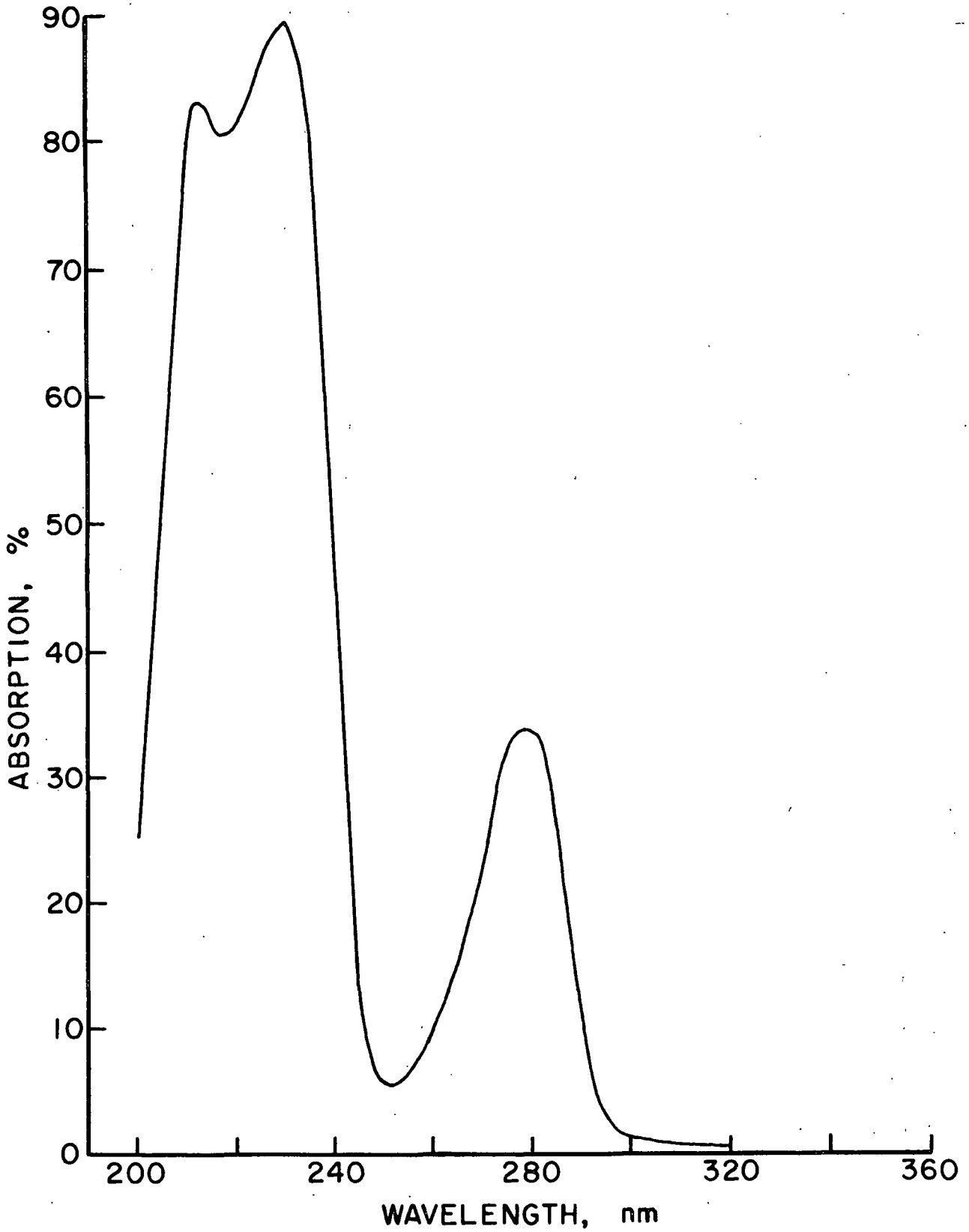


Figure 24. UV Spectrum of XXXIII in Absolute Ethanol

Pew's spectra of simple lignin model compounds, while the spectrum of an ozonized sample of XXXIII displayed increases in absorption in both the trough region (245-275 nm) and the 300-320 nm region, as illustrated by the "difference spectrum" of Fig. 25. Based upon Pew's findings (56), these results could indicate the occurrence of biphenyl condensation of the reaction products during the ozonation of XXXIII.

Alternatively, the increased absorption in the trough region of the ozonized sample could result from the presence of unsaturated carbonyl and carboxyl-containing compounds (57) such as would be expected to arise as the result of ozonolysis of the aromatic rings of XXXIII. In fact, the decrease in absorption at 230 and 280 nm shown in the "difference spectrum" suggests destruction of the aromatic structure of XXXIII, thereby providing corroborative evidence for such a hypothesis. Thus the UV data could be explained in terms of relatively high molecular weight nonvolatile unsaturated compounds such as the proposed initial ozonation products, LVII and LVIII, and/or condensation/polymerization products. The latter products could be formed from the original ozonolysis products *via* such processes as coupling of hydroperoxide radicals, intermolecular esterification, or perhaps the Diels-Alder reaction, as discussed in Appendix III.

Thus, comparison of the UV spectra of an unozonized and an ozonized solution of XXXIII provides additional experimental evidence which is consistent with the hypothesis that the "undetected" products arising from the ozonation of XXXIII are large nonvolatile initial ozonation products and condensation/polymerization products.

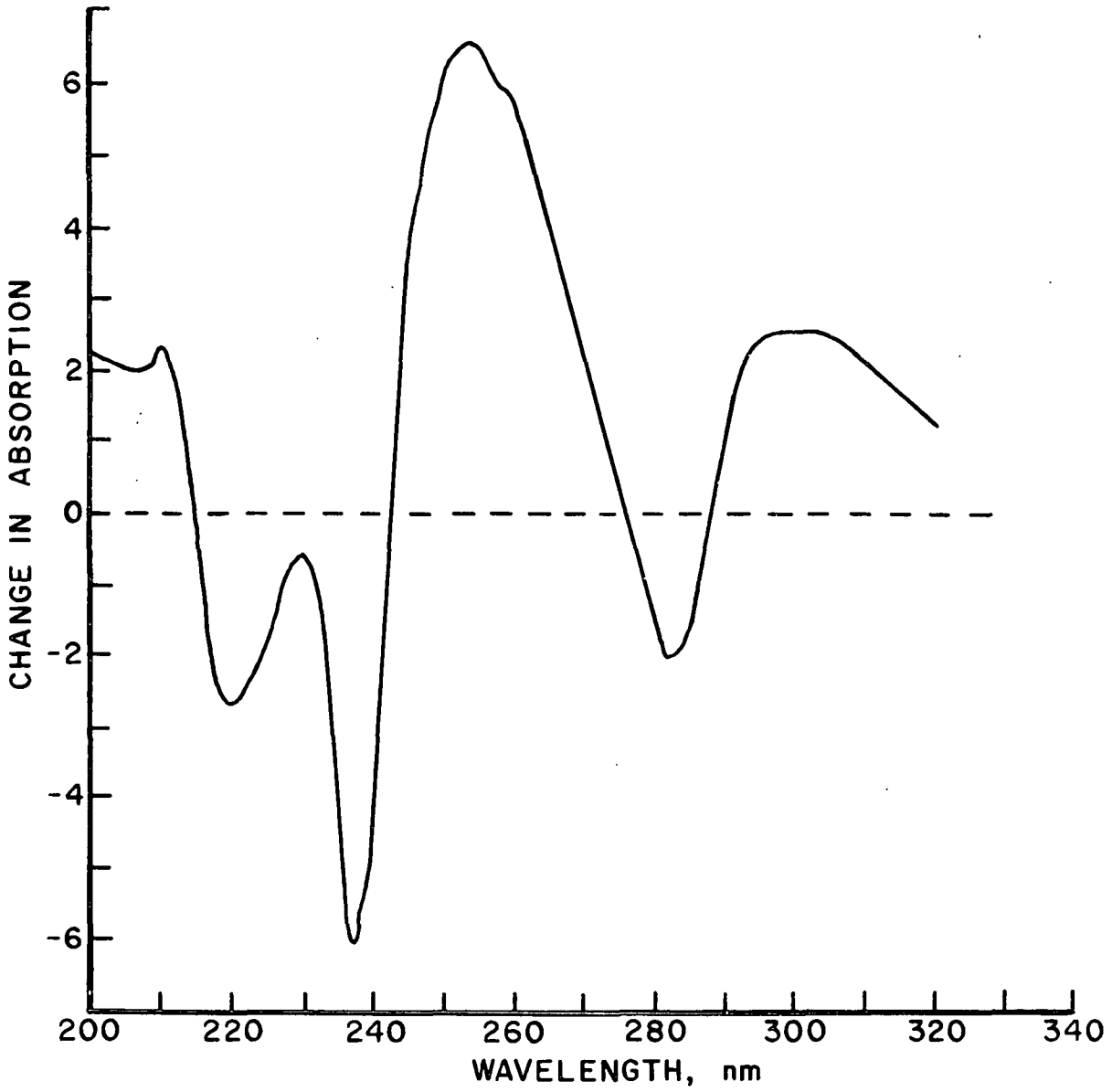


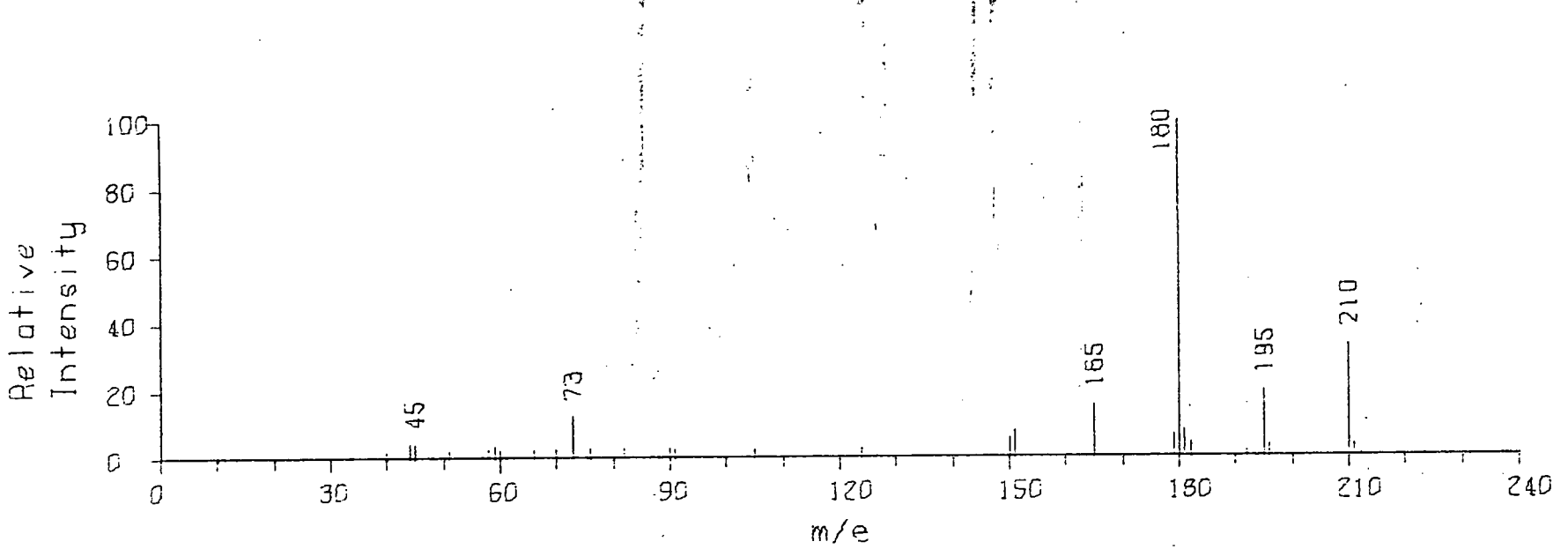
Figure 25. "Difference Spectrum" (i.e., UV Spectrum of an Ozonized Sample of XXXIII Minus the UV Spectrum of an Unozonized Sample of XXXIII)

QUALITATIVE ANALYSIS OF OZONATION PRODUCTS

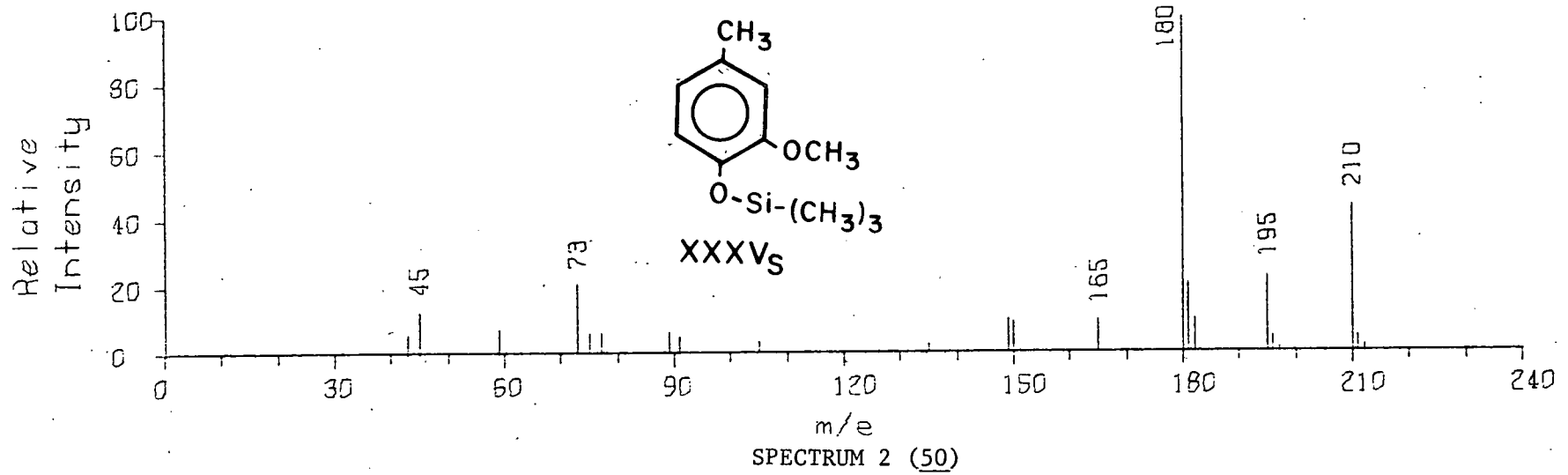
To facilitate the identification of the various ozonation products of XXXIII, a large aliquot comprising about 84% of the ozonized reaction solution of XXXIII was subjected to initial fractionation *via* column chromatography to provide a crude separation of the various reaction solution components. The resultant fractions were subjected to silylation and then analyzed *via* GC, preparative GC, NMR, and GC-MS. The results of the qualitative product analysis, as already discussed, are summarized in Table III (p. 26), and the structures of the positively identified ozonation products are shown in Fig. 15. For the most part, products were identified in the form of trimethylsilyl (TMS) derivatives. The following is a detailed presentation and discussion of the experimental evidence employed to identify the ozonation products of XXXIII detected in this study.

The identification of XXXV as an ozonation product was confirmed by comparison of the relative GC retention times, mass spectra, and NMR spectra of the silylated ozonation product and an authentic sample of the TMS ether of XXXV ($XXXV_s$). As indicated by Fig. 26 and 27, there is excellent agreement between the spectra of the ozonation product and the authentic sample. In addition, a small amount of ozonation material thought to be unsilylated XXXV was also detected, and as shown in Fig. 28, this material yielded a mass spectrum identical to that of an authentic sample of unsilylated XXXV.

Likewise, XXXVI was confirmed as an ozonation product in the same manner as employed for XXXV. Figures 29 and 30 demonstrate the excellent agreement between the mass and NMR spectra of an ozonation product and an authentic sample of the *erythro* isomer of the *bis*-TMS ether of XXXVI ($XXXVIa_s$). In addition, a small amount of an ozonation product with a slightly longer GC



SPECTRUM 1

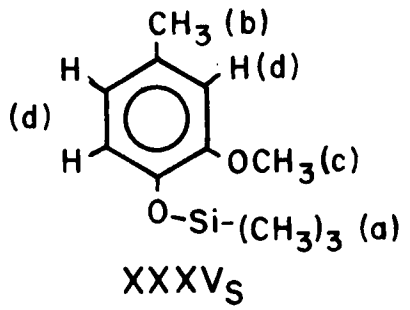


SPECTRUM 2 (50)

Figure 26. Mass Spectra of a Silylated Ozonation Product (SPECTRUM 1) and an Authentic Sample of $XXXV_s$ (SPECTRUM 2)

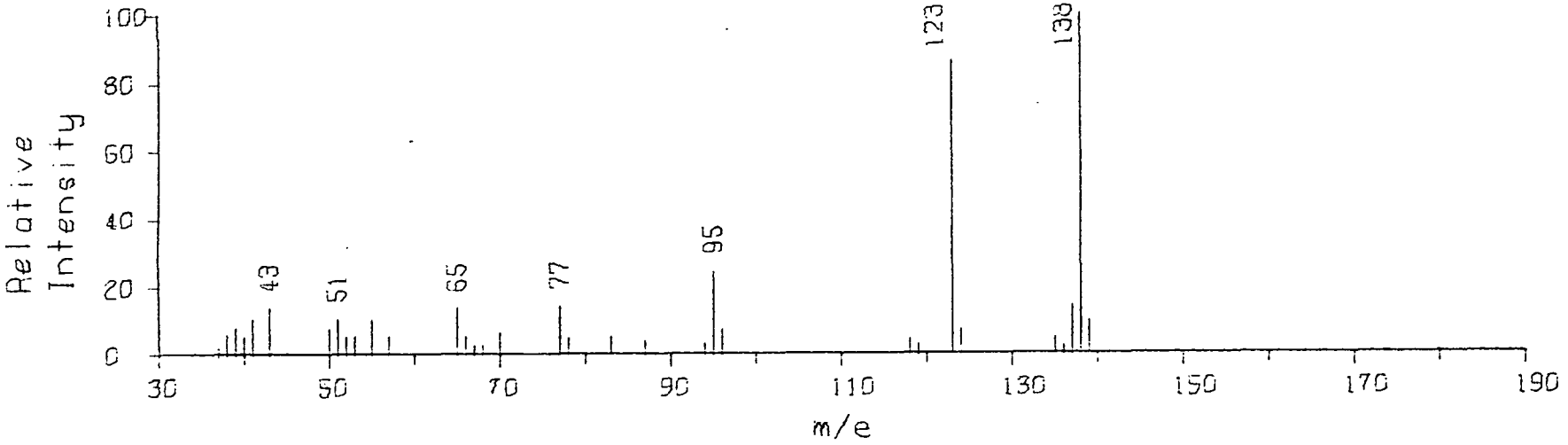
Chemical Shift (ppm)[a]					
Product	Known[b]	Type of Proton	Type of Peak	J(Hz)	Number of Protons
0.23	0.28	(a)	Sing.	---	4[c]
2.29	2.29	(b)	Sing.	---	3
3.79,3.87	3.80,3.86[d]	(c)	Pr. Sing.[e]	---	3
6.60-6.90	6.60-6.90	(d)	Mult.	---	3

[a]Relative to chloroform at 7.26 ppm.
[b]The chemical shift observed for an authentic sample of XXXV, TMS ether (50).
[c]Low value possibly due to degradation of the TMS group.
[d]The chemical shifts for authentic samples of unsilylated and silylated XXXV, respectively (50).
[e]Two methoxyl peaks are obtained as a result of partial hydrolysis of the TMS group.

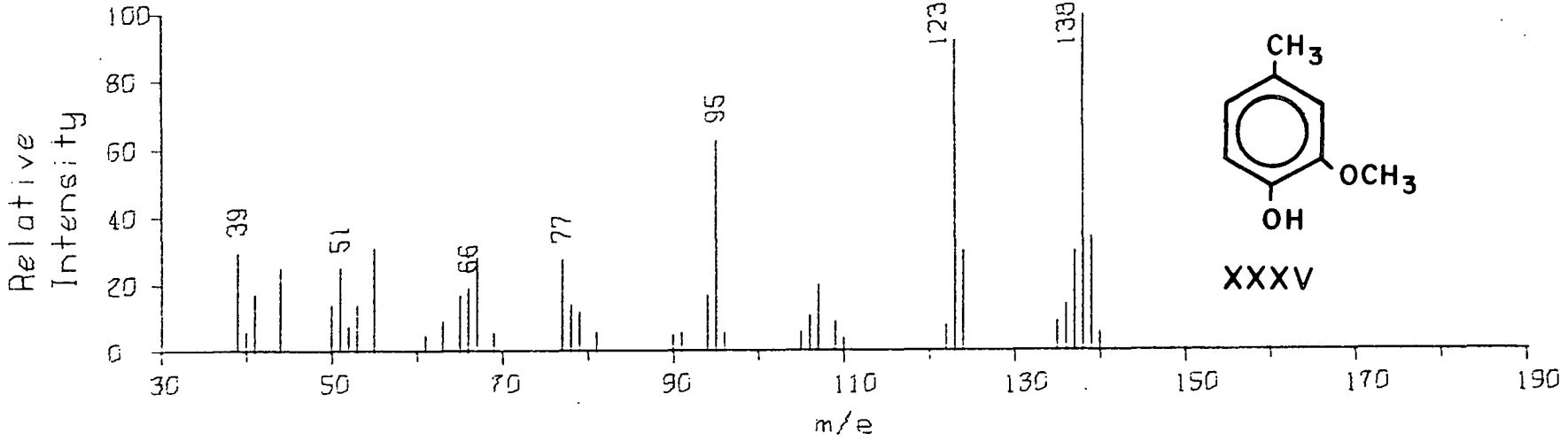


XXXV$_S$

Figure 27. NMR Spectra of the Silylated Ozonation Product and an Authentic Sample of XXXV, TMS Ether



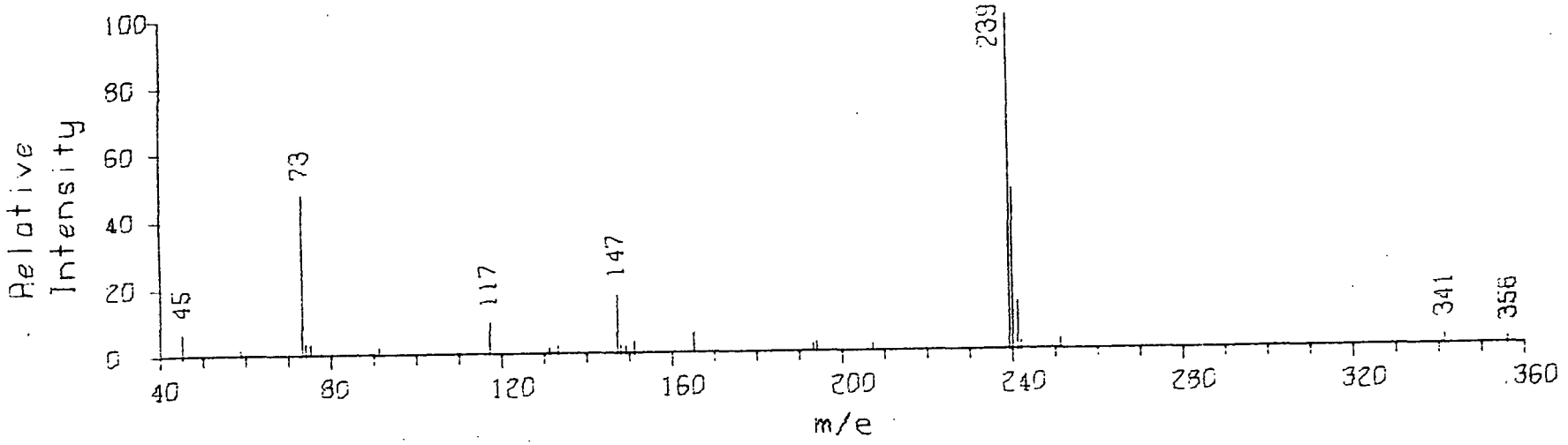
SPECTRUM 3



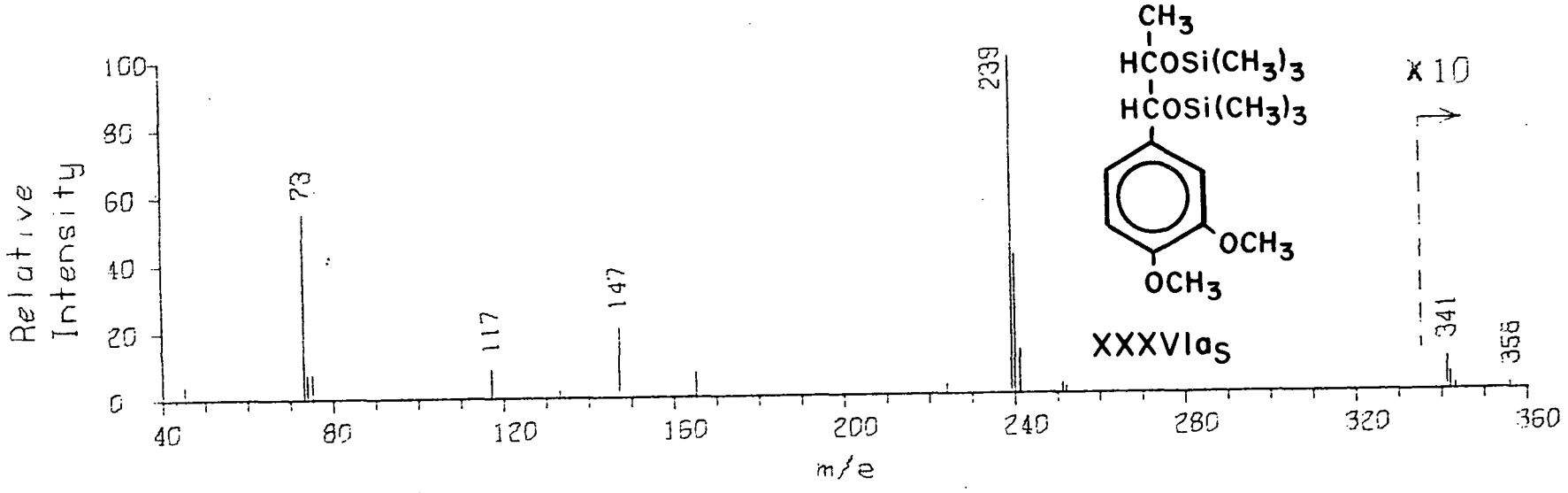
SPECTRUM 4 (58)

XXXV

Figure 28. Mass Spectra of an Ozonation Product (SPECTRUM 3) and an Authentic Sample of XXXV (SPECTRUM 4)



SPECTRUM 5

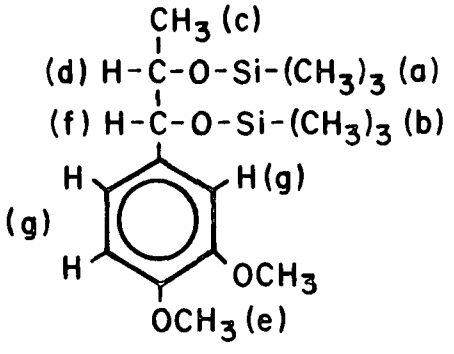


SPECTRUM 6 (50)

Figure 29. Mass Spectra of a Silylated Product (SPECTRUM 5) and an Authentic Sample of XXXVIa$_S$ (SPECTRUM 6)

Chemical Shift (ppm)[a]					
Product	Known[b]	Type of Proton	Type of Peak	J(Hz)	Number of Protons
-0.14	-0.14	(a)	Sing.	---	7
0.01	0.01	(b)	Sing.	---	8
1.17	1.17	(c)	Doub.	6	3
3.69	3.66	(d)	Mult.	---	1
3.85	3.86	(e)	Sing.	---	6
4.27	4.22	(f)	Doub.	6	1
6.74-6.90	6.70-6.86	(g)	Mult.	---	3

[a] Relative to chloroform at 7.24 ppm.
[b] The chemical shift observed for authentic sample of XXXVI, bis-TMS ether.

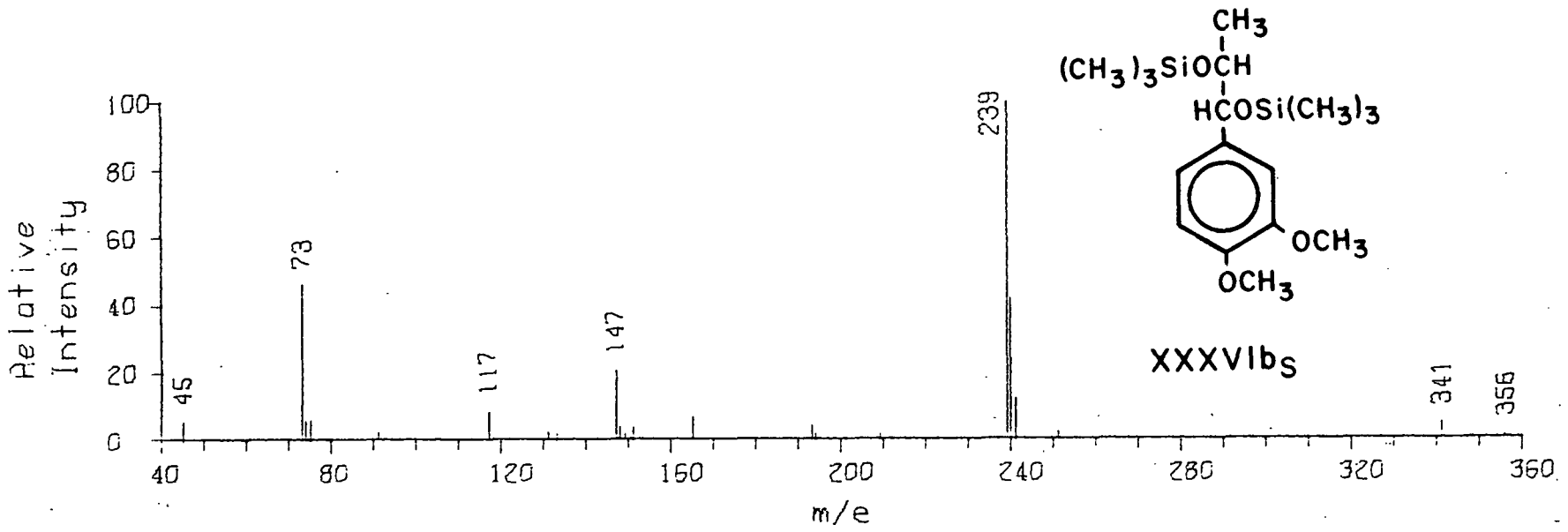


XXXVIa$_S$

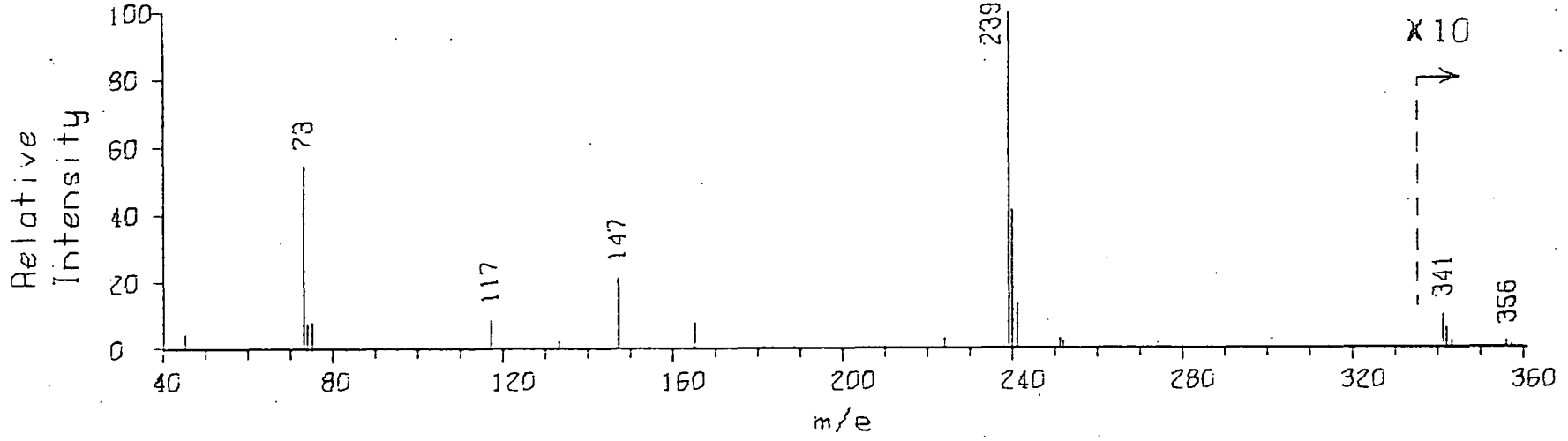
Figure 30. NMR Spectra of the Silylated Ozonation Product and an Authentic Sample of XXXVI, bis-TMS Ether

retention time than $XXXVIa_s$ was detected and shown to yield a mass spectrum identical to that of an authentic sample of the bis-TMS ether of XXXVI (Fig. 31). It was therefore concluded that this ozonation product was the threo isomer of the bis-TMS ether of XXXVI ($XXXVIb_s$). Further evidence for the formation of XXXVI during the ozonation of XXXIII was obtained from the detection of small amounts of ozonation products thought to be LXII and LXIII. Compound LXII most likely arises as a result of the pyrolytic dehydration of unsilylated XXXVI during the GC analysis (58) and, as shown in Fig. 32 and 33, the mass and NMR spectra of the ozonation product and an authentic sample of LXII are in excellent agreement. Likewise, compound LXIII, the mono-TMS ether of XXXVI, would arise from incomplete derivatization of XXXVI. As indicated in Fig. 34, the ozonation product in question yielded a mass spectrum which is consistent with the structure of LXIII. Accordingly, the apparent molecular ion (M) at m/e 284 corresponds to the molecular weight of LXIII, while peaks at m/e 269 (M-15) and m/e 73 are characteristic of TMS derivatives (59). Furthermore, similarly to the bis-TMS ether of XXXVI, the major fragmentation is due to cleavage between the α and β carbon atoms of the propyl side chain to yield the base peak at m/e 239 and a lesser peak at m/e 45.

The ozonation product identified as XXXVII yielded mass and NMR spectra consistent with the structure of the TMS ether of XXXVII ($XXXVII_s$). The apparent molecular ion at m/e 370 in the mass spectrum of the ozonation product (Fig. 35) corresponds to the molecular weight of $XXXVII_s$. Once again the base peak, m/e 239, arises via cleavage between the α and β carbon atoms of the propyl side chain, as was observed for the bis-TMS ether of XXXVI and derivative LXIII, while the major peak at m/e 73 is indicative of a TMS derivative. In addition, the peaks at m/e 59, m/e 267, and m/e 161 provided diagnostic information helpful in establishing the dicarboxylic ester structure of $XXXVII_s$.

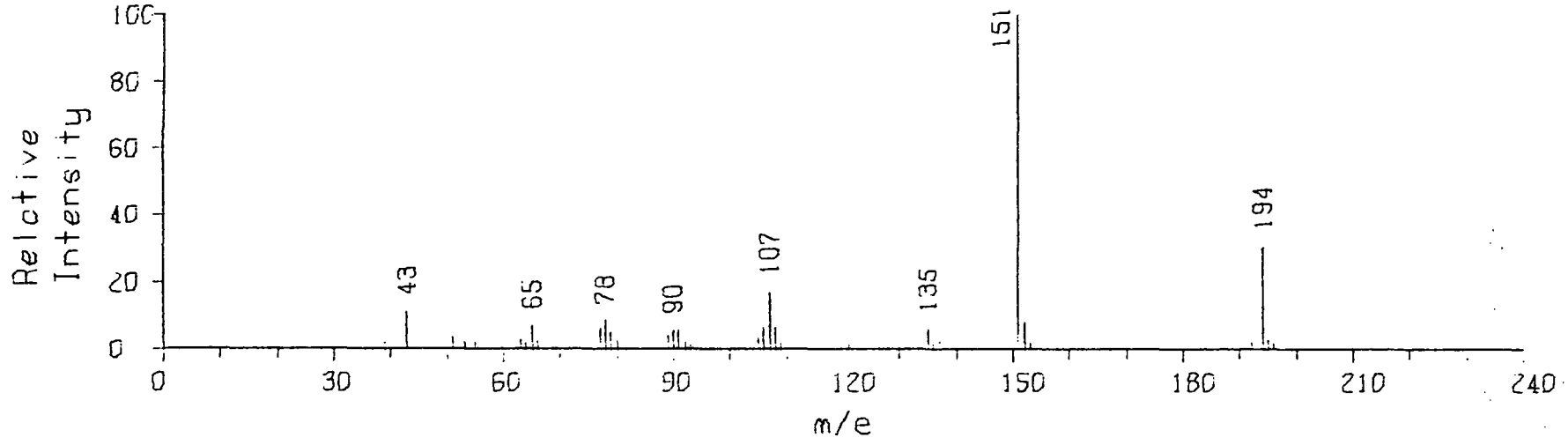


SPECTRUM 7

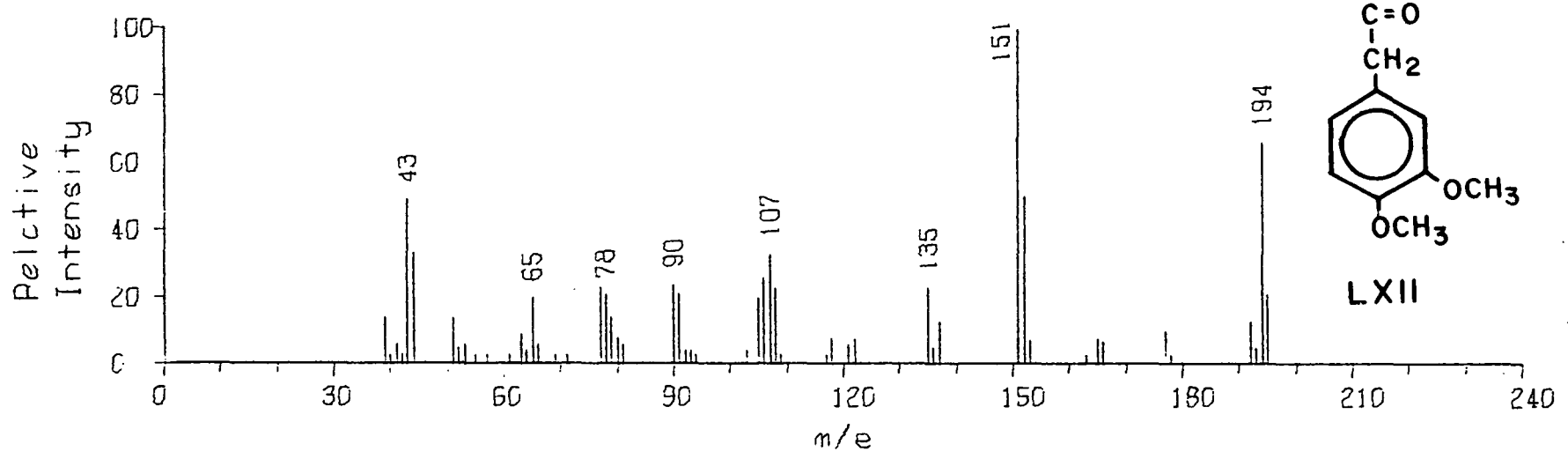


SPECTRUM 8 (50)

Figure 31. Mass Spectra of a Silylated Ozonation Product (SPECTRUM 7) and an Authentic Sample of XXXVIa$_s$ (SPECTRUM 8)



SPECTRUM 9



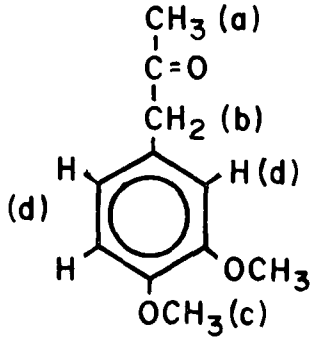
LXII

SPECTRUM 10 (58)

Figure 32. Mass Spectra of an Ozonation Product (SPECTRUM 9) and an Authentic Sample of LXII (SPECTRUM 10)

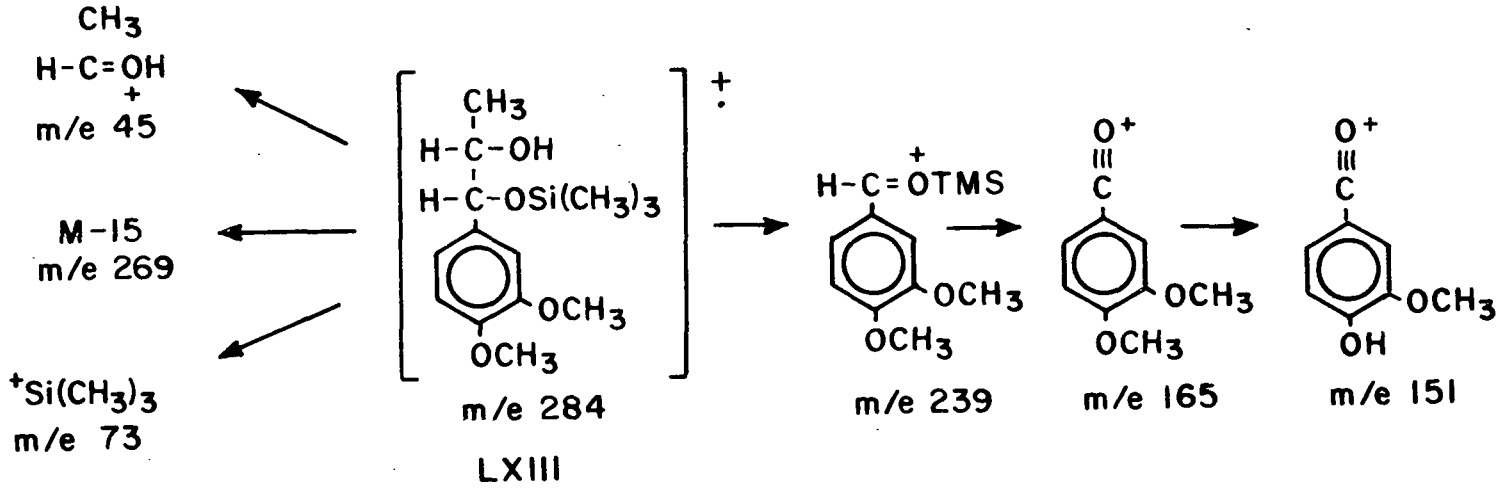
Chemical Shift (ppm)[a]					
Product	Known[b]	Type of Proton	Type of Peak	J(Hz)	Number of Protons
2.15	2.11	(a)	Sing.	---	3
3.63	3.60	(b)	Sing.	---	2
3.87	3.80	(c)	Sing.	---	6
6.69-6.80	6.75	(d)	Mult.	---	3

[a]Relative to chloroform at 7.26 ppm.
[b]The chemical shift observed for an authentic sample of LXII.



LXII

Figure 33. NMR Spectra of the Ozonation Product and an Authentic Sample of LXII



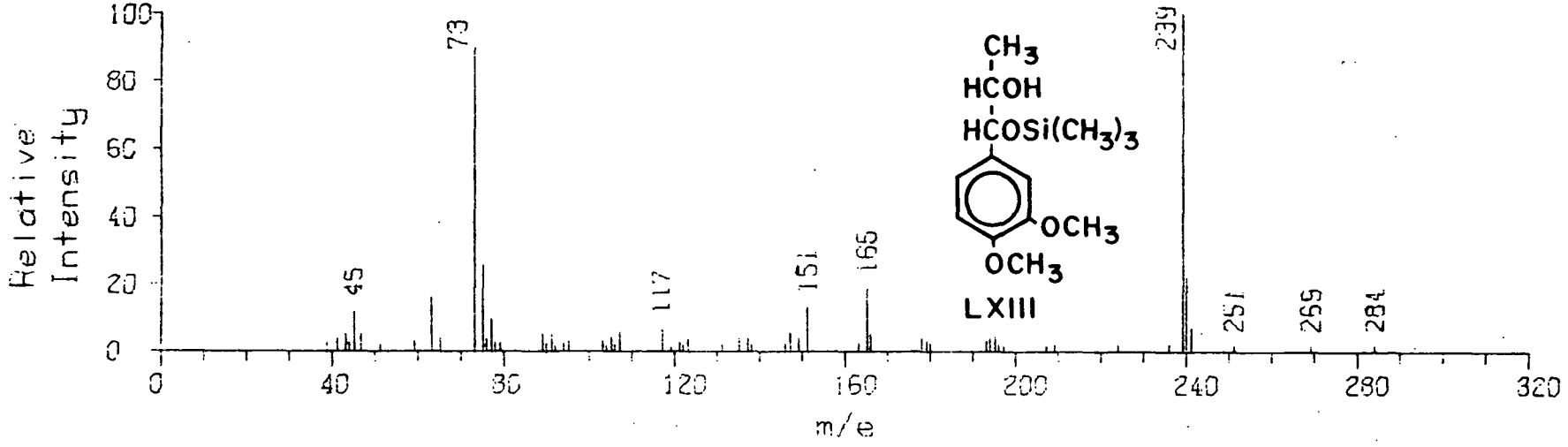
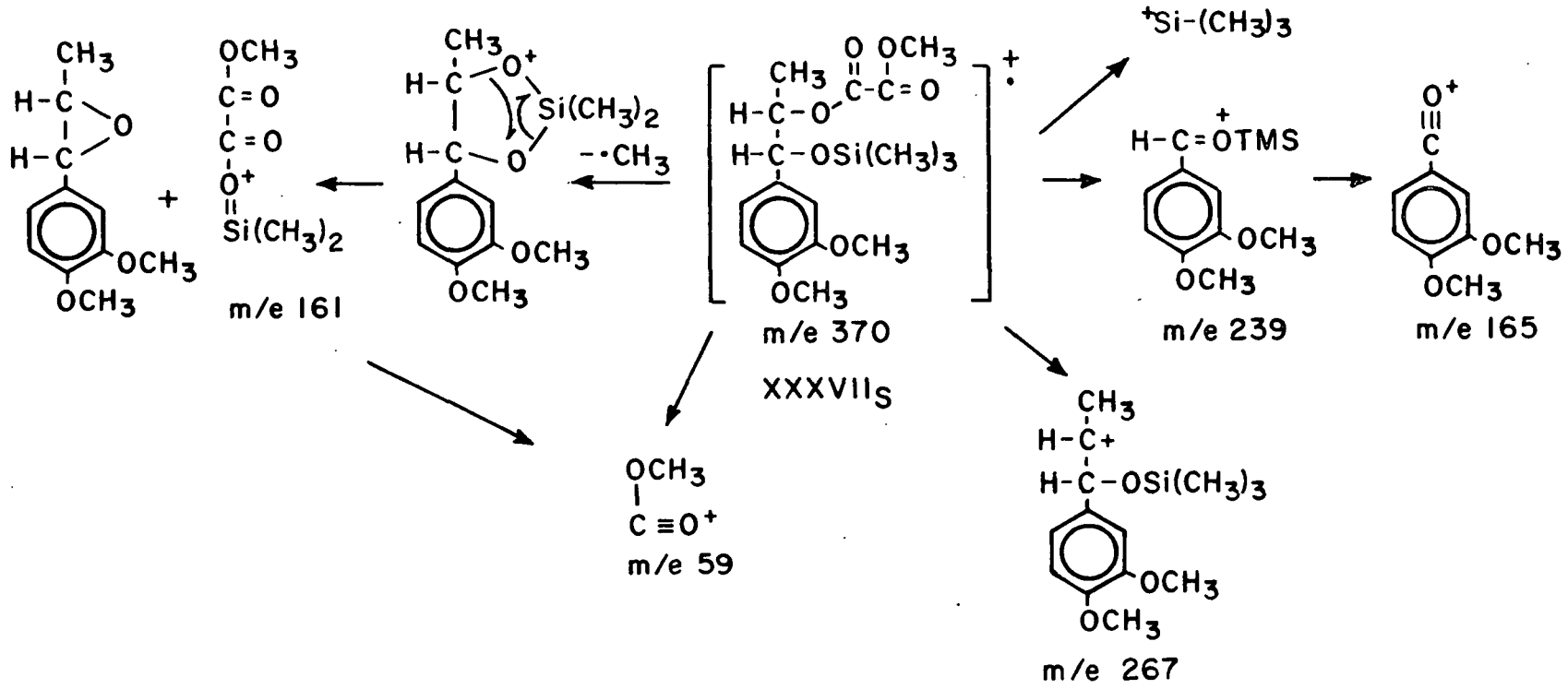


Figure 34. Mass Spectrum of the Ozonation Product Identified as LXIII



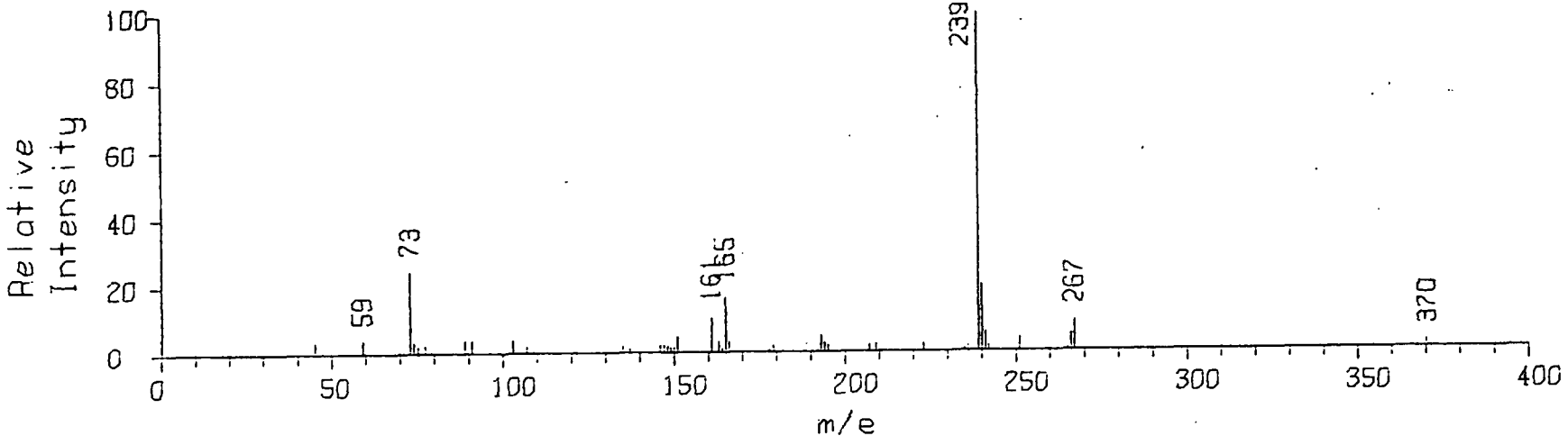


Figure 35. Mass Spectrum of the Ozonation Product Identified as $XXXVII_s$

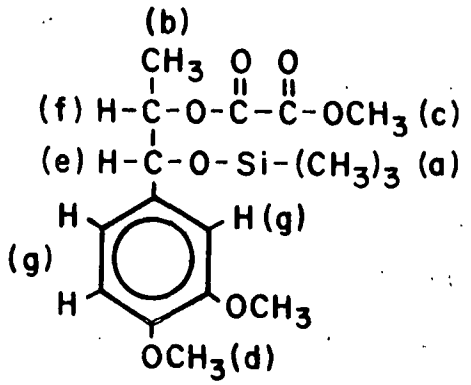
The peak at m/e 59 is characteristic of methyl esters (57,59), while the peak at m/e 267 represents fragmentation that has been observed for esters in which the alcohol moiety is the predominant portion of the molecule (59). The peak at m/e 161 results from loss of a methyl radical with subsequent epoxide formation involving transfer of the dimethylsilyl group to the departing ester ion; major peaks are obtained from a similar fragmentation in the mass spectra of structurally related compounds such as β-phenoxyethyl TMS ether and the TMS derivatives of various diols (59).

The NMR spectrum of the silylated ozonation product identified as XXXVII (Fig. 36) corroborates the mass spectral findings. The peaks at 3.85-3.87 δ confirm the presence of three methoxyl groups most likely of aromatic or ester nature (57). Two of the methoxyl peaks, along with the peaks at 6.76-6.92 δ, can be employed to establish the dimethoxyphenyl type structure, while the third peak could be attributed to the ester methoxyl of $XXXVII_s$. As compared with the NMR spectrum of the bis-TMS ether of XXXVI (Fig. 30), the singlet at 0.06 δ is indicative of a benzylic TMS ether group, while the signals at 1.23, 4.73, and 5.10 δ are consistent with the expected signals for the protons of the propyl side chain of $XXXVII_s$. In particular, the large downfield shift observed for the proton on the β-carbon of this side chain, relative to its counterpart in the bis-TMS ether of XXXVI, was quite useful in confirming the presence of the ester group of $XXXVII_s$ [since replacement of a TMS ether group with an ester group should result in additional deshielding of the methine proton in question (57)].

The ozonation product identified as XXXVIII was also analyzed as the TMS derivative via mass and NMR spectrometry. With an apparent molecular ion at m/e 284, the mass spectrum of the ozonation product appears to be consistent

Chemical Shift[a] (ppm)	Type of Peak	J(Hz)	Number of Protons
0.06 (a)	Sing.	---	8
1.23 (b)	Doub.	6	3
3.85 (c) 3.87, 3.86 (d)	Trio Sing.	---	9
4.73 (e)	Doub.	6	1
5.10 (f)	Mult.	---	1
6.76-6.92 (g)	Mult.	---	3

[a]Relative to chloroform at 7.24 ppm.

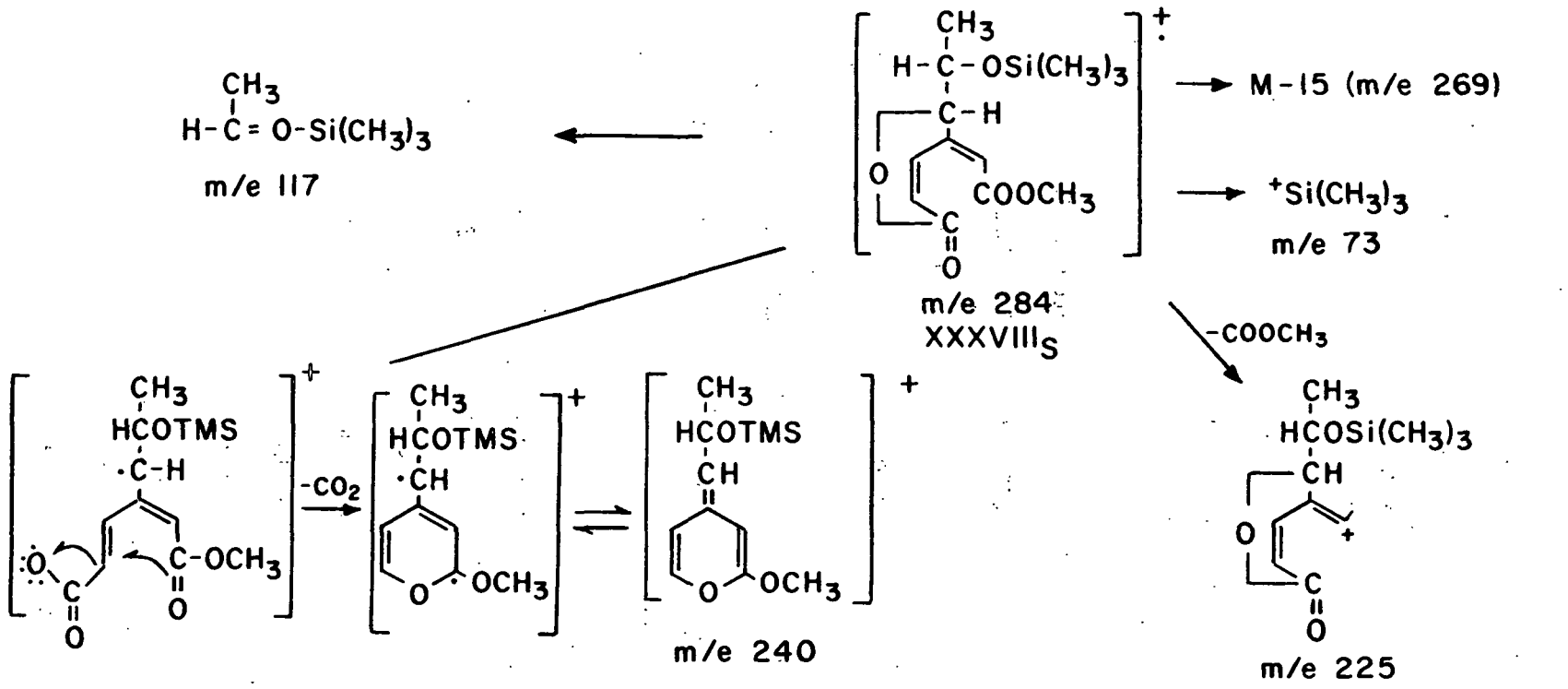


XXXVII$_S$

Figure 36. NMR Spectrum of the Ozonation Product Identified as XXXVII, TMS Ether

with the structure of the TMS ether of XXXVIII (Fig. 37). Based upon previous observations, the base peak at m/e 117 is predictable, and the major peaks at m/e 73 and 269 (M-15) are characteristic of TMS derivatives. Likewise, loss of a carboxylate group to yield the peak at m/e 225 could be expected, based upon the fragmentation pattern of the structurally related compound, ethyl sorbate (57). In addition, the peak at m/e 240 could arise *via* loss of carbon dioxide with subsequent rearrangement to the stable ion, LXIV (60), while the peak at m/e 59 is indicative of a methyl ester.

Likewise, the NMR spectrum of the silylated ozonation product is consistent with the structure of the TMS ether of XXXVIII (Fig. 38). The singlet at 0.03 δ confirms the presence of a TMS ether group similar to those found in the bis-TMS ether of XXXVI (Fig. 30), while the doublet at 1.24 δ and the multiplet at 3.70 δ are reminiscent of the signals obtained for the γ-methyl and β-methine protons on the propyl side chain of the bis-TMS ether of XXXVI. On the other hand, the singlet at 3.76 δ is slightly upfield from the signals observed for the aromatic methoxyl groups of products $XXXV_s$, $XXXVI_s$, and $XXXVII_s$, suggesting that this peak might best be explained in terms of a non-aromatic methoxyl group. At the same time, the signal at 4.56 δ reflects the slight downfield shift expected for proton (e) of $XXXVIII_s$ (Fig. 38), relative to the benzyl methine proton of the bis-TMS ether of XXXVI (Fig. 30), due to the replacement of a TMS ether group by a lactone; moreover, this signal at 4.56 δ comes at the same place as the corresponding methine proton signal in the NMR spectrum of the structurally related compound, γ-valerolactone (57). Finally, the signals at 5.84, 6.08, and 8.23 δ are consistent with the chemical shifts that would be predicted (57) for the three olefinic protons of $XXXVIII_s$ [i.e., protons (f), (g), and (h)]; furthermore, the coupling pattern for these



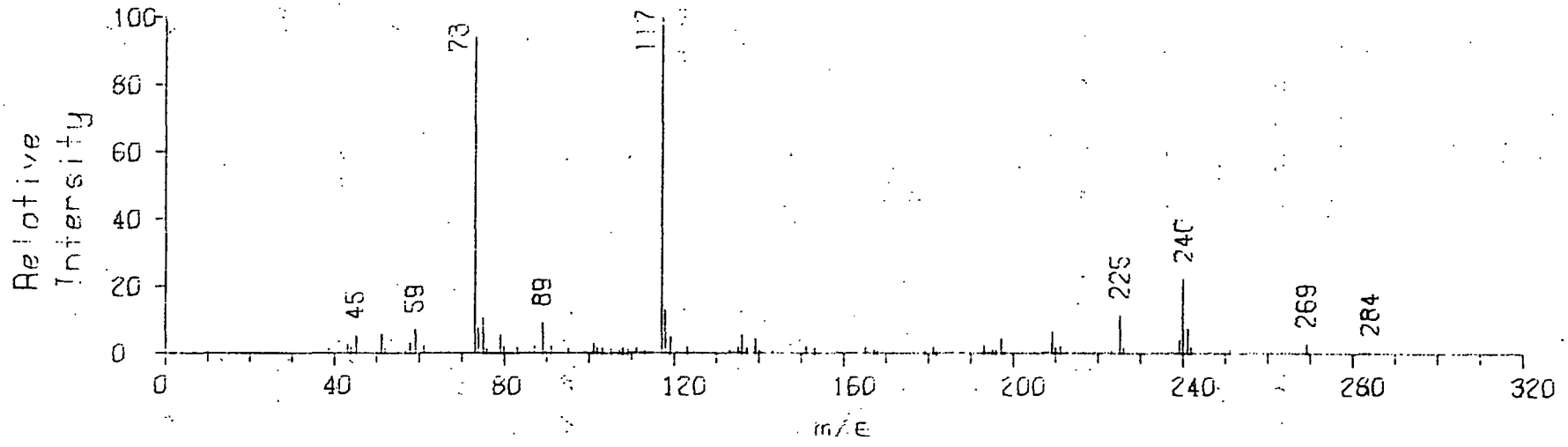
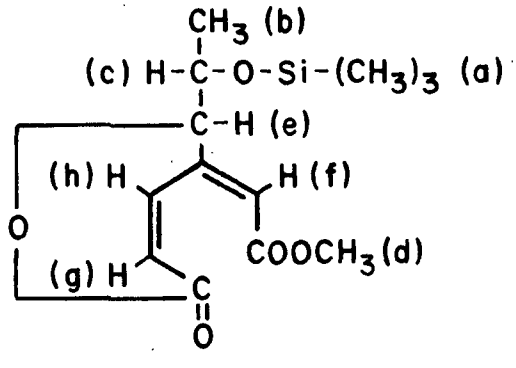


Figure 37. Mass Spectrum of the Ozonation Product Identified as XXXVIII$_s$

Chemical Shift[a] (ppm)	Type of Peak	J(Hz)	Number of Protons
0.03 (a)	Sing.	---	9
1.24 (b)	Doub.	6	b
3.70 (c)	Mult.	---	c + d = 4
3.76 (d)	Sing.	---	
4.56 (e)	Doub.	6	1
5.84 (f)	D of D	1&2	1
6.08 (g)	D of D	10&2	1
8.23 (h)	D of D	10&1	1

[a]Relative to chloroform at 7.24 ppm.
[b]Could not be determined due to impurity interference.

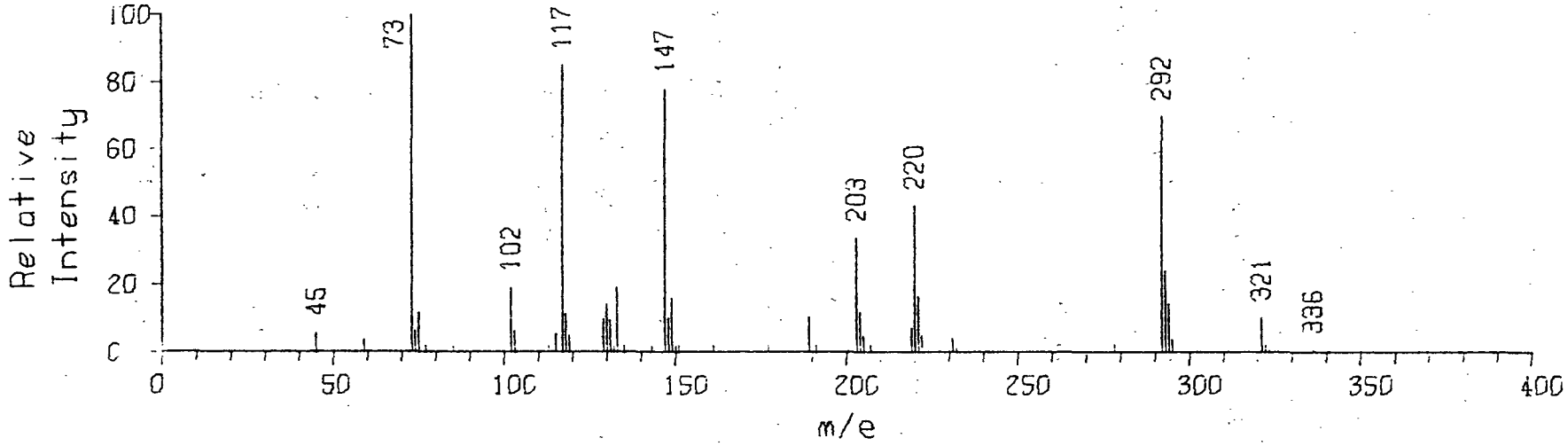


XXXVIII$_S$

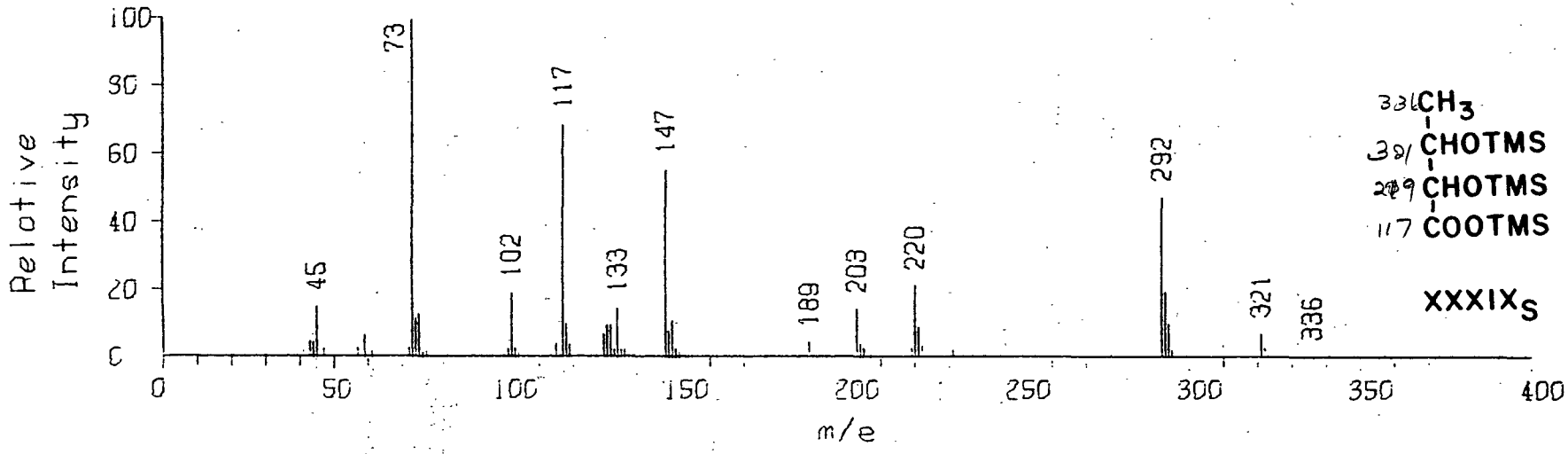
Figure 38. NMR Spectrum of the Ozonation Product Identified as XXXVIII, TMS Ether

three protons, including apparent long-range coupling between protons (f) and (g), and (f) and (h), is consistent with that observed in the NMR spectrum of the structurally related compound, 2-pyrone (61).

The identification of ozonation product XXXIX was confirmed via GC and mass spectral data. A silylated sample of the ozonation product displayed the same GC retention time as an authentic sample of silylated XXXIX. Moreover, there is excellent agreement between the mass spectra of the silylated ozonation product and an authentic sample of the TMS derivative of XXXIX (Fig. 39). Based upon these results it was concluded that the ozonation product was indeed compound XXXIX.



SPECTRUM 11



SPECTRUM 12

Figure 39. Mass Spectra of a Silylated Ozonation Product (SPECTRUM 11) and an Authentic Sample of $XXXIX_s$ (SPECTRUM 12)

EXPERIMENTAL

PREPARATION OF COMPOUNDS

COMMERCIAL AND DONATED CHEMICALS

Creosol (XXXV) was obtained from Eastman Organic Chemicals. The compound 3',4'-dihydroxypropiophenone was purchased from K & K Laboratories, Inc. Tri-Sil concentrate and N,O-bis-trimethylsilyltrifluoroacetamide (BSTFA) were purchased from Pierce Chemical Co. The compound 1-(3,4-dimethoxyphenyl)-propan-2-one was obtained from the collection of Dr. D. C. Johnson, and 1-(3,4-dimethoxyphenyl)ethanol (50) and 2,3-dihydroxybutyric acid (62) were obtained from previous studies.

SYNTHESIS OF COMPOUNDS

The compounds 3',4'-dimethoxypropiophenone (50) and 1-(3,4-dimethoxyphenyl)-2-bromopropan-1-one (63) were prepared as previously described in the literature. The physical constants of these compounds were in good agreement with the values reported in the literature, and their infrared spectra were identical to the spectra of authentic samples obtained from the collection of Lawrence (50).

Preparation of 4'-Benzyloxy-3'-methoxypropiophenone (BMP)

This compound was prepared from propiovanillone and benzyl bromide via the method of Lawrence (50). Recrystallization from isopropanol gave 18.6 g (82.5% yield) of white crystalline material: m.p. 94.5-95.5°C; literature: 94.5-96°C (50). ^{1}H-NMR (100 MHz, $CDCl_3$): δ 1.20 (t, CH_3, 3H, J = 7.2 Hz), 2.92 (q, CH_2, 2H, J = 7.2 Hz), 3.92 (s, OCH_3, 3H), 5.20 (s, OCH_2, 2H), 6.90-7.55 (m, arom., 8H).

Preparation of 1-(3,4-Dimethoxyphenyl)-2-hydroxypropan-1-one (DHP)

According to an adaptation of the method of Hibbert, et al. (64), 1-(3,4-dimethoxyphenyl)-2-bromopropan-1-one (19.3 g) was mixed with 5% aqueous potassium acetate (500 mL) in a round-bottom flask. The mixture was heated to a temperature just below the boiling point and stirred continuously for 10.5 hours. The resultant two-phase mixture was cooled to room temperature and extracted with chloroform (6 x 100 mL), and the combined extracts were dried over anhydrous sodium sulfate. The chloroform phase contains the DHP.

Preparation of 1-(3,4-Dimethoxyphenyl)propan-1,2-diol (XXXVI)

The chloroform phase containing the DHP was concentrated to an oil in vacuo and then dissolved in absolute ethanol (200 mL). Sodium borohydride (5.4 g) was added to the solution, and the mixture was stirred continuously for 4.5 hours. The mixture was next extracted with chloroform (10 x 60 mL), and the combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness in vacuo. The resultant solid was recrystallized from ethyl acetate several times to yield 2.2 g (14.6% yield) of a white crystalline material: m.p. 122-123.5°C; literature: 123°C (50). ^{1}H-NMR (100 MHz, $CDCl_3$): δ 1.11 (d, γ-CH_3, 3H, J = 6.0 Hz), 1.82 (d, β-OH, 1H, J = 6.0 Hz), 2.30 (d, α-OH, 1H, J = 3.0 Hz), 3.86 (pr. s, OCH_3, 6H), 3.96 (m, β-CH, 1H), 4.56 (d of d, α-CH, 1H, J = 3 and 5 Hz), 6.80-7.00 (m, arom., 3H).

Preparation of 1-(3,4-Dimethoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propanol (XXXIII)

This compound was prepared via the method of Lawrence (50). Crystallization from diethyl ether yielded a crystalline material (80.2% yield): m.p. 85-86°C; literature: 85-86°C (50). (Found: C, 68.44; H, 7.22. $C_{19}H_{24}O_5$ requires C, 68.67; H, 7.23%). ^{1}H-NMR (100 MHz, $CDCl_3$): δ 1.18 (d, γ-CH_3, 3H,

J = 6.6 Hz), 2.35 (s, ϕ-CH_3, 3H), 3.5 (s, OH, 1H), 3.85 (s, OCH_3, 9H), 4.32 (m, β-CH, 1H), 4.87 (d, α-CH, 1H, J = 3.0 Hz), 6.70-7.10 (m, arom., 6H).

Acetylation of XXXIII

To check the isomeric purity of XXXIII, the acetyl derivative, XXXIV, was prepared as follows. Compound XXXIII (16 mg) was shaken overnight with acetic anhydride (1.5 mL) and dry pyridine (6 mL) in a 10-mL Erlenmeyer flask. Thin-layer chromatography indicated that the acetylation was complete at this point. Subsequently, the solution was poured into chloroform (30 mL) and extracted with 1N hydrochloric acid (3 x 50 mL) and then distilled water (3 x 50 mL). The chloroform phase was next dried over anhydrous sodium sulfate and then evaporated to near dryness in vacuo at 25-30°C. The resultant residue was then transferred to an NMR tube using small amounts of deuterated chloroform and subsequently subjected to NMR analysis. The acetoxy protons of the threo isomer of XXXIII gave a signal at 2.00 δ while the erythro isomer gave an acetoxy proton signal at 2.10 δ.

ANALYTICAL PROCEDURES

MELTING POINTS AND pH MEASUREMENTS

Melting points were taken on a Thomas-Hoover capillary melting point apparatus. The pH measurements were made with a Beckman Zeromatic pH Meter employing Corning pH and reference (calomel) electrodes.

INFRARED SPECTROPHOTOMETRY

All infrared analyses were conducted on either a Perkin-Elmer Model 700 recording spectrophotometer or a Perkin-Elmer Model 621 grating infrared spectrophotometer.

NUCLEAR MAGNETIC RESONANCE SPECTROMETRY

NMR analysis was performed on a Jeol JNM-FX100 FT NMR spectrometer (100 MHz spectra). The solvents employed were deuterated chloroform containing 1% TMS (Stohler Isotope Chemicals) and 99.8% deuterated chloroform (Aldrich Chemical Company, Inc.). The internal standards employed were the tetramethylsilane proton signal at 0.00 δ or the chloroform proton signal at 7.24 δ.

ULTRAVIOLET SPECTROPHOTOMETRY

UV analysis was performed with a Perkin-Elmer Model 576 ST spectrophotometer.

THERMOGRAVIMETRIC ANALYSIS

The TGA experiments were performed by Dr. Donald Churchill of Appleton Papers, Inc. The operating conditions employed included:

Atmosphere: prepurified nitrogen at 75 mL/min

Initial temperature program: ambient to 83°C at 1°/min

Second temperature program: 83°C to 400°C (or higher) at 5°/min

THIN-LAYER CHROMATOGRAPHY

Thin-layer chromatography (TLC) was performed using microscope slides coated with silica gel GF (Brinkman Instruments Co.). The slides were observed under a UV lamp, and the spots were then visualized by placing the slides in a closed glass jar containing iodine crystals. In addition, some slides were visualized by spraying with 2,4-dinitrophenylhydrazine to determine the presence of carbonyl compounds.

GAS CHROMATOGRAPHY

Quantitative and qualitative gas chromatography was performed on a Varian Aerograph 1200 gas chromatograph with a hydrogen flame ionization detector. The chromatograms were recorded via a Honeywell Electronic 16 recorder equipped with a MOD 227 Disc chart integrator. Prepurified nitrogen (Matheson Gas Products) was employed as the carrier gas. The other operating conditions employed for the various analyses included:

1. Starting Material Analysis

   Internal standard: 4'-benzyloxy-3'-methoxypropiophenone (BMP)

   Column: 4' x 1/8" stainless steel column packed with 5% SE-30 on 60/80 mesh Chromosorb W (AW-DMCS)

   Oven temperature: 205°C isothermal

   Injector temperature: 235°C

   Detector temperature: 295°C

   Flow rate: 30 mL/min

2. Analysis of the Neutral and Phenolic Ozonation Products

   Internal standard: 1-(3,4-dimethoxyphenyl)ethanol (DPE)

   Column: 13' x 1/8" nickel column packed with 3% OV-17 on Supelcoport (80/100 mesh)

   Oven temperature: 60°C for 6 min, then increased at 2°/min to 240°C

   Injector temperature: 230°C

   Detector temperature: 300°C

   Flow rate: 30 mL/min

3. Analysis of Acidic Ozonation Products

   Internal standard: hexanedioic acid

Oven temperature: 50°C for 12 min (or 60°C for 6 min), then increased at 2°/min to 240°C (or increased at 2°/min for 18 min and then 4°/min to 240°C)

All other operating conditions were the same as for the neutral and phenolic ozonation products.

4. Starting Material Analysis for the Competition Reaction

Internal standard: BMP

Column: 5' x 1/8" stainless steel column packed with 5% SE-30 on 60/70 mesh Anakrom ABS

Oven temperature: 170°C for 9 min, then increased at 10°/min to 205°C

All other operating conditions were the same as for the neutral and phenolic ozonation products analysis.

PREPARATIVE GAS CHROMATOGRAPHY

Preparative gas chromatography was performed on a Varian Aerograph 712 gas chromatograph equipped with a stream splitter and a hydrogen flame ionization detector. The chromatograms were recorded via a Perkin-Elmer Model 56 recorder. The operating conditions employed included:

Column: 20' nickel (1/4" o.d.) packed with 3% OV-17 on Supelcoport (80/100 mesh)

Oven temperature: 50-60°C for 6 min, then increase at 1°/min to 250°C and hold

Injector/detector temperatures: 265°C

Carrier gas: prepurified nitrogen at 80-85 mL/min

The fractions were collected in special Pyrex vessels described elsewhere (50). The collection vessels were then sealed with Parafilm M between injections and stored over Drierite until NMR analysis could be conducted (usually within 24

hours). The samples were then rinsed from the collection vessels into NMR tubes using 99.8% deuterated chloroform just prior to the NMR analysis.

GAS CHROMATOGRAPHY-MASS SPECTROMETRY

The mass spectral analyses were accomplished via a Du Pont Model 21-491 mass spectrometer interfaced (via a jet separator) with a Varian Aerograph 1400 gas chromatograph equipped with a hydrogen flame ionization detector and a Hewlett-Packard 7128A recorder. The mass spectra were recorded via a Century GPO 460 oscillographic recorder. Perfluorokerosene (lo-mass) was employed as a mass standard to facilitate assignment of mass-to-charge values to the sample spectra. Other operating conditions included:

GC column: 15' x 1/8" stainless steel column packed with 3% OV-17 on Supelcoport (80/100 mesh)

GC injector temperature: 235°C

GC carrier gas: helium (UHP grade, Matheson Gas Products) at 30 mL/min

GC block temperature: 300°C

GC to MS inlet tube temperature: 300°C

Source temperature: 195-210°C

Sensitivity: 4.0-8.0

Filament: GC

Pressure: less than 3×10^{-7} torr

Scan rate: 100 sec/decade or 40 sec/decade

Chart speed: 4 inches/sec

OZONE PRODUCTION

Ozone for the experiments was generated by passing oxygen (ED grade, Matheson Gas Products) through a Welsbach Model T-816 laboratory ozonator while

maintaining a constant oxygen pressure of 8 psig and a wattage of 70 w. The resultant ozone-oxygen stream (1-3% ozone by weight) was then split between two outlets (i.e., the ozone outlet and the ozone sample outlet), and the flow rate from each was monitored and controlled separately. Equation (6) represents the relationship between the flow rate and ozone content of these two exiting streams, where f_o and f_s are the flow rates from the ozone and ozone sample outlets, respectively, and c_o and c_s are the amounts of ozone offered (over a given period of time) from the ozone and ozone sample outlets, respectively.

$$f_o/f_s = c_o/c_s \qquad (6)$$

The validity of Equation (6) is demonstrated in Appendix IV.

OZONATION OF COMPOUND XXXIII

REACTION CONDITIONS

Compound XXXIII (1 or 3 g) was dissolved in 160 mL of A.C.S. grade acetone (Aldrich Chemical Company, Inc.) in the 250-mL Pyrex wash bottle which was the reactor for this study (Fig. 40). Triply distilled water (40 mL) was then added, and the solution was thoroughly mixed *via* a magnetic stirrer. Duplicate samples (0.7-2 mL) were taken from the resultant solution and weighed into tared 8-mL vials. The reactor was then sealed and allowed to attain a temperature of 25°C in a constant temperature water bath. In some cases the substrate was dissolved in 200 mL of 60% aqueous acetic acid (v/v) rather than aqueous acetone. Extra-dry oxygen was fed through the ozonator to establish the proper oxygen pressure and outlet flow rates, and the exit gas from the ozonator was diverted to large potassium iodide (KI) traps *via* the bypass line (Fig. 40). The reactor was then connected to the rest of the reaction system by placing the reactor top in position (as shown in Fig. 40) and securing it with a clamp.

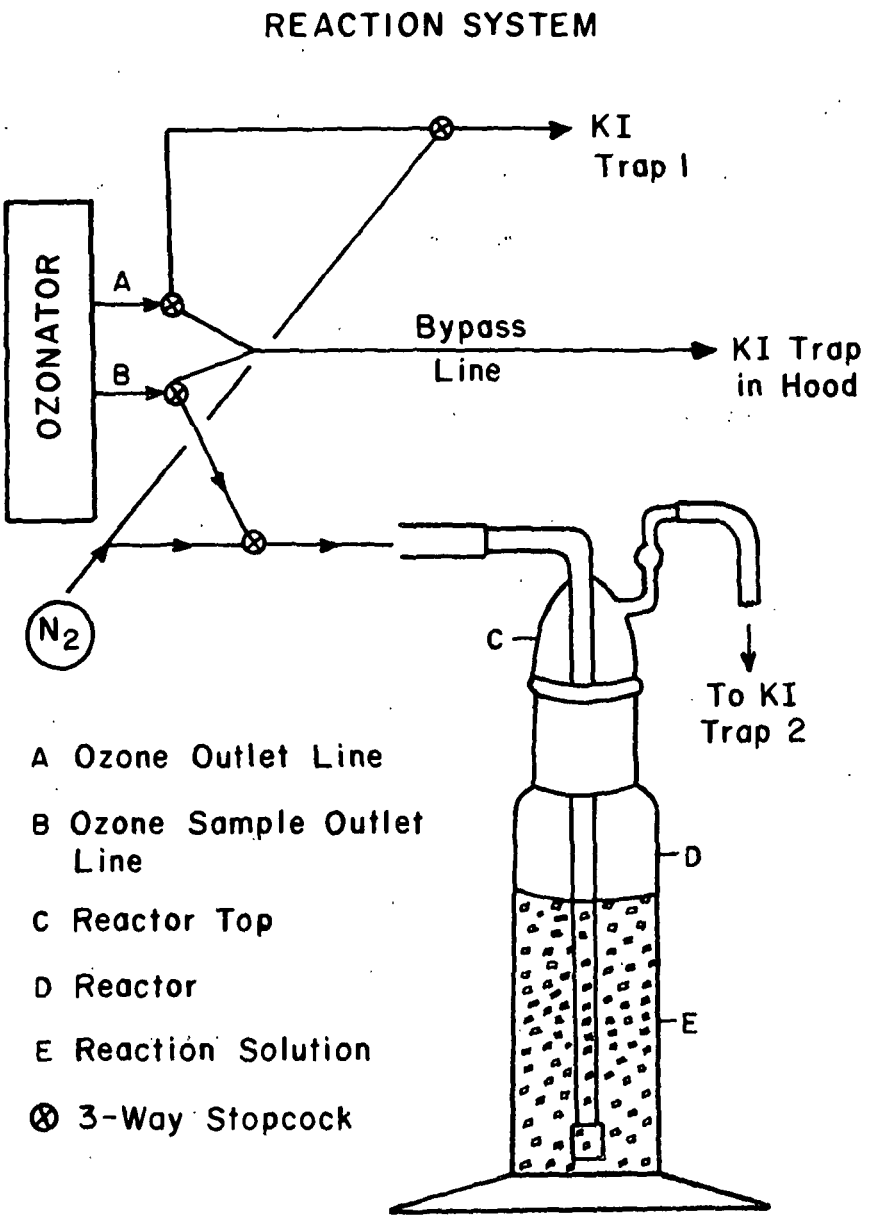


Figure 40. Reaction System Employed for the Ozonation of Compound XXXIII

The KI traps 1 and 2 (500 mL graduated cylinders) were each filled with 400 mL of 5% aqueous potassium iodide solution.

The ozonator was set for the following conditions:

Oxygen pressure: 8 psig

Ozone outlet flow rate: 1.0 liter/min

Ozone sample outlet flow rate: 0.2 liter/min

Once these conditions were established, the ozonator circuit breaker switch was turned on, and the wattage was set at 70 watts. The ozone-oxygen streams from the ozonator were passed through the bypass line for 5 minutes (to allow attainment of a constant level of ozone production). After 5 minutes, the ozone-oxygen streams were diverted to the reactor and KI trap 1 for 5 or 15 minutes. At the end of this time, the streams were diverted back to the bypass line and the ozonator was then switched off. In the meantime, prepurified nitrogen was bubbled through the reactor and KI traps 1 and 2 for 15 minutes. The reactor top was then removed, and duplicate reaction solution samples were weighed into tared 8-mL vials for use in the starting material analysis. The KI traps were sealed with Parafilm and stored in the dark until the ozone analysis could be performed (usually within 2 hours). The reactor was sealed with a ground-glass stopper and Parafilm and stored in a refrigerator pending further analysis of the reaction solution.

STARTING MATERIAL ANALYSIS

Aqueous Acetone Solutions

Into each of the four vials, containing the duplicate reaction solution samples taken before and after the ozonation, was weighed 2 mL of an internal standard, a standard solution of BMP (3.19 mg of BMP/g of solution, in absolute

ethanol). The resultant solutions were concentrated to "dryness" *in vacuo* at 30°C, redissolved in acetone (0.5-2.0 mL), and analyzed in triplicate *via* GC.

In addition, standards containing 2.0, 2.5, or 3.0 mL, respectively, of a standard solution of XXXIII (6.16 mg XXXIII/g of solution, in 80% (v/v) aqueous acetone) and 2 mL of standard BMP solution were prepared by weighing the aliquots of each component solution into tared 8-mL vials. The resultant mixtures were subjected to the sample work-up procedure already described for the starting material analysis and analyzed in triplicate *via* GC. The data obtained from this analysis were then used to determine the GC response factor value for XXXIII *via* Equation (7):

$$F = (A_r/A_s)(W_s/W_r), \qquad (7)$$

where F = response factor value

A_r = GC peak area of the internal standard

A_s = GC peak area of the substrate

W_r = weight of the internal standard

W_s = weight of the substrate

The average response factor value obtained in this manner was 1.19 (±1.1%). This value was then employed with Equation (7) to calculate the amount of starting material present in a given sample.

Aqueous Acetic Acid Solutions

Into each of the four vials, containing the duplicate reaction solution samples taken before and after the ozonation, was weighed 2 mL of standard BMP solution (3.02 mg of BMP/g of solution, in absolute ethanol). Each sample was then transferred (using 25 mL of diethyl ether) to a 60-mL separatory funnel, and the resultant mixture was extracted with 5% aqueous sodium hydroxide solution

(3 x 25 mL). The ether phase was dried over anhydrous sodium sulfate, concentrated to a sirup *in vacuo*, and dissolved in acetone (0.5-2.0 mL). The samples were analyzed in triplicate *via* GC.

As was done for ozonations in aqueous acetone, a response factor value was established for XXXIII. In this case, 2.0, 2.5, or 3.0-mL aliquots of a standard solution of XXXIII in 60% aqueous acetic acid (4.76 mg XXXIII/g of solution) and 2.0 mL of standard BMP solution were weighed into tared 8-mL vials and subsequently subjected to the sample work-up procedure employed for the starting material analysis. The resultant standards were analyzed *via* GC, and a response factor of 1.15 (±0.9%) was obtained *via* Equation (7).

OZONE ANALYSIS

As in previous ozonation studies (19,41,44-47), the amount of ozone offered to the reactor was determined *via* iodometric titration. Accordingly, an aliquot (20-50 mL) of the ozonized potassium iodide solution in KI trap 1 (Fig. 40) was acidified with 2N sulfuric acid (10 mL) in an Erlenmeyer flask. The resultant reddish-brown solution was then titrated with a standard solution of sodium thiosulfate to a colorless end point. The amount of ozone offered to KI trap 1 during the ozonation [i.e., c_o of Equation (6)] was calculated *via* the equation:

$$c_o = 1/2(NV/F_T),$$

where N = normality of the sodium thiosulfate solution

V = volume of sodium thiosulfate solution required for the titration

F_T = fraction of the ozonized potassium iodide solution that was titrated

The amount of ozone offered to the reactor [i.e., c_s of Equation (6)] was then calculated from Equation (6).

For ozonations conducted in aqueous acetic acid, the amount of ozone consumed during an ozonation was likewise determined *via* iodometric titration. Accordingly, the entire 400 mL of ozonized solution in KI trap 2 (Fig. 40) was acidified and then titrated with 0.1N sodium thiosulfate to establish the amount of ozone which reached KI trap 2 during the ozonation (i.e., the amount of ozone offered to the reactor that was not consumed during the ozonation).

For ozonations conducted in aqueous acetone, the amount of ozone consumed during the ozonation was determined as follows. The contents of KI trap 2 were transferred to a 1000-mL Erlenmeyer flask. A 1-mL aliquot of standardized sulfuric acid solution was then added. Subsequently, phenolphthalein solution (3 drops) was added, and the solution was titrated to a faint pink end point with standardized sodium hydroxide solution. The amount of ozone not consumed during the ozonation was then calculated *via* Equation (20) in Appendix II. The amount of ozone consumed during the ozonation was then given by the difference of c_s [Equation (6)] and O_3 [Equation (20)].

PRODUCT ANALYSIS

General Procedure

An aliquot (25-90 mL) of the ozonized reaction solution was placed in a tared 100-mL pear-shaped flask to which had been added known amounts (about 10 mg each) of the internal standards, DPE and hexanedioic acid. The sample was then concentrated *in vacuo* at 30-35°C until all of the acetone was removed. The aqueous mixture was extracted with chloroform (8 x 25 mL), and the chloroform fractions were combined, dried over anhydrous sodium sulfate, concentrated to a sirup *in vacuo* at 30-35°C, redissolved in 1,2-dichloroethane or absolute ethanol (20 mL), and again concentrated to a sirup *in vacuo* (to remove any residual water). The resultant yellowish brown sirup was then dissolved in

anhydrous chloroform (0.3 mL), transferred to a 4-mL vial equipped with a septum-fitted lid, and silylated by addition of Tri-Sil concentrate (0.7 mL) followed by continuous shaking for several hours. The resultant silylated sample (containing the neutral and phenolic products) was ready for analysis *via* GC, GC-NMR, and GC-mass spectrometry.

The aqueous phase was taken to "dryness" *in vacuo* at 35-38°C, dissolved in 1,2-dichloroethane (20 mL), taken to dryness again, dissolved in silylation grade dimethylformamide (0.3 mL), transferred to a 4-mL vial equipped with a septum-fitted lid, and silylated by addition of BSTFA (0.3 mL) followed by continuous shaking for several hours. The resultant silylated sample (containing the water-soluble products) was then ready for analysis *via* GC.

Alternative Method for "Acidic" Product Analysis

An adaptation of the methylation procedure of Merriman, *et al.* (65) was employed. Accordingly, an aliquot (180 mL) of ozonized reaction solution was placed in a beaker containing the internal standards, DPE (21.4 mg) and hexanedioic acid (11.6 mg). The mixture was then neutralized by addition of saturated sodium bicarbonate solution and subsequently concentrated *in vacuo* at 30-33°C until all of the acetone was removed. Chloroform was added to the aqueous mixture and the resultant emulsion was dispersed by addition of a few milliliters of 2*M* sulfuric acid. Saturated sodium bicarbonate solution was added next to reach a pH of eight, and the chloroform phase was then extracted two more times with sodium bicarbonate solution (adjusted to pH 8.5). The combined aqueous phases were extracted with chloroform (5 x 30 mL), and the combined chloroform phases were stored over anhydrous sodium sulfate in the dark.

The aqueous layer (pH 8.3) was taken to dryness *in vacuo* at 30-38°C. The resultant dried salts were then refluxed with 50 mL of anhydrous methanol

(containing 15% by weight of hydrochloric acid) for 3 hours, subsequently neutralized with saturated sodium bicarbonate solution, and extracted with methylene chloride (3 x 25 mL). The combined methylene chloride phases were filtered through anhydrous sodium sulfate, dried over anhydrous magesium sulfate, concentrated to a volume of about 1.5 mL *in vacuo* at 31-33°C, and finally transferred to a 4-mL vial equipped with a septum-fitted lid. The sample was then ready for GC and GC-mass spectrometry analysis.

Column Chromatography Method

An aliquot (155 mL) of the ozonized reaction solution was concentrated to a sirup *in vacuo* at 34-38°C, using absolute ethanol to azeotropically remove any residual water. The sirup was weighed and then passed through a Pyrex column (25 x 1000 mm) that had been "slurry packed" with chromatographic grade silica gel (60-200 mesh). The eluents that were used for the column chromatography were: hexane:diisopropyl ether (1:1, v/v); hexane:diisopropyl ether (1:3, v/v); diisopropyl ether; diisopropyl ether:diethyl ether (1:1, v/v); diethyl ether; diethyl ether:ethyl acetate (1:1, v/v); ethyl acetate; ethyl acetate:acetone (1:1, v/v); acetone; acetone:ethanol (1:1, v/v); ethanol; ethanol:distilled water (1:1, v/v); and distilled water.

Fractions (20 mL) were collected, and all fractions which appeared to be similar *via* TLC were combined, concentrated, and stored in 4-mL vials as "composite" fractions. Each composite fraction was then transferred to a 4-mL vial containing a known amount of internal standard (DPE), taken to dryness *in vacuo*, redissolved in 0.1-0.3 mL of silylation grade chloroform or dimethylformamide, and silylated by addition of either Tri-Sil concentrate or BSTFA (0.3-0.5 mL). The resultant samples were then analyzed *via* GC, GC-NMR, and GC-mass spectrometry.

Ultraviolet Spectrometric Analysis

The samples used to provide the data illustrated in Fig. 24 and 25 were prepared for analysis as follows. Aliquots of unozonized and ozonized reaction solution — possessing equal volumes of solution and initial (i.e., prior to ozonation) concentrations of compound XXXIII — were each placed in 100-mL pear-shaped flasks. Each sample was then concentrated in vacuo to remove the acetone and subsequently dissolved in absolute ethanol (40 mL). Aliquots (1 mL) of the resultant solutions were placed in 10-mL Erlenmeyer flasks and diluted further with absolute ethanol (9 mL/flask) to yield 10-mL samples with a concentration of about 0.1 mg of solute per milliliter of solution. UV spectra of the resultant samples were then obtained scanning from 200 to 320 nm.

Thermogravimetric Analysis

The samples used to obtain the TGA data shown in Fig. 23 were prepared for analysis as follows. The silylated sample from the ozonized reaction solution was prepared as described in the general procedure for product analysis. The unozonized sample was prepared by placing 0.2910 g of XXXIII (the amount required to provide a solution possessing the same concentration of XXXIII as the ozonized sample) into a 4-mL vial equipped with a septum-fitted lid. The XXXIII was then dissolved in anhydrous chloroform (0.3 mL). Next, Tri-Sil concentrate (0.7 mL) was added and the mixture was shaken continuously for several hours to yield the silylated unozonized sample of XXXIII.

The prepared samples were subjected to TGA (with duplicate runs performed on the ozonized sample). Accordingly, an initial temperature program was employed to remove the silylating agents and solvent. The resultant reaction "solids" were then subjected to a second program in which the temperature was raised at a much faster rate (5°/min). In this second program the temperature was allowed to rise until no further weight loss was observed.

Volatile Products Determination

An aliquot (85 mL) of ozonized reaction solution was placed in a tared 100-mL pear-shaped flask to which a known amount (11.0 mg) of internal standard (DPE) had been added. The sample was then concentrated to a heavy sirup *in vacuo* at 30-37°C, after which the flask was weighed. The concentration of the sirup was continued *in vacuo* until no further weight loss was observed, and the final weight of the sirup was recorded. This weight was subtracted from the maximum theoretical weight (defined as the milligrams of XXXIII employed for the ozonation plus the milligrams of ozone consumed during the ozonation) to yield a maximum value for the amount of volatile material lost.

Procedure for Ozonations Conducted in Aqueous Acetic Acid

An aliquot (25-100 mL) of the ozonized reaction solution was placed in a 400-mL beaker, and 2 mL of a standard solution of DPE (1.028 mg DPE/mL of solution, in absolute ethanol) and 2 mL of a standard solution of hexanedioic acid (1.036 mg hexanedioic acid/mL of solution, in absolute ethanol) were added as internal standards. The solution was then neutralized to about pH 7 with saturated sodium bicarbonate solution and extracted with chloroform (5 x 50 mL).

The chloroform phase was dried over anhydrous sodium sulfate, concentrated *in vacuo* at 30-40°C to a sirup, dissolved in anhydrous chloroform (0.3 mL), and transferred to a 4-mL vial equipped with a septum-fitted lid. Tri-Sil concentrate (0.5 mL) was then added, and the mixture was shaken continuously for several hours prior to analysis by GC and GC-mass spectrometry.

The aqueous phase was acidified to about pH 1 with concentrated hydrochloric acid, evaporated to near dryness *in vacuo* at 30-42°C, redissolved in distilled water, and evaporated to dryness *in vacuo* twice more and, finally, continuously

extracted with diethyl ether for over 36 hours. The resultant ether phase was evaporated to near dryness in vacuo at 30-40°C, and the residue was dissolved in silylation grade dimethylformamide (0.4 mL), transferred to a 4-mL vial (equipped with a septum-fitted lid), treated with BSTFA (0.4 mL) and shaken continuously for several hours prior to analysis by GC.

COMPETITION REACTION (SUBSTRATE XXXIII VS. KETOL XLI)

Reaction Conditions

Compounds XXXIII (100 mg) and XLI (100 mg) were dissolved in A.C.S. reagent-grade acetone (32 mL) in a 50-mL graduated cylinder which served as the reactor, and triply distilled water was added. Duplicate samples (2 mL) were taken from the resultant solution and weighed into tared 4-mL vials equipped with septum-fitted lids. The ozone sample outlet line (Fig. 40) was connected to a gas dispersion tube which had a sintered glass disk at the bottom. The gas dispersion tube was then placed in the reactor. The ozone outlet line was connected to KI trap 1 (Fig. 40) which was filled with 400 mL of 5% aqueous potassium iodide solution.

The ozonator was set for the following conditions:

Oxygen pressure: 8 psig

Ozone outlet flow rate: 1.0 liter/min

Ozone sample flow rate: 0.2 liter/min

Once these conditions were established, the ozonator circuit breaker was turned on, and the wattage was set at 70 w. The ozone-oxygen streams from the ozonator were passed through the bypass line (Fig. 40) for 5 minutes and then diverted to the reactor and KI trap 1 for 1.75 minutes. At the end of this time, the streams were diverted back to the bypass line, and the ozonator was then switched off. In the meantime, prepurified nitrogen was bubbled through the reactor and

KI trap 1 for 15 minutes. Duplicate ozonized reaction solution samples (3 mL) were weighed into tared 4-mL vials for use in the starting material analysis. The KI trap was sealed with Parafilm and stored in the dark until the ozone analysis could be performed.

Starting Material Analysis

Into each of the four vials, containing the duplicate reaction solution samples taken before and after the ozonation, was weighed 1 mL of an internal standard, a standard solution of BMP (6.51 mg BMP/g of solution, in absolute ethanol). The resultant solutions were concentrated to near dryness *in vacuo* at 34-39°C, redissolved in anhydrous chloroform (0.3 mL), reacted with Tri-Sil concentrate (0.5 mL) with continuous shaking overnight, and analyzed in triplicate *via* GC.

In addition, standards were prepared by weighing aliquots of a standard solution of XXXIII and XLI (7.12 mg XXXIII and 6.02 mg XLI/g of solution, in 80% (v/v) aqueous acetone) and the standard BMP solution into tared 4-mL vials equipped with septum-fitted lids. These samples were then subjected to the sample work-up procedure already described in this subsection for the starting material and subsequently analyzed in triplicate *via* GC. The data obtained from this analysis were used to determine the GC response factor values for XXXIII and XLI. These values were 0.90 (±0.8%) and 0.85 (±1.9%), respectively.

Ozone Analysis

The amount of ozone offered to the reactor was determined in the usual manner *via* iodometric titration employing a 150-mL aliquot of the ozonized potassium iodide solution in KI trap 1.

CONCLUSIONS

The results of this study indicate that attack by ozone upon a lignin-related model compound containing a β-aryl ether linkage was initiated at several sites and probably proceeded *via* a number of mechanisms.

Ozone-induced cleavage of the β-aryl ether linkage was an important initial mode of degradation and accounted for at least 20% of the starting material consumed during the ozonation of the model compound. This cleavage was initiated at sites on both sides of the β-aryl ether linkage and probably proceeded *via* at least three different reaction mechanisms: 1,3-dipolar insertion of ozone, ozonolysis of an aromatic ring (with subsequent hydrolysis of the resultant ester linkage), and electrophilic attack by ozone upon an aromatic ring.

Oxidative opening (ozonolysis) of the aromatic rings, without consequent cleavage of the β-aryl ether linkage, provided another initial mode of degradation during the ozonation of the model compound. This mode of attack was observed to occur on both aromatic rings of the model compound and was not initiated exclusively between adjacent ring carbons bearing alkoxyl substituents. This finding corroborates the conclusions of Kratzl, *et al.* (41).

Finally, it appears likely that the initial and secondary ozonation products, formed *via* the above reactions, underwent condensation to yield higher molecular weight substances not amenable to analysis *via* gas chromatography. The formation of these substances and some relatively high molecular weight initial ozonolysis products provides a plausible explanation for the low yield of ozonation products detected *via* gas chromatography.

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APPENDIX I

AQUEOUS ACETONE AS AN OZONATION SOLVENT

As already discussed, aqueous acetone was employed as the reaction solvent in this study because of its ability to dissolve the substrate, XXXIII, while at the same time providing an aqueous environment in which to conduct the ozonations. As reported in Table I, distilled water is essentially inert to ozone, and acetone (being a ketone) would not be expected to be particularly reactive to ozone either. However, inasmuch as the reactivity of acetone toward ozone apparently has not been previously reported, an experiment was conducted in this study to determine whether aqueous acetone reacted significantly with ozone in the absence of XXXIII. Accordingly, 80% aqueous acetone was treated with ozone under reaction conditions identical to those utilized in a typical ozonation experiment in which XXXIII was employed as the substrate. The amount of ozone offered to the reactor was determined in the usual manner via iodometric titration while the amount of ozone consumed during the experiment required use of the "double titration" method (see Appendix II). The results of this analysis are summarized in Table VII.

TABLE VII

EXTENT OF OZONE-SOLVENT REACTION

Amount of O_3 Offered	Amount of O_3 Consumed
1.288 mmoles	0.637 mmoles (49%)

These results show that, in the absence of XXXIII, 49% of the ozone offered to the reactor was consumed by the aqueous acetone. It is believed, however,

that in the presence of XXXIII, the extent of the reaction between ozone and the solvent was negligible. This is based on the following observations:

1. If a significant amount of ozone reacted with the acetone, a noticeable decrease in the consumption of XXXIII would be expected for an ozonation conducted in aqueous acetone relative to one conducted in a solvent proven to be inert to ozone. However, based upon the results in Table VIII, it appears that there was no appreciable difference in the consumption of XXXIII between ozonations conducted in aqueous acetone and those conducted in aqueous acetic acid, under otherwise identical reaction conditions.

TABLE VIII

REACTIVITY OF XXXIII IN AQUEOUS ACETONE VS. AQUEOUS ACETIC ACID

Reaction Solvent	Mmoles of XXXIII Offered	Percent of XXXIII Consumed
Aqueous Acetic Acid	2.970 ± 0.017[a]	30.3 ± 2.2[a]
Aqueous Acetone	2.965 ± 0.017[b]	30.2 ± 1.9[b]

[a] The average value obtained from three ozonations.
[b] The average value obtained from four ozonations.

Furthermore, if ozonation of acetone was producing reactive intermediates apt to attack the starting material, significant differences in the reaction products could be expected for an ozonation conducted in aqueous acetone relative to one conducted in an inert solvent. However, the GC chromatogram obtained from the product analysis for the ozonation in aqueous acetic acid was quite similar to those obtained in aqueous acetone. In both solvents, compounds XXXV and XXXVI were by far the predominant products, suggesting that the major reaction mechanisms were the same in both systems.

2. Comparison of the data in Tables I (p. 4) and VII (p. 95) suggests that pure methanol is more reactive toward ozone than is aqueous acetone; however, when employed as the solvent during the ozonation of an aromatic substrate, methanol was not observed to react appreciably with ozone (20,66).

APPENDIX II

THEORY FOR OZONE ANALYSIS VIA THE ACID-BASE TITRATION AND THE DOUBLE TITRATION METHODS

As previously discussed, acetone carry-over from the reactor into the potassium iodide (KI) trap during the ozonation of XXXIII caused interference with the standard iodometric titration method normally employed for ozone analysis. Thus an acid-base titration method was devised to circumvent this problem, based upon the reactions which can occur upon addition of ozone and acetone to an aqueous KI solution. When ozone and acetone are introduced into an aqueous KI solution, Reactions (8) through (15) of the following list of reactions must be considered:

$$O_3 + 2I^- + H_2O \longrightarrow I_2 + 2OH^- + O_2 \quad (8)$$

$$I_2 + 1/3(CH_3)_2CO \longrightarrow 1/3CH_3COCI_3 + I^- + H^+ \quad (9)$$

$$1/3CH_3COCI_3 + 1/3OH^- \longrightarrow 1/3CH_3COO^- + 1/3HCI_3 \quad (10)$$

$$H^+ + OH^- \longrightarrow H_2O \quad (11)$$

$$O_3 + I^- + 1/3(CH_3)_2CO \longrightarrow 1/3CH_3COO^- + 1/3HCI_3 + 2/3OH^- + O_2 \quad (12)$$

$$I_2 + 2OH^- \longrightarrow 1/3IO_3^- + 5/3I^- + H_2O \quad (13)$$

$$O_3 + 1/3I^- \longrightarrow 1/3IO_3^- + O_2 \quad (14)$$

$$1/3IO_3^- + 5/3I^- + 2H^+ \longrightarrow I_2 + H_2O \quad (15)$$

$$2/3H^+ + 2/3OH^- \longrightarrow 2/3H_2O \quad (16)$$

$$O_3 + 2I^- + 2H^+ \longrightarrow I_2 + H_2O + O_2 \quad (17)$$

$$O_3 + I^- + 1/3(CH_3)_2CO + 2/3H^+ \longrightarrow 1/3CH_3COO^- + 1/3HCI_3 + 2/3H_2O + O_2 \quad (18)$$

$$2S_2O_3^= + I_2 \rightleftharpoons S_4O_6^= + 2I^- \quad (19)$$

Any ozone not consumed in the reactor during an ozonation will enter a KI trap and subsequently liberate iodine [Reaction (8)]. Part or all of this

iodine may then react either with acetone [Reactions (9) and (10)] or with hydroxide ion [Reaction (13)] (51). However, during the ozonation of XXXIII there was an excess of acetone present in the trap relative to the amount of iodine liberated (since almost all of the ozone offered was consumed in the reactor), and under these circumstances iodate formation [Reaction (13)] was evidently not important, as addition of excess acid to the ozonized KI solution did not liberate iodine. [Reaction (15) predicts that the iodate ion should be converted to iodine under acidic conditions]. Thus Reaction (12) [the sum of Reactions (8) through (11)] should represent the overall reaction that occurred in the KI trap during the ozonation of XXXIII.

According to Reaction (12), $0.6\overline{6}$ equivalent of hydroxide ion are produced for each equivalent (mole) of ozone consumed in the KI solution, and so if excess acid was added, each equivalent of acid consumed by the hydroxide ion [Reaction (16)] would correspond to 1.5 equivalents of the ozone that was consumed. The acid not consumed via Reaction (16) could then be titrated with base, and the ozone consumed in the KI solution could subsequently be calculated via Equation (20).

$$O_3 = (V_A N_A - V_B N_B)/F_T\ (3/2), \qquad (20)$$

where V_A = volume of standardized acid added to the ozonized KI solution

V_B = volume of standardized base required to titrate the acidified solution

N_A = normality of the acid

N_B = normality of the base

F_T = fraction of the ozonized KI solution that was titrated

O_3 = mmoles of ozone consumed in the KI solution (i.e., the amount of ozone offered to the reactor that was not consumed during the ozonation)

On the other hand, during the solvent stability experiment much more ozone reached the KI trap than during the ozonation of XXXIII (see Table VII of Appendix I) and, as a result, the amount of iodine liberated *via* Reaction (8) exceeded the amount of acetone carry-over into the trap. Consequently, Reaction (13) provided a significant contribution to the overall reaction scheme, as evidenced by the liberation of iodine upon addition of acid to the ozonized KI solution. In this case, Reactions (8), (12), and (14) [the sum of Reactions (8) and (13)] should represent the overall reactions that occurred in the KI trap.

Since Reactions (8) and (12) produced hydroxide ion, and Reaction (14) produced iodate ion, excess acid could be added, and as a result of the subsequent reactions [(15) and (16)], the overall reactions in the acidified ozonized KI solution would be Reactions (17) and (18). The iodine liberated by Reaction (17) could then be titrated with sodium thiosulfate [Reaction (19)], and since 1 mole of ozone produces 1 mole of iodine in Reaction (17), the amount of ozone consumed *via* Reaction (17) would then be calculated *via* Equation (21).

$$[O_3]_{17} = 1/2(NV/F_T), \qquad (21)$$

where V = volume of standard sodium thiosulfate solution required for the titration

N = normality of the sodium thiosulfate solution

F_T = fraction of the ozonized KI solution that was titrated

$[O_3]_{17}$ = mmoles of ozone consumed *via* Reaction (17)

The acid not consumed *via* Reactions (17) and (18) could then be titrated with base, and the total amount of acid consumed by these reactions could subsequently be calculated *via* Equation (22).

$$A_T = V_A N_A - V_B N_B = A_{17} + A_{18}, \qquad (22)$$

where A_T = total amount of acid consumed *via* Reactions (17) and (18)

A_{17} = acid consumed *via* Reaction (17)

A_{18} = acid consumed *via* Reaction (18)

V_A = volume of standardized acid added to the ozonized KI solution

V_B = volume of standardized base required to titrate the acidified solution

N_A = normality of the acid

N_B = normality of the base

Since a 2:1 stoichiometry exists between the acid consumed and the ozone consumed *via* Reaction (17) (i.e., $A_{17} = 2[O_3]_{17}$), the amount of acid consumed *via* Reaction (18) could be calculated from Equation (23). And since there is a 3/2:1 stoichiometry between the ozone consumed and the acid consumed *via* Reaction (18), the amount of ozone consumed *via* Reaction (18) could likewise be calculated from Equation (23).

$$A_{18} = A_T - 2[O_3]_{17} = 2/3[O_3]_{18}, \qquad (23)$$

where $[O_3]_{18}$ = mmoles of ozone consumed *via* Reaction (18)

Thus the total amount of ozone not consumed during the solvent stability experiment ($[O_3]_T$) would be given by Equation (24), where the values for $[O_3]_{17}$ and $[O_3]_{18}$ were determined *via* the "double titration" method.

$$[O_3]_T = [O_3]_{17} + [O_3]_{18} \qquad (24)$$

The validity of this "double titration" method was then proven experimentally as follows. An aqueous KI solution was ozonized. Duplicate samples of this ozonized KI solution were taken. The first of these samples was analyzed for ozone *via* the usual iodometric titration method. Alternatively, acetone was added to the second sample, and the resultant solution was analyzed for

ozone *via* the "double titration" method. The results of these two analyses are summarized in Table IX and demonstrate excellent agreement between the standard iodometric titration method and the "double titration" method. Thus it can be concluded that the "double titration" method provides a valid means of determining ozone consumption when employing acetone as the ozonation solvent.

TABLE IX

RESULTS OF OZONE ANALYSIS COMPARISON:
IODOMETRIC TITRATION *VS.* DOUBLE TITRATION

Analytical Procedure	Mmoles of Ozone Detected
Iodometric Titration	0.820
Double Titration	0.851

APPENDIX III

POSSIBLE MECHANISMS FOR CONDENSATION OF OZONATION PRODUCTS

PERSPECTIVE

The data in Table V (p. 40) indicate that only 40% of the XXXIII consumed during an ozonation could be accounted for in terms of the material detected via GC. This suggests that 60% of the reaction products formed during the ozonation of XXXIII may be present as nonvolatile material not readily analyzable via GC — a notion that is further substantiated by the TGA results reported in Fig. 23. This nonvolatile material could arise as the result of condensation or polymerization of the original ozonation products, and there are several different routes by which this might occur.

DIELS-ALDER REACTION

The Diels-Alder reaction involves the combination of an α,β-unsaturated carbonyl compound (dienophile) with a conjugated diene to form a six-membered ring (52). Thus quinones, muconic acids, and other conjugated carboxyl and carbonyl containing compounds arising from the ozonation of XXXIII could recombine to form higher molecular weight compounds (Fig. 41). Indeed, studies (67-(69) have already established that o-quinones and quinols readily undergo such a reaction, especially in aqueous media. The reaction will also proceed in various organic solvents, including acetone (67). Therefore, it would seem reasonable to expect similar reactions to occur in the ozonized reaction solutions of XXXIII. The occurrence of this type of reaction could explain the failure to detect via GC significant amounts of the unsaturated dicarboxylic and dicarbonyl compounds expected from the ozonolysis of the aromatic rings of XXXIII.

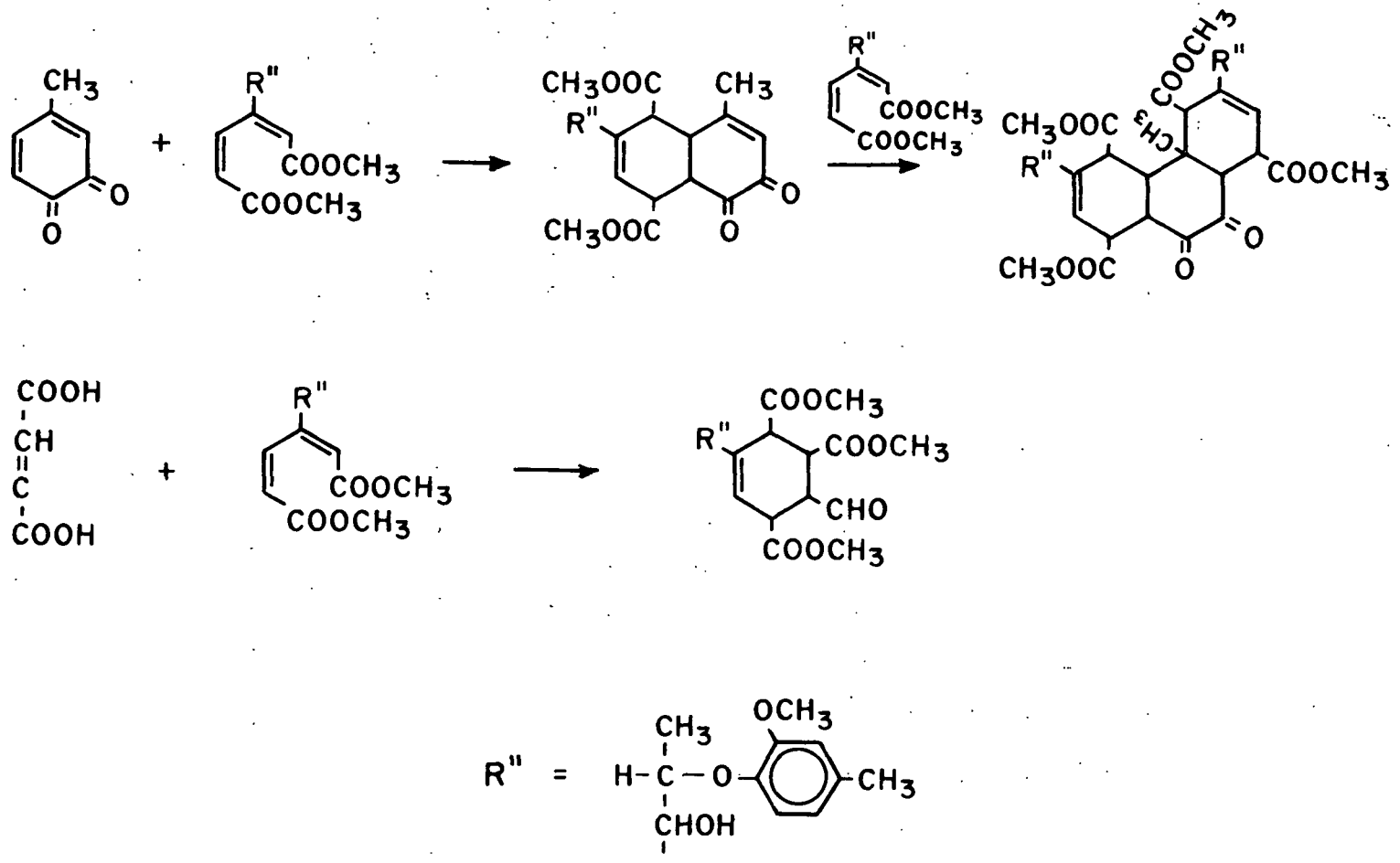


Figure 41. Condensation of Ozonation Products Via the Diels-Alder Reaction

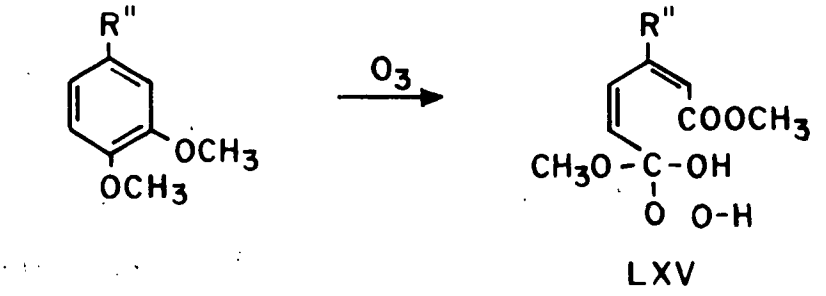
RADICAL COUPLING OF OZONOLYSIS INTERMEDIATES

As discussed in an earlier section, the aqueous solvent employed in this study would tend to favor formation of a hydroxy hydroperoxide, such as LXV (rather than an ozonide or dimer intermediate), during the ozonolysis of an aromatic ring (Reaction (25) of Fig. 42). Intermediate LXV could subsequently be attacked by ozone to yield the radical species LXV• [Reaction (26) of Fig. 42]. Formation of a higher molecular weight compound could then result from coupling of two such radicals [Reaction (28a) of Fig. 42]. Recently, Kurz and Pryor (70) have proposed such a pathway for the ozonation of tert-butyl hydroperoxide (in halogenated solvents at -60 to -4°C), and so it is possible that such a mechanism may be functioning to some extent during the ozonation of XXXIII as well.

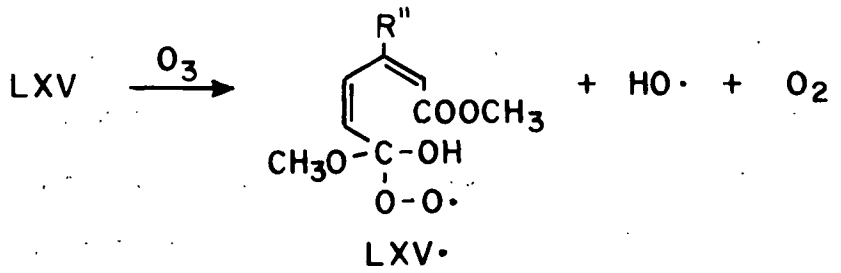
OXIDATIVE COUPLING OF PHENOLIC PRODUCTS (DEHYDROGENATIVE POLYMERIZATION)

Creosol (XXXV) and perhaps other phenolic compounds are produced during the ozonation of XXXIII. Such compounds are a potential source of phenoxy radicals capable of undergoing coupling reactions to form higher molecular weight compounds (71-73). Hindered phenols have been reported (72) to react with the peroxy radical to yield phenoxy radicals [Reactions (31)-(33) of Fig. 43]. Consequently, since the peroxy radical could be generated during the ozonation of XXXIII (Fig. 42), generation of the phenoxy radical should be possible as well. Moreover, hydrogen peroxide could be produced during the ozonation of XXXIII [Reaction (34) of Fig. 43] and subsequently degraded via the Haber-Weiss mechanism (74) [Reactions (35)-(39) of Fig. 43] to provide an additional source of peroxy radicals which could be used in the generation of phenoxy radicals.

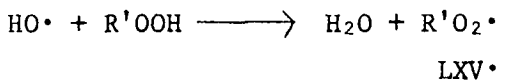
Once generated, the phenoxy radical can couple with peroxy radicals [Reaction (33) of Fig. 43]. In addition, the phenoxy radical is capable of coupling



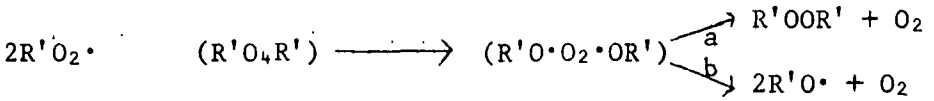
LXV (25)



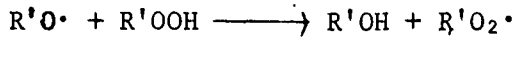
LXV· (26)



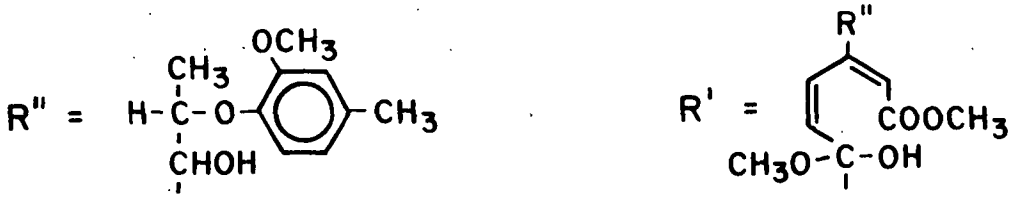
LXV· (27)



(28)



(29)



(30)

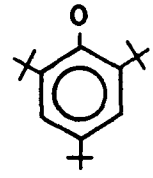
Figure 42. Possible Mechanism for Radical Coupling of Ozonolysis Intermediates

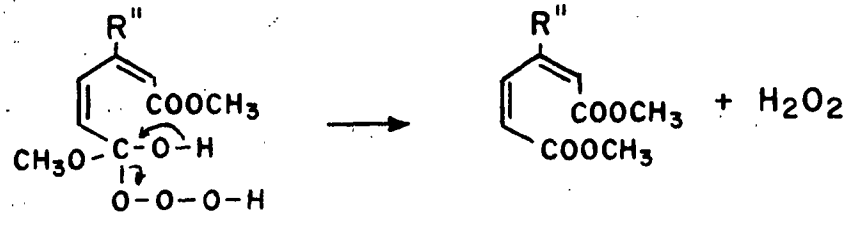
$$RO_2\cdot + R'\text{-}H \longrightarrow R'\cdot + RO_2H \quad (31)$$

$$R'\cdot + RO_2H \longrightarrow R'\text{-}H + RO_2\cdot \quad (32)$$

$$R'\cdot + RO_2\cdot \longrightarrow RO_2R' \quad (33)$$

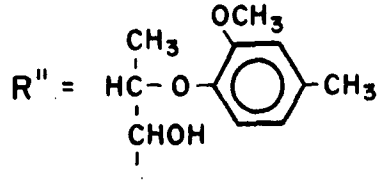
R' =





(34)

R" =



$$M^n + H_2O_2 \longrightarrow M^{n+1} + \cdot OH + OH^- \quad (35)$$

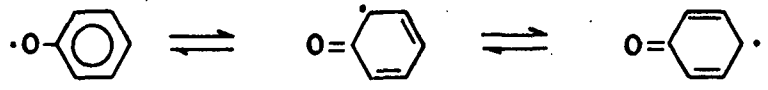
$$M^{n+1} + H_2O_2 \longrightarrow M^n + HO_2\cdot + H^+ \quad (36)$$

$$M^n + \cdot OH \longrightarrow M^{n+1} + OH^- \quad (37)$$

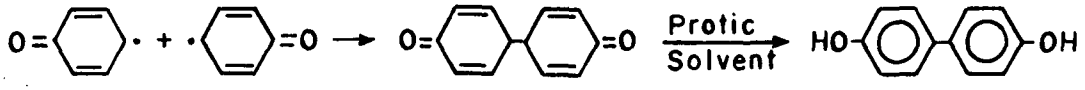
$$M^{n+1} + H_2O \longrightarrow M^n + O_2 + H^+ \quad (38)$$

$$HO\cdot + H_2O_2 \longrightarrow H_2O + HO_2\cdot \quad (39)$$

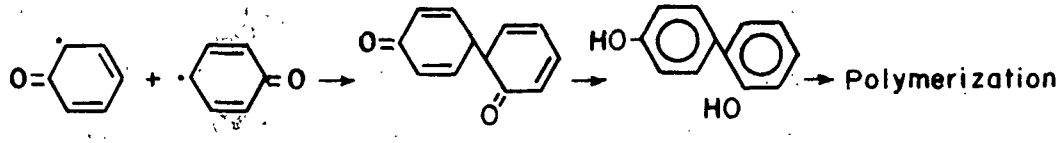
Figure 43. Possible Ways to Generate Phenoxy Radicals



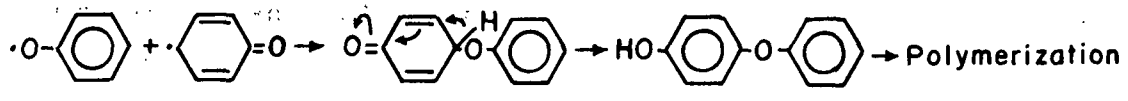
(40)



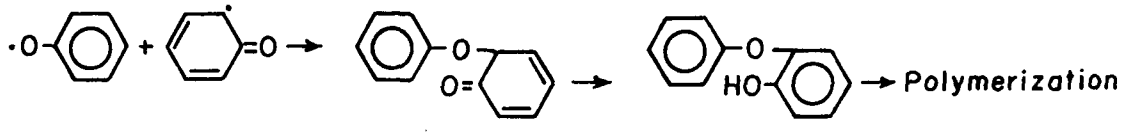
(41)



(42)



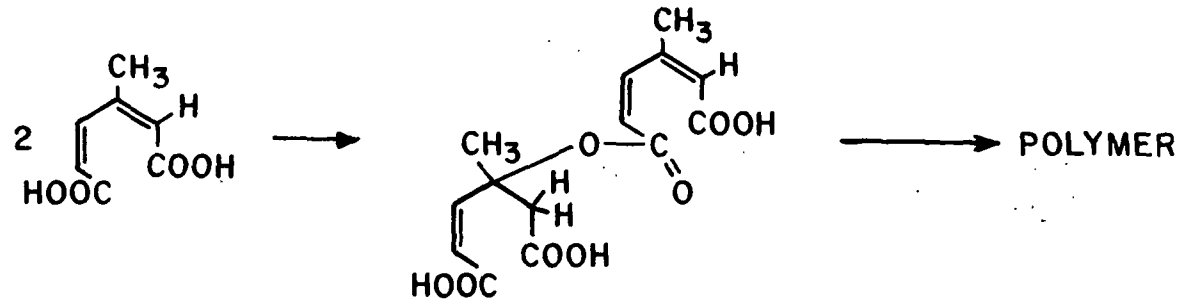
(43)



(44)

Figure 45. Various Modes of Phenolic Coupling

molecule with an unsaturated carbon on a second molecule [in much the same manner that an olefinic carboxylic acid undergoes lactonization to yield γ- and δ-lactones (53,76)]:



As discussed in a previous section, a significant number of muconic acid-related compounds, such as LVII and LVIII, may be produced during the ozonation of compound XXXIII. As depicted in Fig. 46, these products could undergo intermolecular esterification to form high molecular weight compounds not amenable to GC analysis. Consequently, intermolecular esterification provides yet another plausible explanation for the low yield of unsaturated dicarboxylic products detected *via* GC.

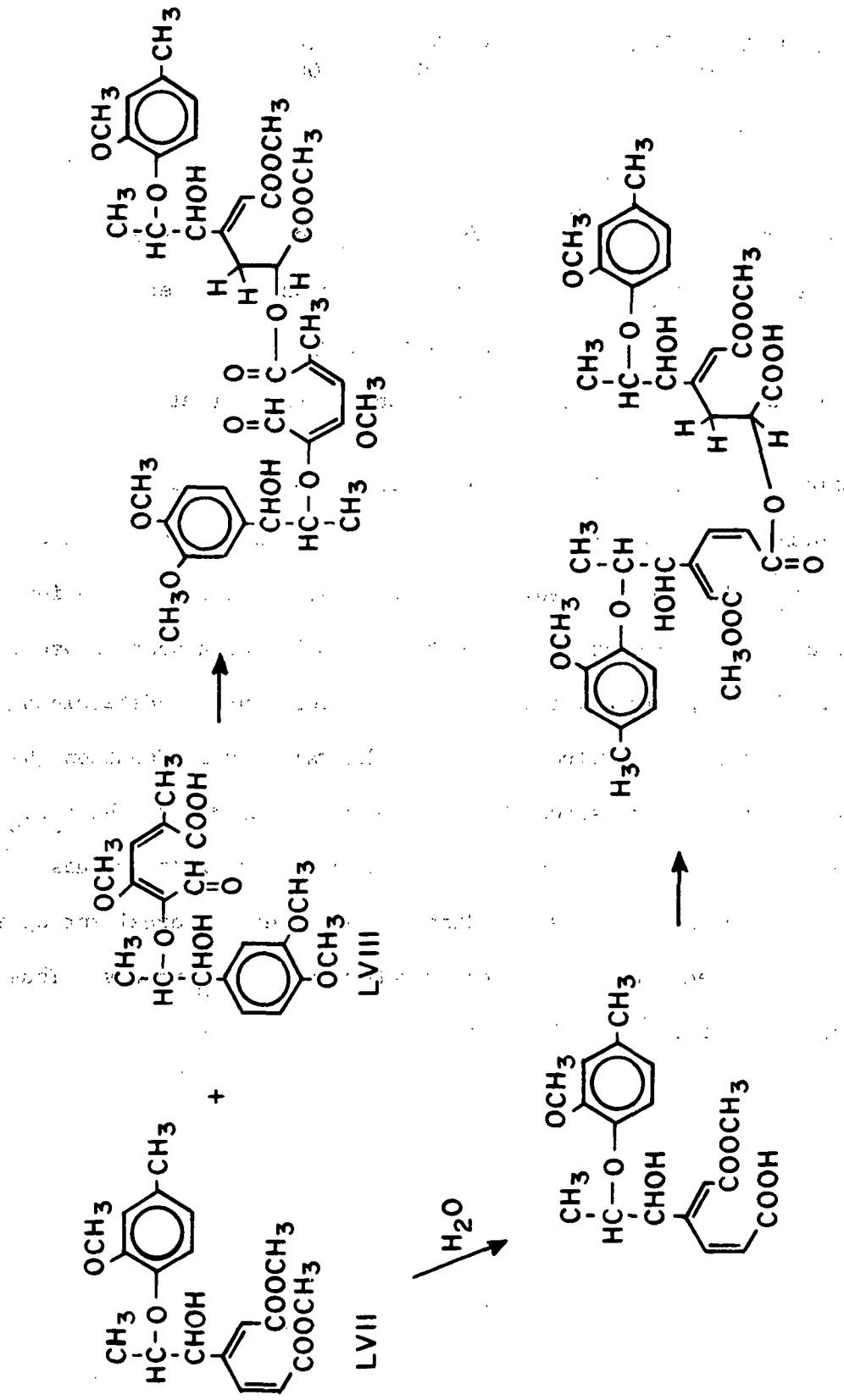


Figure 46. Coupling of Initial Ozonolysis Products Via "Intermolecular Esterification"

APPENDIX IV

EVIDENCE SUPPORTING A RELATIONSHIP BETWEEN FLOW RATE AND OZONE CONTENT DURING OZONE PRODUCTION

$$f_o/f_s = c_o/c_s, \qquad (6)$$

where f_o = ozone-oxygen flow rate, liter/min, from the ozone outlet

c_o = amount of ozone offered, mmoles, from the ozone outlet

f_s = ozone-oxygen flow rate from the ozone sample outlet

c_s = amount of ozone offered from the ozone sample outlet

An experiment was conducted in which ozone-oxygen streams were fed from the ozone and ozone sample outlets directly into KI traps for 5 minutes at given flow rates (i.e., f_o and f_s were known). The resultant ozonized KI solutions were then titrated via the iodometric method to determine the amount of ozone fed to the traps. This experiment, then, provided experimentally-determined values for c_o/c_s at given f_o/f_s values. To test the validity of Equation (6), these experimentally determined values for c_o/c_s were compared with the c_o/c_s values calculated from Equation (6) employing the appropriate f_o/f_s values. This comparison is given in Table X and indicates that there is excellent agreement between the calculated and experimentally determined c_o/c_s values. Thus it can be concluded that Equation (6) is valid.

TABLE X

CALCULATED VS. EXPERIMENTAL VALUES FOR c_o/c_s

Calculated Value[a]	Experimental Value[b]
1.00	1.00
1.50	1.50
2.50	2.60
5.00	4.84

[a] The c_o/c_s ratio calculated via Equation (6).

[b] The c_o/c_s ratio determined experimentally via iodometric titration.

APPENDIX V

RESPONSE FACTOR DETERMINATION FOR PRODUCT ANALYSIS

Four different samples, each containing known amounts of compounds XXXIII, XXXV, XXXVI, and internal standard (DPE), were dissolved in 80% aqueous acetone in tared pear-shaped flasks. The resultant solutions were subjected to the general procedure for product analysis described in the Experimental section, each sample being analyzed in triplicate. Response factor values relative to the internal standard, DPE, were then calculated for compounds XXXIII, XXXV, and XXXVI *via* Equation (45).

$$F_X = (A_I/A_X)(W_X/W_I), \qquad (45)$$

where F_X = response factor for compound X relative to the internal standard

A_I = GC peak area of internal standard

A_X = GC peak area of compound X

W_I = weight of internal standard

W_X = weight of compound X

The response factor values obtained in this manner are summarized in Table XI, and the average response factor values listed were employed in Equation (45) when calculating the amounts of XXXV and XXXVI detected *via* GC in a given ozonized reaction solution. A response factor value of one was assumed for calculating the amounts of all other products detected *via* GC.

TABLE XI

RESPONSE FACTOR VALUES DETERMINED
FOR COMPOUNDS XXXIII, XXXV, AND XXXVI

Compound	Average Response Factor[a]
XXXIII	1.68 (±6.0%)
XXXV	0.72 (±15.1%)
XXXVI	1.01 (±12.0%)
All Others	1.00 (Assumed)

[a]The average value obtained from triplicate injections of four samples.