Thermal, photochemical, and electron impact induced transformations of 1,2-benzisoxazolin-3-ones and related heterocyclic compounds

by

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INTRODUCTION

Mass spectrometry has become an indispensable tool for the organic chemist in the structural characterization of unknown compounds. A major difference between this spectroscopic method and nmr, ir, or uv spectroscopy is the amount of energy imparted to the molecule under examination. In the mass spectrometer this energy is usually applied in the form of electron bombardment. The net result is the removal of an electron from the molecule to produce an ionic species which may behave in one of the following ways: (a) remain intact and be detected as a molecular ion; (b) fragment without rearrangement to give a daughter ion and a neutral species; or (c) undergo an intramolecular rearrangement prior to or in concert with fragmentation. The first two processes are useful in determining the molecular weight and the basic structure of a molecule, respectively. On the other hand, rearrangement of the molecular ion to a different structural species either before or during fragmentation is indeed common and can be very misleading in the characterization of an unknown compound. As a result, a great deal of mechanistic work has emerged recently in order to identify and document some of these interesting unimolecular reactions of positively charged organic molecules (1).

In the present study, the mass spectral fragmentation

processes of a variety of related five-membered heterocyclic compounds are investigated. Some of these molecules are shown to exhibit similar behavior under photolytic and/or pyrolytic conditions. Such correlations serve as a valuable tool in mechanistic mass spectroscopy (see Review of Literature).

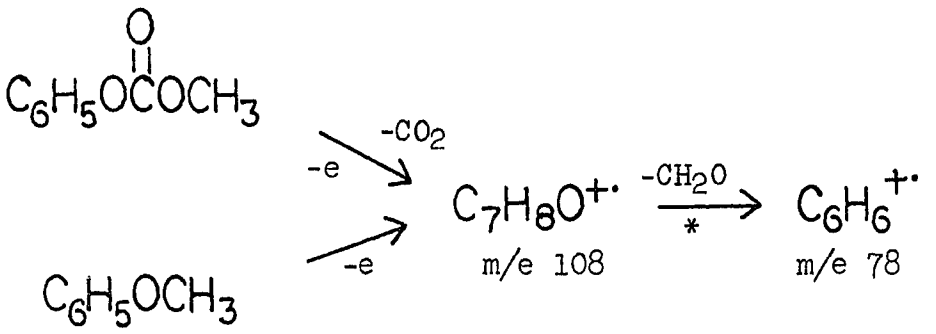
REVIEW OF LITERATURE

Techniques in Mechanistic Mass Spectrometry

A major obstacle encountered by organic mass spectroscopists engaged in mechanistic studies is the lack of structural knowledge of the ions produced upon electron impact. High resolution mass spectroscopy can provide information concerning the elemental compositions of ions, but a variety of other techniques must be utilized by the researcher to obtain inferred structural data. An excellent review has recently been published in which the applications and possible shortcomings of some of these techniques have been presented (2). These methods include the measurement of ionization and appearance potentials, the determination of metastable ion abundance ratios, the use of isotopically labelled compounds, and the study of substituent effects on rates of ion decomposition.

An additional widely used technique is the comparison method in which fragmentation patterns of two isomeric ions of independent origin are compared to determine possible similarities in their decomposition modes. The feasibility of such comparisons has been studied (3), and the conclusions drawn from this work are best illustrated by the following example. The mass spectrum of methyl phenyl carbonate shows an initial loss of CO_2 from the molecular ion to give an ion at m/e 108. This daughter ion then undergoes a subse-

quent metastable fragmentation to produce the $C_6H_6^{+\cdot}$ species

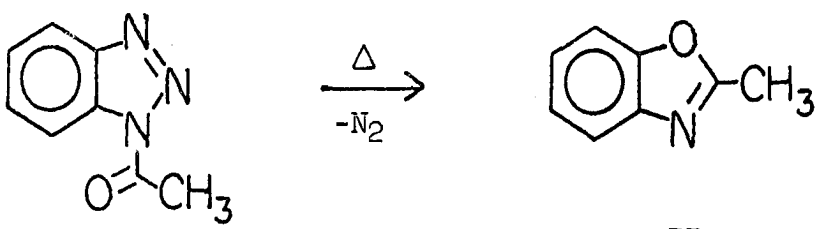


at m/e 78. Since the anisole molecular ion, also at m/e 108, decomposes in a similar manner, it might be reasonable to assume that the $(M-CO_2)^{+\cdot}$ species in the spectrum of methyl phenyl carbonate has a structure similar to that of the anisole radical cation. However, an overall comparison of the two spectra demonstrates a qualitative, but not quantitative, similarity; i.e., the relative ion abundance ratio $[C_7H_8O^{+\cdot}]/[C_6H_6^{+\cdot}]$ from anisole is much greater than the corresponding ratio $[C_7H_8O^{+\cdot}]/[C_6H_6^{+\cdot}]$ from methyl phenyl carbonate over a wide range of electron voltages. This difference in ion intensities is presumed to result from an excess threshold energy imparted to the $C_7H_8O^{+\cdot}$ species upon elimination of CO_2 from the methyl phenyl carbonate ion. This daughter ion would then experience a higher rate of decomposition than the anisole molecular ion, in spite of their possible structural identity.

Numerous attempts have also been made to correlate mass spectral fragmentations with pyrolytic (1, 4) and

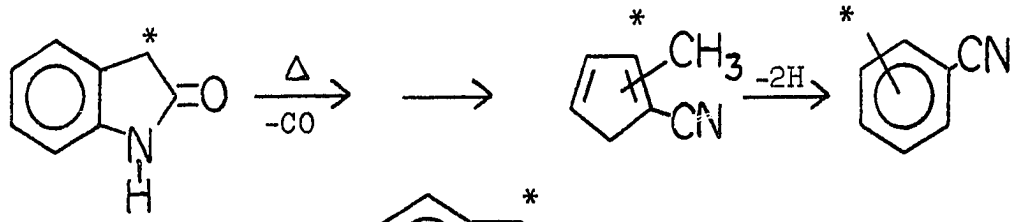
photochemical (1) reactions to obtain inferred information concerning the structures of the positive ions. In many cases such analogies have indeed proved valuable in studying mass spectral processes in a mechanistic sense. Only recently, however, has an empirical method been derived which demonstrates the electronic relationship between these high energy processes (5). Using a Perturbation Molecular Orbital (PMO) approach, electron impact induced reactions have been divided into three classes based on metastable ion characteristics and the electronic states of the ions. This PMO method has been successfully employed to correlate the thermal electrocyclic reaction of hexihelicene, the thermal retro-Diels-Alder reaction, and the photochemical Norrish Type II process with the corresponding mass spectral fragmentations (6).

Other more recent examples of analogies between mass spectral and thermal processes have been reported. For example, the pyrolytic decomposition of 1-acetylbenzotriazole (I) has been shown (7) to result in the formation of 2-methylbenzoxazole (II). The mass spectrum of I demonstrates a similar initial loss of N_2 which is followed by the

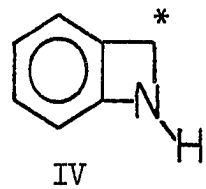


I II

expulsion of CO. A reasonable structure for the $(M-N_2)^{+\cdot}$ species is ionized II, based on its subsequent fragmentation and the known mass spectral decomposition of II. A similar parallel has been noted (8) in the mass spectral and thermal reactions of oxindole (III). Benzonitrile

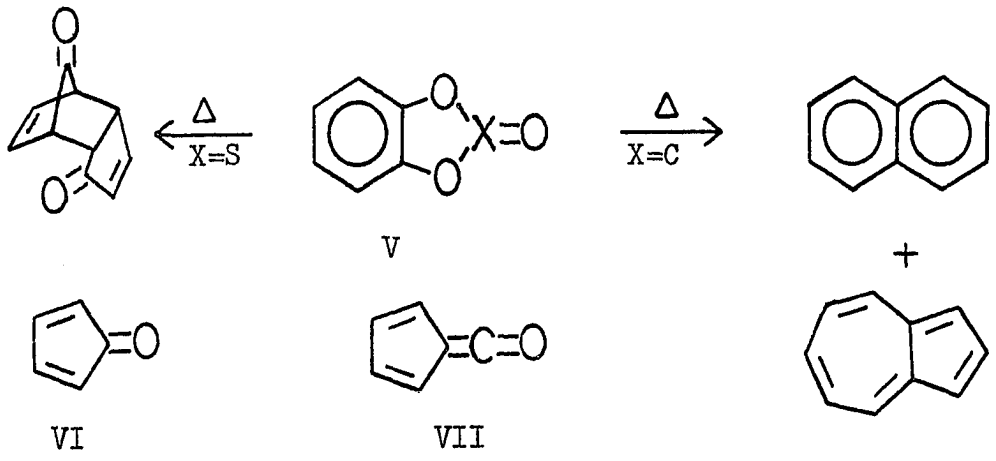


III



IV

is the major product in the pyrolysis of III. The origin of the nitrile carbon atom is the benzene ring of III as determined by C-14 labelling, thus, eliminating IV as a possible intermediate. In the mass spectrometer oxindole fragments with the consecutive losses of CO and HCN. Furthermore, predominantly unlabelled HCN is eliminated from the $(M-CO)^{+\cdot}$ ion of labelled III in agreement with the pyrolytic results. DeJongh and his coworkers (9) have studied similar heterocyclic systems and have found some interesting correlations between the thermal and electron impact induced reactions of V. The pyrolysis of V (X=S) resulted in the successive losses of SO and CO to give cyclopentadienone VI, which was isolated as the dimer. On the other hand, V (X=C) expelled CO_2 thermally and rearranged

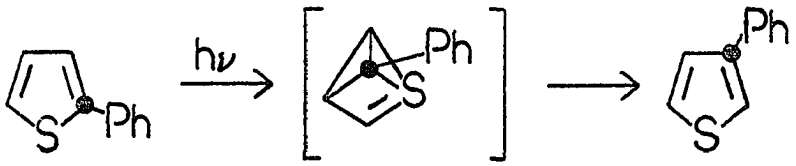


to the ketene VII. Subsequent elimination of CO from VII followed by a dimerization and an isomerization process was proposed to account for the major products, napthalene and azulene. It was of particular interest to find that the mass spectral decomposition of V (X=S) also involved the initial loss of SO followed by CO, whereas that of V (X=C) involved the elimination of CO_2 from the molecular ion. Similar comparisons have been made with other cyclic aromatic sulfites (10, 11) and related heterocyclic systems (12, 13).

It has been estimated that an average molecule upon ionization in the mass spectrometer acquires an internal energy of approximately 5 ev (1). This amount of energy is equivalent to a quantum of light having a wavelength of 250 nm, or light in the ultraviolet region of the spectrum. In view of this, the numerous examples of analogous photochemical and electron impact induced transformations

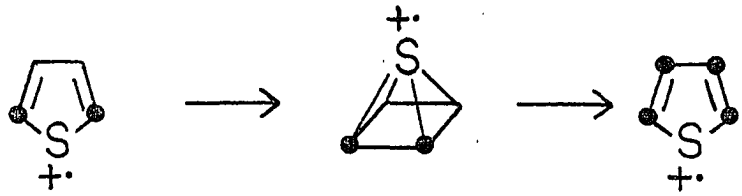
reported in the literature are easily realized (1). Because of the large number and wide diversity of correlations known, only some representative examples involving skeletal rearrangements of heterocyclic compounds will be discussed.

Several years ago Wynberg and his research group (14) reported the photoisomerization of 2-phenyl thiophene. By labelling the substituted carbon of the thiophene ring, it was discovered that the formation of the photoproduct involved a skeletal rearrangement of the thiophene ring, and not a simple 1,2-migration of the phenyl group. Intermediate VIII was postulated for this isomerization.



VIII

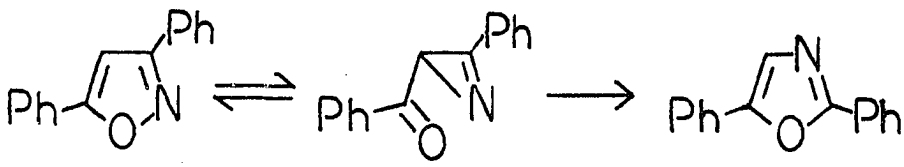
Recently, the mass spectrum of thiophene-2,5-$^{13}C_2$ was studied to determine the possible occurrence of a similar transformation upon electron impact (15). An intense fragment ion in the mass spectrum of thiophene (16) is CHS^+, which, in the case of the labelled material, was found to contain a significant amount of carbon-12. Partial rearrangement of the ionized thiophene ring must occur, therefore, and intermediate IX has been suggested to account for



IX

this isomerization.

A similar ring transformation has been documented by Singh and Ullman (17) in their studies of the photochemistry of 3,5-diphenyl isoxazole (X). The product was 2,5-diphenyl

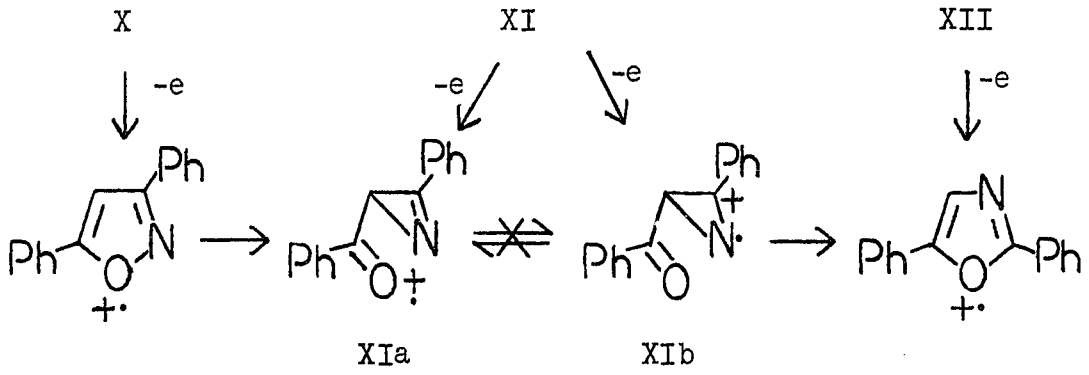


X XI XII

oxazole (XII) which was formed via the acyl azirine XI. This intermediate could be isolated, and it exhibited an unusual wavelength dependence upon photolysis. Irradiation of XI with light of wavelength 334 nm produced X, whereas photolysis under more energetic conditions ($\leq$ 313 nm) resulted in the formation of only XII. This phenomenon has been attributed to selective excitation of the carbonyl and ketimine chromophores.

A related argument has been used to explain the frag-

mentation pattern of the molecular ion of XI in comparison with the mass spectra of X and XII (18).



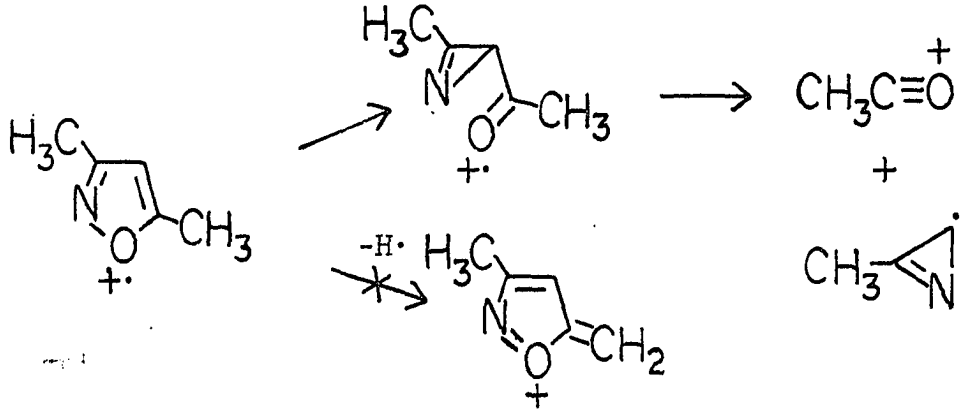
XIa XIb

It has been suggested that selective excitation of XI occurs to give the two charge localized species XIa and XIb. The major decomposition pathway of XIa involves the formation of the benzoyl cation (m/e 105), which is also the base peak in the spectrum of X. For this reason a transformation of the radical cation of X to XIa prior to fragmentation has been postulated. Two of the major ions in the spectrum of XII appear at m/e 166 and m/e 165 corresponding to $(M\text{-}CO\text{-}HCN)^{+\cdot}$ and $(M\text{-}CO\text{-}HCN\text{-}H)^{+}$, respectively. Since these ions also appear in the spectrum of XI, but not in that of X, it has been concluded that XIb partially rearranges to ionized XII prior to fragmentation, but that interconversion of XIa and XIb does not occur. The formation of the ions at m/e 166 and m/e 165 appears to be a general fragmentation pathway characteristic of a large variety of diphenyl-substituted

heterocyclic compounds and has been studied in considerable detail (19).

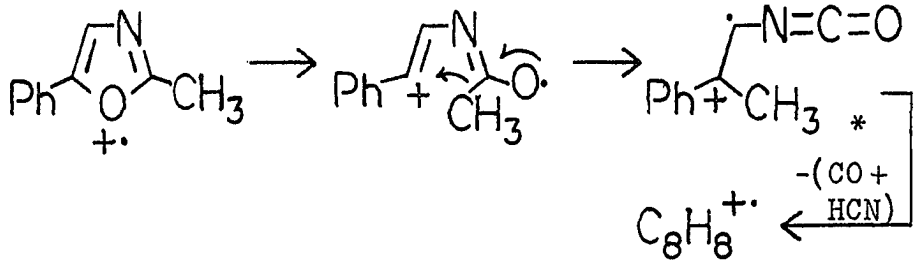
Mass Spectra of Some Five-Membered Heterocycles

The lability of the N-O bond in the isoxazole ring to nucleophilic agents is well known (20). The fragmentation pattern of isoxazoles upon electron impact is also characterized by an initial cleavage of this weak bond. The mass spectrum of 3,5-dimethyl isoxazole, for example, indicates that an isomerization of the molecular ion to an acyl

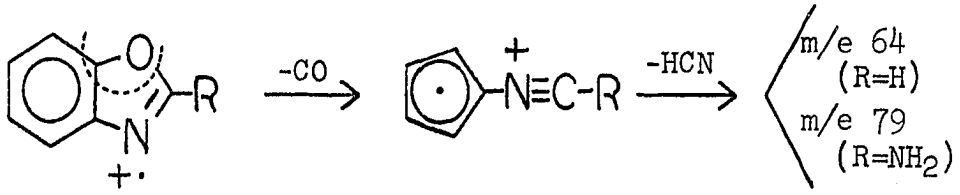


azirine radical cation occurs followed by α-cleavage to give an intense peak at m/e 43 corresponding to the acetyl cation (21). The loss of H· from the molecular ion by β-cleavage, a very important process in dimethyl furans (16, p. 617), is almost nonexistent in the spectra of dimethyl isoxazoles. This also has been postulated to result from the preferred facile ring cleavage reaction. Methyl phenyl isoxazoles exhibit the loss of CO and HCN upon electron impact (22). An isomerization of the

isoxazole radical cation to the corresponding oxazole species via an ionized acyl azirine intermediate is believed to be involved since all of the isomeric methyl phenyl oxazoles also undergo this $M^{+\cdot}$-(CO+HCN) process (23), which has been rationalized as follows:



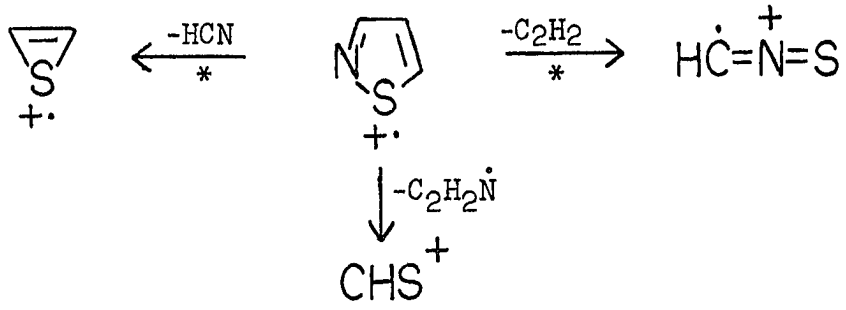
A similar fragmentation involving the loss of CO followed by HCN has been observed in the mass spectrum of benzoxazole (24). The origin of the carbon in the CO loss



presumably is the benzene ring since the 2-amino benzoxazole radical cation undergoes an analogous decomposition. Although numerous other studies of the mass spectra of isoxazoles (25-27) and oxazoles (16, p. 634) have been conducted, the electron impact induced transformations of benzisoxazoles have not been reported.

It is interesting to compare the mass spectral frag-

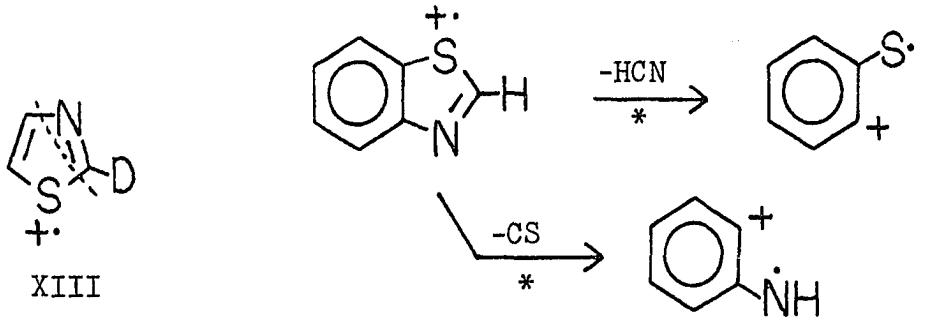
mentation of the isoxazoles with that of the analogous isothiazole ring system. The stability of the isothiazole system is reflected by an intense molecular ion, which is



the base peak in the mass spectrum of the parent compound and in the spectra of most alkyl and aryl derivatives (28). The principal decomposition mode involves cleavage of the N-S and the C_3-C_4 bonds with the elimination of HCN (29), or benzonitrile in the case of 3-phenyl isothiazole (30). Another striking difference between the spectra of isoxazole and isothiazole is the elimination of acetylene from the molecular ion of the latter to yield a daughter ion containing both hetero-atoms. Finally, the formation of the ion at m/e 45 (CHS^+) is reminiscent of a major fragmentation process of the thiophene molecular ion (16, 29).

The mass spectrum of thiazole is very similar to that of its isomer isothiazole, in that the molecular ion is the most intense ion in the spectrum and fragments with the preferential loss of HCN (16, p. 634). The hydrogen involved in this loss has been shown to originate specifi-

cally from the 2-position by examination of the labelled derivative XIII. The loss of HCN from benzothiazole, however, was found to involve the aromatic hydrogens to the extent of ~ 8% (31). Another interesting feature of the

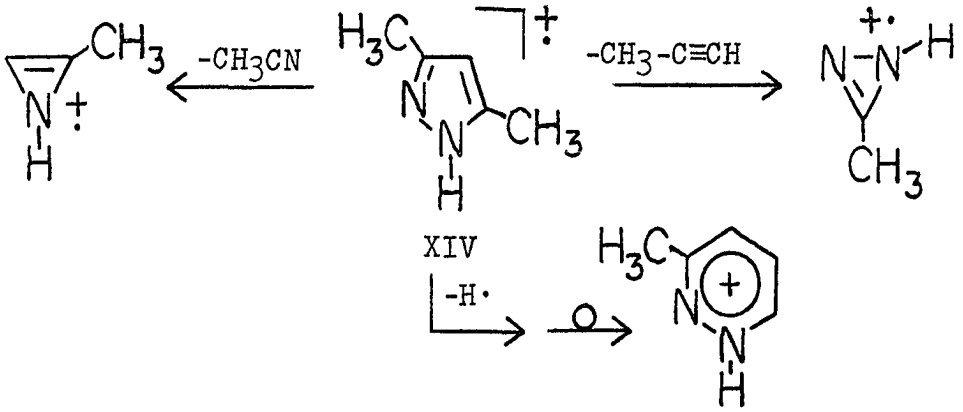


XIII

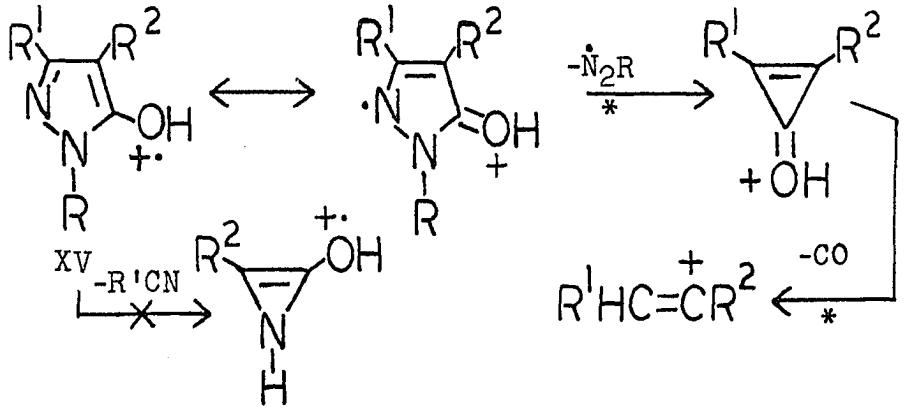
benzothiazole decomposition is the loss of CS which is analogous to the loss of CO from the benzoxazole radical cation (24). The C-2 carbon atom of the thiazole nucleus presumably is involved in this CS loss since this fragmentation pathway does not occur in the spectrum of 2-methyl benzothiazole. Only the loss of an atom of sulfur is observed in the latter case (32). The mass spectra of other alkylated benzothiazoles have recently been reported (33), but no studies have been carried out on the corresponding benzisothiazole system.

A considerable amount of data has accumulated recently concerning the electron impact induced reactions of pyrazoles and related nitrogen-containing heterocycles. The mass spectral decomposition of the pyrazole nucleus is characterized by two major pathways analogous to those described for isothiazoles (29). These are the cleavage

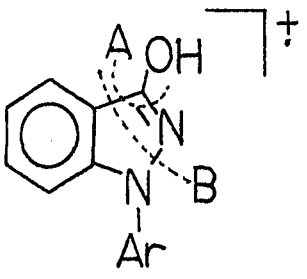
of the 1,2- and 3,4-bonds with expulsion of acetonitrile and the elimination of methyl acetylene by cleavage of the 1,5- and 3,4-bonds, as illustrated in the case of 3,5-dimethyl pyrazole (XIV) (34). The elimination of H· from the molecular ions of various methyl pyrazoles is significant, and ring expanded species have been suggested to explain the subsequent fragmentation of the M-1 ions (35).



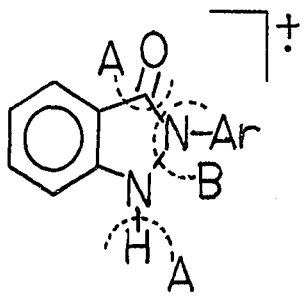
The mass spectra of 5-hydroxy pyrazoles (or 5-pyrazolones) do not resemble those of other pyrazoles, in that the initial cleavage of the N-N bond is generally insignificant. For example, the loss of R'CN from the molecular ion (XV) is not observed. Instead, the spectra



of 5-pyrazolones are characterized by the initial elimination of $\cdot N_2R$ followed by CO (36). A similar breakdown pattern has been shown to occur as the major process in the mass spectra of a variety of alkylated 3-hydroxy indazoles (or 3-indazolinones) (37). However, upon substitution of an aryl group at either the 1- or 2-position of 3-indazolinone, somewhat different fragmentation patterns immerge as illustrated by the dashed lines in XVI and XVII



XVI

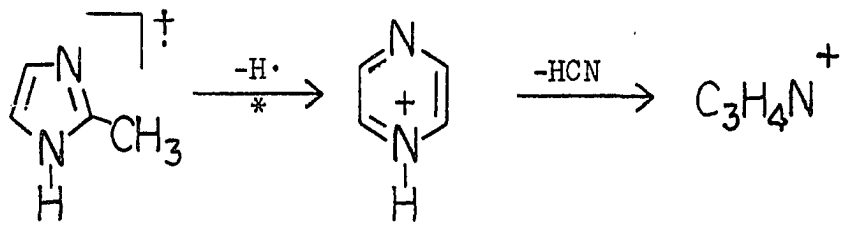


XVII

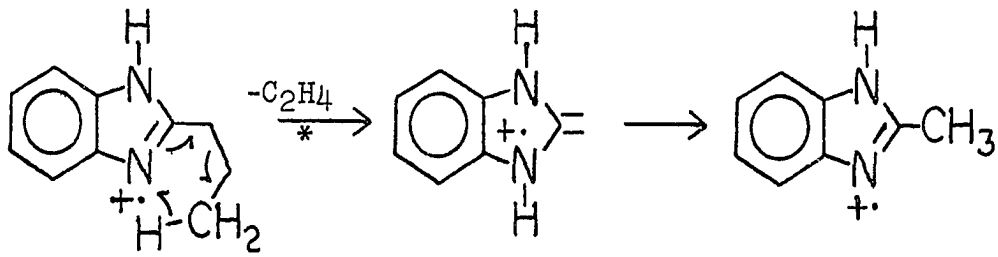
(38). The loss of ĊHO (process A) is characteristic of both systems, but the alternate principal decomposition mode (process B) is highly dependent on the position of ring substitution.

Analogous to the decomposition of the pyrazole radical cation (34), the major fragmentation mode of the molecular ion of imidazole involves the loss of HCN (39, 40, and 16, p. 642). This expulsion of HCN, however, has been shown to be nonspecific by carrying out appropriate deuterium labelling experiments. All of the monomethyl derivates of imidazole fragment upon electron impact with the initial

loss of HCN, the origin of which is largely dependent upon the position of ring substitution. Another important breakdown pattern of the 2-methylimidazole radical cation is the loss of H· to give a presumed protonated pyrazine species



which suffers the loss of a molecule of HCN (39). Similar ring-expanded ions have been postulated to explain the mass spectra of a variety of 2-alkyl benzimidazoles (41, 42). When the 2-alkyl substituent possesses a γ-hydrogen, such as in 2-n-propyl benzimidazole, the preferred process is a



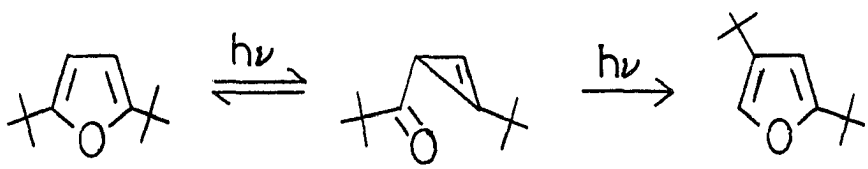
XVIII

McLafferty rearrangement of the molecular ion. The subsequent decomposition of species XVIII suggests that a prior rearrangement of this ion to the 2-methyl benzimidazole molecular ion occurs (43).

Other mass spectral studies of pyrazoles (44-46), pyrazolones (47), 3-indazolinones (48), and imidazoles (49) have been reported.

Photochemistry of Some Five-Membered Heterocycles

The photochemical behavior of a large variety of five-membered heterocyclic compounds has been described in the recent literature (50, 51). The well-known photoisomerization of 2-phenyl thiophene to the corresponding 3-phenyl derivative via a presumed tricyclic intermediate (VIII) was discussed previously (14). A similar transformation has been noted recently in the pyrrole ring system. Irradiation of 2-cyanopyrrole yields 3-cyanopyrrole as the major product, but, as in the case of thiophene, the reverse process apparently does not occur (52). Furans also undergo a related isomerization under photolytic conditions. 2,5-di-t-butylfuran was found to rearrange to the 2,4-di-t-butyl

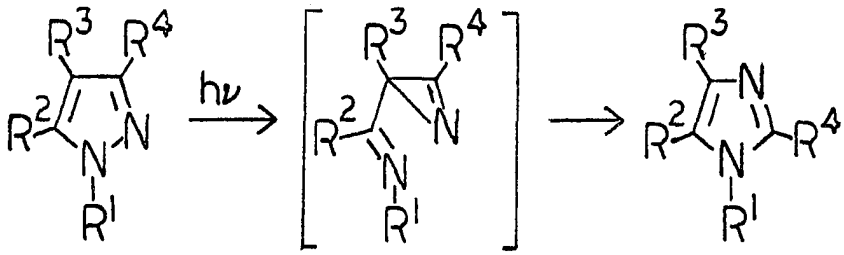


XIX

derivative, and the acylated cyclopropene XIX was an isolable intermediate in this process. Independent irradiation of XIX resulted in the formation of both the 2,5- and

the 2,4-di-t-butyl furans (53, 54).

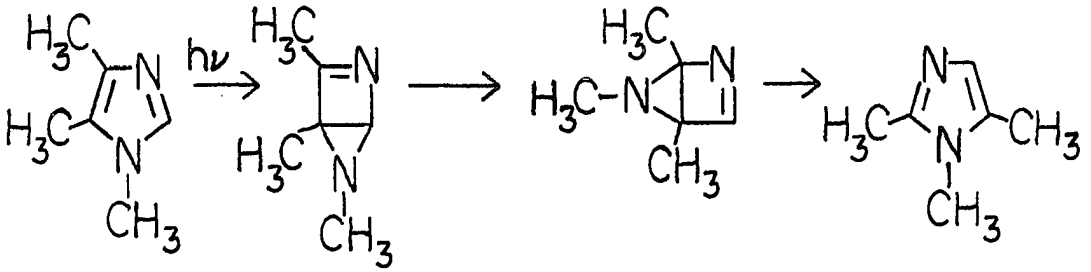
An analogous ring-contraction ring-expansion mechanism has been documented in the isoxazole ⟶ azirine ⟶ oxazole transformation which was discussed in some detail earlier (17). Other examples of photochemical reactions of isoxazolines (55) and isoxazoles (56, 57), whose results have been interpreted by this sequence of valence-bond isomerizations, have been reported. Rearrangements analogous to the isoxazole-oxazole interconversion have also been observed upon irradiation of pyrazoles (58). The products in this case were the corresponding imidazoles. An azirine intermediate XX has been suggested to participate in this rearrangement although no definite evidence for its existence has yet been reported. 5-pyrazolinones similarly have been photochemically transformed to 2-imidazolinones (59).



XX

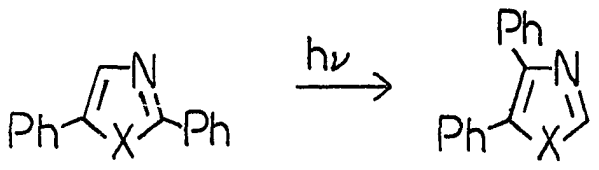
Recently, Beak and Messer reported evidence for an alternative mechanism to account for the photorearrangements of some pyrazoles and imidazoles (60). Irradiation

of 1,4,5-trimethylimidazole gave 1,2,5-trimethylimidazole as the only product. Its formation was rationalized by the intermediacy of the bicyclic structures XXIa and XXIb, which result from an electrocyclic ring closure followed by a 1,3-sigmatropic shift. The same type of mechanism has been proposed to explain the formation of 4,5-



XXIa XXIb

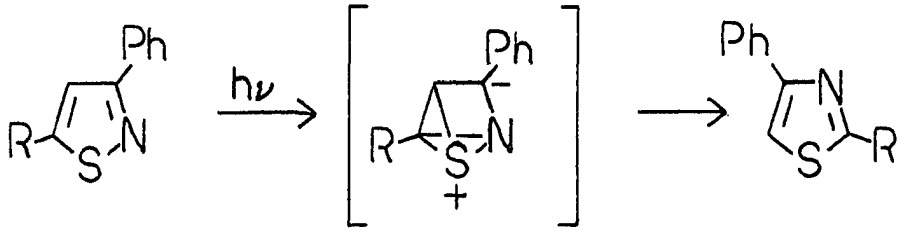
diphenyloxazole (61) and 4,5-diphenylthiazole (62) in the photolysis reactions of the corresponding 2,5-diphenyl substituted precursors XXII. Finally, the photoisomeriza-



XXII

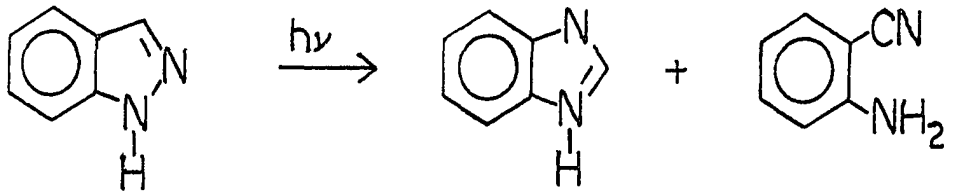
(X = O,S)

tion of isothiazole has also been shown to produce low yields of thiazole (63). A product study of the photochemistry of various derivatives of isothiazole revealed that a pathway somewhat analogous to that proposed in the

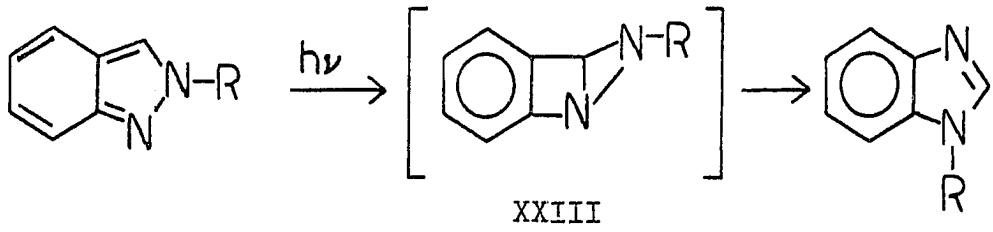


rearrangement of 4,5-diphenylthiazole (62) may also be involved in this system (64).

The photochemistry of the benzo-derivatives of these five-membered heterocyclic systems has received relatively less consideration. Indazole, for example, has been found to photoisomerize to give two products, benzimidazole and 2-aminobenzonitrile (58). Alkyl substitution at the 1-

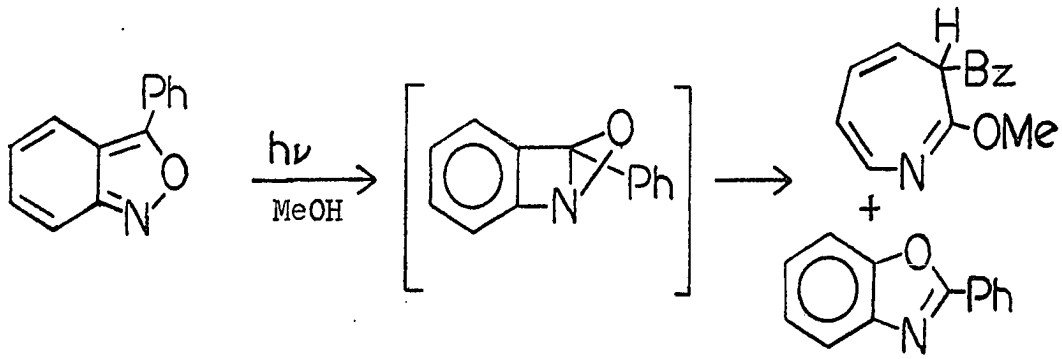


position of indazole was shown to hinder the rearrangement to the benzimidazole product, for in the photolysis of 1-alkyl indazole only the corresponding 2-N-alkylaminobenzonitrile was obtained. On the other hand, irradiation of 2-alkylated indazoles resulted in the formation of substituted benzimidazoles in very high yields. A tricyclic intermediate XXIII, analogous to XXI (see above), has been

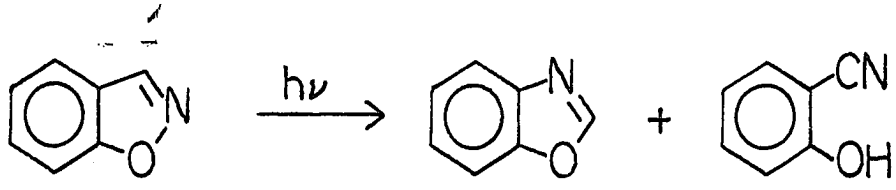


XXIII

invoked to explain this facile isomerization (58, 65). A similar intermediate species may be involved in the photoisomerization of 3-phenyl-2,1-benzisoxazole. The major product was a ring-expanded 3-H-azepine, but a small



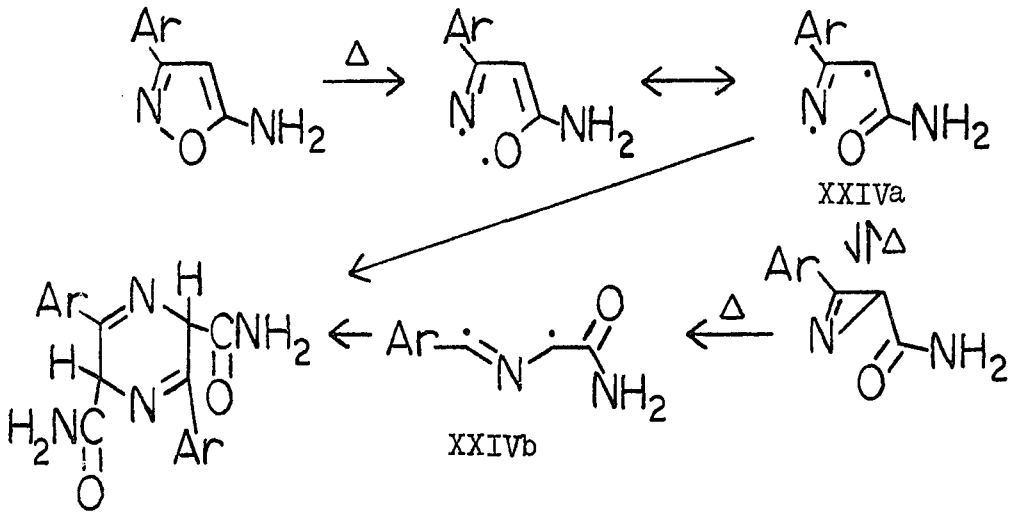
amount of 2-phenylbenzoxazole was also isolated (66). An analogous tricyclic intermediate, however, is not possible in the isomeric system, 1,2-benzisoxazole. The results of the photochemistry of this compound are the same as those reported for indazole. The products obtained in about equal



amounts were benzoxazole and salicylonitrile (67). A ring-contraction ring-expansion mechanism, as proposed in the isomerization of isoxazoles (17), may also be operating in this reaction. It is interesting to note that benz-isothiazole has been shown to be relatively inert under similar photolytic conditions (67).

Thermal Chemistry of Some Five-Membered Heterocycles

Thermally induced transformations of five-membered heterocycles, involving cleavage of the bond between two adjacent ring hetero-atoms, have been reported for derivatives of isoxazoles and isoxazolines. The apparent reason for the almost exclusive interest in only these particular systems is the known lability of the N-O bond (20). One of the earliest studies concerned with the thermolysis of isoxazoles was reported in 1952. A variety of 5-aminoisoxazoles were found to isomerize in urea and other solvents at 140-180° to the corresponding 2-imidazolinones (68). Recent work on the neat pyrolysis of these compounds has led to the isolation of only dihydropyrazine dervia-tives which presumably result from dimerization of the diradical species XXIVa or XXIVb. When the pyrolysis was carried out in solution, azirines could be isolated in certain cases (69, 70). A detailed study on the generation of 3-carboalkoxy-1-azirines from 5-alkoxy isoxazoles by similar thermal methods has been conducted recently,

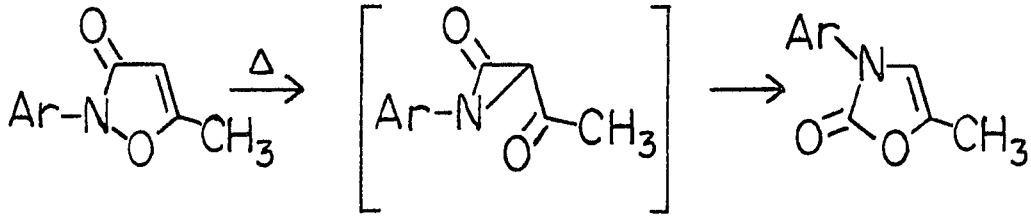


XXIVa

XXIVb

emphasizing the synthetic utility of these reactions (71).

The thermal reactions of a variety of N-aryl isoxazolin-3-ones have been reported to yield the corresponding N-aryl oxazolin-2-ones as the only products (72).

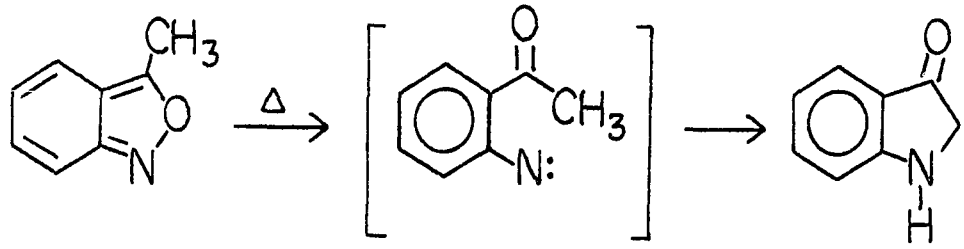


XXV

A ring-contraction ring-expansion sequence involving the acyl aziridinone XXV was suggested as a possible mechanism in the isomerization. Acyl aziridines have been isolated in the thermolysis of 4-isoxazolines (73), and upon subsequent heating they have been converted to oxazolines (74) in support of the mechanism shown above (72). Other

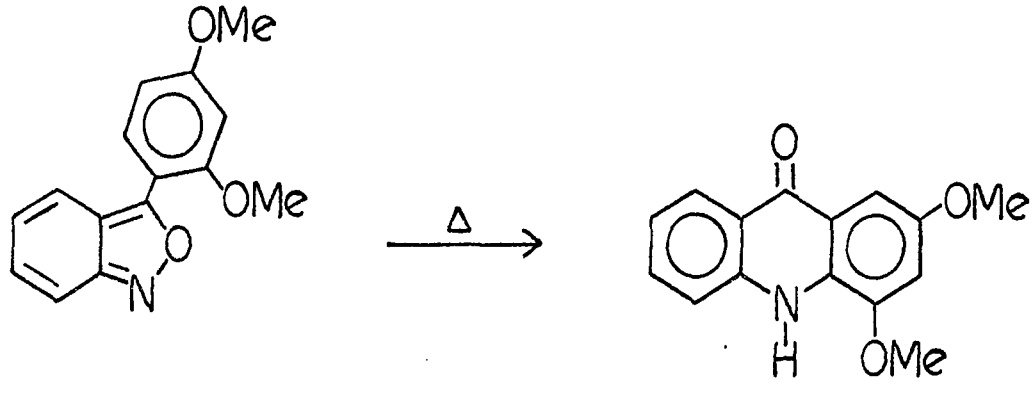
examples of pyrolytic processes involving the conversion of isoxazolines to acyl aziridines have been reported (75, 76).

The pyrolysis of 1,2-benzisoxazole has been studied (77), and salicylonitrile was obtained as the only product. A rearrangement to benzoxazole, which was reported as a major photoproduct (67), could not be detected. Similar results were observed in the thermolysis of 3-methyl-2,1-benzisoxazole (77). The product isolated in this case was indoxyl, whose formation can be rationalized by the nitrene



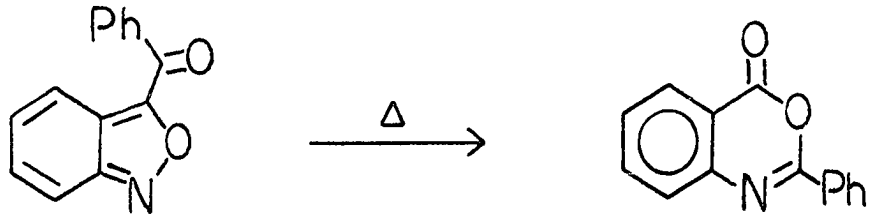
XXVI

intermediate XXVI. Analogous nitrene species have been proposed in the thermal conversions of 3-(2,4-dimethoxy-phenyl)-2,1-benzisoxazole to 2,4-dimethoxy acridone (XXVII)



XXVII

(78) and 3-benzoyl-2,1-benzisoxazole to 2-phenyl-3,1-benzoxazin-4-one (XXVIII) (79).

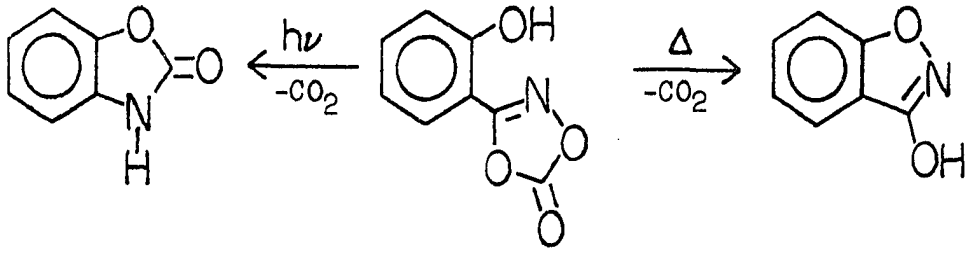


XXVIII

RESULTS AND DISCUSSION

Thermal and Mass Spectral Transformations

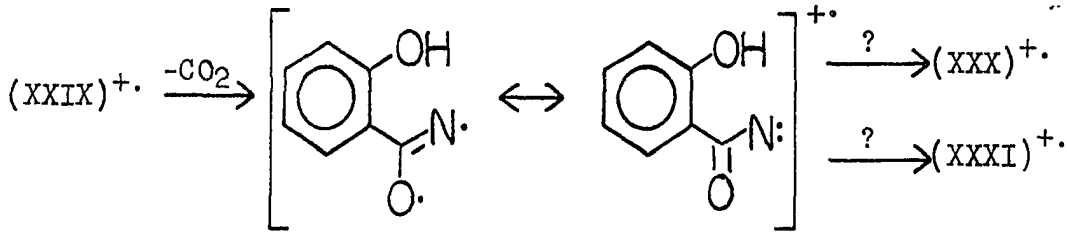
The photochemical decomposition of 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazolin-5-one (XXIX) has been shown to result in the formation of 2-benzoxazolinone (XXX) as the only product.



XXX XXIX XXXI

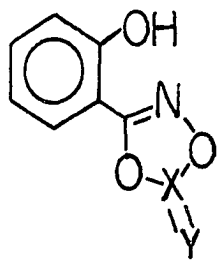
On the other hand, the solution-phase thermolysis (170-180°) of XXIX produces only the isomeric compound, 3-hydroxy-1,2-benzisoxazole (XXXI) (80). In view of the reported analogies between pyrolytic and mass spectral transformations of cyclic carbonates and sulfites (9-11), we initiated a study of the electron impact induced fragmentation of XXIX and related systems.

In particular, we were interested in determining the structure of the ion formed by the loss of CO_2 from the molecular ion of XXIX. In other words, does fragmentation

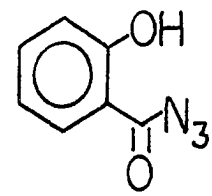


XXXII

of this $(M-CO_2)^{+\cdot}$ species proceed from an ionized acyl nitrene, such as XXXII, or from a rearranged ion related to the molecular ion of either XXX or XXXI analogous to the photolytic or thermal process? Our approach included the comparison method (3) in which the subsequent fragmentation of the $(M-CO_2)^{+\cdot}$ ion of XXIX was compared with the breakdown patterns of authentic XXX and XXXI upon electron impact. The mass spectra of the heterocyclic compounds XXXIIIa and XXXIIIb and of salicyloyl azide (XXXIV) were included in this



XXXIIIa, X=C, Y=S
b, X=S, Y=O



XXXIV

study since the $(XXXIII-XOY)^{+\cdot}$ and $(XXXIV-N_2)^{+\cdot}$ ions may also initially possess a nitrene structure related to XXXII.

The mass spectrum of XXIX (see Figure 1) shows an initial loss of CO_2 from the molecular ion to give an ion at m/e 135 (13%). This daughter ion then undergoes two major decomposition modes which are accompanied by metastable ions. These are: (i) the loss of two molecules of CO to produce the base peak at m/e 79; and (ii) the expulsion of CO_2 to yield an ion at m/e 91 (33%). In process (i), the loss of two CO's may occur in a sequential

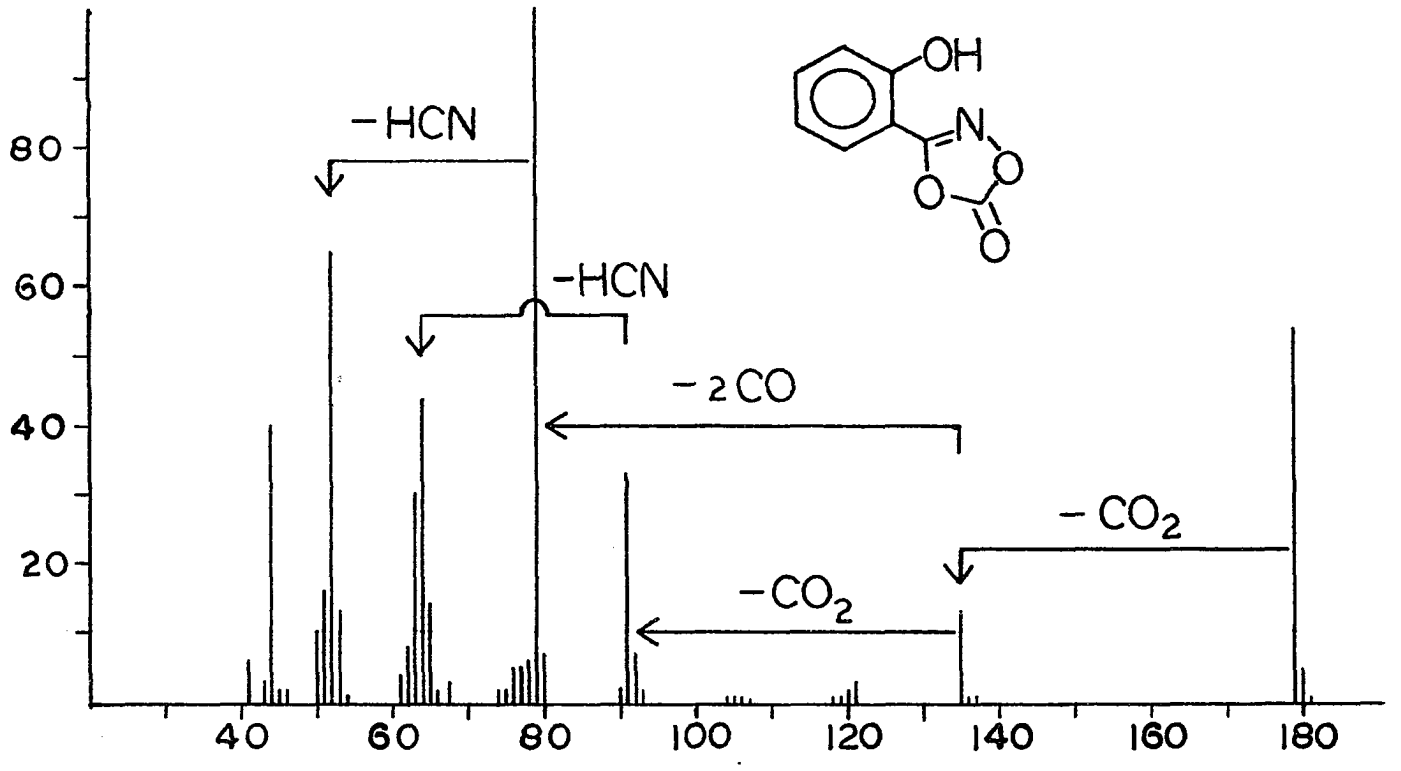


Figure 1. Mass spectrum of 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazolin-5-one (XXIX)

manner, although a metastable ion appears for the combined reaction: 135 → 79. Evidence in support of a stepwise fragmentation is the appearance of a weak ion at m/e 107 (< 1%). Similar observations have been noted in other mass spectral studies, and these are briefly discussed in reference 47. Process (ii), the loss of CO_2 from m/e 135, is particularly interesting and indicates that a substantial amount of rearrangement must occur in the $(M-CO_2)^{+\cdot}$ species. Both of the ions at m/e 91 and m/e 79 undergo further decomposition with the loss of 27 mass units (HCN) to furnish the prominent ions at m/e 64 and m/e 52, respectively.

In the mass spectrum of 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazolin-5-thione (XXXIIIa) the most intense ion appears at m/e 60 corresponding to $(COS)^{+\cdot}$ as shown in Figure 2. The second most abundant ion is the species at m/e 135 (83%) resulting from the metastable loss of neutral COS from the molecular ion. Metastable peaks at m/e 46.2 and m/e 61.3 appear in this spectrum also and correspond to the transitions: 135 → 79 and 135 → 91, respectively. These latter fragmentations are analogous to the major fragmentation patterns (i) and (ii) observed in the mass spectrum of XXIX (Figure 1).

The electron impact induced fragmentation of cyclic carbonates and sulfites has been shown to differ in that

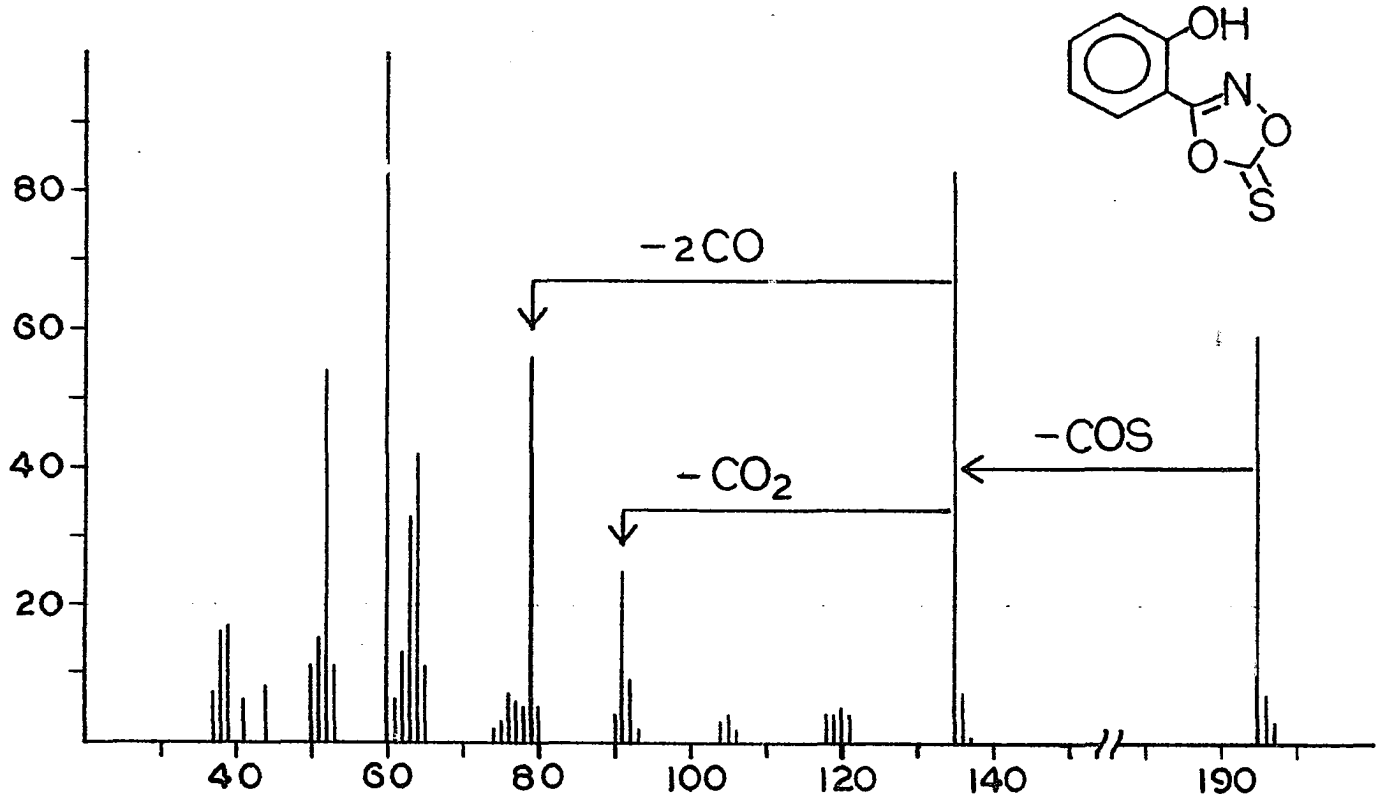


Figure 2. Mass spectrum of 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazolin-5-thione (XXXIIIa)

carbonates exhibit prominent $(M-CO_2)^{+\cdot}$ ions whereas sulfites preferably lose SO from their molecular ions (9). We observe similar results upon comparison of the breakdown patterns of the cyclic carbonate XXIX and 4-(2-hydroxyphenyl)-Δ^3-1,2,5,3-thiadioxazolin-S-oxide (XXXIIIb), a cyclic sulfite (Figure 3). In the spectrum of XXXIIIb an intense peak appears at m/e 121 (54%) corresponding to $(M-SO-NO)^{+\cdot}$. The subsequent fragmentation of this species is in agreement with this formulation and involves the sequential loss of two molecules of CO to give ions at m/e 93 (16%) and m/e 65 (38%). The corresponding ion $(M-CO-NO)^{+\cdot}$ from XXIX, however, is unimportant and has a relative intensity of only 3%.

The expulsion of SO_2 from $(XXXIIIb)^{+\cdot}$ to produce m/e 135 (41%) is also a major pathway. The fragmentation of this ion is responsible for the base peak at m/e 79 and the peak at m/e 91 (40%), processes analogous to (i) and (ii) described in the spectrum of XXIX.

The $(M-N_2)^{+\cdot}$ ion in the mass spectrum of salicyloyl azide (Figure 4) is relatively insignificant (< 2%). However, the appearance of metastable ions at m/e 46.2 and m/e 61.3 substantiate that this ion fragments to produce the species at m/e 79 and m/e 91, respectively.

Competing successfully with the loss of N_2 from $(XXXIV)^{+\cdot}$ are processes which involve the losses of $\cdot N_3$ and

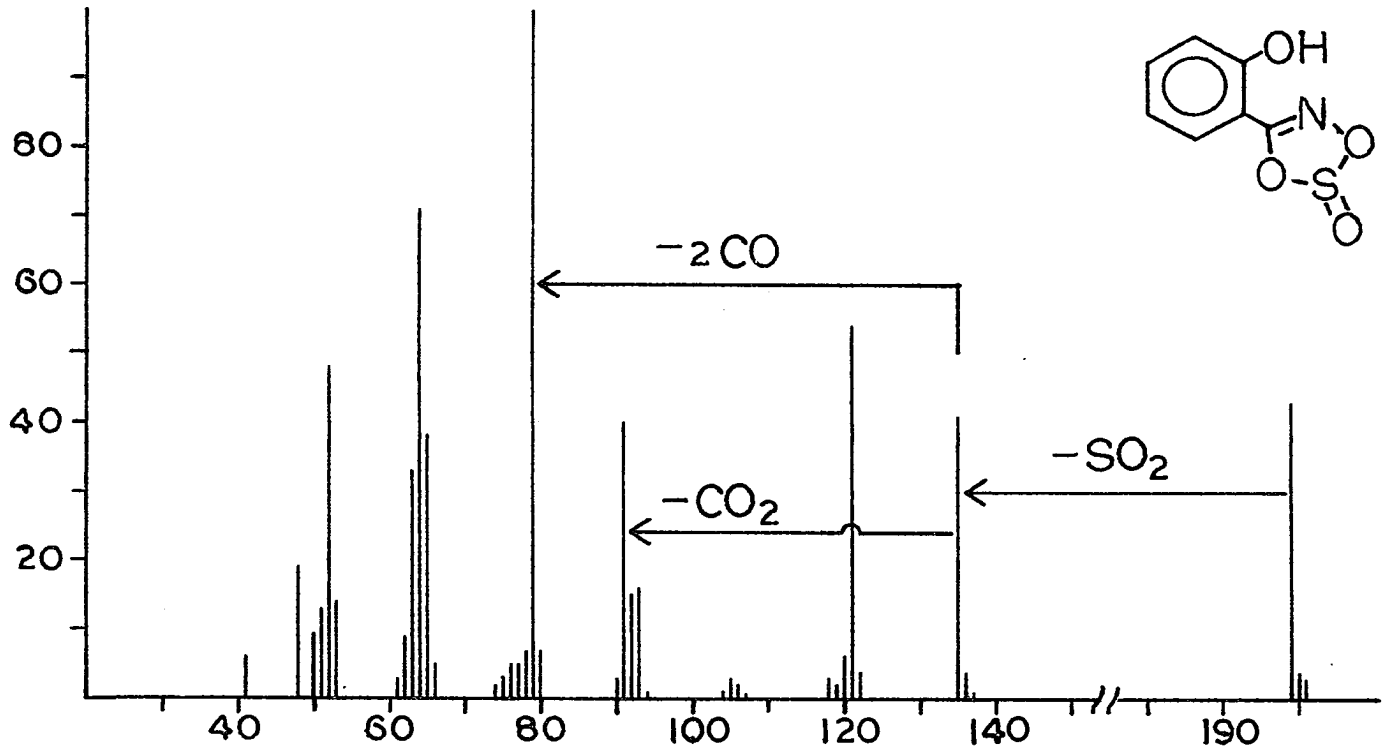


Figure 3. Mass spectrum of 4-(2-hydroxyphenyl)-Δ^3-1,2,5,3-thiadioxazolin-S-oxide (XXXIIIb)

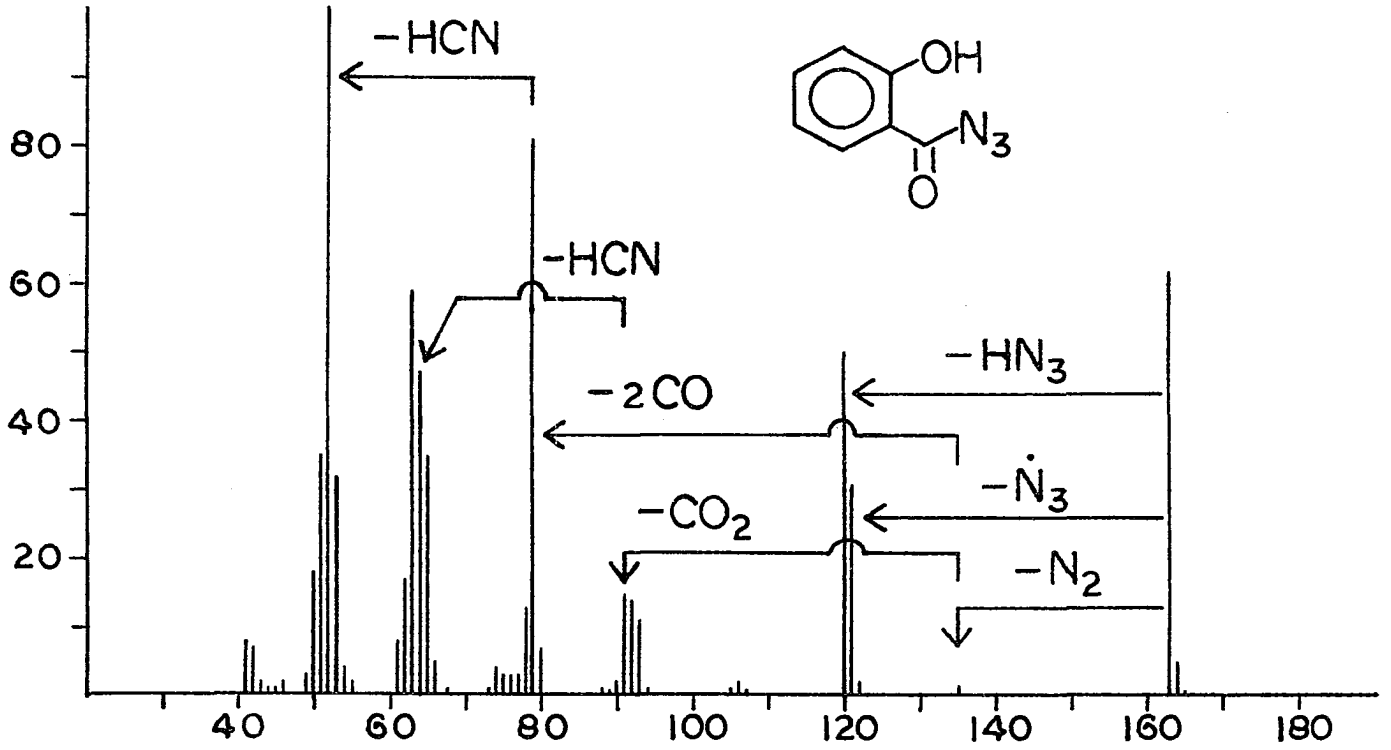
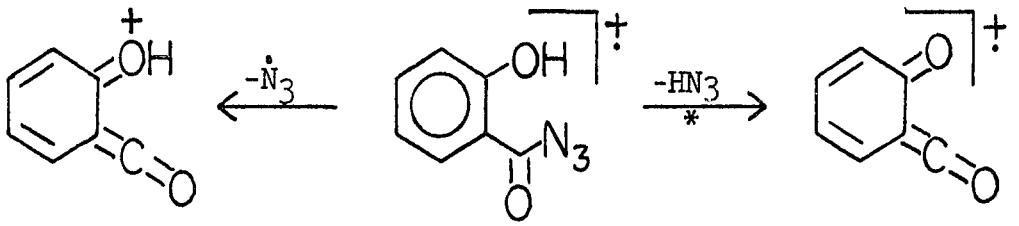


Figure 4. Mass spectrum of salicyloyl azide (XXXIV)

HN_3 to give m/e 121 (31%) and m/e 120 (50%) (see Scheme 1).

Scheme 1



m/e 121 m/e 163 m/e 120

The loss of azide radical has been demonstrated to be the most important process in the mass spectra of a variety of methyl triaryl azides, in which case the $(M-N_2)^{+\cdot}$ ions are also very weak (81). The expulsion of a molecule of hydrazoic acid from $(XXXIV)^{+\cdot}$ may be visualized as occurring by a six-membered transition state analogous to the loss of CH_3OH from the molecular ion of methyl salicylate (16, p. 199). The ions at m/e 121 and m/e 120 both undergo further fragmentation with consecutive losses of two CO molecules.

Since the fragmentation patterns of the m/e 135 ions in mass spectra of compounds XXIX, XXXIIIa, XXXIIIb, and XXXIV are essentially the same and involve the formation of ions at m/e (135-CO-CO) and at m/e ($135-CO_2$), a similar structural species may be involved in each case. In order to obtain added structural information concerning this m/e 135 species, the mass spectral behavior of 2-benzoxazolinone (XXX) and 3-hydroxy-1,2-benzisoxazole (XXXI) was investigated.

In the mass spectrum of 2-benzoxazolinone (Figure 5)

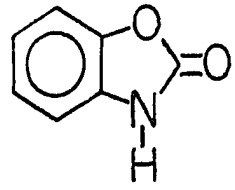


Figure 5. Mass spectrum of 2-benzoxazolinone (XXX)

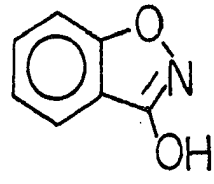
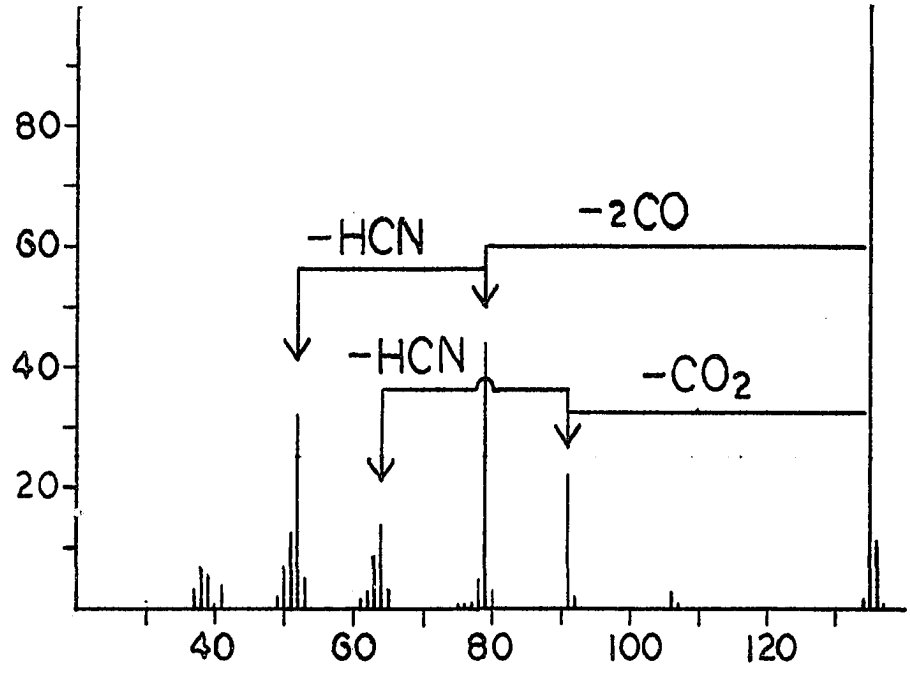
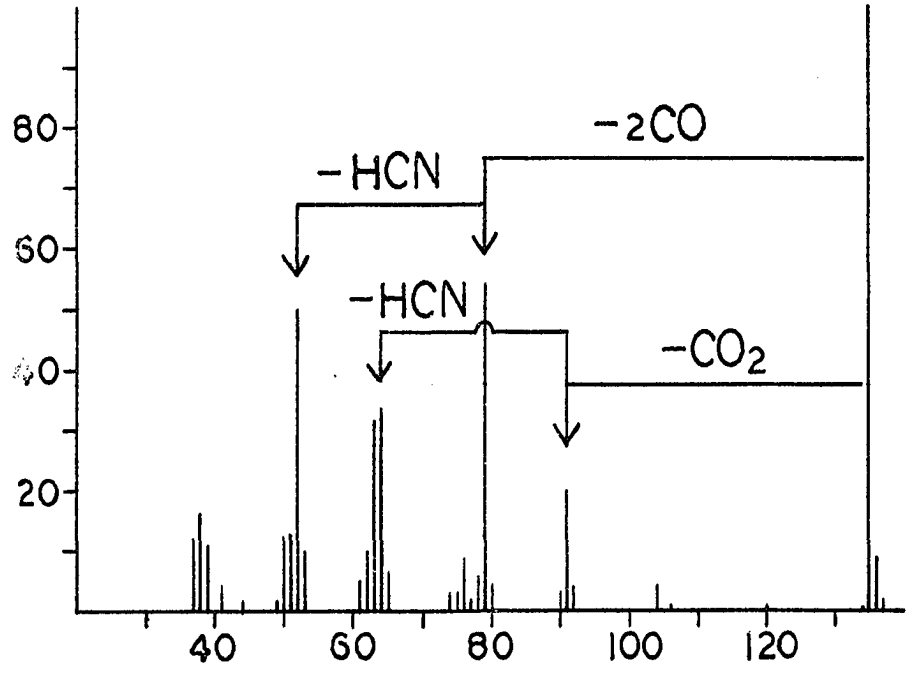


Figure 6. Mass spectrum of 3-hydroxy-1,2-benzisoxazole (XXXI)

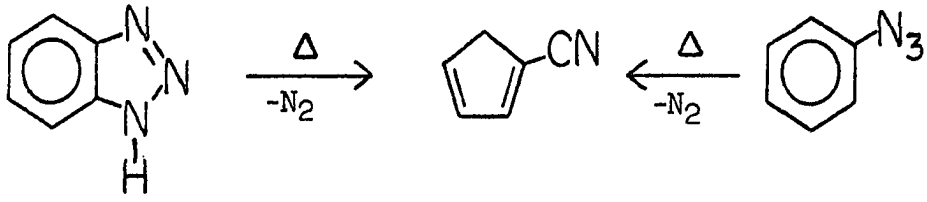

80
60
40
20
-HCN
-2CO
-HCN
-CO2
40
60
80
100
120


80
60
40
20
-HCN
-2CO
-HCN
-CO2
40
60
80
100
120

the molecular ion at m/e 135 produces the base peak in the spectrum. Its decomposition follows the same two major pathways described for the m/e 135 daughter ion in the spectra of XXIX, XXXIIIa, XXXIIIb, and XXXIV (see Figures 1-4). Metastable peaks are observed both for the 135 → 79 transition and for the stepwise loss of two molecules of CO in the following manner: 135 → 107 → 79. High resolution mass spectroscopy (HRMS) verified the empirical formulas of the m/e 107 and m/e 79 species as $(C_6H_5NO)^{+\cdot}$ and $(C_5H_5N)^{+\cdot}$, respectively.

The prominent ion at m/e 91 is formed by the expulsion of a molecule of CO_2 from the molecular ion, a process substantiated both by a metastable ion (m/e 61.3) and by HRMS. A related ionic species is produced by the loss of N_2 from ionized phenyl azide and benzotriazole. Since the gas-phase thermolysis of these compounds affords 1-cyanocyclopentadiene (Scheme 2), it has been postulated that the $(M-N_2)^{+\cdot}$ ion at m/e 91 may also have an ionized

Scheme 2



cyanocyclopentadiene structure which then eliminates a molecule of HCN (82). Recently, Woodgate and Djerassi (83) have shown that considerable skeletal rearrangement occurs in the $(M-N_2)^{+\cdot}$ ion of 1-^{13}C-phenyl azide prior to ejection of HCN and have proposed a seven-membered azepinium ion precursor.

It was of interest, therefore, to study the fragmentation of the $(M-CO_2)^{+\cdot}$ ion produced in the mass spectrum of N-d-2-benzoxazolinone. If only DCN is eliminated from the m/e 92 ion, then one would not expect to observe a significant change in the intensity of m/e 65 relative to m/e 64 upon comparison of the d_0- with the d_1- compound. However, Table 1 illustrates that some hydrogen scrambling does occur in the $(M-CO_2)^{+\cdot}$ species and both DCN and HCN are expelled, accounting for the noticeable increase in the relative abundance of m/e 65. Due to incomplete exchange of the N-H with deuterium and the weak relative intensities of the ions at m/e 65 and m/e 64, it is difficult to determine accurately the degree of hydrogen randomization. Similar H/D scrambling has been noted to occur in the $(M-N_2)^{+\cdot}$ species of 2,4,6-d_3-phenyl azide which was found to undergo random elimination of HCN and DCN (84).

In the spectrum of 2-benzoxazolinone (Figure 5) the ion at m/e 52 is composed of $(C_4H_4)^{+\cdot}$ and $(C_3H_2N)^{+}$ in a 2 to 1 ratio as determined by HRMS. The more intense

Table 1. Relative abundance of m/e 65 and m/e 64 in mass spectra of N-d_0- and N-d_1-2-benzoxazolinone[a]

m/e	Intensity (Σ 64 and 65 = 1.00) d_0	d_1
65	0.18	0.36
64	0.82	0.64

[a]64% d_1, 36% d_0

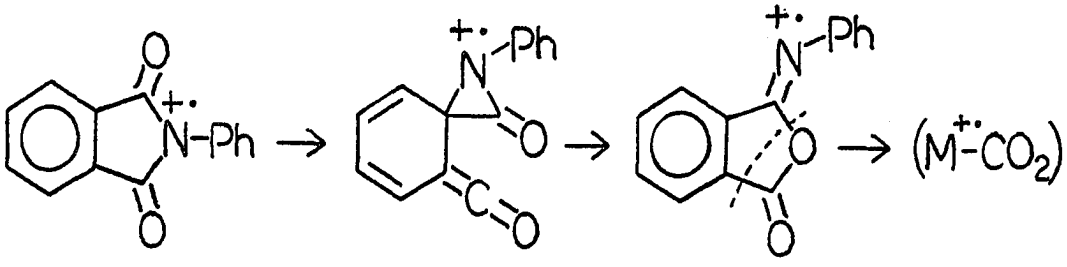
component is produced by the ejection of HCN from m/e 79 and undergoes further fragmentation to give the species $(C_4H_2)^{+\cdot}$ at m/e 50. Both of the above processes are accompanied by appropriate metastable ions.

A comparison of the mass spectrum of 2-benzoxazolinone with that of 3-hydroxy-1,2-benzisoxazole (Figure 6) demonstrates the remarkable similarity in the breakdown patterns of the molecular ions of these two isomeric compounds. Metastable ions appear at m/e 46.2 and m/e 61.3 corresponding to the loss of two CO's (m/e 79) and CO_2 (m/e 91) from the molecular ion, respectively. These transitions are also substantiated by accurate mass measurements. Subsequent decomposition of both fragment ions involves the loss of a molecule of HCN in a manner analogous to that observed in the spectrum of 2-benzoxazolinone.

The expulsion of CO_2 from the molecular ion of XXXI is

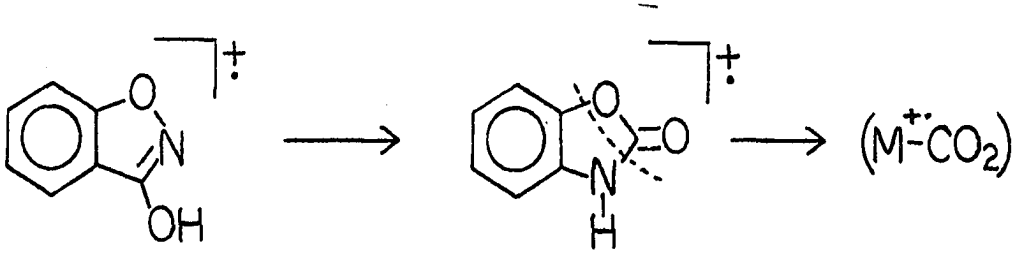
reminiscent of a related process in the mass spectra of phthalimides (85). For example, a prominent ion in the spectrum of N-phenyl phthalimide is the $(M-CO_2)^{+\cdot}$ species which has been explained by the transformation shown in Scheme 3 (86). It is of interest to note that similar isomerizations of phthalimides to isophthalimides have been found to occur thermally (85, 86).

Scheme 3



The principal fragmentation pathways of $(XXXI)^{+\cdot}$ may be explained by a related initial isomerization to a 2-benzoxazolinone radical cation (Scheme 4), from which the

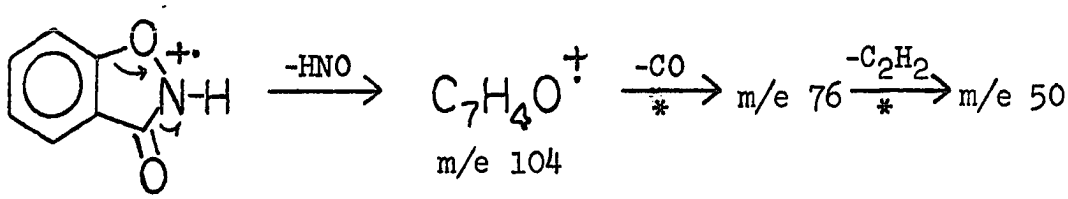
Scheme 4



loss of CO_2 readily occurs. In general, the mass spectra of 3-hydroxy-1,2-benzisoxazole and 2-benzoxazolinone are

virtually the same except for a minor decomposition pathway which appears in the spectrum of XXXI at 70 ev. This involves the loss of HNO from the molecular ion (see Scheme 5) to give a species at m/e 104 (4%) which, in turn, expels a molecule of CO (m/e 76) followed by acetylene (m/e 50).

Scheme 5



A similar fragmentation pathway occurs in the mass spectrum (see Figure 7) of the isomeric heterocycle 2,1-benzisoxazolin-3-one (XXXV). The relative intensity of the $(M\text{-}HNO)^{+\cdot}$ ion is also very small (~ 6%) in the 70 ev spectrum and disappears at lower energy. The primary decompositions of $(XXXV)^{+\cdot}$ involve the losses of two CO's and CO_2, and the overall spectrum of XXXV is qualitatively similar to those of XXX and XXXI. However, a comparison of the relative contributions of the major ions to the total ion current in each of the three spectra (Table 2) indicates a significantly smaller value for the m/e 79 ion in the spectrum of XXXV than in the spectra of XXX and XXXI. This fact is valuable, for example, in differentiating between the mass spectra of XXXI and XXXV since the loss of HNO

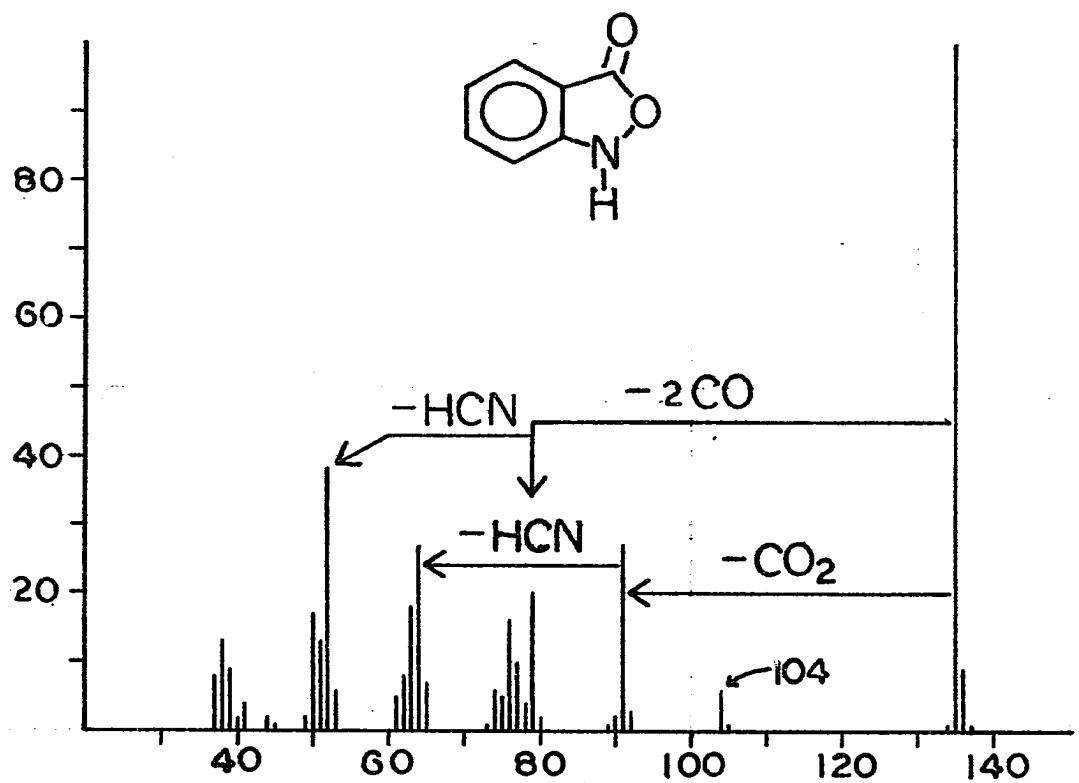


Figure 7. Mass spectrum of 2,1-benzisoxazolin-3-one (XXXV)

Table 2. Contribution of major ions in the mass spectra of XXX, XXXI, and XXXV to the total ion current

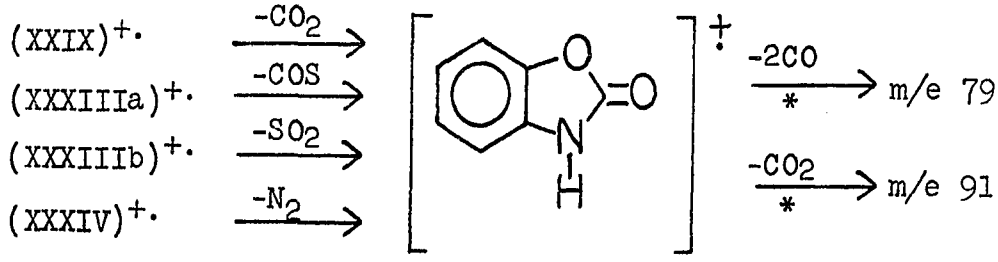
ion	m/e	Fractional ion abundance XXX	XXXI	XXXV
$M^{+\cdot}$	135	0.356	0.256	0.288
$(M-CO_2)^{+\cdot}$	91	0.078	0.051	0.078
$(M-2CO)^{+\cdot}$	79	0.157	0.138	0.058
$(M-CO_2-HCN)^{+\cdot}$	64	0.050	0.087	0.078
$(M-2CO-HCN)^{+\cdot}$	52	0.114	0.128	0.110

occurs as a minor fragmentation pathway in both spectra.

Since 3-hydroxy-1,2-benzisoxazole (XXXI) presumably rearranges upon electron impact to form ionized 2-benzoxazolinone (Scheme 4), it is virtually impossible to determine whether a species such as $(XXXI)^{+\cdot}$ is initially formed upon elimination of the appropriate neutral molecule from the molecular ions of XXIX, XXXIIIa, XXXIIIb, and XXXIV (see Scheme 6). In any case, the expulsion of CO_2 from the m/e 135 ion suggests that a 2-benzoxazolinone radical cation is formed prior to further fragmentation.

It is interesting to note, however, that the m/e 135 ion is the base peak in the mass spectrum of 2-benzoxazolinone (Figure 5) but is relatively less intense in the spectra of XXIX, XXXIIIa, XXXIIIb, and XXXIV

Scheme 6



m/e 135

(Figures 1-4). Furthermore, the fragment ions at m/e 79 and m/e 91 are much more intense than the m/e 135 species in the spectra of XXIX, XXXIIIb, and XXXIV, even though these ions originate from the m/e 135 precursor ion. These results may be explained by the fact that excess threshold energy is imparted to a daughter ion when the molecular ion expels a small neutral molecule, such as N_2 or CO_2 (3) (see Review of Literature). The daughter ion then experiences a higher rate of decomposition and, consequently, a lower relative abundance. This can be illustrated (Table 3) by comparing the relative ion abundance ratio [m/e 91]/[m/e 135] in the spectra of XXIX, XXXIIIa, b, and XXXIV with that found in the spectrum of 2-benzoxazolinone (XXX). This ratio decreases sharply in the spectra of XXXIIIa and XXXIIIb in which large neutral molecules are eliminated from the respective molecular ions.

It was of interest to compare these results with those obtained in a study of the mass spectra of 3-phenyl-Δ^2-1,4,

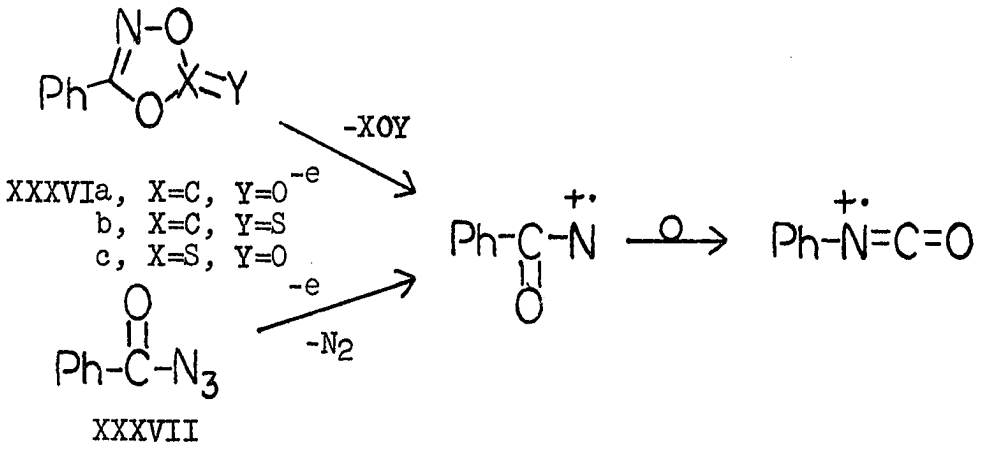
Table 3. Relative ion abundance ratio [m/e 91]/[m/e 135] at 70 ev

Precursor ion	Neutral expelled	Ratio
$(XXXIV)^{+\cdot}$	N_2	11.54
$(XXIX)^{+\cdot}$	CO_2	2.54
$(XXXIIIb)^{+\cdot}$	SO_2	0.98
$(XXXIIIa)^{+\cdot}$	COS	0.30
$(XXX)^{+\cdot}$	-	0.22

2-dioxazolin-5-one (XXXVIa), 3-phenyl-Δ^2-1.4,2-dioxazolin-5-thione (XXXVIb), 4-phenyl-Δ^3-1,2,5,3-thiadioxazolin-S-oxide (XXXVIc), and benzoyl azide (XXXVII). The expulsion of neutral XOY from the molecular ions of XXXVIa-c and N_2 from XXXVII would produce an ionized benzoyl nitrene which could undergo a Curtius rearrangement to afford the phenyl isocyanate radical cation (Scheme 7). The formation of phenyl isocyanate in the thermal and photochemical reactions of these compounds has been reported (80). However, since the electron impact induced Curtius rearrangements have not been studied, the mass spectra of XXXVIa-c and XXXVII were compared (Table 4) with the known (16, p. 420) spectrum of phenyl isocyanate (XXXVIII).

In the mass spectra of both XXXVIa and XXXVIb the most intense peaks correspond to the molecular ions. These

Scheme 7



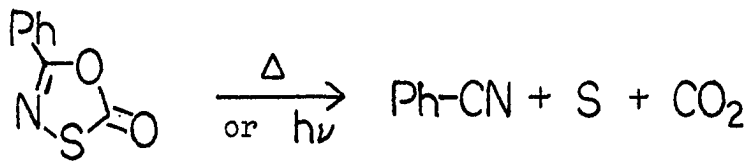
undergo metastable elimination of the corresponding XOY neutral to afford the m/e 119 species whose structure may be ionized phenyl isocyanate. Indeed, the subsequent fragmentation of this ion is the same as that of $(XXXVIII)^{+\cdot}$ and involves the loss of 28 mass units (CO) followed by 27 mass units (HCN) as substantiated by appropriate metastable ions.

An interesting transformation of $(XXXVIb)^{+\cdot}$, which is insignificant in the spectrum of XXXVIa, is the formation of an intense ion at m/e 103. This presumably corresponds to ionized benzonitrile since it undergoes further metastable fragmentation with the loss of 27 mass units (HCN) to give m/e 76. The loss of CO_2S from $(XXXVIb)^{+\cdot}$ may be a stepwise process although the spectrum shows no metastable ions corresponding to the formation of m/e 103. Analogous fragmentation of thiocarbonates has not been observed (16, p. 494). That benzonitrile is not an impurity is indicated by

Table 4. 70 ev mass spectra of XXXVIa-c, XXXVII, and XXXVIII

m/e	Relative intensities				
	XXXVIa	XXXVIb	XXXVIc	XXXVII	XXXVIII
183			50		
179		100			
163	100				
147				19	
120		7	5		
119	81	87	43	4	100
106			9	8	
105	8	4	100	100	
104		2			
103	3	29	5		
92	7	3			10
91	81	36	16	14	74
90	5	2		2	6
89	7	5	2		
78			7	5	
77	33	13	59	74	2
76	9	14	7	6	3
75	6	4	3	5	3
74	7	2	3	7	5
73				2	2
65	16	6	3	7	18
64	73	29	28	31	65
63	29	11	8	14	38
62	8	3	3	4	14
61				2	10
60		8			3
53				2	2
52	13	6	3	8	19
51	51	17	31	49	29
50	32	12	14	30	26
49				4	6
48			9		
44	22	9			2
42			7	4	3
41	14	5		6	11
40				3	10
39				18	52
38				20	56
37				10	35

the absence of nitrile absorption in the ir spectrum of XXXVIb and the sharp decrease in the relative intensity (< 10%) of the m/e 103 ion in the 16 ev spectrum. Furthermore, it is probably not a thermal artifact in the mass spectrometer since it is not a reported product in the thermolysis of XXXVIb (80). It is interesting to note, however, that benzonitrile is formed in the pyrolysis and photolysis reactions of the isomeric compound, 5-phenyl-Δ^4-1,3,4-oxathiazol-2-one (XXXIX) (87).



XXXIX

The mass spectra of the cyclic sulfite (XXXVIc) and benzoyl azide (XXXVII) are very similar in that the ion at m/e 105 is the base peak in both spectra (see Table 4). This corresponds to the benzoyl cation as substantiated by its decomposition to give m/e 77 by the loss of a molecule of CO. The formation of the benzoyl cation is analogous to the generation of the m/e 121 species in the mass spectra of XXXIIIb and XXXIV (see above).

The m/e 119 ions in the spectra of XXXVIc and XXXVII are somewhat less intense. However, metastable ions appear at m/e 69.5 and m/e 45.0 and correspond to the transitions

119 → 91 and 91 → 64, respectively.

Therefore, in the mass spectra of XXXVIa-c and XXXVII, the m/e 119 species is best represented by a phenyl isocyanate radical cation. The similarity in the fragmentation pattern of this ion and that of authentic ionized phenyl isocyanate supports this formulation. However, the wide range of relative intensities of the ions derived from this species indicates that the m/e 119 ion is being formed with varying amounts of internal energy, a phenomonon that can be correlated with the size of the neutral molecule expelled. An illustration of this is shown in Table 5 in which the relative ion abundance ratio [m/e 91]/[m/e 119] for the mass spectrum of phenyl isocyanate (XXXVIII) is

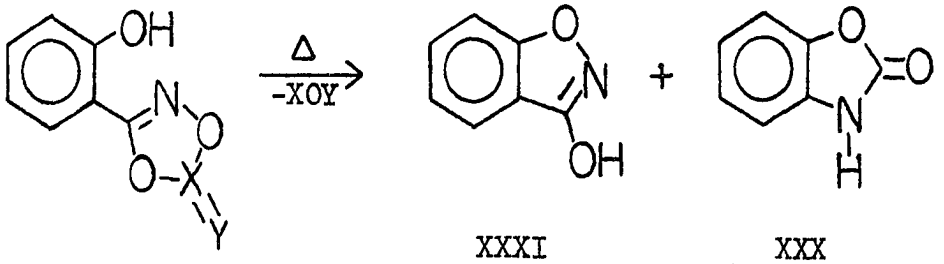
Table 5. Relative ion abundance ratio [m/e 91]/[m/e 119] at 70 ev

Precursor ion	Neutral expelled	Ratio
$(XXXVIII)^{+\cdot}$	-	0.74
$(XXXVII)^{+\cdot}$	N_2	3.50
$(XXXVIa)^{+\cdot}$	CO_2	1.00
$(XXXVIb)^{+\cdot}$	COS	0.41
$(XXXVIc)^{+\cdot}$	SO_2	0.37

compared with the corresponding ratios in the spectra of XXXVIa-c and XXXVII. The results of this comparison are in general agreement with those presented in Table 3 and suggest that molecules such as N_2 and CO_2 are able to absorb less energy from the parent ion upon elimination than the larger molecules, SO_2 and COS (3).

Mechanistic studies in organic mass spectrometry are often plagued by thermal reactions which may occur prior to electron impact in the high temperature inlet system of the spectrometer (16, p. 7). This is of particular importance in compounds XXIX, XXXIIIa, b, XXXIV, XXXVIa-c, and XXXVII since they have been shown to decompose at elevated temperatures (80). In order to alleviate the possibility of such pyrolytic reactions, the mass spectra of these compounds were obtained using the direct inlet probe of the spectrometer whose temperature may range from 50 to 70 °C. Furthermore, both solution- and gas-phase pyrolyses were carried out on several of the above compounds to obtain an estimate of their thermal stabilities.

It has been reported (80) that 3-hydroxy-1,2-benzisoxazole (XXXI) is produced in high yields in the solution-phase thermolysis of the cyclic carbonate (XXIX). However, only starting material is recovered quantitatively when pyrolysis of XXIX is carried out in benzene under reflux for two hours (Table 6). Sublimation of XXIX into



XXIX, XXXIIIa, b

XXXI

XXX

Pyrex furnace tube maintained at 150° results in the formation of XXXI as determined by ir and mass spectroscopy. At higher temperatures significant amounts of 2-benzoxazolinone (XXX) are also produced, and at 450° XXX is the only product in addition to CO_2.

Table 6. Pyrolysis of 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazoline-5-one (XXIX)

Temp. (°C)	% yield[a] XXIX	XXXI	XXX
~ 80[b]	100	0	0
150 (± 5°)[c]	0	77	0
300 (± 5°)[c]	0	58	16
450 (± 5°)[c]	0	0	93

[a]Based on unrecovered XXIX.

[b]Refluxing benezene.

[c]Gas-phase pyrolysis.

The cyclic thiocarbonate XXXIIIa is also recovered virtually unchanged from a benzene solution heated to reflux for one hour (Table 7). However, upon storing this compound at room temperature for approximately two months,

Table 7. Pyrolysis of 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazolin-5-thione (XXXIIIa)

Temp. (°C)	% yield[a] XXXIIIa	XXXI	XXX
~ 80[b]	100	0	0
150[c] (± 5°)	0	82	0
450[c] (± 5°)	0	0	86

[a]Based on unrecovered XXXIIIa.

[b]In benzene under reflux.

[c]Gas-phase pyrolysis.

the presence of a significant amount of 3-hydroxy-1,2-benzisoxazole (XXXI) could be detected by infrared spectroscopy. This is also the major product in the gas-phase pyrolysis of the thiocarbonate at 150°. In general, the thermal behavior of XXIX and XXXIIIa parallel each other closely (see Tables 6 and 7), although the latter compound exhibits more instability by its apparent gradual decomposition at room temperature.

Attempts to study the gas-phase thermolysis of the

cyclic sulfite XXXIIIb were unsuccessful due to the extremely low volatility of this compound at reduced pressures. Böshagen has reported that it is decomposed thermally at 100-120° to give approximately equal amounts of XXX and XXXI (88).

Salicyloyl azide (XXXIV) was found to be surprisingly stable at 150° in the gas-phase and can be isolated unchanged (Table 8). Decomposition is effected at 200-250° to give

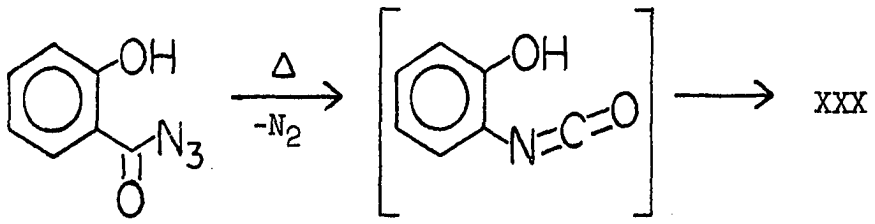
Table 8. Gas-phase pyrolysis of salicyloyl azide (XXXIV)

Temp. °C (± 5°)	% yield[a] XXXIV	XXX
150	96	0
200	63	36
250	0	81

[a]Based on unrecovered XXXIV.

2-benzoxazolinone (XXX). No evidence for the formation of 3-hydroxy-1,2-benzisoxazole (XXXI) could be found in the crude pyrolysate which indicates that a nitrene intermediate is probably not involved in this thermal Curtius rearrangement. Similar conclusions have been reached in studies dealing with solution-phase pyrolyses of XXXIV (89).

It is interesting to note the contrast in the thermal stabilities of XXIX (Table 6) and 3-phenyl-Δ^2-1,4,2-



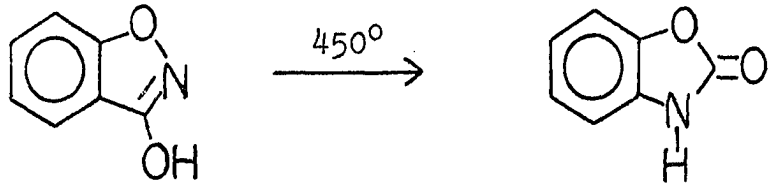
XXXIV

dioxazolin-5-one (XXXVIa). Whereas XXIX is readily decomposed at 150°, XXXVIa can be recovered unchanged at 250° under otherwise identical conditions. A possible explanation may be some type of neighboring-group participation by the hydroxyl group in the elimination of CO_2 from XXIX.

In conclusion, these thermal studies indicate that the transitions shown in Scheme 6 to give m/e 135 and Scheme 7 to give m/e 119 are indeed electron impact induced and are not pyrolytic reactions occurring prior to ionization. This is furthermore substantiated by the appearance of appropriate metastable ions in the mass spectra of XXXIIIa, XXIV, XXXVIa, and XXXVIb and the marked decrease in relative intensities of the m/e 135 and m/e 119 species in the spectra obtained at low energy electron bombardment.

Since the electron impact induced fragmentation of 3-hydroxy-1,2-benzisoxazole (XXXI) is readily explained by an initial isomerization to ionized 2-benzoxazolinone (Scheme 4), it was of particular interest to study the thermal behavior

of these compounds in the gas-phase. Sublimation of XXXI under high vacuum into a Pyrex pyrolysis column packed with glass beads and heated to 450 °C indeed results in essentially quantitative yields of 2-benzoxazolinone (XXX). At lower temperatures a significant amount (see Table 9) of



XXXI XXX

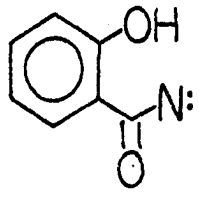
XXXI is recovered unchanged, and at 240-250° no apparent rearrangement can be detected. This indicates that the transformation of ionized XXXI to the radical cation of XXX in the direct inlet probe (50-70 °C) of the mass spectrometer is induced by electron impact and is not a thermal artifact.

Table 9. Effect of temperature on % conversion of XXXI → XXX

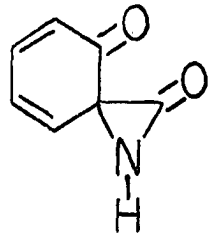
Temp. (°C)	% XXX[a]
240-250	0
340-350	50
440-450	> 95

[a]Determined by nmr integration.

The mechanism of this thermal isomerization may be related to that suggested for the photochemical degradation of 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazolin-5-one (XXIX) which also produces XXX via a postulated acyl nitrene XL (80). A Curtius rearrangement of this nitrene would produce 2-



XL



XLI

hydroxyphenyl isocyanate analogous to the thermal decomposition of salicyloyl azide (XXXIV). Alternatively, the mechanistic pathway may parallel that proposed for the thermal isomerizations of N-aryl isoxazolin-3-ones (72) and 4-isoxazolines (73) which would suggest α-lactam XLI as an intermediate.

In order to elucidate the mechanism involved in the thermal reorganization of XXXI to XXX, we undertook a study of the pyrolytic behavior of a variety of alkyl derivatives of XXXI.

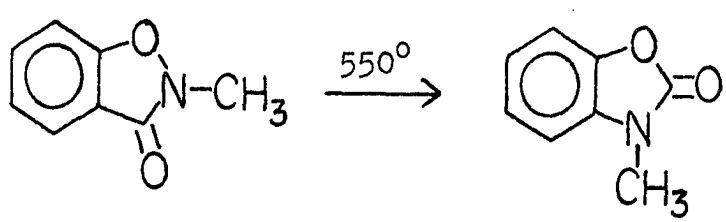
2-methyl-1,2-benzisoxazolin-3-one (XLII) undergoes a quantitative rearrangement at 550 °C in the gas-phase to give essentially pure 3-methyl-2-benzoxazolinone (XLIII). Table 10 shows the relative amounts of XLII and XLIII ob-

Table 10. Pyrolysis of 2-methyl-1,2-benzisoxazolin-3-one (XLII)

Temp. °C (± 10°)	Relative ratio[a] XLII	XLIII
350	96	4
450	32	68
550	0	100

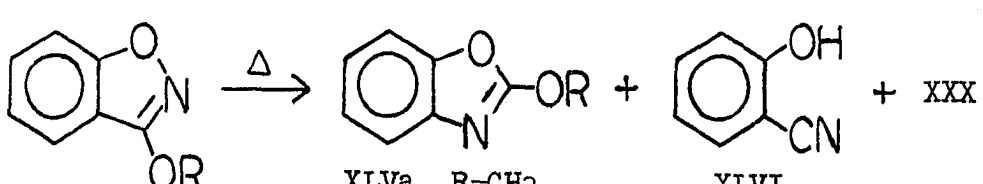
[a]Based on nmr integration.

tained at the temperatures indicated. Greater than 95% of the starting material could be accounted for in all pyrolysis reactions.



XLII XLIII

The isomeric 3-methoxy-1,2-benzisoxazole (XLIVa) is significantly more stable under similar pyrolytic conditions.



XLIVa, R=CH_3
b, R=CH_2CH_3

XLVa, R=CH_3 XLVI

Thermolysis at 500 °C results in essentially quantitative recovery of XLIVa (see Table 11), but at 600 °C some rearrangement product (XLVa) could be detected by nmr spectroscopy of the crude pyrolysate. The major product in

Table 11. Pyrolysis of 3-methoxy-1,2-benzisoxazole (XLIVa)

Temp. °C (± 10°)	% yield[a] XLIVa	XLVa	XXX	XLVI
500	> 95	0	0	0
600	49[b]	4[b]	42	0
700	0	0	69[c]	~ 25[c]

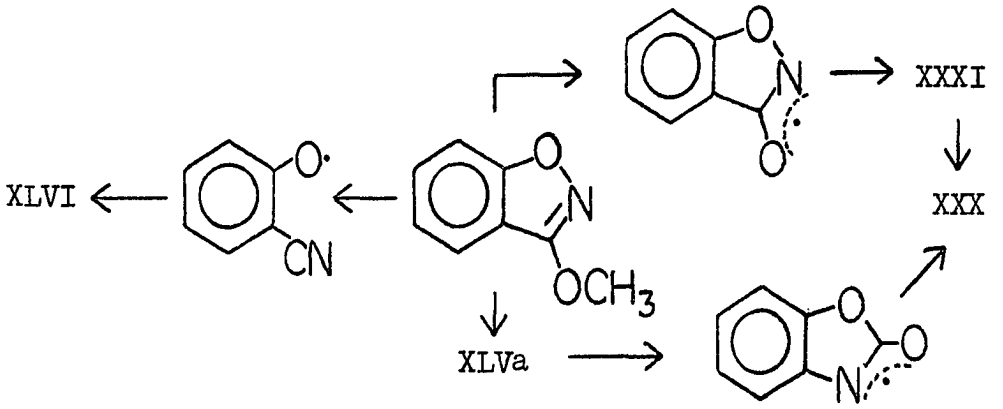
[a]Based on XLIVa.

[b]Ratio determined by nmr integration.

[c]Average of two experiments.

the pyrolyses at 600-700 °C is 2-benzoxazolinone (XXX) which presumably results from cleavage of the O-CH_3 bond in XLIVa followed by a hydrogen abstraction-rearrangement process (Scheme 8). Alternatively, rearrangement of XLIVa to XLVa prior to loss of $\cdot CH_3$ and hydrogen abstraction to form XXX may be occurring. The formation of XLVa at 600° lends support to the latter mechanism although both processes may be occurring simultaneously. Similar gas-phase thermal reactions of anisoles to give the corresponding phenols have been reported (90).

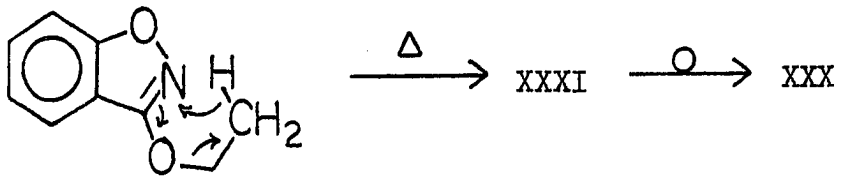
Scheme 8



In addition to 2-benzoxazolinone, the pyrolysis of XLIVa at 700° results in the formation of salicylonitrile XLVI as determined by ir (C≡N absorption at 2230 cm^{-1}) and mass spectroscopy ($M^{+\cdot}$ at m/e 119). This material may be produced by the loss of methoxy radical from XLIVa followed by homolysis of the N-O bond and hydrogen abstraction by a phenoxy radical (see Scheme 8). This process is analogous to the generation of salicylonitrile in the thermolysis of 1,2-benzisoxazole (77).

Similar results are obtained in the gas-phase pyrolysis of 3-ethoxy-1,2-benzisoxazole (XLIVb) at 700°. 2-benzoxazolinone (XXX) and salicylonitrile (XLVI) can be isolated by preparative tlc in yields of 77% and 3%, respectively. The significant decrease in the yield of salicylonitrile with concurrent increase in 2-benzoxazolinone may be explained by the occurrence of yet another mode of decomposition which is available to XLIVb but not to XLIVa. This process (Scheme 9) involves the transfer of a hydrogen

Scheme 9



XLIVb

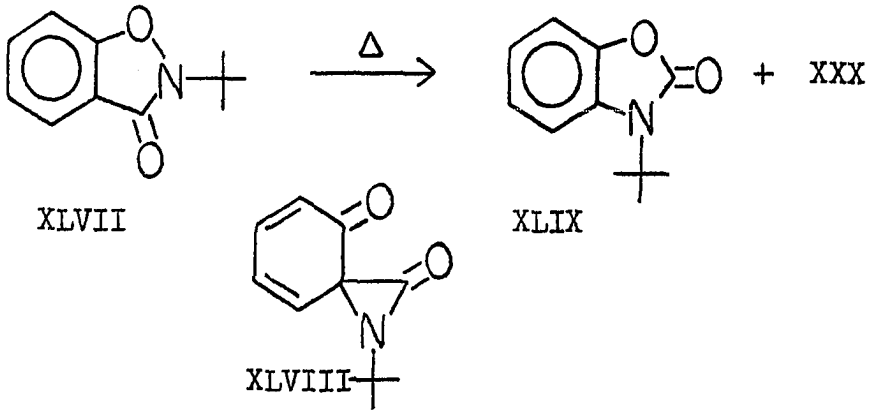
via a six-membered transition state, a well-known thermal reaction of ethers structurally related to XLIVb (91).

It is of particular interest to note the fact that higher temperature is required to effect rearrangement of the O-methyl compound (XLIVa) than is necessary to isomerize the N-methyl derivative (XLII). The greater thermal stability of XLIVa may be explained by the aromatic character of its isoxazole ring as opposed to the nonaromatic isoxazoline structure of XLII. This difference in thermal reactivity of isoxazoles and isoxazolines has been reported previously (71).

The rearrangement of XLII to XLIII and of XLIVa to XLVa clearly cannot be explained by an acyl nitrene intermediate corresponding to XL, since the transfer of a methyl group is highly unlikely. However, the appropriate methyl derivatives of species XLI may be involved in these transformations. Indeed, such an α-lactam intermediate has been proposed in some independent studies dealing with the

thermal and photochemical rearrangements of acylated 3-hydroxy-1,2-benzisoxazoles (92).

Since α-lactams have been shown to exhibit considerable stability upon substitution of a bulky group on nitrogen (93), we synthesized 2-t-butyl-1,2-benzisoxazolin-3-one (XLVII) and studied its thermal behavior in an attempt to generate XLVIII and, thus, to demonstrate whether XLI is an intermediate in the transformation of XXXI to XXX. However, upon thermolysis of XLVII in the gas-phase at temperatures



ranging from 310-500 °C, no evidence for the formation of XLVIII could be detected by ir and nmr spectroscopic measurements carried out on the crude pyrolysate. Instead, 3-t-butyl-2-benzoxazolinone (XLIX) and 2-benzoxazolinone (XXX) are produced in the relative amounts shown in Table 12.

The absence of the α-lactam XLVIII in the pyrolysate of XLVII is not sufficient evidence to exclude it as a possible intermediate in the transformation of XLVII to XLIX.

Table 12. Pyrolysis of 2-t-butyl-1,2-benzisoxazolin-3-one (XLVII)

Temp. °C (± 10°)	Mol %[a] XLVII	XLIX	XXX
310	94	6	0
400	21	35	44
500	0	13	87

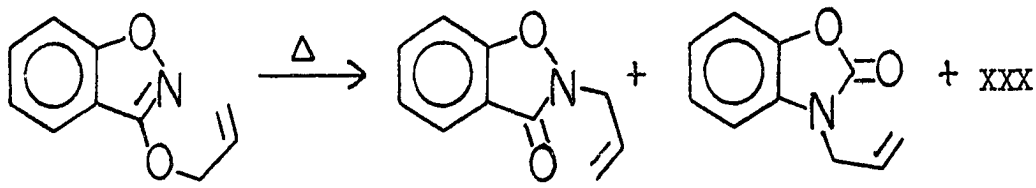
[a]Based on the average of repeated nmr integrations of the pyrolysate.

Due to the length of the pyrolysis column (30 cm) and the necessarily high temperatures involved, a species such as XLVIII might be expected to undergo further reaction prior to condensation (93). It would be of interest, therefore, to study XLVII under flash vacuum pyrolytic conditions in which the residence time is extremely short (94).

The facile formation of 2-benzoxazolinone in the pyrolysis of XLVII at 400-500 °C (Table 12) may be the result of a fragmentation process analogous to that depicted in Scheme 9 producing isobutylene as a by-product. On the other hand, homolysis of the N-t-butyl bond would be favorable in that a relatively stable t-butyl radical is formed. The heterocyclic free radical also produced may then abstract ·H and isomerize (see Scheme 8).

In view of the numerous examples of thermal Claisen

rearrangements in related heterocyclic systems (95), it was of interest to examine the thermal behavior of 3-allyloxy-1,2-benzisoxazole (L) because of its potential to undergo multiple rearrangements.



L LI LII

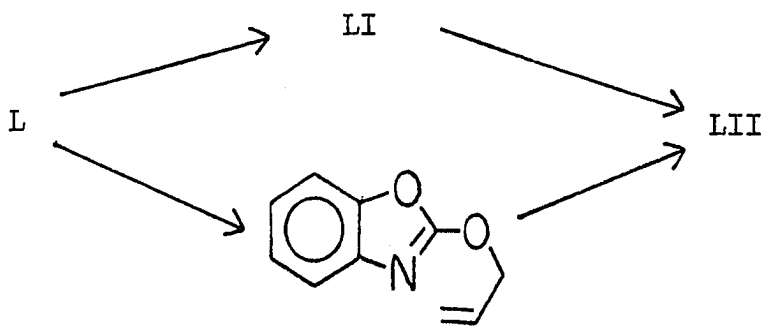
At 310 °C L does undergo a Claisen rearrangement to give 2-allyl-1,2-benzisoxazolin-3-one (LI) in a rather low conversion (Table 13). The anticipated double isomerization occurs at 400-500 °C yielding 3-allyl-2-benzoxazolinone (LII) as the major product. Conceivably, the formation of LII can occur via two pathways which are depicted in Scheme 10. One involves the intermediacy of LI and the other that of

Table 13. Pyrolysis of 3-allyloxy-1,2-benzisoxazole (L)

Temp. °C (± 10°)	Mol %[a] L	LI	LII	XXX
310	92	8	0	0
400	6	19	53	22
500	0	0	66	34

[a]Based on the average of repeated nmr integrations of the pyrolysate.

Scheme 10



LIII

2-allyloxybenzoxazole (LIII) which has been shown to rearrange thermally to give LII (96). However, the absence of LIII in the pyrolysates of L at 310-500 °C and the general unreactivity of the corresponding O-methyl derivative XLIVa at these temperatures suggest that LIII probably is not involved in the transformation of L to LII.

In order to verify that LI is an intermediate in this double isomerization, the thermal behavior of this compound was studied under identical conditions (see Table 14). It is interesting to note that only unchanged LI is isolated at 310°. This indicates that the reverse Claisen process (LI → L) does not occur in this system in agreement with the observations reported for related heterocyclic compounds (95, 96). At 400-500° the major product is LII indicating that the transformation of L to LII (Scheme 10) does occur via LI. A similar mechanism has been proposed in independent studies of the neat thermolysis of L (92).

Table 14. Pyrolysis of 2-allyl-1,2-benzisoxazolin-3-one (LI)

Temp. °C (± 10°)	Mol %[a] LI	LII	XXX
310	100	0	0
400	27	60	13
500	0	77	23

[a]Based on the average of repeated nmr integrations of the pyrolysate.

In view of the striking parallel which has been shown to exist between the mass spectral (Scheme 4) and thermal (Table 8) behavior of 3-hydroxy-1,2-benzisoxazole (XXXI), a study of the electron impact induced transformations of a variety of derivatives of XXXI and XXX was undertaken to determine the effect of substitution on this mass spectral rearrangement process.

The fragmentation pattern of ionized 3-methyl-2-benzoxazolinone (XLIII, Figure 8) is basically similar to that of the radical cation of unsubstituted 2-benzoxazolinone (Figure 5). For example, the loss of CO_2 occurs to give m/e 105 (11%) whose empirical formula is C_7H_7N by accurate mass measurements. This ion then shows a metastable loss of HCN to yield m/e 78 $(C_6H_6)^{+\cdot}$. Also important is the decomposition of the molecular ion with

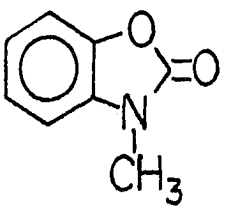


Figure 8. Mass spectrum of 3-methyl-2-benzoxazolinone (XLIII)

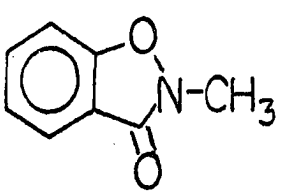
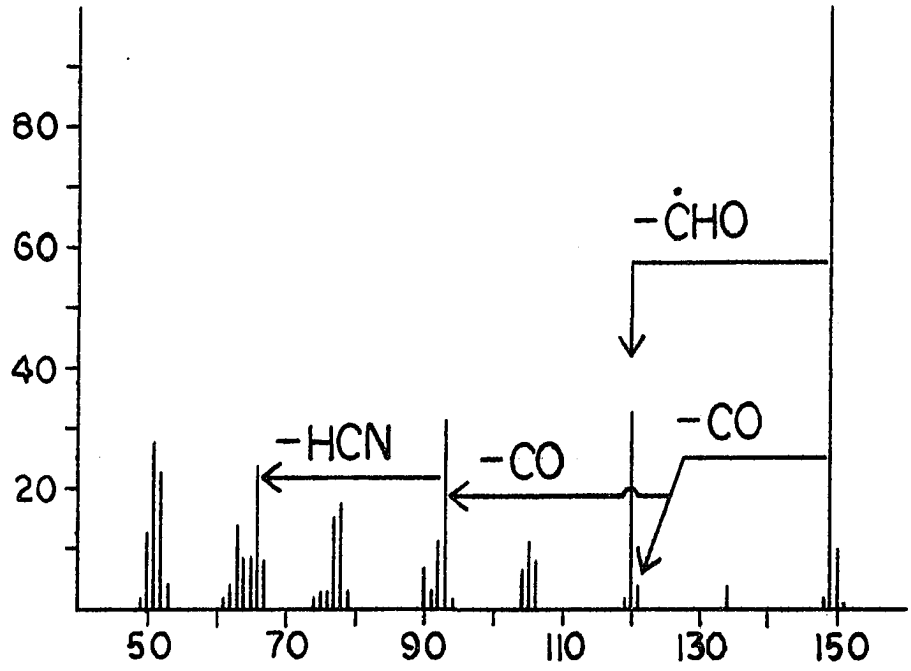
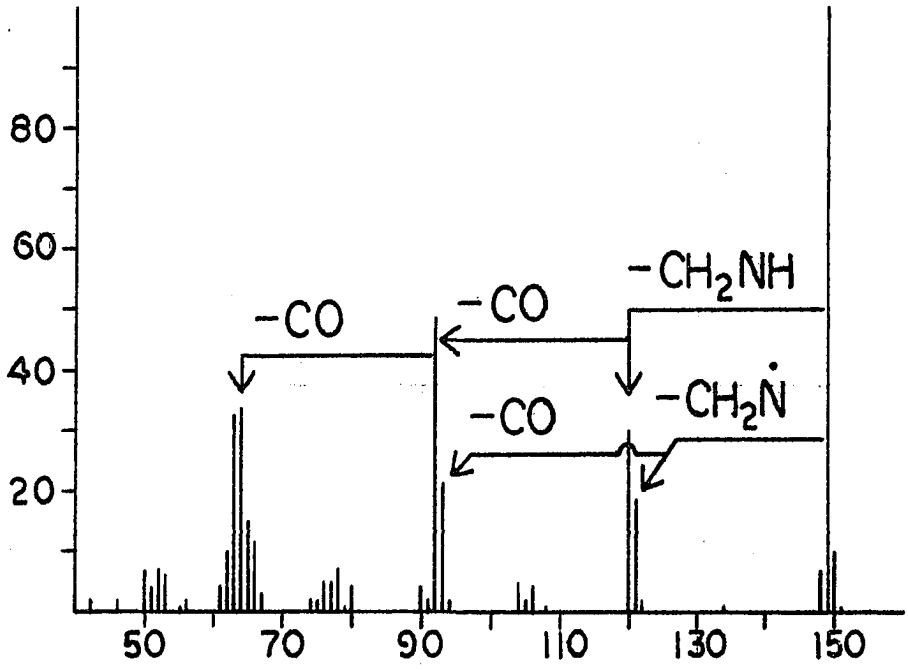


Figure 9. Mass spectrum of 2-methyl-1,2-benzisoxazolin-3-one (XLII)


80
60
40
20
-ĊHO
-HCN
-CO
-CO
50
70
90
110
130
150


80
60
40
20
-CO
-CO
-CH2NH
-CO
-CH2Ṅ
50
70
90
110
130
150

expulsion of two CO's to produce m/e 93 $(C_6H_7N)^{+\cdot}$ whose subsequent fragmentation involves the elimination of HCN (m/e 66). The most intense fragment ion appears at m/e 120 and corresponds to $(M-H\dot{C}O)^+$. The loss of $H\dot{C}O$ may occur in one or two steps as substantiated by appropriate metastable ions. The m/e 120 species is responsible for the formation of m/e 92 $(C_6H_6N)^+$ which undergoes further loss of HCN.

The mass spectrum of 2-methyl-1,2-benzisoxazolin-3-one also shows a prominent loss of 29 mass units from the molecular ion (Figure 9). However, accurate mass measurements of this m/e 120 ion determine its empirical formula to be $C_7H_4O_2$ corresponding to $(M-CH_3N)^{+\cdot}$. This is also substantiated by the metastable fragmentation of this species which involves consecutive losses of two molecules of CO. Elimination of $H_2C\dot{N}$ from the molecular ion also occurs to give $(C_7H_5O_2)^+$ at m/e 121, and the subsequent fragmentation of this ion parallels that of m/e 120 producing ions at m/e 93 $(C_6H_5O)^+$ and m/e 65. The m/e 93 species is actually a doublet, and the other component is $(C_6H_7N)^{+\cdot}$ resulting from the expulsion of two CO's from the molecular ion. This process, which is accompanied by a metastable ion, also occurs in the spectrum of XLIII (Figure 8). However, the ion at m/e 105 $(M-CO_2)^{+\cdot}$ is almost nonexistent in the mass spectrum of XLII. An overall comparison

of the spectra of XLIII and XLII indicates that a rearrangement of $(XLII)^{+\cdot}$ to $(XLIII)^{+\cdot}$, a process observed in the parent unsubstituted compounds, does not occur.

Under pyrolytic conditions 3-methoxy-1,2-benzisoxazole (XLIVa) was found to decompose at temperatures in excess of 500° with the loss of a methyl radical (see Scheme 8). A similar fragmentation of ionized XLIVa occurs in the mass spectrometer to give an intense peak at m/e 134 (Figure 10). The loss of methyl radical is a characteristic process in the mass spectra of methyl aryl ethers (16, p. 237). Subsequent fragmentation of the m/e 134 ion involves the consecutive losses of two CO molecules followed by expulsion of HCN giving rise to m/e 51. All of these processes are accompanied by appropriate metastable ions.

A very similar breakdown pattern is exhibited by the molecular ion of 2-methoxybenzoxazole (XLVa) as demonstrated by comparing Figures 10 and 11. The principal fragmentation mode of ionized XLVa also involves the loss of methyl radical affording the m/e 134 species. The structure of this ion may be the same in both spectra and reasonable possibilities are LIVa and LIVb. The rather low abundance of m/e 90, which would correspond to the loss of CO_2 from m/e 134, lends support to structure LIVa.

A minor fragmentation pathway present in the mass spectra of both XLIVa and XLVa is the expulsion of 29 mass

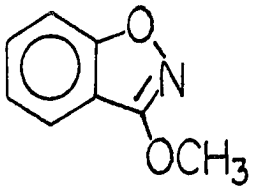


Figure 10. Mass spectrum of 3-methoxy-1,2-benzisoxazole (XLIVa)

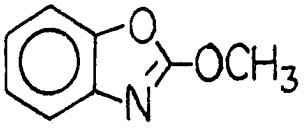
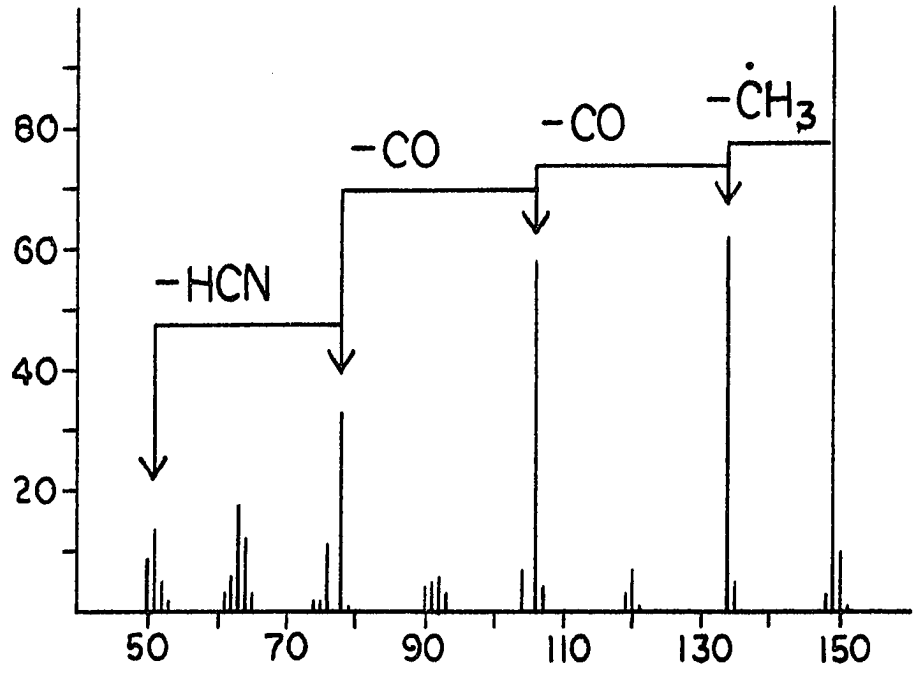
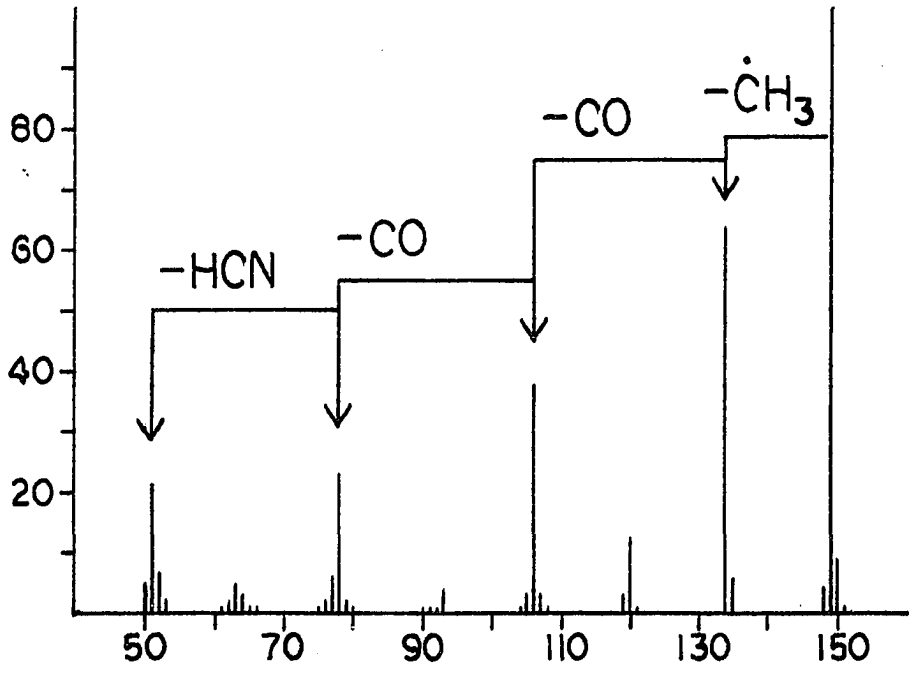
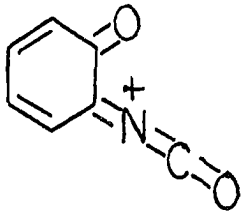


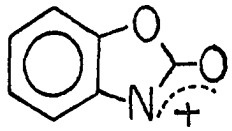
Figure 11. Mass spectrum of 2-methoxybenzoxazole (XLVa)


80
60
40
20
-HCN
-CO
-CO
-ĊH3
50
70
90
110
130
150


80
60
40
20
-HCN
-CO
-CO
-ĊH3
50
70
90
110
130
150



LIVa

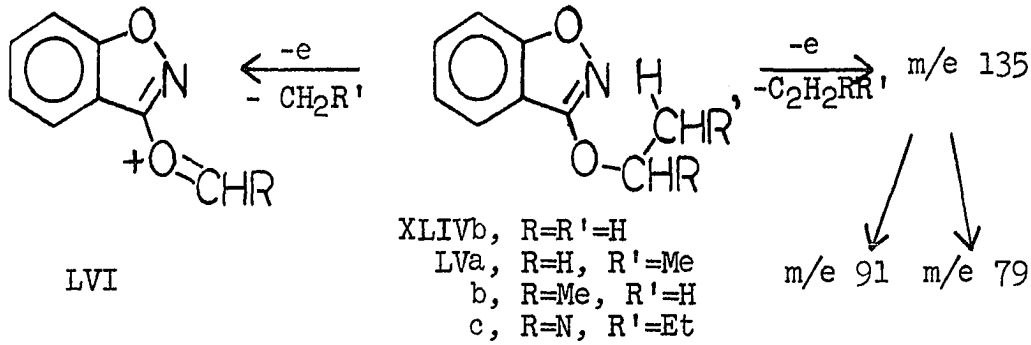


LIVb

units (HCO) from the molecular ion, a process substantiated by a metastable ion at m/e 96.7. The loss of a formyl radical from ionized anisole is also known to occur to a minor extent (16, p. 237).

The mass spectra of a variety of 3-alkoxy-1,2-benzisoxazoles in which the methyl group of XLIVa is replaced with homologous alkyl groups exhibit similar fragmentation patterns which are vastly different than that of XLIVa. The predominant decomposition of the molecular ions of XLIVb and LVa-c occurs via a type of McLafferty rearrangement producing in each case the base peak at m/e 135 (Scheme 11). This ion fragments with metastable losses of CO_2 (m/e 91) and two CO's (m/e 79) in a manner completely analogous to that of ionized 2-benzoxazolinone (Figure 5). Of significantly less importance in the spectra of XLIVb and LVa-c is an α-cleavage reaction to produce species LVI. This process is reminiscent of a prominent decomposition pathway of ethers (16, p. 227).

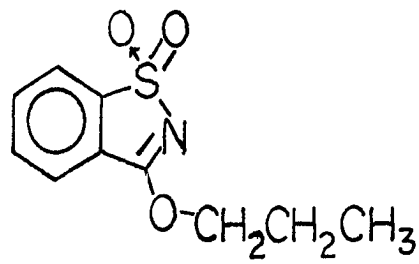
Scheme 11



LVI

XLIVb, R=R'=H
LVa, R=H, R'=Me
b, R=Me, R'=H
c, R=N, R'=Et

An interesting fragmentation occurring in the mass spectra of LVa and LVc is the loss of 30 mass units from the molecular ions to give m/e 147 (10%) and m/e 161 (19%), respectively. Both processes are accompanied by metastable ions. High resolution mass measurements of m/e 161 verify its empirical formula as $C_{10}H_{11}NO$ corresponding to $(M-CH_2O)^{+\cdot}$. A similar fragmentation apparently also occurs

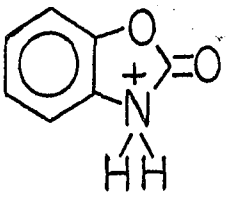


LVII

in the spectrum of LVII, although the origin of the $(M-30)^{+\cdot}$ ion is not discussed in the report (97).

Another interesting facet of the mass spectrum of compound LVc is the intense peak (rel. int. 35% after

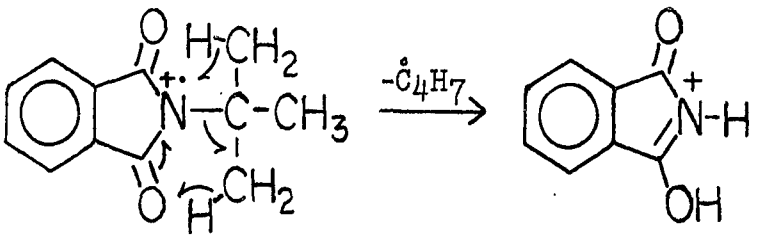
isotopic correction) at m/e 136 resulting from a double hydrogen rearrangement with a metastable loss of $\cdot C_4H_7$. Decomposition of this ion occurs with the expulsion of CO_2 and two CO's suggesting LVIII as a possible structure for this species. Although a double hydrogen rearrangement



LVIII

has been reported in the mass spectrum of LVII (97), a similar process does not occur in the n-propyl derivative LVa.

Numerous other examples of double hydrogen rearrangement in mass spectrometry are known. N-t-butyl phthalimide undergoes an electron impact induced loss of $\cdot C_4H_7$ for which the following mechanism has been proposed (98):

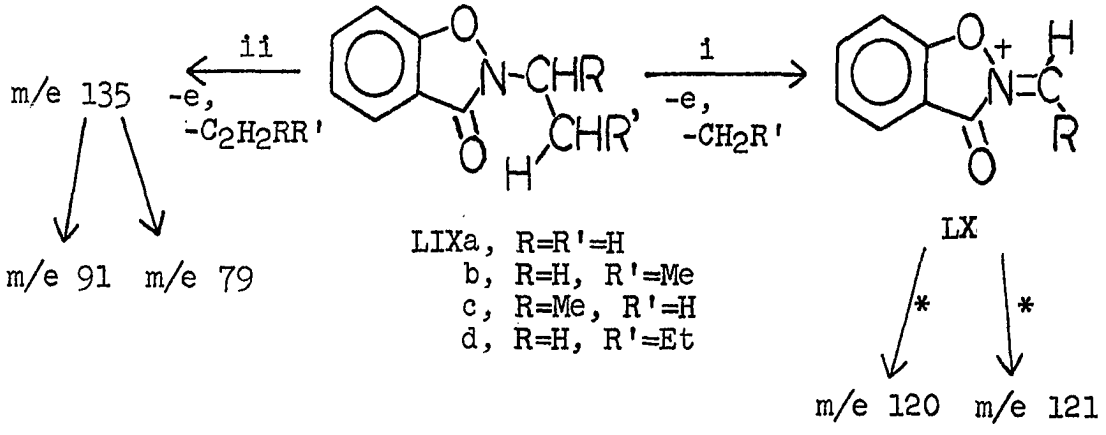


Analogous results have been observed in the spectra of N-n-butyl cyclohexene-1,2-dicarboximide (99) and N-sec-butyl-

and N-t-butyl uracils (100).

The mass spectral behavior of the corresponding N-alkyl derivatives of 3-hydroxy-1,2-benzisoxazole is qualitatively similar to that demonstrated by the O-alkyl compounds described in Scheme 11. Two major fragmentation pathways are followed by compounds LIXa-d upon ionization in the mass spectrometer (Scheme 12). These are: (i) α-cleavage of the alkyl group to furnish the stabilized species

Scheme 12



LX and (ii)the McLafferty rearrangement to give m/e 135.

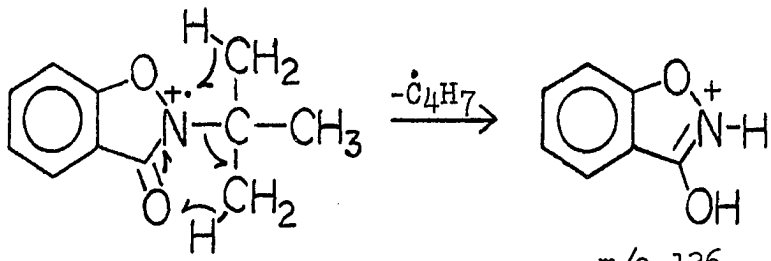
Process (i) is similar to the α-cleavage reactions experienced by amines upon electron impact (16, p. 297). The subsequent fragmentation of species LX includes the metastable losses of RCN and HRCN̈ to give m/e 121 and m/e 120, respectively. These ions may also originate by pathways analogous to those described in the spectrum of the

N-methyl derivative (Figure 9); i.e., a one-step loss of the alkyl group and nitrogen atom (m/e 120) and a similar fragmentation involving a single hydrogen transfer (m/e 121). However, metastable ions corresponding to these processes are absent in the spectra of LIXa-d.

Pathway (ii) is completely analogous to the McLafferty rearrangement for the O-alkyl derivatives (Scheme 11) although of seemingly less importance.

In addition to processes (i) and (ii), the molecular ion of compound LIXd undergoes a metastable transition to produce m/e 136 whose relative intensity is 7% after correcting for isotopic contributions from m/e 135. The significant decrease in importance of this double hydrogen rearrangement process as compared with that observed in the corresponding O-n-butyl derivative LVc is noteworthy and is in line with the observations made in mass spectral studies of the n-propyl derivatives of benzisothiazole-S-dioxides (97).

An interesting result is observed upon examination of the mass spectrum of the corresponding N-t-butyl derivative



(XLVII, Figure 12). In this case, the m/e 136 species resulting from the double hydrogen rearrangement process is the second most intense ion in the spectrum. The formation of this ion may involve a mechanism resembling that suggested for N-t-butyl phthalimide (see above). Subsequent rearrangement of this species to a protonated 2-benzoxazolinone structure (LVIII) probably occurs because it expels a molecule of CO_2 to give $(C_6H_6N)^+$.

That isomerization of ionized XLVII to the radical cation of 3-t-butyl-2-benzoxazolin-one (XLIX) does not occur prior to decomposition is illustrated by a comparison of the spectra of these two compounds (see Figures 12 and 13). The fragmentation pattern of XLIX upon electron impact is indeed simple involving only two major processes. These are the formation of an ion at m/e 135 in a McLafferty rearrangement and a cleavage reaction generating t-butyl cation at m/e 57. However, evidence for a double hydrogen rearrangement is completely lacking in the spectrum.

Finally, it was of interest to study the mass spectrum of 3-allyloxy-1,2-benzisoxazole (L) to investigate possible multiple rearrangements analogous to those demonstrated by L pyrolytically. Furthermore, an electron impact induced Claisen rearrangement has been observed only recently by some Russian workers (101). Previous to this, the only reported rearrangement of this type was a retro-Claisen

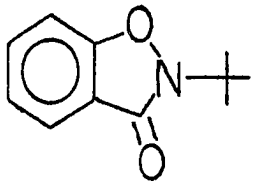


Figure 12. Mass spectrum of 2-t-butyl-1,2-benzisoxazolin-3-one (XLVII)

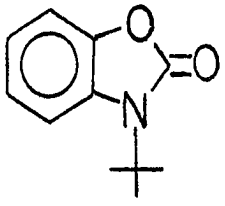
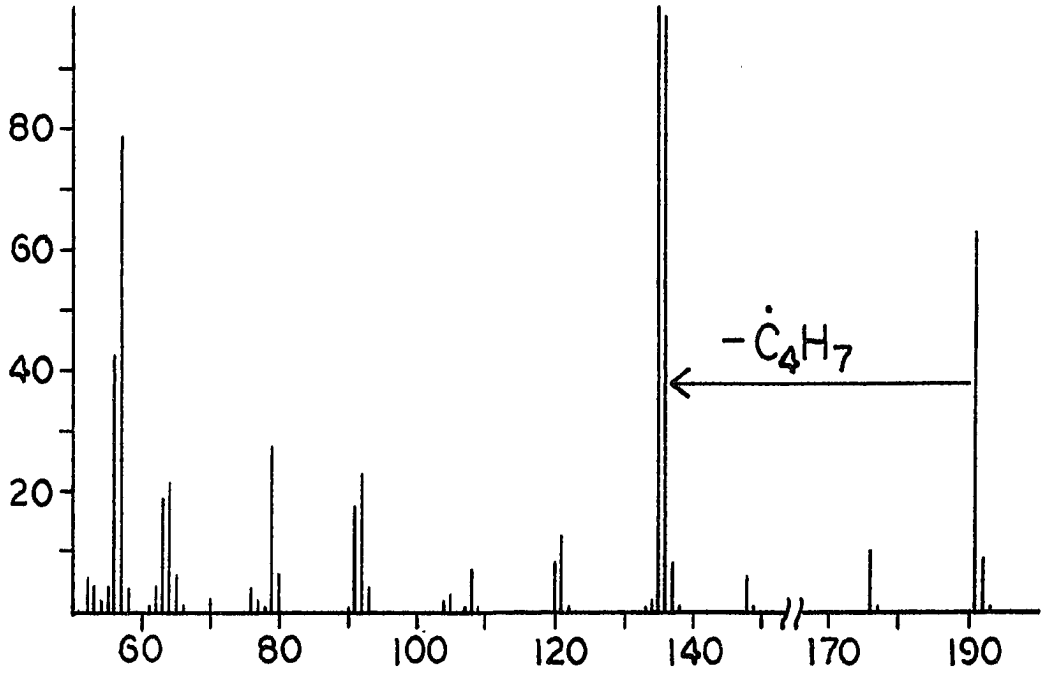
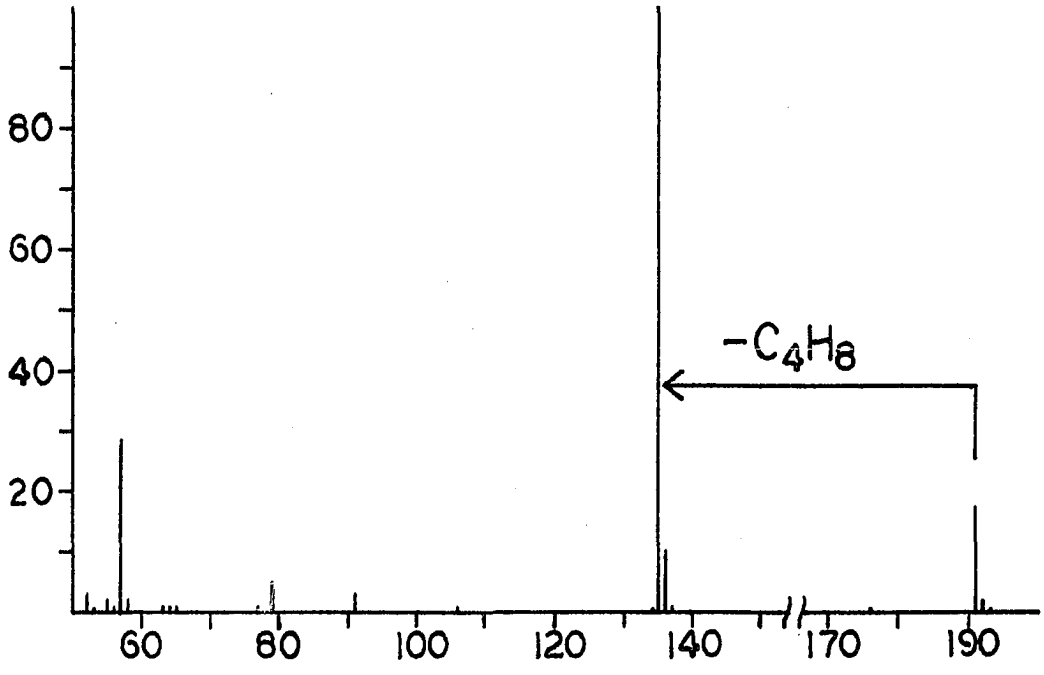
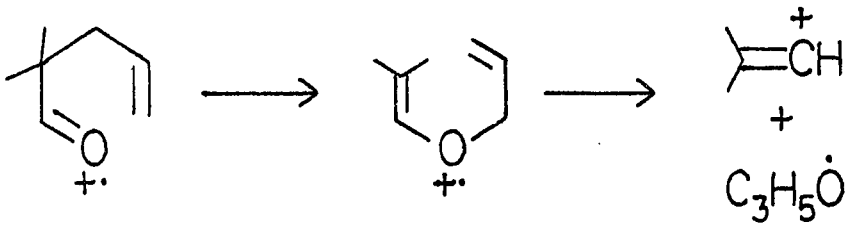


Figure 13. Mass spectrum of 3-t-butyl-2-benzoxazolinone (XLIX)


80
60
40
20
$-\dot{C}_4H_7$
60
80
100
120
140
170
190

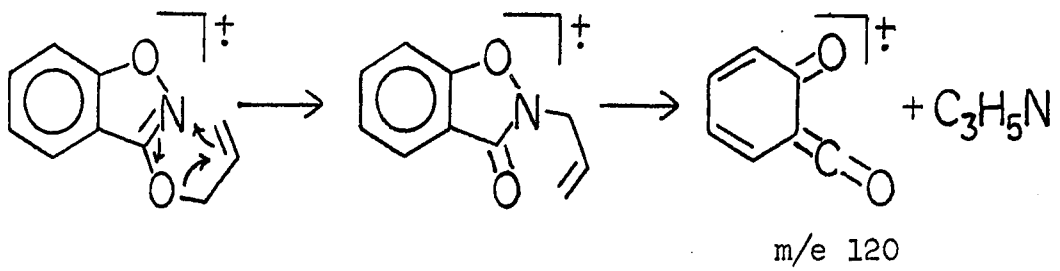

80
60
40
20
$-C_4H_8$
60
80
100
120
140
170
190

process which was postulated to explain the most intense fragment ion in the spectrum of 2,2-dimethylpent-4-en-1-al (16, p. 133).



The base peak in the mass spectrum of L (Figure 14) appears at m/e 120. This ion corresponds to $(C_7H_4O_2)^{+\cdot}$ and is readily explained by an initial isomerization to an ionized 2-allyl-1,2-benzisoxazolin-3-one (LI) structure (Scheme 13) with subsequent expulsion of C_3H_5N. Verifica-

Scheme 13



m/e 120

tion of this is obtained by examination of the breakdown pattern of LI upon electron impact (Figure 15) in which m/e 120 has a relative intensity of 92%. A metastable is observed at m/e 82.3 in both spectra for this transformation.

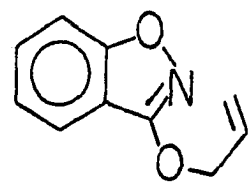


Figure 14. Mass spectrum of 3-allyloxy-1,2-benzisoxazole (L)

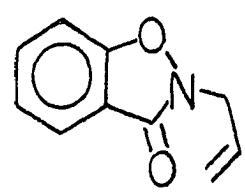
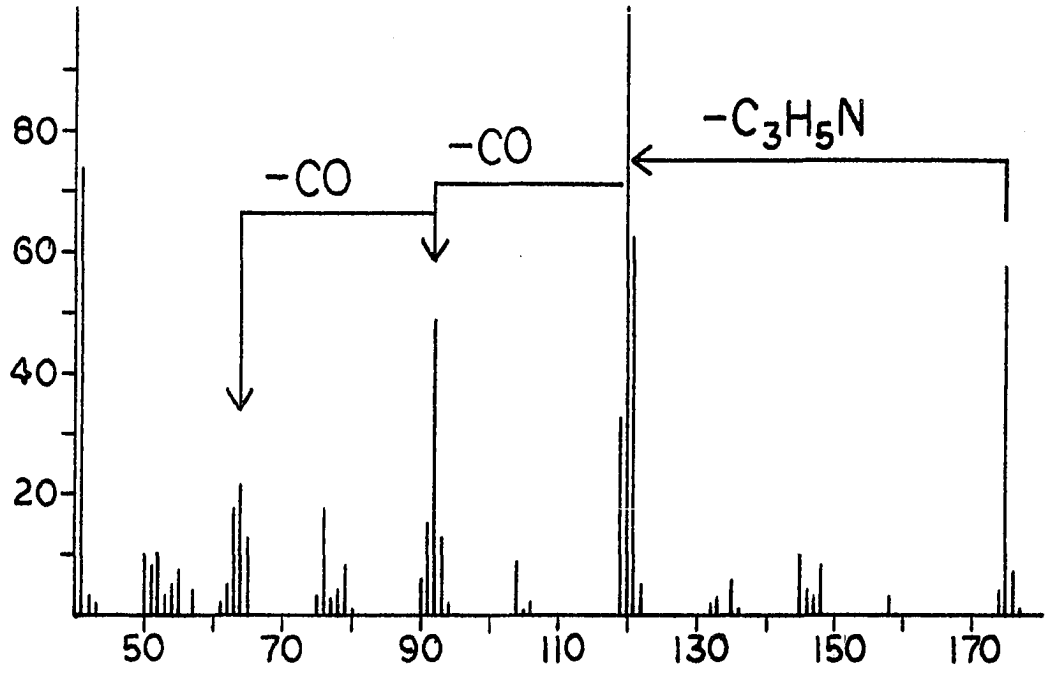
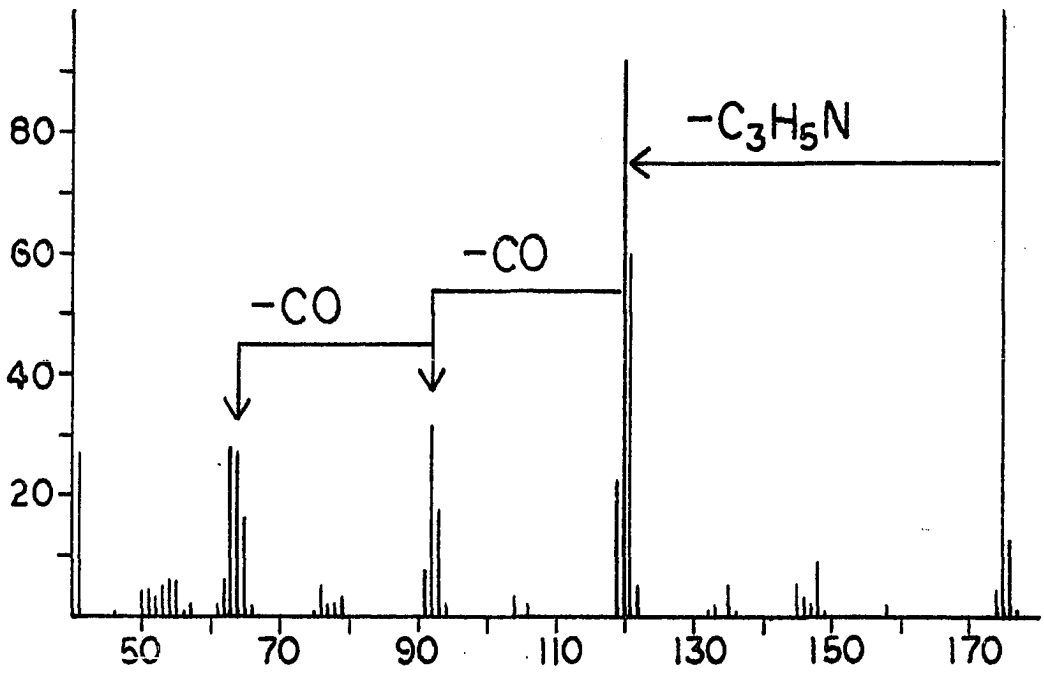


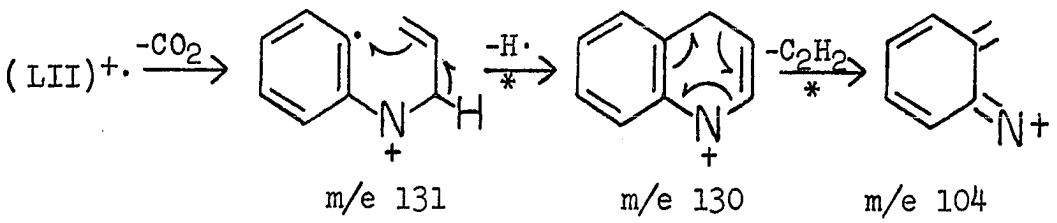
Figure 15. Mass spectrum of 2-allyl-1,2-benzisoxazolin-3-one (LI)


80
60
40
20
-CO
-CO
-C3H5N
50
70
90
110
130
150
170


80
60
40
20
-C3H5N
-CO
-CO
50
70
90
110
130
150
170

An extension of this study included a comparison of the mass spectra of 2-allyloxybenzoxazole (LIII) and 3-allyl-2-benzoxazolinone (LII) to determine whether the isomerization $(LIII)^{+\cdot}$ to $(LII)^{+\cdot}$ also occurs. The spectrum of LII (Figure 16) exhibits an intense loss of allyl radical giving rise to the ion at m/e 134. The structure of this ion may be related to that of the $(M-\dot{C}H_3)^+$ species in the spectrum of 2-methoxybenzoxazole (Figure 11) for the stepwise loss of two CO molecules also accounts for its decomposition. A minor pathway is the expulsion of CO_2 from $(LII)^{+\cdot}$ yielding m/e 131. This ion undergoes loss of H· followed by acetylene as supported by accurate mass measurements and metastable ions. A reasonable mechanism for this fragmentation is shown in Scheme 14.

Scheme 14



m/e 131 m/e 130 m/e 104

A similar loss of CO_2 from the molecular ion occurs in the spectrum of LIII (Figure 17). This indicates that an electron impact induced Claisen rearrangement also takes place in this system. In general, the fragmentation pattern

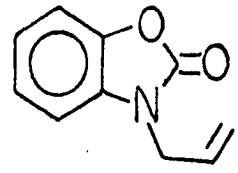


Figure 16. Mass spectrum of 3-allyl-2-benzoxazolinone (LII)

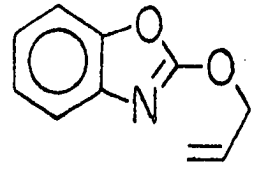
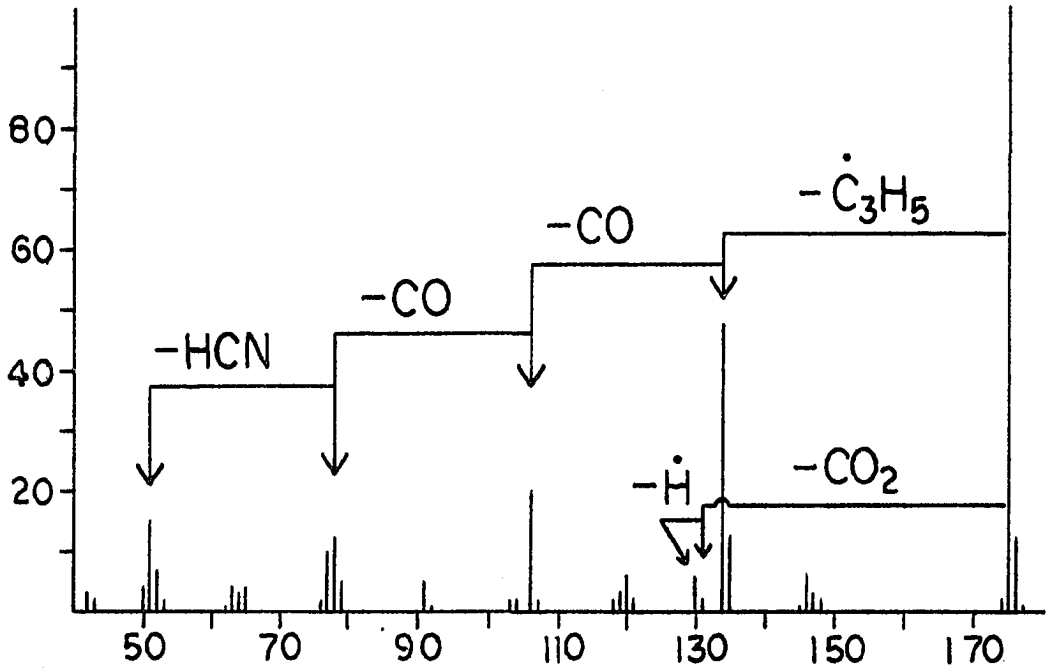
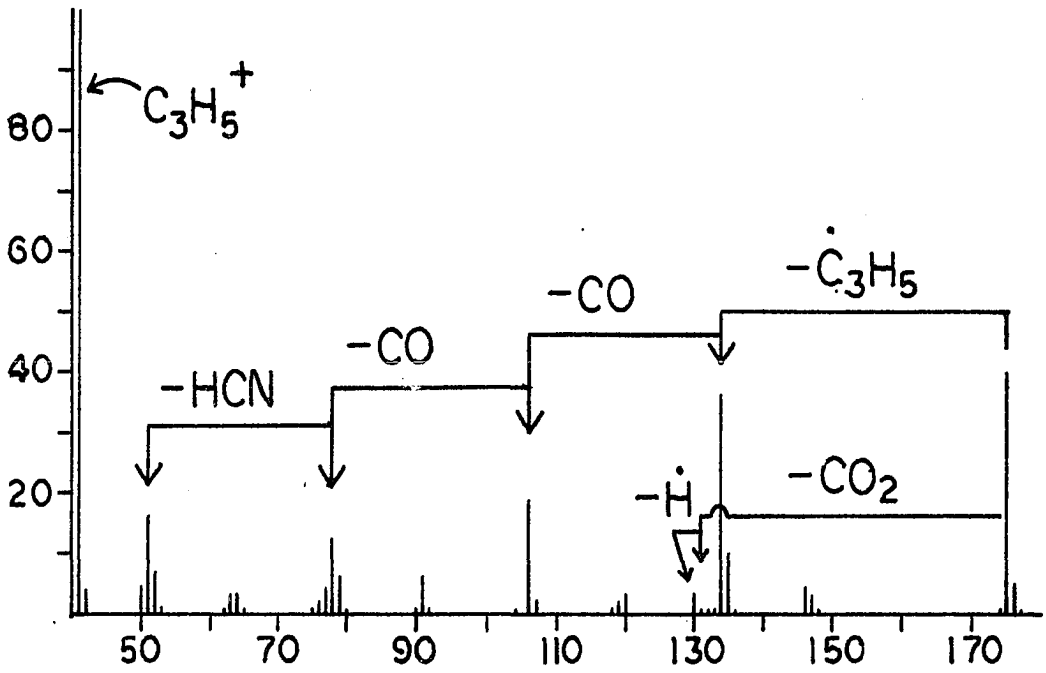


Figure 17. Mass spectrum of 2-allyloxybenzoxazole (LIII)


80
60
40
20
-HCN
-CO
-CO
-$\dot{C}_3H_5$
-$\dot{H}$
-CO_2
50
70
90
110
130
150
170

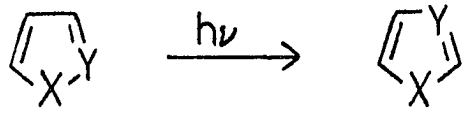

$C_3H_5^+$
80
60
40
20
-HCN
-CO
-CO
-$\dot{C}_3H_5$
-$\dot{H}$
-CO_2
50
70
90
110
130
150
170

of LIII is qualitatively much the same as that observed in the spectrum of LII. Furthermore, a comparison of the spectra of LI and LII indicates that the transformation LI → LII probably does not occur upon electron impact.

Photochemistry

A variety of heterocyclic ring transformations corresponding to the general reaction of Scheme 15 have been reported to occur under photochemical conditions (see Review of Literature). Included in these studies are a number of

Scheme 15



condensed heterocycles, such as indazoles and 1,2- and 2,1-benzisoxazoles. Some mechanistic work has been conducted on the indazole (58, 65) and 2,1-benzisoxazole (66) systems, but analogous studies have not been carried out on 1,2-benzisoxazole (67). In view of this, we investigated in some detail the photochemical behavior of 3-hydroxy-1,2-benzisoxazole (XXXI).

Irradiation of a 0.005 M solution of XXXI in ether for one hour with Corex filtered ultraviolet light results in the formation of 2-benzoxazolinone (XXX) as the only product.

Its isolation and purification could be easily effected by sublimation in vacuo of the crude photolysate. The involatile material is a dark, resinous substance and is more prominent after extended periods of irradiation, especially when higher energy light is used; i.e., replacing the Corex filter with Vycor. This results in concurrent decrease in yields of XXX as illustrated in Table 15 presumably due to a photodecomposition of XXX.

Table 15. Photolysis of 3-hydroxy-1,2-benzisoxazole (XXXI)

Temp. °C	Filter	Solvent	Time (min)	% yield XXXI	% yield XXX
20	Corex	Ether	60	0	80[a]
20	Corex	Ether	180	0	60[a]
20	Vycor	Ether	210	0	59[a]
20	Corex	Methanol	15	~ 20[b]	73[b]
- 72	Vycor	Methanol	120	38[c]	62[c]
20	Pyrex	Acetone	180	49[b]	24[b]
20	Vycor	0.1 M piperylene in ether	180	0	37[d]

[a]Purified by sublimation.

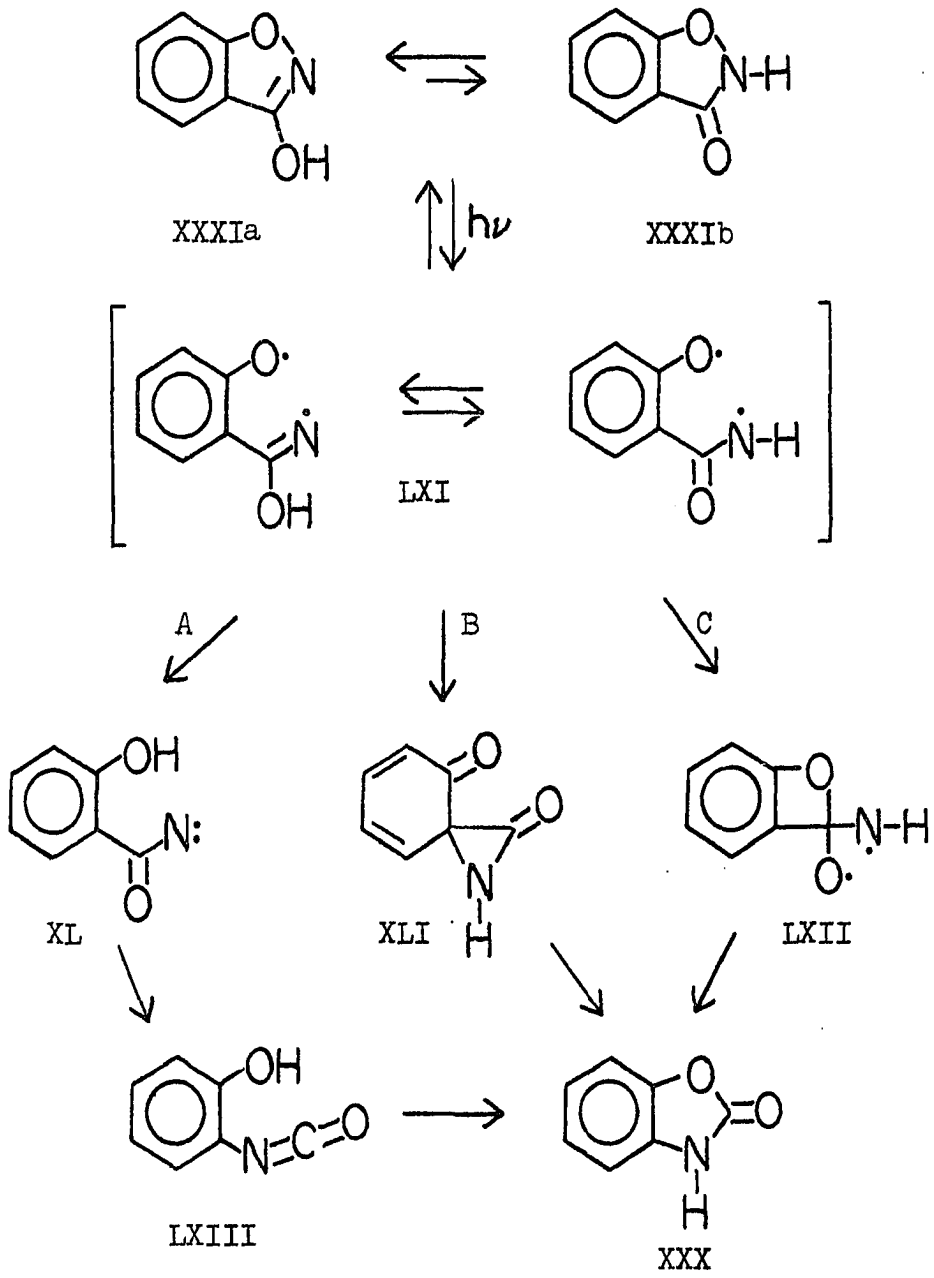
[b]Isolated by column chromatography.

[c]Ratio of products determined by nmr spectroscopy.

[d]Extracted from the concentrated ether solution with aqueous Na_2CO_3.

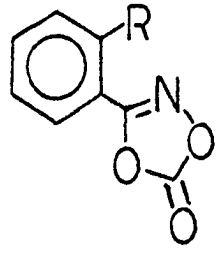
Possible mechanisms for this photoisomerization are presented in Scheme 16. Enol (XXXIa)-keto (XXXIb) equilibria in XXXI follows from an infrared spectral analysis which indicates that the enol form exists exclusively in the solid

Scheme 16



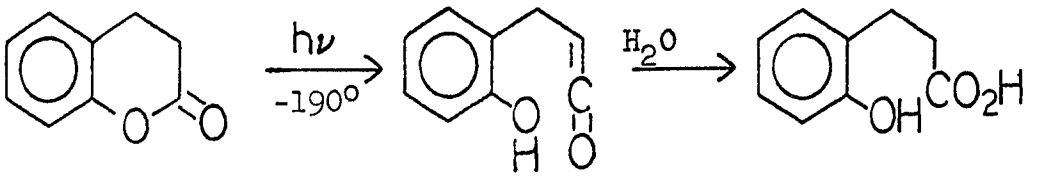
state (strong O-H absorption at 3000-2500 cm^{-1} with complete absence of carbonyl absorption), whereas both forms appear to be present in chloroform solution (O-H absorption as above and weak carbonyl absorption at 1670 cm^{-1}). This is substantiated by comparisons with the ir spectra of the N-alkyl derivatives of XXXI which exhibit carbonyl absorption at approximately 1685-1700 cm^{-1}. Furthermore, methylation of XXXI with either methyl halide or diazomethane yields a mixture of 3-methoxy-1,2-benzisoxazole (XLIVa) and 2-methyl-1,2-benzisoxazolin-3-one (XLII) (88).

The initial step in the photoisomerization of XXXI to XXX presumably involves homolytic cleavage of the weak N-O bond (20) to form diradical species LXI (Scheme 16). A [1,5]-hydrogen migration followed by a type of Curtius rearrangement would produce 2-hydroxyphenyl isocyanate (LXIII), as depicted in pathway A. This isocyanate is known to undergo an intramolecular cyclization to form 2-benzoxazolinone (77, p. 285). As discussed above, the photodecomposition of the cyclic carbonate XXIX yields 2-benzoxazolinone, presumably



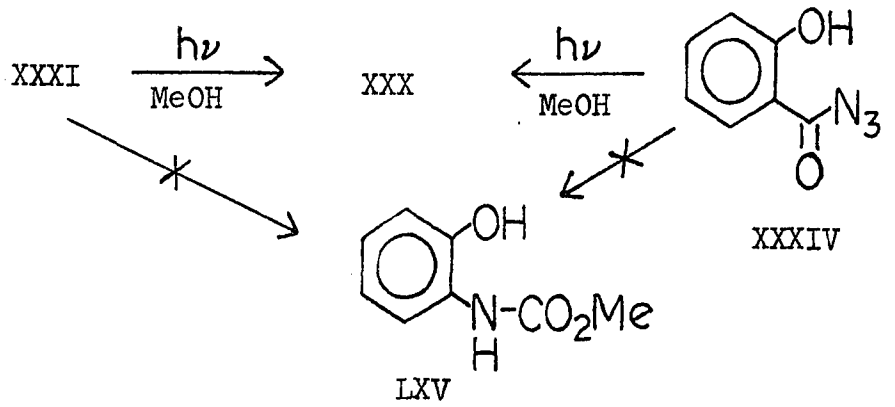
XXIX, R=OH
XXXVIa, R=H

via intermediates XL and LXIII since photolysis of XXXVIa produces phenyl isocyanate (80). LXIII is analogous to ketene LXIV generated at -190 °C in the photolysis of dihydrocoumarin and observed by infrared spectroscopy (102).



LXIV

In attempts to trap isocyanate LXIII, and thus to prove mechanism A, the photolysis of XXXI was carried out in methanol at room temperature and at -72 °C. The only product isolated in both reactions was 2-benzoxazolinone (XXX). No



evidence for the methyl carbamate LXV, the expected diversion product, was shown by ir and nmr analyses of the photolysates.

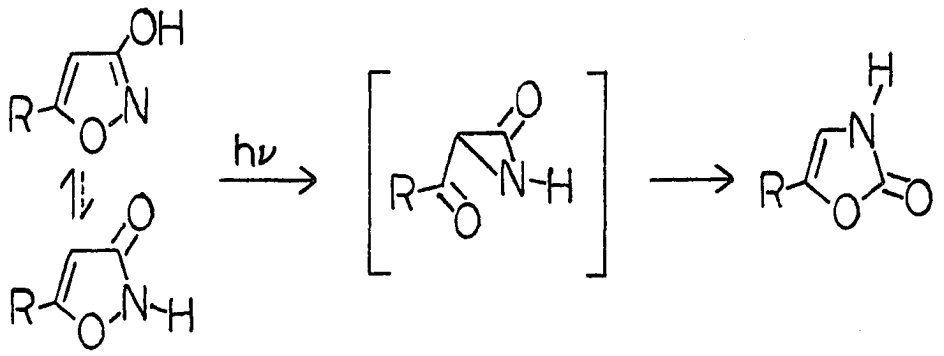
Since the formation of a carbamate related to LXV has been reported in the thermolysis of salicyloyl azide (XXXIV) in the presence of an alcohol (103), it was of interest to

examine the photodecomposition of XXXIV in methanol. However, addition of methanol to the isocyanate group does not occur in the photolysis reaction. Instead, 2-benzoxazolinone can be isolated quantitatively indicating either that an isocyanate is not involved in the photoreaction or that the close proximity of the phenol group overcomes solvolytic action of the methanol. In any case, the thermal reaction should be repeated to determine the accuracy of the reported results (103).

Some thermally reactive intermediates in photochemical reactions have successfully been trapped and observed by special low-temperature irradiation techniques (102). An analogous experiment was conducted on compound XXXI at 77 ^{o}K (see Experimental section). The progress of the photolysis was monitored by infrared spectroscopy. Absorption could not be detected in the region 2240-2260 cm^{-1}, which is characteristic for phenyl isocyanate (104), after irradiation of XXXI. However, the formation of 2-benzoxazolinone (XXX) was evident from the prominent carbonyl absorption at 1740-1780 cm^{-1} which increased with continued irradiation. This suggests that the isocyanate intermediate LXIII is probably not involved in photoisomerization of XXXI to XXX at room temperature.

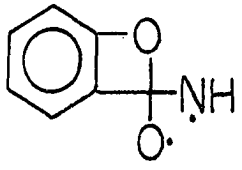
An alternate mechanism is B (Scheme 16) involving a ring-contraction ring-expansion sequence related to that

documented by Singh and Ullman (17) in the photorearrangement of diaryl isoxazoles. Furthermore, an α-lactam has been proposed as an intermediate in the photochemical transformation of a variety of 3-hydroxyisoxazoles to the corresponding 2(3H)-oxazolones (57), as follows:

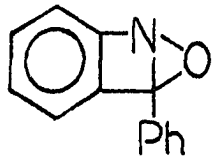


Thus, XLI is a plausible, though expectedly unstable (93) intermediate, which would rearrange under the reaction conditions to XXX.

Finally, a mechanism in which XXX is a primary photoproduct must also be considered, especially since it is produced upon irradiation of XXXI at 77 °K. One possibility is pathway C (Scheme 16) involving diradical species

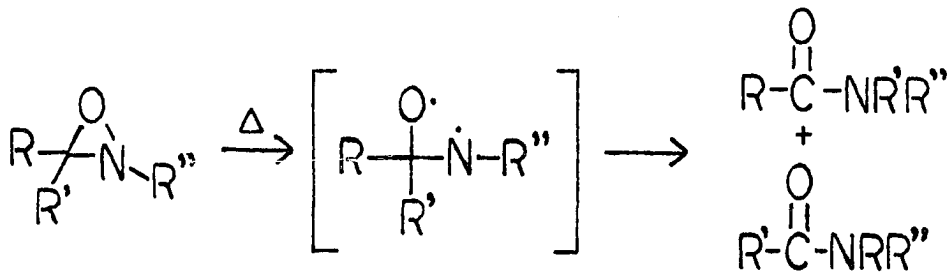


LXII



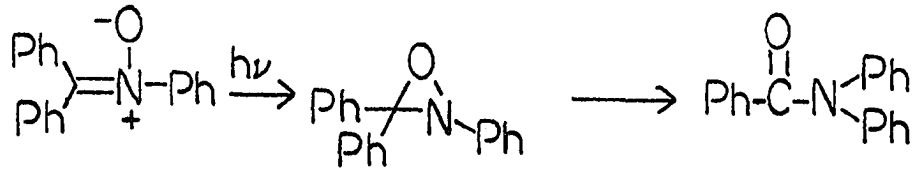
LXII which is reminiscent of the tricyclic intermediate suggested to explain the photolytic products of 3-phenyl-2, 1-benzisoxazole (66).

The formation of XXX from species LXII requires migration of the benzene ring to the radical site on nitrogen. This transformation is analogous to the rearrangements which have been observed in the gas-phase pyrolysis of oxaziridines (105). The suggested mechanism for the formation of the two amide products involves migration of either R or R' to a nitrogen radical in species LXVI. A similar process is known to occur in the photolysis of nitrones.



LXVI

For example, the irradiation product of α, α, N-triphenylnitrone is N,N-diphenylbenzamide consistent with an oxaziridine intermediate which is isolable in this particular case (106).

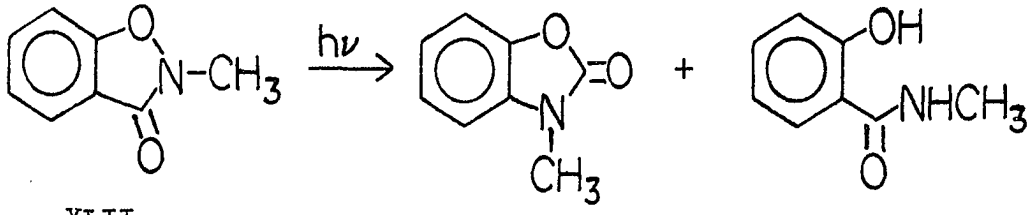


In order to examine the mechanistic aspects of the photoisomerization of XXXI to XXX in greater detail, the photolysis of a variety of alkyl derivatives of XXXI was

investigated.

The results of the photolysis of the N-methyl derivative XLII are illustrated in Scheme 17. Column chromatographic separation of unreacted starting material, rearrangement product XLIII, and N-methyl salicylamide (LXVII) readily

Scheme 17



XLII XLIII LXVII

occurs to give the percentage yields shown in Table 16.

Of particular interest is the formation of amide LXVII when XLII is subjected to direct irradiation in solvents, such as ether, pentane, and methanol. This product substantiates the initial formation of a diradical species by homolysis of the N-O bond analogous to diradical LXI in Scheme 16. Hydrogen abstraction by this species would produce LXVII, whose structure is supported by comparison of the spectral properties of the photoproduct with those of authentic material. This photoreduction is somewhat analogous to the intramolecular hydrogen abstraction products obtained in the photolysis of 1,2-benzisoxazole (67) and indazole (58).

Table 16. Photolysis of 2-methyl-1,2-benzisoxazolinone (XLII)

Filter	Solvent	Time (min)	% yield XLII	% yield XLIII	% yield LXVII
Vycor	Ether	180	50	23	~ 3
Vycor	Pentane	180	31	25	5
Vycor	Methanol	60	4	17	39
Pyrex	Acetone	180	-	92	-
Pyrex	0.01 M acetophenone in benzene	180	67	29	-
Pyrex	0.01 M benzophenone in benzene	180	> 95[a]	< 5[a]	-
Vycor	0.1 M piperylene in ether	180	25	13	3

[a]Determined by nmr spectroscopy of the photolysis product mixture.

Examination of Tables 15 and 16 demonstrates the noticeable increase in rate of consumption of starting material when the photolyses are carried out in methanol rather than ether or pentane. The significance of this solvent effect is unclear. However, a similar relationship between solvent polarity and photochemical reactivity has been noted in related systems (58, 63).

Irradiation of XLII for 3 hours under triplet

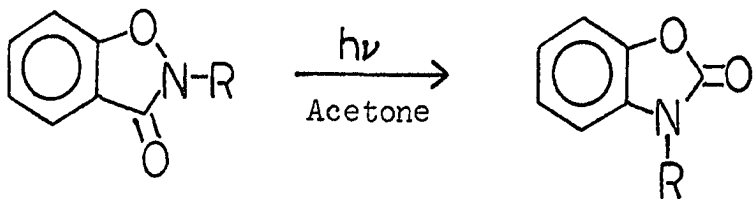
sensitization conditions in benzene containing 0.01 M benzophenone whose triplet energy is 69 kcal/mole (107) results in < 5% conversion to XLIII (see Table 16). Replacement of the sensitizer with acetophenone (E_T = 74 kcal/mole) (107) and photolysis under identical conditions causes substantial rearrangement to occur. However, the highest yield of XLIII is obtained upon irradiation of XLII in (neat) acetone (E_T = 79 kcal/mole) (107). A crude estimate of the triplet energy of this system is 69 to 74 kcal/mole, a value somewhat higher than that estimated for isoxazoles (17).

Phosphorescence spectra were taken of 2-methyl-1,2-benzoxazolin-3-one (XLII) and 3-hydroxy-1,2-benzisoxazole (XXXI) in MTHF glass at 77 ^{o}K. However, the results of these measurements were inconclusive due to extremely weak emission.

Quenching experiments were also conducted on these two compounds (Tables 15 and 16) using 0.1 M piperylene in ether as the triplet quencher. The photolysis reactions were carried out under conditions similar to those used for direct irradiation. Although a significant decrease in yields of the rearrangement product occurred in both cases, the piperylene was unable to quench the photoisomerization. This suggests that if a triplet is involved in the transformations of XXXI to XXX and XLII to LXIII as suggested by the results of triplet sensitization, then it is a suffi-

ciently short-lived species to avoid quenching by piperylene (107).

Photolysis of 2-allyl-1,2-benzisoxazolin-3-one (LI) in acetone with Pyrex filtered uv light for 3 hours also produces high yields (82%) of rearrangement product LII. However, under similar photolytic conditions the t-butyl derivative XLVII affords only trace amounts of XLIX as



LI, R=Allyl
XLVII, R=t-butyl

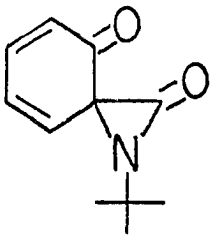
LII, R=Allyl
XLIX, R=t-butyl

determined by nmr spectroscopy. A reasonable yield (50%) of XLIX can be obtained when irradiation of XLVII is carried out in acetone for 6 hours using shorter wavelength light; i.e., a Corex filter.

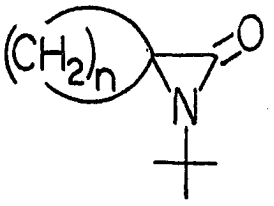
The photoisomerization of the N-alkyl-1,2-benzisoxazolin-3-ones to the corresponding N-alkyl-2-benzoxazolinones clearly cannot occur <u>via</u> a mechanism analogous to pathway A (Scheme 16). Although the photolysis studies of XXXI at 77 ^{o}K indicate the absence of an intermediate in its rearrangement to XXX, the α-lactam XLI (Mechanism B) may be too reactive to exist for a sufficient length of time to be observed even at these low temperatures.

Furthermore, intermediate XLI (H = alkyl) readily accommodates the isomerization of the N-alkyl derivatives.

In view of this, the photochemical behavior of XLVII was investigated at low temperatures to determine the possible formation of α-lactam XLVIII. Spiro-α-lactams stabilized by N-t-butyl functionalities have been isolated and are reasonably stable at room temperature in systems such as LXVIII for which n = 4, 5, or 7. The highly strained



XLVIII



LXVIII

species LXVIII (n = 3) has also been observed spectroscopically at 0 °C but is unstable to isolation (93).

2-t-butyl-1,2-benzisoxazolin-3-one (XLVII) was photolyzed at -70 °C in methylene chloride. The progress of the reaction was followed by infrared spectroscopy. After 60 minutes irradiation, carbonyl absorption appeared at 1750 cm^{-1} corresponding to the rearrangement product XLIX. The intensity of this band increased upon further irradiation at the expense of carbonyl absorption due to starting material. However, no absorption was observed in the region 1820-1850 cm^{-1}, thus ruling out α-lactam XLVIII

as an intermediate under these photolytic conditions.

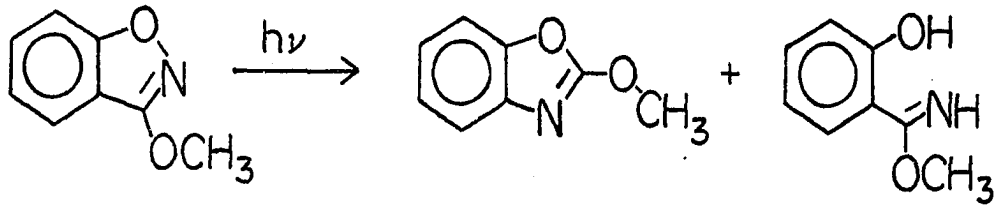
In summary, pathways A and B depicted in Scheme 16 are probably not involved in the photoisomerization of 3-hydroxy-1,2-benzisoxazole (XXXI). This conclusion is based on the rather facile rearrangements observed upon irradiation of the N-alkyl compounds and the failure to detect intermediates LXIII, XLI, or XLVIII in the low temperature photolysis experiments. It is possible that the loss of benzene resonance imposes too great a barrier for the formation of spiro-α-lactam XLI. Therefore, a plausible alternative is mechanism C, although admittedly no direct evidence for diradical species LXII has been found.

The facile photoisomerization of the N-alkyl derivatives of XXXI suggests that the parent compound also undergoes photochemically induced rearrangement via the keto tautomer XXXIb. In support of this is the extremely slow rate of isomerization of 3-methoxy-1,2-benzisoxazole (XLIVa) under similar photolytic conditions (see Table 17). Irradiation of XLIVa in ether for 6 hours produces only 3% of the rearrangement product XLVa and a relatively high yield of imido-ester LXIX. The formation of LXIX presumably results from hydrogen abstraction of a diradical species related to LXI in Scheme 16. Comparison of LXIX with independently synthesized material verified its structure. Photolysis of XLIVa in acetone under triplet sensitization conditions

Table 17. Photolysis of 3-methoxy-1,2-benzisoxazole (XLIVa)

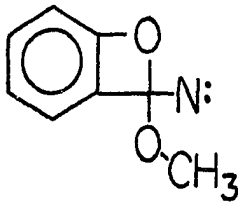
Filter	Solvent	Time (min)	% yield XLIVa	XLVa	LXIX
Vycor	Ether	360	19	3	33
Vycor	Methanol	60	18	24	11
Pyrex	Acetone	180	> 95	-	-
Pyrex	Acetone	540	60	-	-

results in the formation of unidentified decomposition products, since after 9 hours only 60% of the starting material can be recovered by column chromatography. However,



XLIVa XLVa LXIX

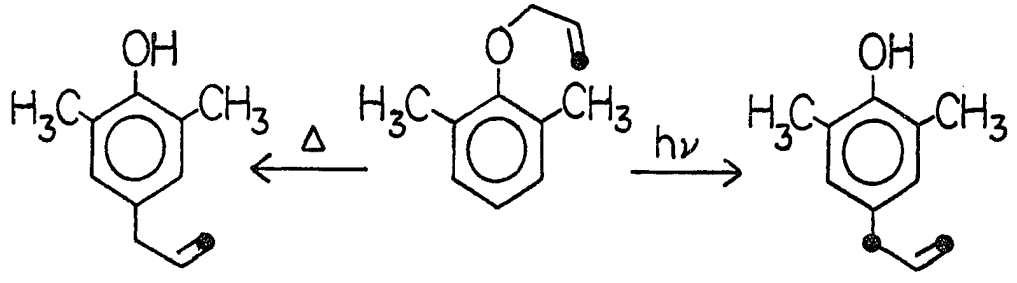
in methanol a rapid isomerization of XLIVa to XLVa occurs, exhibiting a solvent effect similar to that observed upon irradiation of the isomeric N-methyl compound XLII (see above). This photoisomerization of XLIVa to XLVa may involve the intermediate formation of LXX by a mechanism analogous to C (Scheme 16).



LXX

3-allyloxy-1,2-benzisoxazole (L) undergoes both thermal and electron impact induced Claisen rearrangements to afford 2-allyl-1,2-benzisoxazolin-3-one (LI). The photochemical behavior of L was of particular interest since photo-Claisen rearrangements have not as yet been reported in heterocyclic systems.

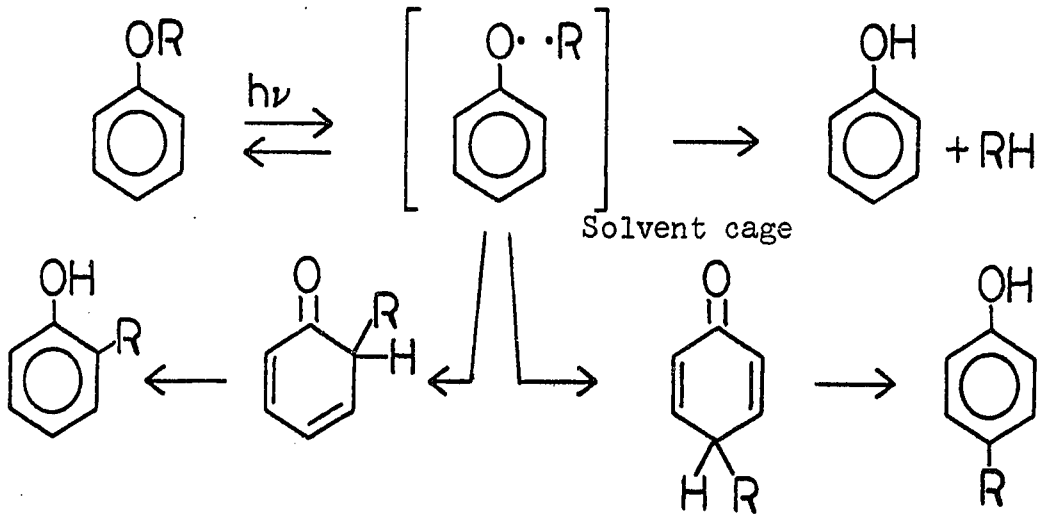
The photo-Claisen rearrangement of phenyl allyl ether was first reported in 1952, and the only products isolated in the reaction were phenol and p-allyl phenol (108). This photoisomerization was later studied by Schmid (109) using (γ-^{14}C) allyl-2,6-dimethyl phenyl ether. The p-allyl phenol



photoproduct was found to contain approximately equal amounts of C-14 in the α- and γ-carbon atoms of the allyl group, whereas the label in the thermal product was located exclu-

sively on the γ-carbon. These results are readily explained by a mechanism involving a radical pair in a solvent cage as shown in Scheme 18 (110). The photo-Fries reaction has been explained by a similar mechanism (111) which recently has been supported by photolysis of phenyl acetate in the vapor-phase (112). As anticipated by such a mechanism,

Scheme 18



unsubstituted phenol was the only product isolated. Numerous other examples of analogous photochemically induced rearrangements of aromatic ethers have recently been reported (113-116).

Irradiation of L (0.005 M) in acetone with Pyrex filtered ultraviolet light results in the formation of the expected double rearrangement product, 3-allyl-2-benzoxazolinone (LII), and unsubstituted 2-benzoxazolinone (XXX). The relative percentage yields of these products along with recovered starting material are shown in Table 18.

Table 18. Photolysis of 3-allyloxy-1,2-benzisoxazole (L)

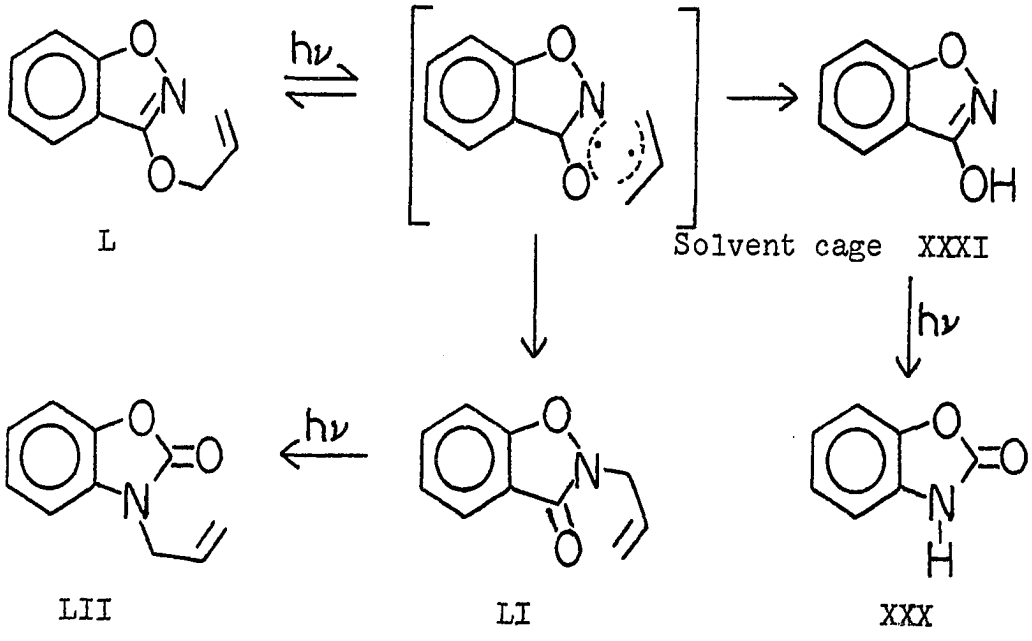
Filter	Solvent	Time (min)	% yield[a] L	LII	XXX	LIII	LXXI
Pyrex	Acetone	540	17	7	19	-	-
Corex	MeOH	30	28[b]	6	14[b]	9[b]	~ 3[b]

[a]Isolated by column chromatography (silica gel).

[b]Ratio determined by nmr spectroscopy.

A reasonable mechanism to explain these results is one involving a solvent cage enclosed radical pair (Scheme 19)

Scheme 19



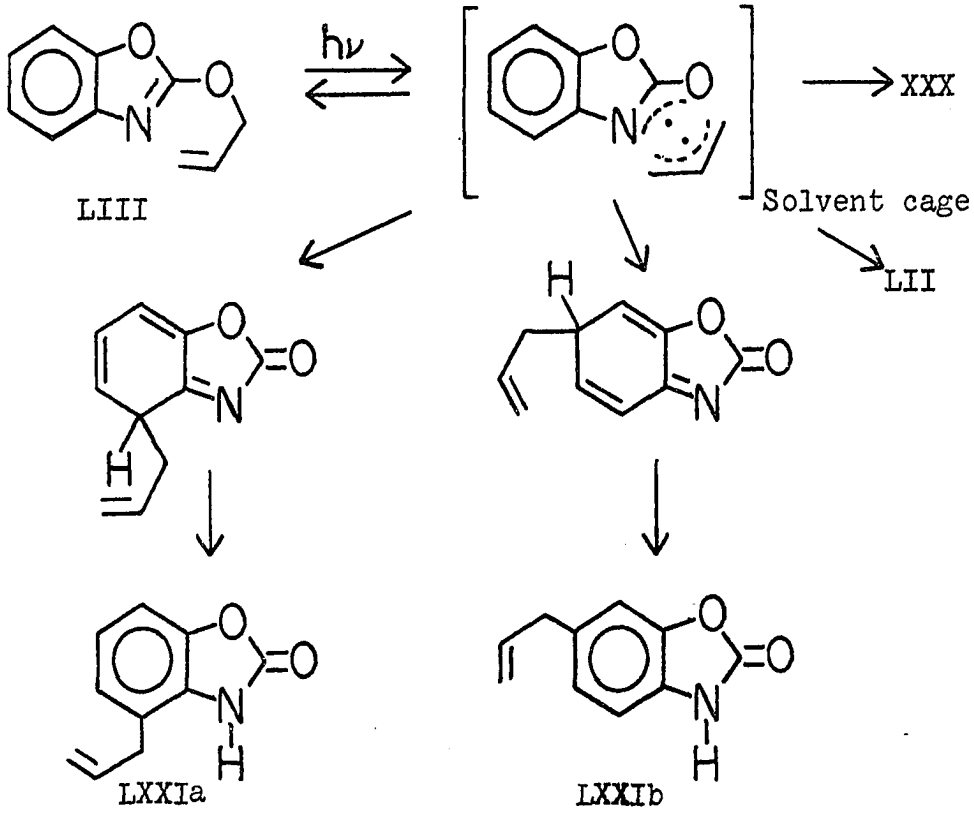
analogous to that postulated for the photo-Fries and -Claisen rearrangements (see Scheme 18). Recombination of this radical pair would afford either starting material or 2-allyl-1,2-benzisoxazolin-3-one (LI). The nmr spectrum of the crude photolysate indicated the presence of trace amounts of LI which is lost in chromatographic work-up. Compound LI is known to undergo a photochemical ring transformation to give LII. However, diffusion of this radical pair from the solvent cage would result in hydrogen abstraction from solvent molecules producing 3-hydroxy-1, 2-benzisoxazole (XXXI) which also has been shown to isomerize to XXX under these photolytic conditions.

An interesting solvent effect is observed upon photolysis of L in methanol. A considerable portion of the starting material is consumed after only 30 minutes irradiation (Table 18). In addition to LIII and XXX, the products obtained in the previous photolysis, 2-allyloxybenzoxazole (LIII) and a small amount of 2-benzoxazolinone containing allylic substitution in the benzene ring (LXXI) are also produced and are readily identified by the chemical shifts of the allyl methylene protons in their nmr spectra.

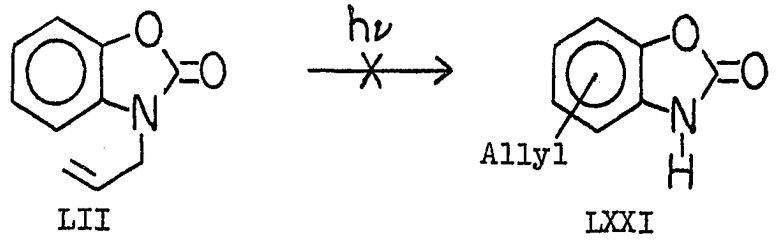
The formation of LIII is plausible in view of the rather facile photoisomerization of the corresponding O-methyl derivative XLIVa to XLVa (see Table 17). Subsequent decomposition of LIII may then occur as illustrated in

Scheme 20 giving rise to isomeric compounds LXXIa and LXXIb analogous to the o- and p-substituted phenols observed in

Scheme 20



the photo-Fries reaction (Scheme 18). Alternatively, LXXI may result from photoisomerization of 3-allyl-2-benzoxazolinone (LII) since N-benzyl aniline has been shown



to afford 2- and 4-aminodiphenyl methane upon photolysis (117). However, irradiation of authentic LII for approximately 4 hours produces only polymeric material, and LII can be recovered to the extent of 70%.

In support of the mechanism shown in Scheme 20, the photolysis of LIII yields 3-allyl-2-benzoxazolinone (LII), 2-benzoxazolinone (XXX), and two isomeric compounds corresponding to LXXI (see Table 19). These latter two compounds can be separated by column chromatography. However, the slower

Table 19. Pyrolysis of 2-allyloxybenzoxazole (LIII)

Filter	Solvent	Time (min)	% yield[a]			
			LIII	LII	XXX	LXXI
Pyrex	Acetone	120	3	10	50	14
Pyrex	Acetone	180	2	11	51	17

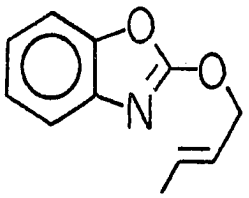
[a]Isolated by column chromatography (silica gel).

moving component has an r_f value almost identical to that of 2-benzoxazolinone rendering these two materials inseparable by chromatographic means. Nmr measurements demonstrate a ratio of ~ 2:1 upon comparison of the amounts of slower to faster moving components of LXXI.

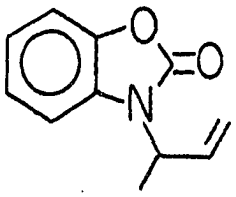
Possible alternate pathways for the photochemically induced isomerizations of L to LI and LIII to LII are

concerted [1,3]- and [3,3]-sigmatropic processes (118). Numerous examples of photochemical allylic rearrangements have been reported as concerted [1,3]-shifts (119). The concerted [3,3]-migration is sterically unfavorable in the first excited singlet electronic state. However, internal conversion to a vibrationally excited ground state would permit the [3,3]-rearrangement to occur in a manner analogous to the thermal Claisen and Cope processes (120).

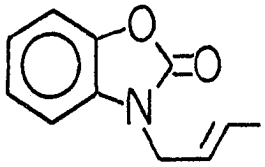
It was of interest to examine the photochemical behavior of 2-crotoxybenzoxazole (LXXII) in order to obtain further mechanistic information concerning this isomerization.



LXXII



LXXIIIa

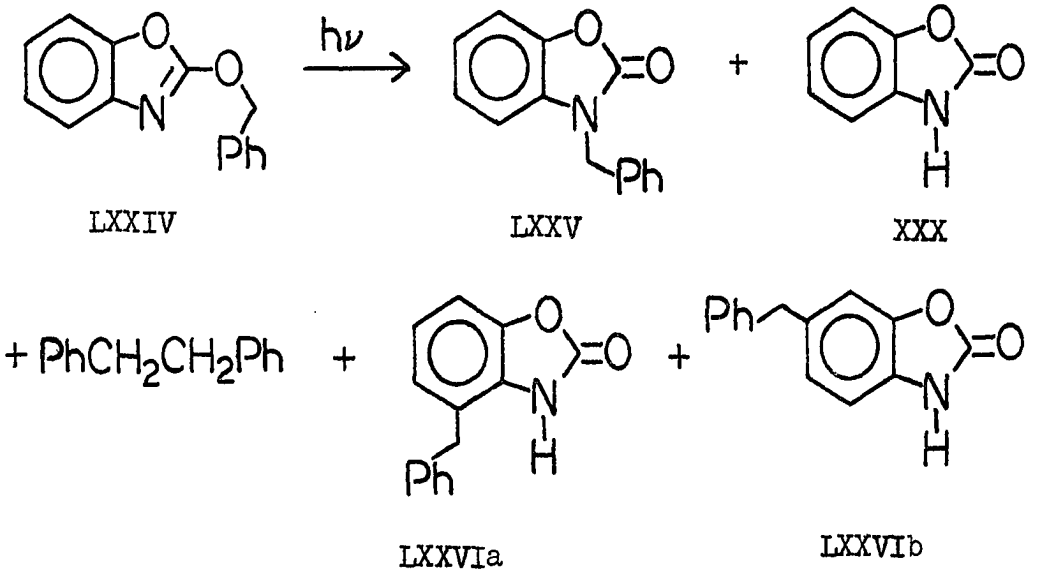


LXXIIIb

A [3,3]-sigmatropic shift of the crotyl group would provide only LXXIIIa, whereas a [1,3]-process would yield LXXIIIb. On the other hand, if a radical pair is involved, then a mixture of these two products should occur. Compound LXXII was synthesized, but, upon attempted purification by distillation or column chromatography, it was rapidly converted by Claisen rearrangement to LXXIIIa and could not be utilized in this mechanistic study of the photo-Claisen rearrangement.

Therefore, the photochemistry of 2-benzyloxybenzoxazole (LXXIV) was investigated, for in this system the [3,3]-process should not be important. Irradiation of 0.01 M solutions of LXXIV for 2 hours at room temperature in ether (Corex filter) and in acetone (Pyrex filter) results in the formation of products analogous to those obtained in the photolysis of the O-allyl compound LIII (see Schemes 20 and 21). Again the products can be isolated by column chromatography, and their relative percentage yields based on

Scheme 21



unrecovered starting material are shown in Table 20. The ratio of the slower to faster moving component of LXXVI is ~ 2:1 in agreement with the results obtained in the case of

Table 20. Photolysis of 2-benzyloxybenzoxazole (LXXIV)

Filter	Solvent	% yield[a] LXXIV	LXXV	LXXVI	XXX
Pyrex	Acetone	0	12	23	42
Corex	Ether	0	14	24	52

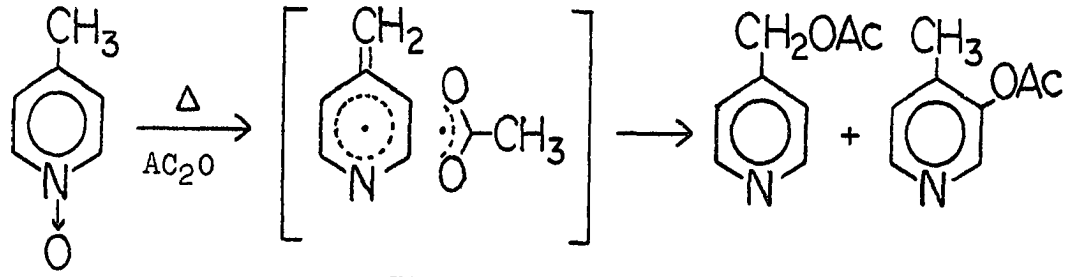
[a]Isolated by column chromatography (silica gel).

the allyl compounds LXXIa and b.

The isolation of considerable amounts of bibenzyl resulting from dimerization of benzyl radicals and the formation of 2-benzoxazolinone substantiate a radical pair mechanism in the photodecomposition of LXXIV. This mechanism may also be responsible for the formation of the N-benzyl derivative LXXV, but the simultaneous operation of a concerted [1,3]-sigmatropic migration cannot be eliminated. Similar conclusions have been reached in a study of the photochemical rearrangements of α-benzyloxystyrenes to β-phenylpropiophenones (121).

An obvious method of distinguishing between these two mechanistic pathways is through the use of chemically induced dynamic nuclear polarization (CIDNP) techniques (122). This method has detected [1,3]-migrations of arylazo groups in 1,3,5-triarylpentazodienes occurring by a radical pair mechanism (123).

Furthermore, the reaction of 4-picoline N-oxide with acetic anhydride at elevated temperatures has been shown by CIDNP to involve to a certain extent radical pair LXXVII in the formation of the acetoxy products (124).



LXXVII

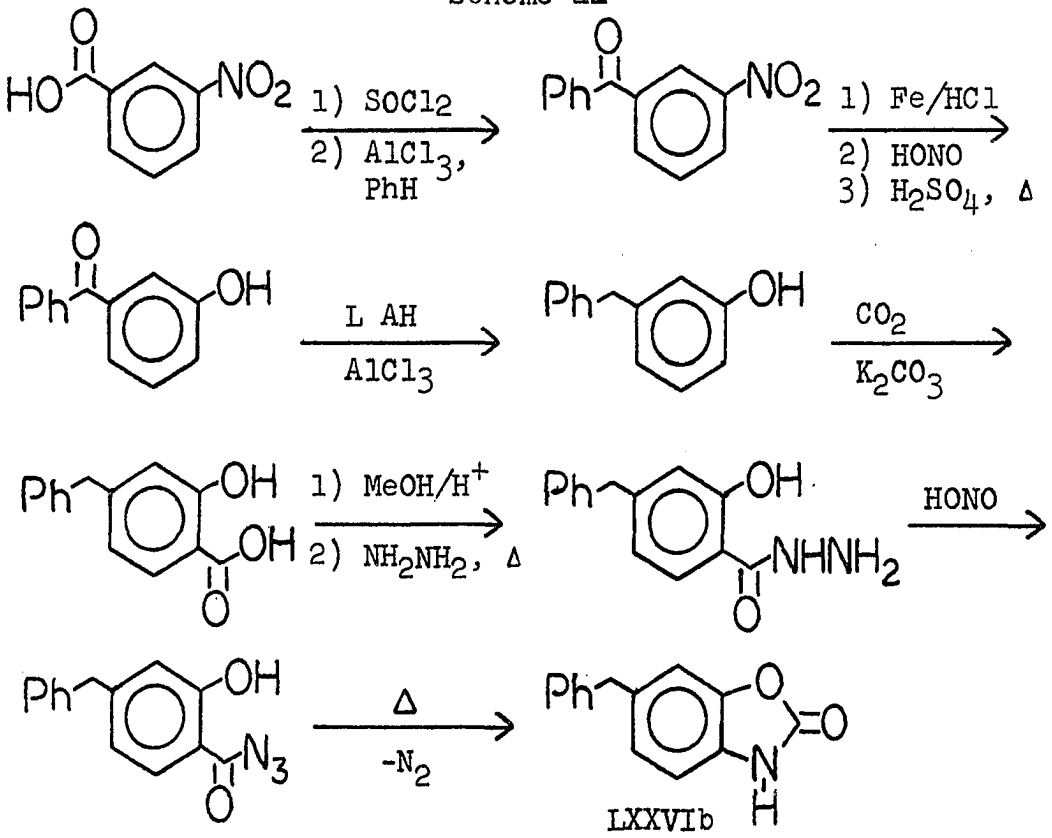
The CIDNP method would also be useful in studying the formation of the benzene ring substituted products LXXVIa and b. These may result from radical recombination processes, as in Scheme 20, or from concerted [1,5]- and [1,7]-sigmatropic rearrangements (118).

As predicted on the basis of the photo-Fries and -Claisen mechanism (Scheme 18) and as indicated in Schemes 20 and 21, the probable positions of ring substitution in compounds LXXIa and b and LXXVIa and b are the 4- and 6-positions in 2-benzoxazolinone. This is indeed substantiated by independent synthesis and chemical and spectral studies of these photoproducts.

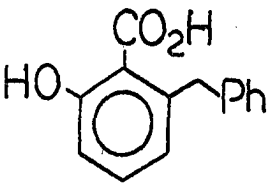
The synthesis of 6-benzyl-2-benzoxazolinone (LXXVIb)

was accomplished starting with 3-nitrobenzoic acid as shown in Scheme 22. The reaction sequence is straightforward, but

Scheme 22

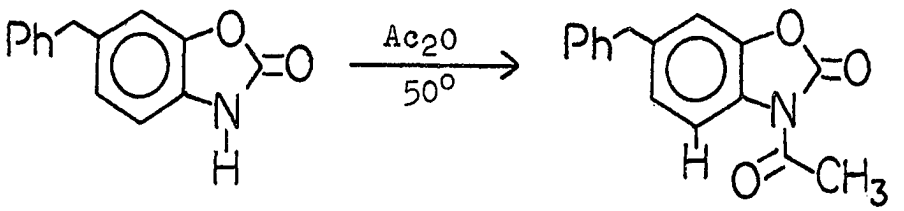


of particular interest is the formation of 4-benzyl salicylic acid in a Marassé modification of the Kolbe-Schmitt reaction. This is carried out in 1000 psi CO_2 in the presence of anhydrous K_2CO_3. The only isomer obtained in 85% yield is 4-benzyl salicylic acid. That the product is not the other possible o-hydroxy acid, 6-benzyl salicylic acid, is readily demonstrated by its nmr spectrum which shows one aromatic proton deshielded by the carboxyl group appearing at 7.83 δ as a doublet. A similar Kolbe-



Schmitt reaction of m-cresol has been shown to yield only the corresponding 4-methyl salicylic acid in comparable yields (125). The 6-benzyl-2-benzoxazolinone (LXXVIb) obtained in this reaction sequence and the photoproduct LXXVI (Scheme 21) with the lower r_f value have identical melting points, nmr, ir, and mass spectra.

Reaction of LXXVIb with acetic anhydride at 50 °C for 2 hours yields the corresponding N-acetyl derivative LXXVIII whose infrared spectrum in chloroform solution shows carbonyl absorptions at 1808 cm^{-1} (2-one) and 1733 cm^{-1} (3-acyl).

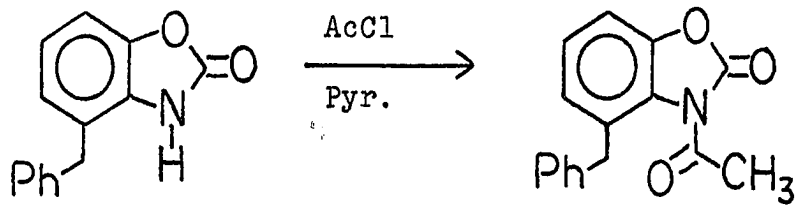


LXXVIb LXXVIII

A comparison of the nmr spectra of LXXVIb and LXXVIII reveals that the carbonyl of the N-acyl group deshields the aromatic proton at the 4-position which experiences a downfield shift of greater than 0.5 ppm appearing as a doublet ($J \approx 8$ Hz)

(92).

This finding is of value in demonstrating that substitution of the benzyl group of the other photoproduct LXXVIa, the component having the larger r_f value, has occurred at the 4-position. Consequently, photoproduct LXXVIa was reacted with acetic anhydride under similar conditions, but only unchanged starting material was recovered indicating possible steric hindrance by the 4-benzyl group.



LXXVIa LXXIX

N-acetylation could be effected by acetyl chloride in the presence of pyridine. The ir spectrum of LXXIX shows carbonyl absorptions at 1800 cm^{-1} (2-one) and 1747 cm^{-1} (3-acyl), and its nmr spectrum substantiates that substitution of the benzyl group has indeed occurred at the 4-position.

These results verify the photochemical reaction sequence displayed in Scheme 21 for 2-benzyloxybenzoxazole (LXXIV). Furthermore, based on the great similarity in the photolysis reaction of LXXIV and the corresponding O-allyl compound LIII, it would be reasonable to conclude

that photoproducts LXXIa and b possess structures as shown in Scheme 20; i.e., that substitution has also occurred at the 4- and 6-positions in this system.

Related Heterocyclic Systems: 3-Indazolinones

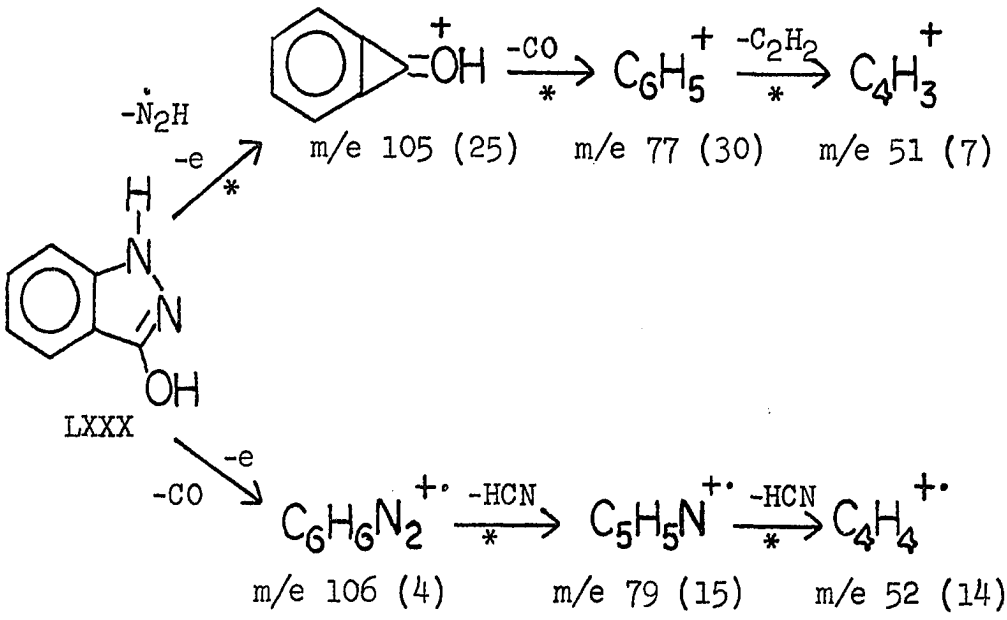
It was of interest to examine the thermal, photochemical, and mass spectral behavior of some related heterocyclic systems, in particular, those in which the ring oxygen of 3-hydroxy-1,2-benzisoxazole (XXXI) has been replaced with nitrogen or sulfur. Photochemically indazole has been shown (58) to isomerize to benzimidazole (Scheme 23, X = NH). However, benzisothiazole was found (67) to be

Scheme 23

relatively stable upon irradiation, and no apparent rearrangement to benzothiazole (Scheme 23, X = S) could be detected.

Mass spectral studies of 3-hydroxy indazole, or 3-indazolinone (LXXX), and of a variety of alkyl and aryl derivatives of LXXX have been reported (37, 38). The major fragmentation pathways of ionized LXXX are shown in Scheme 24 as substantiated by accurate mass measurements of the ions. The relative intensities of the ions appear in

Scheme 24

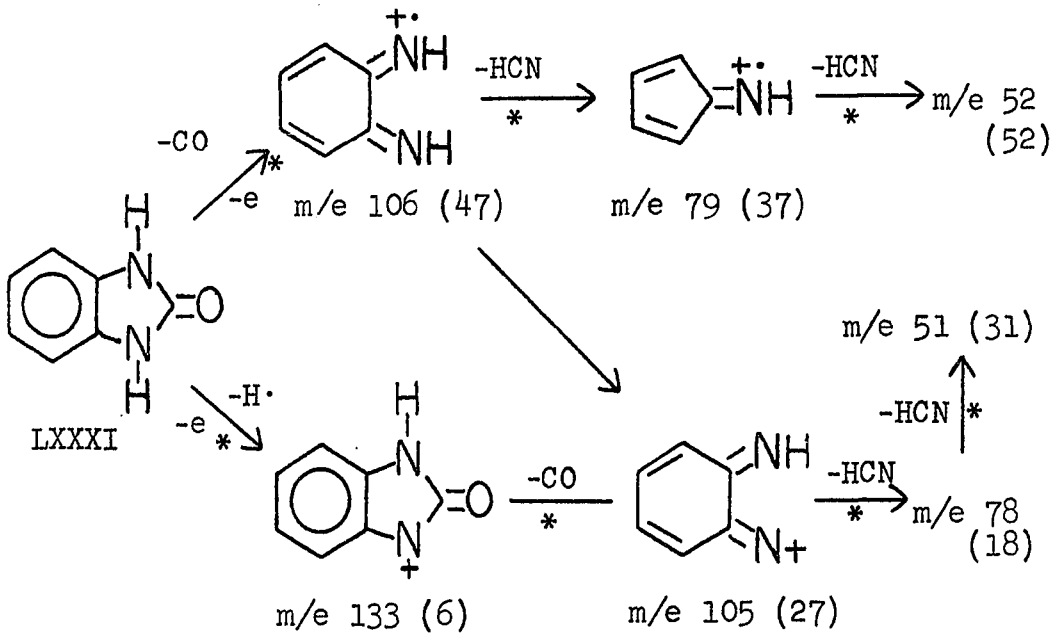


parenthesis, and the metastable processes are indicated with asterisks.

In order to determine whether isomerization of 3-indazolinone (LXXX) to 2-benzimidazolinone (LXXXI) occurs upon electron impact, the spectrum of LXXXI was investigated. The breakdown pattern of ionized LXXXI is depicted in Scheme 25 and involves prominent loss of a molecule of CO, which has also been reported to be an important pathway in the mass spectra of substituted 2-benzimidazolinones (38). This $(M-CO)^{+\cdot}$ species at m/e 106 then fragments with the consecutive losses of two HCN's, each of these processes being accompanied by the appropriate metastable ion.

Also important in the spectrum of LXXXI is the expul-

Scheme 25

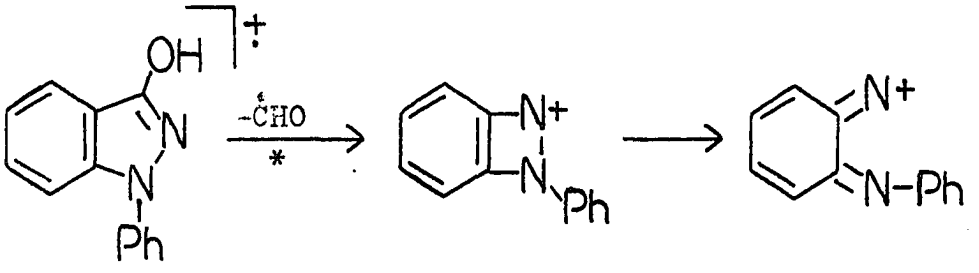


sion of H· from the molecular ion followed by losses of CO and two HCN molecules. The $(M-\dot{C}HO)^+$ ion at m/e 105 is produced alternatively by the elimination of H· from m/e 106 as supported by an intense metastable peak at m/e 104.0.

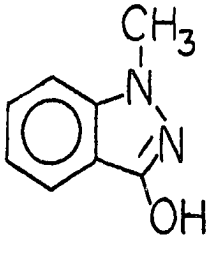
The corresponding ion at m/e 105 in the spectrum of 3-indazolinone (Scheme 24) results predominantly (~ 90%) from the expulsion of $\dot{N}_2H$ from the molecular ion. The loss of $\dot{C}HO$ occurs to a much smaller degree (~ 10%) (37). However, a fragmentation pathway completely analogous to that of 2-benzimidazolinone (Scheme 25) is present in the spectrum of 3-indazolinone and involves the loss of CO and two HCN's from the molecular ion. A possible mechanism to rationalize this process is one in which isomerization of ionized 3-indazolinone (LXXX) to the molecular ion of 2-benzimidazolinone

(LXXXI) occurs, analogous to the electron impact induced transformation of 3-hydroxy-1,2-benzisoxazole (Scheme 4, see above). However, the loss of CO (or ĊHO) from $(LXXX)^{+\cdot}$ does not necessitate such a rearrangement process, and an alternate mechanism has been proposed (38) for this fragmentation reaction in the case of ionized 1-phenyl-3-indazolinone (Scheme 26).

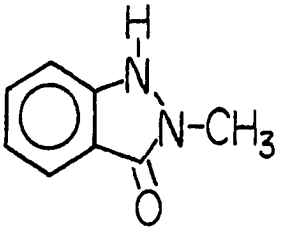
Scheme 26



The mass spectra of the N-methyl derivatives of 3-indazolinone, LXXXIIa and LXXXIIb, have also been reported (37) and their breakdown patterns are very similar. Both



LXXXIIa



LXXXIIb

molecular ions lose ĊHO in both one- and two-step processes to form the major component of the ion at m/e 119. Again this fragmentation may be explained by prior isomerization

to ionized 1-methyl-2-benzimidazolinone (LXXXIII). Indeed, the mass spectrum of LXXXIII (Figure 18) shows an intense peak of m/e 119 corresponding to $(M-\dot{C}HO)^+$. Appropriate metastable ions indicate that this process occurs via both concerted and stepwise mechanisms. Decomposition of the m/e 119 species involves the sequential loss of two HCN molecules to afford ions at m/e 92 and m/e 65.

Of relatively less importance in the spectrum of LXXXIII is the $(M-\dot{C}H_3)^+$ ion at m/e 133 which fragments further with the loss of HCN (m/e 106) as substantiated by a metastable peak at m/e 84.5. This would suggest LXXXIV as

LXXXIV

a possible structure for the $(M-\dot{C}H_3)^+$ species from which expulsion of HCN followed by CO (m/e 78) is plausible. It is interesting to note that metastable ions for the reverse fragmentation process (i.e., the initial loss of CO followed by HCN) are not present in the spectrum of LXXXIII although the $(M-\dot{H})^+$ ion of 2-benzimidazolinone (Scheme 25) appears to favor this pathway.

The loss of methyl radical produces the most intense ion in the spectrum of 1,2-dimethyl-3-indazolinone (LXXXV)

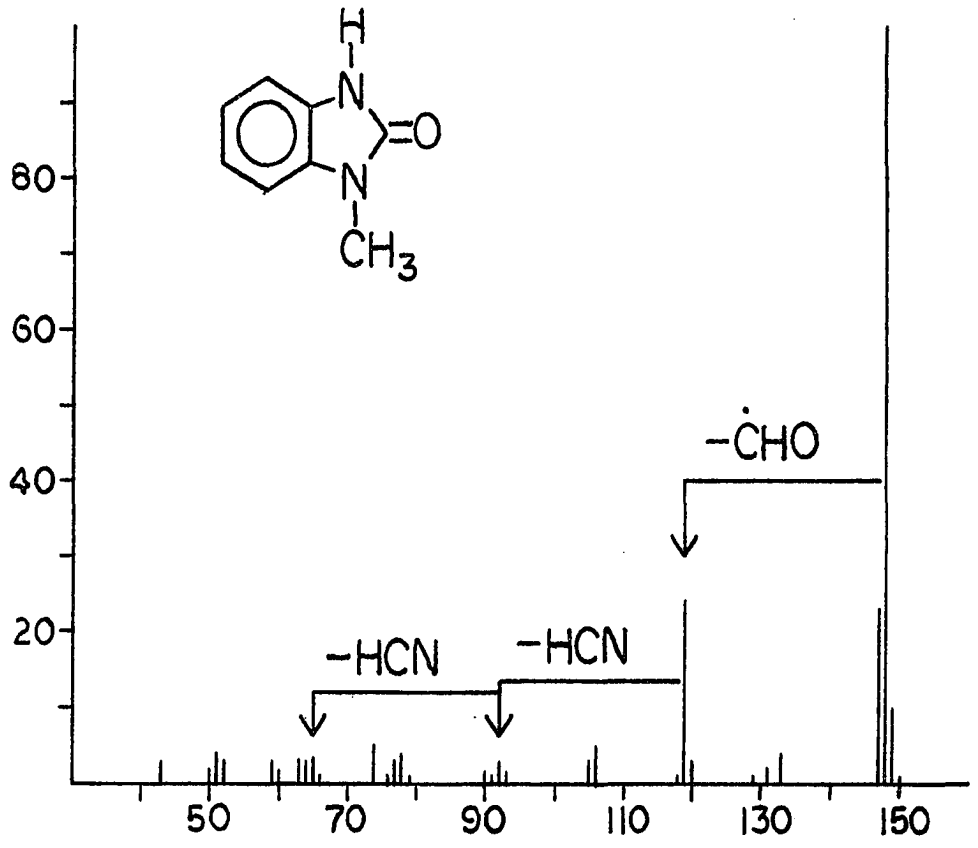


Figure 18. Mass spectrum of 1-methyl-2-benzimidazolinone (LXXXIII)

as shown in Figure 19. The origin of this methyl group is of interest and labelling experiments would be necessary to determine exactly which methyl group is lost in this process. However, upon examination of the mass spectra of the methyl derivatives LXXXIIa and b (37), the contribution of the $(M-\dot{C}H_3)^+$ ion to the total ion current is significantly higher in the spectrum of the 1-methyl derivative LXXXIIa (8.7%) than in that of the 2-methyl compound LXXXIIb (2.7%). This would suggest for compound LXXXV that, although methyl radical presumably is eliminated from both positions to a certain extent, loss from the 1-position is favored, possibly because any positive charge generated at this position is more readily delocalized.

Subsequent decomposition of this $(M-\dot{C}H_3)^+$ species follows two major pathways substantiated by metastable ions. These are: (i) the loss of CO (m/e 119) followed by two consecutive losses of HCN giving rise to ions at m/e 92 and m/e 65; and (ii) elimination of N_2CH_2 producing m/e 105 which expels CO (m/e 77). An almost identical fragmentation pattern has been reported (37) for the m/e 147 ion formed by the loss of carbethoxy radical from ionized 1-carbethoxy-2-methyl-3-indazolinone, thus lending support to the argument that the 1-methyl group is preferentially lost from the molecular ion of 1,2-dimethyl-3-indazolinone (LXXXV).

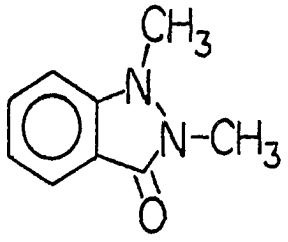


Figure 19. Mass spectrum of 1,2-dimethyl-3-indazolinone (LXXXV)

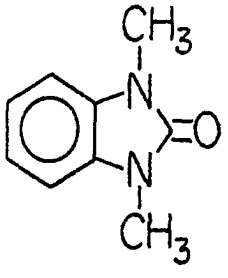
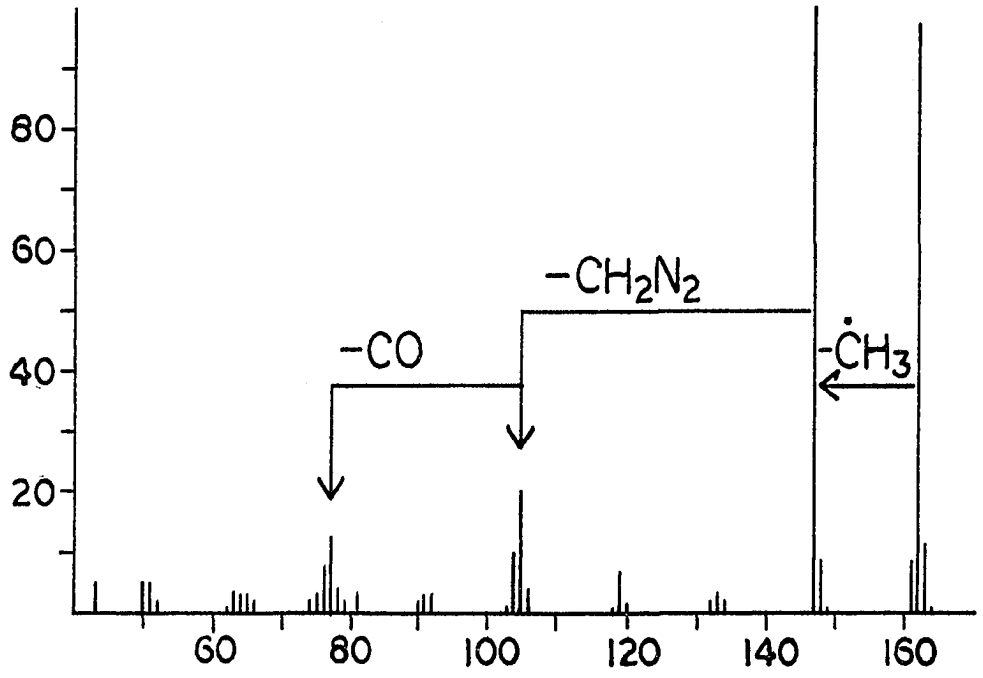
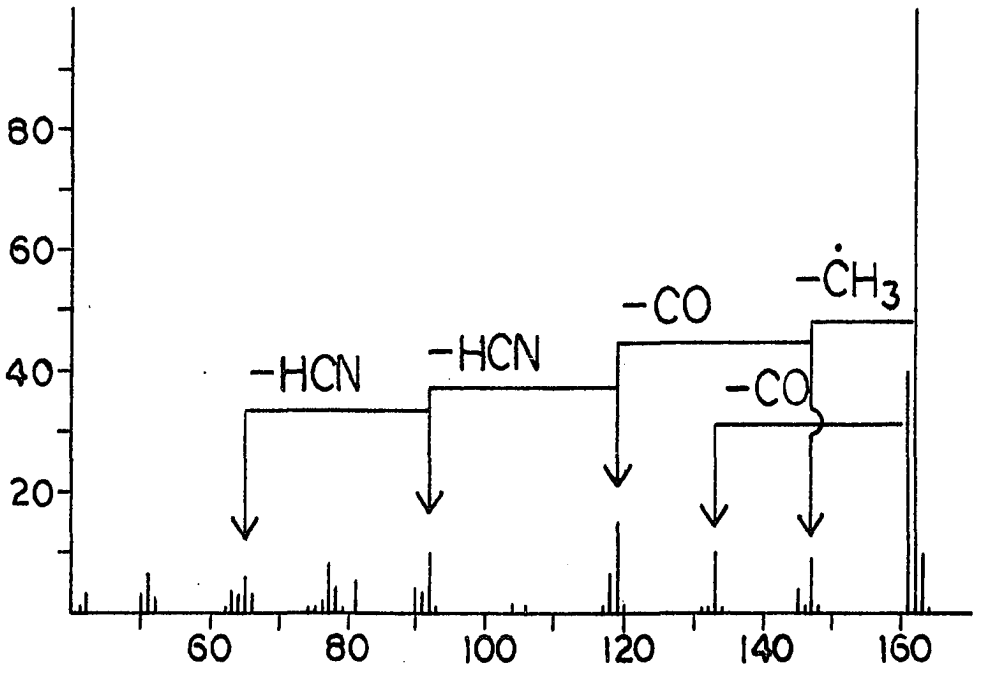
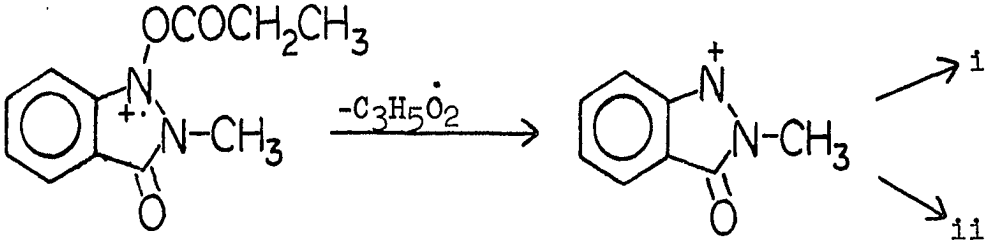


Figure 20. Mass spectrum of 1,3-dimethyl-2-benzimidazolinone (LXXXVI)


80
60
40
20
-CH2N2
-CO
-ĊH3
60
80
100
120
140
160

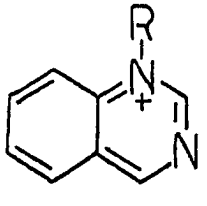

80
60
40
20
-ĊH3
-CO
-HCN
-HCN
-CO
60
80
100
120
140
160



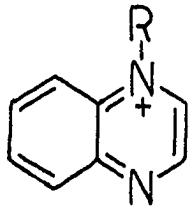
m/e 147

Pathway (i) is also important in the spectrum of 1,3-dimethyl-2-benzimidazolinone (LXXXVI) following the initial expulsion of $\cdot CH_3$ (Figure 20). Another decomposition mode of ionized LXXXVI involves the prominent loss of ·H followed by CO to give the m/e 133 ion, a pathway which also appears in the spectrum of LXXXV (Figure 19).

An interesting fragmentation which is unique to the spectra of the mono- and dimethyl-2-benzimidazolinones is the metastable loss of hydroxyl radical. The hydrogen involved in this loss from 1-methyl-2-benzimidazolinone presumably originates from the methyl group since this process occurs in the spectrum of the dimethyl compound but not in that of unsubstituted 2-benzimidazolinone. These $(M-\dot{O}H)^+$ ions may have ring expanded structures, such as LXXXVIIa or LXXXVIIb, analogous to those proposed to explain



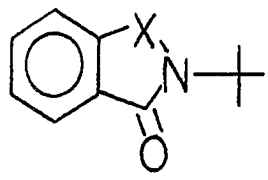
LXXXVIIa



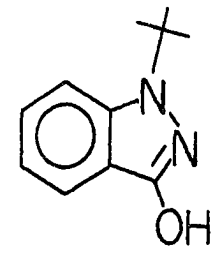
LXXXVIIb

to explain the mass spectra of 2-alkyl benzimidazoles (41, 42). Subsequent decomposition of these ions occurs with step-wise expulsion of two molecules of HCN.

Since double hydrogen rearrangements were noted (see above) in the mass spectra of 2-t-butyl-1,2-benzisoxazolin-3-one (XLVII) and N-t-butyl phthalimide (LXXXVIIIa), it was



XLVII, X=O
LXXXVIIIa, X=(C=O)
b, X=(N-H)



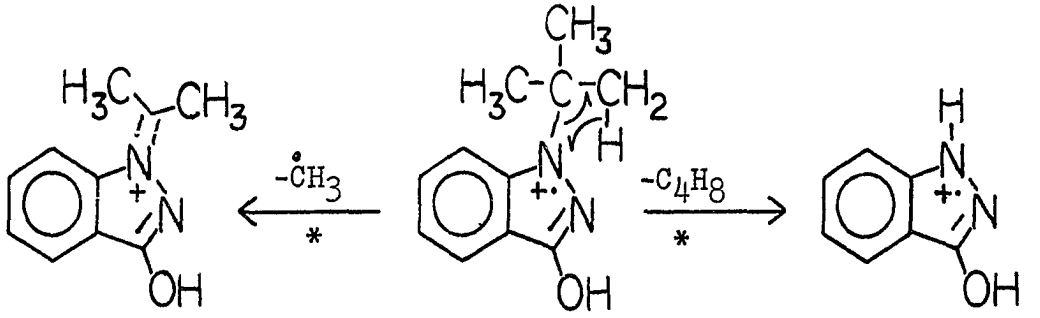
LXXXIX

of interest to synthesize 2-t-butyl-3-indazolinone (LXXXVIIIb) and examine its mass spectral behavior to determine the scope of this process. An attempted synthesis of LXXXVIIIb was carried out following the procedure used to prepare XLVII in a sealed-tube reaction (see Experimental section). In addition to considerable amounts of unreacted starting material, a low yield (6%) of a t-butyl substituted 3-indazolinone was obtained. However, the ir and nmr spectra indicated that substitution had occurred at the 1-position yielding 1-t-butyl-3-indazolinone (LXXXIX).

The mass spectrum of LXXXIX is rather simple and is reminiscent of the spectrum of 3-t-butyl-2-benzoxazolinone (Figure 13). A single hydrogen transfer accounts for the

base peak ion at m/e 134 (Scheme 27). The structure of this m/e 134 ion is probably related to that of ionized

Scheme 27



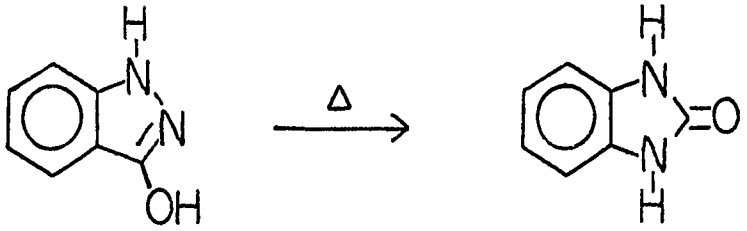
m/e 175 (11) m/e 190 (26) m/e 134 (100)

3-indazolinone since its decomposition also occurs by the loss of $\dot{N}_2H$ (m/e 105) and CO (m/e 106) (see Scheme 24). Loss of methyl radical from the molecular ion of LXXXIX by α-cleavage produces a stabilized species at m/e 175 analogous to the $(M-1)^+$ ion reported in the spectrum of 1-methyl-3-indazolinone (LXXXIIa) (37). Scission of the N-t-butyl bond of ionized LXXXIX with charge retention of the alkyl group gives rise to the ion at m/e 57, the t-butyl cation. However, evidence for a double hydrogen rearrangement is completely lacking in the spectrum.

The electron impact induced rearrangement of 3-hydroxy-1,2-benzisoxazole to 2-benzoxazolinone is evident by the similarity of their spectra (Figures 5 and 6) and, in particular, by the prominent loss of CO_2 from their respective molecular ions. Although a similar transformation of

ionized 3-indazolinone (LXXX) to 2-benzimidazolinone (LXXXI) may occur to a certain extent, a characteristic fragmentation, such as the loss of CO_2 in the previous case, is not available in this system to support such a rearrangement process. A study of the thermal and photochemical behavior of 3-indazolinone was undertaken to determine whether isomerization occurs under these highly energetic conditions.

3-indazolinone (LXXX) is considerably more stable thermally than 3-hydroxy-1,2-benzisoxazole which was found to isomerize at 450° in the gas phase (see Table 9). Sublimation of LXXX under high vacuum into a Vycor tube packed with Vycor chips and heated to 600° results only in slight decomposition to a tarry substance and the recovery of most of the starting material (Table 21). Pyrolysis at 700° does



LXXX LXXXI

result in isomerization to give LXXXI as substantiated by nmr and infrared (C = O at 1733 cm^{-1}, KBr) spectroscopy. Starting material is completely consumed at 800° producing only LXXXI and significant amounts of tar.

Table 21. Pyrolysis of 3-indazolinone (LXXX)

Temp. °C (± 10°)	% yield[a] LXXX	LXXXI
600	88	0
700	36(34)[b]	21(29)[b]
800	0	34

[a]Based on starting LXXX.

[b]Ratio determined by nmr; results of two experiments.

Similar results are obtained upon thermolysis of 2-methyl-3-indazolinone (LXXXIIb). Rearrangement occurs at 650-700° (Table 22) to give 1-methyl-2-benzimidazolinone

Table 22. Pyrolysis of 2-methyl-3-indazolinone (LXXXIIb)

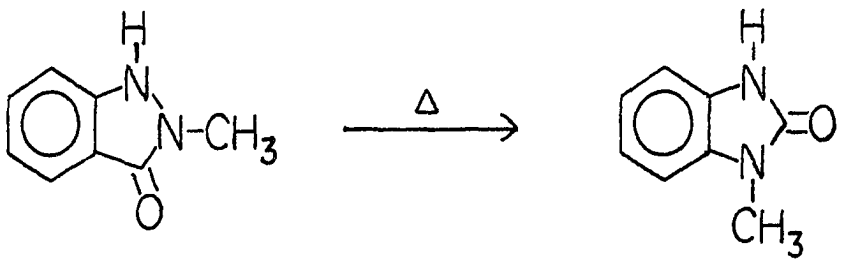
Temp. °C (± 10°)	% yield[a] LXXXIIb	LXXXIII
650	66[b]	16[b]
700	38[c]	28[c]

[a]Based on starting LXXXIIb.

[b]Ratio determined by nmr.

[c]Isolated by preparative tlc.

(LXXXIII) which could be isolated by preparative tlc. Its physical and spectral properties were found to be identical to those of authentic LXXXIII.



LXXXIIb LXXXIII

Pyrolysis of the corresponding 1-methyl-3-indazolinone (LXXXIIa) produces somewhat different results in that loss of the methyl group occurs readily at 650° (Table 23).

Table 23. Pyrolysis of 1-methyl-3-indazolinone (LXXXIIa)

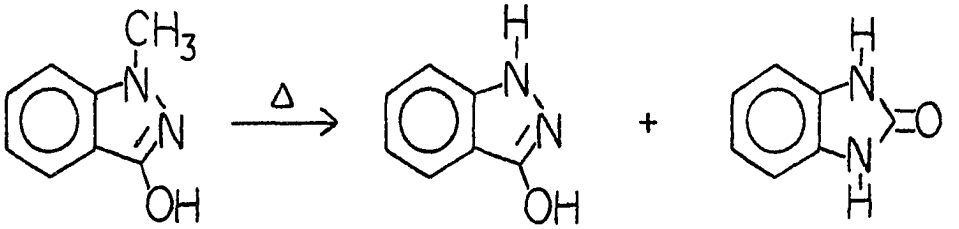
Temp. °C (± 10°)	% yield[a] LXXXIIa	LXXX	LXXXI	LXXXIII
600	83	-	-	-
650	21	58	trace[b]	-
700	trace[b]	35	12	trace[b]

[a]Isolated by preparative tlc or column chromatography.

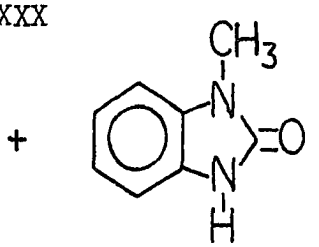
[b]Detected by nmr spectroscopy.

The major product at this temperature is 3-indazolinone (LXXX) which is analogous to the formation of aniline in the thermolysis of N-allyl aniline (126). At higher tempera-

tures (700°) 2-benzimidazolinone (LXXXI) is also formed, presumably via isomerization of LXXX. Alternatively, loss of a methyl group from 1-methyl-2-benzimidazolinone (LXXXIII),



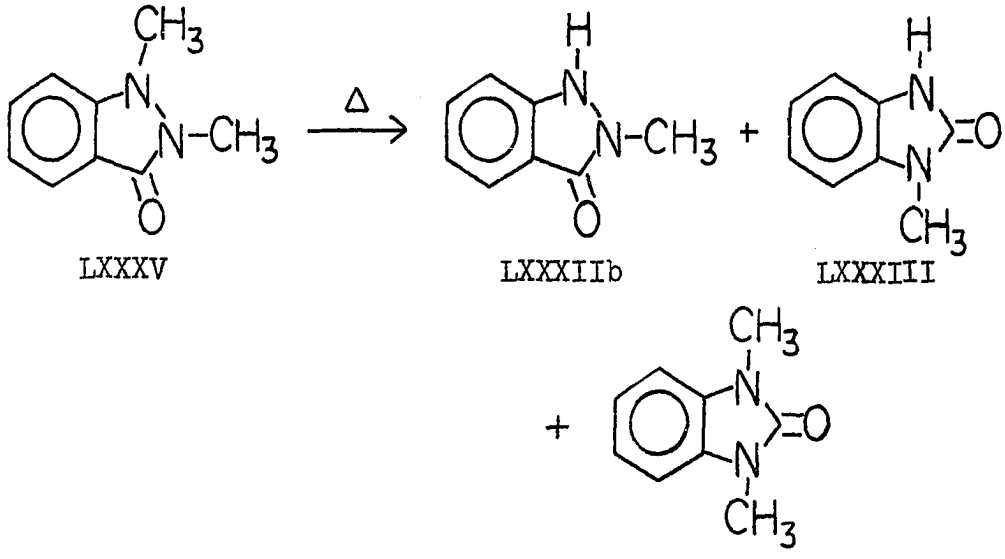
LXXXIIa LXXX LXXXI



LXXXIII

which is formed in trace amounts, may account for LXXXI. However, this appears unlikely since LXXXI is not obtained in the pyrolysis of 2-methyl-3-indazolinone at these temperatures.

1,2-dimethyl-3-indazolinone (LXXXV) also decomposes with the loss of one methyl group when pyrolyzed at 600-650° (Table 24), the major product being 2-methyl-3-indazolinone (LXXXIIb). The rather facile cleavage of the 1-methyl-N bond is in agreement with the pyrolytic results of compounds LXXXIIa and b. Furthermore it lends support to the suggestion that the $(M-\dot{C}H_3)^+$ ion produced upon electron bombardment of LXXXV is formed by preferential loss of the 1-methyl group.



LXXXV LXXXIIIb LXXXIII

LXXXVI

Table 24. Pyrolysis of 1,2-dimethyl-3-indazolnone (LXXXV)

Temp. °C (± 10°)	% yield[a] LXXXV	LXXXIIIb	LXXXIII	LXXXVI
600	32	25	8	trace[b]
650	13	17	6	trace[b]

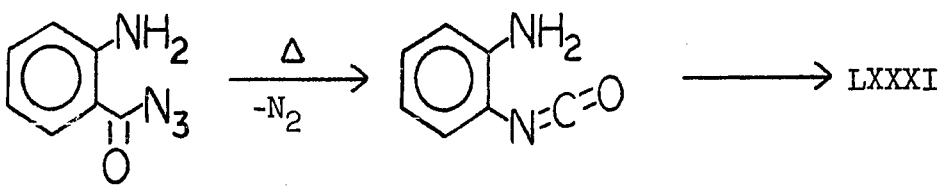
[a]Isolated by column chromatography (silica gel).

[b]Detected by tlc.

It is interesting to note the apparent difference in thermal stabilities of 1-methyl- and 1,2-dimethyl-3-indazolinone (compare Tables 23 and 24). At 600° LXXXIIa is recovered virtually unchanged, whereas the dimethyl compound LXXXV suffers significant loss of the 1-methyl

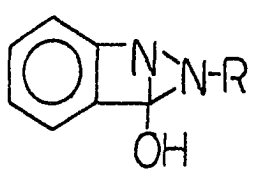
group. A possible explanation of this contrast in behavior is the aromatic nature of the heterocyclic ring in LXXXIIa, which exists predominantly in the enol tautomeric form (127). Delocalization into the benzene ring of the free-radical formed by homolytic scission of the 1-methyl-N bond requires rehybridation of the nitrogen electrons which necessarily destroys aromaticity in the heterocyclic ring of compound LXXXIIa. However, since the heterocyclic ring of the dimethyl derivative LXXXV is not aromatic, stabilization of a free-radical generated at the 1-position in an analogous manner should be favorable. Alternatively, the difference in thermal stabilities of these two compounds may be steric in nature, and the facile loss of a methyl group from LXXXV would be expected to relieve steric interactions of the adjacent methyl groups.

The mechanism of the thermal isomerization of 3-indazolinone (LXXX) to 2-benzimidazolinone (LXXXI) has not been studied in detail. In view of the known (84) Curtius reaction of 2-aminobenzoyl azide whose product is LXXXI, a plausible intermediate in the transformation LXXX → LXXXI is 2-aminophenyl isocyanate (XC). However, such an intermediate must be excluded on the basis of the facile thermally

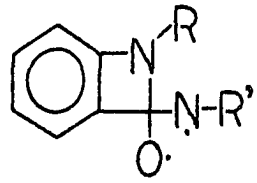


XC

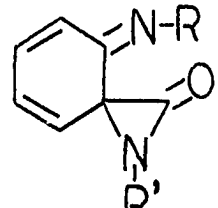
induced rearrangement of 2-methyl-3-indazolinone (LXXXIIb). Therefore, an alternate mechanism involving an intermediate, such as XCIa, b, or c, may be operating.



XCIa



XCIb

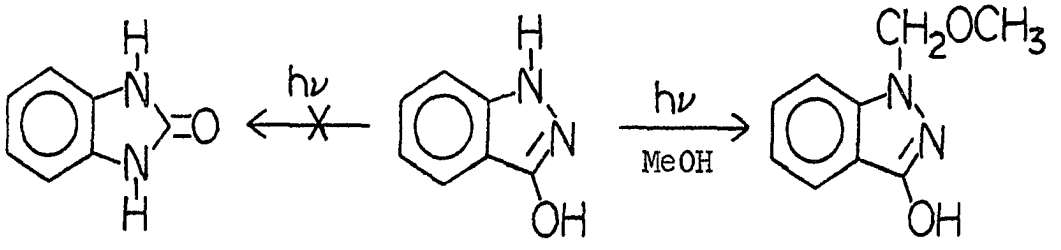


XCIc

The tricyclic structure XCIa is analogous to the intermediate proposed by Schmid et al. (58) in the photoisomerization of indazole. On first consideration, XCIa indeed appears attractive for it readily accommodates the rearrangements of LXXX to LXXXI and LXXXIIb to LXXXIII since it is merely a valence isomer of 3-indazolinone and 2-substituted 3-indazolinones. The loss of the 1-methyl group from LXXXIIa and LXXXV with subsequent rearrangement also seems to indicate the intermediacy of XCIa in these processes. However, among the pyrolysis products of 1-methyl- and 1,2-dimethyl-3-indazolinone are trace amounts of 1-methyl- and 1,3-dimethyl-2-benzimidazolinone, respectively, whose formation cannot be explained by XCIa. Therefore, a related diradical species, such as XCIb, spiro-α-lactam XCIc, or some other intermediate may be involved in this isomerization. Similar conclusions were reached with respect to the mechanism of the thermal conversion of 3-

hydroxy-1,2-benzisoxazole (XXXI) to 2-benzoxazolinone (XXX) (see above).

3-indazolinone (LXXX) is also considerably more reluctant than 3-hydroxy-1,2-benzisoxazole (XXXI) to undergo isomerization photochemically. Irradiation of LXXX under conditions similar to those used to effect photoisomerization of XXXI (see Table 15, above) to 2-benzoxazolinone (XXX) results only in a rather low recovery of unchanged starting material (Table 24). Examination of the nmr spectra



LXXXI LXXX XCII

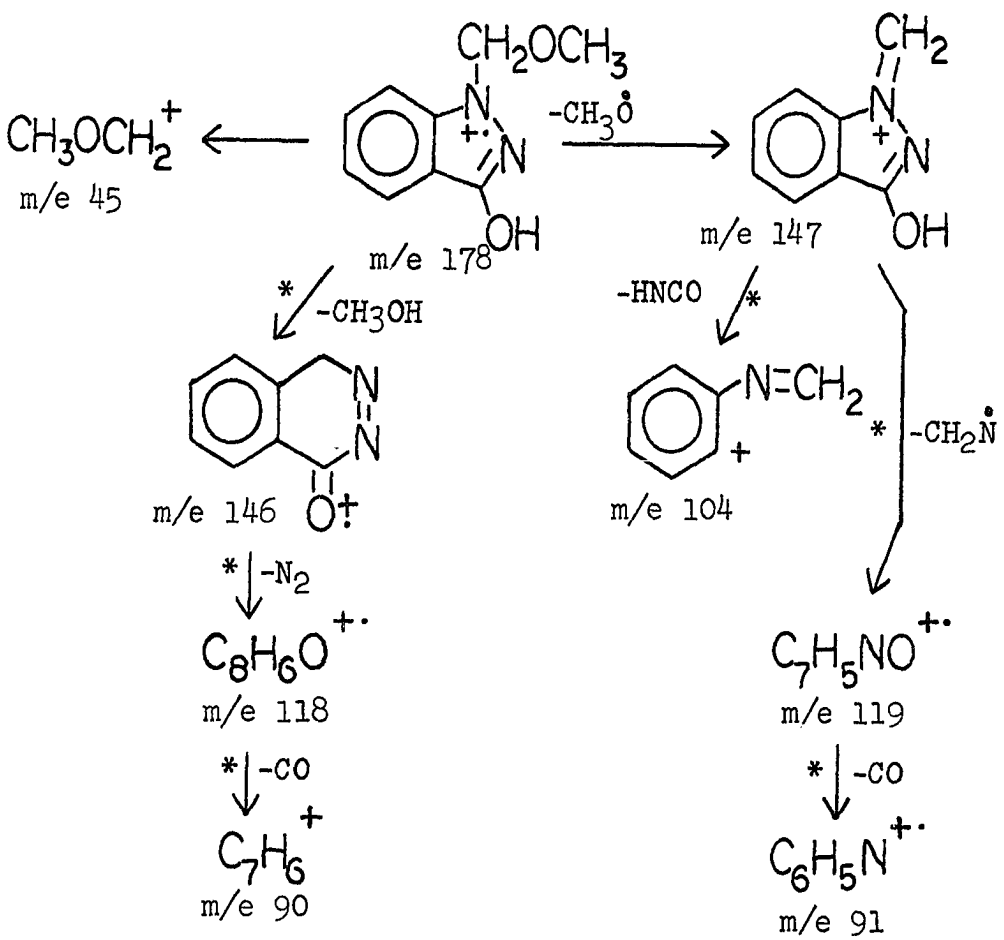
of the crude photolysates gave no evidence for formation of 2-benzimidazolinone (LXXXI). However, a substitution product of LXXX was isolated when the photolysis was conducted in absolute methanol using Corex or Vycor optics. The structure of this photoproduct was determined to be 1-methoxymethyl-3-indazolinone (XCII) from its nmr and infrared spectra. Its mass spectrum was also very definitive showing a molecular ion at m/e 178 and a base peak at m/e 45 which corresponds to $CH_3OCH_2^+$. The major fragmentation pathways of XCII are depicted in Scheme 28

Table 24. Photolysis of 3-indazolinone (LXXX)

Filter	Solvent	Time (min)	% yield[a] LXXX	XCII
Pyrex	Acetone	420	35	-
Corex	MeOH	480	41	14
Vycor	MeOH	600	31	8

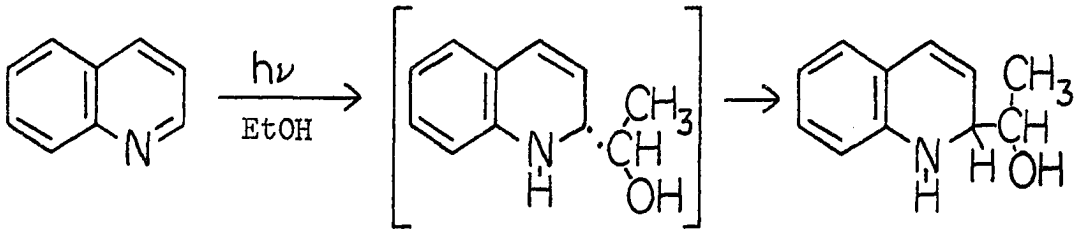
[a]Isolated by column chromatography (silica gel).

Scheme 28



with possible structures of the fragment ions.

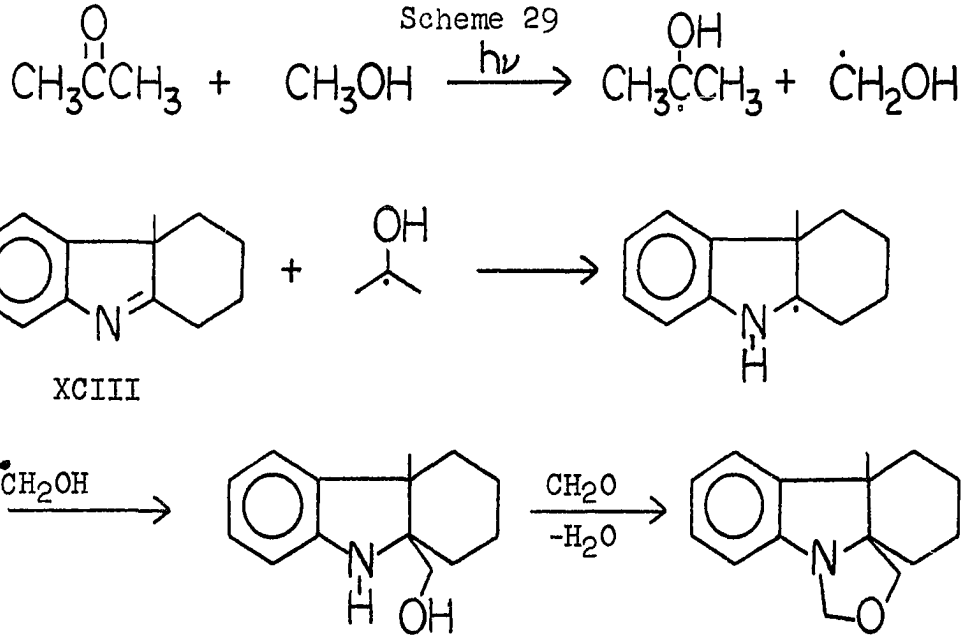
Photoalkylation reactions have been observed to occur upon photolysis of a number of nitrogen containing heterocyclic compounds (50). In most cases this reaction involves addition of a solvent molecule across a C=N bond as exemplified by the recently reported photolysis of quinoline in ethanol (128). A similar mechanism has been proposed to explain the photoreduction of aryl N-alkylimines



although ketyl radicals instead of the excited states of the imines have been shown to be involved (129). Thus, the photoalkylation of the indolene XCIII in methanol-acetone solution may be explained by the mechanism shown in Scheme 29. The last step involves a Mannich condensation of formaldehyde produced by photolysis of methanol (129).

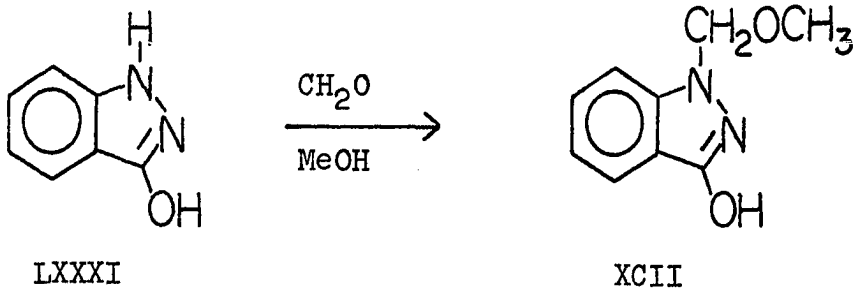
The formation of 1-methoxymethyl-3-indazolinone (XCII) in the photochemical reaction of LXXX in methanol may be rationalized by a similar Mannich condensation. This was validated by reacting 3-indazolinone (LXXX) with formaldehyde in the presence of methanol at room temperature in the dark. The spectral properties of the product obtained were

Scheme 29



XCIII

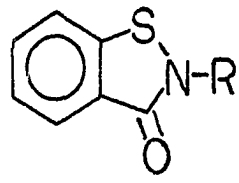
identical to those of the photoproduct.



LXXXI XCII

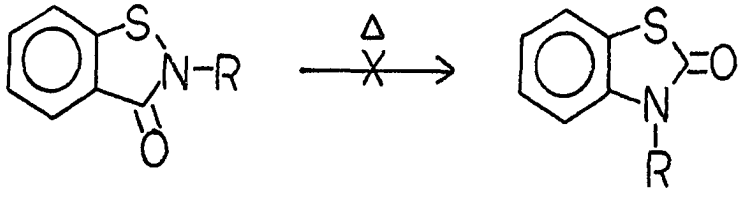
1,2-Benzisothiazolin-3-ones

Replacement of the ring oxygen atom of 3-hydroxy-1,2-benzisoxazole (XXXXI) with sulfur produces 1,2-benzisothiazolin-3-one (XCIVa). Like 3-indazolinone (LXXX), the benzisothiazolinone heterocyclic ring system is thermally much more stable than XXXI. For example, pyrolysis of XCIVa or XCIVb in the gas-phase at temperatures of 500-700°



XCIVa, R=H
b, R=Me

results in almost quantitative recovery of starting material. At temperatures exceeding 700°, considerable decomposition to unidentifiable material occurs, but isomerization to XCVa or XCVb is not observed. This is somewhat surprising in

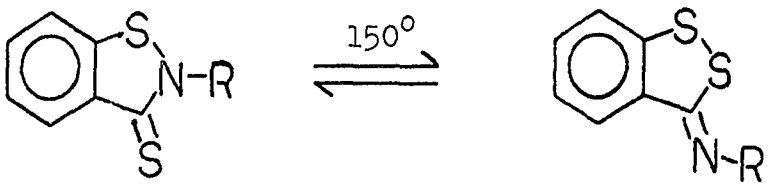


XCIVa, b

XCVa, R=H
b, R=Me

view of the reported equilibria of 1,2-benzisothiazolin-3-thiones (XCVIa) with 3-imino-3H-1,2-benzodithiols (XCVIb) at 150° (130).

It was of interest to study the photochemistry of XCIVa since it has been reported that benzisothiazole does not photoisomerize (67). Irradiation of XCIVa and XCIVb with Vycor filtered ultraviolet light for 9 hours results in the



XCVIa XCVIb

formation of low yields of the corresponding rearrangement products XCVa and XCVb (Table 25). In addition, a significant amount of photo-oxygenation product is obtained in both photolysis reactions. The structures of these products were shown to be XCVIa and XCVIb from spectroscopic analysis and by independent synthesis.

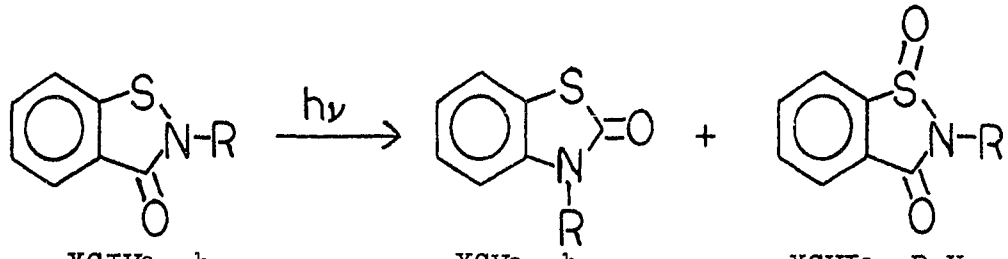
Table 25. Photolysis of 1,2-benzisothiazolin-3-one (XCIVa) and 2-methyl-1,2-benzisothiazolin-3-one (XCIVb)

R	Filter	Solvent	Time (min)	% yield[a] XCIV	XCV	XCVI
H	Vycor	Ether	540	46	9	18
Me	Vycor	Ether	540	70[b]	4	5[b]
Me	Pyrex	Acetone	600	70	4	-

[a]Isolated by column chromatography (silica gel).

[b]Ratio determined by nmr spectroscopy.

The formation of XCVI presumably results from insufficient degassing of the photolysis solutions prior to



XCIVa, b XCVa, b XCVIa, R=H
b, R=Me

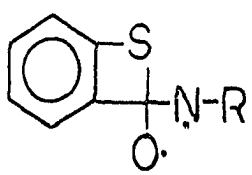
irradiation. Several examples of related photo-oxygenation reactions have been reported. For example, sulfides have been found to yield sulfoxides which, in turn, produce sulfones upon irradiation (131).

Furthermore, oxidation of the sulfur atom of 1,2-benzisothiazolin-3-ones is known to be a rather facile process. Reaction of these compounds with hydrogen peroxide produces the corresponding saccharin derivatives (132). Formation of the sulfoxide is readily achieved by reaction of 1,2-benzisothiazolin-3-ones with nitric acid at room temperature for 30 minutes (133) and is the synthetic procedure used in the preparation of compounds XCVIa and XCVIb.

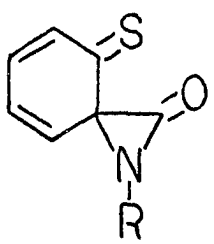
Photolysis of XCIVb in acetone under triplet sensitization conditions also results in a low conversion to the rearrangement product. This suggests that a triplet mechanism is responsible for this ring transposition although more extensive sensitization studies are necessary for verification.

The mechanism of this photoisomerization may be similar

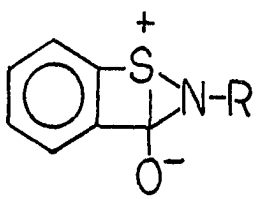
to that proposed for 3-hydroxy-1,2-benzisoxazole (see Scheme 16, pathway C) involving diradical species XCVIIa. Alternatively, a ring-contraction ring-expansion sequence (intermediate XCVIIb) (17) or a mechanism such as that proposed to explain the photorearrangement of isothiazoles (XCVIIc) , (62) cannot be excluded.



XCVIIa



XCVIIb



XCVIIc

The stability of 1,2-benzisothiazolin-3-one is also reflected by its mass spectrum (Figure 21). The base peak of the spectrum is the molecular ion which fragments with the loss of CO to give $(C_6H_5NS)^{+\cdot}$ at m/e 123. This ion then expels H· (m/e 122) or HCN giving rise to the most intense fragment ion at m/e 96 $(C_5H_4S)^{+\cdot}$. This species may also be formed directly from the molecular ion as indicated by a metastable at m/e 61.0. Decomposition of m/e 96 occurs with the expulsion of acetylene producing m/e 70 from which H· is lost to give C_3HS^+. Alternate fragmentation pathways available to ionized XCIVa are the elimination of HNCO to give $(C_6H_4S)^{+\cdot}$ at m/e 108, and the loss of ṄS yielding $(C_7H_5O)^+$ (m/e 105), which is analogous to the $(M-HNO)^{+\cdot}$ species in the spectrum of 3-hydroxy-1,2-

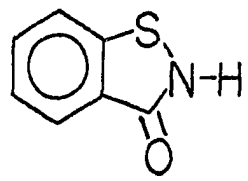


Figure 21. Mass spectrum of 1,2-benzisothiazolin-3-one (XCIVa)

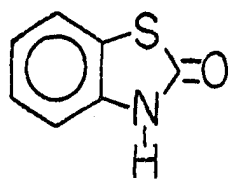
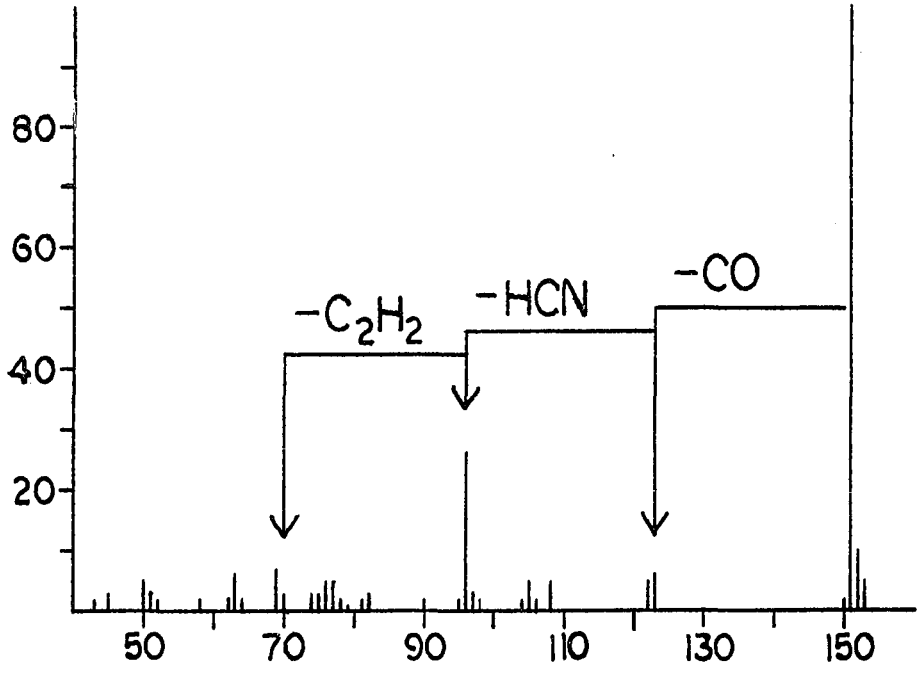
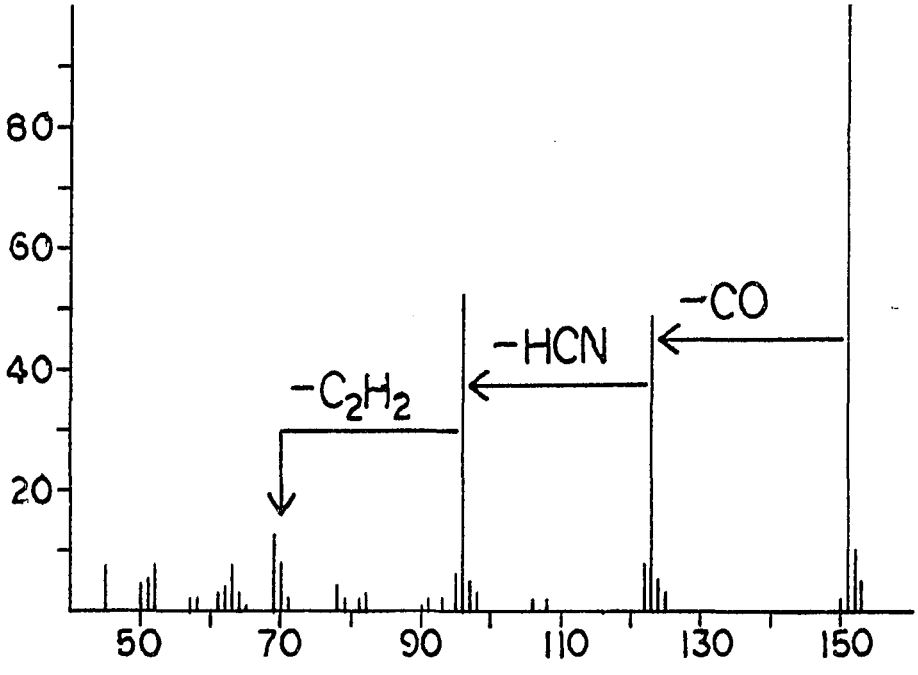


Figure 22. Mass spectrum of 2-benzothiazolinone (XCVa)


80
60
40
20
$-C_2H_2$
-HCN
-CO
50
70
90
110
130
150


80
60
40
20
-CO
-HCN
$-C_2H_2$
50
70
90
110
130
150

benzisoxazole (Figure 6). Appropriate metastable ions for the latter two processes are lacking in the spectrum, but accurate mass measurements substantiate the composition of the ions produced.

The fragmentation of ionized 2-benzothiazolinone (XCVa) (32) occurs along the same pathways (Figure 22). Indeed, the spectra of XCIVa and XCVa are qualitatively similar, except for the loss of ṄS which does not occur in the spectrum of the latter compound. This similarity in breakdown pattern suggests that a common ionic species is being formed prior to fragmentation. With analogy to the photochemical studies of these compounds, a plausible explanation is the occurrence of a rearrangement of XCIVa to XCVa upon electron impact. However, since the loss of COS from $(XCVa)^{+\cdot}$ is essentially nonexistent, there is no easy method to substantiate such an isomerization as is available in the case of 3-hydroxy-1,2-benzisoxazole (see Scheme 4, above).

The fragmentation of 2-methyl-1,2-benzisothiazolin-3-one (XCIVb) is reminiscent of that observed in the analogous system, 2-methyl-1,2-benzisoxazolin-3-one (Cf. Figures 9 and 23). The molecular ion decomposes <u>via</u> two major pathways as substantiated by metastable ions and accurate mass measurements. These are: (i) the loss of CH_2NH to afford $(C_7H_5SO)^{+\cdot}$ at m/e 137; and (ii) the expulsion of

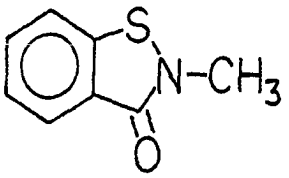


Figure 23. Mass spectrum of 2-methyl-1,2-benzisothiazolin-3-one (XCIVb)

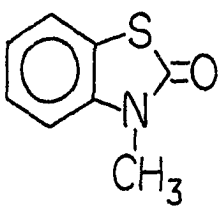
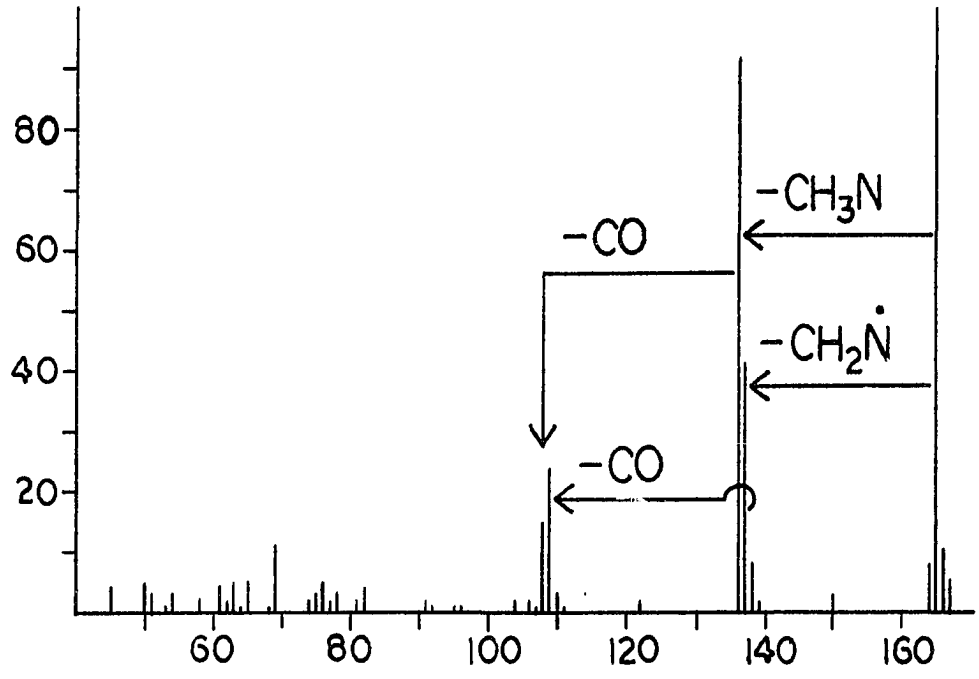
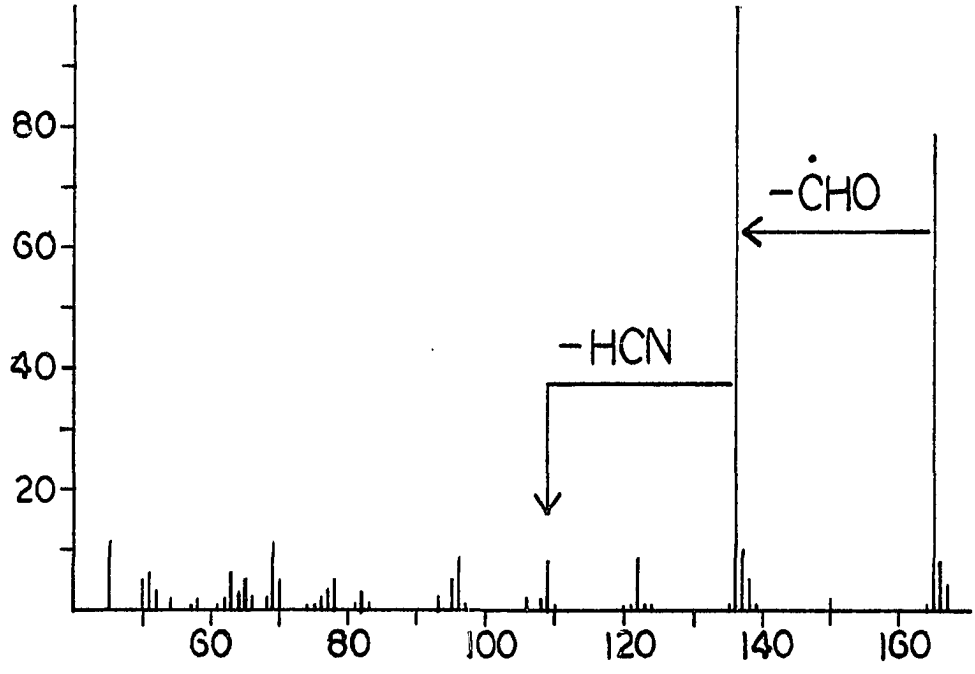


Figure 24. Mass spectrum of 3-methyl-2-benzothiazolinone (XCVb)


80
60
40
20
-CO
-CH3N
-CH2N
-CO
60
80
100
120
140
160

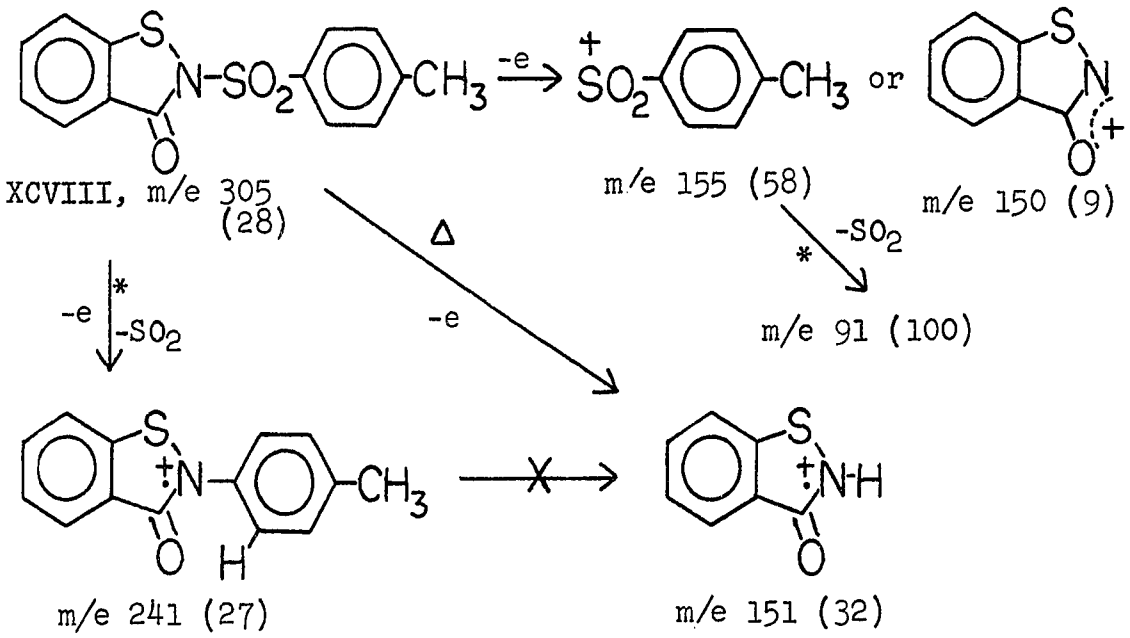

80
60
40
20
-HCN
-CHO
60
80
100
120
140
160

$CH_2\dot{N}$ giving rise to the ion at m/e 136 $(C_7H_4SO)^+$. Both daughter ions undergo a subsequent loss of CO. Furthermore, it should be noted that eliminations of CO and $\dot{C}HO$ from the molecular ion do not occur.

It is interesting to compare this spectrum with that of 3-methyl-2-benzothiazolinone (Figure 24). Again the loss of 29 mass units is the predominant reaction, but the subsequent metastable fragmentation of this m/e 136 ion involves formation of m/e 109, presumably by expulsion of HCN. This indicates that the m/e 136 species corresponds to $(M-\dot{C}HO)^+$ which is analogous to the breakdown pattern of 3-methyl-2-benzoxazolinone (see Figure 8, above). Appropriate metastable ions also support the stepwise loss of H· and CO from the molecular ion. In general, the fragmentation pathways of XCIVb and XCVb are completely different, and rearrangement of $(XCIVb)^{+\cdot}$ to $(XCVb)^{+\cdot}$ is not important although the corresponding photoisomerization occurs.

An interesting fragmentation is observed in the mass spectrum of 2-p-toluenesulfonyl-1,2-benzisothiazolin-3-one (XCVIII). The molecular ion of this compound decomposes with the loss of SO_2 as shown in Scheme 30. The mechanism of analogous SO_2 eliminations from sulfonylureas has been discussed (16, p. 563). The spectrum of XCVIII is dominated by the formation of tosyl cation (m/e 155) from which the base peak at m/e 91 (tropylium ion) originates. Also present

Scheme 30

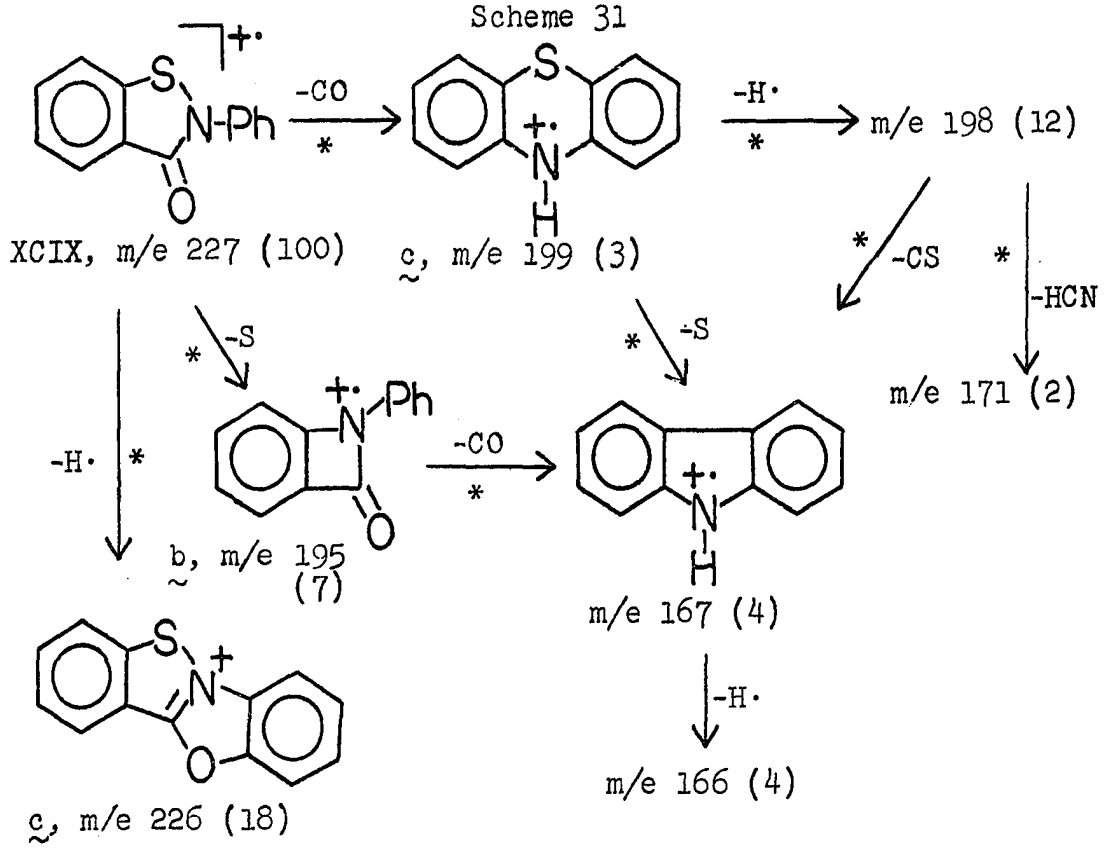


is an ion at m/e 151 corresponding to the molecular ion of 1,2-benzisothiazolinone (XCIVa). Although formation of this ion could conceivably occur by a McLafferty rearrangement process involving an ortho hydrogen of the m/e 241 species, a more reasonable explanation is that m/e 151 is a thermal artifact since considerable heat is necessary to volatilize the sample in the mass spectrometer. Evidence for this is shown by the increase in relative intensity of this ion at low electron voltages. Furthermore, XCIVa is formed quantitatively in the gas-phase pyrolysis of XCVIII (see Experimental section).

Additional support against the generation of m/e 151 from m/e 241 in Scheme 30 is furnished by the mass spectrum of 2-phenyl-1,2-benzisothiazolin-3-one (XCIX) in which the

m/e 151 ion is absent. The principal decomposition modes of the molecular ion of XCIX as supported by metastable ions(*) are depicted in Scheme 31. Possible structures are shown in order to rationalize the fragmentations observed. The low relative intensities of the fragment ions again reflect the general stability of the molecular ion.

Scheme 31



The most intense fragment ion is $(M-H\cdot)^+$ for which structure a is postulated due to the potential stability of such an aromatic species. A similar structure has been proposed for the $(M-1)^+$ ion of N-phenyl dithiophthalimide (86). The molecular ion also loses CO giving rise to a

species at m/e 199 whose structure may be related to that of ionized phenothiazine (c). Indeed, its fragmentation which involves expulsion of sulfur atom and elimination of H· followed by CS or HCN is completely analogous to that reported for phenothiazine (134). Alternatively, $(XCIX)^{+\cdot}$ suffers loss of a sulfur atom producing m/e 195 represented by structure b analogous to the β-lactam structures postulated for the $(M-N_2)^{+\cdot}$ ions of benzotriazinones (135). Decomposition of b occurs with loss of CO to give m/e 167.

In order to investigate possible multiple hydrogen rearrangements similar to those observed in the spectra of the butyl derivatives of 3-hydroxy-1,2-benzisoxazole (see Schemes 11 and 12 and Figure 12, above), the mass spectra of 2-isopropyl- and 2-t-butyl-1,2-benzisothiazolin-3-one were studied.

2-isopropyl-1,2-benzisothiazolin-3-one (XCX) follows three major decomposition pathways upon electron impact (Figure 25). The McLafferty rearrangement with expulsion of propene produces the most intense ion at m/e 151. Subsequent decomposition of this species is the same as that of ionized 1,2-benzisothiazolin-3-one (Figure 21). A second mode of fragmentation involves the formation of ions at m/e 136 and m/e 137 by elimination of C_3H_7N and $C_3H_6\dot{N}$, respectively. This process is also very important in the spectrum of the corresponding N-methyl derivative

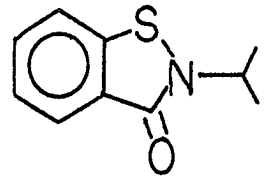


Figure 25. Mass spectrum of 2-isopropyl-1,2-benzisothiazolin-3-one (XCX)

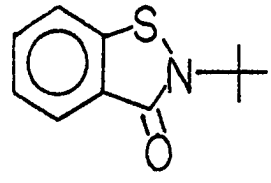
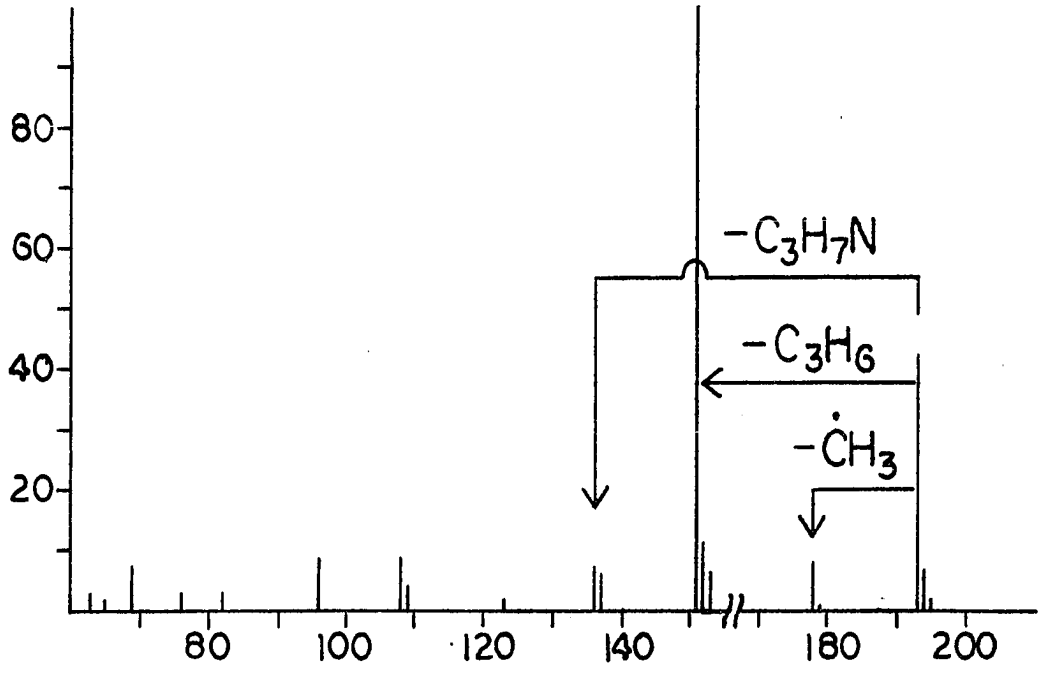
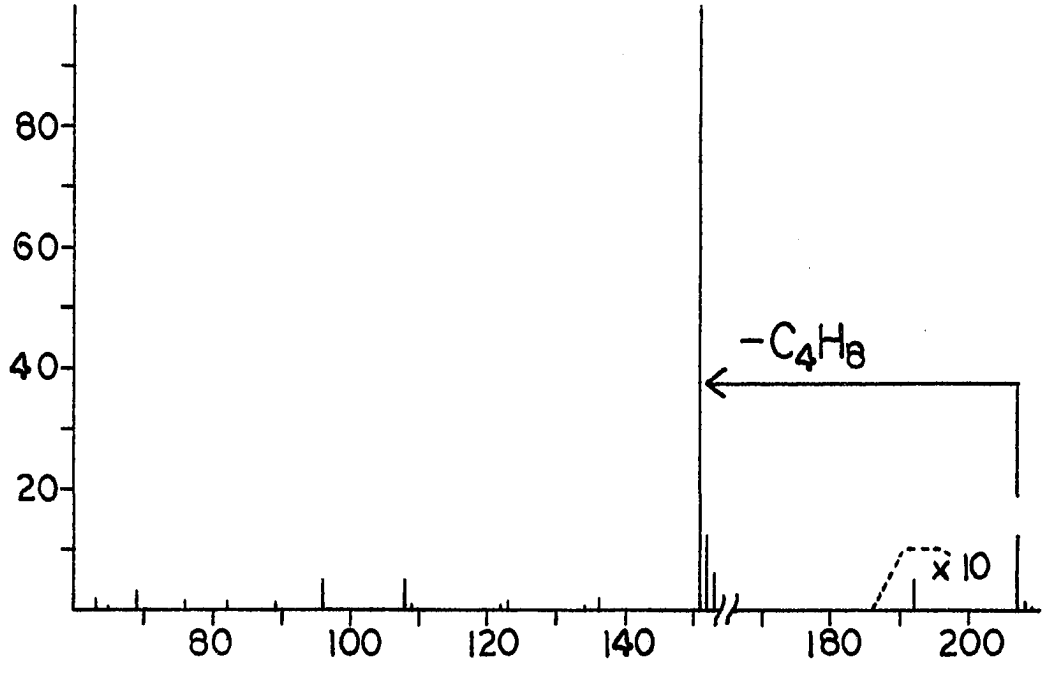


Figure 26. Mass spectrum of 2-t-butyl-1,2-benzisothiazolin-3-one (XCXI)


80
60
40
20
$-C_3H_7N$
$-C_3H_6$
$-\dot{C}H_3$
80
100
120
140
180
200


80
60
40
20
$-C_4H_8$
x 10
80
100
120
140
180
200

(Figure 23). Finally, α-cleavage with the loss of methyl radical is responsible for m/e 178 whose decomposition occurs with further loss of C_2H_3N (m/e 137).

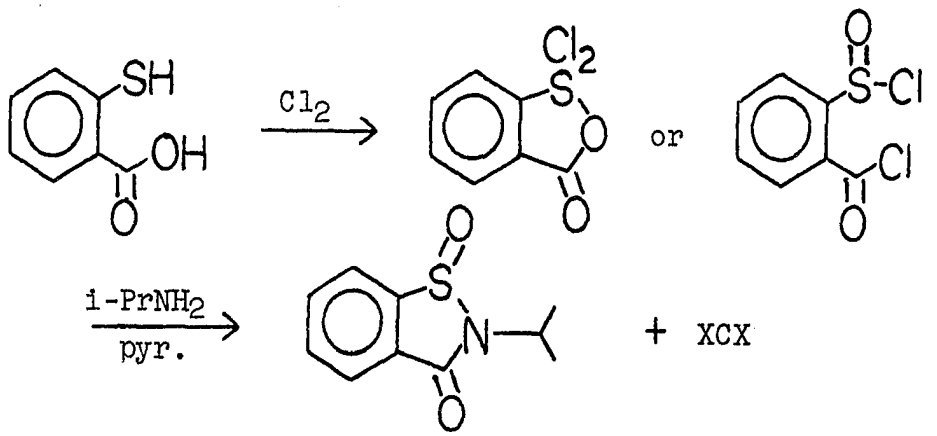
Completely analogous fragmentation is observed in the mass spectrum of 2-t-butyl-1,2-benzisothiazolin-3-one (XCXI) as shown in Figure 26. However, it is interesting to note that double hydrogen rearrangements do not occur in either spectrum.

Such rearrangements have been reported to occur upon electron impact of some saccharin derivatives (97). Since analogous studies of the corresponding S-oxide derivatives have not been conducted, it was of interest to synthesize some compounds in this family and compare their mass spectral behavior with that of 1,2-benzisothiazolin-3-ones and 1,2-benzisothiazolin-3-one-S-dioxides.

2-isopropyl-1,2-benzisothiazolin-3-one-S-oxide (XCXII) was prepared by reacting o-mercaptobenzoic acid with chlorine gas (132, p. 276) and treating the product formed with isopropyl amine in the presence of pyridine (Scheme 32). In addition to XCXII, a significant amount of XCX was also obtained. This mixture could be separated with some difficulty by preparative tlc (see Experimental section).

The synthesis of 2-t-butyl-1,2-benzisothiazolin-3-one-S-oxide (XCXIII) was achieved accidentally in an attempted preparation of XCXI (Scheme 33). The formation of XCXIII

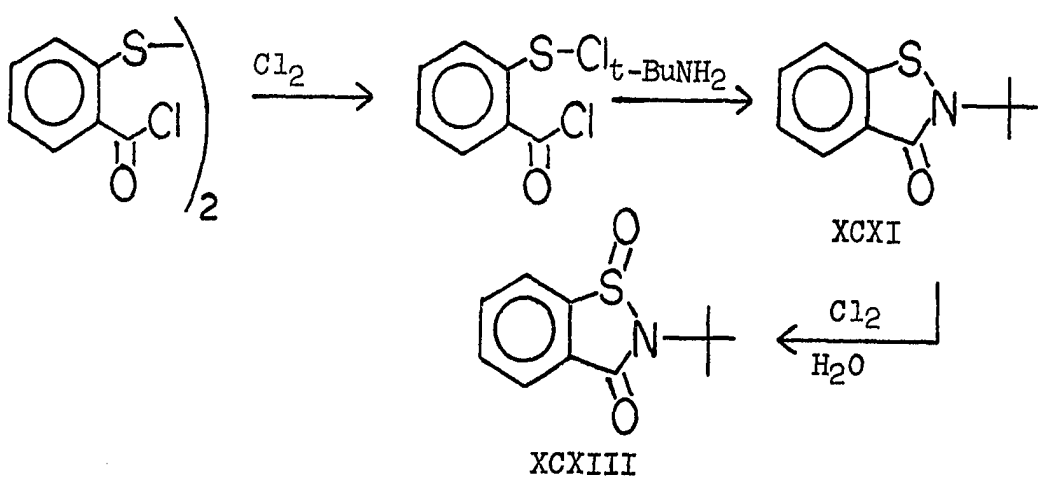
Scheme 32



XCXII

presumably resulted from inadequate removal of excess chlorine from the reaction mixture prior to addition of t-butyl amine. In the presence of trace amounts of water, oxidation of XCXI to XCXIII may occur. A similar reaction has recently been reported (133). Indeed, after degassing the reaction mixture with a stream of dry nitrogen for several hours, reaction with the amine produced only XCXI.

Scheme 33



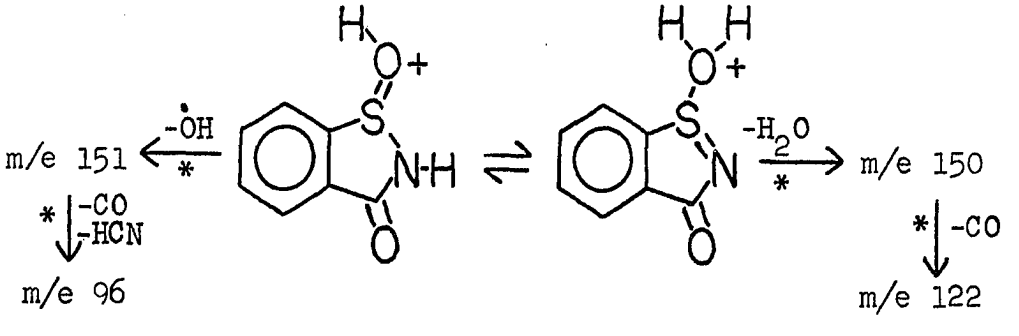
XCXI

XCXIII

The mass spectrum of the isopropyl compound XCXII is, in general, analogous to that of XCX (Cf. Figures 25 and 27). The McLafferty rearrangement (m/e 167), the losses of C_3H_7N and $C_3H_6\dot{N}$ (m/e 152 and m/e 153), and the α-cleavage process (m/e 194) appear in both spectra. However, a double hydrogen rearrangement does occur in the spectrum of the S-oxide derivative XCXII to the extent of 3% (m/e 168).

The m/e 168 species accounts for the base peak in the spectrum of 2-t-butyl-1,2-benzisothiazolin-3-one-S-oxide (Figure 28). Evidence supporting the transfer of hydrogen to the sulfoxide oxygen is furnished by the absence of such a double hydrogen rearrangement in the spectrum of XCXI (Figure 26) and by the subsequent decomposition of the m/e 168 ion (Scheme 34). This ion undergoes loss of ·OH to give m/e 151 $(C_7H_5NOS)^{+\cdot}$, which is also formed from the molecular ion directly as indicated by metastable ions. Fragmentation of m/e 151 occurs with the loss of CO and HCN (m/e 96) in agreement with a structure similar to that of ionized 1,2-

Scheme 34



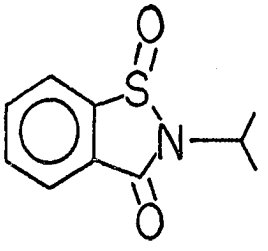


Figure 27. Mass spectrum of 2-isopropyl-1,2-benzisothiazolin-3-one-S-oxide (XCXII)

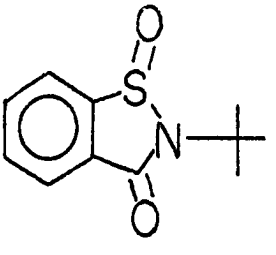
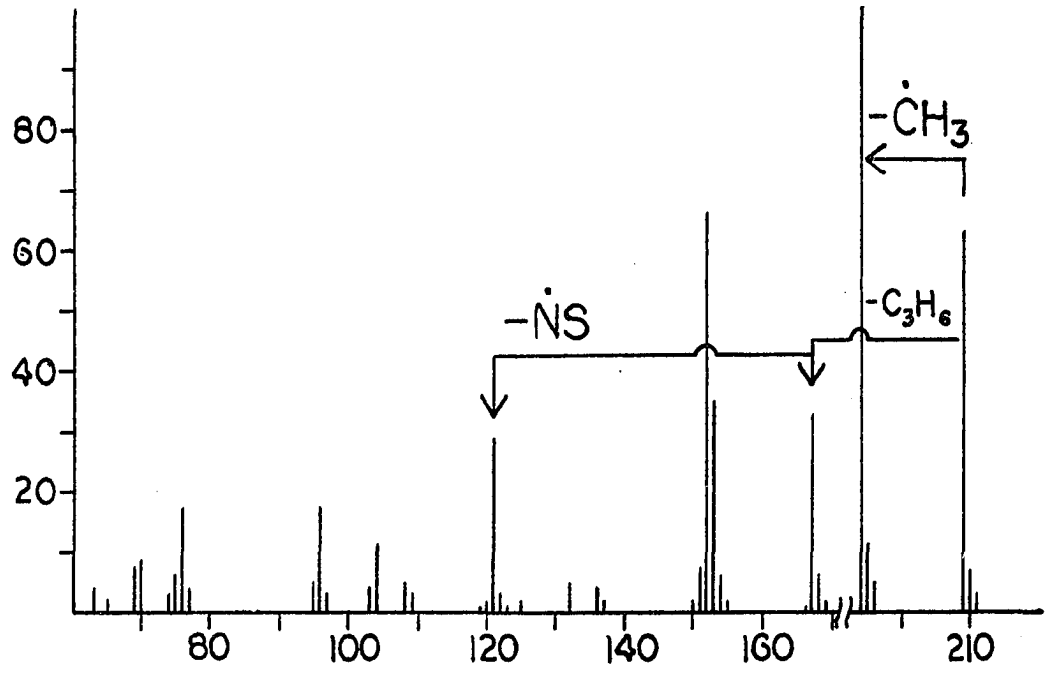
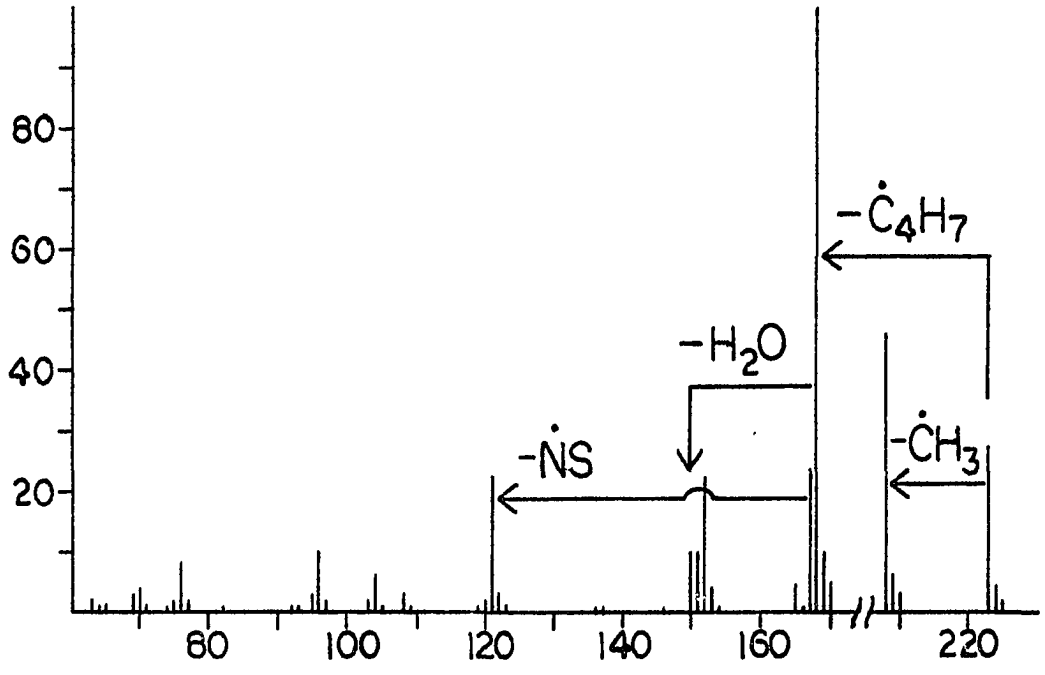


Figure 28. Mass spectrum of 2-t-butyl-1,2-benzisothiazolin-3-one-S-oxide (XCXIII)

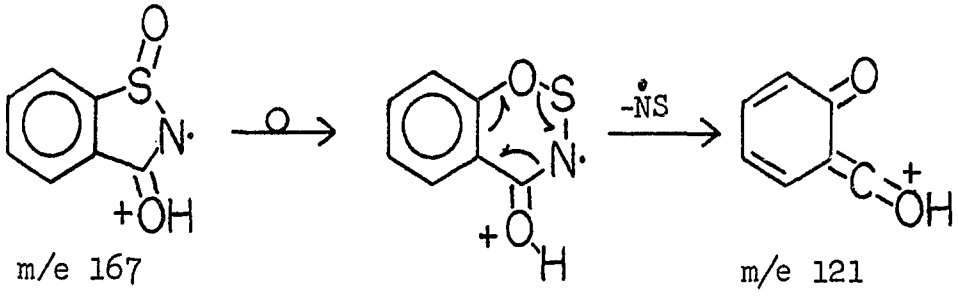

80
60
40
20
-ĊH3
-ṄS
-C3H6
80
100
120
140
160
210


80
60
40
20
-Ċ4H7
-H2O
-ṄS
-ĊH3
60
100
120
140
160
220

benzisothiazolin-3-one (Cf. Figure 21). The m/e 168 ion also eliminates a molecule of water to give m/e 150 $(C_7H_4NOS)^+$ which decomposes further with the loss of CO.

The ion formed by a single hydrogen transfer (m/e 167) is much less prominent, but its fragmentation is particularly interesting. A metastable ion appears at m/e 87.7 corresponding to the transition 167 → 121, and accurate mass measurements confirm the elimination of ṄS in this process. A possible mechanism for this fragmentation reaction is shown in Scheme 35 and involves a 1,2-aryl migration which is common in the spectra of aromatic sulfoxides (16, p. 554).

Scheme 35



m/e 167 m/e 121

A similar process was also observed in the spectrum of unsubstituted saccharin (97).

It was of interest to compare this fragmentation pathway with the mass spectrum of authentic 1,2-benzisothiazolin-3-one-S-oxide (Figure 29). Indeed, a prominent ion appears at m/e 121 which is formed by the metastable loss of ṄS from the molecular ion. This is further substantiated by the consecutive losses of two CO

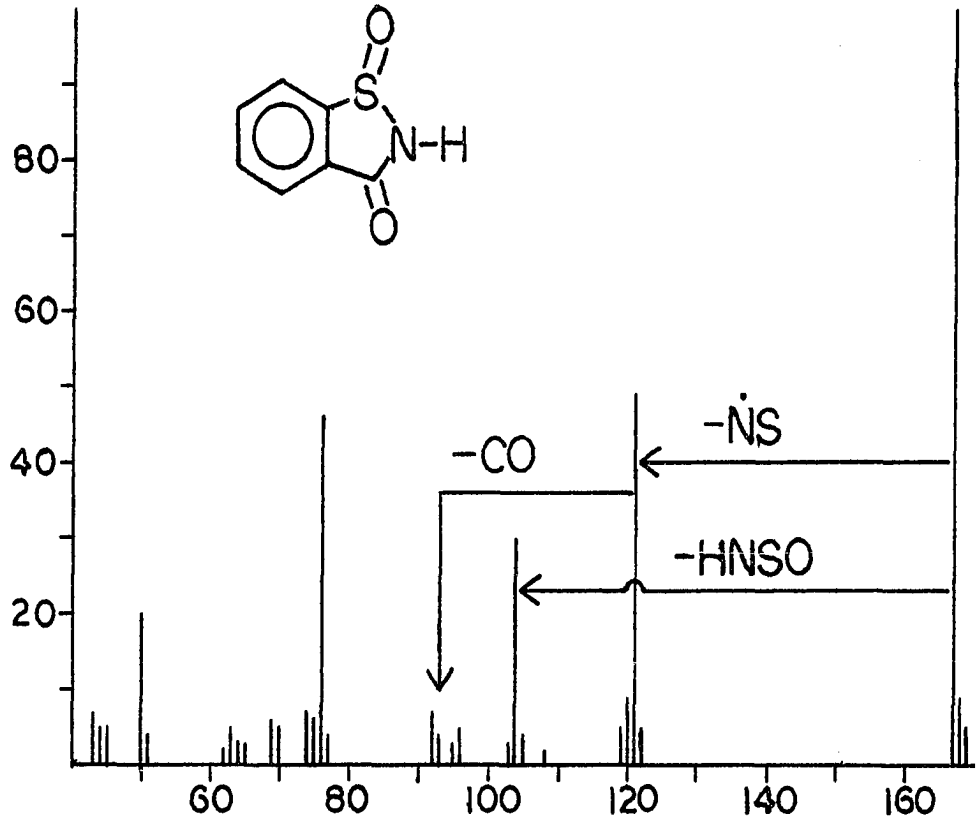


Figure 29. Mass spectrum of 1,2-benzisothiazolin-3-one-S-oxide (XCVIa)

molecules from m/e 121 in agreement with the mechanism shown in Scheme 35. Also important in the spectrum of XCVIa is the $(M-HNSO)^{+\cdot}$ ion at m/e 104. The corresponding ion resulting from loss of HNS in the spectrum of 1,2-benzisothiazolin-3-one (Figure 21) is almost nonexistent.

In summary, 1,2-benzisothiazolin-3-one (XCIVa) is much more stable than the corresponding 1,2-benzisoxazolin-3-one (or 3-hydroxy-1,2-benzisoxazole, XXXI) as shown by the general inertness of XCIVa at temperatures ranging from 500 to 700° and by the completely dominating molecular ion of XCIVa in its mass spectrum. The similarity in breakdown patterns of ionized XCIVa and 2-benzothiazolinone (XCVa) suggests that a common ionic species is produced upon electron impact, which may involve isomerization of $(XCIVa)^{+\cdot}$ to $(XCVa)^{+\cdot}$ with analogy to the observed photochemical isomerization. A similar rearrangement of ionized 3-indazolinone (LXXX) to the molecular ion of 2-benzimidazolinone (LXXXI) may also be involved to explain, in part, the fragmentation of $(LXXX)^{+\cdot}$, again analogous to the demonstrated thermal isomerization.

However, substitution of a methyl group on the nitrogen in compounds XXXI and XCIVa produces drastic changes in the mass spectral fragmentations of these systems. In both cases, loss of CH_2NH from the molecular ion occurs in preference to a heterocyclic ring transformation although

the related thermal and/or photochemical rearrangements persist. In view of this, caution must be exercised in making generalizations concerning electron impact induced processes based on correlations with thermal and photochemical reactions. However, such analogies may be extremely useful as a supplement to other established techniques (2).

EXPERIMENTAL

Instruments and Methods

All low resolution mass spectra were obtained on an Atlas MAT Model CH4 single focusing mass spectrometer at 70 electron volts using the direct inlet probe or vacuum lock system. An accelerating potential of 3 kilovolts and an ionizing current of 1-10 μA were employed. Liquid samples were adsorbed onto molecular sieves prior to insertion into the spectrometer source. High resolution mass spectrometric measurements were performed on an A.E.I. MS 902 double focusing instrument using the technique of peak matching.

Infrared (ir) spectra were obtained on a Perkin-Elmer Model 21 or a Beckman Model IR-12 spectrometer.

60 MHz nuclear magnetic resonance (nmr) spectra were taken on Varian Associates Model A-60 and Hitachi Perkin-Elmer Model R20-B spectrometers. The 100 MHz nmr spectra were recorded on Varian Associates Model HA-100 spectrometer. All chemical shifts are reported in parts per million (ppm), δ units, relative to tetramethylsilane as internal standard.

All melting points were determined with a Kofler (6886-A) Micro Hot Stage melting point apparatus. All melting points, boiling points, and pyrolysis temperatures are uncorrected and are reported in degrees Centigrade. All pressures are expressed in millimeters of mercury.

Vacuum pyrolysis of compounds XXIX-XXXIV, XXXVIa, XLII, and XLIVa was performed with a Pyrex ($\leq 500^{\circ}$) or Vycor ($\geq 500^{\circ}$) tube (17 x 2.5 cm) packed with either Pyrex or Vycor chips. The pyrolysis tube was heated with a tube furnace whose temperature was determined with an iron-constantan thermocouple connected to a potentiometer and located externally approximately midway of the tube. The remaining compounds studied were pyrolyzed with a Vycor tube (30 x 2.5 cm) filled with Vycor chips and heated with a Sola Basic Industries Linberg Hevi-Duty Model 55035-A tube furnace. Vacuum was furnished by a Consolidated Vacuum Corporation Type VMF oil diffusion pump backed by a Welch Duo-Seal vacuum pump. A hollowed aluminum rod (15 x 5 cm) wrapped with Glas-Col heating tape and equipped with a thermometer provided the heat necessary to sublime the samples into the furnace tube. The pyrolysis products were condensed in a U-tube cooled in liquid nitrogen and were washed from the trap with an appropriate organic solvent.

All photolysis experiments were performed using a 450 watt Hanovia lamp (No. 679A36) contained in a water-cooled quartz immersion well which was equipped with the stated filter. All solutions were degassed with nitrogen for ~ 20 minutes prior to irradiation. The photochemical reactions were monitored by tlc, and the products were isolated by the stated procedure.

All column chromatography work was conducted with silica gel (60-200 mesh) using ethyl acetate-Skelly B (petroleum ether, b.p 60-70°) as the eluent. The Skelly B was distilled once prior to use.

Microanalytical data were obtained from Chemalytics, Inc., Tempe, Arizona.

Syntheses

Preparation of salicylohydroxamic acid

A solution of 14 g of sodium hydroxide in 53 ml of water was added with stirring to 10.5 g of hydroxylamine hydrochloride in 110 ml of water in an atmosphere of argon. A solution of 15.2 g of methyl salicylate in 50 ml of dioxane was added slowly to the hydroxylamine which was then stirred at room temperature for 18 hr. The volume of the reaction mixture was halved by evaporation at reduced pressure. Addition of concentrated hydrochloric acid precipitated 11.5 g (76%) of the hydroxamic acid, m.p. 179° (Ethanol; Lit. 179°, decomp., 88).

Preparation of 3-(2-hydroxyphenyl)-Δ^2-1,4,2,-dioxazolin-5-one (XXIX)

A solution of 5 g of salicylohydroxamic acid in 50 ml of dry tetrahydrofuran was placed in a 3-necked 100 ml flask equipped with a condenser, gas-dispersion tube, and magnetic stirrer. The solution was heated to reflux, and phosgene gas was bubbled slowly into the stirred solution for 2.5 hr.

Stirring was continued for another 2 hr at room temperature after which the THF was evaporated in a fume hood at reduced pressure. Recrystallization of the residue from a hexane-ethyl acetate solution returned 5 g (85%) of XXIX, m.p. 118-119° (Lit. 120°, 80); nmr ($CDCl_3$): 6.80-7.70 δ (m); ir ($CHCl_3$): 3400 (O-H) and 1840-1870 cm^{-1} (d, C=O).

Preparation of 2-benzoxazolinone (XXX)

A mixture of 20.2 g of o-aminophenol and 25 g of urea was placed in a 250 ml three-necked flask equipped with a mechanical stirrer. The fused mixture was stirred 3 hr at 140° in an atmosphere of nitrogen. The dark product was washed with 50 ml of 1.5N HCl, decolorized with Norite, and recrystallized from ethyl acetate-hexane producing 5 g (20%); m.p. 143-144° (Lit. 141-142°, 136); nmr ($CDCl_3$): 7.12 (s, 4H) and ~ 10.0 δ (broad s, 1H); ir (KBr): 3250 (N-H) and 1740-1780 cm^{-1} (d, C=O).

250 mg of XXX in 25 ml of anhydrous ether was shaken with 10 ml of D_2O. Separation of the ether layer and evaporation produced XXX-N-d_1 (64% by mass spectroscopy).

Preparation of 3-hydroxy-1,2-benzisoxazole (XXXI)

Triethylamine (6.77 g) was added dropwise to a stirred solution of 4 g of XXIX in 20 ml of dioxane. The reaction mixture was cooled externally to maintain a temperature of ~ 20°. After addition of the triethylamine, the solution

was poured into 70 ml of water, neutralized with 2N HCl, and cooled to precipitate 2.5 g (83%) of XXXI, m.p. 144-5° (aq. methanol; Lit. 144°, 88); ir (KBr): 3000-2500 (O-H) and 1615 cm^{-1} (C=N); nmr ($CDCl_3$): 7.15-7.95 (m, 4H) and ~ 11.0 δ (s, 1H); uv (MeOH): 288.5 mμ (Log ε 3.53), 282 (3.50), 278 (3.50), sh 274 (3.39), and 236 (3.70).

Preparation of 3-(2-hydroxyphenyl)-Δ^2-1,4-2-dioxazolin-5-thione (XXXIIIa)

A stirred mixture of 3 g of salicylohydroxamic acid and 15 ml of thiophosgene was heated to reflux for 3 hr. The homogeneous solution obtained was allowed to cool to room temperature, and the excess thiophosgene was distilled at reduced pressure. Recrystallization of the residue from hexane produced 2.9 g (76%) of XXXIIIa, m.p. 90° (decomp.); nmr (CCl_4): 6.85-7.90 (m, 4H) and 9.5 δ (s, 1H); ir (CCl_4): 3400 (O-H) and 1294 cm^{-1} (C=S); Anal. Calcd. for $C_8H_5NO_3S$: 194.999; Found: 195.002.

Preparation of 4-(2-hydroxyphenyl)-Δ^3-1,2,5,3-thiadioxazolin-S-oxide (XXXIIIb)

A stirred mixture of 0.63 g of salicylohydroxamic acid and 10 ml of thionyl chloride was warmed on an oil bath at 30-35° for 2.5 hr (88). The excess thionyl chloride was then evaporated at reduced pressure, and the residue was recrystallized from a benzene-hexane solution yielding 0.42 g (51%), m.p. 50-2°; nmr (CCl_4): 6.72-7.90 (m, 4H)

and 8.11 δ (s, 1H); ir (CCl_4): 3350 (OH) and 1250-1260 cm^{-1} (S=O).

Preparation of salicyloylhyrazide

A stirred mixture of 15.2 g of methyl salicylate and 15.2 ml of hydrazine-hydrate was heated to reflux in an atmosphere of nitrogen for 15 min. Sufficient absolute ethanol was added through the condenser to produce a homogeneous solution which was heated to reflux for another 2 hr. The ethanol was evaporated at reduced pressure, and ~ 10 ml of water was added to the solution which upon cooling produced 6.3 g (42%) of product, m.p. 152-3° (aq. ethanol; Lit. 144-5°, 137).

Preparation of salicyloylazide (XXXIV)

A solution of 1.54 g of sodium nitrite in 10 ml of water was added dropwise to a stirred mixture of 3.4 g of salicyloylhydrazide in 5.5 ml of conc. HCl and 55 ml of water. The reaction mixture was cooled in an ice bath and stirred at 0-5° for 45 min. The precipitated product was filtered and recrystallized from an aqueous ethanol-ether solution yielding 2 g (55%), m.p. 26° (Lit. 27°, 138); ir ($CHCl_3$): 3200 (O-H) and 2180-2140 cm^{-1} (d, N_3).

Preparation of 2-hydroxylaminobenzoic acid

To a 500 ml three-necked flask equipped with a mechanical stirrer was added 16.7 g of 2-nitrobenzoic acid, 15.7 g of

$Ba(OH)_2$, and sufficient water to produce a 150 ml solution. The solution was cooled to ~ 10° in an atmosphere of argon and 7.5 g of ammonium chloride was added. This was followed by the addition of 15 g of zinc dust over a one-half hr period with strong mechanical stirring maintaining a temperature of ~ 15°. Stirring was continued for approximately 15 min after which the mixture was filtered and the residue washed with 500 ml of warm water. The filtrate was poured into a beaker containing ice. Neutralization of this cooled solution with 6N HCl produced a light yellow precipitate which was collected and washed with cold water yielding 7 g (46%); m.p. 130° (Lit. 142.5°, 139).

Preparation of 2,1-benzisoxazolin-3-one (XXXV)

2-hydroxylaminobenzoic acid (1.5 g) was added at once to 20 ml of boiling 2N H_2SO_4. The solution was heated for 40 sec and then quickly cooled in an ice bath. The light yellow precipitate which formed was collected, washed with cold water, and dried under high vacuum producing 0.5 g (38%). Recrystallization from aqueous ethanol and sublimation gave pure XXXV, m.p. 111-113°, decomp., (Lit. 112°, 139); ir (KBr): 3150 (N-H) and 1750-1725 cm^{-1} (d, C=O).

Preparation of 3-phenyl-Δ^2-1,4,2-dioxazolin-5-one (XXXVIa)

Commercial (Aldrich) benzohydroxamic acid was recrystallized from ethanol, m.p. 133-4°. A solution of 3 g of

benzohydroxamic acid in 50 ml of THF was reacted with phosgene as described in the preparation of XXIX yielding 3 g (86%) of XXXVIa, m.p. 61-2° (hexane; Lit. 61-2°, 80); nmr (CCl_4): 7.35-7.96 δ (m); ir (CCl_4): 1865-1836 cm^{-1} (d, C=O).

Preparation of 3-phenyl-Δ^2-1,4,2-dioxazolin-5-thione (XXXVIb)

This compound was prepared from 3 g of benzohydroxamic acid and thiophosgene by a procedure analogous to that described for XXXIIIa yielding 3.2 g (82%) of XXXVIb, m.p. 52-3° (hexane; Lit. 49-50°, 80); nmr (CCl_4): 7.32-8.02 δ (m); ir (CCl_4): 1313-1290 cm^{-1} (d, C=S).

Preparation of 4-phenyl-Δ^3-1,2,5,3-thiadioxazolin-S-oxide (XXXVIc)

Reaction of 7.5 g of benzohydroxamic acid with thionyl chloride as described for the preparation of XXXIIIb produced 9.7 g (83%) of XXXVIc, m.p. 33-34° (hexane-benzene; Lit. 35°, 80); nmr (CCl_4): 7.16-7.95 δ (m): ir (CCl_4): 1250 cm^{-1} (S=O).

Preparation of benzoyl azide (XXXVII)

A cold solution of 3.7 g of sodium azide in 10 ml of water was added to a solution of 7.0 g of benzoyl chloride in 12.5 ml of reagent-grade acetone at 0 °C. The mixture was stirred at 0° for 30 min and then was poured into a separatory funnel. The acetone layer (top) was poured over crushed ice, where upon the azide crystallized. Recrystallization from aqueous acetone afforded 6.6 g (90%), m.p. 30-1°

(Lit. 32°, 140); ir ($CHCl_3$): 2180-2133 (d, N_3) and 1696 cm^{-1} (C=O); nmr (CCl_4): 7.13-7.66 (m, 3H) and 7.73-8.06 δ (m, 2H).

Preparation of 2-methyl-1,2-benzisoxazolin-3-one (XLII) and 3-methoxy-1,2-benzisoxazole (XLIVa)

A solution of 8.0 g of XXXI in 60 ml of reagent-grade acetone containing 8.0 g of anhydrous, granular potassium carbonate and 10 g of methyl iodide was warmed on an oil bath at 45-50° for 20 hr (88). The insoluble material was removed by filtration, and the filtrate was evaporated at reduced pressure. A chloroform solution of the residue was washed with water, dried over anhydrous magnesium sulfate, and evaporated at reduced pressure producing 7.8 g (89%) of a 1:3 mixture of XLII and XLIVa. Fractional distillation yielded XLIVa, b.p. 27-8° (0.07 mm); ir (film): 1615 cm^{-1} (C=N); nmr (CCl_4): 4.12 (s, 3H) and 7.00-7.65 δ (m, 4H); uv (CH_3OH): 288 mμ (Log ε 3.58), 282 (3.57), 278 (3.57), sh 273 (3.45), and 236 (3.76). XLII was obtained by recrystallization from hexane-ethyl acetate of the solid residue from the distillation, m.p. 74.5-75.5° (Lit. 75-5°, 88); ir (KBr): 1675 cm^{-1} (C=O); nmr ($CDCl_3$): 3.63 (s, 3H) and 7.16-7.92 δ (m, 4H); uv (CH_3OH): 294 mμ (Log ε 3.73), 287 (3.73), sh 254 (3.45), sh 242 (3.73), and end absorption.

Preparation of 3-methyl-2-benzoxazolinone (XLIII)

This compound was prepared from 2.1 g of 2-benzoxazolinone and 2.5 g of methyl iodide following the

procedure described for the synthesis of XLII. Recrystallization from hexane-ethyl acetate afforded 1.6 g (70%) of product, m.p. 83.0-83.5° (Lit. 83-4°, 141); ir (KBr): 1765 cm^{-1} (C=O): nmr ($CDCl_3$): 3.37 (s, 3H) and 6.80-7.30 δ (m, 4H).

Preparation of 2-methoxybenzoxazole (XLVa)

A cold solution of sodium methoxide in 10 ml of dry methanol was added dropwise to 3.07 g of commercial (Eastman) 2-chlorobenzoxazole with stirring and external cooling in an ice bath. The mixture was then stirred at room temperature for 24 hr and filtered. The filtrate was evaporated at reduced pressure. A solution of the residue in 25 ml of ether was washed with water, dried over anhydrous $MgSO_4$, and evaporated at reduced pressure yielding 2.8 g (94%) of crude XLVa. Purification of the product was achieved by column chromatography (silica gel) eluting with 5-7% ethyl acetate in Skelly B, m.p. 32-3° (pentane); ir (CCl_4): 1588 and 1640 cm^{-1}; nmr (CCl_4): 4.13 (s, 3H) and 6.97-7.53 δ (m, 4H); Anal. Calcd. for $C_8H_7NO_2$: 149.048; Found: 149.047.

Preparation of salicylonitrile (XLVI)

A solution of 4.11 g of salicylaldoxime in 15 ml of acetic anhydride was heated to reflux of 2.5 hr. Ten percent aqueous potassium hydroxide was then added slowly until the solution remained slightly basic (phenolphthalein). The solution was acidified with dil. HCl and extracted 3 times

with 25 ml portions of ether. The ether extractions were combined, dried over anhydrous $MgSO_4$, and evaporated at reduced pressure yielding 2.7 g (75%) of XLVI, m.p. 94-5° (benzene; Lit. 99-100°, 142); nmr ($CDCl_3$): 6.73-7.62 (m, 4H) and ~ 9.5 δ (broad s, 1H); ir ($CHCl_3$): 2230 cm^{-1} (C≡N).

Preparation of 2-t-butyl-1,2-benzisoxazolin-3-one (XLVII)

A sealed-tube containing 1.35 g (0.01 mole) of XXXI, 7.4 g (0.08 mole) of t-butyl chloride, and 10 ml of absolute methanol was heated in an oil bath at 100-105° for 4 hr. Evaporation of the methanol and excess t-butyl chloride at reduced pressure returned 1.9 g of a dark oil which was chromatographed on a column of silica gel eluting with 5% ethyl acetate in Skelly B to give 0.9 g (47%) of XLVII, m.p. 48-9° (pentane); ir (KBr): 2975 (C-H) and 1670 cm^{-1} (C=O); nmr (CCl_4): 1.62 (s, 9H) and 7.00-7.82 δ (m, 4H); uv (CH_3OH): 294 mμ (Log ε 3.63), 287 (3.62), sh 255 (3.41), sh 242 (3.65), and end absorption; Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; Found: C, 69.34; H, 6.70.

Preparation of 3-t-butyl-2-benzoxazolinone (XLIX)

An unsuccessful attempt was made to synthesize this compound from XXX and t-butyl chloride via a sealed-tube reaction, but only unchanged starting material was recovered. A significant amount of XLIX was obtained in the photolysis of XLVII (see below). This photoproduct had, m.p. 74-5° (pentane): ir (KBr): 1750 cm^{-1} (C=O); nmr (CCl_4): 1.72

(s, 9H) and 6.85-7.35 δ (m, 4H); Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; Found: C, 68.90; H, 6.79.

Preparation of 3-allyloxy-1,2-benzisoxazole (L) and 2-allyl-1,2-benzisoxazolin-3-one (LI)

These compounds were prepared from 6.75 g of XXXI and 6.5 g of allyl bromide following the procedure described for the synthesis of XLII and XLIVa. Column chromatography (silica gel) of the products afforded 3.2 g (37%) of L eluted with 15% ethyl acetate in Skelly B and 3.4 g (39%) of LI eluted with 20% ethyl acetate in Skelly B. Purification of L was achieved by distillation, b.p. 51° (0.07 mm); ir (film): 1616 and 1540 cm^{-1}; nmr (CCl_4): 4.80-5.00 (m, 2H), 5.13-5.65 (m, 2H), 5.80-6.50 (m, 1H), and 6.97-7.70 δ (m, 4H); uv (CH_3OH): 289 mμ (Log ε 3.59), 283 (3.58), 279 (3.58), sh 273 (3.46), and 238 (3.74); Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; Found: C, 68.18; H, 5.26. LI was recrystallized from hexane, m.p. 32-3°; ir (KBr): 1670 cm^{-1} (C=O); nmr (CCl_4): 4.45-4.65 (m, 2H), 5.08-5.53 (m, 2H), 5.60-6.30 (m, 1H), and 7.00-7.90 δ (m, 4H); uv (CH_3OH): 295 mμ (Log ε 3.73), 289 (3.72), sh 255 (3.50), sh 244 (3.76), and end absorption; Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56, H, 5.18; Found: C, 68.51; H, 5.19.

Preparation of 3-allyl-2-benzoxazolinone (LII)

This compound was synthesized from 2.0 g of XXX and 2.2 g of allyl bromide by the procedure used to prepare XLII and XLIVa yielding 2.1 g (81%) of LII after distillation, b.p. 75-6° (0.07 mm; Lit. 112-114° at 0.5 mm, 141); ir (KBr): 1765 cm^{-1} (C=O); nmr ($CDCl_3$): 4.33-4.55 (m, 2H), 5.06-5.48 (m, 2H), 5.60-6.30 (m, 1H), and 6.83-7.26 δ (m, 4H).

Preparation of 2-allyloxybenzoxazole (LIII)

Sodium alloxide was prepared from 1.52 g of sodium metal and 25 ml of allyl alcohol and was added to 9.21 g of 2-chlorobenzoxazole by the procedure described for the synthesis of XLVa. 10.1 g (96%) of crude LIII was obtained which was purified by column chromatography (silica gel, eluting with 5-7% ethyl acetate in Skelly B) and fractional distillation, b.p. 48-9° at 0.08 mm (Lit. 71-2° at 0.5-0.6 mm, 96); ir (film): 1633 and 1582 cm^{-1}; nmr (CCl_4): 4.85-5.08 (m, 2H), 5.13-5.63 (m, 2H), 5.75-6.43 (m, 1H), and 6.93-7.52 δ (m, 4H); uv (CH_3OH): 277 mμ (Log ε 3.60), 271 (3.65), sh 267 (3.53), and 230 (4.13).

Preparation of 3-ethoxy-1,2-benzisoxazole (XLIVb) and 2-ethyl-1,2-benzisoxazolin-3-one (LIXa)

These compounds were prepared by reacting 1.35 g of XXXI with 1.64 g of ethyl bromide under conditions described for the synthesis of XLII and XLIVa. The product

mixture was chromatographed on a column of silica gel. Elution was 7-10% ethyl acetate in Skelly B produced 1.0 g (61%) of XLIVb, b.p. ~ 50° (0.06 mm); nmr (CCl_4): 1.50 (t, 3H), 4.47 (q, 2H), and 6.96-7.68 δ (m, 4H); ir (film): 1616 and 1544 cm^{-1}; Anal. Calcd. for $C_9H_9NO_2$: 163.063; Found: 163.065. Further elution with 15-25% ethyl acetate-Skelly B yielded 0.45 g (28%) of LIXa, b.p. ~ 65° (0.06 mm); nmr (CCl_4, Cf. ref. 130): 1.35 (t, 3H), 4.02 (q, 2H), and 7.03-7.87 δ (m, 4H); ir (film): 1695 cm^{-1} (C=O).

Preparation of 3-n-propoxy-1,2-benzisoxazole (LVa) and 2-n-propyl-1,2-benzisoxazolin-3-one (LIXb)

The synthesis of these compounds was achieved by the procedure described above for XLII and XLIVa from 0.675 g of XXXI and 1.23 g of n-propyl bromide. Preparative tlc (silica gel) using 15% ethyl acetate-Skelly B as the mobile phase separated the two isomers. The faster moving component was LVb, 0.4 g (45%), b.p. ~ 55° (0.06 mm); nmr (CCl_4): 1.05 (t, 3H), 1.90 (sextet, 2H), 4.36 (t, 2H), and 6.98-7.68 δ (m, 4H); Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; Found: C, 67.88; H, 5.92. The slower component was LIXb, 0.1 g (11%), b.p. ~ 65° (0.06 mm); nmr (CCl_4): 0.99 (t, 3H), 1.82 (sextet, 2H), 3.94 (t, 2H), and 7.03-7.89 δ (m, 4H); Anal. Calcd. for $C_{10}H_{11}NO_2$: 177.079; Found: 177.076.

Preparation of 3-isopropoxy-1,2-benzisoxazole (LVb) and 2-isopropyl-1,2-benzisoxazolin-3-one (LIXc)

These compounds were synthesized by the procedure described above for XLII and XLIVa from 0.4 g of XXXI and 1.23 g of isopropyl bromide. Preparative tlc (silica gel) was utilized to separate the product mixture using 15% ethyl acetate-Skelly B as the solvent. The faster moving component which was further purified by molecular distillation was LVc, 0.035 g (7%); nmr (CCl_4): 1.48 (d, 6H), 5.07 (heptet, 1H), and 6.90-7.62 δ (m, 4H); ir (film): 1616 and 1537 cm^{-1}; Anal. Calcd. for $C_{10}H_{11}NO_2$: 177.079; Found: 177.082. The slower moving component was LIXc, 0.004 g (1%); nmr (CCl_4): 1.43 (d, 6H), 4.76 (heptet, 1H), and 6.9-7.8 δ (m, 4H): ir (CCl_4): 1702 cm^{-1} (C=O); Anal. Calcd. for $C_{10}H_{11}NO_2$: 177.079; Found: 177.078.

Preparation of 3-n-butoxy-1,2-benzisoxazole (LVc) and 2-n-butyl-1,2-benzisoxazolin-3-one (LIXd)

Synthesis of these compounds was achieved from 1.35 g of XXXI and 1.95 g of n-butyl bromide by the procedure described above for XLII and XLIVa. Preparative tlc (silica gel; 25% ethyl acetate-Skelly B) was used to separate the two products which were further purified by molecular distillation. The faster moving component was LVd, 0.53 g (28%); nmr (CCl_4): 0.80-2.13 (m, 7H), 4.40 (t, 2H), and 6.94-7.67 δ (m, 4H); ir (film): 1618 and 1546 cm^{-1}; Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; Found: C, 69.05,

H, 6.59. The slower moving component was LIXd, 0.30 g (16%); nmr (CCl_4): 0.78-2.08 (m, 7H), 4.03 (t, 2H), and 7.03-7.96 δ (m, 4H); ir (film): 1692 cm^{-1} (C=O); Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; Found: C, 68.64; H, 6.52.

Preparation of 2-benzyloxybenzoxazole (LXXIV)

This compound was prepared from sodium benzylate (0.37 g of sodium metal in 15 ml of benzyl alcohol) and 2.17 g of 2-chlorobenzoxazole following the procedure described above for XLVa. Recrystallization from ethyl acetate-pentane returned 1.8 g (57%), m.p. 56.5-57°; nmr (CCl_4): 5.50 (s, 2H) and 6.97-7.60 δ (m, 9H); ir (CCl_4): 1632 and 1583 cm^{-1}; uv (CH_3OH): 276 mμ (Log ε 3.66), 270 (3.72), sh 266 (3.61), and 229 (4.23); Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; Found: C, 74.49; H, 5.02.

Preparation of N-methyl salicylamide (LXVII)

A mixture of 15.2 g of methyl salicylate and 16 g of 40% aqueous methyl amine was heated at reflux for 12 hr. Neutralization with dil. HCl precipitated the amide which was filtered, washed with water, and dried under high vacuum yielding 13.2 g (87%), m.p. 84.5-85.0° (methanol; Lit. 86-7°, 143); nmr ($CDCl_3$): 2.95 (d, 3H) and 6.63-7.58 δ (m, 6H); ir (KBr): 3420 (O-H) and 1643 cm^{-1} (C=O); parent ion at m/e 151.

Preparation of methyl salicylimidate (LXIX)

Dry HCl gas was bubbled into a stirred solution of 1.19 g of salicylonitrile (XLVI) in 5 ml of dry methanol and 5 ml of absolute ether for ~ 0.5 hr. Stirring was continued at room temperature for 3 weeks with periodic addition of HCl. The methanol was evaporated at reduced pressure yielding 0.7 g of the hydrochloride salt which was washed with dry benzene and ether, m.p. 136.5-138°. The salt was added slowly to a stirred mixture of 5 ml of 30% aqueous K_2CO_3 and 5 ml of ether at 0°. The ether layer was separated, dried over anhydrous $MgSO_4$, and evaporated at reduced pressure yielding 0.04 g (3%), m.p. 75.5-76.5° (pentane); ir (CCl_4): 3380 (OH) and 1645 cm^{-1} (C=N); nmr (CCl_4): 3.73 (s, 3H), 6.53-7.78 (m, 4H), and ~ 10.0 δ (broad s, 2H); parent ion at m/e 151; Anal. Calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; Found: C, 63.80; H, 5.66.

Attempted preparation of 2-crotoxybenzoxazole (LXXII)

The procedure described above for the preparation of XLVa was followed starting with 0.033 mole of sodium crotoxide and 4.6 g of 2-chlorobenzoxazole. Distillation of the crude product yielded 4.1 g (73%), b.p. 75-6° (0.05 mm); nmr (CCl_4): 1.62 (d, 3H), 4.70-5.46 (m, 3H), 5.83-6.43 (m, 1H), and 6.90-7.20 δ (m, 4H); ir (film): 1778 cm^{-1} (C=O); parent ion at m/e 189. These spectral data are consistent with structure LXXIIIa, not LXXII.

A second attempt at the synthesis of LXXII was made in which column chromatography was used to purify the product. However, isomerization of LXXII to LXXIIIa occurred rapidly under these conditions also as indicated by tlc and nmr spectroscopy.

Preparation of 3-benzyl-2-benzoxazolinone (LXXV)

A solution of 0.24 g of XXX, 0.12 g of KOH, and 0.26 g of benzyl chloride in 5 ml of ethanol and 0.5 ml of water was heated to 80-5° for 1 hr. Crystallization of the product occurred upon addition of 2 ml of water and cooling to yield 0.16 g (40%), m.p. 119-119.5° (ethyl acetate-hexane; Lit. 127°, 144); ir (CCl_4): 1790 cm^{-1} (C=O); nmr ($CDCl_3$): 4.98 (s, 2H) and 6.72-7.40 δ (m, 9H); parent ion at m/e 225.

Preparation of 6-benzyl-2-benzoxazolinone (LXXVIb)

3-nitrobenzoyl chloride was prepared by heating a mixture of 50 g of 3-nitrobenzoic acid and 50 ml of thionyl chloride under reflux for 4 hr. The excess thionyl chloride was removed by distillation, and the residual oil was vacuum distilled yielding 50.8 g (92%) of product, b.p. 85-6° (0.08 mm).

Benzene (120 ml) was added to a 500-ml 3-necked flask equipped with a mechanical stirrer and reflux condenser containing 46.5 g of 3-nitrobenzoyl chloride. The stirred solution was cooled in an ice bath while adding 37 g of

anhydrous $AlCl_3$ in portions over a 15 min period. An exothermic reaction occurred after removal of the ice bath producing a dark orange solution. The reaction mixture was heated at 85-95° for 3 hr, after which the contents of the flask while still warm were poured over 200 g of crushed ice containing 100 ml of conc. HCl. The benzene layer was separated, washed with 50 ml of 5% aqueous NaOH followed by 50 ml of H_2O, dried over anhydrous $MgSO_4$, and evaporated at reduced pressure yielding 51.7 g (91%) of 3-nitrobenzophenone, m.p. 89-91° (methanol-ethyl acetate; Lit. 94-6°, 145).

A mixture of 51.7 g of 3-nitrobenzophenone and 39 g of powdered iron in 160 ml of 50% aqueous ethanol was introduced into a 500 ml 3-necked flask equipped with a mechanical stirrer, reflux condenser, and addition funnel containing 4.2 ml of conc. HCL in 10 ml of ethanol. After heating the stirred mixture to slow reflux, the HCl-ethanol solution was added dropwise over a 30 min period. Stirring was continued at 85-90° for another 3 hr. The hot mixture was then filtered, and the filtrate having been neutralized with 40% aqueous NaOH was filtered a second time. Volume reduction by evaporation at reduced pressure and cooling yielded 39.9 g (89%) of the yellow product, 3-aminobenzophenone, m.p. 82-4° (aqueous ethanol; Lit. 82°, 146).

Crushed ice (~ 50 g) was added to a solution of 19.7 g

of 3-aminobenzophenone in 40 g of conc. H_2SO_4 and 30 ml of water. The mixture was stirred until a paste of the amine sulfate salt was formed. A cold solution of 7.2 g of sodium nitrite in 16 ml of water was added slowly to the paste which was maintained at 0° until the reaction mixture turned potassium iodide-starch paper purple immediately. Stirring was continued for another 15 min at $0\text{-}5^\circ$, and then the mixture was allowed to stand for another 15 min. The supernatant liquid was decanted into a separatory funnel and was added dropwise (over 30 min period) to a boiling solution ($\sim 160^\circ$) of 66 ml of conc. H_2SO_4 in 60 ml of water. The residual solid diazonium salt was then added to the H_2SO_4, and the mixture was boiled for another 15 min and poured into a 1-liter beaker cooled in an ice bath. This mixture was stirred vigorously for 1 hr, filtered, washed with water, and dried under high vacuum yielding 16.0 g (81%) of 3-hydroxybenzophenone; nmr ($CDCl_3$): 6.80-7.90 (m, 9H) and ~ 6.1 δ (broad s, 1H).

A mixture of 30.7 g of anhydrous $AlCl_3$ in 100 ml of dry ether was added slowly to a suspension of 4.6 g of $LiAlH_4$ in 10 ml of dry ether contained in a 500 ml 3-necked flask equipped with a reflux condenser and mechanical stirrer. A solution of 13 g of 3-hydroxybenzophenone in 225 ml of dry ether was added dropwise over a period of 15 min with stirring in a nitrogen atmosphere.

The mixture was heated to reflux for 30 min. Ethyl acetate was then added slowly to destroy the excess $LiAlH_4$, and the mixture was poured into 100 ml of 20% H_2SO_4. The ether layer was removed, and the aqueous layer was extracted with 100 ml of ether. The combined ethereal solution was washed with H_2O, dried over anhydrous $MgSO_4$, and evaporated at reduced pressure. Distillation afford 9.2 g (76%) of 3-hydroxydiphenylmethane, b.p. 103-5° (0.03 mm; Lit. 183-4° at 11 mm, 147); nmr (CCl_4): 3.75 (s, 2H), 5.84 (broad s, 1H), and 6.37-7.10 δ (m, 9H).

A mixture of 9.2 g of 3-hydroxydiphenylmethane and 20.7 g of anhydrous potassium carbonate (dried at 400° for 2 hr) was placed in a high pressure reactor (125). The reactor was pressurized with 1000 psi of CO_2 and was heated to 175° for 12 hr. The product was dissolved in 100 ml of H_2O, washed 3 times with 30 ml of ether, and acidified with conc. HCl precipitating 9.3 g (82%) of 4-benzylsalicylic acid, m.p. 172-4° (ethyl acetate-pentane); nmr (acetone-d_6): 3.95 (s, 2H), 6.67-6.90 (m, 2H), 7.25 (s, 5H), 7.83 (d, 1H), and 8.35 δ (broad s, 2H); ir ($CHCl_3$): 3400-2800 (O-H) and 1678 cm^{-1} (C=O); parent ion at m/e 228.

A stirred solution of 8.5 g of 4-benzylsalicylic acid and 2 ml of conc. H_2SO_4 in 35 ml of absolute methanol was heated to reflux for 5 hr. The residue obtained upon evaporation of the excess methanol was added slowly to

50 ml of 10% aqueous sodium bicarbonate. The product was extracted with three 25 ml portions of ether which was then dried over anhydrous $MgSO_4$ and evaporated at reduced pressure yielding 6 g (67%) of 4-benzyl methyl salicylate; nmr (CCl_4): 3.75 (s, 3H), 3.80 (s, 2H), 6.40-6.80 (m, 2H), 7.10 (s, 5H), 7.62 (d, 1H), and 10.6 δ (broad s, 1H); ir (film): 1678 cm^{-1} (C=O).

A stirred mixture of 5.4 g of 4-benzyl methyl salicylate and 6 ml of 99% hydrazine hydrate was heated to reflux for 2 hr (137). The solution was cooled and 15 ml of water was added to precipitate 4.9 g (91%) of 4-benzyl salicyloylhydrazide, m.p. 162-3° (ethyl acetate); ir ($CHCl_3$): 3473 (OH) and 1651 cm^{-1} (C=O); parent ion at m/e 242.

4-benzyl salicyloylazide was prepared from 0.76 g of sodium nitrite in 5 ml of water, 2.7 g of 4-benzyl salicyloylhydrazide, and 4 ml of conc. HCl as described above for XXXIV. The product was extracted with benzene yielding 2.28 g (81%); ir ($CHCl_3$): 2192-2140 (d, N_3) and 1652 cm^{-1} (C=O).

A stirred solution of 2.3 g of 4-benzyl salicyloyl-azide in 20 ml of toluene was heated to reflux for 2 hr. The reaction mixture was then cooled in the refrigerator to precipitate 1.5 g (75%) of 6-benzyl-2-benzoxazolinone (LXXVIb), m.p. 149-151° (ethyl acetate-pentane); nmr ($CDCl_3$): 3.98 (s, 2H), 7.00 (s, 3H), 7.23 (s with minor

splitting, 5H), and 9.8 δ (broad s, 1H); ir ($CHCl_3$): 1787 cm^{-1} (C=O); parent ion at m/e 225; Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; Found: C, 74.88; H, 5.26.

Preparation of 3-acetyl-6-benzyl-2-benzoxazolinone (LXXVIII)

A mixture of 0.25 g of LXXVIb and 5 ml of acetic anhydride was stirred at 50° for 2 hr and then poured into 15 ml of water. The precipitate which formed upon cooling was dissolved in ether and washed with dil. aqueous NaOH. Evaporation of the dried (over $MgSO_4$) ether solution produced 0.2 g (70%) of LXXVIII, m.p. 95.5-97.0° (ethyl acetate-pentane); nmr ($CDCl_3$): 2.66 (s, 3H), 3.96 (s, 2H), 6.93-7.32 (m, 7H), and 7.92 δ (d, 1H); ir ($CHCl_3$): 1808 (C=O, 2-one) and 1733 cm^{-1} (C=O, 3-acyl); parent ion at m/e 267.

Preparation of 3-indazolinone (LXXX)

This compound was obtained commercially (Aldrich) and was purified by recrystallization from aqueous methanol, m.p. 245-251° (decomp.; Lit. 242°, decomp., 148); nmr (DMSO-d_6): 6.83-7.83 (m, 4H) and ~ 10.0 δ (broad s, 2H); ir (KBr): 3100-2700 (O-H) and 1640-1613 cm^{-1}; uv (CH_3OH): 309 mμ (Log ε 3.64) and 217 (4.69).

Preparation of 2-benzimidazolinone (LXXXI)

A mixture of 10.8 g of o-phenylenediamine and 6.0 g of urea was heated at 150° with vigorous mechanical stirring

until the fused material solidified. The product was dissolved in 10% NaOH, filtered, and precipitated from the filtrate by adding 5N HCl. Recrystallization from ethanol yielded 3 g (22%) of LXXXI, m.p. 312-4° (Lit. 306-8°, 149); nmr (DMSO-d_6): 6.99 (s, 4H) and ~ 10.7 δ (broad s, 2H); ir (KBr): 1733 cm^{-1} (C=O).

Preparation of 1-methyl- (LXXXIIa), 2-methyl- (LXXXIIb), and 1,2-dimethyl-3-indazolinone (LXXXV)

A stirred solution of 6.7 g of 3-indazolinone, 2.8 g of KOH, and 4.25 g of methyl iodide in 70 ml of absolute methanol was heated to reflux in an atmosphere of nitrogen for 6 hr. The residue obtained by evaporation of the methanol at reduced pressure was chromatographed on a column of silica gel. Elution with 35-55% ethyl acetate-Skelly B afforded 1 g (15%) of the 1-methyl derivative (LXXXIIa), m.p. 155.5-156.5° (ethyl acetate-hexane; Lit. 151-3°, 150); nmr ($CDCl_3$); 3.79 (s, 3H), 6.88-7.88 (m, 4H), and 11.52 δ (s, 1H); ir ($CHCl_3$): 3100-2600 (OH), 1627 and 1558 cm^{-1}. Further elution with 75-95% ethyl acetate-Skelly B produced 1 g (15%) of the 1,2-dimethyl compound (LXXXV), m.p. 66-7° (ethyl acetate-hexane; Lit. 66°, 151); nmr ($CDCl_3$): 3.22 (s, 3H), 3.40 (s, 3H), and 6.98-7.94 δ (m, 4H); ir ($CHCl_3$): 1670 cm^{-1} (C=O). Elution with ethyl acetate yielded 0.5 g (8%) of the 2-methyl isomer (LXXXIIb) which was recrystallized from aqueous methanol,

m.p. 192-200° (decomp.; Lit. 191-202°, decomp., 150); nmr (DMSO-d_6): 3.37 (s, 3H), ~ 3.4 (broad s, 1H), and 6.90-7.75 δ (m, 4H); ir (KBr): 1632 cm^{-1} (C=O).

Preparation of 1-methyl- (LXXXIII) and 1,3-dimethyl-2-benzimidazolinone (LXXXVI)

Compound LXXXIII was prepared from 0.82 g of LXXXI and 1 g of CH_3I by the procedure described above for XLIII. Preparative tlc (silica gel, 75% ethyl acetate-hexane) was used to isolate LXXXIII from the dimethyl compound and starting material yielding 0.26 g (29%), m.p. 193-194.5° (ethyl acetate; Lit. 186°, 152); nmr ($CDCl_3$): 3.32 (s, 3H), 6.72-7.00 (m, 4H), and ~ 10.1 δ (broad s, 1H); ir ($CHCl_3$): 1710 cm^{-1} (C=O). The mother liquor obtained in recrystallization of LXXXIII was evaporated, and the resulting 0.13 g of crude material was reacted with 0.3 ml of methyl iodide under conditions described above. Filtration of the reaction mixture and evaporation of the solvent yielded 0.13 g (91%) of LXXXVI, m.p. 110-5.111° (ethyl acetate-hexane; Lit. 105°, 153); nmr ($CDCl_3$): 3.41 (s, 6H) and 6.80-7.30 δ (m, 4H); ir ($CHCl_3$): 1701 cm^{-1} (C=O).

Preparation of 1-t-butyl-3-indazolinone (LXXXIX)

A sealed-tube containing 1.34 g of LXXX, 8.7 ml of t-butyl chloride, 0.8 ml of pyridine, and ~ 10 ml of absolute methanol was heated at 100-125° for 9 hr. The reaction mixture was acidified with 1.2N HCl and filtered.

Extraction of the filtrate with ether yielded 0.2 g of an oil which was chromatographed on preparative tlc (silica gel, 20% ethyl acetate-hexane) affording 116 mg (6%) of LXXXIX, m.p. 121-132° (decomp.; ethyl acetate-hexane); nmr ($CDCl_3$): 1.66 (s, 9H), 6.90-7.96 (m, 4H), and 10.3 δ (broad s, 1H); ir (CCl_4): 3000-2600 (OH), 1625, and 1590 cm^{-1}; Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; Found: C, 69.43; H, 7.22.

Preparation of 1,2-benzisothiazolin-3-one (XCIVa)

A solution of 15 g of iodine in 100 ml of absolute methanol was added to a stirred suspension of 15.4 g of o-mercaptobenzoic acid in 125 ml of methanol. The mixture was stirred at room temperature for 2 hr, and the precipitated 2,2'-dithiobenzoic acid was filtered, washed with methanol, and dried under high vacuum yielding 11.4 g (75%), m.p. 298-300° (Lit. 293-5°, 154); nmr (DMSO-d_6): 7.16-8.25 (m, 8H) and 10.7 δ (broad s, 2H).

A stirred suspension of 10 g of 2,2'-dithiobenzoic acid in 65 ml of thionyl chloride was heated to vigorous reflux until a homogeneous solution resulted (~ 1.5 hr). The excess thionyl chloride was distilled at reduced pressure, and the residual 2,2'-dithiobenzoyl chloride was recrystallized from benzene-pentane yielding 10.4 g (95%), m.p. 157-9° (Lit. 155-6°, 155).

Chlorine gas was bubbled into a stirred suspension of

6.86 g of the diacid chloride in 50 ml of CCl_4 until a clear yellow solution of 2-chlorosulfenylbenzoyl chloride was obtained. The excess chlorine was expelled with a stream of dry nitrogen gas (~ 1 hr), and the sulfenyl chloride was added dropwise to 55 ml of aqueous ammonia cooled in an ice bath. The precipitated product was filtered, washed with water, and dried producing 5.0 g (83%) of XCIVa, m.p. 155-6° (methanol; Lit. 155-6°, 156); nmr (DMSO-d_6): ~ 6.7 (broad s, 1H) and 7.26-8.10 δ (m, 4H); ir (KBr): 1640 cm^{-1} (C=O); uv (CH_3OH): 316 mμ (Log ε 3.73), sh 260 (3.63), sh 245 (3.88), sh 234 (4.04), and 226 (4.31).

The following compounds were prepared by a similar procedure:

2-methyl-1,2-benzisothiazolin-3-one (XCIVb) was obtained from 6.86 g of 2,2'-dithiobenzoyl chloride and 50 ml of 40% aqueous methyl amine and was isolated from the CCl_4 layer yielding 5.3 g (80%) of XCIVb, m.p. 51-2° (Lit. 51-2°, 156); nmr (CCl_4): 3.36 (s, 3H) and 7.16-8.06 δ (m, 4H); ir (KBr): 1628 cm^{-1} (C=O); uv (CH_3OH): 317 mμ (Log ε 3.83), 245 (4.07), and 227 (4.36).

2-t-butyl-1,2-benzisothiazolin-3-one-S-oxide (XCXIII) was obtained in a similar reaction from 3.43 g of 2,2'-dithiobenzoyl chloride, 5 ml of t-butyl amine, and 10 ml of pyridine. Recrystallization from ethyl acetate-hexane afforded 1.6 g (39%) m.p. 103-4°; nmr (CCl_4):

1.70 (s, 9H) and 7.45-7.94 δ (m, 4H); ir (CCl_4): 1715 (C=O) and 1114 cm^{-1} (S=O); parent ion at m/e 223; Anal. Calcd. for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; Found: C, 59.22; H, 5.85.

2-t-butyl-1,2-benzisothiazolin-3-one (XCXI) was prepared from 12 g of 2,2'-dithiobenzoyl chloride and 75 ml of t-butyl-amine by the same procedure as above, except degassing of the sulfenyl chloride solution with N_2 was extended to 5 hr. Distillation of the product at 0.08 mm yielded 7.7 g (53%), b.p. 95-7° (Lit. 142° at 0.5 mm, 157); nmr (CCl_4): 1.65 (s, 9H) and 7.08-8.02 δ (m, 4H); ir (CCl_4): 1657 cm^{-1} (C=O).

2-isopropyl-1,2-benzisothiazolin-3-one (XCXI) was prepared from 2.28 g of 2,2'-dithiobenzoyl chloride and 10 ml of isopropyl amine. Distillation of the product afforded 2.1 g (82%) b.p. 93.5-95° (0.1 mm); nmr (CCl_4): 1.36 (d, 6H), 4.85 (heptet, 1H), and 7.08-8.00 (m, 4H); ir (film): 1652 cm^{-1} (C=O); Anal. Calcd. for $C_{10}H_{11}NOS$: 193.056; Found: 193.059.

2-p-toluenesulfonyl-1,2-benzisothiazolin-3-one (XCVIII) was obtained from 4.0 g of 2,2'-dithiobenzoyl chloride, 4.0 g of p-toluenesulfonylamide, and 15 ml of pyridine yielding 7.0 g (99%) of crude product which was recrystallized from ethyl acetate-acetone, m.p. 206-9° (decomp.; Lit. 207°, 158); nmr (DMSO-d_6): 2.40 (s, 3H) and 7.17-

8.16 δ (m, 8H); ir (KBr): 1674 cm^{-1} (C=O).

2-phenyl-1,2-benzisothiazolin-3-one (XCIX) was prepared from 2.28 g of 2,2'-dithiobenzoyl chloride and 10 ml of aniline yielding after recrystallization from ethyl acetate-hexane 1.3 g (42%), m.p. 144-5° (Lit. 140°, 156); nmr ($CDCl_3$): 7.18-8.18 δ (m).

Preparation of 1,2-benzisothiazolin-3-one-S-oxide (XCVIa)

A stirred solution of 0.76 g of XCIVa in 5 ml of conc. H_2SO_4 was cooled in a water bath to maintain a temperature of ~ 40° during the slow addition of 0.6 g of potassium nitrate. The reaction mixture was stirred for 30 min and then was poured over 20 g of crushed ice precipitating 0.3 g (28%) of XCVIa, m.p. 162-162.5° (ethanol; Lit. 159°, 159); nmr ($CDCl_3$): 7.53-8.08 (m, 4H) and ~ 11.0 δ (broad s, 1H); ir ($CHCl_3$): 1740 (C=O) and 1105 cm^{-1} (S=O).

Preparation of 2-methyl-1,2-benzisothiazolin-3-one-S-oxide (XCVIb)

This compound was prepared from 0.83 g of XCIVb and 0.6 g of KNO_3 in 5 ml of conc. H_2SO_4 by the procedure described above for XCVIa. Purification by preparative tlc (silica gel, 25% ethyl acetate-hexane) and recrystallization from ethyl acetate-hexane afforded 0.02 g (2.2%) of XCVIb, m.p. 111-112°; nmr ($CDCl_3$): 3.38 (s, 3H) and 7.56-8.04 δ (m, 4H): ir ($CHCl_3$): 1715 (C=O) and 1105 cm^{-1} (S=O); Anal. Calcd. for $C_8H_7NO_2S$: 181.020; Found:

181.020.

Preparation of 2-isopropyl-1,2-benzisothiazolin-3-one-S-oxide (XCXII) (see Scheme 32)

Chlorine gas was bubbled into a suspension of 5 g of o-mercaptobenzoic acid in 50 ml of carbon tetrachloride until a homogeneous solution was obtained. Excess Cl_2 was expelled with a stream of dry N_2, and the solution was added dropwise to 10 ml of isopropyl amine in 10 ml of pyridine with external cooling in an ice bath. The mixture was stirred 30 min at 25° and then was poured into 150 ml of 2.4N HCl. A dark oil (2.7 g) was obtined from the organic layer which was vacuum distilled to give 0.8 g of a mixture of XCX and XCXII by nmr. Purification of XCXII was achieved by preparative tlc (silica gel, 25% ethyl acetate-hexane) and recrystallization from ethyl acetate-hexane, m.p. 53-4°; nmr ($CDCl_3$): 1.56 (d, 6H), 4.46 (heptet, 1H), and 7.55-8.07 δ (m, 4H); ir ($CHCl_3$): 1717 (C=O) and 1102 cm^{-1} (S=O); Anal. Calcd. for $C_{10}H_{11}NO_2S$: 209.051; Found: 209.052.

Preparation of 2-benzothiazolinone (XCVa)

A solution of 12 ml of 2-aminothiophenol in 100 ml of chloroform was treated with gaseous phosgene for 45 min. The chloroform was evaporated at reduced pressure, and the residue was extracted with ether yielding 5.7 g of XCVa, m.p. 136-7° (methanol; Lit. 135°, 160); nmr (DMSO-

d_6): 6.91-7.68 (m, 4H) and ~ 10.5 δ (broad s, 1H); ir (KBr): 1670 cm^{-1} (C=O).

Preparation of 3-methyl-2-benzothiazolinone (XCVb)

This compound was synthesized from 0.76 g of XCVa and 1.4 g of methyl iodide by the procedure described above for XLII and XLIVa yielding 0.8 g (97%) of product, m.p. 77.5-78° (ethyl acetate-hexane; Lit. 74°, 160); nmr (CCl_4): 3.37 (s, 3H) and 6.82-7.46 δ (m, 4H); ir (CCl_4): 1698 cm^{-1} (C=O).

Pyrolyses

Pyrolysis of 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazolin-5-one (XXIX)

A solution of 58 mg of XXIX in 15 ml of benzene was heated to reflux for 2 hr. Evaporation of the solvent returned XXIX quantitatively as shown by ir and tlc. Sublimation of 50 mg of XXIX into a Pyrex furnace tube at 150° and 0.1 mm pressure resulted in the formation of 29 mg of product which was washed out of the U-trap with chloroform. The ir and mass spectra of this product were identical to the corresponding spectra of 3-hydroxy-1,2-benzisoxazole (XXXI). At 300°, 108 mg of XXIX yielded 60 mg of products whose ir and tlc indicated two components. Nmr verified the products to be XXXI and 2-benzoxazolinone (XXX) in a ratio of 78:22. At 450°, 64 mg of XXIX produced 45 mg of material whose ir spectrum was superimposable

with that of authentic XXX.

Pyrolysis of 3-(2-hydroxyphenyl)-Δ^2-1,4,2-dioxazolin-5-thione (XXXIIIa)

A solution of 31 mg of XXXIIIa in 10 ml of benzene was heated to reflux for 1 hr. Evaporation of the solvent yielded only XXXIIIa quantitatively as shown by ir and tlc. Sublimation of 97 mg of XXXIIIa into a heated furnace tube (150°) at 0.1 mm pressure produced 55 mg of product whose nmr and ir spectra were consistent with XXXI and trace amounts of XXX (weak C=O absorption at 1770 cm^{-1}). At 450°, 93 mg of XXXIIIa produced 85 mg of XXX as determined by ir and nmr spectra of the product.

Pyrolysis of salicyloyl azide (XXXIV)

130 mg of XXXIV was pyrolyzed at 150° and 0.01 mm pressure yielding 125 mg of material whose ir spectrum was identical to that of starting XXXIV. At 200°, 96 mg of the azide produced 30 mg of a solid product which condensed near the top of the U-trap. The ir spectrum and tlc of this product were consistent with XXX. 60 mg of starting material was also obtained inside the cold trap. At 250°, 70 mg of the azide resulted in the formation of 47 mg of only XXX by tlc and ir spectroscopy.

Pyrolysis of 3-phenyl-Δ^2-1,4,2-dioxazolin-5-one (XXXVIa)

Sublimation of 97 mg of XXXVIa into a Pyrex furnace tube at 250° and 0.1 mm pressure resulted in essentially quantitative recovery of starting material as shown by superimposable nmr spectra.

Pyrolysis of 2-benzoxazolinone (XXX)

Sublimation of 101 mg of XXX into the furnace tube maintained at 450° and 0.1 mm pressure resulted in recovery of 100 mg of unchanged starting material as shown by nmr, ir, and tlc.

Pyrolysis of 3-hydroxy-1,2-benzisoxazole (XXXI)

51 mg of XXXI was sublimed into the Pyrex furnace tube at 250° and 0.1 mm pressure, and 46 mg of product was obtained whose ir spectrum was superimposable with that of starting material. At 350°, 44 mg of XXXI furnished 40 mg of a 1:1 mixture (by nmr) of XXXI and XXX. This was also verified by ir and tlc. At 450°, 90 mg of XXXI rearranged to afford 87 mg of 2-benzoxazolinone (XXX), m.p. 139-141°. The ir spectrum of the product was superimposable with that of authentic XXX. In each experiment the products were washed out of the U-trap with anhydrous ether.

Pyrolysis of 2-methyl-1,2-benzisoxazolin-3-one (XLII)

A sample (48 mg) of XLII was sublimed in vacuo (0.1 mm) into the pyrolysis tube maintained at 350°. A quantitative

recovery of the material was made whose nmr spectrum showed XLII and 3-methyl-2-benzoxazolinone (XLIII) in a ratio of 96:4. At 450°, 90 mg of XLII yielded ~ 90 mg of a 32:68 mixture (by nmr) of XLII and XLIII. Preparative tlc (silica gel, 50% ethyl acetate-Skelly B) was used to isolate XLIII, m.p. 83-5°. At 550°, pyrolysis of 118 mg of XLII produced 116 mg of XLIII in high purity, m.p. 86-7°. The nmr, ir, and mass spectra of the product were identical to that of authentic material.

Pyrolysis of 3-methoxy-1, 2-benzisoxazole (XLIVa)

27 mg of XLIVa remained essentially unchanged after passing through the furnace tube at 500° (0.1 mm) as determined by ir and nmr spectroscopy. At 600°, 120 mg of XLIVa produced 49 mg of a solid which collected at the top of the U-trap and 63 mg of an oil. Nmr and mass spectroscopy substantiated the solid to be 2-benzoxazolinone (XXX), and the oil was found (by nmr) to be a 9:1 mixture of XLIVa and 2-methoxybenzoxazole (XLVa). At 700°, 187 mg of XLIVa pyrolyzed to give 128 mg of XXX by ir and nmr. In addition, 47 mg of a low melting solid was washed out of the U-trap with $CHCl_3$. The ir spectrum of this product showed absorption at 2230 cm^{-1}, and its mass spectrum had a molecular ion at m/e 119 in agreement with salicylonitrile. Its nmr spectrum ($CDCl_3$) also substantiated this: 6.70-7.60 (m, 4H) and ~ 7.7 δ (broad s, 1H). Trace amounts of certain

unidentified impurities could not be removed by preparative tlc. In a second experiment at 700°, 348 mg of XLIVa produced 190 mg of XXX and 57 mg of an oil whose spectral properties were analogous to those described for salicylonitrile.

Pyrolysis of 3-ethoxy-1,2-benzisoxazole (XLIVb)

Sublimation (sample heater at ~ 40°) of 284 mg of XLIVb into a Vycor furnace tube at 700° and 0.001 mm pressure produced 225 mg of a mixture which was separated by preparative tlc (silica gel, 25% ethyl acetate-Skelly B). The individual bands were extracted (Soxhlet) with ether producing 181 mg of XXX and ~ 7 mg of salicylonitrile (C≡N ir absorption at 2230 cm^{-1}).

Pyrolysis of 2-t-butyl-1,2-benzisoxazolin-3-one (XLVII)

96 mg of XLVII was sublimed (sample heater at 40°) into a furnace tube maintained at 310° and < 0.001 mm pressure yielding 90 mg of product whose nmr indicated a 94:6 ratio of XLVII and 3-t-butyl-2-benzoxazolinone (XLIX). At 400°, 90 mg of XLVII produced 72 mg of a product mixture which was found by nmr to consist of XLVII, XLIX, and XXX in a molar ratio of 21:35:44. Preparative tlc (silica gel, 25% ethyl acetate-Skelly B) separated the components which were individually characterized by nmr and ir. XXX was found to have m.p., 140.5-142°. At 500°, 67 mg of XLVII

resulted in the formation of 43 mg of a 13:87 molar ratio (by nmr) of XLIX and XXX.

Pyrolysis of 3-allyloxy-1,2-benzisoxazole (L)

Distillation (sample heater at ~ 40°) of 158 mg of L into the Vycor furnace tube maintained at 310° and 0.001 mm pressure resulted in the recovery of ~ 158 mg of material whose nmr spectrum indicated 92:8 ratio of L and 2-allyl-1, 2-benzisoxazolin-3-one (LI). At 400°, 138 mg of L produced 24 mg of a white solid (XXX) at the top of the U-trap and 110 mg of a mixture of L, LI and LII in a 6:19:53 molar ratio (by nmr). At 500°, 160 mg of L pyrolysed to give 149 mg of a product mixture of two components (by tlc) whose nmr spectrum indicated LII and XXX in a 66:34 molar ratio.

Pyrolysis of 2-allyl-1,2-benzisoxazolin-3-one (LI)

130 mg of LI was sublimed (sample heater at 55°) at 0.001 mm pressure into a Vycor furnace tube maintained at 310°. A quantitative recovery of starting material resulted as shown by nmr. At 400°, 160 mg of LI produced 17 mg of solid XXX which collected at the top of the U-trap and 128 mg of an oil which condensed inside the trap. The oil consisted of a 27:60 mixture (by nmr) of LI and LII. At 500°, 155 mg of LI pyrolyzed to give 142 mg of a mixture of LII and XXX in a 77:23 molar ratio as determined by nmr spectroscopy.

Pyrolysis of 3-indazolinone (LXXX)

91 mg of LXXX was sublimed (sample heater at 140°) into a Vycor furnace tube at 600° and 0.001 mm pressure yielding 80 mg of a solid product whose nmr (DMSO-d_6) was identical to that of starting material. In addition, ~ 5 mg of an unidentified dark oil was obtained. At 700° under similar conditions, 108 mg of LXXX produced 17 mg of tar and 60 mg of solid material whose ir (KBr) showed carbonyl absorption at 1735 cm^{-1}. The nmr of this pyrolysate indicated a 64:36 mixture of LXXX and 2-benzimidazolinone LXXXI. In a second experiment at 700°, 164 mg of LXXX pyrolyzed to give 23 mg of tar and 106 mg of a 54:46 mixture (by nmr) of LXXX and LXXXI. LXXX (125 mg) was completely isomerized at 800° with the formation of 42 mg of LXXXI, nmr (DMSO-d_6): 6.93 (s, 4H) and 11.6 δ (broad s, 2H); ir (KBr): 1735 cm^{-1} (C=O). 33 mg of tar was also obtained.

Pyrolysis of 2-methyl-3-indazolinone (LXXXIIb)

LXXXIIb (76 mg) was sublimed (sample heater at 125°) at 0.001 mm pressure into a Vycor pyrolysis tube maintained at 650° resulting in the condensation of 62 mg of products in the cold trap. An nmr spectrum (DMSO-d_6) of the pyrolysate indicated an 81:19 mixture of LXXXIIb and 1-methyl-2-benzimidazolinone (LXXXIII). At 700°, 72 mg of LXXXIIb produced 59 mg of essentially the same mixture in an approximate ratio of 40:60. Preparative tlc (silica

gel, 75% ethyl acetate-hexane) separated the two components to give 20 mg of LXXXIIa (higher rf value), ir ($CHCl_3$): 1710 cm^{-1} (C=O). LXXXIIb was also isolated (~ 27 mg) along with minor amounts of unidentified material.

Pyrolysis of 1-methyl-3-indazolinone (LXXXIIa)

62 mg of LXXXIIa was sublimed (sample heater at 95°) at 0.001 mm pressure into a Vycor furnace tube maintained at 600° yielding 55 mg of product. Column chromatography of this material led to the isolation of only LXXXIIa as verified by nmr spectroscopy and tlc. At 650°, 70 mg of LXXXIIa produced 52 mg of a 1:3 mixture (by nmr) of starting material and 3-indazolinone (LXXX). Separation of this mixture by preparative tlc yielded 14 mg of LXXXIIa and ~ 37 mg of LXXX. At 700°, 130 mg of LXXXIIa afforded 56 mg of a product mixture which was separated by column chromatography. Elution with 50-75% ethyl acetate-Skelly B yielded 14 mg of LXXXI, and subsequent washing with ethyl acetate gave 42 mg of LXXX as shown by nmr. Trace amounts of starting material and 1-methyl-2-benzimidazolinone (LXXXIII) could be detected in the nmr spectrum of the crude pyrolysate.

Pyrolysis of 1,2-dimethyl-3-indazolinone (LXXXV)

Sublimation (sample heater at 75°) of 275 mg of LXXXV into a Vycor furnace tube maintained at 600° and 0.005 mm

pressure resulted in the formation of 211 mg of a product mixture which was separated by column chromatography. Elution with 45-70% ethyl acetate-Skelly B gave 15 mg of 1-methyl-2-benzimidazolinone (LXXXIII) containing trace amounts of the dimethyl derivative LXXXVI as indicated by nmr and tlc. Further elution with 80-95% ethyl acetate-Skelly B furnished 65 mg of starting material. Washing the column with ethyl acetate afforded 51 mg of 2-methyl-3-indazolinone (LXXXIIb), m.p. 198-204 (decomp.). At 650°, 145 mg of LXXXV produced 8 mg of LXXXIII, 18 mg of starting material, and 22 mg of LXXXIIb after column chromatography of the 85 mg of pyrolysate obtained. A small amount (~ 13 mg) of unidentified material was also isolated.

Attempted pyrolysis of 1,2-benzisothiazolin-3-one (XCIVa)

95 mg of XCIVa was sublimed (sample heater at 110-115°) at < 0.001 mm pressure into a Vycor furnace tube heated to 500°. The pyrolysate (94 mg) was washed out of the U-trap with reagent acetone and methanol. The nmr spectrum of this material was identical to that of starting material. Similar results were obtained at 600° and 700°. In both experiments > 95% of XCIVa was recovered unchanged as determined by nmr and ir spectroscopy.

Attempted pyrolysis of 2-methyl-1,2-benzisothiazolin-3-one (XCIVb)

Sublimation (sample heater at 70-75°) at 0.001 mm pressure of 233 mg of XCIVb into a Vycor furnace tube heated to 500° resulted in quantitative recovery of unchanged starting material as shown by nmr spectroscopy. Similar results were obtained at 600°. At 700°, XCIVb produced material which was very difficultly soluble in methanol or acetone and was not characterized further.

Pyrolysis of 2-p-toluenesulfonyl-1,2-benzisothiazolin-3-one (XCVIII)

112 mg of XCIVe was sublimed (sample heater at 150°) at 0.001 mm into a Vycor furnace tube at 500° yielding 58 mg of product which was washed out of the cold trap with methanol. The ir and nmr spectra of this material were identical to the corresponding spectra of 1,2-benzisothiazolin-3-one (XCIVa).

Photolyses

Photolysis at low temperature

Irradiation experiments of compounds XXXI and XLVII at 77 °K and (-) 72 °C, respectively, were conducted using the apparatus described in reference 102. The progress of the reactions was monitored by infrared spectroscopy at these temperatures.

Photolysis of 3-hydroxy-1,2-benzisoxazole (XXXI)

A degassed solution of 135 mg of XXXI in 200 ml of ether was irradiated for 1 hr with Corex-filtered uv light. Evaporation of the solvent and sublimation at 0.07 mm yielded 107 mg of 2-benzoxazolinone (XXX), indistinguishable from authentic material by melting point, ir, nmr, and mass spectral criteria. Yields of XXX decreased upon longer irradiation (see Table 15). Photolysis through Vycor for 3 hr of a degassed ether solution of XXXI which was 0.1 M in piperylene produced a 37% yield of XXX. The product was extracted from the concentrated ether solution with aqueous Na_2CO_3.

A solution of 270 mg of XXXI in 180 ml of absolute methanol was degassed and photolyzed (Corex) for 15 min. The residue obtained upon evaporation of the solvent was chromatographed on a column of silica gel. Elution with 25-35% ethyl acetate-Skelly B yielded 197 mg of XXX. Approximately 54 mg of XXXI was recovered by washing the column with 40-50% ethyl acetate-Skelly B. Irradiation of a methanol solution of XXXI for 2 hr at (-) 72° resulted in a product mixture of only XXXI and XXX in a ratio of 38:62 by nmr.

A degassed solution containing 270 mg of XXXI in 180 ml of reagent acetone was irradiated with Pyrex-filtered uv light for 3 hr. Solvent removal and elution from a

silica gel column returned 65 mg of XXX and 133 mg of starting material.

Photolysis of salicyloyl azide (XXXIV)

A solution of 163 mg of XXXIV in 200 ml of absolute methanol was degassed and photolyzed with Pyrex-filtered uv light until effervescence resulting from nitrogen expulsion had subsided (~ 30 min). Evaporation of the methanol produced an essentially quantitative yield of XXX as shown by nmr spectroscopy.

Photolysis of 2-methyl-1,2-benzisoxazolin-3-one (XLII)

Irradiation (Vycor) of a degassed solution of 0.5 g of XLII in 180 ml of ether for 3 hr followed by evaporation of the solvent and column chromatography yielded 114 mg of 3-methyl-2-benzoxazolinone (XLIII) and 267 mg of a mixture (17:1 by nmr) of XLII and N-methyl salicylamide (LXVII). Preparative tlc separated LXVII (molecular ion at m/e 151) from the mixture. Similar results (see Table 16) were obtained by irradiating (Vycor) a 0.006 M solution of XLII in pentane for 3 hr. Irradiation of 149 mg of XLII in 180 ml of absolute methanol 1 hr produced LXVII in 39% yield.

A degassed solution of XLII (149 mg) in 180 ml of benzene containing 0.01 M benzophenone was irradiated for 3 hr with Pyrex-filtered uv light. The concentrated

photolysate was analyzed by nmr spectroscopy which indicated < 5% conversion to XLIII. An experiment carried out under identical conditions using 0.01 M acetophenone as sensitizer yielded 43 mg of XLIII and 100 mg of starting XLII. Irradiation (Pyrex) of XLII (149 mg) in 180 ml of acetone for 3 hr resulted in an almost quantitative conversion (> 92% isolated yield) to XLIII.

A 0.1 M solution of piperlylene in ether (200 ml) failed to quench the photoisomerization of XLII (164 mg) to XLIII. The photolysis was carried out for 3 hr using Vycor optics, and the products (see Table 16) were isolated by column chromatography.

Photolysis of 2-allyl-1,2-benzisoxazolin-3-one (LI)

A degassed solution of 175 mg of LI in 180 ml of acetone was irradiated for 3 hr using Pyrex-filtered uv light. The residue obtained upon solvent evaporation was chromatographed on a silica gel column. Elution with 15-20% ethyl acetate-Skelly B yielded 143 mg of LII.

Photolysis of 2-t-butyl-1,2-benzisoxazolin-3-one (XLVII)

A degassed solution of 191 mg of XLVII in 180 ml of acetone was photolyzed with Corex-filtered uv light for 6 hr. Elution through a silica gel column with 2-4% ethyl acetate-Skelly B separated 95 mg (50%) of XLIX. Further elution with 5-15% ethyl acetate-Skelly B furnished 75 mg

of starting material. Irradiation (6 hr) under similar conditions using a Pyrex filter produced < 5% yields of XLIX.

Photolysis of 3-methyl-2-benzoxazolinone (XLIII)

A solution of 0.5 g of XLIII in 160 ml of pentane and ~ 20 ml of ether was degassed and irradiated with Vycor-filtered uv light for 3 hr. A large amount of dark, insoluble material was obtained. Extensive column chromatography of the photolysate yielded 375 mg of starting material as the only elutible product.

Photolysis of 3-methoxy-1,2-benzisoxazole (XLIVa)

A degassed solution of 149 mg of XLIVa in 180 ml of ether was photolyzed with Vycor-filtered uv light for 6 hr. The products were isolated by silica gel column chromatography. Elution with 5-10% ethyl acetate-Skelly B yielded 33 mg of an oil whose nmr spectrum was consistent with a 6:1 mixture of XLIVa and XLVa. Methyl salicylimidate (LXIX) was obtained (~ 50 mg) by eluting with 15-25% ethyl acetate-Skelly B, m.p. 74.5-6°. Its ir, nmr, and mass spectra were identical with those of authentic LXIX. Irradiation of XLIVa under identical conditions in absolute methanol followed by chromatography of the photolysate yielded 27 mg of starting material, 16 mg of LXIX, and 36 mg of 2-methoxybenzoxazole (XLVa). The

mass spectrum of XLVa had a parent ion at m/e 149, and its ir and nmr spectra were superimposable with those of authentic material. Irradiation of XLIVa (148 mg) in 180 ml of acetone for up to 9 hr using a Pyrex filter resulted in recovery of only starting material.

Photolysis of 3-allyloxy-1,2-benzisoxazole (L)

A degassed solution of 175 mg of L in 190 ml of acetone was irradiated (Pyrex) for 9 hr. Evaporation of the solvent and chromatography of the product mixture produced 29 mg of starting material, 12 mg of 3-allyl-2-benzoxazolinone (LII), and 26 mg of XXX. Photolysis of L (175 mg) in 190 ml of absolute methanol for 30 min produced after column chromatography 36 mg of L, 28 mg of a 46:54 mixture (by nmr) of L and 2-allyloxybenzoxazole (LIII), 10 mg of LII, 25 mg of a 4:1 mixture (by nmr) of XXX and LXXI, and ~ 16 mg of undefined minor products.

Photolysis of 3-allyl-2-benzoxazolinone (LII)

A degassed solution of 350 mg of LII in 190 ml of acetone was irradiated (Pyrex) for 4 hr. Column chromatography of the photolysate yielded 237 mg of LII as the only elutible material

Photolysis of 2-allyloxybenzoxazole (LIII)

LIII (350 mg) was dissolved in 190 ml of acetone and after degassing was irradiated (Pyrex) for 2 hr. Column

chromatography of the photolysate yielded ~ 8 mg of starting material (by ir), 33 mg of LII, 15 mg of LXXI (a or b), and 167 mg of an 84:16 mixture (by nmr) of XXX and LXXI (a or b). The nmr (100 MHz) spectrum of the faster moving component of LXXI had the following resonances: 3.44 (d, 2H), 5.00-5.34 (m, 2H), 5.70-6.16 (m, 1H), 6.70-7.20 (m, 3H) and ~ 10.5 δ (broad s, 1H). Its ir (CCl_4) showed carbonyl absorption at 1772 cm^{-1}, and its mass spectrum had a parent ion at m/e 175. The mass spectrum of the mixture of XXX and the slower moving component of LXXI had molecular ions at m/e 135 and m/e 175. Similar results were obtained upon irradiation of LIII in acetone for 3 hr (see Table 19).

Photolysis of 2-benzyloxybenzoxazole (LXXIV)

A degassed solution of 450 mg of LXXIV in 190 ml of acetone was irradiated (Pyrex) for 2 hr. The photolysis products were isolated by silica gel column chromatography in the following order: 62 mg of bibenzyl, m.p. 51.5-53° (Lit. 53°, 161), nmr ($CDCl_3$): 2.88 (s, 4H) and 7.18 δ (s, 10H), 52 mg of 3-benzyl-2-benzoxazolinone (LXXV), 33 mg of LXXVIa, and 184 mg of a 73:27 mixture (by nmr) of XXX and LXXVIb. LXXVIa had, m.p. 176-8° (ethyl acetate-pentane); nmr ($CDCl_3$): 4.04 (s, 2H), 7.03 (s, 3H), 7.24 (s, 5H), and 9.3 δ (broad s, 1H); ir ($CHCl_3$): 1785 cm^{-1} (C=O); parent ion at m/e 225. Separation of XXX

and LXXVIb was achieved by column chromatography. LXXVIb had, m.p. 149-151°; nmr (100 MHz, $CDCl_3$): 4.00 (s, 2H), 7.00 (s, 3H), 7.22 (d, 5H), and 9.42 δ (broad s, 1H); ir ($CHCl_3$): 1787 cm^{-1} (C=O); parent ion at m/e 225. The photolysis of LXXIV was also performed in ether for 2 hr using a Corex filter producing analogous results as shown in Table 20.

Reaction of photo-product LXXVIa with acetyl chloride

LXXVIa (14 mg) was dissolved in 2 ml of ether and 1 ml of pyridine. Acetyl chloride (0.5 ml) was added slowly to the solution which was then stirred at room temperature for 1.5 hr, poured into 5 ml of water, and extracted with ether. Purification was achieved by preparative tlc (silica gel, 10% ethyl acetate-Skelly B) yielding 11 mg of an oil; nmr ($CDCl_3$): 2.33 (s, 3H), 4.16 (s, 2H), and 6.68-7.30 δ (m, 8H); ir ($CHCl_3$): 1800 (C=O, 2-one) and 1747 cm^{-1} (C=O, 3-acyl); parent ion at m/e 267.

Photolysis of 3-indazolinone (LXXX)

A degassed solution of 268 mg of LXXX in 190 ml of acetone was photolyzed with Pyrex-filtered uv light for 7 hr. Column chromatography of the photolysate returned 93 mg of starting material. Irradiation of LXXX (268 mg) in 190 ml of absolute methanol with Corex-filtered uv light for 8 hr and column chromatography of the products produced

50 mg of XCII, and 110 mg of starting material. XCII had, m.p. 130-1° (ethyl acetate-hexane); nmr ($CDCl_3$): 3.34 (s, 3H), 5.48 (s, 2H), 6.97-7.92 (m, 4H), and 10.55 δ (broad s, 1H); ir ($CHCl_3$): 3100-2600 (OH), 1626, and 1558 cm^{-1}; Anal. Calcd. for $C_9H_{10}N_2O_2$: 178.074; Found: 178.072. Photolysis (Vycor) of 268 mg of LXXX in 190 ml of methanol for 10 hr yielded 28 mg of XCII and ~ 84 mg of starting material.

Reaction of 3-indazolinone (LXXX) with formaldehyde in methanol

Formaldehyde (0.5 ml, 37%) was added dropwise over a period of 10 hr to a solution of 115 mg of LXXX in 95 ml of absolute methanol at room temperature. The solvent was evaporated at reduced pressure, and the residue was separated by preparative tlc. The faster moving component was mainly XCII as shown by nmr ($CDCl_3$) and ir ($CHCl_3$). However, weak absorption in the ir at 1670 cm^{-1} indicated a slight impurity of either the 2- or 1,2-disubstituted compound.

Photolysis of 1,2-benzisothiazolin-3-one (XCIVa)

A degassed solution of XCIVa (0.5 g) in 180 ml of ether was irradiated with Vycor filtered uv light for 9 hr. Column chromatography of the photolysis products was used to isolate 46 mg of 2-benzothiazolinone (XCVa, C=O at 1670 cm^{-1}), 231 mg of starting material, and 97 mg of 1,2-benzisothiazolin-3-one-S-oxide (XCVIa). XCVIa had,

m.p. 158-9°, parent ion at m/e 167, and nmr and ir identical to authentic material.

Photolysis of 2-methyl-1,2-benzisothiazolin-3-one (XCIVb)

Irradiation (Vycor) of a degassed solution of 0.5 g of XCIVb in 190 ml of ether for 9 hr and column chromatography of the products yielded 19 mg of 3-methyl-2-benzothiazolinone (XCVb) and 377 mg of a mixture of starting material and 2-methyl-1,2-benzisothiazolin-3-one-S-oxide (XCVIb). Preparative tlc of this mixture produced 19 mg of XCVIb, m.p. 110-2°. Photolysis of XCIVb (330 mg) in 190 ml of acetone for 10 hr through Pyrex optics afforded by column chromatography 12 mg of XCVb and 230 mg of starting material.

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