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OXIDATION OF ETHYL MICHLER'S KETONE OXIME

Final Report

by

A. F. Fentiman
R. H. Poirier

April, 1966

US Army Edgewood Arsenal
Edgewood Arsenal, Maryland 21010
Contract DA-18-035-AMC-705(A)
Task 1C622401A10204
Battelle Memorial Institute
Columbus Laboratories
505 King Avenue
Columbus, Ohio 43201

Distribution Statement

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FOREWORD

The work described in this report was authorized under Task 1C622104A10204, Detection and Warning Techniques (U). The work reported herein was started in July, 1965, and completed in March, 1966. The experimental data are contained in Battelle Laboratory Record Books Nos. 22643 and 22925.

Acknowledgments

The authors are indebted to R. L. Foltz who determined and assisted in the interpretation of the mass spectra, and to M. K. Scott who conducted certain phases of the chemical work. The authors are also grateful to R. W. Pfeil for the DTA analyses and his assistance in interpreting the results, and to A. H. Adelman for his contribution to the kinetic analysis. The authors acknowledge the work of W. D. Gager, who determined the electron-spin-resonance spectra and T. F. Page, Jr., who determined and aided in the interpretation of the NMR spectra.

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DIGEST

Ethyl Michler's ketone oxime (EMKO) is a reagent that has been useful as a detector of phosphorylating and phosphonylating agents, but its susceptibility to degradation has limited its serviceability. In an effort to overcome this difficulty, it was necessary to consider the oxidative and photochemical degradation of EMKO. Such a study was started on the hypothesis that free radicals, which are important intermediates in the course of many oxidations, are formed in the early stages of EMKO degradation in air or light, or both. Free radicals of EMKO were not detected, but several of its oxidation products were isolated and identified in this work. Subsequently, the photochemical degradation of EMKO on thin-layer supports and in solution was studied and several products isolated and identified. Several mechanisms and intermediates were postulated to account for the observed degradation of EMKO. In addition, the kinetics of the reaction were studied and several analogues of EMKO were prepared in order to test these mechanisms.

The treatment of EMKO with chemical-oxidizing agents leads predominantly to Beckmann rearrangement products, whereas the photochemical degradation of EMKO leads to several products among which are EMK, the anilide, the nor-ethyl anilide, and ethyl Michler's ketimine. The presence of these products did not seem to affect adversely the sensitivity of EMKO toward a model agent.

Through differential thermal analysis (DTA), EMKO was found to be sensitive to acid supports such as silica gel, and less sensitive to neutral and basic supports.

Apparently, the degradation of EMKO by oxygen and light is not accomplished through one simple route, but rather through two or more pathways that lead to several products and complicated kinetics.

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OXIDATION OF ETHYL MICHLER'S KETONE OXIME

by

A. F. Fentiman and R. H. Poirier

INTRODUCTION

Ethyl Michler's ketone oxime (EMKO) is a reagent that has been useful as a detector of phosphorylating and phosphonylating agents, (1)* but its susceptibility to degradation, especially under the influence of sunlight, has limited its serviceability. In an effort to overcome this difficulty, it became necessary to consider the oxidative degradation of EMKO.

In the presence of sunlight and oxygen, EMKO is degraded to the ketone and a yellow substance. In the absence of oxygen, ultraviolet light promotes the Beckmann rearrangement of EMKO, so that the benzanilide is isolated as the principal product. When EMKO is treated with chemical-oxidizing agents, transient-colored compounds are formed, but the benzanilide and the ketone are isolated as the major degradation products.

The purpose of this study was to determine the products that are formed when EMKO is degraded by chemical-oxidizing reagents or by sunlight and oxygen, and to determine whether or not these products affect the response of EMKO toward model agents. In addition, EMKO was to be studied in terms of reactive intermediates, such as free radicals, to determine the mechanism by which it is degraded. An understanding in this area would perhaps allow the design of superior and more stable reagents for the detection of certain CW agents.

RESULTS AND DISCUSSION

Chemical oxidation of EMKO proceeds through transient-colored intermediates. Since these colored intermediates were initially believed to be radicals, their detection and identification were attempted through electron-spin-resonance studies. When these efforts seemed fruitless, attention was directed toward the isolation and identification of the various oxidation products of EMKO. The investigation of the photooxidative fate of EMKO, neat and on supports, by means of differential thermoanalytical techniques was also included in these studies. The mechanistic aspect of the photodegradation of EMKO was considered in a preliminary way, as well as the effects of the degradation products upon the color response of EMKO to a model agent. The results and discussions of these studies are described in the following subsections.

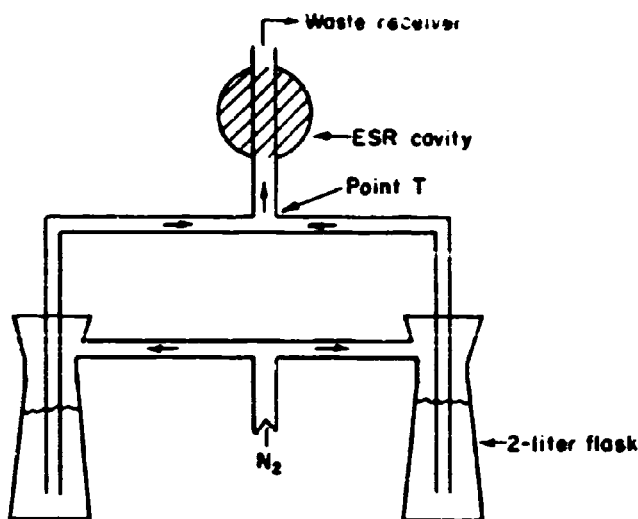
*The literature is cited on page 33.

Electron-Spin-Resonance Studies

A dilute solution of EMKO in methanol when treated with a solution of ceric ammonium nitrate in methanol formed a green color, which rapidly faded and finally became reddish brown. The same colors were observed when either benzene or methylene chloride was used as solvent and lead tetraacetate as the oxidizing agent. When nitrogen was bubbled through the benzene solutions prior to and after mixing, the green color could be preserved for as long as 1 hour. Analysis of this green solution by electron-spin-resonance (ESR) spectroscopy, however, gave no evidence for unpaired electron species.

In another experiment, lead tetraacetate was placed at the bottom of an ESR tube, carbon tetrachloride was added, and EMKO was subsequently floated on top of the carbon tetrachloride. The whole tube was then degassed by freeze thawing under reduced pressure (10^{-4} mm of mercury) and finally sealed under vacuum. When the EMKO and lead tetraacetate crystals were mixed, a blue color formed in the carbon tetrachloride layer. As before, however, no free-radical signals could be detected by ESR spectroscopy.

Since signals have been obtained with other oximes using flow techniques, (2) such a system for use with EMKO was constructed and is diagrammed below.



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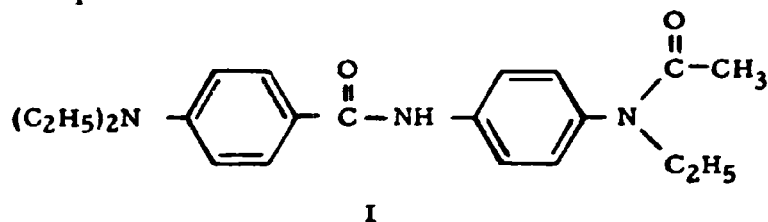
One flask was filled with 0.1-molar EMKO in benzene and the other with 0.1-molar lead tetraacetate in benzene. By careful adjustment of the pressure, the two liquids were forced together at the point T just prior to entering the ESR cavity. The pressure was adjusted so that 2 liters of solution flowed through the ESR cavity in about 3 minutes. This rate of flow allowed sufficient time for a scan of the ESR spectrum. The solution was blue on emerging from the ESR tube but rapidly turned green, then yellow, and finally brown as it proceeded to the waste receiver. Again no unpaired electron signals were detected.

In a final attempt to detect free-radical intermediates in the chemical oxidation of EMKO, a liquid-nitrogen probe connected to the ESR instrument was used. When EMKO in ethanol was cooled to Dry Ice/acetone temperatures with nitrogen bubbling through the solution, and an equally cold solution of ceric ammonium nitrate in ethanol was added, a deep-blue solution resulted. This solution was immediately frozen in liquid nitrogen, and the blue solid that separated was then placed in the liquid-nitrogen probe. Although the blue color was stable indefinitely at these temperatures, no unpaired electrons could be detected.

The fact that ESR signals could not be detected does not preclude the existence of free radicals. It is possible that the radicals are too short lived to be detected under the conditions of the investigation, or that different oxidation conditions are necessary for producing free-radical intermediates from EMKO.

Chemical-Oxidation Studies

Oxidation of EMKO by chemical reagents was conducted in the following way. EMKO (1.36 g) was dissolved in ethanol and treated with ceric ammonium nitrate (2.20 g) in ethanol. After 1/2 hour, the ethanol was poured into an equal volume of water and extracted with ether and benzene. The combined washings were dried and filtered and concentrated in vacuum. The concentrate was placed on a column (1 x 20 cm) of 30 g of alumina and the products eluted with 5 percent methanol in benzene. Five distinct bands formed and were collected. The last band was removed from the column with 50 percent methanol and benzene. The bands were all colored while on the column, but after isolation and purification most of the compounds emerged lightly colored. The compounds, which were identified by means of infrared, ultraviolet, and mass spectrometry, are in the order in which they were eluted from the column, ethyl 4-diethylaminobenzoate, ethyl Michler's ketone (EMK), 4,4'-bis(diethylamino)benzanilide (major product), and two compounds with molecular formulas of $C_{21}H_{27}N_3O_2$ (I) and $C_{21}H_{25}N_3O_3$ (II). The last two compounds appeared to be the benzanilides with one or two of the N-ethyl groups oxidized to acetyl. For example, the first of these anomalous compounds was suspected to be



but this structure was not confirmed.

The initial oxidation experiment using ethanol as solvent and ceric ammonium nitrate as oxidizing agent was repeated, except that oxygen was bubbled through the solution during the reaction. Separation as before gave only a small amount of EMK, I, and II; the product appeared to be almost exclusively the benzanilide.

Oxidation of EMKO by lead tetraacetate in benzene gave fewer reaction products. Thus, upon filtering the reaction mixture, concentrating the filtrate, and chromatographing the concentrate on alumina, two somewhat-colored fractions were collected. However, after these fractions were rechromatographed on silica gel and then recrystallized the colored entities proved to be minor impurities. Thus, EMK, mp 92-94 C (from hexane), was recovered from the first fraction, and the benzanilide, mp 135-137 C (from benzene), was recovered as the major product from the second fraction. The identity of these materials was confirmed by ultraviolet spectroscopy and by mixed melting points with authentic materials.

The observation that the benzanilide is the principal chemical-oxidation product of EMKO is presumably consistent with the report that certain metals or their derivatives promote the Beckmann rearrangement of aldoximes. (3) As a result, it was suspected that further studies of the oxidation of EMKO by metal salts would not necessarily advance the understanding of the aging characteristics of EMKO. Hence, a study of the photochemical effects on EMKO was undertaken.

Photochemical Studies

In these studies, EMKO was irradiated under the following conditions: (1) on thin-layer supports, (2) as a neat solid, and (3) in solution.

Thin-Layer-Support Studies. The aging characteristics of particular interest in this study of EMKO concern those that occur on storage, either as a neat solid or as a solid on a support, in the presence of sunlight and air. A technique especially convenient for the study of the degradation of EMKO in the solid state was the following. Solutions of EMKO were placed on thin-layer chromatographic media, the solvent was evaporated, and the EMKO stain was irradiated and then chromatographed. The fractions that separated were analyzed spectrometrically.

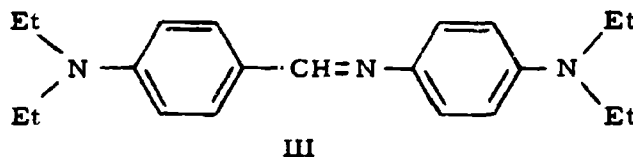
In one series of experiments, EMKO was dissolved in benzene (1.0 to 4.0 $\mu\text{g}/\mu\text{l}$) and spotted on silica-gel thin-layer supports. After the benzene had evaporated the sample was irradiated with a high-pressure broad-spectrum mercury lamp with maximum output at 300 $\text{m}\mu$. Under these conditions, EMKO was essentially unchanged after 1/2 hour but was nearly all degraded after 3 hours. The chromatogram was developed first with 5 percent methanol in ether thereby eluting several spots, and then with 35 percent methanol in ether to give another series of spots. The respective spots were scraped from the sheet, and the product was extracted from the adsorbent using methanol. Ultraviolet spectra were determined on the methanol solution, and the mass spectra on the residue from such solutions. Table 1 summarizes the information obtained on the five fractions collected. Fraction 1 represents the most mobile fraction and Fraction 5 the least mobile.

TABLE 1.
CHEMICAL-OXIDATION PRODUCTS OF EMKO

Fraction	Compound	Absorption Maximum, $m\mu$ (MeOH)	Parent Peak, m/e
1	EMKO	308	339
2	EMK	375	324
3	Benzanilide	323	339
4	$C_{19}H_{25}N_3O^{(a)}$	323	311
5	$C_{21}H_{29}N_3^{(a)}$	437	323

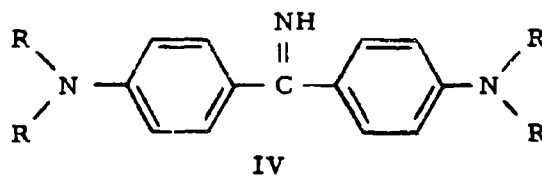
(a) Determined by high-resolution mass spectrometry.

Fraction 5 is of particular interest since its yellow color perhaps accounts for the observed discoloration of aged and irradiated EMKO. On the basis of its color and molecular formula, which was determined by high-resolution mass spectrometry, the Schiff's base III was tentatively postulated for its structure.



However, this compound, which was subsequently prepared from p-diethylamino-benzaldehyde and N,N-diethyl-p-phenylenediamine, proved to be inconsistent spectroscopically with that of Fraction 5 (λ_{max} in methanol, 390 versus 437 $m\mu$).

The next molecular structure considered for the identity of Fraction 5 was the IVa, the ethyl analogue of auramine, IVb.



R = (a) C_2H_5 , (b) CH_3

Auramine is essentially colorless, but its salts, such as the hydrochloride (a well-known dye), is a bright yellow. When initial attempts to prepare ethyl Michler's ketimine hydrochloride failed, supporting evidence for this imine was sought through studies with auramine. Thus, the ultraviolet spectrum of a commercial sample of IVb hydrochloride was determined and found to be very similar to that of Fraction 5 (Figure 1). A hypsochromic shift in the absorption maxima at the longer wavelengths was the only difference in the two spectra. Also, an identical shift in the spectra of both compounds was observed in comparing the maxima of methanol solutions with those of acetonitrile solutions. To further

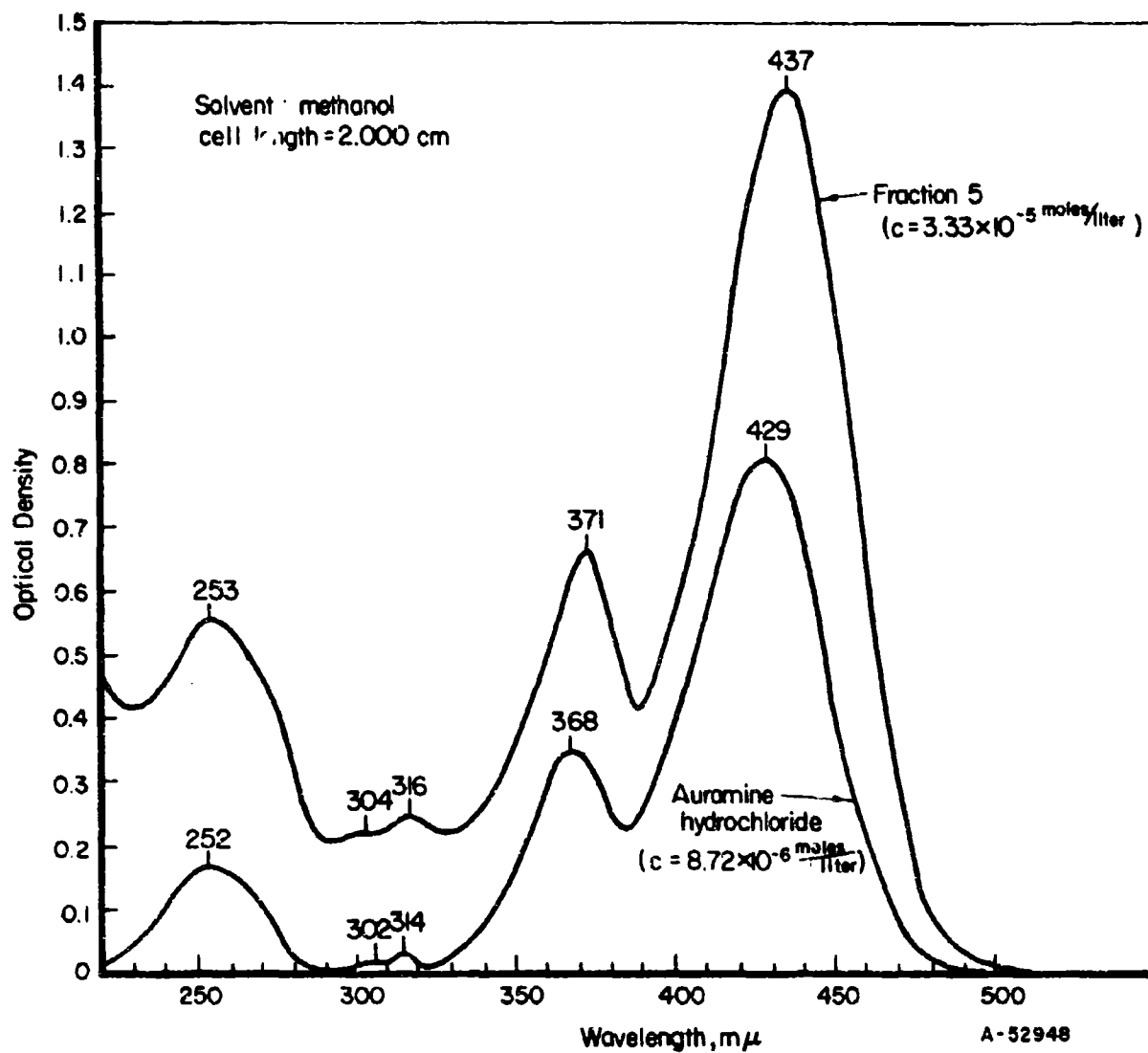


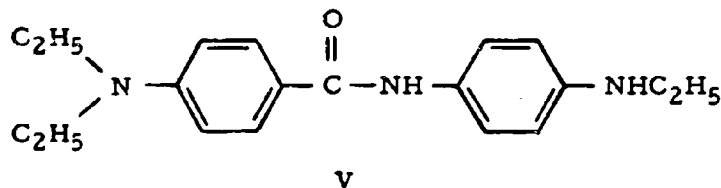
FIGURE 1.
ULTRAVIOLET AND VISIBLE SPECTRA OF KETIMINES

check this similarity, Michler's ketone oxime (MMKO) was irradiated on silica gel, and the yellow photoproduct was isolated and examined spectroscopically. Thus it was shown that the photoproduct of MMKO was identical to auramine.

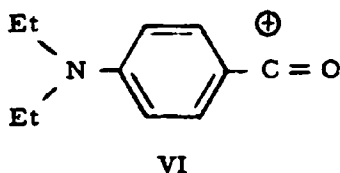
Since auramine base is essentially colorless, the source of proton giving rise to its colored salt under conditions supposedly free of acids was sought. Accordingly, upon making aqueous solutions of auramine hydrochloride basic with sodium hydroxide the yellow color was discharged, but subsequent bubbling of carbon dioxide through the solution restores the yellow form of auramine. Apparently, carbonic acid is strong enough to protonate the imine and produce the yellow color. Similar color transitions were noted after repeating this experiment with Fraction 5.

The ketimine identity of Fraction 5 was eventually confirmed by the preparation of ethyl Michler's ketimine hydrochloride by reaction of p-diethylaminobenzonitrile with p-diethylaminophenyl lithium. The ultraviolet spectrum of this ketimine hydrochloride (λ_{max} in methanol, 437 m μ) and the infrared spectra were identical to those of Fraction 5. Its mass spectrum with a parent peak at 323 was also identical to that of Fraction 5. Occurrence of the parent peak at a mass corresponding to the free base is not unusual, for other amine salts tend to lose the acid moiety under mass-spectrometric conditions. It was therefore concluded that the "450 product", previously identified by Dr. E. J. Poziomek and Mrs. Ethel Hackley* of US Army Edgewood Arsenal as one of the photoproducts of EMKO, corresponds to the ketimine described here.

Fraction 4 was tentatively assigned the nor-ethyl Structure V, an analog of the benzanilide isomer of EMKO, on the basis that



its ultraviolet absorption maximum (323 m μ) occurs at the same wavelength as that of the benzanilide resulting from the Beckmann rearrangement of EMKO, namely, Fraction 3. The base peak of its mass spectrum has an m/e of 176, which corresponds to a molecular formula of $\text{C}_{11}\text{H}_{14}\text{NO}$. This fragment, which was given Structure VI, also arises from fragmentation of the benzanilide.



*Private communication.

Hence, the loss of ethylene necessary to produce the $C_{19}H_{25}N_3O$ compound must have occurred at the nitrogen attached to the other N-phenyl ring of the benzanilide. Fraction 4 was then treated with acetyl chloride in pyridine and the mass spectrum of the product was determined. Although the product was contaminated with the acetyl chloride-pyridine complex, the mass spectrum clearly exhibited the presence of a material with a mass of 353, which corresponds to the N-acetyl derivative of Fraction 4. As expected, Fragment VI with a mass peak at 176 m/e was detected. The deethylation of EMKO apparently occurs thermally as well as photochemically, for Compound V was detected among the products of degradation of EMKO at 205 C for several hours.

Solution Studies. Irradiation studies on solutions of EMKO were undertaken (a) to establish whether or not the minor absorption band at about 370 m μ in the spectrum of the ketimine photoproduct could stem from the presence of EMK and (b) to compare the photodegradation of EMKO in solution with that on solid adsorbents.

A 10^{-5} molar solution of EMKO in acetonitrile was irradiated and the course of reaction monitored via ultraviolet absorption spectroscopy. A prominent band at 360 m μ developed and, since this band always had an absorbance equal to or greater than the one at 450 m μ , it was concluded that this absorbance was not due to the ketimine but rather to the ketone. The reaction followed second-order kinetics for the first 10 minutes during which 63 percent of the EMKO was destroyed. This information apparently corroborates the results obtained earlier by Dr. Poziomek and Mrs. Hackley.

When the concentration of EMKO was increased 1000-fold to 10^{-2} molar and the solution irradiated, kinetics were no longer second order and the reaction was very slow. The drastic change in rate with concentration made the kinetics even more difficult to interpret. Since the role of oxygen had been ignored up until this time, the above experiment was repeated with oxygen bubbled through the solution during the irradiation. These conditions, however, did not change the course of the reaction.

When dilute solutions of EMKO were irradiated in chloroform, EMKO was consumed very rapidly and the products did not absorb in the ultraviolet or visible region of the spectrum. In more concentrated solutions, EMKO was consumed only very slowly and the absorption of EMK appeared in the ultraviolet spectrum.

Irradiation of a concentrated solution of EMKO in spectroscopic-grade acetonitrile produced only a faint yellow color; but dilution of this solution with nonspectroscopic-grade acetonitrile developed a strong yellow color, thereby indicating the presence of appreciable amounts of ketimine. The addition of acetic acid to the irradiated solution had the same effect (Figure 2). The immediate appearance of the 450-m μ band upon irradiation of dilute solutions of EMKO presumably arises from the presence of acid impurities.

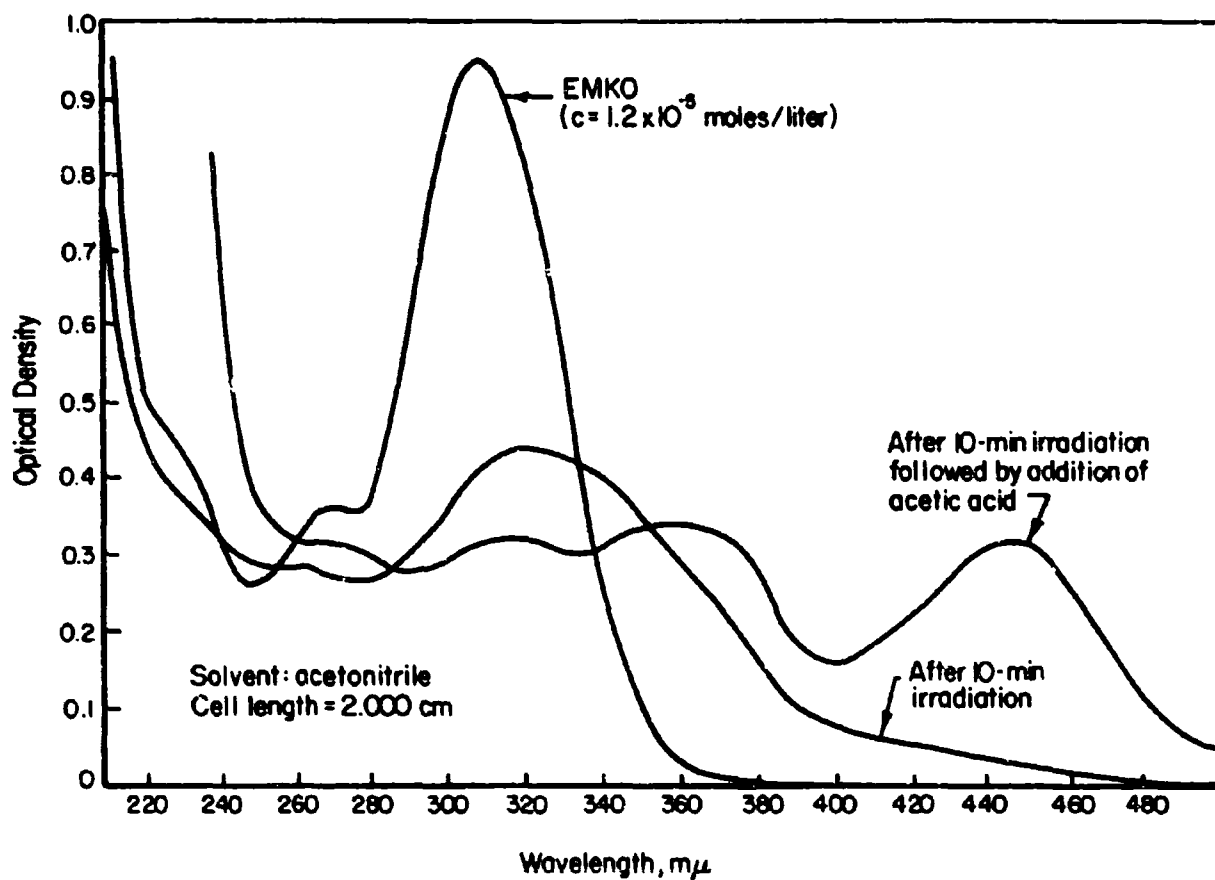


FIGURE 2.
ULTRAVIOLET AND VISIBLE SPECTRA OF EMKO
AND PHOTOPRODUCTS

On continued irradiation of EMKO solutions, both the ketimine and the ketone products are slowly consumed. There is an abundance of literature on the photochemical degradation of benzophenones^(4, 5) the major products are usually benzpinacoles. The photoreactions of ketimines, however, are not so well documented.

Differential-Thermal-Analysis Studies

In conjunction with the thin-layer work, differential thermal analysis (DTA) and thermal gravimetric analysis (TGA) were employed to monitor in situ the behavior of EMKO on chromatographic supports. Thus, it was found that the EMKO used in these studies was at least 99 percent pure, and that it had a melting endotherm at 202 C, which remained unchanged through several successive crystallizations. In fact, EMKO that had been stored for 6 years in a dark bottle, although discolored, contained no detectable amounts of EMK or other impurities; as little as 0.5 percent impurity could have been detected by the DTA assay employed.

When EMKO was deposited onto silica gel from a benzene solution, the melting endotherm of EMKO was no longer present, but in its place there appeared a small broad endotherm at about 50 C, two major endotherms at 175 C, and 215 C and overlapping a small endotherm at 310 C. In contrast, when EMK was placed on silica gel a normal melting endotherm of 96 C was observed with no extraneous endotherms. Unlike EMKO, EMK seemed unchanged by the silica gel.

The photodegradation of EMKO in various forms was next studied by DTA techniques. Accordingly, the thermogram of EMKO in crystal form, as a fused solid, or as an evaporated film, which was irradiated with broad-spectrum ultraviolet light for 1/2 hour, showed no evidence of reaction or decomposition. By contrast, the thermogram of irradiated EMKO on silica gel showed a broad endotherm at 97 C, which corresponded possibly to 10 percent EMK and the anilide, two other major endotherms at 190 and 225 C, and a minor endotherm at 310 C. The latter three endotherms were consistent with the endotherms observed in the thermogram of unirradiated EMKO on silica gel.

Although the anilide and unchanged EMKO were the only two products isolated from chromatograms of EMKO, DTA studies indicated that other materials formed. The unidentified DTA endotherms are suspected to stem from chemisorbed species of EMKO on the acidic silica gel. In an effort to establish this phenomenon, thermograms of EMKO on neutral and basic supports were examined. As anticipated, EMKO exhibited its normal melting endotherm (202 C), when placed onto barium sulfate, an essentially neutral support. Still, the barium sulfate became dark yellow, and on reheating the melting endotherm was slightly lower (196 C), but still rather sharp. A similar experiment was conducted using calcium carbonate, a basic support. In this case, EMKO appeared to be completely stable, and showed a melting endotherm at 202 C even after repeated fusions. The support eventually became very light yellow, but no evidence of decomposition was detectable in the endotherms.

Color Tests

Spot tests were conducted to determine if the presence of photodegradation products affected the color reaction of EMKO, and to determine if any of the compounds prepared during this program gave color reactions with acylating agents. Since ethyl Michler's ketimine was not available in sufficient quantities for such tests, Michler's ketimine was substituted in its place. Toluene sulfonyl chloride was employed as model agent in the tests, which are summarized in Table 2. Apparently, neither the ketone, the anilide, nor the ketimine photodegradation products of EMKO affected perceptibly the color response of EMKO to toluene sulfonyl chloride. It is interesting that the N-methyl EMKO derivative gave a faster color change than did EMKO, and that the O-methyl EMKO derivative gave no color response. The significance of these observations are discussed later. The color response of 4,4'-dinitrobenzophenone oxime is also reported here because it is the only new oxime prepared in the current studies that had not been previously evaluated.

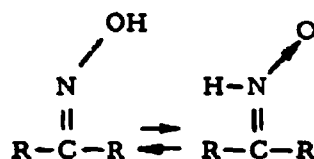
TABLE 2.
REACTION OF p-TOLUENESULFONYL CHLORIDE
WITH VARIOUS REAGENTS(a)

Reagent	Response
EMKO	Yellow → red → black (<2 min)
EMKO and EMK	Yellow → red → black (<2 min)
EMKO + anilide	Yellow → red → black (<3 min)
EMKO + auramine · HCl	Yellow → red → black (<2 min)
Auramine · HCl	No reaction
Auramine (free base)	Slowly turned yellow
N-Methyl EMKO	Red (instantaneous) → orange (>5 min)
O-Methyl EMKO	No change
N-Methyl benzophenone oxime	No change
O-Methyl benzophenone oxime	No change
4,4'-Dinitrobenzophenone oxime	No change

(a) The reagent (~5 mg) or 1:1 mixture of reagents (total, ~5 mg) was mixed with 1 drop of benzene and to this solution was added 1 drop of a 10 percent solution of p-toluenesulfonyl chloride in benzene.

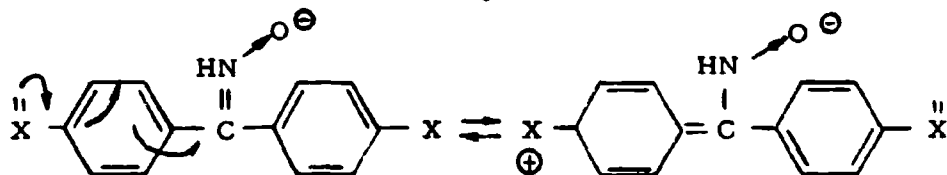
Mechanism of Degradation

In the course of ascertaining the purity of EMKO, its mass spectrum was determined. Unexpectedly, one of the major fragmentation pathways of EMKO involved the loss of an oxygen atom. Loss of oxygen is uncommon in organic molecules. Amine, oxides, such as pyridine N-oxide, and nitrones are among the few classes of compounds that fragment in this manner. The observed fragmentation of EMKO prompted the consideration of tautomeric forms of EMKO, which might fragment with the loss of oxygen. Oxime-nitrone tautomerism was the most obvious isomerization considered.



Some consideration had previously been given to this question. For example, Blatt had prepared molecules of cyclic structure that supposedly arise uniquely from either the nitrone form or the oxime form. (6) The pH values and spectroscopic characteristics of oximes indicate that two forms exist in equilibrium. (7-9)

Since the nitrone form would have a much more electronegative nitrogen, it was believed that electron-releasing groups would provide stability to this structure and increase its contribution to the equilibrium mixture. Thus:

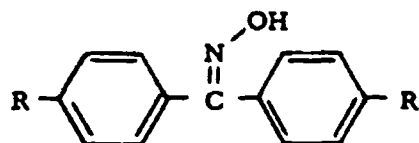


This type of stabilization would not be so effective in the oxime structure since the oxime nitrogen is not so electronegative as the nitrone nitrogen.

Fortuitously, a series of substituted benzophenone oximes was available from earlier work in these laboratories. Their mass spectra were determined in order to establish whether or not oxygen fragmentation was common for diaryl ketoximes. The compounds included in this study along with a summary of the relative mass intensities of some of the peaks in the mass spectra are shown in Table 3.

The loss of oxygen versus the loss of hydroxyl is reflected by the relative intensity of the parent-minus-oxygen peak and the parent-minus-hydroxyl peak. These data do not show conclusively that the nitrone form gives loss of oxygen and the oxime form loss of hydroxyl, but it may be significant that the relative intensities of the parent peaks are related to the electron-releasing, and the electron-withdrawing characteristics of the R-substituent.

TABLE 3.
MASS SPECTROMETRIC FRAGMENTATION OF DIARYL KETOXIMES



R	Relative Intensities(a)	
	$\frac{\text{Parent-O}}{\text{Parent-OH}}$	$\frac{\text{Parent}}{\text{Parent-O}}$
$(\text{CH}_3)_2\text{N}^{(b)}$	1. 22	1. 32
$(i\text{-Pr})_2\text{N}$	4. 50	2. 22
$\text{Et}_2\text{N}^{(c)}$	5. 15	0. 23
H	0. 31	2. 56
NO_2	0. 29	12. 7

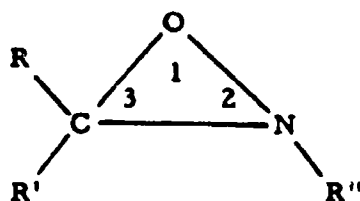
(a) Parent-O is the height of the mass spectra signal corresponding to a molecular weight 16 less than that of the parent molecule, and Parent-OH is the height of the signal at a molecular weight 17 less than that of the parent molecule.

(b) MMKO.

(c) EMKO.

The data reported in the table above were obtained from runs in which the samples were introduced through the hot box of the mass spectrometer. In order to minimize thermal effects on the fragmentation pattern, sampling was also achieved through a direct insertion probe, which permits introduction of the sample directly in the electron beam, and allows for ionization at lower temperatures. The relative intensity of the parent-minus-oxygen peak obtained in this series of experiments was lower, nevertheless, the value of the parent to parent-minus-oxygen ratio still followed the order previously noted. This observation seems to indicate a temperature dependency of the equilibrium with a larger contribution of the species that loses oxygen at higher temperatures.

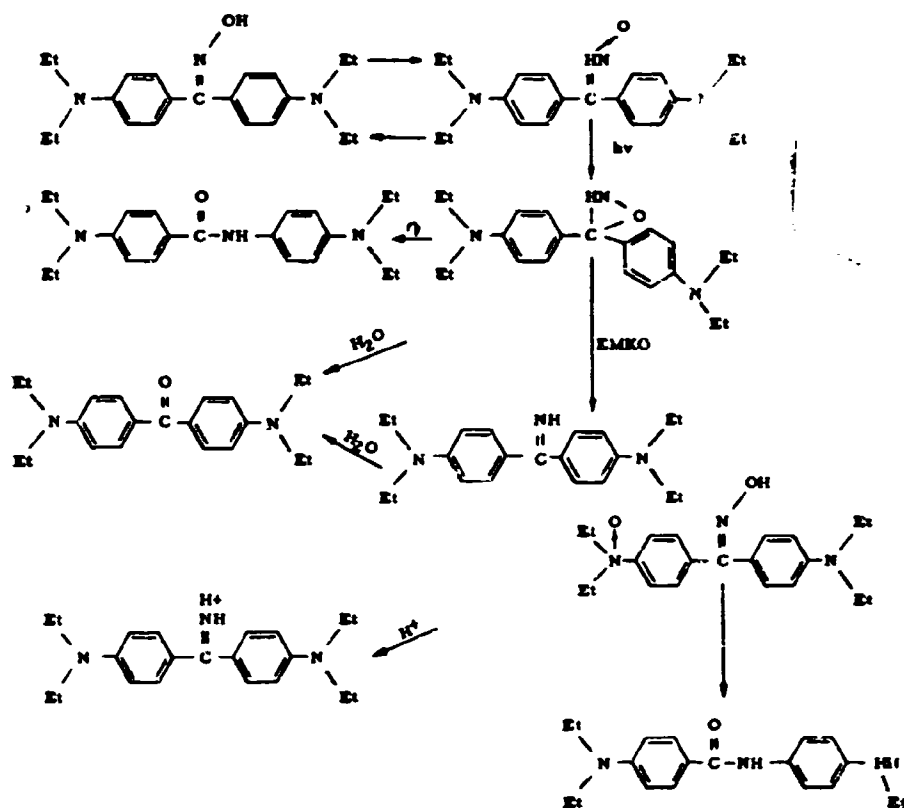
If it is assumed that EMKO can exist in the nitron form as well as in other forms, it is of interest to consider what the consequences of such an assumption are. Recent studies on the irradiation of nitrones have shown that oxaziridines, VI, are among the major photoproducts. (10, 12) Secondary products result from the decomposition of the oxaziridines, and include amides, ketones, and imines. The chemistry of the oxaziridines is summarized in several places. (6-9)



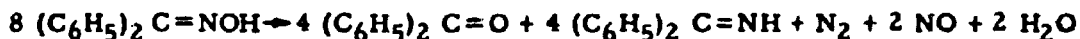
VI

Attempts to prepare oxaziridines isomeric with ketoximes have been unsuccessful, presumably, because of their instability. One example, however, is the oxaziridine derived from cyclohexanone. This compound exists for only a short time and cannot be purified even though the N-methyl compound can be prepared in 50 percent yield. (13) It appears that no 3, 3-diaryloxaziridine compounds have thus far been prepared. Oxaziridines are very active oxidizing agents, and their behavior parallels that of hydrogen peroxide. Thus, oxaziridines oxidize iodide to iodine quantitatively. In fact, this reaction serves for the analysis of oxaziridines. (14, 15) However, their oxidation of tertiary amines to the corresponding N-oxides (15) may be of particular interest to this project.

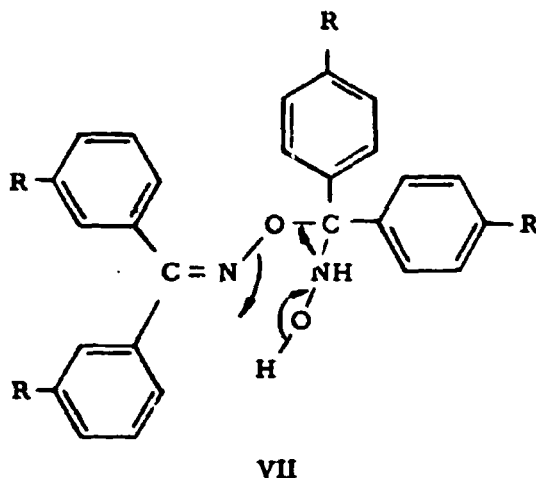
The appearance of an imine in the photodegradation of an oxime is certainly unusual as is the mass spectrometric fragmentation of EMKO to the ketimine. As shown in the following sequence of reactions, the photochemistry of nitrones and the chemistry of oxaziridines account for most of the photoproducts of EMKO, which have thus far been isolated.



There is present in the literature a preparation of diphenylmethane imine by the disproportionation of benzophenone oxime. (16, 17)



The products of this reaction are very similar to the major products obtained from the photochemical degradation of EMKO. A possible mechanism for this reaction that does not involve a nitron or oxaziridine intermediate involves the coupling of two oxime molecules to form Dimer VII, which subsequently disproportionates as shown below to a ketone, an imine, and HNO.

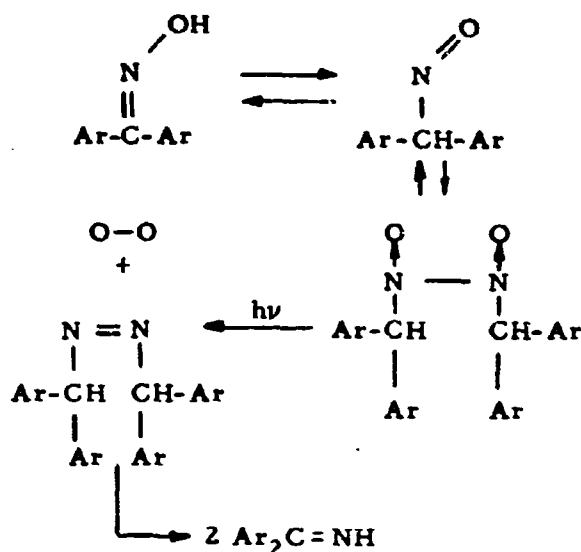


It is possible that the initial dimerization of the oxime occurs thermally when

R is H, or at low temperatures photochemically when R is $N \begin{matrix} \text{Et} \\ \text{Et} \end{matrix}$. Hyponitrous

acid, $H_2N_2O_2$, is a known compound that decomposes readily to nitrogen, oxides of nitrogen, and water. (18) Its formation has been postulated in other photochemical reactions. (19)

A third mechanism, which was suggested by Dr. Arnold Gordon, Chemical Research Laboratories, US Army, Edgewood Arsenal, involves dimerization via an isonitroso form of EMKO as shown below. Such dimerization is apparently common for isonitroso compounds. (20)



The most serious deficiency of the aforementioned schemes perhaps lies in the failure to account for the role of oxygen in the degradation of EMKO.

Kinetic Analysis. In an effort to differentiate among the proposed mechanisms, a kinetic analysis of the photochemical degradation of EMKO was made. Thus, by letting R represent EMKO in the ground state, R* represent EMKO in the excited state, and P represent unspecified products, several photochemical events can be visualized. Among them are the following:



The following cases are then considered: Case I, Equations (1), (2), and (3) operative; Case II, Equations (1), (2), and (4) operative; and Case III, Equations (1), (2), and (5) operative. In each case, the differential equations were derived and the order of the reaction calculated for a high and a low initial concentration of EMKO (Table 4).

TABLE 4.
PREDICTED ORDERS OF REACTION FOR THE
PHOTODEGRADATION OF EMKO

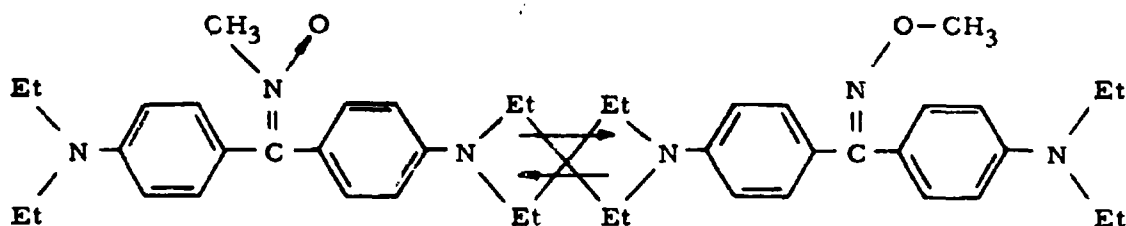
Case	Order of Reaction	
	High Concentration	Low Concentration
I	0	1
II	Fractional	Fractional
III	1	2

At 10^{-5} molar initial concentration of EMKO, the reaction followed second-order kinetics for the first 10 minutes during which 63 percent of the EMKO reacted. When the initial concentration of EMKO was increased 1000-fold to 10^{-2} molar and the solution irradiated, the kinetics were no longer second order and the reaction was very slow. After 2 hours of irradiation, only 17 percent of the EMKO was reacted. The reaction appeared to be first order up until this time, but the reaction rate then diminished even more, and the data could not be interpreted in terms of an integral order of reaction. These results most closely fit those that would result if Case III were operative but, because of the undetermined kinetics above 17 percent reaction at high concentration, the full significance of these results cannot be assessed.

Structure Modification. In a further attempt to distinguish between the various possible mechanisms, selected derivatives of EMKO were prepared and their chemistry investigated. Smith and Robertson have prepared a series of O-methyl and N-methyl benzophenone oximes for a study of factors affecting the site of alkylation of oxime salts. (21) They found that electron-releasing groups favored N-alkylation, whereas electron-withdrawing groups favored O-alkylation. Their chromatographic procedure for the preparation of O-methyl and N-methyl benzophenone oxime was used successfully for the recovery and purification of O-methyl EMKO and N-methyl EMKO from the products of methylation of EMKO.

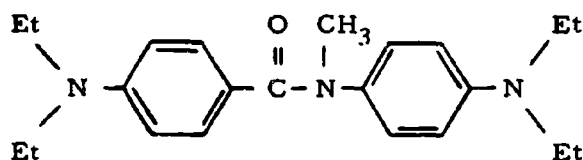
The mass spectra of both O-methyl benzophenone oxime and O-methyl EMKO showed loss of methoxyl group as the major fragmentation pathway, whereas the N-methyl derivatives showed loss of oxygen as a major fragmentation pathway. The NMR spectra showed a downfield shift of the methyl protons in going from the O-methyl to the N-methyl derivative. This shift stems from a deshielding effect caused by the greater electronegativity of the nitrogen atom in the N-methyl compounds.

These two compounds represent a means of locking EMKO in the oxime and the nitron forms, for the methyl group would not be expected to migrate from the oximino oxygen.



In certain cases, nitrones have been induced to rearrange to the O-methyl derivative, but the reaction is not general and the migrating group is one with a greater migratory aptitude than methyl. (22)

When N-methyl EMKO was irradiated in methanol solution, it rapidly degraded as indicated by the disappearance of ultraviolet absorption at 359 m μ and the appearance of new absorption at 320 m μ . The photoproduct was not identified but, based on the work of Calvin and Spitter⁽¹⁰⁾, the main product would be expected to be the N-methylbenzanilide Analogue VIII in protic solvents such as methanol. *



VIII

No imine or ketone was formed, and the addition of acid had no chromophoric effect (no imine as the free base). These results indicate that rearrangement products such as the anilide might form through an oxaziridine intermediate. However, the oxaziridine mechanism is doubtful as an exclusive pathway to all of the products observed, since an oxaziridine of very similar structure to that proposed earlier is almost certainly an intermediate in the photodegradation of N-methyl EMKO.

When O-methyl EMKO was irradiated in methanol, it was quickly and quantitatively converted to the conjugate acid of the ketimine (Figure 3). The structure of the product was confirmed by isolation and comparison of its mass and infrared spectra to those from an authentic sample.

The photochemical degradation of the O-methyl and N-methyl derivatives of EMKO is also inconsistent with the two dimerization mechanisms. The first of such mechanisms considers the addition of O-H across the C=N bond. This mechanism is questionable because of the unfavorable energetics involved in breaking the C-O bond and adding the resulting fragments to a double bond. The second dimerization mechanism, which involves coupling of an isonitroso form

*Compound VIII has since been isolated and identified spectrometrically. methyl p-diethylaminobenzoate was also detected in the product mixture resulting from the ultraviolet irradiation of N-methyl EMKO.

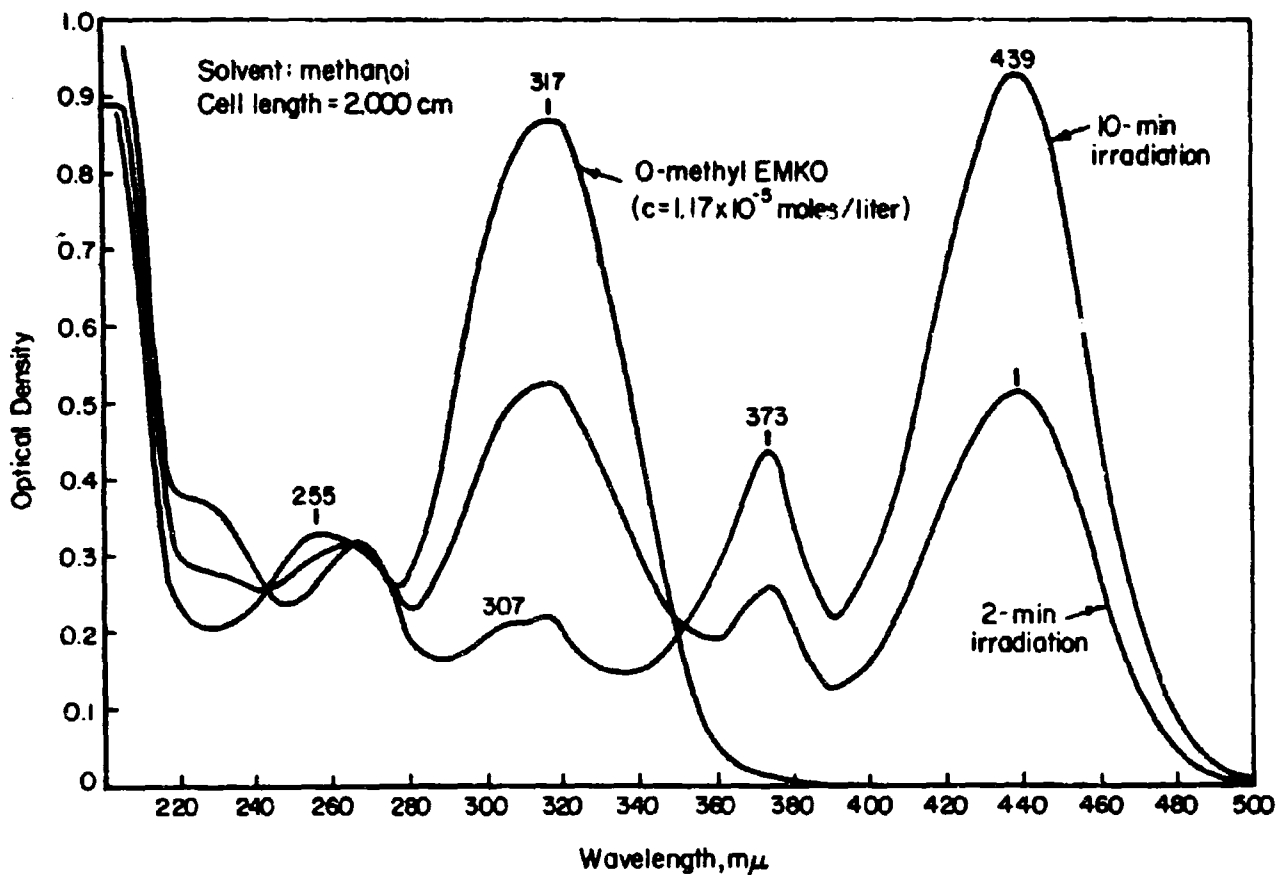
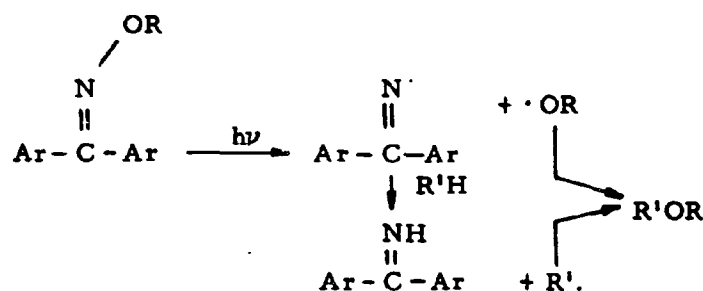


FIGURE 3. ULTRAVIOLET AND VISIBLE SPECTRA OF O-METHYL EMKO AND PHOTOPRODUCT

of EMKO, is also doubtful because it only accounts for the formation of the ketimine. The ketimine can result very readily from a structure (O-methyl EMKO) that cannot isomerize to a nitroso form, which is an essential intermediate in this mechanism. The color tests complicate the picture even more for O-methyl EMKO gives no color-test reaction with toluene sulfonyl chloride, although it gives the same ketimine photoproduct as EMKO. On the other hand, N-methyl EMKO gives a very rapid color test, but it produces at best only one of the products similar to those from EMKO on irradiation.

What then is the mechanism of EMKO degradation and how is it related to color formation in the EMKO detection system? It appears that there are at least two mechanisms operative in the photodegradation of EMKO. The formation of the ketimine in a protic media can be accounted for in terms of a homolytic N-O cleavage.



With EMKO, the tautomer that leads to this photoproduct is inactive as far as color reactions; this is the oxime contribution. The nitron form must, therefore, be the active species as far as color reaction is concerned, and leads to rearrangement products such as the anilide. One possible reason that EMKO gives such good color reactions in the presence of Lewis acids, such as mercuric bromide, is that polarization by these compounds possibly enhances the electro-negative characteristics of the oxime nitrogen, so that it then resembles more closely a nitron nitrogen. In fact, one of the difficulties in preparing the N-methyl derivative of EMKO resulted from the formation of dark-red color bodies, probably from reaction of the nitron with the alkylating agent.

The ketone presumably arises from interactions through the O-H or N-H bond in EMKO as compared with the methyl derivatives of EMKO. For example, if homolytic cleavage is the source of imine in the photoreaction of EMKO, the OH radical, because of its greater reactivity over the CH₃O radical, could attack the same or another EMKO molecule at the oximino carbon. Solvent protonation and subsequent loss of ammonia or nitrogen oxides could ultimately produce the ketone. It is also possible that the ketone results from the interaction of one of these reactive intermediates with molecular oxygen or water.

Future Studies

This investigation raised many questions. The answers to these questions would provide a better understanding of the mechanism of EMKO degradation and color formation with certain agents.

The role of oxygen is not well understood. Experiments in rigorously degassed systems at various initial EMKO concentrations would be helpful in this respect. Experiments in rigorously dried aprotic solvents would provide information on the role of proton donors in these systems. The unusual behavior in chloroform or methylene chloride might be explained in this way.

Even the ultimate products are not known at this time, although this would involve an entirely new set of reactants (the initial products) and products. The off-gases from the irradiation have not been examined. The identification of these products would provide additional helpful information.

Spectrometric studies on EMKO at various concentrations and under various conditions might yield information on the nature of the EMKO molecule - tautomeric mixture, dimer, etc.

As far as the color reactions of EMKO are concerned, there are many factors to be studied. Preliminary tests have indicated that nitrones might be as good or better than EMKO as detection reagents. The effect of catalysts such as mercuric bromide on the color reactions is not known at this time. The stability of EMKO itself in the presence of these additives is not known. It is possible that the degradation of EMKO is accelerated by these compounds. The isolation and identification of color bodies would provide valuable information on the mechanism of color formation.

EXPERIMENTAL

Preparation of Materials

EMKO

This material was prepared by a procedure developed in these laboratories.⁽²³⁾ The EMKO was twice crystallized from ethanol/benzene followed by washing with ethanol, which removed any residual yellow color left by the mother liquor. When dry, the crystals were well formed and perfectly white, mp 194 to 196 C. DTA indicated that this EMKO sample was at least 99 mole percent pure. The NMR, infrared, and ultraviolet spectra of this material were consistent with those previously reported. The mass spectrum was also determined; its interpretation is discussed in the text.

EMK

This material was obtained commercially and was recrystallized several times from ethanol, mp 95.0 to 95.8 C.

4,4'-Bis(diethylamino) benzanilide

The anilide was prepared by condensing p-diethylaminobenzoyl chloride and N,N-diethyl-p-phenylenediamine, (23) mp 137 to 139 C.

Oximes Used for Mass Spectra Determination

All of these oximes were either obtained commercially or were available from an earlier study except 4,4'-dinitrobenzophenone oxime.

4,4'-Dinitrobenzophenone

To 150 ml of glacial acetic acid was added with stirring 2.5 g of chromium trioxide followed by 10 ml of concentrated sulfuric acid. A light-red homogeneous solution resulted. The solution was heated to 35 C and 2.6 g of bis(p-nitrophenyl) methane (commercially available) was added. The temperature rose to 52 C in 10 minutes. During this time, the solution changed from red to green. The temperature then was raised to 55 to 60 C and maintained at this temperature for 1 hour. The solution was cooled and poured into 200 ml of ice water. The precipitate was filtered and washed with water and dried to yield 2.3 g of crude product was crystallized from a mixture of hexane and ethyl acetate yielding 1.8 g (66 percent), mp 186 to 188 C, literature mp 190 to 191 C. (24) This method provides an easy route to this ketone, which otherwise has been prepared by more tedious methods. This procedure is based on conditions worked out during a mechanistic study by Slack and Waters. (25)

4,4'-Dinitrobenzophenone Oxime

The oxime was prepared from the ketone according to a method in the literature. (26) mp 193 to 194 C (dec.) literature mp 195 C(dec.). (26)

N-(4-Diethylaminobenzylidene)-4'-diethylaminoaniline

To 0.89 g of p-diethylaminobenzaldehyde in 5 ml of ethanol was added 0.82 g of N,N-diethyl-p-phenylenediamine in 5 ml of ethanol. The mixture was cooled in ice water, and the precipitated product was filtered. Recrystallization from ethanol gave yellow-orange plates, mp 118 to 120 C. The structure was confirmed by infrared and mass spectra.

4-Diethylaminobenzonitrile

To 35 ml of dimethylformamide was added 40.0 g of p-bromo-N,N-diethylaniline (commercially available) and 16.2 g of copper cyanide and the mixture refluxed for 2-1/2 hours. The mixture was cooled and then poured into 200 ml of saturated ammonium chloride solution containing ice. Ether was added and the mixture filtered. The ether layer was separated and the aqueous layer extracted several times with ether. The ether layers were combined and washed with a saturated solution of ammonium chloride and finally with brine. The ether solution was dried with magnesium sulfate, filtered, and the ether evaporated. Thus, 17 g of an oil, which eventually crystallized, was recovered. Repeated crystallization from petroleum ether (bp 30 to 60 C) finally gave a product with mp 68 to 69 C.

Bis(4-diethylaminophenyl)methane Imine Hydrochloride

In 10 ml of tetrahydrofuran (THF) was placed 0.16 g of lithium wire and to this was added 2.6 g of p-bromo-N,N-diethylaniline in 10 ml of THF. After 2-1/2 hours of refluxing, most of the lithium wire was consumed. Two grams of 4-diethylaminobenzonitrile in 10 ml of THF was added in 10 minutes to the hot organo lithium solution. The mixture was refluxed an additional 1/2 hour, then cooled in ice and treated with 1.2 g of ammonium chloride in 3.0 ml of water. The whole hydrolysis mixture was chromatographed on 100 g of alumina using THF as an eluant. The yellow band that separated was collected and the THF was evaporated to leave a yellow oil, which appeared to be a mixture of the ketone and ketimine hydrochloride. The oil was triturated with water and the water-oil combination filtered. The water was then evaporated leaving a small amount of yellow solid. Infrared, ultraviolet, and mass spectra of this solid appeared to be consistent with the structure of the desired compound.

O-Methyl Benzophenone Oxime and N-Methyl Benzophenone Oxime

These materials were prepared by the method of Smith and Robertson,⁽²¹⁾ except that methyl iodide was used as the alkylating agent and the separation of isomers was accomplished on silica gel.

N-Methyl EMKO

To 23 ml of absolute ethanol was added 0.5 g of sodium metal followed by 4.2 g of EMKO. The mixture was refluxed until all of the EMKO remained in solution upon cooling. Finally, the solution was cooled, 4.0 g of methyl iodide was added, and the mixture was stirred at room temperature overnight. The alcohol was then evaporated and carbon tetrachloride added to precipitate the inorganic salts. Such salts were removed by filtration. The carbon tetrachloride filtrate was concentrated and then chromatographed on 100 g of alumina using benzene as an eluant. Three fractions were thus produced. The first, a clear oil

that would not crystallize, consisted mainly of O-methyl EMKO. The second fraction, a yellow substance, was eluted from the column with 5 percent methanol in benzene. After evaporation of the solvent, this fraction provided a yellow oil that eventually crystallized. The yellow solid was washed with petroleum ether (bp 30 to 60 C) and then crystallized from cyclohexane to give 1.2 g (27 percent) of N-methyl EMKO as a microcrystalline, very light-yellow product, mp 132 to 135 C. Repeated recrystallization gave a pure sample mp 135.5 to 136.5 C. See spectroscopic data in Table 5. The third fraction, a red material, was not identified.

O-Methyl EMKO

A mixture of 10 ml of ethanol, 10 ml of pyridine, 4.2 g of EMK, and 1.7 g of O-methylhydroxylamine hydrochloride was refluxed for 5 hours. Water was added to the hot reaction mixture until a definite cloudiness appeared. The product separated as an oil, but eventually crystallized by rubbing some of the oil against the walls of the flask. The solid was collected on a funnel and washed with a small amount of ethanol. Crystallization from ethanol yielded 2.3 g (50 percent) of a light-yellow solid, mp 74 to 77 C. Several crystallizations from n-hexane produced a white microcrystalline solid, mp 76.5 to 77.5 C.

Spectral Data

The spectral features of the N-methyl and O-methyl derivatives of benzophenone oxime and EMKO are shown in Table 5.

Instrumentation

The instruments used for the various physico-chemical measurements made in this study are described as follows:

<u>Measurement</u>	<u>Instrument Description</u>
Infrared spectra	Perkin-Elmer Infracord, Model 137
NMR spectra	Varian Associates, Model HR-60 High-Resolution Nuclear Magnetic Resonance Spectrometer
ESR spectra	Varian Associates, Model V-4500 Electron-Spin-Resonance Spectrometer
Mass spectra	Associated Electrical Industries (A. E. I.) MS 9 High-Resolution Mass Spectrometer
Ultraviolet - visible spectra	Cary Model 14 M Recording Spectrophotometer
Thermograms	Robert L. Stone Co.'s Model 12 AC DTA Unit

TABLE 5.
SPECTROSCOPIC FEATURES OF N-METHYL AND O-METHYL
DERIVATIVES OF BENZOPHENONE OXIME AND EMKO

	mp, C	Infrared Spectrum, cm ⁻¹			NMR Spectrum; Methyl Protons, τ	Absorption Maximum, m μ (MeOH)
		C-O?	N-O?	C-N? N→O?		
	100-101			1160 1260	6.34	--
	59-61	1050	980		6.09	--
	135-136			1160 1260	6.38	359 ($\epsilon_{\max}$ 36,000)
	76-77	1050	970		6.13	317 ($\epsilon_{\max}$ 37,000)

Ultraviolet irradiations of solutions and thin-layer samples were accomplished using an Hanovia, Type 30620, high-pressure broad-spectrum mercury lamp with maximum output at 300 mμ.

CONCLUSIONS

The treatment of EMKO with chemical oxidizing agents leads predominantly to Beckmann rearrangement products; whereas the photochemical degradation of EMKO leads to several products among which are EMK, the anilide, the nor-ethyl anilide, and ethyl Michler's ketimine. The presence of these products did not seem to affect adversely the sensitivity of EMKO towards a model agent.

Through differential thermal analyses (DTA) EMKO was found to be sensitive to acid supports such as silica gel, and less sensitive to neutral and basic supports. Apparently, the degradation of EMKO by oxygen and light is not accomplished through one simple route, but rather through two or more pathways, which lead to several products and complicated kinetics.

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13. ABSTRACT		
Ethyl Michler's ketone oxime (EMKO) is a reagent that has been useful as a detector of phosphorylating and phosphonylating agents, but its susceptibility to degradation has limited its serviceability. In an effort to overcome this difficulty, it has become necessary to consider the oxidative and photochemical degradation of EMKO. A study of the oxidation of EMKO was started on the hypothesis that free radicals, which are important intermediates in the course of many oxidations, are formed in the early stages of EMKO degradation in air or light or both. Attempts to detect free radicals by means of electron-spin resonance spectroscopy were made and the isolation and identification of oxidation products was attempted. Free radicals were not detected, but several oxidation products were isolated and identified. Subsequently, the photochemical degradation of EMKO on thin-layer supports was studied and several products isolated and identified. Differential thermal analysis (DTA) studies were conducted at the same time. The treatment of EMKO with metal-type oxidizing agents leads predominantly to Beckmann rearrangement products rather than to oxidation products. This unexpected course of action perhaps explains why free-radical products of EMKO were not detected. The photochemical degradation of EMKO leads several products among which are EMKO, the anilide, the nor-ethyl anilide, and ethyl Michler's ketimine. The presence of these compounds was rationalized in several ways and these mechanisms were tested. The kinetics of the photoreaction in solution are complicated and no consistent interpretation is available at this time. Several derivatives were prepared and from their reactions it was concluded that the photochemical degradation of EMKO is accomplished through two or more pathways. DTA studies on EMKO indicate that it is sensitive to acid supports such as silica gel; however, it is more stable on neutral supports and apparently it is completely stable on basic supports.		

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14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Column chromatography						
Differential thermal analysis (DTA)						
Electron spin resonance (ESR)						
Ceric ammonium nitrate						
Lead tetraacetate						
4,4'-Bis(diethylamino) benzanilide						
Ethyl Michler's ketone (EMK)						
Ethyl Michler's ketone oxime (EMKO)						
Thin-layer chromatography						
Silica gel						
Alumina						
Auramine						
Michler's ketone oxime						
Ultraviolet and visible spectra						
Mass spectra						
Infrared spectra						
Kinetics						
Nitrones						
Oxaziridines						
Nuclear magnetic resonance						
4,4'-Dinitrobenzophenone oxime						
N-(4-Diethylaminobenzylidene)-4'-diethylaminoaniline						
Bis(4-diethylaminophenyl) methane imine hydrochloride						
O-Methyl benzophenone oxime						
N-Methyl benzophenone oxime						
N-Methyl EMKO						
O-Methyl EMKO						