The Reaction of Ozone with a Pyrazolone Azomethine Dye

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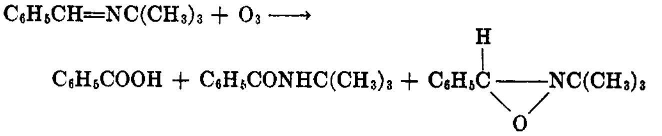
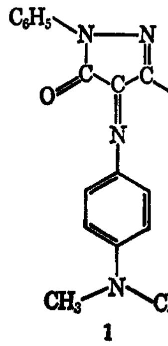
The reaction of the pyrazolone dye, 4-(4-N,N-dimethylaminophenylimino)-3-methyl-1-phenyl-2-pyrazolin-5-one, **1**, with ozone is very rapid and proceeds *via* two paths. The major path produces oxaziridine **2** by adding an oxygen at the azomethine linkage. The second path involves attack at the dimethylamino moiety. Each path leads to a number of demethylated (**3** and **4**) and formylated (**5**, **6**, and **7**) products.

Bailey and coworkers[1] and Miller[2] have reported that ozonation of azomethine compounds, *e.g.*, Schiff bases, results in partial or complete cleavage of the azomethine linkage. Thus reaction of N-benzylidene-*t*-butylamine with ozone gives benzoic acid (40%), N-*t*-butylbenzamide (24%), and 2-*t*-butyl-3-phenyloxaziridine (15%). Emmons has shown that Schiff bases react with peracetic acid to give similar products,[3a] although certain oxaziridines were too subject to acid-catalyzed hydrolysis to isolate.[3b]



$$C_6H_5CH{=}NC(CH_3)_3 + O_3 \longrightarrow C_6H_5COOH + C_6H_5CONHC(CH_3)_3 + C_6H_5\overset{H}{C}\underset{O}{\text{—}}NC(CH_3)_3$$

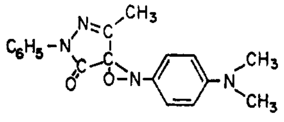
The present report identifies the products of the reaction of ozone with a pyrazolone azomethine dye, **1**, establishes the reactive sites in the molecule in regard to this particular reagent, and discusses possible mechanisms involved.



1

Results

Introduction of a dilute stream of ozone in oxygen (1:20) into a methylene chloride solution of **1** results in rapid reaction of the dye and the formation of the major reaction products, **2–4**, together with other minor products **5–8**. Compound **9** was detected (mass spectral data) in the reaction mixture, but resisted isolation and characterization. The reaction products obtained during the early stages of the reaction indicate that primary attack by ozone occurs at the azomethine and N,N-dimethylamino moieties, and leaves other points of unsaturation or high electron density untouched.



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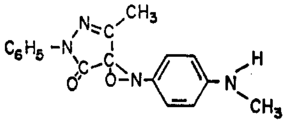

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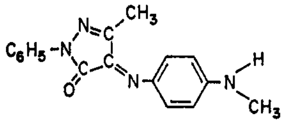

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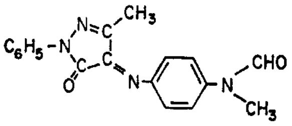

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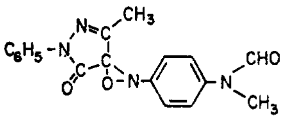

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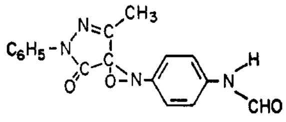

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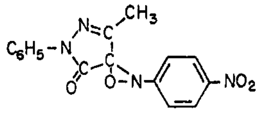

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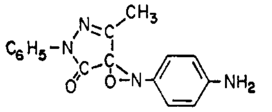

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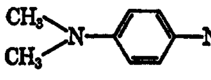

The products were isolated by thin layer (tlc) and adsorption chromatography.[4] Further purification was effected by recrystallization or by liquid–liquid partition chromatography.[5] Azomethine dyes **1** (unreacted) and **4** were identified by comparative tlc and by absorption spectroscopy. The structural proof of **2** is typical of that for the other oxaziridines **3**, **6**, **7**, and **8**. The elemental analysis of **2** indicates the addition of one oxygen atom per dye molecule. Compound **2** is colorless in solution ($\lambda_{\max}$ CH_3OH = 261, 287), thus excluding unsaturation at the 4 position of the pyrazolone ring and N-oxide formation. The parent mass spectrum peak corresponds to $C_{18}H_{18}N_4O_2$ (mol wt 322), which is in agreement with the assigned structure. The characteristic pyrazolone carbonyl stretching band of **1** (1670 cm^{-1} in KBr[6]) is shifted to higher frequencies in **2** (1725 cm^{-1}). This is further evidence of loss of unsaturation at the 4 position of the pyrazolone ring. Analysis of the principle fragment peak, mass 162, by high resolution mass spectroscopy shows the molecular ion to have an empirical formula corresponding to the following structure. The nmr spectrum shows δ values (chemical shifts from tetramethylsilane reference) of 2.4 (s), 3.0 (s), and 6.7–7.7 (m), and integrated peak

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(1) (a) A. H. Riebel, R. E. Erickson, C. J. Abshire, and P. S. Bailey, *J. Amer. Chem. Soc.*, **82**, 1801 (1960); (b) R. E. Erickson, A. H. Riebel, A. M. Reader, and P. S. Bailey, *Ann.*, **658**, 129 (1962); (c) P. S. Bailey, A. M. Reader, P. Kolsaker, H. M. White, and J. C. Barborak, *J. Org. Chem.*, **30**, 3042 (1965).

(2) R. E. Miller, *ibid.*, **26**, 2327 (1961).

(3) (a) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957); (b) R. G. Pews, *J. Org. Chem.*, **32**, 1628 (1967).

(4) B. Loev and K. M. Snader, *Chem. Ind.* (London), 15 (1965); 2026 (1967).

(5) W. F. Smith and K. L. Eddy, *J. Chromatog.*, **22**, 296 (1966).

(6) (a) R. Jones, A. J. Ryan, S. Sternhill, and S. E. Wright, *Tetrahedron*, **19**, 1497 (1963); (b) B. W. Rossiter, unpublished results.

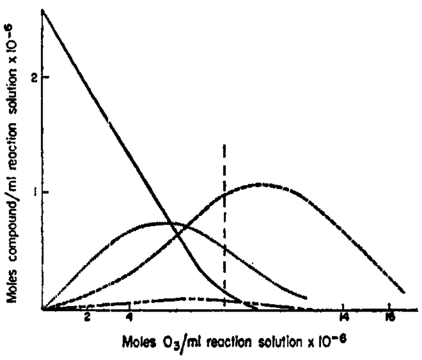


Figure 1.—Ozonation products of dye **1** as a function of the amount of ozone added: ——, **1**; ···, **2**; - - -, **3**; — - —, **4** (solvent, dichloromethane; temperature, 0°).

ratios of 3.0, 6.0, and 9.4 corresponding to the CCH_3, $N(CH_3)_2$, and nine aromatic hydrogens, respectively. The aromatic hydrogen absorption of **2** is shifted upfield relative to that of **1**; thus the nmr spectrum is consistent with saturation of the azomethine linkage without loss or gain of hydrogens. Finally, **2** was independently prepared in 8% yield by the reaction of **1** with alkaline hydrogen peroxide.[7] Surprisingly, the oxaziridine ring of **2** and **3** is resistant to catalytic hydrogenation (15 psi, 25°), and to acid hydrolysis.

Figure 1 shows the concentrations of starting dye **1** and of the major products **2–4**, as a function of the amount of ozone added. It is apparent from the curve that (1) ozone reacts with some of the products in competition with reaction with **1**; (2) products **2** and **4** are formed by parallel reaction paths with the path to the former predominating; and (3) as the concentration of **2** decreases, that of **3** increases. If the reaction is stopped and products are isolated at the point designated by the dotted vertical line, the yields of **1**, **2**, **3**, and **4** are 5, 25, 38, and 2%, respectively.

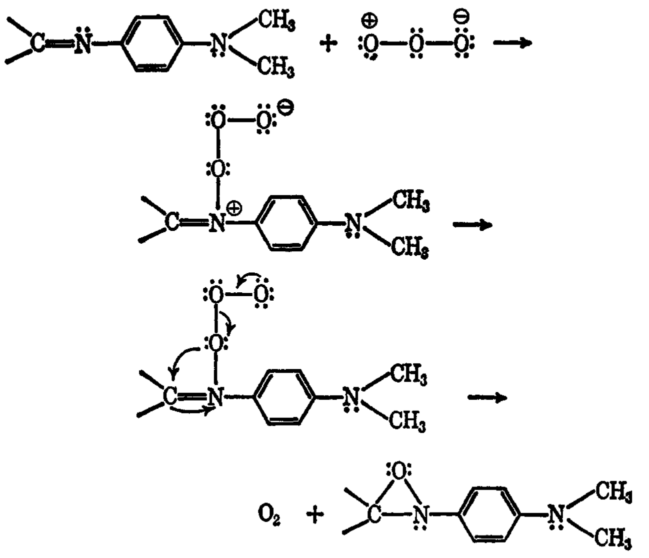
Treatment of the N′,N′-dimethylaminophenyloxaziridine, **2**, with ozone gives formyl derivatives **6** and **7**, desmethyloxaziridine **3**, and nitro derivative **8**. Similarly, ozonation of **3** gives **7** and **8**, and reaction of ozone with **5** produces **6** as the major product.

The ozonation of **1** is independent of the temperature over the range 0–25°. The products and their yields are influenced by the amount and rate of addition of ozone. Several solvents were used, dichloromethane, benzene, ethyl acetate, acetone, nitromethane, methanol, ethanol, isopropyl alcohol, and acetic acid. In general, the solvent does not enter into the reaction, although in the case of dichloromethane, there is mass spectral evidence that chlorinated derivatives of **2** and **8** are formed.

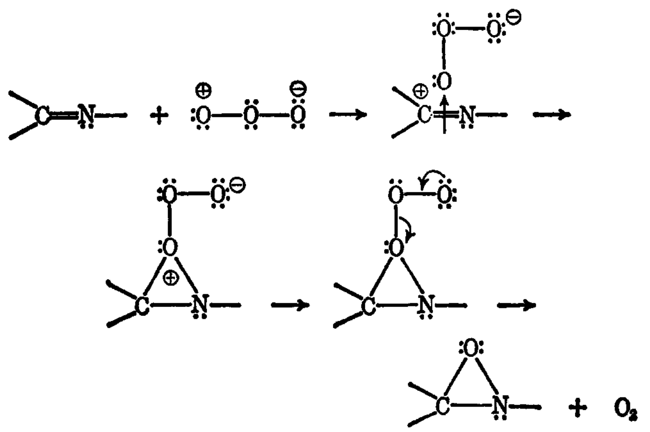
Discussion

Bailey and coworkers have proposed that ozonation of the azomethine linkage of Schiff bases[1a] and of 2,4-dinitrophenylhydrazones[1b] proceeds by nucleophilic attack at the azomethine carbon, which is in contrast to the proposal of electrophilic attack by ozone at carbon–carbon double bonds.[8] Erickson and Myszkiewicz have suggested that ozonation of nitrones involves electrophilic attack.[9] Our evidence suggests electrophilic attack, and is based on the relative rates of disappearance of dyes **1**, **4** and **5** (**1** > **4** > **5**, see Experimental Section). Smith has calculated that the azomethine nitrogen of **1** is considerably more negative than the azomethine carbon atom.[10] It is likely, therefore, that initial attack of ozone is at the azomethine nitrogen (Scheme I). An alternative mechanism involves electrophilic π complex formation of the type proposed for ozonation of carbon–carbon double bonds[8] (Scheme II).

SCHEME I



SCHEME II



No experimental evidence was found for a third possibility, namely, molozonide formation from ozone and the azomethine linkage. Breakdown of a hypothetical molozonide could give oxazirdiines *via* modified Criegee-type intermediates.[11a] Demethylation and oxidation of the dimethylamino moiety can be explained by a number of free radical or ionic reactions[11b,c,d] leading to an intermediate hydroxymethylamino deriva-

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[7] (a) F. D. Gunestone, *Advan. Org. Chem.*, **1**, 132 (1960); (b) L. Fieser, *et al.*, *J. Amer. Chem. Soc.*, **61**, 3216 (1939); **62**, 2866 (1940).

[8] P. S. Bailey and A. G. Lane, *J. Amer. Chem. Soc.*, **89**, 4473 (1967).

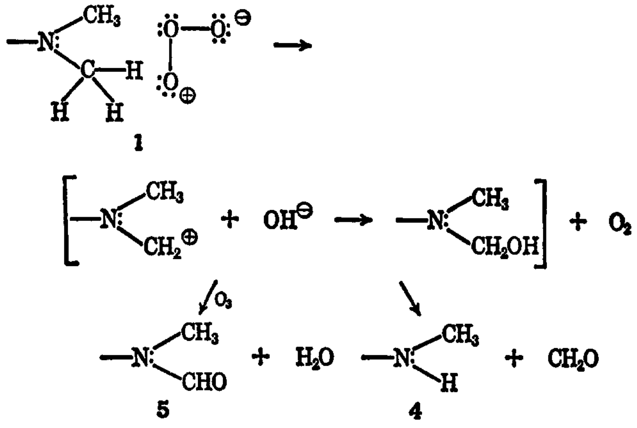
[9] R. E. Erickson and T. M. Myszkiewicz, *J. Org. Chem.*, **30**, 4326 (1965).

[10] W. F. Smith, Jr., *J. Phys. Chem.*, **68**, 1501 (1964).

[11] (a) N. L. Bauld, J. A. Thompson, C. E. Hudson, and P. S. Bailey, *J. Amer. Chem. Soc.*, **90**, 1822 (1968); C. E. Bishop and P. R. Story, *ibid.*, **90**, 1905 (1968); P. R. Story, C. E. Bishop, and J. R. Burgess, *ibid.*, **90**, 1907 (1968); (b) P. S. Bailey, Robert A. Welch Foundation Annual Report, 1965–1966; (c) P. Kolsaker and O. Meth-Cohn, *Chem. Commun.*, 423 (1965); (d) P. S. Bailey, D. A. Mitchard, and A. Y. Khashab, *J. Org. Chem.*, **33**, 2675 (1968).

tive. One such sequence of reactions involving electrophilic attack at the hydrogens α to nitrogen is shown in Scheme III. The intermediate hydroxymethylamino derivative may eliminate formaldehyde, leading to demethylated derivatives,[11b] or be oxidized by ozone to the formyl derivative and other oxidation products. Reaction of **4** and **5** with ozone gives mainly **3** and **6**, respectively. A similar series of reactions is suggested for the ozonation of **2** and for the complete demethylations leading to **9**. Mass spectral evidence for the presence of **9** in the ozonation reaction mixture has been obtained, but **9** has not been isolated or fully characterized.

SCHEME III



Conclusion

Ozone attacks pyrazolone dye **1** at the azomethine and dimethylamino moieties, reaction at the former site predominating. Other points of unsatuaration are left untouched in the initial reactions.

Experimental Section

Solvents were Eastman Grade. Precoated plates for thin layer chromatography were obtained from Brinkmann Instruments Inc. The ozone generator was essentially that described elsewhere.[12]

Ozonation Procedures. For Isolation of Products.—Ozone–oxygen gas (5% ozone) was bubbled into a gas wash bottle equipped with a sintered glass dispersing tube and charged with the solution (between 1 and 5 × 10^{-2} *M*) of the compound to be ozonized. Gas flow was held at a constant rate within the range of 400–1400 ml/min. The extent of decomposition was noted by the amount of ozone used or by the color of the reaction solution. After the desired amount of ozonation, the reaction solution was transferred to a round-bottom flask and the solvent was removed under reduced pressure. The residue was taken up in a minimum of solvent and separated into its components by adsorption chromatography.[4] The compounds were recovered from the adsorbent with a mixture of 15 volumes of methanol and 35 volumes of dichloromethane. Further purification was effected by tlc, liquid–liquid partition chromatography[5] or recrystallization. Table I lists the products obtained by ozonation. The physical data used for the identification of **2–8** are listed below with the specific compounds.

TABLE I

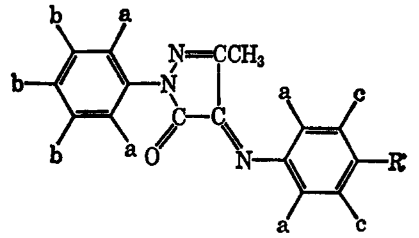
Compd ozonized	Major products isolated from the ozonation
1	**2, 3, 4, 5, 6, 7, 8**
2	**3, 6, 7, 8**
3	**7, 8**
4	**3**
5	**6**
6	**6** (starting material)
7	**7** (starting material)
8	**8** (starting material)

TABLE II

Moles of $O_3 \times 10^{-6}$	Moles of dye **1** $\times 10^{-6}$	Moles of dye **4** $\times 10^{-6}$
0	1.45	1.25
1.1	1.34	1.17
2.2	1.14	1.01
3.3	0.92	0.81
4.4	0.75	0.63
5.5	0.54	0.50
6.6	0.37	0.41
8.8	0.09	0.18
9.9	0.03	0.12
11.0		0.06
12.1		0.03

For Qualitative Identifications.—A solution (2.5 × 10^{-3} *M*) of the compound to be ozonized was treated in an open flask with an ozone–oxygen mixture containing about 5% ozone. The bubbling rate was 25–150 ml/min. Aliquots were removed at various time intervals and spotted onto the tlc plates. Authentic compounds were also spotted onto the tlc plates as references. The plates were developed with a mixture of 10 volumes of ethyl acetate and 90 volumes of dichloromethane. Compounds **1–8** showed the following R_f numbers for development in a glass chamber containing solvent saturated filter paper: 0.58, 0.51, 0.34, 0.52, 0.27, 0.12, 0.07, and 0.55, respectively; without the filter paper the values were 0.82, 0.69, 0.49, 0.74, 0.39, 0.16, 0.09, 0.78, respectively.

The nmr spectra were recorded on a Varian Associates 60-MHz instrument. The chemical shifts (δ) are measured from the reference tetramethylsilane. The band intensities are relative to the pyrazolone ring methyl hydrogens taken as 3.0. The labeling of the aromatic ring hydrogens is illustrated. In the oxaziridines, the aromatic hydrogen bands were bunched together, and were not identified individually. For reasons not clear to the authors, highly purified samples of compounds **1–6** all gave slightly higher values for the integrated peak ratios of the aromatic hydrogens than the expected 9.0.



For Quantitative Measurements.—The ozonation train was equipped with a three-way stopcock permitting the gas flow to be diverted either to the reaction solution or to a 2% KI trap (for analysis of ozone content). A flow meter (Ace Glass Co. Tru-Taper) was included in the train between the ozone generator and the three-way stopcock. The ozone concentration in the gas stream was determined before and after the ozonation of the desired compound. A solution (2.5 × 10^{-3} *M*) of the compound to be ozonized was placed in an erlenmeyer flask equipped with a magnetic stirrer, and the ozone–oxygen gas was then introduced through a sintered glass dispersing tube. Aliquots (1 ml) were removed at various time intervals *via* a pipet filler (Will Scientific Co.), and applied as a stripe to a 20 × 20 cm analytical thickness silica gel tlc plate. After development, the bands were removed individually and the compounds eluted from the adsorbent with EK S467 methanol. The eluates were diluted to volume in appropriate volumetric flasks, and the concentrations determined spectrophotometrically using the extinction coefficients for the compounds.

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(12) L. I. Smith, *et al.*, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 673.

For Competitive Rate Measurements.—A mixture of dyes **1** (1.45×10^{-6} *M*) and **4** (1.25×10^{-6} *M*) in dichloromethane was treated with ozone in a quantitative manner as described above. Analysis of the aliquots gave the data in Table II showing dye **1** was lost slightly faster than dye **4**. As shown in Figure 1, dye **4** is found in the reaction mixtures after all of dye **1** is gone. Similarly, dye **5** is found, by tlc, after both dyes **1** and **4** are gone.

4-(4-N,N-Dimethylaminophenylimino)-3-methyl-1-phenyl-2-pyrazolin-5-one, 1, was prepared according to published procedures,[13] and recrystallized from acetone as deep purple plates: mp 187–188° (lit.[14] mp 188°); λ_{max} (MeOH) 440 nm (ϵ 12,300), 525 (30,000); mass spectrum (70 eV) *m/e* 306; nmr ($CDCl_3$) δ 8.4–7.9 (m, 4.1, aromatic $\mathbf{H}_a$), 7.6–7.1 (m, 3.2, aromatic $\mathbf{H}_b$), 6.7–6.5 (m, 2.1, aromatic $\mathbf{H}_c$), 3.1 (s, 6.1, $>NC\mathbf{H}_3$), 2.3 [s, 3.0, $-N{=}C(C\mathbf{H}_3)-$].

4-[2-(4-N,N-Dimethylaminophenyl)oxaziridine-3-spiro]-3-methyl-1-phenyl-2-pyrazolin-5-one, 2, was isolated from the ozonation mixtures by adsorption chromatography, or was independently synthesized by treating a warm (70°) solution of **1** (0.5 g in 75 ml 95% ethanol) with 5 ml of hydrogen peroxide (25–35%), followed by the addition of six drops of sodium hydroxide (40%). After 3 hr, the reaction mixture was separated by tlc, giving an 8% yield of material identical with **2** (formed by ozonation of **1**) as shown by tlc and by mixture melting point. Compound **2** was recrystallized from alcohol as feathery, pale tan needles: mp 167–168°; uv max (MeOH) 261 nm (ϵ 23,000), 287 (9100); mass spectrum (70 eV) *m/e* 322, 162.0795; nmr ($CDCl_3$) δ 7.7–6.7 (m, 9.4, aromatic **H**), 3.0 (s, 6.0, $>NC\mathbf{H}_3$), 2.4 [s, 3.0, $-N{=}C(C\mathbf{H}_3)-$].

Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.1; H, 5.6; N, 17.4. Found: C, 66.8; H, 5.5; N, 17.5.

4-[2-(4-N-Methylaminophenyl)oxaziridine-3-spiro]-3-methyl-1-phenyl-2-pyrazolin-5-one, 3, was isolated from the ozonation mixtures by adsorption chromatography, and recrystallized from cyclohexane–dichloromethane as a pale yellow powder: mp 213–214°; uv max (MeOH) 255 nm (ϵ 21,700), 287 (8700); mass spectrum (70 eV) *m/e* 308, 148; nmr ($CDCl_3$) δ 7.6–6.5 (m, 9.0, aromatic **H**), 3.9 (s, 1.0, $>N\mathbf{H}$), 2.8 (s, 3.1, $>NC\mathbf{H}_3$), 2.4 [s, 3.0, $-N{=}C(C\mathbf{H}_3)-$].

Anal. Calcd for $C_{17}H_{16}N_4O_2$: C, 66.2; H, 5.2; N, 18.2. Found: C, 66.2; H, 5.5; N, 18.5.

4-(4-N-Methylaminophenylimino)-3-methyl-1-phenyl-2-pyrazolin-5-one, 4, was prepared according to the general procedures of Brown, *et al.*,[13] and recrystallized from chloroform–acetone as feathery red needles: mp 193–194°; λ_{max} (MeOH) 434 nm (ϵ 15,400), 511 (32,000); mass spectrum (70 eV) *m/e* 292; nmr ($CDCl_3$) δ 8.3–7.9 (m, 4.1, aromatic $\mathbf{H}_a$), 7.6–7.1 (m, 3.6, aromatic $\mathbf{H}_b$), 6.6–6.5 (m, 1.8, aromatic $\mathbf{H}_c$), 4.7 (s, 1.0, $>N\mathbf{H}$), 2.9 (s, 3.1, $>NC\mathbf{H}_3$), 2.3 [s, 3.0, $-N{=}C(C\mathbf{H}_3)-$].

Anal. Calcd for $C_{17}H_{16}N_4O$: C, 69.9; H, 5.5; N, 19.2. Found: C, 69.7; H, 5.6; N, 19.2.

4-(4-N-Formyl-N-methylaminophenylimino)-3-methyl-1-phenyl-2-pyrazolin-5-one, 5, was isolated from the ozonation mixtures by adsorption chromatography, and was synthesized by each of the following procedures.

Procedure A.—A poor yield of **5** was obtained by treating a solution of **2** with sufficient formic acid (EK P139) to obtain a color change of the solution (magenta to purple), removing the water by azeotropic distillation, and separating the remaining mixture by adsorption chromatography.

Procedure B.—Compound **5** was obtained in better yield by dissolving 0.3 g of compound **2** in a mixture of 40 ml of ethyl formate (EK P439) and 40 ml of toluene. A small amount of sodium methylate was added. The mixture was heated to boiling and the solvent removed by slow distillation. When the temperature of the distillate had risen to 104° (3–4 hr), the mixture was cooled and separated by adsorption chromatography. The band corresponding to compound **5** was purified further by liquid–liquid partition chromatography, and recrystallized from cyclohexane as a red powder: mp 120–121°; uv max (MeOH) 246 nm (ϵ 26,900), 357 (5600), 493 (1200); mass spectrum (70 eV) 320; nmr ($CDCl_3$) δ 8.6 [s, 0.6, $\mathbf{H}C({=}O)-$], 8.0–6.9 (m, 9.9, aromatic **H**), 3.3 (s, 2.6, $>NC\mathbf{H}_3$), 2.3 [s, 3.0, $-N{=}C(C\mathbf{H}_3)-$].

Anal. Calcd for $C_{18}H_{16}N_4O_2$: C, 67.5; H, 5.0; N, 17.5. Found: C, 67.6; H, 5.2; N, 17.7.

4-[2-(4-N-Formyl-N-methylaminophenyl)oxaziridine-3-spiro]-3-methyl-1-phenyl-2-pyrazolin-5-one, 6, was isolated from the ozonation mixtures by adsorption chromatography and was synthesized by treating compound **3** according to procedure B used to prepare compound **5**. Compound **6** was recrystallized from alcohol as a light tan powder: mp 150–152°; uv max (MeOH) 246 nm (ϵ 23,600), 280 (10,200); mass spectrum (70 eV) 336.1222, 176.0587; nmr ($CDCl_3$) δ 8.6 [s, 1.1, $\mathbf{H}C({=}O)-$], 7.7–7.3 (m, 9.6, aromatic **H**), 3.3 (s, 2.8, $>NC\mathbf{H}_3$), 2.4 [s, 3.0, $-N{=}C(C\mathbf{H}_3)-$].

Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.3; H, 4.8; N, 16.7. Found: C, 64.0; H, 4.7; N, 16.4.

4-[2-(4-N-Formylaminophenyl)oxaziridine-3-spiro]-3-methyl-1-phenyl-2-pyrazolin-5-one, 7, was isolated from the ozonation mixtures by adsorption chromatography, and recrystallized from dichloromethane–cyclohexane as a white powder: mp 250–252°; uv max (MeOH) 241 nm (ϵ 20,400), 280 (8600); mass spectrum (70 eV) 322.1068, 162; nmr ($CDCl_3$) δ 10.3 [s, 1.0, $-N\mathbf{H}C({=}O)-$], 8.6 [s, 0.8, $\mathbf{H}C({=}O)-$], 7.9–7.2 (m, 9.1, aromatic **H**), 2.4 [s, 3.0, $-N{=}C(C\mathbf{H}_3)-$].

Anal. Calcd for $C_{17}H_{14}N_4O_3$: C, 63.3; H, 4.4; N, 17.4. Found: C, 62.8; H, 4.7; N, 17.3.

4-[2-(4-Nitrophenyl)oxaziridine-3-spiro]-3-methyl-1-phenyl-2-pyrazolin-5-one, 8, was isolated from the ozonation mixtures by adsorption chromatography, and recrystallized from cyclohexane as colorless plates: mp 195–196°; uv max (MeOH) 238 nm (ϵ 12,900), 268 (15,700); mass spectrum (70 eV) 324.0843, 164; nmr ($CDCl_3$) δ 7.6–7.4 (m, 6.8, aromatic **H**), 8.4 (m, 2.0, aromatic $\mathbf{H}_c$), 2.4 [s, 3.0, $-N{=}C(C\mathbf{H}_3)-$].

Anal. Calcd for $C_{16}H_{12}N_4O_4$: C, 59.3; H, 3.7; N, 17.3. Found: C, 59.4; H, 3.3; N, 17.5.

Registry No.—Ozone, 10028-15-6; **1,** 1456-89-9; **2,** 19362-39-1; **3,** 19362-40-4; **4,** 13617-66-8; **5,** 19362-42-6; **6,** 19362-43-7; **7,** 19362-44-8; **8,** 19362-45-9.

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