Nitrosation of Methyl and Phenyl Styryl Ketoximes Under Oxygen. Formation of 4-Nitro-1-hydroxypyrazole 2-Oxides and 3,5-Diphenyl-4-nitrato-4,5-dihydroisoxazole

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The nitrosation of the oximes of 4-phenyl-3-buten-2-one and 1,3-diphenyl-2-propen-1-one under oxygen has been reinvestigated. In addition to 4-oxo- and 4-oximino-4H-pyrazole 1,2-dioxides previously reported, the reactions give 4-nitro-1-hydroxypyrazole 2-oxides. In the case of 1,3-diphenyl-2-propen-1-one oxime the nitrosation reaction also gives 3,5-diphenyl-4-nitrato-4,5-dihydroisoxazole. Evidence is presented suggesting that the nitrate ester is formed through the rearrangement of a peroxynitrite intermediate.

Previous studies of the nitrosation of α,β-unsaturated ketoximes of type **1** generally have been focused upon the N-oxygenated pyrazoles which are formed in the reactions [1]. However, isoxazole derivatives have been reported as side products in some of the reactions. In particular, the nitrosation of the oxime **1a** of 1,3-diphenyl-2-propen-1-one under oxygen has been observed to produce 3,5-diphenyl-4-nitrato-4,5-dihydroisoxazole **2a** in addition to 3,5-diphenyl-4-oxo-4H-pyrazole 1,2-dioxide **3a** [2]. Recently we examined the nitrosation of several oximes, including **1a**, with a particular interest in the influence of the geometry of the oxime upon the product distribution. It was found that nitrosation of **1a**, either with sodium nitrite in acetic acid under nitrogen or using butyl nitrite in the presence of copper(II) sulfate and pyridine, gave 3,5-diphenyl-4-oximino-4,5-dihydroisoxazole **4a** as well as N-oxygenated pyrazole derivatives [3]. We have now reinvestigated the effect of oxygen on the nitrosation of **1a** and also of the oxime **1b** of 4-phenyl-3-buten-2-one. We wish to report the formation of 4-nitro-1-hydroxypyrazole 2-oxides **5** as products of the nitrosation of both of the α,β-unsaturated ketoximes under oxygen and to provide evidence regarding the origin of **2a** in the nitrosation of **1a**.

The nitrosation of **1a** was carried out by slow addition of aqueous sodium nitrite to a cooled and vigorously

(1)
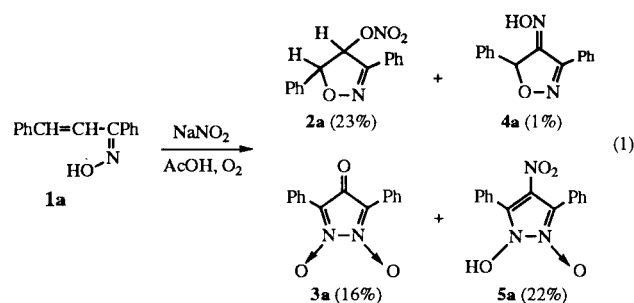
stirred solution of the oxime in acetic acid which had been saturated with oxygen and then kept under an oxygen atmosphere during addition [2]. Following filtration to remove **3a**, the filtrate was evaporated to dryness without heating, and the residue was partitioned between aqueous sodium carbonate and ether. Acidification of the cooled basic solution gave 4-nitro-3,5-diphenyl-1-hydroxypyrazole 2-oxide **5a**, while the ether-soluble material was chromatographed on silica gel to give an additional small amount of **3a**, the nitrate ester **2a**, and **4a** (Equation 1).

The formation of the principal products observed may be explained by the processes shown in Scheme 1, which incorporates and extends suggestions made to explain the results of related nitrosation reactions [2,3,4a-c]. The oxime **1a**, when prepared under typical conditions from

Scheme 1. Proposed Origin of Pyrazole and Isoxazole Derivatives.
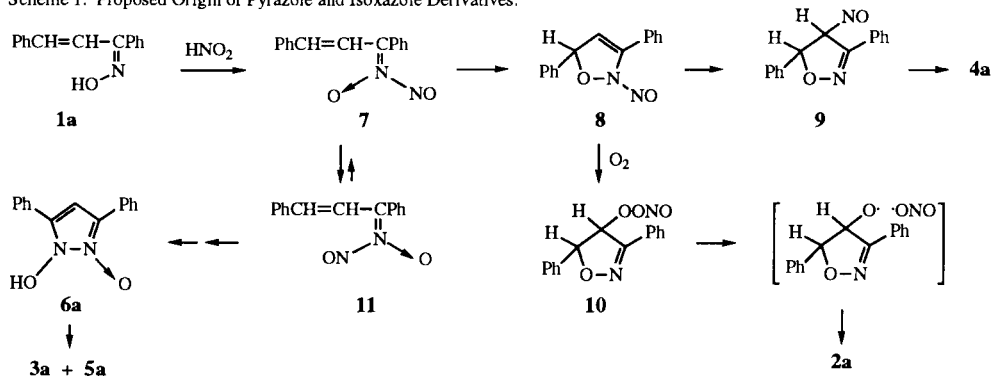
its parent ketone, is obtained primarily as the (E)-stereoisomer [5], in which the hydroxyl group is *syn* with respect to the carbon-carbon double bond. It is believed that nitrosation of **1a** produces the *N*-nitrosonitrone **7**, which may cyclize by bond formation between the nitrone oxygen and the β-carbon, producing a 2-nitroso-2,5-dihydroisoxazole **8**, which rearranges to the 4-nitroso-4,5-dihydroisoxazole **9**, from which **4a** is formed by tautomerization [3]. We suggest that **8** is also involved as an intermediate in the formation of **2a**, reacting with oxygen to give the unstable peroxynitrite **10**, which rearranges spontaneously to **2a**. The details of the suggested conversion of **8** to **10** are open to speculation, since one could visualize a more or less concerted reaction between **8** and oxygen or an alternative process, perhaps involving a hydroperoxyisoxazoline intermediate.

An alternative route to **10** which would not require the intermediacy of **8** would be direct conversion of **1a** to a 4-hydroperoxy-2-isoxazoline by autoxidation, followed by nitrosation to give **10**. However, when **1a** in acetic acid was stirred overnight under oxygen in the absence of sodium nitrite the oxime was recovered unchanged. Although this does not completely rule out some sort of nitrite-mediated autoxidation of **1a** to produce a 4-hydroperoxy-2-isoxazoline intermediate without the intermediacy of **8**, we consider the sequence shown in Scheme 1 as more likely.

Pryor and coworkers have shown that *tert*-butyl hydroperoxide undergoes nitrosation to give *tert*-butyl nitrate. They have proposed that a peroxynitrite intermediate analogous to **10** is formed and undergoes homolysis and radical combination in the fashion shown for the formation of **2a** in Scheme 1 [6]. Although, as discussed above, we doubted that direct oxidation of **1a** to a hydroperoxide intermediate was involved in the formation of **2a** during the nitrosation under oxygen, it was felt that independent formation of such a hydroperoxide and the demonstration that it could be converted to **2a** upon nitrosation would provide support for the intermediacy of **10** suggested in Scheme 1 and validation for the analogy with the work of Pryor which is suggested.

It has been reported that metal ion-catalyzed autoxidation of **1a** gives 3,5-diphenyl-4-hydroxy-4,5-dihydroisoxazole **13** [7], presumably through the intermediacy of a hydroperoxide **12**. We found that when **1a** in ethanol was stirred at room temperature under oxygen in the presence of a large excess of cobalt(II) chloride until consumption of the oxime was complete, followed by separation from inorganic material, a mixture was obtained which consisted of a compound assigned as the hydroperoxide **12**, along with **13**. Pure **12** could not be isolated, but its presence was inferred from the ¹H nmr spectrum of the mixture, which included a pair of doublets for the protons at C4 and C5 which was similar in appearance, but at greater

chemical shift than the signals for the corresponding protons in **13**. Over time the signals assigned for **12** in the nmr spectrum decreased in intensity as those for **13** increased. When a freshly prepared mixture of **12** and **13**, ca. 2:1, was treated with butyl nitrite, a mixture of **13** and **2a** was formed (Equation 2). It is reasonable to assume that conversion of **12** to **2a** in this experiment involves the same peroxynitrite **10** which is proposed as the precursor of **2a** in Scheme 1.
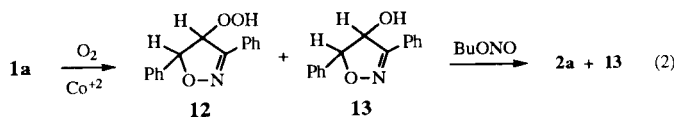
Other compounds which were considered as possible precursors to **2a** were **4a**, **13**, or 4,5-dihydro-3,5-diphenyl-isoxazole. Each of these in turn was submitted to treatment with sodium nitrite in acetic acid under oxygen, and they were all recovered unchanged under the conditions of the reaction.

In the earlier report of the formation of **2a** the question of its stereochemistry was not addressed. In this reinvestigation the major isomer, mp 92-93°, was obtained as reported earlier [2], but the minor isomer, mp 152-154°, was also isolated in very low yield. In the ¹H nmr spectra of 4,5-dihydroisoxazoles, the coupling constant between the protons at C4 and C5 of the *trans* isomer is smaller than that for the *cis* isomer [8]. Since the magnitude of this coupling constant was smaller for the major isomer of **2a** (1.7 Hz) than for the minor isomer (7.3 Hz), it is apparent that the lower-melting major isomer is *trans*-3,5-diphenyl-4-nitrato-4,5-dihydroisoxazole, while the minor isomer has the *cis* stereochemistry.

In order to account for formation of the pyrazole derivatives **3a** and **5a** stereoisomerization of **7** to the *N*-nitrosonitrone **11** is presumed to occur. Such a process has been invoked to explain the production of pyrazoles in other cases where the initial geometry is unfavorable for their formation [3,4b-c]. After isomerization to **11** cyclization occurs as previously proposed [2,3] to give 3,5-diphenyl-1-hydroxypyrazole 2-oxide **6a**, which has been shown to be the likely precursor of **3a** [9].

It is reasonable to assume that **6a** is also involved as an intermediate in the formation of **5a**. One possibility is that **5a** is formed through aromatic nitration of **6a** by nitric acid, which might be formed by oxidation of nitrous acid under the reaction conditions. An alternative to direct nitration of **6a** is nitrosation to **14**, which is converted to **6a** by oxidation of the nitroso group to a nitro group and regeneration of the aromatic pyrazole ring. The intermediacy of **14** has been proposed previously in the formation of the tautomeric 3,5-diphenyl-4-oximino-4H-pyrazole 1,2-dioxide, which is a major product of the nitrosation of

1a under a nitrogen atmosphere [2,3,10]. The formation of 4-methyl-3,5-diphenyl-4-nitro-4H-pyrazole 1,2-dioxide **15** has been reported upon nitrosation of 3,5-diphenyl-4-methyl-1-hydroxypyrazole 2-oxide [2], and the formation of **5a** probably occurs by a closely related mechanism.

14 (R = H, X = NO)   16a (R = Ph)   17
15 (R = Me, X = NO₂)   16b (R = Me)
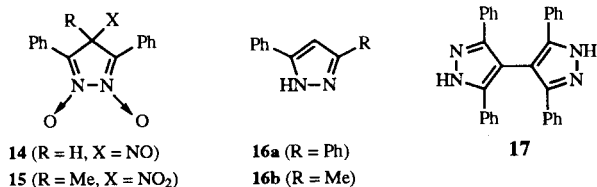
Minor products of the nitrosation of **1a** under oxygen include 3,5-diphenylisoxazole, which could be formed by elimination from **2a**, and 1,3-diphenyl-2-propen-1-one resulting from deoximation of **1a**. Two additional minor products were 3,5-diphenylpyrazole **16a**, and the bipyrazole **17**, which are assumed to be the product of reduction of **5a** and of a dimeric 1-hydroxypyrazole 2-oxide which has been previously reported as a product of the nitrosation of **1a** [11]. Under the reaction conditions, it is possible that the reducing agent is nitrite, which is oxidized to nitrate.

The nitrosation of the (E)-oxime **1b** of benzalacetone under oxygen produces pyrazole derivatives but no isoxazoles (Equation 3). These results are consistent with the stereochemical effect of oxime geometry on product distribution we have recently reported [3]. When the oxime hydroxyl group is oriented *anti* with respect to the carbon-carbon double bond, nitrosation produces an N-nitrosonitrone analogous to **11** (see Scheme 1). In such cases there seems to be an overwhelming preference for pyrazole formation, while isoxazole formation, which would require isomerization to an intermediate analogous to **7** is not commonly observed [3,4b-c]. In addition to the pyrazole derivatives shown in Equation 3, some deoximation of **1b** occurred to give benzalacetone (6%).

(3)
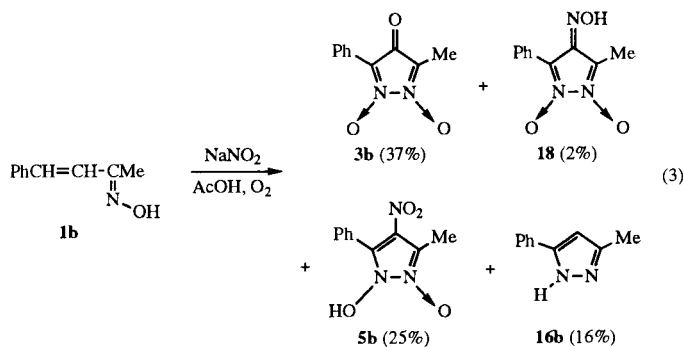
With the exception of **5b**, all of the products shown in Equation 3 were reported for the earlier investigation of the nitrosation of **1b** under oxygen [2]. The pyrazole

derivatives **3b**, **5b**, and **16b** are presumed to be formed through the intermediacy of 3-methyl-5-phenyl-1-hydroxypyrazole 2-oxide **6b**, by the same processes involved in formation of the corresponding products of the nitrosation of **1a**. The formation of **18** has been explained as the result of the nitrosation of **6b** and tautomerization of a 4-nitroso-4H-pyrazole derivative analogous to **14** [2,10].

The 4-nitro-1-hydroxypyrazole 2-oxides **5a** and **5b** have not previously been described in the literature [12]. They are pale yellow solids which exhibit sharp absorptions in the ir at 1561 cm⁻¹ for **5a** and 1575 cm⁻¹ for **5b** assigned as v_{asym} for the nitro groups. The region where v_{sym} would be expected for the nitro groups is obscured by the broad, strong absorption bands characteristic of the 1-hydroxypyrazole 2-oxide system. The compounds do not melt sharply, but decompose upon heating, producing, among other products, the 4-oxopyrazoles **3**. They darken and decompose upon exposure to air and light, and slow decomposition was observed even when stored in the dark under refrigeration. The compounds gave orange sodium or ammonium salts, which were much more stable than the conjugate acids, and it was in this form that samples were typically purified and stored. The ir spectra of the salts were characterized by two very strong absorptions, one around 1460 and the other around 1350 cm⁻¹. The nmr spectra of **5a** and **5b** were not obtained due to their instability and limited solubility in typical solvents, but spectra of the salts were consistent with the assigned structures.

We have carried out a more thorough investigation of the effect of oxygen upon the nitrosation of α,β-unsaturated ketoximes and have isolated 4-nitro-1-hydroxypyrazole 2-oxides which were not previously reported as products of the reactions. We have also confirmed the formation of 3,5-diphenyl-4-nitrato-4,5-dihydroisoxazole from benzalacetophenone oxime and have provided evidence to suggest that it is formed through the rearrangement of an unstable peroxynitrite intermediate. We are pursuing further investigations in the preparation and behavior of 4-nitro-1-hydroxypyrazole 2-oxides.

EXPERIMENTAL

Infrared spectra were run on nujol mulls using a Nicolet 5SXC FT-IR Spectrometer; nmr spectra were run on a Varian Gemini-300 Spectrometer in deuteriochloroform with tetramethylsilane as an internal standard, except where deuterium oxide (D₂O) is specified, in which case the internal standard was sodium 3-trimethylsilyl-1-propanesulfonate. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, DE. Melting point values were obtained using a Thomas Hoover Uni-melt apparatus and are uncorrected.

Nitrosation of 1,3-Diphenyl-2-propen-1-one Oxime **1a** Under Oxygen.

A solution of 10.04 g (0.045 mole) of **1a** (80% *(E)*, 20% *(Z)*) in 150 ml of acetic acid was saturated with oxygen using a gas dispersion tube at room temperature. The solution was kept under an oxygen atmosphere and stirred vigorously at 13-16° [14] while a solution of sodium nitrite, 6.9 g (0.1 mole), in 60 ml of water was added over 180 minutes, followed by continued stirring under oxygen for 60 minutes. The mixture was filtered under suction, and the solid was treated with 25 ml of acetic acid, stirred for a few minutes, and filtered again to give 1.73 g of 3,5-diphenyl-4-oxo-4*H*-pyrazole 1,2-dioxide **3a**, a magenta solid, mp 190-192°, which was identical with an authentic sample [2]. An additional 0.19 g of **3a** was obtained during the chromatographic separation described below, for a total yield of 1.92 g (16%).

The filtrate and wash solutions were combined and evaporated to dryness at room temperature under 0.1 torr. The residual reddish-yellow solid was treated with 200 ml of 5% sodium carbonate solution and 500 ml of ether and stirred, adding more water as needed to dissolve the sodium salt of **5a** which formed. The aqueous layer was separated, and the ether layer was extracted with two 50 ml portions of 5% sodium carbonate, which were added to the aqueous layer. The basic aqueous solution was cooled thoroughly in ice and acidified with hydrochloric acid to a Congo red endpoint, avoiding undue exposure to direct light. The pale yellow solid was collected by suction filtration and washed with cold water which had been acidified with a few drops of hydrochloric acid, then dried overnight at room temperature and 0.1 torr to give 2.98 g (22%) of **5a**, which did not melt sharply, but decomposed to a red solid mixture above 90°, becoming completely liquid by 162° (the melt was found to consist, in part, of **3a**); ir: 1561 cm^{-1}, 1512, 1462, 1329, 1233, 1143, 791, 765, 749, 693. The compound decomposed when exposed to air and light at room temperature, the surface darkening noticably within a few hours.

The sodium salt of **5a** was prepared by suspending the solid in ethanol (absolute), adding a slight excess of sodium hydroxide (40% aqueous solution), stirring and warming gently until homogeneous, then evaporating the solvent under reduced pressure. The crystalline solid was recrystallized from water as yellow needles which became red-orange on drying, or from acetone-hexane. After drying overnight at 90° and 0.2 torr, the salt was obtained as a sesquihydrate, mp 247-249° dec; ir: 1459 cm^{-1}, 1352; ^{1}H nmr (deuterium oxide): δ 7.56 ppm (s); ^{13}C nmr: δ 132.7 ppm, 131.3, 128.8, 126.4, 120.4.

Anal. Calcd. for $C_{15}H_{10}N_3O_4Na \cdot 1.5H_2O$: C, 52.03; H, 3.78; N, 12.13. Found: C, 51.67; H, 3.55; N, 11.73.

The ether solution from above was washed with 50 ml of water and 50 ml of saturated sodium chloride, dried (sodium sulfate), and evaporated. The residual gum was separated by flash chromatography on 150 g of silica gel (Davisil grade 633, 200-425 mesh), starting with 2000 ml of 5% acetone in hexane, followed with 1500 ml of 20% acetone in hexane, and collecting fractions of 100 ml. Fraction 6 contained trace amounts of a mixture of 3,5-diphenylisoxazole and 1,3-diphenyl-2-buten-1-one, identified by ^{1}H nmr comparison with authentic samples. Fractions 7-9 contained a mixture of *trans*-3,5-diphenyl-4-nitrato-4,5-dihydroisoxazole, *trans*-**5a**, and **3a**, which was separated by fractional crystallization from ethanol and from hexane and further chromatography on silica gel. The yield of *trans*-**5a** was 2.66 g (21%), mp 92-93° (from hexane) (reported mp 92-93° [2]); ir: 1650, 1281, 854, 835, 761, 698 cm^{-1}; ^{1}H nmr: δ 7.69 ppm (mult, 2H), 7.33-7.45 (mult, 8H), 6.41 (d, J = 1.7 Hz,

1H), 5.80 (d, J = 1.7 Hz, 1H); ^{13}C nmr: δ 150.5, 135.4, 131.0, 129.1, 129.0, 126.9, 125.5, 91.4, 87.6.

Fractions 10-13 contained additional traces of **3a** along with 0.08 g (1%) of *cis*-**5a**, which was isolated as colorless needles by recrystallization from acetone-hexane, mp 152-154°; ir: 1654, 1274, 936, 840, 693 cm^{-1}; ^{1}H nmr: δ 7.72 (mult, 2H), 7.35-7.50 (mult, 8H), 6.67 (d, J = 7.3 Hz, 1H), 5.67 (d, J = 7.3 Hz, 1H); ^{13}C nmr: δ 152.3 ppm, 131.0, 130.1, 129.5, 129.2, 128.6, 128.4, 127.3, 126.8, 86.2, 83.6.

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.42; H, 4.39; N, 9.62.

Fractions 14-17 gave a mixture which was separated by preparative layer chromatography on 2 mm plates of silica gel, Merck 60 F_{254}, 20 x 20 cm, with chloroform, to give 3,5-diphenyl-4-oximino-4,5-dihydroisoxazole **4a**, 0.12 g (1%) [4c], and 0.10 g of 3,5-diphenylpyrazole [15], which were identical with authentic samples.

Fraction 29 showed much streaking and multiple spots on thin layer chromatography. The major component was separated by preparative layer chromatography in silica gel with 5% ethanol in chloroform and recrystallized as faintly yellow granules, 0.16 g (2%), from acetone-hexane, mp 329-331°. The compound was identical with 3,3',5,5'-tetraphenyl-4,4'-bipyrazole **17** [11].

Nitrosation of 4-Phenyl-3-buten-2-one *(E)*-Oxime **1b** Under Oxygen.

A solution of **1b**, 5.0 g (0.031 mole) in 100 ml of 90% acetic acid was saturated with oxygen at 0° and then treated under an oxygen atmosphere over 150 minutes with 4.5 g (0.065 mole) of sodium nitrite in 40 ml of water. Stirring under oxygen at 0° was continued for 60 minutes, then the orange solid was collected by suction filtration and washed with cold water. The solid was stirred with dichloromethane and filtered to give 0.16 g (2%) of 3-methyl-5-phenyl-4-oximino-4*H*-pyrazole 1,2-dioxide **18**, while evaporation of the dichloromethane solution gave 2.21 g of 3-methyl-5-phenyl-4-oxo-4*H*-pyrazole 1,2-dioxide **3b**. During the chormatographic separation below and additional 0.13 g of **3b** as obtained, for a total yield of 37%. The compounds were identical with authentic samples [2].

The filtrate and wash solution were combined and evaporated without heating under 0.1 torr. The residual material was partitioned between 300 ml of ether and 150 ml of 5% sodium carbonate, and the ether layer was extracted with an additional 25 ml of 5% sodium carbonate. The sodium carbonate solution was cooled in ice and acidified with hydrochloric acid, and the solid was isolated by suction filtration, washed with cold water which was acidified with a few drops of hydrochloric acid, and dried at room temperature under 0.1 torr, avoiding undue exposure to light. This gave 1.79 g (25%) of 3(5)-methyl-5(3)-phenyl-4-nitro-1-hydroxypyrazole 2-oxide **5b** as a pale yellow solid which darkened on heating above 80°, partially melted with decomposition around 115°, and was completely liquified at 143°; ir: 1575, 1505, 1336, 1239, 1200, 1147, 1088, 792, 767, 723, 691 cm^{-1}. The compound was somewhat more stable than **5a**, and an analytical sample was purified by reprecipitation from its ammonium salt.

Anal. Calcd. for $C_{10}H_9N_3O_4$: C, 51.07; H, 3.86; N, 17.87. Found: C, 50.93; H, 3.72; N, 17.95.

The ammonium salt of **5b** was prepared by suspending the solid in ethanol (absolute), adding a slight excess of concentrated aqueous ammonia, warming gently until homogeneous,

and evaporating at reduced pressure. The residual solid was recrystallized from ethanol-ether as orange flakes, mp 173-174° dec; ir: 1463 cm^{-1}, 1347, 1068; ^{1}H nmr (deuterium oxide): δ 7.54 ppm (s, 5H), 2.59 (s, 3H); ^{13}C nmr: δ 132.7 ppm, 132.6, 131.2, 128.7, 126.2, 125.8, 121.1, 12.6. A sample for analysis was dried at room temperature under 0.1 torr for 48 hours.

Anal. Calcd. for $C_{10}H_{12}N_4O_4$•H_2O: C, 44.44; H, 5.22; N, 20.73. Found: C, 44.81; H, 5.08; N, 20.57.

The ethereal solution was washed with saturated sodium chloride, 50 ml, dried (sodium sulfate), and evaporated. The residual gum was submitted to flash chromatography on 20 g of silica gel with 8% acetone in hexane, giving, in order of elution, 0.28 g (6%) of 4-phenyl-3-buten-2-one, an additional 0.13 g of **3b**, and a white solid which was sublimed at 80° and 0.1 torr to give 0.78 g (16%) of 3(5)-methyl-5(3)-phenylpyrazole **16b** (identical with an authentic sample [16]).

Formation of **2a** by Oxidation of **1a** with Oxygen and Cobalt(II) Chloride Followed by Nitrosation.

Oxygen was bubbled for 30 minutes through a stirred solution of 1.76 g (8 mmoles) of cobalt(II) chloride hexahydrate in 30 ml of ethanol (absolute) at room temperature. The oxime **1a**, 0.22 g (1 mmole), was added and vigorous stirring under oxygen was continued for 4 hours at room temperature. The solution was poured into 100 ml of ice water and extracted with 50 ml of ether. The ether extract was washed with two 20 ml portions of water and with 20 ml of saturated sodium chloride, dried (sodium sulfate), and evaporated. Analysis of the residue in deuteriochloroform by nmr spectroscopy showed no remaining oxime but indicated a mixture containing two components, *ca.* 2:1. The minor component was identified as *trans*-3,5-diphenyl-4-hydroxy-4,5-dihydroisoxazole **13** [5,7]; ^{1}H nmr: δ 5.53 ppm (d, J = 3 Hz) and 5.35 (d, J = 3 Hz); ^{13}C nmr: δ 157.3 ppm (isoxazole C3), 90.0 and 84.3 ppm (isoxazole C4 and C5). The major component was assigned as 3,5-diphenyl-4-hydroperoxy-4,5-dihydroisoxazole **12**; ^{1}H nmr: δ 5.94 ppm (d, J = 3 Hz) and 5.64 (d, J = 3 Hz); ^{13}C nmr: δ 152.8 ppm (isoxazole C3), 96.1 and 85.9 (isoxazole C4 and C5).

The crude mixture was dissolved in ethanol (absolute), treated with 0.21 g (2 mmole) of *n*-butyl nitrite, and stirred at room temperature overnight. Evaporation of the solvent gave 0.22 g of a mixture, *ca.* 1:1, of **13** and *trans*-**2a**, which were separated by flash chromatography and identified by comparison with reference samples.

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[12]   Although this seems to be the first time these compounds have been reported, an unidentified reddish solid was previously described from the nitrosation of **1a** [2]. It seems likely that the reddish solid was **5a**, which does become reddish in color when exposed to air and light. Decomposition of **5a** gives **3a**, which was also reported as a decomposition product of the unidentified substance. In a personal communication Professor Freeman has also informed us that several years ago a compound identical with **5b** was isolated in his laboratories from a reaction similar to that described herein, but that those results were not reported [13]. We are indebted to him for this information and for a sample of the compound.

[13]   J. P. Freeman and R. C. Grabiak, unreported results.

[14]   When the nitrosation was performed at 0° much unreacted starting material was recovered. The lower order of reactivity of **1a** compared with **1b** is ascribed to the difference in geometry of the oximes with respect to the carbon-carbon double bond. For example, we have observed that nitrosation at 0° was complete in 5 hours for the *(E)*-oxime of 3,4-dimethyl-3-penten-2-one while a reaction time of 48 hours was required for the *(Z)*-oxime [4b].

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