Stereochemical Effects in the Nitrosation of Some α,β-Unsaturated Ketoximes. Formation of 1-Hydroxypyrazole 2-Oxides and 4-Oximino-4,5-dihydroisoxazoles

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Several α,β-unsaturated ketoximes $R^1CH=CHC(=NOH)R^2$ were nitrosated using butyl nitrite in aqueous ethanol in the presence of copper(II) sulfate and pyridine. The product distribution varied depending on whether the oxime hydroxyl group was *syn* or *anti* with respect to the carbon-carbon double bond. The *anti*-oximes gave the copper complexes of 1-hydroxypyrazole 2-oxides in high yields. The isomeric *syn*-oximes gave lower yields of the pyrazole complexes along with 4-oximino-4,5-dihydroisoxazole derivatives. For the *syn*-oximes where R^1 is phenyl and R^2 is either methyl or ethyl, conversion of the oximes to the parent ketones was also observed. The results may be explained by processes involving *N*-nitrosonitrone intermediates.

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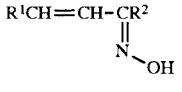
The versatility of the nitrosation of α,β-unsaturated ketoximes as a route to *N*-oxygenated pyrazoles has been discussed in review articles by Freeman [1] and by Kotali and Tsoungas [2]. Although the earliest report of the nitrosation of unsaturated ketoximes by Harries and Gley [3] noted a difference in both reactivity and yields for the nitrosation of the stereoisomeric oximes of 4-methyl-3-penten-2-one, stereochemical considerations have been, for the most part, ignored in subsequent studies. Recently we have observed stereochemical effects in the nitrosation of the (*E*)- and (*Z*)-oximes of 3,4-dimethyl-3-penten-2-one [4] and in the nitrosation of α-bromo-α,β-unsaturated ketoximes [5]. We now wish to report the results of our investigation of the effects of stereochemical factors on the nitrosation of a series of β-phenyl and β–alkyl-α,β-unsaturated ketoximes.

For purposes of the following discussion the terminology suggested by von Auwers for specifying the geometry of stereoisomeric α,β-unsaturated ketoximes has been adopted [6]. The oximes are classified as *anti*-oximes **1** or *syn*-oximes **2** to designate the orientation of the oxime hydroxyl group with respect to the carbon-carbon double bond. In most cases the oximes are known compounds, and the stereochemical assignments have been made [7a-g].



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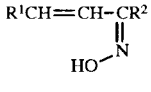

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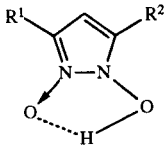
The nitrosation method used in this investigation has been described in previous reports [5,8-10]. This involved the use of butyl nitrite in aqueous ethanol in the presence of copper(II) sulfate and pyridine at room temperature under nitrogen. The main products of the reactions were 1-hydroxypyrazole 2-oxides, which were isolated as the insoluble copper complexes. The 1-hydroxypyrazole 2-oxides **3** could be liberated from the complexes by treatment with aqueous sodium hydroxide, filtration to remove inorganic solids, and acidification of the filtrate to precipitate **3**. Some of the 1-hydroxypyrazole 2-oxides obtained have been reported previously, while new examples were characterized by elemental analysis, infrared and nmr spectral examination, and chemical behavior (*i.e.*, acidity, formation of copper complexes) characteristic of compounds of this class.

In addition to 1-hydroxypyrazole 2-oxides, some of the reactions produced compounds identified as 4-oximino-4,5-dihydroisoxazoles **4**. The formation of **4** ($R^1 = R^2 =$ Ph) has been reported in the nitrosation of 1,3-diphenyl-2-propen-1-one oxime [5,9]. The new compounds **4** were characterized by elemental analysis and infrared and nmr spectral properties. The oxime hydroxyl groups gave broad absorptions in the ir in the region of 3200-3300 cm^{-1} and signals in the ^1H nmr around δ 7.5-9 ppm; the protons attached to C5 of the isoxazole rings gave signals in the region of 5.1-6.1 ppm. The ^{13}C nmr spectra included signals for the carbon atoms of the isoxazole ring at δ 78-90 ppm (C5) and 152-163 ppm (C3 and C4). Although stereoisomerism about the oxime carbon-nitrogen double bond is possible for **4**, only one stereoisomeric form was observed in each case. In two of the nitrosation reactions significant quantities of the parent ketones **5** resulting from deoximation of the starting oximes were observed. Deoximation products were not observed in more than trace amounts in any of the other nitrosation reactions. The results of the nitrosation reactions are summarized in Table 1.

Two types of stereochemical effects are suggested by the data of Table 1. These effects can be seen most clearly in the comparison of the *anti*-oxime **1a-c** and *syn*-oxime **2a-d** derivatives of the alkyl styryl ketones. The nitrosations of the *anti*-oximes **1a-c** give only the 1-hydroxypyrazole 2-oxides **3** in high yields. Although formation of

Table 1

Products of Nitrosation of α,β-Unsaturated Ketoximes



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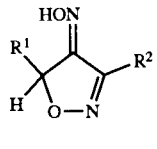

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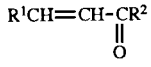


5

Oxime	R^1	R^2	Yield (%) Pyrazole 3 [a]	Isoxazole 4	Ketone 5
1a	Ph	Me	89	0	-
2a	Ph	Me	51	0	25
1b	Ph	Et	90	0	-
2b	Ph	Et	73	<1	10
1c	Ph	*i*-Pr	84	0	-
2c	Ph	*i*-Pr	78	6	-
2d	Ph	*t*-Bu	76 [b]	10	-
1e	Ph	Ph	87	9	-
2e	Ph	Ph	52	44	-
2f	Me	Ph	48	20	-
2g [c]	*t*-Bu	Ph	59 [b]	31	-

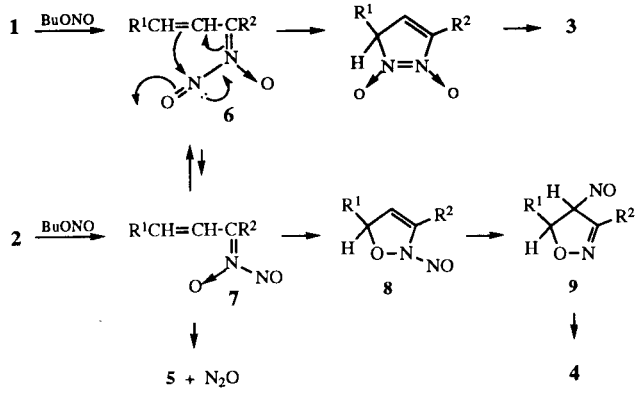
[a] Unless otherwise specified yield given is for the copper complex of the pyrazole. [b] Total yield of pyrazoles including **3** and its 4-nitro-derivative **12.** [c] Contains about 20% of the *anti*-oxime.

3 also represents the principal process in the nitrosations of the *syn*-oximes **2a-d**, the yields of pyrazoles are lower, and two types of competing reactions are observed leading to the 4-oximino-4,5-dihydroisoxazoles **4** and the parent ketones **5.** Furthermore, the relative importance of the two types of competing reactions is influenced by the nature of the alkyl group R^2. These results are consistent with the processes suggested in Scheme 1, which incorporates mechanistic concepts described in earlier reports [1,2,4,5].

The nitrosation of oximes is generally believed to proceed through the intermediacy of *N*-nitrosonitrones formed by attack of the nitrosating agent on the unshared pair of electrons of the oxime nitrogen. In the case of **1** and **2**, this process would be expected to produce the stereoisomeric α,β-unsaturated nitrosonitrones **6** and **7**. In **6** the nitroso group is favorably disposed for electrophilic attack at the β-carbon to produce a 3*H*-pyrazole intermediate as suggested by Freeman, which rearranges to **3.** Lower yields of pyrazoles are obtained from the *syn*-oximes **2** because the intermediate *N*-nitrosonitrone **7** must undergo stereoisomerization to **6** in order for pyrazole formation to occur. Competitive with the stereoisomerization are the processes leading to **4** and **5**.

The mechanism suggested in Scheme 1 for conversion of **7** to the 4-oximino-4,5-dihydroisoxazoles **4** is a variation of that suggested by Freeman in the thermal isomerization of 3,3,5-trimethyl-3*H*-pyrazole 1,2-dioxide to 3,5,5-trimethyl-4-oximino-4,5-dihydroisoxazole [11]. This involves cyclization by attack of the nitrone oxygen at the β-carbon followed by rearrangement of the 2-nitroso-2,5-dihydroisoxazole intermediate **8** to the 4-nitroso-4,5-dihydroisoxazole **9** and tautomeric rearrangement of **9** to **4**. The formation of **8** from **7** is similar to the process proposed by Ooi and Wilson [7d] for the formation of other 2,5-dihydroisoxazoles from α,β-unsaturated nitrones.

Scheme 1: Mechanistic Proposal



The deoximation of oximes to the parent ketones is a common result of the nitrosation of oximes and was first reported by Claisen and Manasse [12]. The deoximation reaction is also believed to proceed through *N*-nitrosonitrone intermediates, and conversion to the ketone is known to be inhibited in sterically-hindered oximes such as pinacolone oxime or camphoroxime [13]. In non-conjugated, sterically-hindered oximes this results in the formation of nitrimines instead of deoximation. Thus, in the current study, it is not surprising that the deoximation process occurs most readily for the least sterically-hindered example of **7** where R^2 is a methyl group but decreases in importance as the steric bulk of R^2 is increased. For **2c** and **2d** the rate of deoximation is decreased to the point where this process is now slower than the cyclization to **4** and is no longer observed to an appreciable extent. Besides decreasing the rate of deoximation to **5**, one might speculate that a bulky group R^2 could also have a favorable effect on the rate of formation of **4** if relief of steric crowding between that group and the nitroso group enhances the rate of cyclization of **7** to **8**.

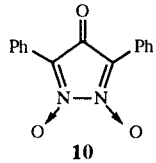
The highest yields of 4-oximino-4,5-dihydroisoxazoles are observed in those *syn*-oximes where R^2 is a phenyl group. Furthermore, **1e**, which is the only *anti*-oxime examined where R^2 is phenyl, is also the only example in which an *anti*-oxime gave a 4-oximino-4,5-dihydroisoxazole, which would require isomerization of an *N*-nitrosonitrone of type **6** to an *N*-nitrosonitrone of type **7**. Perhaps conjugative interactions when R^2 is a phenyl group influence the relative stabilities of **6** and **7** to account for this. The results could also be explained by an effect of the

phenyl group on the relative rates of the cyclization processes by which **3** and **4** are formed from the nitrosonitrone intermediates.

In the discussion to this point the possible effect of the copper ion on the reaction has been ignored. However, it is certainly possible that it may have some involvement beyond its ability to trap the 1-hydroxypyrazole 2-oxide, which is the primary reason for including it in the reaction mixture. To test this possibility, the nitrosations of the *anti*- and *syn*-oximes **1e** and **2e** were examined under different conditions. The stereoisomeric oximes were nitrosated by treatment with sodium nitrite in acetic acid under a nitrogen atmosphere. Under these conditions the 1-hydroxypyrazole 2-oxide cannot be isolated but is converted to a mixture of 3,5-diphenyl-4-pyrazolone 1,2-dioxide **10** and the pyrazolone oxime **11** as reported by Freeman, Gannon, and Surbey [14]. The previous report did not address the stereochemistry of the starting oxime, and the combined yield of **10** and **11** was reported to be about 60%.

The nitrosations of **1e** and **2e** with sodium nitrite in acetic acid under nitrogen gave results shown in Table 2 which were consistent with those observed for their nitrosations with butyl nitrite in the presence of copper sulfate and pyridine. In particular, the ratio of pyrazole products, **10** + **11** to **4e** showed a stereochemical dependence which was similar to what was seen for the nitrosations in the presence of copper sulfate. Thus, although the copper ion may have some influence on the nitrosation reaction beyond the simple trapping of the pyrazole, its mechanistic involvement does not appear to be profound. Furthermore, the stereochemical effects observed in the current studies are similar to effects seen in the nitrosation of the stereoisomeric oximes of 3,4-dimethyl-3-penten-2-one [4] where copper ion was not present.

Table 2
Nitrosation of **1e** and **2e** with Sodium Nitrite in Acetic Acid



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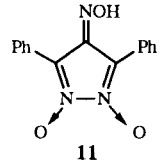

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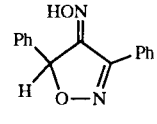
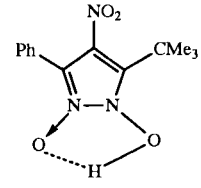


4e

	10	**11**	**4e**
From **1e**	16%	51%	7%
From **2e**	19%	21%	48%

In the processes outlined in Scheme 1 it is suggested that the stereoisomerization required to account for the observations occurs after nitrosation. The possibility that stereoisomerization between the oximes **1** and **2** might precede nitrosation was considered; however, samples of unreacted oximes removed during the course of some of the reactions did not show evidence of any compromise of their stereochemical integrity. These results are consistent with what was observed in the nitrosation of the oximes of 3,4-dimethyl-3-penten-2-one, where there was no indication of stereoisomerization of the unreacted oximes during nitrosation [4]. That stereoisomerization might be more facile for the *N*-nitrosonitrones than for the oximes is consistent with observations reported by Wilson and co-workers [7d,15], that nitrones derived from some α,β-unsaturated ketones undergo stereoisomerization more readily than the structurally related oximes.

In most of the reactions shown in Table 1 the strategy of isolating the 1-hydroxypyrazole 2-oxide as the copper complex was very successful in preventing further reaction of pyrazoles. The strategy was not entirely successful in the nitrosations of **2d** and **2g**, in which a minor product was observed. The same 1-hydroxypyrazole 2-oxide, **3d** or **3g** is formed in both of these reactions. The minor product formed is the 4-nitropyrazole derivative **12**, possibly resulting from nitrosation at C4 of **3** and oxidation of an intermediate nitroso compound. Nitrosation at C4 of 1-hydroxypyrazole 2-oxides has been suggested in the formation of 4-oximino-4*H*-pyrazole 1,2-dioxides under different nitrosation conditions [8,14]. Compound **12** was difficult to isolate from the reaction mixture in pure form due to contamination by **3d**. However, a pure sample of **12** could be prepared by treating **3d** with butyl nitrite. Pure **12** was a pale yellow solid which decomposed upon heating; it was identified from its elemental analysis and spectral properties.



12

These investigations show that the nitrosation of β-substituted-α,β-unsaturated ketoximes is subject to steric effects related both to the geometry about the carbon-nitrogen double bond and to steric crowding in the vicinity of the oxime functional group. The effects observed can be accommodated by processes involving *N*-nitrosonitrone intermediates in accord with the mechanistic hypotheses previously proposed for the nitrosation of oximes.

EXPERIMENTAL

The ir spectra were run as 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, unless other conditions are specified. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, DE. Melting point values were obtained with a Thomas Hoover Uni-melt apparatus and are uncorrected.

4-Methyl-1-phenyl-1-penten-3-one *(E)*- and *(Z)*-Oximes **1c** and **2c**.

A solution of 8.70 g (0.05 mole) of 4-methyl-1-phenyl-1-penten-3-one [7c] in 100 ml of ethanol (95%) was treated with solutions of 5.2 g (0.075 mole) of hydroxylamine hydrochloride in 12 ml of water and of 6.2 g of sodium acetate in 12 ml of water. The solution was heated under reflux for 3 hours, then it was concentrated on a rotary evaporator by removing about 60 ml of solvent. The concentrated mixture was diluted to 200 ml with water and refrigerated overnight.The solid was collected by suction filtration, washed with cold water, and dried to give 7.47 g (79%) of a mixture, *ca.* 4:1 by ^{1}H nmr, of the *(Z)*-oxime and the *(E)*-oxime. Recrystallization from 40 ml of ethanol (95%) gave 4.60 g of the *(Z)*-oxime **2c** as large, colorless shafts, mp 132-134° (reported mp 134-135° [7c]).

The solvent was evaporated from the filtrate, and the residual yellow syrup was submitted to medium-pressure chromatography with 5% acetone in hexane at about 70 psi on a 1000 x 25 mm column of silica gel. After a forerun of 350 ml, fractions of about 25 ml were collected. Fractions 46-52 gave an additional 0.38 g of the *(Z)*-oxime, while fractions 55-73 gave 1.08 g of the *(E)*-oxime **1c**. Recrystallization from hexane gave colorless prisms, mp 76-79°; ^{1}H nmr: δ 7.9 ppm (brd s, 1H), 7.2-7.5 (mult, 5H), 7.08 (d, J = 16 Hz, 1H), 6.66 (d, J = 16, 1H), 3.51 (septet, J = 7 Hz, 1H), 1.24 (d, J = 7 Hz, 6H); ^{13}C nmr: δ 163.3 ppm, 136.2, 134.6, 128.7, 127.1, 120.8, 26.2, 18.9.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.81; H, 7.72; N, 7.39.

General Method for Nitrosation of α,β-Unsaturated Ketoximes.

Oxygen-free solvents were prepared by heating ethanol (95%) or water under reflux for about 60 minutes while a slow stream of nitrogen was passed through the apparatus. Reactions were carried out under a nitrogen atmosphere.

The oxime, 0.05 mole, in 125 ml of oxygen-free ethanol (95%), at room temperature, was treated in rapid succession with 8.0 g (0.1 mole) of pyridine, a solution of 12.5 g (0.05 mole) of copper(II) sulfate pentahydrate in 50 ml of oxygen-free water, and 7.7 g (0.075 mole) of *n*-butyl nitrite. Typically, some transient precipitation of the oxime occurred giving a rather heavy suspension which was agitated manually until it became mobile enough for magnetic stirring. The mixture was stirred at room temperature overnight, then it was treated with 125 ml of water and 250 ml of ether, and stirred for several minutes in an ice bath. The insoluble copper complex was collected by suction filtration, washed with water, with cold ethanol, and with ether, and dried overnight at 0.1 torr. In most cases the yields of the pyrazole products in Table 1 refer to the yields of copper complexes obtained by this method.

The ether layer of the filtrate and wash solutions was separated and the aqueous layer extracted with two 100 ml portions of ether. The ether solutions were combined and washed successively with 50 ml of 5% sodium carbonate, 50 ml of 1.5*M* hydrochloric acid, again with 50 ml of 5% sodium carbonate, then with 50 ml of saturated sodium chloride solution, dried over sodium sulfate, and evaporated. The residue was deposited on 3 g of silica gel (Davisil grade 633, 200-425 mesh) by evaporation of an acetone solution and applied to a column of 20 g of silica gel. Flash chromatography was carried out with 7% acetone in hexane, and fractions of about 20 ml were collected. Typically the first few fractions contained mixtures, usually in only trace amounts except as noted in Table 1, of the 4-pyrazolone 1,2-dioxides and the α,β-unsaturated ketones **5** formed by deoximation. The 4-oximino-4,5-dihydroisoxazoles **4** were in later fractions (typically between 200 and 500 ml of eluate) and were isolated by evaporation, and recrystallized.

The free 1-hydroxypyrazole 2-oxides **3** were obtained by suspending samples of about 2 g of the copper complexes in 25 ml of 5% sodium hydroxide, adding about 10 ml of ethanol (95%), and stirring at room temperature for 30 minutes. The mixtures were filtered under suction through diatomaceous earth to remove inorganic solids, and the filtrates were cooled in ice and acidified to Congo red with hydrochloric acid to precipitate the colorless 1-hydroxypyrazole 2-oxides **3**, which were collected by suction filtration, washed with cold water, and dried under vacuum.

Nitrosation of **1a** and **2a** (R^1 = Ph, R^2 = Me).

The copper complex was a brown solid, mp 219-220° dec, identical with material previously reported [8,16].

Anal. Calcd. for $C_{20}H_{18}N_4O_4Cu$: C, 54.35; H, 4.10; N, 12.68. Found: C, 54.49; H, 3.85; N, 12.30.

Free **3a** was liberated from the copper complex as described above and was identical with a sample previously reported [8].

The deoximation product **5a** was obtained from **2a** and identified by comparison with an authentic sample.

Nitrosation of **1b** and **2b** (R^1 = Ph, R^2 = Et).

The copper complex was a brown solid, mp 209-210° dec.

Anal. Calcd. for $C_{22}H_{22}N_4O_4Cu$: C, 56.22; H, 4.72; N, 11.92. Found: C, 56.03; H, 4.58; N, 11.72.

Free **3b** was a colorless solid, mp 166-167°; ^{1}H nmr: δ 12.2 ppm, 7.89 (d, J = 7.7 Hz, 2H), 7.37-7.50 (mult, 3H), 6.12 (s, 1H), 2.75 (quartet, J = 7.4 Hz, 2H), 1.30 (triplet, J = 7.4 Hz, 3H).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.66; H, 6.02; N, 13.45.

Compound **4b**, 3-ethyl-5-phenyl-4-oximino-4,5-dihydroisoxazole, gave colorless needles from benzene, mp 105-106°; ir: 3213 cm^{-1}, 1458, 988, 894, 765, 700; ^{1}H nmr: δ 8.47 ppm (s, 1H), 7.2-7.4 (mult, 5H), 6.06 (s, 1H), 2.45-2.66 (mult, twelve lines, 2H, diastereotopic CH_2), 1.28 (t, J = 7.5 Hz, 3H); ^{13}C nmr: δ 161.0 ppm, 155.6, 134.7, 128.8, 128.6, 127.4, 82.0, 18.1, 10.7.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.61; H, 5.76; N, 13.41.

The deoximation product **5b** was obtained from **2b** and identified by comparison with an authentic sample.

Nitrosation of **1c** and **2c** (R^1 = Ph, R^2 = *i*-Pr).

The copper complex of **3c** was a pale brown solid, mp 203-204° (reported mp 202° [9]).

Anal. Calcd. for $C_{24}H_{26}N_4O_4Cu$: C, 57.88; H, 5.26; N, 11.25. Found: C, 57.63; H, 5.22; N, 11.13.

Free **3c** was a colorless solid, mp 180-182° (reported mp 193° [9]).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.90; N, 12.78. Found: C, 65.84; H, 6.59; N, 12.98.

Compound **4c**, 3-isopropyl-5-phenyl-4-oximino-4,5-dihydroisoxazole was obtained as colorless prisms from benzene-

pentane, mp 97-99°; ir: 3264 cm^{-1}, 1455, 987, 907; ^1H nmr: δ 8.58 ppm (s, 1H), 7.2-7.4 (mult, 5H), 6.06 (s, 1H), 2.93 (septet, 7 Hz, 1H), 1.32 (d, J = 7 Hz, 3H) and 1.30 (d, J = 7 Hz, 3H) (diastereotopic methyl groups); ^{13}C nmr: δ 160.6 ppm, 158.8, 134.9, 128.7, 128.5, 127.4, 82.0, 25.9, 20.1 and 19.7 (diastereotopic Me_2).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.12; H, 6.32; N, 12.75.

Nitrosation of **1e** and **2e** ($R^1 = R^2 = Ph$).

The copper complex of **3e** was a pale yellow-brown solid, mp 225° dec (reported mp 227° dec [5]).

Anal. Calcd. for $C_{30}H_{22}N_4O_4Cu$: C, 63.65; H, 3.92; N, 9.90. Found: C, 63.88; H, 3.92; N, 9.66.

The free 1-hydroxypyrazole 2-oxide **3e** was liberated as described above and was identical with an authentic sample [8].

The 4-oximino-4,5-dihydroisoxazole **4e** was isolated in the usual way and was identical with a sample reported previously [5].

Nitrosation of **2f** (R^1 = Me, R^2 = Ph).

The reaction gave a copper complex which was identical with that obtained from **1a**, from which the 1-hydroxypyrazole identical with **3a** could be liberated.

Compound **4f**, 5-methyl-3-phenyl-4-oximino-4,5-dihydroisoxazole, was recrystallized from benzene-hexane as colorless granules, mp 144-145°; ir: 3240 cm^{-1}, 1450, 986, 944, 918, 690; ^1H nmr: δ 8.35 ppm (s, 1H), 7.99 (mult, 2H), 7.35-7.50 (mult, 3H), 5.53 (quartet, J = 6.7 Hz, 1H), 1.64 (d, J = 6.7 Hz, 3H); ^{13}C nmr: δ 162.4 ppm, 151.9, 130.4, 128.5, 127.7, 127.1, 78.7, 16.4.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.33; H, 5.31; N, 14.66.

Nitrosation of **2d** (R^1 = Ph, R^2 = *t*-Bu).

A solution of 2.03 g (0.01 mole) of the oxime in 25 ml of deoxygenated ethanol (95%) was stirred under nitrogen at room temperature and treated successively with 1.6 g (0.02 mole) of pyridine, 2.5 g of copper(II) sulfate pentahydrate in 10 ml of water (deoxygenated), and 1.55 g (0.015 mole) of *n*-butyl nitrite. After stirring overnight at room temperature the mixture was cooled in ice and filtered, and the solid was washed with cold ethanol and with water and dried under vacuum to give 1.83 g (70%) of the copper complex as a brown solid, mp 214-216° dec.

Anal. Calcd. for $C_{26}H_{30}N_4O_4Cu$: C, 59.36; H, 5.75; N, 10.65. Found: C, 59.03; H, 5.43; N, 10.47.

The filtrate and wash solutions were combined, treated with 100 ml of water, and extracted with three 75 ml portions of ether. The ether extract was washed with 50 ml of water, 25 ml of 5% sodium bicarbonate, and 50 ml of saturated sodium chloride solution and evaporated without heating under reduced pressure. The residue was held at 0.1 torr overnight to remove 1-butanol. The residue was dissolved in 200 ml of ether and the ether solution was stirred for 15 minutes with 20 ml of 3*M* hydrochloric acid; the aqueous layer was removed and discarded and treatment of the ether layer in the same way with fresh 20 ml portions of 3*M* hydrochloric acid was repeated twice more [17]. The ether solution was then extracted with two 20 ml portions of 5% sodium carbonate solution. Acidification of the sodium carbonate extracts gave a pale yellow solid which was collected, washed with cold water, and dried to give 0.26 g, estimated from ^1H nmr (in deuterium oxide basified with pyridine-d_5) to contain about 0.18 g (8%) of **3d** and 0.08 g (3%) of **12**.

The ether solution was washed with 50 ml of saturated sodium chloride, dried (sodium sulfate), and evaporated. The residue was submitted to flash chromatography on silica gel in the usual way to give a small amount of the 4-pyrazolone 1,2-dioxide [7e] and traces of the ketone **5d**, followed in later fractions by 0.24 g of 3-*tert*-butyl-5-phenyl-4-oximino-4,5-dihydroisoxazole **4d**, which was recrystallized from hexane-acetone as colorless crystals, mp 157-159°; ir: 3228 cm^{-1}, 1458, 977, 903, 692; ^1H nmr: δ 7.93 (s, 1H), 7.22-7.35 (mult, 5H), 6.09 (s, 1H), 1.38 (s, 9H); ^{13}C nmr: δ 160.8 ppm, 160.4, 135.3, 128.6, 128.5, 127.4, 82.4, 33.3, 27.9.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.10; H, 7.06; N, 12.32.

The free 1-hydroxypyrazole 2-oxide **3d** was prepared from the copper complex in the usual way and isolated as a colorless solid, mp 179-181°; ^1H nmr: δ 11.45 ppm (broad s, 1H), 7.92 (d, J = 7.7 Hz, 2H), 7.35-7.50 (mult, 3H), 6.11 (s, 1H), 1.45 (s, 9H).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.22; H, 7.04; N, 12.16.

Nitrosation of **2g** (R^1 = *t*-Bu, R^2 = Ph).

The *syn*-oxime **2g** contained about 20% of the *anti*-oxime [7e,18]. The modification used for **2d** was applied. The copper complex, the 1-hydroxypyrazole 2-oxide, and the 4-nitro-1-hydroxypyrazole 2 oxide **12** which were obtained were the same ones produced in the nitrosation of **2d**. A total of 56% of **3g** was obtained along with 3% of **12**.

Chromatography of the ether-soluble material in the usual way gave 31% of 5-*tert*-butyl-3-phenyl-4-oximino-4,5-dihydroisoxazole **4b**, colorless flakes from benzene-hexane, mp 158-159°; ir: 3214 cm^{-1}, 1455, 1018, 978, 916; ^1H nmr: δ 8.57 ppm (s, 1H), 7.93 (mult, 2H), 7.35-7.50 (mult, 3H), 5.19 (s, 1H), 1.05 (s, 9H); ^{13}C nmr: δ 159.8 ppm, 153.6, 130.4, 128.6, 127.8, 127.0, 88.7, 38.7, 26.7.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.06; H, 6.82; N, 11.93.

3(5)-*tert*-Butyl-5(3)-phenyl-4-nitro-1-hydroxypyrazole 2-Oxide (**12**).

A solution of 0.23 g (1 mmole) of **3d** in 2 ml of acetic acid and 4 ml of ethanol (95%) under nitrogen was cooled in ice, treated with 1.03 g (10 mmole) of *n*-butyl nitrite and stirred with continued cooling overnight. A pale yellow solid was collected and washed with cold ethanol (95%). The solid was stirred at room temperature for several minutes with 25 ml of 3% sodium bicarbonate and filtered to remove insoluble impurities. The filtrate was cooled in ice and acidified to Congo red with 3*M* hydrochloric acid, and the pale yellow solid was collected by suction filtration and washed with cold water which had been acidified with a drop of hydrochloric acid. After drying under 0.1 torr overnight, the yield of **12** was 0.08 g (29%). The compound decomposed violently upon melting at 82°, and it darkened gradually upon exposure to air and light; ir: 1525 cm^{-1}, 1364, 788; ^1H nmr: [19] δ 7.45-7.60 ppm (mult, 5H), 1.53 (s, 9H); ^{13}C: δ 132.5 ppm, 132.1, 131.9, 131.5, 130.4, 128.9, 125.5, 123.0, 36.3, 30.2.

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.65; H, 5.47; N, 15.15.

Nitrosation of **1e** and **2e** with Sodium Nitrite in Acetic Acid.

A solution of 0.45 g (2 mmoles) of the oxime in 20 ml of acetic acid and 2 ml of ethanol (absolute) was purged with nitro-

gen, cooled to 10°, and treated over 10 minutes with a solution of 0.42 g (6 mmoles) of sodium nitrite in 2 ml of water. The temperature was allowed to rise gradually to room temperature and stirring under nitrogen was continued overnight. The mixture was cooled in ice and the orange solid was collected by suction filtration and washed with cold ethanol (95%). The solid was stirred for a few minutes with 10 ml of dichloromethane and filtered, and the solid washed with an additional small quantity of dichloromethane. The insoluble orange solid was identified as 3,5-diphenyl-4-oximino-4*H*-pyrazole 1,2-dioxide **11**, while evaporation of the dichloromethane solution gave 3,5-diphenyl-4-oxo-4*H*-pyrazole 1,2-dioxide **10**. These products were identical with authentic samples [14]. The original filtrate and wash solutions were combined, treated with 100 ml of water, and extracted with three 50 ml portions of ether. The ether extract was washed with four 25 ml portions of water, then with 10 ml portions of 5% sodium carbonate until the wash solution remained basic to litmus, and finally with 50 ml of saturated sodium chloride. After drying over sodium sulfate the ether was evaporated and the residue was separated by flash chromatography on silica gel with 5% acetone in hexane. Early fractions contained an additional small amount of **10**, while later fractions contained **4e**, which was identical with samples described above. Yield data are given in Table 2.

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[17] While most of the copper complexes of **3** were insoluble in ether, those of **3d** and of **12** were soluble in ether to a significant extent. Treatment of the ether solution of the complexes with dilute hydrochloric acid liberated free **3d** and **12**, which were then extracted from the ether solution with dilute sodium carbonate.

[18] Assignment of the major isomer as the *syn*-oxime is based upon the chemical shifts of the vinylic proton signals in the ^{1}H nmr. For the major isomer these appeared as a pair of doublets at δ 6.87 and 6.06 ppm (J = 16.5 Hz), while the corresponding signals for the minor isomer appeared at 6.26 and 5.69 ppm (J = 16.0 Hz). The vinylic protons in the *syn*-oximes typically are deshielded relative to those in the *anti*-oximes of α,β-unsaturated ketoximes [*cf* 7d,15].

[19] The compound decomposed upon attempts to dissolve it in deuteriochloroform or other typical solvents. Its nmr spectra were run in deuterium oxide which was made basic with sodium hydroxide, using sodium 3-trimethylsilylpropane-1-sulfonate as an internal standard. The values reported under these conditions are actually for the conjugate base of **12**.