Preparation and Nitrosation of 3,4-Dimethyl-3-penten-2-one (*E*)- and (*Z*)-Oximes. Formation of 3,3,4,5-Tetramethyl-3*H*-pyrazole 1,2-Dioxide and of 2-Isoxazoline Derivatives

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The stereoisomeric (*E*)- and (*Z*)-oximes of 3,4-dimethyl-3-penten-2-one were prepared and nitrosated with butyl nitrite in methanol. The (*E*)-oxime gave 3,3,4,5-tetramethyl-3*H*-pyrazole 1,2-dioxide in nearly quantitative yield, while the (*Z*)-oxime reacted less readily, giving a lower yield of the same product, with five other products identified as isoxazoline derivatives. Three of these were 4-hydroxy-, 4-methoxy-, and 4-nitro-3,4,5,5-tetramethyl-2-isoxazoline. The fourth was the *O*-(3,4,5,5-tetramethyl-2-isoxazolin-4-yl) derivative of the starting (*Z*)-oxime, and the fifth was 4-methylene-3,5,5-trimethyl-2-isoxazoline.

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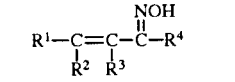
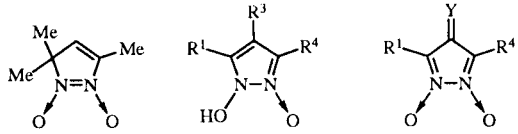
The nitrosation of α,β-unsaturated ketoximes is a versatile method for the synthesis of a variety of *N*-oxygenated pyrazoles. The type of product obtained is influenced by the pattern of substituents attached to the α- and β-carbons of the starting oxime **1** (R is alkyl or aryl except as noted). In the case of the β,β-disubstituted ketoxime, mesityl oxide oxime, **1a** ($R^1 = R^2 = R^4 = Me$), nitrosation produces 3,3,5-trimethyl-3*H*-pyrazole 1,2-dioxide **2** [1,2]. The 3*H*-pyrazole 1,2-dioxide structure has also been suggested for the products of nitrosation of certain cholest-5-en-7-one oximes [3,4]. Nitrosation of ketoximes of type **1b** gives 1-hydroxypyrazole 2-oxides **3** [5], and 1-hydroxypyrazole 2-oxides may also be isolated from the nitrosation of oximes of type **1c** [6,7,8] or types **1d** or **1e** [9] when reactions are carried out under conditions which permit the isolation of **3** as their metal complexes. Under different nitrosation conditions oximes of type **1c** yield 4-pyrazolone 1,2-dioxides **4** (Y = O) or the corresponding oximes **4** (Y = NOH) [10,11]. Until now no one seems to have extended nitrosation studies to α,β,β-trisubstituted-α,β–unsaturated ketoximes. We now wish to report our observations on the nitrosation of such a fully-substituted ketoxime.



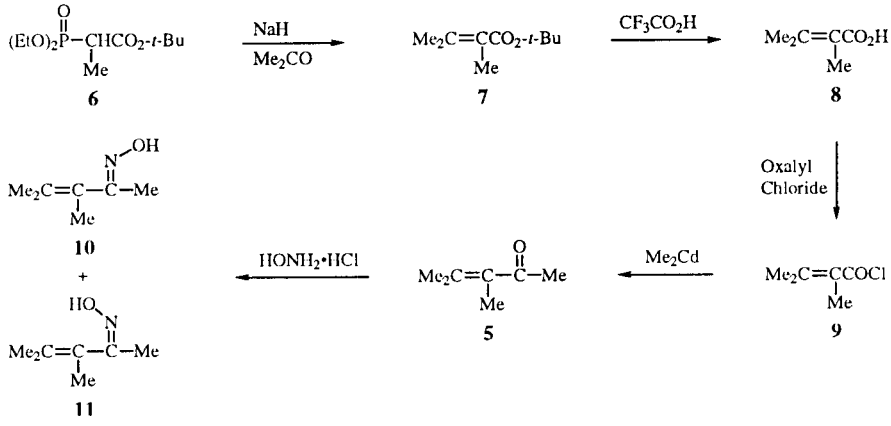
1a ($R^3 = H$)
1b ($R^2 = H$)
1c ($R^2 = R^3 = H$)
1d ($R^1 = R^2 = H$)
1e ($R^1 = R^2 = R^3 = H$)



2 **3** **4**

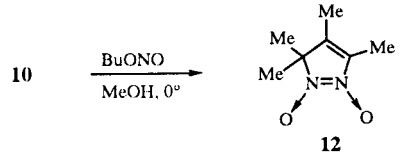
For the purpose of this investigation we prepared 3,4-dimethyl-3-penten-2-one **5** and converted it into its previously unreported oximes. Synthesis of **5** was carried out by the sequence shown in Scheme 1. The route involves a Horner-Emmons reaction followed by cleavage of the

Scheme 1
Preparation of 3,4-Dimethyl-3-penten-2-one Oximes



tert-butyl ester **7** to give 2,3-dimethyl-2-butenoic acid **8**, which could be converted *via* the acyl chloride **9** into **5** using dimethylcadmium. Good yields of **5** were obtained with little contamination by the isomeric 3,4-dimethyl-4-penten-2-one. A sequence similar to that in Scheme 1, starting with the more accessible ethyl ester analogous to **6** was attempted initially, but in that case conditions could not be found to effect hydrolysis of the ethyl ester to **8** without substantial contamination by 2,3-dimethyl-3-butenoic acid. Reaction of **5** with hydroxylamine gave a mixture, *ca.* 3:1; of the isomeric (*E*)- and (*Z*)-oximes **10** and **11**. The configurations of the previously unreported oximes were established by Beckmann rearrangements.

Nitrosation reactions were carried out in methanol with butyl nitrite. In the case of **10** the reaction was complete after about five hours in an ice bath, and a single product **12** was isolated in nearly quantitative yield. The identification of **12** as 3,3,4,5-tetramethyl-3*H*-pyrazole 1,2-dioxide was apparent from its infrared spectrum, which closely resembled that of **2** [2], particularly in the appearance of a strong absorption at 1484 cm^{-1}, and from ^1H and ^{13}C nmr data consistent with the assigned structure.



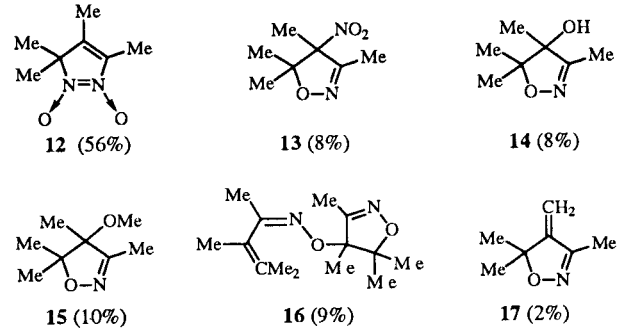
12

The (*Z*)-oxime **11** reacted less readily than **10** with butyl nitrite, consistent with observations by Harries and Gley [1] that the two stereoisomeric oximes of mesityl oxide exhibit a difference in reactivity, as well as in the yield of **2** produced upon nitrosation. At 0°, nitrosation of **11** required about two days for completion. Alternatively, by running the reaction at room temperature, the consumption of **11** was complete in about six hours, giving the product mixture shown in Table 1. The 2-isoxazoline derivatives **13-17** were separated and characterized by elemental analysis and by infrared and ^1H and ^{13}C nmr spectroscopy. The ^{13}C nmr spectra of all five compounds included signals in the region of about δ155-161 ppm and 85-90 ppm, assigned for C3 and C5, respectively, of the isoxazoline ring. For **13-15** signals for four nonequivalent methyl groups were seen in the ^1H nmr spectra.

The infrared spectrum of **13** included as its strongest absorption a peak at 1552 cm^{-1}, along with a weaker absorption at 1346 cm^{-1}. These values fall near the low-frequency ends of ranges of about 1550-1575 and 1350-1370 cm^{-1} reported for ν_{asym} and ν_{sym}, respectively, for the nitro group in a series of 4-nitro-2-isoxazolines [12].

The 2-isoxazolin-4-ol **14** gave a broad, one-proton signal in its ^1H nmr spectrum which was susceptible to exchange with deuterium oxide, and its ir spectrum contained a typical OH stretching band at 3248 cm^{-1}. The methoxy group in **15** gave a three-proton singlet in the ^1H nmr spectrum at δ 3.21 and a signal in the ^{13}C nmr spectrum at δ 52.9 ppm. The relationship between **14** and **15** was confirmed by demonstrating that **15** could be formed from a sample of **14** by treatment with sodium hydride followed by iodomethane.

Table 1
Products of Nitrosation of **11**



12 (56%) **13** (8%) **14** (8%)

15 (10%) **16** (9%) **17** (2%)

In addition to nmr spectral features characteristic of the 3,4,5,5-tetramethyl-2-isoxazolin-4-yl moiety in **16**, the spectra contained additional signals similar to those in the starting oxime **11**. In particular there were three three-proton signals in the region of δ 1.50-1.65 in the ^1H nmr spectrum for the three allylic methyl groups, and the ^{13}C nmr spectrum included signals for the two olefinic carbons at 124.1 and 126.8 ppm. The stereochemical assignment of the oxime ether linkage in **16** as the (*Z*)-isomer was based upon the assumption of retention of the configuration of the starting oxime **11**. This assumption is based upon the observations that no compromise of oxime geometry occurred for either **10** or **11** under the conditions of the nitrosation reactions. Furthermore, the reaction mixture did not contain any material which could be identified as the stereoisomer of **16** with respect to the oxime ether linkage, an observation which is much more consistent with retention rather than with complete stereochemical inversion in the oxime ether.

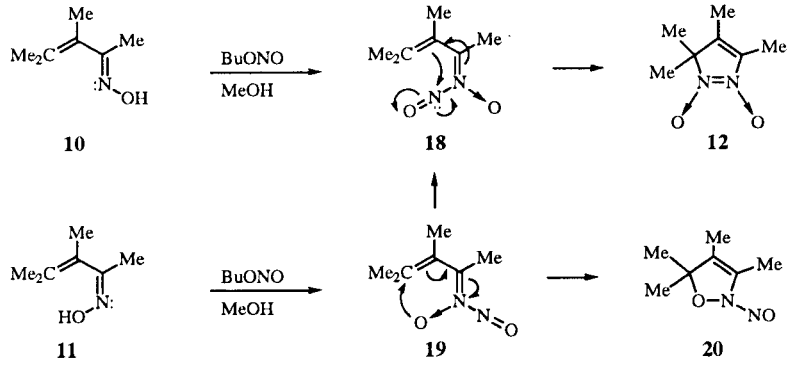
The ^{13}C nmr spectrum of the 4-methylene-2-isoxazoline **17** consisted of only six signals, including one at δ 105.5 for the exocyclic methylene carbon. The number of signals was consistent with the equivalence of the geminal methyl groups on the C5 position, which also was indicated by a six-proton singlet in the ^1H nmr spectrum. The ^1H nmr spectrum also included two one-proton singlets for the two olefinic protons of the exocyclic methylene group, as well as a three-proton singlet for the methyl substituent at C3.

Reactions of samples of the (*E*)- and (*Z*)-oximes with butyl nitrite in deuterated methanol were followed by ^1H nmr analysis. It was observed, starting with pure samples

of the isomeric oximes, that no compromise of oxime geometry occurred for the unreacted oxime. Competitive nitrosation of a mixture of **10** and **11** confirmed that the (*E*)-oxime was consumed more rapidly than the (*Z*)-oxime. Freeman [2,10,13] has suggested a mechanism for the formation of pyrazoles by nitrosation of α,β-unsaturated ketoximes. Scheme 2 represents the extension of this mechanism to the nitrosation of **10** and **11**. It has been suggested that the key intermediates in nitrosation of oximes are *N*-nitrosonitrones formed by attack of the nitrosating agent on the unshared pair of electrons of the oxime nitrogen. Differences in stability and in various other aspects of chemical behavior have been observed for stereoisomeric conjugated ketoximes [*cf* 14], so the fact that **10** and **11** differ in reactivity toward nitrosation is not unexpected.

Scheme 2

Proposed Mechanism for Pyrazole and Isoxazoline Formation



10 **18** **12**

11 **19** **20**

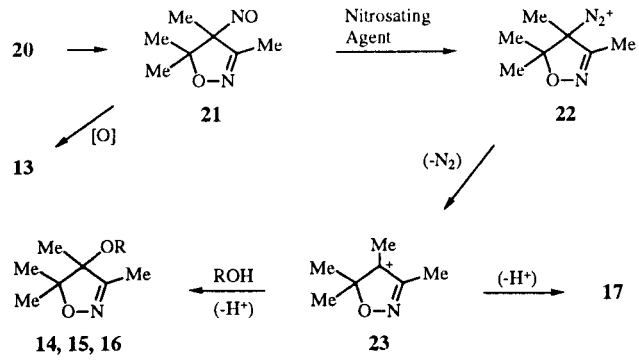
In the case of the (*E*)-*N*-nitrosonitrone **18**, the nitroso group is favorably oriented for electrophilic attack at the β-carbon leading, with appropriate reorganization of electrons as suggested by Freeman, to **12**. The (*Z*)-*N*-nitrosonitrone **19**, on the other hand, must undergo isomerization to **18** before pyrazole formation can occur. An alternative cyclization involving bond formation between the nitrone oxygen and the β-carbon would produce the 2-nitroso-3-isoxazoline **20**, which we suggest may be a reasonable precursor for the products **13-17** observed in the nitrosation of **11**. Indeed, a process analogous to the formation of **20** has been suggested by Freeman in the thermal rearrangement of **2** to 4-oximino-3,5,5-trimethyl-2-isoxazoline [2]. Since the combined yields of the isoxazoline products in the nitrosation of **11** is only slightly less than the yield of **12** in that reaction, it would appear that the rate of cyclization of **19** to **20** is very similar to the rate of isomerization to **18**.

An alternative explanation for the formation of **12** from **11** would be the partial isomerization of **11** to **10** prior to, rather than subsequent to nitrosation. In view of the failure to detect such isomerization in the nmr studies mentioned above, this alternative seems unlikely. That isomerization might be more facile for the nitrosonitrones than the starting oximes is consistent with observations by Ooi and Wilson [15], who have observed greater stereochemical lability for nitrones derived from the (*E*)- and (*Z*)-oximes of 1,3-diphenyl-2-propen-1-one and 1-phenyl-2-propen-1-one than for the parent oximes. Ooi and Wilson also observed the cyclization of α,β–unsaturated nitrones to 3-isoxazolines, providing a precedent for the type of cyclization we suggest for the formation of **20** from **19**.

It is possible to account for the five isoxazoline derivatives isolated from the nitrosation of **11** by processes outlined in Scheme 3. The rearrangement of **20** to **21** is analogous to the process suggested by Freeman in the thermal isomerization of **2** to the 4-oximino-2-isoxazoline mentioned above. In that example, the rearrangement produces a secondary nitroso compound which undergoes tautomerization to the oxime. Since **21** is a tertiary nitroso compound, a similar tautomerization is not possible, and it undergoes different transformations to produce the isoxazolines **13-17**. The formation of **13**, for instance, is easily explained, since a common feature of C-nitroso compounds is the ease with which they are oxidized to nitro compounds.

Scheme 3

Proposed Origin of Isoxazoline Derivatives



The remaining four isoxazoline derivatives could all be accounted for as products derived from the 2-isoxazolin-4-yl cation **23**, which may be formed from the diazonium ion **22**. The formation of diazonium salts by the reaction of *C*-nitroso compounds with nitrosating agents has been suggested in the reactions of nitrosocyclohexane [16] and of nitrosomethane [17], and it has even been possible to produce stable aryldiazonium salts by the nitrosation of nitrosobenzene derivatives [18,19]. Loss of a proton from the methyl group at C4 of **23** could then produce the 4-methylene-2-isoxazoline **17**, while nucleophilic attack by water, methanol, or the oxime **11** and loss of a proton would give **14**, **15**, or **16**, respectively. It is also possible that **14** may be formed through the intermediacy of a nitrite or nitrate ester, since both cyclohexyl nitrite and cyclohexyl nitrate have been reported as products in the nitrosation of nitrosocyclohexane [16]. The nitrite or nitrate ester might be converted into **14** by transesterification with methanol or by reaction with the starting oxime.

Our results show that the formation of *N*-oxygenated pyrazoles by nitrosation of α,β-unsaturated ketoximes can be extended to a system where both of the β-positions as well as the α-position are substituted. We have also demonstrated that the stereochemistry of the oxime has an influence both on its reactivity and on the distribution of products formed during the reaction. We are pursuing further studies of the influence of oxime geometry on nitrosation, and we are proceeding with investigations in the reactions of 3,3,4,5-tetramethyl-3*H*-pyrazole 1,2-dioxide, particularly in comparison with those of 3,3,5-trimethyl-3*H*-pyrazole 1,2-dioxide.

EXPERIMENTAL

The ir spectra were run as nujol mulls, melts or neat films as indicated, 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. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, DE. Melting point values were obtained with a Thomas Hoover Unimelt apparatus and are uncorrected.

tert-Butyl 2,3-Dimethyl-2-butenoate (**7**).

A suspension of 20 g of a 60% sodium hydride dispersion in mineral oil (12.0 g, 0.5 mole of sodium hydride) in 250 ml of 1,2-dimethoxyethane (DME) (distilled from calcium hydride) was cooled intermittently to keep the temperature at 25-35° and stirred while 106 g (0.4 mole) of *tert*-butyl 2-(diethoxyphosphoryl)propanoate **6** [20] in 150 ml of dry DME was added over 60 minutes. The resulting mixture was stirred at room temperature for 120 minutes, then 29 g (0.5 mole) of acetone (anhydrous) was added dropwise, cooling occasionally with an ice bath during addition and for several minutes thereafter to keep the temperature below 35°. The mixture was stirred at room temperature for 12 hours, warmed gradually with continued stirring until the temperature reached 70°, cooled again to room temperature, and poured into 250 ml of ice water, using an additional 100 ml of ice water to complete the transfer. The organic layer was separated, and the aqueous layer extracted with three 200 ml portions of pentane. The organic solutions were combined, washed with 100 ml of saturated sodium chloride solution, and dried (potassium carbonate). The solvent was removed by fractional distillation at ambient pressure. The residual liquid was fractionally distilled (20 cm vigreux column) under reduced pressure, and the product was collected as a colorless liquid, 51.3 g (75%), bp 81-82° at 20 torr; ir (neat): 1710 cm^{-1}, 1638 (wk), 1173, 1101; ^1H nmr: δ 1.95 (s, 3H), 1.82 (s, 3H), 1.76 (s, 3H), 1.50 (s, 9H); ^{13}C nmr: δ 169.1, 139.9, 124.1, 79.9, 28.2, 22.5, 21.9, 15.7.

2,3-Dimethyl-2-butenoic Acid (**8**).

A solution of 85 g (0.5 mole) of the *tert*-butyl ester **7** in 85 ml of trifluoroacetic acid (TFA) was heated under reflux for 30 minutes. After removal of volatile material on a rotary evaporator, the residue was distilled. A low-boiling forerun containing unreacted ester was obtained, after which **8** was collected as a colorless liquid, 44 g, bp 120-22° at 23 torr, which solidified on standing. The forerun yielded an additional 5 g of **8** upon cleavage with a fresh portion of TFA, giving a total yield of 49 g, 86%. Recrystallization from pentane gave colorless crystals, mp 69-71° (reported mp 71° [21]); ir (nujol): 1680 cm^{-1}, 1620; ^1H nmr: δ 12.4 (brd s, 1H), 2.13 (s, 3H), 1.89 (s, 3H), 1.87 (s, 3H) [22]; ^{13}C nmr: δ 175.2, 148.2, 121.6, 23.5, 23.3, 15.5.

2,3-Dimethyl-2-butenoyl Chloride (**9**).

A mixture of 34.2 g (0.3 mole) of **8** in 75 ml of benzene (anhydrous) was stirred at room temperature in a fume hood in a flask equipped with a condenser for reflux topped with a calcium sulfate drying tube, while 42 g (0.33 mole) of oxalyl chloride was added, dropwise, over 75 minutes. The mixture was stirred at room temperature for 30 minutes and was then heated in an oil bath maintained at about 50-60° until gas evolution had ceased (*ca.* 50 minutes), giving a clear yellow solution. The flask was arranged for distillation with a 10 cm vigreux column. and held at about 50° under 80 torr while the solvent and unreacted oxalyl chloride were distilled off. The pressure was reduced further, and the product was distilled as a colorless liquid, 39.5 g, of **9**, shown by nmr to contain about 5% benzene, for a yield of 96%, bp 81° at 50 torr; ir (neat film): 1769 cm^{-1}, 1611; ^1H nmr: δ 2.02 (s, 6H), 1.90 (s, 3H); ^{13}C nmr: δ 168.2, 149.1, 128.2, 23.3 (appears to include both β-Me carbons), 16.6 [23].

3,4-Dimethyl-3-penten-2-one (**5**).

A dried 1000 ml three-neck flask was equipped with an efficient mechanical stirrer, a nitrogen inlet, a thermometer, and a septum. The flask was kept under a nitrogen atmosphere. To the flask was added 170 ml of 3*M* methylmagnesium bromide in ether (0.51 mole) (Aldrich Chemical Co.). The solution was cooled in ice and stirred while 50 g (0.28 mole) of cadmium chloride (anhydrous) was added in portions over 25 minutes, followed by continued stirring and cooling for 15 minutes. A condenser was attached for simple distillation, and the ether was distilled off, adding 250 ml of benzene (anhydrous) gradually to keep the slurry mobile enough for stirring. Stirring was contin-

ued while the thick gray slurry was cooled to room temperature, then the condenser was rearranged for reflux, and a pressure-equalized addition funnel containing 38.4 g (0.29 mole) of **9** in 50 ml of benzene was attached. The acyl chloride solution was added over about 45 minutes to the vigorously stirred mixture, and once the vigorously exothermic reaction had subsided, the mixture was heated under reflux with stirring for 60 minutes. The slurry was poured with stirring into 400 ml of ice-water in a 2000 ml beaker, using additional water and benzene to complete the transfer. The mixture was treated with 3.6*M* sulfuric acid until the inorganic salts dissolved and the aqueous layer was acidic to litmus. The organic layer was separated and the aqueous layer extracted with two 100 ml portions of benzene, which were combined with the original organic solution and washed with 100 ml portions of water, 5% sodium carbonate, and saturated sodium chloride solution, and dried (sodium sulfate). The solvent was removed by distillation under atmospheric pressure, using a 50 cm vigreux column. The residual liquid was transferred to a smaller flask and distilled under reduced pressure using a 30 cm vigreux column. The ketone **5**, 26.6 g (82%), was collected as a colorless liquid, bp 72-73° at 47 torr (reported bp 147° at 1 atm [24]); ir (neat): 1686 cm^{-1}, 1621; ^1H nmr: δ 2.24, 1.88, 1.85, 1.76 (four singlets of equal integration); ^{13}C nmr: δ 204.8, 137.8, 131.3, 29.5, 22.2, 21.5, 15.4.

3,4-Dimethyl-3-penten-2-one (*E*)-Oxime (**10**) and (*Z*)-Oxime (**11**).

A solution of 11.2 g (0.10 mole) of **5** in 60 ml of ethanol (95%) was treated at room temperature with solutions of 12.3 g (0.15 mole) of sodium acetate in 30 ml of water and 10.5 g (0.15 mole) of hydroxylamine hydrochloride in 20 ml of water. After stirring at room temperature for 8 hours, the mixture was treated with 200 ml of water and extracted with three 150 ml portions of ether. The ether extract was washed with three 50 ml portions of 5% sodium bicarbonate until the wash solution remained basic to litmus; it was then washed with 50 ml of saturated sodium chloride, dried (sodium sulfate), and evaporated. The residual liquid was distilled under reduced pressure, giving 11.6 g (91%) of colorless liquid, bp 108-111° at 20 torr. The ^1H nmr spectrum of the product indicated a mixture, *ca.* 3:1, of the (*E*)-oxime **10** and the (*Z*)-oxime **11**. The mixture was dissolved in 25 ml of pentane and cooled in dry ice. The supernatant was drawn off from the white solid which formed, and the solid was recrystallized from pentane at about -20°, giving colorless rhombic plates of **10**, mp 40-42°; ir (melt): 3228 cm^{-1}, 1646 (wk), 923; ^1H nmr: δ 8.5 (brd s, 1 H), 1.95 (s, 3H), 1.75 (s, 3H), 1.71 (s, 6H); ^{13}C nmr: δ 159.7, 130.9, 126.0, 21.7, 20.2, 16.8, 13.8. An analytical sample was distilled at 98° and 10 torr.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.18; H, 10.56; N, 11.05.

The mother liquor was evaporated, and the residue was separated by medium-pressure chromatography with 7% acetone in hexane at a pressure of about 80 psi on a 25 x 1000 mm column of silica gel. After a forerun of 300 ml, fractions of about 20 ml were collected and monitored by tlc on silica gel (Baker-Flex IB2-F) with 15% acetone in hexane, the (*E*)- and (*Z*)-oximes having R_f 0.36 and 0.29, respectively [25]. Fractions 34-47 contained the (*E*)-oxime, fractions 48-55 a mixture, and fractions 56-125 the pure (*Z*)-oxime. The intermediate fractions were rechromatographed to give more of the purified isomers. The (*E*)-oxime was recrystallized from pentane as described above. The (*Z*)-oxime was collected by combining and evaporating the chromatographic fractions, and distilling the residual colorless liquid, bp 88-89° at 10 torr; ir (neat): 3242 cm^{-1}, 1654 (wk), 1019 (str); ^1H nmr: δ 9.35 (brd s, 1H), 1.90 (s, 3H), 1.74 (s, 3H), 1.72 (s, 3H) 1.61 (s, 3H); ^{13}C nmr: δ 159.0, 128.5, 123.9, 21.7, 19.4, 19.0, 15.2.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.16; H, 10.39; N, 11.30.

Beckmann Rearrangements of **10** and **11**.

To an ice-cooled suspension of phosphorus pentachloride, 0.42 g (2 mmoles), in 5 ml of ether (anhydrous) was added a solution of 0.25 g of the oxime in 3 ml of ether. The mixture was stirred in ice for 120 minutes, then 10 ml of 5% sodium carbonate was added and stirring was continued for 10 minutes. An additional 10 ml of ether was added, and the ether layer was separated, washed with saturated sodium chloride, dried (potassium carbonate) and evaporated.

The product from the (*Z*)-oxime **11** was *N*,2,3-trimethyl-2-butenamide, colorless needles from hexane, mp 61-62°, identical with a sample prepared from **9** by reaction with methylamine; ir (nujol): 3288 cm^{-1}, 1666, 1619; ^1H nmr: δ 5.8 (bd s, 1H), 2.85 (d, J = 4.7, 3H, NMe), 1.82 (s, 3H), 1.78 (s, 3H), 1.68 (s, 3H); ^{13}C nmr: δ 173.2, 131.9, 127.1, 26.0, 21.9, 19.9, 16.0.

The crude product from the (*E*)-oxime was a colorless solid, mp 64-68°, which partially decomposed on attempted purification. The crude material was assigned as the *N*-acetyl derivative of 2-amino-3-methyl-2-butene from spectral evidence: ir (nujol): 3242 cm^{-1}, 1648, 1532, 1292; ^1H nmr: δ 7.59 (bd s, 1H), 2.05 (s, 3H), 1.85 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H); ^{13}C nmr: δ 169.1, 125.3, 123.9, 22.7, 19.4 (two overlapping signals), 17.1. The crude product was hydrolyzed by stirring overnight with 5 ml of hexane and a few drops of water acidified with a trace of hydrochloric acid. The hexane layer was separated and the aqueous material extracted with a small portion of ether. Evaporation of the aqueous layer gave 0.02 g of colorless solid identified as acetamide by comparison with an authentic sample. The ether solution was treated with a few ml of 2,4-dinitrophenylhydrazine reagent and stirred for 3 hours at room temperature, giving 0.09 g of orange crystals, mp 119-120°, identical with a sample of the 2,4-DNP derivative of 3-methyl-2-butanone.

3,3,4,5-Tetramethyl-3*H*-pyrazole 1,2-Dioxide (**12**).

A solution of the (*E*)-oxime **10**, 2.54 g (20 mmoles), in 30 ml of anhydrous methanol was cooled in an ice bath, treated with 3.4 g (30 mmoles) of butyl nitrite and allowed to stand with continued cooling under a nitrogen atmosphere. After 5 hours the solvent was removed without heating at 0.2 torr. The residual solid was treated with 15 ml of ether, swirled for several minutes, and kept at -20° overnight. The colorless solid was collected by suction filtration and washed with ether which had been cooled in dry ice, giving 3.04 g (97%) of **12**, mp 109-112°. Evaporation of the filtrate gave 0.07 g of an oily solid, which was mainly an additional small quantity of **12**. Recrystallization from methanol-ether gave colorless prisms, mp 111-112°; ir (nujol): 1699 cm^{-1} (wk), 1484, 1422, 1103, 1030, 891; ^1H nmr: δ 2.17 (s, 3H), 2.00 (s, 3H), 1.59 (s, 6H, CMe_2); ^{13}C nmr: δ 133.8, 131.6, 73.8, 22.6 (gem-di-Me), 9.3, 8.2.

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.73; N, 17.94. Found: C, 54.22; H, 7.29; N, 17.63.

Nitrosation of 3,4-Dimethyl-3-penten-2-one (Z)-Oxime (**11**).

A solution of 2.92 g (23 mmoles) of the (Z)-oxime **11** in 25 ml of methanol (anhydrous, purged with nitrogen) was treated at room temperature under nitrogen with 3.6 g (35 mmoles) of butyl nitrite; a blue-green hue was observed which faded to yellow as the reaction progressed [26]. After standing overnight at room temperature the solution was placed in a fractional distillation apparatus with a 10 cm Vigreux column, and the solvent was removed at 60 torr without heating. The residue was treated with 15 ml of pentane and allowed to stand at -20° for 180 minutes, and 1.49 g of **12** was filtered off and washed with cold pentane.

The pentane was removed from the filtrate, and the 1-butanol was distilled off at 50-55° at 40 torr. The residue was treated again with pentane and allowed to stand at -20° overnight, whereupon a second crop of 0.46 of **12** was deposited. The filtrate was evaporated at 80 torr without heating, and the residue was held at 1 torr for several hours at room temperature, collecting any volatile material in a trap cooled with dry ice. The ^{1}H nmr spectrum of the condensate showed a little 1-butanol along with 0.066 g (2%) of 4-methylene-3,5,5-trimethyl-2-isoxazoline **17** and 0.164 g of 4-methoxy-3,4,5,5-tetramethyl-2-isoxazoline **15**. This mixture was separated by preparative gas chromatography at 170° on a 4 ft by 0.25 in column of Carbowax 20M (20%) on Chrom P; retention times were 75 secounds for 1-butanol, 220 seconds for **17**, and 460 seconds for **15**. An analytical sample of **17** was purified by evaporative distillation; ir (neat): 3090 cm^{-1} (wk), 1718 (wk), 1642 (mod), 903 (v str); ^{1}H nmr: δ 5.19 (s, 1H), 4.98 (s, 1H), 2.05 (s, 3H), 1.38 (s, 6H); ^{13}C nmr: δ 155.5, 153.8, 105.5, 84.9, 27.9 (gem-Me$_2$), 9.9.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.16; H, 8.86; N, 11.19. Found: C, 67.33; H, 9.07; N, 10.91.

The pot residue from above was deposited on 2 g of silica gel by evaporation of an ether solution and applied to a column of 20 g of silica gel (Davisil grade 633, 200-425 mesh). Flash chromatography was carried out using 500 ml of 5% acetone in pentane, followed by 500 ml of 10% acetone in pentane, then 200 ml of 25% acetone in pentane, and finally 100 ml of acetone. Fractions of about 20 ml were collected, evaporated, and checked by ^{1}H nmr analysis. Fractions 2-4 contained 0.266 g (9%) of **16**, the *O*-(3,4,5,5-tetramethyl-2-isoxazolin-4-yl) derivative of the starting (Z)-oxime, which was distilled as a colorless liquid, bp 130° at 5 torr; ir (neat): 1671 cm^{-1} (v wk), 1435, 1134, 1110, 1093, 1015, 935, 905; ^{1}H nmr: δ 1.95 (s, 3H), 1.86 (s, 3H), 1.65 (brd s, 3H), 1.64 (brd s, 3H), 1.52 (brd s, 3H), 1.35 (s, 3H), 1.24 (s, 6H); ^{13}C nmr: δ 159.3, 159.2, 126.8, 124.1, 91.4, 87.1, 23.1, 21.5, 20.1, 19.3, 18.7, 18.6, 15.0, 10.8.

Anal. Calcd. for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.45; H, 9.72; N, 11.61.

Fractions 6-7 gave 0.199 g of **15**, which was combined with that isolated by preparative gc to give a total of 0.363 g (10%). The material was purified by evaporative distillation at 60° and 30 torr; ir (neat): 1108 cm^{-1}, 1059, 850; ^{1}H nmr: δ 3.21 (s, 3H), 1.96 (s, 3H), 1.36 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H); ^{13}C nmr: δ 158.0, 89.3, 87.0, 52.9, 24.4, 18.8, 17.3, 10.6.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.36; H, 9.74; N, 8.71.

Fractions 9-13 yielded 0.302 g (8%) of 3,4,5,5-tetramethyl-4-nitro-2-isoxazoline **13**, mp 45-47° (from pentane); ir (melt): 1552 cm^{-1} (v str), 1387, 1346, 1138, 913; ^{1}H nmr: (four singlets of equal integration) δ 2.04, 1.70, 1.34, 1.33; ^{13}C nmr: δ 153.7, 102.7, 87.9, 23.1, 21.6, 16.5, 10.5.

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 48.82; H, 7.03; N, 16.27. Found: C, 49.18; H, 6.66; N, 15.96.

Fractions 27-37 gave 0.263 g (8%) of 3,4,5,5-tetramethyl-2-isoxazolin-4-ol **14**, as colorless plates, mp 65-66° (from hexane-acetone); ir (nujol): 3248 cm^{-1}, 1628 (wk), 1121, 932, 912; ^{1}H nmr: δ 3.29 (variable between 1.7-3.3; exchanges with deuterium oxide) (brd s, 1H), 1.98 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H); ^{13}C nmr: δ 161.3, 86.4, 84.9, 22.6, 19.1, 18.3, 9.5.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.79; H, 8.71; N, 9.58.

The fraction eluted with acetone contained 0.060 g of the pyrazole **12**, making the total yield of **12** 2.01 g (56%).

4-Methoxy-3,4,5,5-tetramethyl-2-isoxazoline **15**.

A solution of 0.143 g (1 mmole) of the isoxazolinol **14** in 3 ml of 1,2-dimethoxyethane (distilled from calcium hydride) was treated with 0.05 g of a 60% dispersion of sodium hydride in mineral oil (1.25 mmoles of sodium hydride) and stirred at room temperature. After 10 minutes the mixture was treated with 0.17 g (1.2 mmoles) of iodomethane and stirred at room temperature overnight. The yellow solution was treated with 4 ml of water and 25 ml of ether. The ether layer was separated, washed with 5 ml of saturated sodium chloride solution, dried (sodium sulfate) and evaporated. Evaporative distillation at 30 torr and an oil bath temperature of 60° gave 0.053 g (34%) of **15** with spectral properties identical with those described above.

REFERENCES AND NOTES

[1] C. Harries and R. Gley, *Chem. Ber.*, **32**, 1330 (1899).

[2] J. P. Freeman, *J. Org. Chem.*, **27**, 1309 (1962).

[3] Shaffiullah and I. H. Siddiqui, *Indian J. Chem.*, **28B**, 424 (1989).

[4] The structures suggested in [3] have the 3*H*-pyrazole 1,2-dioxide incorporated in a 6,7-diazabicyclo[3.2.1]octane system with a bridgehead double bond. On the basis of Bredt's rule the assigned structures seem unlikely.

[5] J. P. Freeman and J. J. Gannon, *J. Org. Chem.*, **34**, 194 (1969).

[6] J. F. Hansen and D. E. Vietti, *J. Org. Chem.*, **40**, 816 (1975).

[7] J. F. Hansen and D. E. Vietti, *J. Org. Chem.*, **41**, 2871 (1976).

[8] A. A. Fadda, *Indian J. Chem.*, **30B**, 749 (1991).

[9] J. F. Hansen and M. L. Luther, *J. Heterocyclic Chem.*, **30**, 1163 (1993).

[10] J. P. Freeman, J. J. Gannon, and D. L. Surbey, *J. Org. Chem.*, **34**, 187 (1969).

[11] G. R. Stevenson, J. F. Hansen, G. Clark, and J. P. Freeman, *J. Org. Chem.*, **44**, 3211 (1979).

[12] L. A. Demina, G. Kh. Khisamutdinov, S. V. Tkachev, and A. A. Fainzil'berg, *Zh. Org. Khim. USSR (Eng Transl)*, **15**, 654 (1979).

[13] J. P. Freeman, *Chem. Rev.*, **73**, 283 (1973).

[14] J. E. Baldwin and R. K. Norris, *J. Org. Chem.*, **46**, 697 (1981).

[15] N. S. Ooi and D. A. Wilson, *J. Chem. Res.* (*S*), 366, (*M*), 4726 (1980).

[16] L. G. Donaruma and D. J. Carmody, *J. Org. Chem.*, **22**, 635 (1957).

[17] L. Blatt and B. G. Gowenlock, *Trans. Faraday Soc.*, **56**, 682 (1960).

[18] J. M. Tedder, *J. Chem. Soc.*, 4003 (1957).

[19] J . M. Tedder and G. Theaker, *J. Chem. Soc.*, 4008 (1957).

[20] A. Gossauer and G. Kuhne, *Liebigs Ann. Chem.*, 664 (1977).

[21] H. M. R. Hoffmann, K. Haase, Z. M. Ismail, S. Preftitsi, and A. Weber, *Chem. Ber.*, **115**, 3880 (1982).

[22] In [21] ^{1}H nmr data are reported as a 6H singlet at δ 1.86 and a 3H doublet (J = 1.5 Hz) at δ 2.12. We suspect the authors may have inadvertently switched the designation of mutiplicity, while simultaneously incorrectly identifying two closely-spaced singlets as a doublet.

[23] Spectral values are in satisfactory agreement with those reported in [21] for this compound.

[24] Z. Rappoport, Handbook of Tables for Organic Compound Identification, 3rd Ed, CRC Press, Inc, Boca Raton, FL 1967, p 163.

[25] In one case the synthetic sequence was carried out without recrystallizing **8**, and a small amount of another isomeric oxime was obtained which eluted just ahead of and overlapping with **10**. Sufficient amounts of this material were obtained to permit characterization as the oxime of 3,4-dimethyl-4-penten-2-one. The material was a colorless liquid, bp 88-89° at 10 torr; ir (neat): 3266 cm^{-1}, 3087 (wk), 1645, 895; ^{1}H nmr: δ 9.85 (brd s, 1H), 4.90 (s, 1H), 4.85 (s, 1H), 3.02 (q, J = 7 Hz, 1H), 1.79 (s, 3H), 1.67 (s, 3H), 1.22 (d, J = 7 Hz, 3H); ^{13}C nmr: δ 159.7, 145.6, 111.8, 46.8, 20.6, 15.7, 11.1.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.03; H, 10.32; N, 11.04.

[26] The blue-green color may be due to the transient presence of **21**, since blue or green colors are typical of *C*-nitroso compounds. No such color was observed during the nitrosation of **10**.