Pathway Control of Products in the Reaction of Nitrosyl Chloride on Oximes

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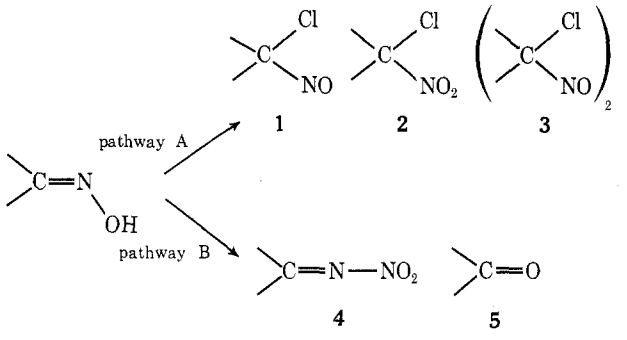
The two pathways of reaction of nitrosyl chloride with oximes were found to be sensitive to three parameters: polarity of solvent, concentration of nitrosyl chloride, and concentration of oxime. Pinacolone oxime, which takes both pathways, was examined with respect to each variable. The two pathways can be controlled over rather wide limits by variation in the three parameters. Pinacolone is produced directly from the oxime by a mechanism which cannot involve hydrolysis since water was excluded from the reaction with nitrosyl chloride. A pathway to account for the production of chloronitroso compound **1**, nitrimine **4**, and ketone **5** is given.

The ambident nature of nitrosyl chloride has been mentioned in a review[1] describing normal and anomalous reaction products in the nitrosochlorination of alkenes. Kadzyauskas and Zefirov point out that slight changes in conditions may produce substantial changes in the pathway of the reaction. We were impressed by the sensitivity of the reagent to changes in reaction conditions in repeating a reaction of nitrosyl chloride not with an alkene but with an oxime, first reported in 1927. Rheinboldt and Dewald[2] reported a 19% yield of the chloronitroso compound, type **1** (Scheme I), as the only

Scheme I



product from a 0.38 M solution of pinacolone oxime in ethyl ether when treated with liquid nitrosyl chloride. We obtained a 51% yield of pinacolone nitrimine, type **4**, from a 0.45 M solution of the same oxime in chloroform with gaseous nitrosyl chloride.[3]

Search of the literature[2-6] (Table I) suggested that many oximes react predominantly by pathway A (Scheme I) to incorporate chlorine; others appear only to react by pathway B; and a few gave products from both pathways (camphor oxime, pinacolone oxime). The results in Table I suggested enough anomalies that generalizations might be forthcoming from closer control over reaction conditions.

Preliminary experiments suggested that a systematic study of the sensitivity of the reagent to solvent polarity, concentration of the oxime, and concentration of the reagent would be worthwhile on an oxime that took both pathways. For this purpose pinacolone oxime was chosen over camphor oxime since it gave all five types of products, **1–5** (Scheme I), which could be conveniently identified.

Since **1** is the initial product in pathway A and subsequently precipitates as dimer (**3**) or is oxidized to **2**, the results obtained from a change of solvent polarity are reported in Figure 1 as a ratio of pathway A to pathway B where pathway A represents the total yield of (1 + 2 + 3). The yield by pathway B includes (4 + 5). The ratios are shown as a function of solvent polarity as measured by the dielectric constants for carbon tetrachloride, chloroform, methylene chloride, and the oxygen-containing solvents, ether and nitromethane. The ratio of products from pathway A to products from pathway B is greater as the dielectric constant increases but it is not a continuous function; oxygen solvents, ether and nitromethane, give an added tilt to the ratio. However, within these results is a hidden anomaly. The ratio of **4** to compound **5** was nearly 5 in carbon tetrachloride and nitromethane while the ratio is approximately 1 in the solvents of intermediate polarity (Table II).

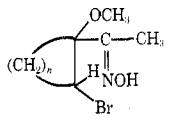
The distribution of products was also found to depend both on the concentration of oxime and concentration of nitrosyl chloride. Chloroform was chosen as solvent for this series of experiments using a molar ratio of 2:1 for nitrosyl chloride to oxime (Figure 2). As the concentration of oxime increased the formation of ketone **5** and nitrimine **4** increased at the expense of chloronitroso compound **1**. At low oxime concentration (up to 1 M), nitrimine and ketone are formed in about equal molar amounts but at a concentration of 2 M, the product mixture was noticeably richer in nitrimine (Table III).

To examine the effect of the molar ratio of nitrosyl chloride to oxime, different molar ratios were used on oxime solutions of the same concentration (1 M), again in chloroform at 25 °C. The results shown in Figure 3 suggest that at a molar ratio of nitrosyl chloride to oxime of 4, chloronitroso compound formation dominates but does not stifle formation of **4** completely. The ratio of nitrimine to ketone remains essentially one at all ratios of reagent to oxime at this concentration (Table IV and Figure 3).

The question of the origin of the ketone in this reaction is relevant since it is known that nitrimines and chloronitroso compounds[7] both hydrolyze to ketones as do oximes. However, water was excluded in the present work and we conclude that the ketone is a primary reaction product. To test this point the reaction of nitrosyl chloride with pinacolone oxime was monitored at intervals to see if the percentage of nitrimine or chloronitroso compound diminished as the reaction progressed. This reaction was carried out at a low molar ratio of reagent to oxime to ensure that nitrimine and ketone were the dominant products. Table V gives the product distribution at approximately one-fourth (29%), half (54%), three-fourths (77%), and completion (100%) of the reaction. Each of the three products **1**, **4**, and **5** increased steadily in amount. There was no decrease in **1** or **4** in any interval. While this does not exclude some formation of ketone from a secondary process it strongly suggests that ketone is mainly formed directly by the reagent. Stirring the reaction mixture with nitrosyl chloride present for 5 h after completion of the reaction also did not change the final product distribution.

When pinacolone oxime was allowed to react with nitrosyl chloride under radiation by an ultraviolet lamp or in the presence of free-radical inhibitors (iodine and hydroquinone) no induction period or change in product distribution was observed.

Table I. Reaction Products of Oximes with Nitrosyl Chloride

Oxime	Pathway A Chloronitroso, %	Pathway B Nitrimine, %	Pathway B Ketone, %
Acetaldehyde	7.4[a]		
α,β-Dibromodihydrocinnamaldehyde	*b*	94[c]	
Diethyl ketone	36[d]		
Ethyl *n*-propyl ketone	48[e]		
Dibenzyl ketone	70[e]		
Cyclohexanone	60[e]		
α-*tert*-Butylcyclohexanone		92[f]	
Methyl 1-chlorocyclohexyl ketone		64[g]	
Methyl 1-chlorocyclopentyl ketone		55[g]	
Benzophenone		20[e]	31,[e] 84[c]
p-Methoxybenzophenone, syn		*h*	*h*
p-Methoxybenzophenone, anti		*h*	*h*
1,3-Diphenyl-2,3-dibromopropanone	*c, i, j*	70[c]	
1-*p*-Methoxyphenyl-1,2-dibromo-3-butanone		*i, k*	
p-Nitrobenzophenone	*h* (chloronitro)	*h*	
Camphor	18	24	
Pinacolone	19[e]	51[f]	
		77[l] (*n* = 3) 89[l] (*n* = 4)	

[a] Reference 2; yields of chloronitroso compound not given on ten other aliphatic aldehydes. [b] 12% yield of 1,3-dichloro-2-bromo-1-nitroso-1-phenylpropane (dimer) and 83% yield of α,β-dibromodihydrocinnamhydroxamic chloride, ref 5. [c] Sealed tube, excess nitrosyl chloride. [d] Reference 2; yields of nitrimines not given on 12 other aliphatic ketones. [e] Reference 2. [f] Reference. 3. [g] Reference 6. [h] Reference 2; yields not given. [i] Reference 5. [j] 26% yield of 1-chloro-1-nitro-1,3-diphenylpropene. [k] 46% yield of 1-*p*-methoxy-1-chloro-2-bromo-3-butanonenitrimine. [l] Reference 4.

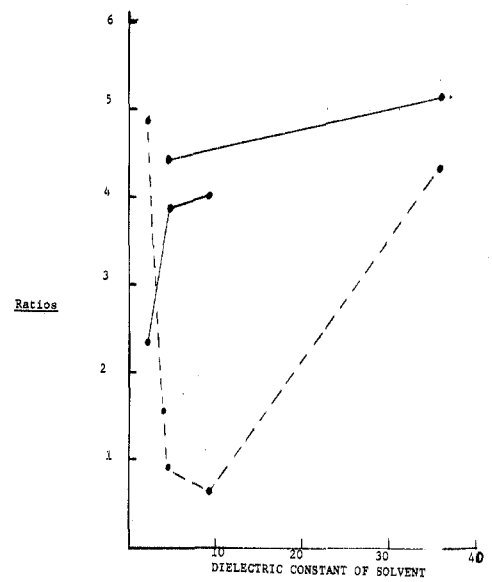


Figure 1. Reaction of nitrosyl chloride with pinacolone oxime (1.43 M) as a function of solvent polarity at 25 °C, [NOCl]/[oxime] = 3. Data from Table II: a, solid line, ratio of product yields of pathway A to pathway B; b, broken line, ratio of nitrimine, 4 to ketone, 5 as a function of dielectric constant of various solvents.

Table II. Products in the Reaction of Nitrosyl Chloride with Pinacolone Oxime (1.43 M) and [NOCl]/[Oxime] = 3 at 25 °C as a Function of Solvent Polarity

Solvent	CCl_4	$CHCl_3$	CH_2Cl_2	$(C_2H_5)_2O$	CH_3NO_2
Dielectric const, ε	2.24	4.81	9.08	4.34	35.8
Pathway A (1 + 2 + 3, %)	70.1	79.6	80.1	81.8	83.7
Pathway B % nitrimine, 4	24.8	9.5	7.8	11.0	13.1
% ketone, 5	5.1	10.9	12.1	7.2	3.2
Pathway A / Pathway B	2.3	3.9	4.0	4.5	5.1
Nitrimine / Ketone	4.9	0.9	0.65	1.5	4.3

Table III. Products in the Reaction of Nitrosyl Chloride with Pinacolone Oxime as a Function of Oxime Concentration in Chloroform at 25 °C with [NOCl]/[Oxime] = 2.0

[Oxime]	0.25 M	0.5 M	1.0 M	2.0 M
% chloronitroso, (1 + 2 + 3)	92.0	78.8	72.7	45.8
% nitrimine, 4	3.5	8.8	14.7	37.1
% ketone, 5	4.5	12.4	12.6	17.1

The results can be rationalized in terms of the polar mechanism proposed by Freeman[8] where the key intermediate is a nitrosonitrone 6 (Scheme II). We add a second molecule of nitrosyl chloride in a pseudo-six-membered ring to account for pathway A predominating to give chloronitroso product with an excess of the reagent. In polar solvents and excess nitrosyl chloride (also strongly polar) ionization to give chloride ion in the pseudo-six-membered ring would be promoted. In less polar solvents and in very low concentrations of reagent the nitrone oxygen competes favorably as a nucleophile with chlorine to give the products of pathway B, ketone and nitrimine. Apparently the methyl and *tert*-butyl groups give the right electronic and steric requirements when pathway B predominates to allow approximately equal probabilities for the two three-membered ring intermediates 7 and 8. The pathway to ketone was shown to include intermediate 7 by Wieland and Grimm[9] with oxygen labeling as shown in Scheme II which resulted in 89% of the label in the nitrous oxide. Freeman[10] has raised objections to the three-membered ring being the only pathway to ketone but it does seem to be the simplest explanation of the results in the absence of water.

A referee suggested that compound 1 could be formed in a

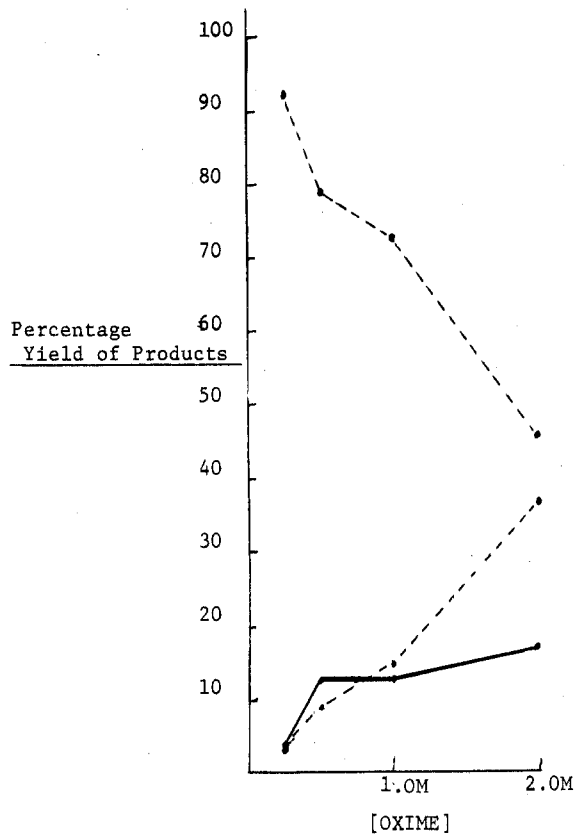
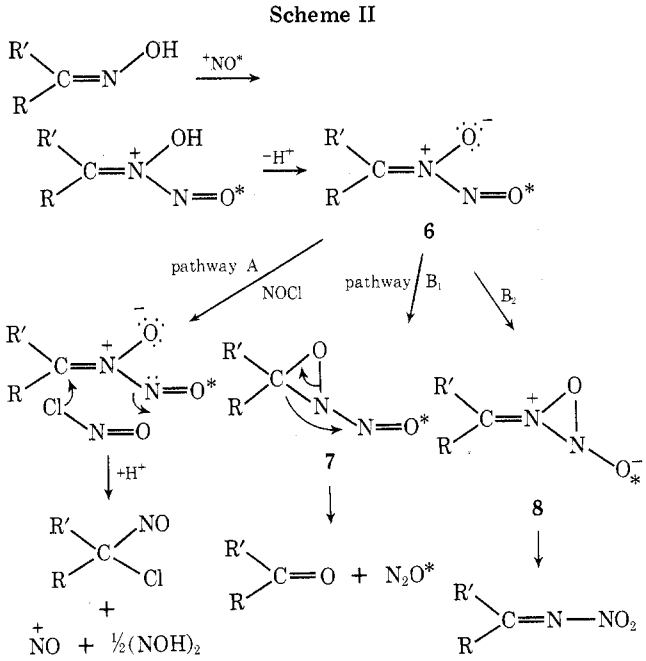
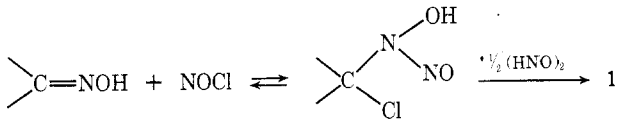


Figure 2. Reaction of nitrosyl chloride with pinacolone oxime as a function of oxime concentration in chloroform at 25 °C, [NOCl]/[oxime] = 2.0. Data from Table III: a, upper broken line, percent chloronitroso product, 1; b, lower broken line, percent nitrimine, 4; c, solid line, percent ketone, 5.

Scheme II



by-pass of 6 with high ratios of nitrosyl chloride to oxime in the following way:



However, the reversible formation of the relatively less polar adduct should not be sensitive to changes in the polarity of solvent, contrary to the findings in this work (Table II and Figure 1). Instead in pathway A, more polar solvents should stabilize our suggested intermediate (Scheme I) and promote ionization of nitrosyl chloride in the pseudo-six-membered ring as was found.

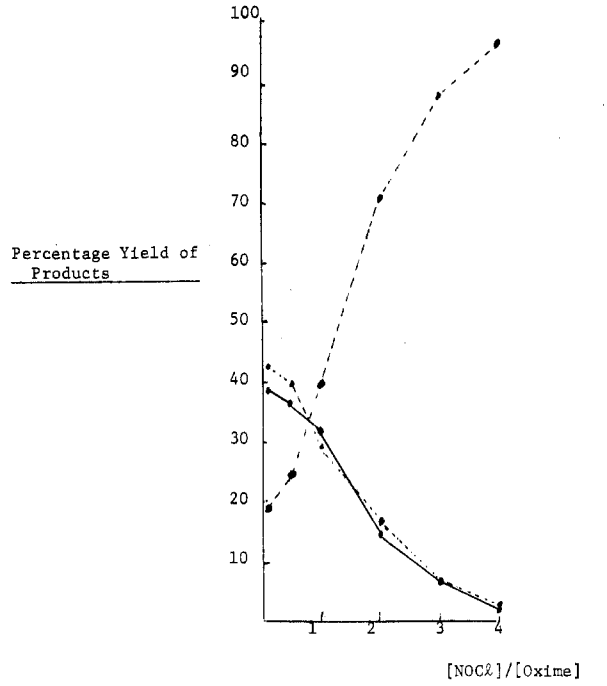


Figure 3. Reaction of nitrosyl chloride with pinacolone oxime as a function of [NOCl]/[oxime] in chloroform at 25 °C, [oxime] = 1.0 M at start. Data from Table IV: a, upper broken line, percent chloronitroso product, 1; b, solid line, nitrimine, 4; c, lower broken line, ketone, 5.

Table IV. Products in the Reaction of Nitrosyl Chloride with Pinacolone Oxime at a Starting Concentration (1 M) in Chloroform at 25 °C as a Function of [NOCl]/[Oxime]

[NOCl]/[Oxime]	0.1	0.5	1.0	2.0	3.0	4.0
% chloronitroso, 1 (+ 2 + 3)	18.5	24.0	39.5	70.2	87.4	96.2
% nitrimine, 4	38.8	36.6	31.8	14.2	6.2	1.7
% ketone, 5	42.7	39.2	28.7	15.6	6.4	2.1

Table V. Distribution of Products of Reaction of Nitrosyl Chloride with Pinacolone Oxime (1.0 M) and Starting Ratio [NOCl]/[Oxime] ≅ 0.5 in Chloroform at 25 °C

% oxime consumed	29	54	77	100
% chloronitroso, 1	4	10	18	21
% nitrimine, 4	13	23	32	41
% ketone, 5	12	21	27	38

Experimental Section

The NMR spectra were taken on a Varian A-60A spectrometer using Me_4Si as internal standard. A standard integration method of determining peak areas was reliable to ±4%. Each experiment with nitrosyl chloride was repeated until consistent results were obtained so that product ratios (Table II) are considered reliable to ±0.4.

Reaction of Pinacolone Oxime and Nitrosyl Chloride in Ether. To a solution of 6.0 g (0.052 mol) of pinacolone oxime in 50 ml of anhydrous ether, 4.5 ml (0.10 mol) of liquid nitrosyl chloride (purified and dried as previously described[5] was quickly added at ice-bath temperature. The solution was stirred mechanically as a white precipitate formed which soon redissolved. After 10 min, 5 g of solid sodium carbonate was added and stirred for 10 min longer. The white salts were removed by filtration and the ether was distilled at ambient pressure. Cooling the remaining green oil gave blue 2-chloro-2-ni-

troso-3,3-dimethylbutane, yield 4.5 g (60%), mp 121–122 °C (recrystallized from methanol[2,11]).

When methanol–water was used for recrystallization the white dimer of the *gem*-chloronitroso compound slowly precipitated. The dimer sublimes, 120–150 °C: ir spectrum (KBr) C–H, 2980 s; N=O, 1544 s; 742 cm^{-1} w. The ir spectra of monomer and dimer are identical except for the absence of the weak line at 742 cm^{-1} in the dimer. However, the NMR spectra of monomer and dimer are substantially different.

NMR spectra ($CDCl_3$): monomer δ 1.64 (s, 3), 1.27 (s, 9); dimer δ 2.15 (s, 3), 1.17 (s, 9).

The pale green filtrate remaining after the removal of the chloronitroso compound was diluted with ether and transferred to a silica gel column. Pinacolone nitrimine was eluted from the column as a colorless oil with a 2:1 mixture of carbon tetrachloride and benzene: yield 0.90 g (13%); bp 40 °C (2.5 mm) [lit.[12] bp 80.5–81.0 °C (12 mm)]; ir spectrum (neat) CH, 2980 br, s; C=N, 1615 m; NO_2, 1560, 1312 cm^{-1} s; NMR spectrum ($CDCl_3$) δ 2.02 (s, 3), 1.21 (s, 9).

Finally, pinacolone was removed from the column by a 1:1 mixture of benzene and chloroform, yield 0.55 g (11%). The pinacolone was identified by the strong carbonyl absorption (1640 cm^{-1}) and the NMR spectrum: ($CDCl_2$) δ 2.12 (s, 3), 1.13 (s, 9).

In this and experiments with other solvents (below), solvents could not be removed at reduced pressure because of loss of the chloronitroso compound, pinacolone, and pinacolone nitrimine in that order of decreasing volatility.

2-Chloro-2-nitro-3,3-dimethylbutane. 2-Chloro-2-nitroso-3,3-dimethylbutane (4.2 g, 0.028 mol) was heated on a steam bath with 10 ml of glacial acetic acid and 5 ml of concentrated nitric acid for 0.5 h. The reaction mixture was poured into 100 ml of cold water and extracted with 50 ml of ether. The ether solution was washed with 5% sodium carbonate solution and then with water. The ether layer was dried over anhydrous sodium sulfate. Removal of the ether by distillation and recrystallization of the product from methanol gave 2.9 g (62%) of 2-chloro-2-nitro-3,3-dimethylbutane: mp 170–172 °C (lit.[2] mp 169–170 °C); ir spectrum (KBr) C–H, 2980 br, s; NO_2, 1560, 1350 cm^{-1} s; NMR spectrum ($CDCl_3$) δ 2.17 (s, 3), 1.21 (s, 9).

Product Distribution. A. Effect of Solvent Polarity. The data for Table II and Figure 1 were obtained as follows. To a solution of 1.65 g (0.014 mol) of pinacolone oxime in 10 ml of carbon tetrachloride, 0.20 ml (0.043 mol) of liquid nitrosyl chloride was quickly added and the solution was stirred mechanically for 20 min. A sample was removed from the reaction mixture and analyzed by integration of the peaks in the NMR spectrum: chloronitroso compound (δ 1.65, 1.27); dimer (δ 2.12, 1.17); chloronitro compound (δ 2.17, 1.21); nitrimine (δ 2.03, 1.21); and ketone (δ 2.12, 1.13).

The same procedure was used with chloroform, methylene chloride, ether, and nitromethane. The dimer and the chloronitro compound appeared in less than 5% total yield in any experiment and did not interfere with the results. Repetition of each experiment more than once suggested that the limits of error in product percentage are ±2.

B. Effect of Concentration of Oxime. Pinacolone oxime (11.5 g) in 50 ml of chloroform (2 M solution) was divided into equal portions. One portion was treated with 1.8 ml (0.04 mol) of liquid nitrosyl chloride and brought to 25 °C. The other portion was diluted with an equal volume of chloroform and half the solution was treated with the same volume of liquid nitrosyl chloride at 25 °C. The second half of this solution was again diluted and so on until five concentrations (Figure 2) had been treated with the same volume of nitrosyl chloride. Each reaction mixture was analyzed as previously described to give the results shown in Figure 2 and Table III.

C. Effect of Excess Nitrosyl Chloride. At a 1 M concentration of pinacolone oxime in chloroform at 25 °C, the effect of different molar ratios of nitrosyl chloride to oxime (0.1–4.0) was analyzed in the same way. The results are given in Table IV and Figure 3.

D. Effect of Nitrosyl Chloride Addition in Small Increments. A solution of 5.8 g (0.05 mol) of pinacolone oxime in 50 ml of chloroform (1.0 M solution) was treated with 0.6 ml (0.012 mol) of liquid nitrosyl chloride. The solution was stirred for 10 min and a sample was removed for an NMR spectrum. The same increment of nitrosyl chloride was added four times more until the oxime disappeared completely from the reaction mixture (Table V). After the reaction was completed, a fifth increment of nitrosyl chloride was added and a sample was removed for an NMR spectrum after 2 and 5 h, respectively. The final product distribution was unchanged.

E. Effect of Free-Radical Inhibitors. The unlikely possibility of a free-radical mechanism being responsible for the results obtained was removed by adding free-radical inhibitors. A 2 M solution of pinacolone oxime in carbon tetrachloride (10 ml) was treated with varying amounts of iodine (0.0, 0.1, 2.5 g) in successive experiments and 1.8 ml (0.04 mol) of liquid nitrosyl chloride. The solution was stirred for 20 min and a sample withdrawn. The solution was washed with saturated sodium hydrogen sulfite solution and dried over sodium sulfate. An NMR spectrum was taken. No noticeable difference in product composition in the three experiments was observed.

The same experiments were repeated with hydroquinone in the quantities given above. The solutions were washed with water to remove unreacted hydroquinone. The same result was obtained as with the iodine inhibitor.

Registry No.—Pinacolone oxime, 2475-93-6; nitrosyl chloride, 2696-92-6; 2-chloro-2-nitroso-3,3-dimethylbutane, 677-58-7; 2-chloro-2-nitroso-3,3-dimethylbutane dimer, 58673-06-6; pinacolone nitrimine, 58673-42-0; 2-chloro-2-nitro-3,3-dimethylbutane, 57484-14-7; pinacolone, 75-97-8.

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