(37) Melting points (hot block) and boiling points are uncorrected. Infrared spectra were obtained on a Beckman IR-8; proton nuclear magnetic resonance spectra on Varian Model A60A and EM360 spectrometers (chemical shifts in ppm on the δ scale, with tetramethylsilane as internal standard); ultraviolet absorption spectra on Cary Model 14 and 15 spectrometers; and mass spectra on Consolidated Electrodynamics 21-104 and Varian M-66 spectrometers. Gas chromatographic analyses and preparative separations were performed on Varian A90-P and Perkin-Elmer 776 instruments. GLC peaks were integrated using a disk integrator or by cut-and-weigh methods.

(38) (a) S. C. Watson and J. F. Eastman, *J. Organometal. Chem.*, **9**, 165 (1967); (b) R. A. Ellison, R. Griffin, and F. N. Kotsonis, *ibid.*, **36**, 209 (1972); (c) G. M. Whitesides, C. P. Casey and J. K. Krieger, *J. Am. Chem. Soc.*, **93**, 1397 (1971).

(39) In the literature,[17b] the amount (0.463 g) of the starting material, 3-acetyl-2-cyclohexenol (misspelled as 3-acetyl-2-cyclohexanol), was miscalculated as 3.81 mmol. The reported yield is therefore probably calculated from the wrong quantity.

(40) "The Sadtler Standard Spectra, Standard Infrared", Sadtler Research Laboratories, Philadelphia, Pa., Spectrum No. 121, 1970.

(41) "Catalog of Mass Spectral Data", American Petroleum Institute Research Project No. 44, Texas A&M University, College Station, Tex., 1970.

Nitrosation in Organic Chemistry. Nitrosolysis, a Novel Carbon–Carbon Bond Cleavage Effected through Nitrosation. Nitrosolysis of Ketones and Ketone Acetals[1]

Milorad M. Rogić,* John Vitrone, and Michael D. Swerdloff

Contribution from the Chemical Research Center, Allied Chemical Corporation, Morristown, New Jersey 07960. *Received June 16, 1976*

Abstract: Nitrosation of cyclohexanone with nitrosyl chloride in liquid sulfur dioxide in the presence of methanol, ethanol, or isopropyl alcohol and at least 1 equiv of hydrogen chloride provides the corresponding 2-alkoxy-3-oximinocyclohexenes. However, when the reaction was carried out without the added hydrogen chloride, the alkyl 6-oximinohexanoates are obtained. This novel carbon–carbon bond cleavage was extended to several other ketones. The successful outcome of this reaction was attributed to an efficient trapping of the α-nitrosohydroxycarbonium ion intermediates with an alcohol and facile in situ cleavage of the resulting α-nitroso hemiacetal. The mechanism of the reaction changes dramatically by changing the nature of the nucleophile associated with the nitrosating reagent. Thus, in the absence of efficient nucleophiles, the α-nitrosocarbonium ion, resulting from the electrophilic addition of the nitrosonium ion to the double bond of an enol or even an olefin, behaves as a 1,3-dipolar ion that can be intercepted with a carbonyl group as a dipolarophile to provide a novel single-step synthesis of various 3-oxazoline *N*-oxides. In this way a reaction of cyclohexanone with *tert*-butyl nitrite and boron trifluoride etherate gave 2,2-dimethyl-1-oxa-4-azaspiro[4.5]dec-3-en 4-oxide. Similarly, a reaction of cyclohexanone with nitrosyl tetrafluoroborate and 1-methylcyclohexene afforded 4,5,6,7-tetrahydro-7a-methylspiro[benzoxazoline-2,1′-cyclohexene] 3-oxide. The same product was also obtained either from a reaction of 1-methylcyclohexyl nitrite with boron trifluoride etherate and cyclohexanone, or 1-methylcyclohexanol with nitrosyl tetrafluoroborate and cyclohexanone. A reaction of cyclohexanone diethyl acetal with ethyl nitrite in liquid sulfur dioxide in the presence of ethanol and a catalytic amount of an acid gave ethyl 5-cyanopentanoate. The diethyl acetals of various cyclic and open chain ketones undergo similar carbon–carbon bond cleavage. The proposed mechanism for the nitrosolysis of cyclohexanone diethyl acetal involves an acid-catalyzed reversible formation of the enol ether from the ketone acetal; an electrophilic addition of the nitrosonium ion, generated from the ethyl nitrite and the acid catalyst, to the double bond of the enol ether; a reaction of the thus produced 1-alkoxy-2-nitrosocarbonium ion with the alcohol to provide the α-nitroso ketone acetal; an acid-catalyzed carbon–carbon bond cleavage to provide the corresponding ω-oximinodiethoxycarbonium ion; a reversible reaction of the carbonium ion with an excess of the alcohol to give the ω-oximinoorthocaproate; and a reaction of the thus produced ortho ester with the oxime to afford the observed ester nitrile.

Nitrosation, a process for the introduction of a nitroso group or its equivalent into an organic structure by a replacement of an activated α-hydrogen by a nitroso group, was discovered by Victor Meyer in 1873.[2,3] Approximately at the same time, Tilden established that a nitroso group can be introduced into an organic structure through the addition of a nitrosating reagent (nitrosyl chloride) across a carbon–carbon double bond.[4,5]

Perhaps the two most prominent features in the chemistry of a nitroso group are unusually facile dimerization to nitroso dimers[6] and the ready isomerization to the corresponding oximes.[6] Thus, primary and secondary aliphatic nitroso compounds generally exist as the corresponding disubstituted diazene 1,2-dioxides,[7] which, in turn, often exist as a pair of interconvertible geometrical *Z* and *E* isomers. It is now well documented that the dimerization initially provides the *Z* isomer, which under thermodynamic conditions isomerizes to the more stable *E* form.[8] It appears that the dimerization process requires fairly low energies of activation in the order of 6–10 kcal/mol,[8f,9] as compared with 20–30 kcal/mol estimated for the energy of activation for the dissociation of the dimers to monomers.[8f,9b,10] Energies of activation for the dimerization of tertiary nitroso compounds, for steric reasons, are significantly higher and they generally exist in monomeric form.[11,12]

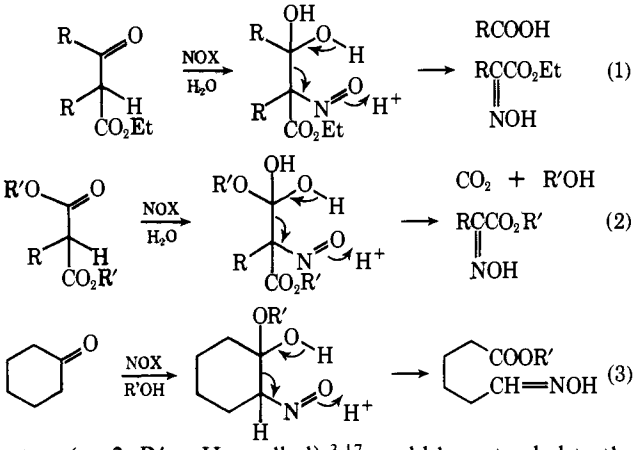
The isomerization of primary and secondary nitroso compounds to the corresponding oximes is not a spontaneous process[6,8c] and in the gas phase requires activation energies in excess of 35 kcal/mol. However, the isomerization of the nitroso compounds in solution is apparently catalyzed both by acids and bases and also appears to be influenced by solvents and heat.[6] Secondary nitroso compounds resulting from an addition of a nitrosating reagent such as nitrosyl chloride or nitrosyl formate across a carbon–carbon double bond dimerize readily and generally exist as the corresponding nitroso dimers.[4,5,12,13] In contrast, nitrosation of ketones usually provides the α-oximino ketones directly. It thus appears that the secondary α-nitroso group in the initially formed α-nitroso ketones, under the condition of the nitrosation reaction undergoes a very facile isomerization to the oxime.[3,5,6]

In addition to its synthetic value as a general method for introducing a nitrogen function into organic molecules, the

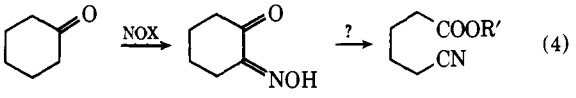
nitrosation reaction has also found use for the carbon–carbon bond cleavage of certain ketones[3,14,15] and in the synthesis of α-amino acids from substituted acetoacetic esters,[3,16] or malonic acids.[3,17] A particular variation of this reaction, nitrosation of cyclohexanecarboxylic acid with nitrosylsulfuric acid in sulfuric acid, constitutes the basic of the Snia-Viscosa technology for the manufacture of caprolactam.[18] These carbon–carbon cleavage reactions are observed only in those systems[19] which are capable of providing a tertiary nitroso group that cannot isomerize to an oxime.

It has been known for quite some time that certain derivatives of α-oximino ketones can undergo the second-order Beckmann rearrangement or, more correctly, the Beckmann fragmentation reaction[23,24] to provide the corresponding esters and nitriles.

Our continuous interest in caprolactam technology led us to explore new synthetic methods for making this monomer. Consequently, we decided to investigate whether the above mentioned in situ cleavage of a carbon–carbon bond in tertiary α-nitroso intermediates, which result from the nitrosation of substituted acetoacetic esters (eq 1),[3,16] or malonic acids and



esters (eq 2, R′ = H or alkyl),[3,17] could be extended to the corresponding *secondary* α-nitroso intermediates, especially those that may be involved in the nitrosation of cyclohexanone (eq 3). If possible, this transformation should provide either ω-oximinocaproic acid (R′ = H) or the ester (R′ = alkyl). We also undertook to find out if it was possible to achieve exclusive mononitrosation of cyclohexanone and, if so, whether it would be possible to convert the thus produced α-oximinocyclohexanone, through a Beckmann fragmentation reaction, to ω-cyanovaleric acid (R′ = H) or the ester (R′ = alkyl) (eq 4).



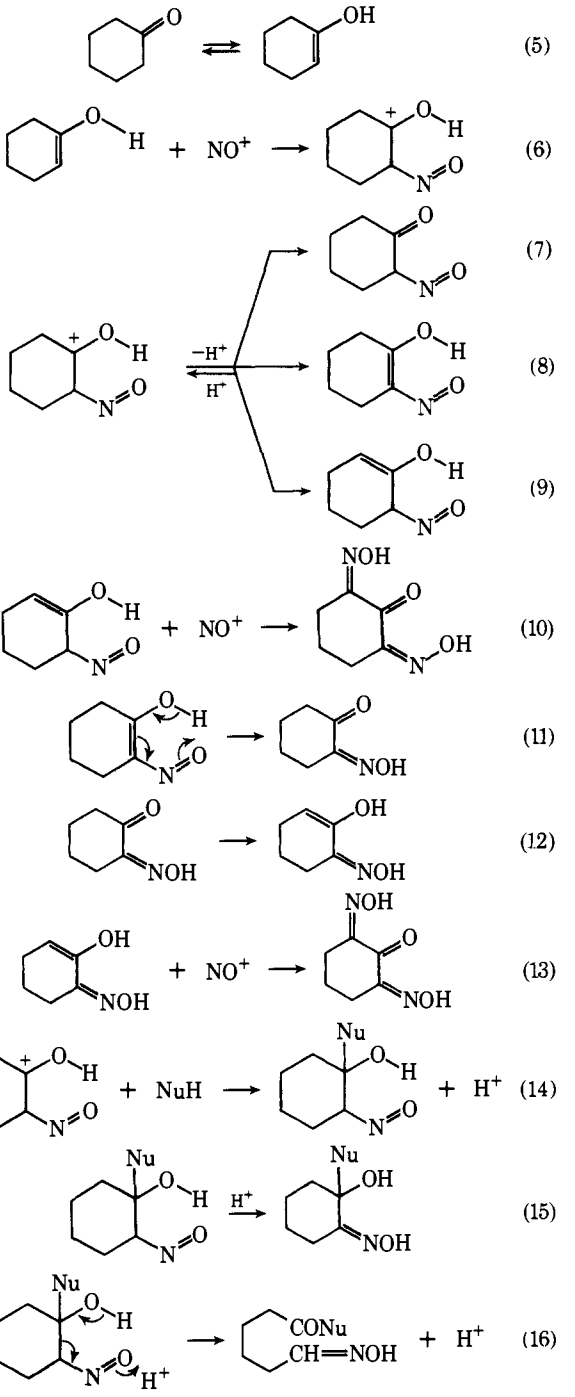
A catalytic hydrogenation of the oximino or the cyano group in the thus produced acids or esters should afford ω-aminocaproic acid or its ester, both of which should easily undergo cyclization to caprolactam.

In the present paper, we shall describe our work that led to the development of the nitrosolysis reaction, a carbon–carbon bond cleavage effected through the nitrosation of ketones or ketone acetals. In the following papers of this series, we will discuss (a) the preparation and mechanism of Beckmann fragmentation of α-nitroso ketone acetal dimers and α-oximino ketone acetals, (b) the stereochemistry of addition of nitrosating reagents to carbon–carbon double bonds, and (c) the homospecific and heterospecific dimerization of nitroso compounds and the ^{13}C NMR spectra of nitroso dimers.

Results and Discussion

1. Mononitrosation of Cyclohexanone. One striking feature of the chemistry of the nitrosation of ketones is that cyclic C(5)–C(8) ketones provide exclusively or predominantly the corresponding α,α′-dioximino ketones,[3] while the larger cyclic[25] and open chain ketones[3] undergo exclusively mononitrosation to give the corresponding α- and/or α′-oximino ketones only. Numerous attempts to achieve mononitrosation of cyclohexanone have not been successful.[25,26] In considering the mechanism of the nitrosation[27] of cyclohexanone (Scheme I), it is reasonable to assume that the reaction involves elec-

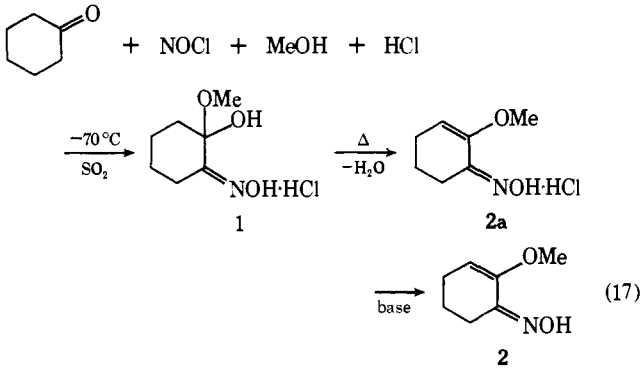
Scheme I



trophilic attack of the nitrosating species on the double bond of the enol present in equilibrium (eq 5, 6), and that the α-nitrosohydroxycyclohexane carbonium ion thus produced can undergo deprotonation to provide α-nitrosocyclohexanone (eq 7). On the other hand, it seems reasonable that the α-oximinocyclohexanone if formed (eq 11) would undergo the required enolization (eq 12), and hence a second nitrosation (eq 13), with difficulty.[28] Consequently, one must consider what can be done to block the pathway leading to the 2-hydroxy-3-ni-

trosocyclohexene (eq 9), so as to achieve mononitrosation. In support of this approach it should be noted that the work of Ogata and co-workers has established that in the nitrosation of cyclohexyl aryl ketones with nitrous acid in concentrated sulfuric acid, the rate-determining step is the rate of deprotonation of the respective conjugate acids, followed by a fast addition of the nitrosating species across the carbon-carbon double bond of the thus generated enols.[14c,d,27] This and other studies suggest that the addition of several nitrosating reagents to carbon-carbon double bonds does indeed show characteristics of an electrophilic addition reaction.[5,12,30-34] *If the nitrosation of ketones (and other activated carbon structures) is a special case of electrophilic addition to a carbon-carbon double bond, it should be possible to intercept the resulting α-nitrosohydroxycarbonium ion with some appropriate nucleophile.* Clearly, if this was possible, then the 2-nitroso-1-hydroxycyclohexane intermediate, resulting from the reaction of the 2-nitrosohydroxycyclohexane carbonium ion with a nucleophile NuH (eq 14), could either isomerize to the α-oximino compound (eq 15), which should be stable toward further nitrosation, or perhaps, undergo a carbon-carbon bond cleavage (eq 16) analogous to the similar cleavage of tertiary α-nitroso intermediates (eq 1, 2), which are not capable of isomerization to the corresponding oximes.

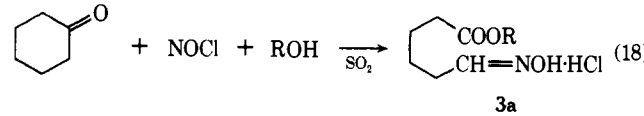
Nitrosation of cyclohexanone with nitrosyl chloride[3] in ether, chloroform, methylene chloride, hexane, or sulfur dioxide gives only 2,6-dioximinocyclohexanone. Even if the nitrosation is carried out in the presence of methanol, the reaction mechanism is not affected significantly and dioximino ketone is still the only product. But when nitrosyl chloride is added to a solution of cyclohexanone *in liquid sulfur dioxide* containing 1 equiv each of methanol and dry hydrogen chloride at −70 °C, decolorization of the nitrosyl chloride occurs after 5-10 min. The resulting solution was stirred for an additional 30 min, the temperature was allowed to rise to about −50 °C, and the sulfur dioxide was evaporated. The resulting tan solid upon treatment with sodium bicarbonate in a minimal quantity of water gave free 2-methoxy-3-oximinocyclohexene **2**, mp 150-151 °C. A 100-MHz NMR spectrum of the reaction solution immediately after mixing the reagents in sulfur dioxide suggested that the initial main reaction product was 1-hydroxy-1-methoxy-2-oximinocyclohexane hydrochloride (**1**). It thus appears that the reaction between cyclohexanone, methanol, and nitrosyl chloride in the presence of hydrogen chloride in sulfur dioxide solution at −70 °C initially affords **1**, which at higher temperature in solution or on isolation undergoes water elimination to give **2a** (eq 17).



(17)

These experiments clearly demonstrate that it is indeed possible to achieve mononitrosation of cyclohexanone by trapping the 1-hydroxy-2-nitrosocyclohexane carbonium ion with methanol.

2. Nitrosolysis of Ketones. (a) Nitrosolysis of Cyclohexanone. When hydrogen chloride was completely omitted, the reaction took a different course, and the methyl ω-oximinocaproate hydrochloride (**3a**) was formed as the major reaction product (eq 18).



3a (18)

Thus, the slow introduction of nitrosyl chloride vapors above a well-stirred solution of cyclohexanone in liquid sulfur dioxide containing 1.5 equiv of ethanol maintained at gentle reflux (~−10 °C) resulted in an immediate decolorization of the nitrosyl chloride. Evaporation of the solvent afforded a 90-95% yield of ethyl ω-oximinocaproate which, according to a 60-MHz NMR spectrum, was a mixture of approximately equal amounts of the *Z* and *E* isomers.

Addition of an equivalent amount of nitrosyl chloride to a solution of ethanol in an excess of liquid sulfur dioxide at −70 °C produced no apparent reaction. The nitrosyl chloride color persisted indefinitely. When, however, such a solution was allowed to warm up to about −20 to −15 °C, depending on the relative concentrations of the reagents, the nitrosyl chloride color quickly disappeared and the solution became slightly yellow. Cooling of the reaction mixture resulted in the reappearance of the nitrosyl chloride color. Presumably, the reaction involves a reversible formation of the corresponding alkyl nitrite and hydrogen chloride,[36] for the same reaction mixture resulted from a solution of ethyl nitrite and hydrogen chloride in sulfur dioxide. Furthermore, it is reasonable to assume that the whole system exists also in equilibrium with the nitrosonium ion, NO^+:[37]

$$NOCl + ROH \underset{SO_2}{\rightleftharpoons} RONO + HCl \rightleftarrows NO^+ + ROH + Cl^- \quad (19)$$

Thus, it appears that the nitrosolysis of cyclohexanone can be explained by the reaction sequence outlined in Scheme I. Presumably, an electrophilic addition of the nitrosonium ion (generated according to eq 19) to a carbon-carbon double bond of the cyclohexanone enol affords the 1-hydroxy-2-nitrosocyclohexane carbonium ion (eq 6), which is trapped with an alcohol to give the α-nitroso hemiacetal (eq 14). An acid-catalyzed carbon-carbon bond cleavage yields the ω-oximinocaproic acid ester (eq 16). Because of its low nucleophilicity on the one hand and very good solvating properties on the other, sulfur dioxide appears to be one of the best solvents for this reaction; it effectively solvates the counterion without any appreciable reaction with the positive charge. This allows a sufficiently high concentration of nitrosonium ion and at the same time provides for the "stabilization" of the intermediate 1-hydroxy-2-nitrosocarbonium ion, thus making the reaction with an alcohol (eq 14) possible. This behavior of sulfur dioxide should be contrasted to other commonly used solvents for the nitrosation reaction, namely water and ether, which because of their basic nature, in addition to solvating anions, effectively react not only with the nitrosonium ion, thus diminishing its electrophilic character significantly, but also with 1-hydroxy-2-nitrosocarbonium ion, assisting its undesirable transformations (eq 8, 9). It is therefore not surprising to find that the nitrosolysis reaction fails in these solvents as well as in many others (carbon tetrachloride, methylene chloride, chloroform, hexane, alcohols, etc). Other polar but nonbasic solvents like nitromethane and sulfolane behave similarly as sulfur dioxide, and, consequently, the nitrosolysis of cyclohexanone in these solvents did take place. For practical purposes, however, there is no advantage in using these solvents in place of sulfur dioxide. Finally, the success of this reaction must be due, at least in part, to the fact that during the reaction cycle only a small amount of free hydrochloric acid is present.

Presumably, the hydrochloric acid generated in the reaction between nitrosyl chloride and the alcohol (eq 19) serves as a catalyst for the enolization of the ketone (eq 5) and the cleavage of the α-nitroso hemiacetal (eq 16) and then becomes "neutralized" by the oxime produced.

When the nitrosation of cyclohexanone was carried out in the presence of an additional equivalent of hydrogen chloride, the competing reaction (eq 15) to give **1**, followed by water elimination to afford 2-alkoxy-3-oximinocyclohexene **2a** (eq 17) becomes more important and the carbon-carbon bond cleavage is suppressed. It is of interest to note that the isomerization (eq 15) took place most readily in the presence of hydrogen chloride or boron trifluoride etherate. In the presence of sulfuric or methanesulfonic acid, the isomerization was not very extensive and the ω-oximinocaproic acid ester was the predominant product. At the present time, it is not quite clear why different acids influence the reaction course differently. It seems reasonable, however, that the nature of the acid rather than the acid concentration is responsible for the changes in the reaction course, but without further information any conclusion would be speculative.

(b) Scope of the Nitrosolysis of Ketones. Since our primary interest in this work was to develop a suitable transformation of cyclohexanone to caprolactam, the bulk of our efforts were centered on a study of the reaction with cyclohexanone itself. Nevertheless, we briefly investigated the nitrosolysis of several other ketones to establish whether the reaction was general in character. The results of these experiments are summarized in Table I. The reaction with cyclohexanone can be carried out equally effectively either with ethanol or methanol. It also appears that *n*-butyl alcohol and isobutyl alcohol can be used but without any apparent advantage. In the past, nitrosyl chloride was usually generated in situ from the reaction of an alkyl nitrite and hydrogen chloride;[3,5a,24] however, in the present reaction such a procedure suffers from the disadvantage that the rate of addition of the hydrogen chloride is not uniform and often results in an accumulation of the acid and, hence, in the concomitant formation of the oximino enol ethers.

It is generally accepted that α-halogenation, α-deuteration, and acid-catalyzed racemization of a ketone all proceed via the rate-determining formation of the enol.[38] Under acidic conditions, the formation of an enol with the more substituted double bond occurs.[39] Since the nitrosolysis of 2-methylcyclohexanone gives ca. equal amounts of 6-oximinohexanoic acid ester and 6-oximinoheptanoic acid ester, it follows that the formation of the enol in this reaction, and perhaps in other nitrosolysis reactions as well, may not be the rate-determining step. Thus it appears that the product distribution in this particular reaction is very likely dictated by the relative rates of the attack of the nitrosating species on the double bond of the respective enols, rather than by the relative rates of the formation of the latter. We will return to this question in a subsequent paper.

Contrary to the cylcic ketones, the 7-tridecanone underwent nitrosolysis to give about 45% of ethyl caproate, 20% of the *n*-hexaldehyde oxime, and as much as 40% of the 6-oximino-7-tridecanone. This probably reflects the earlier mentioned fact that open chain ketones generally undergo mononitrosation.[3] Presumably, a competing isomerization of the α-nitrosohydroxycarbonium ion intermediate to the corresponding α-oximino ketone, a species that is less reactive toward second nitrosation, is much more facile in open chain and large ring cyclic ketones than in the C(5)-C(8) cyclic ketones.[3]

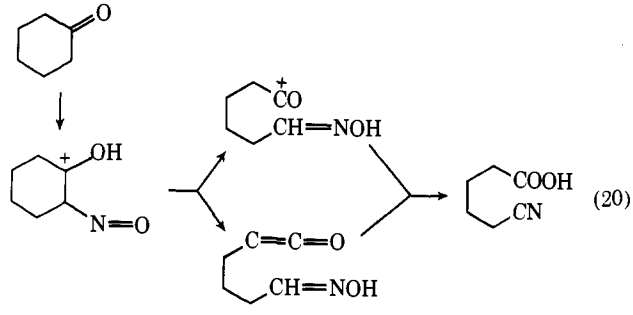
(c) The Importance of the Nature of the Nucleophiles in the Nitrosating Reagent during the Nitrosation of Ketones. At this point, we would like to comment on how *the absence of efficient nucleophiles* in a reaction of a nitrosating reagent with a carbonyl compound affects the mechanism of the reaction and leads to highly unexpected changes in the reaction course.

Table I. Nitrosolysis of Various Ketones[a]

Ketone	Alcohol	Products[b]	Yield,[c] %
Cyclohexanone	EtOH[d]	$HON{=}CH(CH_2)_4COOEt$ 2-Ethoxy-3-oximinocyclohexene	95
	n-BuOH/ i-BuOH[e]	$HON{=}CH(CH_2)_4COOBu\text{-}n$	45
		$HON{=}CH(CH_2)_4COOBu\text{-}i$	45
4-*tert*-Butylcyclohexanone	EtOH	$HON{=}CHCH_2CH(t\text{-}Bu)CH_2CH_2COOEt$	50
		2-Ethoxy-3-oximino-5-*tert*-butylcyclohexene	40
2-Methylcyclohexanone	EtOH	$HON{=}C(CH_3)(CH_2)_4COOEt$	45
		$HON{=}CH(CH_2)_3CH(CH_3)COOEt$	45
Cyclopentanone	EtOH	$HON{=}CH(CH_2)_3COOEt$	70
		2-Ethoxy-3-oximinocyclopentene	25
Cyclododecanone	EtOH	$HON{=}CH(CH_2)_{10}COOEt$	75
		α-Oximinocyclododecanone	25
7-Tridecanone[f]	EtOH	$CH_3(CH_2)_5COOEt$	45
		$CH_3(CH_2)_4CH{=}NOH$	20

[a] For the experimental conditions and the ratios of the reagents, see the Experimental Section. [b] The structures of the products were determined either by comparison with an authentic sample or by the usual spectroscopic and analytical means. [c] By GLC. [d] Essentially the same results were obtained with methanol. [e] 1:1 mixture. [f] As much as 40% of the corresponding α-oximino ketone was also formed.

If the nitrosolysis of cyclohexanone indeed involves the sequence of the reactions outlined in Scheme I and, hence, the formation of α-nitrosohydroxycyclohexane carbonium ion, it was of interest to find what would happen to such an ion in the absence of an efficient nucleophile. It was hoped that under the proper reaction conditions, the α-nitrosohydroxycarbonium ion would undergo carbon-carbon bond cleavage to give either ω-oximinocaproyl carbonium ion or the corresponding ω-oximino ketone, which in situ should undergo dehydration to ω-cyanovaleric acid (eq 20).

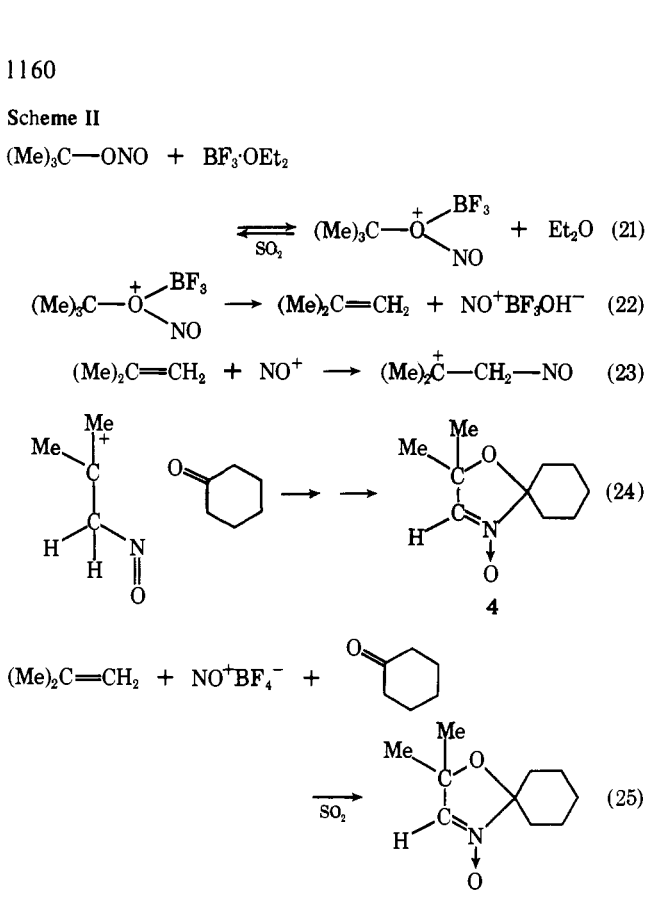


(20)

However, when such a nitrosolysis of cyclohexanone was attempted in liquid sulfur dioxide using *tert*-butyl nitrite and boron trifluoride etherate as the nitrosating reagent, instead of the expected 5-cyanovaleric acid, a white crystalline solid, 2,2-dimethyl-1-oxa-4-azaspiro[4.5]dec-3-ene 4-oxide (**4**), mp 119-121 °C, was obtained in about 50% yield.

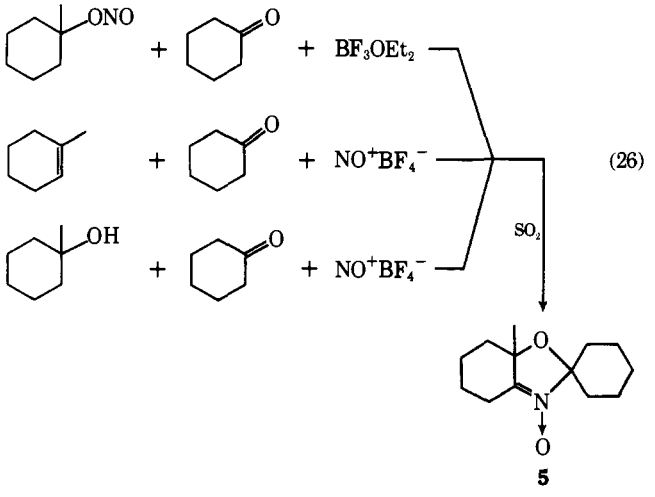
This unexpected formation of **4** may be explained by transformations outlined in Scheme II: (a) a coordination of boron trifluoride etherate with the basic oxygen of the *tert*-

Scheme II



butyl nitrite (eq 21), (b) the formation of isobutylene and a new nitrosating species[40] (eq 22), and (c) the electrophilic addition of the nitrosonium ion to the isobutylene double bond to form the 1-nitroso-2-methylpropane carbonium ion (eq 23). The thus produced carbonium ion, in the absence of efficient nucleophiles, apparently undergoes a 1,3-dipolar addition reaction[41] with the carbonyl group of cyclohexanone to give, after proton expulsion, the observed 2,2-dimethyl-1-oxa-4-azaspiro[4.5]dec-3-ene 4-oxide (**4**) (eq 24). That this indeed may be a plausible mechanism was further indicated by a successful synthesis of **4** by the nitrosation of isobutylene with nitrosyl tetrafluoroborate in liquid sulfur dioxide in the presence of cyclohexanone (eq 25).

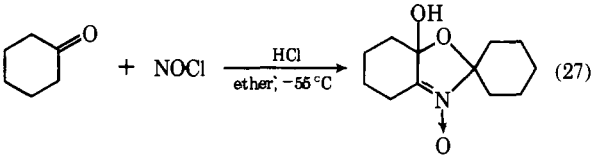
Similarly, a reaction of 1-methylcyclohexene with nitrosyl tetrafluoroborate and cyclohexanone in the same solvent led to 4,5,6,7-tetrahydro-7a-methylspiro[benzoxazoline-2,1′-cyclohexene] 3-oxide, (**5**). Moreover, the same product was also obtained either from a reaction of 1-methylcyclohexyl nitrite with boron trifluoride etherate and cyclohexanone, or 1-methylcyclohexanol with nitrosyl tetrafluoroborate and cyclohexanone in liquid sulfur dioxide[42] (eq 26).



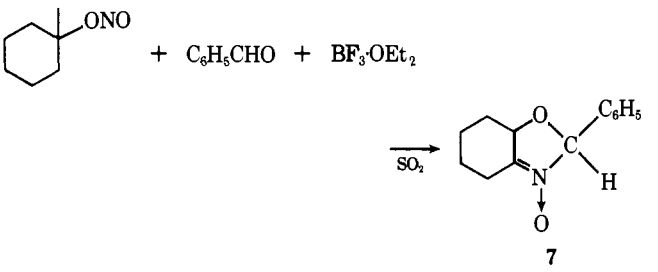
The general nature of the reaction is indicated by preparation of several 3-oxazoline *N*-oxides summarized in Table II.

It is of interest that under these experimental conditions little or no nitrosation products of ketones or aldehydes were detected. This may suggest that under these conditions a reaction of an enol with the nitrosating reagent is not important. It is more likely, however, that because of the absence of an effective base required to remove the α-hydrogen from the conjugate acid of the carbonyl compound, the equilibrium concentration of the enol may be significantly reduced and therefore the usual nitrosation reaction suppressed. On the other hand, the conjugate acid of the carbonyl compound should be and, evidently is, a very effective dipolarophile.

If this argument is correct, then one should be able to intercept even the α-nitrosohydroxycarbonium ion with the parent carbonyl compound under the proper reaction conditions. Indeed, when one carried out the nitrosation of cyclohexanone with nitrosyl chloride in ether saturated with hydrogen chloride at low temperature,[43] one obtains 4,5,6,7-tetrahydro-7a-hydroxyspiro[benzoxazoline-2,1′-cyclohexane] 3-oxide (**6**) as a white crystalline solid, mp 123–124 °C, in up to a 55% yield (eq 27). Heating **6** under vacuum afforded cyclohexanone, leaving as the residue α-oximinocyclohexanone. When an attempted synthesis of **6** was carried out with α-oximinocyclohexanone and cyclohexanone under the same conditions, but in the absence of nitrosyl chloride, no desired product was formed. Evidently, formation of **6** does not involve α-oximinocyclohexanone, and, consequently, it seems that the α-nitrosohydroxycyclohexane carbonium ion was indeed the intermediate in this reaction.

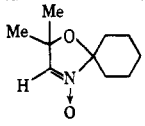
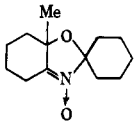
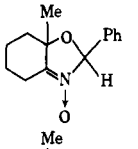
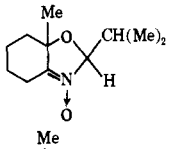
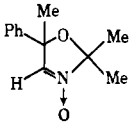
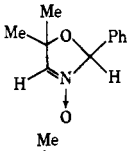
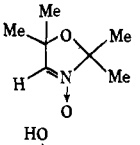
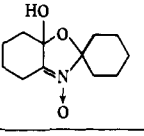


Finally, when a reaction of 1-methylcyclohexyl nitrite with boron trifluoride etherate was carried out in sulfur dioxide in the presence of benzaldehyde, a white crystalline solid, 2-phenyl-4,4,6,7-tetrahydro-7a-methylbenzoxazoline 3-oxide (**7**), mp 144–147 °C, was obtained. While, a priori, the addition of 2-nitrosocyclohexylmethyl carbonium ion across the benzaldehyde carbonyl group can take place from both faces of the carbonyl group to provide both possible diastereoisomers, it appears that the formation of **7** was facialspecific.[44] However, at the present time, the stereochemistry of **7** is not known, and, hence, it is not possible to conclude whether the reaction occurred in a "suprafacial", "antarafacial" or even in a stepwise but stereospecific manner.



Evidently, in the absence of efficient nucleophiles, the α-nitrosocarbonium ion, resulting from the electrophilic addition of the nitrosonium ion to the double bond of an olefin or even an enol, behaves as a 1,3-dipolar ion[41] that can be intercepted with a carbonyl group as a dipolarophile to provide a novel single-step synthesis of various 3-oxazoline *N*-oxides.

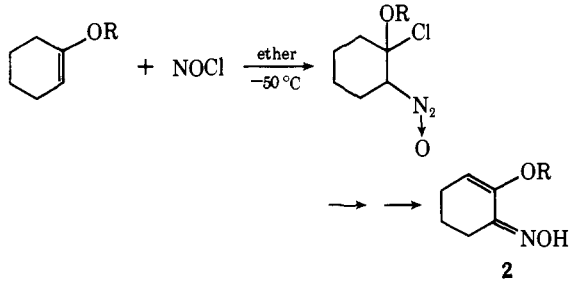
Table II. Preparation of Various 3-Oxazoline *N*-Oxides[a]

No.	Reagents	Solvent	Product	Mp, °C
(1)	Me_3CONO, $(CH_2)_5CO$, $BF_3 \cdot OET_2$	SO_2, $MeNO_2$, $CHCl_2$		119–120
(2)	$CH_2{=}C(Me)_2$, $(CH_2)_5CO$, $NO^+BF_4^-$	SO_2	same	
(3)	$(CH_2)_5C(Me)ONO$, $(CH_2)_5CO$, $BF_3 \cdot OEt_2$	SO_2		104–106
(4)	$CH_2(CH_2)_3CH{=}CMe$, $(CH_2)_5CO$, NO^+BF_4	SO_2	same	
(5)	$(CH_2)_5C(Me)OH$, $(CH_2)_5CO$, $NO^+BF_4^-$	SO_2	same	
(6)	$(CH_2)_5C(Me)ONO$, PhCHO, $BF_3 \cdot OEt_2$	SO_2		144–147
(7)	$(CH_2)_5C(Me)ONO$, Me_2CHCHO, $BF_3 \cdot OEt_2$	SO_2		68–70
(8)	$PhC(Me)_2ONO$, Me_2CO, $BF_3 \cdot OEt_2$	SO_2		64–68
(9)	$Ph(Me)C{=}CH_2$, Me_2CO, $NO^+PF_6^-$	$MeNO_2$	same	
(10)	Me_3CONO, PhCHO, $BF_3 \cdot OEt_2$	SO_2		107–108
(11)	Me_3CONO, Me_2CO, $BF_3 \cdot OEt_2$	$MeNO_2$		bp 42 (0.1 mm)
(12)	$(CH_2)_5CO$, NOCl, HCl	Et_2O		123–124

[a] For further details see the Experimental Section.

3. Nitrosation of Cyclohexanone Enol Ethers. Ogloblin and his co-workers demonstrated that the addition of nitrosyl chloride to the enol ether of isobutyraldehyde in ether at −60 °C occurs in an expected manner, providing 1-chloro-1-methoxy-2-nitroso-2-methylpropane, a thermally unstable product.[20] The addition of methanol to the reaction mixture led to a carbon-carbon bond cleavage, typical for the acid-catalyzed carbon-carbon cleavage of tertiary α-nitroso intermediates in which the nitroso group cannot isomerize to the oxime.[15-19] The products of this carbon-carbon bond cleavage were the expected trimethyl orthoformate and acetone oxime.

We investigated the addition of nitrosyl chloride to cyclohexanone enol ethers, substrates that can give only a secondary 2-nitroso-1-alkoxy-1-chlorocyclohexanes or the corresponding nitroso dimers as the initial reaction products. The addition of nitrosyl chloride to a solution of cyclohexanone enol ether in ether at −50 °C, followed by neutralization with sodium bicarbonate, afforded the 2-methoxy-3-oximinocyclohexene (**2**). Presumably, the reaction initially provides 2-nitroso-1-chloro-1-methoxycyclohexane, present in an equilibrium with the corresponding nitroso dimer. Evidently, the isomerization and acid elimination afforded the observed **2**, R = CH_3 (eq 28).

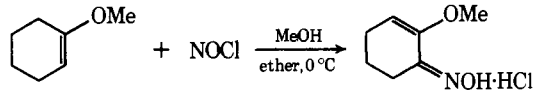


(28)

2

Addition of nitrosyl chloride to a solution of cyclohexanone methyl enol ether in ether containing an equivalent of methanol at −50 °C produced directly **2a**. It appears that this reaction provides the corresponding secondary 2-nitroso-1-methoxy-1-chlorocyclohexane which, perhaps not surprisingly, undergoes the isomerization rather than the carbon-carbon bond

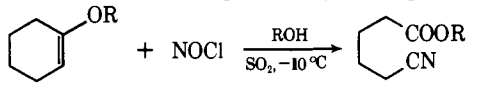
cleavage reaction that would be analogous to the above mentioned tertiary 2-nitroso intermediates (eq 29). However, when



(29)

2a

a similar reaction was carried out in a sulfur dioxide solution containing a slight excess of an alcohol, ω-cyanovaleric acid ester (**8**) was obtained in a significant yield (eq 30).

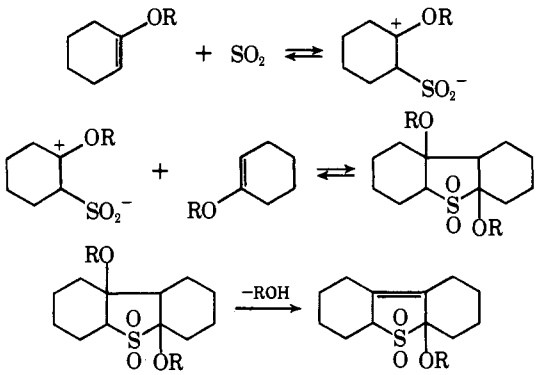


(30)

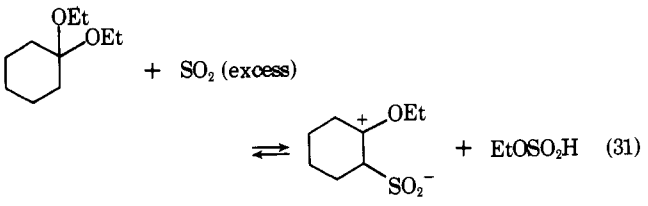
8

Before continuing, it is of interest to note that cyclohexanone enol ethers undergo a fast reaction with sulfur dioxide[45] to give tricyclic sulfone ethers which are evidently formed through a reaction sequence outlined in Scheme III. The reaction can be

Scheme III



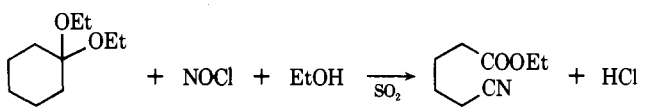
suppressed by the addition of an excess of the alcohol. Presumably, the alcohol should add to the enol ether in the presence of an acid catalyst, including sulfur dioxide, to give the corresponding acetal and thus prevent the sulfone formation. That this may be an oversimplification was indicated by the NMR examination of the corresponding solutions in liquid sulfur dioxide. Thus, a 60-MHz NMR spectrum of a solution of either a 1:1 mixture of 1-ethoxycyclohexene and ethanol or cyclohexanone diethyl acetal in sulfur dioxide showed the presence of a free hydroxyl proton at δ 2.73 (1 H). At 0 °C this proton appeared at δ 3.15 and integrated for only 0.4 H. Clearly, sulfur dioxide cleaves ethanol from diethyl acetal (eq 31).[45,46] Since in both cases no signal for the vinyl proton was



(31)

9

observed, it would appear that the enol ether reacts with sulfur dioxide according to Scheme III to give the indicated 1,3-dipolar ion **9** which exists in equilibrium with the acetal (eq 31). Since the formation of the 1,3-dipolar ion **9** in sulfur dioxide occurs reversibly either from the enol ether or from the acetal, it follows that the acetal solution in sulfur dioxide should also contain the enol ether in the equilibrium. If this is true, then the reaction of cyclohexanone acetal with nitrosyl chloride in sulfur dioxide should also be possible (eq 32), and, if so, this

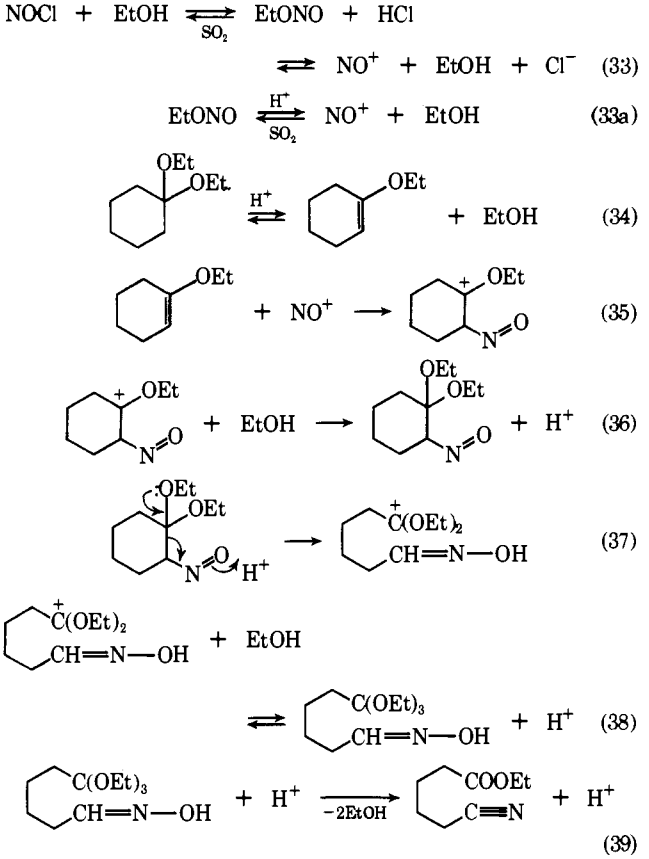


(32)

would eliminate the need to convert the acetal to the enol ether and, hence, save one reaction step.

4. Nitrosolysis of Ketone Acetals. (a) Nitrosolysis of the 1,1-Diethoxycyclohexane. When nitrosyl chloride was added to a solution of 1,1-diethoxycyclohexane in sulfur dioxide containing ethanol, the desired reaction did take place and ethyl ω-cyanovalerate was the major of several reaction products (eq 32). Presumably, the reaction involves the steps outlined in Scheme IV: (a) a fast reversible reaction of nitrosyl

Scheme IV



(33)

(33a)

(34)

(35)

(36)

(37)

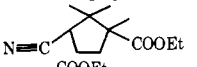
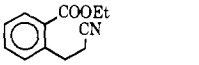
(38)

(39)

chloride and the alcohol (eq 33),[36,37] (b) the acid-catalyzed reversible formation of the enol ether from the ketone acetal (eq 34), (c) the electrophilic addition of the nitrosonium ion generated in step a to the double bond of the enol ether (eq 35), followed by a reaction of the thus produced 1-alkoxy-2-nitrosocarbonium ion with the alcohol to provide the α-nitroso ketone acetal (eq 36), (d) the acid-catalyzed carbon–carbon bond cleavage to provide the ω-oximinodiethoxycarbonium ion (eq 37), (e) a reversible reaction of the carbonium ion with an excess of the alcohol to give the ω-oximinoorthocaproate (eq 38), and (f) the acid-catalyzed reaction of the thus produced ortho ester with the oxime to provide the ethyl ω-cyanovalerate (eq 39).

In the nitrosolysis of ketones with nitrosyl chloride (Scheme I), the hydrochloric acid generated in the reaction of nitrosyl chloride and the alcohol (eq 19) served as the catalyst both for the enolization of the ketone and for the subsequent carbon–carbon bond cleavage. At the end of the reaction cycle, however, the hydrochloric acid was neutralized by the oxime produced. Thus, throughout the entire ketone nitrosolysis reaction cycle, only a trace of the free hydrochloric acid was present. On the other hand, assuming for the moment that the mechanism of the nitrosolysis of cyclohexanone diethyl acetal with nitrosyl chloride is as outlined in Scheme IV, the hydrochloric acid generated in step a (eq 33) should not only serve as the catalyst for the formation of the enol ether (eq 34), for the cleavage of the α-nitroso ketone acetal (eq 37), and for the

Table III. Nitrosolysis of Various Ketone Acetals[a]

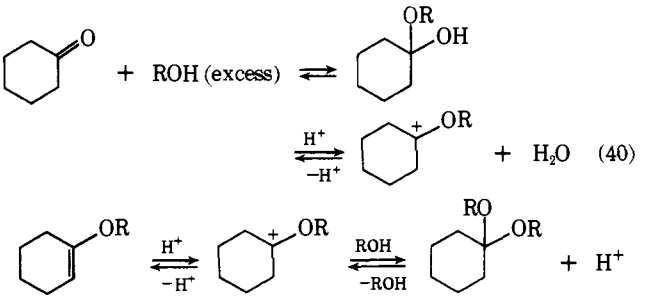
Ketone acetal (R in $>C(OR)_2$)	Alcohol[b]	Products[c]	Yield, %[d]
Cyclohexanone, Et	EtOH	$N{\equiv}C(CH_2)_4COOEt$	87[e]
Cyclohexanone, *n*-Bu	*n*-BuOH	$N{\equiv}C(CH_2)_4COOBu\text{-}n$	87
Cyclohexanone, *i*-Bu	*i*-BuOH	$N{\equiv}C(CH_2)_4COOBu\text{-}i$	87
4-Methylcyclohexanone, Et	EtOH	$N{\equiv}CCH_2CH(CH_3)CH_2CH_2COOEt$	85
4-*tert*-Butylcyclohexanone, Et	EtOH	$N{\equiv}CCH_2CH(tert\text{-}Bu)CH_2CH_2COOEt$	90[f]
2-Methylcyclohexanone, Et	EtOH	$N{\equiv}C(CH_2)_3CH(CH_3)COOEt$	77
		$CH_3CO(CH_2)_4COOEt$	10
Cyclopentanone, Et	EtOH	$N{\equiv}C(CH_2)_3COOEt$	65
Cyclododecanone, Et	EtOH	$N{\equiv}C(CH_2)_{10}COOEt$	88
Camphor, Et	EtOH		50[g]
α-Tetralone, Et	EtOH		60
7-Tridecanone, Et	EtOH	$CH_3(CH_2)_5COOEt$	98[h]
		$CH_3(CH_2)_4CN$	90
4-Heptanone, Et	EtOH	$CH_3CH_2CH_2COOEt$	98[h]
		CH_3CH_2CN	89
2-Heptanone, Et	EtOH	$CH_3(CH_2)_4COOEt$	45
		CH_3COOEt	42
		$CH_3(CH_2)_3CN$	35
Cyclohexyl methyl ketone, Et	EtOH	$C_6H_{11}COOEt$	75

[a] For a representative experimental procedure, see text. [b] The ratio ketone acetal:alcohol:alkyl nitrite was generally the same as in the representative example. [c] The products were characterized either by comparison with authentic samples or by the usual spectroscopic means, or both. [d] By GLC. Generally, the main product is accompanied by the corresponding acetal, which appears to be the major by-product; see the following. [e] Accompanied by 12% of ethyl 6,6-diethoxyhexanoate. Drying the sulfur dioxide solvent increased the yield of the ester nitrile to 93%. [f] Slow reaction. [g] The reaction was very slow and carried out in a sealed ampule overnight at 25°C (CAUTION: excessive pressure!); see ref 49. [h] This reaction was exceptionally fast being complete in less than 1 hr.

dehydration of the oxime by the ortho ester (eq 39), but it should not be consumed in this process and consequently the acid concentration should increase as the reaction progresses. Therefore, since the reaction between nitrosyl chloride and an alcohol to provide the alkyl nitrite and hydrochloric acid (eq 19 or 33) is a reversible process,[36,37] and since the equilibrium in eq 33 could also be approached from the side of alkyl nitrite (eq 33a), then the entire reaction cycle should require only a catalytic amount of an acid. Indeed, when cyclohexanone diethyl acetal was treated with ethyl nitrite and a catalytic amount of hydrogen chloride in a sulfur dioxide/ethanol solution, the desired sequence of reactions (eq 33a-39) did take place and ethyl ω-cyanovalerate was obtained in an 87-93% yield.

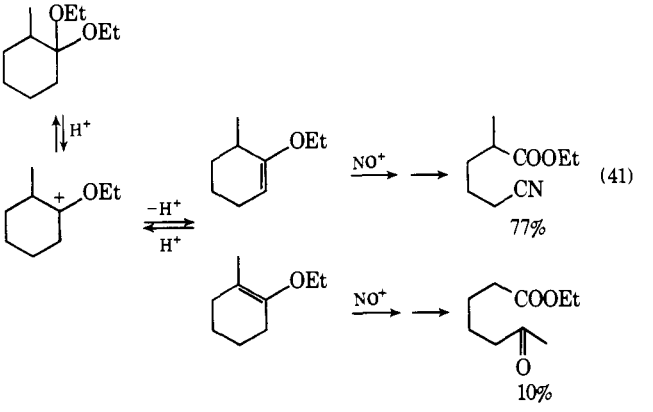
The sequence of reactions outlined in Scheme IV represents an oversimplification of the mechanism of ketone acetal nitrosolysis and a more detailed discussion will be presented later in the text.

(b) Scope of the Nitrosolysis of Ketone Acetals. Cyclohexanone di-*n*-butyl and diisobutyl acetals underwent the nitrosolysis reaction with *n*-butyl nitrite and isobutyl nitrite, respectively, to give the corresponding alkyl ω-cyanovalerates (Table III). However, when the nitrosolysis reaction was attempted with cyclohexanone dimethyl acetal and methyl nitrite under otherwise the identical conditions as above, the dimethyl acetal was isolated essentially unchanged. This difference in the reactivities of the dimethyl and other cyclohexanone dialkyl acetals could be a consequence of the greater thermodynamic stability of the dimethyl acetal since it is known that the reversible formation of an acetal in an acid-catalyzed reaction of cyclohexanone with an alcohol is a function of the steric size of the alkyl group in the alcohol. For example, the formation of cyclohexanone diethyl acetal at equilibrium at room temperature does not exceed 5-10%, while the dimethyl acetal is present at equilibrium in as much as 70%.[47] Therefore, it seems that the inertness of the cyclohexanone dimethyl acetal is due to the less favorable equilibrium between the acetal and the methoxycyclohexane carbonium ion, as compared with the similar equilibrium of the other alkoxycyclohexane carbonium ions and the corresponding acetals (eq 40). Furthermore, since

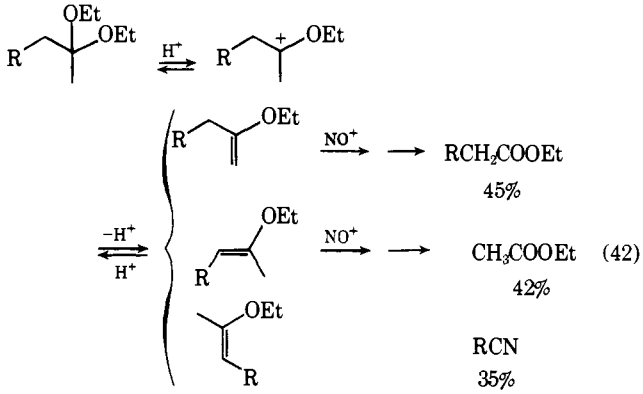


the alkoxycyclohexane carbonium ion is the intermediate in the formation of the enol ether,[48] it follows that the formation of enol ethers would also be dependent on the same equilibrium.

The nitrosolysis of alkyl substituted cyclohexanone diethyl acetals (4-methyl and 4-*tert*-butyl) proceeds similarly as with the acetal of the parent ketone. More interesting is the nitrosolysis of 2-methylcyclohexanone diethyl acetal. This acetal underwent the reaction with ethyl nitrite under the standard reaction conditions to provide 77% of ethyl 5-cyano-2-methylpentanoate and about 10% of ethyl 6-oxoheptanoate. The predominant formation of the ethyl 2-methyl-5-cyanopentanoate vs. the limited amount of the ethyl 6-oxoheptanoate, resulting from the cleavage of the isomeric enol ether (eq 41),



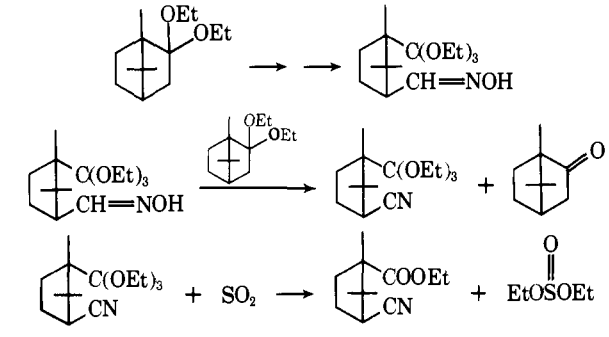
suggests that the rate of formation of the isomeric enol ethers from the ethoxy-2-methylcyclohexane carbonium ion is not the rate-determining step in this nitrosolysis reaction. This contrasts with the fact that in many acid-catalyzed reactions involving enols, the rate-determining step is the rate of deprotonation of the corresponding conjugate acids,[38] a process that generally favors the formation of the isomeric enol with more substituted double bonds.[39] The preferred cleavage of the C(1)-C(6) rather than the C(1)-C(2) carbon-carbon bond seems to suggest preferential electrophilic attack of the nitrosating species at the more nucleophilic double bond of the two enol ethers, thus requiring at least partial equilibration of the latter prior to the reaction with electrophile. Further support for this interpretation comes from the nitrosolysis of the diethyl acetal of 2-heptanone. A relatively high proportion of the C(1)-C(2) vs. C(2)-C(3) carbon-carbon bond cleavage in this reaction suggests that at least partial equilibration of the respective enol ethers did take place before the reaction with the electrophilic nitrosating species (eq 42).



(42)

Nitrosolysis of cyclopentanone diethyl acetal yielded 65% of ethyl 4-cyanobutanoate. The reaction was considerably slower than the reaction with cyclohexanone diethyl acetal. On the other hand, cyclododecanone diethyl acetal reacted much faster, the reaction being essentially over after complete addition of the reagents, providing the ester nitrile in over an 88% yield. The reaction with camphor diethyl acetal was extremely slow under the standard reaction conditions and required higher reaction temperature and increased pressure. While the expected 1-carbethoxy-1,2,2-trimethyl-3-cyanocyclopentane was formed in about a 40-50% yield, camphor as well as diethyl sulfite were also produced in approximately the same yields. This particular reaction has been discussed in some detail elsewhere,[49] and it will suffice to say that the observed reaction products can be accounted for by the reaction sequence outlined in Scheme V. The reaction with α-tetralone

Scheme V



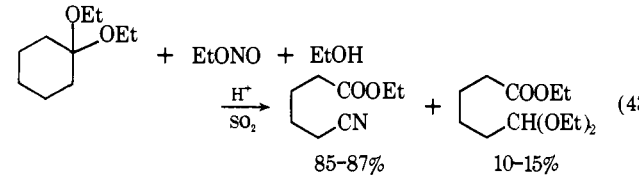
diethyl acetal was also fairly slow and gave the *o*-(ω-cyanoethyl)benzoic acid ester in about a 60% yield.

The nitrosolyses of symmetrical open chain ketones like 4-heptanone and 7-tridecanone were quite fast and generally complete upon the addition of the ethyl nitrite solution. The outcome of the nitrosolysis of "unsymmetrical" open chain ketone acetals has already been mentioned. Finally, the nitrosolysis of cyclohexyl methyl ketone acetal gave a 75% yield of the cyclohexane carboxylic acid ester, further indication of a prerate-determining equilibration of the isomeric enol ether intermediates prior to their capture by the electrophilic nitrosating species.

While a solution of dry hydrogen chloride in an appropriate alcohol was the most frequently used acid catalyst, other strong acids like hydrogen bromide, methanesulfonic acid, sulfuric acid, and boron trifluoride etherate, etc. were also active catalysts.

In concluding this section, it should be mentioned that most of the reactions summarized in Table III were carried out under the standard reaction conditions developed for the nitrosolysis of cyclohexanone diethyl acetal, so that the reported yields are not necessarily the optimal ones.

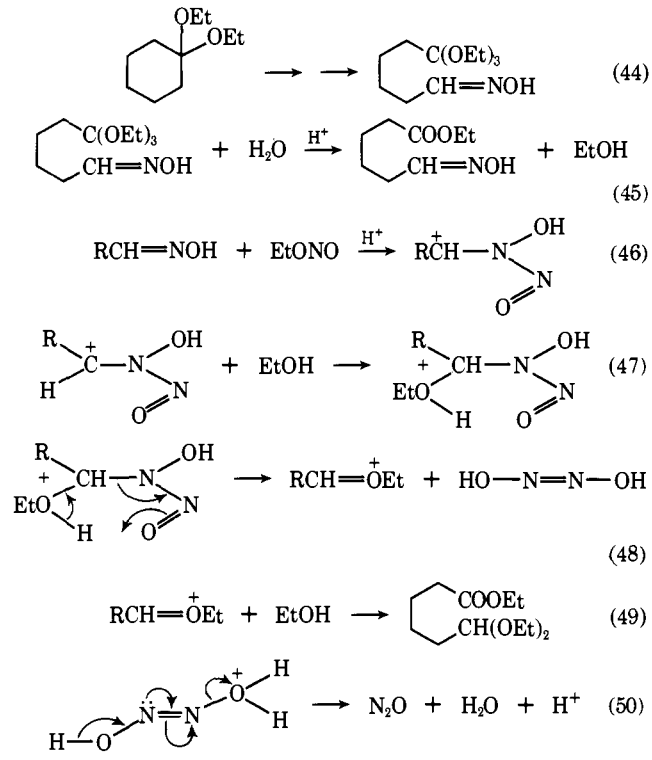
(c) **Side Product Formation.** The nitrosolysis of cyclohexanone diethyl acetal under standard reaction conditions produces an 85-87% yield of ethyl 5-cyanopentanoate. The ester nitrile is generally accompanied with about 10-15% of ethyl 6,6-diethoxyhexanoate (eq 43). The formation of the ester



(43)

acetal may be explained by the sequence of reactions outlined in Scheme VI. A trace of water present in the reaction system

Scheme VI

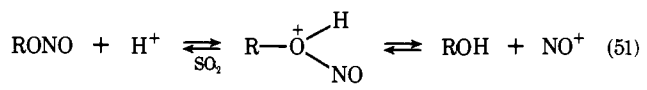


may react with the ortho ester-oxime intermediate (eq 45) before either intramolecular or intermolecular dehydration of the oxime to nitrile takes place. Alternatively, this hydrolysis may occur directly from the 1,1-diethoxy-6-oximinohexane carbonium ion before it becomes converted to the ortho ester. In either case, the oximino group of thus formed ethyl 6-oximinohexanoate becomes a potential site for a reaction with the nitrosating species that may lead to a *N*-nitrosocarbonium ion

(eq 46),[6a,50,51] which in the presence of an excess of ethanol could give the alkoxy ether (eq 47). An acid-catalyzed carbon-nitrogen bond cleavage in the presence of an excess of ethanol would provide the ethyl 6,6-diethoxyhexanoate and HO-N=N-OH (eq 48, 49), which would decompose to dinitrogen oxide and water (eq 50).[6d] Since this sequence of reactions regenerates the water originally present at the beginning of the reaction, it follows that a catalytic amount of water could, depending on the relative rates of the various reactions occurring, significantly reduce the yield of the desired ester nitrile. A careful drying of the entire reaction system and all reagents, particularly the sulfur dioxide solvent, resulted in an increase in the yield of ethyl 5-cyanopentanoate to 93-95%, indicating the importance of the essentially anhydrous conditions for a minimization of the formation of the ester acetal by-products.

(d) Overall Mechanistic Considerations. A probable mechanism for the acid-catalyzed nitrosolysis of cyclohexanone diethyl acetal with ethyl nitrite in sulfur dioxide/ethanol solution was outlined in Scheme IV. A complex sequence of reactions like this one, that proposes several reaction intermediates without providing a firm experimental support for them, by its nature must be largely speculative. Consequently, the credibility of the proposed reaction mechanism must depend upon the indirect evidence and information which taken together should, hopefully, corroborate the available experimental observations. Thus, if the reaction of enol ethers with a nitrosating reagent is indeed an electrophilic addition reaction involving a positively charged intermediate, what are the details of the overall process? Is the addition a reversible or irreversible process? Is the intermediate the corresponding α-nitrosoalkoxycarbonium ion or a cyclic onium ("nitrosonium") ion?[34] Is a reaction of the positively charged intermediate with a nucleophile a stereospecific or nonstereospecific process? What is the overall stereochemistry of this addition reaction? What is the basis for the proposal of the ortho ester-oxime intermediates and dehydration of the latter to the ester nitrile, etc. While the answers to most of these questions will be found in subsequent papers, it is of interest to present some experimental results here because they are pertinent to the general discussion of the mechanism of the nitrosolysis reaction.

The presence of the enol ether in an equilibrium with the cyclohexanone diethyl acetal cannot be verified spectroscopically, but the chemical behavior of this system strongly suggests that such an equilibrium is indeed involved.[47] Similarly, the exact nature of the nitrosating species is also open for speculation. Both nitrosyl chloride and alkyl nitrites are largely covalent compounds and the electrical conductivity of the nitrosyl chloride solution in liquid sulfur dioxide indicates that nitrosyl chloride exists, even in this solvent, predominantly in undissociated form.[37] Cyclohexanone diethyl acetal does not react with ethyl nitrite in sulfur dioxide/ethanol in the absence of added mineral acid. Moreover, ethyl nitrite and cyclohexanone ethyl enol ether do not react under ordinary reaction conditions in the absence of an acid catalyst. This clearly shows that the absence of a reaction between the ketone acetal and ethyl nitrite in sulfur dioxide was not a result of a low equilibrium concentration of the enol ether but rather a consequence of the fact that the ethyl nitrite under these conditions was apparently not reactive enough. It seems reasonable, therefore, that the presence of a strong acid is needed to activate the alkyl nitrite either by polarization or by the generation of the nitrosonium ion through the equilibrium illustrated in eq 51. It is not possible to conclude from the available

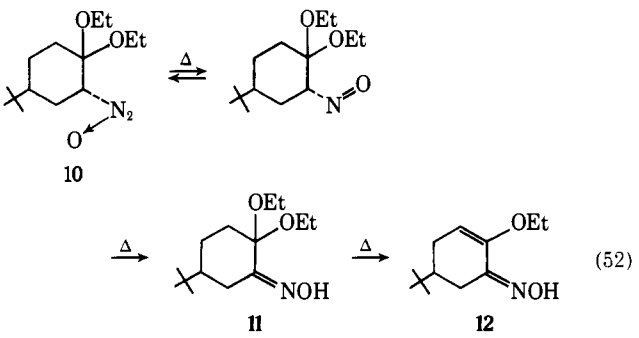


(51)

experimental data whether the enol ether reacts with the NO^+ ions as such or with the "activated" alkyl nitrite.

When the nitrosolysis of 4-*tert*-butylcyclohexanone diethyl acetal was carried out under the standard reaction conditions, it was observed that immediately after the complete addition of the ethyl nitrite solution, a small amount of a crystalline solid separated out and in the course of reaction dissolved again.

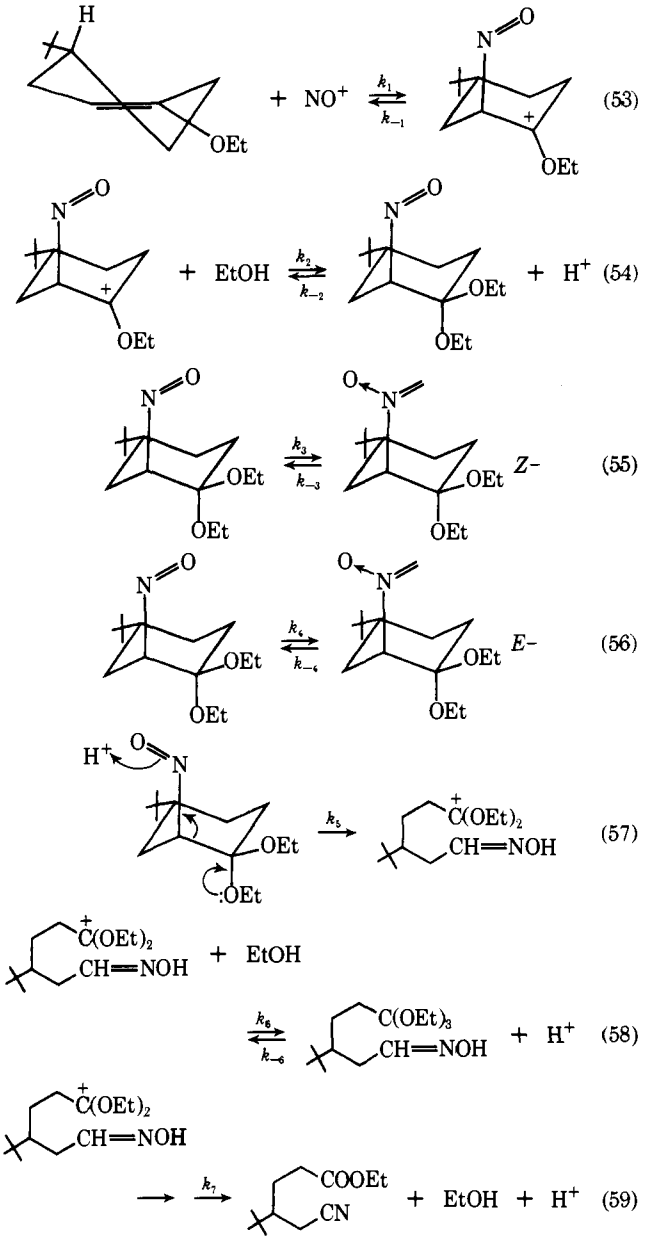
In a separate experiment a small amount of the solid was isolated and characterized as the 1,1-diethoxy-2-nitroso-4-*tert*-butylcyclohexane dimer **10** which on careful heating melted at 130-131 °C to give a deep-blue nitroso monomer. Upon cooling the blue melt resolidified to give the unchanged nitroso dimer. When the blue nitroso monomer was further heated, a relatively fast irreversible color change from blue to yellow occurred. Cooling gave 1,1-diethoxy-2-oximino-4-*tert*-butylcyclohexane (**11**), mp 162-164 °C. However, further heating of the oximino acetal **11**, resulted in an exothermic reaction accompanied by the evolution of a gas. Cooling and crystallization gave 2-ethoxy-3-oximino-5-*tert*-butylcyclohexene (**12**), mp 167-168 °C. The just described transformations can be summarized as in eq 52. While the discussion



(52)

of the NMR spectrum of the nitroso dimer **10** together with the important implications regarding the nature of the dimerization process[13d] will be reported in detail in a subsequent paper,[52] it is important to comment here on several points. From the width-at-half-height of the C_2-H proton at δ 5.80 (4.5 Hz), it is apparent that the proton is in the equatorial position. The IR spectra of both the crude as well as the crystallized dimer **10** established that the configuration of the nitrogen-nitrogen double bond was *E* as expected for the thermodynamically more stable isomer. When the crude **10** was returned to the original reaction solution, it slowly dissolved, and when the reaction was complete, the solution contained ethyl 4-*tert*-butyl-5-cyanopentanoate. These results can be summarized in Scheme VII. Evidently, the electrophilic attack of the nitrosating reagent at the double bond of the enol ether is a facialspecific reaction that occurs exclusively from only one face of the double bond, the face that provides the axial nitroso group (eq 53). The resulting 2-nitrosoalkoxycarbonium ion then reacts with the alcohol to give the 2-nitroso ketone acetal (eq 54). In principle, the reaction with the alcohol could take place from both faces of the 1-alkoxy-2-nitroso-4-*tert*-butylcyclohexyl carbonium ion, being equivalent to either cis or trans overall addition of the alkyl nitrite. While both of these reactions (eq 53 and 54) may be reversible, the experimental evidence, which will be presented in a subsequent paper,[52] indicates that the overall nitrosation is an irreversible and stereospecific process. Since it is well documented that the dimerization of nitroso compounds under kinetic conditions provides the thermodynamically less stable *Z*-nitroso dimers,[8] it follows that the initially produced 1,1-diethoxy-2-nitroso-4-*tert*-butylcyclohexane must first undergo a fast dimerization to the corresponding *Z*-nitroso dimers (eq 55). Under the reaction conditions, the thus produced *Z*-nitroso dimers must dissociate back to the 2-nitroso ketone acetal (eq 55), which then in turn undergoes dimerization (k_4) to the thermody-

Scheme VII



namically more stable *E*-nitroso dimers (eq 56).[7,8] If the rate of the carbon-carbon bond cleavage (k_5) in the 1,1-diethoxy-2-nitroso-4-*tert*-butylcyclohexane is much faster than the rate of dimerization (k_4), no significant amounts of the nitroso dimer should be formed. On the other hand, if the rate k_5 is slower than k_4, the formation of ethyl 4-*tert*-butyl-5-cyanopentanoate will depend on the relative rates k_5 vs. k_4. Thus, it is conceivable that the rate of dissociation of the *E*-nitroso dimer, k_{-4}, may become the rate-determining step of the overall transformation. However, since subsequent conversion of the 1,1-diethoxy-4-*tert*-butyl-6-oximinohexyl carbonium ion to the final ester nitrile product definitely involves several distinct reaction steps (Scheme VIII),[53] the relative rates of

Scheme VIII

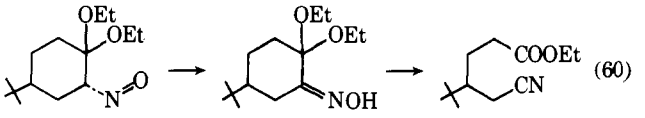
$$RCH{=}NOH + R'C(OEt)_3 \rightleftarrows RCH{=}N{-}O{-}C(OEt)_2R' + EtOH$$

$$RCH{=}N{-}O{-}C(OEt)_2R' + H^+ \rightleftarrows RCH{=}N{-}O{-}C^+(OEt)R' + EtOH$$

$$RCH{=}N{-}O{-}C^+(OEt)R' + RCH{=}NOH \rightleftarrows (RCH{=}N{-}O)_2C(OEt)R' + H^+$$

$$RCH{=}N{-}O{-}C^+(OEt)R' \rightarrow RCN + R'COOEt + H^+$$

which are not known, the assumption that k_{-4} may indeed be the rate-determining step must be taken with reserve. Moreover, if one realizes that the 1,1-diethoxy-2-nitroso-4-*tert*-butylcyclohexane can also isomerize to the 1,1-diethoxy-2-oximino-4-*tert*-butylcyclohexane (eq 60), which con-



ceivably may provide the same ester nitrile product,[52] the decision about the actual reaction mechanism becomes much more difficult. The experimental evidence that the above dehydration of aldoximes with ortho esters to the corresponding nitriles is indeed a facile and general reaction has already been presented.[53] In the subsequent paper[52] we will provide the evidence that, under the same reaction conditions, the formation of the ester nitrile from a 2-nitrosocyclohexanone acetal dimer takes place more readily than from the corresponding 2-oximinocyclohexanone acetal.

Consequently, from the presented experimental evidence, it clearly follows that the mechanism of the nitrosolysis of ketone acetals, as outlined in Scheme IV, is indeed an oversimplification. While the results just discussed do add to the credibility of the main features of the proposed mechanism, at the same time they also suggest that the actual reaction course, depending on the substrate, may involve much more complex chemistry.

Conclusion

Earlier confusion about the dimerization and isomerization of primary and secondary nitroso compounds have apparently been clarified;[54] it is now generally recognized that the isomerization of a nitroso group to an oxime is not a spontaneous transformation.[6] This understanding notwithstanding, it is still widely held that α-nitroso ketones, the intermediates in nitrosation of ketones, are spontaneously isomerized under the reaction conditions to the corresponding α-oximino ketones,[6d,55] which are generally the final products of this reaction. We have now demonstrated that the overall mechanism of the nitrosation of ketones strongly depends on the reaction conditions and the nature of the nitrosating reagent used. Assuming that the nitrosation of ketones is a special case of an electrophilic addition of a nitrosating reagent to a double bond of the enol present in the equilibrium, we have shown that the resulting α-nitrosohydroxycarbonium ion and α-nitrosoalkoxycarbonium ion intermediates can be trapped with an alcohol as a nucleophile. A facile in situ cleavage of the ensuing α-nitroso hemiacetals or α-nitroso acetals provides the basis for the nitrosolysis of ketones and ketone acetals. Clearly, the nitrosolysis reaction is a remarkably simple procedure for the carbon-carbon bond cleavage of a variety of ketones and ketone acetals which provides products with valuable functional groups. In effect, the nitrosolysis of ketones represents an advantageous supplement to a Beckmann fragmentation of the α-oximino ketones.[23] The reaction is carried out under much milder conditions and eliminates the need for the prior preparation of the oximino ketones. It appears particularly useful for the transformation of cyclopentanone, cyclohexanone, and cyclohexanone derivatives where α-oximino ketones are extremely difficult to prepare. In the case of cyclohexanone, a slight variation in the reaction procedure provides for the first time a direct and convenient access to 2-alkoxy-3-oximinocyclohexene, a novel derivative of a mononitrosated cyclohexanone. Furthermore, the nitrosolysis of ketone acetals expands the scope of these cleavage reactions and appears to be particularly attractive because of its very general nature and since it requires very mild reaction conditions and only a cat-

alytic amount of an acid. This development opens up, in effect, a possibility for a new caprolactam process which, contrary to the presently used ones,[56] could operate without the formation of ammonium sulfate as a by-product. ω-Aminocaproic acid esters, which are easily obtained from the corresponding ester nitriles, are effectively a caprolactam equivalent since they can readily be polymerized to nylon-6 polymer.

On the other hand, the mechanism of nitrosation does change dramatically by changing the nature of the nucleophile associated with the nitrosating reagent. Thus, in the absence of efficient nucleophiles, the α-nitrosocarbonium ion, resulting from the electrophilic addition of the nitrosonium ion to the double bond of an olefin or even an enol, behaves as a 1,3-dipolar ion that can be intercepted with a carbonyl group as a dipolarophile to provide a novel single-step synthesis of various 3-oxazoline *N*-oxides.

In the following papers of this series we will describe further developments which have considerably expanded the synthetic value of the nitrosation reaction and, equally important, significantly widen the horizon of our understanding of the mechanistic chemistry of this old reaction.

Experimental Section

All the ketones used in this work were commercial products which were purified when necessary either by distillation or crystallization. The ketone acetals were prepared by the usual procedure using an ortho ester as a dehydrating reagent[57] or by an azeotropic distillation of the water. The enol ethers were prepared by the acid-catalyzed elimination of the alcohol from the corresponding ketone acetals.[57] The nitrosyl chloride was Matheson Cole and Bell product and generally was distilled directly from the cylinder into a delivery flask from which it was introduced into a reaction mixture as a gas. *tert*-Butyl nitrite and *n*-butyl nitrite were commercial products which were freshly distilled before use. Ethyl nitrite was prepared either by an exchange[58] from a higher boiling alkyl nitrite and ethanol or from a water solution of sodium nitrite and ethanol in the presence of sulfuric acid.[59] For convenience, a solution of ethyl nitrite in absolute ethanol was prepared and stored in a refrigerator prior to use. 1-Methylcyclohexyl nitrite[60] and 1-methyl-1-phenylethyl nitrite[61] were prepared from the corresponding alcohol, sodium nitrite, and sulfuric acid and stored in a refrigerator prior to use. Nitrosyl tetrafluoroborate and nitrosyl hexafluorophosphate were commercial samples and were used without further purification. The sulfur dioxide was Matheson Coleman and Bell anhydrous grade and was passed through Linde AW-300 molecular sieves before condensation. Other solvents and alcohols were generally high grade chemicals or freshly purified and distilled samples.

The reported boiling and melting points are uncorrected. GLC analyses were generally carried out on a Hewlett-Packard 5700A instrument using 3- or 6-ft columns of either 10% SE-30 or 10% Carbowax-20M columns packed on Chromosorb W. Proton NMR spectra were recorded on either a Varian A-60 or Varian T60-A 60-MHz or HA-100 MHz instruments, while ^{13}C NMR spectra were recorded on a Varian CFT-20 instrument. All NMR spectra were measured using tetramethylsilane as an internal standard. Routine chemical ionization mass spectra were obtained on a Finnigan 3100D mass spectrometer, while high-resolution mass spectra were obtained on an AEI M.S. 902 instrument.

2,6-Dioximinocyclohexanone. Typical Reaction Procedure. A three-neck, 500-ml flask equipped with a serum capped inlet, a mechanical stirrer, either a dry ice condenser or a regular reflux condenser protected with a nitrogen bubbler, and an inlet for the introduction of a gas (or an addition funnel) was placed in an appropriate bath. The flask was charged with a solvent (about 100 ml) and cyclohexanone (10.4 ml, 100 mmol). The stirrer was started and the reaction carried out by the slow introduction of nitrosyl chloride vapor (14.4 g, 220 mmol) over the well-stirred solution. After the reaction was complete, solid sodium bicarbonate was added in small portions, followed by enough water to neutralize the acid. The organic portion was removed by extraction and, after drying and removal of the solvent, the crude 2,6-dioximinocyclohexanone[24] was obtained as a pale-yellow solid, mp 220–230 °C dec, in yields between 70–95%.

2-Methoxy-3-oximinocyclohexene (2). A three-neck, 500-ml flask equipped with a serum capped inlet, a mechanical stirrer, inlets for the introduction of sulfur dioxide and hydrogen chloride, and a dry ice condenser protected with a nitrogen bubbler was placed in a dry ice–acetone bath at −70 °C. A sulfur dioxide cylinder was connected to one inlet and about 100 ml of sulfur dioxide was distilled into the flask. The stirrer was started and methanol (8.05 ml, 200 mmol) was added by a syringe. Dry hydrogen chloride (110 mmol) was bubbled into the solution[62] and then cyclohexanone (10.4 ml, 100 mmol) was added by a syringe. The hydrogen chloride inlet was replaced with an inlet connected through a stopcock to a precooled flask containing liquid nitrosyl chloride (7.19 g, 110 mmol). The stirrer was started, the stopcock on the nitrosyl chloride flask was then opened, and the nitrosyl chloride container was gently warmed to allow the slow evaporation of the nitrosyl chloride, whose vapor was introduced just above well-stirred reaction solution at −70 °C. After the addition was complete, the pale-yellow solution was stirred for an additional 30 min and the temperature was allowed to rise to about −50 °C. Evaporation of the sulfur dioxide at −40 to −50 °C gave about 20–25 g of a soft, white solid residue. On attempted filtration from a suspension in benzene, this material underwent an apparent change, turning into a slightly tan colored solid, mp 113–115 °C dec. Titration of this solid with sodium hydroxide or with silver nitrate suggested a molecular weight of 174. NMR (D_2O) δ 6.1 (t, 1 H), 4.85 (s, 2 H), 3.69 (s, 3 H), 2.85 (t, 2 H), 2.40 (q, 2 H), and 1.82 (quin, 2 H).

Careful treatment of the hydrochloride with sodium bicarbonate in a minimal quantity of water afforded 12.3 g (87% yield) of 2-methoxy-3-oximinocyclohexene (**2**): mp 150–151 °C; NMR ($CDCl_3$) δ 9.5 (s, 1 H), 5.23 (t, 1 H), 3.69 (s, 3 H), 2.75 (t, 2 H), 2.23 (q, 2 H), and 1.69 (quin, 2 H).

Anal. ($C_7H_{11}NO_2$) C, H, N.

However, titration of a solution of the white, soft solid in water with sodium hydroxide or with silver nitrate indicated a molecular weight of 190–200, suggesting, together with a 100-MHz NMR spectrum at −50 °C of the original sulfur dioxide solution immediately after mixing reagents, that the white soft solid is the unstable 1-methoxy-1-hydroxy-2-oximinocyclohexane hydrochloride (**1**) (a broad singlet at δ 9.1 integrating for 3 H (OH, NOH, HCl), a sharp singlet at δ 3.32 (3 H, OCH_3), and a set of multiplets centered at δ 2.85, 2.15 and 1.95, each integrating approximately for 2 H). On warming the sulfur dioxide solution, an olefinic proton began to appear as a pair of triplets centered at δ 6.51 and 6.63. With time the intensity of the lower field triplet decreased while that of the higher field increased, suggesting that the isomerization of the oxime was taking place. At −10 °C, the spectrum was consistent with the structure of **2a.**

2-Ethoxy-3-oximinocyclohexene was prepared in a 78% yield by the same method and using the same ratios of the reagents as described in preparation of the 2-methoxy analogue: mp 163–163.5 °C; NMR ($CDCl_3$) δ 9.6 (s, 1 H), 5.27 (t, 1 H), 3.78 (q, 2 H), 2.67 (t, 2 H), 2.22 (q, 2 H), 1.67 (quin, 2 H), 1.32 (t, 3 H); mass spectrum (70 eV) *m/e* 155 (M), 140 (M − CH_3), 138 (M − OH), 111 (M − C_2H_4O).

Anal. ($C_8H_{13}NO_2$) C, H, N.

2-Isopropoxy-3-oximinocyclohexene was prepared as above in 70% yield: mp 134–137 °C; NMR ($CDCl_3$) δ 9.4 (s, 1 H), 5.23 (t, 1 H), 4.25 (sept, 1 H), 2.66 (t, 2 H), 2.20 (q, 2 H), 1.65 (quin, 2 H), 1.25 (d, 6 H); mass spectrum (70 eV) *m/e* 169 (M), 152 (M − OH), 127 (M − C_3H_6).

2-Methoxy-3-*N*-acetoxycyclohexene. A 100-ml, three-neck flask equipped with a thermometer, a magnetic stirrer, and a dropping funnel was charged with 14.1 g (100 mmol) of 2-methoxy-3-oximinocyclohexene. Acetic acid anhydride (28.4 ml, 300 mmol) was added dropwise from the addition funnel with stirring. The temperature rose to 45 °C, and the reaction mixture was stirred at 50 °C for an additional 30 min. After evaporation of the acetic acid and the anhydride in vacuo, the residue was crystallized from ether to give 17 g (73%) of the white crystals: mp 49–51 °C; NMR ($CDCl_3$) δ 5.5 (t, 1 H), 3.6 (s, 3 H), 2.72 (t, 2 H), 2.27 (q, 2 H), 2.16 (s, 3 H), 1.73 (quin, 2 H); mass spectrum (70 eV) *m/e* 183 (M), 141 (M − C_2H_2O), 140 (M − C_2H_3O), 124 (M − $C_2H_3O_2$), 111 (M − C_2H_2O, CH_2O).

Anal. ($C_9H_{13}NO_3$) C, H, N.

Typical Procedure for Nitrosolysis of Ketones. Ethyl ω-Oximinocaproate. A three-neck, 500-ml flask equipped with a mechanical stirrer, an inlet for the introduction of sulfur dioxide and nitrosyl chloride, and a dry ice condenser protected with a nitrogen bubbler was placed in a dry ice–acetone bath. A sulfur dioxide cylinder was connected to the inlet and about 200 ml of sulfur dioxide was distilled

into the flask. A solution of cyclohexanone (19.68 ml, 200 mmol) in ethanol (17.6 ml, 300 mmol) was added with the aid of a syringe and the dry ice–acetone bath was removed. Nitrosyl chloride (14.4 g, 220 mmol) was placed in a precooled 50-ml, round-bottom flask protected with a nitrogen bubbler and equipped with an outlet connected via a stopcock to the inlet of the reactor. When the sulfur dioxide started to boil (~−10 °C), the nitrosyl chloride container was gently warmed, and simultaneously the stopcock was opened to introduce the nitrosyl chloride vapors slowly just above the well-stirred solution. The end of the reaction (15–20 min) was indicated by the appearance of a slight yellow color (excess of nitrosyl chloride) which did not decolorize immediately. The reaction mixture was evaporated in vacuo to a small volume, about 150 ml of chloroform was added, and the solution was again briefly concentrated to remove the residual sulfur dioxide. The remaining chloroform solution was transferred to a separatory funnel, diluted with more chloroform to about 200 ml, and washed several times with water to remove the hydrochloric acid. GLC analysis of the solution indicated a 90–95% yield of ethyl ω-oximinocaproate and about a 2% yield of 2-ethoxy-3-oximinocyclohexene. Evaporation of the chloroform afforded 33.0 g (95%) of slightly yellow oximino ester: NMR ($CDCl_3$) δ 9.8 (s, 1 H), 7.37 (t, 0.4 H), 6.66 (t, 0.6 H), 4.12 (q, 2 H), 2.3 (m, 4 H), 1.6 (m, 4 H), 1.22 (t, 3 H); mass spectrum (70 eV) *m/e* 158 (M − CH_3), 156 (M − OH), 155 (M − H_2O), 138 (M − OH, H_2O). A small amount of the ester oxime in a chloroform solution was treated with a slight excess of triethyl orthoformate in the presence of a catalytic amount of hydrogen chloride to give ethyl 5-cyanopentanoate.[53]

Under similar reaction conditions and using the same ratios of the reagents, nitrosolysis of other ketones in the presence of an alcohol afforded the corresponding ester oximes (Table I), which were characterized spectroscopically and by conversion to the corresponding nitriles.[53]

Methyl ω-Oximinocaproate. NMR ($CDCl_3$) δ 9.4 (s, 1 H), 7.37 (t, 0.35 H), 6.66 (t, 0.65 H), 3.65 (s, 3 H), 2.33 (m, 4 H), 1.6 (m, 4 H); mass spectrum (70 eV) *m/e* 159 (M), 160 (M + H), 142 (M − OH), 127 (M − OH, CH_3), 101, 82, 74.

Isobutyl ω-Oximinocaproate. NMR ($CDCl_3$) δ 9.5 (s, 1 H), 7.37 (t, 0.5 H), 6.6 (t, 0.5 H), 3.88 (d, 2 H), 2.35–1.5 (m, 9 H), 0.95 (d, 6 H); mass spectrum (70 eV) *m/e* 184 (M − OH), 146 (M − C_4H_8), 143 (M − C_2H_4NO).

Ethyl 4-*tert*-Butyl-6-oximinohexanoate. NMR ($CDCl_3$) δ 9.6 (s, 1 H), 7.37 (t, 0.3 H), 6.62 (t, 0.7 H), 4.12 (q, 2 H), 2.3–1.2 (m, 7 H), 1.1 (s, 9 H); mass spectrum (70 eV) *m/e* 214 (M − CH_3), 212 (M − OH), 211 (M − H_2O), 196 (M − H_2O, CH_3), 194 (M − OH, H_2O).

Ethyl 2-Methyl-6-oximinohexanoate and Ethyl 6-Oximinoheptanoate. NMR ($CDCl_3$) δ 9.5 (s, 1 H), 7.4 (t, 0.25 H), 6.7 (t, 0.25 H), 4.12 (q, 2 H), 2.3 (m, 4 H), 1.3 (t, 3 H), 1.18 (d, 1.5 H).

Ethyl 5-Oximinopentanoate. NMR ($CDCl_3$) δ 9.5 (s, 1 H), 7.4 (t, 0.6 H), 6.7 (t, 0.4 H), 4.1 (q, 2 H), 2.3 (m, 4 H), 1.9 (m, 2 H), 1.22 (t, 3 H); mass spectrum (70 eV) *m/e* 160 (M + H), 142 (M − OH), 129 (M − NO).

Ethyl **12-oximinododecanoate** was obtained in about a 75% yield together with 2-oximinocyclododecanone: NMR ($CDCl_3$) δ 9.5 (s, 1 H), 7.37 (t, 0.4 H), 6.7 (t, 0.35 H), 4.12 (q, 1.5 H), 2.65–1.25 (m + t, ~23 H); mass spectrum (70 eV) *m/e*, ester: 240 (M − OH), 222 (M − OH, H_2O), 199 (M − C_2H_4NO); ketone: 211 (M), 194 (M − OH), 183 (M − CO). Crystallization of a crude sample afforded the oximino ketone,[25] mp 58 °C, which had the same retention time as the minor component in the reaction mixture.

Nitrosolysis of 7-tridecanone was carried out as above, and the reaction mixture was analyzed by GLC in the presence of an internal standard. The chromatogram showed about a 45% yield of ethyl heptanoate but only about a 20% yield of *n*-hexaldehyde oxime. In addition, about a 40% yield of 6-oximino-7-tridecanone was also formed.

4,5,6,7-Tetrahydro-7a-methylspiro[benzoxazoline-2,1′-cyclohexane] 3-Oxide (5). Typical Procedure. A three-neck, 500-ml flask equipped with a mechanical stirrer, a dry ice condenser, an addition funnel, and an inlet attached to a sulfur dioxide cylinder was placed in a bath maintained at −30 °C and charged with about 100 ml of sulfur dioxide. Cyclohexanone (9.8 g, 100 mmol) and boron trifluoride etherate (14.2 g, 100 mmol) were introduced with a syringe and 1-methylcyclohexyl nitrite (14.3 g, 100 mmol) was added dropwise with stirring over a 30–45 min period. The reaction mixture was stirred at the same temperature for 1.5 h and then at reflux for 1 h. After evaporation of the solvents, the residue was dissolved in 50 ml of methylene chloride and the solution poured into a slurry of sodium bicarbonate (25 g) in 100 ml of wet methylene chloride. After drying and evaporation of the solvent, there was obtained 14.5 g (65%) of **5**: mp 104–106 °C (ether); NMR ($CDCl_3$) δ 3.17 (dm, 1 H, equatorial CH–C=N–), 2.5–1.0 (complex, 17 H), 1.48 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.33 (s, C=N), 105.56 (s, O–C–N), 83.20 (s, Me–*C*), 42.09 (t, CH_2–C=N), 35.64 and 35.00 (t, N–C(CH_2)–), and 25.63–21.99 (Me and other CH_2's); mass spectrum: CI (methane) MH^+ at *m/e* 224, high resolution (70 eV) calcd for $C_{13}H_{21}NO_2$: 223.1572; found: 223.1577; *m/e* 223 (M^+ − O), 192 (M^+ − O, CH_3), 180 (M^+ − $COCH_3$), 163 (M^+ − $COCH_3$, OH), 125 (M^+ − $C_6H_{10}O$). 95 (base, 125^+ − NO), and 81; IR (KBr) 1620 (s, C=N–O), 1162 (s, N–O) cm^{-1}; UV (CH_3OH) λ_{max} 235 nm (ε 13 100).

Anal. ($C_{13}H_{21}NO_2$) C, H, N.

The same compound was also prepared by a slight modification of the above procedure. To a solution of 1-methylcyclohexene (9.6 g, 100 mmol) and cyclohexanone (9.8 g, 100 mmol) in liquid sulfur dioxide (100 ml), an equivalent (11.7 g, 100 mmol) of solid nitrosyl tetrafluoroborate was added in small portions under a blanket of nitrogen, and, after complete reaction, the reaction product **5** was isolated as above in a 57% yield. Alternatively, a similar addition of nitrosyl tetrafluoroborate to a suspension of 1-methylcyclohexanol (11.4 g, 100 mmol), cyclohexanone (9.8 g, 100 mmol), and an excess of anhydrous sodium sulfate (5 g) in 100 ml of sulfur dioxide, followed by the same workup procedure afforded about 15.5 g (a 70% yield) of **5**.

4,5,6,7-Tetrahydro-7a-methylspiro[benzoxazoline-2,1′-cyclohexane] (5a). A solution of *N*-oxide **5** (0.45 g, 2.0 mmol), phosphorus trichloride (40 ml, 46 mmol), and 20 ml of methylene chloride was heated at reflux for 1.5 h.[63] The excess of phosphorous trichloride was evaporated, and the residue was dissolved in methylene chloride and neutralized with dry ammonia at 0 °C. Filtration and evaporation of the solvent gave 0.32 g (a 78% yield) of **5a**: mp 37.5–38.5 °C; NMR ($CDCl_3$) δ 2.59 (dm, 1 H, equatorial CH–C=N), 2.5–1.5 (complex, 17 H) and 1.38 (s, 3 H); high resolution mass spectrum (70 eV) calcd for $C_{13}H_{21}NO$: 207.1622; found: 207.1653; *m/e* 207 (M^+), 192 (M^+ − CH_3), 178, 165, 164 (M − $COCH_3$), 111, 96, 84, 81, and 43 (base); IR (KBr) 1676, 1014, 948 cm^{-1}; UV (CH_3OH) λ_{max} 207.5 nm (ε 3160).

2,2-Dimethyl-1-oxa-4-azaspiro[4.5]dec-3-ene 4-oxide (4), mp 119–121 °C (ether), was prepared according to the typical procedure for synthesis of **5** in a 50% yield: NMR ($CDCl_3$) δ 6.85 (s, CH=N, 1 H), 2.30–2.00 (complex, 3 H), 1.90–1.45 (complex, 7 H), and 1.48 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 132.81 (d, C=N), 106.05 (s, N–C–O), 81.75 (s, O–C–C=N), 35.25 (t, O–C(CH_2)$_2$), 28.0 (q, CH_3), 24.26 and 22.17 (t, –CH_2–); mass spectrum: CI (methane) shows MH^+ at *m/e* 184; EI (70 eV) *m/e* 183 (M^+), 168 (M^+ − CH_3), 167 (M^+ − O), 99 (M^+ − O), 99 (M^+ − $C_4H_{10}O$), 85 (base, M^+ − cyclohexanone), and 81; IR (CCl_4) 1590, (s, C=N→O), 1200, 1150 cm^{-1}; UV (CH_3OH) λ_{max} 235 nm (ε 10 360).

Anal. ($C_{10}H_{17}NO_2$) C, H, N.

The same compound was also prepared by a slight modification of the above procedure. To a solution of cyclohexanone (9.8 g, 100 mmol) and isobutylene (11.2 g, 200 mmol) in sulfur dioxide (100 ml), an equivalent (11.7 g, 100 mmol) of solid nitrosyl tetrafluoroborate was added in small portions, and the reaction mixture was worked up as above to give 5.5 g of **4** (a 30% yield).

2-Phenyl-4,5,6,7-tetrahydro-7a-methylbenzoxazoline 3-oxide (7), mp 144–147 °C (dimethoxyethane), was prepared from 1-methylcyclohexyl nitrite (14.3 g, 100 mmol), benzaldehyde (10.6 g, 100 mmol), and boron trifluoride etherate (14.2 g, 100 mmol) in a 40% yield (9.2 g): NMR ($CDCl_3$) δ 7.47 (m, 5 H), 6.18 (d, J = 2.0 Hz, 1 H, PhOC*H*<), 3.13 (dm, J = 7 Hz, 1 H, equatorial CH_2–C=N), 2.35–1.15 (m, 7 H), 1.47 (s, 3 H). A decoupling experiment indicated that the doublet at δ 6.18 and the equatorial C–H at 3.13 were coupled: ^{13}C NMR ($CDCl_3$) δ 141.64 (s, C=N–), 133.40 (s, *ipso* Ar–C), 128.61, 127.03 and 126.60 (d, other aromatic C's), 97.80 (d, Ph–C–H), 83.75 (s, CH_3–*C*–O), 39.41 (t, CH_2–C=N), 23.82, 21.53, and 20.77 (t, CH_2's), and 20.31 (q, CH_3); mass spectrum (70 eV) *m/e* 231 (M^+), 215 (M^+ − O), 125 (M^+ − C_6H_5CHO), 95 (base, M^+ − C_6H_5CHO–NO), 77, 67, and 55; IR (KBr) 1628 (s, C=N–O), 1175 (s, N→O); UV (CH_3OH) λ_{max} 268 (small), 237.5 (ε 9030), and 213.5 nm. Both the NMR and ^{13}C NMR data suggest only one of the two possible diastereoisomers; however, the relative stereochemistry of the methyl and phenyl groups is not known.

Anal. ($C_{14}H_{17}NO_2$) C, H, N.

2-Isopropyl-4,5,6,7-tetrahydro-7a-methylbezoxazoline 3-oxide, mp 68–70 °C (dimethoxyethane–hexane), was prepared from 1-methylcyclohexyl nitrite (7.2 g, 50 mmol), isobutyraldehyde (3.6 g, 50 mmol), and boron trifluoride etherate (7.1 g, 50 mmol) as above in a 60% yield. Isolation of the pure compound required chromatography on a silica gel column using 1% ethanol–chloroform as the eluent: NMR ($CDCl_3$) δ 5.30 (dd, $J_1 = J_2 = 3.0$ Hz, 1 H, CHN), 3.20 (dm, $J_1 \cong 10.0$ Hz, 1 H, equatorial CHC=N), 2.50 (d-sept, $J_1 \cong 7.0$ Hz, $J_2 = 3.0$ Hz, 1 H, C*H*$(CH_3)_2$), 2.30–1.30 (complex, 7 H), 1.46 (s, 3 H), and 1.06 and 0.85 (d, $J = 15.0$ Hz, 3 H, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 144.93 (s, C=N), 101.81 (d, O–CH–N), 84.12 (s, CH_3-*C*–O), 39.82 (t, *C*H_2–C=N), 28.52 (d, *C*H$(CH_3)_2$), 25.26, 22.90, and 22.05 (t, CH_2's), 21.79 (q, *C*H_3C–O), and 17.56 and 13.77 (q, CH(*C*$H_3)_2$); high resolution mass spectrum (70 eV) calcd for $C_{11}H_{19}NO_2$: 197.1415; found: 197.1415; (*m/e*) 197 (M^+), 138 ($M^+ - C_3H_7O$), 125 ($M^+ - C_4H_8O$), 111 ($M^+ - C_4H_8NO$), 95 (base, $C_7H_{11}^+$), 67 ($C_5H_7^+$), 55 ($C_4H_7^+$), 43 ($C_3H_7^+$), and 41 ($C_3H_5^+$); IR (K(Br) 1638 (s, C=N→O), 1398 and 1371 (m, $(CH_3)_2C$), and 1172 and 1150 cm^{-1} (s, N–O); UV (CH_3OH) λ_{max} 234.5 nm (ϵ 8525).

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, N, 9.70. Found: C, 66.42; H, N, 8.85.

5-Phenyl-2,2,5-trimethyl-3-oxazoline 3-oxide was prepared by the addition of nitrosyl hexafluorophosphate (8.75 g, 50 mmol) to a solution of α-methylstyrene (5.9 g, 50 mmol), and acetone (5.8 g, 100 mmol), in nitromethane (50 ml) in a 10% yield. Alternatively, the same compound was prepared from 1-methyl-1-phenylethyl nitrite (8.25 g, 50 mmol), acetone (5.8 g, 100 mmol), and boron trifluoride etherate (7.1 g, 50 mmol), in a sulfur dioxide solution (50 ml) in a 25% yield (2.6 g). This material was a pale-yellow, unstable, and hygroscopic solid: mp 64–68 °C (ether–pentane); NMR ($CDCl_3$) δ 7.33 (s, 5 H), 7.28 (s, 1 H, H–C=N), 1.71 (s, 6 H), and 1.51 (s, 3 H); mass spectrum: CI (methane) shows MH^+ at 206 for monomer and 411 for dimer; high resolution (70 eV) calcd for $C_{12}H_{15}NO_2$: 205.1102; found: 205.1102; *m/e* 205 (M^+), 190 ($M^+ - CH_3$), 174 ($M^+ - CH_3$, O), 162, 147 (base, $M^+ - (CH_3)_2CO$), 146 ($M^+ - (CH_3)_2CO - H$), 133, 132, and 130. Some higher molecular weight fragments were also observed indicating the presence of dimers; IR (KBr) 1590 (s, C=N→O), 1223, 1203 (s, N–O), 764, 703 cm^{-1} (m, monosubstituted aromatic).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22. Found: 70.75; H, N.

5,5-Dimethyl-2-phenyl-3-oxazoline 3-oxide, mp 107–108 °C (ether), was prepared from *tert*-butyl nitrite (5.2 g, 50 mmol), benzaldehyde (5.3 g, 50 mmol), and boron trifluoride etherate (7.1 g, 50 mmol), in sulfur dioxide (50 ml) in a 45% yield: NMR ($CDCl_3$) δ 7.48 (m, 5 H), 7.04 (d, $J = 2.0$ Hz, 1 H, CH=N), 6.17 (d, $J = 2.0$ Hz, 1 H, PhCH–O), 1.52 (s, 3 H), and 1.48 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 134.35 (s, ipso C-Ar), 133.42 (d, CH=N), 130.14 (d, *p*-C), 128.48 and 127.61 (d, *o*- + *m*-C), 100.14 (d, Ph–CH–), 84.50 (s, O–*C*–C=N), and 26.92 and 25.72 (q, CH_3); mass spectrum (70 eV) *m/e* 191 (M^+), 175 ($M^+ - O$), 141, 107, 106 ($PhCHO^+$), 105, 85 (base, $M^+ - C_7H_6O$), 77, 69, 58, and 55; IR (KBr) 1596 (s, C=N→O), 1385, 1386, 1212, 1180, 1152, 762, and 700; UV (MeOH) λ_{max} 268 (weak), 237.5 (ϵ 8500), and 210 nm.

Anal. ($C_{11}H_{13}NO_2$) C, H, N.

2,2,5,5-Tetramethyl-3-oxazoline 3-oxide, bp 42 °C (0.1 mm), was prepared from *tert*-butyl nitrite (5.8 g, 100 mmol), acetone (10.3 g, 100 mmol), and boron trifluoride etherate (14.2 g, 100 mmol), in a nitromethane solution (75 ml). This is an unstable oil which partially solidifies upon standing (4.3 g, ~30% yield) and undergoes a slow dimerization: NMR ($CDCl_3$) δ 7.11 (s, CHC=N, 1 H), 1.62 (s, 6 H), 1.50 (s, 6 H); mass spectrum: CI (methane) shows MH^+ at 144 for monomer and at 287 for the dimer; high resolution (70 eV) calcd for $C_7H_{13}NO_2$: 143.0945; found: 143.0871; *m/e* 143 (M^+), 127 ($M^+ - O$), 116, 114, 111, 97; 85 ($M^+ - (CH_3)_2CO$), 84 ($M^+ - (CH_3)_2CO - H$), 73, 72, 71, 70, 69, 68, and 58 (base, $(CH_3)_2CO^+$); IR ($CHCl_3$) 1592, (s, C=N→O) 1381, 1370, 1225, 1160, 1015, 925 cm^{-1}; UV (CH_3OH) λ_{max} 234 nm.

4,5,6,7-Tetrahydro-7a-hydroxyspiro[benzoxazoline-2,1′-cyclohexane] 3-Oxide (6).[67] A solution of cyclohexanone (10.8 g, 110 mmol) in ether (100 ml) was saturated with hydrogen chloride at −10 °C. The temperature was lowered to −50 °C, and a solution of nitrosyl chloride (4.6 g, 70 mmol) in ether (20 ml) was added dropwise over a 30-min period. After stirring for 10 min, the reaction mixture was warmed to −10 °C, dry nitrogen gas was bubbled through for 90 min to displace the excess of hydrogen chloride, and the reaction mixture was neutralized (pH 7) with 30% sodium hydroxide solution while maintaining the temperature at −10 °C. The ether layer was separated, and the aqueous layer was extracted with four 100-ml portions of chloroform. After drying over sodium sulfate, the combined organic solutions were evaporated. Dry ether was added to the resulting olive-tan syrup to give 4.4 g (55%) of an off-white solid, mp 117–120 °C. Crystallization from chloroform–ether gave pure **6**: mp 123–124 °C; NMR ($CDCl_3$) δ 4.70 (s, OH, 1 H) 3.20–1.50 (br m, 18 H); ^{13}C NMR ($CDCl_3$) δ 140.91 (s, C=N), 105.79 (s, N–C–O), 102.96 (s, O–C–O), 40.51 (t, CH_2–C=N), 34.87, 34.48 (t, N–C(CH_2)$_2$–), 23.06 (t, CH_2–C–OH), 24.39 (t, CH_2–CH_2C=N), 22.59 (t, 2 C), 22.38 (t), 22.17 (t); IR (KBr) 3120 (OH), 1654 (C=N→O), 995 cm^{-1}; UV (CH_3OH) λ_{max} 231 nm (ϵ 11 047); mass spectrum (70 eV) *m/e* 225 (M^+).

Anal. ($C_{12}H_{19}NO_3$) C, H, N.

Thermal Degradation of 6.[67] The hydroxy *N*-oxide, **6** (0.23 g, 1 mmol), was heated in a short-path distilling apparatus at 0.4–0.5 mm. At 125–130 °C a reaction occurred and cyclohexanone distilled. The residue (an amber oil) was identified as 2-oximinocyclohexanone by IR and NMR.[25]

Reaction of 1-Ethoxycyclohexene with Nitrosyl Chloride. To a stirred solution of the enol ether[57] (7.0 ml, 50 mmol) and ethanol (8.8 ml, 150 mmol) in ether (100 ml) at −15 °C, nitrosyl chloride vapor (3.7 ml, 70 mmol) was introduced slowly. A light-blue color appeared instantaneously but gradually turned green with the separation of a white solid. When all of the nitrosyl chloride was introduced, a large quantity of the solid was present. The stirring was continued for 1 h during which time the color of the solid became slightly tan. The reactior mixture was diluted with more ether and an excess of sodium bicarbonate and small amounts of water were added. GLC analysis of the light brown solution indicated that the 2-ethoxy-3-oximinocyclohexene was the only product in the solution. Evaporation of ether gave 13.8 g of the enol ether (90% yield).

Reaction of 1-Ethoxycyclohexene with Nitrosyl Chloride in a Sulfur Dioxide/Ethanol Solution. A three-neck flask equipped with a mechanical stirrer, a dry ice condenser, and an inlet for the introduction of sulfur dioxide or nitrosyl chloride vapors was placed in a dry ice–acetone bath. Sulfur dioxide (100 ml) was distilled in and the enol ether (6.3 g, 50 mmol)[57] was introduced with a syringe at ~−50 °C. A very intense yellow-orange color developed immediately. Ethanol (4.4 ml, 75 mmol) was added and the intensity of the color weakened significantly. Addition of nitrosyl chloride (3.7 ml, 70 mmol) produced a slightly yellow-green solution. The solvents were removed in vacuo, an excess of chloroform was added, and the solution was again briefly concentrated to remove the residual sulfur dioxide. An excess of solid sodium bicarbonate, followed by a small amount of water, was added to neutralize the acid, and the solution was analyzed by GLC. In addition to cyclohexanone diethyl acetal and three other unidentified compounds, there was about a 30% yield of ethyl 5-cyanopentanoate which was identified by comparison with an authentic sample.

Typical Procedure for the Nitrosolysis of Ketone Acetals. Nitrosolysis of Cyclohexanone Diethyl Acetal. A three-neck, 300-ml flask equipped with a mechanical stirrer, an inlet for the introduction of sulfur dioxide, a dropping funnel, and a dry ice condenser protected with a nitrogen bubbler was placed in a dry ice–acetone bath. A sulfur dioxide cylinder was connected to the inlet and about 75 ml of sulfur dioxide was distilled into the flask. A solution of cyclohexanone diethyl acetal (9.3 ml, 50 mmol)[57] in absolute ethanol (11.4 ml, 195 mmol) was added with the aid of a syringe. A solution of ethyl nitrite (5.0 g, 67 mmol) in absolute ethanol (6.2 ml, 105 mmol) was placed in the dropping funnel, and a catalytic amount of hydrogen chloride (2.0 mmol, 2 ml of 1 N solution in absolute ethanol) was added to the reaction flask. The dry ice bath was removed and, when the sulfur dioxide started to boil (~−10 °C), a solution of ethyl nitrite was added dropwise over a period of 1 h. During this time the reaction mixture became pale blue-green. Stirring was continued for a total of 3.5 h, an internal standard was introduced, and the GLC analysis indicated a 87–93% yield of ethyl ω-cyanovalerate and a 5–12% yield of ethyl 6,6-diethoxyhexanoate. In a larger quantity experiment, when the GLC analysis indicated that the reaction was complete, about 0.5 g of sodium bicarbonate and 30 ml water were added, and the reaction mixture was left at room temperature overnight. GLC analysis of the reaction solution indicated that all of the ester acetal was converted into 5-carbethoxypentanal. The reaction mixture, which still contained large amounts of sulfur dioxide, was diluted with ether and washed

first with brine and then with a saturated solution of sodium bicarbonate. More solid sodium bicarbonate was added until the CO_2 evolution ceased. The white crystalline solid that was formed was filtered off. The ether solution was dried and evaporated, and the residue was distilled to give ethyl 5-cyanopentanoate: bp 98 °C (1.2 mm); NMR ($CDCl_3$) δ 4.12 (q, 2 H), 2.42 (m, 4 H), 1.74 (m, 4 H), 1.25 (t, 3 H); IR (neat) 2270 (C≡N), 1735 (C=O), 1200, 1030 cm^{-1}.

Anal. ($C_8H_{13}NO_2$) C, H, N.

The crystalline bisulfite compound that was filtered off above was suspended in chloroform and hydrolyzed with a 6 N solution of hydrochloric acid. A dried chloroform solution was analyzed by GLC and found to contain the same aldehyde present in the above hydrolyzed reaction mixture. A small amount of triethyl orthoformate was added to the chloroform solution, followed by a drop of sulfuric acid. The neutralized chloroform solution now was found to contain ethyl 6,6-diethoxyhexanoate, which had the same retention time as the minor component in the original reaction mixture before hydrolysis.

A similar reaction procedure was utilized in the nitrosolysis of other ketone acetals, and the results are summarized in Table III.[64]

***n*-Butyl 5-cyanopentanoate,**[64] bp 97 °C (0.3 mm); IR (neat) 2270 (C≡N), 1738 (C=O) cm^{-1}.

Isobutyl 5-cyanopentanoate,[64] bp 91–93 °C (0.3–0.5 mm); IR (neat) 2270 (C≡N), 1735 (C=O) cm^{-1}.

Ethyl 4-methyl-5-cyanopentanoate,[64] bp 76 °C (0.4 mm); IR (neat) 2273 (C≡N), 1735 (C=O) cm^{-1}.

Ethyl 4-*tert*-butyl-5-cyanopentanoate,[64] bp 112–114 °C (0.6 mm); IR (neat) 2275 (C≡N), 1738 (C=O) cm^{-1}.

Nitrosolysis of 2-methylcyclohexanone diethyl acetal[57] gave a mixture of ethyl 2-methyl-5-cyanopentanoate and ethyl 6-oxoheptanoate which were not separated, but were characterized as a mixture by both high- and low-resolution mass spectra. Calcd for $C_9H_{15}NO_2$: 169.2230. Found: 169.1098. Calcd for $C_9H_{16}O_3$: 172.2236. Found: 172.1112.

Ethyl 4-cyanopentanoate,[64] bp 88–90 °C (~2 mm); IR (neat) 2270, (C≡N), 1738 (C=O) cm^{-1}.

The nitrosolysis of cyclododecanone diethyl acetal[57] was much faster than that of the C_6- and C_5-cyclic ketones and gave ethyl 11-cyanoundecanoate:[64] bp 121 °C (0.3 mm); IR (neat) 2270 (C≡N), 1738 (C=O) cm^{-1}.

The nitrosolysis of camphor diethyl acetal[65] gave 1-carbethoxy-1,2,2-trimethyl-4-cyanocyclopentane:[64] bp 80–84 °C (0.4 mm); IR (neat) 2252, 1738 cm^{-1}.

The nitrosolysis of α-tetralone diethyl acetal gave ethyl *o*-(ω-cyanoethyl)benzoate which was characterized as the corresponding benzoic acid.[64]

The nitrosolyses of the diethyl acetals of 7-tridecanone[57] **and 4-heptanone**[57] were both very fast reactions, essentially complete after the addition of the ethyl nitrite solution. The yield of the reaction products was determined by GLC analysis in the presence of an internal standard and ethyl heptanoate or ethyl butyrate, and the corresponding nitriles were identified by comparison with the authentic samples.

The nitrosolysis of 2-heptanone diethyl acetal[57] required ca. 6 h, and the reaction products were again analyzed in the presence of an internal standard and identified by comparison with the authentic samples.

The nitrosolysis of the diethyl acetal of cyclohexyl methyl ketone[57] gave ethyl cyclohexanecarboxylate which was identical with an authentic sample.

Nitrosolysis of Cyclohexanone Di-*n*-butyl Acetal[66] **in Sulfolane.** The reaction was carried out in a similar manner using sulfolane instead of sulfur dioxide as a solvent and at room temperature. After complete reaction, an internal standard was introduced and the reaction mixture was analyzed by GLC analysis. A slightly lower yields of the *n*-butyl 5-cyanopentanoate (78%) was obtained. Similar results were obtained when nitromethane was used as the solvent.

(*E*)-1,1-Dioxidodiazenediylbis(2-diethoxy-5-*tert*-butylcyclohexane) 10. The nitrosolysis of 4-*tert*-butylcyclohexanone diethyl acetal[57] when carried out as above provided the corresponding ester nitrile at a slower rate than the corresponding unsubstituted ketone acetal. In one experiment, after complete addition of the ethyl nitrite, the reaction mixture was cooled to −30 °C causing a solid to separate out. A portion of this solid together with the reaction solution was transferred into an NMR tube, sealed, and allowed to warm to room temperature. After 1 h, the NMR tube was placed in dry ice, opened, and then analyzed by GLC analysis. The result was essentially the same as in the regular experiment. On the other hand, filtration of the solid that separated out at −30 °C gave a white crystalline material (0.5 g), **10,** mp 130–131 °C (as a deep blue melt): NMR ($CDCl_3$) δ 5.86 (m, equatorial C_2-H width-at-half-height 4.5–5.0 Hz), 3.8–3.1 (complex, 2 H), 2.7–1.4 (complex, 7 H), 1.15, 1.06 (2 t, 6 H), 0.83 (s, 9 H); IR ($CHCl_3$) 1227, 1193, 1122, 1105, 1096, 1059 cm^{-1}; high-resolution mass spectrum (70 eV) calcd for $(C_{14}H_{27}NO_3)_2$: (257.3722)$_2$; found: 257.2001; *m/e* 240 (M^+ − OH), 227 (M^+ − NO), 212, 199, 196, 182.

Anal. Calcd for $C_{28}H_{54}N_2O_6$: C, H, N, 5.43. Found: 6.06.

Cooling the blue melt gave a slightly yellow solid which was crystallized from methanol and shown to be unchanged **10.**

1,1-Diethoxy-2-oximino-4-*tert*-butylcyclohexane (11). Continued heating of the blue melt of **10** (0.35 g) causes a rapid color change to yellow. Cooling, followed by crystallization from methanol gave **11** (0.25 g, 71% yield): mp 162–164 °C; NMR ($CDCl_3$) δ ~10.0 (s, 1 H), 3.7–3.1 (complex, 4 H), 2.3 (q, 1 H, equatorial C_3-H), 1.8–1.1 (m, 6 H), 1.23, 1.17 (2 t, 6 H), 0.91 (s, 9 H); high-resolution mass spectrum (70 eV) calcd for $C_{14}H_{27}NO_3$: 257.3722; found: 257.2000; *m/e* 257 (M^+), 240 (M^+ − OH), 225 (M^+ − H, NOH), 213 (M^+ − C_2H_4O), 212 (M^+ − C_2H_5O), 200 (M^+ − C_4H_9), 198 (M^+ − C_2H_5NO).

Anal. ($C_{14}H_{27}NO_3$) C, H, N.

2-Ethoxy-3-oximino-5-*tert*-butylcyclohexene (12). Further heating of the yellow melt from **11** (0.5 g) caused an exothermic reaction followed by the evolution of a gas. Cooling, followed by crystallization from methanol gave 0.3 g of **12** (73%): mp 167–168 °C; NMR (Me_2SO–$CDCl_3$) δ 9.5 (s, 1 H), 5.5 (q, 1 H), 4.1 (q, 2 H), 2.7–1.5 (m, 5 H), 1.6 (t, 3 H), 1.2 (s, 9 H).

Anal. ($C_{12}H_{21}NO_2$) C, H, N.

References and Notes

(1) A part of this work was reported earlier in a preliminary form as a communication to the editor: M. M. Rogić, J. Vitrone, and M. D. Swerdloff, *J. Am. Chem. Soc.*, **97**, 3848 (1975).
(2) V. Meyer, *Ber. Dtsch. Chem. Ges.*, **6**, 1492 (1873).
(3) For a general discussion and summary of the early literature references see O. Touster, *Org. React.*, **7**, Chapter 6 (1953).
(4) W. A. Tilden and W. A. Stenstone, *J. Chem. Soc.*, 554 (1877).
(5) L. J. Beckham, W. A. Tessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951); (b) M. Plungunian and F. E. DeVry, "Nitrosyl Chloride", An Annotated Bibliography, Hercules Technical Information Center, 1970; (c) P. P. Kadzyauskas and N. S. Zefirov, *Usp. Khim.*, **37**, 7 (1968).
(6) B. G. Gowenlock and W. Luttke, *Q. Rev., Chem. Soc.*, **12**, 321 (1958); (b) J. H. Boyer in "The Chemistry of the Nitro and Nitroso Groups", Part I, H. Feuer, Ed., Wiley, New York, N.Y., 1968, p 215; (c) P. A. S. Smith, "Open Chain Nitrogen Compounds", Vol. 2, W. A. Benjamin, New York, N.Y., 1966, Chapter 13; (d) A. T. Austin, *Sci. Prog. (Oxford)*, **49**, 619 (1961).
(7) B. G. Gowenlock and J. Trotman, *J. Chem. Soc.*, 4190 (1955); 1670 (1956); (b) J. W. Smith, *ibid.*, 1124 (1957); (c) G. Collin, R. Hohn, H. G. Hauthal, H. Hubner, W. Pritzkow, W. Rolle, H. Schaefer, and M. Wahren, *Justus Liebigs Ann. Chem.*, **702**, 5 (1967); (d) W. Lutke, *Z. Electrochem.*, **61**, 976 (1956); (c) A. U. Chaudhry and B. G. Gowenlock, *J. Chem. Soc. B*, 1083 (1968).
(8) M. A. Samartsev and K. A. Ogloblin, *J. Org. Chem. USSR (Engl. Transl.)*, **1**, 31 (1965); (b) A. Mackor, Th. A. J. W. Wajer, and Th. J. deBoer, *Tetrahedron Lett.*, 2757 (1967); (c) B. G. Gowenlock, J. Trotman, and L. Batt, *Chem. Soc., Spec. Publ.*, **No. 10**, 75 (1957); (d) V. von Keussler and W. Luttke, *Z. Electrochem.*, **63**, 614 (1959); (e) R. Hoffmann, R. Gleiter, and F. B. Mallory, *J. Am. Chem. Soc.*, **92**, 1460 (1970); (f) Th. A. J. W. Wajer and Th. J. deBoer, *Recl. Trav. Chim.*, **91**, 565 (1972).
(9) E. J. Burrell, Jr., *J. Phys. Chem.*, **66**, 401 (1962); (b) L. Batt and B. G. Gowenlock, *J. Chem. Soc.*, 376 (1960).
(10) E. Baumberger and R. Seligman, *Chem. Ber.*, **36**, 685 (1903); (b) K. D. Anderson and D. L. Hammick, *J. Chem. Soc.*, 30 (1935); (c) J. R. Schwartz, *J. Am. Chem. Soc.*, **79**, 4353 (1957); (d) L. Batt and B. G. Gowenlock, *Trans. Faraday Soc.*, **56**, 1023 (1960).
(11) W. Huckel and M. Blohm, *Justus Liebigs Ann. Chem.*, **502**, 114 (1933); (b) W. G. Dauben, E. C. Martin, and G. Fonken, *J. Org. Chem.*, **23**, 1205 (1958); (c) A. S. Hussey, J. Sauvage, and R. H. Baker, *ibid.*, **26**, 256 (1961); (d) J. Meinwald, Y. G. Meinwald, and T. N. Baker, III, *J. Am. Chem. Soc.*, **86**, 4074 (1964).
(12) A. C. Hamann and D. Swern, *ibid.*, **90**, 6481 (1968).
(13) M. Ohno, M. Okamoto, and K. Nukada, *Tetrahedron Lett.*, 4047 (1965); (b) N. S. Zefirov, P. P. Kadzyauskas, Yu. A. Ustynyuk, and Yu. K. Yur'ev, *Zh. Obshch. Khim.*, **36**, 764 (1966); (c) B. D. Ponder, T. E. Walton, and N. Y. Pollack, *J. Org. Chem.*, **33**, 3957 (1968); (d) M. M. Rogić, T. R. Demmin, R. Fuhrmann, and F. W. Koff, *J. Am. Chem. Soc.*, **97**, 3241 (1975).
(14) J. G. Aston, D. Menard, and M. G. Mayberry, *J. Am. Chem. Soc.*, **54**, 1530 (1932); (b) J. G. Aston and M. G. Mayberry, *ibid.*, **57**, 1888 (1935); (c) Y. Ogata, Y. Furuya, and M. Ito, *ibid.*, **85**, 3649 (1963); (d) Y. Ogata, Y. Furuya, and M. Ito, *Bull. Chem. Soc. Jpn.*, **37**, 1414 (1964); (e) D. T. Manning and H. A. Stansbury, Jr., *J. Am. Chem. Soc.*, **81**, 4885 (1959); (f) E. J. Moriconi, F. J. Creegan, G. K. Donovan, and F. A. Spano, *J. Org. Chem.*, **28**, 2215 (1963); (g) H. Stetter, R. Engl and H. Ranhut, *Chem. Ber.*, **91**, 2882 (1958).
(15) R. B. Woodward and W. von E. Doering, *J. Am. Chem. Soc.*, **67**, 860

(1945).
(16) V. Meyer and J. Zublin, *Chem. Ber.*, **11**, 693 (1878); (b) W. Dieckmann and A. Groeneveld, *ibid.*, **33**, 600 (1898); (c) L. Bouveault and A. Wahl, *Bull. Soc. Chim. Fr.*, **31**, 677 (1904); (d) R. Locquin, *ibid.*, **31**, 1070 (1904); (e) L. Bouveault and R. Locquin, *ibid.*, **31**, 1153 (1904); **35**, 956 (1906); *C. R. Hebd. Seances Acad. Sci.*, **141**, 116 (1905); (f) W. Wislicenus and R. Grutzner, *Chem. Ber.*, **42**, 1940 (1909); (g) N. Hall, J. E. Hynes, and A. Lapworth, *J. Chem. Soc.*, **107**, 136 (1915); (h) H. MacIlwain and G. M. Richardson, *Biochem. J.*, **33**, 44 (1939); (i) M. F. Godfrin, *J. Pharm. Chim.*, **30**, 321 (1939); (j) K. E. Hamlin and W. H. Hartung, *J. Biol. Chem.*, **145**, 349 (1942).
(17) J. Schmidt and K. T. Widmann, *Chem. Ber.*, **42**, 497, 1886 (1909); (b) J. Schmidt and A. Haid, *Justus Liebigs Ann. Chem.*, **377**, 23 (1910); (c) J. Schmidt and H. Dieterle, *ibid.*, **377**, 30 (1910); (d) A. Hantzsch and O. Wohlbruck, *Chem. Ber.*, **20**, 1320 (1887); (e) W. Dieckmann, *ibid.*, **33**, 579 (1900); (f) F. Conrad and C. A. Bischoff, *Justus Liebigs Ann. Chem.*, **209**, 211 (1881); (g) L. Bouveault and R. Locquin, *Bull. Soc. Chim. Fr.*, **31**, 1061 (1904); (h) V. Meyer, *Chem. Ber.*, **10**, 2076 (1877); (i) S. Wleugel, *ibid.*, **15**, 1050, 1057 (1882); (j) A. Furth, *ibid.*, **16**, 2180 (1883); (k) J. Ceresole, *ibid.*, **15**, 1326 (1882); (l) A. C. Onischenko, *Zh. Obshch. Khim.*, **11**, 197 (1941); (m) R. H. Barry and W. H. Hartung, *J. Org. Chem.*, **12**, 460 (1947); (n) R. H. Barry, A. M. Mattocks, and W. H. Hartung, *J. Am. Chem. Soc.*, **70**, 693 (1948).
(18) I. Donati, G. Sioli, and M. Taverna, *Chim. Ind. (Milan)*, **50**, 997 (1968); (b) L. Giuffre, E. Tempesti, G. Sioli, M. Forneroli, and G. Airoldi, *Chem. Ind. Int. (Engl. Transl.)*, 1098 (1971); *Chim. Ind. (Milan)*, **55**, 258 (1973); *Hydrocarbon Process.*, **52**, 199 (1973).
(19) Pritzkow and his co-workers investigated nitrosation and the fragmentation of various α-nitrosocarbonyl systems: (a) K. Smeykal, W. Pritzkow, G. Mahler, K. Fretschmann, and E. Ruhlmann, *J. Prakt. Chem.*, (4), **30**, 126 (1965); (b) W. Pritzkow and W. Rosler, *Justus Liebigs Ann. Chem.*, **703**, 66 (1967); (c) W. Pritzkow and H. Thieme, *J. Prakt. Chem.*, (4), **36**, 180 (1967); (d) K. Lunkwitz, W. Pritzkow, and G. Schmidt, *ibid.*, (4), **37**, 320 (1968); (e) C. Forster, W. Kiersling, M. Liebing, W. Pritzkow, and P. Rudloff, *ibid.*, (3), **311**, 370 (1969). Similarly, *tert*-α-nitroso intermediates which result from the addition of a nitrosating reagent to certain enol ethers[20] and enamines[20,21] are undergoing the carbon–carbon bond cleavage reactions.[22]
(20) K. A. Oglobiin and D. M. Kunovskaya, *J. Org. Chem. USSR (Engl. Transl.)*, **4**, 897 (1968); (b) J. R. Mahajan, G. A. L. Ferreira, and H. C. Araujo, *Chem. Commun.*, 1078 (1972).
(21) J. R. Mahajan, G. A. L. Ferreira, H. C. Araujo, and B. J. Nunes, *Synthesis*, 313 (1973).
(22) See also Y. L. Chow. *J. Am. Chem. Soc.*, **87**, 4642 (1965), and more recent papers by the same author.
(23) A. Werner and A. Piguet, *Chem. Ber.*, **37**, 4295 (1904); (b) A. Werner and T. Detscheff, *ibid.*, **38**, 69 (1905); (c) A. H. Blatt and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 1148 (1934); (d) R. L. Autrey and P. W. Scullard, *ibid.*, **87**, 3284 (1965); (e) R. A. Hill, *J. Org. Chem.*, **27**, 29 (1962); (f) M. Ohno, N. Naruse, S. Torimitsu, and I. Teresawa, *J. Am. Chem. Soc.*, **88**, 3168 (1966); (g) C. W. Shoppee and S. K. Roy, *J. Chem. Soc.*, 3774 (1963); (h) A. Hassner, and N. A. Wentworth, *Chem. Commun.*, 44 (1965), and references therein. For a general discussion of fragmentation reactions, see for example, C. A. Grob in "Theoretical Organic Chemistry", Report on the Kekule Symposium, London, 1958, p 114; *Angew. Chem., Int. Ed. Engl.*, **8**, 535 (1969).
(24) A. F. Ferris, G. S. Johnson, and F. E. Gould. *J. Org. Chem.*, **25**, 496 (1960).
(25) M. Kataoka and M. Ohno, *Bull. Chem. Soc. Jpn.*, **46**, 3474 (1973).
(26) F. M. Jaeger and J. A. Van Dijk, *Proc. Acad. Sci. Amsterdam*, **39**, 384 (1936).
(27) K. Singer and P. A. Vamplew, *J. Chem. Soc.*, 3052 (1957).
(28) A much faster proton elimination from the α'-carbon (eq 9), rather than from the α-carbon atom (eq 8), seems to be a consequence of at least two factors. Evidently, the axial hydrogen of the α'-carbon is well suited for the elimination, because its bonding orbital is parallel with the empty orbital on the sp^2 carbon atom, a well-documented requirement for the facile proton elimination in cyclohexane systems.[29] Furthermore, it seems that the nitroso group in the α-nitrosocyclohexanone, similarly as in the α-nitrocyclohexanone, may be in the axial position. Consequently, the α-hydrogen will be in the equatorial position and, hence, in a less favorable conformation for an efficient elimination. Thus, the indicated elimination leading to 2-hydroxy-3-nitrosocyclohexene, a necessary intermediate for further nitrosation (eq 10) should predominate. However, it is necessary to emphasize that this explanation does not have an experimental support, and hence, the precise reasons for the above mentioned behavior are unknown at this time.
(29) See, for example, H. O. House: "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 336.
(30) It is of interest to note that in the first edition of his well-known book, Ingold considered the addition of nitrosyl chloride to a carbon–carbon double bond a typical electrophilic addition.[31] However, in the period between the first and second editions, the "understanding" of the mechanism of this reaction "advanced" to the point that Ingold was not so sure, one way or the other, and he did not discuss it in the second edition (1969).[38]
(31) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1953, p 669.
(32) D. G. Boller and G. H. Whitfield, *J. Chem. Soc.*, 2773 (1964).
(33) A. Nenz and G. Ribaldone, *Chim. Ind. (Milan)*, **49**, 43 (1967).
(34) L. Kaplan, H. Kwart, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **82**, 234 (1960).
(35) For the formation of 1-hydroxy-2-(ω-carbomethoxybutyl)4,5,6,7-tetrahydrobenzimidazole 3-oxide, an unusual product from the nitrosation of cyclohexanone, see: M. M. Rogić, M. T. Tetenbaum, and M. D. Swerdloff, to be published.
(36) J. A. Leermakers and H. C. Ramsperger, *J. Am. Chem. Soc.*, **54**, 1837 (1932).
(37) C. C. Adison and J. Lewis, *Q. Rev., Chem. Soc.*, **9**, 115 (1955).
(38) E.g., C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2d ed, Cornell University Press, Ithaca, N.Y., 1969, p 832.
(39) H. M. E. Cardwell and A. E. H. Kilner, *J. Chem. Soc.*, 2430 (1951).
(40) The precise structure of the nitrosating agent is not known. It is possible that $NO^+BF_3OH^-$ exists in equilibrium with $NO^+BF_4^-$, $B(OH)_3$, HONO, and $NO^+B(OH)_4^-$.
(41) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **7**, 321 (1968). Strictly speaking, an α-nitrosocarbonium ion is not a 1,3-dipolar ion and this reaction cannot be classified as a *1,3-dipolar cycloaddition reaction;* however, the presence of a free electron pair on the nitrogen makes the indicated addition a definite possibility. An alternative mechanism, which involves an α,β-unsaturated nitroso compound that can arise by proton elimination from the carbonium ion, followed by a 1,4-ene reaction with the carbonyl group, and subsequent isomerization of the 1,3-dioxa-4-azacyclohex-4-ene intermediate to a 1-oxa-4-azacyclopent-3-ene 4-oxide structure, cannot be entirely ruled out.
(42) When a tertiary alcohol was used, the reaction was carried out in the presence of a slight excess of anhydrous sodium sulfate (suspension).
(43) The reaction was carried out under essentially the same reaction conditions as in ref 25, which claims the synthesis of α-oximinocyclohexanone. In our hands, this procedure provides **6** as the major product.
(44) In principle, the reaction of the α-nitrosocyclohexylmethyl carbonium ion with the carbonyl group can take place from both faces of the cyclohexane ring. It is likely, however, that the pathway leading to the equatorial C–O–bond would be favored. Even if the formation of the C–O and N–C bonds is stereospecific and cis, this should not be taken as evidence for the concerted suprafacial process.
(45) M. M. Rogić, and J. Vitrone, *J. Am. Chem. Soc.*, **94**, 8642 (1972).
(46) M. M. Rogić, J. Vitrone, and K. P. Klein, unpublished observations.
(47) D. P. Roelofsen, E. R. J. Wils, and H. Van Bekkum, *Recl. Trav. Chim. Pays-Bas*, **90**, 1141 (1971); (b) N. B. Lorette, W. L. Howard, and J. H. Brown, *J. Org. Chem.*, **24**, 1731 (1959).
(48) E. Schmitz and I. Eichorn in "The Chemistry of the Ether Linkage", S. Patai, Ed., Interscience, New York, N.Y., 1967, Chapter 7.
(49) M. M. Rogić, K. P. Klein, J. M. Balquist, and B. C. Oxenrider, *J. Org. Chem.*, **41**, 482 (1976).
(50) M. P. Doyle, W. Wierenga, and M. A. Zaleta, *J. Org. Chem.*, **37**, 1597 (1972).
(51) J. M. Kliegman and R. K. Barnes, *J. Org. Chem.*, **37**, 4223 (1972).
(52) M. M. Rogić, K. P. Klein, T. R. Demmin, and B. C. Oxenrider, *J. Am. Chem. Soc.*, submitted for publication.
(53) M. M. Rogić, J. F. Van Peppen, K. P. Klein, and T. R. Demmin, *J. Org. Chem.*, **39**, 3424 (1974), and unpublished observations.
(54) See, for example, ref 5c.
(55) J. B. Hendrickson, D. J. Cram, and G. S. Hammond, "Organic Chemistry", 3d ed, McGraw-Hill, New York, N.Y., 1970, p 540.
(56) "Process Survey. Caprolactam", *Eur. Chem. News*, *Caprolactam Suppl.* May 8, 1969.
(57) V. Schmidt and P. Grafen, *Justus Liebigs Ann. Chem.*, **656**, 97 (1962).
(58) A. D. Allen, *J. Chem. Soc.*, 1968 (1954).
(59) W. L. Semon and V. R. Damerell, "Organic Syntheses", Collect. Vol. 2, Wiley, New York, N.Y., 1943, p 204.
(60) P. Gray, P. Rathbone, and A. Williams, *J. Chem. Soc.*, 2620 (1961).
(61) P. Gray and M. J. Pearson, *J. Chem. Soc.*, 5725 (1964).
(62) Hydrogen chloride should be introduced into the solution of methanol in sulfur dioxide; the solubility of hydrogen chloride in sulfur dioxide is not great and it may be difficult to dissolve the needed amount in the absence of the alcohol.
(63) Prepared according to the procedure of F. Agalini and R. Bonnett, *Can. J. Chem.*, **40**, 181 (1962).
(64) The products were characterized by the usual analytical and spectroscopic means and the corresponding spectra were in agreement with the expected structures.
(65) A. Arbuzow, *Chem. Zentralbl.*, **79**, 1340 (1908).
(66) Prepared by an azeothropic distillation of water in the presence of ca. tenfold excess of the alcohol.
(67) We are grateful to Dr. Marvin T. Tetenbaum for performing these experiments.