Nitrosation in Organic Chemistry. General Synthesis of α-Nitroso Ketone Acetal Dimers and α-Oximino Ketone Acetals and Mechanism of Their Fragmentation Reactions

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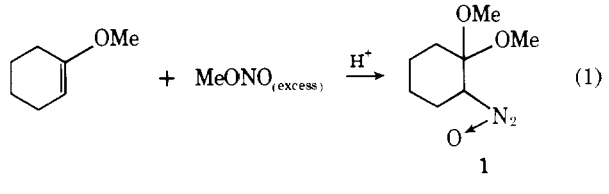
The reaction of 1-methoxycyclohexene with methyl nitrite either in sulfur dioxide solution in the presence of sulfuric acid, boron trifluoride etherate, or some other acid catalyst, or more effectively in an excess of methyl nitrite as solvent, provides 1,1-dimethoxy-2-nitrosocyclohexane dimer in essentially quantitative yield. Other cyclic and open chain enol ethers behave similarly, providing the corresponding α-nitroso ketone acetal dimers in good yields. Transformation of the α-nitroso ketone acetal dimers to the corresponding α-oximino ketone acetals can be easily achieved either by heating in a suitable solvent or in the presence of acid or base catalysts. α-Oximino ketone acetals undergo reaction with ortho esters to give an oxime–ortho ester adduct, which in the presence of an acid catalyst provides an oxime–alkoxycarbonium ion that undergoes rapid fragmentation. For example, 1,1-dimethoxy-2-oximinocyclohexane reacts with trimethyl orthoformate to give the corresponding oxime–orthoformate adduct, which then yields methyl 5-cyanopentanoate and trimethyl orthoformate. This cleavage of α-oximino ketone acetals can be carried out even with a catalytic amount of an ortho ester, or more effectively with dialkoxyalkylcarbonium tetrafluoroborates as catalysts. α-Nitrosocyclohexanone dimethyl acetal dimer underwent a more facile fragmentation to the methyl 5-cyanopentanoate than the α-oximinocyclohexanone dimethyl acetal under the same reaction conditions, suggesting that the previously discussed nitrosolysis reaction involves fragmentation of the α-nitroso ketone acetal monomer rather than the fragmentation of the α-oximinocyclohexanone acetal.

In the preceding paper of this series we described the nitrosolysis reaction—a novel carbon–carbon bond cleavage effected through nitrosation of various ketones and ketone acetals.[1] The success of the nitrosolysis reaction was attributed to an efficient trapping of the corresponding α-nitrosohydroxy- or α-nitrosoalkoxycarbonium ion intermediates with an alcohol and facile in situ cleavage of the resulting α-nitroso hemiacetals or α-nitroso acetals. Our proposed mechanism for the nitrosolysis of ketone acetals involves a multistep reaction sequence. We suggested that the cleavage of α-nitroso acetal involves formation of the corresponding ortho ester–oxime intermediates which is followed by an intermolecular dehydration to the ester nitrile products, although an equally plausible alternative, the competitive isomerization of the intermediate α-nitroso ketone acetals to the α-oximino ketone acetals, followed by a Beckmann fragmentation of the latter to the same product, remained to be considered.[1,2] It was also demonstrated that 1,1-diethoxy-2-nitroso-4-*tert*-butylcyclohexane dimer was the intermediate in the nitrosolysis of the ketone acetal.[1] In the present paper we will describe first a general method for preparation of α-nitroso ketone acetal dimers and α-oximino ketone acetals and then discuss briefly the mechanism of the cleavage of α-oximino ketone acetals.

Results and Discussion

1. Preparation of α-Nitroso Ketone Acetal Dimers. (a) General Consideration. A possible mechanism for the nitrosolysis of cyclohexanone diethyl acetal was presented earlier.[1] In a typical experiment cyclohexanone diethyl acetal provided an 87% yield of the ethyl 5-cyanopentanoate and about 12% ethyl 6,6-diethoxyhexanoate.[1] The formation of the ethyl 6,6-diethoxyhexanoate can be significantly suppressed by carrying out the nitrosolysis reaction under essentially anhydrous conditions.[1] However, even under these conditions, reaction between the ortho ester oxime and ethyl nitrite would still lead to the same side products if the rate of this reaction were sufficiently fast compared to the rate of oxime dehydration. Thus, it appeared that the formation of the ester acetal byproduct could be totally eliminated only if complete reaction between ethyl nitrite and the enol ether intermediate were achieved irreversibly before any significant carbon–carbon bond cleavage takes place. Since secondary nitroso compounds generally dimerize rapidly,[3] an increase in the rate of the α-nitroso ketone acetal formation[1] should also lead to an increase in the rate of nitroso dimer formation. Clearly, if one were able to stop the reaction at the α-nitroso ketone acetal dimer(s) and then to convert the dimer itself to the ester nitrile, the byproduct formation[1] would be eliminated.

(b) α-Nitrosocyclohexanone Dimethyl Acetal Dimer. The failure of cyclohexanone dimethyl acetal to undergo the nitrosolysis reaction under the usual reaction conditions was attributed to an unfavorable equilibrium between the acetal and enol ether.[1] While cyclohexanone enol ethers[4] react readily with liquid sulfur dioxide,[5] addition of cyclohexanone methyl enol ether to a solution of methyl nitrite in liquid sulfur dioxide at −40 °C in the presence of a catalytic amount of either sulfur trioxide, 100% sulfuric acid, or boron trifluoride etherate provided[6] the desired 1,1-dimethoxy-2-nitrosocyclohexane dimer **1** and small amounts of the 1,1-dimethoxy-2-oximinocyclohexane **2**. Crystallization of the crude reaction product afforded pure **1** in 65–75% yield. However, when cyclohexanone methyl enol ether was added dropwise to an excess of methyl nitrite containing a catalytic amount of 100% sulfuric acid or boron trifluoride etherate at −20 °C, an essentially quantitative yield of pure **1** was obtained[6] (eq 1).



(1)

1

The α-nitrosocyclohexanone acetal dimer **1** is a white, stable solid, which on careful heating melted at 108–110 °C to give a blue nitroso monomer. If cooled immediately the blue melt reverts back to the nitroso dimer. IR and UV spectra of both unheated and heated nitroso dimers indicated that the configuration of the nitrogen–nitrogen double bond was *E*. A fast heating of the dimer **1**, or further heating of the blue melt, affords the expected 1,1-dimethoxy-2-oximinocyclohexane (**2**). Further heating of the melted oximino acetal resulted in exothermic reaction accompanied by evolution of a gas.

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Table I. Preparation of Various α-Nitroso Ketone Acetal Dimers[a,b]

enol ether (R) of ketone	registry no.	R in RONO	registry no.	solvent	product	yield, %
cyclohexanone, Me	931-57-7	Me	624-91-9	SO_2	**1**	75–85
cyclohexanone, Me		Me		MeONO	**1**	100
cyclohexanone, Et		Et	109-95-5	EtONO	**1A**[c]	75
cyclohexanone, Et		Me		MeONO	**1B**[d]	70
4-*tert*-butylcyclohexanone, Me	57466-12-3	Me		MeONO	**5**	95
4-*tert*-butylcyclohexanone, Et	3393-97-3	Et		SO_2	**5A**[e]	
4-*tert*-butylcyclohexanone, Et		Me		MeONO	**5B**[f]	(74)
4-*tert*-butylcyclohexanone, Me		Et		EtONO	**5C**[f]	(48)
cyclopentanone, Me	1072-59-9	Me		MeONO	**4**[g]	70
cyclooctanone, Me	50438-51-2	Me		MeONO	**6**	93
cyclododecanone, Me	32400-32-1	Me		MeONO	**7**[h]	100
4-heptanone, Me	61142-44-7	Me		MeONO	**8**[i]	85
6-undecanone, Me	68226-27-7	Me		MeONO	**9**[j]	93
7-tridecanone, Me	64950-77-2	Me		MeONO	**10**[k]	(70)
2-heptanone, Me		Me		MeONO	*l*	
camphor, Me	64950-75-0	Me		MeONO	*l*	

[a] General experimental procedure presented in Experimental Section. [b] Generally, the isolated nitroso dimers were a mixture of the corresponding *dl* pair and *meso* compound; see also ref 6. [c] The product was a mixture of the dimer and the oximino acetal accompanied with 5–10% of **20**. [d] Low-melting solid. [e] This dimer was reported earlier in ref 1. [f] The dimer contaminated with significant amounts of the isomeric α-oximino acetal, see Experimental Section. [g] Contaminated with a small amount of the oximino acetal. [h] Insoluble in common solvents at room temperature. [i] Contaminated with some oximino acetal. [j] Semisolid at room temperature. [k] Crude product as a yellow oil containing predominantly the isomeric oximino acetal. [l] A mixture of several products resulting from further reaction of the initial nitrosation products. Not characterized.

Cooling and crystallization provided a white solid, mp 151–152 °C, which was identical with 2-methoxy-3-oximinocyclohexene (**3**) prepared previously.[1]

(c) Preparation of Other α-Nitroso Ketone Acetal Dimers. Reaction of methyl nitrite with enol ethers of cyclopentanone, 4-*tert*-butylcyclohexanone, cyclooctanone, and cyclododecanone is a convenient procedure for preparation of the corresponding α-nitroso ketone acetal dimers[6] **4, 5, 6,** and **7**, while the reaction with enol ethers of 4-heptanone, 6-undecanone, and 7-tridecanone gave the corresponding open chain dimers **8, 9,** and **10**. The reactions with the enol ether of 2-heptanone or with the hindered camphor enol ether were complex, the major products being either the corresponding α-oximino ketone acetals or products resulting from cleavage. A similar reaction of cyclohexanone ethyl enol ether with ethyl nitrite gave the 1,1-diethoxy-2-nitrosocyclohexane dimer, which was considerably more soluble in ethyl nitrite leading to increased amount of oxime formation. The results of these reactions are summarized in Table I.

2. The Isomerization of α-Nitroso Ketone Acetal Dimers to the α-Oximino Ketone Acetals. The isomerization of α-nitroso ketone acetal dimers to the α-oximino ketone acetals can be accomplished in a variety of ways[3a-d,7,8] (see Experimental Section).

3. (a) Preparation and Fragmentation of Oxime–Ortho Ester Adducts. Earlier we reported on a general method for oxime ortho esters preparations and fragmentation to nitriles, esters, and alcohol.[2] In the absence of an acid catalyst oxime–ortho ester adduct formation does not take place to an appreciable extent. However, heating a mixture with continuous removal of 1 equiv of the alcohol followed by vacuum distillation affords the corresponding oxime ortho ester adducts.[2]

$$RCH{=}NOH + R^1C(OR^2)_3 \overset{\Delta}{\rightleftarrows} RCH{=}NOCR^1(OR^2)_2 + R^2OH \quad (2)$$

The oxime ortho ester adducts are generally stable compounds, under neutral conditions. However, they do undergo a fragmentation reaction (eq 3) in the presence of various acid catalysts including sulfur dioxide.[2]

$$RCH{=}NOCR^1(OR^2)_2 \xrightarrow{H^+} RCN + R^1COOR^2 + R^2OH \quad (3)$$

The precise mechanism of this fragmentation has not yet been established, but it seems reasonable that the reaction proceeds via reversible formation of a conjugate acid intermediate (eq 4), followed by rate-determining formation of an oxime alkoxy carbonium ion and subsequent fast fragmentation of the latter to the reaction products (eq 5 and 6).

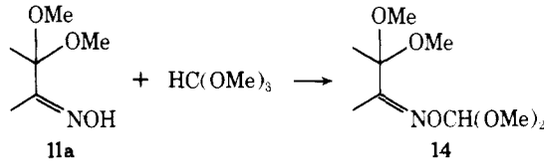
$$RCH{=}NOCR^1(OR^2)_2 + H^+ \rightleftharpoons RCH{=}NOCR^1(OR^2)_2H^+ \quad (4)$$

$$RCH{=}NOCR^1(H,\overset{+}{O}R^2,OR^2) \overset{\text{slow}}{\rightleftharpoons} RCH{=}\overset{+}{N}OCR^1OR^2 + R^2OH \quad (5)$$

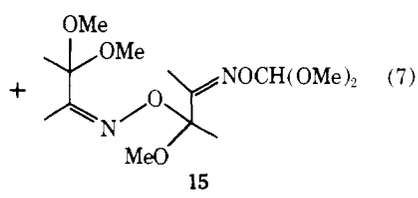
$$RCH{=}\overset{+}{N}OCR^1OR^2 \xrightarrow{\text{fast}} RCN + R^1COOR^2 + H^+ \quad (6)$$

In order to find whether similar mechanisms may operate in the Beckmann fragmentation of α-oximino ketones and α-oximino ketone acetals,[9,10] we prepared several representative members of these systems and briefly investigated their fragmentation reactions.

The commercially available 3-oximino-2-butanone and benzilmonoxime were converted to the corresponding α-oximino ketone acetals **11a** and **11b** by an acid catalyzed reaction with an excess of methanol in the presence of an ortho ester.



11a **14**

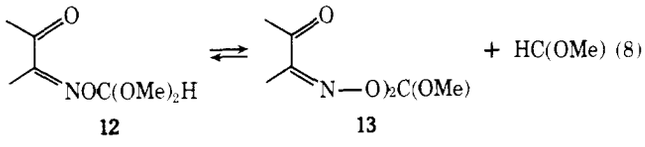


15 (7)

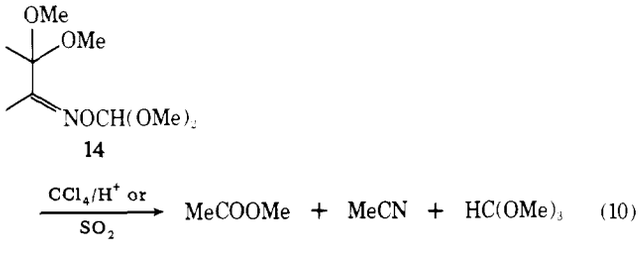
An acid-catalyzed reaction of 3-oximino-2-butanone with an excess of trimethyl orthoformate provided 2,3-butanedione monoxime dimethyl orthoformate **12.** When the α-oximino acetal **11a** was heated with a slight excess of trimethyl orthoformate and the liberated methanol removed by distillation, in addition to the expected α-oximino ketone acetal–orthoformate adduct **14,** a "mixed" dimeric oxime acetal–oxime orthoformate adduct **15** was also formed (eq 7). The formation of the byproduct **15** can be eliminated by carrying the reaction with a large excess of the ortho ester in the presence of a catalytic amount of methanesulfonic acid.

The 2,2-dimethoxy-3-oximinobutane **11a** undergoes Beckmann fragmentation in liquid sulfur dioxide at room temperature to give methyl acetate, acetonitrile, and methanol. Fragmentation of **11b** in sulfur dioxide also occurred at room temperature, although at a slower rate, to give methyl benzoate, benzonitrile, and methanol.

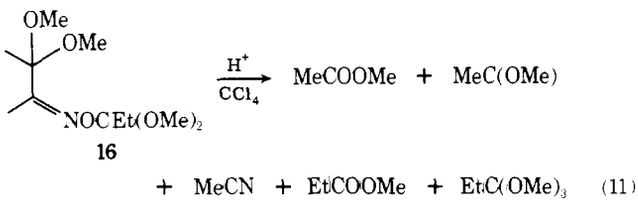
Under similar reaction conditions the oxime–orthoformate adduct **12** underwent a reversible disproportionation to give the corresponding diadduct **13** and trimethyl orthoformate, which was followed by a slower fragmentation to methyl acetate, acetonitrile, and methyl formate (eq 8 and 9).



Surprisingly, a solution of the α-oximino acetal–orthoformate adduct **14,** either in carbon tetrachloride containing a catalytic amount of methanesulfonic acid or in liquid sulfur dioxide, fragmented rapidly and exothermically at room temperature to give *methyl acetate, acetonitrile, and trimethyl orthoformate* (eq 10). Similar treatment of the

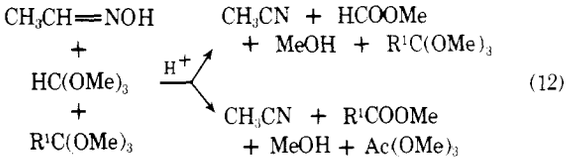


"mixed" ortho ester adduct **15** gave *methyl acetate, acetonitrile, and trimethyl orthoformate in the molar ratios of 2:2:1.* The acid-catalyzed fragmentation of the adduct of 3-oximino-2-butanone dimethyl acetal with trimethyl orthopropionate (**16**) provided a mixture of acetonitrile, methyl acetate, methyl propionate, trimethyl orthoacetate, and trimethyl orthopropionate.



The reaction of 1,1-dimethoxy-2-propanone oxime dimethyl orthoacetate **17,** however, gave only acetonitrile, methyl acetate, and trimethyl orthoformate.

The relative rates at which the various ortho esters dehydrate acetaldoxime deserve brief comment at this point. In a series of competing reactions of acetaldoxime with a 1:1 mixture of trimethyl orthoformate and a different ortho ester in the presence of a catalytic amount of acid (eq 12), we established the following dehydration reactivity sequence: orthopropionate > orthoacetate > orthobenzoate ≫ orthoformate.



The results of these experiments, summarized in Table II, suggest that the rate differences reflect the ability of the substituent R^1 (R^1 = H, Me, Et, Ph) on the "acyl" carbon atom of the oxime–ortho ester adduct to stabilize the developing positive charge on this carbon in the rate-determining step (eq 5).

(b) Mechanism of the Fragmentation of α-Oximino Ketone Acetal–Ortho Ester Adducts.[9,10] Fragmentations

Scheme I

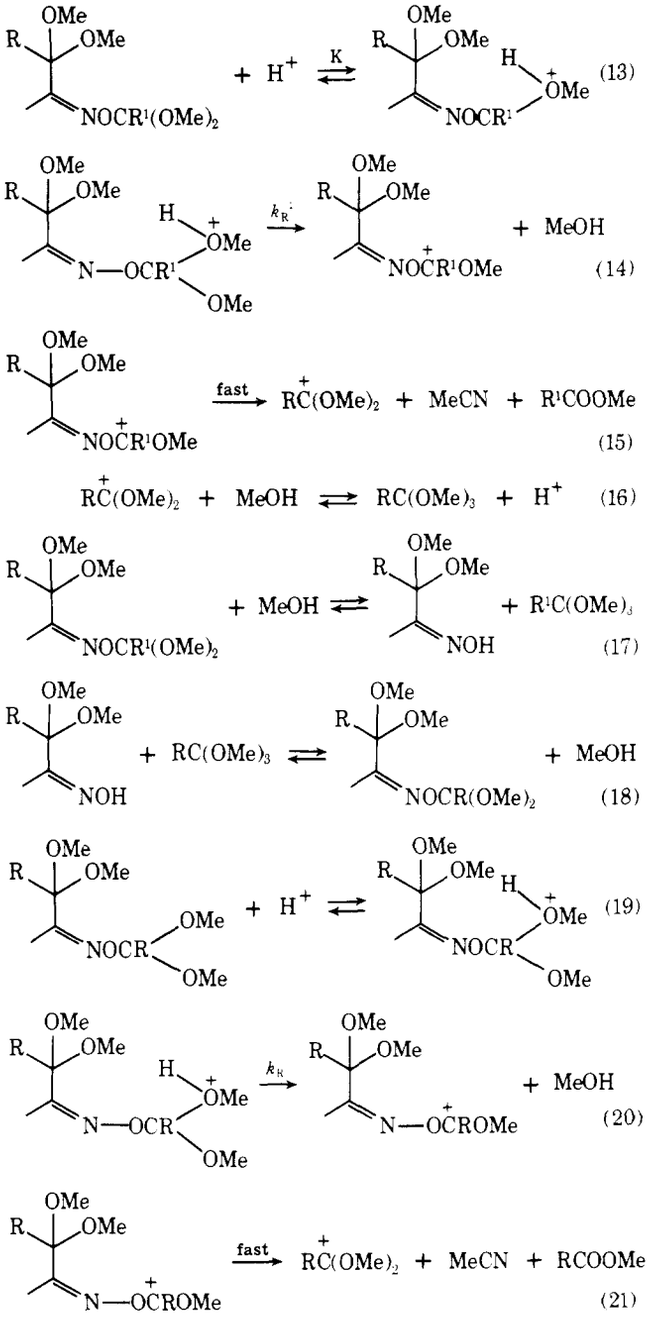


Table II. Relative Reactivities of Ortho Esters in Dehydration of Acetaldoxime[a,b]

$HC(OMe)_3$/ $R^1C(OMe)_3$	MeCN	HCOOMe/ R^1COOMe	$HC(OMe)_3$/ $R^1C(OMe)_3$
$HC(OMe)_3$	100	100	
$HC(OMe)_3$/$MeC(OMe)_3$	100	4/96	96/4
$HC(OMe)_3$/$EtC(OMe)_3$	100	trace/100	100/trace
$HC(OMe)_3$/$PhC(OMe)_3$	100	12/88	88/12

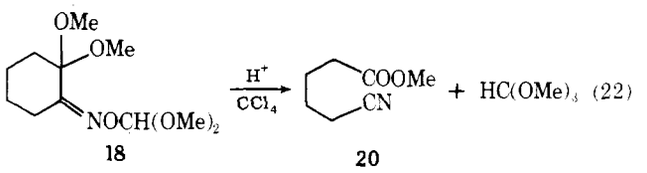
[a] See eq 12. [b] For experimental details see the Experimental Section.

of α-oximino acetal–ortho ester adducts may involve a similar mechanism to the dehydration of aldoxime–ortho ester adducts (eq 4–6). Presumably an intermediate conjugate acid is formed reversibly (Scheme I, eq 13), followed by rate-determining formation of an oxime–alkoxycarbonium ion (eq 14), and subsequent fast fragmentation of the latter to the reaction products (eq 15 and 16).

When the fragmentation affords an ortho ester $RC(OMe)_3$ (eq 16), that is different from the original ortho ester $R^1C(OMe)_3$ used in preparation of the oxime ortho ester adduct, a rapid exchange (eq 16–18) followed by fragmentation will generate again the same ortho ester $RC(OMe)_3$ (eq 19–21). If the relative rates k_R/k_{R^1} of two possible fragmentation processes (i.e., eq 14 vs. eq 20) are dependent on the abilities of the substituents R^1 and R to stabilize the developing positive charge in the respective rate-determining steps, then the fragmentation rate of various oxime–ortho ester adducts should parallel the pattern observed in dehydration of aldoximes with different ortho esters (Table II). Indeed, the experiments with the oxime–ortho ester adducts **14** (eq 10), **16** (eq 11), and **17** clearly established that adducts derived from the ortho ester $RC(OMe)_3$ (R = Me, Et) fragmentated more rapidly than those derived from the trimethyl orthoformate $R^1C(OMe)_3$ (R^1 = H).

This mechanism would predict that the fragmentation of 2,2-dimethoxy-3-oximinobutane (**11a**) and 1,1-dimethoxy-2-oximinocyclohexane (**2**) could be achieved even with a catalytic amount of trimethyl orthoformate or some other ortho ester.[12] It is expected that the initially produced dialkoxycarbonium ion would reenter the reaction cycle and thus drive the reaction to completion. However, this catalyzed fragmentation, unlike the fragmentation of the oxime–ortho ester adduct itself, proceeds with concomitant generation of an equivalent of alcohol which may gradually suppress the formation of the required oxime–ortho ester adduct intermediate (e.g., eq 18), and thereby retard the fragmentation process. In the following section we will discuss practical aspects of this approach.

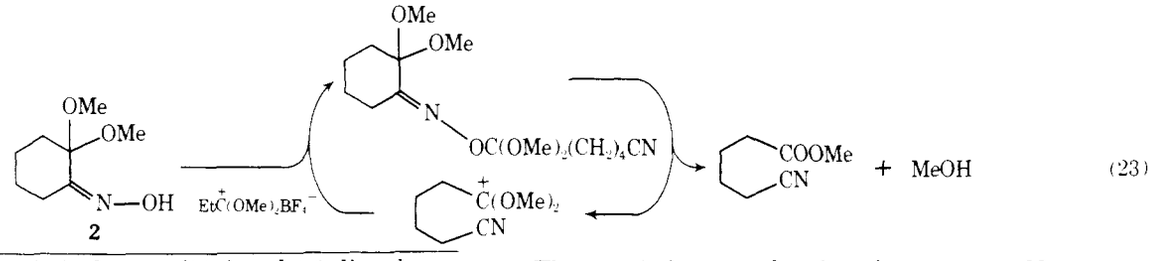
4. Beckmann Fragmentation of 1,1-Dimethoxy-2-oximinocycloalkanes. Reaction of 1,1-dimethoxy-2-oximinocyclohexane (**2**) with an excess of trimethyl orthoformate or trimethyl orthoacetate gave the corresponding adducts **18** and **19.** Addition of a catalytic amount of methanesulfonic acid to a solution of the oxime–orthoformate adduct **18** in carbon tetrachloride at room temperature led to the expected cleavage providing 5-cyanopentanoic acid ester **20,** trimethyl orthoformate, and traces of methyl formate and methanol (eq 22). The same results were also obtained in chloroform or



18 20

sulfur dioxide solutions without added acid catalysts. However, when an attempt was made to achieve the cleavage of the α-oximino acetal **2** with a catalytic amount of trimethyl orthoformate in chloroform at 75 °C, in addition to the desired ester nitrile **20,** a significant amount of the enol ether oxime **3** was also formed. The oxime–orthoacetate adduct **19** under similar reaction conditions provided the ester nitrile **20** and trimethyl orthoacetate in high yield together with methyl acetate and trimethyl 5-cyanoorthopentanoate **21** in a ratio of approximately 7:3. When this reaction was carried out in the presence of an excess of trimethyl orthoacetate, the ortho ester nitrile **21** was formed in more than 90% yield. Interestingly there is no exchange between the oxime–orthoformate **18** and trimethyl orthoacetate, or between oxime–orthoacetate **19** and trimethyl orthoformate in the absence of acid catalyst.

While the attempted cleavage of the 1,1-dimethoxy-2-oximinocyclohexane (**2**) with a catalytic amount of trimethyl orthoformate was only partially successful (vide supra), the acid-catalyzed reaction of **2** with 0.1 equiv of trimethyl orthoacetate in benzene at 80 °C gave a mixture of **20** and **21** in 96% and 3% yield, respectively. Essentially quantitative cleavage was obtained by heating a benzene solution of **2** at 80 °C in the presence of 5 mol % of **21** for 4 h. Finally, the dimethoxyethyl- and dimethoxypropylcarbonium tetrafluoroborates[13,14] were found to be even more efficient catalysts for these transformations. For example, 5 mol % of dimethoxyethylcarbonium tetrafluoroborate converted **2** in methylene chloride solution to the ester nitrile **20** at room temperature in 1 h in essentially quantitative yield (eq 23).



The α-oximino acetals of cyclopentanone **22,** 4-*tert*-butylcyclohexanone **23,** cyclooctanone **24,** and cyclododecanone **25** in methylene chloride in the presence of dimethoxyethylcarbonium tetrafluoroborate as the catalyst all reacted in the same manner providing a high yield of the corresponding ester nitriles **26, 27, 28,** and **29,** respectively. Thus, it appears that the dimethoxyethylcarbonium tetrafluoroborate is the catalyst of choice for converting α-oximino ketone acetals to the corresponding ester nitriles. The transformations of α-oximino ketone acetals and the corresponding oxime–ortho ester adducts discussed above are summarized in Table III.

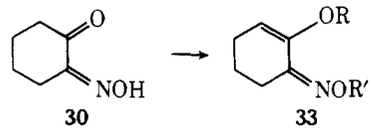
The cleavage of the α-oximino ketone acetals can, of course, be achieved with typical reagents for Beckmann fragmentation of α-oximino ketones, e.g., thionyl chloride in sulfur dioxide at −10 °C or in ether at 0 °C, or tosyl chloride in pyridine at 0 °C. However, the 2-methoxy-3-oximinocyclohexene **3** failed to fragment under all of these conditions. This is perhaps not surprising since it is known that vinyl carbons migrate poorly under standard Beckmann conditions.[15]

Table III. Fragmentation of α-Oximino Ketone Acetals and Oximino Ketone Acetal Ortho Ester Adducts[a]

compd[b]	registry no.	solvent	reagent, mol	catalyst	conditions	products (%)[c]
11a	68226-28-8	SO_2			RT; 6 h	MeCN (100); MeCOOMe (100); MeOH (100)
11b	68226-29-9	SO_2			75 °C; 48 h	PhCN (100); PhCOOMe (100); MeOH (100)
12	68226-30-2	SO_2			RT; 1 week	MeCN (100); MeCOOMe (100); HCOOMe (100)
14	66977-24-0	CCl_4		$MeSO_3H$	RT; 1 h	MeCN (100); MeCOOMe (97); $HC(OMe)_3$ (97); HCOOMe (trace); $MeC(OMe)_3$ (trace)
14		SO_2			RT; 1 h	
16	68226-31-3	CCl_4		$MeSO_3H$	RT; 1 h	MeCN (100); MeCOOMe (~50); EtCOOMe (~50); $MeC(OMe)_3$ (~50); $EtC(OMe)_3$ (~50)
17	66977-25-1	$CHCl_3$		$MeSO_3H$	75 °C; 2 h	MeCN (~60); MeCOOMe (~60); $HC(OMe)_3$ (~60); $MeC(OMe)_3$ (~10); **17** (~10); $((MeO)_2CHC(Me)=NO-)_2CMe(OMe)$ (~10)
2	52540-36-0	SO_2			RT; 24 h	**2** (23); **3** (38);[e] **20** (16)[f]
2		SO_2	1 $HC(OMe)_3$		RT; 24 h	**20** (97); $HC(OMe)_3$ (97); MeOH (100); HCOOMe (trace)
18	66977-21-7	CCl_4		$MeSO_3H$	RT; 24 h	**20** (93); $HC(OMe)_3$ (93); HCOOMe, **21** (traces)
18		SO_2			RT; 1 h	**20** (95); $HC(OMe)_3$ (95); HCOOMe (traces)
19	66977-22-8	$CDCl_3$		$MeSO_3H$	RT; 1 h	**20** (70); **21** (30);[g] $MeC(OMe)_3$ (70); MeCOOMe (30)
19		CCl_4	3 $MeC(OMe)_3$	$MeSO_3H$	RT; 1 h	**21** (90)[c]
2		$CHCl_3$	0.1 $HC(OMe)_3$	$MeSO_3H$	75 °C; 24 h	**20** (~25); **3** (~65)
2		C_6H_6	0.1 $MeC(OMe)_3$	$MeSO_3H$	80 °C; 6 h	**20** (96); **21** (3)
2		CCl_4	1 **21**		80 °C; 24 h	**20** (~100)
2		CCl_4	1 **21**	$MeSO_3H$	RT; 30 min	**20** (~100)
2		C_6H_6	0.05 **21**	$MeSO_3H$	80 °C; 4 h	**20** (~100)
2		CH_2Cl_2		0.05 $EtC(OMe)_2^+BF_4^-$	RT; 1 h	**20** (~93)[c]
22	64950-85-2	CH_2Cl_2		0.05 $EtC(OMe)_2^+BF_4^-$	RT; 1 h	**26** (~90)[d,h]
23	68226-32-4	CH_2Cl_2		0.05 $EtC(OMe)_2^+BF_4^-$	RT; 1 h	**27** (~95)[d,i]
24	64950-92-1	CH_2Cl_2		0.05 $EtC(OMe)_2^+BF_4^-$	RT; 1 h	**28** (~95)[d,j]
25	68226-33-5	CH_2Cl_2		0.05 $EtC(OMe)_2^+BF_4^-$	RT; 1 h	**29** (100)[d,k]
2		SO_2	$SOCl_2$		−10 °C; 25 h	**20** (~100)
2		C_5H_5N	TsCl		0 °C; 3 h	**20** (~61)[d]

[a] For more detail see Experimental Section. [b] Compound **2** stands for 1,1-dimethoxy-2-oxminocyclohexane. Similarly **11a** and **11b** are α-oximino ketone acetals of 3-oximino-2-butanone and benzilmonoxime; **12** = 2,3-butanedione monoxime dimethyl orthoformate; **14** = orthoformate adduct of 2,2-dimethoxy-3-oximinobutane; **16** = orthopropionate adduct of 2,2-dimethoxy-3-oximinobutane; **17** = orthoacetate adduct of 1,1-dimethoxy-2-oximinopropane; **18** = orthoformate adduct of 1,1-dimethoxy-2-oximinocyclohexane; **19** = orthoacetate adduct of 1,1-dimethoxy-2-oximinocyclohexane; **20** = methyl ester of 5-cyanopentanoic acid; **21** = trimethyl 5-cyanoorthopentanoate; **22** = 1,1-dimethoxy-2-oximinocyclopentane; **23** = 1,1-dimethoxy-2-oximino-4-*tert*-butylcyclohexane; **24** = 1,1-dimethoxy-2-oximinocyclooctane; **25** = 1,1-dimethoxy-2-oximinocyclododecane; **26** = methyl 4-cyanobutanoate; **27** = methyl 5-cyano-4-*tert*-butylpentanoate; **28** = methyl 7-cyanoheptanoate; **29** = methyl 11-cyanoundecanoate. [c] By NMR and GLC. [d] Isolated yields. [e] Registry no. 52841-56-2. [f] Registry no. 3009-88-9. [g] Registry no. 2568-83-4. [h] Registry no. 41126-15-2. [i] Registry no. 68226-34-6. [j] Registry no. 61831-05-8. [k] Registry no. 22915-49-7.

(b) Fragmentation of α-Oximinocyclohexanone. Ready access to α-oximinocyclohexanone acetal **2** makes α-oximinocyclohexanone itself readily available. In the past this compound was prepared with considerable difficulty.[16-18] Acid-catalyzed hydrolysis of the α-oximino acetal in wet isopropyl alcohol or tetrahydrofuran provided 2-oximinocyclohexanone (**30**). Acid-catalyzed exchange with ethylene glycol gave the α-oximinocyclohexanone ethylene glycol ketal **31** in high yield. Since previous reports indicated that α-oximinocyclohexanone **30** was stable toward Beckmann fragmentation with sulfuric and phosphoric acid, we briefly investigated several reactions of **30**. First, the above mentioned hydrolysis of the α-oximinocyclohexanone acetal **2** produced only a single isomer of **30** as indicated by ^{13}C NMR analysis. Reaction of **30** with trimethyl orthoformate in chloroform containing an acid catalyst gave the corresponding oxime–orthoformate **32** which was converted to methyl ester nitrile **20** and methyl formate. On the other hand, treatment of the α-oximinocyclohexanone **30** with 1 equiv of tosyl chloride in methylene chloride in the presence of triethylamine afforded **33a** in high yield (eq 24). Base-catalyzed hydrolysis of **33a** gave 5-cyanopentanoic acid and the tosylate of the α-oximinocyclohexanone enol **33b**, which was acylated to the corresponding *N*-acetate **33c**. Reaction of α-oximinocyclohexanone with benzoyl chloride gave **33d**, and similar reaction with ethyl chloroformate led to **33e**.



30 **33**

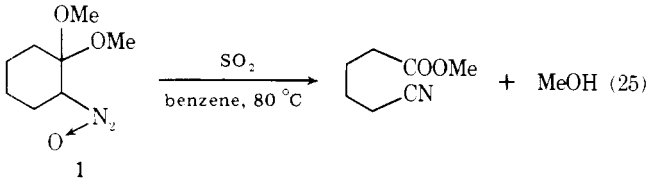
(24)

33a, R = Ts; R′ = $CO(CH_2)_4CN$
b, R = Ts; R′ = H
c, R = Ts; R′ = Ac
d, R = R′ = COPh
e, R = R′ = COOEt

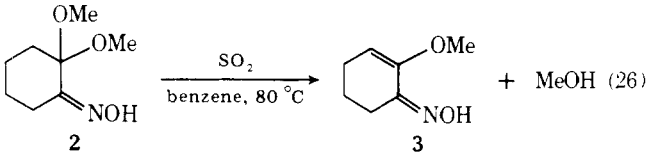
5. Is the α-Oximinocyclohexanone Acetal an Intermediate in the Overall Nitrosolysis of Cyclohexanone Diethyl Acetal? In view of the facile transformations of the α-oximino ketone acetals to the corresponding ester nitriles, it was of interest to establish whether the previously discussed nitrosolysis reaction[1] involves an acid-catalyzed carbon–carbon bond cleavage in the intermediate α-nitroso ketone acetal, followed in situ by dehydration[2] of the resulting ortho ester oxime to the corresponding ester nitrile, rather than the Beckmann fragmentation[9,10] of the isomeric α-oximino ketone acetals resulting from the isomerization of the α-nitroso ketone acetal intermediates.

Beckmann fragmentation of the dimer **1** in sulfur dioxide/methanol containing a catalytic amount of hydrogen chloride gave only a moderate yield of methyl 5-cyanopentanoate **20.** A solution of **1** in liquid sulfur dioxide at room temperature overnight provided the ester nitrile **20** in about 85% yield. NMR analysis of a solution of the α-oximino acetal **2** in liquid sulfur dioxide at room temperature *after 24 h* indicated that in addition to about 23% of unchanged α-oximino ketone acetal **2**, there was about 38% of the enol ether oxime **3**, and only about 16% of the ester nitrile **20.**

When a solution of the nitroso acetal dimer **1** was heated in benzene at 80 °C in the presence of a small quantity of sulfur dioxide, the ester nitrile **20** was obtained in high yield without significant amounts of byproducts (eq 25). On the other hand, the α-oximino ketone acetal **2** under identical conditions afforded only the oximino enol ether **3** (eq 26).



1



2 3

Consequently, the transformations of the nitroso acetal dimer **1** to the ester nitrile **20** in liquid sulfur dioxide and in benzene in the presence of sulfur dioxide were both significantly faster than the similar transformations of the α-oximino ketone acetal **2** under the same conditions, suggesting that the α-oximino ketone acetals probably are not important intermediates[11] in the overall nitrosolysis of ketone acetals.[1]

Conclusion

Reaction of enol ethers of cyclic and symmetrical open chain ketones with methyl nitrite in the presence of a catalytic amount of acid provides the corresponding α-nitroso acetal dimers. The dimers can be converted to the α-oximino ketone acetals in a variety of ways. Under carefully defined conditions α-nitrosocyclohexanone dimethyl acetal undergoes fragmentation to methyl 5-cyanopentanoate more readily than the isomeric α-oximinocyclohexanone dimethyl acetal, suggesting that the α-oximino ketone acetals are not important intermediates in the nitrosolysis reaction. α-Oximino ketone acetals react with ortho esters to give α-oximino ketone acetal ortho ester adducts. In the presence of acid catalysts these adducts fragment to the corresponding nitrile, ester, and the ortho ester, showing that the cleavage reaction can also be achieved directly from the α-oximino ketone acetals in the presence of a catalytic amount of an ortho ester or a dialkoxyalkyl tetrafluoroborate. Similar transformations of the α-oximino ketone acetals of C_5, C_8, C_{12}, and other cyclic ketones provide a convenient preparation of the corresponding ω-nitrogen alkyl esters, which previously were not always readily available. Mechanistic studies have clearly demonstrated that Beckmann fragmentation of α-oximino ketone acetals can be carried out under mild reaction conditions using readily available catalysts. In effect, these transformations represent mild alternatives to the typical Beckmann conditions which generally require strong acids or highly reactive acylating reagents. The readily available α-oximinocyclohexanone dimethyl acetal offers for the first time a simple synthesis of α-oximinocyclohexanone.

Experimental Section

The ketone acetals used in this work were prepared by the usual procedure using an ortho ester as a dehydrating agent,[19] and the enol ethers were prepared from the ketone acetals by acid-catalyzed elimination of the alcohol.[19] The nitrosyl chloride was Matheson Coleman and Bell high purity grade product, and it was generally distilled first from the cylinder into a delivery flask, from which then it was introduced into a reaction mixture as a gas. The ethyl nitrite and methyl nitrite were prepared either by an exchange from a higher boiling alkyl nitrite and the alcohol[20] or from a water solution of sodium nitrite and the alcohol in the presence of sulfuric acid.[21] The sulfur dioxide was Matheson Coleman and Bell anhydrous grade and was passed through Linde AW-300 molecular sieves before condensation.

Boiling and melting points reported are uncorrected. GLC analyses were carried out generally on Hewlett-Packard 5700A instrument 3- or 6-ft columns of either 10% SE-30 on Chromosorb W or the corresponding 10% Carbowax-20M columns. ^{1}H NMR spectra were recorded on either Varian A-60 or Varian T60-A 60 MHz and 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.

1,1-Dimethoxy-2-nitrosocyclohexane Dimer, 1. A 1-L three-neck flask equipped with a mechanical stirrer, a dry ice condenser, and an addition funnel protected with a dry nitrogen atmosphere was placed in a dry ice/acetone bath. The sulfur dioxide (250 mL) was distilled directly into the flask, and then methyl nitrite (29.75 g, 0.487 mol) was distilled into the sulfur dioxide. Freshly distilled boron trifluoride etherate (0.25 mL) was added via syringe and the solution warmed to −15 °C. The addition funnel was charged with 1-methoxycyclohexene (45.8 g, 0.407 mol), and the enol ether was added dropwise with stirring over 20 min. After stirring for an additional 20 min at −15 °C, the deep blue-green solution became yellow-green. The reaction mixture was cooled to −76 °C and poured into 200 mL of cold pentane containing sodium bicarbonate (1–2 g). Evaporation at room temperature left a yellow-green gummy residue, which after treatment with pentane and filtration gave 35 g (50%) of **1**, mp 108–110 °C (see below). Evaporation of the mother liquor followed by similar treatment increased the yield to ca. 65–70%.

The Addition of Methyl Nitrite to 1-Methoxycyclohexene in Methyl Nitrite. General Procedure for the Syntheses of α-Nitroso Ketone Acetal Dimers. A 500-mL, three-neck flask equipped with a mechanical stirrer, a dry-ice condenser, and an addition funnel protected with a dry nitrogen atmosphere was placed in a dry ice/acetone bath. Methyl nitrite (125 g, 2.05 mol) was distilled into the flask, and 20% oleum (0.32 mL) was added as the catalyst. The enol ether (75.4 g, 0.674 mol) was added dropwise from the addition funnel over 1–2 h with stirring at −20 °C. The resulting heavy suspension of a white solid in a blue-green liquid was diluted with petroleum ether (bp 30–60 °C) and ca. 6.0 g of solid sodium bicarbonate was added. Excess methyl nitrite was allowed to distill off, the reaction mixture filtered, and the white solid washed with petroleum ether. The solid was dissolved in dry methylene chloride and the solution was filtered to remove the inorganic materials and evaporated at 0 °C to give 114 g, 97% yield, of **1** as a white powder, mp 108–110 °C: NMR ($CDCl_3$) δ, 5.80 (t, CH-N, 1 H, width at half-height ca. 5.5 Hz), 3.20 (s, OCH_3, 3 H), 3.14 (s, OCH_3, 3 H), and 2.50 and 1.20 (mb, $-(CH_2)_4-$, 8 H); ^{13}C NMR ($CDCl_3$) δ 99.69 (s, $C(OCH_3)_2$), 60.63 (d, CHN), 48.30 (q, OCH_3), 47.64 (q, OCH_3), 28.46 (t, $CC(OMe)_2$), 26.62 (t, CCN), 21.83 (t, CCO), 19.95 (t, CCN).[22]

Anal. ($C_{16}H_{30}N_2O_6$): C,H,N.

1,1-Dimethoxy-2-oximinocyclohexane, 2. (a) From 1 by

Heating. Careful heating of **1** (0.5 g) in a large test tube resulted in melting at 108–110 °C. The deep blue melt was heated until a sudden exothermic color change to yellow occurred. The solid that appeared on cooling was crystallized from ethyl acetate to give **2**, mp 116–117 °C: NMR ($CDCl_3$) δ 9.8 (bs, NOH, 1 H), 3.17 (s, OCH_3, 6 H), 2.5 (m, CH_2=CN, 2 H), 1.6 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 153.19 (s, C=N), 99.44 (s, C=N), 99.44 (s, **C**$(OMe)_2$), 48.52 (q, 2 OCH_3), 35.24 (t, **C**H_2C=N), 25.38 (t, **C**$H_2C(OMe)_2$), 22.84 and 22.25 (2t, -**C**H_2-**C**H_2CC=N).[23]

Anal. ($C_8H_{15}NO_3$): C,H,N.

A similar result was obtained by heating a suspension of **1** (8.6 g, 50 mmol) in 50 mL of methanol until a homogenous solution resulted. Evaporation of a slightly yellow solution left a solid, mp 103–115 °C, which after crystallization as above gave 7.8 g of **2**, mp 116–117 °C (90%).

(b) Base Catalyzed. Addition of a small amount of sodium methoxide to a methanol solution of **1** (1.7 g, 10 mmol in 10 mL) gave 1.6 g of **2** (95%) at room temperature after several hours.

Acid Catalyzed. A solution of **1** in chloroform or methanol containing a catalytic amount of hydrogen chloride was stirred at room temperature and periodically analyzed by NMR. Complete formation of **2** depended on the relative concentration and the amount of the catalyst used. Extended reaction time often led to small amounts of **3**, mp 151–152 °C.

Acid-Catalyzed Equilibration of 2 and 3. A solution of **2** in carbon tetrachloride (ca. 10%) in an NMR tube containing a catalytic amount of methanesulfonic acid and an internal standard was analyzed by NMR at 25 °C. From the relative ratio of the methoxy and olefin signals the change from **2** to **3** was followed. The equilibrium ratio **2**–**3** of 58:42 was reached after 10 days. The same equilibrium was observed when the reaction was carried out with 1 equiv each of **3** and methanol in carbon tetrachloride in an NMR tube containing the acid catalyst.

A list of various α-nitroso ketone acetals, prepared by the above method, is given in Table I, and physical and spectroscopic data are summarized below.

1,1-Diethoxy-2-nitrosocyclohexane Dimer, 1A. The dimer was prepared by addition of the ethyl enol ether (6.3 g, 50 mmol) to an excess of ethyl nitrite (48 g, 640 mmol). Workup as above gave **1a** in 75% yield as a low-melting solid contaminated with a small amount of the isomeric oximinoacetal: NMR ($CDCl_3$) δ 5.83 (s, CHN, 1 H), 3.50 (m, $-OC\mathbf{H}_2CH_3$, 4 H), 3.0–1.4 (bm, 8 H), 1.0 (m, $-OCH_2C\mathbf{H}_3$, 6 H).

1-Ethoxy-1-methoxy-2-nitrosocyclohexane Dimer, 1B. This dimer was prepared as above from the ethyl enol ether (20.4 g, 162 mmol) and methyl nitrite (30.5 g, 500 mmol) in 70% yield: NMR ($CDCl_3$) δ 5.87 (s, CHN, 1 H), 3.48 (dq, $OC\mathbf{H}_2CH_3$, 2 H), 3.23 (s, OCH_3, 3 H), 1.8 (m, 4 H), 1.17 (dt, $C\mathbf{H}_3CH_2$–, 3 H).

Anal. ($C_{18}H_{32}N_2O_6$): C,H,N.

1,1-Dimethoxy-2-nitroso-4-*tert*-butylcyclohexane dimer, 5: mp 146–148 °C; 95% yield; NMR ($CDCl_3$) δ 5.87 (m, C**H**N, 1 H), 3.19 and 3.12 (2 s, OCH_3, 6 H), 2.5–1.0 (bm, 7 H), 0.83 (s, *t*-Bu, 9 H).

Anal. ($C_{24}H_{46}N_2O_6$): C,H,N.

1,1-Diethoxy-2-nitroso-4-*tert*-butylcyclohexane dimer, 5A, was reported earlier.[1]

***r*-1-*tert*-Butyl-*t*-4-ethoxy-*c*-4-methoxy-*t*-3-nitrosocyclohexane Dimer, 5B.** Addition of 1-ethoxy-4-*tert*-butylcyclohexene (3.23 g, 17.7 mmol) to an excess of methyl nitrite (7 mL) with fuming sulfuric acid as catalyst followed by a workup as above gave 3.2 g of **5B** contaminated with significant quantities of the corresponding oximino acetal. The dimer was not characterized as such but it was converted to the oxime (see below).

***r*-1-*tert*-Butyl-*c*-4-ethoxy-*t*-4-methoxy-*t*-3-nitrosocyclohexane Dimer, 5C.** Addition of 1-methoxy-4-*tert*-butylcyclohexene (2.76 g, 16.5 mmol) to an excess of ethyl nitrite (7 mL) with fuming sulfuric acid as catalyst followed by a workup as above gave 1.9 g of **5C** contaminated with significant quantities of the corresponding oximino acetal. This mixture was converted to the oxime which was then characterized (see below).

1,1-Dimethoxy-2-nitrosocyclopentane dimer, 4, was prepared as above from the methyl enol ether (15.9 g, 162 mmol) and methyl nitrite (30.5 g, 500 mmol) in about 90% yield: NMR ($CDCl_3$) δ 5.93 (m, C**H**N, 1 H), 3.33 and 3.22 (2 s, OCH_3, 6 H), 2.2–1.7 (bm, 6 H).

1,1-Dimethoxy-2-nitrosocyclooctane dimer, 6: mp 127–128 °C; 93% yield; NMR ($CDCl_3$) δ 6.0 + 5.83 (2 m, CHN, 1 H), 3.23 and 3.20 (2 s, OCH_3, 6 H), 2.33 (m, 4 H), 2.3–1.2 (m, 8 H).

Anal. ($C_{20}H_{38}N_2O_6$): C,H,N.

1,1-Dimethoxy-2-nitrosocyclododecane dimer, 7: mp 142–143 °C; 100% yield. Because of very poor solubility, no NMR spectrum was recorded.

Anal. ($C_{28}H_{54}N_2O_6$): C,H,N.

6,6-Dimethoxy-5-nitrosoundecane dimer, (9): semisolid at room temperature; 93% yield; NMR ($CDCl_3$) δ 5.9 (dd, C**H**N, 1 H), 3.23 (s, OCH_3, 6 H), 2.23–0.9 (m, 20 H).

4,4-Dimethoxy-3-nitrosoheptane dimer, 8: white-bluish solid; 85% yield; NMR ($CDCl_3$) δ 6.0 (dd, C**H**N, 1 H), 3.37 and 3.36 (2 s, OCH_3, 6 H), 1.83 (m, 6 H), 1.0 (t, $C\mathbf{H}_3CH_2$, 6 H).

Reaction of 7-Methoxy-6-tridecene with Methyl Nitrite. A reaction of enol ether (28.0 g, 132 mmol) with an excess of methyl nitrite (25.0 g, 406 mmol) in the presence of fuming sulfuric acid as catalyst, followed up by workup as above, gave about 25 g of a yellow oily product whose NMR indicated it to be predominantly the 7,7-dimethoxy-6-oximinotridecane **10** ($CDCl_3$); δ 9.5 (bs, NOH, 1 H), 3.20 (s, OCH_3, 6 H), 2.19 (m, 2 H), 2.0–0.9 (m, 22 H).

Reaction of 2-Methoxy-2-octene and 2-Methoxy-1-octene with Methyl Nitrite. A mixture of ca. 80% of 2-methoxyoct-2-ene and ca. 20% of 2-methoxyoct-1-ene (18.7 g, 135 mmol) with an excess of methyl nitrite (25.0 g, 406 mmol) in the presence of boron trifluoride etherate (0.3 mL), followed by standard workup, gave 23 g of a yellow liquid which according to the NMR analysis was predominantly a mixture of 2,2-dimethoxy-3-oximinooctane and 2,2-dimethoxy-1-oximinooctane accompanied by a small amount of the cleavage products.

Reaction of 2-Methoxycamphene with Methyl Nitrite. Reaction of 2-methoxycamphene (18.9 g, 114 mmol) with an excess of methyl nitrite (25.0 g, 406 mmol), followed by workup as above, gave a complicated mixture of products, which according to NMR analysis and mass spectrum were cleaved products resulting from the initial nitrosation reaction. No attempt to separate and characterize any of the products was made.

1-Methoxy-1-ethoxy-2-oximinocyclohexane. Heating the dimer **1B** (2.0 g, 1.06 mmol) in benzene at 80 °C for 30 min, followed by evaporation of the solvent, afforded the oximino acetal, mp 86–88 °C, in 90% yield: NMR ($CDCl_3$) δ 9.6 (b, NOH, 1 H), 3.62 (dq, $OC\mathbf{H}_2CH_3$, 2 H), 3.22 (s, OCH_3, 3 H), 2.57 (m, 2 H), 1.72 (m, 6 H), 1.22 (t, $-CH_2C\mathbf{H}_3$, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.9 (s, C=N), 98.9 (s, C$(OR)_2$), 56.1 (t, $-OCH_2-$), 48.4 (q, OCH_3), 35.5, 24.9, 21.5, 20.8 (4t, $-CH_2-$), 14.7 (q, $\mathbf{C}H_3CH_2-$).[23]

1,1-Diethoxy-2-oximinocyclohexane, mp 98–104 °C, was prepared from the crude dimer as above in 80% yield: NMR ($CDCl_3$) δ 9.4 (s, NOH, 1 H), 3.43 (dq, $-OC\mathbf{H}_2CH_3$, 4 H), 2.5 (m, $-CH_2C$=N, 2 H), 2.0–1.4 (m, 6 H), 1.18 (t, $-CH_2CH_3$, 6 H); ^{13}C NMR ($CDCl_3$) δ 156.00 (s, C=N), 99.04 (s, **C**$(OEt)_2$), 56.26 (t, $-OCH_2CH_3$), 36.18 (t, $-\mathbf{C}H_2C$=N), 25.30 (t, $-CH_2C(OEt)_2$), 22.79 and 22.37 (2t, $-CH_2CH_2-$), 15.23 (q, $\mathbf{C}H_3CH_2-$).[23]

Anal. ($C_{10}H_{19}NO_3$): C,H,N.

1,1-Dimethoxy-2-oximinocyclopentane, 22, was prepared in 85% yield from the nitroso dimer **4** (29.6 g, 186 mmol) by refluxing in methanol (60 mL): NMR ($CDCl_3$) δ 9.4 (vb, NOH, 1 H), 3.30 (s, OCH_3, 6 H), 2.55 (t, 2 H), 2.2–1.7 (m, 4 H). The crude product was not characterized further, but it was converted to methyl 4-cyanobutanoate (see below).

1,1-Dimethoxy-2-oximino-4-*tert*-butylcyclohexane, 23. Heating the dimer **5** as above, or stirring in the presence of base (sodium methoxide in methanol), produced the oximino acetal **23** in quantitative yield: mp 186–188 °C; NMR ($CDCl_3$) δ 9.4 (bs, NOH, 1 H), 3.31 and 3.12 (2 s, OCH_3, 6 H), 2.28 (m, C**H**C=N, 1 H), 1.9–1.5 (m, 6 H), 0.91 (s, C$(CH_3)_3$, 9 H); ^{13}C NMR ($CDCl_3$) δ 156.51 (s, C=N), 99.14 (s, **C**$(OCH_3)_2$), 49.00 and 48.17 (2 q, OCH_3), 47.38 (d, **C**H**C**$(CH_3)_3$), 34.75 (t, **C**H_2C=N), 32.69 (s, **C**$(CH_3)_3$), 23.92 and 23.16 (2t, $-CH_2CH_2-$).[23]

Anal. ($C_{12}H_{23}NO_3$): C,H,N.

***r*-1-*tert*-Butyl-*t*-4-ethoxy-*c*-4-methoxy-3-oximinocyclohexane, 23B.** Isomerization of the crude nitroso dimer **5B** as above gave **23B,** mp 161–173 °C, in 77% yield: NMR ($CDCl_3$) δ 9.5 (bs, NOH, 1 H), 3.57 (q, $-OC\mathbf{H}_2CH_3$, 2 H), 3.14 (s, OCH_3, 3 H), 2.32 (m, CHC=N, 1 H), 2.0–0.9 (m, 6 H), 1.24 (t, $-CH_2C\mathbf{H}_3$, 3 H), 0.92 (s, C$(CH_3)_3$, 9 H); ^{13}C NMR ($CDCl_3$) δ 156.09 (s, C=N), 99.01 (s, **C**$(OR)_2$), 55.82 (t, $-OCH_2CH_3$), 49.07 (q, OCH_3), 47.32 (d, **C**H**C**$(CH_3)_3$), 35.55 (t, **C**H_2C=N), 32.69 (s, **C**$(CH_3)_3$), 27.41 (q, C(**C**H_3)), 23.82 and 23.29 (t, $-CH_2-$), 15.24 (q, $\mathbf{C}H_3CH_2-$);[23] mass spectrum (CI) (NH_3) *m/e* 244 (MH^+), 212 ($MH^+ - CH_3OH$), 198 ($MH^+ - C_2H_5OH$).

Anal. ($C_{13}H_{25}NO_3$): C,H,N.

***r*-1-*tert*-Butyl-*c*-4-ethoxy-*t*-4-methoxy-3-oximinocyclohexane, 23C.** Isomerization of the crude nitroso dimer **5C** as above gave **23C,** 146–146.5 °C, in 36% yield: NMR ($CDCl_3$) δ 9.4 (bs, NOH, 1 H), 3.45 (m, $-OC\mathbf{H}_a\mathbf{H}_bCH_3$, 2 H), 3.35 (s, OCH_3, 3 H), 2.35 (bd, -CHC=N, 1 H), 1.9–1.05 (m, 6 H), 1.18 (t, $\mathbf{C}H_3CH_2-$, 3 H), 0.92 (s, C$(CH_3)_3$, 9 H); ^{13}C NMR ($CDCl_3$) δ 157.40 (s, C=N), 99.06 (s, **C**$(OR)_2$), 56.98 (t, $-OCH_2CH_3$), 48.29 (q, $-OCH_3$), 47.41 (d, $-$**C**H**C**$(CH_3)_3$), 34.96 (t,

$-CH_2C{=}N$), 32.72 (s, $-C(CH_3)_3$), 27.40 (q, $C(CH_3)_3$), 23.95 and 23.19 (t, $-CH_2-$), 15.18 (q, $-CH_2CH_3$);[23] mass spectrum (CI) (NH_3) *m/e* 244 (MH^+), 212 ($MH^+ - CH_3OH$), 198 ($MH^+ - C_2H_5OH$).

Anal. ($C_{13}H_{25}NO_3$): C,H,N.

1,1-Dimethoxy-2-oximinocyclooctane, 24. A solution of the dimer **6** (22.0 g, 54.7 mmol), in dry toluene (100 mL), was heated at 45 °C in the presence of a catalytic amount of sodium methoxide. When the deep blue color changed to pale yellow (ca. 5–10 min), the reaction mixture was filtered from a small amount of insoluble material and evaporated to dryness to give 19.3 g of **24:** mp 132–134 °C (95% yield); NMR ($CDCl_3$) δ 9.83 (bs, NOH, 1 H), 3.16 (s, OCH_3, 6 H), 2.42 (m, 2 H), 1.98 (m, 2 H), 1.63 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 158.08 (s, C=N), 102.07 (s, $C(OMe)_2$), 48.77 (q, 2 OCH_3), 29.46 (t, $-CH_2C{=}N$), 25.34 (t, $-(CH_2)_3-$), 24.70 and 21.83 (t, $-CH_2-$);[23] mass spectrum (CI) (CH_4) *m/e* 202 (MH^+), 187 ($MH^+ - CH_3$), 184 ($MH^+ - H_2O$), 170 ($MH^+ - CH_3OH$).

Anal. ($C_{10}H_{19}NO_3$): C,H,N.

1,1-Dimethoxy-2-oximinocyclododecane, 25. Stirring dimer **7** in boiling *n*-butyl alcohol in the presence of a catalytic amount of sodium methoxide for 1 h gave a solid, which by NMR analysis appeared to be a mixture of 1,1-dimethoxy-2-oximinocyclododecane (**25**), 1-methoxy-1-*n*-butoxy-2-oximinocyclododecane (**25a**), and 1,1-di-*n*-butoxy-2-oximinocyclododecane (**25b**). Isomerization of **7** (31.0 g, 60.3 mmol) was obtained in refluxing toluene (300 mL) in the presence of a catalytic amount of sodium methoxide to give pure **25** in quantitative yield: mp 124–125 °C; NMR ($CDCl_3$) δ 9.67 (bs, NOH, 1 H), 3.17 (s, OCH_3, 6 H), 2.41 (m, 4 H), 1.33 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 157.61 (s, C=N), 104.00 (s, $C(OMe)_2$), 48.67 (q, OCH_3);[23] mass spectrum (CI) (ammonia) *m/e* 258 (MH^+), 240 ($MH^+ - H_2O$), 226 ($MH^+ - MeOH$).

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

4,4-Dimethoxy-3-oximinoheptane, mp 106–108 °C, was prepared from the corresponding nitroso dimer in 84% yield: NMR ($CDCl_3$) δ 9.73 (s, NOH, 1 H), 3.1 (s, OCH_3, 6 H), 2.27, 1.67, 0.97 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 159.14 (s, C=N), 103.49 (s, $C(OMe)_2$), 48.83 (q, OCH_3), 35.87 (t, $CH_2C{=}N$), 18.81, 16.63 (2t, $-CH_2CH_2-$), 13.94, 10.06 (2 q, CH_3).[23]

Anal. ($C_9H_{19}NO_3$): C,H,N.

6,6-Dimethoxy-5-oximinoundecane was prepared from the corresponding nitroso dimer in about 80% yield. Crude yellow oil was not purified further: NMR ($CDCl_3$) δ 9.5 (bs, NOH, 1 H), 3.13 (s, OCH_3, 6 H), 2.3, 1.23, 0.92 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 158.57 (s, C=N), 103.58 (s, $C(OMe)_2$), 48.89 (q, OCH_3), 33.79, 31.85, 27.74, 25.67, 23.63, 22.88, 22.56 (7 t, $-CH_2-$), 14.02 and 13.82 (2 q, CH_3-).[23]

Preparation of 3-Oximino-2-butanone Dimethyl Acetal, 11a. A solution of 3-oximino-2-butanone (5.05 g, 50 mmol), trimethyl orthoformate (6.0 g, 60 mmol), and methanesulfonic acid (0.05 g) in 30 mL of methanol was heated at reflux under nitrogen. GLC analysis indicated that the oximino ketone reacted completely after 45 min. The reaction mixture was cooled, neutralized with sodium methoxide, and concentrated in vacuo. The residue was recrystallized from hexane to yield 3.6 g (49%) of **11a:** mp 55–58 °C; NMR ($CDCl_3$) δ 10.1 (s, NOH, 1 H), 3.27 (s, OCH_3, 6 H), 1.92 (s, $CH_3C{=}N$, 3 H), 1.44 (s, $CH_3C(OMe)_2$, 3 H).

Anal. ($C_6H_{13}NO_3$): C,H,N.

Preparation of Benzil Monoxime Dimethyl Acetal, 11b. A solution of benzil monoxime (6.65 g, 30 mmol), trimethyl orthoformate (4.24 g, 40 mmol), and methanesulfonic acid (0.03 g) in 30 mL of methanol was heated under nitrogen at reflux for 24 h. On cooling a solid precipitated out and filtration followed by crystallization from methanol gave ca. 43% yield of **11b:** mp 220–221 °C; NMR ($CDCl_3$) δ 7.2 (m, C_6H_5, 10 H), 3.20 (s, OCH_3, 6 H); mass spectrum (70 eV) *m/e* 271 (M^+), 254 ($M^+ - OH$), 151, etc.

Anal. ($C_{16}H_{17}NO_3$): C,H,N.

Fragmentation of 3-Oximino-2-butanone Dimethyl Acetal 11a in Sulfur Dioxide. A heavy-walled NMR tube was charged with about 0.1 g of **11a** and ca. 1 mL of sulfur dioxide and sealed at −76 °C. The reaction at room temperature was followed by NMR analysis (about 50% complete after 1 h at room temperature), and when all starting material reacted, the NMR spectrum showed the following peaks at δ 3.64 and 2.02 (2 s, CH_3COOMe, 6 H), 3.37 and 2.75 (2 s, CH_3OH, 3 + 1 H), and 1.98 (s, CH_3CN, 3 H). The NMR tube was cooled and opened and the material poured into chloroform and analyzed by GLC. The GLC analysis indicated that acetonitrile, methyl acetate, and methanol were the only products in this reaction.

Fragmentation of Benzil Monoxime Dimethyl Acetal 11b in Sulfur Dioxide. A sample of the acetal (0.1 g) was placed in a heavy-walled NMR tube and about 1 mL of the sulfur dioxide was added at −70 °C. The NMR tube was sealed and the solution heated at 75 °C for 48 h: NMR (SO_2) δ 7.2–8.2 (m, 2 C_6H_5 + OH, 11 H), 3.9 (s, CH_3OOCPh, 3 H), 3.37 (s, CH_3OH, 3 H). The GLC analysis showed that benzonitrile, methyl benzoate, and methanol were the only reaction products.

Preparation of 3-Oximino-2-butanone Dimethyl Orthoformate Adduct 12. 3-Oximino-2-butanone (5.1 g, 50 mmol) was dissolved in 10 mL of trimethyl orthoformate (10 g, 95 mmol) under nitrogen with stirring. Within 5 min after addition of 1 drop of methanesulfonic acid at room temperature GLC analysis indicated complete formation of the oxime–ortho ester adduct. The reaction mixture was neutralized with sodium methoxide and then distilled in vacuo. There was obtained 5.6 g of **12** (70% yield): bp 45–48 °C (1.5 mm); NMR (CCl_4) δ 5.70 (s, CH, 1 H), 3.37 (s, OCH_3, 6 H), 2.32 (s, $CH_3C{=}N$, 3 H), 1.93 (s, CH_3CO, 3 H).

Anal. ($C_7H_{13}NO_4$): C,H,N.

Fragmentation of 3-Oximino-2-butanone Dimethyl Orthoformate Adduct 12 in Sulfur Dioxide. The oxime ortho ester adduct **12** (0.1 g) was dissolved in 1 mL of sulfur dioxide and sealed in a heavy-walled NMR tube. At room temperature NMR analysis indicated that in addition to the expected fragmentation, a disproportionation of **12** to the corresponding dioxime methyl orthoformate adduct **13** and trimethyl orthoformate was also taking place (δ 6.50 (s, $(=NO)_2CHOMe$), 4.92 (s, $HC(OMe)_3$)). After standing for 1 week at room temperature fragmentation was complete: δ 8.0 (s, **H**COOMe, 1 H), 3.75 (s, $HCOOCH_3$, 3 H), 3.63 and 2.02 (2 s, CH_3COOCH_3, 3 + 3 H), 1.98 (s, CH_3CN, 3 H). GLC analysis showed that acetonitrile, methyl formate, and methyl acetate were the only reaction products.

Preparation of 3,3-Dimethoxy-2-butanone Oxime Dimethyl Orthoformate, 14. To a solution of 3,3-dimethoxy-2-butanone oxime (3.7 g, 25 mmol) in trimethyl orthoformate (5.3 g, 50 mmol) under nitrogen, one drop of methanesulfonic acid was added. After 1 h at room temperature, the reaction mixture was dissolved in ether and washed with several portions of dilute sodium hydroxide to remove unreacted oximino acetal, dried over magnesium sulfate, and distilled. There was obtained about 50% yield of **14,** bp 54–59 °C (0.1 mm). When the same amounts of the reagents were heated *in the absence of the acid catalyst,* an equivalent amount of methanol distilled off and distillation of the residue afforded about 50% of **14,** bp 54–59 °C (0.1 mm), and about 15% of a mixed oxime acetal/oxime ortho ester adduct **15,** bp 114–125 °C. On the other hand, heating of the 3,3-dimethoxy-2-butanone oxime (3.7 g, 25 mmol) with a tenfold excess of trimethyl orthoformate (26.5 g, 250 mmol) in the absence of the acid catalyst, to remove 1 equiv of methanol, followed by vacuum distillation, gave 4.7 g of **14:** bp 56–58 °C (0.1 mm) (85% yield); NMR (CCl_4) δ 5.58 (s, CH, 1 H), 3.29 (s, $HC(OCH_3)$, 6 H), 3.15 (s, $C(OCH_3)_2$, 6 H), 1.82 (s, $CH_3C{=}N$, 3 H), 1.37 (s, CH_3CO, 3 H).

Anal. ($C_9H_{19}NO_5$): C,H,N.

15: NMR (CCl_4) δ 5.52 (s, CH, 1 H), 3.29 (s, $CH(OCH_3)_2$, 6 H), 3.22 (s, NOC (OCH_3), 3 H), 3.15 (s, $CH_3C(OCH_3)_2$, 6 H), 1.87 (s, $CH_3C{=}N$, 3 H), 1.82 (s, $CH_3C{=}N$, 3 H), 1.58 (s, $CH_3C(OMe)ON{=}$, 3 H), 1.37 (s, $CH_3C(OMe)_2$, 3 H).

Fragmentation of 3,3-Dimethoxy-2-butanone Oxime Dimethyl Orthoformate, 14. A sample of **14** (0.1 g) was dissolved in carbon tetrachloride (1 mL) in an NMR tube and a catalytic amount of methanesulfonic acid was added. A mild exothermic reaction occurred and NMR analysis indicated complete disappearance of the starting material and formation of equimolar amounts of acetonitrile, methyl acetate, and trimethyl orthoacetate.

Similarly, a solution of **14** (0.1 g) in sulfur dioxide (1 mL) sealed in a heavy-walled NMR tube at −76 °C underwent the fragmentation reaction at room temperature to give acetonitrile (δ 1.98), methyl acetate (δ 1.97 and 3.60), and trimethyl orthoformate (δ 4.92 and 3.21). Methanol (δ 3.32) and methyl formate (δ 8.00 and 3.72) were also present in trace amounts.

Fragmentation of the Mixed Oxime–Acetal/Oxime Orthoformate Adduct 15. A similar reaction of **15** in carbon tetrachloride in the presence of a catalytic amount of methanesulfonic acid gave acetonitrile, methyl acetate, and trimethyl orthoformate in the molar ratio of 2:2:1 in essentially quantitative yield.

Relative Reactivities of Ortho Esters in a Reaction with Acetaldehyde Oxime. Equimolar amounts of trimethyl orthoformate with trimethyl orthoacetate, or trimethyl orthopropionate, or trimethyl orthobenzoate, respectively, were mixed with an equimolar amount of acetaldehyde oxime in the presence of a catalytic amount of methanesulfonic acid and the reaction was followed by NMR analysis at 70 °C. From the relative ratios of methyl formate vs. methyl acetate, methyl propionate, or methyl benzoate on the one hand, and the relative ratios of unreacted ortho esters on the other, the relative reactivities of these ortho esters were determined and summarized in Table II.

Preparation of 3,3-Dimethoxy-2-butanone Oxime Dimethyl Orthopropionate, 16. 3,3-Dimethoxy-2-butanone oxime (7.4 g, 50 mmol) and trimethyl orthopropionate (13.4 g, 100 mmol) were heated under nitrogen at 120 °C for 4 h. When GLC analysis indicated reaction was complete, the mixture was made basic by addition of a small amount of sodium methoxide and distilled to give 8.5 g (68% yield) of **16:** bp 61–63 °C (0.1 mm); NMR (CCl_4) δ 3.20 (s, $CH_3C(OCH_3)_2$, 6 H), 3.16 (s, $C(OCH_3)_2$, 6 H), 1.85 (q, CH_3CH_2, 2 H), 1.83 (s, $CH_3C{=}N$, 3 H), 1.38 (s, $CH_3C(OMe)_2$, 3 H), 0.8 (t, CH_3CH_2, 3 H).

Anal. ($C_{11}H_{23}NO_5$); C,H,N.

Fragmentation of 3,3-Dimethoxy-2-butanone Oxime Dimethyl Orthopropionate, 16. To a solution of **16** in carbon tetrachloride in an NMR tube a catalytic amount of methanesulfonic acid was added. A mild exothermic reaction occurred and the NMR spectrum, as well as GLC analysis, indicated that fragmentation had occurred to give acetonitrile and approximately equimolar amounts of methyl acetate and methyl propionate, as well as trimethyl orthoacetate and trimethyl orthopropionate.

2-Oximinopropionaldehyde Dimethyl Acetal. To a stirred solution of pyruvic aldehyde dimethyl acetal (11.8 g, 100 mmol) in ether (100 mL) at 0 °C, a solution of hydroxylamine hydrochloride (8.3 g, 120 mmol) and potassium hydroxide (8.4 g, 150 mmol) in 30 mL of water was added dropwise. After 15 min, the ether layer was separated, dried over magnesium sulfate, and distilled. There was obtained 12.3 g (92% yield) of 2-oximinopropionaldehyde dimethyl acetal: bp 85–87 °C (5 mm); NMR (CCl_4) δ 9.75 (s, NOH, 1 H), 4.50 (s, CH, 1 H), 3.28 (s, OCH_3, 6 H), 1.76 (s, $CH_3C{=}N$, 3 H).

Anal. ($C_5H_{11}NO_3$): C,H,N.

1,1-Dimethoxy-2-propanone Oxime Dimethyl Orthoacetate, 17. 2-Oximinopropionaldehyde dimethyl acetal (6.7 g, 50 mmol) was heated under reflux with trimethyl orthoacetate (15 g, 125 mmol). After GLC analysis indicated complete reaction, the reaction mixture was cooled and washed with dilute sodium hydroxide solution. The product was dissolved in ether, dried over magnesium sulfate, and distilled to give 65% yield of **17:** bp 59–61 °C (0.1 mm); NMR ($CDCl_3$) δ 4.55 (s, CH, 1 H), 3.33 (s, OCH_3, 6 H), 1.83 (s, CH_3CN, 3 H), 1.57 (s, $CH_3C(OMe)_2$, 3 H).

Anal. ($C_9H_{19}NO_5$): C,H,N.

Fragmentation of 1,1-Dimethoxy-2-propanone Oxime Dimethyl Orthoacetate, 17. A solution of oxime dimethyl orthoacetate **17** (0.1 g) in chloroform was placed in an NMR tube. After the addition of a catalytic amount of methanesulfonic acid the NMR tube was heated at 75 °C for 2 h. The NMR spectrum indicated ca. 60% of methyl acetate, acetonitrile, and trimethyl orthoformate, ca. 10% of trimethyl orthoacetate and the dioxime methyl orthoacetate, and ca. 5–10% of unreacted **17**. There was no evidence of any methyl formate. GLC analysis confirmed the NMR results.

Preparation of 2,2-Dimethoxycyclohexanone Oxime Dimethyl Orthoformate, 18. A solution of the α-oximino acetal **2** (5.8 g, 34 mmol) in trimethyl orthoformate (6.0 g, 60 mmol) was heated at 100 °C under nitrogen for 48 h. The reaction mixture was made alkaline with sodium methoxide and distilled to give 7.5 g (90% yield) of **18:** bp 88–89 °C (0.1 mm); NMR (CCl_4) δ 5.50 (s, CH, 1 H), 3.27 and 3.12 (2 s, OCH_3, 6 + 6 H), 2.47 (m, CH_2CN, 2 H), 6.1 (m, $(CH_2)_3$, 6 H).

Anal. ($C_{11}H_{21}NO_5$): C,H,N.

Fragmentation of 2,2-Dimethoxycyclohexanone Oxime Dimethyl Orthoformate, 18. A solution of the oxime orthoformate **18** (0.1 g) was dissolved in carbon tetrachloride in an NMR tube and treated with a catalytic amount of methanesulfonic acid. The peaks of **18** were gradually replaced by new singlets at δ 4.85 and 3.23 ($HC(OCH_3)_2$) and 3.62 ($CH_3OCO(CH_2)_4CN$). After 15 min the reaction was approximately 75% complete and after 24 h there was slightly more than 93% of the nitrile ester **20** and trimethyl orthoformate formed. In addition, trace amounts of methyl formate and trimethyl 5-cyanoorthopentanoate **21** were also present. The GLC analysis confirmed the NMR findings.

In a similar experiment, a sample of **18** was placed in a heavy-walled NMR tube, the sulfur dioxide was added, and the NMR tube sealed at −76 °C. The reaction was followed by NMR at room temperature and it was essentially complete in 1 h to give more than 70% of **20** and trimethyl orthoformate, together with traces of methyl formate and **21**.

Preparation of 2,2-Dimethoxycyclohexanone Oxime Dimethyl Orthoacetate, 19. A solution of the oximino acetal **2** (1.73 g, 10 mmol) in trimethyl orthoacetate (12.0 g, 100 mmol) was heated at 100 °C under nitrogen for 16 h. The reaction mixture was made basic with sodium methoxide and distilled to afford 2.4 g (90% yield) of **19:** bp 80–82 °C (0.1 mm); NMR ($CDCl_3$) δ 3.25 and 3.20 (2 s, OCH_3, 6 + 6 H), 2.5 (m, 2 H), 2.0–1.4 (m, 6 H), 1.56 (s, CH_3C, 3 H).

Anal. ($C_{12}H_{23}NO_5$): C,H,N.

Fragmentation of 2,2-Dimethoxycyclohexanone Oxime Dimethyl Orthoacetate, 19. To a sample of the oxime orthoacetate adduct **19** in deuteriochloroform in an NMR tube, a catalytic amount of methanesulfonic acid was added. An exothermic reaction occurred and the NMR spectrum indicated formation of **20** and methyl acetate together with trimethyl orthoacetate and **21**. The GLC analysis confirmed this finding and showed that the ratio of **21** and methyl acetate vs. trimethyl orthoacetate and **20** was ca. 7:3.

Preparation of Trimethyl 5-Cyanoorthopentanoate, 21. To a solution of the oxime orthoacetate adduct, **19** (11.7 g, 45 mmol), in trimethyl orthoacetate (18 g, 150 mmol), and 50 mL of carbon tetrachloride a catalytic amount of methanesulfonic acid was added. After 1 h at room temperature the reaction mixture was made basic with sodium methoxide and distilled. There was obtained 7.6 g (90% yield) of **21:** bp 80–81 °C (0.25 mm); NMR (CCl_4) δ 3.16 (s, OCH_3, 9 H), 2.35 (m, 2 H), 1.60 (m, 6 H); IR (neat) 2270 cm^{-1}.

Anal. ($C_9H_{17}NO_3$): C,H,N.

Preparation of Ethyldimethoxycarbonium Tetrafluoroborate. The catalyst was prepared according to the procedure published by Borch.[13]

Fragmentation of 2-Oximinocyclohexanone Dimethyl Acetal, 2, Catalyzed by Dimethoxyethylcarbonium Tetrafluoroborate.[13,14] To a solution of the oximino acetal **2** (8.7 g, 50 mmol) in methylene chloride (100 mL) in a flask immersed in a water bath at room temperature a solution of the dimethoxyethylcarbonium tetrafluoroborate[14] in the same solvent (ca. 5 mol equiv %) was added. An exothermic reaction occurred, and after 30 min at room temperature both GLC and NMR analyses indicated essentially quantitative formation of **20.** Workup as above gave 6.6 g (93% yield) of **20,** bp 95–97 °C (1.5 mm).

Using essentially the same reaction procedure α-oximino acetals **22, 23, 24,** and **8** were converted to the corresponding ester nitriles **26, 27, 28, 29,** respectively. (See also Table III.)

Methyl-4-cyanobutanoate, 26: bp 92–93 °C (6.2 mm); 90% yield; NMR ($CDCl_3$) δ 3.7 (s, OCH_3, 3 H), 2.5 (m, 4 H), 1.95 (m, 2 H); IR (neat) 2230, 1749 cm^{-1}.

Anal. ($C_6H_9NO_2$): C,H,N.

Methyl 4-*tert*-butyl-5-cyanopentanoate, 27: bp 110–111 °C (1.8–2.0 mm), 93% yield; NMR ($CDCl_3$) δ 3.67 (s, OCH_3, 3 H), 2.4 (m, 4 H), 2.3–1.3 (bm, 3 H), 0.97 (s, 9 H); IR (neat) 2250, 1740 cm^{-1}.

Anal. ($C_{11}H_{19}NO_2$): C,H,N.

Methyl 7-cyanoheptanoate, 28: bp 142 °C (8 mm); 95% yield; NMR ($CDCl_3$) δ 3.67 (s, OCH_3, 3 H), 2.42 (m, 4 H), 1.5 (m, 8 H); IR (neat) 2220, 1730 cm^{-1}.

Anal. ($C_9H_{15}NO_2$): C,H,N.

Methyl 11-cyanoundecanoate, 29: bp 160–161 °C (2.5 mm); 100% yield; NMR ($CDCl_3$) δ 3.65 (s, OCH_3, 3 H), 2.25 (m, 4 H), 1.3 (m, 16 H); IR (neat) 2220, 1730 cm^{-1}.

Anal. ($C_{13}H_{23}NO_2$): C,H,N.

2-Oximinocyclohexanone, 30. To a solution of the oximino acetal **2** (12.1 g, 70 mmol) in tetrahydrofuran and water (150 mL + 30 mL) 1 mL of 10% hydrochloric acid was added and the solution left at room temperature for 60 h. Neutralization with an excess of solid sodium bicarbonate, drying with magnesium sulfate, and evaporation afforded 7.1 g of **30** as a viscous oil (80% yield). Careful chromatography over sephadex LH-20/THF gave pure **30:** mp 70–73 °C; NMR ($CDCl_3$) δ 9.8 (bs, NOH, 1 H), 2.80 (t, J = 6 Hz, $CH_2C{=}N$, 2 H), 2.59 (t, J = 7 Hz, $CH_2C{=}O$, 2 H), 2.1–1.65 (m, $-CH_2CH_2-$, 4 H); IR (prior to crystallization, neat) 3275 (NOH), 1710 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 204.05 (s, C=O), 153.88 (s, C=N), 40.91 (t, $CH_2C{=}N$), 25.12 (t, $CH_2C{=}O$), 22.58, 21.74 (2 t, $-CH_2CH_2-$).[23]

6-Hydroxyimino-1,4-dioxospiro[4.5]decane, 31. Oximino acetal **2** (1.73 g, 10 mmol) and ethylene glycol (3.1 g, 50 mmol) were refluxed in 10 mL of benzene containing 1 drop of methanesulfonic acid for 9 h. Ether (200 mL) was added and the solution neutralized with an excess of sodium bicarbonate. After drying, evaporation gave 0.52 g of **31:** mp 97–98 °C; NMR ($CDCl_3$) δ 10.0 (bs, NOH, 1 H), 3.98 (s, $-OCH_2O-$, 4 H), 2.64 (t, $CH_2C{=}N-$, 2 H), 1.95–1.55 (m, 6 H).

Anal. ($C_{10}H_{13}NO_3$): C,H,N.

Reaction of Oximino Acetal 2 with Thionyl Chloride. A solution of oxime acetal **2** (0.4 g, 2.3 mmol) in sulfur dioxide (5 mL) containing excess thionyl chloride (1.2 g, 10 mmol) was refluxed for 2.5 h. Evaporation of 0 °C gave 0.34 g (ca. 100% yield) of **20,** identical in every respect with an authentic sample. Similarly, treating a solution of **2** (0.4 g, 2.3 mmol) in 10 mL of dry ether with an excess of thionyl chloride (0.55 g, 4.6 mmol) at 0 °C for 30 min followed by evaporation at 0 °C gave **20** in quantitative yield.

Reaction of Oximino Acetal 2 with Tosyl Chloride. To a solution of **2** (0.4 g, 2.3 mmol) in dry pyridine (3 mL) tosyl chloride (0.48

g, 2.5 mmol) was added and the reaction mixture stirred at 0 °C for 3.5 h. After usual workup, evaporation afforded 0.2 g (61% yield) of **20**.

Attempted Beckmann Fragmentation of the Enol Ether Oxime 3. A solution of the tosylate of **3**, mp 90–94 °C (prepared in a standard manner using tosyl chloride/pyridine), in pyridine/ethanol (0.1 g in 0.2 mL of pyridine and 5 mL of ethanol) was refluxed for 1.5 h. Standard workup afforded unreacted tosylate. Similarly, a reaction of **3** (1.4 g, 10 mmol) with an excess of trimethyl orthoformate (10 mL), at 90 °C, gave the corresponding oxime–ortho ester adduct, mp 145–148 °C. A sample of the adduct (0.2 g) was refluxed in benzene (6 mL) in the presence of a catalytic amount of methanesulfonic acid. Neutralization with excess sodium bicarbonate, followed by evaporation, gave 0.17 g of a brown oil, which according to NMR analysis was a 1:1 mixture of unreacted oxime orthoformate adduct and the corresponding dioxime orthoformate.

Reaction of 2-Oximinocyclohexanone with Trimethyl Orthoformate. A mixture of **30** (7.43 g, 58.5 mmol) and trimethyl orthoformate (8.1 g, 76.0 mmol) was stirred under reflux until approximately 50 mmol of methanol distilled off. The crude reaction mixture was chromatographed on Sephadex LH-20/CH_3CN to give **32** as an oil: NMR ($CDCl_3$) δ 5.85 (s, $HC(OMe)_2$, 1 H), 3.50 (s, OCH_3, 6 H), 3.05–1.4 (bm, 8 H); ^{13}C NMR ($CDCl_3$) δ 195.93 (s, C=O), 155.75 (s, C=N), 118.21 (s, $HC(OMe)_2$), 52.35 (q, OCH_3), 41.31 (t, CH_2C=N), 26.37 (t, CH_2CO), 22.69 and 21.82 (2 t, $-CH_2CH_2-$).[23]

A solution of **32** in deuteriochloroform, containing a catalytic amount of sulfuric acid, gave methyl formate and **20** in essentially quantitative yield.

2-(*p*-Toluenesulfonyloxy)cyclohex-2-ene Oxime ω-Cyanopentanoate, 33a. To a solution of **30** (2.59 g, 20.4 mmol) and triethylamine (10 mL) in methylene chloride (60 mL) a solution of tosyl chloride (5.83 g, 30.6 mmol) in methylene chloride (40 mL) was added. After 3 h at reflux, 200 mL of 10% potassium carbonate was added and left at room temperature overnight. After washing and drying, evaporation afforded 6.3 g (80%) of **33a**: mp 126–128 °C; NMR ($CDCl_3$) δ 8.05–7.25 (ArH, 4 H), 6.40 (t, $-CH$=CO–, 1 H), 2.80–2.20 + 2.40 (m + s, CH_3, 17 H).

Anal. ($C_{19}H_{22}N_2O_5S$): C,H,N,S.

2-(*p*-Toluenesulfonyloxy)cyclohex-2-en-1-one Oxime, 33b. A mixture of **33a** (0.12 g, 0.3 mmol) and sodium hydroxide (0.5 g) in 10 mL of water was heated at 80 °C until a homogeneous solution resulted. A slight excess of 6 N hydrochloric acid was added and the resulting solid, 0.06 g, 70% yield, was recrystallized from hexane–chloroform to give **33b**: mp 153–154 °C; NMR ($CDCl_3$) δ 9.35 (bs, NOH, 1 H), 7.85–7.25 (ArH, 4 H), 6.13 (t, CH=C, 1 H), 2.8–2.15 + 2.5 (s, CH_3) (m, 9 H).

Anal. ($C_{13}H_{15}NO_4S$): C,H,N,S.

2-(*p*-Toluenesulfonyloxy)cyclohex-2-en-1-one Oxime Acetate, 33c. A reaction between the oxime **33b** (2.0 g, 7.1 mmol) and acetic anhydride (4.36 g, 42.6 mmol) at 50 °C for 2 h followed by a usual workup gave **33c**: mp 116–118 °C (98% yield); NMR ($CDCl_3$) δ 8.05–7.35 (ArH, 4 H), 6.45 (t, –CH=C, 1 H), 2.85 (t, $-CH_2C$=N, 2 H), 2.55–1.65 (m + s, 10 H).

Anal. ($C_{15}H_{17}NO_5S$): C,H,N,S.

2-Benzoyloxycyclohex-2-en-1-one oxime benzoate, 33d, mp 109–111 °C, was prepared from **28** and benzoyl chloride, in a similar manner as **33a**, in 67% yield: NMR ($CDCl_3$) δ 8.25–7.35 (m, 10 H), 6.30 (t, –CH=C–, 1 H), 3.25–1.70 (m, 6 H).

Anal. ($C_{20}H_{17}NO_4$): C,H,N.

2-Ethoxycarbonyloxycyclohex-2-en-1-one oxime ethyl carbonate, 33e, bp 130 °C (0.25 mm), was obtained in a 60% yield from **30** and ethyl chloroformate, as above: NMR ($CDCl_3$) δ 6.2 (t, $-CH$=C–, 1 H), 4.2 (q, CH_3CH_2O–, 4 H), 2.9–1.6 (m, 6 H), 1.30 (t, CH_3CH_2–, 6 H).

Anal. ($C_{12}H_{17}NO_6$): C,H,N.

Transformation of 1,1-Dimethoxy-2-nitrosocyclohexane Dimer, 1. (a) In Sulfur Dioxide. Methyl 5-Cyanopentanoate, 20. A heavy-walled NMR tube was charged with the nitroso dimer **1**, chloroform (as an internal standard), and sulfur dioxide as a solvent. The NMR tube was sealed at −76 °C and analyzed periodically at room temperature by NMR. After standing overnight the starting material was consumed and the relative ratio of the ester methoxy signal and the chloroform internal standard indicated an 85% yield of **20**. The NMR tube was placed in dry ice and opened. GLC analysis confirmed the above finding and showed several other minor higher boiling materials. The same reaction on a larger scale (5.2 g, 30 mmol in 30 mL of sulfur dioxide) in a Fisher pressure bottle equipped with a pressure gauge gave a dark liquid after evaporation of sulfur dioxide. The liquid was dissolved in ether, washed with several portions of saturated sodium bicarbonate solution, and dried over magnesium sulfate. Evaporation of ether followed by distillation gave 3.4 g of **20** (80% yield): bp 91–93 °C (1.3 mm); NMR ($CDCl_3$) δ 3.65 (s, OCH_3, 3 H), 2.37 (m, 4 H), 1.72 (m, 4 H); IR (neat) 2270, 1735 cm^{-1}.

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

(b) In Benzene Solution Catalyzed with Sulfur Dioxide. A heavy-walled NMR tube was charged with a solution of the dimer **1** in benzene containing a catalytic amount of sulfur dioxide. The NMR tube was sealed and heated at 80 °C for 1 h and then analyzed by NMR. The analysis indicated that all dimer was converted into the ester nitrile **20** without evidence for significant formation of other byproducts.

Transformations of 1,1-Dimethoxy-2-oximinocyclohexane, 2. (a) In Sulfur Dioxide. A heavy-walled NMR tube was charged with oximino acetal **2**, chloroform (internal standard), and sulfur dioxide as solvent. A NMR spectrum taken immediately at room temperature showed the following signals: δ 7.43 ($CHCl_3$, internal standard), 7.2 (s, NOH, 1 H), 3.19 (s, $-OCH_3$, 6 H), 2.55 (m, 2 H), 1.7 (m, 6 H). In addition there was a small singlet at 3.35. Ten minutes later, the hydroxyl proton moved to δ 7.0, and the singlet at δ 3.35 became more intense. After 75 min, the hydroxyl proton appeared at δ 6.3, a new singlet at δ 3.62 started to appear, while the intensities of the singlets at δ 3.38 and 3.19 were almost the same. The NMR tube was placed in dry ice, opened, and after evaporation of the solvents analyzed again by NMR as well as by GLC. Both analyses showed that the isolated material was essentially unchanged **2** contaminated by small amounts of **3** and **20**. The experiment was repeated and after 24 h at room temperature the NMR spectrum indicated that there was now about 1.5 hydroxyl proton (δ 6.2), accompanied by a triplet at δ 5.7 ($-CH$=C(OCH_3)–, 0.38 H), two singlets at δ 3.62 and 3.61 (C=$COCH_3$, $COOCH_3$, ~1.6 H), and two singlets at δ 3.35 (~3 H) and 3.19 (~1.4 H). Evidently, in addition to about 23% of unchanged **2**, there was about 38% of **3**, and only about 16% of **20**. The GLC analysis substantiated the NMR findings.

(b) In Benzene Solution Catalyzed with Sulfur Dioxide. A heavy-walled NMR tube was charged with a solution of the oximino acetal **2** in benzene containing a catalytic amount of sulfur dioxide. The NMR tube was sealed and heated at 80 °C for 3.5 h. The NMR analysis indicated that essentially all oximino acetal was converted to the oximino enol ether **3**, without appreciable formation of **20**.

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Registry No.—*dl*-**1**, 68226-35-7; *meso*-**1**, 68226-36-8; *dl*-**1A**, 68226,37-9; *meso*-**1A**, 68226-38-0; **1B**, 64950-84-1; *dl*-**4**, 68226-39-1; *meso*-**4**, 68297-96-1; **5B**, 68226-40-4; **5C**, 68296-41-3; *dl*-**6**, 68226-41-5; *dl*-**5**, 68297-95-0; *meso*-**6**, 68226-42-6; *dl*-**7**, 68226-43-7; *meso*-**7**, 68226-44-8; *dl*-**8**, 68226-45-9; *meso*-**8**, 68226-46-0; *dl*-**9**, 68297-94-9; *meso*-**9**, 68226-47-1; **10**, 64950-89-6; **13**, 68226-48-2; **15**, 68226-49-3; **30**, 24858-28-4; **31**, 68226-50-6; **32**, 66977-23-9; **33a**, 68297-93-8; **33b**, 68226-51-7; **33c**, 68226-52-8; **33d**, 68226-53-9; **33e**, 68226-54-0; 2-methoxy-2-heptene, 61142-43-6; 2-methoxy-1-heptene, 61142-46-9; 2-methoxy-2-octene, 61142-42-5; 2-methoxy-1-octene, 42367-31-7; 2,2-dimethoxy-3-oximinooctane, 68226-55-1; 2,2-dimethoxy-1-oximinooctane, 64950-94-3; 1-methoxy-1-ethoxy-2-oximinocyclohexane, 68226-56-2; 1,1-diethoxy-2-oximinocyclohexane, 58158-89-7; *r*-1-*tert*-butyl-*t*-4-ethoxy-*c*-4-methoxy-3-oximinocyclohexane, 68226-57-3; *r*-1-*tert*-butyl-*c*-4-ethoxy-*t*-4-methoxy-3-oximinocyclohexane, 68226-58-4; 1-methoxy-1-*n*-butyoxy-2-oximinocyclododecane, 68226-59-5; 1,1-di-*n*-butoxy-2-oximinocyclododecane, 68226-60-8; 4,4-dimethoxy-3-oximinoheptane, 68226-61-9; 6,6-dimethoxy-5-oximinoundecane, 68226-62-0; 2-oximinopropionaldehyde dimethyl acetal, 68226-63-1; pyruvic aldehyde dimethyl acetal, 6342-56-9; hydroxylamine hydrochloride, 5470-11-1; trimethyl orthoacetate, 1445-45-0; ethyldimethoxycarbonium tetrafluoroborate, 64950-83-0; ethylene glycol, 107-21-1.

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(23) ^{13}C NMR assignments of the methylene carbon atoms adjacent to the oxime and acetal functions are consistent, but remain tentative at this time.

Isoquinolines. 8. Ethylene Oxide Mediated Conversion of Isoquinolines to Isoquinolones and Oxazolidines. Its Extension to Related Nitrogen Heterocycles[1]

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Treatment of 1-(3-methoxy-2-nitrobenzyl)isoquinoline (**1b**) with ethylene oxide in acetic acid afforded stable 10b-(3-methoxy-2-nitrobenzyl)oxazolo[2,3-*a*]isoquinoline (**3b**). Similarly, 1-cyanoisoquinoline (**1c**) yielded *N*-(2-hydroxyethyl)-1-isoquinolone (**6a**) and *N*-(2-acetoxyethyl)-1-isoquinolone (**6b**). In the latter instance no competitive formation of lactone **4** was observed. When quinoline was treated with ethylene oxide in acetic acid, novel labile 10b*H*-oxazolo[3,2-*a*]quinoline (**7**) was obtained, but similar treatment of 2-methylquinoline gave no reaction.

In an earlier communication[4] we reported that isoquinoline **1a** reacts with ethylene oxide in acetic acid at room temperature to afford after workup oxazolidine **3a** (Scheme I). Supporting the intermediacy of zwitterion **2a** in this conversion was the known cyclization of *N*-(2-hydroxyethyl)-3,4-dihydroisoquinolinium salts with bases to 5,6-dihydro analogues of **3a**[5a-e] and the reported synthesis of 2,3-disubstituted analogues of **3a** by treating *N*-benzylisoquinolinium halides with aldehydes and base.[6a,b] Herein we report further on the scope of this reaction with other isoquinolines and its partially successful extension to several related nitrogen heterocycles.

A possible explanation for the previously observed instability of oxazolidine **3a**[4] was the presence of an oxidizable 10b position. To test this explanation and probe the possible steric limitations of the ethylene oxide insertion reaction with isoquinolines, 1-(3-methoxy-2-nitrobenzyl)isoquinoline (**1b**) was treated with ethylene oxide in acetic acid to afford after workup an oxazolidine (69%) whose spectral data and combustion analyses are compatible with structure **3b** (for ^{13}C NMR consult Table I). In contrast to labile oxazolidine **3a** (where R^1 = H), 10b-substituted oxazolidine **3b** was isolated as a stable crystalline substance, mp 139–142 °C. Ethylene oxide mediated oxazolidine formation in the isoquinoline series appears to be a facile reaction even with appreciable steric hindrance in the isoquinoline 1 position.

The observation[4] that bromine substitution in the 1 position of isoquinolines facilitated ethylene oxide mediated isoquinolone conversion (presumably via oxazolidine **3** and oxazolinium salt **5** intermediates of Scheme I) prompted us to investigate whether putative cyano intermediate **2c** functioned similarly or underwent intramolecular ring closure to afford lactone **4** (Scheme I). Treatment of **1c** with ethylene oxide in acetic acid yielded after chromatography a mixture of isoquinolones **6a** (48%) and **6b** (34%). Basic hydrolysis of crude mixture **6a** and **6b** immediately after reaction of **1c** with

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