Table IV. Kinetic Parameters for Formation of Syn and Anti Isomers, Ester Hydrolysis, and Syn–Anti Isomerization in H_2O at 30 °C (μ = 1.6 M (KCl))[a]

pH	[buffer]	$k_{ds} \times 10^2$, s^{-1}	$k_{da} \times 10^2$, s^{-1}	$k_{sh} \times 10^3$, s^{-1}	$k_{ah} \times 10^5$, s^{-1}	$k_{sa} \times 10^4$, s^{-1}	$k_{as} \times 10^4$, s^{-1}
6.8	0.3[b,c]	6.5	7.0	1.8		6.5	
	0.2[b,d]				4.7	2.5	1.7
	0.2 (^{31}P)[b]				6.4		
8.2	0.3 (^{31}P)[e]				3.6		
9.0	0.2[f,c]	0.32	0.32	1.3		3.0	
	0.2 (^{31}P)[g,d]				4.2	1.1	0.66
	0.2 (^{31}P)[e]				3.0		

[a] Obtained by means of ^{1}H NMR unless otherwise indicated. [b] Sodium phosphate buffer. [c] Iterative method of calculation; see text. [d] Nonlinear least-squares method of calculation, see text. [e] Boric acid buffer. [f] *p*-Hydroxybenzoic acid buffer. [g] Diazabicyclooctane buffer.

To compare the intramolecular assistance of ester hydrolysis with the intermolecular process, the hydrolysis of 0.075 M *O*-methyloxime of DKP in the presence of 0.075 M acetone oxime at pH 7.5 (0.2 M phosphate) was studied. After 2143 h no ester hydrolysis was detected, although about 16% of the acetone oxime had hydrolyzed. Since about 5% ester hydrolysis could have been detected, the effective molarity[9] of the oxime hydroxyl group is $>10^4$ M. It would appear that this group is more effective in assisting phosphonate ester hydrolysis than the amide group, which requires strongly acidic conditions to promote conveniently rapid rates of hydrolysis[2] and presumably has a very slow rate at neutral pH. This difference in effectiveness may be due in part to the presence of the oxime OH proton, which can be transferred to the phosphoryl oxygen as described above. Finally, hydrolysis of the monoester SH is not observed, probably because the presence of the negative charge makes the phosphorus in this compound much less reactive than in the diester. Presumably, removal of the negative charge by lowering the pH would promote monoester hydrolysis as has been observed for the amide case.[2]

Acknowledgment. We are grateful to the National Research Council of Canada for partial support of this work, to Dr. A. Woon-Fat for the ^{31}P spectra, and to Professor M. Zerner for some helpful suggestions concerning the iterative program. We also are indebted to R. Dudley for suggesting the oxazolidine of DKP as a model compound.

Registry No.—CA, 66417-89-8; methoxyamine hydrochloride, 593-56-6; acetone oxime, 127-06-0; acetone, 67-64-1; hydroxylamine hydrochloride, 5470-11-1.

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A Useful, Regiospecific Synthesis of Isoxazoles

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Isoxazoles have been obtained in excellent yield by acylation of *syn*-1,4-dilithio oximes with amides (DMF, ArCONMe$_2$) followed by a mineral acid induced cyclization–dehydration. The process is exemplified by the conversion of cyclohexanone oxime to 3,4-tetramethyleneisoxazole in 87% yield by successive treatment with *n*-butyllithium, DMF, and acid and by the similar isolation of 5-*p*-anisyl-3,4-trimethyleneisoxazole (67% yield) from cyclopentanone oxime and *N*,*N*-dimethyl-*p*-anisamide. Acylation with DMF of the dilithio salt from (*E*)-benzylacetone oxime afforded 3-(2-phenylethyl)isoxazole in 91% yield uncontaminated by the isomeric 4-benzyl-3-methylisoxazole. An extension of the general scheme permitted the preparation of the latter in 82% yield from acetone oxime. By these procedures, classes of isoxazoles, previously among the most difficult to synthesize (3-substituted, 5-unsubstituted, or aryl), are now among the easiest to make.

Today, the isoxazole ring system is generally considered to be the most broadly useful heteroaromatic precursor and intermediate in preparative organic chemistry.[2] However, the synthetic potential of isoxazoles has not yet been realized fully because of limitations in the structural variations now readily available.[3]

Classically, isoxazoles are made by reaction of 1,3-dicarbonyl compounds (**1**) with hydroxylamine followed by dehydrative cyclization of an intermediate monooxime.[3] When R and R″ in **1** are not the same, two isomeric isoxazoles (**2**) are possible. Both are obtained when R and R″ are similar, a complication which usually leads to major separation prob-

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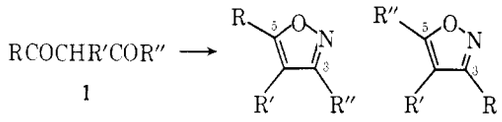
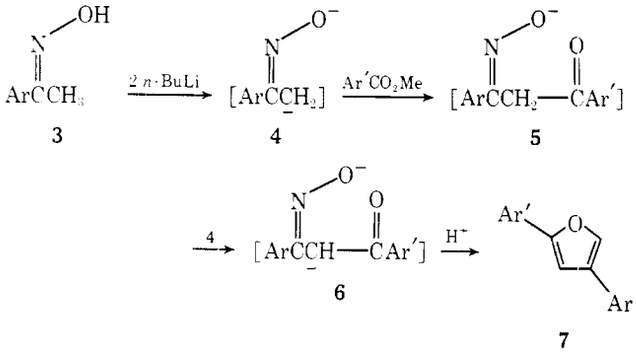


1 2

lems. When R and R″ are quite different, only small amounts of the second isomer are formed. Thus, some unsymmetrical isoxazoles are easily and cleanly synthesized, while others are created only as minor reaction product contaminants. For example, attack on 1 (R″ = H) by hydroxylamine occurs almost exclusively at the aldehyde carbonyl. As a consequence, 3-unsubstituted isoxazoles are readily made, while useful syntheses of most 5-unsubstituted isoxazoles are unknown.[4]

Because our own interest in the latter has been frustrated by difficulties in obtaining desired compounds, we have developed and will describe here a useful, regiospecific route to these and other unsymmetrical isoxazoles.[5]

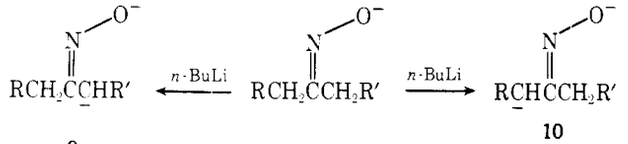
In 1970, Beam, Dyer, Schwarz, and Hauser[6] reported an unequivocal synthesis of unsymmetrical 3,5-diarylisoxazoles which provided the basis for our scheme. They deprotonated acetophenone oximes (3) to the dilithio salts 4, which on acylation with benzoate esters yielded the dianions 6. These cyclized to the isoxazoles 7 on treatment with acid. Cyclopentanone and cyclohexanone oximes were similarly converted to the 5-arylisoxazoles 8. Overall yields were only



3 4 5 6 7

10–40% based on the more expensive oxime component. This deficiency was primarily caused by the loss of half of 4 used up in the thermodynamically required deprotonation 5 → 6.[7] Later, the method was extended to more examples of 7 and 8,[8,9] but waste of the dilithio salt remained an unsolved problem. Still the procedure was recognized as the best available for the synthesis of 7.[9]

The consequences of oxime geometry were not considered: whether the second proton would be abstracted from the carbon syn (→ 9) or anti (→ 10) to the oxygen in an unsymmetrical oxime.[10] Thermally, most oximes are reasonably stable to geometric isomerism and are formed from ketone precursors exclusively or at least primarily in one of the two possible forms. The preferred isomer can usually be predicted from steric factors, but this is ordinarily unnecessary since



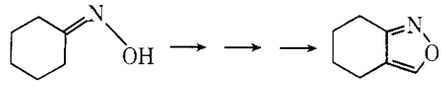
9 10

simple NMR methods are available for identifying and determining the ratio of *E* and *Z* isomers in any sample.[11]

Recently Kofron and Yeh[12] deomonstrated by some elegant alkylation studies[12,13] that the geometry of the starting oxime is retained in the 1,4-dilithio salt and that the second proton is abstracted from the carbon syn to the oxygen (→ 9). For example, a 72% *E* to 28% *Z* mixture of butanone oximes afforded $PhCH_2CH_2COEt$ and $MeCOCHMeCH_2Ph$ in a ratio of 73:27 on treatment with 2 equiv of *n*-BuLi followed by alkylation with $PhCH_2Cl$ and subsequent oxime hydrolysis. Kofron and Yeh argued that syn selectivity is a result of chelation with the Li^+, but this explanation has been excluded in related systems by Fraser et al.[14] They preferred an orbital symmetry rationalization originally formulated by Hoffmann and Olofson in 1966[15] to explain (among other phenomena) the known thermodynamic preference for syn vs. anti geometries in other linear 4-atom π systems containing six electrons (e.g., butadienyl dianions, enediolates, and 1,2-dialkoxy- or 1,2-dihaloethylenes).

Results and Discussion

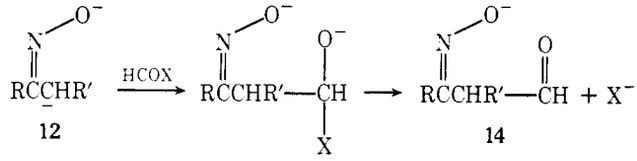
Adaptation of the process of Hauser, Beam, and collaborators to the formation of 5-unsubstituted isoxazoles requires substitution of a formate ester for the benzoate ester. When cyclohexanone oxime was treated in succession with (a) *n*-BuLi (2 equiv) at 0 °C, (b) ethyl formate, and (c) hydrochloric acid–dioxane at reflux, 3,4-tetramethyleneisoxazole (11) was



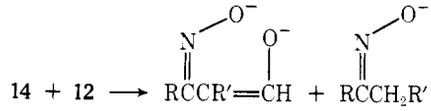
11

isolated in 22% overall yield. Though the yield was poor, the result was encouraging. No published synthesis had ever given 11 unadulterated by the isomeric 4,5-tetramethyleneisoxazole.

To eliminate the waste of dilithio oxime, modification of the leaving group in the formylating agent (HCOX) seemed to offer the best opportunity for success. If 13 could be prevented from fragmenting to 14 until the later acid treatment (when X would be lost as HX), the dianion 12 would not be used up in producing 15. To achieve this end, X^- should be



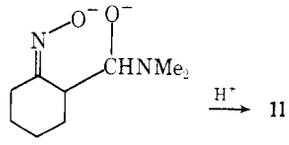
12 13 14



15 16

much worse at stabilizing a negative charge than the O^- in 13 or the EtO^- eliminated with HCO_2Et as the acylating agent. Then X^- would necessarily be a very strong base, and a most attractive formylating agent would be *N*,*N*-dimethylformamide (DMF).[16] The Me_2N^- anion is a much poorer leaving group than alkoxide; Me_2NH is over 15 powers of ten less acidic than ethanol.[17]

Acylation of dilithiocyclohexanone oxime in THF with excess DMF (2 equiv) at 0 °C followed by cyclization with sulfuric acid in aqueous THF at reflux gave the desired isoxazole 11 in 87% distilled yield from the oxime. That the intermediate 17 was stable in the basic reaction medium was shown by bubbling anhydrous N_2 through that medium. Less

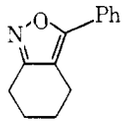


17

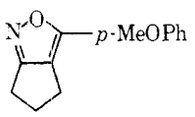
than 2% of the theoretical amount of Me_2NH was isolated from the effluent (as HCl salt).

The excellent yield of **11** by the DMF process has obvious implications with regard to the original Hauser–Beam 5-arylisoxazole synthesis. To see if the yield advantage would hold up, the new methodology was tested in three systems.

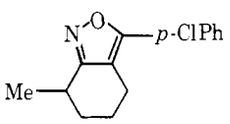
Treatment of dilithiocyclohexanone oxime with *N,N*-dimethylbenzamide[18] afforded the 5-phenylisoxazole **18** in 67% yield when 2 equiv of amide was added and in 64% yield with 1.1 equiv of amide. In the first Hauser-Beam paper,[6] a



18 (67%)



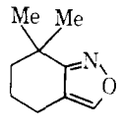
19 (67%)



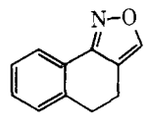
20 (64%)

31% yield for the analogous methyl benzoate reaction was reported, but in a more recent publication the yield was 15%.[8b] By the new amide method, the recrystallized isoxazole **19** from cyclopentanone oxime[19] and *N,N*-dimethyl-*p*-anisamide[20] also was obtained in 67% yield. The published yield of this highly strained isoxazole[21] by the ester process was 15%.[8b] Finally, (*E*)-2-methylcyclohexanone oxime[22] and *N,N*-dimethyl-*p*-chlorobenzamide[23] were converted to **20** in 64% recrystallized yield. Note that the presence of the chloro substituent did not cause complications such as benzyne formation.[24] From the syntheses of **18–20**, it is evident that replacement of the ester in the Hauser–Beam scheme by the *N,N*-dimethylamide increases the 5-arylisoxazole yield by factors of at least two to more than four.

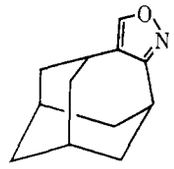
Other 5-unsubstituted isoxazoles also were made with DMF as the acylating agent. For example, 2,2-dimethylcyclohexanone oxime[25] was converted to **21** in 85% distilled yield; α-



21 (85%)



22 (87%)



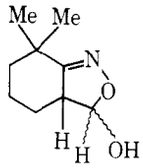
23 (59%)

tetralone oxime[26] similarly afforded pure **22** in 87% yield; and homoadamantanone oxime[27] gave **23** in 59% yield. All three oxime precursors were obtained as single pure syn isomers from reaction of the ketone with hydroxylamine.

Isoxazoles such as **11** and **18–23** generally were made most efficiently when the dilithio oxime was formed with *n*-BuLi in THF at 0 °C. The monolithio salt, which precipitated as the first *n*-BuLi equivalent was added, redissolved as the addition was continued. Substitution of 1,2-dimethoxyethane (DME) for THF generally had little effect on yield: 87% of **11** in THF and 81% in DME. However, in the synthesis of **21**, the monoanion salt precipitated in DME and did not react on continued addition of *n*-BuLi.

Next the DMF was added, also at 0 °C. Though 2 equiv were usually used, the isoxazole yield dropped only slightly if the amount was reduced: 81% of **11** with 2 equiv of DMF in DME and 75% with 1.2 equiv. Formylation was complete in less than an hour, but it ordinarily proved convenient to wait until the next day to perform the cyclization. This was best carried out by pouring the acylation reaction mixture into a somewhat larger volume of 4:1 THF–water made 3 M in H_2SO_4 and refluxing the mixture for 60–90 min. Substitution of 3 M HCl for the H_2SO_4 had little effect on yield. However, the lower boiling products such as **11** were contaminated by 4-chlorobutanol[28,29] from cleavage of some THF by the HCl. Dioxane–HCl also could be utilized for cyclization.

In the synthesis of **11**, the yield was not reduced by replacing the 3 M H_2SO_4 by 1.5 M. However, the product from di-



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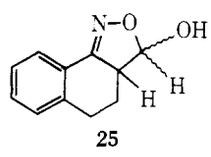

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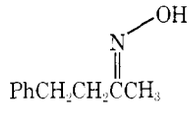
methylcyclohexanone oxime when refluxed with 1.5 M H_2SO_4 was a mixture of the isoxazole **21** (35%) and the two intermediate 5-hydroxyisoxazoline diastereomers **24** (1:1, 31%, mp 68.5–69.5 °C). Similarly, in the preparation of **22** with 1.5 M H_2SO_4 from α-tetralone oxime, the product was a single isoxazoline diastereomer (72% yield) of undetermined stereochemistry (**25**).[30] As part of the structure proofs, **24** and **25** were dehydrated to the isoxazoles with neat trifluoroacetic acid. Thus, the most difficult step in the cyclization process must be the final dehydration to the heteroaromatic system, a somewhat unexpected and surprising result.

In the preceding experiments, only one isoxazole product is possible, even if the starting oxime has the wrong geometry. As a first test of regiospecificity, benzylacetone was converted to its oxime which is obtained entirely in the *E* configuration (**26**).[31] When **26** was treated with *n*-BuLi and DMF and then



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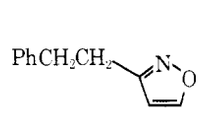

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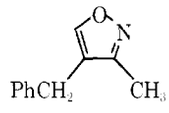

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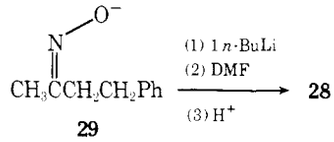
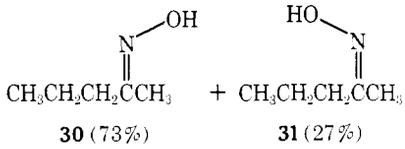
cyclized, the previously unknown isoxazole **27** was isolated in 91% distilled yield. Though searched for, none of the other possible isomer (**28**) was found. This could be prepared, however, from acetone oxime by conversion to its dilithio salt, which was then alkylated with benzyl chloride to give the monolithio salt **29**. Reaction of **29** (note *Z* configuration) with



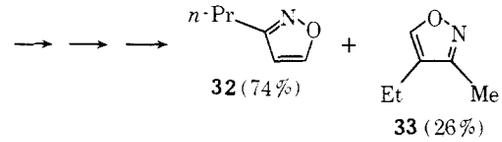
29

another equivalent of *n*-BuLi deprotonated it to the dilithio salt, which was formylated with DMF and cyclized to **28**. The overall yield of distilled **28** from acetone oxime was an excellent 82%, and none of the isomeric **27** was found. Thus, both isomeric isoxazoles **27** and **28** can be obtained in separate, completely regiospecific reactions. Moreover, the scheme, acetone oxime to **28**, illustrates a powerful extension of the standard process to the unambiguous production of the normally disfavored isoxazole isomer.

A few unsymmetrical ketones yield oxime mixtures when treated with hydroxylamine. One example is 2-pentanone, which is converted to a mixture containing 73% of the *E* oxime **30** and 27% of the *Z* oxime **31**.[32] Reaction of this mixture with *n*-BuLi, DMF, and acid gave 3-*n*-propylisoxazole[33] (**32**) and



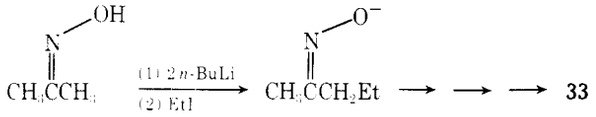
30 (73%) + **31** (27%)



32 (74%)

33 (26%)

4-ethyl-3-methylisoxazole (**33**) in the predicted ratio (found 74:26; combined yield 83%). The minor isomer **33** was formed



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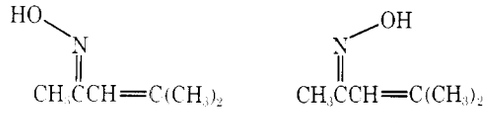
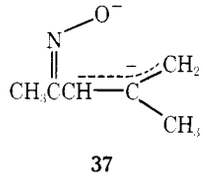
free of **32** by reacting acetone oxime in sequence with (a) 2 *n*-BuLi, (b) EtI, (c) 1 *n*-BuLi, (d) DMF, and (e) acid. By this route, the overall yield of **33** via the *Z* intermediate **34** was 77%.

Thus, both **32** and **33** could be obtained in good yield. However, some effort was expended attempting to increase the ratio **32/33** in the first scheme. The reasoning was as follows. Normally, a methyl group is a stronger C–H acid than a methylene group.[17] If this kinetic acidity difference applies to **30** vs. **31**, then relatively more of **30** than **31** would be doubly deprotonated if less than the full amount of *n*-BuLi were used. Then, if the concentration relationship between the two dianions was retained on trapping by DMF, the final result would be an increase in the ratio **32/33**. The best result was obtained when a 73:27 mixture of **30** and **31** was reacted with 1.6 equiv of *n*-BuLi at −78 °C. Then the observed isoxazole ratio **32/33** was 89:11. The effect is less than anticipated but in the right direction. Other attempts to change this ratio are outlined in the Experimental Section (the ratio could be increased to 94:6, but only at an unacceptable sacrifice in isoxazole yield).

Some interesting discoveries were made when this chemistry was extended to the oximes of mesityl oxide. Oximation of this ketone under standard basic conditions affords a liquid oxime mixture, 77% *E* (**35**) and 23% *Z* (**36**).[34,35] The *Z* oxime hydrochloride also can be prepared,[35] and neutralization of this yields the crystalline *Z* oxime **36**.[35] The latter is somewhat unstable (after 6 weeks at 3–4 °C, the remaining oily solid had a *Z*/*E* ratio of 57:43).



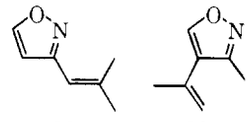
35 (*E*) **36** (*Z*)



37

Though normal ionization at the α carbon syn to the oxime OH is impossible in **36**, deprotonation at the γ carbon would give the ambident dianion **37**, from which an isoxazole could be formed if acylation occurred at the α carbon. Products from γ-carbon formylation should be destroyed during the acid treatment.

Reaction of a 77:23 **35/36** oxime mixture with *n*-BuLi, DMF, and acid gave an isoxazole mixture containing a 59% yield of the *E*-derived product[36] **38** and a 1% yield of the *Z*-derived product[37] **39**. It would seem that **35** is an even more efficient isoxazole precursor vs. **36** than might have been expected. This



38 **39**

35 (77%) + **36** (23%) → (59%) + (1%)

36 (ca. 100%) → (4%) + (35%)

observation was confirmed when the crystalline *Z* oxime **36** was subjected to the same treatment. Then the yield of **39** was 35%, and the product was contaminated by a 4% yield of **38**. The source of **38** in the **36** reaction is not known. The process might not be completely regiospecific, or some component of the reaction mixture might catalyze the isomerism **36** → **35** or the same process in one of the intermediate anions. It is unlikely that the starting **36** contained enough **35** as an impurity.

Two final comments on reaction limitations are the following. Based on the alkylation studies of Kofron and Yeh,[12] aldoximes should not react cleanly, thus excluding the scheme as a useful route to 3-unsubstituted isoxazoles. However, these are most easily made by classical methods.[3] More serious is our inability to obtain isoxazoles with *N*,*N*-dimethylacetamide and *N*,*N*-dimethylisobutyramide as the amide components, possibly because of competing deprotonation of the amides to their enolates by the dilithio oxime. Thus, most 5-alkylisoxazoles are unavailable by this process.

In summary contrast, it is also noteworthy that the yields of the seven previously known 5-unsubstituted isoxazoles and 5-arylisoxazoles, whose synthesis is described here, are at least a factor of two and often a factor of four or more greater than the values reported by earlier methods.

Experimental Section

Melting points were taken in a Thomas-Hoover apparatus equipped with a calibrated thermometer. Infrared spectra were obtained on a Perkin-Elmer 267 spectrophotometer, NMR spectra on a Varian A60-A spectrometer, and mass spectra on an AEI MS-902 high-resolution spectrometer. Gas chromatographic analyses were performed on a Varian "Aerograph" Model 920 chromatograph equipped with thermal conductivity detectors and fitted with a 5 ft × 0.25 in SE-30 on Gas Chrom Q column (A) or a same size 20% Carbowax 20 M on Gas Chrom Q column (B). When used as reaction solvents, the THF and DME were refluxed over and distilled from $LiAlH_4$ before use. Dimethylformamide (DMF) was allowed to stand overnight with BaO and then filtered and distilled at reduced pressure. The *n*-butyllithium (*n*-BuLi) used to form the dianions was obtained as a ca. 2 M solution in hexane and was periodically analyzed by the method of Ellison.[38]

All ground glassware utilized in the preparation and subsequent acylations of the dilithio oximes was dried in an oven at 150 °C, assembled while hot, and allowed to cool under a stream of dry N_2. The apparatus was designed to ensure that all subsequent reactions were performed under a slight N_2 pressure.

Oximes. Commercial acetone oxime was recrystallized from hexane before use. Cyclohexanone oxime [recrystallized from hexane, mp 89.5–90.5 °C (lit.[39] mp 89.5–90.5 °C)], (*E*)-2,2-dimethylcyclohexanone oxime[11c,f,g] [from ethanol–water, mp 93.5–94 °C (lit.[25] mp 92–93 °C)], α-tetralone oxime [from ethanol–water, mp 102.5–103.5 °C (lit.[26] mp 102–103 °C)], cyclopentanone oxime [from hexane, mp 57–58.5 °C (lit.[19] mp 58.5 °C)], (*E*)-benzylacetone oxime [from ethanol–water, mp 85–86 °C (lit.[31] mp 86–87 °C)], (*E*)-homoadamantan-4-one oxime[11d] [from ethanol–water, mp 145–146 °C (lit.[27] mp 145–146 °C)], and (*E*)-2-methylcyclohexanone oxime[11f] [from hexane, mp 41.5–43 °C (lit.[22] mp 43 °C)] were made from the ketones and hydroxylamine hydrochloride by the standard procedure[40] (or for the last two oximes by the minor variations described in the melting point references). The references to the source of the stereochemical assignments follow the oxime names. The benzylacetone oxime was assigned the *E* structure because the α-CH_2 NMR resonance shifted further downfield than the methyl peak in the presence of $Eu(DPM)_3$:[11g] NMR ($CDCl_3$) δ 1.87 (3 H, s), 2.25–2.65 (2 H, m), 2.7–3.0 (2 H, m), 7.13 (5 H, s), 8.6–9.4 (1 H, broad); NMR (0.001 mol in 0.5 mL of $CDCl_3$ containing 20 mg of Eu reagent) δ 2.16 (3 H, s), 2.75–3.15 (4 H, broad s), 7.13 (5 H, s), 9.8–10.3 (1 H, broad).

The 2-pentanone oxime mixture[40] was isolated by distillation at reduced pressure, bp 71–73 °C at 12 Torr (lit.[32] bp 165 °C at 725 Torr). The 73:27 *E*/*Z* ratio found by Berlin[11g] was confirmed by europium shift NMR analysis.

Mesityl oxide was converted to its *Z* oxime hydrochloride [mp 118.5–120 °C dec (lit.[35] mp 123 °C dec)]. Addition of Na_2CO_3 (0.10 mol) in portions to a solution of this salt (0.07 mol) in 40 mL of water precipitated the free *Z* oxime as a white solid. Recrystallization from petroleum ether (35–60 °C) gave colorless radiating sheets of mp 47–48 °C (lit.[35] mp 49 °C): 71% yield; NMR (CCl_4) δ 1.77 (3 H, d, *J* = 1.5 Hz), 1.83 (3 H, d, *J* = 1.5 Hz), 1.99 (3 H, s), 5.96 (1 H, m), 9.6–9.9

(1 H, broad). After 6 weeks at 3–4 °C, the originally pure *Z* oxime was an oily solid which analyzed as a 57:43 *Z*/*E* mixture (NMR).

The mesityl oxide *E* and *Z* oxime mixture[34] was isolated as a clear, colorless oil of bp 87–89 °C at 13 Torr (lit.[35] bp 85 °C at 10 Torr): NMR ($CDCl_3$) δ 1.78 (d, *J* = 1.5 Hz) and 1.83 (d, *J* = 1.5 Hz) (6 H, γ-methyls), 1.93 (s, *E* oxime) and 2.00 (s, *Z* oxime) (3 H, α-methyls), 5.60 (0.77 H, m, vinyl H of *E* oxime), 5.96 (0.23 H, m, vinyl H of *Z* oxime), 9.7–10.1 (1 H, broad). The 77:23 *E*/*Z* ratio was calculated from the NMR vinyl absorption areas. The product was contaminated by 4% of isomesityl oxide oximes (NMR m's at δ 2.9, 3.1, and 4.9).

3,4-Tetramethyleneisoxazole (11). *n*-Butyllithium (*n*-BuLi) in hexane (0.055 mol) was added (30 min) to a rapidly stirred solution of cyclohexanone oxime (2.83 g, 0.025 mol) in 50 mL of THF cooled to 0 °C (ice bath). A white solid which precipitated during addition of the first equivalent of *n*-BuLi largely dissolved as the addition continued. After an hour at 0 °C, no solid remained and the dilithio salt solution was light yellow. DMF (3.66 g, 0.05 mol) in 15 mL of THF was added over 15 min, and stirring was continued at 0 °C for another hour. Then the solution was allowed to warm to room temperature, left overnight (though the reaction was over after less than an hour; see below), and poured into a rapidly stirred solution of 11.0 g of concentrated H_2SO_4 diluted to 75 mL with 4:1 THF–water (3 N in H_2SO_4). This mixture was refluxed for an hour and cooled, and the layers were separated. The organic layer was set aside, and the aqueous phase was carefully basified with solid $NaHCO_3$, diluted with enough water to dissolve any precipitated inorganic salts, and extracted with ether (3 × 25 mL). All of the organic layers were combined, washed successively with 5% aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), and dried ($MgSO_4$). Vacuum distillation afforded **11**: 2.72 g (88%); bp 85–87 °C at 9 Torr (lit.[41] bp 87–88 °C at 14 Torr); NMR (CCl_4) δ 1.5–2.0 (4 H, m), 2.35–2.85 (4 H, m), 8.07 (1 H, s); trace of (2%) DMF contamination.

In another experiment, the ice bath was removed immediately after the DMF addition and the reaction mixture was reacted with acid 75 min later: acid made up by diluting 22 g of concentrated H_2SO_4 to 75 mL with 4:1 THF–water (6 N in H_2SO_4). In the final workup, hexane was substituted for ether. Vacuum distillation afforded **11** uncontaminated by DMF; yield 2.68 g (87%).

When the first experiment was repeated with DME as the solvent and 3 N HCl in aqueous dioxane in the acid cyclization step, an 81% yield of pure **11** was obtained. With 1.5 and 1.2 equiv of DMF, the yields were 76 and 75%, respectively. When the reaction was carried out with THF as the solvent and using 4 N aqueous HCl in dioxane in the acid cyclization step, vacuum distillation gave **11** in 80% corrected yield. However, it was contaminated by 27% of 4-chlorobutanol[28] (NMR and VPC comparison[29]).

An attempt was made to trap Me_2NH by allowing N_2 to bubble slowly through the reaction solution during the DMF addition and for another 5 h. The gas stream was passed through a KOH drying tube into 20 mL of 4 N HCl. Evaporation of the acid solution in vacuo yielded only 0.03 g (1.5%) of Me_2NH·HCl (IR comparison).

In the ethyl formate test experiment, the ester (dried over K_2CO_3 and distilled) (0.93 g, 0.0125 mol) in DME (10 mL) was added (5 min) to the dilithiocyclohexanone oxime in DME. After 30 min at 0 °C, the mixture was poured into 25 mL of concentrated HCl diluted by 75 mL of dioxane and refluxed for an hour. Workup as already described yielded 1.07 g of an oil, bp 86–87.5 °C at 8 Torr, shown by VPC (column A) to contain 63% of **11** (yield 22%), 31% of cyclohexanone oxime, and 6% of cyclohexanone. Cyclohexanone oxime was the main component (IR) of the substantial pot residue.

7-Aza-5,5-dimethyl-8-oxabicyclo[4.3.0]-6,9-nonadiene (21). (In the syntheses of this and other isoxazoles which follow, the main procedure described above was followed with minor variations.) DMF (3.66 g, 0.05 mol) in THF (15 mL) was added (15 min) to a well-stirred THF–hexane solution of the dilithio salt from (*E*)-2,2-dimethylcyclohexanone oxime (2.82 g, 0.025 mol). No solid precipitated during the *n*-BuLi addition. However, a white solid appeared while the mixture was stirred for another 6.5 h after removal of the ice bath. The mixture was poured into a rapidly stirred solution of 22 g of concentrated H_2SO_4 diluted to 75 mL with 4:1 THF–water (6 N in H_2SO_4). After 75 min at reflux, the reaction was worked up as above (except replacement of ether by hexane[42]). Vacuum distillation gave **21**: 3.23 g (85% yield; no DMF contaminant[42]); bp 92.5–94 °C at 11 Torr; NMR (CCl_4) δ 1.32 (6 H, s), 1.5–2.0 (4 H, m), 2.35–2.7 (2 H, m), 7.98 (1 H, t, *J* = 1 Hz); mass spectrum, *m/e* (relative intensity) 151.0996 (M^+, 10; calcd *m/e* 151.0997), 136.0777 ($M^+ - Me$, 5; calcd *m/e* 136.0762), 69 (100).

When the acid-induced ring closure was performed by refluxing for an hour with 75 mL of 3 N H_2SO_4 in 4:1 THF–water, a 35% yield of **21** was isolated by vacuum distillation. The pot residue solidified upon cooling, and recrystallization from ether–pentane afforded a white solid, mp 68.5–69.5 °C, identified as a 1:1 mixture of the **24** diastereomers: 1.32 g (31%); IR (CH_2Cl_2) 2.77–3.08 μm (w with m spike at 2.79 μm); NMR ($CDCl_3$) δ 1.0–2.5 (12 H, m with large spikes of similar intensity at δ 1.15, 1.23, 1.30, and 1.33), 2.85–3.45 (1 H, m), 4.1–4.65 (1 H, broad), 5.57 (0.5 H, d, *J* = 2.5 Hz), 5.83 (0.5 H, d, *J* = 7 Hz); mass spectrum, *m/e* (relative intensity) 169.1087 (M^+, 12; calcd *m/e* 169.1102), 154.0861 ($M^+ - Me$, 1; calcd *m/e* 154.0867), 153 (6), 152.1063 ($M^+ - OH$, 4; calcd *m/e* 152.1075), 151.0989 ($M^+ - H_2O$, 2; calcd *m/e* 151.0997), 69 (31), 55 (23), 44 (39), 40 (100).

The NMR spectrum of the **24** pair in CF_3CO_2H was the same as that of **21** in the same solvent: NMR δ 1.52 (6 H, s), 1.7–2.2 (4 H, m), 2.55–2.9 (2 H, m), 8.41 (1 H, t, *J* = 1 Hz).

When DME was used as the initial reaction solvent, the white precipitate which formed on addition of the first equivalent of *n*-BuLi did not dissolve when more *n*-BuLi was added. After 90 min at 0 °C, the DMF was added. The solid remained even after stirring overnight at 25 °C. Acid cyclization and workup yielded 2,2-dimethylcyclohexanone as the only high-boiling product.

4,5-Dihydronaphth[1,2-*c*]isoxazole (22). Ring closure of the formylation intermediate from α-tetralone oxime (4.03 g, 0.025 mol) (in THF–hexane) was achieved by refluxing for an hour with 75 mL of a solution of concentrated H_2SO_4 in 4:1 THF–water (6 N in H_2SO_4). **22** was isolated as a yellow oil: 3.56 g (83%); bp 96–98 °C at 0.2 Torr (lit.[21] bp 114–117 °C at 0.3 Torr); NMR (CCl_4) δ 2.55–3.1 (4 H, m), 7.1–7.65 (3 H, m), 7.75–8.0 (1 H, m), 8.07 (1 H, t, *J* = 1 Hz).

Attempted dehydration–cyclization by refluxing for an hour with 3 N H_2SO_4 in 4:1 THF–water yielded a light yellow oil which crystallized upon standing. Two recrystallizations from 95% EtOH afforded a single **25** diastereomer: 3.38 g (72%); small white needles of mp 129–131.5 °C; IR ($CHCl_3$) 2.77–3.04 μm (w with m spike at 2.79 μm); NMR (CD_3CN) δ 1.65–2.3 (2 H, m), 2.7–3.5 (3 H, m), 4.45–4.75 (1 H, m, washed out with D_2O), 5.5–5.9 (1 H, m; became d, *J* = 6 Hz, after D_2O wash), 7.05–7.35 (3 H, m), 7.6–8.0 (1 H, m); mass spectrum, *m/e* (relative intensity) 189.0792 (M^+, 100; calcd *m/e* 189.0789), 172.0750 ($M^+ - OH$, 7; calcd *m/e* 172.0762), 171.0672 ($M^+ - H_2O$, 2; calcd *m/e* 171.0683), 161 (31), 144 (74), 143 (55), 116 (57), 115 (38).

The NMR spectrum of **25** in CF_3CO_2H was the same as that of **22** in the same solvent: NMR δ 2.75–3.5 (4 H, m), 7.25–8.1 (4 H, m), 8.80 (1 H, t, *J* = 1 Hz).

An 87% yield of **22** was obtained when the reaction was run on twice the above scale and the ring closure was carried out by refluxing the mixture for 90 min in 33 mL of concentrated HCl diluted by 67 mL of THF.

Tricyclo[4.3.1.1^{3,8}]undecan[4,5-*c*]isoxazole (23). The dilithio salt was prepared by adding (50 min) *n*-BuLi (0.0276 mol) to homoadamantan-4-one oxime (2.16 g, 0.012 mol) in 45 mL of THF at 0 °C. After stirring for 3 h at 0 °C, DMF (3.50 g, 0.048 mol) in THF (10 mL) was added and stirring was continued at 0 °C for another 2.5 h. The solution was stirred overnight at 25 °C and then refluxed (90 min) with 17 mL of concentrated HCl and 33 mL of dioxane. A standard extraction workup gave a concentrate from which most of the 4-chlorobutanol was removed in vacuo (oil bath at 60 °C, pressure 0.3 Torr). The remaining oil crystallized upon dissolution in CH_2Cl_2 followed by evaporation. Two recrystallizations from aqueous EtOH gave colorless needles of mp 92.5–93.5 °C: 1.35 g (59%); NMR ($CDCl_3$) δ 1.2–2.35 (12 H, m), 2.85–3.45 (2 H, m), 7.95 (1 H, d, *J* = 1 Hz); mass spectrum, *m/e* (relative intensity) 189.1158 (M^+, 53; calcd *m/e* 189.1153), 162 (100), 161.1201 ($M^+ - CO$, 57; calcd *m/e* 161.1204), 79 (63), 41 (72).

5-Phenyl-3,4-tetramethyleneisoxazole (18). The procedure for the preparation of **11** was followed substituting *N*,*N*-dimethylbenzamide[18] (7.46 g, 0.05 mol) for DMF. The dark yellow oil obtained after ring closure and extraction workup crystallized from 95% EtOH; white sheets of mp 65–67 °C (lit.[6] mp 65–67 °C) were obtained after recrystallization, 2.30 g (46%). Chromatography (silica gel with CCl_4) of the combined filtrates yielded another 1.36 g (21%) of **18** after recrystallization: mp 63.5–65.5 °C; NMR ($CDCl_3$) δ 1.5–2.1 (4 H, m), 2.4–3.1 (4 H, m), 7.2–7.95 (5 H, m).

5-*p*-Methoxyphenyl-3,4-trimethyleneisoxazole (19). Synthesis of **19** as above from *N*,*N*-dimethyl-*p*-methoxybenzamide[20] and cyclopentanone oxime (2.48 g, 0.025 mol) gave, after chromatography and recrystallization from 95% EtOH, a yellow solid of mp 92–93.5 °C (lit.[8b] mp 91–94 °C): 3.58 g (67%); NMR ($CDCl_3$) δ 2.15–3.0 (6 H, m), 3.78 (3 H, s), 6.85 (2 H, d from AB q, *J* = 9 Hz), 7.55 (2 H, d from AB q, *J* = 9 Hz). Another 4% of **19** was present in the crystallization filtrate (NMR analysis).

Similarly, (*E*)-2-methylcyclohexanone oxime and *N*,*N*-dimethyl-*p*-chlorobenzamide[23] were converted to the isoxazole **20** as white plates from 95% EtOH: yield 3.95 g (64%); NMR ($CDCl_3$) δ

Table I. Isoxazoles from (*E*)- and (*Z*)-2-Pentanone Oxime Mixture: Reaction Condition Variations

n-BuLi, equiv	Reaction temp[a]	DMF, equiv	Isoxazole mixture yield,[b] %	32:33
2.20	0 °C	2.0	83	74:26
1.75	0 °C	1.5	86	83:17
1.65	−78 °C[c]	1.5	81	89:11
1.65	0 °C, then reflux[d]	1.5	40	94:6
1.65	−78 °C, then 50 °C[e]	1.5	64	89:11
1.60	0 °C	1.2	84	83:17

[a] During and after *n*-BuLi addition. [b] Based on possible yield from *n*-BuLi (e.g., 1.8 mol of *n*-BuLi could yield 0.8 mol of product). [c] Mixture is warmed to 25 °C before DMF is added. [d] Dilithio oxime mixture is refluxed for 1.2 h and then cooled to ca. 25 °C before DMF is added. [e] Dilithio oxime mixture is heated at 50 °C for 1.5 h and then cooled to ca. 25 °C before DMF is added.

1.3–2.2 (m) and 1.40 (d, J = 6 Hz) (total of 7 H), 2.55–3.2 (3 H, m), 7.35 (2 H, d from AB q, J = 9 Hz), 7.62 (2 H, d from AB q, J = 9 Hz); mass spectrum, m/e (relative intensity) 249.0816 (M^+ + 2, 35; calcd m/e 249.0794), 247.0777 (M^+, 88; calcd m/e 247.0763), 193 (12), 191 (41), 141 (35), 139 (100), 113 (15), 111 (35).

3-(2-Phenylethyl)isoxazole (27). With (*E*)-benzylacetone oxime (4.08 g, 0.025 mol) as the oxime component, the procedure for **11** was followed, yielding **27** as an oil: 3.95 g (91%; VPC pure); bp 74–76 °C at 0.1 Torr; NMR (CCl_4) δ 2.87 (4 H, s), 5.90 (1 H, d, J = 1.5 Hz), 7.07 (5 H, s), 8.02 (1 H, d, J = 1.5 Hz); mass spectrum, m/e (relative intensity) 173.0831 (M^+, 55; calcd m/e 173.0840), 172 (33), 144 (25), 130.0652 ($M^+ - C_2H_3O$, 11; calcd m/e 130.0656), 129 (5), 115 (3), 104 (50), 103 (11), 91 (100), 77 (22).

4-Benzyl-3-methylisoxazole (28). Benzyl chloride (dried over $MgSO_4$ and distilled) (3.33 g, 0.0263 mol) in THF (15 mL) was added (20 min) to a solution prepared from acetone oxime (1.83 g, 0.025 mol) and *n*-BuLi (0.0525 mol). The solution was stirred at 0 °C (30 min), warmed to 25 °C (30 min), and stirred for an hour. The solution was cooled again to 0 °C, *n*-BuLi (0.0263 mol) was dripped in (20 min), and the resulting burgundy solution was stirred at 0 °C for 45 min. DMF (3.66 g, 0.05 mol) in THF (15 mL) was added (15 min), and then the solution was warmed to 25 °C and stirred overnight. **28** was isolated by vacuum distillation after the acid cyclization (reflux 90 min) and standard extraction workup: 3.57 g (82%); bp 81–82 °C at 0.2 Torr; NMR (CCl_4) δ 2.02 (3 H, s), 3.62 (2 H, s), 6.9–7.4 (5 H, m), 7.95 (1 H, s); mass spectrum, m/e (relative intensity) 173.0842 (M^+, 100; calcd m/e 173.0840), 172.0745 ($M^+ - H$, 18; calcd m/e 172.0762), 144.0801 ($M^+ - CHO$, 26; calcd m/e 144.0812), 131 (47), 130 (18), 115.0548 ($M^+ - C_2H_4NO$, 5; calcd m/e 115.0547), 104 (18), 103 (34), 91.0537 ($C_7H_7^+$, 68; calcd m/e 91.0547), 77 (29). None of the isomeric **27** was obtained (VPC analysis).

4-Ethyl-3-methylisoxazole (33). The above procedure was followed substituting ethyl iodide (3.90 g, 0.0263 mol) for benzyl chloride. **33** was isolated as a colorless oil: 2.15 g (77%); bp 84–86 °C at 54 Torr; NMR (CCl_4) δ 1.18 (3 H, t, J = 7 Hz), 2.16 (3 H, s), 2.37 (2 H, q, J = 7 Hz), 8.07 (1 H, s); mass spectrum, m/e (relative intensity) 111.0675 (M^+, 88; calcd m/e 111.0683), 110.0607 ($M^+ - H$, 9; calcd m/e 110.0605), 96.0448 ($M^+ - Me$, 65; calcd m/e 96.0449), 68.0269 ($C_4H_4O^+$, 71; calcd m/e 68.0261), 42 (100). None of the isomer **32** was found (VPC analysis).

Mixture of 3-Propylisoxazole (32) and 4-Ethyl-3-methylisoxazole (33) from (*E*)- and (*Z*)-2-Pentanone Oxime Mixture. The procedure for the synthesis of **11** was followed using the 73% (*E*)- to 27% (*Z*)-2-pentanone oxime mixture. The isoxazole product mixture was isolated by vacuum distillation: 2.30 g (yield 83%; corrected for ca. 7% of DMF contaminant; NMR and IR analysis); bp 82–87 °C at 65 Torr. A product ratio of 74% of **32** and 26% of **33** was determined by NMR (relative areas of isoxazole 5-H peaks) and VPC (column B at 110 °C and flow rate of 60 cm^3/min; **32** retention time, 10.1 min; **33**, 12.9 min) analyses. **33**: (lit.[33] bp 74–75 °C at 40 Torr) NMR (CCl_4) δ 0.98 (3 H, t, J = 7 Hz), 1.4–2.1 (2 H, m), 2.68 (2 H, t, J = 7 Hz), 6.22 (1 H, d, J = 1.5 Hz), 8.40 (1 H, d of t, J = 0.5 and 1.5 Hz). Reaction condition variations are summarized in Table I.

4-Isopropenyl-3-methylisoxazole (39) and 3-(2-Methyl-1-propenyl)isoxazole (38) from (*Z*)-mesityl Oxide Oxime. With (*Z*)-mesityl oxide oxime (2.83 g, 0.025 mol) as the reactant, the procedure for **11** was used with the following modification. The *n*-BuLi was added to the oxime solution at −78 °C (dry ice–acetone bath), and the mixture was then warmed to 0 °C (45 min). During this period a white solid, which later dissolved, appeared. Vacuum distillation gave the **38–39** mixture: 1.20 g (39%; corrected for ca. 3% of unidentified impurities); bp 69–72 °C at 10 Torr. A product ratio of 89% of **39** to 11% of **38** was calculated from VPC peak areas (column B at 130 °C; flow rate 55 cm^3/min) and NMR analysis (relative areas of 5-H peaks). Compound **39**: (lit.[37] bp 70–71 °C at 17 Torr) retention time, 9.8 min; NMR (CCl_4) δ 2.02 (3 H, d of d, J = 1 and 1.5 Hz), 2.33 (3 H, s), 4.9–5.2 (2 H, m), 8.18 (1 H, broad s). Compound **38**: retention time, 12.7 min; NMR (CCl_4) δ 1.90 (3 H, d, J = 1.5 Hz), 2.00 (3 H, d, J = 1.0 Hz), 6.0–6.2 (1 H, m), 6.25 (1 H, d, J = 1.5 Hz), 8.32 (1 H, d of d, J = 0.5 and 1.5 Hz). Mass spectrum, m/e (relative intensity) 123.0687 (M^+, 100; calcd m/e 123.0684), 122.0610 ($M^+ - H$, 26; calcd m/e 122.0605), 108 (9), 94.0650 ($M^+ - CHO$, 60; calcd m/e 94.0656), 55 (26), 53 (29), 39 (46).

38, was identical with a sample separated from a mixture[36] [bp 79–84 °C at 6 Torr (lit.[36] bp 65–69 °C at 6 Torr)] with the isomeric 5-(2-methyl-1-propenyl)isoxazole: NMR (CCl_4) δ 1.92 (3 H, d, J = 1.5 Hz), 2.00 (3 H, d, J = 1.0 Hz), 6.13–6.37 (2 H, m with d at δ 6.15, J = 1.5 Hz), 8.25 (1 H, d of d, J = 0.5 and 1.5 Hz).

When (*Z*)-mesityl oxide oxime dianion was made at 0 °C, the yield dropped to 28% and the isoxazole mixture contained 85% of **39** and 15% of **38**.

4-Isopropenyl-3-methylisoxazole (39) and 3-(2-Methyl-1-propenyl)isoxazole (38) from (*E*)- and (*Z*)-Mesityl Oxide Oxime Mixture. Repetition of the standard synthesis using the normally obtained mixture of mesityl oxide oximes (77% *E* and 23% *Z*) (2.83 g, 0.025 mol) afforded the product isomer mixture: 1.86 g (60%; corrected for ca. 5% of unidentified impurities); bp 77–80 °C at 15 Torr; **38/39** ratio was 98:2 (VPC and NMR analysis, see above).

Attempted Synthesis of 5-Methyl-3,4-tetramethyleneisoxazole. The process used for **11** was followed substituting *N*,*N*-dimethylacetamide (distilled) for DMF (3 N HCl used in acid cyclization). Vacuum distillation after workup yielded only 4-chlorobutanol, *N*,*N*-dimethylacetamide, and cyclohexanone (NMR and VPC analyses). The results were similar when the acetamide was added to the dilithiocyclohexanone oxime at −63 °C (liquid N_2–$CHCl_3$ bath) or at +53 °C. Similar failure was encountered in attempts to prepare the isoxazole from dilithio-(*E*)-2-methylcyclohexanone oxime and *N*,*N*-dimethylisobutyramide.[43]

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Registry No.—**11**, 2305-78-4; **18**, 24097-27-6; **19**, 61054-32-8; **20**, 66417-90-1; **21**, 20108-84-3; **22**, 66417-91-2; **23**, 66482-61-9; *cis*-**24**, 66482-62-0; *trans*-**24**, 66482-63-1; **25**, 66482-64-2; **26**, 66417-92-3; **27**, 66417-93-4; **28**, 66417-94-5; **30**, 26306-10-5; **31**, 26306-11-6; **32**, 30842-94-5; **33**, 66417-95-6; **35**, 28052-09-7; **36**, 28052-10-0; **38**, 54316-28-8; **39**, 66417-96-7; mesityl oxide, 141-79-7; (*Z*)-mesityl oxime HCl, 66417-97-8; cyclohexanone oxime, 100-64-1; (*E*)-2,2-dimethylcyclohexanone oxime, 66417-98-9; α-tetralone oxime, 3349-64-2; (*E*)-homoadamantan-4-one oxime, 26770-89-8; *N*,*N*-dimethylbenzamide, 611-74-5; *N*,*N*-dimethyl-*p*-methoxybenzamide, 7291-00-1; cyclopentanone oxime, 1192-28-5; (*E*)-2-methylcyclohexanone oxime, 32179-89-8; *N*,*N*-dimethyl-*p*-chlorobenzamide, 14062-80-7; benzyl chloride, 100-44-7; acetone oxime, 127-06-0; ethyl iodide, 75-03-6; 5-(2-methyl-1-propenyl)isoxazole, 66417-99-0.

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Conformations of Azocane (Azacyclooctane)

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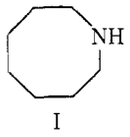
The ^{1}H and the natural-abundance ^{13}C NMR spectra of azocane (azacyclooctane) (I) have been measured from −10 to −180 °C. A dynamic NMR effect is observed in the ^{1}H NMR spectra of I in the vicinity of −120 °C, and is attributed to ring inversion in a boat–chair, which is the predominant conformation of I. The free energy of activation ($\Delta G^{\ddagger}$) for this process is 7.3 ± 0.2 kcal/mol. The ^{13}C NMR spectra of I show a dynamic NMR effect which does not arise from ring inversion in the boat–chair, but rather from the interconversion of this conformation with a small concentration (3% at −112 °C) of a crown–family conformation. The thermodynamic and kinetic parameters for the boat–chair to crown process are as follows: ΔG° = 1.2 ± 0.1 kcal/mol, $\Delta G^{\ddagger}$ = 10.5 ± 0.2 kcal/mol.

Lambert and Khan[1] have recently measured the ^{1}H and ^{13}C NMR spectra of azocane (I) and related compounds from room temperature to −120 °C. We have also studied the dynamic NMR behavior of I at low temperatures,[2] but our results, which we now report, differ in some important respects from those obtained by these authors.



I

Lambert and Khan[1] found that the α resonance of azocane in the 270 MHz ^{1}H NMR spectrum splits into two bands of equal intensities at low temperatures. The two bands were well resolved at −107 °C and coalesced to a single band at about −95 °C. These authors concluded that azocane has a boat–

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