(because of the instability of **5** toward handling in the pure state, quantitative extinction coefficients were not obtained); nmr ($CDCl_3$) τ 1.95–3.50 (m, 6, Ar H), 3.28 (s, 2, CH=CH), and 6.98 (s, 3, NCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 237 (100) and 208 (26).

Anal. Calcd for $C_{15}H_{11}NS$: mol wt, 237.061. Found: (high-resolution mass spectrum), 237.061.

Thermal Decomposition of 5.—A solution of 8 mg of **5** in 0.5 ml of benzene was placed in a thick-walled tube, degassed, sealed, and heated in an oil bath maintained at 203 ± 0.5° for 20 hr. After the tube had been cooled, it was opened and the solution was concentrated. Analysis of the residue by tlc over silica gel using benzene for elution showed five components. The major component, also the one of highest R_f value (0.8), had a characteristic bright blue fluorescence. This was separated and rerun in a tlc comparison with an authentic sample of **19**. Both showed the same blue fluorescence and both were identical in their tlc behavior.

Registry No.—**5**, 29939-42-2; **8**, 29939-43-3; **10**, 4063-33-6; **11**, 29939-45-5; **12**, 29939-46-6; **13**, 29939-47-7; **14**, 30115-51-6; **15**, 29939-48-8; **16**, 29939-49-9.

Intramolecular Nitrone–Olefin Cycloadditions. The Stereochemistry of Hexahydro-2,1-benzisoxazoline Formation[1]

NORMAN A. LEBEL* AND EUGENE G. BANUCCI

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

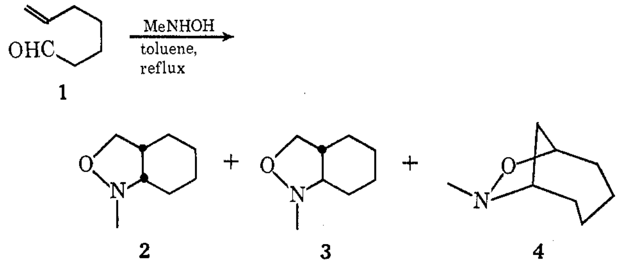
Received February 4, 1971

The stereochemistry of the intramolecular, 1,3-dipolar cycloaddition of several methyl-substituted *N*-methyl-*C*-6-heptenylnitrones was studied. The major product isoxazolidines were confirmed to have the 7-aza-8-oxabicyclo[4.3.0]nonane (3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline, hydrindan) skeleton. The stereochemistry at the ring fusion was assigned primarily on the basis of nmr spectral evidence. It was found that cyclization of the nitrones at 76° gave primarily the trans-fused isomers in all cases, and the ratio between cis and trans isomers was influenced mainly by substitution in the five-membered isoxazolidine ring. Interconversion of the isoxazolidines in the temperature range 180–300° occurred by retro-1,3-dipolar cycloaddition. At these temperatures the thermodynamically more stable cis-fused isomers predominated. These results correlate well with what is known concerning the relative stabilities of *cis*- and *trans*-hydrindan. The retro-1,3-dipolar cycloaddition of bicyclic isoxazolidines promises to be a valuable method for relative stability studies of fused heterobicyclo[*n*.3.0] derivatives.

Part A

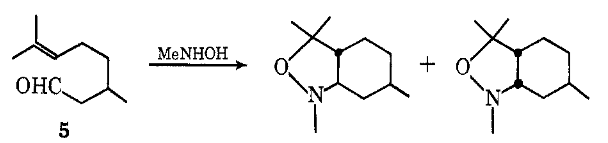
In the intramolecular 1,3-cycloaddition of *N*-alkyl-*C*-5-hexenyl- and -6-heptenylnitrones to give fused bicyclic isoxazolidine products, cis–trans isomerism at the ring juncture is a source of configurational ambiguity. For every case of product formation involved with the creation of a 2-aza-3-oxabicyclo[3.3.0]octane skeleton (*N*-alkyl-*C*-5-hexenylnitrones) a cis fusion was noted. Ring closure to give the more highly strained trans isomer would require a transition state of prohibitive energy.[2] However, with the homologous series mixtures of isomers having the azaoxabicyclo[4.3.0]nonane (5-aza-6-oxahydrindanyl, 3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline) ring system were obtained,[2a] and the relative amounts of the isomers were shown to be temperature dependent in at least one case.[2b]

For example, the unsubstituted compound **1** led to a 3:1:1 mixture of cis (**2**), trans (**3**), and bridged bicyclic isomers **4**, respectively.[2a] On the other hand,



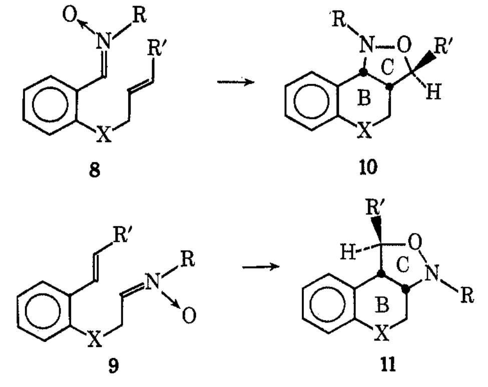
1 **2** **3** **4**

condensation of (+)-citronellal (**5**) with *N*-methylhydroxylamine gave isomer ratios for **6**:**7** ranging from 97:3 at 25° to 87:13 at 138°.[2] In this case, predom-



5 **6** **7**

inant formation of the trans isomer is found. Very recently, a series of papers has revealed the intramolecular cyclizations of nitrones of the types **8** and **9**.[3] The products, tetrahydrobenzopyrano[4,3-*c*]isoxazoles (**10**, X = O), the analogous quinoline analogs (**10**, X = NH), and the tetrahydrobenzopyrano[3,4-*c*]isoxazoles (**11**, X = O), were found in almost every case to contain a cis juncture between the B and C rings. In only



8 **10** **9** **11**

(1) We gratefully acknowlege the National Science Foundation for support under Grant No. GP14114.

(2) (a) N. A. LeBel, M. E. Post, and J. J. Whang, *J. Amer. Chem. Soc.*, **86**, 3759 (1964); (b) M. E. Post, unpublished data.

(3) (a) W. Oppolzer and K. Keller, *Tetrahedron Lett.*, 1117, 4313 (1970); (b) W. Oppolzer and H. P. Weber, *ibid.*, 1121 (1970).

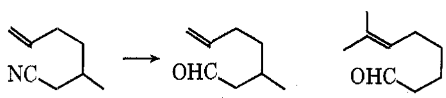
one example was a trans B/C ring fusion noted, and the product ratio was 51:17, cis to trans, respectively.[3a]

Any attempt at rationalization of these divergent data must take into account that nitrone–olefin cycloadditions are reversible.[4–6] We have shown previously that isoxazolidines **6** and **7** are configurationally stable at all temperatures used in their preparation (<200°) but that they are in equilibrium with a third isomer at higher temperatures. However, it was emphasized that the two isomers produced in the *nonstereoselective* cyclization of an analog of **8** (*vide supra*) were not interconverted at 110°.[3a] There remains, of course, the possibility that equilibrium had already been attained in this last example.

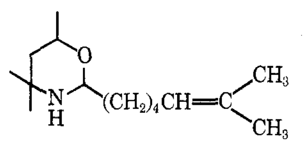
In this manuscript we summarize data which amplify and explain the stereochemical observations encountered in the formation of 6,5-fused heterocycles by way of this intramolecular cyclization reaction.

Results

Two additional olefinic aldehydes (**12** and **13**) intermediate in substitution between the two extremes **1** and **5**, were selected, and an analysis of the stereochemistry of the products from intramolecular 1,3 cycloaddition of the nitrones was conducted. The synthesis of 3-methyl-6-heptenal (**12**) was straightforward,



14 **12** **13**

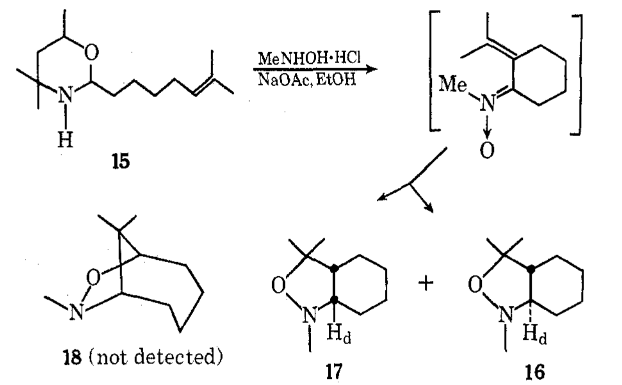


15

because the commercially available allylacetone could be easily homologated by way of the alcohol and then the bromide or tosylate to 5-cyano-1-hexene. Alcoholysis of this nitrile gave an ester which was reduced with lithium aluminum hydride to 2-methyl-5-hexen-1-ol. The *p*-toluenesulfonate of this alcohol was subjected to displacement with cyanide to obtain nitrile **14**. Reduction of 1-cyano-2-methyl-5-hexene (**14**) with diisobutylaluminum hydride (DIBAH) gave the desired aldehyde **12** (68% yield) which was characterized as the 2,4-dinitrophenylhydrazone.

Initial attempts to synthesize adequate quantities of 7-methyl-6-octenal (**13**) by a similar sequence proved unrewarding. The difficulty was encountered in the last step involving reduction of 7-cyano-2-methyl-2-heptene[7] with DIBAH which led to large amounts of tar. The Meyers' synthesis of aldehydes[8] seemed to offer a satisfactory alternative approach, and to this end quantities of the tetrahydro-1,3-oxazine (**15**) were prepared by borohydride reduction of the dihydrooxazine obtained by alkylation of the lithio salt of 2,4,4,6-tetramethyl-4,5-dihydro-1,3-oxazine[8] with 6-bromo-2-methyl-2-hexene. However, acid-catalyzed hydrolysis of **15** resulted in the production of substantial amounts of nonvolatile residues, again attesting to the sensitivity of the olefinic aldehyde **13**. An obvious consideration was the possibility that the aldehydes from cleavage of tetrahydro-1,3-oxazines such as **15** could be trapped as nitrones if the reaction was carried out in the presence of N-substituted hydroxylamines. This hope was realized in the isolation of the known *N*-methyl-*C*-phenylnitrone from reaction between 4,4,6-trimethyl-2-phenyltetrahydro-1,3-oxazine and *N*-methylhydroxylamine hydrochloride in 95% ethanol containing some sodium acetate. Moreover, when the same reaction was carried out with 2-(5-hexen-1-yl)-4,4,6-trimethyltetrahydro-1,3-oxazine, the nitrone of 6-heptenal (**1**) was not isolated; rather, intramolecular 1,3-dipolar cycloaddition occurred *in situ;* and the isomeric isoxazolidines **2**, **3**, and **4** were obtained. Extension of this technique to other tetrahydrooxazines having olefinic C-2 substituents should greatly extend the scope of the intramolecular nitrone–olefin reaction.

Reaction of **15** with *N*-methylhydroxylamine under the same conditions gave a 23% yield of isoxazolidines **16** and **17** in the ratio 85:15, respectively. The two isomeric tetrahydrobenzisoxazolines **16** and **17** could be



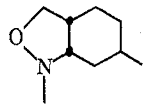
separated by elution chromatography. The major isomer **16** was collected and shown to be homogeneous by vpc and tlc. Reaction of the slightly impure **17** with methyl iodide in ether selectively removed all traces of the trans compound **16**, giving the homogeneous cis isomer **17**. Elemental analysis and spectral evidence showed that the two components were saturated isoxazolidines. As with the case of 6-heptenal (which leads to **2**, **3**, and **4**, *vide supra*), three isoxazolidines are theoretically possible: **16**, **17**, and the bridged bicyclic isomer **18** resulting from orientation in the opposite direction. Both of the isoxazolidines **16** and **17** were confirmed to have the fused (hexahydro-2,1-benzisoxazoline) skeleton rather than the alternative bridged bicyclic structure **18** because of the absence in their nmr spectra of proton absorption at lower field than δ 3.30. It was expected that the bridgehead hydrogen atom of **18** (α to oxygen, *i.e.*, at C-6) would result in absorption in the region around δ 4.5 (*cf.* **4**, δ 4.3[2a]).

The stereochemistry of the fused products **16** and **17** was deduced from the close nmr spectral similarities to those isoxazolidines resulting from condensation of (+)-citronellal and *N*-methylhydroxylamine. The de-

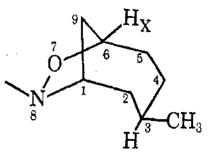
(4) G. Delpierre and H. Lamchen, *J. Chem. Soc.*, 4693 (1963).
(5) N. A. LeBel and T. A. Lajiness, *Tetrahedron Lett.*, 2173 (1966).
(6) R. Huisgen, R. Grashey, H. Hauck, and H. Seidl, *Chem. Ber.*, **101**, 2548, 2559, 2568 (1968).
(7) Prepared by sequential homologation from 5-bromo-2-methyl-2-pentene, or by Beckmann fragmentation of 2,2-dimethylcycloheptanone oxime: R. T. Conley and B. E. Novak, *J. Org. Chem.*, **27**, 3196 (1962).
(8) A. I. Meyers, A. Nabeya, H. W. Adikes, and I. R. Politzer, *J. Amer. Chem. Soc.*, **91**, 763 (1969).

tails of the structural analysis are given in Part B, p 2445.

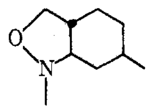
The condensation between 3-methyl-6-heptenal (**12**) and *N*-methylhydroxylamine afforded four isoxazolidines in the ratio 19.4:5.0:60.1:15.5 when the reaction was carried out in refluxing toluene (110°). The distribution in refluxing ethanol (76°) was 14.3:3.5:74.0:8.2. The products were separated by elution chromatography and were characterized as **19**, **20**, **21**, and **22**, respectively. Vpc indicated that the sep-



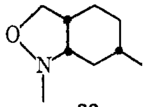
19



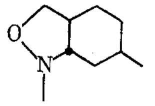
20



21



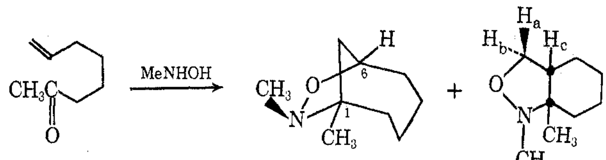
22



23 (not detected)

arated products (in order of elution) were homogeneous (except for **20**, which was about 89% pure), and elemental analysis combined with spectral evidence showed them to be saturated isoxazolidines. Six bicyclic isoxazolidines are theoretically possible. Four of these, represented by **19**, **21**, **22**, and **23**, have fused rings. Two, represented by the two possible isomers at C-3 of **20**, would have bridged structures. Structural assignments to all of these isomers were made on the basis of nmr comparisons with analogs of known stereochemistry and also by comparisons of the order of elution from alumina. The specifics are given in Part B.

Cyclization of the keto nitrone derived from 7-octen-2-one (**24**)[2a] was reexamined. A product was obtained which seemed homogeneous by vpc and tlc, but whose nmr indicated the presence to two isomeric isoxazolidines in the ratio 63:38. Over a limited temperature range (76–116°) this kinetic ratio does not seem to be temperature dependent. Assignment of structure to the minor isomer **25** was made possible by the presence of a distinctive doublet centered at δ 4.6 indicative of a single hydrogen on a bridgehead carbon next to oxygen (O–C-6–H). The nmr spectrum of the major compo-



24 **25** **26**

nent **26** shows a quartet for H_a but a triplet for H_b, which with higher resolution can also be shown to be a quartet. The rationale for the assignment is similar to that used for assigning the structure of isomer **22**, which is conformationally identical with that of **26**. The kinetic product ratios at 76° are summarized in Table I.

Thermal Isomerizations.—Most of the pure bicyclic isoxazolidines were pyrolyzed either neat or as 33% (w/w) solutions in tridecane or hexadecane at temperatures ranging from 180 to 235°. Mixtures of isomers

Table I

Kinetic Product Distributions for the Intramolecular Cycloadditions of *N*-Methyl-*C*-6-heptenylnitrones at 76°

Carbonyl compd	Ratio, trans:cis
5	93 (**6**):7 (**7**)
13	85 (**16**):15 (**17**)
12	76 (**21**):24 (**19** + **22**)
1	66 (**3**):34 (**2**)
24	0:100 (**26** only)

were recovered and the relative compositions were determined by vpc analysis. These isomerizations can be attributed to retro-1,3-dipolar cycloadditions,[5] and approximate equilibrium values are summarized in Table II.

Table II

Approximate Equilibrium Product Distributions of Bicyclic Isoxazolidines

Starting isoxazolidine	Temp, °C	Ratio (% compd) trans:cis:bridged
3	200	0 (**3**):100 (**2** only):0
6 or **7**	300	50 (**6**):50 (34% **7**, 16% **30**):0
16	300	30 (**16**):70 (**17**):0
21, **19**, or **22**	235	0 (**21**):92 (62% **19**, 30% **22**):8 (**20**)
26 + **25**	285	0:100 (**26** only):0

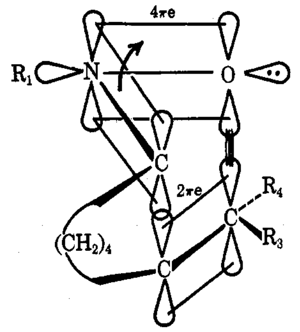
Discussion

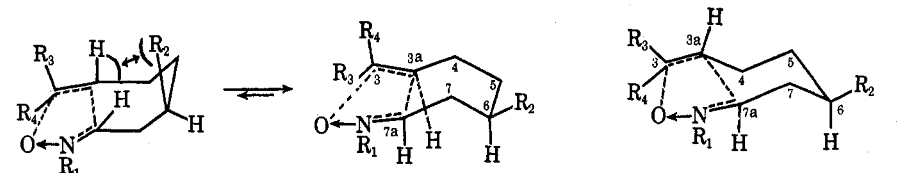
The steric course of the intramolecular reaction to form the bicyclo[4.3.0]nonane system may now be considered. In the cyclization itself, two transition states, **27** leading to a cis ring fusion and **28** leading to the trans isomer, appear to have the most favorable conformations. Two different possibilities for orbital overlap leading to cis-fused products **29** and **30** are represented. Both of these require the incipient six-membered carbocyclic ring to adopt a twist conformation. On the other hand, **28** assumes a slightly deformed chair arrangement for this portion of the molecule in order to lead to trans-fused product **31**. In this analysis, we assume that syn ⇄ anti interconversions of the intermediate nitrones are rapid under the reaction conditions[9] and that the product ratios are dependent only upon the respective transition state energies (however, the rationale would not be significantly different if this were not the case). Apparently in the unsubstituted case (**1** → **3** + **2**), the transition states are nearly equivalent in energy, since kinetic ring closure leads to only a slight favoring for trans (**3**) over cis (**2**) product. Introduction of a methyl substituent (R_2) in the methylene chain imparts a slight additional favoring of "trans" transition state **28** (relative to **27**) [**12** → **21** (major) + **19** + **22**], probably because of the increased eclipsed interaction in **27** that would result when R_2 is methyl as opposed to hydrogen. This same effect can be seen in comparing **13** (R_2 = H) → **16** + **17** and **5** (R_2 = CH_3) → **6** + **7** (Scheme I).

A different effect is observable upon the introduction of the *gem*-dimethyl (3,3-dimethyl) grouping in the potential five-membered ring. In terms of steric bulk, the group extending from C-3a in transition states **27** and

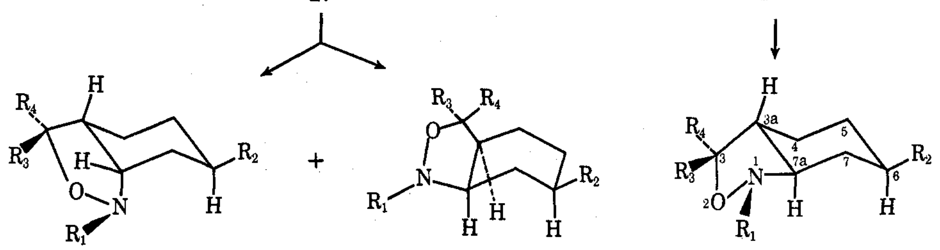
(9) For a review of such isomerizations, see M. Lamchen in "Mechanisms of Molecular Migrations," Vol. I, B. S. Thyagarajan, Ed., Wiley, New York, N. Y., 1968, pp 54–58.

SCHEME I





27 28



29 (7, 17, 19, 2, 26) 30 (22) 31 (6, 16, 21, 3)

28 (R_1 = R_3 = R_4 = CH_3; R_2 = H) should approximate a *tert*-butyl group. An equatorial position is therefore demanded by this grouping, eliminating any transition state conformation with axial orientation of this group and restricting considerably the flexibility of both cis products and cis transition states. In addition, the twist arrangement of the tetramethylene side chain will be associated with a C-4 methylene, C-3 methyl group (R_4 = CH_3) interaction. Transition state **28**, however, accommodates a more favorable equatorial position for the *gem*-dimethyl grouping and minimizes serious eclipsing interactions. Experimentally, the trans:cis (**16**:**17**) distribution of 85:15 is not unexpected. Finally, in the cyclization of the nitrone derived from citronellal (**5**) both effects reinforce each other accounting for the overwhelming formation of the trans,trans product **6**.

With the nitrone from ketone **24**, a transition state similar to **28** would require the C-7a methyl group to be axial, a situation that is sufficiently unfavorable to cause transition state **27** leading to cis product **26** to become dominant (note also the high proportion of bridged bicyclic compound **25** formed).

The temperature effect, which results in increased proportion of the cis isomers in these examples, is readily understandable in terms of a higher entropy for the "cis" transition state(s) **27**.

The conditions of the thermal isomerizations, involving for the most part high temperatures, sealed tubes, and vapor as well as condensed phases, mitigated against determination of accurate thermodynamic quantities. Nevertheless, it is quite apparent that the relative stabilities of the various isoxazolidine isomers at lower temperatures correspond fairly closely to the situation with hydrindan itself. Furthermore, the effect of substitution on these equilibria parallels the kinetic trends: *gem*-dimethyl in the five-membered heterocyclic ring and/or methyl substitution (not at the ring fusion) in the six-membered carbocyclic ring favor the trans isomers.

The data available for hydrindan indicate an enthalpy difference of only 1.07 ± 0.09[10a] or 0.58 ± 0.05 kcal/mol[10b] between *cis*- and *trans*-hydrindan, with the cis isomer having the higher enthalpy.[10] On the other hand, $-\Delta H^0$ (cis ⇄ trans) amounts to 2.7 kcal/mol for the decalins.[11] The difference in the two systems has been ascribed to the fact that in *cis*-hydrindan an axial and an equatorial bond of the adjacent ring-juncture atoms in the six-membered ring must be twisted toward one another to accommodate the more nearly planar five-membered ring. With *trans*-hydrindan, the corresponding twist involves two equatorial bonds, a distinctly higher energy process.[10a,12]

The relative stabilities of the hydrindans is highly dependent upon the relative entropies of the isomers. Below 466°K, *trans*-hydrindan predominates; however, above this temperature *cis*-hydrindan becomes more favorable.[10a] The entropy of the cis isomer is higher than that of the trans by 1.0[10b]–2.3 eu.[10a] Apparently with *trans*-hydrindan, the five-membered ring is more rigid than the same ring in *cis*-hydrindan; thus the five-membered ring is more capable of pseudorotation in the latter isomer leading to a higher entropy.

(10) (a) N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.*, **82**, 2553 (1960); (b) K. R. Blanchard and P. v. R. Schleyer, *J. Org. Chem.*, **28**, 247 (1963).

(11) N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.*, **81**, 4080 (1959).

(12) W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 37.

It is probable that the vicinal substitution of small heteroatoms (*e.g.*, oxygen, nitrogen) in the five-membered ring of the hydrindanyl system has no large quantitative effect on the relative stabilities of the cis and trans ring junctures.[13] On this basis, the higher stability of **2** (cis) over **3** at temperatures above 100° (373°K) is reasonable. The same logic holds well for the methyl-substituted isoxazolidines **19**, **21**, and **22**. Here again, the cis-fused ring juncture is favored in pyrolysis to the virtual exclusion of the trans isomer. In the case of the *gem*-dimethyl compounds, **6** and **7** from **5** and **16** and **17** from **13**, the substitution of two methyl groups on the five-membered ring should lower substantially the entropy difference between the cis and trans isomers, since the large steric bulk of this grouping should inhibit pseudorotation in the cis compound. Stereomodels confirm this logic since the *gem*-dimethyl grouping must maintain an equatorial position. As entropy effects diminish, the slight enthalpy difference favoring the trans isomer appreciates. Therefore, in the citronellal system, the additional methyl group in the carbocyclic ring only slightly increases the free energy of the cis isomers, but this appears to be sufficient to allow this to be the one case where the trans isomer is the most thermodynamically stable up to 300°.

The 8-methylhydrindan system may be approached in the same way as were the previous cases. It is clear from equilibration studies that the cis isomer has the more negative free energy in this system.[14] Substitution of the 8-methyl group into *trans*-hydrindan would be expected to increase its heat content more than would the same substitution in the cis system, because only in the latter can the methyl group be put into a favorable equatorial position[15] (*i.e.*, there are more gauche butane interactions in the trans). Thus, in this work we find that *cis*-1,7a-dimethylhexahydrobenzisoxazoline (**26**) is the kinetically and thermodynamically favored isoxazolidine from 7-octen-2-one (**24**).

As for the cyclizations of compounds **8** and **9**,[3] it seems reasonable to expect that the observed cis isomers are favored both kinetically and thermodynamically, probably because of the two sp^2 hybridized carbon atoms associated with the fused benzene ring and also because of the additional heteroatom. In our own work, this effect has been noted in that *cis*-1,3,3,6-tetramethyl-3a,4,5,7a-tetrahydro-2,1-benzisoxazoline (analogous to **7** but with a Δ^6 double bond) was the major kinetic product from the intramolecular cycloaddition of the nitrone from citral, and this cis-fused compound was the only isomer found after thermal isomerization.[5]

Experimental Section[16]

N-**Methylhydroxylamine.**—The zinc dust–ammonium chloride procedure of Beckmann[17] for the reduction of nitro compounds to hydroxylamines was employed. Alternatively, commercial grade *N*-methylhydroxylamine hydrochloride (Aldrich Chemical Co.) was used without further purification.

3-Methyl-6-heptenal (**12**).—Into a three-necked, round-bottomed flask equipped with an addition funnel, low temperature thermometer, stirrer, and a Friedrich's condenser with a nitrogen outlet was placed a solution of 24.0 g (0.195 mol) of 1-cyano-2-methyl-5-hexene (**14**) in 250 ml of ether. The system was flushed with nitrogen, and a solution of 33.5 g (0.234 mol) of diisobutylaluminum hydride (DIBAH) (Texas Alkyls, Inc.) in 50 g of hexane was added dropwise at 0°. After the addition was completed, the ice bath was removed and the mixture was stirred for 0.5 hr at room temperature. The mixture was then recooled and 10% sulfuric acid was added slowly until the mixture became acidic. After stirring for 0.5 hr at 25°, the organic layer was separated and the aqueous solution was extracted twice with ether. The extract was washed with saturated sodium bicarbonate solution followed by brine, dried (Na_2SO_4), concentrated, and distilled to give 18.0 g (65%) of aldehyde **12**: bp 35–36° (6 mm); ir 2720, 1715, 1625, 985, and 900 cm^{-1}.

Anal. Calcd for $C_8H_{14}O$: C, 76.19; H, 11.11. Found: C, 76.19; H, 11.14.

Treatment of the aldehyde, with ethanolic 2,4-dinitrophenylhydrazine produced the 2,4-dinitrophenylhydrazone, which melted at 64.5–66.0° after recrystallization from ethanol.

Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.90; H, 5.87; N, 18.30. Found: C, 54.84; H, 5.92; N, 18.06.

1,6-Dimethylhexahydro-2,1-benzisoxazoline (**19–22**). **Method A.**—To a 500-ml flask, equipped with a stirrer, Dean-Stark water separator, Friedrich's condenser, and addition funnel, was added 220 ml of dry toluene. The toluene was heated to reflux and 12.6 g (0.10 mol) of 3-methyl-6-heptenal (**12**) was added all at once followed immediately by the dropwise addition of a solution of *N*-methylhydroxylamine, prepared in the following manner.

To a cold solution of 10.0 g (0.12 mol) of *N*-methylhydroxylamine HCl in 15 ml of dry, reagent grade methanol was added rapidly 9.84 g (0.18 mol) of dry sodium methoxide with vigorous stirring. The cooling bath was removed, and the mixture was stirred at room temperature for 0.5 hr and filtered, and the filter cake was washed with 4 ml of methanol. The combined filtrate and wash were refiltered and mixed with 65 ml of toluene. The resultant two-phase system was then added to the aldehyde in refluxing toluene over a 3-hr period. Two 25-ml portions of azeotrope were removed during the addition, combined, and recycled. Following the recycle, an additional 40 ml of distillate was removed.

The mixture was stirred at reflux overnight and was then cooled to room temperature (total reaction time, 19 hr). The solution was extracted with four 40-ml portions of 10% HCl. The acid extract was back-washed with 60 ml of pentane, 60 ml of ether, and again with 60 ml of pentane. The aqueous acidic solution was basified with 30% KOH and was extracted with six 70-ml portions of pentane. The pentane extract was washed twice with 100 ml of water and dried ($MgSO_4$). The extract was concentrated and the residue was distilled at 72–74° (5 mm) to give 12.41 g (80.5%) of distillate. Examination of the distillate by vpc (column C) at 110° showed the four products **19**, **20**, **21**, and **22** in the ratio 19.4:5.0:60.1:15.5, respectively. The isomers were separated by elution chromatography using Merck alumina (acid washed) and were shown to be homogeneous by vpc.

cis,*trans*-**1,6-Dimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline** (**19**): bp 72.0° (5.0 mm); $n^{25}D$ 1.4682; mass spectrum *m/e* (rel intensity) 155 (98, M^+), 154 (45), 140 (10), 98 (100), 84 (35), 73 (35), 70 (55), 67 (25), 60 (15), 57 (20), 55 (30), 42 (45), 41 (30); nmr δ 0.94 (d, 3, J = 6 Hz, C-6 CH_3), 2.77 (dd, 1, J = 7.5, 2.5 Hz, H_b), 4.20 (dd, 1, J = 7.5, 6 Hz, H_a).

3,8-Dimethyl-7-oxa-8-azabicyclo[4.2.1]nonane (**20**): bp 72.5° (5.0 mm); $n^{25}D$ 1.4711; mass spectrum *m/e* (rel intensity) 155 (70), 154 (11), 140 (11), 109 (27), 100 (18), 98 (30), 84 (100),

(13) For recent comments, see (a) C. Romers, C. Altona, H. R. Buys, and E. Havinga in "Topics in Stereochemistry," Vol. IV, E. L. Eliel and N. L. Allinger, Ed., Wiley, New York, N. Y., 1969, Chapter 2; (b) E. L. Eliel, *Accounts Chem. Res.*, **3**, 1 (1970).

(14) W. E. Backmann and A. S. Dreiding, *J. Amer. Chem. Soc.*, **72**, 1323 (1950).

(15) N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956).

(16) Melting points and boiling points are uncorrected. The ir spectra were determined with a PE Model 237-B Infracord recording spectrophotometer, using sodium chloride plates for the liquid films and 0.1-mm matched cells for CCl_4 or $CHCl_3$ solutions. The analyses were by Midwest Microlabs, Indianapolis, Ind. Nmr determinations were carried out on Varian Models A-60A or T-60 instruments. Approximately 30% (w/v) solutions in CCl_4 or $CHCl_3$ were employed with TMS as the internal standard. Mass spectra were determined with a AEI Model MS-902 double focusing spectrometer at 70-eV ionization potential and 100-μA emission. Vpc analyses were carried out on an HP Model 5750 dual flame ionization unit with a 6 ft × 1/8 in. aluminum column containing 8% (w/w) Dow Polyglycol E-20M on Chromosorb W (column A) and an 8 ft × 1/8 in. aluminum column containing 20% (w/w) E-20M on Chromosorb W (column B). Additional vpc analyses were performed on a PE Model F-11 flame ionization unit with a 50 ft × 0.020 in. stainless steel column containing XE-60 liquid phase (column C). Nitrogen was the carrier gas at 4 psig.

(17) E. Beckmann, *Justus Liebigs Ann. Chem.*, **365**, 204 (1909).

81 (16), 73 (50), 70 (16), 67 (27), 57 (30), 55 (26); nmr δ 1.0 (d, 3, $J \leqq 2$ Hz, C-3 CH_3), 2.67 (s, 3, NCH_3), 4.70 (d br, 1, $J \sim 7$ Hz, O-C-6-H).

***trans,trans*-1,6-Dimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline (21)**: bp 73.5° (5.0 mm); $n^{25}D$ 1.4681; mass spectrum *m/e* (rel intensity) 155 (96), 154 (67), 140 (9), 112 (16), 109 (34), 98 (88), 95 (18), 86 (56), 84 (100), 81 (30), 73 (53), 70 (30), 68 (26), 67 (42), 57 (98), 56 (87); nmr δ 1.03 (d, 3, J = 6 Hz, C-6 CH_3), 2.73 (s, 3, NCH_3), 3.62 (m, 1, H_b), 4.08 (m, 1, H_a).

***cis,cis*-1,6-Dimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline (22)**: bp 73.0° (5.0 mm); $n^{25}D$ 1.4705; mass spectrum *m/e* (rel intenstiy) 155 (89), 154 (56), 99 (23), 98 (100), 85 (23), 84 (39), 81 (27), 73 (32), 70 (23), 68 (24), 67 (30), 57 (24), 55 (41), 42 (64), 41 (56); nmr δ 0.97 (d, 3, C-6 CH_3), 2.70 (s, 3, NCH_3), 3.63 (dd, 1, J = 7.3, 8 Hz, H_b), 4.20 (dd, 1, J = 7.3, 9 Hz, H_a).

Isoxazolidine **21** on treatment with methyl iodide in ether gave a methiodide, which on recrystallization from ethanol showed mp 135.5–136.5°.

Anal. Calcd for $C_{10}H_{20}NOI$: C, 40.40; H, 6.73; N, 4.71. Found: C, 40.64; H, 6.70; N, 4.70.

Method B.—A mixture of 9.8 g (0.12 mol) of anhydrous sodium acetate and 200 ml of absolute ethanol was brought to reflux, and 12.6 g (0.10 mol) of 3-methyl-6-heptenal (**12**) was added all at once, followed immediately by the dropwise addition of 10.0 g (0.12 mol) of *N*-methylhydroxylamine HCl in 65 ml of absolute ethanol over a period of 1 hr. After 75% of the *N*-methylhydroxylamine solution had been added, 42.6 g (0.30 mol) of anhydrous sodium sulfate was added, and the addition was completed. The mixture was stirred at reflux for 40 hr, cooled to 50°, and filtered. The filtrate was concentrated at atmospheric pressure to 30 ml and poured into 200 ml of pentane. The solution was then extracted with five 20-ml portions of 10% HCl and the extracts were combined and back-washed with ether. The aqueous acidic layer was basified with 40% KOH and extracted with pentane. The combined extract was washed with brine, dried, concentrated, and distilled at 72–74° (5 mm) to give 10.7 g (69.2%) of product. Examination of the distillate by vpc (column C, 110°) showed the four isomers **19**, **20**, **21**, and **22** in the ratio 14.3:3.5:74.0:8.2.

2-(6-Methyl-5-hepten-1-yl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine.—A 500-ml, three-necked flask equipped with a magnetic stirring bar, an addition funnel topped with a rubber septum, and a nitrogen-inlet tube was successively evacuated and flushed with nitrogen. Anhydrous THF (100 ml) and 14.1 g (0.10 mol) of 2,4,4,6-tetramethyl-4,5-dihydro-1,3-oxazine[18] was added from a syringe. The stirred solution was cooled to −78° and 47 ml (0.11 mol, 2.35 *M*) of *n*-butyllithium in hexane (Lithium Corp.) was injected into the funnel. The *n*-butyllithium solution was added dropwise over 1 hr. Upon complete formation of the anion, 19.5 g (0.11 mol) of 6-bromo-2-methyl-2-hexene in 25 ml of anhydrous THF was injected into the funnel and was slowly added over 0.5 hr. The mixture was allowed to warm to room temperature and was stirred overnight. The mixture was then poured into 100 ml of ice water and acidified with 9 *N* HCl. The acidic solution was extracted with pentane and then made basic by the slow addition of 40% NaOH. The resulting oil was extracted with ether and the extract was dried (K_2CO_3). The solution was concentrated to give the crude dihydro-1,3-oxazine in 89% yield (21.0 g), ir 1660 cm^{-1} (C=N). The product was used without further purification.

2-(6-Methyl-5-hepten-1-yl)-4,4,6-trimethyltetrahydrooxazine (15).[18]—In a 600-ml beaker were placed 100 ml of THF, 100 ml of 95% ethanol, and the crude dihydrooxazine (21 g) obtained in the preceding experiment. The mixture was cooled to between −35 and −40°, and HCl (9 *N*) was added to the stirred solution until an approximate pH of 7 was obtained. Sodium borohydride solution was prepared by dissolving 3.78 g (0.10 mol) in a minimum amount of water to which 1 drop of 40% NaOH was added. The sodium borohydride solution and the 9 *N* HCl were added alternately to the stirred mixture so that pH 6–8 was maintained. During the addition care was taken to maintain a temperature between −35 and −45°. After addition of the borohydride was completed, the solution was stirred with cooling for an additional hr (a pH 7 was maintained by the occasional addition of HCl). The contents were then poured into 100 ml of water, made basic, and extracted with ether. The organic extract was washed with brine, dried, and concentrated to give 20.8 g of crude tetrahydrooxazine **15** which was used without further purification.

***cis*- and *trans*-1,3,3-Trimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline (16 and 17). *In Situ* Formation and Cyclization of Nitrones Derived from Substituted Tetrahydrooxazines.**—In a three-necked, round-bottomed flask equipped with a magnetic stirrer, a condenser, and an addition funnel were placed 23.9 g (0.1 mol) of crude tetrahydrooxazine **15**, 3.28 g (0.04 mol) of anhydrous sodium acetate, and 200 ml of 95% ethanol. *N*-Methylhydroxylamine HCl (8.35 g, 0.1 mol) in 100 ml of ethanol was added dropwise over 1 hr. The solution was brought to reflux and stirred for 24 hr. The mixture was allowed to cool and was poured into 200 ml of water. After acidification to pH 2 with 10% HCl, the mixture was extracted with ether and basified with 20% NaOH. The basic solution was then extracted with ether, and the extract was washed with brine, dried, and concentrated. Distillation at 72–78° (15 mm) afforded 7.8 g of basic materials, determined to be three components by vpc on column C (110°). Further purification by elution chromatography using Merck alumina (acid washed) and pentane as eluent gave 3.8 g [22.5% overall yield, 58.5% based on the amount of aldehyde **13** (DNP, mp 90–91°) produced in separate experiments] of material showing no hydroxyl absorbance in the ir. Only two components were seen on vpc, **16** and **17**, in the ratio 85.0:15.0, respectively. The isomers were separated by chromatography and were shown to be homogeneous by vpc and tlc on silica gel using a chloroform–hexane solvent system.

***cis*-1,3,3-Trimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline (17)**: bp 76.0° (5 mm); $n^{25}D$ 1.4633; mass spectrum *m/e* (rel intensity) 169 (76), 168 (14), 155 (27), 154 (100), 152 (17), 140.5 (m*), 123 (94), 112 (28), 98 (46), 95 (42), 86 (89), 81 (62), 73 (49), 70 (62), 68 (49), 67 (65), 60 (42), 58 (68), 43 (99); nmr δ 1.23 (s, 3, CH_{3b}), 1.32 (s, 3, CH_{3a}), 2.78 (s, 3, NCH_3), 3.05 (m, 1, H_d).

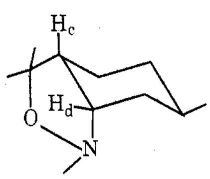
***trans*-1,3,3-Trimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline (16)**: bp 76.0° (5 mm); $n^{25}D$ 1.4621; mass spectrum *m/e* (rel intensity) 169 (14), 156 (10), 155 (81), 154 (60), 123 (54), 109 (19), 99 (20), 98 (100), 95 (26), 86 (33), 84 (39), 82 (24), 81 (41), 67 (47), 55 (69), 43 (70), 42 (91), 41 (69); nmr δ 1.00 (s, 3, CH_{3b}), 1.23 (s, 3, CH_{3a}), 2.57 (s, 3, NCH_3).

The latter compound, when stirred in ether with methyl iodide, formed a methiodide. After recrystallization from ethanol it showed mp 188.5–189.5°.

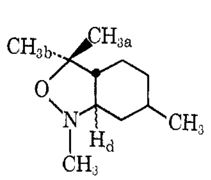
Anal. Calcd for $C_{11}H_{22}NOI$: C, 42.44; H, 7.07; N, 4.50. Found: C, 42.60; N, 6.89; N, 4.34.

Part B

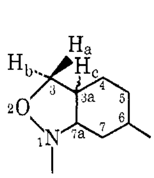
Structural Assignments of Bicyclic Isoxazolidines.—Condensation of citronellal and *N*-methylhydroxylamine followed by *in situ* cyclization in ethanol provided a 93:7 ratio of trans,trans (**6**) and cis,trans (**7**) isomers, respectively. This first study established the absolute configuration of the major isomer **6** by degradation to (−)-*N*,*N*-dimethylmenthylamine,[2a] and the cis,trans structure for **7** was confirmed later, primarily (but not exclusively) on the basis of the unique low field resonance (δ 2.78) for the equatorial hydrogen α to nitrogen (see H_d in conformational structure **32**).[5]



32 = 7



33



34 (19, 21, 22)

By analogy, therefore, assignment of cis stereochemistry to isoxazolidine **17** is readily made by its distinctive H_d resonance at δ 2.95. No absorbance below δ 2.50 is found in the spectrum of **16**. Additional evidence is found in the relative chemical shifts of the geminal methyl substituents. In a series of eight, pre-

(18) Procedures for the preparation, alkylation, and reduction of dihydro-1,3-oxazines were kindly supplied by Professor A. I. Meyers; see also ref 8.

viously synthesized,[2,5] fused bicyclic isoxazolidines with this grouping (structure **33**) $\Delta\nu_{trans}$ (CH_{3a}, CH_{3b}) = 10–14 Hz, whereas $\Delta\nu_{cis}$ (CH_{3a}, CH_{3b}) = 4–6 Hz. For isoxazolidine **16**, $\Delta\nu$ (CH_{3a}, CH_{3b}) = 12 Hz supporting the trans ring fusion assignment. Isoxazolidine **17** shows this value as 4 Hz, confirming cis stereochemistry. The stereochemical assignments are further supported by the observation of a greater thermodynamic stability at temperatures above 200° (*vide infra*) for **17** relative to **16**, and the fact that **17** (axial R_3N:) is eluted from alumina before **16** (equatorial R_3N:).

Examination of **20** by nmr showed a distinctive doublet at δ 4.65, characteristic of a single bridgehead hydrogen (H_x) adjacent to oxygen. The area around δ 3.1 also showed an isolated multiplet, undoubtedly due to the bridgehead hydrogen adjacent to nitrogen (C-1 H). Further evidence providing a distinction between isomers at C-3 was not available; however, the exo stereochemistry for the C-3 methyl group of **20** is most reasonable.

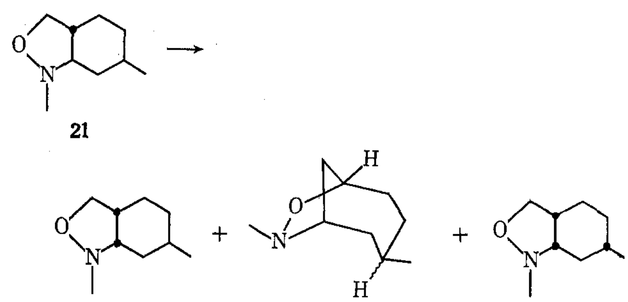
Assignment of structure to the remaining fused, bicyclic isomers was made possible through examination of the nmr spectra between δ 3.3 and 4.3. In this region, resonance characteristic of the methylene protons of the $NOCH_2$ moiety absorb. The multiplets for each of these hydrogens (H_a and H_b in structure **34**) are well separated, and from earlier work[5] we assign the lower field resonance to the exo C-3 proton H_a. For both the compounds **19** and **22** (general structure **34**), two well-spaced multiplets are seen. The absorbances for these protons in **34** can be treated as the AM portion of a AMX spectrum. Examination of stereomodels of the two cis diastereomers **19** and **22** indicates that H_c is in a bisecting conformation relative to H_a and H_b for isomer **19**. This is not the case for **22**, since the methylene group in question is now axially oriented as opposed to the equatorial position it occupies in **19**. Utilizing the Karplus equations, a predicted pattern may be derived for each compound. These predicted spectral patterns are very closely approximated by the experimental spectra; the multiplet for H_b of **19** appears as a pair of doublets, whereas the pattern for H_b of **22** resembles a triplet. This latter occurs since the coupling constant for J_{H_c,H_b} ($\phi \sim 150°$) is nearly equal to J_{H_a,H_b}; the two center lines overlap resulting in the observation of a near 1:2:1 triplet. The H_a resonance of **22** shows as a doublet of doublets rather than a triplet because J_{H_a,H_c} ($\phi \sim 30°$) is smaller than J_{H_a,H_b}.

Assignment of stereochemistry to the final isomer **21** was more difficult because of the poorer resolution of the H_a and H_b multiplets. However, further examination of stereomodels indicated that the other possibility, isomer **23**, would be forced to adopt a twist conformation in order to maintain the methyl group of the cyclohexane ring in an equatorial position. Thus, **23** would be a higher energy stereoisomer, and the transition state leading to it would be of higher energy than that leading to **21** (to the extent that the transition states resemble the respective products). Newman projections of the predicted most stable conformations of **21** and the alternative **23** suggest substantial differences in the comparative dihedral angles between H_a and H_c and H_b and H_c. An analysis similar to that used above would suggest that the H_a,H_b pattern for **21** should very much resemble that of **22**, except that H_a (the lower field multiplet) would now appear as a near triplet, and H_b would show the four-line pattern. The experimental spectrum of the only isolated trans isomer is not inconsistent with this prediction.

An isomer having the same relative stereochemistry as **23** is a possible product from the intramolecular cycloaddition of (+)-citronellal-*N*-methylnitrone; however *this compound was not produced* in the ring closure reaction. This compound was obtained by an alternative route;[5] however, it was not present to any extent in the interconversion studies of **6** and **7**, and it was very readily hydrogenolyzed. Thus the cis,trans stereochemistry present in structures like **33** and **34** represents an unstable isomer, and the trans-fused compound isolated in this work must be **21** rather than **23**.

The order of elution of the isomers from acid-washed alumina also supports the stereochemical assignments; **19** (cis fusion, axial R_3N–equatorial CH_2O) is eluted before **22** (cis fusion, equatorial R_3N–axial CH_2O) which is eluted before **21** (trans fusion, equatorial R_3N–equatorial CH_2O). Finally, the trans,trans isomer **21** reacts rapidly with methyl iodide to give the quaternary salt in the presence of **19** and **22**, which undergo only slow conversion.

Equilibration Studies.—Pyrolysis of pure **21**, either neat or as a 33% (w/w) solution in tridecane resulted in the formation of **19**, **20**, and **22**. After the complete



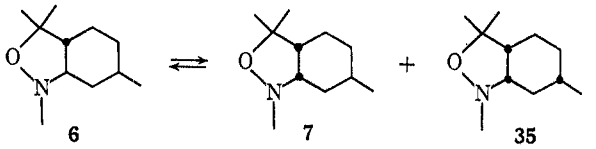
21 19 20 22

disappearance of isomer **21** (219 hr at 180°, 12 hr at 200°, 0.75 hr at 235°), a distribution consisting of compounds **19**, **20**, and **22** in the approximate ratio 39:10:51, respectively, was obtained. Further pyrolysis of this mixture led to a 62:8:30 mixture of the respective isomers. Interconversion at 235° of each of the pure isomers **19**, **20**, and **22** also led to this final approximate ratio.

Pyrolysis of pure **16** (trans, 3,3-dimethyl) in hexadecane resulted in a thermal isomerization of the isoxazolidine to an equilibrium concentration of isomers **16** and **17** (cis). At 300° the isomer ratio was found to be approximately 30:70 trans (**16**):cis (**17**) isomers, respectively. This equilibrium could also be attained at lower temperatures (235°, 270°) by longer reaction times. However, at temperatures above 300° rapid decomposition of material occurs. At reaction temperatures less than 235°, the rate of isomerization was found to be extremely slow.

The isomerization of isoxazolidine **3** (trans, unsubstituted), on the other hand, was extremely rapid even at temperatures around 200°. The thermal equilibrations resulted only in the recovery of **2**, showing that the cis isomer **2** is the more thermodynamically stable species at these temperatures.

Previous studies with isoxazolidine **6** (trans,trans) indicated that the thermal isomerizations can be attributed to retro-1,3-dipolar additions which regenerate the unsaturated nitrones from the isoxazolidines.[5] In this series, pyrolysis of **6** resulted in the formation of two additional isomers, **7** (cis,trans) and **35** (cis,cis).



6 **7** **35**

The equilibrium concentration of isomers **6**, **7**, and **35** at 300° was found to be approximately 50:34:16, respectively, representing a trans:cis-fused ratio of about 50:50.

Finally, when the 62:38 mixture of **26** (cis, 7a-methyl) and **25**, respectively, the products of the keto nitrone cyclization, was pyrolyzed at 285° for 0.5 hr, the only detectable product was the cis-fused isomer **26**.

Experimental Supplement[16]

5-Cyano-1-hexene.—Allylacetone was reduced with sodium borohydride in 89% yield to give 5-hexen-2-ol, bp 138–139° (atmospheric pressure) (lit.[19] bp 138°). Reaction of this alcohol with phosphorus tribromide and pyridine in ether gave 5-bromo-1-hexene (58%), bp 131–134° (lit.[19] bp 142°). Conversion of 30.74 g (0.188 mol) of the bromide to the nitrile was carried out by heating at 80° with a solution of 10.2 g (0.21 mol) of sodium cyanide in 80 ml of dry DMSO for 0.5 hr. After work-up, distillation afforded 18.1 g (83%) of 5-cyano-1-hexene: bp 55–56° (6 mm); ir 3060, 2240, and 1650 cm^{-1}. This compound was also made by reaction of the *p*-toluenesulfonate of 5-hexen-2-ol with sodium cyanide in DMSO at 90°.

1-Cyano-2-methyl-5-hexene (14).—Alcoholysis of 5-cyano-1-hexene with refluxing anhydrous ethanol saturated with hydrogen chloride to which slightly more than 1 equiv of water was slowly added gave, after work-up, ethyl 2-methyl-5-hexenoate: bp 74–75° (6 mm); ir 3060, 1725, 1640, 990, and 910 cm^{-1}. Reduction with lithium aluminum hydride in ether afforded an 89% yield of 2-methyl-5-hexen-1-ol: bp 84–85° (8 mm); ir 3350, 3060, and 1645 cm^{-1}. The *p*-toluenesulfonate was prepared (89%, crude oil). Displacement of 86.0 g of the tosylate with sodium cyanide in DMSO at 90° gave 36.5 g (89%) of nitrile **14**: bp 65–66° (7 mm); ir 3075, 2240, 1630, 995, and 910 cm^{-1}.

Anal. Calcd for $C_8H_{13}N$: C, 78.04; H, 10.56; N, 11.36. Found: C, 78.00; H, 10.66, N, 11.24.

Vpc analysis on column B at 130° showed one peak. The identical compound was also prepared by pyrolysis at 550° of 1-cyano-1-carboethoxy-2-methyl-5-hexene, which in turn was obtained by alkylation of ethyl sodiocyanoacetate with 5-bromo-1-hexene.

5-Methyl-4-hexen-1-ol.—2-Methyl-3-carboxy-5,6-dihydropyran (mp 115°)[20] was decarboxylated by distillation at 150° and a 60% yield of 2-methyl-5,6-dihydropyran was obtained: ir 1670 cm^{-1} (sharp fingerprint region). Bromination of 98 g (1.0 mol) of this compound in 250 ml of ether at −55° gave a suspension of the dibromide which was added slowly to a stirred solution of 1.0 mol of methylmagnesium bromide. After 90-min additional stirring, the mixture was poured onto crushed ice and ammonium chloride. Separation of layers and work-up gave 165 g (86%) of crude 2,2-dimethyl-3-bromotetrahydropyran, which was used without further purification. To a stirred solution of 50 g (2.2 g-atoms) of finely divided sodium in ether was added dropwise 193 g (1.00 mol) of 2,2-dimethyl-3-bromotetrahydropyran in 500 ml of ether.[21] After completion of the addition water was added until two clear phases were obtained. The mixture was extracted with ether and the extract was dried, concentrated, and distilled at 62–63° (13 mm), yielding 98 g (86%) of 5-methyl-4-hexen-1-ol: ir 3350 (broad), 1385, and 1375 cm^{-1}.

Alternatively, this compound could be prepared as follows. Reaction of methylmagnesium bromide with methylcyclopropyl ketone (Aldrich Chemical Co.) gave dimethylcyclopropyl carbinol. The alcohol was then rearranged to 5-bromo-2-methyl-2-pentene with 48% HBr in 80% yield.[22] The bromide was subsequently homologated by the regular route of cyanide displacement, hydrolysis, and reduction to give 5-methyl-4-hexen-1-ol in 23% overall yield.

6-Bromo-2-methyl-2-hexene.—A solution of 41.4 g (0.152 mol) of phosphorus tribromide in 100 ml of dry ether was slowly treated with 7.25 g (0.091 mol) of pyridine. The reaction mixture was cooled to −20° by means of a carbon tetrachloride–Dry Ice bath. 5-Methyl-4-hexen-1-ol (42.4 g, 0.372 mol), containing 2.5 g of pyridine, was added, and the mixture was stirred for 24 hr at room temperature. The mixture was transferred to a 500-ml side-necked flask, the ether was distilled, and the residue was pyrolyzed at 150° (50 mm). The pyrolysate was collected in a Dry Ice trap and diluted with an equal amount of water. The organic layer was separated and was washed with 10% HCl, followed by brine. The extract was dried, concentrated, and distilled to give 61.0 g (93%) of bromide: bp 67–68° (20 mm); ir 1665, 1385, and 1375 cm^{-1}.

1-Methyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline (2, 3).—Reaction of tetrahydrofurfuryl chloride with sodium metal in ether produced 4-penten-1-ol, which was converted to 1-bromo-4-pentene by the phosphorus tribromide–pyridine procedure. The bromide was used to alkylate 2,4,4,6-tetramethyl-4,5-dihydro-1,3-oxazine in the manner previously described for the production of **15**. The crude dihydrooxazine was subsequently reduced to the tetrahydrooxazine, which was used without further purification.

A method similar to that described for the production of **16** and **17** was employed to convert the crude tetrahydrooxazine to a mixture of isomeric isoxazolidines. Reaction of 4.18 g (0.050 mol) of *N*-methylhydroxylamine HCl, 3.28 g (0.04 mol) of sodium acetate, and 23.9 g (0.11 mol) of tetrahydrooxazine in 200 ml of 95% ethanol gave 5.0 g (38.5%) of a 30:57:13 ratio of isomers **2**:**3**:**4**, respectively. The compounds were identified by admixture on vpc and spectral comparisons with a mixture of isomers prepared by the condensation of 6-heptenal and *N*-methylhydroxylamine.[2a] The latter cyclization, conducted in refluxing toluene for 4 hr, gave an isomer ratio of 42.4:42.3:15.3 for **2**:**3**:**4**, respectively. Continued refluxing in toluene for 15 hr converted this ratio to approximately 50:40:10. Pyrolysis of this mixture at 250° for 15 min gave only the cis isomer **2**.

Separation of Isomers. A. Elution Chromatography.—Generally, it was found that Merck acid-washed alumina provided the best separation for the isoxazolidines prepared in this study. A column was constructed of 1095 g of alumina. Purified pentane was the solvent and 35.0 g of the mixture of isomers **19–22** was placed on the column. Fractions of 1 l. were collected (see Table III). Rechromatography of fractions 8 and 9–11 afforded pure samples of isomers **20** and **22**, respectively.

TABLE III

Fraction	Eluent (%)	Wt, g	% composition by vpc **19**	**20**	**21**	**22**
1	Pentane					
2–4	Ether (1)	0.5	Only			
5	Ether (1)	0.8	95	5		
6	Ether (1)	1.3	93	5		2
7	Ether (2)	1.7	81	15		4
8	Ether (2)	0.7	5	85		10
9	Ether (2)	1.2		15		85
10	Ether (5)	3.9		10		90
11	Ether (5)	3.6		5		95
12–15	Ether (5)	6.2			60	40
16	Ether (10)	4.6			95	5
17–23	Ether (50)	6.7			Only	
		32.2 = 89.5%				

In similar fashion, a mixture of **16** and **17** could be separated. The column contained 425 g of alumina, with pentane as the solvent, and an 8.5-g quantity of the isomer mixture **16** and **17**

(19) H. B. Wood and E. C. Horning, *J. Amer. Chem. Soc.*, **75**, 5511 (1953).

(20) J. Perkin, *J. Chem. Soc.*, **51**, 702 (1887).

(21) R. P. Linstead and H. N. Rydon, *ibid.*, 1995 (1934).

(22) A. M. Moreno and G. I. Fernandez, *Bol. Inst. Quim. Univ. Nac. Auton. Mex.*, **16**, 59 (1964); *Chem. Abstr.*, **63**, 4333*f* (1965).

Table IV
Equilibration of 17 in Hexadecane

Time, hr	Temp, °C	% 16	% 17	% dec
3	235	4	96	5
25		37	63	25
48		44	56	33
60		60	40	38
74		67	33	45
91		70	30	62
1.2	270	25	75	11
2.5		65	35	36
6.5		69	31	64
8.5		71	29	84
2.7	300	69	31	62
3.7		70	30	81
6.5		70	30	95

Table V
Thermal Isomerizations of 21 in Tridecane

Time, hr	Temp, °C	% 19	% 20	% 21	% 22	% dec
31	180	3.4	0.5	91.6	4.5	3
43.5		6.0	0.4	86.9	6.7	6
48		6.6	2.1	84.5	6.8	10
52		10.2	3.2	74.3	12.3	10
65		10.7	3.3	73.1	12.9	12
78.5		13.2	4.1	66.5	16.2	15
103		17.5	5.6	52.0	24.8	17
130		24.0	8.3	38.8	28.9	19
175.5		34.0	9.7	9.4	46.9	20
219		38.0	11.0		51.0	25
219		37.8	11.5		50.6	25
2	200	5.5	1.6	85.2	7.7	10
4.5		18.1	5.1	51.1	25.7	20
7		18.9	7.7	42.8	30.6	25
12		39.0	10.6		50.4	34
24		39.6	12.4		48.0	48
0.25	235	3.5		96.5		12
0.50		27.0	5.3	40.6	27.0	40
0.75		36.1	11.3	2.0	50.6	49
1.00		48.0	10.5		41.5	69
1.50		56.7	9.6		33.7	76
2.00		59.7	8.6		31.7	80

in the ratio 85.0:15.0 was separated. Fractions of 350 ml were collected, and a 90.5% recovery was realized.

B. Preferential Methiodide Formation.—To a solution of 0.37 g (0.0022 mol) of an isomer mixture containing **16** and **17** in the ratio 20:80, respectively, in 10 ml of ether, was added 0.38 g (0.0027 mol) of methyl iodide. The mixture was stirred at room temperature overnight and then filtered, and the filter cake was washed with ether. The combined filtrate and wash was concentrated and the residue was distilled at 76° (5 mm) to give 0.28 g (94.5%) of pure **17**.

***cis*-1,7a-Dimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline (26) and 1,8-Dimethyl-7-oxa-8-azabicyclo[4.2.1]nonane (25).**—From 8.3 g (0.066 mol) of 7-octen-2-one and an excess of *N*-methylhydroxylamine according to method A, there was obtained 7.0 g (68%) of basic material, bp 71° (4.5 mm), $n^{25}D$ 1.4767. Vpc analysis on a variety of columns and tlc suggested that the material was homogeneous. However, the nmr spectrum indicated two isomers present in the ratio 62 (**26**):38 (**25**): nmr (100 MHz) δ 2.58 (s, **26** NCH_3), 2.63 (s, **25** NCH_3), $\Delta\nu = 6$ Hz.

Anal. Calcd for $C_9H_{17}NO$ (a 38:62 mixture of isomers): C, 69.63; H, 11.04; N, 9.02. Found: C, 69.64; H, 11.16; N, 8.89.

Interconversions of Bicyclic Isoxazolidines at Various Temperatures.—The thermal rearrangements were conducted in a Wood's metal bath. Samples were placed in 8 × 10 × 200 mm

Table VI
Thermal Isomerizations of 6 in Tridecane

Time, hr	Temp, °C	% 7 + 35	% 6	% dec
3	235	3	97	5
25		39	61	16
60		43	59	19
91		45	55	25
1.2	270	21	79	12
2.5		37	63	12
6.5		46	54	13
8.5		47	53	17
2.7	300	47	53	24
3.7		50	50	33
6.5		49	51	55

Pyrex No. 8640 combustion tubes and purged with argon, and the tubes were sealed. The samples were generally prepared as 33% by weight solutions in hexadecane or tridecane, although limited samples of the minor isomers necessitated 10% by weight solutions. The solvent also functioned as an internal standard on vpc. In all cases runs in triplicate were performed, and periodic checks of the spectral properties of the components confirmed the vpc analyses. The results are given in Tables IV–VI.

Thermal Interconversions of 19, 20, and 22 at 235°.—Solutions of pure **19**, **20**, and **22** (10% by weight) in tridecane were employed and the results are tabulated in Table VII. No **21** was detected in any of the equilibrations.

Table VII
Equilibration of 19, 20, and 22

Time, hr	% 19	% 20	% 22	% dec
		Equilibration of 19		
2.5	95.1	1.5	4.4	3
5.0	90.5	2.5	7.0	10
7.5	79.3	3.6	17.1	15
12.5	70.3	4.2	25.4	20
25.0	65.3	4.8	29.9	28
		Equilibration of 20		
2.5	31.9	22.4	45.7	11
5.0	50.4	16.4	33.2	29
7.5	62.8	6.2	31.0	38
		Equilibration of 22		
1.0	5.4	1.4	93.2	2
2.5	12.8	2.0	85.2	5
5.0	30.0	3.8	66.2	12
7.5	36.8	4.7	58.5	20
10.0	45.0	5.3	49.7	24
15.0	53.7	6.3	40.0	29
25.0	58.3	8.5	33.2	43

Thermal Equilibration of 16.—Pyrolysis of **16** in hexadecane at 300° for 2 hr gave a 70.5:29.5 ratio of **16** to **17**, respectively.

Thermal Interconversion of Isoxazolidines 26 and 25.—Pyrolysis of a 62:38 mixture of *cis*-isoxazolidine **26** and bicyclic isoxazolidine **25**, respectively, in a sealed tube at 280° gave only the cis isomer **26** after 2 hr: nmr δ 1.12 (s, 3, C-7a CH_3), 2.57 (s, 3, NCH_3), 3.69 (t, 1, $J = 7.5$ Hz, H_b), 4.10 (dd, 1, $J = 7.5$, ~ 10 Hz, H_a).

Registry No.—**6**, 6501-80-0; **12**, 30315-97-0; **12** 2,4-DNP, 30315-98-1; **14**, 30315-99-2; **16**, 30318-71-9; **16** methiodide, 30318-72-0; **17**, 30318-73-1; **19**, 30318-74-2; **20**, 30318-75-3; **21**, 30318-76-4; **21** methiodide, 30318-77-5; **22**, 30318-78-6; **25**, 30477-03-3; **26**, 30318-79-7; 5-cyano-1-hexene, 30316-00-8; 2-methyl-5-hexen-1-ol, 30315-99-2; 6-bromo-2-methyl-2-hexene, 30316-02-0.