(4)

cyclooctane would rearrange to 4-vinylcyclohexene in a single step as a deep-seated rearrangement would be necessary to open the four- and five-membered rings in tricyclooctane and close again to give a six-membered ring. Hence, it is more reasonable to conclude that the 1,5-cyclooctadiene is an intermediate in the isomerization of tricyclooctane to 4-vinylcyclohexene. The data in Table I show that in the decomposition of tricyclooctane the amount of 1,5-cyclooctadiene that remains is a maximum at the shortest time a measurement can be made. It can be calculated from the experimental first-order rate constants (at 327.3°) that the amount of 1,5-cyclooctadiene would go through a maximum at only 98/1000 sec. after the reaction had started, and the ratio of 1,5-cyclooctadiene to tricyclooctane would have been 0.034.

It is much more difficult to decide whether 1,3-butadiene is formed via 1,5-cyclooctadiene or directly in the decomposition of tricyclooctane. Mechanistically it can be seen that the pathway which does not involve 1,5-cyclooctadiene as an intermediate requires the simultaneous cleavage of four bonds as is shown.
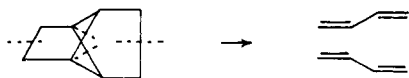
The breaking of these bonds in a stepwise fashion does not seem to lead to an energetically favored pathway except in the one instance in which 1,5-cyclooctadiene is formed. Hence, it is reasonable to conclude that the sequence of reactions is
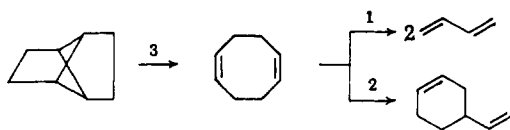
In common with the decomposition of cyclobutane,[2] alkyl substituted cyclobutanes,[2] and bicyclo[2.1.1]-

hexane,[4] the isomerization of tricyclooctane appears to be a homogeneous, unimolecular process which is unaffected by the presence of molecules which act as free-radical traps. The activation energy for the reaction is the same as that for bicyclo[2.1.1]hexane within experimental error. While at first sight it may appear that the tricyclooctane is a more strained system than bicyclo[2.1.1]hexane, molecular models show that the addition of a second two-carbon bridge diagonally to a cyclobutane ring can be achieved with little or no additional distortion. The fact that the activation energy remains the same is either due to all of the strain energy not being available for the rupture of the cyclobutane system during pyrolysis, or due to the increase in strain energy being no more than the experimental error in the activation energy. It is surprising that the pre-exponential factor in this instance is larger than for bicyclo[2.1.1]hexane by a factor of 3 which corresponds to a difference of more than 2 e.u. of entropy of activation. Since the isomerization of bicyclo[2.1.1]hexane involves a reaction from a bicyclic to an open-chain system while the isomerization of tricyclooctane involves a reaction from a tricyclic to a monocyclic system, a smaller ratio of pre-exponential factors would have been predicted.

In view of the complexity in the decomposition of 1,5-cyclooctadiene, very little can be said about the mechanism of this process. The ratio of 4-vinylcyclohexene to 1,3-butadiene is seen to decrease with an increase in temperature. From a plot of the logarithm of this ratio vs. the reciprocal of this temperature, it can be calculated that the difference in the activation energies for the formation of these products $(E_1 - E_2)$ equals 6.2 kcal./mole. If the activation energy of the first-order process from 299.5 to 327.3° is identified with reaction 2, then the activation energy for reaction 1 is probably (49 + 6) = 55 kcal./mole. This value is of the same order of magnitude as the activation energy of 61.8 kcal./mole for the unimolecular decomposition of 4-vinylcyclohexene to two molecules of 1,3-butadiene.[9]

(9) N. E. Duncan and G. J. Janz, J. Chem. Phys., 20, 1644 (1952).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY, DETROIT 2, MICH.]

The Addition of Nitrones to Olefins. Fused Bicyclic Isoxazolidines[1]

By NORMAN A. LeBEL, MARY ELLEN POST, AND JONG JAI WHANG

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The oxidation of N-methyl-N-5-hexenylhydroxylamine with mercuric oxide and the condensation between 5-hexenal and N-methylhydroxylamine afforded cis-N-methyl-3-oxa-2-azabicyclo[3.3.0]octane (2). Other bicyclic isoxazolidines have been synthesized by the condensation reaction employing unsaturated aldehydes and unsaturated ketones. The structures of these compounds were proved by hydrogenolysis and, in some cases, independent synthesis of the amino alcohols. The mechanism of the cyclization reactions are postulated as intramolecular 1,3-additions of an unsaturated nitrone intermediate. The scope of this preparative route to fused bicyclic isoxazolidines is discussed in terms of reactivity, orientation, and stereochemistry.

The pyrolysis of a mixture of the isomeric N-methyl-α-pipecoline oxides produced, in addition to the predicted unsaturated hydroxylamine, an unexpected bicyclic base.[2] This product was identified as N-

methyl-3-oxa-2-azabicyclo[3.3.0]octane (2), and was postulated as having arisen from an unsaturated nitrone intermediate (1). The nitrone may have been produced from N-methyl-N-5-hexenylhydroxylamine by an oxidation–reduction reaction. However, this unsaturated hydroxylamine was obtained in good

(1) A preliminary communication concerning a part of this work has appeared: J. Am. Chem. Soc., 81, 6334 (1959). This work was reported in part: Abstracts, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 1960, p. 85-O.

(2) A. C. Cope and N. A. LeBel, J. Am. Chem. Soc., 82, 4656 (1960).

yield from *trans*-N-methyl-α-pipecoline oxide and N-methylhexamethylenimine oxide, without the accompanying formation of 2.[2] In order to verify the occurrence of the intermediate nitrone 1, and to investigate the utility of such reactions as preparative routes to bicyclic isoxazolidines, we have studied the intramolecular cyclization of 1 and other related compounds.

It was recognized that, although several routes are available for the synthesis of aliphatic nitrones such as 1, their preparation in pure form would be difficult. Various types of dimeric products are often obtained.[3–5] Several monofunctional, nonaromatic nitrones have been reported, but they are alicyclic compounds.[6–8] Recently, the preparation of relatively stable δ-hydroxy nitrones has been accomplished.[9] We have made no attempt to isolate the reactive nitrone intermediates described in this work. Compound 1 was generated *in situ* by two different methods, and its monomeric rearrangement products were studied.
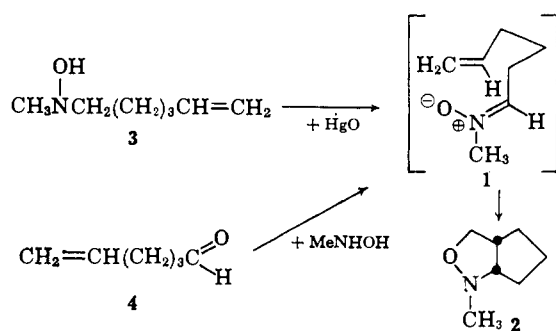
Oxidation of an ether or alcoholic solution of N-methyl-N-5-hexenylhydroxylamine (3) with excess mercuric oxide afforded 2 in 18–24% yield. The isoxazolidine was identified as 2 by its infrared spectrum, by gas chromatography, and by preparation of derivatives. In addition, 5-hexenal (4) was isolated and characterized as its 2,4-dinitrophenylhydrazone. Alternatively, 2 was prepared by the condensation of 5-hexenal (4) and freshly prepared N-methylhydroxylamine (Table I).

Further proof for the structure of 2 was furnished by zinc and acetic acid hydrogenolysis. The amino alcohol
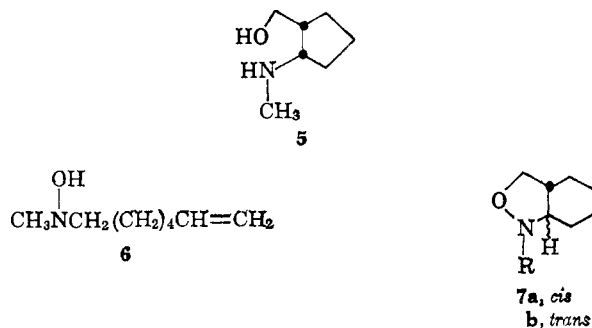
(3) F. H. Banfield and V. Kenyon, *J. Chem. Soc.*, 1612 (1926).

(4) J. Thesing and H. F. Meyer, *Ber.*, **89**, 2159 (1956).

(5) H. Hellmann and K. Teichmann, *ibid.*, **89**, 1134 (1956).

(6) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2094 (1959).

(7) J. Thesing and W. Sirenberg, *Ber.*, **92**, 1748 (1959), and earlier papers.

(8) We have, however, prepared and characterized N-ethylcyclohexane carboxaldoxime: M. E. Post, unpublished studies.

(9) A. A. R. Sayigh and H. Ulrich, *J. Org. Chem.*, **27**, 4662 (1962).

RCHO, R =	R'NHOH, R' =	Isoxazolidine	Yield %	B.p. °C	Mm.
CH2=CH(CH2)3—	CH3	2^a	41	79–80	30
	C2H5	11a^b	42	95–97	28
	(CH3)2CH	11b^c	44	93–95	25
CH2=CH(CH2)4—	CH3	7^{d,e}	48	70–72	15
CH3CH=CH(CH2)3— (trans)	CH3	11c^f	55	77–78	33
	C3H7	11d^g	77	88	26
CH3CH=CH(CH2)3— (cis)	CH3	11e^{h,i,k}	42	78–80	18
CH3CH=CH(CH2)4— (trans)	(CH3)2CH	12a^j	45	78–80	15
CH3\C=C/H, /CH3 (CH2)3\CH3CHCH2— (+)	CH3	12b^{l,p}	65	116–118	20
	C2H5	12c^{m,p}	71	104–105	16
	(CH3)2CH	12d^n	74	107–108	12
	C6H5	12e^o	31	144–145 (m.p.)	

product was identified as N-methyl-*cis*-2-hydroxymethylcyclopentylamine (5) by comparison with an authentic sample.[2]

The reaction was extended to include the homolog 7. The mercuric oxide oxidation of N-methyl-N-6-heptenylhydroxylamine (6) afforded *cis*-N-methyl-8-oxa-7-azabicyclo[4.3.0]nonane (1-methyloctahydroanthranil, 7) in 18% yield. From the neutral fraction of this oxidation it was possible to isolate 6-heptenal (8) as its 2,4-dinitrophenylhydrazone.

An authentic sample of 8 was prepared from the known 5-hexen-1-ol.[10] The condensation of 8 and N-methylhydroxylamine proceeded smoothly to produce an isoxazolidine mixture which was shown to be identical with 7 by infrared and gas chromatographic analyses, and by comparison of derivatives.

The isolation of the unsaturated aldehydes 5-hexenal (4) and 6-heptenal (8) in the oxidation reactions in over 60% yield as their derivatives lends additional support to the preferential formation of the most highly substituted nitrone groups.[5]

(10) R. R. Burford, F. R. Hewgill, and P. R. Jeffries, *ibid.*, 2937 (1957).

The compound 7 isolated from these reactions was determined to be a mixture of two components in a ratio approximately 2:1. The major component was determined to be the *cis* isomer **7a**, since hydrogenolysis afforded a crystalline, low-melting amino alcohol which was identical with N-methyl-*cis*-2-hydroxymethylcyclohexylamine (**9**), formed by lithium aluminum hydride reduction of N-*cis*-2-carboxycyclohexylformamide (**10**).
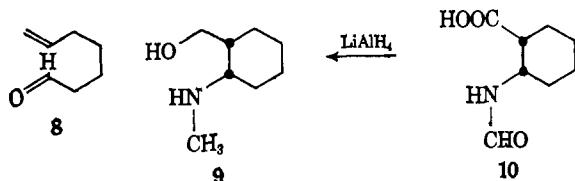
The formation of the bicyclic products 2 and 7 from the olefinic nitrones (*cf.* 1) is representative of the intramolecular addition of a nitrone to an olefin.[1] Several laboratories have now reported examples of intermolecular additions.[11-13] Numerous analogies in the general category of 1,3-dipolar addition reactions have been reviewed and reported.[14a,b]

We have been successful in preparing additional analogs of the bicyclic isoxazolidines 2 and 7. These compounds have the general formulas given by 11 and 12, and are summarized in Table I. In most cases, the appropriate unsaturated aldehyde was condensed with a monoalkylhydroxylamine in benzene or toluene solvent with azeotropic distillation of the water, and the products were isolated by extraction with acid. The reaction proceeded smoothly with N-methyl-, N-ethyl-, and N-isopropylhydroxylamines. The composition of the products was determined by gas chromatography and by the preparation of derivatives. The several new aldehydes employed in these condensations reactions were synthesized from known starting materials by well-established sequences.
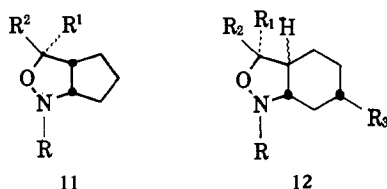
11a, R = C_2H_5, R_1 = R_2 = H
 b, R = $(CH_3)_2CH$, R_1 = R_2 = CH_3
 c, R = CH_3, R_1 = H, R_2 = CH_3
 d, R = C_2H_5, R_1 = H, R_2 = CH_3
 e, R = CH_3, R_1 = CH_3, R_2 = H
12a, R = $(CH_3)_2CH$, R_1 = R_3 = H, R_2 = CH_3
 b, R = CH_3, R_1 = R_1 = R_3 = CH_3
 c, R = C_2H_5, R_1 = R_2 = R_3 = CH_3
 d, R = $(CH_3)_2CH$, R_1 = R_2 = R_3 = CH_3
 e, R = C_6H_5, R_1 = R_2 = R_3 = CH_3

Under comparable reaction conditions, the intramolecular addition reaction appeared to give products in superior yield with the more highly substituted olefins (*cf.* Table I). These results lend qualitative support to the suggestions that the rate of addition of nitrones to unconjugated (*e.g.*, simple) olefins reflects the elec-

(11) C. W. Brown, K. Marsden, M. A. T. Rogers, C. M. B. Tylor, and R. Wright, *Proc. Chem. Soc.*, 254 (1960).

(12) R. Grashey, R. Huisgen, and H. Leitermann, *Tetrahedron Letters*, No. 12, 9 (1960).

(13) G. R. Delpierre and M. Lamchen, *Proc. Chem. Soc.*, 386 (1960).

(14) (a) R. Huisgen, *ibid.*, 357 (1961); (b) R. Huisgen, *Angew. Chem.*, 75, 604, 742 (1963).

trophilic nature of the nitrone group,[15-17] and that the rate increases with higher polarizability of the double bond.[14a,b] A comprehensive treatment of relative reactivities in intermolecular 1,3-dipolar addition reactions, including those of nitrones, has been given.[14b] Despite the absence of supporting experimental details, the data presented suggest certain trends. Most evident are the low reactivity of simple olefins, the higher reactivity of *p*-substituted styrenes containing electron-attracting groups, and the effects of steric hindrance in the olefin.

Substitution of N-phenyl for N-alkyl in a nitrone will provide resonance stabilization of the ground state and should affect the reaction rate for addition to a weakly polarizable olefin. Huisgen has provided evidence supporting the fact that replacement of N-methyl by N-phenyl in a nitrone results in an increase in the rate of reaction with ethyl crotonate.[14b] When either of the aldehydes 4 or 8 was condensed with N-phenylhydroxylamine, N-phenylisoxazolidines could not be isolated. Instead, intractable, acid-labile oils were obtained which suggested a nitrone (or dimer). A steric effect of the phenyl group does not seem to be a significant factor since N-isopropylnitrones afforded good yields of cyclized products. When citronellal was employed, however, the condensation with N-phenylhydroxylamine led to the formation of a compound (poor yield) identified as N-phenyl-*trans*,*trans*-4,9,9-trimethyl-8-oxa-7-azabicyclo[4.3.0]nonane (12e). The structure of 12e, the stereochemistry of which was inferred by analogy (*vide infra*), was deduced from its infrared and ultraviolet (λ_{max} 239 mμ, ϵ 9000) spectra and from the fact that it consumed 1 mole of hydrogen on catalytic hydrogenation to give an amino alcohol (14). These and other available data[14b,18] seem to indicate that factors influencing the rate of 1,3-dipolar additions of nitrones will differ if the substrate olefin is a simple one rather than the highly polar double bond of a conjugated ester, the intra- or intermolecular pathway notwithstanding. Further speculation is entirely inappropriate at this time and must await the results of kinetic studies of the intramolecular reaction that are currently under way.

Orientation in nitrone additions to unsymmetrical olefins poses an interesting question. It is important to note that the formation of the fused products 2, 7, 11, and 12 results from predominant attachment of the oxygen atom at the carbon atom most remote from the nitrone group—regardless of the direction of polarization of the olefin. We have been unable to isolate or identify the bridged bicyclic products that

(15) N. A. LeBel, L. A. Spurlock, and G. M. J. Slusarczuk, *J. Am. Chem. Soc.*, 84, 4360 (1962).

(16) Undoubtedly, the "*gem*-dimethyl effect" must also play a significant part in facilitating ring closure; *cf.* N. L. Allinger and V. Zalkow, *J. Org. Chem.*, 25, 701 (1960).

(17) Three canonical forms a, b, and c are often used to depict the nitrone linkage. A simple Hückel LCAO treatment (courtesy of Professor N. L. Allinger) of the parent nitrone system has led to the following approximate values for π-electron density (*cf.* d). From this approach, it is obvious that the ground state charge distribution of an aliphatic nitrone is more closely represented by a and b.
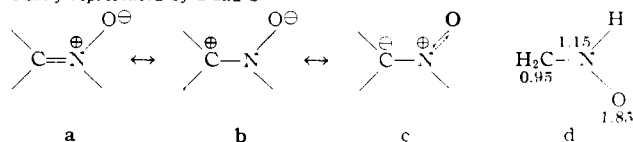
(18) G. R. Delpierre and M. Lamchen, *J. Chem. Soc.*, 4693 (1963).

would arise from addition in the opposite direction. Steric effects must be involved with destabilization of the transition states for formation of the alternate bridged structures.

The stereochemical course of the intramolecular reaction must now be considered. Compound 2 is homogeneous and contains a *cis* ring fusion. When the condensation was carried out with the isomeric olefinic aldehydes *trans*- and *cis*-5-heptenal, two different isoxazolidines, 11c and 11e, respectively, were obtained. The product 11c was found to be homogeneous. Although 11e contained a small amount of isomer 11c, the amount corresponded very closely to the contaminent *trans*-aldehyde present in *cis*-5-heptenal. It is apparent from these results that the intramolecular addition is kinetically controlled and that the configuration of the olefin is retained in the product isoxazolidine. That 11c and 11e differed only in configuration at the carbon atom bearing the methyl substituent was proved by hydrogenolysis and oxidation of each compound to the same amino ketone, N-methyl-*cis*-2-acetylcyclopentylamine (15, as the N-acetyl derivative).[19] In all cases, compounds 2 and 11 contain the *cis* fused bicyclo[3.3.0]octane skeleton as implied in stereoformula 1. Closure to give the highly strained *trans* isomer would involve a transition state of much higher energy.
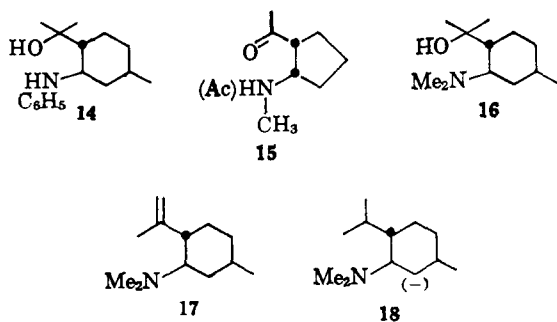
Similar considerations are not appropriate for the homologous hydrindanyl-type products 7 and 12. The unsubstituted compound 7 was formed as a 2:1 mixture of *cis* (7a) and *trans* (7b) isomers. On the other hand, 12b, c, and d were found to be at least 97% pure.[20] The stereochemistry of 12b was confirmed by the following sequence of reactions. Catalytic hydrogenolysis of the methiodide produced, after basification, an N,N-dimethylamino alcohol (16), which was dehydrated with acetic anhydride. The olefinic amine 17 was hydrogenated to a saturated tertiary amine (18) which proved to be identical with (—)-N,N-dimethylmenthylamine.

Rationalization of these apparently divergent data is made on the following grounds. Of the two most favorable transition states for cyclization, that (19) leading to *cis* ring fusion requires the potential six-membered carbocyclic ring to adopt a twist conformation. In 20, a slightly deformed chair arrangement is possible leading to the *trans* isomer. Examination of models indicates that orbital overlap for 1,3-addition is favorable *via* 19 to give a *cis* ring juncture for both

(19) These experiments were carried out by N. D. Ojha and W. Luinna, Jr.

(20) Cf. footnote p in Table 1. Some decomposition and rearrangement was noted on repeated distillation of 12b and 12c.

syn and *anti* configurations of the intermediate nitrone. On the other hand, effective overlap in the transition state for formation of a *trans* fused product is essentially precluded with an *anti*-nitrone; and 20 represents only the more favorable *syn* arrangement. Considering the reaction only in terms of the ratio of two isomeric products and the probability that there is little difference in thermodynamic stability of these products,
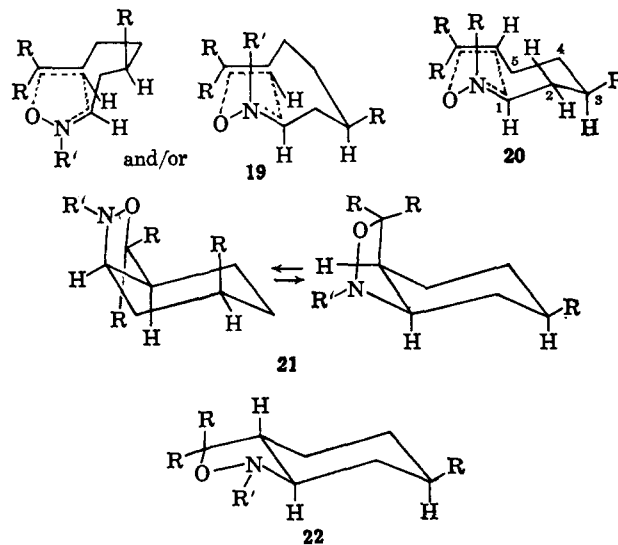
two situations can be envisioned. The ground state equilibrium composition of the nitrone must certainly favor the *anti* configuration. If the barrier to *syn* → *anti* isomerism is of the order of magnitude of the activation energies for intramolecular addition, then *cis* product would be favored (at least for the unsubstituted compound). However, if the barrier to rotation in the nitrone is low (a likely possibility), then the ratio of products would depend only on the difference in free-energy levels of the respective transition states. In 20, a significant interaction develops between the C-1 hydrogen atom and the C-5 methylene group which should allow the seemingly less favorable twist arrangement of the tetramethylene chain of 19 to compete successfully. The result is the observed isomer ratio of *ca.* 2:1 for 7a:7b in the condensation of 6-heptenal and methylhydroxylamine. These products correspond to 21 and 22 (R = H), respectively. However, when the R substituents do not equal H (*cf.* citronellal), the *trans* product 22 would appear to be much more stable than the *cis* compound 21 and product development control dominates.

Condensation of methylhydroxylamine with 2,6-dimethyl-5-heptenal ("melonal," 23) afforded the highly methylated isoxazolidine 24 in 55% yield. The stereochemistry of 24 seems reasonable on steric grounds.

Two unsaturated ketones have also been utilized. The condensations of 6-hepten-2-one (25) and 7-octen-

2-one (27) with N-methylhydroxylamine afforded the isoxazolidines 26 and 28, respectively. The isolated yields were excellent. Compound 26 was found to be homogeneous. Gas chromatography analysis suggested 28 to be isomerically pure as well, but n.m.r. analysis[21]
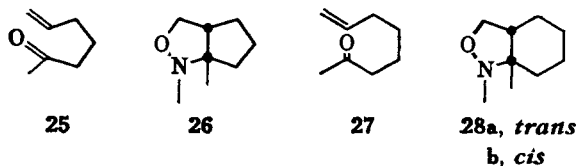
indicated two isomers in the ratio 2:1. The major isomer was assigned the *cis* structure 28b on the basis of its rigid geometry and similar n.m.r. spectrum to that of 26. The result is not inconsistent with the stereochemical considerations given earlier.

The condensation between citral and N-ethyl-hydroxylamine posed a very interesting case. Two double bonds are present to which the nitrone may add in an intramolecular manner. The condensation was carried out in the usual manner and the basic products were isolated. After removal of acid-labile compounds, a pure bicyclic isoxazolidine (29) was isolated. Hydrogenation gave 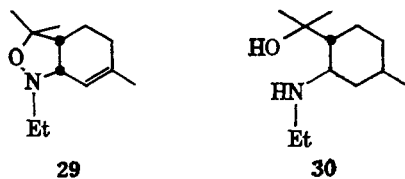two dihydro compounds, *neither* of which was identical with 12c. In other preparations, the *trans* isomer of 29 was detected as comprising 17–20% of the isoxazolidine fraction. It was separated by g.c. and was exhaustively hydrogenated to give racemic amino alcohol 30. Compound 29 must therefore contain a *cis* ring fusion.

The isoxazolidines were mobile liquids which showed the properties of weak bases. Determinations of the pK'_a have been carried out with compounds 11b and 12c, and values of 5.83 and 5.87 were obtained. Suitable crystalline derivatives of these products are the picrate and hydrogen oxalate salts. Methiodide salts are very useful derivatives of isoxazolidines, particularly for those systems which contain a six-membered ring fused to the five-membered heterocycle (*cf.* compounds 12). Because of the steric hindrance involved, it was not unexpected to observe that the 3-oxa-2-azabicyclo-[3.3.0]octane analogs (compounds 11) formed methiodides at much slower rates and in poorer yield, or not at all.

Hydrogenolysis of the isoxazolidine rings have been effected with a variety of reagents, and, in general, the yields of 1,3-aminoalcohols were excellent. Suitable conditions involve the use of hydrogen and platinum or palladium catalysts at atmospheric

pressure; hydrogen and Raney nickel at *ca.* 30 p.s.i.g.; lithium aluminum hydride in tetrahydrofuran solvent; and zinc and acetic acid. These reactions are summarized in Table III. Reductions of the methiodides have also been carried out efficiently under catalytic conditions and with lithium aluminum hydride (Table III). Several other modes of cleavage of isoxazolidines—which when coupled with the intramolecular addition reaction represent synthetic routes of wide utility—have been observed and will be discussed in a later manuscript.

The infrared spectra of the pure isoxazolidines are devoid of absorption bands in the N—H, O—H, C=O, and C=C regions, but are rather complex in the fingerprint region. However, relatively consistent bands occur at about 950 cm.$^{-1}$, a region that has been generally assigned to the normal N—O single bond frequency.[22] Another absorption band that has occurred repeatedly is found in the vicinity of 1070 cm.$^{-1}$.

Experimental[23]

N-Alkylhydroxylamines.—The zinc dust–ammonium chloride procedure of Beckman[24] for the reduction of nitro compounds to hydroxylamines was employed. N-Methylhyroxylamine hydrochloride was obtained in yields of 33–40%, m.p. 87° (lit.[24] m.p. 83–83.5°), after two recrystallizations from ethanol. Prior to use, pure N-methylhydroxylamine, b.p. 60–63° (20 mm.), n^{25}D 1.4151 (lit.[24] b.p. 62° at 15 mm., n^{20}D 1.4164), was obtained by treating a methanol solution of the hydrochloride with an equivalent amount of sodium methoxide, followed by distillation. N-Ethylhydroxylamine, m.p. 58–59° (lit.[24] m.p. 59°), was similarly obtained, as was N-isopropylhydroxylamine, m.p. 85–86° (lit.[24] m.p. 89°). The N-ethyl and N-isopropyl compounds were stored as ether solutions, and were sublimed just prior to use. N-Phenylhydroxylamine was prepared according to the procedure given in ref. 25.

Aldehydes.—Four of the olefinic aldehydes employed as starting materials for the ring-closure reaction were synthesized *via* reaction of a Grignard reagent, prepared from the homologous bromide, with ethyl orthoformate. Steam distillation of the diethyl acetal from 10% aqueous sulfuric acid gave the desired aldehyde. Alternatively, reduction of the nitrile with diisobutyl-aluminum hydride has also been employed.[26]

trans-5-Heptenal.—*trans*-4-Hexen-1-ol (98% pure by gas chromatography) was prepared in 83% yield by cleavage of 2-bromo-3-methyltetrahydropyran with sodium[27]; b.p. 102° (78 mm.), n^{25}D 1.4396 (lit.[28] b.p. 158–159°, n^{20}D 1.4402). The reaction of 100 g. (1.0 mole) of this alcohol with phosphorus tribromide and pyridine in ether[29] gave 89 g. (55%) of *trans*-1-bromo-4-hexene, b.p. 98–100° (95 mm.), n^{25}D 1.4658 (lit.[25] b.p. 63–65° at 35 mm., n^{25}D 1.4652). The Grignard reagent was prepared from 32.6 g. (0.2 mole) of the bromide, and was allowed to react with freshly distilled ethyl orthoformate.[30] The reaction mixture was hydrolyzed with dilute sulfuric acid, the upper oily layer was taken up in ether, and the ether was removed by distillation. Steam distillation from 10% sulfuric acid and subsequent work-up gave 8.5 g. (38%) of *trans*-5-heptenal, b.p. 90–92° (85 mm.), n^{25}D 1.4360, infrared absorption at 1730 and 962 cm.$^{-1}$;

(21) N.m.r. spectra were obtained with approximately 15% w./v. solutions in carbon tetrachloride, containing tetramethylsilane as the internal standard. A Varian DP-60 spectrometer was used. Chemical shifts were determined by means of the audio-sideband technique. Pertinent data are for 26: 3.70 (1H, J = 8.1), O-CH; 3.14 two doublets (1 H, J₁ = 4.6, J₂ = 8.1), O-CH; 2.39s (3H), N-CH₃; 1.11s (3H), C-CH₃ for 28, major isomer: 3.88 two doublets (J₁ = 6.9, J₂ = 8.5), O-CH; 3.46 (J = 6.9), O-CH; 2.38s, N-CH₃; 1.06s, C-CH₃; minor isomer: 4.42d broad, O-CH₂; 2.45, N-CH₃, 1.14, C-CH₃. Chemical shift values are in p.p.m., coupling constants in c.p.s.

(22) S. Califano and W. Luttke, Z. physik. Chem., 6, 83 (1956).

(23) Melting points are corrected and boiling points are uncorrected. Infrared spectra were determined with a Beckman IR-4 recording spectrophotometer. Microanalyses were by Midwest Microlabs, Inc., Indianapolis, Ind. Gas chromatography analyses were carried out with 6 ft. × 8 mm. glass columns packed with 25% by weight of silicone 550 Fluid on base-washed firebrick (A), 25% by weight of tris-β-cyanoethoxypropane on firebrick (B), GE XF 1150 Fluid (silicone-nitrile) on base-washed firebrick (C). Helium was the carrier gas.

(24) E. Beckman, Ann., 365, 304 (1909).

(25) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 723.

(26) A. I. Zakharkin and I. M. Khorlina, Dokl. Akad. Nauk SSSR, 116, 422 (1957); Chem. Abstr., 52, 8040 (1958).

(27) C. L. Stevens, B. Cross, and T. Toda, J. Org. Chem., 28, 1283 (1963).

(28) L. Crombie and S. H. Harper, J. Chem. Soc., 1707 (1950).

(29) R. P. Linstead and N. N. Rydon, ibid., 1898 (1934).

(30) Reference 25, p. 701.

g.c. analysis on column B at 170° showed only slight contamination by the *cis* isomer.

Anal. Calcd. for $C_7H_{12}O$: C, 74.86; H, 10.79. Found: C, 74.60; H, 10.89.

The 2,4-dinitrophenylhydrazone was recrystallized from 95% ethanol; m.p. 109.5–110°.

Anal. Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.35; H, 5.34; N, 19.24.

A second method was also employed in which a solution of 1-bromo-4-hexene (17.8 g., 0.11 mole) in 25 ml. of redistilled ethylene glycol was added dropwise to a solution of 8.8 g. (0.2 mole) of potassium cyanide in 60 ml. of ethylene glycol. The mixture was heated at 90–95° for 4 hr. After dilution with water, the product was extracted with ether. The solution was washed with brine, dried, and concentrated. Distillation afforded 10.9 g. (92%) of *trans*-1-cyano-4-hexene, b.p. 78–81° (19 mm.), n^{25}D 1.4339.

A solution of 7.06 g. (0.065 mole) of *trans*-1-cyano-4-hexene in 60 ml. of anhydrous ether under a nitrogen atmosphere was stirred efficiently at 0°, and a solution of 10.1 g. (0.077 mole) of diisobutylaluminum hydride in 30 ml. of dry hexane was added dropwise. When addition was complete, the cooling bath was removed, and the mixture was allowed to stir for 0.5 hr. Sulfuric acid (10%) was added slowly with cooling until the aqueous phase remained acidic. After an additional 0.5-hr. stirring, the organic layer was separated. The aqueous layer was extracted with three 25-ml. portions of ether. The combined organic phase was washed with saturated sodium bicarbonate solution and brine, and was dried and concentrated. Distillation gave 4.6 g. (64%) of *trans*-5-heptenal, b.p. 55–58° (18 mm.), n^{25}D 1.4335; g.c. analysis and infrared spectra showed the product to be identical with that prepared *via* the Grignard method.

cis-5-Heptenal.—The same sequence of reactions was applied to *cis*-4-hexen-1-ol[28] (containing about 4% of the *trans* isomer and 11% of hexanol as shown by gas chromatography on column B at 160°). *cis*-1-Bromo-4-hexene was obtained (63%), b.p. 58–60° (20 mm.), n^{25}D 1.4681 (*Anal.* Calcd. for $C_6H_{11}Br$: C, 44.19; H, 6.80. Found: C, 44.43; H, 6.77); gas chromatography on column B at 146° showed about 5% *trans* isomer and 13% 1-bromoheptane. Conversion to *cis*-5-heptenal by the Grignard method was effected in 40% yield, b.p. 58° (20 mm.), n^{25}D 1.4356. Gas chromatography on column A at 170° showed several impurities, and the sample for analysis was collected by gas chromatography.

Anal. Calcd. for $C_7H_{12}O$: C, 74.86; H, 10.79. Found: C, 73.07; H, 10.78.

The 2,4-dinitrophenylhydrazone was recrystallized from absolute ethanol; m.p. 94–95°. A mixture melting point with the *trans* isomer was depressed (90–95°).

Anal. Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.68; H, 5.58; N, 18.74.

cis-1-Bromo-4-hexene (8.6 g., 0.053 mole) was treated with potassium cyanide in ethylene glycol to give 4.83 g. (84%) of *cis*-1-cyano-4-hexene, b.p. 82–85° (20 mm.), n^{23}D 1.4360 (g.c. analysis on column B at 147° showed 84% *cis*-nitrile and 16% *trans*-nitrile. Pure *cis* isomer was separated by g.c. (*Anal.* Calcd. for $C_7H_{11}N$: C, 77.07; H, 10.09; N, 12.84. Found: C, 76.84; H, 10.08; N, 12.85). Reduction of 4.7 g. of *cis*-1-cyano-4-hexene (84% *cis*, 16% *trans*) with diisobutylaluminum hydride according to the procedure used for the pure *trans* isomer gave 1.47 g. (31%) of *cis* 5-heptenal, b.p. 58° (20 mm.), n^{24}D 1.4358; g.c. analysis on column B at 150° showed 80% *cis*-5-heptenal and 20% *trans*-5-heptenal.

6-Heptenal (8).—5-Hexen-1-ol[31] was converted to 6-bromo-1-hexene by the phosphorus tribromide–pyridine procedure[28]; b.p. 88–90° (95 mm.), n^{25}D 1.4638 (lit.[26] b.p. 47–51° at 16 mm., n^{25}D 1.4632). The bromide was converted to the aldehyde *via* the Grignard reagent, and there was obtained 4.95 g. (39%) of 6-heptenal, b.p. 88–90° (80 mm.), n^{25}D 1.4261; infrared spectra: 1730, 1639, 991, and 910 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{12}O$: C, 74.95; H, 10.79. Found: C, 74.67; H, 10.97.

The 2,4-dinitrophenylhydrazone was prepared and was recrystallized three times from 95% ethanol; m.p. 95–95.8°.

Anal. Calcd. for $C_{13}H_{16}O_4N_4$: C, 53.41; H, 5.51; N, 19.16. Found: C, 53.25; H, 5.64; N, 19.33.

(31) R. E. Lyle, E. J. DeWitt, and I. C. Pattison, *J. Org. Chem.*, **21**, 61 (1956).

trans-6-Octenal.—*trans*-1-Cyano-4-hexene (22.2 g., 0.2 mole) was treated with ethanol containing the calculated amount of water in the presence of sulfuric acid catalyst, and there was obtained 25 g. (81%) of ethyl *trans*-5-heptenoate, b.p. 85–89° (20 mm.), $n^{24.5}$D 1.4256 (*Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.29; H, 10.24). Reduction with lithium aluminum hydride afforded *trans*-5-hepten-1-ol, b.p. 109–111° (45 mm.), n^{24}D 1.4426 (*Anal.* Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.38. Found: C, 73.76; H, 12.33). When the alcohol was treated with phosphorus tribromide in pyridine, *trans*-7-bromo-2-heptene, b.p. 108–110° (88 mm.), n^{23}D 1.4675, was obtained (19.5 g., 58%) (*Anal.* Calcd. for $C_7H_{13}Br$: C, 47.47; H, 7.40. Found: C, 47.48; H, 7.70).

From 15 g. (0.086 mole) of *trans*-7-bromo-2-heptene, 4.0 g. (37%) of *trans*-6-octenal was obtained by employing the Grignard reagent–ethyl orthoformate procedure; b.p. 86–88° (50 mm.), $n^{24.5}$D 1.4362.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.38; H, 11.12.

The 2,4-dinitrophenylhydrazone was recrystallized three times from ethanol; m.p. 100–101°.

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.91; H, 5.92; H, 18.62. Found: C, 55.04; H, 6.05; N, 18.62.

5-Hexenal (4). Procedure A.—To a solution of 18 g. (0.156 mole) of a mixture of *cis*- and *trans*-3-aminocyclohexanol[10] in 900 ml. of 25% aqueous acetic acid was added a solution of 18 g. of sodium nitrite in 150 ml. of water and the reaction was maintained at 0° for 6 hr. Sulfamic acid (30 g.) was added slowly followed by 700 ml. of methylene chloride. Sodium carbonate and methylene chloride were added simultaneously until the aqueous layer was nearly neutral to litmus. The layers were separated and the aqueous solution was extracted with four 200-ml. portions of methylene chloride. The combined extract was dried over magnesium sulfate and concentrated. The light yellow solution was distilled to yield 5.75 g. (37.5%) of 5-hexenal, b.p. 118–121°, n^{25}D 1.4113 (lit.[32] b.p. 118–118.5°, n^{20}D 1.4109 .

The 2,4-dinitrophenylhydrazone was recrystallized from aqueous ethanol and melted at 99–100° (lit.[10] m.p. 96°).

Procedure B.—The Grignard reagent was prepared from 22 g. (0.135 mole) of 5-bromo-1-pentene[33] and the solution was treated with ethyl orthoformate. Work-up in the usual manner afforded, after careful fractionation, 6.15 g. (41%) of 5-hexenal.

6-Hepten-2-one (25).—A sample of 6-hepten-2-one (25) was supplied by Professor N. C. Yang, University of Chicago. Additional material was synthesized by alkylation of ethyl acetoacetate with 4-bromo-1-butene to give ethyl 2-acetyl-5-hexenoate (65%), b.p. 103–110° (22 mm.). Saponification and decarboxylation furnished 6-hepten-2-one (25, 67%), b.p. 71–73° (50 mm.), n^{25}D 1.4223, identical with the earlier sample.

7-Octen-2-one (27).—Alkylation of ethyl acetoacetate with 5-bromo-1-pentene afforded 73% yield of ethyl 2-acetyl-6-heptenoate, b.p. 69–72° (2 mm.), n^{25}D 1.4422 (lit.[34] b.p. 118–121° at 12 mm., n^{25}D 1.4402). Saponification and decarboxylation gave 7-octen-2-one (27), 88%, b.p. 81–86° (35 mm.), n^{25}D 1.4282 (lit.[34] b.p. 82° at 34 mm., n^{25}D 1.4262).

Mercuric Oxide Oxidations. A. N-Methyl-N-5-hexenylhydroxylamine (3).—To a well-stirred suspension of 16 g. of yellow mercuric oxide and 60 ml. of absolute ethanol was added dropwise a solution of 3.5 g. (0.026 mole) of N-methyl-N-5-hexenylhydroxylamine (3) in 15 ml. of absolute ethanol over a period of 20 min. The reaction flask was kept in an ice bath during the addition, and was stirred for an additional 5 hr. at room temperature. After filtration the filtrate was concentrated and the pale yellow residue was distilled to yield 1.05 g. of crude product, b.p. 64–66° (20 mm.). Purification was effected by solution in cold 10% hydrochloric acid, followed by several washings with ether. The product was liberated by basification with 25% sodium hydroxide solution and was extracted with four 25-ml. portions of ether. The extract was dried and concentrated. The residue was distilled to yield 0.75 g. (22%) of the isoxazolidine 2, b.p. 62–64° (18 mm.), n^{25}D 1.4644 (lit.[2] b.p. 79–80° at 30 mm., n^{25}D 1.4642).

The infrared spectrum of this product was identical with that of the product obtained from the reaction of N-methylhydroxylamine with 5-hexenal and that of 2 obtained previously,[2] and g.c. on column A at 138° confirmed the assignment.

(32) M. S. Kharasch, B. M. Kuderna, and W. Nudenberg, *ibid* **18**, 1225 (1953).

(33) A. Juvala, *Ber.*, **63**, 1989 (1930).

(34) The procedure and an authentic sample were generously provided by Professor P. E. Peterson, St. Louis University.

TABLE II
DERIVATIVES OF BICYCLIC ISOXAZOLIDINES

Isoxazolidine derivative	Formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
7 hydrogen oxalate	$C_{10}H_{17}NO_5$	95–95.8	51.93	51.77	7.42	7.16	6.06	6.04
11a picrate	$C_{14}H_{18}N_4O_8$	155–156	45.40	45.66	4.90	4.85	15.13	15.00
11b picrate	$C_{15}H_{20}N_4O_8$	130–133	46.87	47.15	5.25	5.37	14.58	14.27
11b hydrogen oxalate	$C_{11}H_{19}NO_5$	87–87.5	53.86	53.67	7.81	7.68	5.71	5.71
11c picrate	$C_{14}H_{18}N_4O_8$	130–131	45.40	45.58	4.90	5.04	15.13	14.94
11d picrate	$C_{15}H_{20}N_4O_8$	108–109	46.87	46.79	5.25	5.20	14.58	14.41
11e picrate	$C_{14}H_{18}N_4O_8$	149–150	45.40	45.70	4.90	5.00	15.13	14.65
12a hydrogen oxalate	$C_{10}H_{17}NO_5$	95–95.8	51.93	51.77	7.42	7.16	6.06	6.04
12a picrate	$C_{17}H_{21}N_4O_8$	156–157	49.51	49.66	5.87	5.79	13.59	13.67
12b picrate	$C_{17}H_{24}N_4O_8$	168–169	49.51	49.37	5.87	6.13	13.59	13.64
12b methiodide	$C_{12}H_{24}NOI$	198–199	44.28	44.35	7.44	7.65	4.31	4.53
12c picrate	$C_{18}H_{26}N_4O_8$	156–157	50.70	50.74	6.15	6.17	13.14	13.15
12d picrate	$C_{19}H_{28}N_4O_8$	144–145	51.81	51.99	6.41	6.45	12.72	12.84
12e picrate	$C_{22}H_{26}N_4O_8$	183–184	55.69	55.54	5.53	5.58	11.81	11.72
24 picrate	$C_{16}H_{22}N_4O_8$	125.5–126	48.24	48.47	5.57	5.81	14.07	13.94
26 picrate	$C_{14}H_{18}N_4O_8$	~200 dec.	45.40	45.62	4.90	5.07	15.13	14.83
28 picrate	$C_{15}H_{20}N_4O_8$	~220 dec.	46.87	47.13	5.25	5.48	14.58	14.36

The hydrogen oxalate was prepared in the usual manner and was recrystallized from ethyl acetate; m.p. 82–82.5° (lit.[2] m.p. 81–81.9°). A mixture melting point was undepressed.

In a separate experiment, 2 g. of 3 was oxidized with 10 g. of yellow mercuric oxide as described above. After removal of the inorganic contaminants, the alcoholic solution was treated with the calculated amount of 2,4-dinitrophenylhydrazine solution (2.94 mg. per ml. of solution). The precipitate was chromatographed through Merck acid-washed alumina employing a mixture of hexane and benzene as the eluent. Only 5-hexenal-2,4-dinitrophenylhydrazone (2.56 g., 59%) was isolated. This product was identified from its infrared spectrum and mixture melting point (99.5–100°).

B. N-Methyl-N-6-heptenylhydroxylamine (6).—The oxidation of 3 g. (0.021 mole) of N-methyl-N-6-heptenylhydroxylamine (6) with 15 g. of yellow mercuric oxide was carried out in the manner described above. There was obtained 0.52 g. (17.5%) of 7 (R = CH₃), b.p. 70–72° (15 mm.), $n^{25}D$ 1.4671.

In order to effect purification, this product was treated with oxalic acid in ether to form the hydrogen oxalate. After two recrystallizations from ethyl acetate, the salt was dissolved in water and basified with 25% sodium hydroxide solution. The product was taken up in ether and the dried solution was concentrated. Distillation of the residue furnished an analytical sample of N-methyl-8-oxa-3-azabicyclo[4.3.0]nonane (7), $n^{25}D$ 1.4672.

The hydrogen oxalate, prepared and recrystallized in the usual manner, melted at 95–95.8°.

The methiodide, unlike that of the bicyclo[3.3.0] homolog, was formed easily by reaction with methyl iodide in ether solution; m.p. 148–149°.

An additional oxidation experiment was carried out in which 2 g. of 6 was oxidized with mercuric oxide as described above. The filtrate was treated with calculated amount of freshly prepared 2,4-dinitrophenylhydrazine solution and the precipitate was chromatographed. Again, only one product (2.78 g., 73%), formulated as 6-heptenal-2,4-dinitrophenylhydrazone, m.p. 95.5–96°, was isolated. A mixture melting point with an authentic sample (vide infra) was undepressed.

Condensation of Aldehydes and Ketones with N-Alkylhydroxylamines.—The unsaturated aldehydes and ketones, prepared as described above, and the redistilled commercially available aldehydes (+)-citronellal and citral were condensed with N-alkylhydroxylamines by one of several procedures. Typical experiments are described as follows.

Method A. Ether and Magnesium Sulfate. N-Methyl-cis-3-oxa-2-azabicyclo[3.3.0]octane (2).—To a well-stirred suspension of 8 g. of anhydrous magnesium sulfate in 50 ml. of ether, containing 0.96 g. (0.02 mole) of freshly prepared N-methylhydroxylamine, was added a solution of 2.0 g. (0.02 mole) of 5-hexenal over a period of 2 hr. The mixture was heated at reflux for 8 hr., and then was filtered. The product was extracted with 10% hydrochloric acid. After basification, the liberated organic base was taken up in pentane. After back-washing with water, the pentane solution was dried and concentrated. Distillation afforded 0.98 g. (38%) of the isoxazolidine 2, b.p. 62–64° (20 mm.),

identical with that obtained previously. The product was found to be homogeneous by gas chromatography on column A at 138°.

Method B. Toluene. trans, trans-1,3,3,6-Tetramethyl-3a,4,-5,6,7,7a-hexahydro-2,1-benzisoxazoline (12b).—A mixture of 10.0 g. (0.06 mole) of citronellal and 200 ml. of toluene was heated to reflux in a flask to which was attached a Stark water separator. A solution of 5.0 g. (0.11 mole) of N-methylhydroxylamine in 50 ml. of toluene and 10 ml. of absolute methanol was added dropwise over a period of 2 hr. The theoretical amount of water was collected (1.2 ml.) and the mixture was heated under reflux for an additional 16 hr. The cooled solution was extracted with six 35-ml. portions of 10% hydrochloric acid. The acid extract was washed with ether and then was basified with 20% sodium hydroxide solution. The liberated organic product was extracted with ether. The combined ether extract was washed with water, dried (MgSO₄), and concentrated. Distillation of the residue through a spinning-band column afforded 8.2 g. (70%) of the isoxazolidine 12b, b.p. 102–104° (16 mm.). The product was found by g.c. (column C at 162°) to consist of a major isomer (12b, 86%) contaminated with 12% of a second isomer.

Benzene was also employed as a solvent in these condensations. The yields were usually lower than those obtained with toluene under comparable conditions. Ethanol at reflux temperature for 24 hr. also gave good yields.

Method C. Ethanol at Room Temperature. Preparation of 12b.—A solution of 3.05 g. (0.065 mole) of N-methylhydroxylamine in 50 ml. of absolute ethanol was added dropwise with stirring to a solution of 12.81 g. (0.07 mole) of citronellal in 200 ml. of ethanol. After 24 hr., the mixture was acidified to pH 2 and was concentrated at reduced pressure. The acidic solution was washed thoroughly with ether to remove citronellal. Basification and extraction with ether, followed by drying and concentration, gave the crude product 12b; g.c. analysis indicated 97% purity; contamination by 3% of an isomer was noted. Distillation afforded a 25% yield of 12b, b.p. 102–103° (16 mm.), $n^{25}D$ 1.4607.

Similar results were obtained with toluene as a solvent.

The products from these condensation reactions are summarized in Table I.

cis,trans-1,3,3,7-Tetramethyl-2-oxa-1-azabicyclo[3.3.0]octane (24).—Condensation between 2,6-dimethyl-5-heptenal (melanal,[35] 3 g.) and 2.5 g. of N-methylhydroxylamine in toluene gave 1.91 g. (54%) of isoxazolidine 24, b.p. 101° (45 mm.), $n^{25}D$ 1.4539.

The picrate is given in Table II.
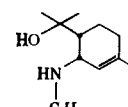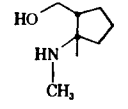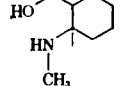
cis-1,8-Dimethyl-2-oxa-1-azabicyclo[3.3.0]octane (26).—Condensation of 5.52 g. (0.05 mole) of 6-hepten-2-one (25) and 5 g. (0.1 mole) N-methylhydroxylamine by the toluene method afforded 5.58 g. (80%) of isoxazolidine 26, b.p. 87–88° (40 mm.), $n^{21}D$ 1.4627; g.c. on column C at 150° showed only one component.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.16; H, 10.87; N, 10.20.

The picrate is given in Table II.

(35) Generously supplied by Professor L. Friedman, Case Institute of Technology.

Table III

Amino Alcohols from Reduction of Isoxazolidines

Amino alcohol	Proce-dure^a	Yield, %	Properties	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
5	A	32							
9	A^b	85	45–46^d	67.08	66.93	11.96	11.73	9.78	9.79
31, R_1 = H, R_2 = CH_3	A	56	104–104.5^d	71.30	71.38	12.51	12.58	7.56	7.43
	B	45							
	C	82							
	D	41							
16, R_1 = R_2 = CH_3	E	81	77–81 (1)^c	72.30	72.59	12.64	12.63	7.03	6.94
30, R_1 = H, R_2 = C_2H_5	B	78	75–78 (0.5)^c	72.30	72.18	12.64	12.47	7.03	7.04
32, R_1 = CH_3, R_2 = C_2H_5	E	72	88–90 (2)^c	73.18	73.00	12.75	12.58	6.57	6.62
14, R_1 = H, R_2 = C_6H_5	C	97	129–130^d	78.86	79.04	10.19	10.44	5.66	5.75
33	F	Poor	88–90 (2)^c	73.87	73.59	11.92	11.83	6.63	6.92
34	C	80	68–71 (1.3)^c						
35	C	88	70 (1.5)^c						

^a Procedure A = Zn–HOAc; B = LiAlH_4 in THF; C = H_2, Pd–C; C = H_2–Pt; E = H_2–Pt reduction of the methiodide; F = LiAlH_4 reduction of the methiodide in THF suspension. ^b Properties are those of the alcohol from reduction of N-cis-2-carboxycyclo-hexylformamide (10). ^c B.p., °C (mm.). ^d M.p., °C..

1,7a-Dimethyl-3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline (28).—From 8.3 g. (0.066 mole) of 7-octen-2-one (27) and an excess of N-methylhydroxylamine there was obtained 7.08 g. (69%) of 28, b.p. 105–106° (37 mm.), n^25D 1.4768; g.c. on column C at 150° indicated that 28 was homogeneous, but the n.m.r. spectrum (ref. 21) suggested two isomers.

Anal. Calcd. for C_9H_17NO: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.64; H, 11.16; N, 8.89.

The picrate is given in Table II.

Isoxazolidine Derivatives.—Several derivatives were appropriate for the characterization of the isoxazolidines, and those employed are summarized in Table II. Picrates were usually recrystallized from 95% ethanol, methiodides from acetone or alcohol–ether mixtures, hydrogen oxalates from ethyl acetate or methanol-ethyl acetate mixtures.

The Condensation of Citral and N-Ethylhydroxylamine.—Employing the usual apparatus for the cyclization reaction,' 11.1 g. (0.073 mole) of citral in benzene was treated with 4.45 g. (0.073 mole) of N-ethylhydroxylamine. The theoretical amount of water was collected and the reaction mixture was worked up as described previously. There was obtained 4.58 g. of product, b.p. 82- 90° (13 mm.), n^25D 1.4721. A viscous residue (2.78 g.) remained. The distillate was a clear liquid which became dark on standing. It gave positive triphenyltetrazolium chloride and 2,4-dinitrophenylhydrazone tests. For purification, the crude product was dissolved in 25 ml. of 12% hydrochloric acid and the solution was heated at 100° for 2 hr. After cooling, the solution was extracted with ether and basified; the product was extracted with pentane. Distillation gave 2.2 g. (15%) of 1-ethyl, 3,3,6-trimethyl-cis-3a,4,5,7a-tetrahydro-2,1-benzisoxazoline (29), b.p. 108–110° (15 mm.), n^25D 1.4752. The liquid material was shown to be homogeneous by gas chromatography on column A at 182°; infrared bands at 1670 (m), 1380 (s), 1365 (s), 1290 (m), 1235 (m), 1200 (m), 1165 (s), 1075 (m), 985 (w), 965 (w), 935 (s), 906 (s), 875 (s), 850 (m), 785 (m), 720 (m) cm.^-1. Other preparations, avoiding the acid purification procedure, afforded 4:1 mixtures of cis (29) and trans isomers, respectively, in yields up to 27%.

Anal. Calcd. for C_12H_21NO: C, 73.79; H, 10.64; N, 7.17. Found: C, 73.50; H, 10.94; N, 7.29.

The picrate was recrystallized twice from ethanol; m.p. 136–137°.

Anal. Calcd. for C_18H_24N_4O_8: C, 50.91; H, 5.70; N, 13.20. Found: C, 50.99; H, 5.77; N, 13.24.

The methiodide formed readily and was recrystallized from acetone; m.p. 158.5–159°.

Anal. Calcd. for C_13H_24NOI: C, 46.29; H, 7.17; N, 4.17; I, 37.63. Found: C, 46.16; H, 7.41; N, 4.33; I, 37.50.

A solid remained from the distillation of 29 and weighed 0.18 g. It was recrystallized twice from ether–pentane mixtures, m.p. 180–181° and was formulated as N-ethyl-4,9,9-trimethyl-8-oxa-7-azabicyclo[4.3.0]nonan-4-ol.

Anal. Calcd. for C_12H_23NO_2: C, 67.56; H, 10.86; N, 6.59. Found: C, 67.21; H, 10.82; N, 6.94.

The Condensation of Citronellal with N-Phenylhydroxylamine. Twenty-five grams (0.162 mole) of citronellal was condensed with 17.7 g. (0.162 mole) of N-phenylhydroxylamine. The pentane extract was dried and concentrated and a crystalline solid (9.1 g., 23%) was obtained. After two recrystallizations from aqueous ethanol followed by sublimation, the product, N-phenyl-trans,-trans-4,9,9-trimethyl-8-oxa-7-azabicyclo[4.3.0]nonane (12e), had m.p. 147-148°, λ_max^EtOH 248 mμ (ε 7850).

N-cis-2-Carboxycyclohexylformamide (10).—cis-Hexahydro-anthranilic acid was prepared by hydrogenation of anthranilic acid over 5% rhodium-on-alumina or 10% rhodium-on-charcoal catalyst.[36] It was recrystallized from aqueous acetone; m.p. 232–233° dec. (lit.[37] m.p. 234–234.5° with dec.). A mixture of 3.0 g. (0.021 mole) of cis-hexahydroanthranilic acid and 1.28 g. (0.025 mole) of 90% formic acid was heated for 4 hr. The resulting solution was kept at room temperature for 2 hr. and crystals were deposited. The product was recrystallized twice from water to furnish 1.93 g. (54%) of product, m.p. 200–201°. An analytical sample was obtained by sublimation, m.p. 201°.

Anal. Calcd. for C_8H_13NO_3: C, 56.12; H, 7.65; N, 8.18. Found: C, 56.25; H, 7.93; N, 8.21.

Hydrogenolysis of the Isoxazolidines.—Several different procedures were found suitable for the reductive cleavage of the isoxazolidines or their methiodides. These procedures are summarized below.

Zinc and Acetic Acid Reduction. N-Methyl-trans,trans-2-(2'-hydroxy-2'-propyl)-5-methylcyclohexylamine (31).—A solution of 500 mg. of isoxazolidine 12b in 0.5 ml. of glacial acetic acid was added to a stirred suspension of 420 mg. of zinc dust in 4 ml. of 1:1 acetic acid–water. After 5 hr. at 50–60°, the mixture was

(36) We wish to thank Professor A. C. Cope for informing us of a procedure for the preparation of this acid.

(37) S. Hunig and H. Kahanek, Ber., 86, 518 (1953).

TABLE IV

DERIVATIVES OF AMINO ALCOHOLS

Compound	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
5 oxalate	181–181.5	55.15	54.98	9.26	9.20	8.04	8.13
9 hydrogen oxalate	104–105	51.49	51.72	8.21	8.13	6.00	5.77
9 bisbenzoate	118–119						
30 picrate	154–155	51.57	51.86	6.83	6.59	12.67	12.63
14 picrate	196–197	55.45	55.74	5.93	6.05	11.76	11.80
31 hydroiodide	203–204	44.36	43.91	8.01	8.02	4.26	4.43
34 bisbenzoate	94.5–95	75.18	75.11	7.17	7.39	3.99	3.88
35 bisbenzoate	117–117.5	75.58	75.23	7.45	7.64	3.83	3.66

filtered and the excess zinc was washed with 5% hydrochloric acid. Basification, followed by continuous extraction with methylene chloride, gave 354 mg. of crude product. Chromatography over a small quantity of alumina and elution with ether gave 277 mg. (56%) of the amino alcohol **31**, m.p. 104–104.5°.

Catalytic Hydrogenation. A. Palladium-on-Carbon. Reduction of 12b to 31.—A solution of 500 mg. of **12b** in 15 ml. of ethanol was added to 200 mg. of prereduced 10% palladium-carbon catalyst in 10 ml. of ethanol; 90% of the theoretical amount of hydrogen was taken up in 45 min. *After filtration and evaporation of the solvent, 440 mg. of crude product was obtained. Chromatography on alumina gave 415 mg. (81.5%) of **31**, m.p. 104–104.5°.

N-Phenyl-*trans,trans*-2-(2'-hydroxy-2'-propyl)-5-methylcyclohexylamine (14).—Hydrogenation of 1.4 g. (0.006 mole) of **12f** in the presence of 0.33 g. of 10% palladium–carbon catalyst gave 1.37 g. (97%) of a solid amino alcohol **14**, m.p. 121–123°. Recrystallization from hexane raised the melting point to 129–130°.

Catalytic Reduction. B. Platinum Oxide. Reduction of 12b to 31.—A solution of 500 mg. of isoxazolidine in 25 ml. of ethanol was hydrogenated in the presence of 250 mg. of prereduced platinum oxide. After 18 hr., an additional 195 mg. of catalyst was added. The total uptake of hydrogen amounted to 66%. The crude product was chromatographed to give a 59% yield of amino alcohol **31**, m.p. 104–104.5°.

N-Ethyl,N-methyl-*trans,trans*-2-(2'-hydroxy-2'-propyl)-5-methylcyclohexylamine.—The methiodide of **12c** (6.13 g., 0.19 mole) was hydrogenated in 200 ml. of ethanol with prereduced platinum oxide as the catalyst. Evaporation of the solvent gave a crystalline hydroiodide of the amino alcohol, m.p. 203–204°. The salt was dissolved in water, basified, and extracted with methylene chloride. Distillation gave a liquid amino alcohol **32**, b.p. 88–90° (2 mm.), n^{22}D 1.4669.

Lithium Aluminum Hydride Reduction of 12b.—A mixture of 1 g. of **12b**, 0.2 g. of lithium aluminum hydride, and 50 ml. of tetrahydrofuran was heated at reflux for 20 hr. Work up was effected by the addition of 0.2 g. water, 0.6 g. of 15% potassium hydroxide solution, and 0.2 g. of water. After removal of the salts by filtration, the filtrate and washings were dried and concentrated to give 0.86 g. of crude material. Chromatography on alumina gave 0.56 g. of recovered starting material (54.5%) and 0.46 g. (45.5%) of amino alcohol **31**, m.p. 104–104.5°

The amino alcohol products and derivatives are given in Tables III and IV.

N,N-Dimethyl-*trans,trans*-2-(2'-propenyl)-5-methylcyclohexylamine (17).—A mixture of 5.97 g. (0.025 mole) of amino alcohol

31 and 10 ml. of acetic anhydride was heated at reflux for 10 hr. The solution was chilled and was basified with 20% potassium hydroxide solution. After extraction with ether, the extract was dried and concentrated. Distillation gave 4.23 g. (75%) of **17**, b.p. 69–70° (3.5 mm.), n^{25}D 1.4658, [α]^{25}D +9.15°.

Anal. Calcd. for $C_{12}H_{23}N$: C, 79.48; H, 12.76; N, 7.73. Found: C, 79.52; H, 13.01; N, 7.29.

The n.m.r. spectrum and infrared spectrum of **17** confirmed the presence of the terminal methylene group.

The picrate was prepared and was recrystallized from 95% ethanol; m.p. 153.5–154°.

Anal. Calcd. for $C_{18}H_{26}N_4O_7$: C, 52.68; H, 6.39; N, 13.65. Found: C, 52.77; H, 6.33; N, 13.94.

N,N-Dimethyl-1-methylamine (18).—The amine **17** was hydrogenated in methanol solution in the presence of 10% prereduced Pd–C catalyst. Upon distillation, there was obtained 0.69 g. (69%) of **18**, b.p. 75–76° (4.9 mm.), n^{25}D 1.4565, [α]^{25}D −49.6° (lit.[38] b.p. 85° at 7 mm., n^{25}D 1.4552, [α]^{25}D −51.20°).

Trimethyl-1-methylammonium Iodide.—The methiodide of **18** was prepared and was recrystallized from acetone; m.p. 192.5–193.5, [α]^{25}D (H₂O, 1.55) −18.7° (lit.[38] m.p. 192.3–192.5°, 193–194°, [α]^{25}D −40.5°, −37.6°), m.m.p. 193–194°.

N,N-Dimethyl-*l*-menthylammonium Picrate.—The picrate of **18** was prepared; m.p. 128.5–129°. The picrate of synthetic N,N-dimethyl-*l*-menthylamine[38] ([α]^{20}D −47.6°) melted at 127.5–128°, m.m.p. 127.5–128°.

Relative Configurations of Isoxazolidines 11c and 11e.—Samples of 131 mg. each of isomeric isoxazolidines **11c** and **11e** were hydrogenated with 10% Pd–C in absolute ethanol to the corresponding amino alcohols (infrared spectra different). Each amino alcohol was acetylated to the diacetyl derivative (infrared spectra different). The diacetates were saponified with 1 N sodium hydroxide at room temperature and the N-acetylamino alcohols were isolated (infrared spectra different). Oxidation with potassium dichromate and sulfuric acid in a two-phase system with ether gave N-methyl-N-acetyl-*cis*-2-acetylcyclopentylamine (15) (infrared spectra nearly identical). The 2,4-dinitrophenylhydrazones were prepared and were recrystallized from benzene; m.p. 189–190° (from 11c), 189–190° (from 11e), m.m.p. 190°.

(38) N. L. McNiven and J. Reed, *J. Chem. Soc.*, 153 (1952); A. C. Cope and E. M. Acton, *J. Am. Chem. Soc.*, **80**, 357 (1958).

Phenonium Ions as Discrete Intermediates in Certain Wagner–Meerwein Rearrangements

BY DONALD J. CRAM

The case is stated for the existence of phenonium ions in certain Wagner–Meerwein rearrangements.

Thirteen years after the original evidence for the existence of ethylene phenonium ions was published,[1] H. C. Brown has in print[2] questioned the validity of the

(1) (a) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3863 (1949); (b) **71**, 3875 (1949).

original interpretations.[3] This event requires a summation of the case for the existence of ethylene pheno-

(2) H. C. Brown, "The Transition State," Special Publication No. 16, The Chemical Society, London. 1962, p. 140.

(3) In numerous seminars, colloquia, and symposia since 1958, H. C. Brown has enthusiastically attacked bridged phenonium ion interpretations.