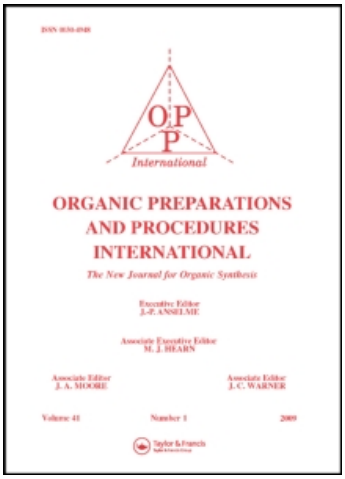


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# SYNTHESIS OF AZIRIDINES BY REDUCTION OF OXIMES WITH LITHIUM ALUMINUM HYDRIDE A REVIEW

Katsumi Kotera[a]; Keizo Kitahonoki[a]
[a] Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan

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ORGANIC PREPARATIONS AND PROCEDURES 1(4), 305-324 (1969)

# SYNTHESIS OF AZIRIDINES BY REDUCTION OF OXIMES WITH LITHIUM ALUMINUM HYDRIDE A REVIEW

Katsumi Kotera and Keizo Kitahonoki*

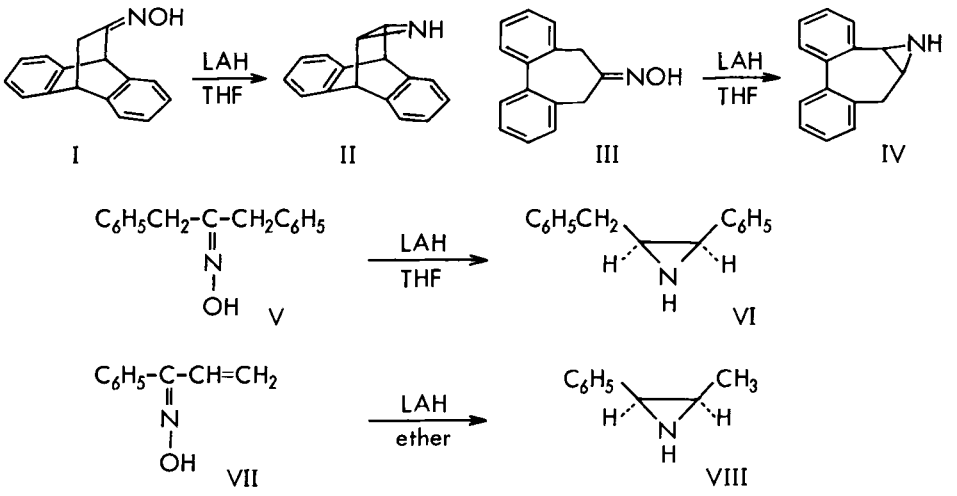
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan



The synthesis and the chemistry of aziridines have attracted considerable attention in recent years from the academic as well as from the practical point of view. We wish to describe here a new synthetic method for aziridines, which was discovered in our laboratories.

The reduction of oximes with lithium aluminum hydride (LAH) usually gives the corresponding primary amines[1] although the yields vary over a wide range. It has also been reported that the reduction of certain aryl ketoximes[2] and strained alicyclic ketoximes[3] yields the rearranged secondary amines together with the primary amines. No other unusual path of the reduction of oximes with that reagent had been known. Our keen interest on the LAH reduction of ketoximes[4] led us to investigate this reaction further. Thus, in 1965, we reported that certain types of ketoximes are reduced mainly to aziridines with LAH in suitable solvents, especially in tetrahydrofuran (THF).[5] For example, dibenzobicyclo[2.2.2]octadienone oxime (I), dibenzo-(a,c)cycloheptadien-6-one oxime (III) and dibenzyl ketoxime (V) were reduced with

* To whom correspondence should be directed.




LAH in boiling THF to the corresponding aziridines II, IV and VI, in 35, 79, and 77% yield, respectively;[5,6] the yields of the accompanying primary amines in the reaction being only 3, 12.1, 7.6%, respectively. From further study we succeeded in working out a new and simple synthetic method for the preparation of aziridines directly from some oximes. At almost the same time, Shandala et al.[7] reported one similar example of this reaction type: phenyl vinyl ketoxime (VII) gave cis-2-phenyl-3-methyl-aziridine (VIII) in 50% yield with LAH in boiling ether.

Among the methods reported hitherto for the syntheses of aziridines,[8] ones in which ketoximes or their derivatives are used as starting compounds, as in the present reaction, are limited to the Hoch-Campbell synthesis,[9] the Neber and related rearrangements.[10] The former is the reaction of ketoximes with Grignard reagents forming aziridines in which the alkyl or aryl group of the reagent is introduced. Eguchi and Ishii[11] reported that this reaction proceeds through an azirine intermediate, and recently Laurent and Muller[12] investigated the effect of oxime configuration on this reaction, which was shown to be closely related to that of the present reaction. In the Neber reaction aminoketones (or intermediate azirines) are formed from

ketoxime O-tosylates (or imino derivatives) by basic reagents. Although azirines,[13a] or aziridine intermediates in which an alkoxy substituent was introduced,[13b] have been isolated in some instances of this reaction, there have been no reports on the utility of this reaction for aziridine synthesis. Only mechanistic investigations of this reaction had been carried out to clarify the above intermediates in limited examples and aziridines were obtained on LAH reduction of them. It should also be recognized that the Neber and related rearrangements proceed independently of the configuration of the ketoxime O-tosylates or other imino derivatives used,[14] this being one of the characteristics of the reaction, different from both our reaction and the Hoch-Campbell method. Though the new reaction reported here can be classified in the category of the Neber rearrangement or the Hoch-Campbell synthesis, we believe that the mechanism and/or scope of the reaction are different from the above two methods. A short review on the new synthesis of aziridines from oximes is given here, based on the results obtained so far.



## General Procedure, Scope and Limitation of the Present Reaction

### 1. General procedure

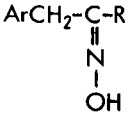
In general, two to three moles of LAH are used for one mole of the oxime. Use of less than two moles of LAH is inadequate, giving delayed completion of the reaction or poor yield of aziridines. When boiling THF is used as solvent, the reaction is usually complete within one to two hours. LAH and THF should be purified according to the method of Davis et al.[15] and the method given in Organic Syntheses,[16] respectively, to obtain maximum yields of aziridines. The consumption of oximes can be checked by TLC on $SiO_2$, using the solvent system chloroform : methanol (95 : 5) and spray reagents, 5% potassium dichromate in 40% sulfuric acid, platinic chloride-

iodine solution, or iodine vapor, or their combination. The spot of the aziridine formed usually appears at a position not far from that of the oxime. As a typical example, the procedure for the LAH reduction of dibenzyl ketoxime (V) to cis-2-benzyl-3-phenylaziridine (VI) is described.[6c,d] "To a slurry of LAH (3.80 g, 0.10 mole) in THF (350 ml), a solution of dibenzyl ketoxime (V) (11.27 g, 0.05 mole), mp 123-124° in dry THF (80 ml) was added dropwise with stirring at 20° over a 10-min period. The mixture was refluxed for 3 hours, showing a color change from the initial pale green to a permanent light chocolate color. The mixture was cooled with ice water and decomposed by gradual addition of $H_2O$ (12 ml) at a temperature below 20°. The precipitate was filtered off and washed three times with ether (400 ml). The ethereal washings were combined with the original filtrate, dried over $Na_2SO_4$ and evaporated in vacuo to give a pale yellow oil (11.0 g), which was dissolved in petroleum ether (100 ml) and chromatographed on $SiO_2$ (75 g, Merck). Fractions eluted with petroleum ether : benzene (1 : 1 — 0 : 1) were combined and evaporated to leave a crystalline residue (9.0 g), which was recrystallized from petroleum ether to give cis-2-benzyl-3-phenylaziridine (VI) (7.8 g, 74%), mp 44-45°, as needles."

## 2. Scope and limitation

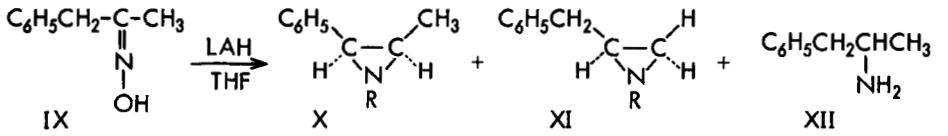
In order to examine the applicability of this reaction, LAH reduction of several classes of oximes was carried out. Based on the results so far obtained, the scope and limitation of this reaction will be described.

(a) Formation of aziridines from ketoximes of the type A:[5,6a,c,e]



A R = aryl or alkyl

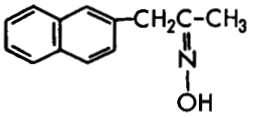
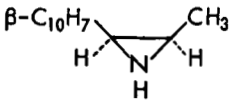
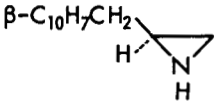
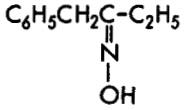
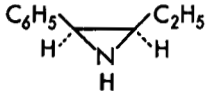
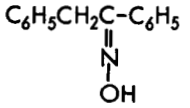
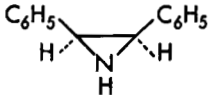
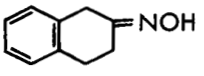
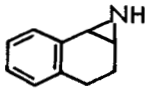
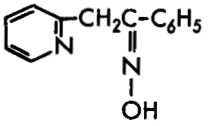
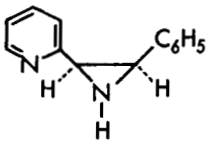
The ketoximes III and V are included in this type. From these oximes, the corresponding aziridines have been obtained in good yields as already stated. As another example, LAH reduction of 1-phenylpropan-2-one oxime (IX) should be mentioned.




IX X XI XII

anti : syn = 3 : 1 a: R = H b: R = -CONHC$_6$H$_5$ a: R = H b: R = -COC$_6$H$_4$NO$_2$-p

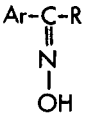
Table I
Aziridine Formation from Type A Oximes

| Oxime | Aziridine | | | |
|---|---|---|---|---|
| | Structure | mp, °C | Yield, % | C$_6$H$_5$NHCO- or p-O$_2$N·C$_6$H$_4$·CO- derivative, mp, °C |
|  |  | 83-84 | 25.0 | 147-148 |
| |  | (oil) | 7.0 | 94.5-95.5[a] |
|  |  | 45-46 | 24.4 | 95-96<br>62-63[a] |
|  |  | 83-84 | 25.0 | 163-164 |
|  |  | 52-53.5 | 40.0 | 157-158 |
|  |  | 66-67 | 22.3 | 123-125 |

[a] p-NO$_2$C$_6$H$_4$CO-derivative.

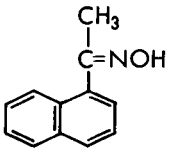
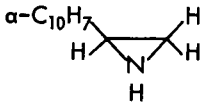
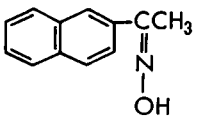
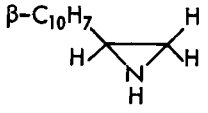
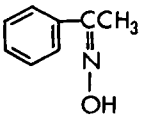
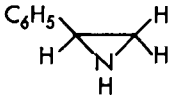
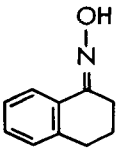
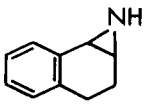
The ketoxime IX used here consists of a mixture of anti- and syn-isomers (ca 3 : 1). LAH reduction of IX in boiling THF yielded cis-2-phenyl-3-methylaziridine (Xa), 2-benzylaziridine (XIa) and 3-phenyl-2-aminopropane (XII) in 23.9, 8.8, and 56.0% yield, respectively. The aziridines, Xa and XIa, were also characterized by conversion to their derivatives Xb, mp 92-94°, and XIb, mp 92.5-94.5°. Other examples of LAH reduction of ketoximes belonging to this type are shown in Table I.

(b) Formation of aziridines from ketoximes of the type B:[6e]

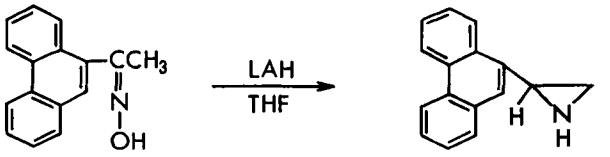


B R = alkyl

Table II
Aziridine Formation from Type B Oximes

| Oxime | Aziridine | | | |
|---|---|---|---|---|
| | Structure | mp, °C | Yield, % | $C_6H_5NHCO$- derivative, mp, °C |
|  |  | 66-67 | 63.7 | 133.5-135 |
|  |  | 102.5-103.5 | 16.2 | 145-146 |
|  |  | (oil) | 17.3 | 96.5-97.5 |
|  |  | 52-53.5 | 11.0 | 157-158 |

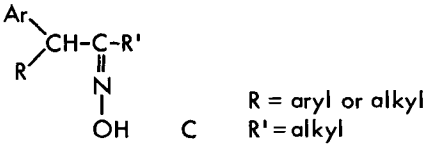
The ketoximes described are of the acetophenone oxime type. For example, 9-acetylphenanthrene oxime (XIII) was reduced with LAH to 2-(9-phenanthryl)aziridine (XIV), mp 90-91°, in 40% yield.




XIII XIV

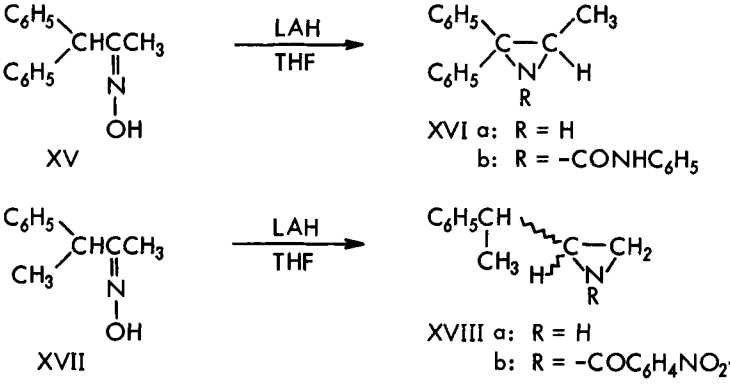
Several ketoximes of this type were reduced with LAH and the results obtained are shown in Table II.

(c) Formation of aziridines from ketoximes of the type C:[6e]



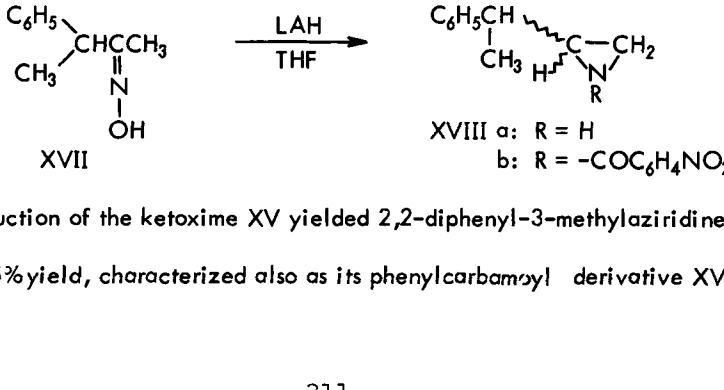

C R = aryl or alkyl
R' = alkyl

It has been reported that the Neber rearrangement of ketoxime O-tosylates of this type was unsuccessful.[10] However, our reaction proceeded successfully as shown in the following examples.




XV

XVI a: R = H
b: R = -CONHC$_6$H$_5$



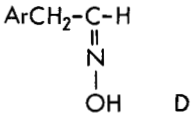

XVII

XVIII a: R = H
b: R = -COC$_6$H$_4$NO$_2$-p

LAH reduction of the ketoxime XV yielded 2,2-diphenyl-3-methylaziridine (XVIa) in 40.5% yield, characterized also as its phenylcarbamoyl derivative XVIb.

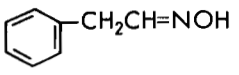
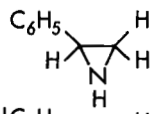
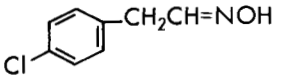
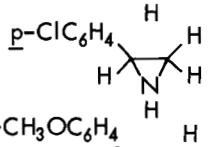
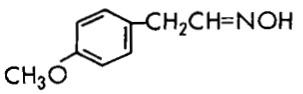
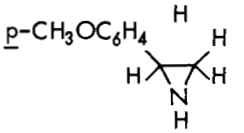
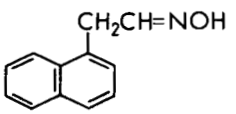
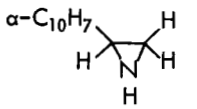
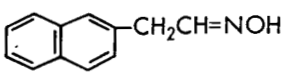
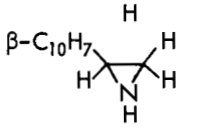
On the other hand, the ketoxime XVII, having a methyl group instead of one of the phenyl groups in XV, was reduced to the aziridine XVIIIa in 38.3% yield, cyclizing only towards the terminal methyl group. No aziridine cyclized to the benzylic position was found among the reduction products. The aziridine XVIIIa was found to consist of a mixture of erythro- and threo-isomers, which could be separated as the p-nitrobenzoyl derivatives XVIIIb, mp 65-66° (main) and 178-179° (minor).

(d) Formation of aziridines from aldoximes of the type D:[6e]



D

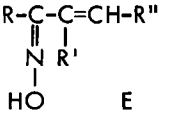
Table III
Aziridine Formation from Type D Aldoximes

| Aldoxime | Aziridine | | | |
|---|---|---|---|---|
| | Structure | mp, °C | Yield, % | $C_6H_5NHCO$- derivative mp, °C |
|  |  | (oil) | 34.0[a] | 96.5-97.5 |
|  |  | (oil) | 28.0[a] | — |
|  |  | (oil) | 23.0[a] | — |
|  |  | 66-67 | 20.4 | 133.5-135.0 |
|  |  | 101.5-102.5 | 12.0 | 145-146 |

[a] The yield of the isolated thiazolidine-2-thione derivative which was obtained by the reaction of the crude aziridine with carbon disulfide.[10]

Aldoximes were reported not to undergo the Neber reaction.[10] In contrast to this, as shown in Table III, LAH reduction in THF proceeds to give the expected aziridines.

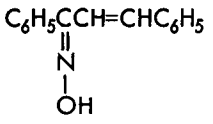
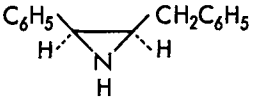
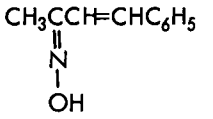
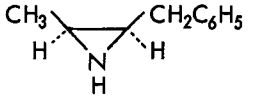
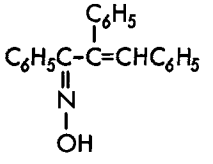
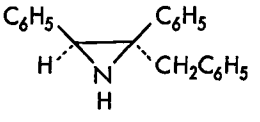
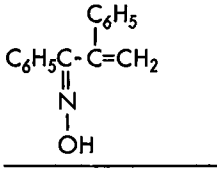
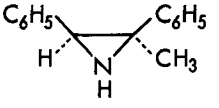
(e) Formation of aziridines from α,β-unsaturated ketoximes of the type E:[6c,17]



R = Aryl or alkyl
R' = H or aryl
R" = H, alkyl or aryl

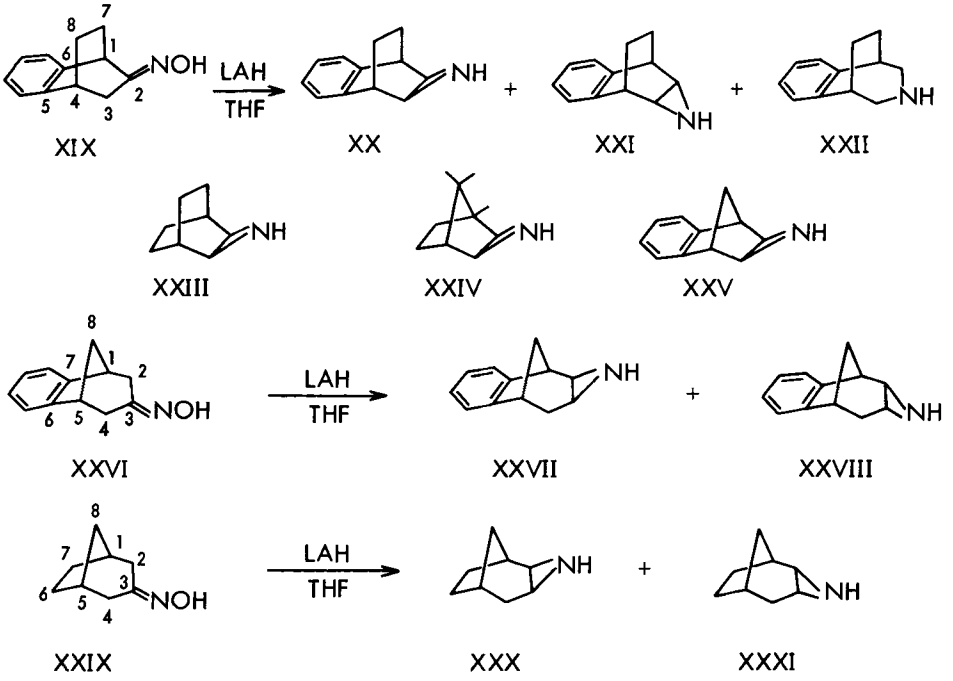
The α,β-unsaturated ketoximes listed in Table IV were reduced with LAH in THF to the corresponding aziridines in appreciable yields. Prior to our research, only one example of this category had been reported.[7] Table IV summarizes our results obtained so far.[17]

Table IV
Aziridine Formation from Type E Oximes

| α,β-Unsaturated oxime | Aziridine | | |
|---|---|---|---|
| | Structure | mp, °C | Yield, % |
|  |  | 46.5-47 | 31 |
|  |  | (oil) | 33 |
|  |  | 85.5-86 | 86 |
|  |  | 58.5-59 | 90 |

(f) Formation of aziridines from ketoximes of bridged ring systems[6b,18]

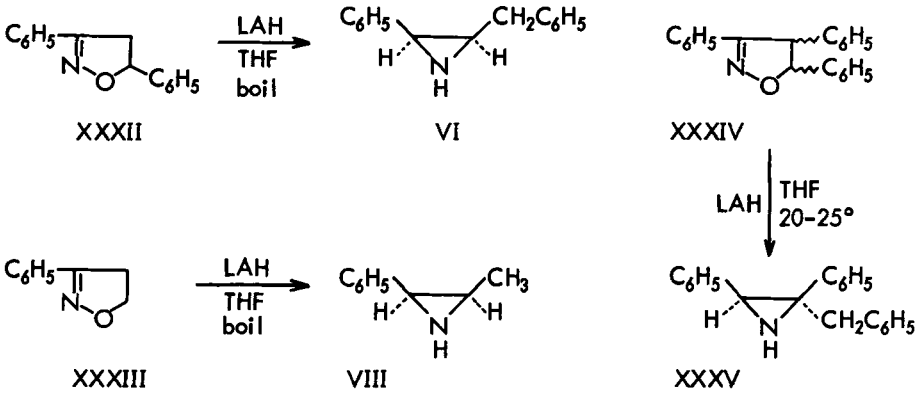
Ketoximes of bridged ring systems were also converted to aziridines by the present method, as in the example of dibenzobicyclo[2.2.2]octadienone oxime (I) mentioned before. 5,6-Benzobicyclo[2.2.2]octenone oxime (XIX) was reduced with LAH to exo-aziridine XX, endo-aziridine XXI, exo- and endo-primary amines, and the rearranged secondary amine XXII in 46, 4, 25 and 4% yield, respectively. However, LAH reduction of bicyclo[2.2.2]octanone oxime having no fused benzene ring afforded only a low yield of the aziridine XXIII.[6b,19] LAH reduction of 6,7-benzobicyclo[3.2.1]octen-3-one oxime (XXVI), for which no syn and anti isomers exist,[20] yielded almost exclusively aziridines: exo-aziridine XXVII (36.8%) and endo-aziridine XXVIII (54.7%).[18b] Similar reduction of bicyclo[3.2.1]octan-3-one oxime (XXIX), in spite of the absence of a fused benzene ring, was found to give



fair yields of the expected aziridines XXX (25.3%) and XXXI (44.6%), together with some epimeric primary amines.[21] In this case, too, as the effect of the configuration of the ketoxime on aziridine formation can be ignored, the unexpectedly good results may be attributable to other factors.

(g) Formation of aziridines from 2-isoxazolines[17]

We recently reported that the O-Me and O-Ac derivatives of dibenzyl ketoxime as well as dibenzyl ketoxime (V) itself were reduced with LAH to cis-2-benzyl-3-phenylaziridine (VI) in almost the same yields.[6c] Since 2-isoxazolines can be regarded as internal O-alkyl oximes, the possibility of aziridine formation from




XXXII VI XXXIV

XXXIII VIII XXXV

2-isoxazolines by LAH reduction was expected. This was found to be the case, and LAH reduction of 3,5-diphenyl- (XXXII) and 3-phenyl-2-isoxazoline (XXXIII) gave the desired aziridines, VI and VIII, in 31 and 36% yield, respectively. The yields of the accompanying aminoalcohols, which are usual reduction product from 2-isoxazolines,[22] were 26 and 50%. cis- and trans-3,4,5-Triphenyl-2-isoxazoline (XXXIV) gave the aziridines XXXV in excellent yields (94 and 97%, respectively as determined by GLC analyses). The mechanism of this new reaction is somewhat different from that of the aziridine formation from oximes.[17]

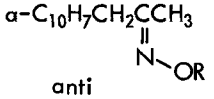
Summarizing this section, aryl ketoximes and oximes having an aromatic ring attached to the carbon α to the oxime group gave aziridines. Some bridged ring ketones gave aziridines even when they have no aromatic ring. Some phenyl-substituted 2-isoxazolines as well as O-acyl and O-alkyl derivatives of an oxime were converted to aziridines by this method.

Oximes of monocyclic 5-7 membered ring ketones failed to give aziridine.

## Effect of Oxime Configuration on Aziridine Formation

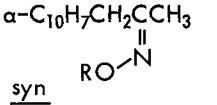
The Neber rearrangement has been reported to proceed independently of the configuration of ketoximes used.[14] However, the investigation of the effect of oxime configuration on the present reaction clearly indicated that it has characteristics different from the Neber and related rearrangements, the configuration of oximes used being an important factor for the direction of cyclization to aziridines.

### 1. On aralkyl alkyl ketoximes and their O-tosylates[23]



anti

XXXVI a: R = H
b: R = Tos

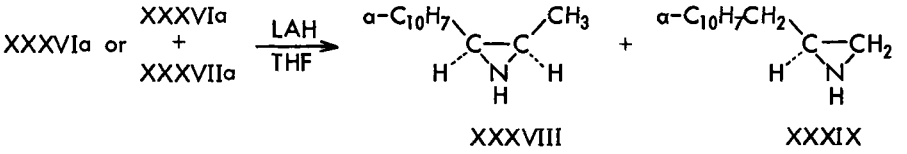


syn

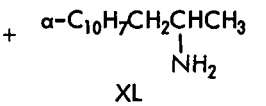
XXXVII a: R = H
b: R = Tos

Pure anti-1-(α-naphthyl)propan-2-one oxime (XXXVIa) could be separated from a mixture of the two isomers (ca 1.5 : 1), but the syn-oxime XXXVIIa was not obtained pure. Treatment of the anti-oxime XXXVIa with tosyl chloride and pyridine gave the anti-oxime O-tosylate XXXVIb, mp 90° (dec). Tosylation of a mixture of XXXVIa and XXXVIIa, followed by treatment of the mixture of the tosylates with neutral alumina gave unrearranged syn-oxime O-tosylate XXXVIIb, mp 101° (dec). The configurations of the two oxime isomers XXXVIa and XXXVIIa were determined from their NMR data. The chemical shifts of the methyl and methylene protons differed

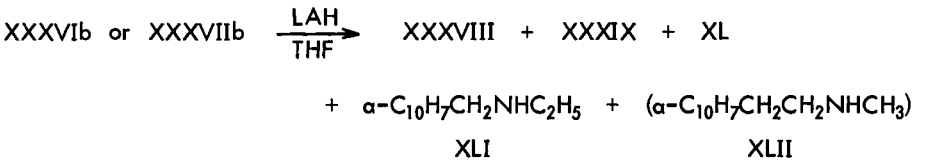
between the syn and anti isomers, closer proximity of the hydroxyl group causing a down field shift of their methylene or methyl protons respectively. The determination of the configuration of the oxime O-tosylates, XXXVIb and XXXVIIb, also based on NMR data, was further backed by the results obtained from Beckmann rearrangement of the separated isomers.




XXXVIII XXXIX




XL




XLI XLII

While LAH reduction of the ketoximes, XXXVIa or XXVIa + XXXVIIa, gave the two aziridines, XXXVIII and XXXIX, and the primary amine XL, the reduction of the ketoxime O-tosylates, XXXVIb or XXXVIIb, yielded the above three products together with the rearranged secondary amines, XLI and XLII.[24] GLC analyses of the reduction

Table V
GLC Analyses of LAH Reduction Products of the Oximes, XXXVIa and XXXVIa + XXXVIIa

| Isomer (ratio) of the oxime | Product; yield, % XXXVIII | XXXIX | XL |
|---|---|---|---|
| anti XXXVIa | 15.2 | 28.9 | 53.5 |
| anti : syn (XXXVIa : XXXVIIa) = 3.6~3.8 : 1 | 26.1 | 23.3 | 41.1 |
| anti : syn (XXXVIa : XXXVIIa) = 1.3~1.4 : 1 | 39.0 | 15.0 | 33.3 |

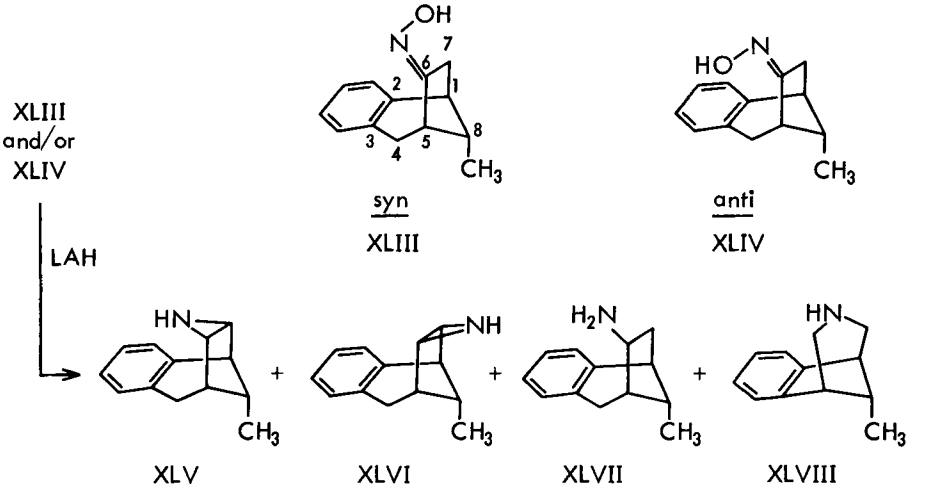
Table VI
GLC Analyses of LAH Reduction Products of the Oxime-tosylate XXXVIb and XXXVIIb

| Isomer of oxime tosylate | Product; yield, % XXXVIII | XXXIX | XL + XLII[24] | XLI |
|---|---|---|---|---|
| anti (XXXVIb) | 7.4 | 22.1 | 36.9 | 2.4 |
| syn (XXXVIIb) | 20.7 | 1.5 | 44.6 | 1.1 |

products are shown in Tables V and VI. The data show that the reaction is strongly influenced by the configuration of the ketoxime or the oxime O-tosylate used.

2. On ketoximes of bridged ring systems[18a,b]

The dependence of aziridine formation on the configuration of ketoximes used was also recognized in bicyclic ketoximes such as 8-endo-Me-2,3-benzobicyclo-[3.2.1]octen-6-one oxime. This oxime was successfully separated into the syn-isomer XLIII and the anti-isomer XLIV. LAH reduction of the pure isomers and of their mixtures was carried out and the products were analyzed by GLC.



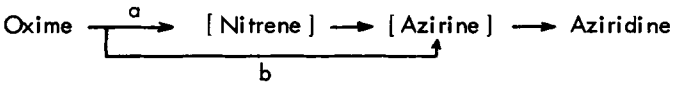

As shown in Table VII, the syn-oxime gave more aziridine than did the anti-oxime.[25]

Table VII
GLC Analyses of LAH Reduction Products of the Oximes XLIII and XLIV

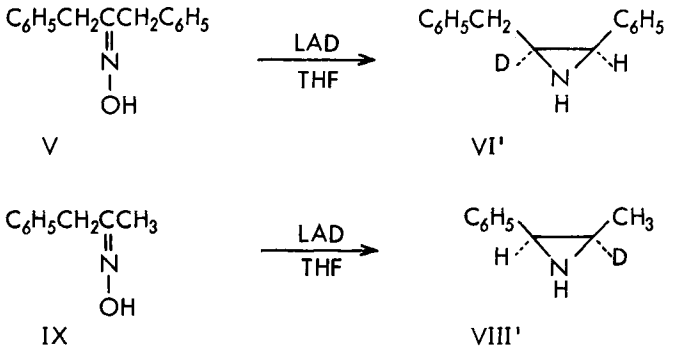
| Isomer (ratio) of the oxime | Product; yield, % XLV | XLVI | XLVII | XLVIII |
|---|---|---|---|---|
| syn (XLIII) | 42.2 | 12.0 | 19.3 | 13.3 |
| syn : anti = 1 : 1 | 23.5 | 9.1 | 22.7 | 17.2 |
| anti (XLIV) | 7.7 | 5.2 | 39.4 | 23.6 |

## Kinetics and Mechanism

Because of certain similarities with the Neber rearrangement and the Hoch-Campbell synthesis, we initially thought that our reaction might follow one of the paths (a) or (b):[5,6b]




However, studies on the effect of oxime configuration on the reaction seem to indicate that a nitrene intermediate is not involved. From the results obtained so far, the following five points are probably useful for the elucidation of the reaction mechanism: (1) aziridines obtained by LAH reduction have stereospecifically a cis-configuration; (2) aziridine formation is influenced strongly by the configuration of ketoximes used, the aziridine ring being preponderantly formed with the carbon which is closer to the hydroxyl of the oximes; (3) further to point (2), ring closure to a benzylic position is favored over that to an aliphatic one; (4) in the $LiAlD_4$ (LAD) reduction of ketoximes, deuterium was introduced to the carbon originally carrying the oximino group, as indicated in the formulae, VI' and VIII'; (5) the reaction does not go through a hydroxylamine stage.[26]



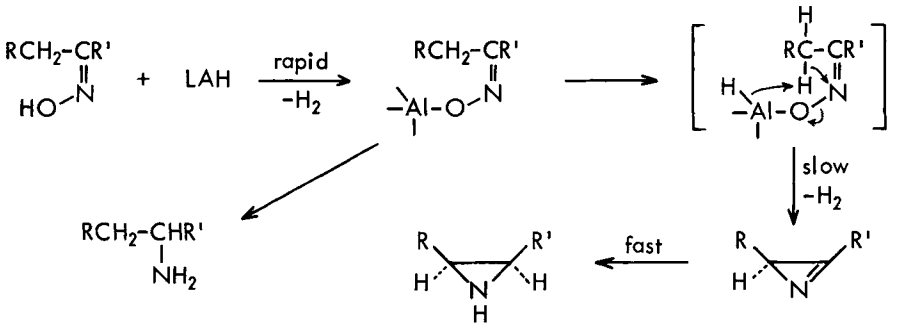

Considering the above results, mechanistic studies involving kinetics and stoichiometry were made using dibenzyl ketoxime (V) and acetophenone oxime.[27]

The stoichiometry of the reaction of the ketoxime V was followed using gasometry. One mole of hydrogen was evolved immediately followed by the slow evolution of another mole of hydrogen. One more equivalent of hydride was taken up by the substrate, a total of three equivalents of hydride being consumed. Next, GLC analyses of starting material and reduction products were carried out with the ketoxime V and acetophenone oxime. From the data obtained, the following conclusions can be drawn.

1. Aziridine formation is independent of the initial concentration of LAH.

2. Aziridine formation is autocatalyzed by the primary amine which is a side product of the reaction.

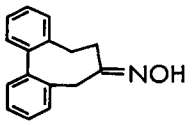
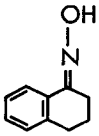
Accordingly, the following mechanism can be suggested for the present reaction.



## Effect of Added Amines and Solvent

Further study revealed that the addition of N-methyl-n-butylamine (in situ) markedly increases the reaction rate and the yield of aziridines. Table VIII shows the effect of amine addition on the yield. The order of catalytic efficacy of amines on aziridine formation was secondary amine > primary amine > tertiary amine.[27]

Table VIII
Effect of Added N-Methyl-n-butylamine on Aziridine Formation

| Ketoxime | Product; yield, %[a] | | | |
|---|---|---|---|---|
| | Without amine | | With N-(Me-n-Bu)amine | |
| | Aziridine | Primary amine | Aziridine | Primary amine |
| $C_6H_5CH_2CCH_3$ ‖ N, OH | 30[b] | 60 | 75[b] | 15 |
| $C_6H_5CCH_3$ ‖ N, OH | 30 | 60 | 73 | 20 |
|  | 12 | 60 | 50 | 20 |
|  | 20 | 75 | 60 | 30 |

[a] Yield found from GLC analyses.

[b] Total yield of the aziridines, X and XI.

Solvent effects on the reaction were considerable,[5,6a,b] as shown in Table IX for the product distribution from the ketoxime V.

Table IX
Solvent Effects on Aziridine Formation from the Oxime V

| Solvent | pKa | Product; yield, %[a] | |
|---|---|---|---|
| | | Aziridine VI | Primary amine[b] |
| THF | -2.02 | 86 | 13 |
| 2-Me-THF | -2.08 | 68 | 23 |
| Tetrahydropyran | -2.79 | 71 | 21 |
| Glyme | -3.27 | 86 | 9 |
| Ether | -3.59 | 25 | 70 |

[a] Yield found from GLC analyses.

[b] 2-Amino-1,3-diphenylpropane.



## Acknowledgment

The authors are indebted to Dr. K. Takeda, Prof. E. Ochiai and Dr. H. Tanida for their interest and valuable discussions. We also thank our co-workers cited in the references to our papers, for their devoted efforts in making this work possible.

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[4] Cf. K. Kitahonoki and Y. Takano, Tetrahedron Lett., 1597 (1963); Tetrahedron, 25, 2417 (1969).

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[27] K. Kotera, H. Tanida and T. Okada, presented at the 19th meeting on the symposium of organic reaction mechanism, Oct. 10, 1968, Yamagata. Details will be reported in the near future.

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