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TRANSFORMATION OF ISOXAZOLINES INTO AZIRIDINES BY LITHIUM ALUMINUM HYDRIDE REDUCTION

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Recently, our group reported a new method for the synthesis of aziridines by reduction of oximes with lithium aluminum hydride (LAH) (1a-h). It was also demonstrated in an example that the reduction of not only the oxime itself but also its O-acylate and O-Me ether yielded the same aziridine in almost equal yields. Namely, the LAH reduction of dibenzylketoxime (IVa) in tetrahydrofuran (THF) gave cis-2-phenyl-3-benzylaziridine (II) in 93% yield and the same treatment of the O-Me ether IVb afforded the identical aziridine in 90% yield (2). These findings led us to the expectation that the LAH reduction of 2-isoxazolines may provide the possibility of its transformation into aziridine derivatives, since 2-isoxazolines can be regarded as the compounds having an O-alkyl oxime function in the molecules, although being fixed in the ring system. Actually, the reduction of suitable 2-isoxazolines with LAH was found to give the aziridines, inspite of the facts that there have been a few papers concerning the LAH reduction of 2-isoxazolines, which reported the formation of only the corresponding 3-aminopropanols (3a-d).

Perold and von Reiche reported (3a) that the LAH reduction of 3,5-diphenyl-2-isoxazoline (I) in ether gave 1,3-diphenyl-3-aminopropanol (III) in 62% yield.*[1] However, when THF was used instead of ether as a solvent for the LAH reduction of I, the expected cis-2-phenyl-3-benzylaziridine (II) was obtained in 31% yield accompanied with the reported amino-alcohol III in 26% yield. The aziridine II was identical with the one obtained from IVa and IVb mentioned above as well as from chalcone oxime (V), m.p. 107.5-111° (2). Similarly, the LAH reduction of 3-phenyl-2-isoxazoline (VI) yielded cis-2-phenyl-3-methylaziridine (VII) in 36% yield, which was identical with the aziridine obtained from 1-phenylpropan-

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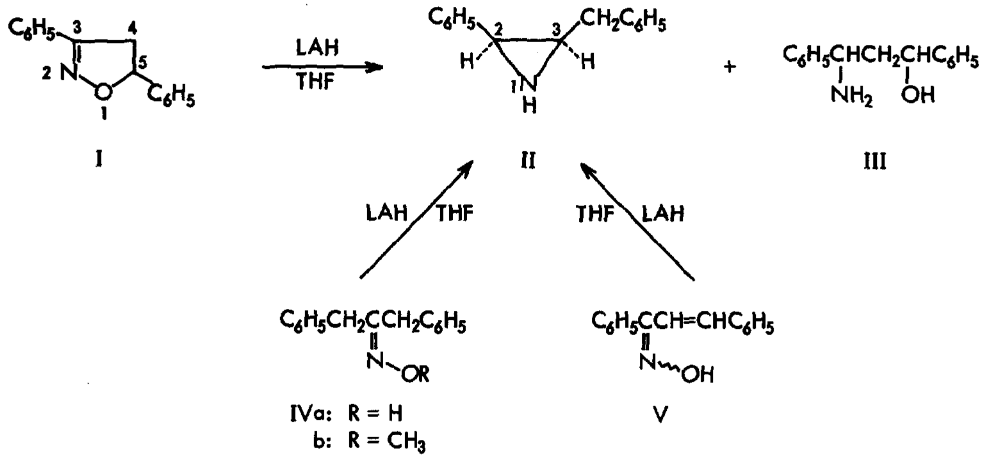
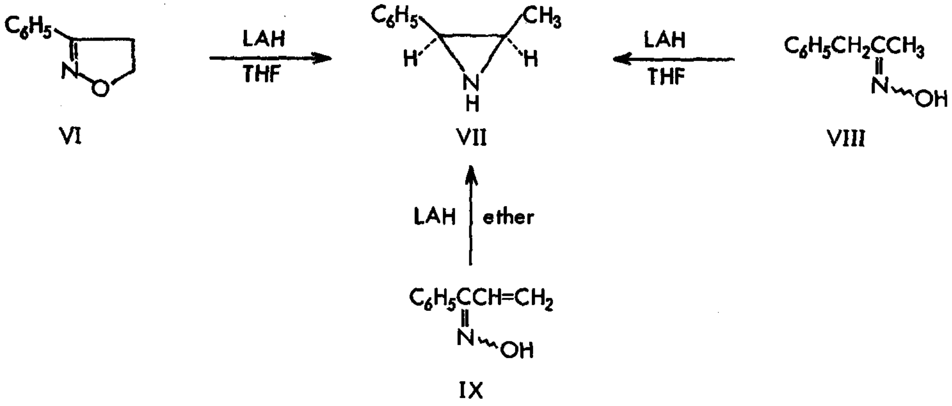
*[1] Reinvestigation of the LAH reduction of I in boiling ether showed that the aziridine II, which could be analyzed by GLC, was formed in 4.6% yield together with the crude amino-alcohol III, isolated in ca 90% yield.

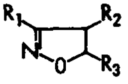
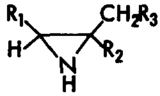
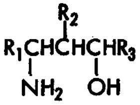




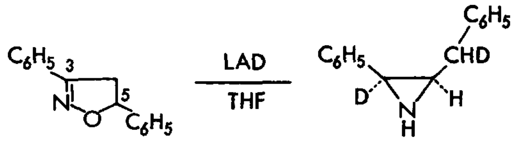
2-one oxime (VIII) (1a,e) and phenylvinylketoxime (IX) (1h). Several other 2-isoxazolines, X-XIII (Table I) synthesized also by 1,3-dipolar addition using suitable nitrile oxides and olefins except for XIII were reduced with LAH in THF in appropriate reaction conditions. All of the 2-isoxazolines tested gave aziridines, although in a wide range of yields, as summarized in Table I. The reduction products were separated into the aziridines and amino-alcohols by elution-chromatography. Some aziridines produced were also analyzed by GLC. As the data show, preponderant aziridine formation from 2-isoxazolines having phenyl groups both at the C_4- and C_5-positions was observed in the examples, X, XI and XIII. These results suggest the effects of the substituents for the aziridine formation from isoxazolines.

In order to inspect the reaction mechanism, the LAD reduction was carried out on 2-isoxazolines, I

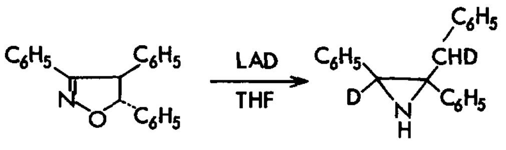
Table I. Aziridine Formation from 2-Isoxazolines with LAH in THF

				LAH reduction		
					Product % [a]	
	R_1	R_2	R_3	Reaction condition		 $\underset{NH_2}{R_1CH}\overset{R_2}{C}H\underset{OH}{CHR_3}$
I(4)	C_6H_5	H	C_6H_5	reflux	31 (40 [b]) (cis)	26
VI(5)	C_6H_5	H	H	reflux	36 (50 [b]) (cis)	50
X(6)	C_6H_5	C_6H_5 (trans)	C_6H_5	20-25°	83[c](97)	13
XI(6)	C_6H_5	C_6H_5 (cis)	C_6H_5	20-25°	(94)	
XII [d]	C_6H_5	CH_3 (trans)	C_6H_5	30-35°	4[c]	68
XIII [d]	CH_3	C_6H_5 (trans)	C_6H_5	35-40°	70[c]	15

[a] Isolated yields, but the percentages in the parentheses show the yields analyzed by GLC. [b] Reaction temp: 40°. [c] The configurations of these aziridines remain to be solved. [d] The compound XII (m.p. 81-82°) and XIII (b.p. 137°/0.1 mm) are newly synthesized.



I II'



X XIV

and X. The obtained aziridines, II' and XIV, were proved to be the dideuterated products at the C_3- and C_5-positions of the 2-isoxazolines by the NMR data. These results may provide a clue to solve the reaction mechanism of this reaction, which probably involves the azirine intermediate as in the case of the reduction of oximes (1a,b).

Aziridine formation from 2-isoxazolines, which are easily derived by 1,3-dipolar addition with nitrile oxides and olefins, gives a new method for the synthesis of aziridines. These findings also suggest the possibility of aziridine formation from other suitable heterocyclic compounds. We continue to explore these developements including the mechanistic study.

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