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STEREOCHEMISTRY OF AZIRIDINE FORMATION BY LITHIUM ALUMINUM HYDRIDE REDUCTION OF KETOXIMES OF BRIDGED RING SYSTEMS. ON BENZOBICYCLO[3.2.1]OCTENONE OXIMES

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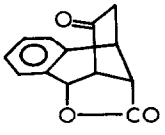
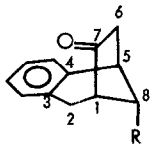
In our previous communication (1), it was reported that lithium aluminum hydride (LAH) reduction of some ketoximes in refluxing tetrahydrofuran (THF) provided a new method for the synthesis of aziridines.

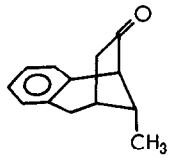
This paper is concerned with separation of syn- and anti-isomers of ketoximes and stereochemistry of aziridine formation by LAH reduction in instances of benzobicyclo[3.2.1]octenone oximes having bridged ring system.



I



IIa: R = H
b: R = CH_3



III

For this purpose, we synthesized benzobicyclo[3.2.1]octenones*[2] such as benzobicyclo[3.2.1]-octene 7-one (IIa), 8-endo-methyl-benzobicyclo[3.2.1]octene 7-one (IIb) and 8-endo-methyl-benzo-bicyclo[3.2.1]octene 6-one (III), starting from the keto-lactone I (2).

The oxime IV showed two spots (R_f-values, 0.64 and 0.70) on TLC using silica gel and ether : n-hexane (3:1), and was separated into the respective components, syn-isomer (R_f 0.64) IVa, m.p. 112-112.5° and anti-isomer (R_f 0.70) IVb, m.p. 115° by combination of column-chromatography and preparative TLC

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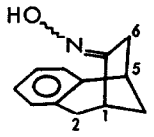
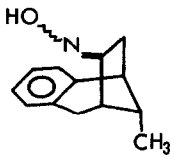
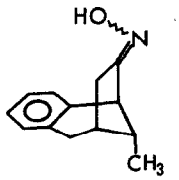
*[2] The syntheses of these ketones will be reported elsewhere in details.



IVa: syn-isomer
b: anti-isomer



Va: syn-isomer
b: anti-isomer

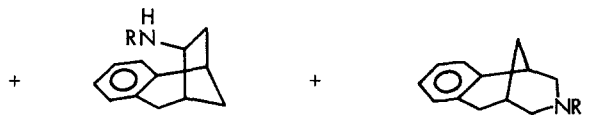


VIa: syn-isomer
(b: anti-isomer)

over silica gel.*3 The stereochemistry of the separated oximes was established from their NMR data. The proton signal of C_1-hydrogen in IVa appears near 7.00 τ as a multiplet obscured with those of C_5-hydrogen and C_2-hydrogens, but that of IVb appears at 6.43 τ as an isolated multiplet, which shifts to low field owing to deshielding effect by the proximity of the hydroxyl group. Regarding proton signals of the C_6-methylene group of IVa and IVb, reverse findings were observed (3). Similarly, the oxime V was successfully separated into the isomers, the syn- form Va, m.p. 115-116° and the anti- form Vb, m.p. 149-151°, the stereochemistry of which was established from the chemical shifts of the respective C_1-protons in the NMR spectra. As to the oxime VI, only the syn-oxime VIa, m.p. 135.5-136° could be isolated.*4

VIIa: R = H
b: R = p-$NO_2C_6H_4CO$

VIIIa: R = H
b: R = p-$NO_2C_6H_4CO$



IXa: R = H
b: R = CHO

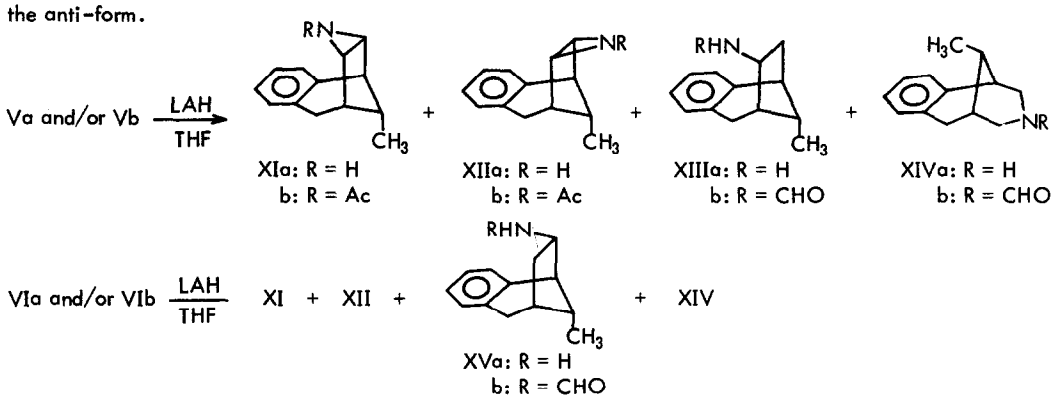
Xa: R = H
b: R = CHO

*3 Separation of isomers of ketoximes having bridged ring systems has been hitherto unreported. In this paper, the prefixes, syn and anti, were used in the sence that the oxime having the hydroxyl group directed to the methylene group at C_6 is syn and the oxime with reverse orientation is anti.

*4 Content ratio of the components in a mixture of the syn- and anti- forms, VIa and VIb, was determined from the proton signals of the C_5-hydrogens, which appear at 6.58 τ in VIa and at 5.83 τ in VIb as a multiplet respectively (60 Mc, C_6H_6).

In order to investigate the stereochemistry of aziridine formation from ketoximes of bridged ring systems, preliminary test was carried out with the oxime IV. The LAH reduction of a mixture of IVa and IVb gave the endo-aziridine VIIa (p-nitrobenzoyl derivative VIIb, m.p. 139-140°), the exo-aziridine VIIIa (p-nitrobenzoyl derivative VIIIb, m.p. 159-160°), the endo-primary amine IXa (N-formate IXb, m.p. 141.5-142.5°) and a secondary amine Xa (N-formate Xb, m.p. 107-107.5°).*5

The syn-oxime IVa was reduced with 4 molar equivalents of LAH in refluxing THF for 3 hr. Reduction products were separated by chromatography on alumina into the primary amines (IXa, main) and the aziridines (VIIa, main) in 22 and 33% yields, respectively. The similar treatment of the anti-oxime IVb gave the primary amines (IXa, main) (59%) and a small amount of the aziridines (VIIa, main). In these reductions, when the technique of GLC was used for the analyses of the products, relative ratios of the primary amines and the aziridines were 56 : 44 from the syn-form IVa and 99 : 1 from the anti-form IVb. These results showed clearly predominant aziridine formation from the syn-form in comparison with from the anti-form.



The LAH reduction of a mixture of the oxime isomers, V or VI, gave, besides the endo-primary amine XIIIa (N-formate XIIIb, m.p. 156-157°) from V or the endo-primary amine XVa (N-formate XVb, m.p. 74-76°) from VI, the endo-aziridine XIa, m.p. 92-92.5°, the exo-aziridine XIIa, m.p. 89-89.5° and a secondary amine XIVa (N-formate XIVb, m.p. 105-106°) as common products. The structures and stereochemistry of the aziridines, XIa and XIIa, were determined on the basis of their IR spectra and the NMR

*5 Elucidation of the structures and stereochemistry of these products will be omitted, because it was made based on analytical and spectral data in the similar manner to the cases of the oximes, V and VI, described later.

TABLE I
Hydrogen Bonding of the Aziridines, XIa and XIIa, and Proton Signals of Methyl Groups in their N-Acetates, XIb and XIIb

Product IR	XIa	XIIa
Hydrogen bonding[a]	3298 cm^{-1} +	3316 cm^{-1} -
Product NMR (τ)	XIb	XIIb
$NCOCH_3$	8.32[b]	7.88

[a] Hydrogen bonding was measured under grating using 20 mm cell in CCl_4 solution.

[b] Owing to the shielding effect of the benzene ring.

data of their N-acetates, XIb and XIIb. As shown in TABLE I, the measurement of hydrogen bonding on the free aziridines and chemical shifts of the methyl groups of their N-acetates permit the assignment of the endo-aziridines XIa and the exo-aziridine XIIa. Catalytic reduction of XIa with Pd-carbon in ethanol gave the endo-amine XIIIa, m.p. 51-53° and the endo-amine XVa. Beckmann rearrangement of the anti-oxime Vb followed by the LAH reduction of the lactam produced, m.p. 133-135° gave the same secondary amine as XIVa.*6

Detailed study for the stereochemistry of aziridine formation by LAH reduction was performed with the oxime isomers, Va and/or Vb, and VIa and/or VIb. The corresponding products were quantitatively analyzed by the technique of GLC. As portrayed in TABLE II, the aziridine isomers, XIa and XIIa, were predominantly

TABLE II
GLC Analyses of LAH Reduction Products of 8-endo-Methyl-benzobicyclo-[3.2.1]octenone Oximes, V and VI[a]

Isomer ratio of the oxime	Product, %			
	Aziridine		Primary amine	Secondary amine
	XIa	XIIa	XIIIa or XVa	XIVa
Va (syn)	42.2	12.0	19.3 (XIIIa)	13.3
	54.2			32.6
Va : Vb = 1:1	23.5	9.9	22.7 (XIIIa)	17.2
	33.4			39.9
Vb (anti)	7.7	5.2	39.4 (XIIIa)	23.6
	12.9			63.0
VIa (syn)	19.3	39.2	11.9 (XVa)	8.5
	58.5			20.4
VIa : VIb = 1.1 : 1	10.5	20.9	44.1 (XVa)	18.1
	31.4			62.2

[a] In each case, 50 mg of the oxime was reduced under heating at 90° with 37 mg (4 molar equiv) of LAH in 5 ml of THF in a sealed tube for 4 hr and the products were analyzed by GLC using diphenylether as an internal reference.

*6 Beckmann rearrangement with the syn-oximes, Va and VIa, gave different lactams, m.p. 248-249° (dec) and m.p. 200-201°, from the lactam, m.p. 133-135° mentioned here.

obtained from the syn-oximes in comparison with from the anti-oximes. This agrees well with the results obtained from aralkyl alkyl ketoximes (4). The most interesting finding is that total yields of the aziridine isomers produced from both of the syn-oximes, Va and VIa, are almost the same (ca. 55%), but product ratio between the endo- and exo-isomers varies reversely.*7

These facts can not be interpreted only by the probable homobenzylic character of the methylene group adjacent to the carbonyl function (1). For reasonable interpretation, further investigations involving the detailed mechanistic study may be necessary.

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2. K. Kitahonoki, and Y. Takano, Tetrahedron Letters 1597 (1963).
3. Refer to: A. C. Huitric, D. B. Roll and J. R. DeBoer, J. Org. Chem. 32, 1661 (1967) and references cited therein.
4. K. Kotera, T. Okada and J. Miyazaki, Tetrahedron Letters 841 (1967).

*7 In this connection, the LAH reduction of benzobicyclo[2.2.2]octenone oxime (1), of which the stereochemistry is probably syn, afforded the endo- and exo-aziridines in 5 and 45% yields, respectively, indicating the result similar to that from VIa. On the other band, the result obtained from IVa was in good agreement with that from Va in view of predominant formation of the endo-aziridines.