STEREOCHEMISTRY OF AZIRIDINE FORMATION BY REDUCTION OF OXIMES WITH LITHIUM ALUMINUM HYDRIDE ON ARALKYL ALKYL KETOXIMES AND THEIR TOSYLATEDS*

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Abstract—Separation of syn- and anti-isomers of aralkyl alkyl ketoximes and their tosylates has been carried out using 1-triethylpropen-2-one and 1-naphthaldehydepropen-2-one. With the individual configurations, LAH reduction of the oximes and their tosylates has been performed and the products have been analysed by GLC. The results clearly indicate that aziridine formation is strongly influenced by the configurations of the oximes and the oxime tosylates used.

Recently, our group reported a new method for the synthesis of aziridines by LAH reduction of ketoximes. The details and further extention are successively being presented. At the earlier stage, it seemed that the general mode of this reaction may be reminiscent of the Neber and the related rearrangements. The investigation of the stereochemistry of aziridine formation, however, indicates clearly that our reaction is of different type from the above reactions. This is the subject of the paper.

(a) Separation of syn- and anti-isomers of ketoximes and oxime tosylates

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_3 & \quad \text{C}_6\text{H}_5\text{CH}_2\text{COCH}_3 \\
\text{N} & \quad \text{N} \\
\text{OR} & \quad \text{OTs} \\
\text{a: } R & = \text{H} \\
\text{b: } R & = \text{Si}_3\text{C}_6\text{H}_4\text{CH}_3 \\
\text{anti-isomer} & \\
\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_3 & \quad \text{C}_6\text{H}_5\text{CH}_2\text{COCH}_3 \\
\text{N} & \quad \text{N} \\
\text{OR} & \quad \text{OTs} \\
\text{a: } R & = \text{H} \\
\text{b: } R & = \text{SO}_2\text{C}_6\text{H}_4\text{CH}_3 \\
\text{syn-isomer} & \\
\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_3 & \quad \text{C}_6\text{H}_5\text{CH}_2\text{COCH}_3 \\
\text{N} & \quad \text{N} \\
\text{OR} & \quad \text{OTs} \\
\text{a: } R & = \text{H} \\
\text{b: } R & = \text{SO}_2\text{C}_6\text{H}_4\text{CH}_3 \\
\text{IVa: } R & = \text{H} \\
\text{b: } R & = \text{SO}_2\text{C}_6\text{H}_4\text{CH}_3
\end{align*}
\]

* The part of this paper was presented at our preliminary symposium.

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In order to study the stereochemistry of aziridine formation, separation of the isomers of the oximes and the tosylates was first undertaken with some aralkyl alky ketones, such as 1-phenylpropan-2-one and 1-phenylpropan-2-one. Reaction of 1-phenylpropan-2-one with hydroxylamine gave a liquid mixture of anti- and syn-oximes in ratio of ca. 3:1, which was analysed by the NMR data. Pure anti-oxime Ia, m.p. 62-63°, was separated from a mixture of two isomers, but syn-oxime Ila was not obtained pure.* Treatment of Ia with tosyl chloride and pyridine afforded the anti-oxime tosylate Ib, m.p. 76-79° (dec), which was rearranged into N-benzyl acetamide by acetylation of basic alumina for 1 hr. The syn-oxime tosylate 1Ib, m.p. 89-89° (dec) was isolated from a mixture of anti- and syn-oxime tosylates after the contact with basic alumina for 3 hr, since the anti-oxime tosylate Ib was more readily rearranged by action of basic alumina than the syn-oxime. The Beckmann rearrangement of IIb with basic alumina for 40 hr gave as sole product, N-methyl phenylacetamide, indicating the syn-configuration. Similarly, anti-1-2-naphthylethylpropan-2-one oxime (IIla, m.p. 96-97°) could be separated from a mixture of two isomers. IIla and IVa (ca. 1:5:1). The configuration of the oximes was based on the NMR data, which involve low shift owing to deshielding effect by the proximity of the OH group, as shown in Fig. 1. However, the syn-oxime IVa was not isolated in a pure state. Treatment of IIla with tosyl chloride and pyridine afforded the anti-oxime tosylate, IIlb, m.p. 90° (dec), which was characterized by the rearrangement to N-naphthylmethylacetamide, m.p. 125-126° with basic alumina. Tosylation of a mixture of IIla and IVa followed by contact with neutral alumina gave the syn-oxime tosylate, IVb, m.p. 101° (dec), accompanied with N-naphthylmethyl acetamide (from IIlb) and a small amount of N-methyl-naphthylacetamide, m.p. 139-141° (from IVb). In this case, the use of basic alumina was unsuitable, because of concomitant rearrangements of two oxime tosylates. While characterization of the oxime tosylates thus separated was achieved by the Beckmann rearrangement with basic alumina, their NMR data also support the conclusion, indicating a greater deshielding effect by the proximity of the OH function than by the proximity of the unshared pair of electrons on the nitrogen, as summarized in Table 1. 

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical shift (ppm)</th>
<th>Chemical shift (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-CH_3</td>
<td>-CH_3</td>
</tr>
<tr>
<td>Ia</td>
<td>6.66</td>
<td>6.32</td>
</tr>
<tr>
<td>Ila</td>
<td>6.33</td>
<td>6.39</td>
</tr>
<tr>
<td>Ila</td>
<td>6.20</td>
<td>6.31</td>
</tr>
<tr>
<td>IVa</td>
<td>5.87</td>
<td>6.50</td>
</tr>
<tr>
<td>lb</td>
<td>6.97</td>
<td>6.62</td>
</tr>
<tr>
<td>lb</td>
<td>6.87</td>
<td>6.60</td>
</tr>
<tr>
<td>IIlb</td>
<td>6.55</td>
<td>6.69</td>
</tr>
<tr>
<td>IVb</td>
<td>6.20</td>
<td>6.62</td>
</tr>
</tbody>
</table>

* Recently, the same finding was independently reported by two groups.  

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**Table 1. NMR Spectral Data on 1-Substituted Propan-2-One Oximes (Ia, Ila, IIla and IVa) and their Tosylates (IIb, IIIb, IVb and IVb) (60 MHz, CDCl\_3)**
Fig. 1 NMR spectra of 1-naphthylpropan-2-one oximes (IIIa and IVa) (60 Mc, benzene).
(b) Aziridine formation by LAH reduction of 1-phenylpropan-2-one oxime and 1-azirino-2-naphthalpropan-2-one oxime

LAH reduction of a mixture of two isomers of 1-phenylpropan-2-one oxime (Is): This was done in boiling tetrahydrofuran (THF) affording three basic products, which showed three spots (Rf values: 0.85, 0.65 and 0.23) on TLC using SiO2, and the solvents being CH3OH/MeOH (20:1). Elution chromatography over SiO2 separated the products into three components in ratio of ca. 2:3:5, of which the product (Rf: 0.85) was proved to be cis-2-phenyl-3-methylaziridine (Va), m.p. 41-45°, based on the analytical and spectral data. The product Va corresponded to the molecular formula, C12H14N, with the IR band at 3300 cm⁻¹ (NH). In the NMR spectrum, the proton signals of Va appear at δ 4.02 (s, broad, NH), 1.02 (d, J1,2 = 5.5 c/s, -CH2), 7.65 (d, J1,2 = 5.5 c/s, C6-H) and 6.82 (d, J1,2 = 6.5 c/s, C3-H), respectively. The NMR spectrum of its phenacylbenzoyl derivative Vb, m.p. 92-94°, shows the proton signal patterns similar to those of Va, such as 8.95 (d, J1,2 = 5.5 c/s, -CH2), 7.06 (d, J1,2 = 5.5 c/s, C6-H) and 6.65 (d, J1,2 = 5.5 c/s, C5-H), but the proton signals due to the secondary amino group, which appears at high field in the spectrum of Vb, is not recognized at all in Vb. These facts strongly suggest the presence of an aziridine ring in Va and further,
the above coupling constants ($J_{H1-H2} = 6.5$ Hz) also permit the assignment of cir-
configuration of the aziridine. The assigned structure Va is also supported by the
following chemical evidence. Refluxing of Va with 5% sulphuric acid gave an amo-
 alcohol VIIIa, which was converted to IX through the intermediates, VIIIb and VIIIc.
In a similar manner, the ketone IX was also derived from the known di-norbornadi-
ene (Xa). This shows that VIIia must be di-norbornepropeadine, resulting from trans-
clavage of the aziridine ring with the acid. Furthermore, treatment of Va with
hydrobromic acid afforded a chiral-amine XI, which was reduced to the primary
amine VIIia with Pd-carbon catalyst. The amine VIIia was identical with the product
($R_2$, 0.23) from the LAH reduction of 1-phenylpropane-2-one oxime. The amine VIIia
was also characterized as its acetate (VIIb) and phenylcarbamoyl derivative (VIIc).
Furthermore, the structure and stereochemistry of Va was unequivocally established
by the comparison of its N-methyl derivative Vc with an authentic specimen as the
picrate. The third product ($R_2$, 0.65), characterized as its p-nitrobenzoyl derivative,
Vlb, m.p. 92.5-94.5°C, was found to be another aziridine Via, reversely cyclized towards
the terminal Me group. Refluxing of Vla with 5% sulphuric acid afforded an amor-
phous VIIIa as major product, characterized as its O,N-diazoate Xb, m.p. 114-115°C,
which was identical with the O,N-diazoate derived from the known diazidalanine
methylster. This permits the assignment of the structure Vla. Ultimately, the structure
was determined by the synthesis of the aziridine Vla and its phenylcarbamoyl
derivative Vlb by the known method. In order to inspect the reaction mechanism,
LAD reduction of a mixture of the oxime isomers was carried out in boiling THF.
Among, reduction products, cis-2-phenyl-3-methyl-3-deuteroaziridine ( prefers,
m.p. 40-42°C, was isolated. The location of deuterium introduced was determined by
the comparison of the NMR spectrum of Vla with that of Va. The spectrum of Vla
shows the proton signals at 7 08 (s, $-CH_3$), 8.97 (s, broad, $-NH$) and 6.78 (s,
broad, $C_2H_3$) respectively, and the proton signal near 7 65 attributable to the
C2 hydride in Va disappears.

\[ \text{LAD in THF} \]

\[ \text{H} \]

\[ \text{XIVa, R = H} \]

\[ \text{b: R = COCH_2NO_2} \]

\[ \text{NR} \]

\[ \text{XVb, R = H} \]

\[ \text{b: R = COCH_2NO_2} \]

\[ \text{HNR} \]

\[ \text{XIVA, 5-H_2O} \]

\[ \text{c: C\textsubscript{6}H_5CH_2CH \_3} \]

\[ \text{OR} \]

\[ \text{XVla, R = H} \]

\[ \text{b: R = Ac} \]

* We wish to thank Dr. H. Nicolais for providing valuable sample of Vc-picrate.
† Waugh et al. reported the synthesis of Va by LAH reduction of phenyl vinyl ketone.
In a manner similar to the case of 1-phenylpropyl-2-one oxime, LAH reduction of a mixture of 1-α-naphthylpropyl-2-one oxime (Ila: 1Va, ca. 1:5:1) was carried out in boiling THF. The products were separated into the following three basic compounds: cis-2-α-naphthyl-3-methylaziridine (XIIIa), m.p. 77–79°, characterized as its phenylcarbamoyl derivative, XIIIb, m.p. 139–140° and 2-α-naphthylmethylaziridine (XIVa), characterized as its p-nitrobenzoyl derivative, XIVb, m.p. 121°–122° and 1-α-naphthyl-2-aminopropene (XVa), characterized as its hydrochloride, m.p. 214–215° and phenylcarbamoyl derivative, XVa, m.p. 181–182°. The analytical and spectral data support the assignments of the structures, XIIIa, XIVa and XVa.*

(c) Stereochemistry of aziridine formation by LAH reduction

(i) With 1-phenylpropyl-2-one oximes (Ia and Iib) and their tosylates (Ib and Iib) as described above, and 1Va = Vla + Vla + Vla

<table>
<thead>
<tr>
<th>Isomer ratio of the oxime</th>
<th>Product</th>
<th>Vla</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-iso-I (Ia)</td>
<td>1Va</td>
<td>18%</td>
</tr>
<tr>
<td>α-syn-I (Ia: Iib) = 5:7:1</td>
<td>13</td>
<td>56%</td>
</tr>
<tr>
<td>α-syn-I (Ia: Iib) = 2:3:1</td>
<td>23</td>
<td>88%</td>
</tr>
</tbody>
</table>

* In each case, 300 mg of the oxime was reduced with 166 mg (2.2 molar equiv.) of LAH in 10 ml of THF for 2 hr.

Details were described in the experimental section.
For further confirmation, LAH reduction was carried out with purely isolated anti- and syn-oxime tosylates (Ib and IIb) under similar conditions and the products were analyzed by GLC. In these cases, the reduction products were more complicated, because N-phenylbenzylamine (XVII), presumably arising from the anti-isomer (Ib), was actually recognized in the reaction mixture. Although the presence of another secondary amine, N-methyl-phenethylamine (XVIII) was expected from the syn-isomer (IIb), it could not be confirmed, because the peak of XVIII overlapping with that of VIIa. The data from Ib and IIb, shown in Table 3, indicates that the aziridine formation depends on the configuration of the oxime-tosylate, with the same tendency as the oxime itself.
In both cases, even though pure anti-isomer (Ia or Ib) was used, a considerable amount of Va was still formed. This fact may be rationalized by a probable equilibrium between the anti- and the syn-isomers during the reduction.*

<table>
<thead>
<tr>
<th>Isomer of oxide tosylate</th>
<th>Va</th>
<th>Product</th>
<th>VIIa (XVIII)</th>
<th>XVII</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti (Ib)</td>
<td>21%</td>
<td>1.5</td>
<td>55.7</td>
<td>6.4</td>
</tr>
<tr>
<td>syn (Ib)</td>
<td>69%</td>
<td>11.0</td>
<td>4.4</td>
<td>4.4</td>
</tr>
</tbody>
</table>

* Reduction procedure: oxide tosylate, 50 mg; LAH 19 mg (10 mole equiv.); THF 1.5 ml; refluxed for 4 hr.

(ii) With 1-<i>o</i>-napthylphenyl-2-one oximes (IIIa and IVa) and their tosylates (IIIB and IVB) LAH reduction of 1-<i>o</i>-napthylphenyl-2-one oximes (IIIa and/or IVa) IIIB and/or IVB are carried out as for the oxime isomers (Ia and Ib) and their tosylates (Ib and Ib) and the products were analyzed by GLC as previously. The results are recorded in Table 4 and the data regarding similar treatment of the oxime tosylates (Ib or IVb) are given in Table 5.

### Table 4: GLC analyses of LAH reduction products of 1-<i>o</i>-napthylphenyl-2-one oximes (IIBa and/or IVBa)

<table>
<thead>
<tr>
<th>Isomer ratio of the oxime</th>
<th>Product</th>
<th>XIlla</th>
<th>XIVa</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti only (IIBa and/or IVBa)</td>
<td>3/9.5:1</td>
<td>26</td>
<td>23.5</td>
</tr>
<tr>
<td>anti: syn (IIBa and/or IVBa)</td>
<td>1.3:1.4:1</td>
<td>390</td>
<td>150</td>
</tr>
<tr>
<td>anti only (IIBa and/or IVBa)</td>
<td>1.3:1.4:1</td>
<td>390</td>
<td>150</td>
</tr>
<tr>
<td>anti: syn (IIBa and/or IVBa)</td>
<td>3/9.5:1</td>
<td>26</td>
<td>23.5</td>
</tr>
</tbody>
</table>

* Reduction procedure: oxide, 150 mg; LAH, 75 mg (2.66 mole equiv.); THF, 6 ml; refluxed for 3 hr.

### Table 5: GLC analyses of LAH reduction products of 1-<i>o</i>-napthylphenyl-2-one oximes tosylates (Ib or IVb)

<table>
<thead>
<tr>
<th>Isomer ratio of oxide tosylate</th>
<th>Product</th>
<th>XIlla</th>
<th>XIVa (XIX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti (Ib)</td>
<td>207</td>
<td>22.1</td>
<td>446</td>
</tr>
<tr>
<td>syn (Ib)</td>
<td>7/6%</td>
<td>15</td>
<td>4.1</td>
</tr>
</tbody>
</table>

* Reduction procedure: oxide tosylate, 70 mg; LAH, 19 mg (2.5 mole equiv.); THF 2 ml; refluxed for 3 hr.

It was actually found that when pure one-oxime 1a was refluxed in THF for 2 hr without LAH, about one-tenth of the oxime isomerized to syn-isomer Ib. |
In both cases, satisfactory results were obtained regarding the TLC analysis of the respective products. For example, the products, XIIIa, XIVa, XVI (XVIII) and XIX show the corresponding peaks having the respective retention times 30, 56, 18 and 14 min under the conditions used. As an example, the gas chromatogram of the products from the anti-oxidant toluylate IIIb is shown in Fig. 3.

(d) Mechanism and conclusion

As this new method for aziridine formation may be classified as similar to the Grignard reaction of ketoximes (the Hoch–Campbell Syntheses) or the Neber and the related rearrangements, the following two mechanisms, tentatively proposed, are based on the reaction mechanism of the Hoch–Campbell syntheses or the Neber reaction. The first involves the formation of the aziridine intermediate through the unsaturated nitrene and the stereoselective reduction of the azirine to the ciss-aziridine. The second consists of the concerted $\gamma$-elimination with the retention of the configuration about the nitrogen, like the Beckmann rearrangement, and the direct formation of the aziridine without the nitrene intermediate. However, the results obtained here can not be reasonably interpreted by either of the two mechanisms.

* In the competitive reaction, the same conclusion was obtained regarding the stereochemistry of aziridine formation by LAH reduction of ketoximes of bridged ring systems.
A balanced mechanism must be proposed. Although the detailed mechanistic study is being continued and the aspect of this reaction becomes clearer gradually, these features remain uncertain. However, cyclic intermediates such as in cyclopentene formation reactions 13 or the mechanism of concerted γ-elimination leading to the retention of the configuration about the nitrogen atom may be speculated.
chloride, m.p. 144–215°C as plates. (Found: C, 70.40; H, 7.16; N, 6.41; Cl– H2C=CH-CH2-NCl requires C, 64.5; H, 7.27; N, 10.99%). Furthermore, crust XVII (50 mg) was treated with phenylisocyanate (36 mg) in ether (9 ml) at room temp for 1.5 hr. The resulting crude XVIII was recrystallized from methanol to give pure XVIII (66 mg, m.p. 161–162°C as needles. c=0.330 in (N0H), 1629 cm–1 (CO=O) (Found: C, 71.85; H, 6.70; N, 5.9, Cl-C-NH2 requires C, 74; 72; H, 6.95; N, 5.9, 220%).

Action of XVIII with epichlorohydrin: The mixture of XVIII (50 mg) was refluxed with 15% HOCl (16 ml) for 2 hr. Working up in a manner similar to the case of Via left (a crystalline residue (183 mg) which was recrystallized from ethanol to yield an amorphous solid XVII (130 mg, m.p. 123–124°C as needles. (Found: C, 71.76; H, 7.27; N, 4.9, C2O2H-NH2 requires C, 71.71; H, 7.11; N, 4.8, 220%). The product XVIII (96 mg) was recrystallized with AcOH (0.1 ml) and pyridine (3 ml) The resulting crude O-acetate (50 mg) was recrystallized from x-hexane-AcOH to give pure XVIII (31 mg, m.p. 127–128°C as needles. c=0.328 in (N0H), 1720 cm–1 (C=O) (Found: C, 71.87; H, 6.71; N, 4.8, C2O2H-NH2 requires C, 71.86; R, 6.71; N, 4.91%).

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