A NOVEL REARRANGEMENT OF N-CYANOMETHYLHYDROXY-
TETRAHYDROISOQUINOLINIUM METHIODIDES UNDER BASIC
CONDITIONS

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Abstract --- Reaction of N-cyanomethylisoquinolinium methiodide (2a) with
sodium methoxide gave a rearranged tetrahydroisoquinolin-8-ol (5a) in high yield.
With 1- or 4-substituted N-cyanomethylisoquinolinium (2b-d) and 8-hydroxy-
tetrahydroisoquinolinium methiodides (2f), similar rearrangement was observed.
Plausible mechanism on formation of the products was discussed.

In the course of our study on synthesis of dibenzopyranazepine alkaloid, clavizepine (1), reaction of N-cyanomethyl-6- or 8-hydroxytetrahydroisoquinolinium methiodides (2) under basic conditions revealed a novel rearrangement instead of a ring expansion to a 3-benzazepine (3). Here we wish to report an alkoxide-promoted
C-N bond fission and recyclization of N-cyanomethyl-6-hydroxytetrahydroisoquinolinium methiodides to
tetrahydroisoquinolin-8-ols substituted in a different pattern from the starting isoquinolines.
The tetrahydroisoquinolinium iodide (2a) (0.2 mmol), readily available from isocorypalline (4a) and iodoacetoni-
trile, was heated with sodium methoxide (NaOMe) (2 mmol) in MeOH (10 ml) for 2 h. Usual work-up and
purification by preparative tlc afforded 8-hydroxy-7-methoxy-5-methoxymethyl-2-methyltetrahydroisoquino-
line (5a) in the yield of 97%. In the 1H-nmr spectrum, six singlet peaks [2.47 (3H, NMe), 3.36 (3H, OMe),
3.56 (2H, 1-H2), 3.84 (3H, OMe), 4.34 (2H, ArCH2O), and 6.74 (1H, ArH)] were observed. Occurrence of
a methylene and an aliphatic methoxyl groups and disappearance of one aromatic proton led the structure to 5a.
The structure was confirmed by an alternative synthesis of an authentic specimen by conventional procedure.
That is, a mixture of 8-hydroxy-7-methoxy-2-methyltetrahydroisoquinoline (4f), 35% formalin, and 50% aq.
NaOMe (10 eq.) – R4 MeOH

Temperature reflux, 2 h

Yield (%) of 5

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>Yield (%) of 5</th>
<th>100MHz 1H-NMR [ppm in CDCl3, J (Hz)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>OMe</td>
<td>97</td>
<td>2.47(3H, s), 3.36(3H, s), 3.56(2H, s), 3.84(3H, s), 4.34(2H, s), 6.74(1H, s)</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
<td>OMe</td>
<td>80</td>
<td>1.34(3H, d, J=5.5), 2.52(3H, s), 3.17(3H, s), 3.63 (2H, s), 3.84(3H, s), 4.44(1H, q, J=5.5), 6.80(1H, s)</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>Ph</td>
<td>OH</td>
<td>OMe</td>
<td>66</td>
<td>2.34(3H, s), 2.76(2H, d, J=4), 3.16(3H, s), 3.84(3H, s), 6.76(1H, s)</td>
</tr>
<tr>
<td>d</td>
<td>CH2Ar</td>
<td>H</td>
<td>OH</td>
<td>OMe</td>
<td>67b</td>
<td>2.52(3H, s), 3.63(2H, s), 3.86, 3.88, 3.91(each 3H, s), 6.73(1H, d, J=16), 6.97(1H, s)</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>59</td>
<td>2.46(3H, s), 3.28(3H, s), 3.54(2H, s), 4.28(2H, s), 6.32, 6.85(each 1H, d, J=8)</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>OMe</td>
<td>49</td>
<td>2.48(3H, s), 3.34(3H, s), 3.56(2H, s), 3.81(3H, s), 4.54(2H, s), 6.44(1H, s)</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>Ph</td>
<td>OH</td>
<td>OMe</td>
<td>61</td>
<td>2.29(3H, s), 2.75(2H, d, J=4), 3.12(3H, s), 3.85(3H, s), 4.24(2H, s), 6.54(1H, s)</td>
</tr>
</tbody>
</table>

*a* Ar=3,4-dimethoxyphenyl, *b* yield of the stilbene (6)
KOH in MeOH was heated for 4 h to give the 5-methoxymethylisoquinoline, which was identical with the recyclized product (5a) by comparison of the spectral data.

This novel rearrangement was applied to various 1- or 4-substituted isocorypalline (4b, 4c, 4d) to investigate the generality. Similar reaction of cyanomethiodides (2b,c) with NaOMe yielded the corresponding 8-ols (5b,c). Compound (2d) gave a trans-stilbene (6), which was formed by elimination of methanol. The results are listed in Table. Reaction of a quaternary iodide (2e) bearing no methoxyl group on 7-position also proceeded giving rise to an isoquinolin-8-ol (5e).

A plausible mechanism is depicted in Scheme. A C-N bond fission caused by electron-donation from the phenolate anion (2a'), generates a p-quinone methide (7), to which the Michael addition of methoxide anion takes place to give the methoxymethylphenolate anion (8'). Then, intramolecular nucleophilic substitution of the cyanomethyl group in 8' to the activated arene proceeds to form the final product (5a). This assumption was supported by the following evidence. When 2a was treated with NaOMe at 25°C, the intermediary compound (8) was isolated. On further heating with NaOMe compound (8) gave the recyclized isoquinoline (5a). In the present reaction no formation of 3-benzazepine (3) by intramolecular reaction of the quinone methide (7) with a carbanion, which could be generated from the cyanomethyl group, was observed.

8-Hydroxy-7-methoxy-2-methyltetrahydroisoquinolinium salt (2f), a regioisomer of 2a, should be a precurser of the o-quinone methide (9). Actually, similar base treatment of 2f gave 6-hydroxy-7-methoxy-5-methoxymethyl-2-methyltetrahydroisoquinoline (5f), which was identical with an authentic methoxymethyl derivative of isocorypalline (4a) prepared from 4a in a manner similar to that described for 5a. 4-Phenyl congener (2g) also reacted with methoxide anion to give a recyclized product (5g).
Thus, it is noteworthy that in the present reaction the modified Pictet-Spengler reaction of N-cyanomethylphenols under basic conditions takes place, although some limitations exist. Application of this novel methodology for synthesis of isoquinoline alkaloids is now in progress.

REFERENCES AND NOTES
4. All new compounds were characterized by their $^1$H-nmr and high resolution mass spectral measurements or elemental analysis. Melting points of crystalline compounds are as follows. 2a, 191-192° C (MeCN); 2e, 186° C (MeCN); 2f, 178-180° C (EtOH-hexane).
11. Kametani et al. have reported recyclization via C-N bond fission of a dihydroxytetrahydroprotoberberinium methiodide under basic conditions; T. Kametani, K.Takemura, K. Fukumoto, T. Terui, and A. Kozuka, J. Chem. Soc., Perkin Trans. 1, 1974, 2678. On the other hand, acid catalyzed cyclization with decyanation of N-cyanomethyl moiety has been reported; M. Rubiralta, A. Diez, and J. Bosch, Heterocycles, 1988, 27, 785.

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