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

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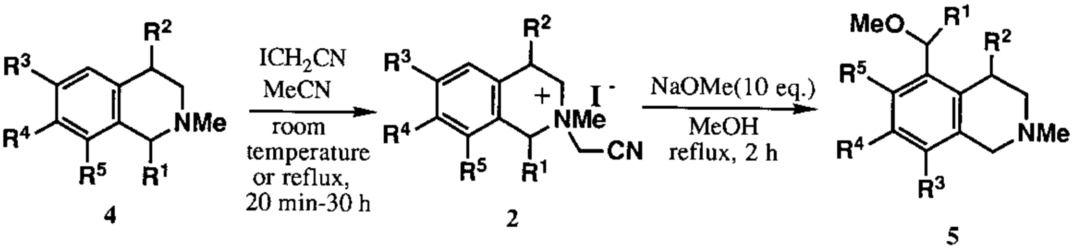
Abstract --- Reaction of *N*-cyanomethylisoquinolinium methiodide (**2a**) with sodium methoxide gave a rearranged tetrahydroisoquinolin-8-ol (**5a**) in high yield. With 1- or 4-substituted *N*-cyanomethylisoquinolinium (**2b-d**) and 8-hydroxy-tetrahydroisoquinolinium methiodides (**2f**), similar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

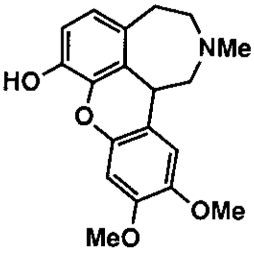
In the course of our study[1] on synthesis of dibenzopyranazepine alkaloid, clavizepine (**1**),[2] reaction of *N*-cyanomethyl-6- or 8-hydroxytetrahydroisoquinolinium methiodides (**2**) under basic conditions revealed a novel rearrangement instead of a ring expansion to a 3-benzazepine (**3**).[3] 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**)[4] (0.2 mmol), readily available from isocorypalline (**4a**)[5] and iodoacetonitrile, 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-methyltetrahydroisoquinoline (**5a**)[4] in the yield of 97 %. In the ^{1}H-nmr spectrum, six singlet peaks [2.47 (3H, NMe), 3.36 (3H, OMe), 3.56 (2H, 1-H_2), 3.84 (3H, OMe), 4.34 (2H, $ArCH_2O$), 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.[6] That is, a mixture of 8-hydroxy-7-methoxy-2-methyltetrahydroisoquinoline (**4f**),[7] 35% formalin, and 50% aq.



	R^1	R^2	R^3	R^4	R^5	Yield(%) of 5	100MHz ^{1}H-NMR [ppm in CDCl$_3$, J (Hz)]
a	H	H	OH	OMe	H	97	2.47(3H,s),3.36(3H,s),3.56(2H,s),3.84(3H,s), 4.34(2H,s),6.74(1H,s)
b	Me	H	OH	OMe	H	80	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)
c	H	Ph	OH	OMe	H	66	2.34(3H,s),2.76(2H,d,J=4),3.16(3H,s),3.84(3H, s),6.76(1H,s)
d	CH$_2$Ar^a	H	OH	OMe	H	67^b	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)
e	H	H	OH	H	H	59	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)
f	H	H	H	OMe	OH	49	2.48(3H,s),3.34(3H,s),3.56(2H,s),3.81(3H,s), 4.54(2H,s),6.44(1H,s)
g	H	Ph	H	OMe	OH	61	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)

[a] Ar=3,4-dimethoxyphenyl, [b] yield of the stilbene (**6**)



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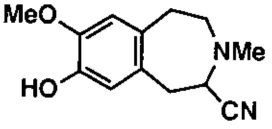

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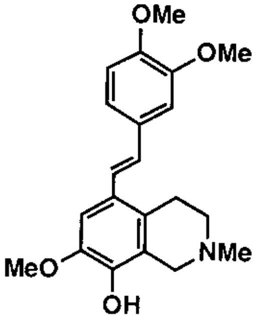

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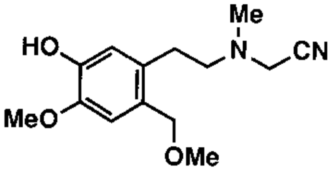

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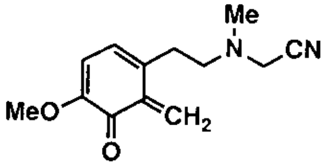

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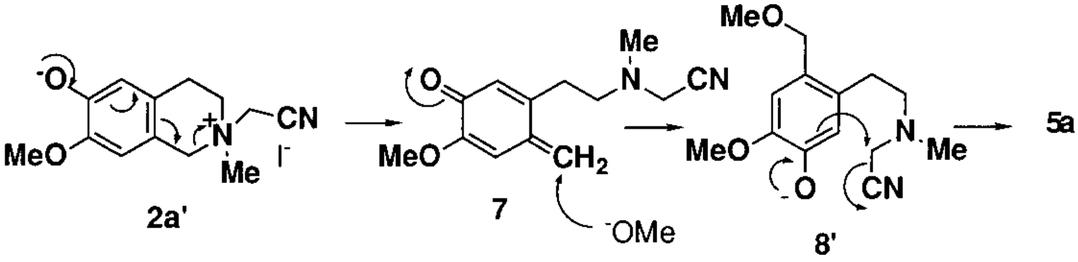
KOH in MeOH was heated for 4 h to give the 5-methoxymethylisoquinoline, which was identical with the recyclized product (**5a**) by comparison of the spectral data.

This novel rearrangement was applied to various 1- or 4-substituted isocorypalline (**4b**,[8] **4c**[9] or **4d**[10]) to investigate the generality. Similar reaction of cyanomethiodides (**2b,c**)[4] with NaOMe yielded the corresponding 8-ols (**5b,c**).[4] Compound (**2d**)[4] gave a *trans*-stilbene (**6**),[4] which was formed by elimination of methanol. The results are listed in Table. Reaction of a quaternary iodide (**2e**)[4] bearing no methoxyl group on 7-position also proceeded giving rise to an isoquinolin-8-ol (**5e**).[4]

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**)[4] 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.



Scheme

8-Hydroxy-7-methoxy-2-methyltetrahydroisoquinolinium salt (**2f**),[4] 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**),[4] 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**)[4] also reacted with methoxide anion to give a recyclized product (**5g**).[4]

Thus, it is noteworthy that in the present reaction the modified Pictet-Spengler reaction of *N*–cyanomethylphenols under basic conditions takes place,[11] although some limitations exist. Application of this novel methodology for synthesis of isoquinoline alkaloids[12] is now in progress.

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