

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

Hiroshi Hara,* Masaki Endoh, Ken-ichi Kaneko, and Osamu Hoshino*

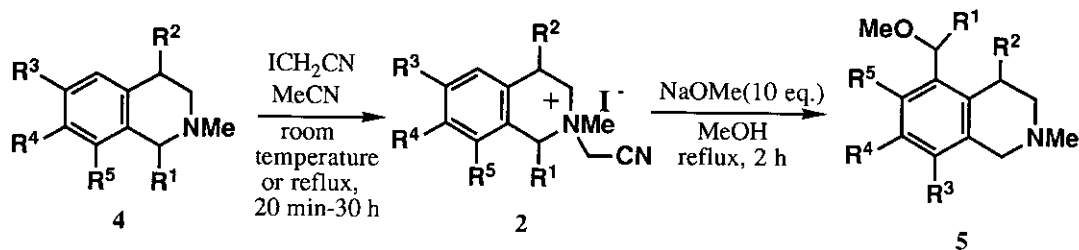
Faculty of Pharmaceutical Sciences, Science University of Tokyo

12 Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

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.

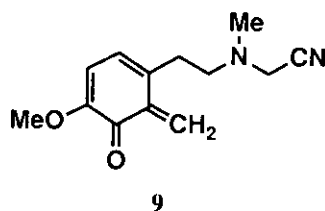
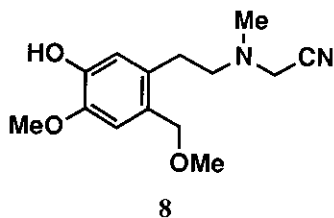
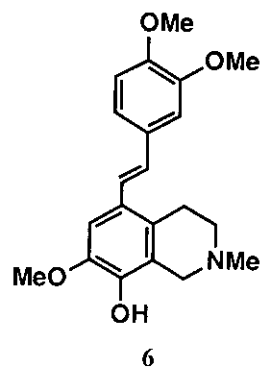
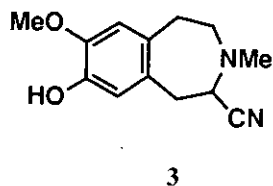
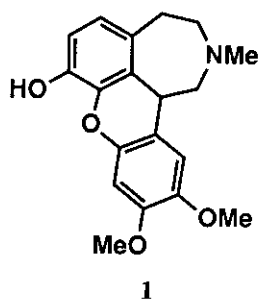
In the course of our study¹ on synthesis of dibenzopyranazepine alkaloid, clavizepine (**1**),² reaction of *N*-cyanomethyl-6- or 8-hydroxytetrahydroisoquinolinium methiodides (**2**) under basic conditions revealed a novel rearrangement instead of a ring expansion to a 3-benzazepine (**3**).³ Here we 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 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.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)

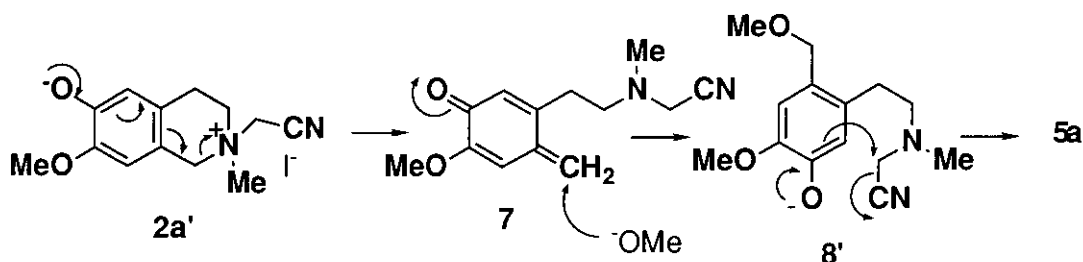
^a Ar=3,4-dimethoxyphenyl, ^b yield of the stilbene (6)



KOH in MeOH was heated for 4 h to give the 5-methoxymethylisoquinoline, which was identical with the cyclized 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 cyclized 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 precursor 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 cyclized 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 alkaloids¹² is now in progress.

REFERENCES AND NOTES

1. H. Hara, M. Kishigami, M. Endoh, K. Kaneko, and O. Hoshino, *Heterocycles*, 1992, **33**, 219.
2. J. M. Boente, L. Castedo, D. Dominguez, and M. C. Ferro, *Tetrahedron Lett.*, 1986, **27**, 4077.
3. cf. S. Smith, Jr., V. Elango, and M. Shamma, *J. Org. Chem.*, 1984, **49**, 581.
4. All new compounds were characterized by their ¹H-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).
5. J. M. Bobbitt, D. N. Roy, A. Marchand, and C. W. Allen, *J. Org. Chem.*, 1967, **32**, 2225.
6. cf. M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, 1957, **22**, 1435.
7. J. M. Bobbitt and C. P. Dutta, *J. Org. Chem.*, 1969, **34**, 2001.
8. O. Hoshino, K. Ohyama, M. Taga, and B. Umezawa, *Chem. Pharm. Bull.*, 1974, **22**, 2587.
9. H. Hara, R. Shirai, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.*, 1985, **33**, 3107.
10. O. Hoshino, M. Taga, and B. Umezawa, *Heterocycles*, 1973, **1**, 223.
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. I*, **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.
12. cf. Y.-C. Wu, J.-Y. Liou, C.-Y. Duh, S.-S. Lee, and S.-T. Lu, *Tetrahedron Lett.*, 1991, **32**, 4169.

Received, 3rd September, 1992