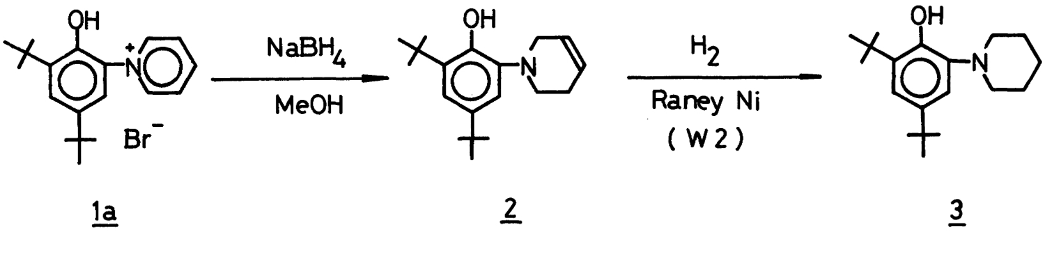
CHEMISTRY LETTERS, pp. 1345-1348, 1981.

REDUCTION OF 1-(3,5-DI-TERT-BUTYL-2-HYDROXYPHENYL)PYRIDINIUM HALIDES WITH RANEY Ni-Al ALLOY IN AN ALKALINE SOLUTION AFFORDING 2,4-DI-TERT-BUTYLBENZOXAZOLO[3,2-a]-5a,6,7,8,9,10-HEXAHYDROPYRIDINES

Gouki FUKATA,[†,††] Takashi ITOH,[††] and Masashi TASHIRO*[†,††]
† Research Institute of Industrial Science, Kyushu University
†† Department of Molecular Science and Technology, Graduate School of Engineering Sciences, Kyushu University
Hakozaki, Higashi-ku, Fukuoka 812

Treatment of 1-(3,5-di-tert-butyl-2-hydroxyphenyl)pyridinium halides (1a-1c) with Raney Ni-Al alloy in an alkaline solution afforded the corresponding 2,4-di-tert-butylbenzoxazolo[3,2-a]-5a,6,7,8,9,10-hexahydropyridines (4a-4c). In the case of 1b, 2,4-di-tert-butylbenzoxazolo[3,2-a]-5a,6,7,10-tetrahydro-8-methylpyridine (5) was also obtained as a by-product.

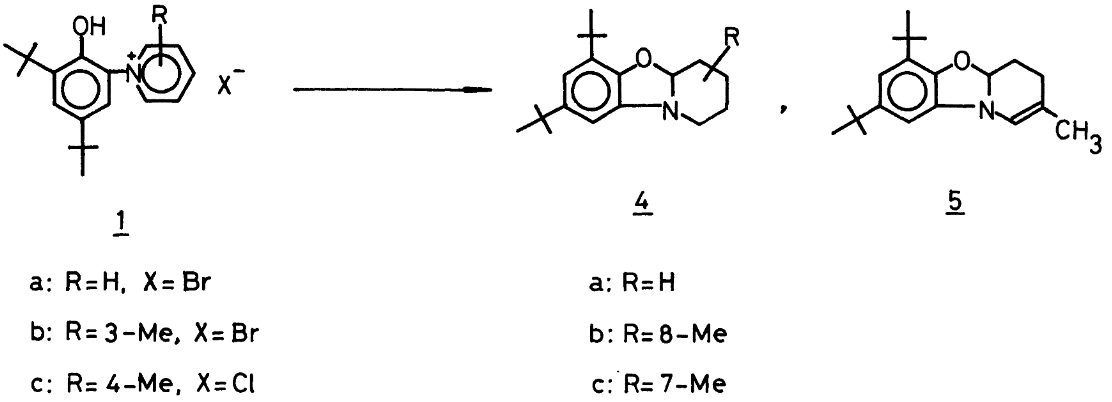
It has been previously reported that[1,2] the reduction of 1-(3,5-di-tert-butyl-2-hydroxyphenyl)pyridinium bromide (1a) with $NaBH_4$ in methanol afforded a good yield of 2,4-di-tert-butyl-6-(1,2,3,6-tetrahydro-1-pyridyl)phenol (2), which was easily reduced to 2,4-di-tert-butyl-6-piperidinophenol (3) by hydrogenation with a Raney Ni (W2) catalyst (Scheme 1).



Scheme 1

Furthermore, Raney Ni-Al alloy in an alkaline solution has been known to be a powerful reductive reagent for the reduction of phenol derivatives.[3-5]

In the present work, the reduction of the title compounds 1a-1c was carried out with Raney Ni-Al alloy in an alkaline solution to obtain piperidinophenols such as 3 directly from 1. The expected compounds were not formed, however, but the reductive cyclization occurred and yielded the novel products shown in Scheme 2.[6] The yields of the products are summarized in Table 1.



Scheme 2

Table 1. Reduction of 1 with Raney Ni-Al Alloy in an Alkaline Solution[a)]

Substrate	Product (%)[b)]
1a	4a (90)
1b	4b (34), 5 (16)
1c	4c (20)

a) Reaction conditions: one gram each of 1 and of the alloy was used. Temperature: refluxing temperature of methanol for 10 min. Solvent: methanol (10 ml).

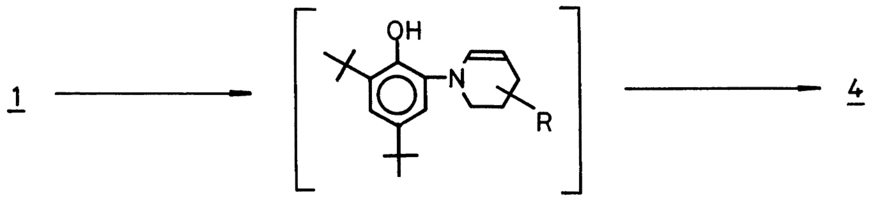
b) Isolated yields are shown.

The reduction of 1a afforded 2,4-di-tert-butylbenzoxazolo[3,2-a]-5a,6,7,8,9,10-hexahydropyridine (4a) in 90% yield, while the cases of 1b and 1c gave the corresponding 8-methyl-(4b) and 7-methyl-(4c) derivatives in low yields together with a large amount of tarry materials. In the case of 1b, 2,4-di-tert-butylbenzoxazolo[3,2-a]-5a,6,7,10-tetrahydro-8-methylpyridine (5) was also obtained as a by-product.

The structures of the products were determined by their elemental analyses and spectral data.[7] The hydrogenation of 4a in the presence of Raney Ni (W2) afforded 3 in 89% yield. This result supports the structure proposed for 4a.

$$\underline{4a} \xrightarrow[\text{Raney Ni (W2)}]{H_2} \underline{3}$$

Treatment of 2 with Raney Ni-Al alloy under conditions identical to those[6] of the reduction of 1a did not give any product, but the starting compound 2 was recovered in an almost quantitative yield. This finding suggests that 4 might be formed from enamine intermediate 6 by intramolecular Michael-type addition of the hydroxy groups to the activated double bond as shown below.



6

The compounds 4a-4c may be pharmologically interesting, because they share part of their structure with vomicine,[8,9] which is characterized by strychinine-like biological activity. Indeed, we experienced numbness throughout the oral cavity even when 4a was handled with extreme care.

References

*. To whom all inquiries should be addressed.

1. M. Tashiro and G. Fukata, Heterocycles, 12, 1551 (1979).
2. M. Tashiro, G. Fukata, and T. Itoh, J. Org. Chem., in press.
3. M. Tashiro, K. Nakayama, and G. Fukata, Chem. Letters, 1981, 359.
4. M. Tashiro, T. Sumida, and G. Fukata, Heterocycles, 14, 675 (1980).
5. M. Tashiro, A. Iwasaki, and G. Fukata, J. Org. Chem., 43, 196 (1978).

6. Typical procedure (on a large scale): to a solution of 36.4 g of 1a and 80 ml of aq.30% KOH in 700 ml of methanol 25 g of Raney Ni-Al alloy at room temperature was added in small portions. After the reaction mixture was refluxed for 10 min, the excess alloy was filtrated off. The filtrate was poured into a large amount of water to give 24.5 g of 4a, which was recrystallized from MeOH-H_2O.

7. 4a: mp. 107-110°C (d), colorless needles (MeOH-H_2O), ^{1}H-NMR ($CDCl_3$): δ 1.28, 1.36 (each s, 9H), 1.40-2.15 (m, 6H), 2.56-2.88 (m, 1H), 3.40-3.68 (m, 1H), 4.98 (d.d, J = 8 and 3 Hz, 1H), 6.32,6.57 (each d, J = 2.5 Hz, 1H); Mass: m/e 287 (M^+).

   4b: mp. 195°C (d), colorless prisms (MeOH-H_2O); ^{1}H-NMR ($CDCl_3$): δ 0.95 (d, J = 6 Hz, 3H), 1.27, 1.32 (each s, 9H), 1.40-2.16 (m, 5H), 2.16-2.52 (m, 1H), 3.40-3.66 (m, 1H), 5.00 (d.d, J = 8.5 and 3.5 Hz, 1H), 6.30, 6.56 (each d, J = 2 Hz, 1H); Mass: m/e 301 (M^+).

   4c: mp. 63-66°C, colorless crystalline powders; ^{1}H-NMR ($CDCl_3$): δ 1.00 (d, J = 6 Hz, 3H), 1.13, 1.28 (each s, 9H), 1.40-1.72 (m, 4H), 1.80-2.08 (m, 1H), 2.60-2.92 (m, 1H), 3.45-3.72 (m, 1H), 5.06 (d.d, J = 9 and 3 Hz, 1H), 7.32, 7.56 (each d, J = 2 Hz, 1H); Mass: m/e 301 (M^+).

   5: mp. 103-105°C, colorless prisms (MeOH-H_2O); ^{1}H-NMR ($CDCl_3$): δ 1.27, 1.32 (each s, 9H), 1.65 (s, 3H), 1.76-2.44 (m, 4H), 5.76 (d.d, J = 9.5 and 3 Hz, 1H), 6.20 (b.s, 1H), 6.42, 6.56 (each d, J = 2 Hz, 1H); Mass: m/e 299 (M^+).

8. H. Wieland and L. Hormer, Ann., 528, 73 (1937).
9. R. Huisgen, H. Wieland, and H. Eder, Ann., 561, 193 (1949).

(Received July 13, 1981)