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# 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

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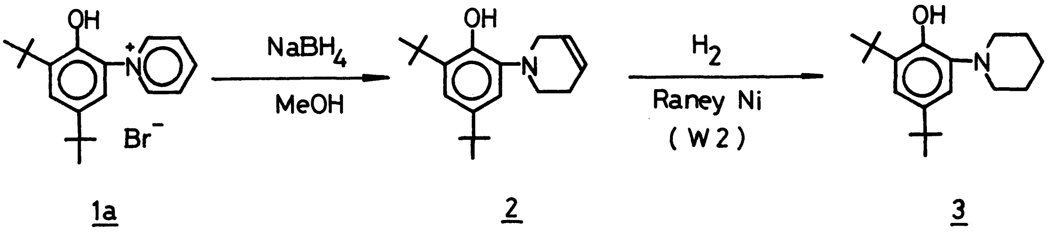
Treatment of 1-(3,5-di-tert-butyl-2-hydroxyphenyl)pyridinium halides (1a-1c) with Raney Ni-Al alloy in an alkaline solution afforded the corresponding 2,4-di-tert-butylbenzoxazolo[3,2-a]-5a,6,7,8,9,10-hexahydropyridines (4a-4c). In the case of 1b, 2,4-di-tert-butylbenzoxazolo[3,2-a]-5a,6,7,10-tetrahydro-8-methylpyridine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

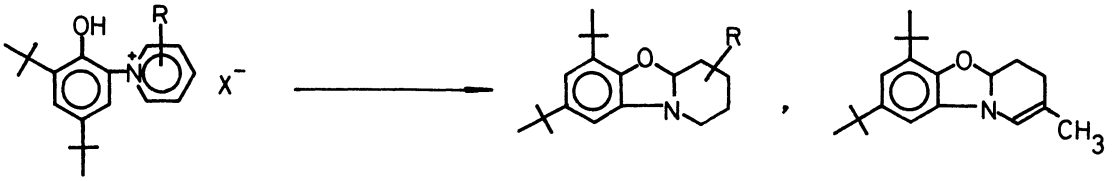
It has been previously reported that[1,2] the reduction of 1-(3,5-di-tert-butyl-2-hydroxyphenyl)pyridinium bromide (1a) with $NaBH_4$ in methanol afforded a good yield of 2,4-di-tert-butyl-6-(1,2,3,6-tetrahydro-1-pyridyl)phenol (2), which was easily reduced to 2,4-di-tert-butyl-6-piperidinophenol (3)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



1

a: R=H, X=Br

b: R=3-Me, X=Br

c: R=4-Me, X=Cl

4

a: R=H

b: R=8-Me

c: R=7-Me

5

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).

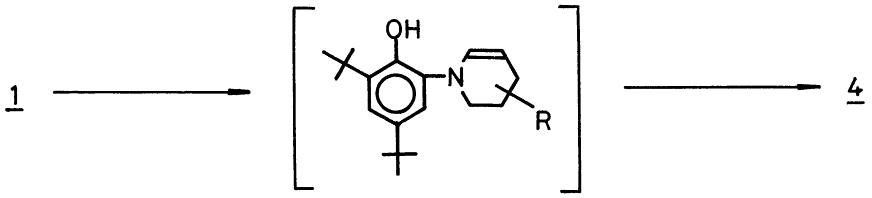
b) Isolated yields are shown.

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.

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

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.

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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$_2$O.
7. 4a: mp. 107-110°C (d), colorless needles (MeOH-H$_2$O), $^1$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$_2$O); $^1$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$_2$O); $^1$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 ($M^+$).
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