Tetrahedron Letters,Vol.25,No.33,pp 3615-3616,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A NOVEL SYNTHESIS OF 9-HYDROXYAPORPHINE

H. Hara, F. Hashimoto, O. Hoshino, and B. Umezawa*

Faculty of Pharmaceutical Sciences, Science University of Tokyo,
12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

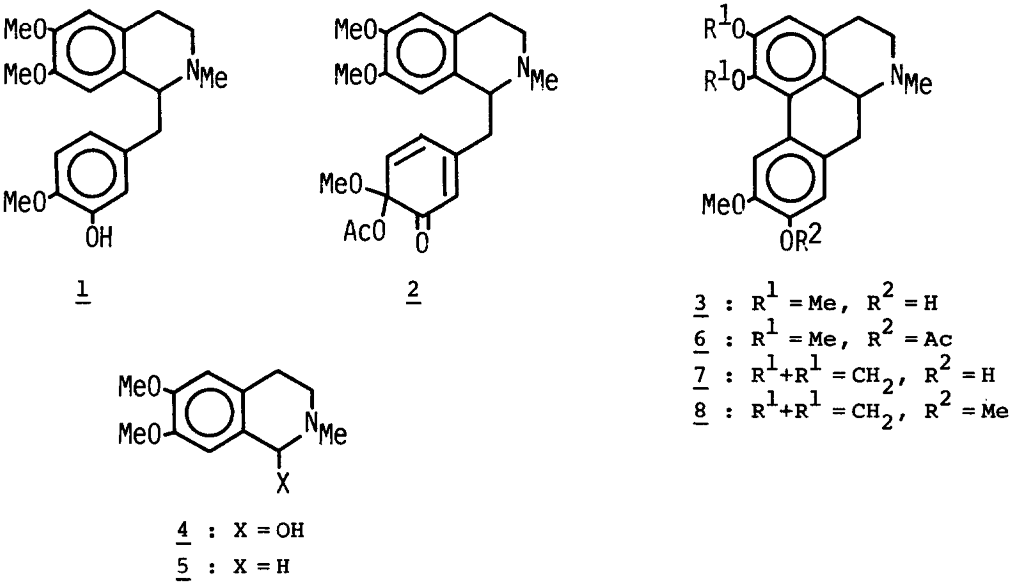
Abstract: (±)-N-Methyllaurotetanine (3) was readily prepared *via* the *o*-quinol acetate (2), which was obtained from the 1-(3'-hydroxybenzyl)-tetrahydroisoquinoline (1) by lead tetraacetate oxidation.

Since the protection of the hydroxyl group in the starting 1-(3'-hydroxybenzyl)-tetrahydroisoquinolines during lead tetraacetate oxidation was a crucial prerequisite, the synthesis of the title aporphines was so far rather tedious by our methodology.1)

Here, we wish to report another approach to the preparation of a 9-hydroxy aporphine. (±)-Laudanine (1)2) was oxidized with lead tetraacetate in CH_2Cl_2 at 0°C for 1 min to give the *o*-quinol acetate (2) [NMR ($CDCl_3$): δ 2.05 (OAc), 3.37 (aliphatic OMe); IR ($CHCl_3$): 1725 cm^{-1} (OAc), 1665 cm^{-1} (dienone)], quantitatively. Without purification, 2 was treated with CF_3CO_2H in CH_2Cl_2 for 1 h to afford (±)-N-methyllaurotetanine (3)1b) (20%, mp 143-144°C) and the 1-hydroxytetrahydroisoquinoline (4) (32%). The structure of the latter was determined as follows. Namely, hydrogenation of 4 on 10% Pd-C in MeOH yielded the known tetrahydroisoquinoline (5).3) A mechanistic pathway for the genaration of 4 could be visualized as shown in the Scheme, the key step being a vinylogous retro-Mannich reaction. Presumably, the nitrogen in CF_3CO_2H was not so tightly fastened to a proton as to prohibit the electron movement, the undesirable reaction being effected. To avoid the side reaction, conditions with a strong acid were employed, *i.e.* treatment of the *o*-quinol acetate (2) with Ac_2O-c.H_2SO_4 gave exclusively (±)-O-acetyl-N-methyllaurotetanine (6) and even a trace of 4 was detected. Hydrolysis of 6 with 5% KOH-MeOH gave (±)-N-methyllaurotetanine (3) in 34% yield from 1.

The present procedure seems to be a very useful alternative for the synthesis of other 9-hydroxyaporphines, and its application to the synthesis of 1,2-methylenedioxyaporphines (7 and 8) is currently in progress.

Acknowledgement: The authors gratefully acknowledge the financial support of this work by a Grant-in-Aid for scientific research (No. 58570890) from the Ministry of Education.



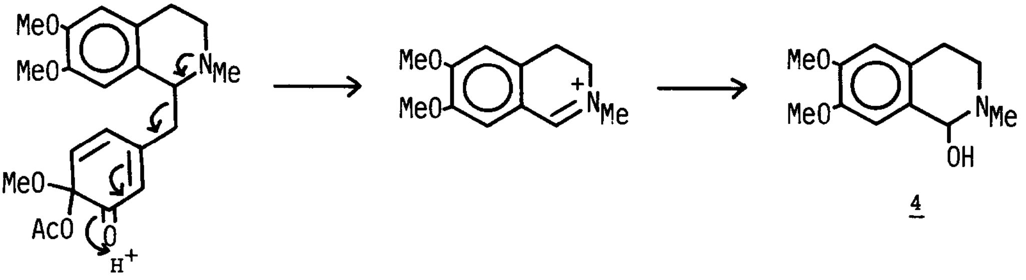
1

2

3 : R^1 = Me, R^2 = H
6 : R^1 = Me, R^2 = Ac
7 : R^1+R^1 = CH_2, R^2 = H
8 : R^1+R^1 = CH_2, R^2 = Me

4 : X = OH
5 : X = H

Figure



2

4

Scheme

References

1) a) H. Hara, O. Hoshino, and B. Umezawa, Chem. Pharm. Bull., 24, 262 (1976).
   b) H. Hara, O. Hoshino, and B. Umezawa, ibid., 24, 1921 (1976).
   c) O. Hoshino, M. Ohtani, and B. Umezawa, ibid., 27, 3101 (1979).
2) B. Frydman, R. Bendisch, and V. Deulofeu, Tetrahedron, 4, 342 (1958).
3) J. S. Buck, J. Amer. Chem. Soc., 56, 1769 (1934).

(Received in Japan 24 April 1984)