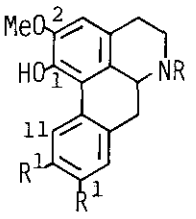
A NOVEL SYNTHESIS OF (±)-NORAPORPHINE ALKALOIDS, (±)-WILSONIRINE AND (±)-NORDOMESTICINE#

Osamu Hoshino, Hiromichi Ogasawara, Masaji Suzuki, and Bunsuke Umezawa
Faculty of Pharmaceutical Sciences, Science University of Tokyo,
12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

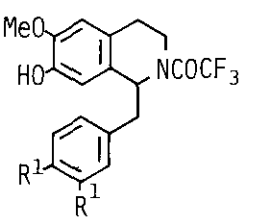
Abstract— (±)-Wilsonirine (1a) and (±)-nordomesticine (1b) were synthesized in moderate yields on acid treatment, followed by alkaline hydrolysis of o-quinol acetates (o-QAs)(3) readily obtained by lead tetraacetate oxidation of (±)-N-trifluoroacetyltetrahydroisoquinolin-7-ols (2).

Noraporphine alkaloids have been expected to be useful key compounds for synthesis of biologically active compounds[1]. However, only a few papers[2] have been published on their synthesis so far. In continuation of our studies[3] on application of lead tetraacetate [$Pb(OAc)_4$] oxidation to synthesis of isoquinoline alkaloids, we found that (±)-N-trifluoroacetyltetrahydroisoquinolin-7-ols (2) were readily oxidized with the oxidant in CH_2Cl_2 to give rise to the corresponding (±)-N-trifluoroacetyl-6-acetyl-6-methoxy-7-oxo-$\Delta^{4a,5,8,8a}$-hexahydroisoquinolines [o-quinol acetates (o-QAs)](3), which could be converted into (±)-noraporphines. We now wish to report a novel synthesis of (±)-wilsonirine (1a)[4] and (±)-nordomesticine (1b)[5].



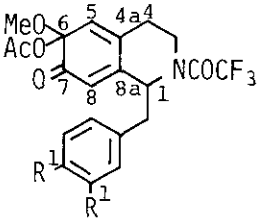
1 : R^1=H

4 : R=$COCF_3$



2

a : R^1=OMe b : R^1+R^1=OCH_2O



3

Dedicated to Professor G. Stork on the occasion of his sixty-fifth birthday.

A typical example is as follows. $Pb(OAc)_4$ (127 mg) was added in one portion to an ice-cold, stirred solution of 2a[2b] (mp 149-151°C)(100 mg) in CH_2Cl_2 (1 ml) and stirring was continued at 0-5°C for 0.5 h. A careful work-up of the reaction mixture gave quantitatively a 1:1.2 diastereoisomeric mixture of 3a (oil)[IR[6] ν:1735, 1680 cm^{-1}; ^{1}H-nmr[6] δ:2.10, 2.12 (1:1.2)(3H, each s, 6-OCOMe), 3.42, 3.43 (1.2:1)(3H, each s, 6-OMe)]. CF_3COOH (5 ml) was added dropwise to an ice-cold, stirred solution of crude 3a in CH_2Cl_2 (5 ml) and the mixture was stirred at room temperature for 1 h. Usual work-up of the reaction mixture gave quantitatively a solid, which was purified on preparative thin-layer chromatography (SiO_2; developing solvent; $CHCl_3$) to give 4a[6] (61 mg, 61%), mp 190-191°C(CH_2Cl_2-n-hexane)(lit.[2b], 196.5-197°C). ^{1}H-Nmr spectra datum of 4a was identical with that noted in literature[2b].

From the above results, it was proved that $Pb(OAc)_4$ oxidation of 2a gave o-QA (3a), acid treatment of which afforded (±)-N-trifluoroacetylwilsonirine (4a) in a moderate yield.

Similarly, 2b (mp 137-138°C) gave o-QA (3b)[6], which was converted into 4b[6] in 21% overall yield.

Alkaline hydrolysis (aq.K_2CO_3-MeOH, reflux, 2 h) of 4a and 4b afforded 1a[6] (93%), mp 210-213°C(CH_2Cl_2)(lit.[4], 211-213°C) and 1b[6] (98%), mp 205-207°C(CH_2Cl_2-n-hexane), respectively.

Thus, a novel synthesis of (±)-noraporphine alkaloids was accomplished *via* o-QAs (3) of (±)-N-trifluoroacetyltetrahydroisoquinolin-7-ols (2). *Further development of the present method is in progress.*

ACKNOWLEDGEMENTS

The authors are indebted to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for his kind supply of vanillin and piperonal. Thanks are also due to Professor M. Ishikawa and Dr. A. Sugimoto of Tokyo Medical and Dental University for high resolution ms spectral measurements, to Sankyo Co., Ltd. for elemental analysis, and to Misses N. Sawabe and N. Yamatani of this Faculty for ^{1}H-nmr and ms spectral measurements.

REFERENCES AND NOTES

1. J.L.Neumeyer, F.E.Gramchelli, C.N.Filer, A.H.Soloway, and S.-J.Law, J. Med. Chem., 1980, 23, 1008 and refs. cited therein.
2. a) Pschorr cyclization; P.Tschesche, P.W.R.Moll, and G.Legler, Tetrahedron, 1964, 20, 1435. Oxidative coupling; b) VOF_3-TFA-TFAA; S.M.Kupchan, O.P.Dhingra, and C.-K.Kim, J. Org. Chem., 1976, 43, 4076; c) Ph_2SeO; J.P.Marino and A.Schwartz, Tetrahedron Lett., 1979, 3243. d) Selective demethylation of norglaucine; L.Castedo, A.R.de Lera, J.M.Saá, R.Suau, and C. Villaverde, Heterocycles, 1980, 14, 1135.
3. B.Umezawa and O.Hoshino, Heterocycles, 1975, 3, 1005; O.Hoshino, M.Ohtani, and B.Umezawa,

Chem. Pharm. Bull., 1979, 27, 3101; H.Hara, F.Hashimoto, O.Hoshino, and B.Umezawa, Tetrahedron Lett., 1984, 25, 3615; idem, Chem. Pharm. Bull., 1984, 32, 4154; H.Hara, O.Hoshino, and B.Umezawa, ibid, 1985, 33, 2705; H.Hara, A.Tsunashima, H.Shinoki, T.Akiba, O.Hoshino, and B.Umezawa, ibid, 1986, 34, 66.

4. S.R.Johns, J.A.Lamberton, C.S.Li, and A.A.Sioumis, Aust. J. Chem., 1970, 23, 363.
5. As (+)-nordomesticine; S.R.Johns, J.A.Lamberton, and A.A.Sioumis, Aust. J. Chem., 1966, 19, 2331.
6. IR spectra were taken with a Hitachi 260-10 spectrophotometer in $CHCl_3$ solution. ^{1}H-Nmr spectra were measured with a JEOL-JNM-FX-100(100MHz) instrument in $CDCl_3$ solution using TMS as internal standard. 3a; δ: 2.10, 2.12 (1:1.2)(3H, each s, 6-OCOMe), 3.42, 3.43 (1.2:1)(3H, each s, 6-OMe), 3.82, 3.83, 3.84 (9H, each s, 3xOMe), 5.15 (1H, dd, J=4.3, 8.5 Hz, 1-H), 5.14, 5.99 (2H, each br s, 2xolefinic H), 6.60-6.70 (3H, m, 3xAr-H). 4a; δ: 3.94 (3H, s, OMe), 3.96 (3H, s, 2xOMe), 5.08 (1H, dd, J=5.4, 12.9 Hz, 6a-H), 6.60, 6.80 (2H, each s, 2xAr-H), 8.15 (1H, s, 11-H). 1a; δ: 3.95 (9H, s, 3xOMe), 6.58, 6.77 (2H, each s, 2xAr-H), 8.10 (1H, s, 11-H). 3b (oil); ν: 1730, 1680 cm^{-1}; δ: 2.10, 2.12 (1:1.2)(3H, s, 6-OCOMe), 3.42 (3H, s, 6-OMe), 4.96-5.24 (1H, m, 1-H), 5.46, 5.57 (1:1.2)(1H, each s, olefinic H), 5.90 (2H, s, OCH_2O), 5.96-6.08 (1H, m, olefinic H), 6.44-6.78 (3H, m, 3xAr-H). 4b; δ: 3.97 (3H, s, 2-OMe), 5.05 (1H, dd, J=5.7, 12.8 Hz, 6a-H), 6.00 (2H, s, OCH_2O), 6.60, 6.78 (2H, each s, 2xAr-H), 8.04 (1H, s, 11-H). 1b; δ: 3.95 (3H, s, 2-OMe), 5.98 (2H, s, OCH_2O), 6.57, 6.76 (2H, each s, 2xAr-H), 8.00 (1H, s, 11-H).

Received, 29th May, 1986