A NOVEL SYNTHESIS OF 5- OR 13-OXYGENATED TETRAHYDROPROTOBERBERINES§

Hiroshi Hara, Machiko Hosaka, Osamu Hoshino, and Bunsuke Umezawa*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, Shinjuku-ku, Tokyo, 162, Japan

In order to introduce O-functional groups at the 5- or 13-position in tetrahydroprotoberberine, we tried lead tetraacetate oxidation of (±)-2-hydroxy-3,10,11-trimethoxy (3)- or (±)-10-hydroxy-2,3,11-trimethoxy (12)-tetrahydroprotoberberine, a moiety of which was 1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-isoquinoline convertible to the corresponding 4,7-diacetate via p-quinol acetate.

(±)-2-Phenol (3) yielded a p-quinol acetate (4), which was transformed to several 5-oxygenated tetrahydroprotoberberines (6,7,8,9,10, and 11). Similarly, some 13-oxygenated derivatives (14,15, and 16) were prepared from (±)-10-phenol (12).

Protoberberine alkaloids carrying a hydroxyl group at the

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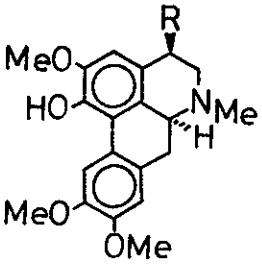
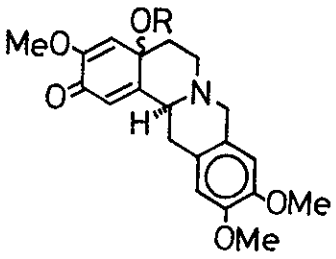
5-[1] or 13-[2] position have been known and their syntheses have also been achieved by several methods such as Pomeranz-Fritsch type cyclization leading to 5-hydroxy compounds[3], hydroboration-oxidation to a 5-[4] or 13[5]-hydroxy compound, and conversion of phthalide isoquinolines[6], Mannich reaction of α-hydroxybenzylisoquinolines[7] or hydride reduction of the oxidation products of berberine-acetone[8a], berberine[8b], and dihydroberberine[2b,8c] to 13-hydroxy compounds.

Our success that (±)-thaliporphine (1) has on oxidation with lead tetraacetate [$Pb(OAc)_4$] been stereospecifically transformed in one step to (±)-4β-acetoxythaliporphine (2)[9] encouraged us to carry out similar reactions on 2- or 10-phenolic tetrahydroprotoberberine in an anticipation to introduce oxygen functions at the 5- or 13-position. This communication deals with a novel synthesis of the title compounds in a stereoselective manner by use of $Pb(OAc)_4$.

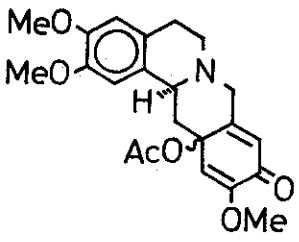
To a solution of (±)-2-hydroxy-3,10,11-trimethoxy-tetrahydroprotoberberine (3)[10] (400 mg) in acetic acid (4 ml) was added $Pb(OAc)_4$ (624 mg, 1.1 eq.) in one portion and the whole was stirred for 30 min at room temperature. Contrary to the anticipation, usual work-up[12] gave a p-quinol acetate (4) [mp 159-161°; IR[13]: 1740 ($OCOCH_3$), 1670, 1645, 1630 cm^{-1} (dienone)] (455 mg, quantitative). The p-quinol acetate was by no means a mixture of diastereoisomers because it displayed a sole spot on TLC and a simple pattern consisting of all singlet peaks [NMR[13] δ: 2.02 (3H, s, NCH_3), 3.66, 3.78, 3.80 (each 3H, s, $3xOCH_3$), 5.88, 6.28 (each 1H, s, 2 x olefinic H), 6.50, 6.61 (each 1H, s, 2 x aromatic H)] ascribable to a diastereoisomer. However, attempted hydrolysis of 4 failed to give a p-quinol



	R
1	H
2	OAc



	R
4	Ac
5	H



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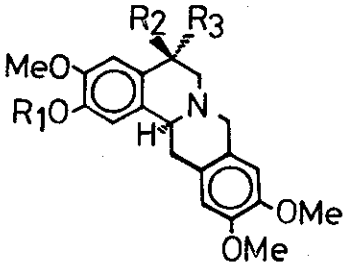
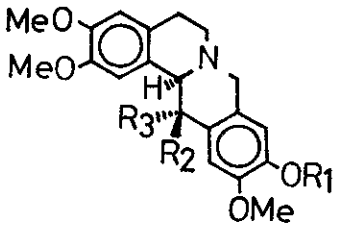
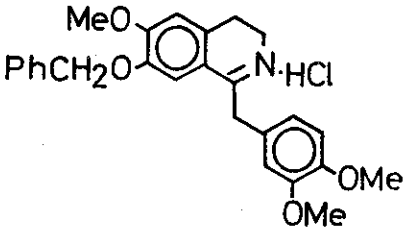


	R_1	R_2	R_3
3	H	H	H
6	Ac	OAc	H
7	H	OH	H
8	Me	OH	H
9	Me	OAc	H
10	H	H	OMe
11	H	OMe	H



	R_1	R_2	R_3
12	H	H	H
14	Ac	OAc	H
15	Ac	H	OAc
16	H	H	OMe



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(5) leaving stereochemistry of 4 unsolved.

Accordingly, a usual rearrangement technique in this region[12] was next tried. Namely, to a stirred suspension of the unpurified 4 (455 mg) in acetic anhydride (4 ml) under ice-cooling, was added conc. sulfuric acid (0.8 ml) drop by drop during 30 sec. The whole was stirred for 1 hr at room temperature and work-up as usual gave stereospecifically (±)-2, 5β-diacetate (6) [IR: 1760, 1725 cm^{-1}; NMR δ: 6.00 (1H, t, J=2,5Hz)] (468 mg, 91%). Purification on a silica gel short column and repeated recrystallization from acetone-pet. ether yielded colorless fine needles, mp 150-151°. Hydrolysis with conc. hydrochloric acid of 6 gave (±)-2, 5β-diol (7) [mp 165-170°; IR: 3540 cm^{-1} (OH); NMR (in d_5-pyridine) δ: 4.84 (1H, t, J=2.5Hz)], re-acetylation of which with acetic anhydride and pyridine led back to 6. For further confirmation of their structures, two derivatives of the diol (7) were prepared by convensional methods; (±)-5β-hydroxy-2,3,10,11-tetramethoxytetrahydroprotoberberine (8)[14] [mp 189-190° (lit.[3a] mp 194-195°)] and (±)-5β-acetate (9)[14] [mp 184-186° (lit.[3a] mp 188-189°)].

Treatment[12] of a suspension of 6 in MeOH with 5% KOH and purification on preparative TLC[15] ($CHCl_3$: MeOH=30:1) gave rise to (±)-5α-methoxy (10)-[mp 179-181° (dec.); IR: 3540 cm^{-1}; NMR δ: 4.58 (1H, dd, J=5, 10Hz)] and (±)-5β-methoxy (11)-[mp 137.5-138°; IR: 3540 cm^{-1}; NMR δ: 4.20 (1H, t, J=2.5Hz)] 2-hydroxy-3,10,11-trimethoxytetrahydroprotoberberines in 29% and 35% yield, respectively.

Similarly, $Pb(OAc)_4$ oxidation of (±)-10-hydroxy-2,3,11-trimethoxytetrahydroprotoberberine (12)[16] gave quantitatively an oily p-quinol acetate (13) [IR: 1740, 1675, 1645, 1630 cm^{-1},

NMR δ: 2.12 ($OCOCH_3$), 3.67, 3.83, 3.86 (each 3H, s, 3xOCH_3), 5.87, 6.24 (each 1H, s, 2 x olefinic H), 6.58, 6.59 (each 1H, s, 2 x aromatic H)], stereochemistry of which was unknown though homogeneous. Similar acid treatment with acetic anhydride and conc. sulfuric acid followed by purification on a silica gel column[15] gave (±)-10, 13β-diacetate (14)[17] [mp 166-167°; IR: 1765, 1730 cm^{-1}; NMR δ: 6.54 (1H, d, J=2.5Hz)] and (±)-10, 13α-diacetate (15)[17] [mp 168.5-169°; IR: 1760, 1730 cm^{-1}; NMR δ: 6.14 (1H, d, J=7.5Hz)] in a ratio of 3:1. This result was consistent with a suggestion on relative steric effect between 13α- and 13β-hydroxytetrahydroprotoberberines[5].

Although attempted hydrolysis of 14 and 15 to their respective diols was futile, reaction with 5% KOH in MeOH of 14 and 15 took place to give solely (±)-10-hydroxy-13α-methoxy-2,3,11-trimethoxytetrahydroprotoberberine (16) [mp 146-148°; IR: 3530 cm^{-1}; NMR δ: 4.64 (1H, d, J=9Hz)] in 28% and 27% yield, respectively. However, the reason why the reaction lacked stereoselectivity as observed in the case of the rearrangement of 13 remained unexplained in spite of the common belief that these reactions proceeded through a p-quinone methide[12].

Thus, 5- and 13-oxygenated tetrahydroprotoberberines were synthesized stereoselectively (partly stereospecifically) starting from 2- and 10-phenolic congeners according to an entirely different method from hitherto known ones. In particular, synthesis of the 13-acetoxytetrahydroprotoberberines in the manner described above could be referred as biomimetic[18]. One step synthesis of 5- or 13-acetoxytetrahydroprotoberberine on $Pb(OAc)_4$ oxidation of 3- or 11-phenolic congener is currently investigated.

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10. Compound (3) was prepared from 3,4-dihydroisoquinoline hydrochloride (17)[11] with $NaBH_4$ reduction, cyclization (98% HCOOH/37% HCHO) and debenzylation (H_2/Pd-C, MeOH, $H^{\oplus}$). All new compounds gave satisfactory analytical data.

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13. NMR spectra were taken with a Japan Electron Optics Labs. Model JNR-4H-100 spectrometer in $CDCl_3$ solution by using $(CH_3)_4Si$ as an internal standard, unless otherwise noted. IR spectra were run on a Hitachi 225 spectrometer in $CHCl_3$.

14. NMR and IR spectroscopic data of 8 and 9 were consistent with those given in the literature[3a].

15. Preparative TLC was run on silica gel HF_{254} (Merck). Column chromatography was performed on silica gel (Kanto Chemical), eluant: $CHCl_3$.

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17. Configuration of the 13-acetoxyl group was determined by values of the coupling constant of the 13-hydrogen and these were well accordant with those of other models[2b,6b,8b].

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