Studies on Tetrahydroisoquinolines. XVI.¹⁾ Preparation of 2-Hydroxyaporphines *via* *o*-Quinol Acetates²⁾

OSAMU HOSHINO, MINORU OHTANI, and BUNSUKE UMEZAWA

Faculty of Pharmaceutical Sciences, Science University of Tokyo³⁾

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2-Hydroxylated aporphines, ($\pm$)-predicentrine (**4a**), ($\pm$)-isodomeesticine (**4b**), ($\pm$)-boldine (**4c**) and ($\pm$)-2,10-dihydroxy-1,9-dimethoxyaporphine (**4d**), were prepared. The key step is acid-catalyzed cyclization of the appropriate *o*-quinol acetates (**2**).

Keywords—1-benzyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolines; Pb(OAc)₄ oxidation; CH₂Cl₂; Ac₂O-conc.H₂SO₄; KOH-MeOH; IR; NMR

Careful treatment of the lead tetraacetate oxidation product of ($\pm$)-1-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**1a**) was found to yield a 1:1 diastereoisomeric *o*-quinol acetate (**2a**), formation of which had not previously noted in our laboratory.⁴⁾ The structure was well supported by the spectral data (infrared spectrum (IR), nuclear magnetic resonance (NMR), and ultraviolet spectrum (UV)), and especially by the presence of an aliphatic methoxy [δ 3.27, 3.36 (1:1)] and two olefinic protons [δ 5.32, 5.56 (1:1), 5.91, 5.93 (1:1)] as well as a homoannular vinylogous conjugated enone system (calcd. λ : 324 nm; obs. λ : 321 nm).

The *o*-quinol acetate (**2a**) was considered as a potential precursor to a 2-hydroxylated aporphine, ($\pm$)-predicentrine, because the activated benzene ring might attack at the vinylogous conjugated enone (Michael type reaction) directly, leading to the alkaloid or at an allylic acetate (*Sn* 2' type reaction) owing to a favored 5-exo-Trig process⁵⁾ leading to a dienone, isomerization⁶⁾ of which would take place readily. The present report deals with a novel synthesis of some 2-hydroxylated aporphines by acid treatment of *o*-quinol acetates.

- 1a** : R₁=R₂=CH₃
1b : R₁+R₂=CH₂
1c : R₁=CH₃, R₂=C₇H₇
1d : R₁=C₇H₇, R₂=CH₃

Chart 1

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After preliminary experiments, it was found that the cyclization could be best achieved by the use of acetic anhydride–conc. sulfuric acid. Eventually, when **2a** was treated with the above mixture, an O-acetylporphine was produced in 31.8% yield. The presence of three one-proton singlets, one of which was appreciably deshielded appearing at δ 7.97 in the NMR spectrum, was a strong indication that the desired cyclization had occurred to yield ($\pm$)-O-acetylpredicentrine (**3a**). As expected, hydrolysis of **3a** with methanolic potassium hydroxide gave ($\pm$)-predicentrine (**4a**),⁷⁾ methylation of which with diazomethane led to ($\pm$)-glaucine (**5a**)⁸⁾ further supporting the structure **3a**.

Similarly, *o*-quinol acetate (**2b**) gave in 16.1% yield ($\pm$)-O-acetylisodomeesticine (**3b**), which was converted into ($\pm$)-isodomeesticine (**4b**).⁹⁾ ($\pm$)-Nantenine (**5b**)¹⁰⁾ was obtained by methylation of **4b**.

Furthermore, ($\pm$)-boldine (**4c**) and ($\pm$)-2,10-dihydroxy-1,9-dimethoxyaporphine (**4d**) were synthesized *via o*-quinol acetates.

The starting material (**1c** or **1d**) was prepared as follows. Refluxing of a mixture of β -(3-hydroxy-4-methoxyphenyl)ethylamine hydrochloride¹¹⁾ and sodium β -(3-benzyloxy-4-methoxyphenyl)-¹²⁾ or β -(4-benzyloxy-3-methoxyphenyl)-¹³⁾ glycidate in acetic acid and aqueous methanol, followed by N-methylation (a modified Eschweiler-Clark reaction) gave **1c** (mp 100–101°) or **1d** (mp 125–127°).

o-Quinol acetates (**2c** and **2d**) were obtained in a similar manner. Acetic anhydride–conc. sulfuric acid treatment of **2c** and **2d** gave ($\pm$)-O,O-diacetylboldine (**3c**) and ($\pm$)-2,10-dia-

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Chart 3

toxy-1,9-dimethoxyaporphine (**3d**) in 41.7 and 36.9% yields, respectively. A precedent¹⁴ for the cleavage of aryl benzyl ether by the acetyl cation has been well documented. Successive hydrolysis of **3c** and **3d** with methanolic potassium hydroxide led readily to ($\pm$)-boldine (**4c**)¹⁵ and **4b**.

Thus, 2-hydroxylated aporphines were successfully synthesized by a procedure having possible biogenetic implications.¹⁶

Experimental¹⁷

($\pm$)-1-(3-Benzoyloxy-4-methoxybenzyl)- and ($\pm$)-1-(4-Benzoyloxy-3-methoxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (**1c** and **1d**)— β -(3-Hydroxy-4-methoxyphenyl)ethylamine.HCl¹¹ (500 mg, 2.46 mmol) and sodium β -(3-benzoyloxy-4-methoxyphenyl) glycidate¹² (1.03 g, 3.20 mmol) were refluxed for 3 hr in a mixture of MeOH (30 ml), AcOH (0.2 ml) and H₂O (1 ml). After cooling, most of the MeOH was removed under reduced pressure and the residue was made alkaline with saturated NaHCO₃ solution and extracted with CHCl₃. Usual work-up of the CHCl₃ extract gave an amorphous mass, crystallization of which from MeOH gave ($\pm$)-1-(3-benzoyloxy-4-methoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (264 mg, 26.5%), mp 163–166°. Another crop (15 mg) of the tetrahydroisoquinoline, mp 171–174° (MeOH), was obtained by chromatographic purification of the mother liquor. The total yield amounted to 279 mg (28%) and an analytical sample gave mp 176–177° (MeOH). IR ν (cm⁻¹): 3530 (OH). NMR δ : 3.81, 3.88 (each 3H, s, 2 $\times$ OCH₃), 5.12 (2H, s, OCH₂Ph). Anal. Calcd. for C₂₅H₂₇NO₄: C, 74.05; H, 6.71; N, 3.46. Found: C, 74.07; H, 6.60; N, 3.55.

The tetrahydroisoquinoline (500 mg, 1.23 mmol) was dissolved in a warm mixture of MeOH (10 ml) and 37% HCHO (1 ml) and the whole was stirred at room temperature for 1 hr. NaBH₄ (442 mg, 11.7 mmol) was added portionwise under ice cooling and stirring was continued at room temperature for 1 hr. Usual work-up gave an amorphous mass (478.7 mg, 93%), crystallization of which from acetone–H₂O led to **1c** (336.1 mg, 65.3%), mp 98–99°. An analytical sample gave mp 100–101°. IR ν (cm⁻¹): 3530 (OH); NMR δ : 2.48 (3H, s, NCH₃), 3.56, 3.86 (each 3H, s, 2 $\times$ OCH₃), 5.06 (2H, s, OCH₂Ph), 5.93 (1H, s, 8-H). Anal. Calcd. for C₂₆H₂₉NO₄: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.75; H, 6.68; N, 3.21.

($\pm$)-1-(4-Benzoyloxy-3-methoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (15.5%), mp 157.5–159° (EtOH), was obtained similarly. IR ν (cm⁻¹): 3540 (OH). NMR δ : 3.80, 3.86 (each 3H, s, 2 $\times$ OCH₃), 5.15 (2H, s, OCH₂Ph). Anal. Calcd. for C₂₅H₂₇NO₄: C, 74.05; H, 6.71; N, 3.16. Found: C, 73.84; H, 6.53; N, 3.48. **1d** (92.2%), mp 125–127° (acetone–H₂O). IR ν (cm⁻¹): 3540 (OH). NMR δ : 2.53 (3H, s, NCH₃), 3.50, 3.80 (each 3H, s, 2 $\times$ OCH₃), 3.66 (1H, dd, $J=4, 8$ Hz, 1-H), 5.12 (2H, s, OCH₂Ph), 5.92 (1H, s, 8-H). Anal. Calcd. for C₂₆H₂₉NO₄: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.26; H, 6.77; N, 3.52.

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17) All melting points were measured on a Büchi melting point measuring apparatus and are uncorrected. IR spectra were taken on a Hitachi 215 infrared spectrometer in CHCl₃ solution, unless otherwise noted. NMR spectra were run on a JEOL JNM-FX 100 spectrometer in CDCl₃ solution using (CH₃)₄Si as an internal standard. The following abbreviations are used: s: singlet; bs: broad singlet; d: doublet; dd: doublet of doublets. UV spectrum was measured on a Hitachi 200-10 spectrometer in CH₂Cl₂ solution. Preparative thin-layer chromatography (TLC) was performed on Silica gel HF₂₅₄ (Merck) Column chromatography was carried out on silica gel (Kanto Kagaku Co., Ltd.).

TABLE I. Spectral Data for *o*-Quinol Acetates (*o*-QA) (2)

<i>o</i> -QA	IR ν (cm ⁻¹)	NMR δ (ppm)	UV λ (nm)
2a	1735 (OCOCH ₃) 1680 (dienone)	2.03, 2.04 (3H, each s, OCOCH ₃ ^a), 2.47, 2.55 (3H, each s, NCH ₃ ^a), 3.27, 3.36 (3H, each s, 7-OCH ₃ ^a), 3.84, 3.87 (each 3H, s, 2 × OCH ₃), 5.32, 5.56 (1H, each s, 8-H ^a), 5.91, 5.93 (1H, each s, 5-H ^a)	232 285 321
2b	1735 (OCOCH ₃) 1675 (dienone)	2.06, 2.09 (3H, each s, OCOCH ₃ ^a), 2.46, 2.51 (3H, each s, NCH ₃ ^a), 3.14, 3.37 (3H, each s, 7-OCH ₃ ^a), 5.31, 5.59 (1H, each s, 8-H ^a), 5.92, (2H, s, OCH ₂ O), 5.97, 5.99 (1H, each s, 5-H ^a)	—
2c	1735 (OCOCH ₃) 1680 (dienone)	2.03, 2.06 (3H, each s, OCOCH ₃ ^a), 2.41, 2.48 (3H, each s, NCH ₃ ^a), 3.24, 3.36 (3H, each s, 7-OCH ₃ ^a), 3.86 (3H, s, 4-OCH ₃), 5.13 (2H, s, OCH ₂ Ph), 5.28, 5.50 (1H, each s, 8-H ^a), 5.93 (1H, bs, 5-H)	—
2d	1740 (OCOCH ₃) 1680 (dienone)	1.97, 2.05 (3H, each s, OCOCH ₃ ^a), 2.48, 2.55 (3H, each s, NCH ₃ ^a), 3.21, 3.36 (3H, each s, 7-OCH ₃ ^a), 3.86, 3.89 (3H, each s, 3-OCH ₃ ^a), 5.13 (2H, s, OCH ₂ Ph), 5.30, 5.54 (1H, each s, 8-H ^a), 5.94 (1H, bs, 5-H)	—

^a) A 1:1 peak ratio was observed.

General Procedure for the Formation of *o*-Quinol Acetates (2)—Pb(OAc)₄ (1.1 eq.) was added to a stirred solution of **1** (200 mg) in CH₂Cl₂ (40–60 ml) at 5° in a single portion, and stirring was continued for 1 min. The reaction mixture was poured into saturated NaHCO₃ solution and extracted with CH₂Cl₂. The CH₂Cl₂ extract was rinsed with brine and dried over MgSO₄. The solvent was first removed on a water bath maintained at 30° under reduced pressure to give a volume of ca. 10 ml, then the remainder was evaporated off as quickly as possible at room temperature using a water aspirator and finally a vacuum pump, leaving an amorphous mass of diastereoisomeric *o*-quinol acetates (**2**) in quantitative yield. Their spectral data are shown in Table I.

General Procedure for Synthesis of (±)-O-Acetylporphines (3)—Conc. H₂SO₄ (0.2 ml) was added drop by drop to an ice-cooled, stirred solution in Ac₂O (2 ml) of **2** obtained from **1** (200 mg) as described above and the whole was stirred at room temperature for 1 hr. Chipped ice was added and stirring was continued at room temperature for 0.5–1 hr. The mixture was made basic with NaHCO₃ (powder) and usual work-up gave an oil, which was purified chromatographically.

(±)-O-Acetylpredicentrine (**3a**): Column chromatography of an oil (243 mg) gave oily **3a** (71 mg, 31.8%) (eluted with CHCl₃–MeOH=100:1). IR ν (cm⁻¹): 1760 (OCOCH₃). NMR δ : 2.37 (3H, s, OCOCH₃), 2.57 (3H, s, NCH₃), 3.58, 3.90–3.94 (each 3H, s, 3 × OCH₃), 6.76, 6.79 (each 1H, 3-, 8-H), 7.97 (1H, s, 11-H). Methiodide, mp 230–231° (dec.) (EtOH). Anal. Calcd. for C₂₃H₂₈NO₅I·1/4H₂O: C, 52.09; H, 5.41; N, 2.64. Found: C, 52.04; H, 5.35; N, 2.61.

(±)-O-Acetylisodomesticine (**3b**): Purification of an oil (239.5 mg) on preparative TLC (developing solvent; benzene–MeOH=8:1) gave oily **3b** (36 mg, 16.1%). IR ν (cm⁻¹): 1750 (OCOCH₃). NMR δ : 2.36 (3H, s, OCOCH₃), 2.57 (3H, s, NCH₃), 3.58 (3H, s, OCH₃), 5.95, 5.98 (each 1H, d, *J*=1.5 Hz, OCH₂O), 6.76 (2H, s, 3-, 8-H), 7.87 (1H, s, 11-H). Methiodide, mp 239–242° (dec.) (EtOH). Anal. Calcd. for C₂₂H₂₄NO₅I·1/4H₂O: C, 51.42; H, 4.80; N, 2.73. Found: C, 51.47; H, 4.76; N, 2.77.

(±)-O,O-Diacetylboldine (**3c**): Column chromatography of an oil (258.3 mg) gave benzyl acetate (66.3 mg, 90.5%) (eluted with CHCl₃) and oily **3c** (81.8 mg, 41.7%) (eluted with CHCl₃–MeOH=100:1) [IR ν (cm⁻¹): 1760 (OCOCH₃). NMR δ : 2.35, 2.37 (each 3H, s, 2 × OCOCH₃), 2.56 (3H, s, NCH₃), 3.60, 3.85 (each 3H, s, 2 × OCH₃), 6.82, 6.97 (each 1H, s, 3-, 8-H), 8.07 (1H, s, 11-H). Methiodide, mp 243–246° (dec.) (EtOH). Anal. Calcd. for C₂₄H₂₈NO₆I: C, 52.09; H, 5.10; N, 2.53. Found: C, 52.33; H, 5.11; N, 2.50].

(±)-2,10-Diacetoxy-1,9-dimethoxyaporphine (**3d**): Column chromatography of an oil (250.7 mg) gave benzyl acetate (69.5 mg, 97.1%) (eluted with CHCl₃) and an amorphous mass (**3d**) (72.4 mg, 36.9%) (eluted with CHCl₃–MeOH=100:1) [IR ν (cm⁻¹): 1760 (OCOCH₃). NMR δ : 2.32, 2.36 (each 3H, s, 2 × OCOCH₃), 2.56 (3H, s, NCH₃), 3.59, 3.89 (each 3H, s, 2 × OCH₃), 6.77, 6.88 (each 1H, s, 3-, 8-H), 8.07 (1H, s, 11-H). Methiodide, mp 222–223° (dec.) (MeOH). Anal. Calcd. for C₂₄H₂₈NO₆I·1/4H₂O: C, 51.67; H, 5.15; N, 2.51. Found: C, 51.61; H, 5.19; N, 2.31].

(±)-Predicentrine (**4a**), (±)-Isodomesticine (**4b**), (±)-Boldine and (±)-2,10-Dihydroxy-1,9-dimethoxy-

aporphine (4d)—A mixture of **3** and 1.7% KOH–MeOH was stirred under ice cooling for 0.5 hr. Acidification with AcOH, followed by basification with saturated Na_2CO_3 solution and usual work-up gave ($\pm$)-2-hydroxyaporphines (**4**).

4a: an oil. IR ν (cm^{-1}): 3520 (OH). NMR δ : 2.58 (3H, s, NCH_3), 3.60, 3.91, 3.93 (each 3H, s, $3 \times \text{OCH}_3$), 6.64, 6.78 (each 1H, s, 3-, 8-H), 7.91 (3H, s, 11-H). **4a**·HCl, mp 214–216° (dec.) (MeOH–ether) [lit.⁷⁾ 215–217° (dec.)].

4b: mp 180–182° (ether–*n*-hexane) (lit.⁹⁾ 180–183°). IR ν (cm^{-1}): 3500 (OH). NMR δ : 2.53 (3H, s, NCH_3), 3.59 (3H, s, OCH_3), 5.95, 5.98 (each 1H, d, $J=1.5$ Hz, OCH_2O), 6.64, 6.76 (each 1H, s, 3-, 8-H), 7.82 (1H, s, 11-H). **4b**·HCl, mp 241–244° (dec.) (MeOH–ether) (lit.⁹⁾ 245–250°).

4c: mp 158–160° (benzene) (lit.¹⁵⁾ 159–162°). IR¹⁸⁾ ν (cm^{-1}): 3480 (br) (OH). NMR δ : 2.55 (3H, s, NCH_3), 3.60, 3.92 (each 3H, $2 \times \text{OCH}_3$), 6.64, 6.81 (each 1H, s, 3-, 8-H), 7.90 (1H, s, 11-H).

4d: mp 179–180.5° (benzene). IR¹⁸⁾ ν (cm^{-1}): 3450 (OH). NMR δ : 2.56 (3H, s, NCH_3), 3.60, 3.94 (each 3H, s, $2 \times \text{OCH}_3$), 6.65, 6.78 (each 1H, s, 3-, 8-H), 7.92 (1H, s, 11-H). *Anal.* Calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_4 \cdot 1/3\text{C}_6\text{H}_6$: C, 71.37; H, 6.56; N, 3.95. Found: C, 71.10, 71.21; H, 6.48, 6.46; N, 3.92, 4.19.

($\pm$)-**Glaucine (5a)** and ($\pm$)-**Nantenine (5b)**—Methylation of **4a** and **4b** was effected with excess CH_3N_2 -ether in MeOH to give **5a** (oil) [NMR δ : 2.55 (3H, s, NCH_3), 3.66, 3.89, 3.91, 3.93 (each 3H, s, $4 \times \text{OCH}_3$), 6.58, 6.78 (each 1H, s, 3-, 8-H), 8.08 (1H, s, 11-H). Picrate, mp 190–193° (dec.) (EtOH) (lit. 193–194°;^{8a)} 191–193° (dec.)^{8b)}] and **5b** [mp 138–139° (*n*-hexane) (lit.¹⁰⁾ 140–142°). NMR δ : 2.53 (3H, s, NCH_3), 3.66, 3.87 (each 3H, s, $2 \times \text{OCH}_3$), 5.96, 5.97 (each 1H, d, $J=1.5$ Hz, OCH_2O), 6.58, 6.74 (each 1H, s, 3-, 8-H), 7.91 (1H, s, 11-H)], respectively.

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18) The spectra were taken in KBr discs.