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Studies on Tetrahydroisoquinolines. XVI.[1] Preparation of 2-Hydroxyaporphines *via* *o*-Quinol Acetates[2]

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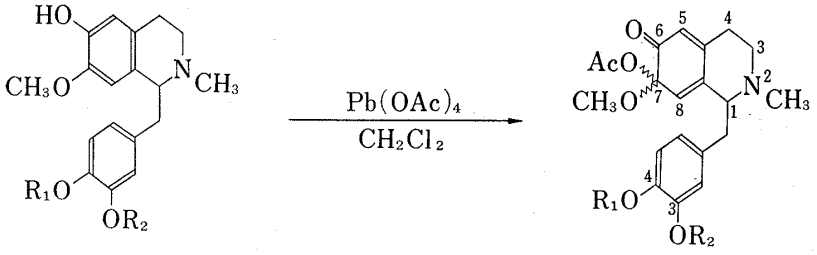
2-Hydroxylated aporphines, (±)-predicentrine (**4a**), (±)-isodomesticine (**4b**), (±)-boldine (**4c**) and (±)-2,10-dihydroxy-1,9-dimethoxyaporphine (**4d**), were prepared. The key step is acid-catalyzed cyclization of the appropriate *o*-quinol acetates (**2**).

Keywords——1-benzyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolines; $Pb(OAc)_4$ oxidation; CH_2Cl_2; Ac_2O–conc.H_2SO_4; KOH-MeOH; IR; NMR

Careful treatment of the lead tetraacetate oxidation product of (±)-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, (±)-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 process[5] leading to a dienone, isomerization[6] 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.



2

1a : $R_1=R_2=CH_3$
1b : $R_1+R_2=CH_2$
1c : $R_1=CH_3$, $R_2=C_7H_7$
1d : $R_1=C_7H_7$, $R_2=CH_3$

Chart 1

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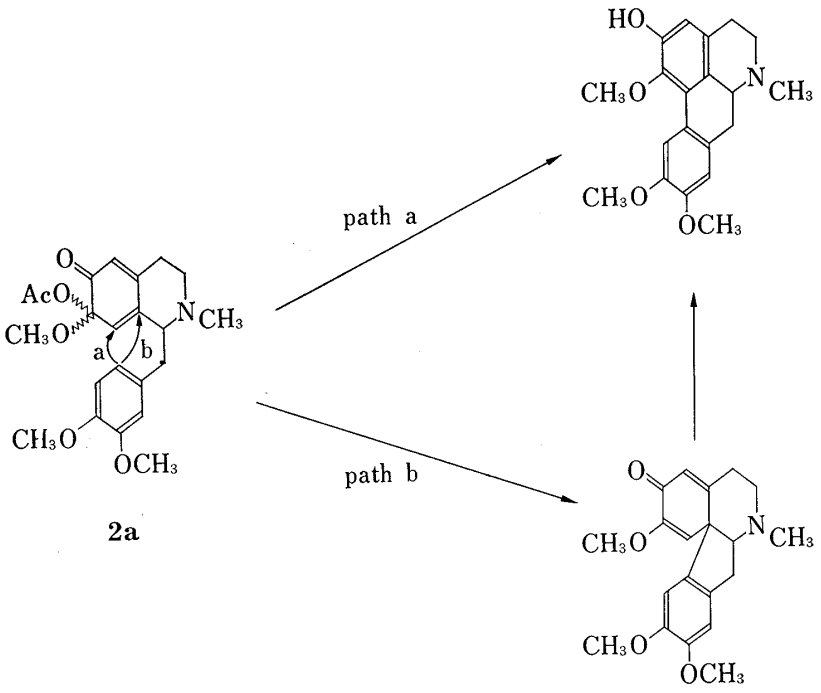

Chart 2

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-acetylaporphine was produced in 31.8% yield. The presence of three one-proton singlets, one of which was appreciablly deshielded appearing at δ 7.97 in the NMR spectrum, was a strong indication that the desired cyclization had occurred to yield (±)-O-acetylpredicentrine (**3a**). As expected, hydrolysis of **3a** with methanolic potassium hydroxide gave (±)-predicentrine (**4a**),[7] methylation of which with diazomethane led to (±)-glaucine (**5a**)[8] further supporting the structure **3a**.

Similarly, *o*-quinol acetate (**2b**) gave in 16.1% yield (±)-O-acetylisodomesticine (**3b**), which was converted into (±)-isodomesticine (**4b**).[9] (±)-Nantenine (**5b**)[10] was obtained by methylation of **4b**.

Furthermore, (±)-boldine (**4c**) and (±)-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 hydrochloride[11] 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 (±)-O,O-diacetylboldine (**3c**) and (±)-2,10-diace-

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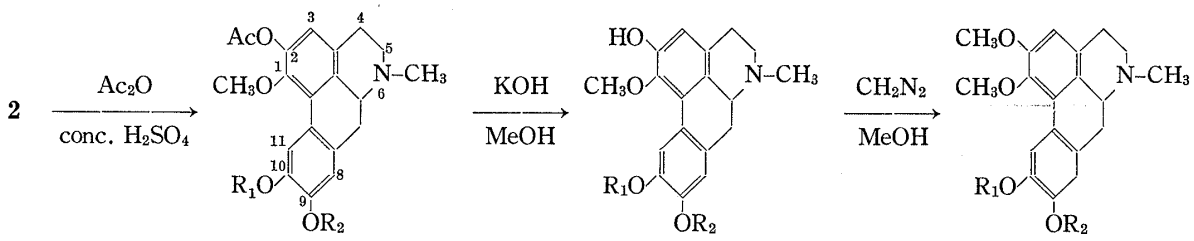

3a : $R_1=R_2=CH_3$
3b : $R_1+R_2=CH_2$
3c : $R_1=CH_3$, $R_2=Ac$
3d : $R_1=Ac$, $R_2=CH_3$

4a : $R_1=R_2=CH_3$
4b : $R_1+R_2=CH_2$
4c : $R_1=CH_3$, $R_2=H$
4d : $R_1=H$, $R_2=CH_3$

5a : $R_1=R_2=CH_3$
5b : $R_1+R_2=CH_2$

Chart 3

toxy-1,9-dimethoxyaporphine (**3d**) in 41.7 and 36.9% yields, respectively. A precedent[14] 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 (±)-boldine (**4c**)[15] and **4b**.

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

Experimental[17]

(±)-1-(3-Benzyloxy-4-methoxybenzyl)- and (±)-1-(4-Benzyloxy-3-methoxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (1c and 1d)——β-(3-Hydroxy-4-methoxyphenyl)ethylamine.HCl[11] (500 mg, 2.46 mmol) and sodium β-(3-benzyloxy-4-methoxyphenyl) glycidate[12] (1.03 g, 3.20 mmol) were refluxed for 3 hr in a mixture of MeOH (30 ml), AcOH (0.2 ml) and H_2O (1 ml). After cooling, most of the MeOH was removed under reduced pressure and the residue was made alkaline with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave an amorphous mass, crystallization of which from MeOH gave (±)-1-(3-benzyloxy-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, $2\times OCH_3$), 5.12 (2H, s, OCH_2Ph). *Anal.* Calcd. for $C_{25}H_{27}NO_4$: 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. $NaBH_4$ (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–H_2O 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, NCH_3), 3.56, 3.86 (each 3H, s, $2\times OCH_3$), 5.06 (2H, s, OCH_2Ph), 5.93 (1H, s, 8-H). *Anal.* Calcd. for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.75; H, 6.68; N, 3.21.

(±)-1-(4-Benzyloxy-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, $2\times OCH_3$), 5.15 (2H, s, OCH_2Ph). *Anal.* Calcd. for $C_{25}H_{27}NO_4$: 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–H_2O). IR ν (cm^{-1}): 3540 (OH). NMR δ: 2.53 (3H, s, NCH_3), 3.50, 3.80 (each 3H, s, $2\times OCH_3$), 3.66 (1H, dd, $J=4$, 8 Hz, 1-H), 5.12 (2H, s, OCH_2Ph), 5.92 (1H, s, 8-H). *Anal.* Calcd. for $C_{26}H_{29}NO_4$: 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 $CHCl_3$ solution, unless otherwise noted. NMR spectra were run on a JEOL JNM-FX 100 spectrometer in $CDCl_3$ solution using $(CH_3)_4Si$ 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 CH_2Cl_2 solution. Preparative thin-layer chromatography (TLC) was performed on Silica gel HF_{254} (Merck). Column chromatography was carried out on silica gel (Kanto Kagaku Co., Ltd.).

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

o-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_2O), 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_2Ph), 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_2Ph), 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 CH_2Cl_2 (40—60 ml) at 5° in a single portion, and stirring was continued for 1 min. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The CH_2Cl_2 extract was rinsed with brine and dried over $MgSO_4$. 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-Acetylaporphines (3)——Conc. H_2SO_4 (0.2 ml) was added drop by drop to an ice-cooled, stirred solution in Ac_2O (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 $NaHCO_3$ (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 $CHCl_3$–MeOH=100:1). IR ν (cm^{-1}): 1760 ($OCOCH_3$). NMR δ: 2.37 (3H, s, $OCOCH_3$), 2.57 (3H, s, NCH_3), 3.58, 3.90 3.94 (each 3H, s, 3×OCH_3), 6.76, 6.79 (each 1H, 3-, 8-H), 7.97 (1H, s, 11-H). Methiodide, mp 230—231° (dec.) (EtOH). *Anal.* Calcd. for $C_{23}H_{28}NO_5I \cdot 1/4H_2O$: 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 ($OCOCH_3$). NMR δ: 2.36 (3H, s, $OCOCH_3$), 2.57 (3H, s, NCH_3), 3.58 (3H, s, OCH_3), 5.95, 5.98 (each 1H, d, J=1.5 Hz, OCH_2O), 6.76 (2H, s, 3-, 8-H), 7.87 (1H, s, 11-H). Methiodide, mp 239—242° (dec.) (EtOH). *Anal.* Calcd. for $C_{22}H_{24}NO_5I \cdot 1/4H_2O$: 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 $CHCl_3$) and oily **3c** (81.8 mg, 41.7%) (eluted with $CHCl_3$–MeOH=100:1) [IR ν (cm^{-1}): 1760 ($OCOCH_3$). NMR δ: 2.35, 2.37 (each 3H, s, 2×$OCOCH_3$), 2.56 (3H, s, NCH_3), 3.60, 3.85 (each 3H, s, 2×OCH_3), 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 $C_{24}H_{28}NO_6I$: 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 $CHCl_3$) and an amorphous mass (**3d**) (72.4 mg, 36.9%) (eluted with $CHCl_3$–MeOH=100:1) [IR ν (cm^{-1}): 1760 ($OCOCH_3$). NMR δ: 2.32, 2.36 (each 3H, s, 2×$OCOCH_3$), 2.56 (3H, s, NCH_3), 3.59, 3.89 (each 3H, s, 2×OCH_3), 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 $C_{24}H_{28}NO_6I \cdot 1/4H_2O$: 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 (±)-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, $3\times OCH_3$), 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°). IR[18] ν (cm^{-1}): 3480 (br) (OH). NMR δ: 2.55 (3H, s, NCH_3), 3.60, 3.92 (each 3H, $2\times OCH_3$), 6.64, 6.81 (each 1H, s, 3-, 8-H), 7.90 (1H, s, 11-H).

4d: mp 179—180.5° (benzene). IR[18] ν (cm^{-1}): 3450 (OH). NMR δ: 2.56 (3H s, NCH_3), 3.60, 3.94 (each 3H, s, $2\times OCH_3$), 6.65, 6.78 (each 1H, s, 3-, 8-H), 7.92 (1H, s, 11-H). *Anal.* Calcd. for $C_{19}H_{21}NO_4\cdot 1/3C_6H_6$: 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.

(±)-Glaucine (5a) and (±)-Nantenine (5b)——Methylation of **4a** and **4b** was effected with excess CH_2N_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, $4\times OCH_3$), 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, $2\times OCH_3$), 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.