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Studies on Tetrahydroisoquinolines. XXVII.[1] A Synthesis of 3-Hydroxyaporphines and 3-Hydroxyhomoaporphines[2]

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Acid treatment of *o*-quinol acetates (**2a** and **2b**) derived from 5-hydroxy-1-benzyltetrahydroisoquinolines (**3a** and **3b**) gave the corresponding 3-hydroxyaporphines (**4a** and **4b**) in high yield. Similarly, the 3-hydroxyhomoaporphines (**4c**, **4d**, and **4e**) were exclusively synthesized from the corresponding 1-phenethyl *o*-quinol acetates (**2c**, **2d**, and **2e**). On the other hand, no *C*-noraporphine was formed from the 1-aryl *o*-quinol acetate (**2f**); instead, the *p*-quinone (**11**) was generated.

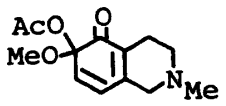
Keywords——*o*-quinol acetate; lead tetraacetate oxidation; 3-hydroxyaporphine; 3-hydroxyhomoaporphine; cyclization

As an extension of our program directed towards the elucidation of the reactivity of *o*- and *p*-quinol acetates derived from guiacol-type 1,2,3,4-tetrahydroisoquinolines, we have recently carried out the lead tetraacetate (LTA) oxidation of 1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinolin-5-ol to obtain the expected *o*-quinol acetate (**1**) and have confirmed that the 8-position of **1** can be attacked by acetic acid intermolecularly.[3] The present report deals with the successful cyclization of the *o*-quinol acetates (**2**) to 2,3-dioxygenated aporphines and homoaporphines as an application of the similar cyclization of *p*-quinol acetates.[4]

The 1-benzyl-6-methoxytetrahydroisoquinolin-5-ols (**3a** and **3b**) were prepared by the usual procedure[5] starting from 2-benzyloxy-3-methoxy-β-phenethylamine and the corresponding phenylacetic acids [i) Bischler–Napieralski reaction, ii) $NaBH_4$ reduction, iii) *N*-methylation, and iv) debenzylation]. Similarly, the 1-phenethyl analogs (**3c**, **3d**, and **3e**) were derived from the same phenethylamine as above and the corresponding dihydrocinnamic acids.

Oxidation of the phenolic amine (**3a**) with LTA in CH_2Cl_2 gave the *o*-quinol acetate (**2a**) as a mixture of diastereomers[6]; the structure was consistent with the spectral data [infrared (IR) cm^{-1}: 1730 (OAc), 1670 (dienone); proton nuclear magnetic resonance (^{1}H-NMR) δ: 2.04 (OAc), 3.32 and 3.35 (3H, a pair of s, aliph. OMe)[6]]. The *o*-quinol acetate (**2a**) was treated with CF_3CO_2H in CH_2Cl_2 to give the 3-hydroxyaporphine (**4a**), mp 213—214 °C (lit.[7] 214—215 °C), in 73% yield. The ^{1}H-NMR spectrum of **4a** showed three aromatic protons (δ 6.82, 7.07, 7.16) each as a singlet, demonstrating the formation of the aporphine ring.

Similarly, oxidation of the 1-piperonyltetrahydroisoquinolin-5-ol (**3b**) and subsequent acid treatment afforded 3-hydroxy-2-methoxy-9,10-methylenedioxyaporphine (**4b**), mp 206 °C, in 87% yield. Moreover, the 1-homoveratryltetrahydroisoquinolin-5-ol (**3c**) was oxidized to give the *o*-quinol acetate (**2c**), which was treated with CF_3CO_2H, affording 3-hydroxy-2,10,11-trimethoxyhomoaporphine (**4c**), mp 199—200 °C, in 91% yield. 3-Hydroxy-2-methoxy-10,11-methylenedioxy- (**4d**) and 3-hydroxy-2,10,11,12-tetramethoxy- (**4e**) homoaporphines were similarly synthesized from the corresponding 1-phenethyltetrahydro-



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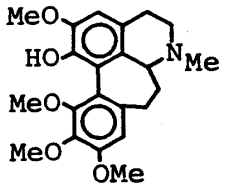

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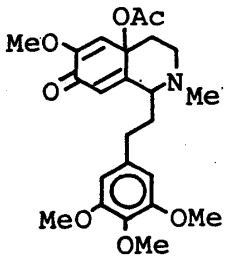

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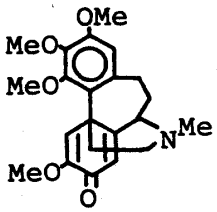

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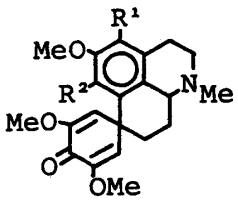
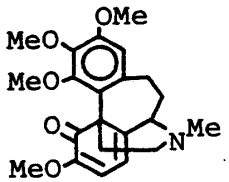


8 : R^1=H, R^2=OH

10 : R^1=OH, R^2=H



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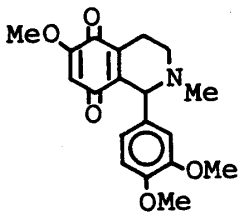

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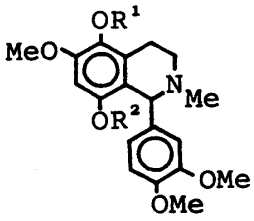
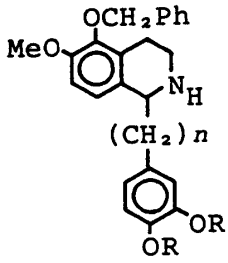


12 : R^1=R^2=Ac

13 : R^1=H, R^2=$COCF_3$

14 : R^1=R^2=H

15 : R^1=H, R^2=Ac



18a : R=Me, n=1

18b : R+R=CH_2, n=1

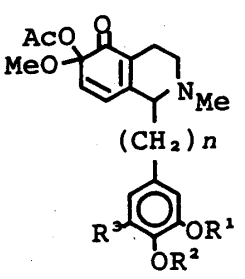
18f : R=Me, n=0

Fig. 1

isoquinolin-5-ols (**3d** and **3e**), in 87% and 90% yields, respectively.

In a previous total synthesis of (±)-kreysigine (**5**) *via* the appropriate *p*-quinol acetate (**6**), we have observed that (±)-*O*-methylandrocymbine (**7**) and the homoproaporphine (**8**) are also formed as by-products.[8] Therefore, formation of such by-products was also expected in the present case. However, the *o*-quinol acetates (**2c—e**) gave solely the homoaporphines (**4c—e**). Presumably, steric and/or electrostatic repulsion between the carbonyl group and the activated benzene ring prevented the cyclization of the *o*-quinol acetate (**2e**) to the homomorphinandienone (**9**).

In order to construct the *C*-noraporphine skeleton (**4f**), we applied the above methodology to 1-aryltetrahydroisoquinolin-5-ol (**3f**). Namely, LTA oxidation of **3f**, which was prepared by the usual procedure,[5] gave the *o*-quinol acetate (**2f**). Acid treatment of **2f** furnished the *p*-quinone (**11**) as an isolable product, unexpectedly. The structure of **11** was determined from the spectroscopic data [IR cm^{-1}: 1645, 1600 (quinone); ^{1}H-NMR δ: 5.65 (olefinic H)] and the reduction below. Reduction of the *p*-quinone (**11**) with zinc in Ac_2O gave the diacetate (**12**), the ^{1}H-NMR spectrum of which showed a signal due to one of the acetoxyl groups at δ 1.88. The upfield-shifted acetoxyl group could readily be assigned to C-8. The absence of *C*-noraporphine (**4f**) formation was perhaps ascribable to its highly strained structure, and the *p*-quinone (**11**) was generated through the intermediacy of the tri-



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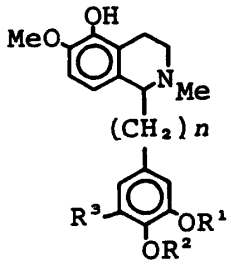

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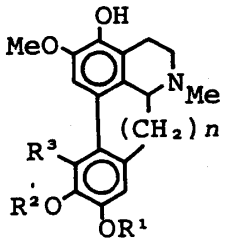

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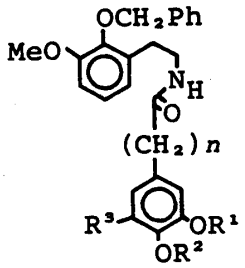

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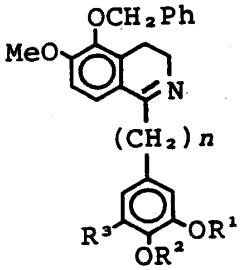

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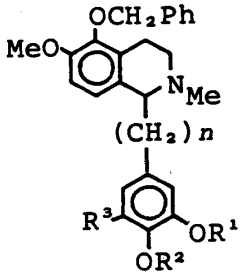

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	n	R^1	R^2	R^3
a:	1	Me	Me	H
b:	1	$-CH_2-$		H
c:	2	Me	Me	H
d:	2	$-CH_2-$		H
e:	2	Me	Me	OMe
f:	0	Me	Me	H

Fig. 2

fluoroacetate (**13**),[9] which was successively hydrolyzed to afford 5,8-dihydroxy-6-methoxy-2-methyl-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**14**). The hydroquinone (**14**) was so sensitive to air oxidation that the *p*-quinone was gradually formed in the course of work-up.[10] Actually, the crude product obtained by the above CF_3CO_2H treatment of **2f** was also a mixture of two compounds (**11** and **14**). To establish the structures, the mixture wa acetylated to give rise to a stable but intractable mixture, which consisted to two compounds, **11** and **12**.[11] The precursor of the diacetate (**12**) is almost certainly the unstable hydroquinone (**14**).

Thus, the *o*-quinol acetates (**2**) proved to be key compounds for the preparation of 3-hydroxyaporphines and 3-hydroxyhomoaporphines.

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken with a JEOL JNM-FX-100 (100 MHz) or Hitachi R-24B instrument in $CDCl_3$ solution with Me_4Si as an internal standard, and IR spectra were run on a Hitachi model 260 spectrometer in $CHCl_3$ solution, unless otherwise noted. High-resolution mass spectral data were measured with a Hitachi RMU-6E mass spectrometer. Preparative thin-layer chromatography (TLC) was performed on precoated Silica gel 60 F_{254} plates (Merck), 2.0 mm thick.

General Procedure for the Preparation of 1,2,3,4-Tetrahydroisoquinolin-5-ols (3a, 3b, and 3f)——A mixture of 2-benzyloxy-3-methoxyphenethylamine and homoveratric acid or homopiperonylic acid was heated at 160 °C (bath temperature) for 5 h to give an amide (**16a** or **16b**). Schotten–Baumann reaction of the same amine and 3,4-dimethoxybenzoyl chloride afforded an amide (**16f**). Bischler–Napieralski reaction of **16a**, **16b**, and **16f** yielded the hydrochlorides of the 3,4-dihydroisoquinolines (**17a**, **17b**, and **17f**), respectively. Sodium borohydride reduction of **17a**·HCl, **17b**·HCl, or **17f** in MeOH gave the corresponding tetrahydroisoquinoline (**18a**, **18b**, or **18f**). Reaction of the amine (**18a**, **18b**, or **18f**) with 37% formalin in MeOH and subsequent reduction with sodium borohydride

afforded the corresponding *N*-methylamine (**19a**, **19b**, or **19f**). Hydrogenolysis of the bases with palladium on carbon gave **3a**, **3b**, and **3f**, respectively. Yields and physical data are as follows. **16a**: 65%, mp 73—74 °C (*n*-hexane); *Anal.* Calcd for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.57; H, 6.66; N, 3.20. IR cm^{-1}: 1645 (CONH–). ^{1}H-NMR δ: 3.35 (2H, s, $COCH_2Ar$), 3.80, 3.85, 3.87 (each 3H, s, OMe), 4.92 (2H, s, OCH_2Ph). **16b**: 49%, mp 83.5—84 °C (*n*-hexane); *Anal.* Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.51; H, 6.02; N, 3.45. ^{1}H-NMR δ: 3.20 (2H, s, $COCH_2Ar$), 3.79 (3H, s, OMe), 4.85 (2H, s, OCH_2Ph), 5.76 (2H, s, OCH_2O). **16f**: 81%, mp 113—114 °C (PhH–$CHCl_3$); *Anal.* Calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.40; H, 6.23; N, 3.29. **18a**: 83% (from **16a**), an oil. ^{1}H-NMR δ: 3.84 (3H, s, OMe), 3.86 (6H, s, 2 × OMe), 4.96 (2H, s, OCH_2Ph). **18b**: 96% (from **16b**), an oil. ^{1}H-NMR δ: 3.78 (3H, s, OMe), 4.88 (2H, s, OCH_2Ph), 5.80 (2H, s, OCH_2O). Oxalate: mp 200—201 °C (MeOH); *Anal.* Calcd for $C_{27}H_{27}NO_8$: C, 65.71; H, 5.52; N, 2.84. Found: C, 65.67; H, 5.52; N, 2.76. **19a**: 91%, an oil. ^{1}H-NMR δ: 2.47 (3H, s, NMe), 3.76, 3.83, 3.89 (each 3H, s, OMe), 4.96 (2H, s, OCH_2Ph). **19b**: 97%, an oil. ^{1}H-NMR δ: 2.35 (3H, s, NMe), 3.70 (3H, s, OMe), 4.87 (2H, s, OCH_2Ph), 5.69 (2H, s, OCH_2O). Methiodide: mp 120 °C (H_2O); *Anal.* Calcd for $C_{27}H_{30}INO_4 \cdot H_2O$: C, 56.36; H, 5.61; N, 2.09. Found: C, 56.48; H, 5.49; N, 2.41. **3a**: 97%, mp 121—122 °C (acetone–MeOH); *Anal.* Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.79; H, 7.34; N, 4.12. IR cm^{-1}: 3525 (OH). ^{1}H-NMR δ: 2.50 (3H, s, NMe), 3.77, 3.83, 3.85 (each 3H, s, OMe). **3b**: 92%, an oil. ^{1}H-NMR δ: 2.40 (3H, s, NMe), 3.73 (3H, s, OMe), 5.74 (2H, s, OCH_2O). Methiodide: mp 224—225 °C (iso-PrOH); *Anal.* Calcd for $C_{20}H_{24}INO_4$: C, 51.18; H, 5.15; N, 2.98. Found: C, 50.99; H, 5.34; N, 2.79. **3f**: 85% (from **16f**), mp 164—165 °C (acetone–ether); *Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 68.92; H, 7.04; N, 4.23. ^{1}H-NMR (CD_3OD) δ: 2.20 (3H, s, NMe), 3.73, 3.78, 3.84 (each 3H, s, OMe), 4.16 (1H, s, 1-H).

General Procedure for the Preparation of 1-Phenethyl-1,2,3,4-tetrahydroisoquinolin-5-ols (3c, 3d, and 3e)——A mixture of 2-benzyloxy-3-methoxyphenethylamine and the appropriate dihydrocinnamic acid was heated at 160 °C (bath temperature) for 5 h to give the amide (**16c**, **16d**, or **16e**). Bischler–Napieralski reaction of **16c**, **16d**, or **16e** in CH_2Cl_2 afforded the 3,4-dihydroisoquinoline (**17c**, **17d**, or **17e**), which was reacted with CH_3I and reduced with sodium borohydride, giving the *N*-methylamine (**19c**, **19d**, or **19e**). Hydrolysis of the base by refluxing with 20% HCl in benzene gave **3c**, **3d**, or **3e**, respectively. Yields and physical data are as follows. **16c**: 84%, mp 82—83 °C (AcOEt–*n*-hexane); *Anal.* Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.12. Found: C, 72.29; H, 7.07; N, 3.12. IR cm^{-1}: 1660 (CONH–). ^{1}H-NMR δ: 3.86, 3.88, 3.92 (each 3H, s, OMe), 5.04 (2H, s, OCH_2Ph). **16d**: 85%, mp 90—91 °C (EtOH–iso-PrOH); *Anal.* Calcd for $C_{26}H_{27}NO_5$: C, 72.04; H, 6.28; N, 3.23. Found: C, 72.29; H, 6.37; N, 3.16. IR cm^{-1}: 1665 (CONH–). ^{1}H-NMR δ: 3.93 (3H, s, OMe), 5.03 (2H, s, OCH_2Ph), 5.93 (2H, s, OCH_2O). **16e**: 70%, an oil. IR cm^{-1}: 1650 (CONH–). **15e**·methiodide: mp 164—165 °C (acetone–ether); *Anal.* Calcd for $C_{29}H_{34}INO_5$: C, 57.72; H, 5.68; N, 2.32. Found: C, 57.73; H, 5.65; N, 2.11. **19c**: 92% (from **16c**), an oil. ^{1}H-NMR δ: 2.45 (3H, s, NMe), 3.88, 3.90, 3.92 (each 3H, s, OMe), 5.05 (2H, s, OCH_2Ph). **19d**: 81% (from **16d**), an oil. ^{1}H-NMR δ: 2.43 (3H, s, NMe), 3.90 (3H, s, OMe), 5.04 (2H, s, OCH_2Ph), 5.92 (2H, s, OCH_2O). **3c**: 50%, an amorphous mass. IR cm^{-1}: 3540 (OH). ^{1}H-NMR δ: 2.46 (3H, s, NMe), 3.84 (3H, s, OMe), 3.86 (6H, s, 2 × OMe). Methiodide: mp 100—102 °C (MeOH–AcOEt); *Anal.* Calcd for $C_{22}H_{30}INO_4 \cdot 0.5H_2O$: C, 52.00; H, 6.15; N, 2.75. Found: C, 52.06; H, 6.25; N, 2.57. **3d**: 54%, an oil. IR cm^{-1}: 3550 (OH). ^{1}H-NMR δ: 2.49 (3H, s, NMe), 3.90 (3H, s, OMe), 5.92 (2H, s, OCH_2O). Methiodide: mp 108—110 °C (MeOH–AcOEt); *Anal.* Calcd for $C_{21}H_{26}INO_4 \cdot H_2O$: C, 50.31; H, 5.84; N, 2.80. Found: C, 50.47; H, 5.64; N, 2.55. **3e**: 60% (from **16e**), an oil. IR cm^{-1}: 3525 (OH). ^{1}H-NMR δ: 2.46 (3H, s, NMe), 3.80, 3.84 (each 3H, s, OMe), 3.82 (6H, s, 2 × OMe), 6.36 (2H, s, 2′- and 6′-H), 6.54, 6.68 (each 1H, d, J = 8 Hz, 7- and 8-H).

General Procedure for Preparation of the 3-Hydroxyaporphines and Homoaporphines (4a, 4b, 4c, 4d, and 4e)——LTA (1.2 eq) was added to an ice-cooled solution of a phenolic base (**3a**, **3b**, **3c**, **3d**, or **3e**) (100 mg) in CH_2Cl_2 (5 ml), and the mixture was stirred at the same temperature for 1 min. The resulting precipitate was removed by filtration and the filtrate was washed with sat. $NaHCO_3$ aq. solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with brine. The extract was dried over K_2CO_3, and the solvent was removed under reduced pressure below 30 °C to give the *o*-quinol acetate (**2a**, **2b**, **2c**, **2d**, or **2e**, respectively). Without purification, each *o*-quinol acetate was dissolved in CH_2Cl_2 (10 ml), and CF_3CO_2H (1 ml) was added to the solution. The mixture was stirred at room temperature for 2 h. Usual work-up gave a crude product, which was purified by recrystallization or preparative TLC [developing solvent: $CHCl_3$–MeOH (100 : 15)]. Yields and physical data are as follows. **2a**: an oil. IR cm^{-1}: 1730 (OAc), 1670 (dienone). ^{1}H-NMR δ: 2.04 (3H, s, OAc), 2.41 (3H, s, NMe), 3.32, 3.35 (3H, each s, aliph. OMe), 3.77 (6H, s, 2 × arom. OMe), 5.68, 5.77 (1H, each s, olef. H), 5.85 (1H, s, olef. H), 6.60 (3H, s, arom. H). **2c**: an oil. IR cm^{-1}: 1730 (OAc), 1675 (dienone). ^{1}H-NMR δ: 2.05 (3H, s, OAc), 2.38 (3H, s, NMe), 3.38 (3H, s, aliph. OMe), 3.76 (6H, s, arom. H), 5.90 (2H, s, olef. H). **2d**: an oil. IR cm^{-1}: 1735 (OAc), 1675 (dienone). ^{1}H-NMR δ: 2.01 (3H, s, OAc), 2.32 (3H, s, NMe), 3.34 (3H, s, aliph. OMe), 5.70 (2H, s, OCH_2O), 5.90 (2H, s, olef. H). **4a**: 73% (from **3a**), mp 213—214 °C (*n*-hexane–$CHCl_3$) (lit.[7] 214—215 °C). ^{1}H-NMR δ: 2.55 (3H, s, NMe), 3.84, 3.89, 3.92 (each 3H, s, OMe), 6.82, 7.07, 7.16 (each 1H, s, arom. H). **4b**: 87% (from **3b**), mp 206 °C (ether); *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.21; H, 5.87; N, 4.30. ^{1}H-NMR δ: 2.52 (3H, s, NMe), 3.94 (3H, s, OMe), 5.92 (2H, br s, OCH_2O), 6.70, 6.92, 7.08 (each 1H, s, arom. H). **4c**: 91% (from **3c**), mp 199—200 °C (MeOH–AcOEt); *Anal.* Calcd for $C_{21}H_{25}NO_4 \cdot 0.5H_2O$: C, 69.20; H, 7.19; N, 3.84. Found: C, 69.24; H, 7.32; N, 3.72. ^{1}H-NMR δ: 2.42 (3H, s, NMe), 3.91 (6H, s, 2 × OMe), 3.93 (3H, s, OMe), 6.72, 6.74, 6.81 (each 1H, s, arom. H). **4d**: 87% (from **3d**), mp 188—190 °C (MeOH). High-resolution mass spectrum (MS): Calcd for $C_{20}H_{21}NO_4$ (339.1468).

Found: 339.1447 (M^+). ^{1}H-NMR δ: 2.44 (3H, s, NMe), 3.95 (3H, s, OMe), 6.00 (2H, s, OCH_2O), 6.75, 6.77, 6.86 (each 1H, s, arom. H). **4e**: 90% (from **3e**), mp 240—245 °C; MS *m/z*: 385 (M^+). ^{1}H-NMR (CF_3CO_2D) δ: 3.92, 4.09 (each 3H, s, OMe), 4.03 (6H, s, 2 × OMe), 6.85, 7.13 (each 1H, s, arom. H). Acetate: an oil. High-resolution MS: Calcd for $C_{24}H_{29}NO_6$ (427.1992). Found: 427.1971 (M^+). IR cm^{-1}: 1750 (OAc). ^{1}H-NMR δ: 2.36, 2.40 (each 3H, s, OAc and NMe), 3.53, 3.82, 3.91, 3.92 (each 3H, s, OMe), 6.55, 6.98 (each 1H, s, arom. H). Methiodide of the acetate: mp 204—205 °C (MeOH–ether); *Anal.* Calcd for $C_{25}H_{32}INO_6 \cdot 0.5C_4H_{10}O$: C, 53.55; H, 6.16; N, 2.31. Found: C, 53.35; H, 6.04; N, 2.15.

Oxidation of 3f and Subsequent Acid Treatment——LTA (1.2 eq) was added to an ice-cooled solution of **3f** (120 mg) in CH_2Cl_2 (10 ml) in one portion, and the whole was stirred at the same temperature for 1 min. The same work-up gave the *o*-quinol acetate (**2f**) [IR cm^{-1}: 1735 (OAc), 1670 (dienone); ^{1}H-NMR δ: 2.00, 2.05 (3H, a pair of s, OAc), 2.16, 2.20 (3H, a pair of s, NMe), 3.37, 3.42 (3H, a pair of s, aliph. OMe), 5.80 (2H, br s, olef. H)] as an oil. Without purification, **2f** was dissolved in CH_2Cl_2 (15 ml), and CF_3CO_2H (0.7 ml) was added to the solution. The mixture was stirred at room temperature for 2 h. Usual work-up and purification by preparative TLC [developing solvent: $CHCl_3$–MeOH (15 : 1)] afforded the *p*-quinone (**11**) (82 mg, 66%) as unstable reddish brown crystals. High-resolution MS: Calcd for $C_{19}H_{21}NO_5$ (343.14196). Found: 343.14437 (M^+). IR cm^{-1}: 1645, 1600 (quinone). ^{1}H-NMR δ: 2.25 (NMe), 3.74, 3.80, 3.84 (each 3H, s, OMe), 4.48 (1H, s, 1-H), 5.65 (1H, s, 7-H), 6.65 (3H, br s, arom. H).

Reduction of 11 by Zinc in Acetic Anhydride[3]——Zinc powder (350 mg) was added to a solution of **11** (82 mg) in Ac_2O (6 ml), and the mixture was stirred at room temperature for 12 h. The reaction mixture was filtered, and water (10 ml) was added to the filtrate. The whole was stirred for 1 h and then basified with sat. $NaHCO_3$ aq. solution. The product was extracted with $CHCl_3$ and work-up as usual gave an oily product, which was purified by preparative TLC [developing solvent: $CHCl_3$–MeOH (15 : 1)] to give the diacetate (**12**) (52 mg, 50%), an oil. IR cm^{-1}: 1755 (OAc). ^{1}H-NMR δ: 1.88 (3H, s, 8-OAc), 2.34, 2.36 (each 3H, s, 5-OAc and NMe), 3.76, 3.80, 3.84 (each 3H, s, OMe), 4.54 (1H, s, 1-H), 6.50, 6.58 (each 1H, s, 7-H and 2′-H), 6.54, 6.72 (each 1H, d, J = 8 Hz, 5′- and 6′-H). Methiodide: mp 238—240 °C (MeOH–ether); *Anal.* Calcd for $C_{24}H_{30}INO_7$: C, 50.45; H, 5.29; N, 2.45. Found: C, 50.17; H, 5.10; N, 2.32.

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References and Notes

1) Part XXVI: H. Hara, A. Tsunashima, H. Shinoki, T. Akiba, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.*, **34**, 66 (1986).
2) Preliminary report: see H. Hara, H. Shinoki, O. Hoshino, and B. Umezawa, *Heterocycles*, **20**, 2155 (1983).
3) H. Hara, H. Shinoki, O. Hoshino, and B. Umezawa, *Heterocycles*, **20**, 2149 (1983).
4) H. Hara, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.*, **24**, 262 (1976).
5) H. Hara, R. Shirai, O. Hoshino, B. Umezawa, and Y. Iitaka, *Chem. Pharm. Bull.*, **31**, 4236 (1983).
6) The ratio of two products was approximately 1 : 1 as estimated from the integral values of ^{1}H-NMR signals.
7) S. M. Kupchan and C. K. Kim, *J. Org. Chem.*, **41**, 3210 (1976).
8) H. Hara, O. Hoshino, B. Umezawa, and Y. Iitaka, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2657.
9) The structure of **13** was assumed by analogy with the reaction described below. Treatment with AcOH (2.5 ml)[3] of **2f** derived from **3f** (100 mg) at room temperature overnight, followed by purification of the products over silica gel column [eluent: $CHCl_3$–MeOH (50 : 1)] gave 8-acetoxy-5-hydroxy-6-methoxy-2-methyl-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**15**), mp 141—142 °C (MeOH) (106 mg, 90%); *Anal.* Calcd for $C_{21}H_{25}NO_6 \cdot 0.5H_2O$: C, 63.62; H, 6.61; N, 3.52. Found: C, 63.64; H, 6.57; N, 3.53. IR cm^{-1}: 3545 (OH), 1750 (OAc). ^{1}H-NMR δ: 1.85 (3H, s, OAc), 2.33 (3H, s, NMe), 3.78 (3H, s, OMe), 3.82 (6H, s, 2 × OMe), 4.55 (1H, s, 1-H), 6.40 (1H, s, 7-H).
10) In order to isolate the hydroquinone (**14**), hydrolysis of the monoacetate (**15**) with conc. HCl was carried out. The crude product showed two spots on TLC [developing solvent: $CHCl_3$–MeOH (10 : 1)]. The upper spot was identical with the *p*-quinone (**11**) and the lower one was presumed to be the hydroquinone (**14**). Attempted separation of the reaction mixture by preparative TLC failed to give **14**: the eluate of the lower zone, which should have contained **14**, again exhibited two spots, showing that a part of **14** changed to **11** during the elution.
11) Attempts at separation of the *p*-quinone (**11**) and the diacetate (**12**) by preparative TLC [developing solvent: $CHCl_3$–MeOH (10 : 1) or $CHCl_3$–MeOH–AcOEt (10 : 1 : 1)] failed. The ratio of the products (**11** and **12**) was roughly estimated as 1 : 3 by inspection of the ^{1}H-NMR spectrum. High-pressure liquid chromatography [AQUASIL column (Senshu Kagaku Co., Ltd.); eluent, MeOH–$CHCl_3$ (75 : 25)] of the mixture showed two peaks, of which the front peak was identified as the diacetate (**12**) and the rear one, the *p*-quinone (**11**) by comparison with authentic samples.