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Studies on Tetrahydroisoquinolines. XXIX.[1] Reaction of 7-Acetoxy-1,2,3,4,6,7-hexahydro-1-(2-(3′,4′-dimethoxy- or 3′,4′-methylenedioxyphenyl)ethyl)-7-methoxy-2-methyl-6-oxo-isoquinoline (*o*-Quinol Acetate) with Acetic Anhydride in the Presence of Acid

Osamu Hoshino,[a] Kyoko Kikuchi,[a] Hideto Ogose,[a] Bunsuke Umezawa,*,[a] and Yoichi Iitaka[b]

Faculty of Pharmaceutical Sciences, Science University of Tokyo,[a] 12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan and Faculty of Pharmaceutical Sciences, University of Tokyo,[b] 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan

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Treatment of *o*-quinol acetates (**5a**, **b**) of 1,2,3,4-tetrahydro-1-phenethylisoquinolin-6-ols (**6a**, **b**) with acetic anhydride in the presence of an acid (concentrated H_2SO_4, $BF_3 \cdot Et_2O$ or CF_3COOH) gave 2-acetoxyhomoaporphines (**4a**, **b**) and/or aldehyde-amides (**7a**, **b**), and the ratio of the products was strongly dependent on the choice of the acid and the solvent. A mechanistic pathway is proposed.

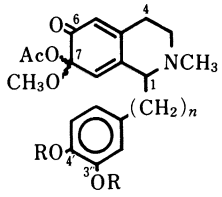
Keywords——lead tetraacetate oxidation; X-ray analysis; *o*-quinol acetate; 1,2,3,4-tetrahydro-1-phenethylisoquinolin-6-ol; aldehyde-amide; 2-acetoxyhomoaporphine; acetic anhydride; concentrated sulfuric acid; boron trifluoride etherate; trifluoroacetic acid

Previously, we have reported that reaction of *o*-quinol acetates (*o*-QAs) (**1**) with acetic anhydride (Ac_2O) containing concentrated sulfuric acid (conc. H_2SO_4) or with Ac_2O–conc. H_2SO_4 in acetonitrile (CH_3CN) gives rise to 2-acetoxyaporphines (**2**)[2] or 1,2-diacetoxyaporphines (**3**).[3] In order to extend the methodology to the synthesis of 2-acetoxyhomoaporphines (**4a**, **b**), which are of interest pharmacologically, reaction of *o*-QAs (**5a**, **b**) derived from 1,2,3,4-tetrahydro-1-phenethylisoquinolin-6-ols (**6a**, **b**) was explored. The present paper is concerned with the formation of 2-acetoxyhomoaporphines (**4a**, **b**) and/or aldehyde-amides (**7a**, **b**) from *o*-QAs (**5a**, **b**) by treatment with Ac_2O containing an acid.

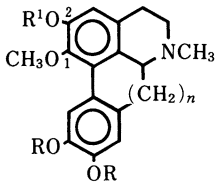
The starting material (**6a**) was prepared as follows. Heating of 2-(3-benzyloxy-4-methoxyphenyl)ethylamine[4] and 3-(3,4-dimethoxyphenyl)propionic acid[5] at 160 °C for 6 h gave an amide (**8a**),[6] Bischler–Napieralski reaction of which afforded 3,4-dihydroisoquinoline hydrochloride (**9a** · HCl)[6] in 68% overall yield (based on the amine oxalate). Reduction of **9a** with sodium borohydride ($NaBH_4$) followed by *N*-methylation gave 6-benzyloxy-1,2,3,4-tetrahydro-2-methylisoquinoline (**10a**), which was debenzylated by catalytic hydrogenolysis over palladium on carbon to give 1,2,3,4-tetrahydroisoquinolin-6-ol (**6a**) in 68.4% overall yield. Analogously, **6b** was prepared starting from the phenethylamine and 3-(3,4-methylenedioxyphenyl)propionic acid.[7]

As reported previously,[2] oxidation of **6a**, **b** with lead tetraacetate in methylene chloride (CH_2Cl_2) gave quantitatively 1 : 1 diastereomeric mixtures of *o*-QAs (**5a**, **b**), which rapidly decomposed on standing at room temperature to leave complex mixtures containing 4-acetoxytetrahydroisoquinolin-6-ols (**11a**, **b**). The spectral data for **5a**, **b** are shown in Table I.

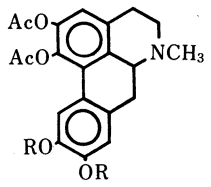
Treatment of *o*-QA (**5a**) with Ac_2O–conc. H_2SO_4 at room temperature for 30 min gave



1 : n=1
5 : n=2



2 : n=1, R^1=Ac
4 : n=2, R^1=Ac
13 : n=2, R^1=H
14 : n=2, R^1=CH_3



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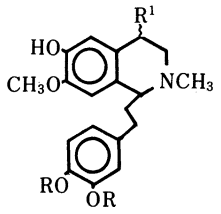
a : R=CH_3 b : R+R=CH_2



6 : R^1=H
11 : R^1=OAc

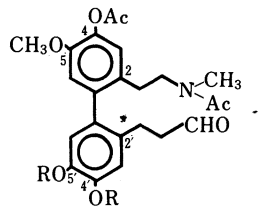


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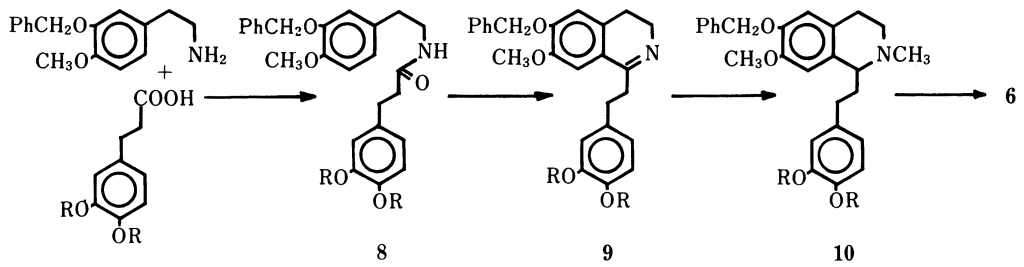
Chart 1



8 9 10

a : R=CH_3 b : R+R=CH_2

Chart 2

oily products, which were subjected to preparative thin layer chromatography (TLC) to afford an aldehyde-amide (**7a**) (20.5%) and 2-acetoxyhomoaporphine (**4a**) (25.3%). The mass spectrum (MS) of the former (**7a**) indicated a molecular formula of $C_{25}H_{31}NO_7$ and the proton nuclear magnetic resonance (^{1}H-NMR) spectrum (Table II) showed the signals of a formyl group as a singlet (1H) at δ 9.59, the acetyl group of an acetamido grouping as a pair of singlets[8] (3H) at δ 1.67 and 1.99, and of an *N*-methyl group as a pair of singlets[8] (3H) at δ 2.66 and 2.71. The infrared (IR) spectrum (Table II) exhibited absorption bands due to phenolic acetoxyl, formyl, and amido groups at 1770, 1730, and 1635 cm^{-1}, respectively.

On the basis of these spectral data, the structure of the aldehyde-amide (**7a**) was deduced to be 4-acetoxy-2-(2-(*N*-acetyl-*N*-methylamino)ethyl)-5-methoxyphenyl-2′-(2-formylethyl)-4′,5′-dimethoxybenzene. Furthermore, the position of the acetoxyl group in **7a** was confirmed by the X-ray crystallographic analysis of a methoperchlorate (**12**) derived from **7a**. An ORTEP drawing of **12** is depicted in Fig. 1.

The ^{1}H-NMR spectrum (Table II) of the latter (**4a**) showed a singlet signal (3H) due to a methoxyl group at the 1-position at δ 3.28 and of three singlet signals (each 1H) due to aromatic protons at δ 6.75, 6.80, and 7.03. From these spectral data, microanalysis, and

TABLE I. Spectral Data for *o*-Quinol Acetates (**5a**, **b**)

o-QA	IR (cm^{-1})	^{1}H-NMR δ (100 MHz)		
		NCH_3[a]	OAc[a]	7-OCH_3[a]
5a	1745, 1690	2.38 (s)	2.08 (s)	3.43 (s)
		2.44 (s)	2.11 (s)	3.44 (s)
5b	1745, 1685	2.36 (s)	2.08 (s)	3.44 (s)
		2.43 (s)	2.12 (s)	3.45 (s)

a) A 1 : 1 ratio was observed. Abbreviation: s, singlet.

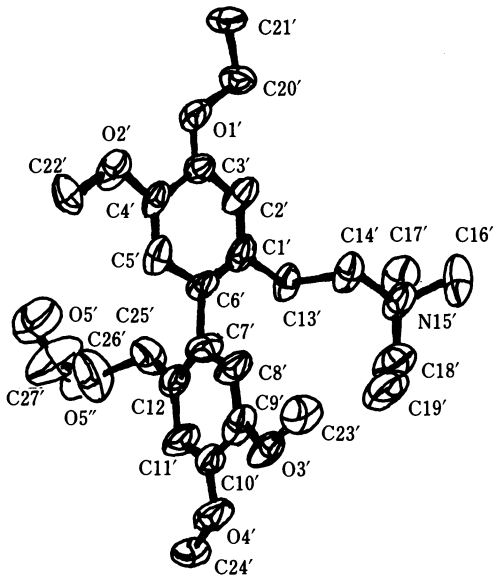
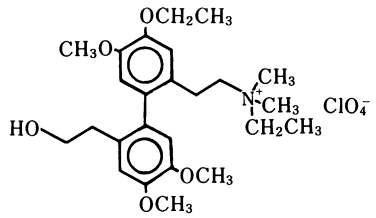


Fig. 1. An ORTEP Drawing of **12**



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chemical conversion into a known compound 1,2,10,11-tetramethoxyhomoaporphine (**14a**),[6] the structure of **4a** was determined to be 2-acetoxy-1,10,11-trimethoxyhomoaporphine.

In contrast to the case of *o*-QAs (**1**),[2] the reaction of **5a** was proved to give 2-acetoxyhomoaporphine (**4a**) accompanied with aldehyde-amide (**7a**).

Although shortening of the reaction time did not change the ratio of products, employment of boron trifluoride etherate ($BF_3 \cdot Et_2O$) instead of conc. H_2SO_4 increased the yield of **4a**. With trifluoroacetic acid (TFA), however, the ratio of products dramatically changed to afford **7a** mainly. The results are summarized in Table III.

The pathway of formation of **4a** and **7a** may be as depicted in Chart 3. Namely, the ring closure of **5a** would occur through an intermediate A (7-*endo*-trigonal process)[9] and/or B (6-*exo*-trigonal process),[9] followed by rearrangement of the C6′–C8a to C6′–C8 bonds to give **4a**. On the other hand,[10] cleavage of the C1–C8a bond in B through a vinylogous retro-aldol type reaction would lead to an intermediate C. Further hydrolysis and acetylation of C would give rise to **7a**.[11]

The above mechanistic considerations strongly suggested that fixing the lone pair electrons on nitrogen would favor the formation of **4** over **7**. Therefore, preferential formation of **4** was expected to be possible by the use of conc. H_2SO_4 or $BF_3 \cdot Et_2O$ in aprotic

TABLE II. Spectral Data and Elemental Analysis of 2-Acetoxyhomoaporphines (**4a, b**) and Aldehyde-Amides (**7a, b**)

Products	IR (cm^{-1})	^{1}H-NMR δ (100 MHz)[a]							mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found)		
		NAc	NCH_3	OAc	OCH_3	OCH_2O	ArH	CHO			C	H	N
4a	1760	—	2.39 (s)	2.35 (s)	3.23 (s) 3.87 (s) 3.94 (s)	—	6.75 (1H, s) 6.80 (1H, s) 7.03 (1H, s)	—	210.5—211.5[b] (MeOH)	$C_{29}H_{29}N_4O_{12}$	55.68 (55.50	4.67 4.90	8.96 8.97)
7a	1770 1730 1635	1.67 (s) 1.99 (s) (1:1)	2.66 (s) 2.71 (s) (1:1)	2.34 (s)	3.79 (s) 3.80 (s) (1:1) 3.85 (s) 3.90 (s)	—	6.60—6.96 (4H, m)	9.59 (br s)	—[c]	$C_{25}H_{31}NO_7$	457.2098 (457.2090)[d]		
4b	1765	—	2.39 (s)	2.34 (s)	3.33 (s)	5.93 (1H, d) 5.96 (1H, d) (J=1)	6.72 (1H, s) 6.80 (1H, s) 6.95 (1H, s)	—	220—220.5[b] (MeOH)	$C_{28}H_{25}N_4O_{12}$	55.18 (55.06	4.13 4.39	9.19 9.09)
7b	1775 1735 1640	1.77 (s) 2.00 (s) (1:1)	2.71 (s) 2.75 (s) (1:1)	2.33 (s)	3.78 (s) 3.79 (s) (1:1)	5.95 (2H, s)	6.56—6.96 (4H, m)	9.59 (br s)	—[c]	$C_{24}H_{27}NO_7$	441.1785 (441.1770)[d]		

a) Abbreviations are as follows: s, singlet; br s, broad singlet; d, doublet; m, multiplet. *b*) A picrate. *c*) An oil. *d*) High-resolution mass spectrum m/z (M^+).

TABLE III. Reaction Conditions and Yields of 2-Acetoxyhomoaporphines (**4a, b**) and Aldehyde-Amides (**7a, b**)

o-QA	Reaction conditions[a]		Yields (%)	
	Acid (ml)	Reaction time (min)	**4**	**7**
5a	Conc. H_2SO_4 (0.3)	30	25.3	20.5
	Conc. H_2SO_4 (0.3)	10	24.3	10.7
	$BF_3 \cdot Et_2O$ (0.82)	60	55.6	14.8
	TFA[b] (0.5)	30	6.0	44.8
5b	Conc. H_2SO_4 (0.3)	10	26.9	20.5
	Conc. H_2SO_4 (0.3)[c]	60	62.0	5.2
	TFA[b] (0.5)	30	4.2	49.5

a) *o*-QAs (**5**) prepared from **6** (100 mg) (see Experimental) and Ac_2O (1 ml) were used. *b*) TFA: CF_3COOH. *c*) CH_3CN (50 ml) was used.

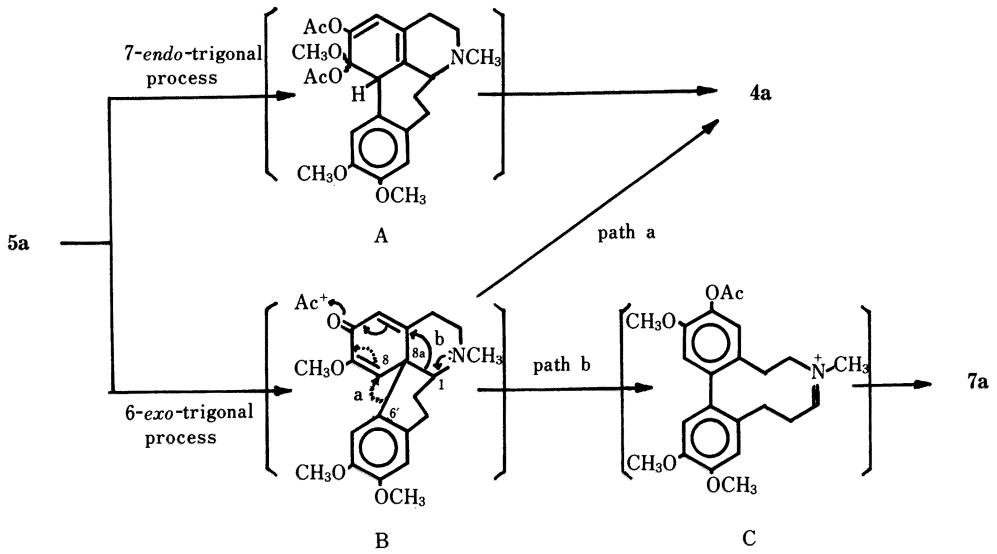

Chart 3

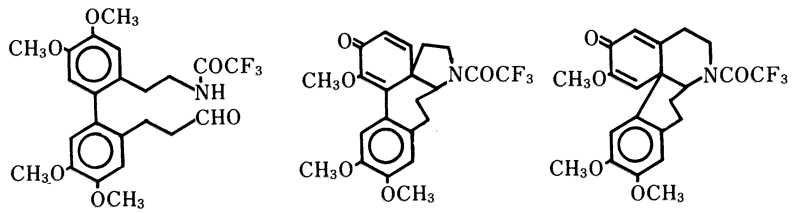

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Chart 4

TABLE IV. Reaction Conditions and Yields of 2-Acetoxyhomoaporphine (**4a**) and Aldehyde-Amide (**7a**)

Entry	Reaction conditions[a]			Yield (%)	
	Solvent (ml)	Acid (ml)	Reaction time (min)	**4a**	**7a**
1	CH_2Cl_2 (50)	Conc. H_2SO_4 (0.3)	60	53.8	—
2	CH_3CN (50)	Conc. H_2SO_4 (0.3)	60	69.8	10.2
3	CH_3NO_2 (50)	Conc. H_2SO_4 (0.3)	10	80.2	—
4	CH_3NO_2 (10)	Conc. H_2SO_4 (0.3)	60	62.3	—
5	CH_3CN (50)	$BF_3 \cdot Et_2O$ (0.82)	60	61.0	12.3
6	CH_3NO_2 (50)	$BF_3 \cdot Et_2O$ (0.82)	60	78.6	—
7	CH_2Cl_2 (30)	TFA[b] (0.5)	30	—	50.5
8	CH_3CN (50)	TFA[b] (0.5)	60	—	29.3

a) *o*-QA (**5a**) prepared from **6a** (100 mg) (see Experimental) and Ac_2O (1 ml) were used. *b*) TFA: CF_3COOH.

polar solvents, which would be effective to fix the lone pair electrons on nitrogen. Indeed, treatment of **5a** with Ac_2O–conc. H_2SO_4 in CH_2Cl_2 gave only **4a** in 53.8% yield. Although employment of CH_3CN increased the yield of **4a**, the formation of **7a** was also observed (entry

2). With nitromethane (CH_3NO_2), however, **4a** was obtained in a good yield (entry 3). Furthermore, with Ac_2O–$BF_3 \cdot Et_2O$ in CH_3CN or CH_3NO_2 a similar trend was observed (entries 5 and 6). On the other hand, with Ac_2O–TFA in CH_2Cl_2 or CH_3CN, **7a** was formed as a sole product (entries 7 and 8). The results are listed in Table IV. Analogously, treatment of **5b** with Ac_2O containing acid was carried out to afford **4b** and **7b**, respectively (Table III). Acidic hydrolysis of **4a**, **b** gave 2-hydroxyhomoaporphines (**13a**, **b**) in good yields.

In conclusion, treatment of *o*-QAs (**5a**, **b**) with Ac_2O in the presence of an acid gave 2-acetoxyhomoaporphines (**4a**, **b**) and/or aldehyde-amides (**7a**, **b**). This is the first report of the formation of the latter products in the reaction of *o*-QAs with Ac_2O containing an acid.

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. IR spectra were measured on a Hitachi 215 infrared spectrometer in $CHCl_3$ solution. ^{1}H-NMR spectra were taken with a JEOL-FX 100 spectrometer (100 MHz) in $CDCl_3$ solution using Me_4Si as an internal standard. MS were run on a Hitachi RMU-7M instrument at 70 eV. Preparative TLC was performed on Kieselgel HF_{254} (0.5 mm thick) (Merck) with $CHCl_3$–MeOH–AcOEt (8 : 1 : 1) as a developing solvent, unless otherwise noted.

***N*-2-(3-Benzyloxy-4-methoxyphenyl)ethyl-3-(3′,4′-dimethoxyphenyl)propionamide (8a)**——A mixture of 2-(3-benzyloxy-4-methoxyphenyl)ethylamine[4] (22.8 g), obtained from the oxalate (34.9 g), and 3-(3,4-dimethoxyphenyl)propionic acid[5] (23.7 g) was heated at 160 °C for 6 h. The product was taken up in $CHCl_3$ (250 ml). Usual work-up of the $CHCl_3$ solution gave a colorless solid (**8a**) (38.1 g, 84% based on the oxalate), mp 96—98 °C (benzene) (lit.[6] 88.3—89.8 °C). IR cm^{-1}: 3430 (NH), 1660 (CONH). ^{1}H-NMR δ: 3.69 (9H, s, 3 × OCH_3), 4.98 (2H, s, OCH_2Ar). *Anal.* Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.12. Found: C, 72.20; H, 6.75; N, 3.03.

***N*-2-(3-Benzyloxy-4-methoxyphenyl)ethyl-3-(3′,4′-methylenedioxyphenyl)propionamide (8b)**——A mixture of 2-(3-benzyloxy-4-methoxyphenyl)ethylamine[4] (4.0 g) and 3-(3,4-methylenedioxyphenyl)propionic acid[7] (3.7 g) was heated at 160 °C for 2.5 h. Usual work-up of the reaction mixture gave colorless crystals (**8b**) (6.0 g, 89.8%), mp 132.5—133.5 °C (benzene–hexane). IR cm^{-1}: 3430 (NH), 1665 (CONH). ^{1}H-NMR δ: 3.84 (3H, s, OCH_3), 5.06 (2H, s, OCH_2Ar), 5.86 (2H, s, OCH_2O). *Anal.* Calcd for $C_{26}H_{27}NO_5$: C, 72.04; H, 6.28; N, 3.23. Found: C, 72.27; H, 6.23; N, 3.18.

6-Benzyloxy-3,4-dihydro-7-methoxy-1-(2-(3′,4′-dimethoxyphenyl)ethyl)isoquinoline Hydrochloride (9a·HCl)——A solution of the amide (**8a**) (2.5 g) and $POCl_3$ (10 ml) in CH_2Cl_2 (25 ml) was refluxed for 3 h. Removal of the solvent *in vacuo* gave an oil, which was crystallized by trituration in a mixture of hexane, ether, and iso-PrOH to give pale yellow crystals (**9a**·HCl) (2.13 g, 82%), mp 188—189 °C (iso-PrOH) (lit.[6] 173.8—174.7 °C). *Anal.* Calcd for $C_{27}H_{30}NO_4 \cdot HCl$: C, 69.30; H, 6.64; N, 2.99. Found: C, 69.09; H, 6.49; N, 3.04.

6-Benzyloxy-3,4-dihydro-7-methoxy-1-(2-(3′,4′-methylenedioxyphenyl)ethyl)isoquinoline Hydrochloride (9b·HCl)——A solution of the amide (**8b**) (1.4 g) and $POCl_3$ (6 ml) in CH_2Cl_2 (15 ml) was refluxed for 3 h. Work-up of the reaction mixture as noted for **8a** gave pale yellow crystals (**9b**·HCl) (1.05 g, 72%), mp 198—199 °C (MeOH–iso-PrOH). IR cm^{-1}: 2700—2300 (br), 1660, 1575 (C=N). ^{1}H-NMR δ: 3.87 (3H, s, OCH_3), 5.24 (2H, s, OCH_2Ar), 5.88 (2H, s, OCH_2O), 7.38 (5H, s, C_6H_5). *Anal.* Calcd for $C_{26}H_{26}NO_4 \cdot HCl$: C, 67.74; H, 5.79; N, 3.04. Found: C, 67.59; H, 5.90; N, 3.04.

1,2,3,4-Tetrahydro-6-hydroxy-7-methoxy-1-(2-(3′,4′-dimethoxyphenyl)ethyl)-2-methylisoquinoline (6a)——$NaBH_4$ (1.4 g) was added portionwise to an ice-cooled, stirred solution of the free amine (**9a**) (22.2 g) in MeOH (240 ml) and the whole was stirred at room temperature for 2 h. Removal of the solvent *in vacuo* gave an oil. H_2O was added to the oil and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave an oil (22 g, 99%). A solution of the crude oil (22 g) and 37% aqueous formaldehyde (20 g) in MeOH (220 ml) was stirred at room temperature for 2 h. $NaBH_4$ (9.6 g) was added portionwise to the ice-cooled, stirred mixture over a period of 2.5 h and stirring was continued at room temperature for 1 h. Usual work-up of the reaction mixture gave an oil (**10a**) (20.5 g, 90%). A solution of the crude **10a** (5.5 g), 2% aqueous $PdCl_2$ (14 ml), and active carbon (1.36 g) in MeOH (200 ml) was shaken with H_2 at room temperature for 1.4 h. After filtration to remove the catalyst, usual work-up of the reaction mixture gave pale yellow crystals (**6a**) (3.3 g, 76.7%) mp 113—114 °C (ether–hexane). IR cm^{-1}: 3550 (OH). ^{1}H-NMR δ: 2.46 (3H, s, NCH_3), 3.80, 3.83, 3.84 (each 3H, s, 3 × OCH_3), 6.47, 6.60 (each 1H, s, 2 × ArH), 6.64—6.82 (3H, m, 3 × ArH). High-resolution MS Calcd for $C_{21}H_{27}NO_4$ (M^+) *m/z*: 357.1937. Found: 357.1915.

1,2,3,4-Tetrahydro-6-hydroxy-7-methoxy-2-methyl-1-(2-(3′,4′-methylenedioxyphenyl)ethyl)isoquinoline (6b)——$NaBH_4$ (0.4 g) was added portionwise to an ice-cooled, stirred solution of the free amine (**9b**) (8.7 g) in MeOH (150 ml) and the whole was stirred at room temperature for 2 h. Usual work-up of the reaction mixture gave an oil (9.6 g), which was methylated as noted for **9a** to give an oil (**10b**) (9.0 g, 99%). A mixture of the crude **10b** (4.1 g), 2% aqueous $PdCl_2$ (12 ml), and active carbon (1.1 g) in MeOH (200 ml) was shaken with H_2 at room temperature for

TABLE V. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors

No.	Atom	x	y	z	B_{eq} (Å^2)
1	Cl	7342 (4)	501 (3)	8936 (4)	8.2 (0.1)
2	O1(Cl)	6949 (20)	773 (11)	9864 (16)	24.5 (0.7)
3	O2(Cl)	8315 (14)	445 (15)	9000 (30)	29.3 (1.0)
4	O3(Cl)	6930 (17)	−143 (10)	8509 (19)	21.7 (0.6)
5	O4(Cl)	7224 (22)	1029 (11)	8277 (16)	22.7 (0.7)
6	Cl′	2508 (3)	2844 (2)	1375 (4)	7.5 (0.1)
7	O1(Cl′)	3002 (20)	3332 (12)	2160 (21)	24.2 (0.8)
8	O2(Cl′)	1963 (13)	2457 (10)	1948 (19)	18.1 (0.6)
9	O3(Cl′)	1940 (14)	3222 (15)	715 (21)	25.1 (0.8)
10	O4(Cl′)	3327 (12)	2487 (8)	889 (14)	14.2 (0.4)
11	C1	4677 (10)	2828 (7)	8044 (11)	4.6 (0.3)
12	C2	4785 (10)	3214 (7)	9152 (12)	5.1 (0.3)
13	C3	5496 (11)	3752 (7)	9356 (11)	4.9 (0.3)
14	C4	6131 (10)	3880 (7)	8504 (11)	4.5 (0.3)
15	C5	6046 (10)	3478 (7)	7448 (11)	4.7 (0.3)
16	C6	5326 (10)	2926 (7)	7232 (12)	4.9 (0.3)
17	C7	5312 (10)	2477 (7)	6095 (11)	4.5 (0.3)
18	C8	6119 (10)	1945 (6)	5928 (11)	4.3 (0.2)
19	C9	6185 (10)	1554 (7)	4832 (11)	4.7 (0.3)
20	C10	5466 (11)	1709 (7)	3937 (11)	5.2 (0.3)
21	C11	4687 (11)	2224 (7)	4125 (12)	5.3 (0.3)
22	C12	4578 (11)	2621 (7)	5221 (11)	5.0 (0.3)
23	C13	3876 (11)	2233 (7)	7855 (12)	5.0 (0.3)
24	C14	4338 (10)	1587 (7)	8429 (12)	5.0 (0.3)
25	N15	3665 (9)	916 (6)	8205 (9)	5.4 (0.2)
26	C16	2598 (11)	1120 (9)	8688 (15)	7.3 (0.4)
27	C17	4196 (13)	329 (8)	8843 (14)	7.3 (0.4)
28	C18	3441 (12)	656 (8)	6950 (13)	7.2 (0.3)
29	C19	4438 (14)	455 (9)	6352 (15)	8.4 (0.4)
30	C20	5008 (12)	4047 (9)	11262 (11)	6.5 (0.3)
31	C21	5416 (13)	4575 (9)	12286 (13)	7.5 (0.4)
32	C22	7389 (13)	4642 (9)	7923 (13)	7.3 (0.4)
33	C23	7648 (12)	848 (9)	5524 (13)	7.2 (0.3)
34	C24	5057 (16)	1569 (10)	1938 (12)	9.5 (0.4)
35	C25	3703 (12)	3202 (8)	5367 (14)	6.5 (0.3)
36	C26	4106 (15)	3913 (8)	5051 (17)	9.0 (0.4)
37	C27	3202 (20)	4455 (10)	5093 (26)	15.8 (0.8)
38	O1	5682 (7)	4162 (5)	10390 (7)	5.6 (0.2)
39	O2	6797 (7)	4448 (5)	8807 (8)	5.8 (0.2)
40	O3	6940 (7)	1027 (5)	4607 (8)	6.0 (0.2)
41	O4	5669 (8)	1329 (5)	2903 (8)	6.9 (0.2)
42	O5	3658 (17)	5053 (11)	4827 (15)	18.5 (0.6)
43	C1′	−211 (10)	2079 (7)	−2767 (11)	4.6 (0.3)
44	C2′	−59 (10)	1329 (7)	−2829 (11)	4.6 (0.3)
45	C3′	597 (10)	963 (7)	−3586 (11)	4.3 (0.3)
46	C4′	1108 (10)	1343 (7)	−4326 (12)	4.9 (0.3)
47	C5′	971 (11)	2090 (7)	−4272 (11)	5.0 (0.3)
48	C6′	326 (10)	2459 (7)	−3455 (11)	4.5 (0.3)
49	C7′	251 (10)	3270 (7)	−3376 (11)	4.7 (0.3)
50	C8′	1054 (11)	3655 (7)	−2706 (12)	5.5 (0.3)
51	C9′	1016 (10)	4408 (8)	−2608 (12)	5.3 (0.3)
52	C10′	186 (12)	4783 (8)	−3169 (12)	6.0 (0.3)
53	C11′	−598 (11)	4416 (7)	−3809 (12)	5.7 (0.3)
54	C12′	−543 (11)	3648 (8)	−3905 (11)	5.5 (0.3)
55	C13′	−972 (10)	2481 (8)	−1933 (11)	5.0 (0.3)

TABLE V. (continued)

No.	Atom	x	y	z	B_{eq} (Å^2)
56	C14′	−460 (11)	2408 (8)	−735 (12)	6.1 (0.3)
57	N15′	−1114 (10)	2798 (7)	210 (10)	6.5 (0.3)
58	C16′	−2200 (15)	2481 (12)	131 (17)	11.1 (0.5)
59	C17′	−551 (15)	2659 (12)	1319 (14)	10.0 (0.5)
60	C18′	−1368 (16)	3589 (9)	117 (16)	9.6 (0.4)
61	C19′	−396 (17)	4005 (10)	35 (17)	11.0 (0.5)
62	C20′	309 (12)	−176 (8)	−2921 (15)	7.2 (0.4)
63	C21′	790 (14)	−953 (8)	−3128 (16)	8.4 (0.4)
64	C22′	2156 (13)	1292 (9)	−5902 (14)	7.8 (0.4)
65	C23′	2515 (11)	4455 (9)	−1288 (15)	7.7 (0.4)
66	C24′	−690 (12)	5927 (8)	−3505 (15)	7.3 (0.4)
67	C25′	−1459 (13)	3232 (9)	−4539 (13)	7.2 (0.3)
68	C26′	−1720 (24)	3412 (16)	−5554 (19)	19.1 (0.8)
69	C27′	−2604 (21)	3149 (18)	−6435 (34)	23.7 (1.1)
70	O1′	814 (7)	222 (5)	−3684 (8)	6.0 (0.2)
71	O2′	1692 (7)	927 (5)	−5084 (8)	5.9 (0.2)
72	O3′	1759 (8)	4831 (5)	−1955 (9)	7.6 (0.2)
73	O4′	215 (8)	5539 (5)	−3030 (9)	7.0 (0.2)
74	O5′[a]	−2428 (20)	2621 (15)	−6675 (27)	12.4 (0.7)
75	O5″[a]	−3305 (21)	3325 (14)	−5937 (23)	10.9 (0.6)
76	W1[a]	891 (29)	1099 (20)	784 (33)	17.3 (1.0)
77	W2[a]	204 (33)	773 (23)	139 (32)	19.5 (1.2)

a) Atoms with half occupancy factor.

1.75 h. Work-up of the reaction mixture as noted above afforded pale yellow crystals (**6b**) (2.4 g, 75%), mp 89—90 °C (MeOH–hexane). IR cm^{-1}: 3550 (OH). ^{1}H-NMR δ: 2.44 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), 5.84 (2H, s, OCH_2O), 6.46, 6.56 (each 1H, s, 2 × ArH), 6.56—6.68 (3H, m, 3 × ArH). *Anal.* Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.23; H, 6.79; N, 4.09.

General Procedure for Preparation of *o*-QAs (5)——$Pb(OAc)_4$ (1.1 eq) was added in one portion to an ice-cooled, stirred solution of **6** (100 mg) in CH_2Cl_2 (16 ml) and stirring was continued at the same temperature for 4—5 min. A precipitate was filtered off and H_2O (4—5 drops) was added to the filtrate. The mixture was swirled well and dried over anhydrous K_2CO_3 for 5 min. After filtration to remove the K_2CO_3, the solvent was removed at below 5 °C under vacuum to give *o*-QA (**5**) as an oil, quantitatively. As *o*-QA rapidly decomposed on standing at room temperature to give complex mixtures containing 4-acetoxytetrahydroisoquinolin-6-ols (**11**), work-up of the reaction mixture was carried out under ice-cooling and the *o*-QA was used without purification. The spectral data for **5** are listed in Table I.

General Procedure for Reaction of *o*-QA (5) with Ac_2O in the Presence of an Acid——(i) Without Solvent: *o*-QA (**5**), obtained from **6** (100 mg) as noted above, was dissolved in Ac_2O. Acid was added to the ice-cooled, stirred solution and stirring was continued at room temperature for an appropriate time. The reaction mixture was poured into ice-water. It was made alkaline with 5% aqueous $NaHCO_3$ and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract furnished an oil, which was purified by preparative TLC. Spectral data, reaction conditions, yields and elemental analyses of **4** and **7** are listed in Tables II and III.

(ii) With Solvent: Ac_2O was added to an ice-cooled, stirred solution of *o*-QA (**5**), obtained from **6** (100 mg) as noted above, in an appropriate solvent and the acid was added to the mixture. The whole was stirred at room temperature. Work-up as noted above afforded **4** and/or **7**. The results are listed in Tables III and IV.

Preparation of Methoperchlorate (12)——A solution of **7a** (196 mg) and $NaBH_4$ (19 mg) in MeOH (3.5 ml) was stirred at room temperature for 50 min. K_2CO_3 (60.5 mg) was added to the mixture and the whole was refluxed for 45 min. After filtration to remove the K_2CO_3, H_2O was added to the filtrate and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract afforded quantitatively an oil [IR cm^{-1}: 3525 (OH), 1620 ($NCOCH_3$). MS *m/z*: 417 (M^+)]. A mixture of the oil (84 mg), K_2CO_3 (40 mg) and EtI (0.1 ml) in EtOH (3 ml) was refluxed with stirring for 1.5 h. After filtration to remove the K_2CO_3, the solid was washed with hot benzene. Removal of the solvent from the combined organic layers *in vacuo* gave an oil (77 mg, 85.9%) [IR cm^{-1}: 3600, 3380 (OH), 1620 ($NCOCH_3$). MS *m/z*: 445 (M^+)]. A mixture of the crude product (70.8 mg) and $LiAlH_4$ (19 mg) in THF (5 ml) was stirred for 5 min and refluxed for 0.5 h. Usual work-up of the reaction mixture gave an oil (64 mg), which was purified by preparative TLC (developing solvent; $CHCl_3$: MeOH = 7 : 1) to give an oil (39 mg, 56.3%). IR cm^{-1}: 3300 (OH). ^{1}H-NMR δ: 0.95 (3H,

t, J=7.5 Hz, $NCH_2\underline{C}H_3$), 1.49 (3H, t, J=7.5 Hz, $OCH_2\underline{C}H_3$), 2.41 (3H, s, NCH_3), 3.81, 3.83, 3.90 (each 3H, s, 3×OCH_3), 6.61, 6.77 (each 2H, s, 4×ArH). MS m/z: 431 (M^+). A mixture of the oil (39 mg) and MeI (1 ml) in MeOH (3 ml) was refluxed for 3.5 h. Removal of the solvent gave a methiodide, which was treated with aqueous $NaClO_4$ to afford colorless needles (**12**) (27.8 mg, 56.3%), mp 153.5—154 °C (EtOH–ether). *Anal.* Calcd for $C_{26}H_{40}NO_5 \cdot ClO_4 \cdot 0.5H_2O$: C, 56.25; H, 7.26; N, 2.53. Found: C, 55.85; H, 7.13; N, 2.46.

Structural Determination of 12——(i) Crystal Data: $C_{26}H_{40}NO_5 \cdot ClO_4 \cdot 0.5H_2O$ (M_r=555.1); triclinic, space group, $P\bar{1}$, Z=4, unit cell dimensions; a=13.071 (7), b=18.633 (9), c=11.984 (6)Å, α=97.75 (5), β=94.39 (5), γ=87.06 (4)°, U=2881.1 Å^3, D_{cal}=1.280 g cm^{-3}.

(ii) X-Ray Crystallographic Analysis: A single crystal with approximate dimensions of 0.02×0.11×0.4 mm was chosen for the X-ray study from crystals grown in EtOH–ether solutions. The intensity data were obtained using Cu K_α radiation monochromated by the use of a graphite plate. The crystal data are given above (i). The intensities of 3150 reflections were measured as above the $2\sigma(I)$ level out of 5468 within the 2θ angle range of 6° through 120°. A set of trial structures was obtained by the direct method, and the one which agreed best with the Patterson function was refined by difference Fourier synthesis and least-squares calculations. The final refinement, including two solvate water molecules of half weight and the disordered hydroxyl group 05′ and 05″ gave an R value of 0.113.[12] Hydrogen atoms were not included. Atomic coordinates and equivalent isotropic temperature factors are given in Table V and an ORTEP drawing of **12** is depicted in Fig. 1.

The crystal contains two independent molecules in the asymmetric unit, and the two molecules are very similar to each other in dimensions and conformation.

2-Hydroxy-1,10,11-trimethoxy-6-methyl- and 2-Hydroxy-1-methoxy-6-methyl-10,11-methylenedioxyhomoaporphines (13a and 13b)——**13a**: A solution of **4a** (145 mg) and 10% HCl (10 ml) in MeOH (10 ml) was refluxed for 0.5 h. Removal of the solvent *in vacuo* gave an oil, which was basified with 5% aqueous $NaHCO_3$. The product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave an oil, which was crystallized by trituration in a mixture of benzene and hexane to give pale yellow crystals (**13a**) (125.2 mg, 96.6%), mp 170—171 °C (benzene–hexane). IR cm^{-1}: 3550 (OH). ^{1}H-NMR δ: 2.34 (3H, s, NCH_3), 3.28 (3H, s, 1-OCH_3), 3.80, 3.86 (each 3H, s, 2×OCH_3), 6.58, 6.66, 6.96 (each 1H, s, 3×ArH). *Anal.* Calcd for $C_{21}H_{25}NO_4 \cdot 0.25C_6H_6$: C, 72.00; H, 7.07; N, 3.73. Found: C, 72.32; H, 7.11; N, 3.53. **13b**: A solution of **4b** (122 mg) and 10% HCl (10 ml) in MeOH (10 ml) was refluxed for 0.5 h. Work-up of the reaction mixture as noted for **13a** afforded pale yellow crystals (**13b**) (86 mg, 85%), mp 178—181 °C (hexane). IR cm^{-1}: 3520 (OH). ^{1}H-NMR δ: 2.40 (3H, s, NCH_3), 3.32 (3H, s, 1-OCH_3), 5.94, 5.96 (each 1H, d, J=0.8 Hz, OCH_2O), 6.67, 6.72, 6.94 (each 1H, s, 3×ArH). *Anal.* Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.68; H, 6.09; N, 4.10.

1,2,10,11-Tetramethoxyhomoaporphine (14a)——A solution of **13a** (100 mg) in MeOH (3 ml) was treated with excess CH_2N_2–ether solution (10 ml) at room temperature for 12 h. Removal of the solvent afforded an oil, which was purified by preparative TLC (developing solvent; $CHCl_3$: MeOH = 8 : 1) to furnish an oil (**14a**) (60.4 mg, 58%) and **13a** (22 mg). **14a**: ^{1}H-NMR δ: 2.40 (3H, s, NCH_3), 3.42 (3H, s, 1-OCH_3), 3.86, 3.88, 3.93 (each 3H, s, 3×OCH_3), 6.64, 6.73, 7.06 (each 1H, s, 3×ArH). MS m/z: 369 (M^+). **14a**·HCl, mp 243—245 °C (dec.) (MeOH–ether) (lit.[6] 242—244 °C (dec.)). The ^{1}H-NMR spectral data and the melting point of **14a**·HCl were identical with those given in the literature.[6]

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References and Notes

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10) S. M. Kupchan *et al.*[6] have reported that oxidative coupling of non-phenolic 1-phenethyltetrahydroisoquinolines gives aldehyde-amide (i), homoneospirenedienone (ii), and homoproerythrinadienone (iii), and

they proposed an analogous mechanistic pathway for the formation of (i).

11) In the case of *o*-QAs (**1**), the formation of an intermediate such as B, which would lead to a noraldehyde-amide similar to **7**, might be unfavorable, because steric hindrance would be greater in the formation of the five-membered ring than in that of the six-membered one. Therefore, the noraldehyde-amide would not be formed in the similar reaction of **1**.

12) A list of F_O and F_C values may be obtained from one (Y.I.) of the authors upon request.