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Studies on Tetrahydroisoquinolines. XXI.[1] A Synthesis of (±)-1-Hydroxy-2-methoxyhomoproaporphine and Stereochemistry of 4-Oxygenated 1,2,3,4-Tetrahydroisoquinolines

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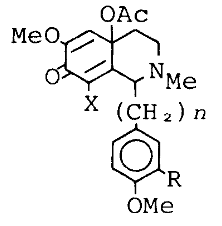
Acid treatment of the *p*-quinol acetate (**23**), obtained from the phenolic amine (**14**) gave (±)-2-hydroxy-3-methoxyhomoproaporphine (**20**) in excellent yield. However, similar treatment of other *p*-quinol acetates (**24** and **25**) afforded no cyclized products. Reaction of **24** or **25** with Ac_2O–conc. H_2SO_4 gave two diastereoisomeric 4,7-diacetates (**36a** and **36b** or **38a** and **38b**). The stereostructures of **36a** and **36b** were decided by nuclear magnetic resonance study, while those of **38a** and **38b** were determined by chemical transformations and X-ray analyses. The stereoselectivity of acetoxylation is discussed.

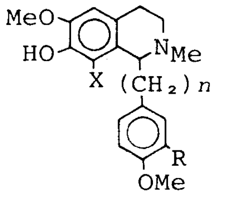
Keywords——lead tetraacetate oxidation; *p*-quinol acetate; cyclization; homoproaporphine; trifluoroacetic acid; acetic anhydride–conc. sulfuric acid; X-ray analysis; 1,4-disubstituted tetrahydroisoquinoline; stereoselectivity

We have already reported that the cyclization reaction of *p*-quinol acetate (**1** or **2**) derived from 1-benzyl or 1-phenethyltetrahydroisoquinolin-7-ol (**3** or **4**) gives aporphine (**5**) or homoaporphine (**6**), homomorphinandienone (**7**), and homoproaporphine (**8**).[2] The *o*-quinonoid cation (**9** or **10**) has been assumed to be a genuine intermediate. Baldwin's rule[3] holds well for this cyclization. Namely, aporphine (**5**) is solely afforded according to the 6-*endo-trig* mode of cyclization. In spite of a favorable mode of cyclization (6-*exo-trig*), no morphinandienone (**11**) is obtained, probably due to steric factors. No cyclization to proaporphine (**12**) was observed. However, the possibility of conversion of the initially generated quinonoid cation (**13**) into aporphine (**5**) by a dienone–phenol type-rearrangement still remains. On the other hand, in the case of the 1-phenethyl *p*-quinol acetate (**2**), three kinds of cyclized products are produced according to Baldwin's rule; *i.e.* homoaporphine (**6**), homomorphinandienone (**7**), and homoproaporphine (**8**) are afforded through the 7-*endo-trig*, 7-*exo-trig*, and 6-*endo-trig* modes, respectively. To investigate further the mode of cyclization, we chose three tetrahydroisoquinolines, 1-(4-methoxyphenethyl) (**14**)-, 1-(4-methoxybenzyl) (**15**)-, and 1-(3,4-dimethoxyphenyl) (**16**)-1,2,3,4-tetrahydro-6-methoxy-2-methyl-7-isoquinolinols.

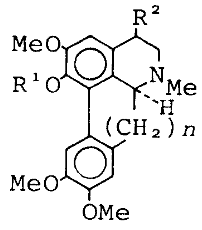
Because of the coupled effect of Baldwin's rule and the fact that the C-8 carbon was attacked by the carbon *para* to the activating ether group in ring C, the result of acid treatment of the *o*-quinonoid cations, **17**, **18**, and **19** was expected to be as follows. Namely, **17** would afford homoproaporphine (**20**) through the favorable 6-*endo-trig* mode. On the other hand, the other two, **18** and **19**, would give no cyclized products, proaporphine (**21**) and C-noraporphine (**22**), because the 5-*endo-trig* mode is disfavored. The present report deals with the confirmation of this prediction and with stereochemical aspects of the reaction of *p*-quinol acetates (**23**, **24**, and **25**) Ac_2O–conc. H_2SO_4.



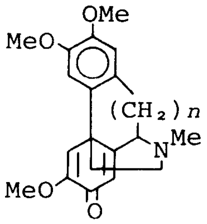
1: $n=1$, R=OMe, X=H
2: $n=2$, R=OMe, X=H
23: $n=2$, R=X=H
24: $n=1$, R=X=H
25: $n=0$, R=OMe, X=H
44: $n=0$, R=OMe, X=Br



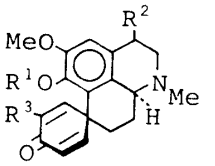
3: $n=1$, R=OMe, X=H
4: $n=2$, R=OMe, X=H
14: $n=2$, R=X=H
15: $n=1$, R=X=H
16: $n=0$, R=OMe, X=H
45: $n=0$, R=OMe, X=Br



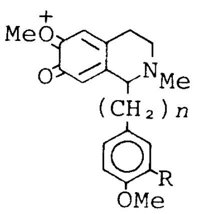
5: $n=1$, $R^1=R^2=H$
6: $n=2$, $R^1=R^2=H$
34: $n=1$, $R^1=Ac$, $R^2=OAc$
35: $n=1$, $R^1=Ac$, $R^2=H$



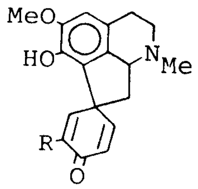
7: $n=2$
11: $n=1$



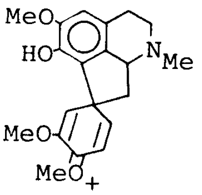
8: $R^1=R^2=H$, $R^3=OMe$
20: $R^1=R^2=R^3=H$
31: $R^1=Ac$, $R^2=R^3=H$
32: $R^1=Ac$, $R^2=OAc$, $R^3=H$



9: $n=1$, R=OMe
10: $n=2$, R=OMe
17: $n=2$, R=H
18: $n=1$, R=H
19: $n=0$, R=OMe



12: R=OMe
21: R=H



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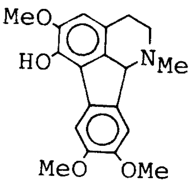

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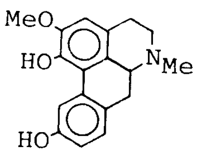

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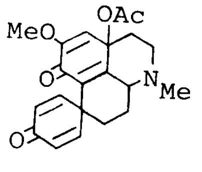

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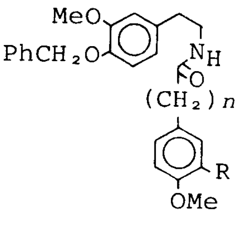
Fig. 1



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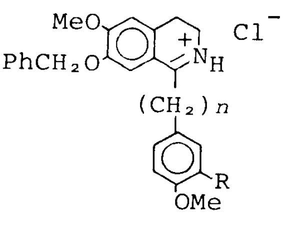

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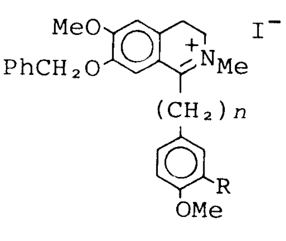

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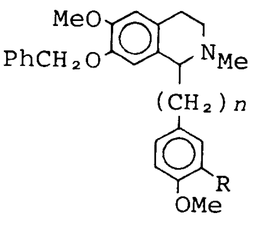

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c: $n=2$, R=H
d: $n=0$, R=OMe

Fig. 2

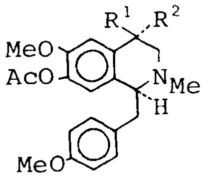
The starting 7-phenolic tetrahydroisoquinolines (**14**, **15**, and **16**) were prepared from the amides (**26**) *via* **27**, **28**, and **29** by a standard sequence of reaction[2] [Bischler–Napieralski cyclization, *N*-methylation, $NaBH_4$ reduction, and debenzylation]. Lead tetraacetate oxidation of **14**, **15**, and **16** as usual[2] gave the *p*-quinol acetates (**23**, **24**, and **25**) quantitatively; infrared (IR) spectral data are listed in Table I.

Treatment of **23** with CF_3CO_2H in CH_2Cl_2 gave (±)-1-hydroxy-2-methoxyhomoproaporphine (**20**) in high yield, as expected. Spectral data for **20** were coincident with those in the literature.[4] On the other hand, treatment of **24** with CF_3CO_2H gave neither proaporphine (**21**) nor aporphine (**30**), which could be produced by the dienone-phenol rearrangement of the former. Similarly, treatment of **25** with the same acid did not give even a trace of *C*-noraporphine (**22**), as predicted. Thus, Baldwin's rule holds here.

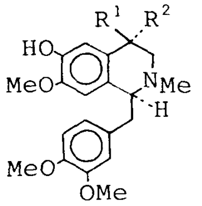
Next we tried to treat the *p*-quinol acetates (**23**, **24**, and **25**) with Ac_2O–conc. H_2SO_4 instead of CF_3CO_2H. Treatment of **23** with Ac_2O–conc. H_2SO_4 gave (±)-1-acetoxy-2-methoxyhomoproaporphine (**31**) and a small amount of (±)-1,4β-diacetoxy-2-methoxyhomoproaporphine (**32**). Identity of **31** with the acetate of **20** was confirmed by mixed melting point determination and spectral comparisons. The structure of **32** was supported by an alternative synthesis; *i.e.* the *p*-quinol acetate (**33**) obtained on lead tetraacetate oxidation of **20** gave the same product as **32** when treated with Ac_2O–conc. H_2SO_4. β-Orientation of

TABLE I. IR Spectral Data for the *p*-Quinol Acetates (in $CHCl_3$)

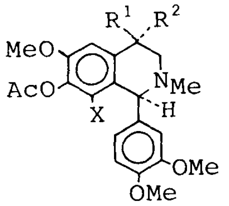
Compound	OAc (cm^{-1})	Dienone (cm^{-1})		
23	1740	1665	1640	1620
24	1740	1670	1650	1630
25	1750	1680	1660	1640
33	1735	1680	1620	
44	1740	1690	1660 (sh.)	



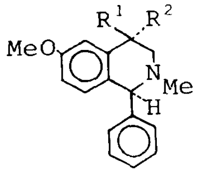
36a: $R^1=H$, $R^2=OAc$
36b: $R^1=OAc$, $R^2=H$



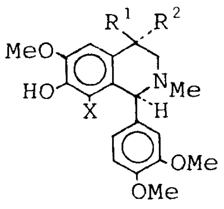
37a: $R^1=H$, $R^2=OAc$
37b: $R^1=OAc$, $R^2=H$



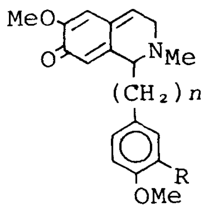
38a: $R^1=X=H$, $R^2=OAc$
38b: $R^1=OAc$, $R^2=X=H$
46: $R^1=H$, $R^2=OAc$, $X=Br$



39a: $R^1=H$, $R^2=OH$
39b: $R^1=OH$, $R^2=H$



40a: $R^1=X=H$, $R^2=OMe$
40b: $R^1=OMe$, $R^2=X=H$
41a: $R^1=H$, $R^2=OMe$, $X=Br$
41b: $R^1=OMe$, $R^2=H$, $X=Br$
47: $R^1=H$, $R^2=OH$, $X=Br$



42: $n=1$, $R=H$
43: $n=0$, $R=OMe$

Fig. 3

TABLE II. NMR Chemical Shifts and Coupling Constants of C-4 Protons on 4-Substituted 1-Aryl-1,2,3,4-tetrahydroisoquinolines

Configuration	Compound			
	38	39	40	41
a series (1,4-*trans*)	δ 6.15 (dd, $J=6$ and 8 Hz)	δ 5.12 (dd, $J=5.3$ and 7.5 Hz)	δ 4.67 (dd, $J=6$ and 9 Hz)	δ 4.21 (t, $J=3$ Hz)
b series (1,4-*cis*)	δ 5.91 (br t, $w/2=$ 5.7 Hz)	δ 5.45 (t, $J=2.3$ Hz)	δ 4.23 (t, $J=3$ Hz)	δ 4.60 (dd, $J=7$ and 9 Hz)

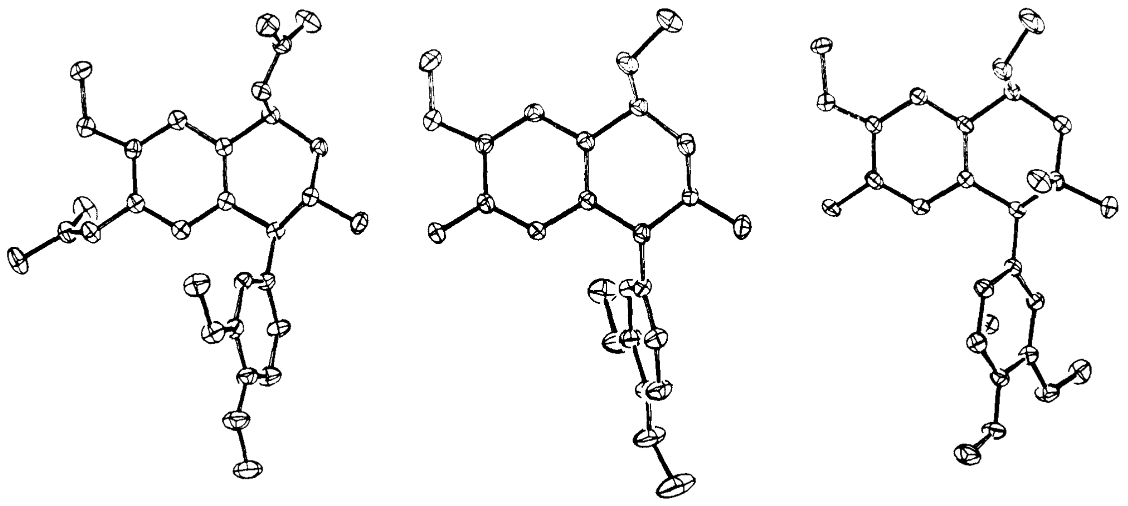
the 4-acetoxyl group was proved on the basis of the nuclear magnetic resonance (NMR) coupling constant (dd, $J=2.5$ and 5.0 Hz) of the pseudoequatorial C-4 hydrogen[5] at δ 5.95. Previously, 4β-acetoxy-*O*-acetylaporphine (**34**) was obtained as a minor product in addition to *O*-acetylaporphine (**35**) by treatment of the *p*-quinol acetate (**1**) with Ac_2O–conc. H_2SO_4. Hence, the formation mechanism of **32** is probably analogous to that of **34**.[5]

Similarly, **24** was treated with Ac_2O–conc. H_2SO_4 to afford two kinds of diastereoisomers (**36a** and **36b**) in 36 and 10% yields, respectively. Both **36a** and **36b** were shown to possess two acetoxyl groupings, aromatic and aliphatic, and the C-4 hydrogen of **36a** appeared at δ 5.74 as a triplet[6] ($J=3.5$ Hz), whereas that of **36b** appeared at δ 5.88 as a triplet ($J=6$ Hz). Orientation of the 4-acetoxyl group was determined by analogy to that of 4-acetoxy-1,2,3,4-tetrahydro-7-methoxy-2-methyl-1-veratryl-6-isoquinolinols (**37a** and **37b**).[7] Namely, by comparison of the coupling patterns of two pairs of 4-acetoxy derivatives, the stereostructure of **36a** was determined as 1,4-*trans* diacetate and that of **36b** as 1,4-*cis*.

Similar treatment of **25** with Ac_2O–conc. H_2SO_4 gave two diastereoisomeric 4-acetoxy derivatives, 4,7-diacetoxy-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinolines (**38a** and **38b**) in a ratio of 2:5. The presence of the aromatic and aliphatic acetoxyl groupings in **38a** and **38b** was evident in their IR spectra. On the basis of the NMR data and the assumption that the 1-phenyl group in **39a** and **39b** was quasi-equatorially disposed, Kametani *et al.*[8] claimed that the 4-hydroxy and 1-phenyl groups of 1,2,3,4-tetrahydro-4-hydroxy-6-methoxy-2-methyl-1-phenylisoquinolines, **39a** [δ 5.12 (dd, $J=5.3$ and 7.5 Hz)] and **39b** [δ 5.45 (t, $J=2.3$ Hz)], were oriented *trans* and *cis*, respectively. By comparison of the coupling patterns of the C-4 hydrogens of **38a** [δ 6.15 (dd, $J=6$ and 8 Hz)] and **38b** [δ 5.91 (br t, $w/2=5.7$ Hz)] with those of **39a** and **39b**, the stereostructure of **38a** and **38b** could be assigned as 1,4-*trans*- and 1,4-*cis*-4,7-diacetoxy-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinolines, respectively. In order to check this, two diastereoisomeric 4-methoxy derivatives (**40a** and **40b**) and their brominated products (**41a** and **41b**) were prepared as follows and the coupling patterns of the C-4 hydrogens were compared. Treatment of **38a** or **38b** with 5% aq. KOH in MeOH[9] gave two diastereoisomeric 1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-4,6-dimethoxy-2-methyl-7-isoquinolinols (**40a** and **40b**), in a ratio of approximately 1:1. Bromination of **40a** and **40b** gave 8-bromo-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-4,6-dimethoxy-2-methyl-7-isoquinolinols (**41a** and **41b**), respectively. The coupling pattern of the C-4 hydrogen in **41a** and **41b** was dramatically changed when compared with that in the starting **40a** or **40b** as shown in Table II. The reversal was explicable in terms of conformational change of the Δ^3-piperideine moiety. Namely, the quasi-equatorially oriented 1-phenyl group in **40a** and **40b** was forced to dispose quasi-axially owing to severe steric repulsion with the C-8 bromine atom. Thus the validity of Kametani's assumption was verified; *i.e.* the 1,4-disubstituents in the a series were *trans*-oriented, and in the b series, *cis*.

For unequivocal confirmation, X-ray crystallographic analyses of **38a**, **40a**, and **40b** were carried out. Perpendicularity of the two benzene planes in these three compounds was a prominent feature, indicating that a kind to allylic strain was actually operating.

As mentioned above, the *trans vs. cis* ratios in the reaction of **24** and **25** with Ac_2O–conc. H_2SO_4 were markedly different; *i.e.* **36a**:**36b**=7:2 and **38a**:**38b**=2:5. This phenomenon is worthy of some comment. Up to the present, the most convincing reaction mode was considered to be the conjugated addition of acetic acid to the intermediary *p*-quinone methides (**42** and **43**) or the like, and the preferred direction of addition was expected to be governed by the lone pair electrons on the nitrogen atom. Our X-ray analysis[10)] of 1,2,3,4-tetrahydro-7-methoxy-2-methyl-1-(3,4-methylenedioxybenzyl)-6-isoquinolinol revealed that the benzyl group at C-1 was quasi-axially oriented. In view of this result and the fact that



38b **40a** **40b**·methiodide

Fig. 4

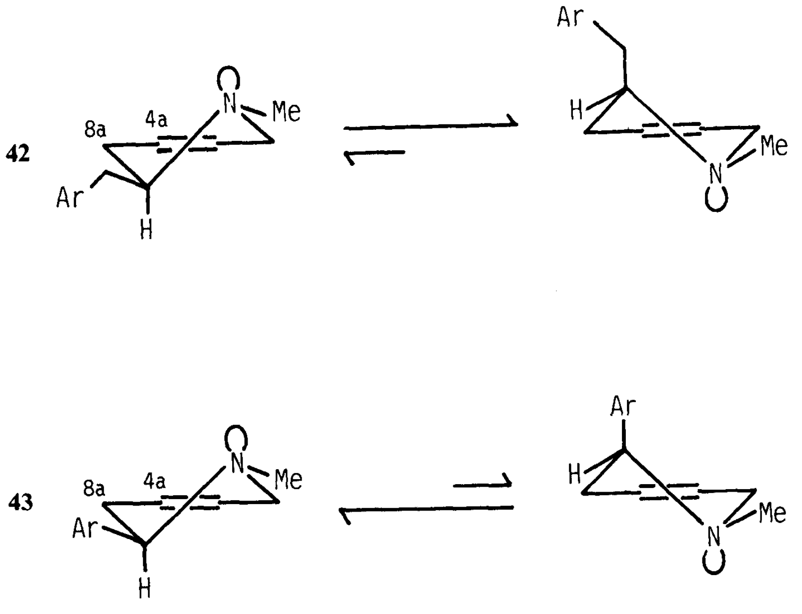


Fig. 5

Table III. Microanalytical or High Resolution Mass Spectral Data for New Compounds

Compound	Formula	Molecular weight	Analysis (%) Calcd (Found)		
			C	H	N
16	$C_{19}H_{23}NO_4$	329.38	69.28	7.04	4.25
			(69.15	7.05	3.99)
20	$C_{19}H_{21}NO_3$	311.37	73.29	6.80	4.50
			(72.92	6.77	4.65)
31	$C_{21}H_{23}NO_4$	353.40	71.37	6.56	3.96
			(71.63	6.51	4.03)
32	$C_{23}H_{25}NO_6$	411.44	67.14	6.12	3.40
			(66.90	6.08	3.25)
36a[a]	$C_{24}H_{30}INO_6$	555.40	51.90	5.44	2.52
			(51.90	5.40	2.57)
36b[a]	$C_{24}H_{30}INO_6 \cdot 0.25H_2O$	559.90	51.48	5.49	2.50
			(51.42	5.23	2.59)
38a[a]	$C_{24}H_{30}INO_7 \cdot MeOH$	603.45	49.84	5.29	2.32
			(49.82	5.27	2.27)
38a	$C_{23}H_{27}NO_7$	429.1786		(429.1791[b])	
38b[a]	$C_{24}H_{30}INO_7 \cdot MeOH$	603.45	49.84	5.29	2.32
			(49.63	5.21	2.36)
38b	$C_{23}H_{27}NO_7$	429.1786		(429.1775[b])	
40a	$C_{20}H_{25}NO_5$	359.43	66.84	7.01	3.90
			(67.14	6.96	3.87)
40b[a]	$C_{21}H_{28}INO_5 \cdot H_2O$	537.40	48.56	5.82	2.70
			(48.62	5.82	2.61)
41a	$C_{20}H_{24}BrNO_5$	438.33	54.80	5.52	3.20
			(54.78	5.47	3.07)
41b	$C_{20}H_{24}BrNO_5$	437.0836		(437.0820[b])	
	$C_{20}H_{24}Br^{*}NO_5$	439.0817		(439.0815[b])	
45	$C_{19}H_{22}BrNO_4$	408.30	55.89	5.43	3.43
			(55.77	5.33	3.11)
46[c]	$C_{24}H_{29}BrClNO_{11}$	622.86	46.28	4.69	2.25
			(46.10	4.52	2.19)
26d	$C_{25}H_{27}NO_5$	421.47	71.24	6.46	3.32
			(71.03	6.49	3.08)
27c	$C_{25}H_{28}ClNO_3$	425.94	70.49	6.63	3.29
			(70.72	6.77	3.19)
28d	$C_{26}H_{29}INO_4$	546.41	57.15	5.35	2.56
			(56.99	5.24	2.20)

a) Methiodide.
b) High resolution mass spectral data.
c) Methoperchlorate.

nitrogen inversion and ring reversal of piperidine and piperideine inevitably occur in certain solvents,[11] the above ratio is most probably a reflection of the actual nitrogen inversion that occurred (Fig. 5). Thus the β-quasi-axial conformation of the benzyl group at C-1 in **42** was relatively stable enough to permit attack of the hydrogen-bonded acetic acid from the α side to a larger extent. On the other hand, the β quasi-equatorial conformation of the aryl group at C-1 in **43** was so stable that the 1,4-*cis* diastereoisomer (**38b**) was formed preferentially.

Treatment of **38a** and **38b** with 5% aq. KOH in MeOH gave a 1 : 1 mixture of **40a** and **40b**, showing that the selectivity was lost due to the preferred hydrogen bonding of methanol to hydroxide ion over the nitrogen atom.

Treatment of the *p*-quinol acetate (**44**), which was derived from 8-bromo-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6-methoxy-2-methyl-7-isoquinolinol (**45**), with Ac_2O–conc. H_2SO_4 gave the 4α,7-diacetate (**46**; 1,4-*trans*) as a sole product. Since the β quasi-axially oriented aryl group at C-1 in the intermediary *p*-quinone methide was frozen or the conformation was rigid enough to permit no nitrogen inversion, α-oriented lone pair electrons of nitrogen were wholly responsible for the selectivity in this case. Treatment of **46** with 5% aq. KOH in MeOH gave **41a** exclusively. Presumably, the β-face attack of methoxide ion and/or methanol was hindered by the β quasi-axially oriented aryl group at C-1 in the intermediary *p*-quinone methide. Thus, the stereochemical features of the reaction of *p*-quinol acetates, **24**, **25**, **33**, and **44**, with Ac_2O–conc. H_2SO_4 can be rationally explained.

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. NMR spectra were taken with a JEOL JNR-4H-100 (100 MHz), JEOL JNM-FX-100 (100 MHz), or Hitachi R-24B instrument in $CDCl_3$ solution with Me_4Si as an internal standard. IR spectra were run on a Hitachi model 215 spectrometer. High resolution mass spectrum (MS) data were measured with a Hitachi RMU-6E mass spectrometer. Preparative thin-layer chromatography (TLC) was performed on Silica gel HF_{254} or precoated Silica gel 60 F_{254} plates (Merck) 2.0 mm thick. Microanalytical data for all new compounds are listed in Table III.

General Procedure[2] for the Synthesis of 1,2,3,4-Tetrahydro-7-isoquinolinols (14 and 15)——A mixture of 4-benzyloxy-3-methoxyphenethylamine and 4-methoxydihydrocinnamic acid was heated for 3 h to give an amide (**26c**). Schotten–Baumann reaction of the same amine and 3,4-dimethoxybenzoyl chloride afforded an amide (**26d**). Bischler–Napieralski reaction of **26c** and **26d** yielded the 3,4-dihydroisoquinoline hydrochlorides (**27c** and **27d**). Quaternization of the free bases with methyl iodide gave the metho salts (**28c** and **28d**), sodium borohydride reduction of which yielded 7-benzyloxy-1,2,3,4-tetrahydroisoquinolines (**29c** and **29d**). Hydrogenolysis of the bases with palladium on carbon gave **14** and **16**. Yields and physical data are as follows. **26c**: 58%, mp 144—145 °C (MeOH) [lit. 139—141 °C,[12] 135—136 °C[13]]; IR ν_{max}^{KBr} cm^{-1}: 3275 (NH), 1640 (C=O). **26d**: 83%, mp 178 °C (iso-PrOH); IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1640 (C=O). **27c**: 75%, mp 157—159 °C (ether–MeOH); IR ν_{max}^{KBr} cm^{-1}: 1640 ($C=N^+H$). **27d**: 92%, mp 144.5 °C (ether–MeOH); IR ν_{max}^{KBr} cm^{-1}: 1640 ($C=N^+H$). **28c**: 94%, mp 112—115 °C (MeOH–iso-PrOH) [lit. 141—143 °C,[12] 126—127 °C[13]]; IR ν_{max}^{KBr} cm^{-1}: 1630 ($C=N^+<$). **28d**: 79%, mp 188—189 °C (iso-PrOH); IR ν_{max}^{KBr} cm^{-1}: 1610 ($C=N^+<$). **29c**: 100%, oil; NMR δ: 2.40 (NMe), 3.70, 3.79 (each OMe), 5.07 (OCH_2Ph), 6.55 (2H, s, 5- and 8-H), 6.76 (2H, d, *J*=10 Hz, 3′- and 5′-H), 6.98 (2H, d, *J*=10 Hz, 2′- and 6′-H). **29d**: 84%, oil; NMR δ: 2.02 (NMe), 3.58, 3.68, 3.72 (each OMe), 3.80 (1-H), 4.68 (OCH_2Ph), 5.95 (8-H), 6.42 (5-H). **14**: 93%, amorphous mass; IR ν_{max}^{KBr} cm^{-1}: 3530 (OH); NMR δ: 2.40 (NMe), 3.70, 3.75 (each OMe), 6.50, 6.62 (each 1H, s, 5- and 8-H), 6.76 (2H, d, *J*=10 Hz, 3′- and 5′-H), 7.06 (2H, d, *J*=10 Hz, 2′- and 6′-H). **16**: 88%, mp 168 °C (ether); IR ν_{max}^{KBr} cm^{-1}: 3350 (OH); NMR δ: 2.05 (NMe), 3.68, 3.70, 3.74 (each OMe), 3.92 (1-H), 6.12 (8-H), 6.48 (5-H), 6.72 (br s, 2′-, 5′-, and 6′-H).

Synthesis of (±)-1-Hydroxy-2-methoxyhomoproaporphine (20)——$Pb(OAc)_4$ oxidation of **14** (100 mg) and subsequent treatment with CF_3CO_2H were carried out as described previously[2] to give **20**: 94.3 mg (98%), mp 239—241 °C ($CHCl_3$–MeOH) [lit.[4] 248—249 °C (dec.)]; IR ν_{max}^{KBr} cm^{-1}: 3520 (OH), 1655, 1620 (dienone); NMR δ: 2.43 (NMe), 3.77 (OMe), 6.15—6.35 (2H, complex, 10- and 12-H), 6.52 (3-H), 6.80—7.08 (2H, complex, 9- and 13-H).

Ac_2O–conc. H_2SO_4 Treatment of *p*-Quinol Acetates (23, 24, 25, 33, and 44)——$Pb(OAc)_4$ oxidation and subsequent treatment with Ac_2O–conc. H_2SO_4 were carried out as described previously.[14] The amounts of the starting phenols (**14**, **15**, **16**, **20**, and **45**), methods of purification, melting points and yields of the products, and spectroscopic data are given below. **14** (100 mg): preparative TLC (development with $CHCl_3$: MeOH = 20 : 1, mobility **32** > **31**), **32** [6 mg (5%), mp 214—215 °C (acetone–ether); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1720 (OAc), 1655, 1620 (dienone); NMR δ: 2.00, 2.14 (each OAc), 2.47 (NMe), 3.74 (OMe), 5.95 (dd, *J*=2.5, 5 Hz, 4-H), 6.19—6.40 (2H, complex, 10- and 12-H), 6.92 (3-H), 6.79—7.14 (2H, complex, 9- and 13-H)] and **31** [57 mg (53%), mp 194—195 °C (iso-PrOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (OAc), 1650, 1620 (dienone); NMR δ: 1.99 (OAc), 2.45 (NMe), 3.73 (OMe), 6.15—6.37 (2H, complex, 10- and 12-H), 6.69 (3-H), 6.82—7.13 (2H, complex, 9- and 13-H)]. **15** (123 mg): preparative TLC (first development with $CHCl_3$: MeOH = 100 : 7 and second with benzene : AcOEt = 3 : 5, mobility **36a** > **36b**), **36a** [54 mg (36%), oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1725 (OAc); NMR δ: 2.07, 2.21 (each OAc), 2.55 (NMe), 3.72, 3.74 (each OMe), 5.74 (1H, t, *J*=3.5 Hz, 4-H), 6.26 (8-H), 6.72 (2H, d, *J*=8.8 Hz, 3′- and 5′-H), 6.82 (5-H), 6.91 (2H, d, *J*=8.8 Hz, 2′- and 6′-H); methiodide: mp 168—170 °C (MeOH)] and **36b** [15 mg (10%), oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1755, 1720

TABLE IV. Crystallographic Parameters

Compound	**38b**	**40a**	**40b**·methiodide
Formula	$C_{23}H_{27}NO_7 \cdot 0.5C_3H_7OH$	$C_{20}H_{25}NO_5$	$C_{21}H_{28}$ NO_5
Formula weight	503.6	359.4	501.4
Crystal system	Triclinic	Orthorhombic	Triclinic
Space group	$P\bar{1}$	P_{cab}	$P\bar{1}$
a (Å)	12.388 (6)	13.153 (7)	10.888 (6)
b (Å)	11.828 (6)	22.374 (11)	11.765 (6)
c (Å)	11.163 (6)	12.629 (6)	9.651 (5)
α (°)	68.97 (3)		112.36 (6)
β (°)	114.28 (6)		92.79 (5)
γ (°)	120.47 (6)		96.99 (5)
U (Å^3)	1261	3716.5	1129
Z	2	8	2
D_{calc} (g cm^{-3})	1.326	1.285	1.475

TABLE V. Final Atomic Coordinates (× 10^4) and Thermal Parameters for Non-hydrogen Atoms of **38b**, with Their e.s.d.'s in Parentheses

Atom	X	Y	Z	B_{eq} A 2
C1	484 (7)	6728 (7)	388 (8)	5.03 (.15)
N2	−289 (6)	7496 (6)	−566 (6)	5.72 (.13)
C3	−1632 (8)	6536 (8)	−1152 (8)	5.24 (.16)
C4	−2369 (8)	5746 (8)	−92 (8)	5.63 (.16)
C4A	−1547 (7)	5265 (7)	1216 (8)	4.57 (.15)
C5	−2172 (8)	4348 (8)	2210 (8)	5.15 (.16)
C6	−1449 (8)	3893 (7)	3433 (8)	5.44 (.16)
C7	−107 (8)	4329 (8)	3650 (8)	4.81 (.16)
C8	523 (8)	5231 (8)	2694 (8)	5.23 (.16)
C8A	−209 (7)	5724 (7)	1450 (8)	4.59 (.15)
C9	1875 (7)	7655 (7)	1012 (8)	5.21 (.15)
C10	2114 (8)	8526 (7)	1770 (8)	5.13 (.15)
C11	3396 (8)	9368 (8)	2337 (8)	5.62 (.16)
C12	4441 (8)	9341 (9)	2166 (9)	5.61 (.18)
C13	4203 (9)	8489 (10)	1432 (11)	7.69 (.21)
C14	2907 (8)	7638 (9)	839 (10)	7.24 (.19)
C15	2691 (10)	10286 (11)	3335 (11)	8.97 (.25)
C16	6750 (10)	10201 (14)	2663 (13)	9.01 (.30)
C17	319 (9)	8398 (9)	−1660 (9)	9.49 (.20)
C18	−3844 (8)	6681 (8)	−517 (9)	6.84 (.17)
C19	−4066 (10)	7566 (10)	−46 (11)	10.27 (.22)
C20	−3251 (9)	2807 (11)	4364 (11)	10.55 (.23)
C21	494 (9)	2662 (9)	5330 (9)	7.54 (.19)
C22	1301 (11)	2441 (11)	6753 (10)	10.47 (.25)
O1	−2695 (5)	6623 (5)	222 (6)	5.30 (.11)
O2	−4582 (7)	6084 (8)	−1413 (7)	7.69 (.17)
O3	−1931 (6)	3069 (6)	4489 (6)	7.83 (.13)
O4	664 (6)	3964 (6)	4916 (6)	5.43 (.12)
O5	−210 (8)	1860 (7)	4622 (7)	9.20 (.17)
O6	3733 (6)	10267 (6)	3076 (7)	5.69 (.14)
O7	5650 (6)	10213 (7)	2775 (8)	5.92 (.16)
O(S)	539 (7)	604 (6)	−212 (8)	10.39 (.16)

TABLE VI. Final Atomic Coordinates ($\times 10^4$) and Thermal Parameters for Non-hydrogen Atoms of **40a**, with Their e.s.d.'s in Parentheses

Atom	X	Y	Z	B_{eq} A 2
C(1)	860 (2)	2459 (1)	5100 (2)	2.93 (.04)
N(2)	−255 (2)	2340 (1)	5008 (2)	3.01 (.03)
C(3)	−398 (2)	1687 (1)	5000 (3)	3.79 (.04)
C(4)	−33 (2)	1422 (1)	3958 (2)	2.91 (.04)
C(4A)	1007 (2)	1655 (1)	3683 (2)	2.69 (.04)
C(5)	1566 (2)	1378 (1)	2871 (2)	2.64 (.04)
C(6)	2552 (2)	1558 (1)	2645 (2)	3.04 (.04)
C(7)	2994 (2)	2019 (1)	3240 (2)	2.82 (.04)
C(8)	2419 (2)	2314 (1)	3986 (2)	2.44 (.04)
C(8A)	1420 (2)	2135 (1)	4224 (2)	2.78 (.04)
C(9)	1073 (2)	3125 (1)	5126 (2)	2.88 (.04)
C(10)	975 (2)	3476 (1)	4214 (3)	2.69 (.04)
C(11)	1150 (3)	4084 (1)	4242 (3)	3.15 (.05)
C(12)	1418 (3)	4356 (1)	5206 (3)	3.09 (.05)
C(13)	1542 (3)	4013 (2)	6099 (3)	3.28 (.06)
C(14)	1380 (3)	3394 (2)	6056 (3)	3.31 (.05)
C(15)	−778 (3)	2596 (2)	5945 (3)	4.14 (.05)
O(16)	45 (2)	785 (1)	4047 (2)	4.63 (.04)
C(17)	−906 (3)	487 (2)	4116 (4)	4.63 (.07)
O(18)	3164 (2)	1307 (1)	1881 (2)	3.43 (.03)
C(19)	2684 (3)	920 (2)	1135 (3)	3.91 (.06)
O(20)	3994 (2)	2167 (1)	3061 (2)	3.12 (.03)
O(21)	1089 (2)	4458 (1)	3393 (2)	3.90 (.04)
C(22)	784 (3)	4205 (2)	2404 (3)	4.57 (.07)
O(23)	1544 (3)	4962 (1)	5165 (2)	4.55 (.05)
C(24)	1613 (5)	5271 (2)	6121 (4)	6.41 (.11)

(OAc); NMR δ: 2.07, 2.23 (each OAc), 2.48 (NMe), 3.72, 3.75 (each OMe), 5.88 (1H, t, $J=6$ Hz, 4-H), 6.42 (8-H), 6.73 (2H, d, $J=8.8$ Hz, 3′- and 5′-H), 6.82 (5-H), 6.98 (2H, d, $J=8.8$ Hz, 2′- and 6′-H); methiodide: mp 181—182 °C (MeOH)]. **16** (480 mg): preparative TLC (development with *n*-hexane : AcOEt = 1 : 2, mobility **38a** > **38b**), **38a** [116 mg (19%), mp 149.5—150 °C (MeOH); IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1755, 1725 (OAc); NMR δ: 2.18 (3H, s, NMe or OAc), 2.20 (6H, s, 2 × OAc or OAc and NMe), 3.79 (6H, s, 2 × OMe), 3.86 (3H, s, OMe), 4.18 (1-H), 6.15 (1H, dd, $J=6$, 8 Hz, 4-H), 6.32 (8-H), 6.63 (br s, 2′-H), 6.74 (2H, br s, 5′- and 6′-H), 6.79 (5-H)] and **38b** [298 mg (48%), mp 118.5—120.5 °C (iso-PrOH); IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1755, 1725 (OAc); NMR δ: 2.18, 2.19, 2.21 (each 3H, s, 2 × OAc and NMe), 3.80, 3.82, 3.88 (each 3H, s, OMe), 3.95 (1-H), 5.91 (1H, br t, $w/2=5.7$ Hz, 4-H), 6.28 (8-H), 6.74 (br s, 2′-H), 6.80 (2H, br s, 5′- and 6′-H), 6.92 (5-H); methiodide: mp 182—184 °C (MeOH)]. **20** (200 mg): **32** [248 mg (94%), mp 214—215 °C (acetone–ether)], all spectral data were consistent with those of an authentic sample reported above. **45** (126 mg): preparative TLC (development with *n*-hexane : AcOEt = 1 : 2), **46** [64 mg (41%), oil; IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1760, 1720 (OAc); NMR δ: 2.16, 2.31, 2.45 (each 3H, s, 2 × OAc and NMe), 3.81, 3.83, 3.84 (each 3H, s, OMe), 5.05 (1-H), 5.89 (1H, d, $J=3$ Hz, 4-H), 6.28 (1H, dd, $J=2$, 8 Hz, 6′-H), 6.55 (1H, d, $J=2$ Hz, 2′-H), 6.70 (1H, d, $J=8$ Hz, 5′-H), 6.97 (5-H); methoperchlorate: mp 154—157 °C (EtOH)].

Acetylation of 20——Acetylation on **20** (30 mg) with $\mathrm{Ac_2O}$ (0.3 ml) and pyridine (0.3 ml) gave 1-acetoxy-2-methoxyhomoaporphine (**31**) (31 mg), mp 193.5—194 °C, which was identical with an authentic sample (**31**) reported above.

Reaction of Diacetates (38a and 38b) with 5% aq. KOH in MeOH——A 5% aq. KOH solution (1.5 ml) was added to a solution of **38a** (74 mg) in MeOH (3 ml). The whole was stirred at room temperature for 30 min. Usual work-up gave an amorphous mass (52 mg), which was separated into two diastereoisomeric 4-methoxy derivatives (**40a** and **40b**) by preparative TLC (development with $\mathrm{CHCl_3}$: MeOH = 10 : 1, mobility **40a** > **40b**). **40a** [15 mg (24%), mp 158.5—160.5 °C (MeOH); NMR δ: 2.22 (NMe), 3.55 (4-OMe), 3.75, 3.84, 3.85 (each 3H, s, OMe), 4.08 (1-H), 4.67 (1H, dd, $J=6$, 9 Hz, 4-H), 6.15 (8-H), 6.68 (br s, 2′-H), 6.75 (2H, br s, 5′- and 6′-H), 6.94 (5-H)]. **40b** [15 mg (24%), oil; NMR δ: 2.10 (NMe), 3.53 (4-OMe), 3.77 (OMe), 3.84 (6H, s, 2 × OMe), 3.92 (1-H), 4.24 (1H, t, $J=3$ Hz, 4-H), 6.19 (8-H), 6.75 (4H, br s, ArH); methiodide: mp 166—171 °C ($\mathrm{H_2O}$). The same treatment of **38b** (130 mg) with MeOH

TABLE VII. Final Atomic Coordinates and Thermal Parameters for Non-hydrogen Atoms of **40b**·Methiodide, with Their e.s.d.'s in Parentheses

Atom	X 10 5	Y 10 5	Z 10 5	B_{eq} A 2
I	−3304 (8)	5295 (7)	77089 (9)	5.67 (.01)
Atom	**X 10 4**	**Y 10 4**	**Z 10 4**	**B_{eq} A 2**
C1	3011 (10)	2386 (10)	3530 (11)	4.39 (.16)
N2	3516 (9)	1998 (9)	1970 (10)	4.91 (.15)
C3	2476 (11)	1945 (10)	841 (12)	4.43 (.18)
C4	2021 (11)	3202 (10)	1167 (12)	4.62 (.17)
C4A	2021 (10)	3954 (10)	2823 (11)	3.56 (.16)
C5	1450 (10)	5028 (10)	3220 (11)	4.27 (.17)
C6	1419 (10)	5758 (10)	4723 (11)	4.02 (.16)
C7	1963 (11)	5447 (10)	5838 (11)	4.39 (.18)
C8	2519 (10)	4384 (10)	5435 (11)	4.81 (.17)
C8A	2542 (9)	3633 (9)	3923 (11)	3.78 (.15)
C9	3878 (10)	2297 (10)	4727 (12)	4.03 (.16)
C10	3535 (10)	1328 (10)	5199 (12)	4.42 (.17)
C11	4211 (10)	1253 (10)	6398 (12)	5.13 (.18)
C12	5253 (10)	2130 (11)	7153 (12)	4.50 (.17)
C13	5594 (10)	3100 (11)	6695 (13)	4.63 (.19)
C14	4921 (10)	3174 (11)	5469 (12)	4.34 (.18)
C15	3813 (13)	678 (12)	1500 (15)	7.37 (.23)
C16	4677 (12)	2851 (14)	1963 (14)	6.71 (.24)
C17	2521 (20)	3634 (16)	−992 (15)	10.17 (.37)
C18	306 (13)	7215 (12)	4183 (14)	8.30 (.22)
C19	6940 (13)	2832 (14)	9096 (16)	5.07 (.26)
C20	2900 (12)	−614 (12)	6170 (16)	6.36 (.23)
O1	1954 (9)	6146 (9)	7319 (8)	7.73 (.17)
O2	879 (8)	6820 (7)	5265 (9)	6.42 (.14)
O3	2807 (9)	3963 (8)	602 (9)	6.76 (.16)
O4	5830 (8)	1988 (8)	8336 (9)	5.29 (.15)
O5	3930 (8)	361 (8)	6968 (10)	6.52 (.15)

(6 ml) and 5% aq. KOH (3 ml) gave **40a** [31 mg (28%)] and **40b** [31 mg (28%)]. Both products were identified by comparison with authentic samples reported above.

Bromination of 16, 40a, and 40b——Ice-cooled 1% (w/v) Br_2–$CHCl_3$ (12 ml) was added portion by portion to a stirred solution of **16** (100 mg) in $CHCl_3$ (2 ml) at 0 °C, and the stirring was continued for 5 min. After addition of sat. aq. $Na_2S_2O_3$ (excess), the mixture was basified with aq. ammonia. Extraction with $CHCl_3$ followed by usual work-up gave 8-bromo-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6-methoxy-2-methyl-7-isoquinolinol (**45**) [126 mg (100%), mp 190—192 °C (MeOH); NMR δ: 2.42 (NMe), 3.82 (6H, s, 2×OMe), 3.88 (OMe), 4.85 (1-H), 6.29—6.75 (4H, complex, ArH)]. Bromination of **40a** (106 mg) with 1% Br_2–$CHCl_3$ (12 ml) and of **40b** (60 mg) with 1% Br_2–$CHCl_3$ (7 ml) gave 1,4-*trans*- and 1,4-*cis*-8-bromo-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-4,6-dimethoxy-2-methyl-7-isoquinolinols (**41a** and **41b**), respectively. **41a** [130 mg (100%), mp 174—178 °C (dec.) (MeOH); NMR δ: 2.43 (NMe), 2.87 (2H, d, J=3 Hz, 3-H_2), 3.48 (4-OMe), 3.81, 3.83, 3.85 (each 3H, s, OMe), 4.21 (1H, t, J=3 Hz, 4-H), 4.96 (1-H), 6.30 (1H, dd, J=2, 8 Hz, 6′-H), 6.58 (1H, d, J=2 Hz, 2′-H), 6.69 (1H, d, J=8 Hz, 5′-H), 6.93 (5-H)]. **41b** [71 mg (97%), oil; NMR δ: 2.39 (NMe), 2.73 (1H, dd, J=9, 12 Hz, 3-ax. H), 2.96 (1H, dd, J=7, 12 Hz, 3-eq. H), 3.51 (4-OMe), 3.80, 3.83, 3.92 (each 3H, s, OMe), 4.60 (1H, dd, J=7, 9 Hz, 4-H), 4.86 (1-H), 6.47 (1H, dd, J=2, 8 Hz, 6′-H), 6.64 (1H, d, J=2 Hz, 2′-H), 6.72 (1H, d, J=8 Hz, 5′-H), 7.00 (5-H)].

Reaction of 46 with 5% aq. KOH in MeOH——Treatment of the diacetate (**46**) (64 mg) with MeOH (2.4 ml) and 5% aq. KOH (1.2 ml), by the same procedure as above, gave **41a** [14 mg (25%)] and 1,4-*trans*-8-bromo-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-6-methoxy-2-methyl-isoquinolin-4,7-diol (**47**) [25 mg (47%), oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH); NMR δ: 2.35 (NMe), 3.78, 3.82, 3.90 (each 3H, s, OMe), 4.52 (1H, br d, J=3 Hz, 4-H), 4.93 (1-H), 6.30 (1H, dd, J=2, 8 Hz, 6′-H), 6.45 (1H, d, J=2 Hz, 2′-H), 6.68 (1H, d, J=8 Hz, 5′-H), 6.92 (5-H)]. The former product (**41a**) was shown to be identical with an authentic sample reported above by comparison of NMR spectra. The latter product (**47**) was transformed into a diacetate, which was identical with the starting materials (**46**).

Structure Determination by X-Ray Analysis——Intensities were measured by a θ–2θ scan method with a scan speed as specified below (degree min^{-1} in θ) on a Phillips PW 1100 diffractometer using Cu-$K\alpha$ radiation monochromated by means of graphite plates. The structure of **40b**·methiodide was solved by the heavy atom method, and those of **38b** and **40a** by the direct method using the MULTAN[16] program. The data were refined by the least-squares method with block diagonal matrix approximations. The final R values were obtained excluding hydrogen atom contributions. The crystallographic parameters are listed in Table IV, and the atomic coordinates and thermal parameters in Tables V, VI, and VII.[17]

38b: μ for Cu-$K\alpha = 7.62\,\text{cm}^{-1}$; scan speed $= 8°\ \text{min}^{-1}$; 3795 reflections were measured out of about 4300 theoretically possible reflections within the 2θ range of 6—156°. The final R value was 0.122. The rather poor R value may be due to (1) the very fast scan speed which was chosen to shorten the total measuring time, (2) disorder of the solvent molecules as discussed below, (3) exclusion of hydrogen atom contributions. The final difference electron-density map showed a peak near the center of symmetry. The coordinates and temperature factor of this peak were refined by the least-squares method to reasonable values on the assumption that the peak was an oxygen atom. The distance between the symmetry-related peaks across the center of symmetry was 1.47 Å, corresponding to a O–C bond length. It may therefore be assumed that two molecules of isopropanol with 1/2 weight are distributed over the symmetry center, with oxygen and the C-1 carbon atoms superposed on the peak. Two carbon atoms corresponding to the two methyl groups were smeared out and appeared as very broad low peaks in the difference-electron density map, which may indicate the occurrence of free rotation about the O–C_1 bond.

40a: μ for Cu-$K\alpha = 7.17\,\text{cm}^{-1}$; scan speed $= 4°\ \text{min}^{-1}$; 2603 reflections were observed out of 3930 theoretically possible reflections with the 2θ range of 6—156°. The final R value was 0.054.

40b·methiodide: μ for Cu-$K\alpha = 134\,\text{cm}^{-1}$; scan speed $= 9°\ \text{min}^{-1}$; 4064 reflections were measured out of 4765 theoretically possible ones within the 2θ range of 6—157°. The final R value was 0.085.

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