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Studies on Tetrahydroisoquinolines. XXX.[1,2] A Synthesis of Mixed Tetrahydroisoquinoline Dimers *via* *p*-Quinol Acetates

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Acid treatment of the *p*-quinol acetate (**1**) and a variety of phenols gave the coupling compounds. A mechanistic consideration of the reaction is also presented.

Keywords——tetrahydroisoquinoline dimer; radical reaction; *p*-quinol acetate; atropisomer; X-ray analysis; biphenyl; C–C bond formation

We have previously demonstrated that the *p*-quinol acetate (**1**), derived from corypalline (**2a**), reacted with **2a** in the presence of trifluoroacetic acid (TFA) to give a corypalline dimer (**3a**).[3] At that time, the reaction was considered as a nucleophilic attack of **2a** on **1**, the attacking site being the carbon at the C-8 position, *i.e. ortho* to the phenolic hydroxyl group. Since the *para* position to the C-7 hydroxyl group is substituted in **2a**, the carbon at that site is not available. We considered that the carbon at the *para* position to a hydroxyl group might be another possible attacking site if it is unsubstituted.

To examine this possibility, 5-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**4a**) was chosen as a phenol. This paper deals with the results using several phenols. A mechanistic pathway is proposed for the reaction.

Thus, reaction of **1** with **4a** in the presence of TFA and subsequent acetylation gave 8-(5-acetoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-7-acetoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5**), 5-acetoxy-1,2,3,4-tetrahydro-8-(1,2,3,4-tetrahydro-6-methoxy-2-methyl-7-isoquinolyloxy)-2-methylisoquinoline (**6b**), *O*-acetylcorypalline (**2b**), and 5-acetoxy-1,2,3,4-tetrahydroisoquinoline (**4b**).

Accordingly, three characteristics of the present reaction become evident. First, the carbon *para* to the phenolic hydroxyl group did not attack the carbon at the C-8 position of **1**, but instead became linked to the carbonyl oxygen of **1**, giving **6b**, to our surprise. Second, the carbon *ortho* to the phenolic hydroxyl group attacked the carbon at the C-8 position of **1** as before. Third, **1** was reduced to **2a**.

Hydrolysis of **6b** gave 5-hydroxy-1,2,3,4-tetrahydro-8-(1,2,3,4-tetrahydro-6-methoxy-2-methyl-7-isoquinolyloxy)-2-methylisoquinoline (**6a**), which was identical with an authentic sample prepared *via* the Ullmann reaction of 8-bromo-5-benzyloxy-1,2,3,4-tetrahydroisoquinoline and **2a**.

To test the generality of the above three characteristics, we next examined the same reaction of **1** and the phenol as above to obtain 7-hydroxy-6-methoxy-2-methyl-8-(2-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**7a**), 6-methoxy-2-methyl-7-(4-hydroxyphenyloxy)-1,2,3,4-tetrahydroisoquinoline (**8a**), and **2a**. The structures of the former two were deduced by inspection of proton nuclear magnetic resonance (^{1}H-NMR) spectral data. Thus, the above characteristics were proved to be general in the reaction.[4]

Reaction of isocorypalline (**9**), 6-hydroxy-, or 7-hydroxy-1,2,3,4-tetrahydro-2-methylisoquinoline with **1** was similarly carried out to reveal that the expected dimers (**10**, **11**, **12**, **13**, and **14**) were also formed in this case, and **2a** or **2b** was always obtained as a by-product.

The fact that reduction of **1** occurred in the reaction was suggestive of the involvement of a hydrogen radical. To confirm this, the following experiments were undertaken. First, intermediacy of a *p*-quinone methide (**15**) was proved as follows. Namely, treatment of **1** with TFA in methylene chloride gave 4,7-dihydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline and a trace of unchanged **1**. Formation of the former provided strong support for the intermediacy of **15**. Second, reaction of **1** and **9** in the presence of 4,4′-thiobis(2-*tert*-butyl-6-methylphenol) gave none of the dimer (**10**), showing that the reaction proceeded radically.Third, the same treatment of the *p*-quinol acetate (**16**) derived from 1-phenylcorypalline (**17a**) and **2a** gave the dimer (**3a**), **17a**, and **2a**.

Thus, the role of the *p*-quinol acetate (**16**) as an oxidizing agent was proved, *i.e.*, an intermolecular oxidation–reduction took place between the *p*-quinone methide derived from **16** and **2a**. At this stage, we considered that the formation of **7a** and **8a** might occur as indicated in Fig. 1. Namely, the *p*-quinone methide (**15**) and phenol would lie face to face for intermolecular oxidation–reduction, and coupling would occur in two ways, *i.e.*, along the dotted line *a* to give **7a**, and along the dotted line *b* to give **8a**.

The same reaction of **1** and (±)-*N*,4′-*O*-dimethylisococlaurine (**18**) gave two diastereoisomeric 5-(7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-7-methoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolines (**19** and **20**) in a ratio of 2:1, together with **18** and **2a**. Compounds **19** and **20** might have been formed as a consequence of atropisomerism. Actually, X-ray analysis of **19**·2CH_3I unequivocally established its structure as depicted in the scheme. Therefore, the stereostructures of **19** and **20** were determined. The ratio of the two isomers was probably a reflection of the following effects. First, formation of the hydrogen bond between the lone pair electrons of the nitrogen in **15** and the phenolic hydrogen in **18** was prerequisite for the reaction. Second, since the 1-benzyl group of **18** was oriented axially,[5] access of the *p*-quinone methide **15** to **18** from the less hindered side was roughly twice as favorable as from the more hindered side (Fig. 2). Steric repulsion of the methoxyl group of **15** and the benzyl group of **18** is illustrated on the right. Third, the counterclockwise rotation around the newly formed C–C bond was favored over the clockwise one

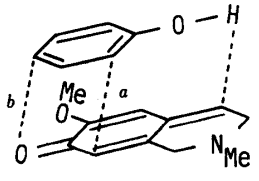
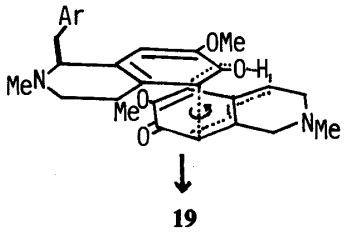


Fig. 1



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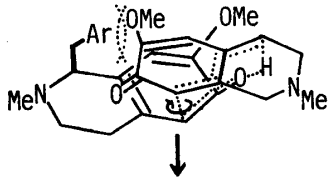

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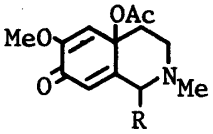
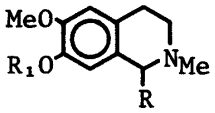
Fig. 2



1 : R=H

16 : R=Ph

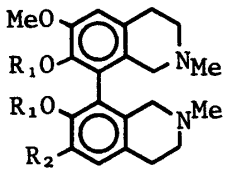


2a : $R_1=R_2=H$

2b : R_1=Ac, R_2=H

17a : R_1=H, R_2=Ph

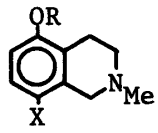
17b : R_1=Ac, R_2=Ph



3a : R_1=H, R_2=OMe

3b : R_1=Ac, R_2=OMe

13 : R_1=Ac, R_2=H

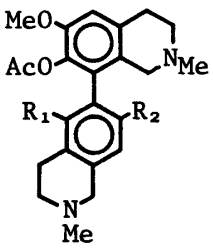


4a : R=X=H

4b : R=Ac, X=H

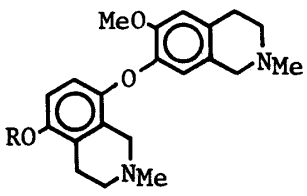
4c : $R=CH_2Ph$, X=H

22 : $R=CH_2Ph$, X=Br



5 : R_1=OAc, R_2=H

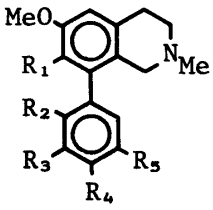
14 : R_1=H, R_2=OAc



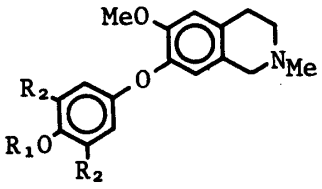
6a : R=H

6b : R=Ac

6c : $R=CH_2Ph$



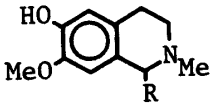
	R_1	R_2	R_3	R_4	R_5
7a :	OH	OH	H	H	H
7b :	OAc	OAc	H	H	H
21 :	OH	H	OMe	OMe	H
24 :	OH	H	Me	OH	Me



8a : $R_1=R_2=H$

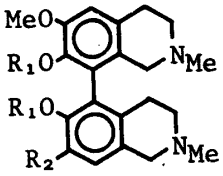
8b : R_1=Ac, R_2=H

23 : R_1=H, R_2=Me



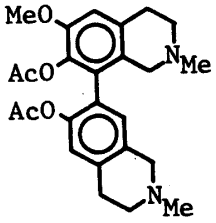
9 : R=H

18 : $R=CH_2$-C$_6$H$_4$-OMe



10 : R_1=H, R_2=OMe

11 : R_1=Ac, R_2=H



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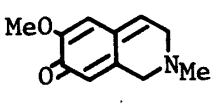

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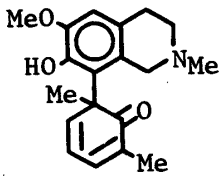

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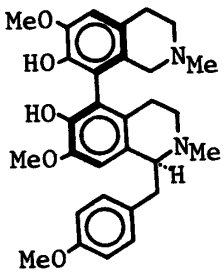

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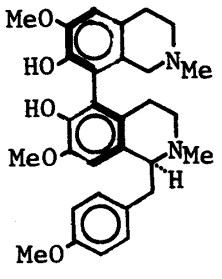

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Chart 1

owing to the stereoelectronic effect of the lone pair electrons (located at the β-side) of the nitrogen in **15** and the oxygen in **18** as depicted in Fig. 2 (left). The reverse was true for the other transition state (right).

Since the intermolecular oxidation–reduction between *p*-quinol acetates and phenols was proved to occur in general, the reaction[3] of **1** and veratrol should have given **2a** to some extent, because the first-formed product, 7-hydroxy-6-methoxy-8-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**21**), should be able to act as a hydrogen donor. Eventually, careful reexamination of the above reaction resulted in a 3.1% yield of **2a**. Though the yield of **2a** was much lower in this case as compared to the reaction of *p*-quinol acetates and phenols, where the yield of **2a** was amounted to *ca.* 18%, the result clearly indicated that oxidation–reduction always occurred in the reaction of *p*-quinol acetate and phenols.

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken with a JEOL JNX-FX-100 (100 MHz) or with a Hitachi R-24B (60 MHz) instrument with Me_4Si as an internal standard. Infrared (IR) spectra were run on a Hitachi 260 spectrometer in $CHCl_3$ solution unless otherwise noted. Mass spectra (MS) were run on a Hitachi RMU-7M mass spectrometer. Preparative thin layer chromatography (TLC) was performed on Silica gel 60 F_{254} plates (Merck), 2.0 mm thick.

General Procedure for the Reaction of the *p*-Quinol Acetate (1) with Phenols——The *p*-quinol acetate (**1**) was prepared quantitatively by $Pb(OAc)_4$ oxidation of corypalline (**2a**) (100 mg, 0.52 mmol), as described previously.[3] Without purification, the *p*-quinol acetate (**1**) and a phenol (1 eq) were dissolved in CH_2Cl_2 (10 ml). Trifluoroacetic acid (1 ml) was added to the solution and the whole was stirred at room temperature for 1 h. The reaction mixture was basified with saturated aqueous $NaHCO_3$ and the product was extracted with CH_2Cl_2. The extract was washed with brine and dried over K_2CO_3. The solvent was removed under reduced pressure to give a mixture of products. The mixture was separated by preparative TLC or column chromatography. In the case of inseparable products, separation of the mixture was carried out after acetylation.

Reaction of 1 and the Tetrahydroisoquinolin-5-ol (4a)[6]——The reaction product was acetylated and separated by preparative TLC [developing solvent, $CHCl_3$–MeOH (10:1)] to give three products, A, B, and C (polarity: A < B < C). A: *O*-Acetylcorypalline (**1b**), 15 mg (12%), mp 77—78 °C (ether–hexane). *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.29; H, 7.28; N, 6.22. ^{1}H-NMR δ: 2.28 (3H, s, OAc), 2.44 (3H, s, NMe), 3.50 (2H, s, 1-H), 3.78 (3H, s, OMe), 6.64 (2H, s, ArH). Product A was identical with an authentic sample [mp 77—78 °C (ether–hexane)]. B: 5-Acetoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**4b**), 59 mg (56%), an oil. High-resolution MS. Calcd for $C_{12}H_{15}NO_2$: 205.1101. Found: 205.1078 (M^+). ^{1}H-NMR δ: 2.27 (3H, s, OAc), 2.42 (3H, s, NMe), 3.53 (2H, s, 1-H). Product B was identical with an authentic sample [bp 140—145 °C (bath temperature)/3 mmHg]. Product C was further developed three times on preparative TLC (developing solvent, $CHCl_3$–MeOH = 10:1) to give the biphenyl (**5**) and the biphenyl ether (**6b**). **5**: an oil, 8.5 mg (4%). High-resolution MS. Calcd for $C_{25}H_{30}N_2O_5$: 438.2152. Found: 438.2142 (M^+). ^{1}H-NMR δ: 1.95, 1.98 (each 3H, s, OAc), 2.33, 2.48 (each 3H, s NMe), 3.80 (3H, s, OMe), 6.68 (1H, s, ArH), 6.89 (2H, s, 2 × ArH). **6b**: an oil 23 mg (11%). MS *m/z*: 396 (M^+). IR cm^{-1}: 1750 (OAc), 1260 (ArOAr). ^{1}H-NMR δ: 2.28 (3H, s, OAc), 2.43, 2.47 (each 3H, s, NMe), 3.77 (3H, s, OMe), 6.44, 6.73 (each 1H, d, J = 9 Hz, ArH), 6.52, 6.66 (each 1H, s, ArH).

Reaction of 1 and Phenol——The reaction products were separated by preparative TLC [developing solvent, $CHCl_3$–MeOH (10:1)] to give corypalline (**2**), 39 mg (19.3%) and a mixture of two compounds. The latter was acetylated with Ac_2O and pyridine to afford an oily acetate, which was separated by preparative TLC [developing solvent, benzene–AcOEt–MeOH (7:5:3)], giving the diacetate (**7b**) and the monoacetate (**8b**). **7b**: an oil, 96.4 mg (25.2%). ^{1}H-NMR δ: 1.94 (3H, s, OAc), 2.01 (3H, s, OAc), 2.33 (3H, s, NMe), 3.15 (2H, s, $ArCH_2N$–), 3.82 (3H, s, OMe), 6.71 (1H, s, 5-H), 7.04—7.46 (4H, m, 4 × ArH). **8b**: an oil, 34 mg (10%). ^{1}H-NMR δ: 2.28 (3H, s, OAc), 2.43 (3H, s, NMe), 3.44 (2H, s, $ArCH_2N$–), 3.78 (3H, s, OMe), 6.62, 6.67 (each 1H, s, ArH), 6.89 (4H, m, 4 × ArH).

Hydrolysis of 7b——Methanolic KOH (5%) (1 ml) was added to a solution of **7b** (96 mg) in MeOH (8 ml), and the mixture was stirred at room temperature for 30 min. Usual work-up gave 8-(2′-hydroxyphenyl)corypalline (**7a**) (72 mg, 96%), mp 112—113 °C (hexane). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.72; H, 6.92; N, 4.84. ^{1}H-NMR δ: 2.41 (3H, s, NMe), 3.27 (2H, s, $ArCH_2N$–), 3.94 (3H, s, OMe), 6.71 (1H, s, 5-H), 6.82—7.41 (4H, m, 4 × ArH).

Hydrolysis of 8b——Hydrolysis of **8b** (34 mg) under the same conditions as above gave *O*-(4-hydroxyphenyl)corypalline (**8a**) (27 mg, 91%), mp 200—202 °C (benzene). *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.50; H, 6.64; N, 4.85. ^{1}H-NMR δ: 2.46 (3H, s, NMe), 3.54 (2H, s, $ArCH_2N$–), 3.78 (3H, s, OMe), 6.37 (2H, d, J = 8.5 Hz, 2 × ArH), 6.57 (1H, s, ArH), 6.60 (2H, s, J = 8.5 Hz, 2 × ArH), 6.65 (1H, s, ArH).

Reaction of 1 and Isocorypalline (9)[7]——The reaction products were separated by column chromatography [silica gel; eluent, $CHCl_3$–MeOH (20 : 1→10 : 3)] to give the mixed dimer (**10**) and a mixture of two compounds. The latter was recrystallized from benzene to afford isocorypalline (**9**), 31 mg (31%), mp 162—164 °C, and concentration of the mother liquor gave corypalline (**2a**), 7 mg (7%), mp 169—170 °C). **10**: 108 mg (54.3%), mp 230—240 °C (dec.). ^{1}H-NMR (D_2O–NaOD) δ: 2.18, 2.32 (each 3H, s, NMe), 3.76 (6H, s, 2×OMe), 6.56, 6.64 (each 1H, s, ArH). Dimethiodide of **10**: mp 290—291 °C (dec.) (MeOH). *Anal.* Calcd for $C_{22}H_{28}N_2O_4 \cdot 2CH_3I$: C, 43.13; H, 5.13; N, 4.19. Found: C, 43.10; H, 5.18; N, 4.03. ^{1}H-NMR (D_2O) δ: 3.09 (6H, s, 2×NMe), 3.15, 3.22 (each 3H, s, NMe), 3.90 (6H, s, OMe), 6.89, 7.01 (each 1H, s, ArH).

Reaction of 1 with 1,2,3,4-Tetrahydro-2-methylisoquinolin-6-ol——The reaction products were dissolved in Ac_2O (4 ml) and pyridine (2 ml) and the whole was allowed to stand overnight at room temperature. Usual work-up gave an oil (200 mg), which was separated by preparative TLC [developing solvent, $CHCl_3$–MeOH (10 : 1)] to afford *O*-acetylcorypalline (**2b**), 22 mg (18%), 6-acetoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, 53 mg (50%), and a mixture of two compounds. The former two compounds were identified by comparison with authentic samples. The mixture was separated by preparative TLC [developing solvent, $CHCl_3$–MeOH (20 : 3)] to give the mixed dimers (**11** and **12**). 6-Acetoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline: a viscous oil, bp 145—150 °C (bath temperature)/3 mmHg. High-resolution MS. Calcd for $C_{12}H_{15}NO_2$: 205.1101. Found: 205.1074. 8-(6-Acetoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-5-yl)-7-acetoxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**11**): an oil, 48.3 mg (21.3%). ^{1}H-NMR δ: 1.92, 1.96 (each 3H, s, OAc), 2.31, 2.43 (each 3H, s, NMe), 3.82 (3H, s, OMe), 6.70 (1H, s, 5-H), 6.92, 7.04 (each 1H, d, J=8 Hz, 7′- and 8′-H). IR ν_{max} cm^{-1}: 1750 (OAc). Dimethiodide: mp 215 °C. *Anal.* Calcd for $C_{25}H_{30}N_2O_5 \cdot 2CH_3I \cdot 0.5H_2O$: C, 44.34; H, 5.10; N, 3.83. Found: C, 44.44; H, 5.25; N, 3.87. 8-(6-Acetoxy-2-methyl-1,2,3,4-tetrahydroisoquinoin-7-yl)-7-acetoxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**12**): an oil, 37 mg (16.3%). ^{1}H-NMR δ: 1.98 (6H, s, 2×OAc), 2.37, 2.46 (each 3H, s, NMe), 3.80 (3H, s, OMe), 6.68, 6.76, 6.88 (each 1H, s, ArH). IR ν_{max} cm^{-1}: 1750 (OAc). Dimethiodide: mp 228 °C (dec.). *Anal.* Calcd for $C_{25}H_{30}N_2O_5 \cdot 2CH_3I \cdot 0.5H_2O$: C, 44.34; H, 5.10; N, 3.83. Found: C, 44.23; H, 5.34; N, 3.85.

Reaction of 1 with 1,2,3,4-Tetrahydro-2-methylisoquinolin-7-ol——The reaction products (180 mg) were acetylated with Ac_2O (4 ml) and pyridine (2 ml) to give an oily acetate (201 mg), which was separated into three fractions by preparative TLC [developing solvent, $CHCl_3$–MeOH (10 : 1)]. Two of them were identified as *O*-acetylcorypalline (**2b**) and 7-acetoxy-1,2,3,4-tetrahydro-2-methylisoquinoline, by comparison with authentic samples. The remaining products were separated by preparative TLC [developing solvent, $CHCl_3$–MeOH (20 : 3)] to afford the mixed dimers (**13** and **14**). 7-Acetoxy-1,2,3,4-tetrahydro-2-methylisoquinoline: an oil (45%), bp 150—155 °C (bath temperature)/3 mmHg. High-resolution MS. Calcd for $C_{12}H_{15}NO_2$: 205.1101. Found: 205.1082. ^{1}H-NMR δ: 2.22 (3H, s, OAc), 2.41 (3H, s, NMe). 8-(7-Acetoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-7-acetoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**13**): an oil, 70 mg (30.8%). ^{1}H-NMR δ: 1.95, 1.96 (each 3H, s, OAc), 2.32 (6H, s, 2×NMe), 3.83 (3H, s, OMe), 6.72 (1H, s, 5-H), 6.94, 7.12 (each 1H, d, J=8 Hz, 5′- and 7′-H). IR ν_{max} cm^{-1}: 1750 (OAc). Dimethiodide: mp 270 °C (MeOH). *Anal.* Calcd for $C_{25}H_{30}N_2O_5 \cdot 2CH_3I \cdot 2H_2O$: C, 42.75; H, 5.32; N, 3.69. Found: C, 43.05; H, 5.00; N, 3.71. 8-(7-Acetoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-7-acetoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**14**): an oil, 9 mg (4%). High-resolution MS. Calcd for $C_{25}H_{30}N_2O_5$: 438.2152. Found: 438.2138. ^{1}H-NMR δ: 1.98 (6H, s, 2×OAc), 2.32, 2.48 (each 3H, s, OMe), 6.68, 6.80, 6.84 (each 1H, s, ArH). IR ν_{max} cm^{-1}: 1750 (OAc).

Trifluoroacetic Acid Treatment of the *p*-Quinol Acetate in the Absence of a Phenolic Compound——Trifluoroacetic acid (1 ml) was added to a solution of the *p*-quinol acetate (**1**), derived from corypalline (100 mg), in CH_2Cl_2 (8 ml). The whole was stirred at room temperature for 1 h, and usual work-up gave an oil (95 mg), which was separated by preparative TLC [developing solvent, $CHCl_3$–EtOH (9 : 3)] to afford the *p*-quinol acetate (**1**) (4 mg, 3%) and 4-hydroxycorypalline (18 mg, 21%), mp 158 °C (dec.) ($CHCl_3$) (lit.[10] 153—155 °C). ^{1}H-NMR δ: 2.43 (3H, s, NMe), 3.87 (3H, s, OMe), 4.50 (1H, t, J=3 Hz, 4-H), 6.53, 6.84 (each 1H, s, ArH). IR ν_{max}^{KBr} cm^{-1}: 3350, 3075 (OH).

Reaction of the *p*-Quinol Acetate (1) with Isocorypalline (9) in the Presence of 4,4′-Thiobis(2-*tert*-butyl-6-methylphenol)——Corypalline (100 mg) was oxidized by $Pb(OAc)_4$ to give the *p*-quinol acetate (**1**), which was dissolved in CH_2Cl_2 (8 ml) with isocorypalline (**9**) (100 mg) and the thiobisphenol (186 mg). Trifluoroacetic acid (1 ml) was added to the solution and the whole was stirred at room temperature for 1 h. Usual work-up gave an oil (385 mg), which was purified by column chromatography [silica gel; eluent, $CHCl_3$→$CHCl_3$–MeOH (10 : 3)] to give crystals (114 mg). The product was proved to be a mixture of corypalline (**2a**) and **9** in a ratio of 1 : 1 on the basis of ^{1}H-NMR spectral analysis. Separation of the mixture was unsuccessful by column chromatography or preparative TLC.

Reaction of the 1-Phenyl *p*-Quinol Acetate (16) and Corypalline (2a)——The *p*-quinol acetate (**16**) (684 mg), which was prepared from 1-phenylcorypalline (**17a**),[10] was dissolved in CH_2Cl_2 (40 ml) together with corypalline (**2a**) (404 mg). Trifluoroacetic acid (4 ml) was added to the solution, and the whole was stirred at room temperature for 1 h. Usual work-up gave an oil (1.07 g), which was acetylated with Ac_2O (4 ml) and pyridine (4 ml) to give an oil (1.2 g). The product was separated by column chromatography [silica gel; eluent, $CHCl_3$→$CHCl_3$–MeOH (10 : 1)] to give *O*-acetyl-1-phenylcorypalline (**17b**) (240 mg, 37%), *O*-acetylcorypalline (**2b**) (162 mg, 33%), and the dimer of *O*-acetylcorypalline (**3b**) (162 mg, 17%). All of the products were identified by comparison with authentic samples prepared by acetylation of the corresponding phenols. 4a-Acetoxy-6-methoxy-2-methyl-7-oxo-1-phenyl-1,2,3,4,4a,7-

TABLE I. Fractional Atomic Coordinates (x, y and z) and Equivalent Isotropic Temperature Factors (B_{eq} in Å^2)

No.	Atom	x ($\times 10^5$)	y ($\times 10^5$)	z ($\times 10^5$)	B_{eq} (Å^2)
1	I1	79572 (6)	−30701 (9)	38729 (7)	5.88 (0.02)
2	I2	59434 (5)	39927 (8)	69156 (5)	4.16 (0.01)

No.	Atom	x ($\times 10^4$)	y ($\times 10^4$)	z ($\times 10^4$)	B_{eq} (Å^2)
3	C1	8488 (5)	2204 (9)	3250 (7)	2.1 (0.2)
4	C2	8480 (5)	1493 (9)	2508 (7)	2.2 (0.2)
5	C3	8020 (6)	361 (10)	2507 (7)	2.9 (0.2)
6	N4	8145 (4)	−459 (8)	1771 (6)	2.8 (0.1)
7	C5	7546 (6)	−1320 (12)	1681 (8)	4.4 (0.2)
8	C6	8787 (6)	−1205 (11)	1916 (8)	4.0 (0.2)
9	C7	8178 (7)	318 (11)	985 (7)	3.9 (0.2)
10	C8	8788 (6)	1167 (11)	1015 (7)	3.5 (0.2)
11	C9	8812 (5)	1881 (10)	1821 (7)	2.4 (0.2)
12	C10	9190 (5)	2980 (10)	1847 (7)	2.8 (0.2)
13	C11	9204 (5)	3665 (9)	2579 (7)	2.8 (0.2)
14	O12	9536 (4)	4767 (7)	2673 (5)	3.8 (0.1)
15	C13	9775 (7)	5352 (12)	1924 (8)	4.6 (0.2)
16	C14	8849 (5)	3287 (9)	3276 (7)	2.5 (0.2)
17	O15	8844 (4)	3993 (7)	3972 (5)	3.4 (0.1)
18	C16	8057 (5)	1896 (9)	3962 (6)	1.8 (0.2)
19	C17	8298 (5)	1075 (9)	4571 (7)	2.2 (0.2)
20	O18	8905 (3)	514 (7)	4489 (5)	3.1 (0.1)
21	C19	7908 (5)	864 (9)	5273 (6)	2.2 (0.2)
22	O20	8208 (4)	74 (7)	5837 (4)	3.0 (0.1)
23	C21	7833 (6)	−183 (12)	6571 (7)	3.9 (0.2)
24	C22	7292 (5)	1424 (9)	5359 (7)	2.4 (0.2)
25	C23	7034 (5)	2162 (9)	4695 (7)	2.0 (0.2)
26	C24	6314 (5)	2576 (9)	4785 (7)	2.8 (0.2)
27	C25	5799 (6)	1540 (11)	4486 (8)	3.5 (0.2)
28	C26	5873 (5)	459 (10)	5071 (8)	3.4 (0.2)
29	C27	6201 (6)	−615 (10)	4795 (8)	4.0 (0.2)
30	C28	6276 (6)	−1599 (11)	5334 (8)	4.2 (0.2)
31	C29	6028 (6)	−1531 (10)	6151 (9)	4.1 (0.2)
32	O30	6118 (5)	−2546 (8)	6661 (6)	5.6 (0.2)
33	C31	5935 (9)	−2460 (14)	7504 (10)	6.6 (0.3)
34	C32	5694 (6)	−473 (10)	6440 (8)	3.8 (0.2)
35	C33	5623 (5)	520 (10)	5870 (8)	3.3 (0.2)
36	N34	6190 (4)	3747 (8)	4256 (6)	3.1 (0.1)
37	C35	5443 (6)	4083 (12)	4222 (9)	4.7 (0.2)
38	C36	6586 (7)	4790 (10)	4671 (8)	3.9 (0.2)
39	C37	6417 (6)	3568 (11)	3374 (7)	3.1 (0.2)
40	C38	7164 (5)	3284 (10)	3344 (7)	2.7 (0.2)
41	C39	7413 (5)	2409 (9)	4014 (7)	2.1 (0.2)
42	C40	9740 (7)	7485 (17)	5048 (11)	7.2 (0.3)
43	O41	9139 (5)	8131 (9)	5227 (6)	6.1 (0.2)

Centrosymmetric space group. Equivalent positions: and their inverted coordinates.

x	y	z
$-x$	$1/2+y$	$1/2-z$

TABLE II. Anisotropic Thermal Parameters for Each Atom

No.	Atom	$U11$	$U22$	$U33$	$U12$	$U13$	$U23$
		$U(ij)$'s are multiplied by $\times 10^4$					
1	I1	971 (7)	607 (6)	648 (7)	−187 (5)	−79 (6)	121 (6)
2	I2	738 (5)	450 (4)	396 (6)	34 (4)	36 (5)	41 (5)
		$U(ij)$'s are multiplied by $\times 10^3$					
3	C1	27 (5)	29 (5)	22 (7)	3 (4)	−1 (5)	3 (5)
4	C2	26 (5)	29 (5)	29 (7)	1 (4)	−2 (5)	4 (5)
5	C3	50 (7)	32 (6)	30 (8)	−8 (5)	8 (6)	−14 (6)
6	N4	49 (5)	33 (5)	26 (6)	−7 (4)	0 (5)	−9 (5)
7	C5	59 (8)	50 (8)	57 (10)	−22 (6)	−5 (7)	−15 (7)
8	C6	47 (7)	45 (7)	59 (10)	14 (6)	1 (7)	−7 (7)
9	C7	76 (9)	43 (7)	28 (8)	−9 (6)	−7 (7)	5 (7)
10	C8	69 (8)	45 (7)	18 (7)	−12 (6)	9 (6)	−7 (6)
11	C9	41 (6)	36 (6)	16 (7)	−1 (5)	−1 (5)	8 (6)
12	C10	34 (6)	41 (6)	32 (8)	2 (5)	−2 (6)	1 (6)
13	C11	34 (6)	31 (6)	41 (8)	−6 (5)	−3 (6)	8 (6)
14	O12	55 (5)	39 (4)	52 (6)	−18 (4)	5 (4)	−4 (4)
15	C13	67 (9)	59 (8)	51 (10)	−28 (7)	1 (7)	28 (8)
16	C14	29 (5)	37 (6)	28 (7)	5 (5)	−1 (5)	7 (6)
17	O15	64 (5)	40 (4)	26 (5)	−4 (4)	5 (4)	−11 (4)
18	C16	37 (6)	25 (5)	7 (6)	−1 (4)	−1 (5)	−5 (5)
19	C17	32 (5)	27 (5)	25 (7)	1 (5)	−4 (5)	−8 (6)
20	O18	37 (4)	44 (4)	40 (5)	14 (3)	8 (4)	4 (4)
21	C19	41 (6)	26 (5)	14 (7)	−3 (5)	−1 (5)	1 (5)
22	O20	50 (4)	39 (4)	25 (5)	11 (4)	−4 (4)	9 (4)
23	C21	58 (8)	58 (8)	31 (8)	−1 (6)	10 (7)	28 (7)
24	C22	32 (5)	24 (5)	37 (8)	−2 (4)	−5 (6)	−6 (6)
25	C23	27 (5)	27 (5)	23 (7)	1 (4)	−4 (5)	−6 (5)
26	C24	30 (5)	30 (6)	46 (8)	4 (5)	−4 (6)	7 (6)
27	C25	44 (7)	40 (7)	48 (9)	−8 (5)	−5 (6)	7 (7)
28	C26	34 (6)	41 (6)	55 (9)	−12 (5)	−4 (6)	−6 (7)
29	C27	51 (7)	34 (6)	67 (10)	−3 (5)	−6 (7)	−11 (7)
30	C28	64 (8)	45 (7)	51 (9)	−7 (6)	5 (7)	−18 (7)
31	C29	48 (7)	34 (6)	74 (10)	−5 (6)	−11 (7)	4 (7)
32	O30	92 (7)	35 (5)	86 (8)	10 (5)	−1 (6)	7 (5)
33	C31	141 (15)	53 (9)	59 (11)	11 (9)	19 (10)	13 (9)
34	C32	45 (7)	36 (6)	63 (10)	−4 (5)	−2 (7)	−6 (7)
35	C33	38 (6)	40 (6)	48 (9)	−6 (5)	0 (6)	−7 (6)
36	N34	45 (5)	32 (5)	41 (7)	8 (4)	−6 (5)	4 (5)
37	C35	45 (7)	62 (8)	70 (10)	28 (7)	1 (7)	8 (8)
38	C36	78 (9)	28 (6)	41 (9)	0 (6)	−7 (7)	−15 (6)
39	C37	52 (7)	48 (7)	19 (7)	14 (6)	6 (6)	0 (6)
40	C38	42 (6)	35 (6)	26 (8)	13 (5)	1 (6)	11 (6)
41	C39	30 (5)	29 (5)	21 (7)	−3 (4)	2 (5)	−3 (5)
42	C40	63 (9)	108 (13)	104 (14)	21 (9)	40 (10)	2 (12)
43	O41	93 (7)	60 (6)	79 (8)	11 (6)	−7 (6)	−9 (6)

Temperature factor T is in the form of

$$T=\exp\{-2\pi^2(U11h^2a^{*2}+U22k^2b^{*2}+U33l^2c^{*2}+2U12kha^*b^*+2U13hla^*c^*+2U23klb^*c^*)\}.$$

TABLE III. Bond Lengths in Å

Atom 1	Atom 2	Length (S.T.D.)	Atom 1	Atom 2	Length (S.T.D.)
C1	–C2	1.428 (15)	C19	–C22	1.378 (14)
C1	–C14	1.386 (14)	O20	–C21	1.446 (14)
C1	–C16	1.492 (14)	C22	–C23	1.425 (14)
C2	–C3	1.539 (14)	C23	–C24	1.510 (14)
C2	–C9	1.373 (15)	C23	–C39	1.377 (14)
C3	–N4	1.515 (14)	C24	–C25	1.591 (15)
N4	–C5	1.521 (15)	C24	–N34	1.556 (14)
N4	–C6	1.525 (15)	C25	–C26	1.518 (17)
N4	–C7	1.530 (15)	C26	–C27	1.422 (16)
C7	–C8	1.526 (18)	C26	–C33	1.398 (18)
C8	–C9	1.516 (15)	C27	–C28	1.390 (18)
C9	–C10	1.418 (15)	C28	–C29	1.423 (19)
C10	–C11	1.398 (16)	C29	–O30	1.390 (15)
C11	–O12	1.381 (13)	C29	–C32	1.420 (17)
C11	–C14	1.407 (16)	O30	–C31	1.421 (19)
O12	–C13	1.460 (16)	C32	–C33	1.428 (17)
C14	–O15	1.364 (13)	N34	–C35	1.526 (15)
C16	–C17	1.405 (14)	N34	–C36	1.528 (15)
C16	–C39	1.401 (14)	N34	–C37	1.519 (15)
C17	–O18	1.362 (12)	C37	–C38	1.517 (16)
C17	–C19	1.411 (15)	C38	–C39	1.515 (15)
C19	–O20	1.377 (12)	C40	–O41	1.424 (19)

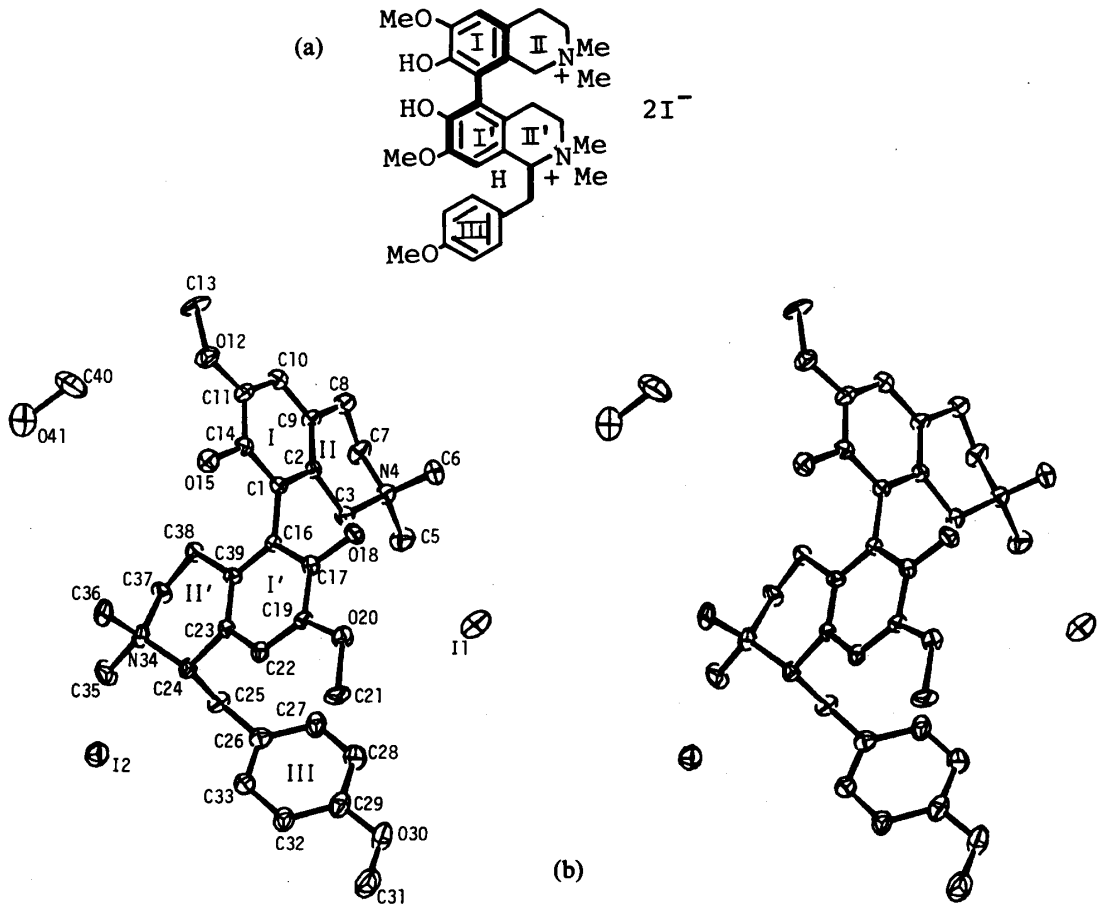

Fig. 3. (a) Chemical Structure and (b) a Stereoscopic View of the Molecule (**19**·Dimethiodide)

TABLE IV. Bond Angles in Degrees

Atom 1	Atom 2	Atom 3	Angle (S.T.D.)	Atom 1	Atom 2	Atom 3	Angle (S.T.D.)
C2	–C1	–C14	118.9 (9)	O20	–C19	–C22	125.4 (9)
C2	–C1	–C16	122.1 (9)	C17	–C19	–C22	121.3 (9)
C14	–C1	–C16	118.6 (9)	C21	–O20	–C19	116.1 (8)
C3	–C2	–C1	115.5 (9)	C23	–C22	–C19	118.4 (9)
C3	–C2	–C9	123.2 (9)	C24	–C23	–C22	114.6 (9)
C1	–C2	–C9	121.0 (9)	C24	–C23	–C39	124.0 (9)
N4	–C3	–C2	111.5 (8)	C22	–C23	–C39	121.3 (9)
C5	–N4	–C3	107.3 (8)	C25	–C24	–C23	111.0 (9)
C5	–N4	–C6	109.2 (9)	C25	–C24	–N34	109.4 (8)
C5	–N4	–C7	108.6 (9)	C23	–C24	–N34	109.2 (8)
C3	–N4	–C6	110.7 (8)	C26	–C25	–C24	108.6 (9)
C3	–N4	–C7	109.5 (8)	C27	–C26	–C25	119.1 (10)
C6	–N4	–C7	111.5 (9)	C27	–C26	–C33	120.5 (11)
C8	–C7	–N4	111.5 (9)	C25	–C26	–C33	120.4 (10)
C9	–C8	–C7	110.2 (10)	C28	–C27	–C26	119.0 (11)
C10	–C9	–C2	120.3 (10)	C29	–C28	–C27	120.5 (12)
C10	–C9	–C8	117.7 (9)	O30	–C29	–C28	117.6 (11)
C2	–C9	–C8	122.0 (10)	O30	–C29	–C32	120.8 (11)
C11	–C10	–C9	118.5 (10)	C28	–C29	–C32	121.6 (11)
O12	–C11	–C10	124.0 (10)	C31	–O30	–C29	118.7 (11)
O12	–C11	–C14	114.7 (9)	C33	–C32	–C29	116.7 (11)
C10	–C11	–C14	121.3 (10)	C35	–N34	–C24	110.8 (8)
C13	–O12	–C11	117.2 (9)	C35	–N34	–C36	108.7 (9)
O15	–C14	–C1	119.5 (9)	C35	–N34	–C37	108.2 (8)
O15	–C14	–C11	120.6 (9)	C24	–N34	–C36	107.8 (8)
C1	–C14	–C11	119.9 (9)	C24	–N34	–C37	111.1 (8)
C17	–C16	–C1	119.5 (9)	C36	–N34	–C37	110.1 (8)
C17	–C16	–C39	120.5 (9)	C38	–C37	–N34	112.0 (9)
C1	–C16	–C39	120.0 (9)	C39	–C38	–C37	113.9 (9)
O18	–C17	–C16	120.2 (9)	C16	–C39	–C23	119.3 (9)
O18	–C17	–C19	120.9 (9)	C16	–C39	–C38	119.3 (9)
C16	–C17	–C19	118.8 (9)	C23	–C39	–C38	121.3 (9)
O20	–C19	–C17	113.3 (9)	C26	–C33	–C32	121.7 (11)

hexahydroisoquinoline (**16**): an oil. ^{1}H-NMR δ: 2.17 (6H, s, OAc and NMe), 3.63 (3H, s, OMe), 5.32, 5.34 (each 0.5H, s, olefinic H), 5.85 (1H, s, olefinic H), 7.17 (5H, s, PhH). *O*-Acetyl-1-phenylcorypalline (**17b**): mp 103—104 °C (ether–hexane). *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.28; H, 6.69; N, 4.53. ^{1}H-NMR δ: 2.14 (3H, s, OAc), 2.18 (3H, s, NMe), 3.74 (3H, s, OMe), 6.15 (1H, s, 8-H), 6.54 (1H, s, 5-H), 7.12 (5H, s, PhH). 7,7′-Diacetoxy-1,2,3,4,1′,2′,3′,4′-octahydro-6,6′-dimethoxy-2,2′-dimethyl-8,8′-bisisoquinoline (**3b**): mp 202 °C (MeOH–ether). High-resolution MS. Calcd for $C_{26}H_{32}N_2O_6$: 468.2258. Found: 468.2249. ^{1}H-NMR δ: 1.99 (6H, s, 2×OAc), 2.31 (6H, s, 2×NMe), 3.82 (6H, s, 2×OMe), 6.70 (2H, s, 2×ArH). IR ν_{max} cm^{-1}: 1755 (OAc).

Preparation of *O,O′*-Diacetyl-8,8′-bicorypallyl (3b)——The corypalline dimer (**3a**)[3] (39 mg) was allowed to stand with Ac_2O (2 ml) and pyridine (1 ml) overnight. Usual work-up gave the diacetate (**3b**) (40 mg, 84.1%), mp 202 °C (MeOH–ether), spectral data of which were coincident with those of the above-mentioned dimer.

Reaction of 1 with (±)-6-Hydroxy-7-methoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (18)——The reaction products (266 mg) were separated by preparative TLC [developing solvent, $CHCl_3$–MeOH (10 : 3)] to give corypalline (15 mg), the 1-benzylcorypalline (98 mg), and two mixed dimers [**19**: 50.3 mg (19%) and **20**: 25 mg (9.7%)]. **19**: mp 178—180 °C (MeOH–ether). *Anal.* Calcd for $C_{30}H_{36}N_2O_5 \cdot 0.25H_2O$: C, 70.77; H, 7.23; N, 5.50. Found: C, 70.81; H, 7.13; N, 5.46. ^{1}H-NMR δ: 2.36, 2.51 (each 3H, s, NMe), 3.67, 3.77, 3.88 (each 3H, s, OMe), 6.16, 6.60 (each 1H, s, ArH), 6.76, 6.99 (each 2H, d, J=8 Hz, ArH). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH). **20**: mp 170—174 °C (MeOH–ether). *Anal.* Calcd for $C_{30}H_{36}N_2O_5 \cdot 0.25H_2O$: C, 70.77; H, 7.23; N, 5.50. Found: C, 70.72; H, 7.11; N, 5.66. ^{1}H-NMR δ: 2.32, 2.56 (each 3H, s, NMe), 3.61, 3.79, 3.81 (each 3H, s, OMe), 6.04, 6.62 (each 1H, s, ArH), 6.76, 7.03 (each 2H, d, J=8 Hz, ArH). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH).

Dimethiodide of 19——A solution of **19** and CH_3I (excess) in MeOH was refluxed for 2 h. Removal of the solvent gave crystals, which were recrystallized from MeOH to give colorless prisms [mp 234 °C (dec.)]. *Anal.* Calcd for $C_{30}H_{36}N_2O_5 \cdot 2CH_3I \cdot CH_3OH \cdot H_2O$: C, 47.26; H, 5.65; N, 3.34. Found: C, 47.29; H, 5.55; N, 3.42.

Structure Determination of 19·Dimethiodide by X-Ray Analysis——The crystals were grown in methanol solutions as pale yellow small plates. The X-ray specimen was about $0.6 \times 0.3 \times 0.12$ mm in size and was mounted on a Philips PW 1100 diffractometer. All the measurements were made using MoK_α radiation monochromated by a graphite plate. The crystal data were: monoclinic, space group $P2_{1/c}$, $Z=4$. Lattice constants, $a=19.845$ (10), $b=10.950$ (6), $c=16.132$ (8) Å, $\beta=91.76$ (5)°, $V=3504$ Å^3, μ for Mo$K_\alpha=18.2$ cm^{-1}, $D_{calc}=1.555$ gcm^{-3}. Intensities were measured by the 2θ-ω scan method with the scan speed of 0.6 °s^{-1} in θ. Scans were repeated twice when the total counts in the first scan were less than 3000. A total of 3364 reflections were measured as above the $2\sigma(I)$ level within the 2θ angle of 50°, which corresponds to about 82% of the number of theoretically possible reflections. The crystal structure was determined by the heavy atom method and refined by the block-diagonal matrix least-squares procedure. The final R value was 0.063 assuming anisotropic thermal parameters for all the atoms taken into the structure factor calculations.[11] Hydrogen atoms were not included. The weight percentages of C, H, and N obtained by elemental analysis agree well with the chemical formula $C_{30}H_{36}N_2O_5 \cdot 2CH_3I \cdot CH_3OH \cdot H_2O$. The present X-ray determination, however, showed no electron density peaks higher than 0.3 electron/Å^3 which can be assigned to water oxygen atoms. Probably, water molecules were lost by evaporation during the storage of the crystal specimen or during the X-ray measurement. We therefore describe the chemical formula as a monohydrate, but the X-ray structure as a simple methanol solvate.

Bond lengths and bond angles (Tables II and III) are consistent with the chemical structure shown in Fig. 3(a). Figure 3(b) shows a stereoscopic view of the molecule which indicates that the two phenyl rings (I and I′) are connected by a single bond (C1–C16) like biphenyl, and the two rings are twisted at about 90°. The torsion angle, C14–C1–C16–C17, is calculated to be 99.5 (9)°. Such a large twist is clearly the consequence of the close contacts between exocyclic atoms. Thus, the interatomic distances from C3 to O18 and C38 are found to be 3.603 (13) Å and 3.885 (15) Å, respectively, and the corresponding distances from O15 to C38 and O18 are 3.539 (13) Å and 3.900 (10) Å, respectively, and the molecule is relieved from the repulsions between these atoms by the twisting about the C1–C16 bond. N-14 and N-34 are puckered from the respective six-membered rings (II and II′) in such a way that they are *endo* with respect to the substituent groups (OH and OMe) of the confronting phenyl ring (N4 *versus* I′ and N34 *versus* I). The phenyl ring III extends from ring II′, keeping some interaction with the I′ ring and its substituents. Thus the torsion angle N34–C24–C25–C26 is nearly in *trans* conformation [173.5 (6)°] and that of C24–C25–C26–C27 is 106.3 (10)°. The latter causes ring III to face the methoxyl group (O20–C21H_3).

5-Hydroxy-1,2,3,4-tetrahydro-8-(1,2,3,4-tetrahydro-6-methoxy-2-methyl-7-isoquinolyloxy)-2-methylisoquinoline (6a)——The acetate (**6b**) (32 mg) was dissolved in MeOH (1 ml), and aqueous 1 N NaOH–MeOH (MeOH : H_2O = 3 : 1) (0.1 ml) was added to the ice-cooled solution. The whole was stirred at the same temperature for 15 min, Reaction mixture was alkalinized with saturated aqueous NH_4Cl and the product was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over K_2CO_3. The solvent was evaporated off under reduced pressure to give the phenolic amine (**6a**) (30 mg, 94%), mp 188 °C (acetone). *Anal.* Calcd for $C_{21}H_{26}N_2O_5$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.16; H, 7.38; N, 7.89. ^{1}H-NMR δ: 2.43, 2.46 (each 3H, s, NMe), 3.76 (3H, s, OMe), 5.85, 6.04 (each 1H, d, $J=9$ Hz, ArH), 6.43, 6.62 (each 1H, s, ArH). IR ν_{max} cm^{-1}: 3400 (OH), 1260 (ArOAr).

5-Benzyloxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (4c)——Sodium hydride (60%, 1 eq) was added to a stirred solution of **4a** (1.5 g) in *N*,*N*-dimethylformamide (DMF) (50 ml) at room temperature. Stirring was continued for 1 h, then benzyl chloride (1.28 g) was added to the mixture, and the whole was stirred at 70—80 °C for 2 h. The reaction mixture was poured into water and the product was extracted with $CHCl_3$. Usual work-up gave an oil (2.2 g), which was purified by silica gel column chromatography (eluent, $CHCl_3$) to yield **4c** (1.7 g, 73%) as an oil. ^{1}H-NMR δ: 2.44 (3H, s, NMe), 5.03 (2H, s, OCH_2Ph), 6.60, 6.67 (each 1H, d, $J=8$ Hz, 6- and 8-H), 7.03 (1H, t, $J=8$ Hz, 7-H), 7.20—7.60 (5H, m, PhH). IR ν_{max} cm^{-1}: 1260, 1070 (ArOCH_2Ph).

5-Benzyloxy-8-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (22)——Bromine–$CHCl_3$ [2% solution, 125 ml (2.5 eq)] was slowly added to a stirred solution of **4c** (1.6 g) in $CHCl_3$ (80 ml) under ice-cooling, and the whole was stirred for 2 h at the same temperature. Excess $Na_2S_2O_3$ was added to the reaction mixture and the whole was stirred vigorously. After alkalization with saturated aqueous $NaHCO_3$, the product was extracted with $CHCl_3$. Usual work-up gave an oil (2.3 g), which was purified by silica gel column chromatography (eluent, $CHCl_3$) to afford **22** (1 g, 44%), mp 104—105 °C (AcOEt). *Anal.* Calcd for $C_{17}H_{18}BrNO$: C, 61.48; H, 5.42; N, 4.22. Found: C, 61.51; H, 5.56; N, 4.15. ^{1}H-NMR δ: 2.49 (3H, s, NMe), 5.01 (2H, s, OCH_2Ph), 6.57, 7.24 (each 1H, d, $J=8$ Hz, 6- and 7-H), 7.24—7.40 (5H, m, PhH). IR ν_{max} cm^{-1}: 1250 (ArOCH_2Ph).

5-Benzyloxy-1,2,3,4-tetrahydro-8-(1,2,3,4-tetrahydro-6-methoxy-2-methyl-7-isoquinolyloxy)-2-methylisoquinoline (6c)——A mixture of **22** (150 mg), corypalline (262 mg), K_2CO_3 (94 mg), and pyridine (10 ml) was heated under stirring. At the beginning of reflux, CuO (100 mg) was added to the mixture and the whole was refluxed for 7 h. Further CuO (50 mg) was added and the whole was refluxed for another 3 h. The reaction mixture was filtered, and the filtrate was dissolved in ether. The ether solution was washed with aqueous 10% NaOH and brine, successively. The organic layer was dried over K_2CO_3, and the solvent was evaporated off under reduced pressure to give an oily

product, which was purified by preparative TLC [developing solvent, $CHCl_3$–MeOH (10 : 1)] to give **6c**, as an oil (150 mg, 75%). MS *m/z*: 444 (M^+). ^{1}H-NMR δ: 2.40, 2.45 (each 3H, s, NMe), 3.82 (3H, s, OMe), 4.99 (2H, s, OCH_2Ph), 6.35, 6.64 (each 1H, s, ArH), 6.50, 6.63 (each 1H, d, J=9 Hz, ArH), 7.22—7.42 (5H, m, PhH). IR ν_{max} cm^{-1}: 1250 (ArOAr).

Debenzylation of 6c——Debenzylation of **6c** (139 mg) was carried out by hydrogenolysis [2% $PdCl_2$ (0.5 ml), C (23 mg), and MeOH (20 ml)] to give the hydroxybiphenyl ether (**6a**) (98.4 mg, 89%), mp 186—188 °C (acetone). This compound was identical with the product (**6a**) prepared by coupling of the *p*-quinol acetate (**1**) and the 5-hydroxytetrahydroisoquinoline (**4a**).

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References and Notes

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4) Reaction with CF_3CO_2H of the *p*-quinol acetate (**1**) and 2,6-dimethylphenol gave 7-(4-hydroxy-3,5-dimethylphenoxy)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**23**), mp 143—144 °C (benzene) (7.6%) [*Anal.* Calcd for $C_{19}H_{23}NO_3$ (313.382): C, 72.82; H, 7.40; N, 4.47. Found: C, 72.90; H, 7.63; N, 4.37. ^{1}H-NMR δ: 2.17 (6H, s, 2 × $ArCH_3$), 2.41 (3H, s, NMe), 3.41 (2H, s, $ArCH_2N$), 3.81 (3H, s, OMe), 6.47 (1H, s, 8-H), 6.54 (2H, s, 2′- and 6′-H), 6.64 (1H, s, 5-H)], 7-hydroxy-6-methoxy-8-(4-hydroxy-3,5-dimethylphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**24**), mp 195—196 °C (benzene) (18.3%) [*Anal.* Calcd for $C_{19}H_{23}NO_3$ (313.382): C, 72.82; H, 7.40; N, 4.47. Found: C, 72.88; H, 7.43; N, 4.56. ^{1}H-NMR δ: 2.26 (6H, s, 2 × $ArCH_3$), 2.33 (3H, s, NMe), 3.12 (2H, s, $ArCH_2N$), 3.87 (3H, s, OMe), 6.56 (1H, s, 5-H), 6.80 (2H, s, 2′- and 6′-H)], corypalline (**2a**) (19.2%), and a small amount of 2,6-dimethylphenol. Probably **24** was produced from the initially formed C–C coupling compound (**25**).
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11) The final atomic parameters (Table I) were deposited with the Cambridge Crystallographic Data Center and will be available as a data base. Final *Fo*, *Fc* tables may be obtained on request from one of the authors (Y. Iitaka).