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# Studies on Tetrahydroisoquinolines. XXXII.[1] Conversion of 7-Hydroxy-6-methoxytetrahydroisoquinolines to 6-Hydroxy-7-methoxytetrahydroisoquinolines

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The 7-hydroxy-6-methoxytetrahydroisoquinolines (**2** and **8**) were transformed to the corresponding 6-hydroxy-7-methoxytetrahydroisoquinolines (**4** and **14**) *via* the *p*-quinol acetates (**1** and **9**), the *p*-quinol ethers (**3a** or **3b**, and **10a**), and the 6-alkoxy-7-ols (**5** or **7**, and **13**), respectively.

**Keywords**——tetrahydroisoquinolinol; *p*-quinol acetate; *p*-quinol ether; reductive aromatization; transposition

We have already reported that the *p*-quinol acetate (**1**), derived from corypalline (**2**) by lead tetraacetate oxidation, reacts with various alcohols in the presence of $BF_3 \cdot Et_2O$ or concentrated $H_2SO_4$ to give rise to the corresponding *p*-quinol ether (**3**), as a result of elimination of the methoxyl group at the C-6 position.[2]

If the *p*-quinol ether (**3**) has a readily removable alkyl group at the C-6 position, it may be a key precursor leading to the 6-hydroxy-7-methoxytetrahydroisoqinoline (**4**). Here we wish to report a procedure for conversion of 7-hydroxy-6-methoxytetrahydroisoquinolines to 6-hydroxy-7-methoxytetrahydroisoquinolines *via* the following steps; oxidation, ether-formation, reductive aromatization, methylation of the 7-hydroxyl group, and hydrolysis.

First, a conversion of corypalline (**2**) into the isomer (**4**) *via* the 4a,6-diallyl *p*-quinol ether (**3a**) was undertaken. Treatment of the *p*-quinol ether (**3a**), which was obtained by the reaction of **1** and allyl alcohol,[2] with $NaBH_4$ followed by heating on a boiling water bath, gave the allyloxy phenol (**5**) in a yield of 88%. The structure of the product was supported by its infrared (IR) and proton nuclear magnetic resonance ($^1$H-NMR) spectral data.

Methylation of **5** with diazomethane afforded the ether (**6**), then the allyl ether was cleaved by treatment with 10% Pd–C and *p*-TsOH $\cdot H_2O$[3] to give the expected 6-hydroxy-7-methoxytetrahydroisoquinoline (**4**) in an overall yield of 3.5% from **2**. The product (**4**) was identical with an authentic specimen.[4] The low overall yield was mainly due to the final step (22% yield). Hence isopropanol was employed for the formation of the *p*-quinol ether (**3**) instead of allyl alcohol. Thus, the *p*-quinol ether (**3b**)[2] was reduced with $NaBH_4$ followed by heating at 100°C (bath temperature) to give the isopropoxy phenol (**7**), which was subjected to methylation and subsequent hydrolysis with 48% HBr in AcOH[5] to yield **2a** in an overall yield of 8.2%.

The procedure was applied to the 1-benzyl corypalline (**8**). Namely, the *p*-quinol acetate (**9**),[6] readily obtained from **8** as a mixture of two diastereoisomers, was treated with isopropanol in the presence of $BF_3 \cdot Et_2O$ at room temperture to give a single *p*-quinol ether (**10a** or **10b**) (14%) and a diastereoisomeric mixture of the 4,6-diisopropoxytetrahydroisoquinolines (**11**) (18%) on the basis of $^1$H-NMR spectral analysis. This can presumably be explained in terms of the stereochemical 1,3-relationship of the two substituents at C-1 and C-

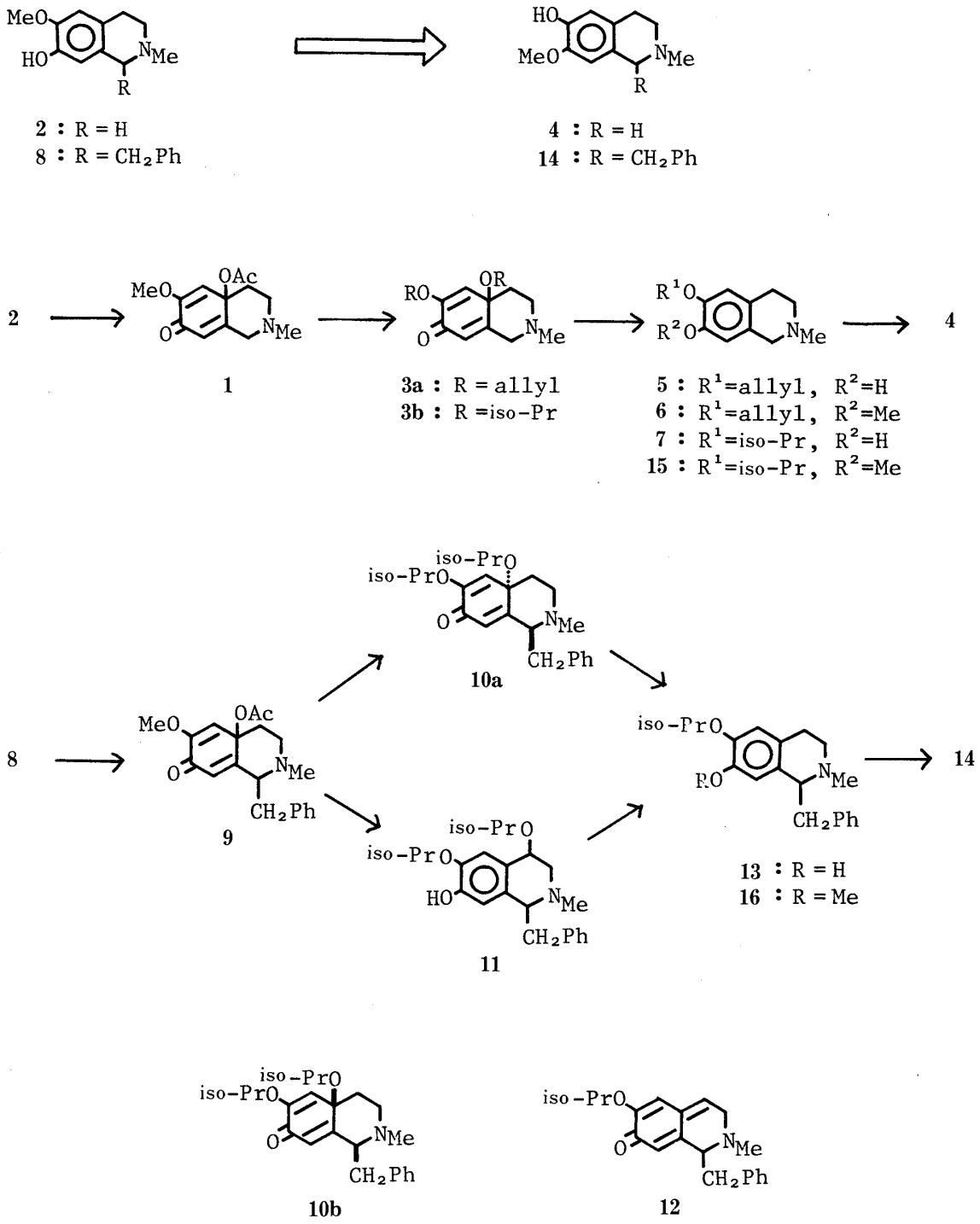


Chart 1

4a. Namely, two *p*-quinol ethers (**10a** and **10b**) were formed initially. One of these, the 1,4a-*trans* ether (**10a**), remained unchanged, while the other, the 1,4a-*cis* ether (**10b**), was further transformed into the 4,7-diisopropoxy derivatives (**11**) *via* the *p*-quinone methide (**12**) owing to its instability caused by repulsion between the two bulky groups in the 1,3-relationship.

Reductive aromatization of the *p*-quinol ether (**10a**) gave the 6-isopropoxy derivative (**13**) in 46% yield. The mixture of the diethers (**11**) was also converted to **13** by hydrogenolysis ($H_2$/10% Pd–C, 6N HCl) in 38% yield. Compound **13** was methylated and subsequently hydrolyzed with 48% HBr in AcOH, giving the 1-benzyl-6-hydroxy-7-methoxytetrahydro-

isoquinoline (**14**) in 55% yield (overall yield of 7.4% from **8**). Compound **14** was identical with an authentic sample[4] based on a comparison of their spectral data and mixed melting point determination.

Thus, an efficient procedure for transposition of the hydroxyl and methoxyl groups of 7-hydroxy-6-methoxytetrahydroisoquinolines has been developed.

## 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) instrument in $CDCl_3$ solution with $Me_4Si$ as an internal standard unless otherwise noted. IR spectra were run on a Hitachi 260 spectrometer in $CHCl_3$ solution. 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.

**Reaction of the *p*-Quinol Acetate (9) with Isopropanol in the Presence of Borontrifluoride Etherate**——The *p*-quinol acetate (**9**) was prepared quantitatively by $Pb(OAc)_4$ oxidation of 1-benzylcorypalline (**8**)[6] (300 mg), as described previously.[6] Without purification, **9** was dissolved in a mixture of iso-PrOH (36 ml) and $BF_3 \cdot Et_2O$ (3.6 ml). The whole was stirred at room temperature for 2.5 h, and the reaction mixture was poured into 10% aqueous $Na_2CO_3$ to be alkalinized. The product was extracted with $CHCl_3$, and the extract was washed with brine and dried over $K_2CO_3$. The solvent was evaporated off under reduced pressure to give an oil (298.3 mg), which was separated by preparative TLC [developing solvent, $CHCl_3$–AcOEt–MeOH (25 : 1 : 1)] to afford the *p*-quinol ether (**10a**) (55.8 mg, 14%) and the diisopropoxyphenol (**11**) (70.8 mg, 18%) (polarity: **10a** < **11**). **10a**: An oil. High-resolution MS, Calcd for $C_{23}H_{30}NO_3$ ($M^+ - 1$): 368.2224. Found: 368.2232. $^1$H-NMR $\delta$: 0.93, 1.06, 1.35, 1.37 (each 3H, d, $J$=5.7 Hz, $OCH\underline{Me}_2$), 2.17 (3H, s, NMe), 3.27, 4.36 (each 1H, septet, $J$=5.7 Hz, $OC\underline{H}Me_2$), 5.66 (1H, s, 5-H), 6.36 (1H, s, 8-H), 7.30 (5H, s, PhH). IR $\nu_{max}$ cm$^{-1}$: 1665, 1640, 1620 (dienone). **11**: An oil. High-resolution MS, Calcd for $C_{24}H_{31}NO_3$: 369.2302. Found: 369.2333. $^1$H-NMR $\delta$: 1.22, 1.25, 1.37, 1.38 (each 3H, d, $J$=5.7 Hz, $OCH\underline{Me}_2$), 2.54, 2.58 (3H, each s, 3 : 5,[7] NMe), 3.69—3.96 (*ca.* 1.5H, m, $C_4$-H and $OC\underline{H}Me_2$), 4.22 (*ca.* 0.5H, t, $C_4$-H), 4.58 (1H, septet, $J$=5.7 Hz, $OCHMe_2$), 6.24, 6.44 (1H, each s, 3 : 5,[7] ArH), 6.88, 6.95 (1H, each s, 5 : 3,[7] ArH), 7.00—7.40 (5H, m, ArH). IR $\nu_{max}$ cm$^{-1}$: 3535 (OH).

**6-Allyloxy-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (5)**——Sodium borohydride (7.5 mg) was added to a solution of the *p*-quinol ether (**3a**)[2] (36.2 mg) in MeOH (4 ml) and the whole was stirred at room temperature for 2 h. The solvent was evaporated off under reduced pressure and the residue was made alkaline with 10% aqueous $Na_2CO_3$. The product was extracted with a mixture of $CHCl_3$ and iso-PrOH (4 : 1), and the organic layer was washed with brine and dried over $K_2CO_3$. The solvent was evaporated off under reduced pressure to give a yellow oil (35 mg), which was heated on a boiling water bath under reduced pressure for 2 h to afford an oil (32.5 mg). The oil was purified by preparative TLC [developing solvent $CHCl_3$–AcOEt–MeOH (6 : 1 : 1)] to give the allyloxyphenol (**5**) (25.4 mg, 88%), mp 130—132°C (hexane). High-resolution MS, Calcd for $C_{13}H_{17}NO_2$: 219.1257. Found: 219.1243. $^1$H-NMR $\delta$: 2.42 (3H, s, NMe), 3.48 (2H, s, $C_1$-H), 4.57 (2H, dt, $J$=5.7, 1.4 Hz, $OC\underline{H}_2CH=CH_2$), 5.29 [1H, dq, $J$=10, 1.4 Hz, $OCH_2CH=C\underline{H}_2$ (*trans* H)], 5.39 [1H, dq, $J$=17, 1.4 Hz, $OCH_2CH=C\underline{H}_2$ (*cis* H)], 6.08 (1H, ddt, $J$=17, 10, 5.7 Hz, $OCH_2C\underline{H}=CH_2$), 6.56, 6.59 (each 1H, s, ArH). IR $\nu_{max}$ cm$^{-1}$: 3545 (OH).

**7-Hydroxy-6-isopropoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (7)**——Sodium borohydride (18 mg, 1.5 eq) was added to a solution of the *p*-quinol ether (**3b**)[2] (89 mg) in MeOH (6 ml) and the whole was stirred at room temperature for 2 h. Usual work-up gave a yellow oil (90 mg), which was heated on a boiling water bath under reduced pressure for 2 h to afford an oil. The oil was purified by preparative TLC [developing solvent, $CHCl_3$–AcOEt–MeOH (6 : 1 : 1)] to give the isopropoxyphenol (**7**) (38 mg, 54%), mp 114—114.5 °C (AcOEt). *Anal.* Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.69; H, 8.57; N, 6.25. $^1$H-NMR $\delta$: 1.35 (6H, d, $J$=5.7 Hz, $OCH\underline{Me}_2$), 2.46 (3H, s, NMe), 3.51 (2H, s, 1-H), 4.53 (1H, septet, $J$=5.7 Hz, $OC\underline{H}Me_2$), 6.58, 6.61 (each 1H, s, ArH), IR $\nu_{max}$ cm$^{-1}$: 3540 (OH).

**1-Benzyl-7-hydroxy-6-isopropoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (13)**——(a) Sodium borohydride (5 mg) was added to the solution of the *p*-quinol ether (**10a**) (27 mg) in MeOH (4 ml) and the whole was stirred at room temperature for 3.5 h. Usual work-up gave a yellow oil (29 mg), which was heated on a boiling water bath under reduced pressure for 2 h to afford an oil (30 mg). The oil was purified by preparative TLC [developing solvent, $CHCl_3$–AcOEt–MeOH (15 : 1 : 1)] to give **13** (11 mg, 46%), as an oil. High-resolution MS, Calcd for $C_{20}H_{25}NO_2$: 311.1884. Found: 311.1894. $^1$H-NMR $\delta$: 1.36, 1.38 (each 3H, d, $J$=5.7 Hz, $OCH\underline{Me}_2$), 2.50 (3H, s, NMe), 3.78 (1H, t, $J$=5.7 Hz, $C_1$-H), 4.55 (1H, septet, $J$=5.7 Hz, $OC\underline{H}Me_2$), 6.39, 6.56 (each 1H, s, ArH), 7.00—7.46 (5H, m, PhH). IR $\nu_{max}$ cm$^{-1}$: 3540 (OH).

(b) The isopropoxyphenol (**11**) (36 mg) was dissolved in 6 N HCl and the mixture was shaken with 10% Pd–C (20 mg) in an atmosphere of hydrogen until uptake of the gas ceased. After the catalyst was removed by filtration, the filtrate was alkalized by adding 15 N $NH_4OH$. The product was extracted with $CHCl_3$, and the extract

was washed with brine and dried over $K_2CO_3$. The solvent was evaporated off under reduced pressure to give an oil (43 mg), which was purified by preparative TLC [developing solvent, $CHCl_3$–AcOEt–MeOH (15 : 1 : 1)] to afford the 6-isopropoxy-7-ol (**13**) (12 mg, 38%), as an oil. The product was identical with **13** prepared by procedure (a).

**6-Hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (4)**——(a) A solution of **5** (72 mg) and diazomethane (excess) in ether (30 ml) and MeOH (8 ml) was allowed to stand at room temperature for 3 d. Evaporation of the solvent gave an oil, which was purified by preparative TLC [developing solvent, $CHCl_3$–AcOEt–MeOH (10 : 1 : 1)] to afford the methyl ether (**6**) (36.4 mg, 47%), as an oil. High-resolution MS, Calcd for $C_{14}H_{19}NO_2$: 233.1414. Found: 233.1399. $^1$H-NMR $\delta$: 2.48 (3H, s, NMe), 3.55 (2H, s, $C_1$-H), 3.85 (3H, s, OMe), 4.58 (2H, dt, $J$=5.7, 1.4 Hz, $OC\underline{H}_2CH=CH_2$), 6.10 (1H, ddt, $J$=17, 10, 5.7 Hz, $OCH_2C\underline{H}=CH_2$), 6.53, 6.62 (each 1H, s, ArH). The methyl ether (**6**) (22 mg) was dissolved in a mixture of MeOH (2 ml) and water (0.4 ml), and 10% Pd–C (20 mg) and *p*-TsOH (20 mg) was added. The whole was refluxed with stirring for 24 h. After removal of the catalyst by filtration, the filtrate was alkalized with 10% aqueous $Na_2CO_3$. The product was extracted with a mixture of $CHCl_3$ and iso-PrOH (4 : 1) and the extract was dried over $K_2CO_3$. Evaporation of the solvent gave a brown oil (14 mg), which was purified by preparative TLC [developing solvent, $CHCl_3$–AcOEt–MeOH (6 : 1 : 1)] to afford **4** (4 mg, 22%), mp 152—154 °C (MeOH). $^1$H-NMR [$CDCl_3$–$CD_3OD$ (1 : 1)] $\delta$:2.59 (3H, s, NMe), 3.73 (2H, s, $C_1$-H), 3.87 (3H, s, OMe), 6.56, 6.64 (each 1H, s, ArH). The product was identical with an authentic specimen as judged by mixed melting point determination and comparison of their spectral data.

(b) Methylation of the 6-isopropoxy-7-ol (**7**) (18 mg) with diazomethane (excess) in ether–MeOH for 3 d gave a crude product (18 mg), which was purified by preparative TLC [developing solvent $CHCl_3$–AcOEt–MeOH (10 : 1 : 1)] to afford the methyl ether (**15**) (12.3 mg, 64%), as an oil. $^1$H-NMR $\delta$: 1.35 (6H, d, $J$=5.7 Hz, $OCH\underline{Me}_2$), 2.48 (3H, s, NMe), 3.54 (2H, s, $C_1$-H), 3.84 (3H, s, OMe), 4.48 (1H, septet, $J$=5.7 Hz, $OC\underline{H}Me_2$), 6.52, 6.64 (each 1H, s, ArH). The methyl ether (**15**) (11.2 mg) was dissolved in a mixture of AcOH (2 ml) and concentrated HBr (0.4 ml), and the whole was heated at 80 °C with stirring for 3 h. The reaction mixture was made alkaline with 10% aqueous $Na_2CO_3$, and the product was extracted with a mixed solvent [$CHCl_3$–iso-PrOH (4 : 1)]. After drying over $K_2CO_3$, the solvent was evaporated off under reduced pressure to give an oil (15 mg). Purification by preparative TLC [developing solvent $CHCl_3$–AcOEt–MeOH (6 : 1 : 1)] afforded **4** (4.6 mg, 50%), which was identical with an authentic sample prepared by procedure (a).

**1-Benzyl-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (14)**——The isopropoxy phenol (**13**) (60 mg) was dissolved in MeOH (8 ml), and diazomethane–ether solution (excess) was added to the solution. The whole was allowed to stand at room temperature for 1 d and the solvent was evaporated off under reduced pressure to give an oil (61 mg), which was purified by preparative TLC [developing solvent $CHCl_3$–AcOEt–MeOH (15 : 1 : 1)] to afford 1-benzyl-6-isopropoxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**16**) (51.7 mg, 83%), as an oil. $^1$H-NMR $\delta$: 1.34, 1.36 (each 3H, d, $J$=5.7 Hz, $OCH\underline{Me}_2$), 2.56 (3H, s, NMe), 3.50 (3H, s, OMe), 4.47 (1H, septet, $J$=5.7 Hz, $OC\underline{H}Me_2$), 5.96, 6.59 (each 1H, s, ArH), 7.00—7.40 (5H, m, PhH). Concentrated HBr (2 ml) was added to a solution of the methyl ether (**16**) (32.4 mg) in AcOH (5 ml), and the whole was heated at 80 °C with stirring for 2.5 h. The reaction mixture was basified with 10% aqueous $Na_2CO_3$, and the product was extracted with $CHCl_3$. The organic layer was washed with brine and dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure gave a yellow oil (28 mg), which was purified by preparative TLC [developing solvent, $CHCl_3$–AcOEt–MeOH (10 : 1 : 1)] to afford **14** (15.5 mg, 55%), mp 160—162°C (lit.[4] 161—163 °C). The product was identical with an authentic sample.[4] $^1$H-NMR $\delta$: 2.60 (3H, s, NMe), 3.51 (3H, s, OMe), 5.83, 6.64 (each 1H, s, ArH), 7.02—7.40 (5H, m, PhH). IR $\nu_{max}$ $cm^{-1}$: 3545 (OH).

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7) These ratios indicate the existence of two diastereoisomers.