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Studies on Tetrahydroisoquinolines. XX.[1] A Novel Synthesis of 8-Aryl-1,2,3,4-tetrahydroisoquinolines[2]

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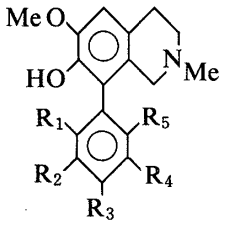
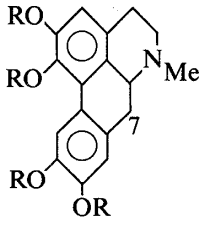
Treatment of a mixture of the *p*-quinol acetate (**4**) and aryl ethers with trifluoroacetic acid gave 8-aryl-1,2,3,4-tetrahydroisoquinolines (**1a**—**f**) in good yields. Similar reaction of **4** and corypalline (**3**) afforded a corypalline dimer (**5**).

Keywords——oxidation; lead tetraacetate; *p*-quinol acetate; trifluoroacetic acid; deuterium-exchange; NMR; arylation; nucleophilic substitution; tetrahydroisoquinoline

8-Aryl-1,2,3,4-tetrahydroisoquinolines (**1**) are regarded as the lower homologs of aporphines (**2**); that is, the former compounds lack the C-7 methylene group in the C-ring of the latter compounds. In spite of the potencial biological activity[3] of the former compounds, an efficient synthesis has not yet been developed. A significant drawback in the known methods[4] is the difficulty of preparing **1**, which possesses the same oxygenation pattern as the natural aporphines, in addition to the large number of reactoin steps. Here we wish to report a convenient synthetic method starting from 7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (corypalline) (**3**).

As an extension of the intermolecular nucleophilic reaction[5] at the C-8 position of 1,2,3,4-tetrahydroisoquinolines *via* *p*-quinol acetate (**4**), phenylation with phenyl ethers or a phenol was tried. The key compound **4**, which was prepared from corypalline (**3**) as usual,[6] smoothly reacted with veratrole in the presence of trifluoroacetic acid in CH_2Cl_2 to give 8-(3,4-dimethoxyphenyl)corypalline (**1a**) in 70% yield. Structure assignment was based on nuclear magnetic resonance (NMR) spectroscopic evidence. Namely, three methoxyl signals at δ 3.86, 3.89, and 3.93 showed that veratrole was substituted at the C-5 or C-8 position. Moreover, the up-field shift of the C-1 methylene protons (δ 3.18) of **1a** as compared to those (δ 3.44) of





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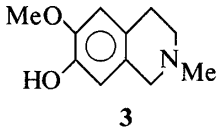
	R_1	R_2	R_3	R_4	R_5
1a :	H	OMe	OMe	H	H
1b :	OMe	OMe	OMe	H	H
1c :	H	OCH_2O		H	H
1d :	OMe	H	OMe	H	H
1e :	OMe	H	H	OMe	H
1f :	OMe	H	OMe	H	OMe



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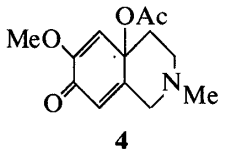

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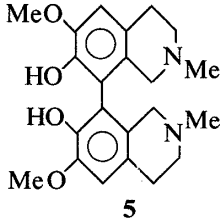

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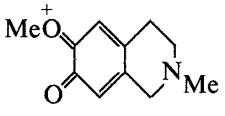

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Chart 1

TABLE I. Melting Points and Yield of the Products

Compound	mp (°C)	Recryst. solvent	Yield (%)
1a	183—185	iso-PrOH	70
1b	129—130	Ether–acetone	42
1c	203—204	iso-PrOH	52
1d	163—166	*n*-Hexane	43
1e	152—155[a]	MeOH	29
1f	207—210	iso-PrOH–ether	36
5	227—229	iso-PrOH	22

a) Methiodide of the acetate.

TABLE II. IR and NMR Spectral Data for the Products (**1a**—**f**)

Compound	IR (cm^{-1}) OH	NMR (δ) NMe	1-H_2	OMe	Others
1a	3535	2.34	3.18	3.86, 3.89, 3.93	
1b	3540	2.41	3.26	3.66, 3.90, 3.91, 3.93	6.65 (5-H), 6.74,[a] 6.84[a]
1c	3525	2.37	3.21	3.90	6.01 (OCH_2O)
1d	3200—3500	2.38	3.37	3.75 (2×OMe), 3.80	
1e	3530	2.32	3.17	3.67, 3.73, 3.83	
1f	3250,[b] 3560[b]	2.31	3.09	3.68 (2×OMe), 3.82 (2×OMe)	6.19 (3'-and 5'-H), 6.55 (5-H)

a) Doublet, J=8.6 Hz.
b) Broad absorption.

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

Compound	Formula	Molecular weight	Analysis (%) Calcd C	H	N	Found C	H	N
1a	$C_{19}H_{23}NO_4$	329.38	69.28	7.04	4.25	69.24	7.19	4.07
1b	$C_{20}H_{25}NO_5$	359.41	66.83	7.01	3.90	66.66	7.09	3.76
1c	$C_{18}H_{19}NO_4$		313.1314			313.1306[b]		
1d	$C_{19}H_{23}NO_4$	331.40	69.28	7.04	4.25	69.08	7.10	4.09
1e[a]	$C_{22}H_{28}NO_5^+ \cdot I^-$		386.1967			386.1956[b]		
1f	$C_{20}H_{25}NO_5 \cdot 0.25H_2O$	363.91	66.00	7.06	3.85	65.91	7.03	3.77

a) Methiodide of the acetate.
b) High resolution mass spectral data measured with a Hitachi model RMU-6E mass spectrometer.

corypalline is clearly due to the anisotropic effect induced by the newly introduced C-8 phenyl group.

The position of substitution in the present reaction was also clarified by a deuterium-exchange experiment. When corypalline (**3**) was heated in 1N NaOD-D_2O at 100°C for 8 h, the signal intensity at δ 6.29 was reduced markedly. Thus, 43 % of the original hydrogen was replaced by deuterium. On the other hand, 8-(2,3,4-trimethoxyphenyl)corypalline (**1b**), which was prepared analogously from **4** and 1,2,3-trimethoxybenzene, was found to have no replaceable hydrogen by the same treatment as above. Accordingly, the absence of hydrogen *ortho* to the C-7 phenolic group in **1b** was confirmed unequivocally.

p-Quinol acetate (**4**) reacted with corypalline (**3**) to give a dimer (**5**), which was identical with an authentic sample[7] obtained by the phenol coupling of **3**. This reaction further verified the position of substitution, confirming the above assignment.

The intermediate in the present reaction was suppose to be an *o*-quinonoid cation (**6**),[5] which was attacked immediately by the activated benzene nucleophile.

A variety of phenyl ethers could be used as the nucleophile with satisfactory results. Yields and spectral data of the products are shown in Tables I and II.

The similar reaction of **4** with other phenolic 1,2,3,4-tetrahydroisoquinolines is currently being investigated in order to obtain mixed dimers.

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. NMR spectra were taken with a JEOL model JNR-4H-100 (100 MHz) or a Hitachi model R-24B irstrument in $CDCl_3$ solution with Me_4Si as an internal standard. Infrared (IR) spectra were run on a Hitachi model 215 spectrophotometer in $CHCl_3$ solution. Preparative thin-layer chromatography (TLC) was performed on Silica gel HF_{254} (Merck). Microanalytical data for all new compounds are listed in Table III.

General Procedure for the Preparation of 8-Aryl-1,2,3,4-tetrahydroisoquinolines (1)——Trifluoroacetic acid (0.5 ml) was added to a CH_2Cl_2 (10 ml) solution of an aryl ether (1.5 eq) and the *p*-quinol acetate (**4**) obtained from corypalline (**3**) (100 mg) as described previously,[6] and the whole was stirred at room temperature for 1 h. The reaction mixture was washed with sat. $NaHCO_3$ aq. and brine, and the CH_2Cl_2 solution was dried over anhydrous K_2CO_3. Evaporation of the solvent under reduced pressure gave a crude product which was purified by preparative TLC (developing solvent; $CHCl_3$: MeOH=10:1).

Preparation of Corypalline Dimer (5)——Trifluoroacetic acid (1 ml) was added to a stirred mixture of corypalline (**3**) (100 mg) and *p*-quinol acetate (**4**) obtained from **3** (100 mg) in CH_2Cl_2 (20 ml) and stirring was continued at room temperature for 1 h. Usual work-up gave an amorphous mass (188 mg), which was separated by preparative TLC (developing solvent; $CHCl_3$: MeOH=20:3) to yield recovered corypalline (**3**) (55 mg), mp 164—166°C, from the upper zone, and the dimer (**5**) (43 mg, 22%), mp 227—229°C (iso-PrOH), from the lower zone. The latter product was shown to be identical with an authentic sample[7] by mixed melting point determination and spectral comparison.[8]

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8) NMR in 1N NaOD-D_2O.