THE SYNTHESIS OF 8-ARYL-1,2,3,4-TETRAHYDROISOQUINOLINES†

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Abstract— Treatment of a mixture of the p-quinol acetate (1a) and aryl alkyl ethers with trifluoroacetic acid gave the 8-aryl-1,2,3,4-tetrahydroisoquinolines (5a-f) in good yields. Similar reaction of 1a and corypalline (2a) afforded the corypalline dimer (7).

The p-quinol acetate (1)[1], readily obtained from 7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (2) by lead tetraacetate oxidation, has been proved in our hand[2] to be a reactive intermediate for the synthesis of aporphine (3)[3] and 8-chlorotetrahydroisoquinoline (4).[4] In order to explore a further synthetic utility of 1, 8-aryltetrahydroisoquinolines (5) were chosen as the next target. The present communication deals with a novel synthesis of 8-aryl-1,2,3,4-tetrahydroisoquinolines (5).[5]

A mixture of the crude p-quinol acetate (1a)[1,3], obtained from corypalline (2a) (48.2 mg), and veratrole (52 mg, 1.5 eq.) in methylene chloride (5 ml) was treated with trifluoroacetic acid (0.3 ml) at room temperature for 1 hr to give 8-(3,4-dimethoxyphenyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (5a)[6] (58 mg, 70%), m.p. 183-185°, the structure of which was assigned on the basis of its nuclear magnetic resonance spectrum showing that three methoxyl groups (δ 3.86, 3.89, 3.93) existed and that the C-1 methylene protons (δ 3.18) resonated at apparently higher field than those (δ 3.44) of the starting phenol (2a) by the anisotropic effect of the entering benzene ring. It was interesting that the site of substitution in this arylation was entirely analogous to that in the chlorination.[4] Similarly, reaction of 1a with several other activated benzene derivatives was carried out to give the corresponding 8-aryl derivatives (5b-f) in good yields. The yield and spectral data of the products are shown in Tables I and II, re-

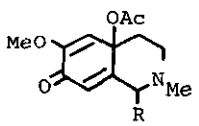
† Dedicated to Prof. T. Kametani on the occasion of his retirement.

spectively.

A key intermediate in this reaction would be the o-quinonoid cation (6), as already shown in the chlorination[4b], which would be attacked by an activated benzene at the 8-position through conjugate addition followed by enolization.

As a matter of course, reaction of 1a with corypalline (2a) was anticipated to result in the formation of the corypalline dimer. In reality, 1a reacted with 2a (1 eq.) to give the known corypalline dimer (7)[7], m.p. 227-229°, in 22% yield. Thus substitution in the present reaction was in part synthetically proved to take place at the 8-position.

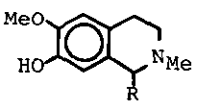
We are currently engaging in the synthesis of some mixed tetrahydroisoquinoline dimers.



1

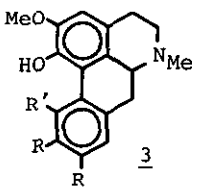
1a : R=H

1b : R=CH_2Ar



2

2a : R=H



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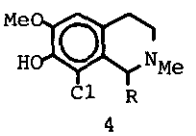

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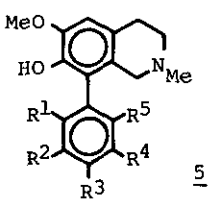
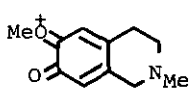


5

	R^1	R^2	R^3	R^4	R^5
5a	H	OCH_3	OCH_3	H	H
5b	H	$-OCH_2O-$		H	H
5c	OCH_3	OCH_3	OCH_3	H	H
5d	OCH_3	H	OCH_3	H	H
5e	OCH_3	H	H	OCH_3	H
5f	OCH_3	H	OCH_3	H	OCH_3



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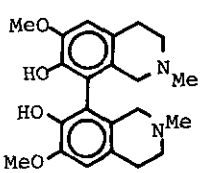

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Table I The Melting Point and Yield of the Products (5a-f)

	m.p. (°C)	yield (%)
5a	183 - 185	70
5b	203 - 204	52
5c	129 - 130	42
5d	163 - 166	43
5e	152 - 155§	29
5f	207 - 210	36

§ Methiodide of the acetate.

Table II The Spectral Data of the Products (5a-f)

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

¶ Each doublet, J=8.6 Hz.

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6. All new compounds gave satisfactory analytical data. NMR and IR spectra were taken in $CDCl_3$ and $CHCl_3$ solution, respectively. Preparative t.l.c. was run on silica gel HF_{254} (Merck).

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