A SYNTHESIS OF MIXED TETRAHYDROISOQUINOLINE DIMERS VIA p-QUINOL ACETATE

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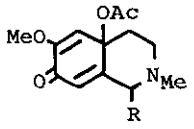
Abstract --- Several mixed tetrahydroisoquinoline dimers (4, 6, 7, 10b, 11b, 12b, and 13b) were prepared by reaction of the p-quinol acetate (1a) and the corresponding phenolic tetrahydroisoquinolines. In the case of 5-hydroxytetrahydroisoquinoline (14), a different kind of dimer (16) was obtained together with 15. A radical mechanism was presented for these reactions.

Preliminarily we have reported a novel synthesis of 8-aryl-1,2,3,4-tetrahydroisoquinolines by acid treatment of the p-quinol acetate (1a) with aryl ethers.[1] In connection with the synthesis, we found a facile method for the preparation of the mixed tetrahydroisoquinoline dimer which could hardly be prepared using the usual phenol coupling of two different phenols.

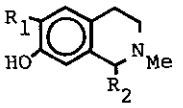
This paper presents a novel synthesis of several mixed dimers and an oxidizing capability of the p-quinol acetate (1).

The reaction of p-quinol acetate (1a), readily obtained from corypalline (2a),[2] with isocorypalline (3a)[3] in the presence of trifluoroacetic acid gave the mixed dimer (4) (dimethiodide: mp 290-291°C) in 54% yield. The structure of the dimer was determined as 4 by NMR spectral assignment. Signals of two methoxyl groups were overlapped at δ 3.76 and those of two N-methyl groups appeared separately at δ 2.18 and 2.32, thus excluding the structure of 5 for the dimer.

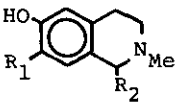
Similarly, acid treatment of 1a with (±)-N-4'-O-dimethylisococlaurine (3b)[4]



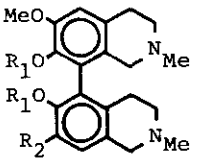
1a : R=H
1b : R=Ph



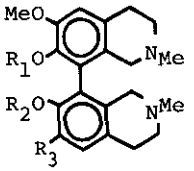
2a : R_1=OMe, R_2=H
2b : R_1=OMe, R_2=Ph
9 : R_1=R_2=H



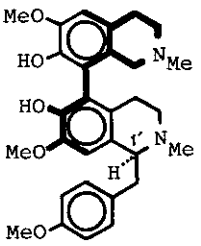
3a : R_1=OMe, R_2=H
3b : R_1=OMe
R_2=$CH_2C_6H_4OMe$(p)
8 : R_1=R_2=H



4 : R_1=H, R_2=OMe
10a : R_1=R_2=H
10b : R_1=Ac, R_2=H



	R_1	R_2	R_3
5 :	H	Me	OH
12a :	H	H	H
12b :	Ac	Ac	H
22 :	H	H	OMe



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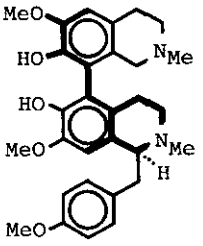

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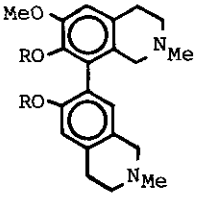
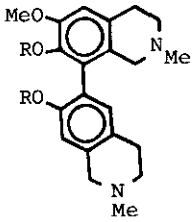
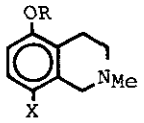


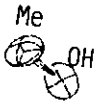
11a : R=H
11b : R=Ac



13a : R=H
13b : R=Ac



14 : R=X=H
17 : R=CH_2Ph, X=H
18 : R=CH_2Ph, X=Br



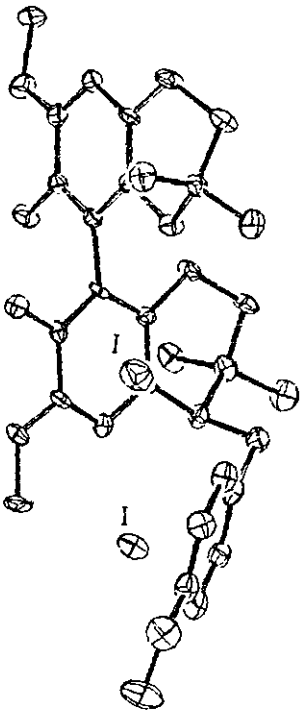
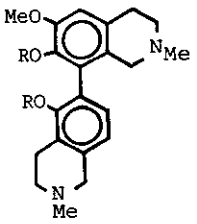
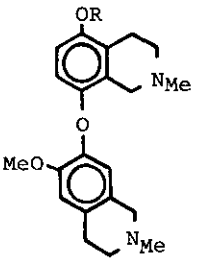


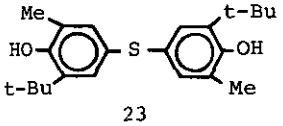
Fig. 1 The Structure of Dimethiodide of Compound 6



15 : R=Ac
21 : R=H



16 : R=Ac
19 : R=CH_2Ph
20 : R=H



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yielded a pair of diastereomers [6 (19%) and 7 (10%)], the formation of which was attributable to the presence of axial dissymmetry and an asymmetric carbon at 1'-position. The stereostructure of the former (6) was determined by X-ray crystallographic analysis of its dimethiodide (Fig. 1).

Next, 6- or 7-hydroxytetrahydroisoquinoline (8[5] or 9[6]) reacted with 1a to afford two regioisomers (10a and 11a, or 12a and 13a), which were separated as their diacetates (10b and 11b, or 12b and 13b). Yields of these products are shown in Table I. Structure assignment of the dimers was based on NMR spectroscopic evidences. Namely, three aromatic proton signals of 10b and 12b appeared as a singlet and an AB-quartet (J=8 Hz), while those of 11b and 13b as three singlets.

On the other hand, the reaction of 5-hydroxytetrahydroisoquinoline (14)[7] with 1a and subsequent acetylation unexpectedly afforded the mixed dimer (15)(4%) and different kind of dimer (16)(11%) having a biphenyl ether linkage. The structure of the former (15) was determined by NMR study, that is, two acetoxyl signals were shifted to upper field (δ 1.95 and 1.98) by the anisotropic effect of twisted biphenyl benzene rings. However, NMR spectrum of 16 showed one normal acetoxyl signal at δ 2.28 and four aromatic protons, two of which appeared as an AB-quartet (J=8 Hz). Accordingly, the structure of the latter product was presumably shown as the biphenyl ether (16). For confirmation, the authentic sample of 16 was prepared as follows. Bromination of 5-benzyloxytetrahydroisoquinoline (17) gave the 8-bromo derivative (18), which was subjected to the Ullmann reaction with corypalline (2a) affording the benzyloxybiphenyl ether (19). Catalytic debenzylation of 19 yielded the hydroxybiphenyl ether (20), the acetate of which was completely identical with the above product (16) by comparison of their IR and NMR spectral charts and TLC behavior.

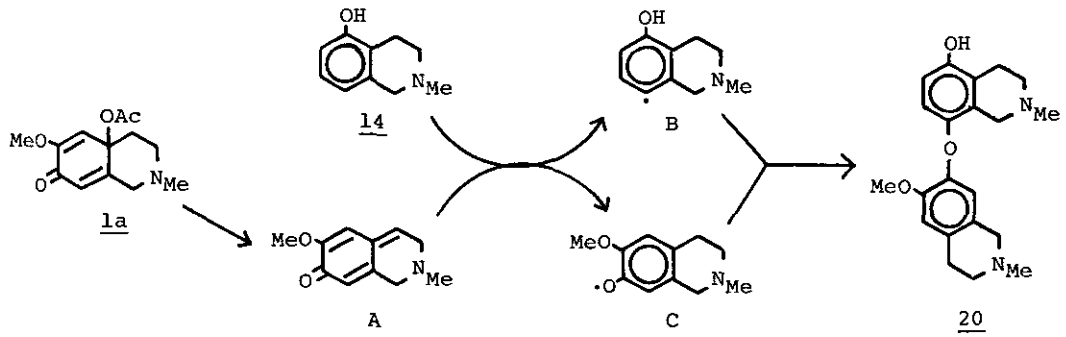
The formation of the biphenyl ether (20) was of great interest. As in the case of 8-aryltetrahydroisoquinolines,[1] 21 was most likely formed through S_N reaction. However, the formation of the biphenyl ether (20) was hardly explicable in terms of ionic mechanism. It is probable that the initially generated p-quinone methide (A) oxidized 5-hydroxytetrahydroisoquinoline (14) into the phenol radical (B), leaving the corypalline radical (C) which would couple with B to give the biphenyl ether (20) (Scheme 1).

Actually, the p-quinol acetate (1b), obtained from 2b,[2] reacted with corypalline (2a) in the presence of CF_3CO_2H giving corypalline dimer (22)[8](17%) and 2b[8](37%). The structure of the former (22) was confirmed by direct comparison with the au-

thentic sample.[9] As 8-position of the p-quinol acetate (1b) was sterically hindered by the bulky 1-phenyl group, attack of phenol on the position was inhibited giving no mixed dimer. Another possible dimer, i.e. the biphenyl ether like 16 could not be detected in spite of numerous attempts. In any event, 1b was to be clearly modified as an oxidizing agent for the coupling reaction of corypalline.

In order to establish the proper mechanism, ionic or radical, for the formation of the mixed dimer (4), the reaction of the p-quinol acetate (1a) with isocorypalline (3a) in the presence of 4,4'-thiobis(2-tert-butyl-6-methylphenol) (23) as radical scavenger was carried out, but giving no dimer (4).[10]

Therefore it is assumed that a radical mechanism is more suitable than the ionic one for the reaction of the p-quinol acetate (1) with phenolic tetrahydroisoquinolines in the presence of CF_3CO_2H.



Scheme 1

Table I : Yields of Mixed Tetrahydroisoquinoline Dimers

Starting material		Products			
p-QA[§]	Phenol	Mixed Dimer		Others	
1a	3a	4 (54%)		3a (31%)	2a (7%)
1a	3b	6 (19%)	7 (10%)	3b (60%)	2a (15%)
1a	8	10b (21%)	11b (16%)	8† (50%)	2a† (18%)
1a	9	12b (31%)	13b (4%)	9† (45%)	2a† (18%)
1a	14	15 (4%)	16 (11%)	14† (56%)	2a† (12%)
1b	2a	22† (17%)		2a† (33%)	2b† (37%)

[§]p-Quinol acetate

†Isolated as acetate or diacetate

ACKNOWLEDGEMENT --- The authors are indebted to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for his kind supply of the starting vanillin. Thanks are also due to Sankyo Co., Ltd. for elemental analyses and to Miss N. Sawabe of this Faculty for NMR spectral measurements.

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8. The dimers 22 and 2b were separated as acetates.
9. An authentic diacetate of 22 was prepared from 22[1] by usual acetylation.
10. Treatment of the p-quinol acetate (1a) with CF_3CO_2H in the presence of 23 gave corypalline (2a) (47%), showing that a redox reaction occurred.

Received, 27th June, 1983