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A FRAGMENTATION REACTION OF 4a-ACETOXY-6-METHOXY-2-METHYL-7-OXO-1,2,3,4,4a,7-HEXAHYDROISOQUINOLINE

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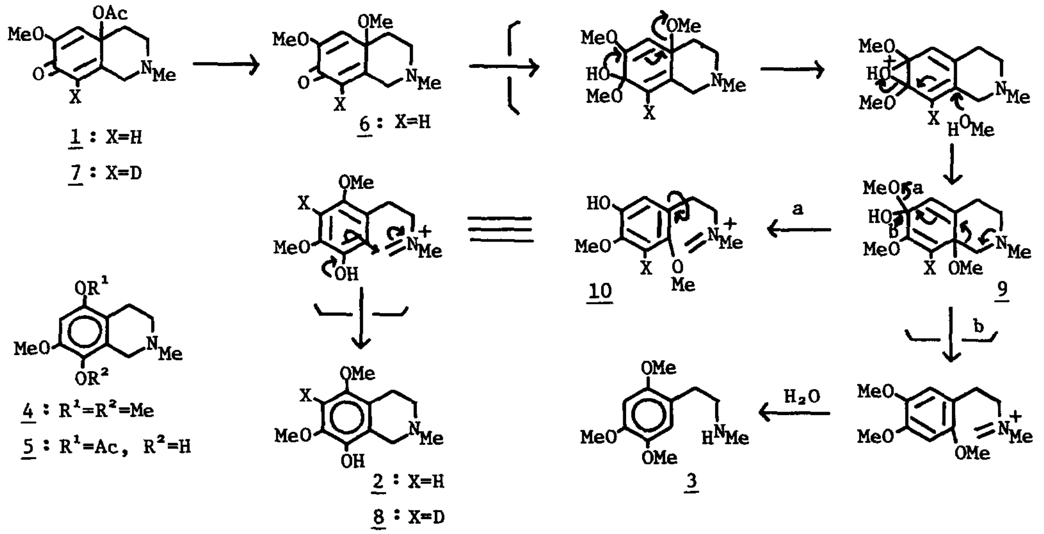
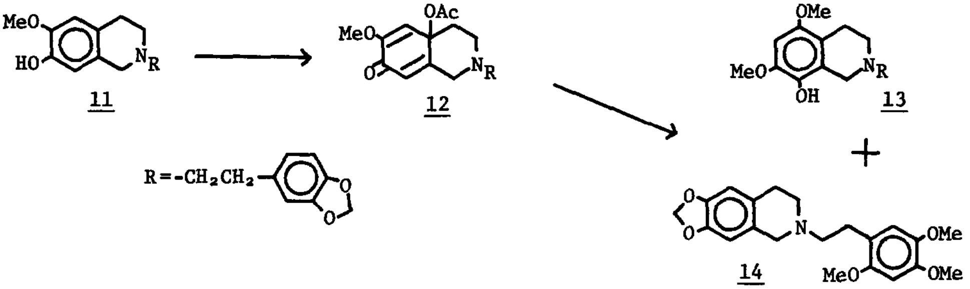
Summary: Treatment of the p-quinol acetate (1) with boiling MeOH in the presence of $BF_3\cdot Et_2O$ gave the 8-hydroxy-5,7-dimethoxytetrahydroisoquinoline (2). A mechanism via the phenethylammonium intermediate (10) was proposed.

In the course of our continued study on the reactivity[1] of the p-quinol acetate (1), a fragmentation (C_1-C_{8a} bond cleavage) reaction of 1 was encountered in boiling MeOH in the presence of $BF_3\cdot Et_2O$ to yield the 8-hydroxy-5,7-dimethoxytetrahydroisoquinoline (2)[2] (mp 171-172°C, 43% yield) together with 2,4,5-trimethoxyphenethyl methylamine (3) (an oil, 12% yield). Structure of 2 was determined by its conversion to the methyl ether (4),[3] and no incorporation of a deuterium atom on heating 2 with 5% NaOD-D_2O.[6]

Since treatment of the p-quinol ether (6)[1c] with MeOH under the same conditions afforded 2, a dienone-phenol rearrangement of 6 leading to 2 appeared to be the most plausible mechanism for the transformation. However, the same reaction of the 8-deuterio p-quinol acetate (7) gave the 6-deuterioisoquinolinol (8) instead of 2, ruling out the above mechanism. Thus, the reaction is best explained in terms of the fragmentation of a common intermediate (9)[7] followed by the Mannich-type reaction as shown in the scheme.



In order to verify the mechanism, the N-homopiperonyltetrahydroisoquinoline (11)[8] was converted into the corresponding p-quinol acetate (12) and treated in the same way. Two recyclized products 13[2] (mp 127°C) and 14[2] (mp 78-82°C) were obtained in 39% and 23% yield, respectively. Structure of the latter (14) was confirmed by comparison with an authentic specimen prepared by condensation of 1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline and methyl 2,4,5-trimethoxyphenylacetate and subsequent reduction. Formation of 14 was clearly indicative of recyclization via the fragmentation.



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References and Notes

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2) All new compounds gave satisfactory combustion analytical values and their ^{1}H-NMR spectral data (δ values in $CDCl_3$ solution) are as follows. 2: 2.51 (NMe), 3.60 ($ArCH_2N$), 3.81, 3.91 (each OMe), 6.41 (ArH); 13: 3.69 ($ArCH_2N$), 3.76, 3.83 (each OMe), 5.88 (OCH_2O); 14: 3.63 ($ArCH_2N$), 3.80, 3.82, 3.87 (each OMe), 5.86 (OCH_2O), 6.47, 6.49, 6.53, 6.72 (each 1H, s, ArH).

3) The authentic sample (4) was prepared from the 5-acetoxy-8-hydroxy-7-methoxytetrahydroisoquinoline (5)[4] by usual methylation.[5]

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7) The initially formed hemiketal is likely to be transformed to the intermediate. Fragmentation involving the removal of methoxyl group (route a) yields the isoquinolinol (2). The trimethoxyphenethylamine (3) was considered to be formed via the fragmentation (route b).

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