ON THE REACTION OF 1-BENZYL-7-ACETOXY-7-METHOXY-2-METHYL-6-OXO-$\Delta^{4a,5,8,8a}$-HEXAHYDROISOQUINOLINES (O-QUINOL ACETATES) WITH METHANOL IN THE PRESENCE OF SULFURIC ACID†

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Abstract—— Reaction of o-quinol acetate (1) with MeOH-conc. H_2SO_4 proceeded unexpectedly to give 1-(3,4-dimethoxybenzyl)-4a,6-dimethoxy-2-methyl-7-oxo-$\Delta^{5,6,8,8a}$-hexahydroisoquinoline (6) and 4-methoxytetrahydroisoquinolin-6-ol (7). A brief account for the stereochemical course of the reaction was presented.

Our continuing interest in the chemistry of o-quinol acetate (o-QA)[1] of 6-tetrahydroisoquinolinol stimulated us to examine its reaction with MeOH-conc.H_2SO_4. Here we wish to describe the unusual formation of a p-quinol methyl ether, 1-(3,4-dimethoxybenzyl)-4a,6-dimethoxy-2-methyl-7-oxo-$\Delta^{5,6,8,8a}$-hexahydroisoquinoline (6) and a stereochemical feature of the reaction.

A methanolic solution of o-QA (1)[1], prepared from 1-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline was treated with conc.H_2SO_4-MeOH at room temperature for 1 hr. Usual work-up of the reaction mixture followed by column chromatography over silica gel gave a diastereomeric mixture of 6a and 6b (40% yield) and that of 1-(3,4-dimethoxybenzyl)-6-hydroxy-4,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (7)(12.4% yield)[7a (9.4%) and 7b (3.0%)][2] [methiodide [3], m.p. 216-218° (dec.)(EtOH)]. The former was separated by preparative thin

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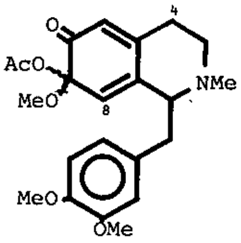
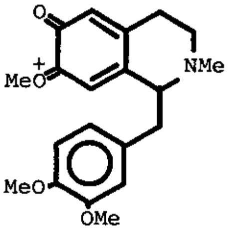
† Cordially dedicated to Professor Kyosuke Tsuda on the occasion of 75th birthday.



1



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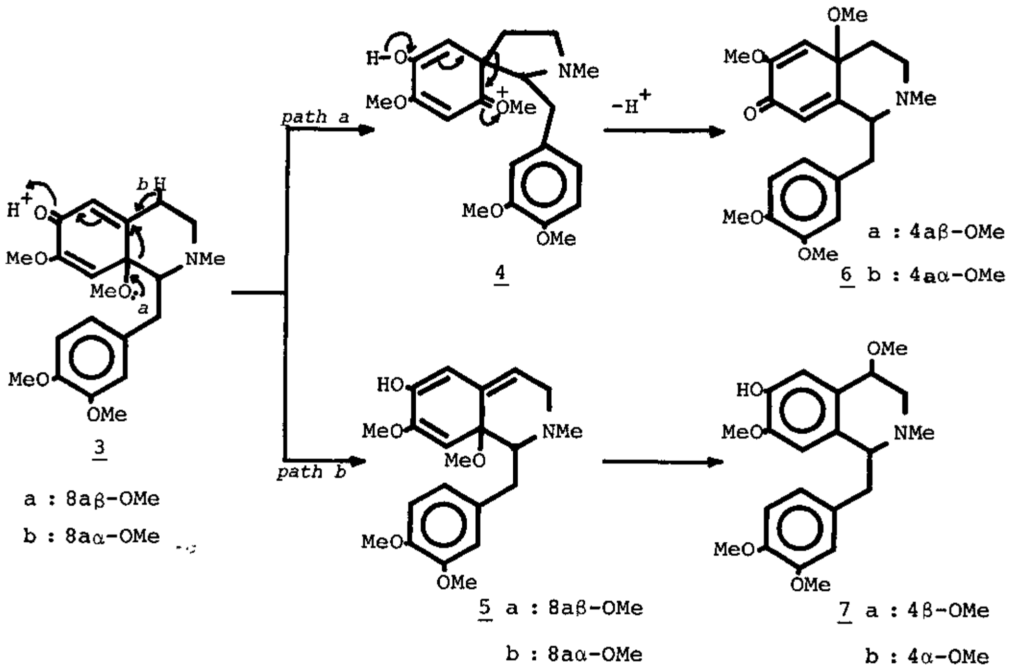


3

a : 8aβ-OMe

b : 8aα-OMe

4

6 a : 4aβ-OMe

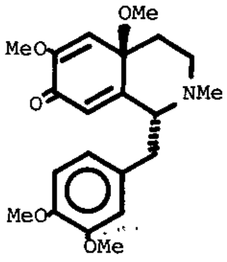
b : 4aα-OMe

5 a : 8aβ-OMe

b : 8aα-OMe

7 a : 4β-OMe

b : 4α-OMe



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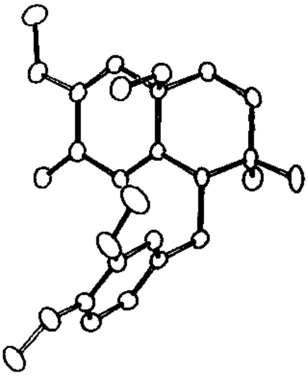

Perspective Drawing of the Molecular Structure of Methiodide of 6a chromatography[4] to give oily 6a [16.3%; methiodide, m.p. 214-217° (dec.)(EtOH)] and oily 6b [17.3%; methiodide, m.p. 218-221° (dec.)(EtOH)]. Attempts to separate the latter were unsuccessful.

To ascertain the stereostructure of 6a, a single crystal (0.30 x 0.35 x 0.35 mm) recrystallized from absolute EtOH was subjected to X-ray crystallographic analysis. Crystal data: 6a · MeI, $C_{22}H_{30}INO_5$, mol. wt. = 515.4, m.p. 237-239° (dec.). Monoclinic, space group C2/c, Z = 8, Dcal = 1.468 gm^{-3}, a = 20.124(10), b = 19.539(10), c = 14.685(7) Å, $\beta = 126.14(6)°$, U = 466.9 $Å^3$, μ for MoKα = 13.86 cm^{-1}. The iodine atoms were found at the two special positions with half weight; one at (1/4, 1/4, 0) on the center of symmetry and another at (0, y, 1/4) on the diad axis. The final R value was 0.065 including anisotropic thermal parameters for all non-hydrogen atoms. The analysis established the stereostructure as 8, where the nitrogen-containing six membered ring adopted a chair conformation and the orientations of C_{4a}-methoxyl and C_1-benzyl groups were β-axial and α-equatorial, respectively.

The net trans vs. cis ratio, 6a + 7a : 6b + 7b, in the reaction was 5:4, when calculated from the above yields.

Thus a rational mechanistic pathway for the reaction would be as follows. Namely, acid-catalyzed detachment of the acetoxyl group in 1 gave an onium ion (2), on the C_{8a}-position of which MeOH attacked to result in the transient formation of a p-quinol methyl ether (3a and 3b). Subsequently, the pathway was devided into two routes; one (path a) involved the C_{8a}-C_1 bond shift assisted by the tertiary methoxyl group to C_{4a} giving a spiro intermediate (4) and another (path b) the enolization giving an allylic methyl ether (5). The bond alteration in 4 and the allyic or 1,3-sigmatropic rearrangement in 5 afforded 6 and 7, respectively. Steric influence imposed on the incoming methoxyl group at C_{8a}- and C_4-positions by the α-oriented C_1-benzyl group was probably reflected in the product ratio.

As to the o-QA derived from 1-(3,4-methylenedioxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, the reaction took the same course as above and a similar trend was observed, the trans vs. cis ratio being 5:4.

Scope of the reaction is currently pursued and the results will be published shortly.

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REFERENCES AND NOTES

1. O. Hoshino, M. Ohtani, and B. Umezawa, Chem. Pharm. Bull., 1979, **27**, 3101.
2. The yields were calculated on the basis of the peak areas of NCH_3 groups of 7a and 7b. Tentatively, the assignment was made according to that of 4-acetoxy congeners (details will be published elsewhere). Namely, NCH_3 group of 1,4-*trans* compound resonated at higher field than that of 1,4-*cis* by a value of 0.04-0.06 ppm.
3. All new compounds gave satisfactory NMR spectroscopic data and correct combustion analyses were obtained for their crystalline derivatives.
4. Two developments were carried out on silica gel plates [silica gel HF_{254} (Merck)] by use of C_6H_6-MeOH (10:1) as a developing solvent.

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