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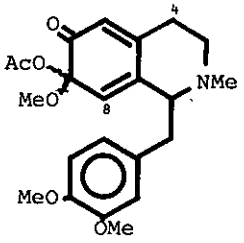
Abstract—— Reaction of o-quinol acetate (1) with MeOH-conc. H_2SO_4 proceeded unexpectedly to give 1-(3,4-dimethoxybenzyl)-4a,6-dimethoxy-2-methyl-7-oxo-$\Delta^{5,6,8,8a}$-hexahydroisoquinoline (6) and 4-methoxytetrahydroisoquinolin-6-ol (7). A brief account for the stereochemical course of the reaction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

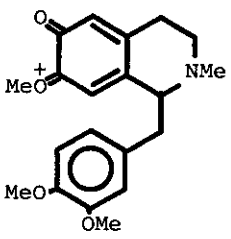
Our continuing interest in the chemistry of o-quinol acetate (o-QA)[1] of 6-tetrahydroisoquinolinol stimulated us to examine its reaction with MeOH-conc.H_2SO_4. Here we wish to describe the unusual formation of a p-quinol methyl ether, 1-(3,4-dimethoxybenzyl)-4a,6-dimethoxy-2-methyl-7-oxo-$\Delta^{5,6,8,8a}$-hexahydroisoquinoline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

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



1



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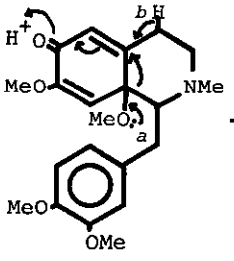


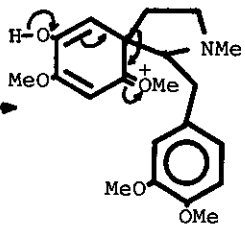
3

a : 8aβ-OMe

b : 8aα-OMe

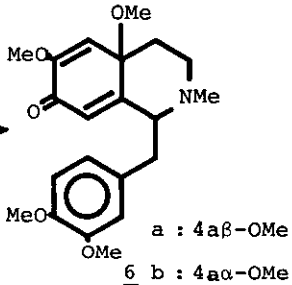
path a

path b



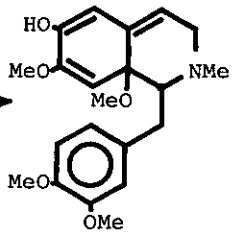
4

$-H^+$



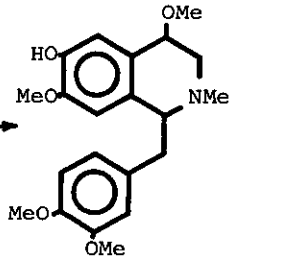
6 a : 4aβ-OMe

b : 4aα-OMe



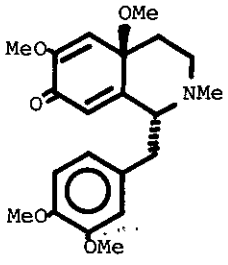
5 a : 8aβ-OMe

b : 8aα-OMe



7 a : 4β-OMe

b : 4α-OMe



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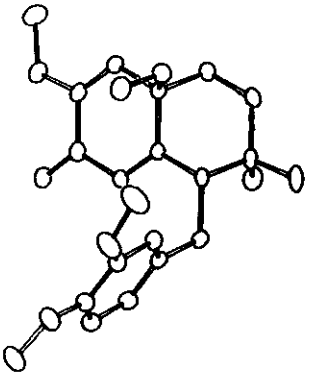

Perspective Drawing of the Molecular Structure of Methiodide of 6a

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, β = 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 combusion 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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