A COMMENT ON LEAD TETRAACETATE OXIDATION OF FOUR GUIACOL-TYPE 1,2,3,4-TETRAHYDROISOQUINOLINES

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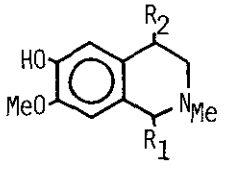
Abstract —— Lead tetraacetate oxidation of four guiacol-type tetrahydroisoquinolines (1a, 2a, 6, and 7a) in CH_2Cl_2 at 0°C gave the respective o-quinol acetates (4a, 12, 8, and 13). On the other hand, oxidation of them in AcOH at room temperature afforded the acetoxy derivatives (14a, 3a, 9, and 14a), respectively. Treatment of the o-quinol acetate (4a, 12, 8, or 13) with AcOH yielded the same product (14a, 3a, 9, or 14a) as above. The o-quinol acetate (4a or 13) was thermally transformed into the 4-acetoxy derivative (5a or 15).

Lead tetraacetate oxidation of 6- or 7-hydroxy-1,2,3,4-tetrahydroisoquinoline (1 or 2) having a guiacol moiety gives a useful synthetic intermediate. Namely, the p-quinol acetate (3) is obtained from 2, and the o-quinol acetate (4) or the 4-acetoxy derivative (5) from 1. By acid treatment of 3, 4, or 5, many isoquinoline alkaloids have been biomimetically synthesized.[1] However, no report is available on the lead tetraacetate oxidation of 5-hydroxy-6-methoxy- (6) or 8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (7).

Here we wish to report newly on the oxidation of 6 and 7 and on a recent development concerning the tetrahydroisoquinoline oxidative rearrangement.[2]

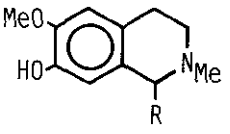
Lead tetraacetate oxidation of 5-hydroxy-6-methoxytetrahydroisoquinoline (6) in CH_2Cl_2 at 0°C for 2 min and subsequent work-up with care at a low temperature (<30°C) gave an oily o-quinol acetate (8), the structure of which was determined by spectral data. IR spectrum showed absorption bands of ester (1720 cm^{-1}) and dienone (1660 cm^{-1}), and two olefinic protons appeared at δ 6.00 as a singlet on NMR



1

1a : R_1=R_2=H

1b : R_1=H, R_2=Ph



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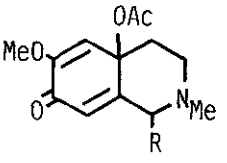
2a : R=H



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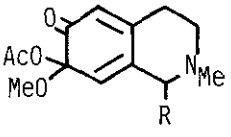
3a : R=H



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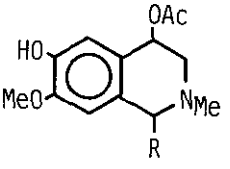
4a : R=H



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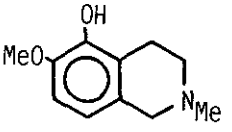
5a : R=H



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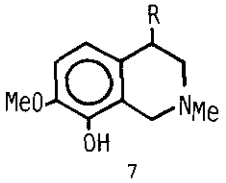
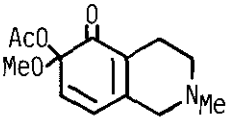


7

7a : R=H

7b : R=Ph



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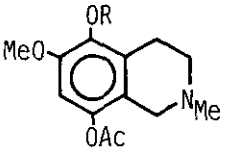
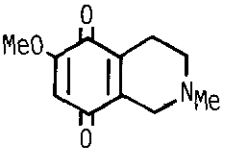


9 : R=H

10 : R=Ac



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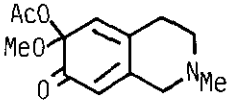

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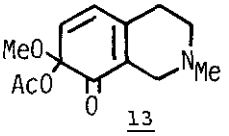

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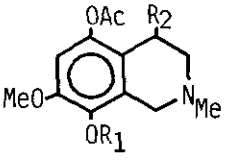
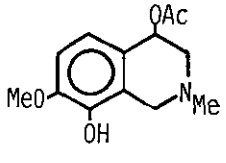


14a : R_1=R_2=H

14b : R_1=H, R_2=Ph

16a : R_1=Ac, R_2=H

16b : R_1=Ac, R_2=Ph



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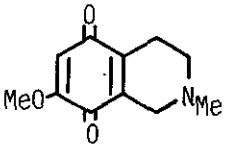

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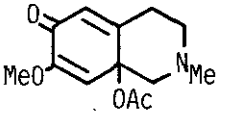


18

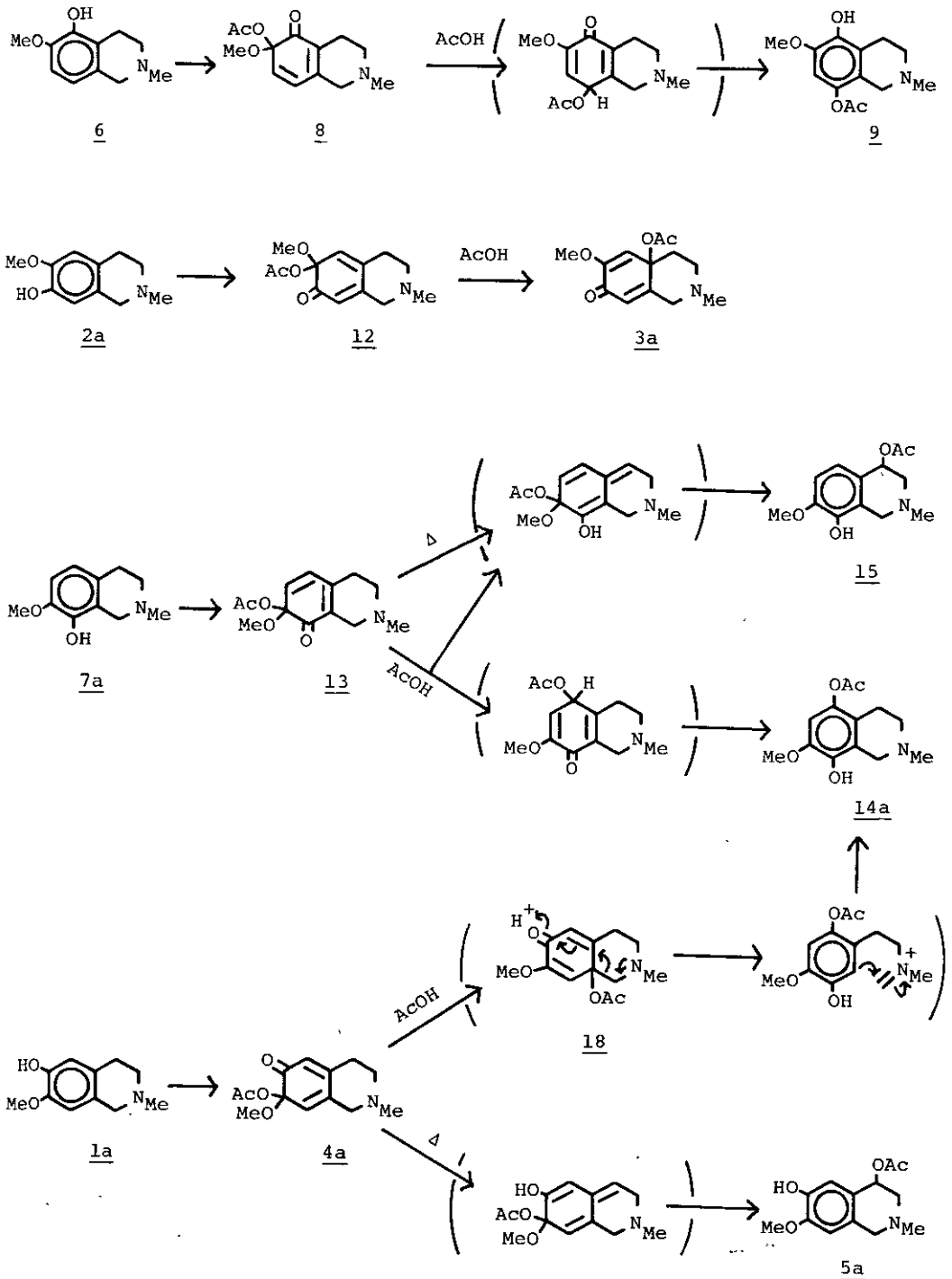
spectrum. Treatment of 8 with AcOH at room temperature gave the monoacetate (9) (51% yield from 6), mp 147-148°C, having one aromatic acetoxyl group [1750 cm^{-1} (IR) and δ 2.28 (NMR)], one aromatic proton (δ 6.44), and one hydroxyl group (3540 cm^{-1}), the last of which was assignable as phenolic by acetylation; the diacetate (10), mp 105-106°C [1750 cm^{-1} (IR)]. In order to confirm structure of 9, an authentic sample of 10 was prepared. Oxidation of 6 with Fremy's salt[3] afforded the p-quinone (11) [1625 and 1605 cm^{-1} (IR)] as an oil. Reduction of 11 by Zn in Ac_2O[4] yielded a diacetate, which was coincident with the diacetate (10) by comparison of spectra (IR and NMR) and a mixed melting point determination.

In addition, 5-hydroxy-6-methoxytetrahydroisoquinoline (6) was oxidized by lead tetraacetate in AcOH at room temperature to give rise to the monoacetate (9), directly. Treatment of the o-quinol acetate (8) with Ac_2O-c.H_2SO_4 gave the diacetate (10). However, thermal treatment of 8 in CH_2Cl_2 yielded a complicated mixture. These behaviors of 6 as above were similar to those of 7-hydroxy-6-methoxytetrahydroisoquinoline (2a) as shown in Scheme.

Lead tetraacetate oxidation of corypalline (2a) in CH_2Cl_2 at 0°C gave the o-quinol acetate (12) (1730 and 1675 cm^{-1}), which was treated with AcOH to afford the p-quinol acetate (3a).[5] Thermal treatment of 12 gave a complicated mixture.

On the other hand, oxidation of 8-hydroxy-7-methoxy congener (7a) in CH_2Cl_2 at 0°C for 1 min gave the o-quinol acetate (13) [1730 (ester), 1680 cm^{-1} (dienone)] as an oil. Without purification, 13 was treated with AcOH to give two monoacetate (14) (36%) and 15 (14%), and the structure of the former [δ 6.44 (Ar-H); 3530 (OH), 1750 cm^{-1} (OAc)] and its acetate (16), mp 121-122°C [1760 cm^{-1} (OAc)], were determined in a similar manner as above. Fremy's salt oxidation of 7a gave the p-quinone (17) [1630, 1600 cm^{-1} (IR)]. 17 was reduced by Zn in Ac_2O to afford a diacetate, which was identical with 16. The latter product (15) showed absorption bands corresponding to alcoholic ester (1710 cm^{-1}) and hydroxyl groups (3530 cm^{-1}) on IR spectrum, and two aromatic protons [δ 6.70 and 6.80 (each doublet, J=8 Hz)] and one proton (δ 5.92, triplet, J=4 Hz) on NMR spectrum. The latter proton signal was assignable to a benzylic methine hydrogen geminal to the acetoxyl function. On the basis of these data and chemical correlation,[6] structure of 15 was reasonably assigned. A likely passway was shown in the Scheme.

Oxidation of 7a in AcOH yielded 14 and 15 in a ratio of 2.3 : 1, showing that the o-quinol acetate (13) was a key intermediate in this reaction, since the ratio of products 14 and 15 on treatment of 13 with AcOH was 2.6 : 1. The o-quinol acetate



Scheme

(13) was allowed to stand in CH_2Cl_2 without any added nucleophile at 30°C for 5 h giving solely the monoacetate (15), formation of which was most reasonably considered to be due to two successive [3,3]-sigmatropic rearrangements after enolization as shown in the Scheme. This chemical behavior of 13 was very similar to that of the o-quinol acetate (4a).[7]

Finally, in order to clarify the scope of the tetrahydroisoquinoline oxidative rearrangement,[2] we carried out the oxidation of a 6-hydroxy congener, 6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1a). At that time we considered that the bulky aryl group at the 3-position was responsible for the rearrangement. Therefore, we chose 1a as the simplest representative to check the above consideration. Thus it was revealed that treatment of the o-quinol acetate (4a) with AcOH and the oxidation in AcOH of 1a gave unexpectedly the monoacetate (14a) in 41% and 65% yield, respectively. Possibly, the rearrangement occurred according to route in the Scheme, that is, the p-quinol acetate (18) was a transient intermediate, although hypothetical.

In addition, the oxidation in AcOH of both 1b and 7b,[9] which possessed phenyl group at the 4-position, gave the monoacetate (14b) in 29 and 7% yield, respectively. The monoacetate (14b) was easily transformed into the diacetate (16b). Structure of both products 14b and 16b was reasonably assigned on the basis of IR and NMR data.

Thus an essential requirement for the rearrangement to occur was that a given tetrahydroisoquinoline had no substituent at the 1-position, disproving the above consideration.

Conclusively, since the o-quinol acetates could be isolated by lead tetraacetate oxidation in CH_2Cl_2 of the corresponding guiacol-type tetrahydroisoquinolines, the initial oxidation products in AcOH must have also been the o-quinol acetates, which were then transformed to the final products via the p-quinol acetates by way of aromatization, enolization, or the retro-Mannich and Mannich reactions. On the other hand, the o-quinol acetates 4a and 13 were thermally transformed into the 4-acetoxy derivatives 5a and 15, respectively.

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5. B. Umezawa, O. Hoshino, Y. Terayama, K. Ohyama, Y. Yamanashi, T. Inoue, and T. Toshioka, Chem. Pharm. Bull., 1971, 19, 2138.
6. The starting phenol (7a) was easily obtained by hydrogenolysis of 15 on 10% Pd-C.
7. Oxidation of 1a in CH_2Cl_2 at 0°C gave the o-quinol acetate (4a),[1b] which was readily transformed at 30°C (1 h) into the 4-acetoxy derivative (5a).[8]
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