A SYNTHESIS OF 3-HYDROXYAPORPHINE AND HOMOAPORPHINE

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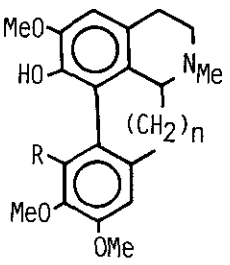
Abstract —— 3-Hydroxy-2,9,10-trimethoxyaporphine (8) and 3-hydroxy-2,10,11,12-tetramethoxyhomoaporphine (9) were synthesized via the corresponding o-quinol acetates (13 and 14).

A facile synthesis of 1-hydroxyaporphine (1) and homoaporphine (2) via the corresponding p-quinol acetates (3 and 4) have been already established.[1] Recently, we reported that lead tetraacetate oxidation in CH_2Cl_2 of 5-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (5) has given the o-quinol acetate (6), which has been treated with AcOH to afford the 8-acetoxy derivative (7),[2] showing that the 8-position is susceptible to the nucleophilic attack and the reaction should be applicable to ring closure. Here we wish to report a novel synthesis of 3-hydroxyaporphine (8) and homoaporphine (9).

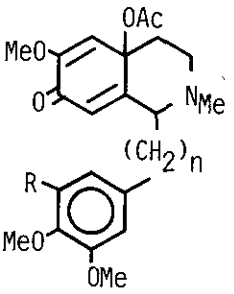
Three starting phenols (10, 11, and 12) were prepared by a conventional method.[1,3] Lead tetraacetate oxidation of 10 in CH_2Cl_2 at 0°C for 2 min and careful work-up[2] (<30°C) gave the o-quinol acetate (13) [IR: 1730 cm^{-1} (OAc) and 1670 cm^{-1} (dienone)], quantitatively. Without purification, 13 was treated with CF_3CO_2H in CH_2Cl_2 at room temperature for 2 h to give an oil, which was purified on preparative TLC affording 3-hydroxy-2,9,10-trimethoxyaporphine (8), mp 213-214°C (lit.[4] 214-215°C), in 73% yield (from 10). Three aromatic protons at δ 6.82, 7.07, and 7.16 on NMR spectrum reasonably proved the aporphine structure for 8.

Similarly, oxidation of 11 gave the o-quinol acetate (14), acid treatment of which furnished 3-hydroxy-2,10,11,12-tetramethoxyhomoaporphine (9), mp 240-245°C (methiodide of the acetate: mp 204-205°C), in 90% yield (from 11).[5] NMR spectrum of 9 showed signals of four methoxyl groups [δ 3.92, 4.03 (6H), 4.09] and two aromatic protons (δ 6.85, 7.13). Evidently, one aromatic proton at δ 7.13 assignable to the



1 : n=1, R=H

2 : n=2, R=OMe



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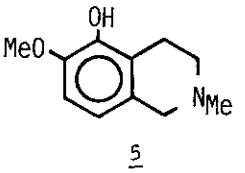

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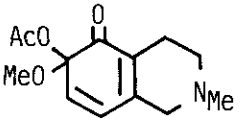

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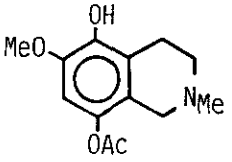

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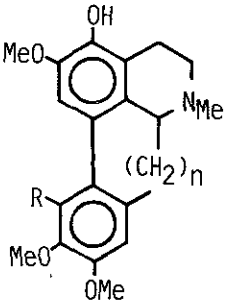
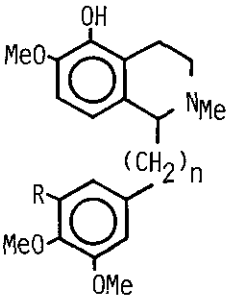


8 : n=1, R=H

9 : n=2, R=OMe

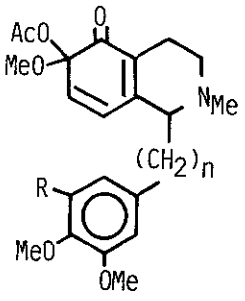
18 : n=0, R=H



10 : n=1, R=H

11 : n=2, R=OMe

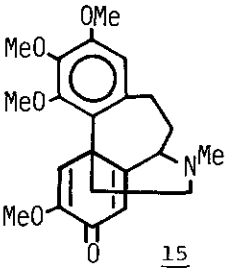
12 : n=0, R=H



13 : n=1, R=H

14 : n=2, R=OMe

17 : n=0, R=H



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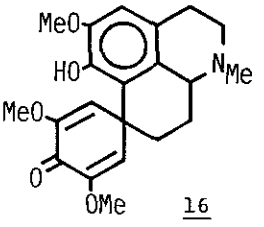

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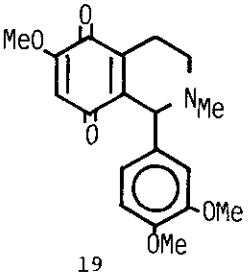

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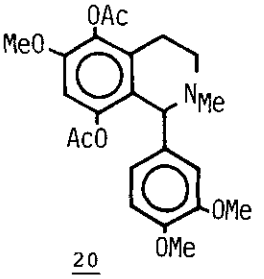

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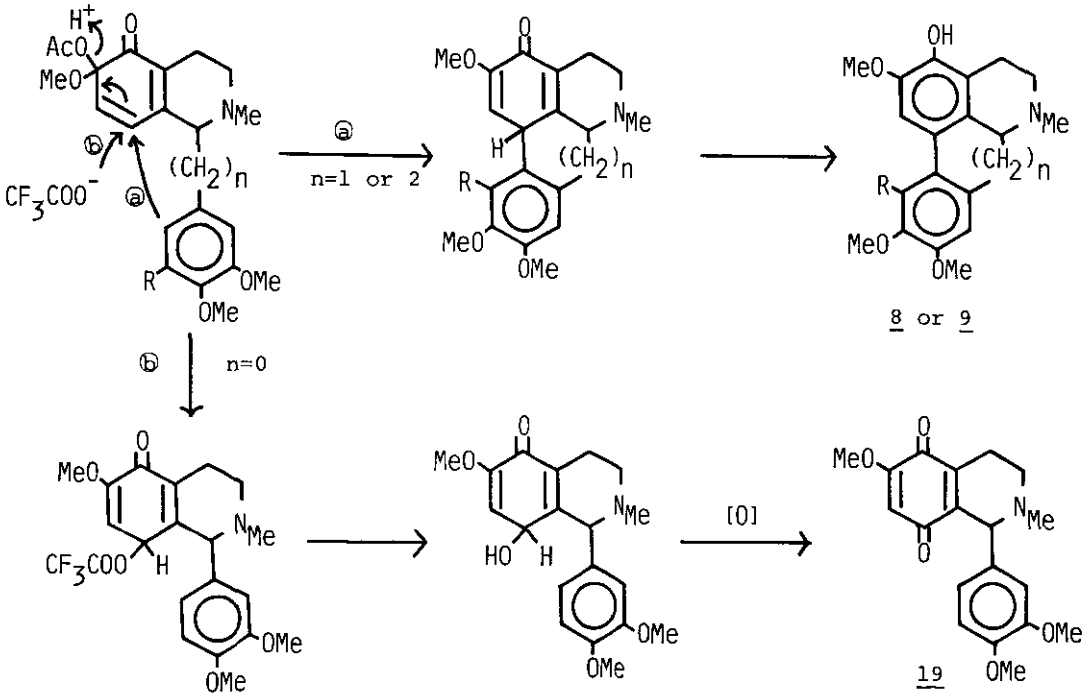
C-1 position was deshielded by the C-12 methoxyl group.

Analoguously, oxidation of the 1-aryltetrahydro-5-isoquinolinol (12) gave the o-quinol acetate (17), cyclization of which however was unsuccessful. Namely, 17 was treated with CF_3CO_2H in CH_2Cl_2 to give rise to no cyclized product (18) but the p-quinone (19) in 66% yield (from 12). Structure of 19 was determined both spectroscopically and chemically. One olefinic proton [δ 5.65 (NMR)] and two absorption bands [1645, 1600cm^{-1} (IR)] pointed out clearly the p-quinone structure. Reduction of 19 with Zn in Ac_2O[2] gave the diacetate (20) (methiodide: mp 238-240°C), spectral data of which showed aromatic acetoxyl function (1750cm^{-1}) on IR and four aromatic protons and two singlets of acetoxyl groups on NMR. Signal due to the C-8 acetoxyl protons was shifted to higher field owing to the anisotropic effect caused by the C-1 benzene ring.

Mechanism of the aporphine cyclization and the formation of p-quinone could be illustrated as shown in the Scheme. Especially, in the case of 17, steric strain imposed by the five membered ring in 18 probably prohibited the intramolecular arylation, allowing the nucleophilic attack by CF_3COO^-. Hydrolysis of trifluoroacetate and subsequent oxidation gave the quinone 19.



Scheme

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REFERENCES AND NOTES

1. a) H. Hara, O. Hoshino, and B. Umezawa, Chem. Pharm. Bull., 1976, 24, 262; b) H. Hara, O. Hoshino, and B. Umezawa, Chem. Pharm. Bull., 1976, 24, 1921; c) H. Hara, O. Hoshino, and B. Umezawa, J. Chem. Soc. Perkin I, 1979, 2657; d) H. Hara, O. Hoshino, T. Ishige, and B. Umezawa, Chem. Pharm. Bull., 1981, 29, 1083.
2. H. Hara, H. Shinoki, O. Hoshino, and B. Umezawa, Heterocycles, submitted.
3. All new compounds gave reasonable spectroscopic data and satisfactory combusion analytical values.
4. S. M. Kupchan and C. K. Kim, J. Org. Chem., 1976, 41, 3210.
5. The sole formation of 9 from 14 was interesting when compared with the result that the p-quinol acetate (4)[1c] gave three products, the 1-hydroxyhomoaporphine [(±)-kreysigine] (2), the homomorphinandienone [(±)-O-methylandrocymbine] (15), and the homoproaporphine (16) under similar conditions.

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