A BIOMIMETIC SYNTHESIS OF (±)-TETRAHYDROTAKATONINE, (±)-O-METHYLGIGANTINE, AND TEHAUNINE†

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Abstract—— Treatment of 7-acetoxy-7-methoxy-2-methyl-6-oxo-$\Delta^{4a,5,8,8a}$-hexahydroisoquinolines (6a-c) with conc.H_2SO_4 in Ac_2O and subsequent hydrolysis followed by methylation produced the title alkaloids (9a-c), although in low yields.

It has been reported that as to the isoquinoline alkaloid biosynthesis[1] the C_5-oxygen function of 5,6,7-trimethoxytetrahydroisoquinoline such as thalifendlerine (1) would be introduced into a p-quinol cation (2) derived from the corresponding guiacol-type tetrahydroisoquinoline. However, there are no in vitro or in vivo evidences for supporting the speculation. In the course of our studies on the reaction of quinol acetates of tetrahydroisoquinolinols, we have recently found that the reaction of 4a-acetoxy-6-methoxy-2-methyl-7-oxo-$\Delta^{5,6,8,8a}$-hexahydroisoquinolines (p-quinol acetates) with hydrochloric acid[2,3] gives 8-chloro-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (4) via o-quinoid cation (3) and that lead tetraacetate oxidation of 1-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline gives a reactive 7-acetoxy-7-methoxy-2-methyl-6-oxo-$\Delta^{4a,5,8,8a}$-hexahydroisoquinoline (o-quinol acetate)(o-QA)(6d)[4]. On the other hand, o-QA (6) was expected to generate another o-quinoid cation (5), which was eventually equivalent to 2. Thus, 5 would be a feasible candidate to testify the above speculation and its reaction with Ac_2O containing conc.H_2SO_4 was examined. Here, we wish to describe a successful synthesis of the title alkaloids (9a-c) by the unprecedented methodology.

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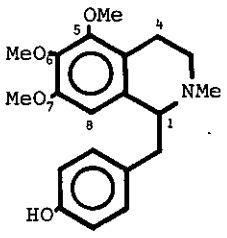
† Cordially dedicated to Professor Kyosuke Tsuda on the occasion of 75th birthday.



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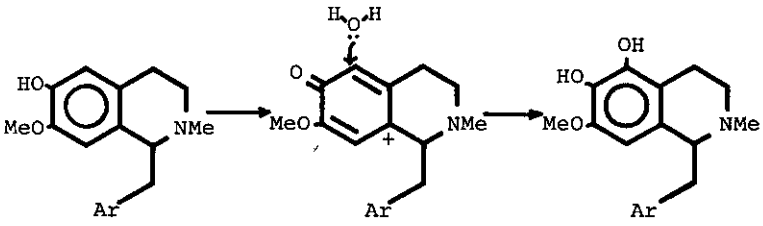

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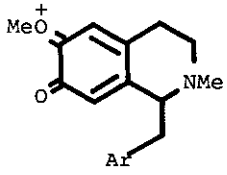

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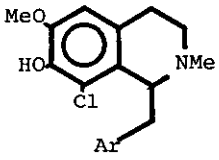

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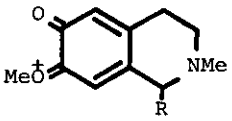

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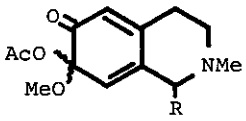

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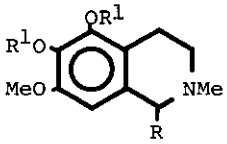
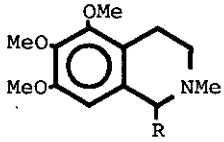


7 : R^1 = OAc

8 : R^1 = H



9

a : R = 4-$MeOC_6H_4CH_2$ b : R = Me c : R = H

d : R = 3,4-$(MeO)_2C_6H_3CH_2$

A diastereomeric mixture of o-QA (6a)[5] derived from 1-(4-methoxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (500 mg) in the similar manner[6] as described previously[3] was treated with conc.H_2SO_4 in Ac_2O (1:10v/v, 15 ml) at room temperature for 1 hr to afford oily 5,6-diacetate (7a)(18.2 mg, 2.7% from the starting phenolic base). Attempts to identify the other products were unfruitful. Hydrolysis of 7a with 20%HCl [50°C (bath temperature), 1 hr] gave hygroscopic 5,6-diol (8a)·HCl.[7] Methylation of 8a with diazomethane in MeOH afforded oily (±)-tetrahydrotakatonine (9a)(17.6%, from 7a)[9a·HCl, m.p. 185-187° (lit.[8] 188-192°)]. A similar sequence of reactions of 6-hydroxy-7-methoxy-1,2-dimethyl- and 6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines gave oily 5,6-diacetates (7b) (19.6%) and (7c)(19.4%). Acidic hydrolysis followed by methylation as mentioned above afforded oily (±)-O-methylgigantine (9b)(22.2%) and oily tehaunine (9c)(22.1 %), respectively. For unambiguous characterization, 9b and 9c were converted to methopicrate[9], m.p. 201°, and to hydrochloride, m.p. 228-229° (lit.[10] 229-230°), respectively.

Thus, 5,6,7-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (9a-c) were explicitly shown to be derivable from the corresponding 7-methoxy-6-phenolic bases by the intermediary of heterocyclic o-QA (6a-c), whose fact proved both an *in vitro* experimental support to Dyke's speculation[1] and a considerable biogenetic implication. Synthetic endeavours to improve the yield of 7a-c and to prepare (±)-thalifendlerine (1) by the methodology are currently under way.

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REFERENCES AND NOTES

1. S.F. Dyke, Heterocycles, 1977, 6, 1441.
2. H. Hara, O. Hoshino, and B. Umezawa, Chem. Pharm. Bull., 1981, 29, 51.
3. Recently, the similar reaction of o-QA was found to give a 5-chloro compound. Details will be reported in due course.
4. O. Hoshino, M. Ohtani, and B. Umezawa, Chem. Pharm. Bull., 1979, 27, 3101.
5. All new compounds gave reasonable spectroscopic data.
6. Removal of the solvent was performed in an ice-water bath under reduced pressure.
7. The product was dried in a desiccator overnight.
8. S. Kubota, T. Masui, E. Fujita, and S.M. Kupchan, J. Org. Chem., 1966, 31, 516.
9. Satisfactory combusion analytical value was obtained.
10. The authors thank Professor G.J. Kapadia of Howard University for communicating the melting point and for sending the copy of its IR spectral chart.

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