

THE TETRAHYDROISOQUINOLINE OXIDATIVE REARRANGEMENT

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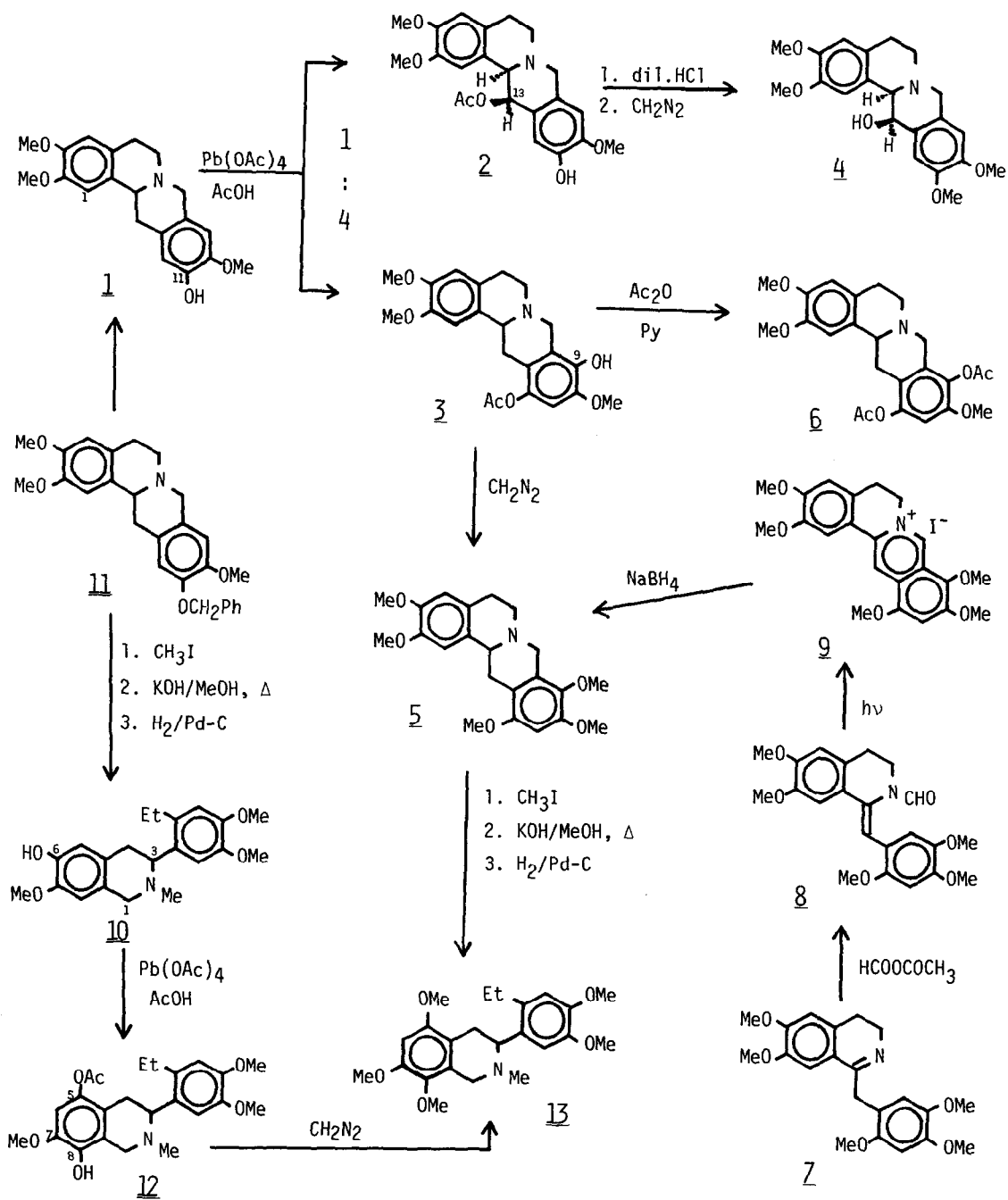
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Since ( $\pm$ )-11-hydroxy-2,3,10-trimethoxytetrahydroprotoberberine (1) incorporates a 6-hydroxy-7-methoxytetrahydroisoquinoline moiety as an integral part of rings C and D, its lead tetraacetate oxidation<sup>1)</sup> was expected to cause the direct introduction of acetoxy group at the 13-position. Interestingly, however, the reaction took in large part a different course resulting in the unexpected formation of a D-ring acetoxyated product. Here we wish to report on its structure and a scope of the novel reaction.

To a stirred solution in AcOH (3 ml) of 1<sup>2)</sup> (300 mg, 0.88 mmole) at room temp., was added lead tetraacetate (468 mg, 1.2 eq.) in one portion and the whole was stirred for 30 min at the same temp. Usual work-up of the reaction mixture gave a brown oil (412 mg), which was separated into ( $\pm$ )-13 $\beta$ -acetoxy-11-hydroxy- (2) (50 mg, 12.5%), mp 104-114°, [ IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3530 (OH), 1720 (aliph. OCOCH<sub>3</sub>); NMR  $\delta$  (CDCl<sub>3</sub>): 1.71 (3H, s, OCOCH<sub>3</sub>), 6.53 (1H, d, J=2.5 Hz, 13 $\alpha$ -H) ] and ( $\pm$ )-12-acetoxy-9-hydroxy-2,3,10-trimethoxytetrahydroprotoberberine (3) (207 mg, 51.9%), mp 172-179°, [ IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3530 (OH), 1760 (arom. OCOCH<sub>3</sub>); NMR  $\delta$  (CDCl<sub>3</sub>): 2.27 (3H, s, OCOCH<sub>3</sub>), 6.50, 6.60, 6.70 (each 1H, s, arom. H)].

The structure of the former was proved by its transformation to ( $\pm$ )-13 $\beta$ -hydroxy-2,3,10,11-tetramethoxy compound (4), mp 200-203° (lit.<sup>3)</sup> mp 198-200°, [NMR  $\delta$  (CDCl<sub>3</sub>): 4.80 (1H, broad s, 13 $\alpha$ -H)], while that of the latter by some reactions and finally by the synthesis of (+)-2,3,9,10,12-pentamethoxytetrahydroprotoberberine (5).

The major product of the lead tetraacetate oxidation provided a diacetate (6) upon acetylation, mp 164-169°, [ IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 1760 (OCOCH<sub>3</sub>); NMR  $\delta$  (CDCl<sub>3</sub>):



2.27, 2.30 (each 3H, s, OCOCH<sub>3</sub>), 6.61 (2H, s, 2 x arom. H), 6.67 (1H, s, arom. H)], and a pentamethyl ether (5), mp 187-189°, [NMR  $\delta$  (CDCl<sub>3</sub>): 3.78, 3.79, 3.88 (each 3H, s, OCH<sub>3</sub>), 3.85 (6H, s, 2 x OCH<sub>3</sub>), 6.38, 6.59, 6.78 (each 1H, s, arom. H); MS m/e: 385 (M<sup>+</sup>), 194, 189] after treatment with diazomethane in methanol.<sup>4)</sup>

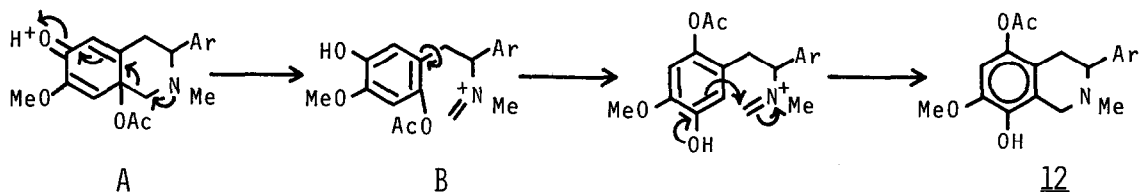
3,4-Dihydroisoquinoline (7) derived from  $\beta$ -(3,4-dimethoxyphenyl)ethylamine and methyl 2,4,5-trimethoxyphenylacetate by a conventional method was formylated with acetic-formic anhydride to yield an enamide (8) (56.1%), mp 143-143.5°, [IR  $\nu_{\text{max}}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 1660 (NCHO); NMR  $\delta$  (CDCl<sub>3</sub>): 6.51, 6.60 (each 1H, s, arom. and olef. H), 6.87 (2H, s, 2 x arom. H), 7.25 (1H, s, arom. H), 8.10 (1H, s, NCHO)], which was irradiated in a mixture<sup>5)</sup> of dioxane, t-BuOH, and 47% HI with a 400W mercury lamp (pyrex filter) under Ar stream for 5 hr to lead to 2,3,9,10,12-pentamethoxyprotoberberine iodide (9) (65.4%), mp 230-234°, [NMR  $\delta$  (CF<sub>3</sub>COOD): 7.04, 7.36, 7.64, 8.85, 9.51 (each 1H, s, arom. H)]. NaBH<sub>4</sub> reduction of the iodide (9) yielded after purification on preparative TLC authentic ( $\pm$ )-tetrahydroprotoberberine (5) (81.6%), mp 185-188°, which was identical with the above pentamethyl ether.

The oxidation of 6-phenolic tetrahydroisoquinolines possessing no substituent at the 3-position has never given such a rearranged product as 3.

To gain an insight into the essential features of the reaction, ( $\pm$ )-6-hydroxy-7-methoxy-2-methyl-3-phenyl-tetrahydroisoquinoline (10) derived from ( $\pm$ )-11-benzyloxy-2,3,10-trimethoxytetrahydroprotoberberine (11) was subjected to the oxidation and purification of the product on preparative TLC yielded ( $\pm$ )-5-acetoxy-8-hydroxy-7-methoxy-tetrahydroisoquinoline (12) (86.6%), mp 167-168°, [IR  $\nu_{\text{max}}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 3530 (OH), 1755 (OCOCH<sub>3</sub>); NMR  $\delta$  (CDCl<sub>3</sub>): 2.19 (6H, s, OCOCH<sub>3</sub> and NCH<sub>3</sub>), 6.50, 6.68, 7.05 (each 1H, s, arom. H); MS m/e: 415 (M<sup>+</sup>), 208]. On methylation with diazomethane<sup>4)</sup> the monoacetate (12) was transformed to the corresponding ( $\pm$ )-5,7,8-trimethoxy-tetrahydroisoquinoline (13), a brown oil, [NMR  $\delta$  (CDCl<sub>3</sub>): 3.59, 3.64 (each 3H, s, OCH<sub>3</sub>), 3.71 (9H, s, 3 x OCH<sub>3</sub>), 6.21, 6.48, 6.78 (each 1H, s, arom. H)], which was spectroscopically and chromatographically (TLC) identical with an authentic specimen prepared from pentamethyl ether (5).

The reaction pathway must involve a retro-Mannich reaction of a *p*-quinol acetate (A) as shown in Scheme I to generate the immium B, which recycles *ortho* to the phenolic function to supply a 5-acetoxy-8-hydroxy-7-methoxy-tetrahydroiso-

quinoline (12).



Scheme I

The present reaction appeared to widen the scope of the oxidation in the field of isoquinoline alkaloids implying a possible occurrence of tetrahydroprotoberberines possessing such an oxygenation pattern in the D-ring as pictured above.

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#### REFERENCES AND FOOT NOTES

1. O. Hoshino, K. Ohyama, M. Taga, and B. Umezawa, *Chem. Pharm. Bull. (Tokyo)*, 22, 2587 (1974); B. Umezawa and O. Hoshino, *Heterocycles*, 3, 1005 (1975).
2. T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc. (C)*, 112 (1968).
3. M. Shamma and V. St. Georgiev, *Tetrahedron*, 32, 211 (1976).
4. H. Brederbeck, R. Sieber, L. Kamphenkel, *Chem. Ber.*, 89, 1169 (1956).
5. G. R. Lenz, *J. Org. Chem.*, 42, 1117 (1977).

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