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A Novel Synthesis of Aporphine Alkaloids *via o*-Quinol Acetates

Lead tetraacetate oxidation of 1-(3',4'-dimethoxy- or 3',4'-methylenedioxy-benzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**1a** or **1b**) in CH_2Cl_2 was found to give quantitatively a diastereomeric mixture (1:1) of an *o*-quinol acetate (**2a** or **2b**), treatment of which with Ac_2O -conc. H_2SO_4 at room temperature led to ($\pm$)-*O*-acetyl-predicentrine (**5a**) or -isodomeesticine (**5b**). Furthermore, hydrolysis of **5a** or **5b** with 1.7% KOH - MeOH afforded ($\pm$)-predicentrine (**6a**) or ($\pm$)-isodomeesticine (**6b**).

Keywords—lead tetraacetate oxidation; Ac_2O -conc. H_2SO_4 ; 1-benzyl-1,2,3,4-tetrahydro-7-methoxy-6-isoquinolinols; ($\pm$)-*O*-acetylpredicentrine; ($\pm$)-*O*-acetylisodomeesticine; ($\pm$)-predicentrine; ($\pm$)-isodomeesticine

Careful reexamination on lead tetraacetate (LTA) oxidation of 1-(3',4'-dimethoxybenzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**1a**) revealed that a reactive *o*-quinol acetate (**2a**) was the genuine intermediate leading to a 4-acetoxy derivative (**3a**) obtained in our early experiment.^{1,2)} Thus the *o*-quinol acetate was anticipated to be of a potential use for the synthesis of aporphine alkaloid, when treated with acid, through the agency of dienone-phenol rearrangement³⁾ of a dienone (**4**) formally derivable from **2a** or

Chart 1

- 1) Details including the oxidation of 1-benzyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline will be published in due course.
- 2) O. Hoshino, K. Ohyama, M. Taga, and B. Umezawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 2587 (1974).
- 3) There are some reports on the rearrangement of a dienone such as **4** [cf. M.P. Cava, I. Noguchi, and K.T. Buck, *J. Org. Chem.*, **38**, 2394 (1973); S.M. Kupchan and C.-K. Kim, *ibid.*, **41**, 3210 (1976); S.M. Kupchan, C.-K. Kim, and K. Miyano, *J.C.S. Chem. Comm.*, **1976**, 91].

direct coupling between C-6' and C-8 positions in **2a**. We now wish to report a novel synthesis of aporphine alkaloids *via o*-quinol acetates.

To a stirred solution of **1a** (200 mg) in CH_2Cl_2 (60 ml) was added LTA (285 mg) in one portion at 5°. After agitation for 1 min, the whole was poured into sat. aq. NaHCO_3 solution and extracted with CH_2Cl_2 . Usual work-up of the extract followed by prompt removal of the solvent at reduced pressure below 30° afforded quantitatively a diastereomeric mixture (1:1) of **2a** (oil); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1735, 1680; NMR δ (CDCl_3): 2.03, 2.04 [each s, 3H, OCOCH_3 (1:1)], 3.27, 3.36 [each s, 3H, 7- OCH_3 (1:1)].

To convert **2a** into an aporphine Ac_2O -conc. H_2SO_4 was proved efficacious after several attempts. Thus, to a stirred, ice-cold solution of the crude **2a** in Ac_2O (2 ml) was added conc. H_2SO_4 (0.2 ml) dropwise and stirring was continued at room temperature for 1 hr. On quenching by ice-water followed by stirring for 0.5 hr, the reaction mixture was made basic with NaHCO_3 (powder) and the product was taken up in CHCl_3 . Usual work-up of the CHCl_3 extract gave an oil (243 mg), silica gel column chromatography of which with CHCl_3 -MeOH (100:1) yielded oily ($\pm$)-O-acetylpredicentrine (**5a**) (71 mg, 31.8%); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1760; NMR δ (CDCl_3): 2.37 (s, 3H, OCOCH_3), 6.76, 6.79 (each s, 2H, arom. H), 7.97 (s, 1H, 11-H); methiodide, mp 230–231° (dec.) (EtOH).

Hydrolysis of **5a** with 1.7% KOH-MeOH at room temperature for 0.5 hr gave oily ($\pm$)-predicentrine (**6a**) (96.5%); HCl salt, mp 214–216° (dec.) (MeOH-ether) [lit.⁴⁾ 215–217° (dec.)]. Methylation with diazomethane of **6a** gave ($\pm$)-glaucine (**7a**) (77%); picrate, mp 190–193° (dec.) (EtOH) [lit. 193–194°, ^{5a)} 191–193° (dec.) ^{5b)}].

By the same sequence of reactions starting from **1b**, **2b** (oil); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1735, 1675; NMR δ (CDCl_3): 2.06, 2.09 [each s, 3H, OCOCH_3 (1:1)], 3.14, 3.37 [each s, 3H, 7- OCH_3 (1:1)], ($\pm$)-O-acetylisodomeesticine (**5b**) (oil, 16.1%); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1750; NMR δ (CDCl_3): 2.36 (each s, 3H, OCOCH_3), 5.95, 5.98 (AB q, 2H, $J=1.5$ Hz, OCH_2O), 6.76 (s, 2H, 3- and 8-H), 7.87 (s, 1H, 11-H); methiodide, mp 239–242° (dec.) (EtOH), ($\pm$)-isodomeesticine (**6b**) (quant.); mp 180–182° (ether-*n*-hexane) (lit.⁶⁾ 180–183°), and ($\pm$)-nantenine (**7b**) (95.8%); mp 138–139° (*n*-hexane) (lit.⁷⁾ 140–142°), were obtained.

As a result, we succeeded in a novel synthesis of some aporphine alkaloids *via o*-quinol acetates and the synthesis of ($\pm$)-boldine (**6c**) and aporphine (**6d**) by this methodology appears to locate within a shooting range.

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Faculty of Pharmaceutical Sciences,
Science University of Tokyo
12 Ichigaya Funagawara-machi,
Shinjuku-ku, Tokyo, 162
Japan

OSAMU HOSHINO
MINORU OHTANI
BUNSUKE UMEZAWA

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