Communications to the Editor

Chem. Pharm. Bull. 26(12)3920—3921(1978)

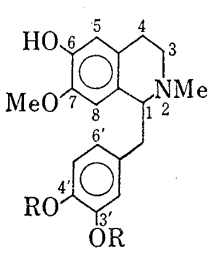
UDC 547.944.04.057 : 547.833.9.04

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

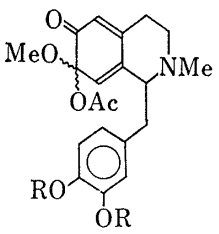
Lead tetraacetate oxidation of 1-(3′,4′-dimethoxy- or 3′,4′-methylenedioxy-benzyl)-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**1a** or **1b**) in CH_2Cl_2 was found to give quantitatively a diastereomeric mixture (1 : 1) of an *o*-quinol acetate (**2a** or **2b**), treatment of which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

Keywords——lead tetraacetate oxidation; Ac_2O–conc.H_2SO_4; 1-benzyl-1,2,3,4-tetrahydro-7-methoxy-6-isoquinolinols; (±)-O-acetylpredicentrine; (±)-O-acetylisodomesticine; (±)-predicentrine; (±)-isodomesticine

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 rearrangement[3] of a dienone (**4**) formally derivable from **2a** or



1 **a** : R=Me
b : R+R=CH_2



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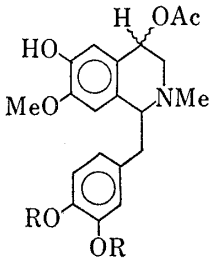

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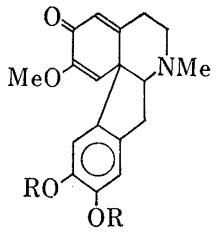

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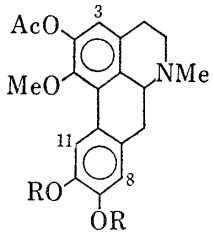

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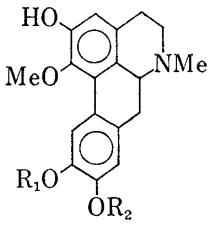

6 **a** : R_1=R_2=Me
b : R_1+R_2=CH_2
c : R_1=Me, R_2=H
d : R_1=H, R_2=Me

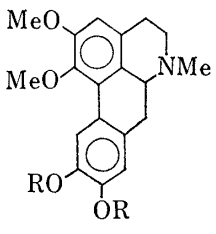

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Chart 1

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 $\nu_{max}^{CHCl_3}$ 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 (±)-O-acetylpredicentrine (**5a**) (71 mg, 31.8%); IR $\nu_{max}^{CHCl_3}$ 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 (±)-predicentrine (**6a**) (96.5%); HCl salt, mp 214—216° (dec.) (MeOH–ether) [lit.[4] 215—217° (dec.)]. Methylation with diazomethane of **6a** gave (±)-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 $\nu_{max}^{CHCl_3}$ 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)], (±)-O-acetylisodomesticine (**5b**) (oil, 16.1%); IR $\nu_{max}^{CHCl_3}$ 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), (±)-isodomesticine (**6b**) (quant.); mp 180—182° (ether–*n*-hexane) (lit.[6] 180—183°), and (±)-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 (±)-boldine (**6c**) and aporphine (**6d**) by this methodology appears to locate within a shooting range.

Acknowledgement We are indebted to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for his kind supply of the starting material. Thanks are also due to Miss N. Sawabe of this Faculty for NMR spectral measurement and to Sankyo Co., Ltd. for elemental analysis.

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Received October 6, 1978

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5) *a*) A.H. Jackson and J.A. Martin, *J. Chem. Soc.* (*C*), **1966**, 2061; *b*) S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), **18**, 1224 (1970); O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Commun.*, **1971**, 1533; *idem*, *Chem. Pharm. Bull.* (Tokyo), **22**, 1302 (1974).
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