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Synthesis of Higenamine, A Cardiotonic Principle of Aconite Root

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Abstract □ Higenamine (**I**), a cardiotonic principle of Aconite root, was synthesized from 4-methoxyphenylacetic acid (**II**) and β-(3, 4-dimethoxyphenyl)-ethylamine (**IV**). Condensation of **IV** with 4-methoxyphenylacetyl chloride (**III**) was followed by cyclodehydration yielding 1-(4′-methoxybenzyl)-6, 7-dimethoxy-3, 4-dihydroisoquinoline (**VI**). Reduction of **VI** to 1, 2, 3, 4-tetrahydroisoquinoline (**VII**) and subsequent demethylation provided desired product higenamine, 1-(4′-hydroxybenzyl)-6, 7-dihydroxy-1, 2, 3, 4-tetrahydroisoquinoline.

Keywords □ Higenamine, 1-(4′-hydroxybenzyl)-6, 7-dihydroxy-1, 2, 3, 4-tetrahydro isoquinoline, 4-Methoxyphenylacetic acid, β-(3, 4-Dimethoxyphenyl) ethylamine.

Higenamine (**I**), 1-(4′-hydroxybenzyl)-6, 7-dihydro-1, 2, 3, 4-tetrahydroisoquinoline, is a potent cardiotonic component isolated from the root of *Aconitum* spp. (Ranunculaceae).[1,2] It was also isolated from the seed embryo of *Nelumbo nucifera* (Nymphaeceae) as a smooth muscle and uterine relaxing component.[3]

Considerable interests have been placed upon the investigation of the action mechanism of higenamine on cardiac muscle.[4-7] Higenamine was found to increase the slow inward calcium current through the sarcolemma. The cardiac effect of higenamine was also potentiated by extracellular calcium and was competitively blocked by propranolol. The results were indicative that the mechanism of positive inotropic action of higenamine was different from that of cardiac glycosides and the cardiotonic effects were likely exerted through the stimulation of cardiac adrenoceptors. However, only few other pharmacological and toxicological works have been done.

The higenamine contents in plants are quite low to provide enough higenamine for biological testings in vivo. In addition, the separation and purification of higenamine from plant sources are complex and time comsuming. Higenamine was also reported to be partially synthesized by demethylation of coclaurine (methylhigenamine) with hydrobromic acid.[3,8]

This paper describes the total synthesis of higenamine from the commercially available, inexpensive starting materials with fairly good overall yield. 4-Methoxyphenylacetyl chloride (**III**) prepared from 4-methoxyphenylacetic acid (**II**) was condensed with β-(3, 4-dimethoxyphenyl) ethylamine (**IV**). Bischler-Napieralski cyclodehydration of the resulting N-(3′, 4′-dimethoxyphenylethyl)-4-methoxyphenylacetamide (**V**) with phosphorus oxychloride yielded 1-(4′-methoxybenzyl)-6, 7-dimethoxy-3, 4-dihydroisoquinoline (**VI**). The 3, 4-dihydroisoquinoline (**VI**), with the treatment of sodium borohydride, was easily reduced to the corresponding 1, 2, 3, 4-tetrahydroisoquinoline (**VII**) almost quantitatively. Tridemethylation of 1-(4′-methoxybenzyl)

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-6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline (**VII**) was achieved by refluxing with 47% hydriodic acid providing desired product higenamine (**I**) as its hydriodide salt. The overall yield from **II** was approximately 50%. Comparison of IR, UV, NMR and Mass data with the literature values comfirmed the structure of higenamine. The result of the elemental analysis was also consistant with the theoretical values. The free base of higenamine could also be obtained with the treatment of ammonium hydroxide as reported.[8]

EXPERIMENTAL METHODS

The IR spectra were taken with Perkin-Elmer 283, UV with Gilford 2600, NMR with Varian FT-80A and the Mass spectra were taken with Hewlett-Packard 5985B. Elemental analysis was done with Perkin-Elmer 240 at The Korean Chemical Research Institute.

N-(3′, 4′-Dimethoxyphenylethyl)-4-methoxyphenylacetamide (V)

4-Methoxyphenylacetyl chloride was prepared from 4-methoxyphenylacetic acid (8.3g, 0.05 mole) by the procedure of Sims et al.[9] After removal of the solvent and excess thionyl chloride, the crude 4-methoxyphenylacetyl chloride (**III**), IR ν_{max}^{neat} 1795cm^{-1}, was directly utilized for the next reaction without furthur purification. The above crude acid chloride (**III**) was dissolved in 30ml of benzene and was added dropwise to the solution of β-(3, 4-dimethoxyphenyl) ethylamine (18.2g, 0.1 mole) in 40ml benzene. The reaction mixture was refluxed for 5 hrs. After cooling, the precipitate was filtered. It was dissolved in chloroform and washed with d-HCl. Removal of the solvent from the organic layer and recrystallization from ethanol provided amide (**V**) (12.2g, yield 75%). mp 122~123°C; IR ν_{max}^{neat} 1640cm^{-1} (CONH); NMR δ($CDCl_3$) 7.04 (2H, d, J=8Hz), 6.78 (2H, d, J=8Hz), 6.65 (1H, s), 6.55 (2H, s), 5.3 (1H, b, NH), 3.83 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.45 (2H, s, $COCH_2$), 3.36 (2H, t, J=7Hz, CH_2), 2.65 (2H, t, J=7Hz, CH_2); Anal. Calcd. for $C_{19}H_{23}NO_4 \cdot 1/4H_2O$; C, 68.43; H, 7.11; N, 4.19; Found; C, 68.43; H, 7.05; N, 4.21

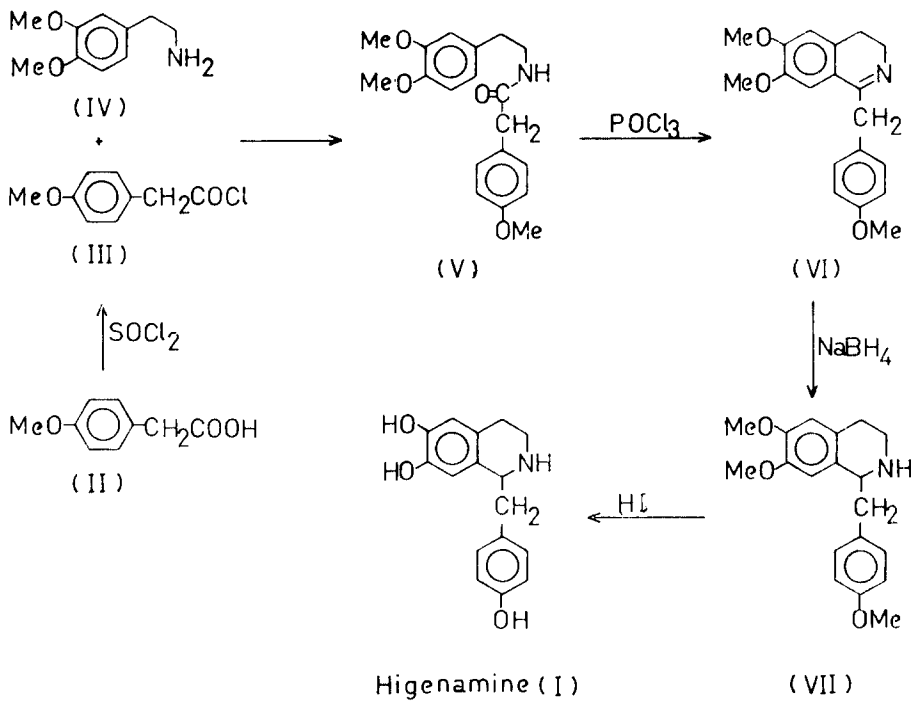
1-(4′-Methoxybenzyl)-6, 7-dimethoxy-3, 4-dihydroisoquinoline (VI) hydrochloride

The mixture of 5g (0.015 mole) of N-(3′, 4′-dimethoxyphenylethyl)-4-methoxyphenyl acetamide (**V**) and 2g (0.013 mole) of phosphorous oxychoride in 50ml of dry toluene was refluxed for 2 hrs. Toluene and phosphoryl chloride were removed under the reduced pressure and the mixture was trituated with d-HCl and ether. Crude product was collected and recrystallized from isopropanol providing comp **VI** as hydrochloride salt (4.3g, yield 82%) mp 139~140°C; IR ν_{max}^{KBr} 1634cm^{-1} (C=NH); NMR δ(D_2O) 7.4 (1H, s), 7.31 (2H, d, J=8Hz), 7.01 (1H, s), 6.95 (2H, d, J=8Hz), 4.41 (2H, s, ϕ-CH_2), 3.92 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.8 (2H, m, CH_2), 3.08 (2H, t, J=8Hz, CH_2); Anal. Calcd. for $C_{19}H_{22}NO_3Cl \cdot 3/2 H_2O$: C, 60.85; H, 6.73; N, 3.73; Found; C, 60.51; H, 6.47; N, 3.79

The above hydrochloride was dissolved in water, basified with d-NH_4OH and extracted with $CHCl_3$. After drying with anhydrous Na_2SO_4 and evaporation of the solvents from the $CHCl_3$ layer, comp **VI** was obtained as free base.

1-(4′-Methoxybenzyl)-6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline (VII) hydrochloride

To the solution of 3.1g (0.01 mole) of 1-(4′-methoxybenzyl)-6, 7-dimethoxy-3, 4-dihydroisoquinoline (**VI**) in 30ml of ethanol, was added



sodium borohydride (0.8g) in 30ml of ethanol slowly with cooling. the reaction mixture was treated as usual and the base was extracted with chloroform. Removal of the solvent from the dried extract gave crude 1-(4′-methoxybenzyl)-6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline (**VII**). Comp **VII** was purified in the form of hydrochloride by recrystallization from isopropanol (3.3g, yield 93%). mp 104~106°C; IR ν_{max}^{KBr} 1608cm^{-1}; NMR (free base) δ($CDCl_3$) 7.14 (2H, d, J=8Hz), 6.81 (2H, d, J=8Hz) 6.6 (1H, s), 6.55 (1H, s), 3.81 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 2.6-3.3 (7H, m); Anal. Calcd. for $C_{19}H_{24}NO_3Cl \cdot 3/4\ H_2O$; C, 62.78; H, 7.08; N, 3.85; Found; C, 62.60; H, 7.10; N, 3.96.

1-(4′-Hydroxybenzyl)-6, 7-dihydroxy-1, 2, 3, 4-tetrahydroisoquinoline (Higenamine) (I) hydriodide

1-(4′-Methoxybenzyl)-6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline (**VII**) hydrochloride (3.5 g, 0.01 mole) was refluxed with 15ml of 47% hydriodic acid for 2 hrs. On cooling, crude product was precipitated out. It was recrystallized from the mixture of ethanol and ether to provide higenamine hydriodide (3.2g, yield 83%) mp 234~235°C; IR ν_{max}^{KBr} 1605cm^{-1}; UV λ_{max}^{EtOH} nm 225, 286.5; NMR δ(DMSO) 8.3~9.3 (3H, m), 7.16 (2H, d, J=8Hz), 6.77 (2H, d, J=8Hz), 6,60 (1H, s), 6.55 (1H, s), 4.55 (1H, m), 2.7~3.6 (6H, m); MS (m/e) 271, 178, 164, 149, 128 (HI), 107; Anal. Calcd. for $C_{16}H_{18}NO_3I$; C, 48.13, H, 4.55; N, 3.51; Found C, 48.28 H, 4.66; N, 3.62

LITERATURE CITED

1) Kosuge, T. and Yokota, M.: Studies on cardiac principle of Aconite root. *Chem. Pharm. Bull.* **24**, 176-178 (1976).

2) Kosuge, T. Yokota, M. and Nagasawa, M.: Studies on cardiac principle in Aconite roots. I. Isolation and structural determination of higenamine. *Yakugaku Zasshi* **98**, 1370-1375 (1978).

3) Koshiyama, H., Ohkuma, H., Kawaguchi, H. Hsü H.-Y. and Chen, Y.-P.: Isolation of 1-(*p*-hydroxybenzyl)-6, 7-dihydroxy-1, 2, 3, 4-tetrahydroisoquinoline (demethylcoclaurine), an active alkaloid from *Nelumbo nucifera*. *Chem. Pharm. Bull.* **18**, 2564-2568 (1970).

4) Chang, K.C., Lim, J.K., Park, C.W., and Kim, M.S.: Studies on the mechanism of positive inotropic action on higenamine. *Kor. J. Pharmacol.* **17**, 59-68 (1981).

5) Kwon, P.J., Cho, S.I., Uhm, D.Y., and Rhee, S.D.: Effects of higenamine on action potential and contractility of cardiac muscle. *Chung Ang J. Med.* **6**, 543-550 (1981).

6) Kim, J.H., Lee, Y.K., Kim, H.W., Kim, M.S., Park, C.W. and Lee, J.K.: The effect of higenamine on the calcium transport of cardiac sarcoplasmic reticulum. *Kor. J. Pharmacol.* **18**, 79 (1982).

7) Park, C.W., Chang, K.C., and Lim, J.K.: Effects of higenamine on isolated heart adrenoceptor of rabbit. *Ach. Int. Pharmacody. Therap.* **267**, 279-288 (1984).

8) Yamaguchi, H.: Studies on the alkaloids of Menispermaceus plants. CLXV. Alkaloids of *Cocculus latifolius* DC. (Suppl. 13). Synthesis of coclaurine derivatives. *Yakugaku Zasshi* **78**, 692-694 (1958).

9) Sims, J.J., Selman, L.H. and Cadogan, M.: 6-Methoxy-β-tetralone. *Org. Syn.* **51**, 101-112 (1971).