

SYNTHESIS OF *N*_a-METHOXYINDOLE AND *N*_a-METHOXY- OXINDOLE ALKALOIDS HAVING YOHIMBINE SKELETON

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Abstract - Indoloquinolizidine (1) and yohimbine (7) were converted to the corresponding *N*_a-methoxyindoles and *N*_a-methoxyoxindoles by the oxidation of the dihydroindole derivatives with H₂O₂ and sodium tungstate.

The genus *Gelsemium*, belonging to the family *Loganiaceae*, has been used in traditional Chinese medicine and more recently has been used as an analgesic for the palliation of various acute cancer pains.¹ Recent intensive research on the chemical components of this plant by our group and others resulted in the isolation of many new indole and oxindole alkaloids of various skeletal type.² On the basis of the structures of the isolated alkaloids, we have proposed the biogenetic route of the *Gelsemium* alkaloids.^{2d} Along this biogenetic speculation, we have already succeeded in the synthesis of sarpagine-type alkaloids,³ humantenine-type oxindole alkaloids,⁴ gelsedine skeleton,⁵ and koumines.⁶ In the course of this study,⁷ the introduction of an oxygen function onto the *N*_a position of the oxindole alkaloids has been strongly required, since twenty-nine *N*_a-methoxyoxindole alkaloids of various skeletal type have been isolated from the *Gelsemium* species up to date (Figure 1). Our initial attempts at the direct introduction of an oxygen function on the *N*_a position in oxindole derivatives by utilizing the known procedures⁸ were unsuccessful. Recently, Somei *et al.* have developed a new method for the synthesis of *N*_a-hydroxyindoles having relatively simple structures from the corresponding indoles.⁹ We applied this procedure to two indole alkaloids, indoloquinolizidine (1) and yohimbine (7), and succeeded in the preparation of the desired *N*_a-methoxyoxindole derivatives. Here we would like to report the results of this investigation.

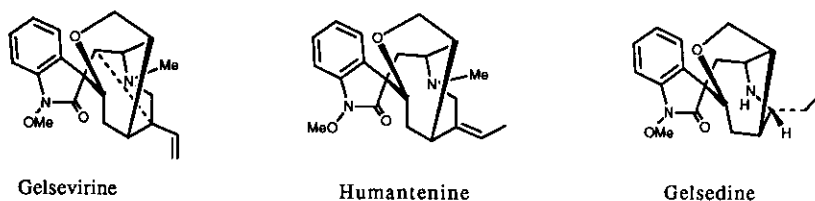
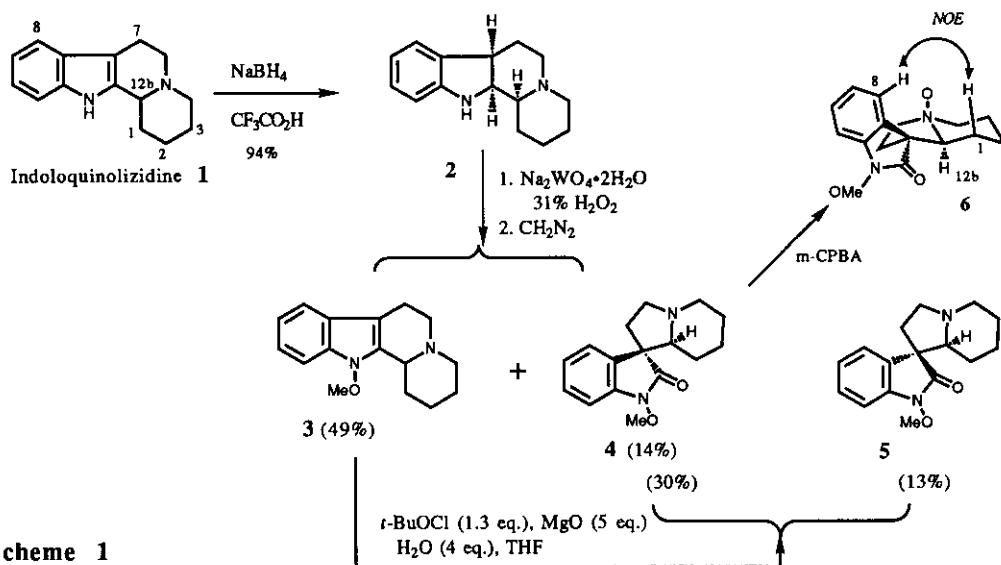


Figure 1 Representative *Gelsemium* Alkaloids Having a *N*_a-Methoxyoxindole Moiety

Initially, according to the method reported by Gribble¹⁰ indoloquinolizidine (1) was reduced with sodium borohydride (NaBH_4) in trifluoroacetic acid ($\text{CF}_3\text{CO}_2\text{H}$) to give the indoline derivative (2) in 94% yield. On oxidation with 10 equiv. of 31% aqueous hydrogen peroxide (H_2O_2) in methanol- H_2O (10:1) at 15°C for 15 min in the presence of 0.2 equiv. of sodium tungstate ($\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$) and successive treatment with ethereal diazomethane (CH_2N_2),⁹ 2 afforded the N_A -methoxyindole (3) and N_A -methoxyoxindole (4) in 49 and 14% yields, respectively. The structure of 3¹¹ was confirmed by the indolic uv absorption and characteristic signal of an N_A -methoxy group (δ 3.91, 3H, s) in the ^1H nmr spectrum. The second product (4)¹¹ showed the uv absorption at 255 nm, indicating that it possessed an oxindole nucleus. The ^1H nmr spectrum reveals the presence of an N_A -methoxy group (δ 4.01) in 4. The stereochemistry of 4 was deduced by the ^1H nmr spectrum of the N -oxide derivative (6), which was prepared by *m*-chloroperbenzoic acid oxidation of 4. The signal due to H-8 (δ 8.22) was observed downfield 0.8 ppm lower than the corresponding signal of 4. This phenomenon can be interpreted by the anisotropy effect of N -oxide function, indicating that 6 might take the configuration at the spiro position having *syn*-relationship between the benzene ring and the N -oxide function. 6% Enhancement observed in difference NOE experiment between the H-8 and the C-1 axial proton reveals that the N -oxide and the angular proton (H-12b) in the octahydroindolizine system adopts the *trans* configuration. The N_A -methoxyindole (3) could be converted to the corresponding N_A -methoxyoxindoles (4 and 5) in 30 and 13% yields, respectively, by treating with *t*-butyl hypochlorite (*t*-BuOCl) in aqueous THF in the presence of magnesium oxide (MgO). By the use of the known procedure (1. *t*-BuOCl, Et_3N , dry CH_2Cl_2 , 2. AcOH - H_2O - MeOH)¹² for the conversion of indoles into the oxindole derivatives, we could not obtain the N_A -methoxyoxindoles from 3.



Scheme 1

From the pharmacological point of view as well as recent findings of the biologically active *N*_a-methoxyindoles from natural source,^{9d} we were interested in the synthesis and the biological activities of *N*_a-methoxyyohimbine and its oxindole derivatives. According to the reported procedure yohimbine (7) was reduced with NaBH₄ in CF₃CO₂H to yield the dihydro derivatives (8 and 9)¹³ in 68 and 1% yields, respectively. Dihydroyohimbine (8) was oxidized with 31% aqueous H₂O₂ in the presence of Na₂WO₄·2H₂O and then the reaction mixture was directly treated with CH₂N₂ to afford three products, *N*_a-methoxyyohimbine (10, 45% yield)¹⁴ and two *N*_a-methoxyoxindole derivatives (11, 2% yield and 12, 2% yield).¹⁴ The stereochemistry of the spiro position in 11 and 12 was deduced by the comparison of their cd spectra with those of authentic yohimbine-oxindoles (13 and 14).¹² (Figure 2) The isomer (12) was predominantly epimerized to 11 in hot pyridine. A similar behavior was observed in two

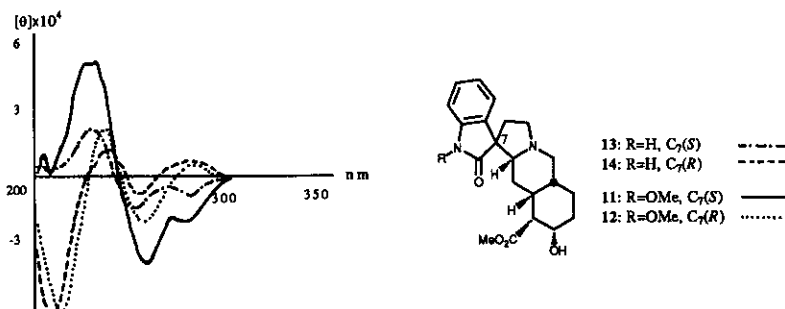
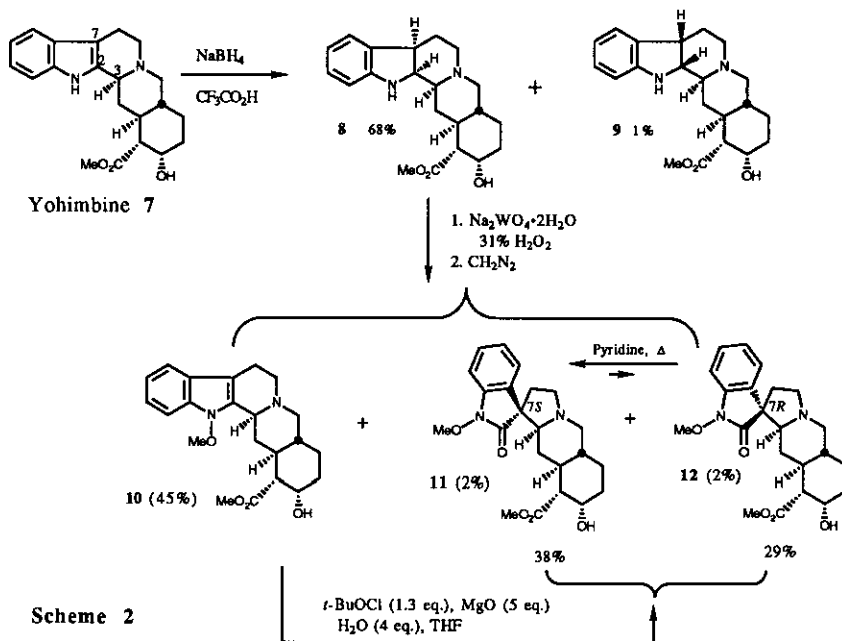


Figure 2 Cd spectra of the yohimbine-oxindole derivatives

yohimbine-oxindoles (13 and 14),¹² also supporting that 11 has 7S and 12 has 7R configuration, respectively. *N*_a-Methoxyyohimbine (10) was successfully converted into *N*_a-methoxyoxindole derivatives (11 and 12) in 38 and 29% yields, respectively, by treating with *t*-BuOCl in aqueous THF in the presence of MgO.

The plausible mechanism of the direct formation of *N*_a-hydroxyoxindoles from the dihydroindoles by the oxidation with H₂O₂/Na₂WO₄ system can be considered as follows. On attempts at the oxidation of the *N*_a-methoxyindole (3) with H₂O₂/Na₂WO₄ system, the formation of the corresponding *N*_a-methoxyoxindoles (4) and/or (5) was not observed at all. Therefore, onto the benzylic position of the nitron intermediate (16),¹⁵ an OH or OOH function might be oxidatively introduced and subsequent pinacol-type rearrangement might give the *N*_a-hydroxyoxindole (19).

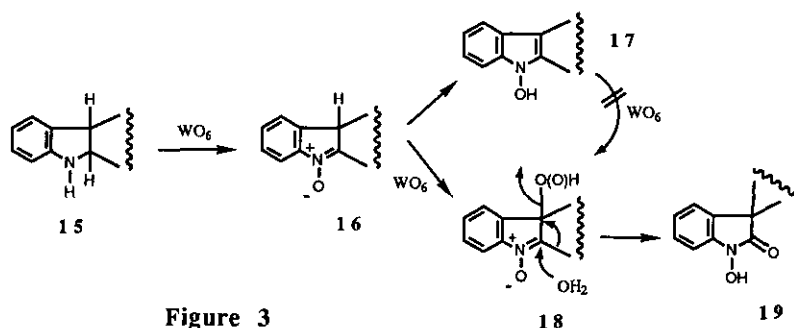


Figure 3

The application of this procedure for the synthesis of the *Gelsemium* alkaloids having the *N*_a-methoxyoxindole moiety is under investigation.

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11. **3**: mp 96°C (hexane). Ei-ms m/z (%): 256 (M^+ , 25), 225 (M^+ -OMe, 100), 169 (24). Uv $\lambda_{\max}$ (EtOH); 227, 276 nm. 1H Nmr ($CDCl_3$, 500 MHz) δ : 7.44 (1H, d, $J=7.6$ Hz), 7.36 (1H, dd, $J=8.0, 0.8$ Hz), 7.18 (1H, td, $J=8.0, 0.8$ Hz), 7.08 (1H, td, $J=7.6, 0.8$ Hz), 3.91 (3H, s), 3.43 (1H, br d, $J=11.0$ Hz, H-12b). **4**: mp 113-117°C (ether). Ei-ms m/z (%): 272 (M^+ , 55), 241 (M^+ -OMe, 100), 158 (44). Uv $\lambda_{\max}$ (EtOH); 207, 255 nm. Ir (KBr) $\nu_{\max}$ 2940, 1720 cm^{-1} . 1H Nmr ($CDCl_3$, 500 MHz) δ : 7.41 (1H, d, $J=7.4$ Hz), 7.27 (1H, t, $J=7.7$ Hz), 7.07 (1H, t, $J=7.4$ Hz), 6.96 (1H, d, $J=7.7$ Hz), 4.01 (3H, s), 3.17 (1H, d, $J=11.0$ Hz, H-12b). **5**: amorphous powder. 1H Nmr ($CDCl_3$, 270 MHz) δ : 4.00 (3H, s). Uv $\lambda_{\max}$ (EtOH); 204, 256 nm. **6**: amorphous. Ei-ms m/z (%): 288 (M^+ , 44), 257 (M^+ -OMe, 58). Uv $\lambda_{\max}$ (EtOH); 204, 255 nm. 1H Nmr ($CDCl_3$, 500 MHz) δ : 8.22 (1H, dd, $J=7.5, 1.0$ Hz), 4.02 (3H, s), 3.52 (1H, dd, $J=12.2, 2.6$ Hz, H-12b), 2.00 (1H, m, H-1).
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14. **10**: mp 198-201°C (acetone). Ei-ms m/z (%): 384 (M^+ , 9), 353 (M^+ -OMe, 100), 169 (16). Uv $\lambda_{\max}$ (EtOH); 227, 277 nm. Ir (KBr) $\nu_{\max}$ 1740 cm^{-1} . 1H Nmr ($CDCl_3$, 500 MHz) δ : 7.44 (1H, d, $J=8.0$ Hz), 7.35 (1H, d, $J=8.0$ Hz), 7.19 (1H, td, $J=8.0, 1.1$ Hz), 7.08 (1H, td, $J=8.0, 1.1$ Hz), 4.21 (1H, s), 3.89 (3H, s), 3.50 (1H, dd, $J=11.3, 1.9$ Hz, H-3), 3.76 (3H, s), 3.36 (1H, s). **11**: mp 89-95°C (MeOH). Ei-ms m/z (%): 400 (M^+ , 41), 369 (M^+ -OMe, 100), 224 (88). Uv $\lambda_{\max}$ (EtOH); 207, 255 nm. Ir (KBr) $\nu_{\max}$ 3450, 2920, 1720 cm^{-1} . 1H Nmr ($CDCl_3$, 500 MHz) δ : 7.39 (1H, d, $J=7.4$ Hz), 7.28 (1H, t, $J=7.7$ Hz), 7.08 (1H, t, $J=7.4$ Hz), 6.96 (1H, d, $J=7.7$ Hz), 4.08 (1H, s), 3.99 (3H, s), 3.56 (3H, s), 3.27 (1H, td, $J=8.8, 2.5$ Hz), 3.09 (1H, dd, $J=10.9, 3.5$ Hz), 3.05 (1H, s). **12**: mp 177-179°C (ether). Ei-ms m/z (%): 400 (M^+ , 45), 369 (M^+ -OMe, 100), 224 (86). Uv $\lambda_{\max}$ (EtOH); 205, 257 nm. Ir (KBr) $\nu_{\max}$ 3450, 2920, 1720 cm^{-1} . 1H Nmr ($CDCl_3$, 500 MHz) δ : 7.28 (1H, td, $J=7.7, 0.8$ Hz), 7.20 (1H, d, $J=7.4$ Hz), 7.09 (1H, td, $J=7.5, 0.8$ Hz), 6.93 (1H, d, $J=7.7$ Hz), 4.10 (1H, s), 3.97 (3H, s), 3.57 (3H, s), 3.35 (1H, s), 3.17 (1H, dd, $J=10.7, 3.0$ Hz).
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