SYNTHESIS OF N_a-METHOXYINDOLE AND N_a-METHOXYOXINDOLE ALKALOIDS HAVING YOHIMBINE SKELETON

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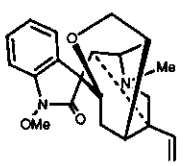
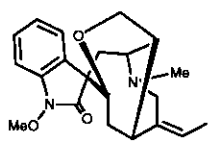
Abstract - Indoloquinolizidine (1) and yohimbine (7) were converted to the corresponding N_a-methoxyindoles and N_a-methoxyoxindoles by the oxidation of the dihydroindole derivatives with H_2O_2 and sodium tungstate.

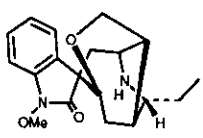
The genus *Gelsemium*, belonging to the family *Loganiaceae*, has been used in traditional Chinese medicine and more recently has been used as an analgesic for the palliation of various acute cancer pains.[1] Recent intensive research on the chemical components of this plant by our group and others resulted 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 procedures[8] 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.



Gelsevirine



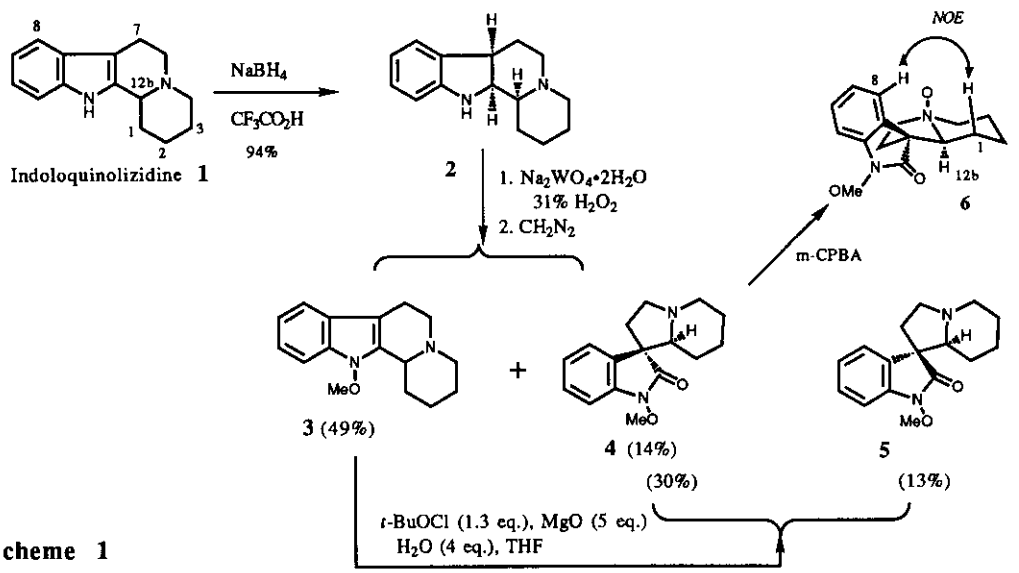
Humantenine



Gelsedine

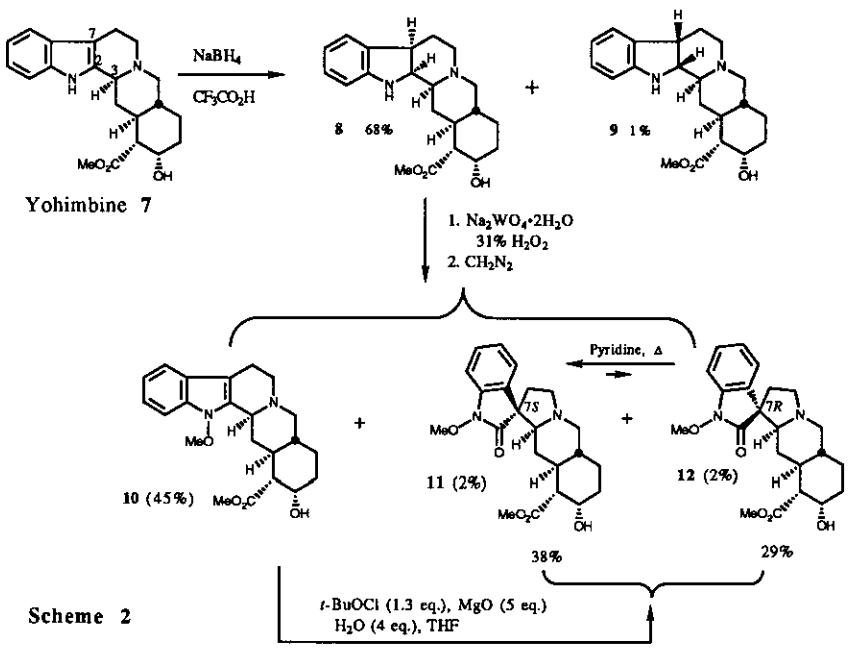
Figure 1 Representative *Gelsemium* Alkaloids Having a N_a-Methoxyoxindole Moiety

Initially, according to the method reported by Gribble[10] indoloquinolizidine (**1**) was reduced with sodium borohydride ($NaBH_4$) in trifluoroacetic acid (CF_3CO_2H) 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 ($Na_2WO_4 \cdot 2H_2O$) 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 **3**[11] 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 $NaBH_4$ in CF_3CO_2H to yield the dihydro derivatives (**8** and **9**)[13] in 68 and 1% yields, respectively. Dihydroyohimbine (**8**) was oxidized with 31% aqueous H_2O_2 in the presence of $Na_2WO_4 \cdot 2H_2O$ and then the reaction mixture was directly treated with CH_2N_2 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



Scheme 2

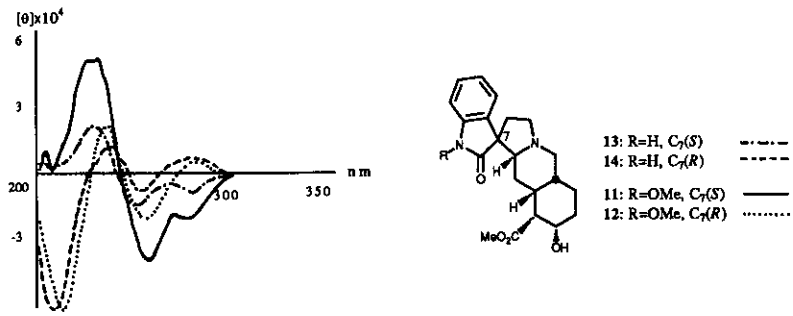
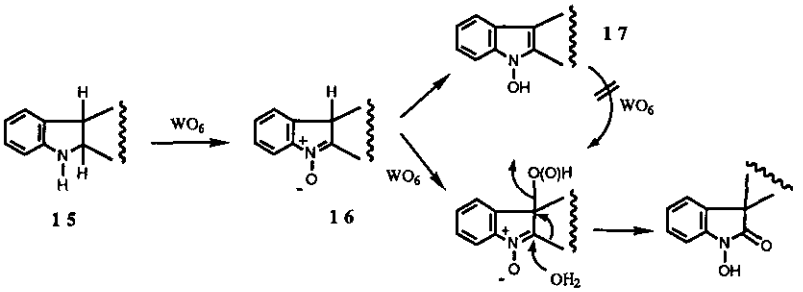


Figure 2 Cd spectra of the yohimbine-oxindole derivatives

yohimbine-oxindoles (**13** and **14**),[12] also supporting that **11** has 7*S* and **12** has 7*R* 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-hydroxyindoles from the dihydroindoles by the oxidation with H_2O_2/Na_2WO_4 system can be considered as follows. On attempts at the oxidation of the N_a-methoxyindole (**3**) with H_2O_2/Na_2WO_4 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 nitrone intermediate (**16**),[15] an OH or OOH function might be oxidatively introduced and subsequent pinacol-type rearrangement might give the N_a-hydroxyoxindole (**19**).



15 16 18 19

Figure 3

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

REFERENCES

1. Z-J. Liu and R. -R. Lu, 'The Alkaloids', Vol. 33, ed. by A. Brossi, Academic Press, New York, 1988, Chap. 2.
2. a) Y. Shun, G. A. Cordell, and M. Garland, *J. Nat. Prod.*, 1986, **49**, 806. b) S. Sakai, S. Wongseripipatana, D. Ponglux, M. Yokota, K. Ogata, H. Takayama, and N. Aimi, *Chem. Pharm. Bull.*, 1987, **35**, 4668. c) D. Ponglux, S. Wongseripipatana, H. Takayama, K. Ogata, N. Aimi, and S. Sakai, *Tetrahedron Lett.*, 1988, **29**, 5395. d) D. Ponglux, S. Wongseripipatana, S. Subhadhirasakul, H. Takayama, M. Yokota, K. Ogata, C. Phisalaphong, N. Aimi, and S. Sakai, *Tetrahedron*, 1988, **44**, 5075. e) L. -Z. Lin, G. A. Cordell, C. Z. Ni, and J. Clardy, *J. Nat. Prod*, 1989, **52**, 588. f) L. -Z. Lin, G. A. Cordell, C. Z. Ni, and J. Clardy, *Phytochemistry*, 1989, **28**, 2827. g) L. -Z. Lin, G. A. Cordell, C. Z. Ni, and J. Clardy, *Tetrahedron Lett.*, 1989, **30**, 1177 and 3354. h) L. -Z. Lin and G. A. Cordell, *J. Org. Chem.*, 1989, **54**, 3199. i) F. Sun, Q. Y. Xing, and X. T. Ling, *J. Nat. Prod.*, 1989, **52**, 1180. j) L. -Z. Lin, G. A. Cordell, C. Z. Ni, and J. Clardy, *Phytochemistry*, 1990, **29**, 965 and 3013. k) L. -Z. Lin, G. A. Cordell, C. Z. Ni, and J. Clardy, *Phytochemistry*, 1991, **30**, 679 and 1311.
3. a) H. Takayama, M. Kitajima, S. Wongseripipatana, and S. Sakai, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1075. b) H. Takayama and S. Sakai, *Chem. Pharm. Bull.*, 1989, **37**, 2256. c) M. Kitajima, H. Takayama, and S. Sakai, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1773.
4. H. Takayama, K. Masubuchi, M. Kitajima, N. Aimi, and S. Sakai, *Tetrahedron*, 1989, **45**, 1327.

5. a) H. Takayama, M. Horigome, N. Aimi, and S. Sakai, *Tetrahedron Lett.*, 1990, **31**, 1287. b) H. Takayama, H. Odaka, N. Aimi, and S. Sakai, *Tetrahedron Lett.*, 1990, **31**, 5483.
6. a) S. Sakai, E. Yamanaka, M. Kitajima, M. Yokota, N. Aimi, S. Wongseripipatana, and D. Ponglux, *Tetrahedron Lett.*, 1986, **27**, 4585. b) H. Takayama, M. Kitajima, and S. Sakai, *Heterocycles*, 1990, **30**, 325.
7. H. Takayama and S. Sakai, *J. Synth. Org. Chem. Jpn.*, 1990, 48, 876.
8. a) S. A. Matlin, P. G. Sammes, and R. M. Upton, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2481. b) D. A. Aue and D. Thomas, *J. Org. Chem.*, 1974, **39**, 3855.
9. a) M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251. b) T. Kawasaki and M. Somei, *Heterocycles*, 1990, **31**, 1605. c) T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, *Heterocycles*, 1991, **32**, 221. d) M. Somei, *J. Synth. Org. Chem. Jpn.*, 1991, **49**, 205.
10. a) G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, *J. Am. Chem. Soc.*, 1974, **96**, 7812. b) G. W. Gribble, J. L. Johnson, and M. G. Saulnier, *Heterocycles*, 1981, **16**, 2109.
11. **3**: mp 96°C (hexane). Ei-ms m/z (%); 256 (M^+, 25), 225 (M^+-OMe, 100), 169 (24). Uv λ_{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 λ_{max} (EtOH); 207, 255 nm. Ir (KBr) ν_{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 λ_{max} (EtOH); 204, 256 nm. **6**: amorphous. Ei-ms m/z (%); 288 (M^+, 44), 257 (M^+-OMe, 58). Uv λ_{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).
12. N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, 1962, **84**, 3871.
13. J. Le Men, L. Le Men-Oliver, J. Levy, M. C. Levy-Appert-Colin, and J. Hannart, *Ger. Offen.* 2410651 (Cl. C07d) [*Chem. Abstr.*, 1975, **82**, 43640u].
14. **10**: mp 198-201°C (acetone). Ei-ms m/z (%); 384 (M^+, 9), 353 (M^+-OMe, 100), 169 (16). Uv λ_{max} (EtOH); 227, 277 nm. Ir (KBr) ν_{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, 1.9Hz, 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 λ_{max} (EtOH); 207, 255 nm. Ir (KBr) ν_{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 λ_{max} (EtOH); 205, 257 nm. Ir (KBr) ν_{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).
15. H. Mitsui, S. Zenki, T. Shiota, and S. Murahashi, *J. Chem. Soc., Chem. Commun.*, 1984, 874.

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