SYNTHESIS OF $N_\alpha$-METHOXYINDOLE AND $N_\alpha$-METHOXYOXINDOLE ALKALOIDS HAVING YOHIMBINE SKELETON

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Abstract - Indoloquinolizidine (1) and yohimbine (7) were converted to the corresponding $N_\alpha$-methoxyindoles and $N_\alpha$-methoxyoxindoles by the oxidation of the dihydroindole derivatives with $\text{H}_2\text{O}_2$ 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.²⁴ 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 $N_\alpha$ position of the oxindole alkaloids has been strongly required, since twenty-nine $N_\alpha$-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 $N_\alpha$ position in oxindole derivatives by utilizing the known procedures⁸ were unsuccessful. Recently, Somei et al. have developed a new method for the synthesis of $N_\alpha$-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 $N_\alpha$-methoxyoxindole derivatives. Here we would like to report the results of this investigation.

![Figure 1](image-url)

**Figure 1** Representative Gelsemium Alkaloids Having a $N_\alpha$-Methoxyoxindole Moiety
Initially, according to the method reported by Gribskov\textsuperscript{10} indoloquinolizidine (1) was reduced with sodium borohydride (NaBH\textsubscript{4}) in trifluoroacetic acid (CF\textsubscript{3}CO\textsubscript{2}H) to give the indoline derivative (2) in 94\% yield. On oxidation with 10 equiv. of 31\% aqueous hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) in methanol-H\textsubscript{2}O (10:1) at 15°C for 15 min in the presence of 0.2 equiv. of sodium tungstate (Na\textsubscript{2}WO\textsubscript{4}•2H\textsubscript{2}O) and successive treatment with ethereal diazomethane (CH\textsubscript{2}N\textsubscript{2}),\textsuperscript{9} 2 afforded the Na\textsubscript{a}-methoxyindole (3) and Na\textsubscript{a}-methoxyoxindole (4) in 49 and 14\% yields, respectively. The structure of 3\textsuperscript{11} was confirmed by the indolic uv absorption and characteristic signal of an Na\textsubscript{a}-methoxy group (δ 3.91, 3H, s) in the \textsuperscript{1}H nmr spectrum. The second product (4)\textsuperscript{11} showed the uv absorption at 255 nm, indicating that it possessed an oxindole nucleus. The \textsuperscript{1}H nmr spectrum reveals the presence of an Na\textsubscript{a}-methoxy group (δ 4.01) in 4. The stereochemistry of 4 was deduced by the \textsuperscript{1}H 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 Na\textsubscript{a}-methoxyindole (3) could be converted to the corresponding Na\textsubscript{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\textsubscript{3}N, dry CH\textsubscript{2}Cl\textsubscript{2}, 2. AcOH-H\textsubscript{2}O-MeOH)\textsuperscript{12} for the conversion of indoles into the oxindole derivatives, we could not obtain the Na\textsubscript{a}-methoxyoxindoles from 3.

\begin{center}
\begin{tikzpicture}[scale=0.8]
  \node (1) at (0,0) {Indoloquinolizidine 1};
  \node (2) at (2,0) {Indoline 2};
  \node (3) at (2,-1) {Na\textsubscript{a}-methoxyindole 3 (49\%)};
  \node (4) at (4,-1) {Na\textsubscript{a}-methoxyoxindole 4 (14\%) (30\%)};
  \node (5) at (6,-1) {Na\textsubscript{b}-methoxyoxindole 5 (13\%)};

  \draw[->] (1) -- (2);
  \draw[->] (2) -- (3);
  \draw[->] (2) -- (4);
  \draw[->] (2) -- (5);

  \draw[->] (1) -- node[above] {NaBH\textsubscript{4}} (2);
  \draw[->] (2) -- node[above] {CF\textsubscript{3}CO\textsubscript{2}H} (2);
  \draw[->] (2) -- node[below] {1. Na\textsubscript{2}WO\textsubscript{4}•2H\textsubscript{2}O, 31\% H\textsubscript{2}O\textsubscript{2}, 2. CH\textsubscript{2}N\textsubscript{2}} (3);
  \draw[->] (2) -- node[below] {m-CPBA} (4);

  \draw[->] (2) -- node[above] {t-BuOCl (1.3 eq.), MgO (5 eq.), H\textsubscript{2}O (4 eq.), THF} (5);

  \node at (7.5,0) {Scheme 1};
\end{tikzpicture}
\end{center}
From the pharmacological point of view as well as recent findings of the biologically active $\text{Na}_8$-methoxyindoles from natural source, we were interested in the synthesis and the biological activities of $\text{Na}_8$-methoxyyohimbine and its oxindole derivatives. According to the reported procedure yohimbine (7) was reduced with NaBH$_4$ in CF$_3$CO$_2$H to yield the dihydro derivatives (8 and 9) in 68 and 1% yields, respectively. Dihydroxyyohimbine (8) was oxidized with 31% aqueous H$_2$O$_2$ in the presence of Na$_2$WO$_4$·2H$_2$O and then the reaction mixture was directly treated with CH$_2$N$_2$ to afford three products, $\text{Na}_8$-methoxyyohimbine (10, 45% yield) and two $\text{Na}_8$-methoxyoxindole derivatives (11, 2% yield and 12, 2% yield). 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). 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), also supporting that 11 has $7S$ and 12 has $7R$ configuration, respectively. Na-Methoxyyohimbine (10) was successfully converted into Na-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 Na-hydroxyindoles from the dihydroindoles by the oxidation with $\text{H}_2\text{O}_2/\text{Na}_2\text{WO}_4$ system can be considered as follows. On attempts at the oxidation of the Na-methoxyindole (3) with $\text{H}_2\text{O}_2/\text{Na}_2\text{WO}_4$ system, the formation of the corresponding Na-methoxyoxindoles (4) and/or (5) was not observed at all. Therefore, onto the benzylic position of the nitrone intermediate (16), an OH or OOH function might be oxidatively introduced and subsequent pinacol-type rearrangement might give the Na-hydroxyoxindole (19).

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

REFERENCES


11. 3: mp 96°C (hexane). Ei-ms m/z (%): 256 (M+, 25), 225 (M+OMe, 100), 169 (24). UV \( \lambda_{\text{max}} \) (EtOH): 227, 276 nm. \( ^1\text{H} \) Nmr (CDCl3, 500 MHz) \( \delta \): 7.44 (1H, d, J=7.6 Hz), 7.36 (1H, dd, J=8.0, 0.8 Hz), 7.18 (1H, dd, J=6.8 Hz), 7.08 (1H, d, J=7.6, 0.8 Hz), 3.91 (3H, s), 3.43 (1H, br d, J=1.0 Hz, H-12b). 4: mp 113-117°C (ether). Ei-ms m/z (%): 272 (M+, 55), 241 (M+OMe, 100), 158 (44). UV \( \lambda_{\text{max}} \) (EtOH): 207, 255 nm. Ir (KBr) \( \nu \): 2940, 1720 (cm-1). \( ^1\text{H} \) Nmr (CDCl3, 500 MHz) \( \delta \): 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. \( ^1\text{H} \) Nmr (CDCl3, 270 MHz) \( \delta \): 4.00 (3H, s). UV \( \lambda_{\text{max}} \) (EtOH): 204, 256 nm: 6: amorphous. Ei-ms m/z (%): 288 (M+, 44), 257 (M+OMe, 58). UV \( \lambda_{\text{max}} \) (EtOH): 204, 255 nm. \( ^1\text{H} \) Nmr (CDCl3, 500 MHz) \( \delta \): 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).


14. 10: mp 198-201°C (acetone). Ei-ms m/z (%): 384 (M+, 9), 353 (M+OMe, 100), 169 (16). UV \( \lambda_{\text{max}} \) (EtOH): 227, 277 nm. Ir (KBr) \( \nu \): 1740 cm-1. \( ^1\text{H} \) Nmr (CDCl3, 500 MHz) \( \delta \): 7.44 (1H, d, J=8.0 Hz), 7.35 (1H, d, J=8.0 Hz), 7.19 (1H, d, 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): \( ^{13}\text{C} \) nmr (CDCl3, 500 MHz) \( \delta \): 179.9, 168.7, 133.9, 131.1, 127.3, 125.0, 120.5, 115.0, 114.8, 110.4, 78.0, 53.2, 51.9, 41.9, 41.7, 39.2, 39.1, 37.8, 37.1, 35.0, 29.9, 29.8. 11: \( ^{13}\text{C} \) nmr (MeOD) 49.0 (M+, 41), 40.4 (M+OMe, 40), 30.1 (M+OMe, 100). 


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