Synthesis of 1-hydroxyyohimbine and its novel skeletal rearrangement reaction into oxindole derivatives

SYNTHESIS OF 1-HYDROXYYOHIMBINE AND ITS NOVEL SKELETAL REARRANGEMENT REACTION INTO OXINDOLE DERIVATIVES [1]

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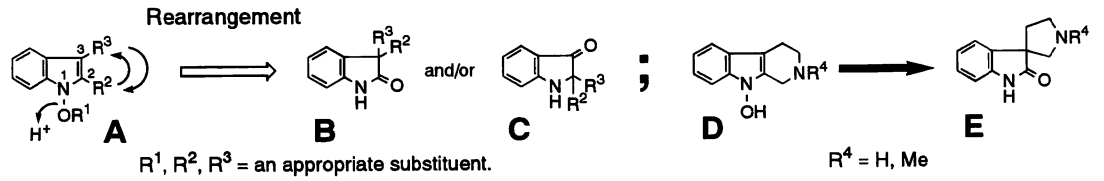
Abstract — 1-Hydroxyyohimbine was prepared for the first time. Its skeletal rearrangement reaction either directly into 2-oxindole or into 3-oxindole derivatives by a series of reaction is reported. 1-Hydroxyyohimbine and some of its derivatives showed potent α2 blocking activity.

We have supposed[2a] that 1-hydroxyindoles (**A**) undergo the rearrangement reaction as illustrated in Scheme 1 to provide 2-oxi- (**B**) and/or 3-oxindoles (**C**) regarding their possible role in biological processes.[2] In our continuing efforts to realize it chemically, we have succeeded in finding such example that 1,2,3,4-tetrahydro-9-hydroxy-β-carbolines (**D**) tranform to 3,3-disubstituted 2-oxindoles[3] (**E**) under acidic conditions. As a result, whether the same type of rearrangement occurs in the cases of more complex natural products has been an interesting and important subject for us to verify our "1-Hydroxyindole Hypotheses".[2] Now, we wish to report that the predicted rearrangement actually occurs in the case of yohimbine alkaloids.

Scheme 1



First, we needed a novel 1-hydroxyyohimbine (**1**). According to the reported procedure,[4] we tried the reduction of yohimbine (**2**) with $NaBH_3CN$ in TFA to give 2β,7β- (**3**) and 2α,7α-dihydroyohimbine (**4**) in 9 and 89% yields, respectively. Subsequent application of our $Na_2WO_4 \cdot 2H_2O$ and 30% H_2O_2 method[5] to **4** afforded the desired **1** for the first time in 86% yield as stable crystals.

The formation of by-product (**3**) in the first step is not only the cause of lowering the yield of **4** but also a troublesome problem for its separation. Therefore, in order to improve the process, we explored the reduction of yohimbine hydrochloride (**2** · **HCl**) as a substrate with $NaBH_3CN$ in TFA and discovered the stereoselective production of **4** in an quantitative yield without any detectable amount of **3**. Consequently, by conducting the two procedures sequentially, **1** was readily available from **2** · **HCl** in 86% yield.

Syntheses of some derivatives of **1** were examined with an aim to develop biologically active substances. Thus, methylation with CH_2N_2 afforded 1-methoxy compound[6] (**5**) in 77% yield. Utilizing K_2CO_3 as a base in DMF, allyl bromide, butyl iodide, and *p*-nitrobenzyl bromide reacted successfully with **1** to afford **6**, **7**, and **8** in 93, 99, and 90% yields, respectively. These compounds including **1** itself showed potent α2 blocking activity and the details will be reported in due course.

Scheme 2

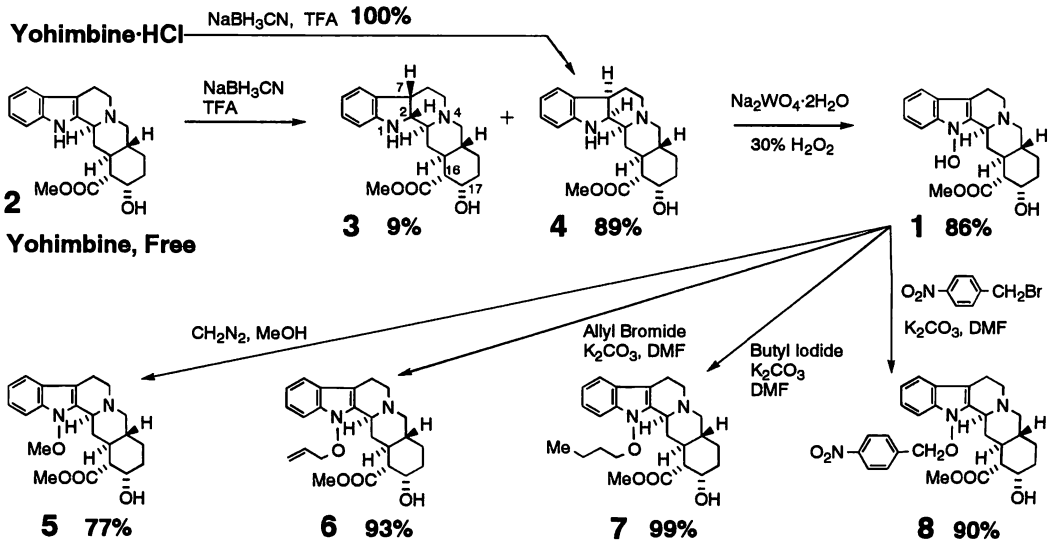
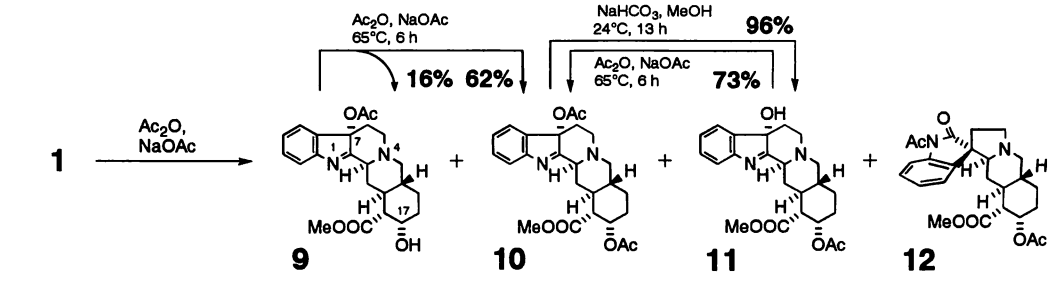


Table 1



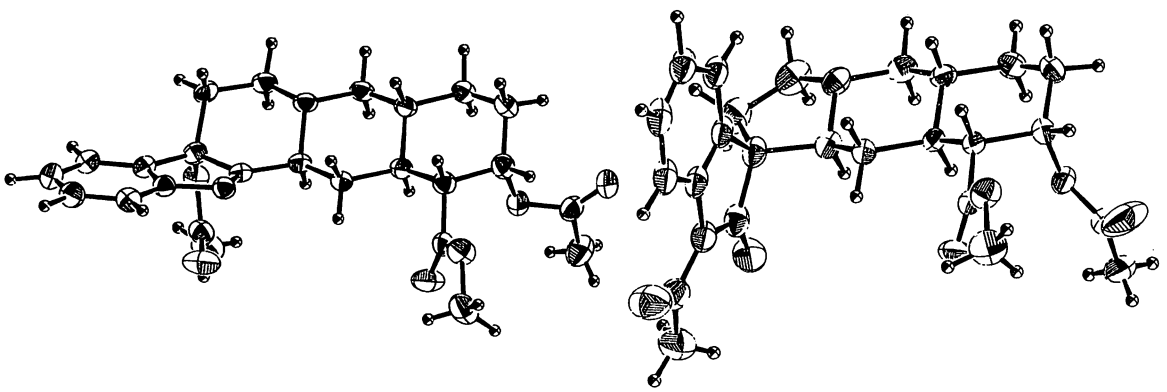
Entry	NaOAc (mol eq)	Reaction Conditions Temp. (°C)	Time (h)	Yield (%) of 9	10	11	12
1	2	63	0.5	52	12	0	0
2	2	65	1	71	8	0	0
3	"	"	6	23	41	0	9
4	"	"	40	0	40	0	15
5	20	"	6	0	0	12	12
6	—	"	48	9	44	0	16

With **1** in hand, we next tried its reaction with Ac_2O in the presence of NaOAc which is a suitable condition for promoting rearrangement[7] of 1-hydroxy group and the results are summarized in Table 1. As can be seen from the Table, possible four products were produced stereoselectively such as 7α-acetoxy-[8] (**9**), 7α-acetoxy-17-*O*-acetyl- (**10**), 17-*O*-acetyl-7α-hydroxyyohimbines (**11**), and the predicted 2-oxindole (**12**). The rearrangement of 1-acetoxy group to 7α-position was best achieved under the reaction conditions described in Entry 2 providing **9** (71%) and **10** (8%). As the reaction time became longer (Entries 1-4), the yield of **9** decreased, while the yield of **10** increased. In the cases of Entries 3 and 4, the expected formation of 2-oxindole (**12**) was observed. Use of excess amount of NaOAc made the reaction dirty and as a result total yield of prod- ucts (**11** and **12**) decreased (Entry 5). The slight improvement in the yield of **12** (16%) was observed by carrying out the reaction without using NaOAc, together with **9** and **10** in the respective yields of 9 and 44% (Entry 6).

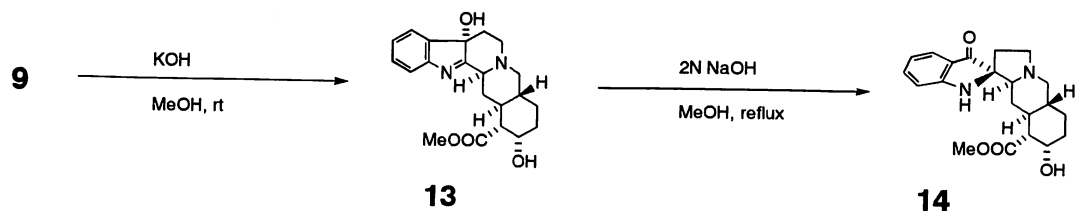
Figure 1. X-Ray Single Crystallographic Analyses

ORTEP Drawing of **10** (R = 0.030)

ORTEP Drawing of **12** (R = 0.031)



Scheme 3



The structures of **10** and **12** were determined unequivocally by X-Ray single crystallographic analyses and their results are shown in Figure 1. Structures of **9** and **11** were confirmed by chemical correlations to **10**. Thus, treatment of **9** with Ac_2O and pyridine at 65 °C for 6 h afforded **10** and unreacted **9** in 62 and 16% yields, respectively. Under similar reaction conditions, **11** provided **10** in 73% yield, while **11** was obtained in 96% yield from **10** by a regioselective hydrolysis of 7α-acetoxy group by treatment with

$NaHCO_3$ in MeOH at room temperature.

On the other hand, a facile rearrangement of **9** to spiroindoxyl compound[8a] (3-oxindole,[8b] **14**) was already repoted by Finch and co-workers[8c] through **13** by the hydrolysis of 7α-acetoxy group, followed by alkaline treatment (Scheme 3). Therefore, we have succeeded in realizing the skeletal rearrangement of **1** into both 2-oxi- and 3-oxindole derivatives as predicted.[2] Attempts to improve their yields, preparations of various kinds of 1-hydroxyyohimbine derivatives, and their biological evaluations are currently in progress.

ACKNOWLEDGMENT

The authors express their cordial gratitude to Prof. H. Shigenobu (Toho University School of Pharmaceutical Science) for biological evaluations.

REFERENCES AND NOTES

1. a) This is Part 106 of a series entitled " The Chemistry of Indoles". b) Part 105: K. Yamada, T. Kawasaki, T. Fujita, and M. Somei, *Heterocycles*, 2001, **55**, 1151. All new compounds gave satisfactory spectral and elemental analysis data. **1**, mp 224—226°C (decomp); **5**, mp 201—203°C (lit.[6] mp 198—201℃); **6**, mp 126.0—128.5℃ (decomp); **7**, mp 150—152℃ (decomp); **8**, mp 148—149℃ (decomp); **9**, mp 120—122°C (lit.[8b] mp 123—124℃); **10**, mp 190—191℃; **11**, mp 193—195°C (decomp); **12**, mp 213—215°C (decomp).
2. a) Review; M. Somei, *J. Synth. Org. Chem. Jpn.*, 1991, **49**, 205; b) M. Somei and M. Natsume, *Tetrahedron Lett.*, 1973, 2451; c) M. Somei and Y. Fukui, *Heterocycles*, 1993, **36**, 1859; c) Review; M. Somei, *ibid.*, 1999, **50**, 1157 and references cited therein.
3. M. Somei, K. Noguchi, R. Yamagami, Y. Kawada, K. Yamada, and F. Yamada, *Heterocycles*, 2000, **53**, 7 and references cited therein.
4. J. Le Men, L. Le Men-Oliver, J. Levy, M. C. Levy-Appert-Colin, and J. Hannart, *Ger. Offen.* 2,410,651 (Cl. C07d) [*Chem. Abstr.*, 1975, **82**, 43640u]. See also reference 6.
5. M. Somei and T. Kawasaki, *Heterocycles*, 1989, **29**, 1251; M. Somei, T. Kawasaki, K. Shimizu, Y. Fukui, and T. Ohta, *Chem. Pharm. Bull.*, 1991, **39**, 1905.
6. H. Takayama, N. Seki, M. Kitajima, N. Aimi, H. Seki, and S. Sakai, *Heterocycles*, 1992, **33**, 121.
7. M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *Heterocycles*, 1992, **34**, 1877.
8. a) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, 1951, **73**, 2188. b) H. Takayama, M. kurihara, S. Subhadhirasakul, M. Kitajima, N. Aimi, and S. Sakai, *Heterocycles*, 1996, **42**, 87. c) N. Finch, C. W. Gemenden, I. H.-C. Hsu, and W. I. Taylor, *J. Am. Chem. Soc.*, 1963, **85**, 1520; N. Finch, C. W. Gemenden, I. H.-C. Hsu, A. Kerr, G. A. Sim, and W. I. Taylor, *ibid.*, 1965, **87**, 2229.

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