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

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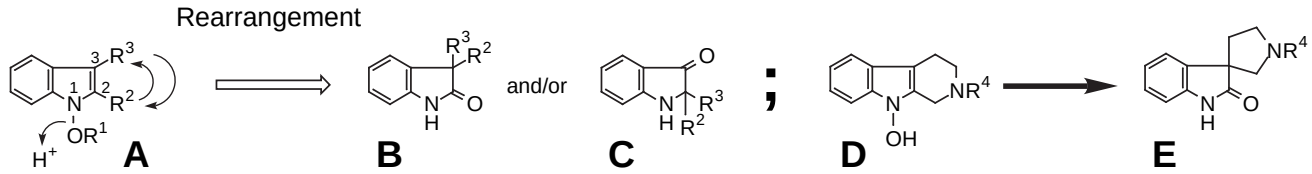
Abstract — 1-Hydroxyyohimbine was prepared for the first time. Its skeletal rearrangement reaction either directly into 2-oxindole or into 3-oxindole derivatives by a series of reaction is reported. 1-Hydroxyyohimbine and some of its derivatives showed potent α2 blocking activity.

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

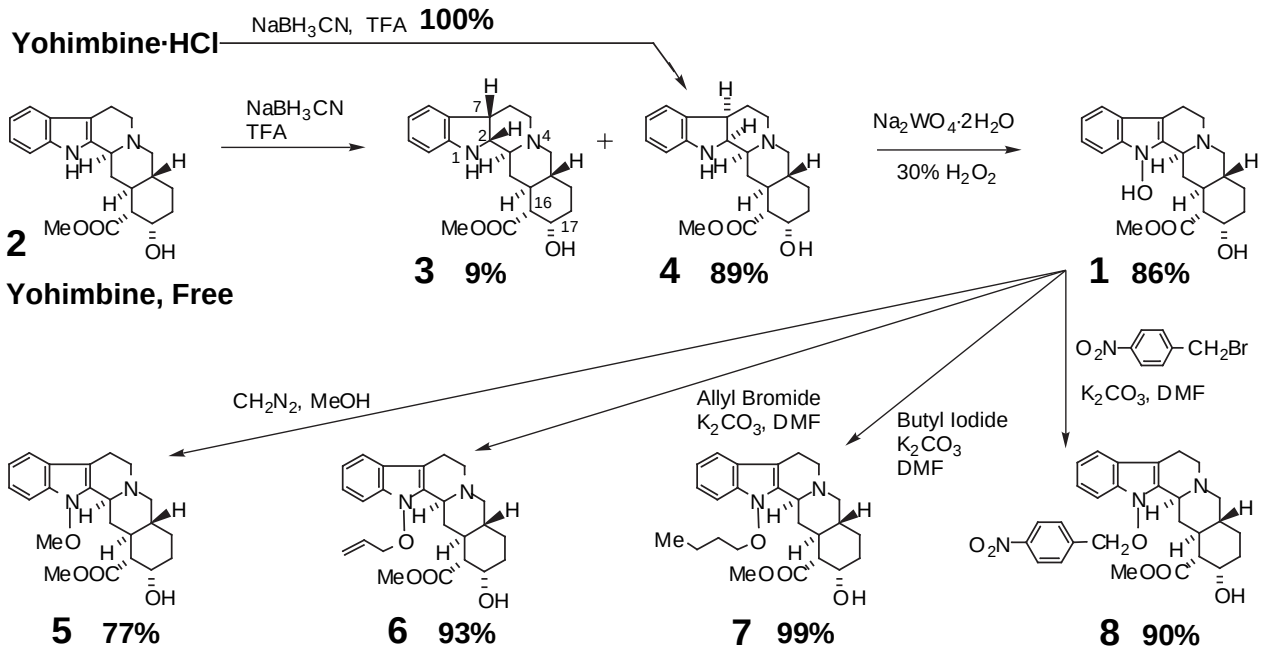
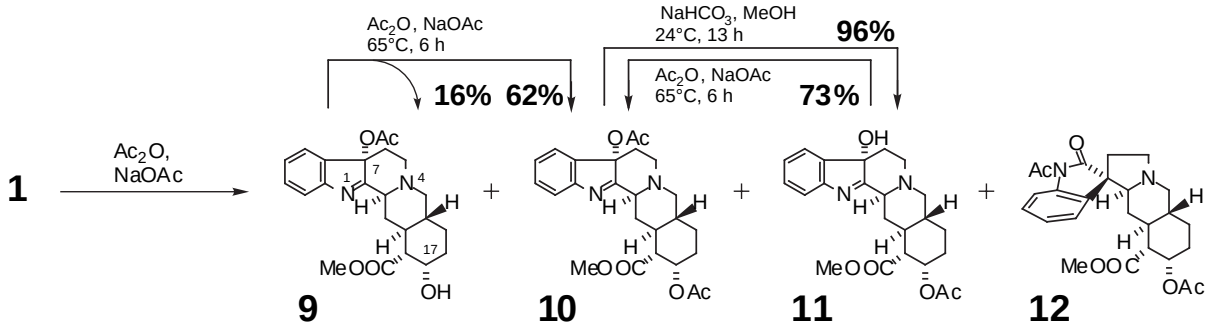


Table 1



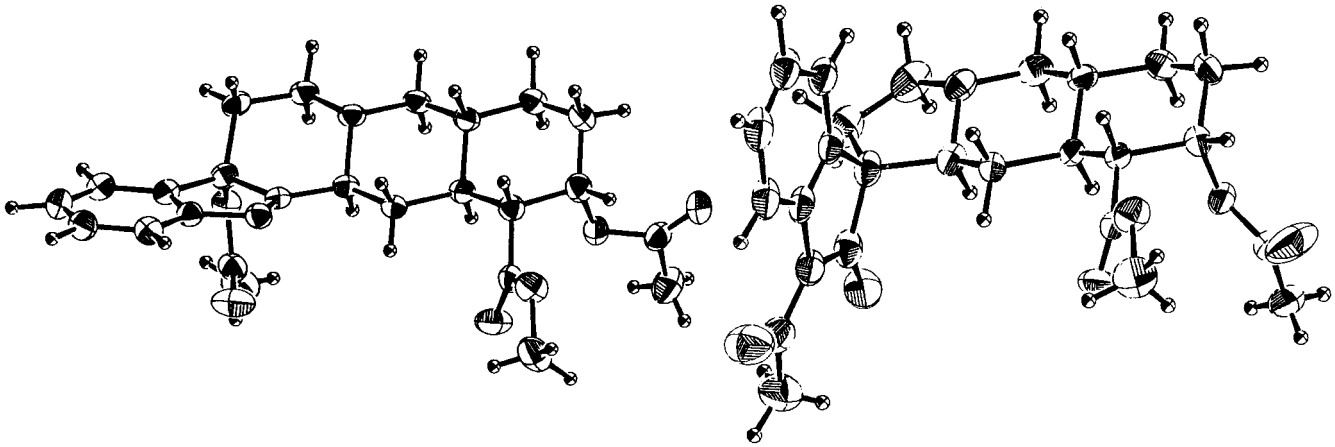
Entry	NaOAc (mol eq)	Reaction Conditions Temp. (°C)	Time (h)	Yield (%) of **9**	**10**	**11**	**12**
1	2	63	0.5	52	12	0	0
2	2	65	1	71	8	0	0
3	"	"	6	23	41	0	9
4	"	"	40	0	40	0	15
5	20	"	6	0	0	12	12
6	—	"	48	9	44	0	16

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).

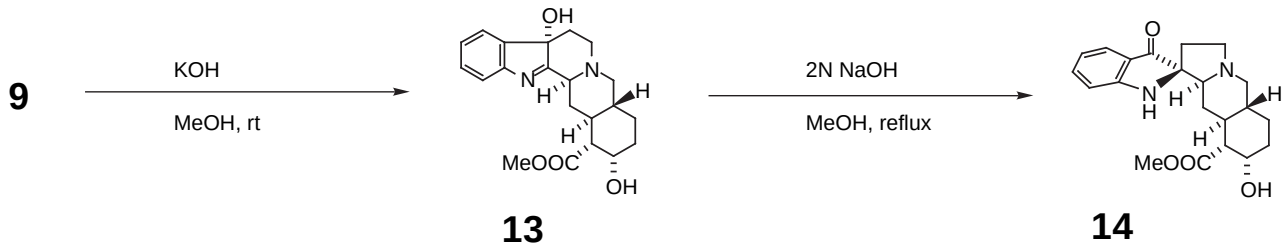
Figure 1. X-Ray Single Crystallographic Analyses

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

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