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

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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 \( \alpha_2 \) blocking activity.

We have supposed\(^2\) 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-\( \beta \)-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.

First, we needed a novel 1-hydroxyyohimbine (1). According to the reported procedure,\(^4\) we tried the reduction of yohimbine (2) with NaBH\(_3\)CN in TFA to give 2\( \beta \),7\( \beta \)- (3) and 2\( \alpha \),7\( \alpha \)-dihydroyohimbine (4) in 9 and 89% yields, respectively. Subsequent application of our Na\(_2\)WO\(_4\)-2H\(_2\)O and 30% H\(_2\)O\(_2\) 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\(_3\)CN 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 CH₂N₂ afforded 1-methoxy compound⁶ (5) in 77% yield. Utilizing K₂CO₃ 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.

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>NaOAc (mol eq)</th>
<th>Reaction Conditions</th>
<th>Yield (%) of</th>
<th>Reaction Conditions</th>
<th>Yield (%) of</th>
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<td>9</td>
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With 1 in hand, we next tried its reaction with Ac₂O in the presence of NaOAc which is a suitable condition for promoting rearrangement 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 products (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**

9 \[\text{KOH} \quad \text{MeOH, rt}\] \[\rightarrow \]

13

14 \[\text{2N NaOH} \quad \text{MeOH, reflux}\]

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 Ac₂O 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
NaHCO₃ in MeOH at room temperature.

On the other hand, a facile rearrangement of 9 to spiroindoxy compound⁸a (3-oxindole,⁸b 14) was already reported by Finch and co-workers⁸c 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.

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REFERENCES AND NOTES


