Preparation and a novel rearrangement reaction of 1, 2, 3, 4-tetrahydro-9-hydroxy-β-carboline, and their applications for the total synthesis of (±)-coerulescine

PREPARATION AND A NOVEL REARRANGEMENT REACTION OF 1,2,3,4-TETRAHYDRO-9-HYDROXY-β-CARBOLINE, AND THEIR APPLICATIONS FOR THE TOTAL SYNTHESIS OF (±)-COERULESCINE[1]

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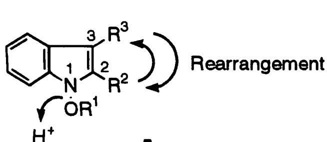
Abstract — Novel 9-hydroxy-β-carboline derivatives were produced for the first time. A novel rearrangement reaction of 1,2,3,4-tetrahydro-9-hydroxy-β-carbolines was discovered to give 3,3-disubstituted oxindoles, which was successfully applied to the total synthesis of (±)-coerulescine.

1-Hydroxyindoles undergo various types of reactions depending on the structures and reaction conditions.[2] We have designed 1,2,3,4-tetrahydro-9-hydroxy-β-carbolines (**1a–d**, Scheme 1) as key substrates to elucidate whether the rearrangement of the 2-substituent to the 3-position[3a] or *vice versa*, predicted by our 1-hydroxyindole hypotheses,[3] occurs or not as illustrated in a general formula **A** of 1-hydroxyindoles (Figure 1).

Figure 1

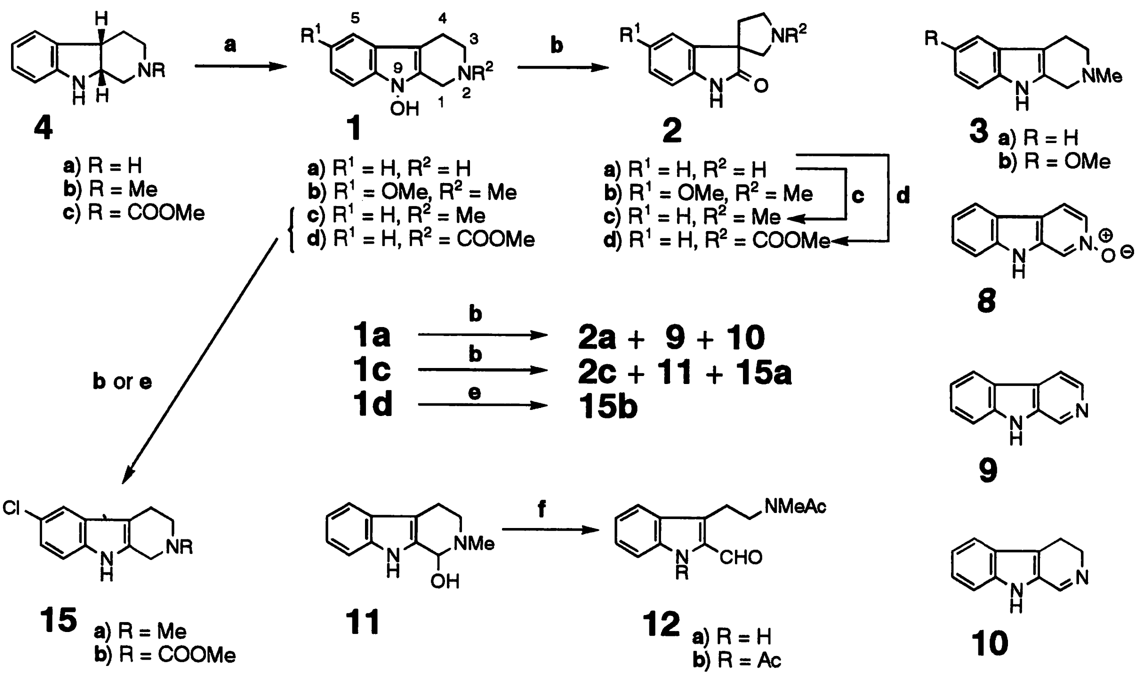


A

Quite recently, Colegate and co-workers[4] isolated and determined (−)-coerulescine (**2c**) from *Phalaris coerulescens*. We have noticed that *Phalaris* species generally contain 1,2,3,4-tetrahydro-β-carbolines (**3a, b**), because our hypotheses assumed[3a] biosyntheses of the related alkaloid, (−)-horsfiline[5] (**2b**) and **2c** from **3b** and **3a**, respectively, through the corresponding 9-hydroxy-β-carbolines (**1b** and **1c**). Now, we wish to report successful preparations of **1a** and **1c**, and their novel rearrangement achieving a total synthesis of 3,3-disubstituted oxindole alkaloid, (±)- coerulescine (**2c**).

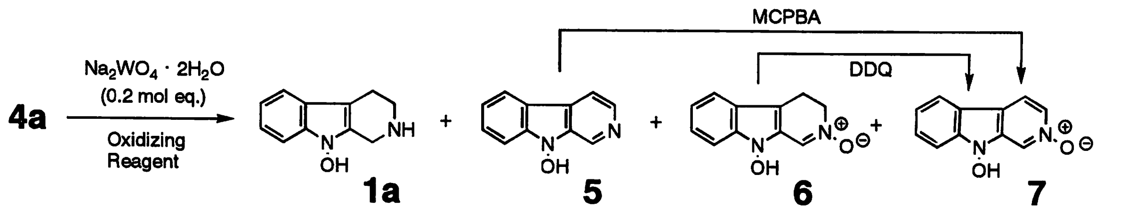
We have already developed the preparation of 1,2,3,4-tetrahydro-9-hydroxy-2-methoxycarbonyl-β-carboline[6] (**1d**) from the corresponding 1,2,3,4,4a,9a-hexahydro compound (**4c**) by $Na_2WO_4 \cdot 2H_2O$–30% H_2O_2 method.[7] According to the procedure, oxidation of **4a** was examined and typical results are summarized in Table 1. As can be seen from the Table, reaction time was found to be an important factor for preparing **1a**. In cases (Entries 1 and 2) where reaction times were 25 min, even a trace amount of **1a** was not detected in the reaction mixture, instead 9-hydroxy-β-carboline (**5**), 3,4-dihydro-9-hydroxy-β-carboline *N*-oxide (**6**), and 9-hydroxy-β-carboline *N*-oxide (**7**) were produced. When the reaction time was longer than 25 min, total yield of the three 9-hydroxy-β-carbolines (**5–7**) decreased, while the production of **1a** was observed in 11% yield when it was shortened to 10 min (Entry 3). Better yield of **1a** (55%) was attained by reacting **4a** for only 5 min as shown in Entry 4. As for oxidizing reagent, urea hydrogen peroxide was a reagent of choice to give satisfactory result (65%, Entry 5) as discovered in our previous report.[8] Similarly,

Scheme 1



a) $Na_2WO_4{\cdot}2H_2O$, 30% H_2O_2; b) MeOH-c-HCl (1:3, v/v), reflux; c) HCHO/AcOH/$NaBH_3CN$; d) ClCOOMe, Et_3N; e) MeOH-c-HCl, under various reaction conditions; f) Ac_2O, pyridine.

Table 1



Entry	Oxidizing Reagent (mol eq)	Reaction Conditions Solvent System	Temp. (°C)	Time (min)	Yield (%) of 1a	5	6	7
1	30% H_2O_2 (10)	MeOH-H_2O (10:1, v/v)	19	25	0	14	21	7
2	"	*t*-BuOH-H_2O (4:1, v/v)	22	25	0	5	25	21
3	"	"	21	10	11	trace	22	15
4	"	MeOH-H_2O (9:1, v/v)	27	5	55	trace	5	5
5	98% Urea·H_2O_2 (10)	"	25.5	5	65	trace	5	2

oxidation of 1,2,3,4,4a,9a-hexahydro-2-methyl-β-carboline (**4b**) afforded 1,2,3,4-tetrahydro-9-hydroxy-2-methyl-β-carboline (**1c**) in 69% yield.

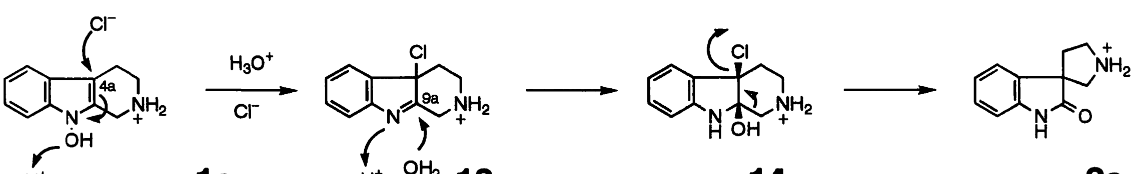
On the other hand, oxidation of **5** with MCPBA afforded **7** in 29% yield in addition to β-carboline *N*-oxide[9] (**8**) and β-carboline (**9**) in 31 and 11% yields, respectively. Dehydrogenation of **6** with DDQ provided 75% yield of **7**. Interestingly, treatment of **6** with chloroacetyl chloride produced **8** and **9** in 60 and 33% yields, respectively. Thus, four novel 9-hydroxy-β-carboline compounds (**1a** and **5**–**7**) and **8** are now readily available. Since these compounds are useful building blocks for β-carboline alkaloids syntheses, their applications are currently in progress.

With **1a**,**c** and **1d** in hand, we treated them with MeOH-c-HCl (1:3,v/v). Although no reaction took place at room temperature, the desired reaction of **1a** occurred under refluxing for 1 h resulting in the formation of **2a** in 47% yield together with **9** and **10** in 2 and 36% yields, respectively. Subsequent methylation of **2a** with HCHO-AcOH-$NaBH_3CN$ afforded (±)-**2c** in 91% yield, while the reaction of **2a** with methyl chloroformate gave **2d** in 99% yield. Similarly, treatment of **1c** with refluxing MeOH-c-HCl (1:3,v/v) for 3 h produced (±)-**2c**, **11**, and 6-chloro-1,2,3,4-tetrahydro-2-methyl-β-carboline (**15a**) in 42, 46, and 9% yields, respectively.

The structure of (±)-**2c** was confirmed by the direct comparison with the authentic sample prepared alternatively according to the reported procedure.[4c] Spectral data of our samples, authentic sample, and the reported ones of (–)-**2c** were identical in every respects. The structure of relatively unstable **11** was deduced based on its spectral data and the fact that it yielded formyl compounds (**12a** and **12b**) by the reaction with Ac_2O-pyridine.

The mechanism of the rearrangement would be explained as shown in Scheme 2. Initial protonation of 9-hydroxy group, followed by its elimination and chloride attack at the 4a carbon generates chloroindolenine (**13**). After addition of water to the 9a imine carbon atom of **13** giving **14**, concerted elimination of chloride and rearrangement of the alkyl side chain attached to the 9a carbon atom result in 3,3-disubstituted oxindole structure (**2a**).

Scheme 2



Protonated **1a** **13** **14** Protonated **2a**

It should be noted that **2d** was not formed in the reaction of **1d** with methanolic HCl under various examined reaction conditions. In these cases, nucleophilic substitution reaction took place affording 6-chloro-1,2,3,4-tetrahydro-2-methoxycarbonyl-β-carboline (**15b**, 8–16%) together with 1,2,3,4-tetrahydro-2-methoxycarbonyl-β-carboline (21–30%).[10]

In conclusion, we could prepare novel 9-hydroxy-β-carbolines which would be utilized as useful building blocks for the syntheses of β-carboline compounds. We have also discovered a novel rearrangement reaction on 1-hydroxyindole skeletons providing valuable means for the preparation of 3,3-disubstituted oxindole alkaloids. The present findings suggest chemists to be very careful to use acids for isolation of indole alkaloids from natural resources, otherwise oxindole alkaloids might be obtained as artifacts of genuine 1-hydroxy- or 1-methoxyindole alkaloids, if they happen to exist.[1b,2b,3a]

ACKNOWLEDGMENT

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REFERENCES AND NOTES

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8. M. Somei and T. Kobayashi, *Heterocycles*, 1992, **34**, 1295.
9. Synthesis of **8** from **9** in 78% yield: M. Natsume and R. Tanabe, *Ann. Rept. ITSUU Lab.*, 1968, **15**, 21 and references cited therein.
10. Remarkable differences observed in the reactivities of **1a**, **c** and **1d** might be explained by the protonation of β-nitrogen. The detailed elucidation of the results is an interesting future subject.

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