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New oxindole and indole alkaloids from *Gelsemium rankinii*

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ABSTRACT

Six new humantenine-type (**1**–**6**) and two new gelsemine-type (**7**, **8**) oxindole alkaloids and one new indole alkaloid (**9**) were isolated from the leaves and branches of *Gelsemium rankinii*. The structures of the new alkaloids were determined by spectroscopic analyses. Among them, 6-hydroxyhumantenine (**5**) is the first example of a *Gelsemium* alkaloid with an oxygen function at C-6 position, and is a plausible biogenetic precursor of gelsemine-type alkaloids.

1. Introduction

The genus *Gelsemium* comprises three species: *G. elegans*, which is widely distributed in Southeast Asia, and *G. sempervirens* and *G. rankinii*, which are distributed in North America. All of them are known to be rich sources of indole alkaloids. To date, more than seventy alkaloids have been isolated and classified into six types on the basis of their chemical structures.[1–3] Recently, we have found a new type of oxindole alkaloid from *G. rankinii* called rankiniridine, which has a nitrogen–carbon linkage between a humantenine-type alkaloid and an iridoid unit.[4] In our continuing chemical studies on the *Gelsemium* alkaloids,[5] we isolated six new humantenine-type (**1**–**6**), two new gelsemine-type (**7**, **8**), and one new sarpagine-type (**9**) alkaloids from *G. rankinii* (Fig. 1). In this paper, we report the structure elucidation of these new alkaloids.

2. Results and discussion

New alkaloid **1** was found to have the molecular formula $C_{20}H_{22}N_2O_3$ from HRFABMS [*m/z* 339.1737 (MH^+)]. It possesses two hydrogens less than rankinidine (**10**),[6,7] the main alkaloid of this plant. The UV spectrum exhibited a characteristic oxindole chromophore. ^1H and ^{13}C NMR spectra (Table 1) revealed some readily assignable signals due to the rankinidine skeleton, including signals assigned to an oxindole system with a non-substituted A ring [δ_H 7.48 (d, H-9), δ_H 7.32 (ddd, H-11), δ_H 7.14 (ddd, H-10), δ_H 6.98 (d, H-12); δ_C 171.4 (C-2)], an ethylidene group [δ_H 5.41 (m, H-19), δ_H 1.67 (3H, d, H_3-18)], an N_a-methoxy group [δ_H 3.98 (3H, s)], an oxymethylene group [δ_H 4.61 (d), δ_H 4.16 (dd); δ_C 64.9 (C-17)], an oxymethine group [δ_H 3.59 (d); δ_C 75.2 (C-3)] and a methylene group bearing a nitrogen atom [δ_H 4.91 (d), δ_H 3.76 (br d) (H_2-21)]. Comparison of the ^1H NMR data of **1** with those of rankinidine (**10**) indicated the lack of a nitrogen-bearing methine proton due to H-5 and the downfield shift of the signals due to H_2-6, H-16 and H_2-21 in **1**. Furthermore, a signal at δ 173.2 corresponding to an imine carbon was observed in the ^{13}C NMR spectrum of **1**. The above data implied the existence of an imine residue between N_4 and C-5 in **1**. The W-coupling (J=3.0 Hz) between H-6 and H-16 in the ^1H NMR spectrum and the HMBC correlations between the protons of H-17 and H-21 and the imine carbon at δ 173.2 supported the existence of an N_4–C-5 imine residue (Fig. 2). The anisotropy effect of this imine group might have caused the ^1H NMR signals of H-6 and H-21 to shift to the lower field. The *Z* configuration of the ethylidene group at C-19–C-20 was confirmed by the NOE correlation of H-19 to H-15. Therefore, compound **1** was deduced to be 4,5-dehydrorankinidine. This is the first example of a *Gelsemium* alkaloid with an imine moiety between N_4 and C-5 position.

New alkaloid **2** was shown to have the molecular formula $C_{20}H_{24}N_2O_4$ from HRFABMS [*m/z* 357.1844 (MH^+)], which indicated that **2** has an extra oxygen atom compared to rankinidine (**10**). The ^1H NMR spectrum was very similar to that of rankinidine (**10**) and included signals assignable to an N_a-methoxy oxindole system with a non-substituted A ring, an ethylidine group, an oxymethylene group (H_2-17), an oxymethine group (H-3), and methylene (H_2-21) and methine (H-5) groups bearing a nitrogen atom. However, the H-14 signal was observed as a methine proton in the lower field [δ 4.64 (d, H-14)] relative to that of **10**. In addition, an oxygenated methine

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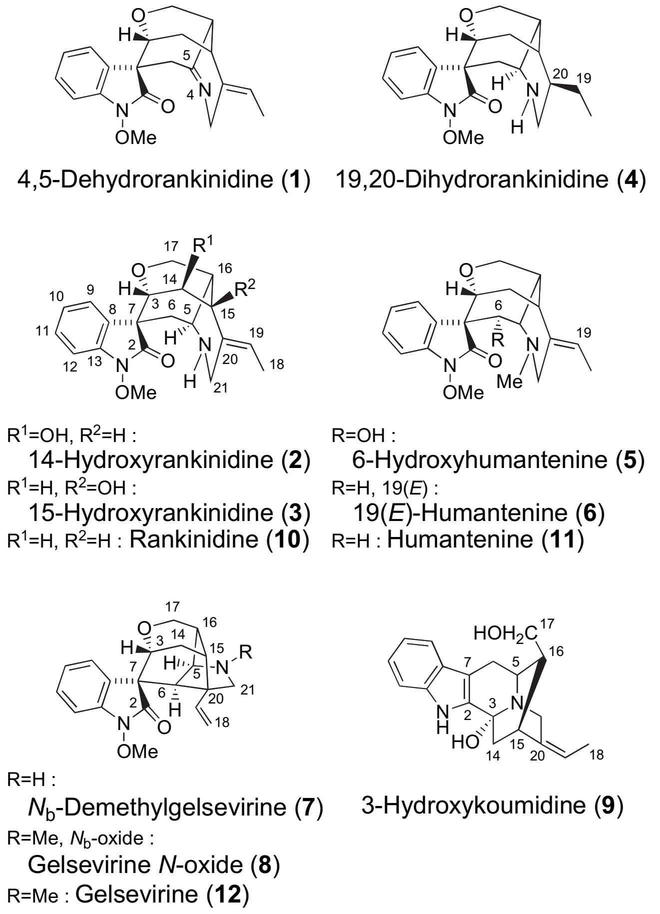

4,5-Dehydrorankinidine (**1**)

19,20-Dihydrorankinidine (**4**)

R^1=OH, R^2=H : 14-Hydroxyrankinidine (**2**)
R^1=H, R^2=OH : 15-Hydroxyrankinidine (**3**)
R^1=H, R^2=H : Rankinidine (**10**)

R=OH : 6-Hydroxyhumantenine (**5**)
R=H, 19(*E*) : 19(*E*)-Humantenine (**6**)
R=H : Humantenine (**11**)

R=H : N_b-Demethylgelsevirine (**7**)
R=Me, N_b-oxide : Gelsevirine *N*-oxide (**8**)
R=Me : Gelsevirine (**12**)

3-Hydroxykoumidine (**9**)

Figure 1. Structures of new (**1**–**9**) and known (**10**–**12**) alkaloids.

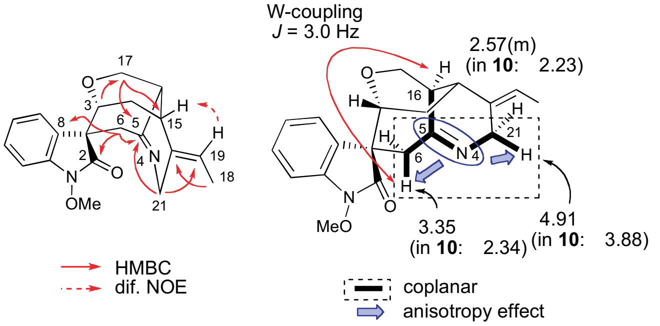
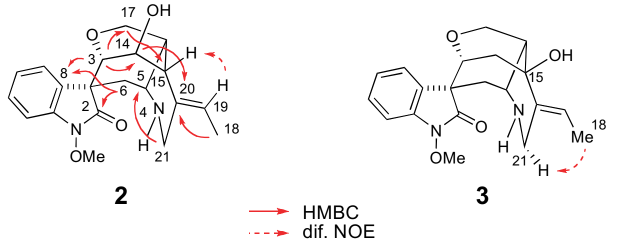


Figure 2. Selected HMBC and NOE correlations and NMR analysis of 4,5-dehydrorankinidine (**1**).

carbon signal was observed at δ_C 71.2 besides C-3 and C-17 oxygenated carbon signals in the ^{13}C NMR spectrum, suggesting the existence of an additional hydroxyl group. HMBC correlation of the proton at δ 3.51 due to H-3 to the carbon at δ 71.2 and that of the proton at δ 4.64 to the carbon at δ 137.5 (C-20) indicated that the hydroxyl group was attached to C-14 (Fig. 3). The configuration of the hydroxyl group at C-14 was shown to be β on the basis of the coupling constant of H-14 ($J_{14,15}$=5.8 Hz) that shows coupling only with H-15 and not with H-3; the dihedral angle between H-14 and H-3 is ca. 90 degrees. The *Z* configuration of the ethylidene group at C-19–C-20 was confirmed by the NOE correlation of H-19 to H-15. From these data, compound **2** was deduced to be 14-hydroxyrankinidine.


2

3

Figure 3. Selected HMBC and NOE correlations of 14-hydroxyrankinidine (**2**) and 15-hydroxyrankinidine (**3**).

New alkaloid **3** was found to have the molecular formula $C_{20}H_{24}N_2O_4$ from HRFABMS [*m/z* 357.1822 (MH$^+$)], which is the same as that of compound **2**. The ^{1}H NMR spectrum was very similar to that of rankinidine (**10**) except for the lack of a signal due

Table 1
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data for **1**–**4** in CDCl$_3$

Position	**1**		**2**		**3**		**4**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2		171.4		173.7		173.9		174.8
3	3.59 (d, 8.9)	75.2	3.51 (s)	81.8	3.65 (d, 8.5)	73.2	3.68 (d, 8.3)	72.8
5		173.2	3.67 (m)	53.0	3.76 (m)	53.9	3.60 (m)	54.8
6	3.35 (dd, 13.5, 3.0) 2.89 (d, 13.5)	41.7	2.40 (dd, 16.0, 5.3) 2.15 (dd, 16.0, 2.7)	34.4	2.43 (dd, 16.0, 5.8) 2.17 (dd, 16.0, 4.0)	34.5	2.54 (dd, 15.8, 7.6) 1.86 (dd, 15.8, 9.5)	31.4
7		50.2		54.8		55.9		55.7
8		129.8		130.7		131.0		129.8
9	7.48 (d, 7.7)	125.2	7.42 (d, 7.6)	125.1	7.45 (d, 7.6)	125.3	7.42 (d, 7.7)	125.7
10	7.14 (ddd, 7.7, 7.7, 1.1)	123.3	7.15 (ddd, 7.6, 7.6, 1.1)	123.9	7.15 (dd, 7.6, 7.6)	123.7	7.11 (ddd, 7.7, 7.7, 1.1)	123.1
11	7.32 (ddd, 7.7, 7.7, 1.1)	128.4	7.32 (ddd, 7.6, 7.6, 1.1)	128.5	7.32 (dd, 7.6, 7.6)	128.3	7.31 (ddd, 7.7, 7.7, 1.1)	128.1
12	6.98 (d, 7.7)	107.1	6.99 (d, 7.6)	107.4	6.98 (d, 7.6)	107.3	7.00 (d, 7.7)	107.3
13		138.8		138.2		138.3		138.9
14	2.30 (dd, 14.9, 7.6) 2.18 (ddd, 14.9, 8.9, 8.9)	30.2	4.64 (d, 5.8)	71.2	2.97 (d, 16.2) 2.15 (overlapped)	38.3	2.35 (dd, 14.8, 8.1) 1.98 (ddd, 14.8, 10.7, 8.3)	21.9
15	2.75 (m)	33.6	2.38 (overlapped)	46.1		68.4	2.16 (m)	28.8
16	2.57 (m)	38.6	2.29 (m)	32.7	2.19 (overlapped)	41.4	2.11 (m)	39.7
17	4.61 (d, 10.9) 4.16 (dd, 10.9, 4.2)	64.9	4.35 (d, 10.7) 4.14 (dd, 10.7, 4.9)	66.8	4.56 (dd, 10.4, 4.6) 4.23 (d, 10.4)	62.5	4.20 (d, 11.0) 4.02 (dd, 11.0, 5.5)	67.6
18	1.67 (3H, d, 7.0)	13.2	1.64 (3H, d, 6.7)	12.8	1.65 (3H, d, 7.0)	12.6	0.95 (3H, dd, 7.4, 7.4)	11.4
19	5.41 (m)	119.0	5.46 (br q, 6.7)	119.1	5.86 (br q, 7.0)	116.0	1.36 (2H, dq, 7.4, 7.4)	23.1
20		137.3		137.5		144.2	1.70 (m)	41.9
21	4.91 (d, 17.6) 3.76 (br d, 17.6)	49.6	3.88 (d, 17.0) 3.32 (d, 17.0)	41.4	3.90 (d, 16.7) 3.45 (d, 16.7)	41.6	3.11 (dd, 13.6, 11.4) 2.77 (dd, 13.3, 5.0)	40.6
N_a-OMe	3.98 (3H, s)	63.2	4.01 (3H, s)	63.6	3.98 (3H, s)	63.5	4.00 (3H, s)	63.4