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FOUR MONOTERPENE ALKALOID DERIVATIVES FROM *INCARVILLEA SINENSIS*

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Key Word Index—*Incarvillea sinensis*; Bignoniaceae; incarvine D; methoxyincarvillateine; incarvillateine *N*-oxide; incarvine A *N*-oxide; anti-rheumatism.

Abstract—Two new derivatives of monoterpene alkaloids, named incarvine D and methoxycarvillateine, and two novel *N*-oxides, incarvillateine *N*-oxide and incarvine A *N*-oxide were isolated from the aerial parts of *Incarvillea sinensis* LAM. On the basis of chemical and spectroscopic evidence, incarvine D was characterized as the ester of a monoterpene alkaloid, incarvilline, and a monoterpene, tetrahydro-alcohol compound corresponding to Hildebrandt's acid; methoxycarvillateine was established as the methoxy derivative of incarvillateine, and the two oxides were determined to be *N*-oxide derivatives of incarvillateine and incarvine A, respectively. © 1997 Elsevier Science Ltd

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INTRODUCTION

Incarvillea sinensis LAM., one of the well-known Chinese crude drugs, has been used to treat rheumatism and to relieve pain. In studies on its pharmacological active substance(s), we have isolated and characterized five new alkaloids, incarvilline (**5**), incarvillateine (**6**) and incarvine A–C [1–4]. The present paper describes the isolation and structure elucidation of two new alkaloids, incarvine D (**1**) and methoxyincarvillateine (**2**), and two novel *N*-oxides, incarvillateine *N*-oxide (**3**) and incarvine A *N*-oxide (**4**).

RESULTS AND DISCUSSION

Incarvine D (**1**) showed peaks at *m/z* (rel. int.) 351 $[M]^+$ (66), 183 $[\text{incarvilline}]^+$ (70), 182 $[\text{incarvilline-H}]^+$ (100) and 166 $[\text{incarvilline-OH}]^+$ (100) in its mass spectrum. Its ^{13}C NMR signals at δ 57.5, 57.7, 30.6, 37.7, 29.9, 76.0, 41.0, 46.1, 46.2, 17.3 and 14.9 could be assigned, respectively, to C-1, C-3–9, *N*-Me, Me-4 and Me-8 of the monoterpene alkaloid moiety, incarvilline (**5**). The structure of (**5**) was previously determined by X-ray analysis [1], and whose absolute configuration was determined recently [5]. The proton signals were also attributed as follows: δ 0.86 (3H, *d*, $J = 6.7$ Hz, 4-Me), 0.96 (3H, *d*, $J = 7.3$ Hz, 8-Me), 1.55–1.64 (2H, *m*, 1-H*a*, 6-H*a*), 1.68 (1H, *t*, $J = 11.6$ Hz, 3-H*a*), 1.91–2.22 (4H, *m*, 6-H*b*, 8, 9, 4-H), 2.23 (3H, *s*, *N*-Me), 2.39 (1H, *m*, 5-H), 2.50 (1H, *m*, 3-H*b*), 2.66 (1H, *m*, 1-H*b*), 5.28 (1H, *m*, 7-H). The remaining carbon signals at δ 12.3 (*q*), 19.4 (*q*), 26.2 (*t*), 29.4 (*d*), 35.8 (*t*), 39.7 (*t*), 60.8 (*t*), 127.8 (*s*), 142.2 (*d*) and 167.8 (*s*) established the presence of a monoterpene moiety whose ^1H–^{13}C COSY led to the assignment of one methyl at δ 0.94 (3H, *d*, $J = 6.7$ Hz); one olefinic methyl at 1.83 (3H, *s*); one olefinic proton at 6.73 (1H, *t*, $J = 7.3$ Hz); six methylene protons at 1.30 (1H, *m*), 1.40 (1H, *m*), 1.44 (1H, *m*), 1.55–1.64 (2H, *m*), 1.91–2.22 (2H, *m*) and two oxygenated methylene protons at δ 3.66 (2H, *m*). The monoterpene moiety was characterized as a tetrahydro-alcohol compound corresponding to Hildebrandt's acid [6], by comparing the chemical shifts with those of incarvine A (**7**) [3].The bond between incarvilline (**5**) and the monoterpene moiety was elucidated by the HMBC spectrum, in which a cross peak between C-1′ of the monoterpene moiety and H-7 of the incarvilline (**5**) moiety was observed. The chemical shift of the signal at δ_H 5.28 (1H, *m*), assignable to H-7 of **5**, also established that the 7-hydroxyl group was acylated. Consequently, the structure of incarvine D (**1**) has been established as shown in the formula.

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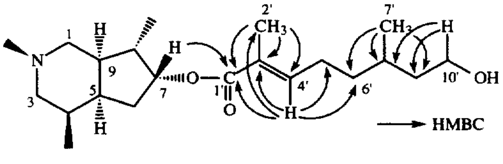
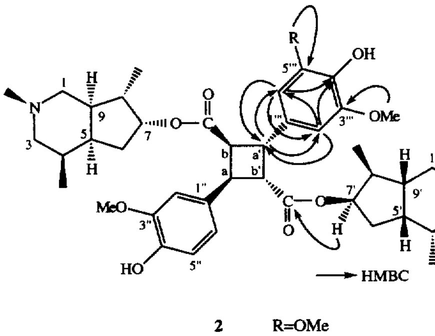


1

Methoxyincarvillateine (**2**) showed peaks at m/z (rel. int.) 748 $[M]^+$ (13), 182 (73) and 166 (54) in its EI mass spectrum. The ^{13}C NMR signals (Table 1) suggested the presence of two molecules of monoterpene alkaloid moiety, incarvilline (**5**) [1]. The proton signals also supported the occurrence of the two moles of the incarvilline moiety (Table 2). The remaining carbon signals (Table 1) disclosed the presence of a 3-methoxy-4-hydroxy-benzyl moiety and a 3,5-dimethoxy-4-hydroxybenzyl moiety. The signals at δ 41.2, 42.2, 47.9 and 48.0 indicated the presence of a four-membered ring which was confirmed by ^{1}H–^{1}H and ^{1}H–^{13}C COSY. Consequently, the structure of **2** has been established as shown in the formula, named methoxyincarvillateine. Its structure was also verified by the aid of ^{1}H–^{1}H, ^{1}H–^{13}C COSY and HMBC, and by comparison with incarvillateine (**6**), whose structure was previously determined by X-ray analysis [2].

Incarvillateine *N*-oxide (**3**) seemed as a pure substance according to TLC, UV and FABMS; however, the multiplicity of the ^{1}H and ^{13}C NMR spectral data (Table 3) showed it to be a mixture of two *N*-oxides. Attempts to separate them by HPLC under various conditions were unsuccessful. The positive FAB-mass spectrum of **3** showed an $[M+1]^+$ peak at m/z 735, and intense fragments due to half molecular moieties at m/z 360 and 376, as well as the fragment ion $[M-16]^+$ at m/z 718. These were typical for *N*-oxides [7]. All other prominent signals were similar to those found in the spectrum of incarvillateine (**6**) [2].

On comparison of the ^{1}H and ^{13}C NMR spectra of **3** with those of **6** (Table 3), noticeable shifts were observed not only for two of the *N*-Me groups, but also for their neighbouring methylene groups, whereas the other signals were similar to those of **6**. The *N*-Me δ_H signals were shifted downfield to δ 3.09 (+0.92 ppm), while their neighbouring methylene groups were also shifted downfield; however, their chemical shifts could not be assigned accurately due to overlapping of the signals. The ^{13}C NMR signals of the two *N*-Me groups were shifted to δ 61.44 (+15.44 ppm) (*av*.), C-1, -1′ to δ_C 66.52 (+9.47 ppm) (*av*.), and C-3, -3′ to δ_C 67.66 (+10.31 ppm) (*av*.), respectively. These shifts were indicative of the influence of the *N*-O dipole.



2 R=OMe
6 R=H

Oxidation of **3** and **6**, respectively, with *m*-chloroperbenzoic acid, yield incarvillateine *N*,*N*′-dioxide (**8**), whose positive FAB mass spectrum showed $[M+1]^+$ at m/z 751, and $[M-O+1]^+$ at m/z 735, suggesting that both *N* and *N*′ were oxidized. The ^{1}H and ^{13}C NMR spectra of **8** were similar to those of **6** except that all of the *N*-Me signals were shifted downfield to δ 3.13 (+0.96 ppm), 1-, 1′-H*a* to δ 2.78 (+1.36 ppm), 1-, 1′-H*b* to δ 3.10 (+0.55 ppm), 3-, 3′-H*a* to δ 2.94 (+1.36 ppm) and 3-, 3′-H*b* to δ 2.94 (+0.49 ppm) and in the ^{1}H NMR spectrum, and all of the *N*-Me signals were shifted downfield to δ 6.15 (+15.5 ppm), C-1, -1′ to δ 66.4 (+9.3 ppm) and C-3, -3′ to δ 67.6 (+10.2 ppm) in the ^{13}C NMR spectrum (Table 3). These facts suggested that **3** was a mixture of **3a** and **3b**.

The ^{1}H NMR spectrum of incarvine A *N*-oxide (**4**) was similar to that of **7** [4] except for the downfield shifts of *N*-Me groups (+1.05 ppm), and their neighbouring methylene groups. The ^{13}C NMR spectrum (Table 4) also supported the above facts: two *N*-Me signals were shifted downfield to δ 61.25 (+15.35 ppm), C-1, −1′ to δ 67.23 (+10.13 ppm), and C-3, −3′ to δ 66.16 (+8.86 ppm). The occurrence of $[M+1]^+$ at m/z 545 and $[M]^+$ at m/z 544 in the positive FAB mass spectrum of **4**, as well as a fragment ion $[M-O+1]^+$ at m/z 529, was typical of *N*-oxides [7]. The multiplicity observed in the ^{1}H NMR spectrum and the duplicate ^{13}C-signals indicated that **4** was a mixture of **4a** and **4b**.

Oxidation of **4** and **7** with *m*-chloroperbenzoic acid, individually, afforded incarvine A *N*,*N*′-dioxide (**9**). This confirmed that **4** was composed of **4a** and **4b**. The positive FAB mass spectrum of **9** showed $[M+1]^+$ at m/z 561 suggesting both *N* and *N*′ were oxidized. The ^{1}H and ^{13}C NMR spectra of **9** were similar to that of **7** except that all *N*-Me signals were shifted downfield to δ_H 3.19 (+0.90 ppm), 1-, 1′-H*a* to δ 3.00 (+1.34 ppm), 1-, 1′-H*b* to δ 3.17 (+0.45 ppm), 3-, 3′-H*a* to δ 3.00 (+1.24 ppm) and 3-, 3′-H*b* to δ_H 3.10 (+0.52 ppm) and to δ_C 60.96 (+15.06 ppm), δ_C 67.41 (+10.31 ppm), and δ_C 66.31 (+9.01 ppm), respectively (Table 4).

EXPERIMENTAL

General. ^{1}H and ^{13}C NMR: JEOL JNM-GX 500 NMR, int. standard (TMS); EIMS: JEOL DX-303 HF spectrometer; TLC: precoated Kieselgel 60 F_{254} plate (0.2 mm Merck), detection by spraying Dragendorff and 10% aq. H_2SO_4; CC: Kieselgel 60 (70–230 and 230–400 mesh, Merck), Aluminium oxide 90

Table 1. ^{13}C NMR data for compounds **2** and **6**

Incarvilline moieties			C_6–C_3 units		
C	**6**	**2**	C	**6**	**2**
4, 4′, 8, 8′-Me	14.4	14.4	a, a′-C	40.3	41.2
	14.8	14.8		41.7	42.2
	16.8	16.8	b, b′-C	47.2	47.9
	17.0	17.1		47.8	48.0
C-6,6′	29.1	29.2	COO, COO′	171.7	171.6
	29.6	29.7		171.9	171.9
C-4, 4′	30.1†	30.3†	3″, 3‴-OMe	55.6	55.8
	30.1†	30.3†		55.7	56.2†
C-5, 5′	37.2†	37.3†	C-2″, 2‴	110.8	110.9
	37.2†	37.3†		110.9	104.4
C-8, 8′	40.1†	40.3	C-5″, 5‴	114.7†	114.6
	40.1†	40.4		114.7†	147.2
N, *N*′-Me	45.9	46.1	C-6″, 6‴	119.8	119.9
	46.0	47.4		120.3	104.6
C-9, 9′	45.6	45.8	C-1″, 1‴	130.2	129.7
	45.7	45.9		130.4	130.5
C-1, 1′	57.1	57.2	C-3″, 3‴	145.3	145.2
	57.3	57.3		145.5	147.1
C-3, 3′	57.4†	57.5	C-4″, 4‴	146.8	146.8
	57.4†	57.6		146.9	134.3
C-7, 7′	76.2	76.4	5″ (or 5‴)-OMe		56.2†
	76.5	76.6			

† Overlapped signals.

Table 2. ^{1}H NMR data for compounds **2** and **6**

6	**2**
0.58 (1H, *m*, 6-H*a*)	0.59 (1H, *m*, 6-H*a*)
0.60 (3H, *d*, *J* = 7.3 Hz, 8-Me)	0.59 (3H, *d*, *J* = 7.3 Hz, 8-Me)
0.71 (3H, *d*, *J* = 6.7 Hz, 4-Me)	0.72 (3H, *d*, *J* = 6.1 Hz, 4-Me)
0.76 (3H, *d*, *J* = 6.7 Hz, 4′-Me)	0.76 (3H, *d*, *J* = 6.7 Hz, 4′-Me)
0.81 (3H, *d*, *J* = 7.0 Hz, 8′-Me)	0.82 (3H, *d*, *J* = 7.3 Hz, 8′-Me)
1.06 (1H, *m*, 6′-H*a*)	1.02 (1H, *m*, 6′-H*a*)
1.42 (2H, *m*, 1, 1′-H*a*)	1.44 (2H, *t*, *J* = 12.2 Hz, 1, 1′-H*a*)
1.58 (4H, *m*, 3, 3′-H*a*, 6, 6′-H*b*)	1.59 (3H, *m*, 3, 3′-H*a*, 6-H*b*)
1.72 (2H, *m*, 8′, 8-H)	1.72 (2H, *m* 6′-H*b*, 8-H)
1.84 (2H, *m*, 9, 9′-H)	1.84 (3H, *m*, 9, 9′, 8′-H)
1.97 (2H, *m*, 4, 4′-H)	1.96 (3H, *m*, 4, 4′, 5-H)
2.13 (2H, *m*, 5, 5′-H)	2.14 (1H, *m*, 5′-H)
2.17 (6H, *s*, *N*, *N*′-Me)	2.19 (6H, *s*, *N*, *N*′-Me)
2.45 (2H, *m*, 3, 3′-H*b*)	2.46 (2H, *m*, 3, 3′-H*b*)
2.55 (2H, *m*, 1, 1′-H*b*)	2.57 (2H, *m*, 1, 1′-H*b*)
3.81–3.89 (2H, *m*, b, b′-H)	3.83 (2H, *m*, b, b′-H)
3.88, 3.89 (each, 3H, *s*, 3″, 3‴-OMe)	3.88, 3.89, 3.90 (each, 3H, *s*, 3″, 3‴, 5″ (or 5‴)-OMe × 3)
4.30–4.38 (2H, *m*, a, a′-H)	4.34 (2H, *m*, a, a′-H)
4.89 (2H, *m*, 7, 7′-H)	4.90 (2H, *m*, 7, 7′-H)
6.77 (6H, *m*, 2″, 2‴, 5″, 5‴, 6″, 6‴-H)	6.53 (2H, *m*, 2‴, 6‴-H)
	6.81 (3H, *m*, 2″, 5″, 6″-H)

* Assignments may be interchanged between two incarvilline moieties.

aktiv (70–230 mesh, Merck) and Bondapak C_{18} (Water Associates, Inc.).

Extraction and separation. The aerial parts of *Incarvillea sinensis* collected in Hebei province, China, were exhaustively extracted with EtOH. The EtOH extract was concd under red. pres. to a syrup, which was dissolved in 2% HCl and filtered. The filtrate was adjusted to pH 11 by adding NH_4OH, and the alkaloids extracted into $CHCl_3$. After removal of solvent *in vacuo*, the residue was repeatedly chromatographed over an Al_2O_3 column with $CHCl_3$–MeOH (10:0.4), Bondapak C_{18} with 70–100% MeOH, and a silica gel

Table 3. ^{13}C NMR data for compounds **3** (CD_3OD), **6** ($CDCl_3$) and **8** ($CD_3OD + D_2O$)

Incarvilline moieties				C_6–C_3 units			
C	**6**	**3**	**8**	C	**6**	**3**	**8**
8, 8′-Me	14.4	15.91	15.9	a, a′-C	40.3	43.21	43.7
	14.8	16.06	16.0		41.7	44.06	44.0
4, 4′-Me	16.8	17.01	17.0	b, b′-C	47.2	48.96	48.8
	17.0	18.05			47.8	50.05	50.0
		18.08				50.08	
C-6, 6′	29.1	31.10	31.1	O, O′-Me	55.6	57.30	57.4
	29.6	31.21	31.4		55.7		55.7
		31.41		C-2″, 2‴	110.8	113.53	113.4
		31.53			110.9	113.68	113.5
C-4, 4′	30.1	27.47	27.4	C-5″, 5‴	114.7	116.98	117.0
		31.80				117.06	
		31.85		C-6″, 6‴	119.8	121.70	121.5
C-5, 5′	37.2	38.17	38.1		120.3	121.73	122.1
	37.3	39.18				122.26	
		39.23		C-1″, 1‴	130.2	132.55	132.5
C-9, 9′	45.6	43.86	43.0		130.4	132.58	132.6
	45.7	43.92	44.0			132.66	
		47.24		C-3″, 3‴	145.3	147.65	147.3
		47.29			145.5	147.85	147.5
N, *N*′-Me	45.9	46.39	61.5	C-4″, 4‴	146.8	149.67	149.7
	46.0	46.42			146.9	149.72	
		61.44		COO, COO′	171.7	174.06	174.5
C-8, 8′	40.1	41.80	41.7		171.9	174.15	174.8
		42.59				174.38	
C-1, 1′	57.0	58.03	66.4			174.46	
	57.1	58.13					
		66.50					
		66.53					
C-3, 3′	57.3	58.53	67.6				
	57.4	58.58					
		67.66					
C-7, 7′	77.2	77.76	78.2				
	76.5	78.11	78.5				
		78.25					
		78.50					

column with cyclohexane–MeOH–Et_2NH (30:1:1–5:1:1) to afford compounds **1** (40.1 mg), **2** (62.5 mg), **3** (47.0 mg) and **4** (41.0 mg).

Incarvine D (**1**). White powder, $[\alpha]_D^{26}$ −4.2° ($c = 0.60$, $CHCl_3$). EIMS *m/z* (rel. int.): 352 $[M+1]^+$ (100), 351 $[M]^+$ (66), 336 (10), 250 (59), 183 (70), 182 (100), 166 (100), 84 (16), 81 (22), 58 (88); ^1H NMR ($CDCl_3$); Monoterpene moiety: δ 0.94 (3H, *d*, $J = 6.7$ Hz, 7′-Me), 1.30 (1H, *m*, 6′-H*a*), 1.40 (1H, *m*, 6′-H*b*), 1.44 (1H, *m*, 9′-H*a*), 1.55–1.64 (2H, *m*, 8′-H, 9′-H*b*), 1.83 (3H, *s*, 2′-Me), 1.91–2.22 (2H, *m*, 5′-H_2), 3.66 (2H, *m*, 10′-H_2), 6.73 (1H, *t*, $J = 7.3$ Hz, 4′-H). ^{13}C NMR ($CDCl_3$); Monoterpene moiety: δ 167.8 (C-1′), 12.3 (C-2′), 127.8 (C-3′), 142.2 (C-4′), 26.2 (C-5′), 35.8 (C-6′), 19.4 (C-7′), 29.4 (C-8′), 39.7 (C-9′), 60.8 (C-10′).

Methoxyincarvillateine (**2**). White powder, $[\alpha]_D^{20}$ −4.0° ($c = 0.61$, $CHCl_3$), EIMS *m/z* (rel. int.): 748 $[M]^+$ (13), 390 (44), 389 (19), 361 (25), 360 (100), 359 (47), 182 (73), 166 (54), 58 (27).

Incarvillateine N-*oxide* (**3**). White powder, $[\alpha]_D^{18}$ −19.2° ($c = 0.50$, CH_3OH). Positive FAB-MS *m/z* (rel. int.): 735 $[M+1]^+$ (100), 717 (18), 376 (96), 375 (15), 361 (26), 360 (92); ^1H NMR (CD_3OD): δ 0.66 (2H, *d*, $J = 7.9$ Hz, 6-H*a*), 0.71, 0.75, 0.77, 0.79, 0.80, 0.83, 0.88, 0.91 (24H, *d*, $J = 7.3, 7.3, 6.7, 7.3, 6.7, 7.3, 7.3, 7.3$ Hz, 4, 4′-Me × 2, 8, 8′-Me × 2), 1.04 (2H, *m*, 6′-H*a*), 1.58 (4H, *m*, 6, 6′-H*b*), 1.68–1.90 (10H, *m*, 1, 3-H*a*, 8, 8′, 9-H), 2.01, 2.15 (6H, *m*, 4, 5, 5′-H), 2.28 (6H, *s*, *N*-Me), 2.32 (2H, *m*, 9′-H), 2.57 (4H, *m*, 3-H*b*, 4′-H), 2.67–2.99 (10H, *m*, 1-H*b*, 1′, 3′-H), 309 (6H, *s*, *N*′-Me), 3.82–3.95 (4H, *m*, b, b′-H), 3.86, 3.88 (12H, *s*, OMe), 4.29–4.39 (4H, *m*, a, a′–H), 4.93 (4H, *m*, 7, 7′-H), 6.77 (8H, *m*, 5″, 5‴, 6″, 6‴-H), 6.87, 6.92 (4H, *m*, 2″, 2‴-H).

Oxidation of **3** *and* **6** *with* m-*chlorperbenzoic acid*. A soln of *m*-chloroperbenzoic acid (3.4 mg) in $CHCl_3$ (1 ml) was added gradually to the stirred soln of **3** (5.2 mg) in $CHCl_3$ (1 ml), and stirring continued for 2 hr. After evapn of the solvent, the residue was subjected

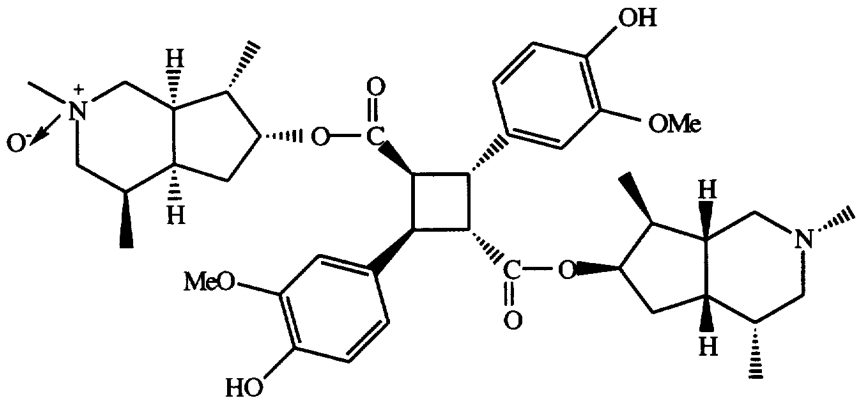
Table 4. ^{13}C NMR data for compounds **4** ($CDCl_3+CD_3OD$), **7** ($CDCl_3$) and **9** (CD_3OD)

Incarvilline moiety				Hildebrant's acid moiety			
C	**7**	**4**	**9**	C	**7**	**4**	**9**
8, 8′-Me	14.6	15.83	15.98	C-1″	167.3	169.29	169.68
		15.92	16.04	C-2″	12.2	12.19	13.42
4, 4′-Me	17.1	17.10	19.67			13.58	
		19.99		C-3″	128.9	129.89	130.55
C-6, 6′	29.6	30.92	31.50			130.04	
	29.7	31.04		C-4″	139.9	142.00	142.97
		31.10				142.36	
C-4, 4′	30.2	26.85	27.67	C-5″	26.4	27.85	28.20
		31.22				27.91	
C-5, 5′	37.3	37.60	38.46	C-6″	39.3	40.69	41.05
	37.4	38.72		C-7″	18.6	18.23	17.09
		38.78		C-8″	157.9	160.09	161.22
C-9, 9′	45.7	43.21	43.95			160.58	
		43.61		C-9″	116.2	117.23	117.92
		46.43				117.53	
N, *N*′-Me	45.9	46.49	60.96	C-10″	166.2	168.02	168.43
		46.64				168.06	
		61.25					
C-8, 8′	40.6	41.33	42.26				
	40.7	41.42					
		42.12					
		42.27					
C-1, 1′	57.1	57.75	67.41				
		67.23					
C-3, 3′	57.3	58.12	66.31				
		66.16					
C-7, 7′	75.1	76.21	76.87				
	75.9	76.64	77.81				
		77.09					
		77.52					

to CC on silica gel eluted with $CHCl_3$–MeOH–H_2O (8:2:0.2–7:3:0.5) to provide compound **8** (3.3 mg). By the same method, **8** (28.5 mg) was prepd from incarvillateine (**6**) (51.7 mg). $[\alpha]_D^{28}$ -20.0° ($c = 0.37$, CH_3OH+H_2O (1:1)). Positive FAB-MS *m/z* (rel. int.): 751 $[M+1]^+$ (45), 376 (50), 360 (10), 182 (100); ^{1}H NMR (CD_3OD+D_2O): δ 0.67 (1H, *m*, 6-H*a*), 0.79 (3H, *d*, $J = 7.3$ Hz, 8-Me), 0.80 (3H, *d*, $J = 7.3$ Hz, 8′-Me), 0.83 (3H, *d*, $J = 6.7$ Hz, 4-Me), 0.91 (3H, *d*, $J = 6.7$ Hz, 4′-Me), 0.98 (1H, *m*, 6′-H*a*), 1.62 (1H, *m*, 6-H*b*), 1.72 (1H, *m*, 6′-H*b*), 1.89 (1H, *m*, 8-H), 1.96 (1H, *m*, 8′-H), 2.06 (1H, *m*, 5-H), 2.15 (1H, *m*, 5′-H), 2.32 (2H, *m*, 9, 9′-H), 2.55 (2H, *m*, 4,4′-H), 2.78 (2H, *m*, 1, 1′-H*a*), 2.94 (4H, *m*, 3, 3′-H), 3.10 (2H, *m*, 1, 1′-H*b*), 3.13 (6H, *s*, *N*, *N*′-Me), 3.85–3.99 (2H, *m*, b, b′-H), 3.88, 3.90 (6H, *s*, O, O′-Me), 4.30–4.41 (2H, *m*, a, a′-H), 4.94 (2H, *m*, 7, 7′-H), 6.77 (4H, *m*, 5″, 5‴, 6″, 6‴-H), 6.87, 6.92 (2H, *m*, 2″, 2‴-H).

Incarvine A N-*oxide* (**4**). White powder, $[\alpha]_D^{27}$ -14.8° ($c = 0.45$, $CHCl_3$). Positive FABMS *m/z* (rel. int.): 545 $[M+1]^+$ (200), 544 $[M]^+$ (21), 543 (31), 529 $[M-O+1]^+$ (10), 527 (20), 380 (23), 364 (8), 281 (12), 265 (6); EIMS *m/z* (rel. int.): 545 $[M+1]^+$, 543, 529 $[M-O+1]^+$ (61), 528 $[M-O]^+$ (51), 364 (18), 347 (18), 182 (76), 166 (65), 164 (40), 163 (100), 110 (42); ^{1}H NMR ($CDCl_3+CD_3OD$): δ 0.87, 0.91, 0.93, 0.94, 0.96, 0.98, 1.27, 1.28 (24H, *d*, $J = 7.0$, 7.0, 6.5, 8.4, 6.2, 7.3, 7.3, 7.3 Hz, 4, 4′-Me × 2, 8, 8′-Me × 2), 1.57–1.84 (8H, *m*, 1, 3-H*a*, 6, 6′-H*a*), 1.84 (6H, *s*, 2″-Me), 1.84–2.17 (12H, *m*, 6, 6′-H*b*, 4, 9, 8′-H), 2.17 (6H, *s*, 7″-Me), 2.29–2.46 (10H, *m*, 5, 5″, 6″-H), 2.36 (6H, *s*, *N*-Me), 2.50–2.63 (6H, *m*, 5′-H, 1, 3-H*b*, 9′-H), 2.78–2.94 (4H, *m*, 4′-H, 3′-H*a*), 3.00–3.18 (4H, 1′-H*a*, 1′-H*b*), 3.34 (8H, *s*, *N*′-Me, 3′-H*b*), 5.29 (4H, *m*, 7, 7′-H), 5.68 (2H, *s*, 9″-H), 6.70 (2H, *m*, 4″-H).

Oxidation of **4** *and* **7** *with* m-*chloroperbenzoic acid.* A soln of *m*-chloroperbenzoic acid (10.0 mg) in $CHCl_3$ (1 ml) was added gradually to the stirred soln of **4** (7.0 mg) in $CHCl_3$ (1 ml), and stirring was continued for 2 hr. After evapn of the solvent, the residue was subjected to CC on silica gel eluted with $CHCl_3$–MeOH–H_2O (9:1:0.1–7:3:0.5) to provide compound **9** (2.6 mg). By the same method, **9** (2.0 mg) was prepd from incarvine A (**7**) (5.0 mg). $[\alpha]_D^{27}$ -6.0° ($c = 0.44$, CH_3OH). Positive FAB-MS *m/z* (rel. int.): 561 (44) $[M+1]^+$, 380 (7), 281 (7), 182 (100); ^{1}H NMR (CD_3OD): δ 0.95 (each 3H, *d*, $J = 7.3$ Hz, 4, 4′-Me), 0.97, 1.00 (each 3H, *d*, $J = 7.3$ Hz, 8, 8′-Me), 1.66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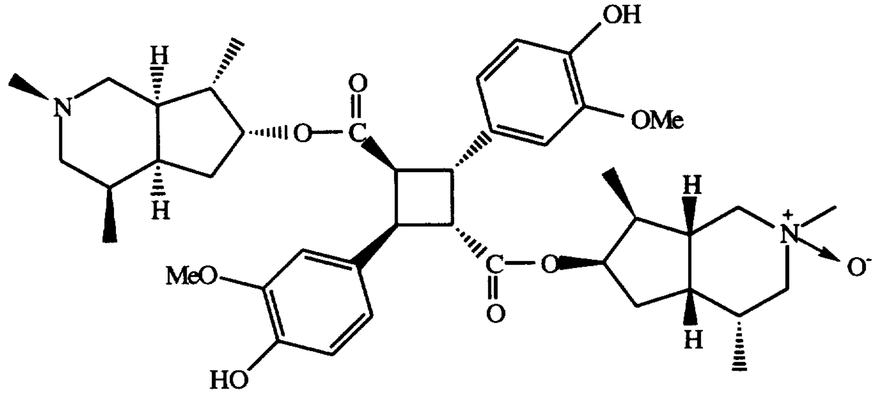
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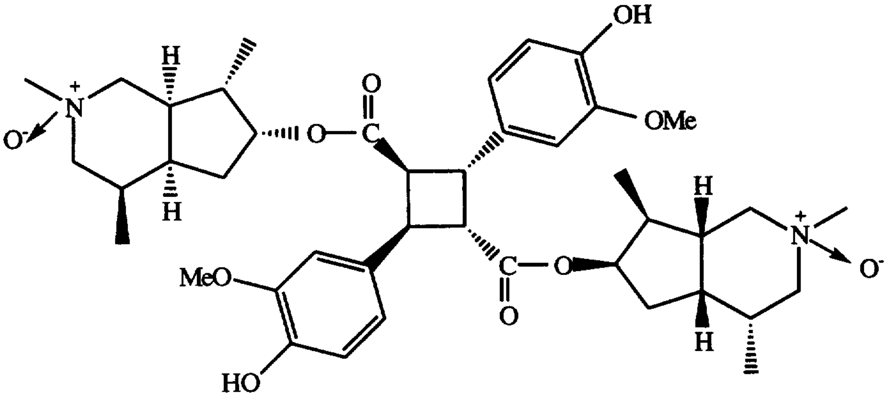
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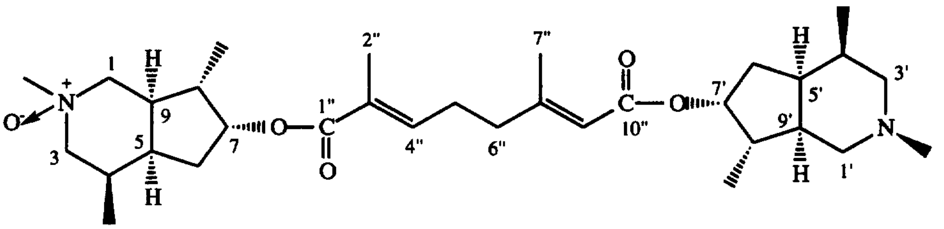
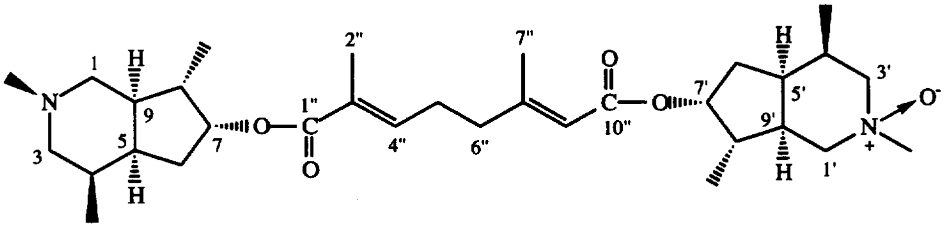


4 a



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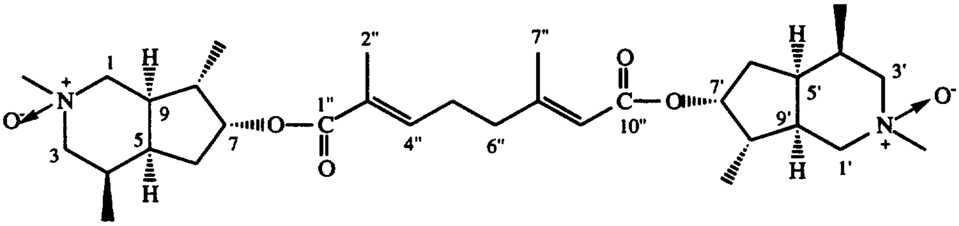

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(2H, *m*, 6, 6′-H*a*), 1.84 (3H, *s*, 2″-Me), 1.94–2.12 (4H, *m*, 6, 6′-H*b*, 8, 8′-H), 2.17 (3H, *d*, *J* = 1.2 Hz, 7″-Me), 2.34 (2H, *m*, 6″-H), 2.45 (6H, *m*, 5, 5′, 9, 9′,5″-H), 2.71 (2H, *m*, 4, 4′-H*a*), 3.00 (4H, *m*, 1, 1′, 3, 3′-H*a*), 3.10 (2H, *m*, 3, 3′-H*b*), 3.17 (2H, *m*, 1, 1′-H*b*), 3.19 (6H, *s*, *N*, *N*′-Me), 5.29 (2H, *m*, 7, 7′-H), 5.71 (1H, *m*, 9″-H), 6.73 (1H, *m*, 4″-H).

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