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EPIMERIC PAVINE *N*-OXIDES FROM *THALICTRUM SIMPLEX*

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Key Word Index—*Thalictrum simplex*; Ranunculaceae; pavine alkaloid *N*-oxides; aporphine alkaloid *N*-oxides; thalimonine *N*-oxide A; thalimonine *N*-oxide B; leucoxylonine *N*-oxide.

Abstract—Two novel epimeric *N*-oxides, (−)-thalimonine *N*-oxide A and (−)-thalimonine *N*-oxide B isolated as mixture from *Thalictrum simplex* were separated by reverse-phase HPLC. The structures of the epimers were established by spectral analysis and confirmed by synthesis. The IR spectral absorption band of Me–N^+–O^- group of each epimer was ascertained. The known aporphine alkaloid (+)-leucoxylonine was isolated for the first time from a member of the Ranunculaceae, together with the new (+)-leucoxylonine *N*-oxide.

INTRODUCTION

Two pavine *N*-oxides, (−)-argemonine *N*-oxide and (−)-eschscholtzine *N*-oxide isolated from the Papaveraceae, are the pavine alkaloids known so far [1]. Recently, argemonine *N*-oxide was found in *Thalictrum minus* and *T. foetidum* of the Ranunculaceae [2, 3]. Aporphine *N*-oxides have been isolated from the Annonaceae, Berberidaceae, Lauraceae, Magnoliaceae, Menispermaceae, Monimiaceae, Papaveraceae and Ranunculaceae [4–7]. The phenanthrene derivative, thalicthuberine *N*-oxide, was also found in species of the Ranunculaceae [8].

The main alkaloid in the aerial parts of *T. simplex* is the pavine base, (−)-thalimonine [9]. Two other laevorotatory pavine bases, (−)-2-demethylthalimonine and (−)-9-demethylthalimonine, were isolated as minor components from the same species [10]. Ongoing studies of the alkaloid content of *T. simplex* have now allowed the isolation and structural elucidation of two novel laevorotatory epimeric pavine *N*-oxides, (−)-thalimonine *N*-oxide A (**1**) and (−)-thalimonine *N*-oxide B (**2**), together with the known aporphine base, (+)-leucoxylonine (**4**), and a novel dextrorotatory (+)-leucoxylonine *N*-oxide (**5**).

RESULTS AND DISCUSSION

A polar fraction eluted from column chromatography of the crude alkaloid mixture of *T. simplex* was subjected to gel filtration on a Sephadex LH-20 column. Several fractions separated according to molecular size were collected. One of these fractions looked as a pure substance according to TLC behaviour, IR and UV spectral examinations. Because of its false multiplicity, its ^{1}H NMR spectrum led us to suppose that the sample represents a mixture of diastereoisomeric *N*-oxides of (−)-thalimonine (Table 1). The mixture was separated by preparative reverse-phase HPLC. The IR spectra of the separated isomers **1** and **2** are similar in all absorptions except for one, situated at 1080 cm^{-1} in the spectrum of **1** and at 1090 cm^{-1} in the spectrum of **2**. Both absorptions are present in the spectrum of the mixture but they are absent in the IR spectra of the previously isolated free pavine bases, (−)-thalimonine, (−)-2-demethylthalimonine and (−)-9-demethylthalimonine [9, 10]. Comparison of the IR spectra of free pavine bases with those of the mixture from epimeric pavine *N*-oxides and of individual pavine epimer *N*-oxides allowed us to ascribe the absorption band at 1080 to Me–N^+–O^- of **1** and that at 1090 cm^{-1} to the same group in **2**.

Both alkaloids show the same EI mass spectral fragmentation pattern, with only the intensity of some signals being different. A weak $[M]^+$ is present in both cases, together with the base fragment at *m/z* 204 and the next most intensive fragment at *m/z* 218. All other important signals are similar to those found in the spectrum of (−)-thalimonine itself [9]. Spectra of both epimers show the expulsion of 16 amu from $[M]^+$, which is typical for *N*-oxides [11], as well as the $[M]^+$ of dehydrogenation products at *m/z* 383 $[M-2]^+$. The signal of highest mass but of low intensity under soft ionization condition like chemical ionization (Cl; NH_3) at *m/z* 386 can be attributed to $[M+1]^+$.

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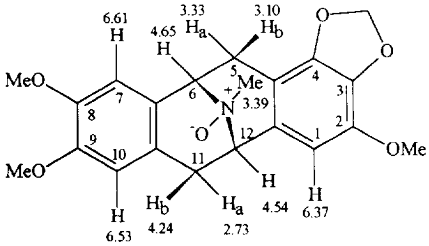
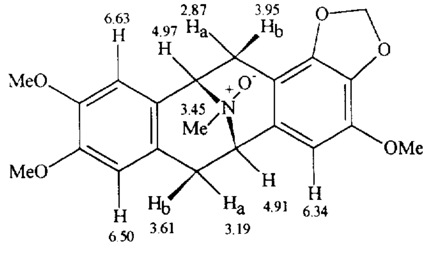


1

(-)-Thalimonine *N*-oxide A



2

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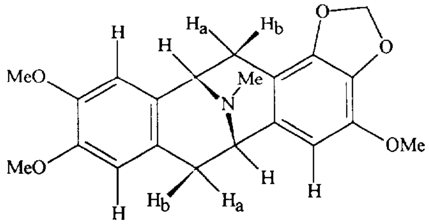
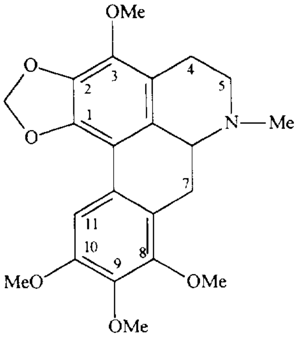


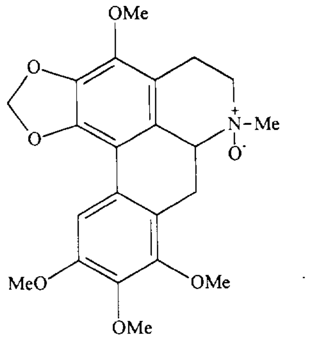
3

(-)-Thalimonine



4

(+)-Leucoxylonine



5

(+)-Leucoxylonine *N*-oxide

In the ^{1}H NMR spectrum of each epimer, a noticeable chemical shift from those of (−)-thalimonine (**3**) is observed not only for the signals of the MeN group but also for the two sets of aliphatic AMX spin systems (H-5a, H-5b, H-6 and H-11a, H-11b, H-12), which are characteristics of pavine alkaloids [12]. There is no big difference between chemical shifts of MeN signals of **1** and **2**. The signal of the MeN group of **1** is found at $\delta 3.39$ ($\delta(\mathbf{1}) - \delta(\mathbf{3}) = 0.86$) and of **2** at $\delta 3.45$ ($\delta(\mathbf{2}) - \delta(\mathbf{3}) = 0.92$). The downfield shifts involving the bridgehead protons H-6 and H-12 greater in **2** than those of **1**. Thus, the H-6 proton of **2** is shifted to $\delta 4.97$ ($\delta(\mathbf{2}) - \delta(\mathbf{3}) = 0.94$) and H-12 to $\delta 4.91$ ($\delta(\mathbf{2}) - \delta(\mathbf{3}) = 0.88$), respectively, while the H-6 proton of **1** is found at $\delta 4.65$ ($\delta(\mathbf{1}) - \delta(\mathbf{3}) = 0.62$) and at H-12 at $\delta 4.54$ ($\delta(\mathbf{1}) - \delta(\mathbf{3}) = 0.51$). The H-5b methylene proton of **2** is shifted downfield to $\delta 3.95$ ($\delta(\mathbf{2}) - \delta(\mathbf{1}) = 0.85$) but, on the other hand, the H-11b proton of **1** is shifted more downfield at $\delta 4.24$ ($\delta(\mathbf{1}) - \delta(\mathbf{2}) = 0.63$ ppm) than the H-11b of **2**. The H-5a proton of **1** is shifted downfield from the H-5a proton of **2** at $\delta 3.33$ ($\delta(\mathbf{1}) - \delta(\mathbf{2}) = 0.46$) and conversely the H-11a proton of **2** is shifted downfield more than H-11a of **1** at $\delta 3.19$ ($\delta(\mathbf{2}) - \delta(\mathbf{1}) = 0.46$). The different downfield shifts between H-5b and H-11b protons of epimers **1** and **2** could be due to the influence of the neighbouring oxygen atom and allowed us to suppose the relative configuration of the nitrogen atom of **1** and **2**. Partial NOE experiments were carried out in order to confirm the structures **1** and **2**. Irradiation of the MeN group ($\delta 3.39$) of **1** affects enhancement of the H-5b proton

Table 1. ^{1}H NMR spectral data of alkaloids **1**–**3** (δ in $CDCl_3$ at 300 MHz)

H	Compound **1**	 **2**	 **3**
1	6.37 *s*	6.34 *s*	6.32 *s*
5a	3.33 *d* (17.2)	2.87 *d* (16.3)	2.63 *s*
5b	3.10 *d* (5.9)	3.95 *dd* (5.8, 16.3)	3.20 *dd* (5.9, 16.5)
6	4.65 *d* (5.7)	4.97 *t*	4.03 *t*
7	6.61 *s*	6.63 *s*	6.61 *s*
10	6.53 *s*	6.50 *s*	6.45 *s*
11a	2.73 *d* (16.0)	3.19 *d* (17.5)	2.56 *s*
11b	4.24 *dd* (5.8, 16.0)	3.61 *dd* (6.1, 17.5)	3.41 *dd* (5.9, 16.2)
12	4.54 *d* (5.7)	4.91 *dd* (6.8, 16.3)	4.03 *t*
2-OMe	3.90 *s*	3.89 *s*	3.86 *s*
8-OMe	3.85 *s*	3.86 *s*	3.84 *s*
9-OMe	3.80 *s*	3.81 *s*	3.78 *s*
3,4-OCH_2O	5.95 *dd* (1.4, 26.7)	5.91 *dd* (1.4, 13.0)	5.88 *dd* (1.4, 23.2)
NMe	3.39 *s*	3.45 *s*	2.53 *s*

Coupling constants (*J* in Hz) given in parentheses.

Table 2. ^{13}C NMR spectral data of alkaloids **1**–**3** (δ in $CDCl_3$ at 75.5 MHz)

C	Compound **1**	 **2**	 **3**
1	106.0	106.2	106.3
2	146.2	146.1	146.3
3	143.4	143.2	142.3
4	142.9	142.2	142.3
4a	135.0	135.5	132.5
5	31.5	29.9	27.6
6	69.9	70.0	56.4
6a	126.0	124.4	129.8
7	111.1	111.0	110.4
8	148.2	147.9	147.8
9	148.6	148.1	148.2
10	110.0	110.0	111.3
10a	121.4	121.5	123.9
11	35.0	35.7	34.2
12	70.6	69.8	56.7
12a	129.6	129.6	129.8
2-OMe	56.7	56.5	55.9
8-OMe	56.1	56.0	55.4
9-OMe	55.8	55.8	55.7
3,4-OCH_2O	101.8	101.5	101.3
N-Me	76.6	77.0	40.8

(δ3.10), of H-6 (δ4.65) and of H-12 (δ4.54). Irradiation of the aromatic singlet H-7 (δ6.61) of **1** shows the adjacent relationships with H-5a (δ3.33) and H-6 (δ4.65) aliphatic protons. The MeN signal of **2** (δ3.45) correlated with H-11b (δ3.61), H-6 (δ4.97) and H-12 (δ4.91). Irradiation of H-11a (δ3.19) of **2** affects the aromatic singlets H-1 (δ6.34) and H-10 (δ6.50) and shows strong coupling with the other geminal proton H-11b (δ3.61). On the other hand, irradiation of the methine H-12 proton (δ4.91) of **2** effects H-1 (δ6.34), MeN (δ3.45) and gave reversed NOE on H-11b (δ3.61). The results of partial NOE experiments thus allowed us to ascertain the structures **1** and **2** for each of the epimeric *N*-oxides.

In the ^{13}C NMR spectra of the both epimeric *N*-oxides are observed, as expected, downfield shifts for the MeN C atoms, resulting from the influence of the N–O dipole. The MeN C atom of **1** is shifted at δ76.6 ($\delta(\mathbf{1}) - \delta(\mathbf{3}) = 35.8$) and of **2** at δ77.0 ($\delta(\mathbf{2}) - \delta(\mathbf{3}) = 36.2$). The large downfield shifts involve the methine C-6 atoms of **1** at δ69.9 ($\delta(\mathbf{1}) - \delta(\mathbf{3}) = 13.5$) and of **2** at δ70.0 ($\delta(\mathbf{1}) - \delta(\mathbf{3}) = 13.6$) and C-12 of **1** at δ70.6 ($\delta(\mathbf{1}) - \delta(\mathbf{3}) = 13.9$) and C-12 of **2** at δ69.8 ($\delta(\mathbf{2}) - \delta(\mathbf{3}) = 13.1$), respectively. The methylene atoms C-5 and C-11 are also shifted downfield compared with those of the free base **3** (Table 2). These are the first published ^{13}C NMR spectra of pavine *N*-oxides.

Authentic samples of (−)-thalimonine *N*-oxides were prepared by oxidation of the free base at 4° and 22°. Only 60% of the free base was successfully oxidized during one week regardless of temperature. These experiments showed that oxidation of pavine base is difficult and a time-consuming process. It excludes the artificial formation of the *N*-oxides during extraction and separation. Oxidation of the free base yielded a mixture of the two epimers. The synthetic mixture was subjected to the same procedure of purification and separation as the natural one. All spectral data as well as R_t value on analytical HPLC of the synthetic epimers are identical with those of the natural products, (−)-thalimonine *N*-oxide A (**1**) and (−)-thalimonine *N*-oxide B (**2**). Both alkaloids have the same absolute configuration as (−)-thalimonine, which is still unknown [9].

Two dextrorotatory alkaloids, **4** and **5**, were isolated as minor components. Alkaloid **4** was eluted with MeOH–Et_2O (1 : 1) from a column of neutral alumina. All physical data of **4** were similar to those published for the known alkaloid (+)-leucoxylonine, found previously only in *Ocotea leucoxylon* (Lauraceae) [5]. Thus, alkaloid **4** was identified as (+)-leucoxylonine. It is the first aporphine alkaloid isolated from a plant species of the

Ranunculaceae with six additional substituents in the aromatic rings. The other aporphine alkaloid **5** was separated from (−)-thalimonine *N*-oxides by gel filtration on a Sephadex LH-20 column. The IR spectrum of **5** is similar to that of (+)-leucoxylonine. Only two absorptions of **5** are different from those of **4**, the band at 1120 cm^{-1} ($\tilde{\nu}(5) - \tilde{\nu}(4) = 10$ cm^{-1}) and those at 949 cm^{-1} ($\tilde{\nu}$ (5) − $\tilde{\nu}$ (4) = 9 cm^{-1}). The ^{1}H NMR spectrum of **5** is also similar to that of **4** with the exception of the signal of MeN which is shifted downfield to δ3.25 ($\delta(5) - \delta(4) = 0.68$). The [M]$^+$ is absent in the EI mass spectrum of **5** but the [M − 16]$^+$ at *m/z* 399, typical for *N*-oxides, is present [11]. The [M + H]$^+$ ion of **5** at *m/z* 416 is of low intensity. Compound **5** showed dextrorotation as does (+)-leucoxylonine (**4**). The ^{1}H NMR and mass spectral data, as well as the right-handed optical property of **5**, established the structure of this alkaloid as the new (+)-leucoxylonine *N*-oxide.

EXPERIMENTAL

Plant material. Aerial parts of *T. simplex* were collected near Ulan Bator during the full flowering period at the end of July 1991. The species was identified by Prof. Ch. Sanchill and Prof. E. Ganbold (Institute of Botany, Mongolian Academy of Sciences). A voucher specimen (No 83) is deposited in the Herbarium of the Institute of Botany, Mongolian Academy of Sciences, Ulan Bator.

Extraction and isolation. Dried and ground plant material (1.5 kg) was extracted successively with cold petrol and EtOH. The EtOH extracts were evapd *in vacuo* and the residue treated as described previously [8–10]. Gel filtration on a column of Sephadex LH-20 using Me_2CO as eluent yielded 20 mg of a mixt. of epimers **1** + **2** and 1.5 mg of **5**. The mixt. of epimers was subjected to prep. reverse-phase HPLC (EtOH–1.5% aq. soln ortho H_3PO_4, 3:17) to obtain the pure pavine *N*-oxides epimers, **1** and **2**.

(−)-*Thalimonine* N-*oxide A* [= (−)-2,8,9-*trimethoxy*-3,4-*methylenedioxypavinane* N-*oxide A*, $C_{21}H_{23}NO_6$ (**1**, 3 mg)]. $[\alpha]_D^{21}$ − 53.3° (MeOH; *c* 0.05). CD: $\Delta\varepsilon_{294}$ + 0.10, $\Delta\varepsilon_{288}$ − 0.14, $\Delta\varepsilon_{276}$ + 1.61, $\Delta\varepsilon_{261}$ + 0.45 (sh), $\Delta\varepsilon_{236}$ − 8.12, $\Delta\varepsilon_{218}$ + 15.22, $\Delta\varepsilon_{205}$ − 39.70. UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 284 (3.28), 251 (3.27). IR $\tilde{\nu}_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3000, 2920, 2845, 1730, 1650, 1610, 1519, 1465, 1345, 1250, 1135, 1080 [Me–N$^+$–O]$^-$, 1055, 1000, 980, 905, 870, 850, 820. ^{1}H NMR: Table 1. NOE correlations (rel. %): H-1/H-11a (2.7), H-1/H-12 (6.0), H 1/2-OMe (7.6), H-7/H-5a (2.5), H-7/H-6 (4.7), H-7/8-OMe (8.2), H-10/H-11a (3.4), H-10/9-OMe (9.0), H-11b/H-11a (25.8), H-11b/H-12 (6.3), MeN/H-5b (6.0), MeN/H-6 (5.8), MeN/H-12 (5.6). ^{13}C NMR: Table 2. EIMS 70 eV *m/z* (rel. int.): 385 [M]$^+$ (2), 383 (3), 370 (6), 369 (21), 368 (9), 355 (6), 354 (8), 218 (53), 205 (13), 204 (100), 191 (10), 190 (32), 188 (8), 77 (13), 57 (11), 55 (11). CIMS (NH_3) 70 eV *m/z* (rel. int.): 386 [M + H]$^+$ (6), 371 (18), 370 (100), 369 (8), 356 (22).

(−)-*Thalimonine* N-*oxide B* [= (−)-2,8,9-*trimethoxy*-3,4-*methylenedioxypavinane* N-*oxide B*, $C_{21}H_{23}NO_6$ (**2**, 3 mg)]. $[\alpha]_D^{21}$ − 80.0° (MeOH; *c* 0.02). CD: $\Delta\varepsilon_{294}$ + 0.05, $\Delta\varepsilon_{287}$ − 0.23, $\Delta\varepsilon_{274}$ + 1.17, $\Delta\varepsilon_{262}$ + 0.32 (sh), $\Delta\varepsilon_{237}$ − 8.86, $\Delta\varepsilon_{219}$ + 11.47, $\Delta\varepsilon_{206}$ − 36.25. UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 277 (3.34), 246 (3.34). IR $\tilde{\nu}_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3000, 2920, 2845, 1730, 1650, 1610, 1519, 1465, 1345, 1250, 1135, 1090 [Me–N$^+$–O]$^-$, 1055, 1000, 980, 905, 870, 850, 820. ^{1}H NMR: Table 1. NOE correlations (rel. %): H-1/2-OMe (7.5), H-5a/H-5b (21.4), H-5b/H-5a (23.8), H-5b/H-6 (7.4), H-6/H-5b (3.9), H-6/H-5a (1.9), H-6/H-7 (6.1), H-6/NMe (4.3), H-7/8-OMe (8.8), H-10/9-OMe (9.9), H-11b/H-11a (12.1), H-11a/H-11b (19.2), H-11a/H-1 (5.9), H-11a/H-10 (5.9), H-11b/H-12 (3.7), H-12/H-11b (2.5), H-12/H-1 (5.8), H-12/MeN (8.0). MeN/H-11b (3.2), MeN/H-12 and MeN/H-6 (6.7). ^{13}C NMR: Table 2. EIMS 70 eV *m/z* (rel. int.): 385 [M]$^+$ (3), 383 (4), 370 (5), 369 (21), 368 (12), 355 (7), 354 (8), 218 (48), 205 (13), 204 (100), 191 (5), 190 (29), 188 (6), 77 (10), 57 (6), 55 (6). CIMS (NH_3) 70 eV *m/z* (rel. int.): 386 [M + H]$^+$ (1), 371 (7), 370 (100).

Prepn of (−)-*thalimonine* N-*oxides.* To 1 ml of a cooled stirred soln of (−)-thalimonine (16 mg, 0.043 mmol) in EtOH (UV grade) were slowly added 0.3 ml H_2O_2 30% v/v during 1 hr. The soln was stirred 48 hr at 4°, then 6 mg K_2CO_3 was added and stirring continued during the next 24 hr at 4° and then 4 days at 22°. The solvent was evapd under red. pres. and the residue treated with a satd soln of K_2CO_3 and extracted with $CHCl_3$. The solvent was evapd *in vacuo* and the residue purified by prep. TLC yielded 9.6 mg of (−)-thalimonine *N*-oxides and 5.5 mg unoxidized (−)-thalimonine. In the second expt, only the procedure during the first hr was performed at 4° and all further procedures were performed at 22° during 7 days. The isolated mixtures of *N*-oxides were sepd by prep. HPLC.

(+)-*Leucoxylonine* N-*oxide* [= (−)-3,8,9,10-*tetramethoxy*-1,2-*methylenedioxyaporphine* N-*oxide*, $C_{22}H_{25}NO_7$ (**5**), 1.5 mg]. $[\alpha]_D^{21}$ = + 30.9° (MeOH; *c* 0.06). CD: $\Delta\varepsilon_{305}$ − 2.17, $\Delta\varepsilon_{297}$ − 2.40, $\Delta\varepsilon_{295}$ − 2.40, $\Delta\varepsilon_{283}$ − 3.43, $\Delta\varepsilon_{245}$ + 20.03, $\Delta\varepsilon_{222}$ − 8.63, $\Delta\varepsilon_{216}$ − 6.93 (sh), $\Delta\varepsilon_{209}$ − 4.34, UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 280 (3.63). IR $\tilde{\nu}_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3600, 3000, 2930, 2850, 1730, 1630, 1600, 1580, 1495, 1465, 1425, 1400, 1350, 1260, 1140, 1120, 1055, 1000, 949, 920, 850, 660. ^{1}H NMR (300 MHz): δ7.40 (1H, *s*, H-11), 5.91 and 6.16 (2H, *dd*, *J* = 1.2 Hz OCH_2O), 4.08 (3H, *s*, 3-OMe), 3.92 (3H, *s*, OMe), 3.90 (3H, *s*, OMe), 3.89 (3H, *s*, OMe), 3.25 (3H, *s*, NMe). EIMS 70 eV *m/z* (rel. int.): 399 [M − 16]$^+$ (91), 398 (100), 385 (11), 384 (22), 368 (13), 356 (18), 325 (6), 298 (4), 169 (3), 139 (10), 97 (20), 91 (12), 83 (51), 58 (8). CIMS (NH_3) 70 eV *m/z* (rel. int.): 416 [M + H]$^+$ (2.5), 402 (4), 401 (22), 400 (100), 399 (10), 398 (28), 386 (11), 384 (3), 306 (5).

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