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Banyingela Kanyinda, Renee Vanhaelen-Fastre, Maurice Vanhaelen, and Robert Ottinger

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IDENTIFICATION BY TWO-DIMENSIONAL NMR SPECTROSCOPY OF TWO NEW BENZYLISOQUINOLINE ALKALOIDS FROM LEAVES OF *ANISOCYCLA CYMOSA*

BANYINGELA KANYINDA, RENEE VANHAELEN-FASTRE, MAURICE VANHAELEN,*

Department of Pharmacognosy and Bromatology, U.L.B., CP 205/4, Boulevard du Triomphe, B-1050 Bruxelles, Belgium

and ROBERT OTTINGER

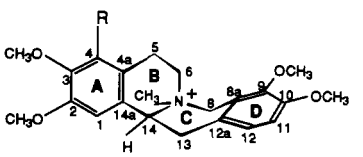
Department of Organic Chemistry, Ecole polytechnique, U.L.B., CP 165, av. F.D. Roosevelt, 50, B-1050 Bruxelles, Belgium

ABSTRACT.—Two new *N*-methyltetrahydroprotoberberines, (−)-*N*-*O*-dimethylthaicanine [**1**] and (−)-*N*-methylthaicanine [**2**] were isolated from *Anisocycla cymosa* leaves together with four other known alkaloids: (−)-*N*-methyltetrahydropalmatine [**3**], anisocycline [**4**], palmatine [**5**], and stephenanthrine [**6**]. Their structures and stereochemistry were determined by chemical and spectrometric methods, including 2D nmr experiments (^{13}C-^{1}H COSY and ^{1}H-^{1}H COSY).

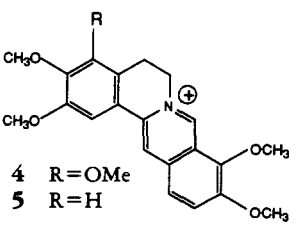
Anisocycla cymosa Troupin (Menispermaceae), a woody climber growing in Zaire (1), is used, according to the Zairian folkloric tradition, as a tonic, antipyretic, analgesic, and antirheumatic. We have previously identified in the roots several isoquinoline alkaloids: two protoberberines, anisocycline [**4**] and palmatine [**5**]; three bis-benzylisoquinolines, cocsoline, 1,2-dehydroapateline, and 1,2-dehydrotelobine; and one aporphine, remrefidine (2). This paper details the isolation from *A. cymosa* leaves and the structure elucidation of two new *N*-methyltetrahydroprotoberberine alkaloids, (−)-*N*-*O*-dimethylthaicanine [**1**] and (−)-*N*-methylthaicanine [**2**], as well as the identification of four known alkaloids: three protoberberine alkaloids (−)-*N*-methyltetrahydropalmatine [**3**], anisocycline [**4**], and palmatine [**5**]; and one phenanthrene alkaloid, stephenanthrine [**6**].

RESULTS AND DISCUSSION

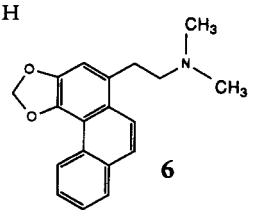
The MeOH extract of dry leaves of *A. cymosa* was fractionated as described in the Experimental, affording alkaloidal fractions B and C, which were further purified by combined cc and preparative tlc. Compounds **1**, **3**, **4**, **5**, and **6** were isolated from fraction B and compound **2** from fraction C.



1 R=OMe
2 R=OH
3 R=H



4 R=OMe
5 R=H



6

Uv spectra of **1** and **2**, which presented maxima at 230 and 280 nm, were in agreement with those observed for tetrahydroprotoberberine (3,4). Eims of **1** presented a weak molecular ion at *m/z* 400, corresponding to $C_{23}H_{30}O_5N$, and the typical fragmentation attributable to trisubstituted A and B rings of tetrahydroprotoberberine (ion at *m/z* 220) (5) as compared with **3** (ion at *m/z* 190) (5). The mol wt was ascertained by fabms, which was characterized by an $[M]^+$ ion at the expected *m/z* 400. The eims also exhibited the characteristic retro-Diels-Alder fragmentation associated with a tetrahydroprotoberberine skeleton, showing two methoxyl groups on the D ring and at least two methoxyl groups on the A ring (*m/z* 164) (6). Moreover, this spectrum was characterized by a prominent ion $[M-14]^+$ *m/z* 386 which suggested the loss of the *N*-methyl substitution. The ^{1}H-nmr spectrum gave further evidence to confirm these propositions: an *N*-methyl singlet at δ 3.66 (3H), five MeO singlets at δ 3.85, 3.86, 3.88, 3.94, and 3.95, an aromatic singlet at δ 6.71, and two aromatic doublets at δ 6.84 and 6.90 ($J=8.5$ Hz, AB system) assignable to H-11 and H-12, respectively. Consistent with the above data and biogenetic considerations, a substitution of the A ring at positions 1, 2, and 3 by MeO groups was presumed (7). With an MeO group substitution on the 1 position, the corresponding singlet characteristically appears downfield at δ about 4.11 (8–10). The absence of any MeO signal at δ about 4.11 in the ^{1}H-nmr spectrum of **1** suggested that the third MeO group was fixed on the 4 position of the A ring. Further evidence for this localization was deduced from the ^{13}C-nmr spectrum whose data are given in Table 1 and compared with those of cyclanoline, a related *N*-methyltetrahydroprotoberberine. The C-5 resonance of **1** appeared at δ 19.0; this carbon is strongly shielded because of the presence of an oxygen substituent on C-4, whereas in absence of such a substitution, the C-5 signal appears at δ 23–25.6 (10–16). Furthermore, the 2D direct ^{13}C-^{1}H chemical shift correlation (hetero COSY) spectrum showed a cross peak at δ 105.98/6.71 indicating that the aromatic singlet proton resonating at δ 6.71 (H-1) was attached to the carbon resonating at δ 105.98 (C-1). Therefore, the third MeO group was definitely located on C-4. Further examination of the hetero COSY spectrum showed that the ^{13}C-nmr resonances at δ 123.50, 113.65, 105.98, 59.94, 52.14, 19.04, 64.85, and 33.90 were to be associated to the ^{1}H-nmr resonances at δ 6.84 (H-12), 6.90 (H-11), 6.71 (H-1), 5.45 and 5.01 (H_a-8 and H_b-8), 4.06 and 3.65 (H_b-6 and H_a-6), 3.15 and 3.25 (H_a-5 and H_b-5), 3.00 and 3.51 (H_a-13 and H_b-13), and 5.66 (H-14), respectively.

Finally, structure **1** was unambiguously supported by the complete interpretation of the results of the hetero COSY and ^{1}H-^{1}H COSY spectra (data not shown) and of the ^{1}H-nmr spectrum.

The stereochemistry of **1**, and further of **2**, was deduced from ^{1}H-nmr and ^{13}C-nmr data. The ^{1}H-nmr spectrum of cis-fused quinolizidine *N*-metho salts showed the *N*-methyl singlet at δ 3.22–3.50, whereas for the trans-fused form this signal is shielded up to δ 2.83–3.06 (10, 16–19). Therefore, the *N*-methyl signal of **1** appearing at δ 3.65 suggested a cis-B/C fused protoberberine system. Furthermore, this hypothesis was enhanced by ^{13}C-nmr data; indeed, the *N*-methyl carbon of **1** was observed at δ 50.3, confirming the assignment of a cis-B/C fusion since the *N*-methyl resonance of the trans form shifts to higher fields (δ 39.0–44.5) than that of the cis form (δ 51.8–52.4) (11,13,20). In addition, this assignment of a cis-B/C fusion for **1** was also supported by the resonance values of C-6 and C-13; the C-6 signal of the cis form resonates at higher fields (δ 52.1–56.0) than that of the trans form (δ 61.8–63.8 (11,13,17), whereas the C-13 signal of the trans form shifts to higher field (δ 30–33) than that of the cis form (δ 34–35) (11,13,17,20).

The chemical correlation between **1** and *N*-methyltetrahydroanisocycline was established. This last pentasubstituted tetrahydroprotoberberine was obtained by hydro-

TABLE 1. ^{13}C-nmr (62.89 MHz) Chemical Shift Assignments[a] of **1**, **2**, and (−)-Cyclanoline.

Carbon	Compound		
	1[b]	**2**[c]	(−)-Cyclanoline[d]
C-1	106.0	108.4	113.2
C-2[e]	151.5	148.8	143.8
C-3[e]	142.0	153.6	147.6
C-4[e]	153.6	146.0	113.5
C-4a[f]	123.5	122.0	122.8
C-5	19.0	19.3	24.5
C-6	52.1	53.3	54.9
C-8	59.9	68.1	61.7
C-8a[f]	113.1	122.0	125.1
C-9[g]	151.3	152.6	145.7
C-10[g]	145.7	145.2	150.1
C-11	113.6	115.8	113.5
C-12	123.5	126.3	114.5
C-12a[f]	127.1	128.5	125.1
C-13	33.9	35.0	34.9
C-14	64.8	67.9	68.6
C-14a[f]	119.7	119.8	122.0
N-Me	50.3	51.6	52.0
2-OMe[h]	56.1	56.7	—
10-OMe[h]	56.6	56.8	57.2
3-OMe[h]	60.7	62.1	57.7
9-OMe[h]	60.9	62.1	—
4-OMe[h]	61.7	—	—

[a]In ppm, $\delta_{TMS} = 0$.
[b]In $CDCl_3$.
[c]In CF_3COOD-$CDCl_3$ (4:0.01).
[d]In CF_3COOD; data are from Yoshikawa *et al.* (11).
[e–h]Assignments may be interchanged.

genation and further *N*-methylation of **4** by MeI (2), affording a mixture (1:1) of *trans*- and *cis*-*N*-methyltetrahydroanisocycline. The ^{1}H-nmr spectrum of the mixture displayed all the signals recorded with **1**.

On the basis of all collected experimental results, we propose for this new alkaloid structure **1**, for which we suggest the name *N*-*O*-dimethylthaicanine.

Compound **2** in eims displayed a weak molecular ion at *m/z* 386 consistent with ($C_{22}H_{28}O_5N$), and gave, as described for **1**, a typical fragmentation for A and B rings of trisubstituted tetrahydroprotoberberine. The ion at *m/z* 206 was attributable to a retro-Diels-Alder fission and corresponded to A and B rings bearing two MeO groups and one OH (2,5). The phenolic nature of this last one was supported by the bathochromic shift observed in the uv spectrum after alkalinization. The fragment at *m/z* 164 corresponds to the D ring substituted by two MeO groups. Furthermore, the ms exhibited a peak $[M-14]^+$ *m/z* 372, suggesting the loss of an N-Me group. This was in agreement with the ^{1}H-nmr spectrum, which exhibited an N-Me singlet at δ 3.31, four MeO singlets at δ 3.82, 3.88, and 3.92, two aromatic doublets at δ 6.97 and 7.02 ($J = 14.3$ Hz, AB system) assignable to H-11 and H-12, and an aromatic singlet at δ 6.50 attributable to H-1.

A comparative interpretation of the ^{1}H- and ^{13}C-nmr spectra of **1** and **2** showed that the signal corresponding to a fifth MeO group at δ 61.69 was lacking in **2**. Further

evidence of the lower methoxylation degree of **2** was obtained from spectral data of its methyl ether, prepared with CH_2N_2. The uv, ms, and ^{1}H-nmr data of the methylated derivative were identical with those recorded for **1**. Compound **2** was thus identical with **1**, with the exception of the MeO group fixed on C-4 of **1**, substituted in **2** by an OH. Thus, structure **2** was assigned for this new alkaloid for which we proposed the name (−)-*N*-methylthaicanine; the stereochemistry was identical with that of **1**.

Other isolated alkaloids, *N*-methyltetrahydropalmatine [**3**], anisocycline [**4**], palmatine [**5**], and stephenanthrine [**6**], were identified by direct comparison of their tlc behavior as well as their uv, ^{1}H-nmr, and eims with those of authentic samples previously isolated (2,9,10).

EXPERIMENTAL

PLANT MATERIAL.—Leaves of *A. cymosa* were collected near Yangambi, Zaire, in April 1990, and identified by Mr. Tentula, Department of Botany, Institut de Recherches Agronomiques de Yangambi. A voucher specimen has been deposited in the Herbarium of the Institut de Recherche en Sciences de la Santé, Kinshasa, Zaire.

GENERAL EXPERIMENTAL PROCEDURES.—Mp's were measured with a Gallenkamp mp apparatus. Uv spectra were recorded on a Shimadzu UV-265FS spectrophotometer and ir spectra on a Perkin-Elmer 177 spectrophotometer. Ms were recorded wiht a VG Micromass 7070F apparatus (ei at 70 eV) and, for fab, on an AEI MS902S (glycerol as matrix). All nmr spectra were recorded, at 250 MHz for ^{1}H nmr and at 62.89 MHz for ^{13}C nmr, on a Brüker WP 250 spectrometer, using TMS as internal reference. Optical rotations were measured on a Perkin-Elmer 141 Polarimeter. Ion exchange resin Amberlite® IRA 400 (Cl^-) (Aldrich, Milwaukee, WI), silicic acid (Union Chimique Belge, RPL, Belgium), Si gel 60 (E. Merck, Darmstadt, Germany), and neutral Al_2O_3 (M. Woelm, Eschwege, Germany) were used for cc, and Si gel $60PF_{254}$ (E. Merck, Darmstadt, Germany) (layer thickness: 1.0 mm) for preparative tlc. The tlc chromatograms were visualized under uv at 254 nm and/or sprayed with Dragendorff's and potassium iodoplatinate reagents.

EXTRACTION AND ISOLATION.—Powdered dry leaves (700 g) were extracted exhaustively with MeOH (5 liters) by percolation. The MeOH extract was evaporated to dryness under reduced pressure, and the residue was taken up with 5% aqueous HCl (200 ml). After filtration, the solution was extracted several times with petroleum ether (1 liter). After alkalinization with aqueous 25% NH_4OH, the aqueous phase A was extracted seven times with $CHCl_3$ (50 ml). These combined $CHCl_3$ extracts were washed with H_2O and dried on anhydrous Na_2SO_4, then evaporated to dryness yielding the alkaloidal fraction B (30 g). The aqueous solution A, after extraction by $CHCl_3$, was acidified by 3 N aqueous HCl, and the quaternary alkaloids were then precipitated by Mayer's reagent. The precipitate was centrifuged and dissolved in

TABLE 2. Chemical Shifts and Coupling Constants of the C-1, C-5, C-6, C-8, C-11, C-12, C-13, and C-14 Protons of **1**[a].

Proton (multiplicity)	δ (ppm)	*J* (Hz)	Proton (multiplicity)	δ (ppm)	*J* (Hz)
H-1 (s)	6.71	—	H-11 (d)	6.90	—
$J_{C\text{-}1,H\text{-}1}$	—	159.8	$J_{H\text{-}11,H\text{-}12}$	—	8.5
H_a-5 (m)	3.15	—	$J_{C\text{-}11,H\text{-}11}$	—	160.1
H_b-5 (m)	3.25	—	H-12 (d)	6.84	—
$J_{C\text{-}5,H_a\text{-}5,H_b\text{-}5}$	—	132.0	$J_{H\text{-}12,H\text{-}11}$	—	8.5
H_a-6 (m)	3.65	—	$J_{C\text{-}12,H\text{-}12}$	—	161.5
H_b-6 (m)	4.06	—	H_a-13 (dd)	3.00	—
$J_{C\text{-}6,H_a\text{-}6,H_b\text{-}6}$	—	144.5	H_b-13 (dd)	3.51	—
H_a-8 (d)	5.01	—	H-14 (dd)	5.66	—
$J_{H_a\text{-}8,H_b\text{-}8}$	—	15.8	$J_{H_a\text{-}13,H_b\text{-}13}$	—	18.8
H_b-8 (d)	5.45	—	$J_{H_a\text{-}13,H_b\text{-}14}$	—	10.0
$J_{H_b\text{-}8,H_a\text{-}8}$	—	15.9	$J_{H_b\text{-}13,H\text{-}14}$	—	6.5
$J_{C\text{-}8,H_a\text{-}8,H_b\text{-}8}$	—	145.6	$J_{C\text{-}14,H\text{-}14}$	—	149.8
			$J_{C\text{-}13,H_a\text{-}13,H_b\text{-}13}$	—	132.0

[a]Spectra obtained at 250 MHz in $CDCl_3$ with TMS as an internal standard.

Me_2CO-MeOH-H_2O (6:2:1); this solution passed through an ion-exchange resin column of Amberlite® IRA 400 (Cl^-). The eluate and the column washings with Me_2CO-MeOH-H_2O (6:2:1) were combined and evaporated to dryness to afford the quaternary alkaloidal fraction C (3 g).

TREATMENT OF FRACTION B.—A fraction B aliquot (5 g), fixed on cellulose, was transferred to the top of a neutral Al_2O_3 (activity III, 150 g) column. Elution was performed with $CHCl_3$ added with increasing amounts of MeOH. Ultimate purification was obtained by preparative tlc on Si gel, using the following mobile phases: S_1, $CHCl_3$–MeOH–2-butanone–petroleum ether (20:10:4:7) and S_2, $CHCl_3$-MeOH-Me_2CO-25% aqueous NH_4OH (27:3:10:0.5). This procedure permitted the isolation of **1** (380 mg, with S_1), **3** (52 mg, with S_1), **4** (1 g, with S_1), **5** (120 mg, with S_1), and **6** (10 mg, with S_2).

TREATMENT OF FRACTION C.—Fraction C (3 g) was fractionated by cc on silicic acid (50 g) and eluted with $CHCl_3$ added with increasing percentages of MeOH. Further purification by preparative tlc on Si gel, using as solvent system $CHCl_3$-MeOH-Et_2O-25% aqueous NH_4OH (14:13:1.5:1.5), afforded **2** (120 mg).

(−)-N-O-*Dimethylthaicanine* [**1**].—White needles ($CHCl_3$): mp 218°; $[\alpha]^{20}D$ −102.8° (c = 0.020, $CHCl_3$); uv λ max (MeOH) nm (log ε) 230 (4.38), 280.9 (3.49); ir ν max (KBr) cm^{-1} 3460, 2940, 2838, 1606, 1498, 1462, 1282, 1238, 1122, 1106, 1002, 984, 920, 844, 728; ir ν max ($CHCl_3$) cm^{-1} 3446, 2942, 2840, 1606, 1498, 1462, 1282, 1238, 1122, 1024, 986, 730, 642; ^1H nmr ($CDCl_3$, 250 MHz) δ 3.0 (1H, dd, J = 18.8 Hz, H_a-13), 3.51 (1H, dd, J = 18.8 Hz, H_b-13), 3.15–3.25 (2H, m, H_a-5 and H_b-5), 3.62 (3H, s, N-Me), 3.65 (1H, m, H_a-6), 4.06 (1H, m, H_b-6), 3.84, 3.86, 3.88, 3.92, and 3.93 (15H, s, 5 × OMe), 5.02 (1H, d, J = 15.9 Hz, H_a-8), 5.45 (1H, d, J = 15.8 Hz, H_b-8), 5.66 (1H, dd, J = 6.5 and 10.0 Hz, H-14), 6.71 (1H, s, H-1), 6.85 (1H, d, J = 8.5 Hz, H-12), 6.91 (1, d, J = 8.5 Hz, H-11); ^{13}C nmr ($CDCl_3$, 62.89 MHz) see Table 1; ^1H-^{13}C-nmr and ^1H-^1H COSY data not shown; eims *m/z* (rel. int.) $[M]^+$ 400 (0.8), $[M-14]^+$ 386 (27.3), 385 (100), 384 (65.2), 369 (15.2), 354 (31.1), 222 (12.9), 220 (37.1), 164 (93.9), 149 (81.8); fabms *m/z* (rel. int.) $[M]^+$ 400 (100), $[M-14]^+$ 386 (11.9), 370 (11.9), 236 (86.9), 220 (17.9), 206 (26.2).

(−)-N-*Methylthaicanine* [**2**].—White amorphous powder: $[\alpha]^{20}D$ −102.1° (c = 0.014, MeOH); uv λ max (MeOH) nm (log ε) 230 (4.01), 279.1 (3.20); uv λ max (MeOH + NaOH) nm (log ε) 286.4 (3.44); ^1H nmr [$CDCl_3$-CD_3OD (3.9:0.1), 250 MHz] δ 3.0–3.25 (3H, m, H_a-13, H_a-5, H_b-5), 3.31 (3H, s, N-Me), 3.32–3.80 (3H, m, H_b-13, H_a-6, H_b-6), 3.82, 3.88, 3.92 (12H, s, 4 × OMe), 4.73–4.89 (3H, m, H_a-8, H_b-8, -14), 6.50 (1H, s, H-1), 6.97–7.02 (2H, dd, J = 14.3 Hz, AB system, H-11, -12); ^{13}C-nmr [CF_3COOD-$CDCl_3$ (4:0.01), 62.89 MHz] see Table 1; eims *m/z* (rel. int.) $[M]^+$ 386 (1.4), $[M-14]^+$ 372 (21.4), 371 (62.8), 370 (100), 369 (42.8), 355 (15.7), 339 (18.6), 206 (17.1), 165 (24.3), 164 (84.3), 149 (70).

METHYLATION OF **2**.—Compound **2** (8 mg) was treated with CH_2N_2 in Et_2O during 24 h; further purification by preparative tlc on Si gel afforded a product (6 mg) whose spectroscopic data (uv, ^1H nmr) were in agreement with those recorded for **1**.

REDUCTION OF **4**.—Anisocycline [**4**] (200 mg), reduced by $NaBH_4$ according to a previously described procedure (2), afforded (±)-tetrahydroanisocycline (150 mg) identical (tlc, uv, ms, nmr data) with an authentic sample of the same alkaloid we have previously identified in *A. cymosa* roots (2).

N-METHYLATION OF (±)-TETRAHYDROANISOCYCLINE.—To (±)-tetrahydroanisocycline (300 mg) in Me_2CO (10 ml), MeI (1 ml) was added and allowed to stand overnight. The insoluble material (500 mg) was filtered and crystallized from $CHCl_3$ to give white needles (200 mg), which were further recrystallized from MeOH to yield a mixture of *trans*- and *cis*-*N*-methyltetrahydroanisocycline salts. The ^1H-nmr spectrum ($CDCl_3$) of this mixture displayed two *N*-methyl signals, at δ 2.79 (trans) and δ 3.20 (cis). The ^1H-nmr spectrum of the mixture displayed all the signals recorded with **1**.

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