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BISBENZYLISOQUINOLINE ALKALOIDS FROM *ANISOCYCLA CYMOSA* ROOTS

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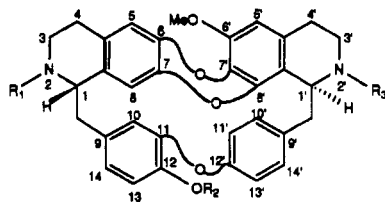
ABSTRACT.—Three new bisbenzylisoquinoline alkaloids, (+)-2'-norcocosoline [**1**], (+)-12-O-methylcocosoline-2'- β -N-oxide [**2**], and (+)-cocosoline-2'- β -N-oxide [**3**], were isolated from cc polar fractions of the roots of *Anisocyclus cymosa*, in addition to eight known bisbenzylisoquinoline, aporphine, protoberberine, and phenanthrene alkaloids previously reported. Their structures were elucidated by spectroscopic and chemical methods.

The phytochemical investigation of *Anisocyclus cymosa* Troupin (Menispermaceae), a woody climber growing in Zaire, has led to the isolation of several benzylisoquinoline alkaloids (1,2). Using Si gel cc, three new bisbenzylisoquinoline alkaloids were isolated from the CHCl₃-MeOH (1:1) fraction of the roots. All the individual alkaloids gave a green-blue color test with concentrated HNO₃-H₂SO₄ (1:9) for a dibenzodioxin system (3,4). Therefore, they all possess three diaryl ether bridges.

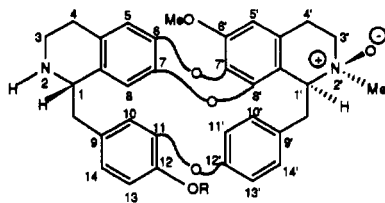
The first new alkaloid is the monophenolic (+)-2'-norcocosoline [**1**], whose spectral characteristics point to a close structural relationship with (+)-cocosoline previously isolated (1). Its eims spectrum indicated clearly a molecular peak at *m/z* 534, which was 14 mass units less than for (+)-cocosoline. An important peak at *m/z* 335, representing the upper half of the molecule due to double benzylic cleavage (5,6), was also 14 mass units less than the corresponding peak for (+)-cocosoline. The mass units difference was therefore located in the upper half of the molecule. From the comparison of the ¹H-nmr spectra of **1** and (+)-cocosoline, two notable features were observed: the absence of an N-Me group signal at δ 2.58 and the downfield shift of H-1' from δ 4.02 (cocosoline) to 4.48 in **1**. These changes are typical of the replacement of

an N-Me group by an NH function (7). Treatment of (+)-norcocosoline [**1**] with formalin and formic acid afforded compound **4** with two N-Me groups, identical by direct comparison (uv, ¹H nmr, eims) to authentic (+)-cocosoline (8-11). Compound **1** is therefore identified as (+)-2'-norcocosoline.

The second new alkaloid is (+)-12-O-methylcocosoline-2'- β -N-oxide [**2**]. Its eims spectrum showed a small molecular peak at *m/z* 578 together with a somewhat stronger *m/z* 576 [M-2]⁺. This molecular peak was 16 mass units more than that of (+)-12-O-methylcocosoline [**5**] (1,6,12). Such an [M-2]⁺ ion is often encountered in bisbenzylisoquinoline N-oxides (7). The prominent [M-16]⁺ ion was related to the loss of oxygen from the molecular ion; it is characteristic for N-oxides (13-15). The other major fragmentation pattern was similar to the one found in the ms spectrum of (+)-12-O-methylcocosoline [**5**]. The ¹H-nmr spectrum was very close to that of **5**. However, a remarkable difference prevailed with the absorption for the 2'-N-methyl group at δ 3.31 and that for H-1' at δ 4.47, which were both shifted downfield. The 2'-N-methyl singlet at δ 3.31 and the H-1' at δ 4.50 are characteristic for a trans relationship between the N-oxide oxygen and H-1' (7, 15-17). The presence of an nOe effect between H-1' (δ



- 1** $R_1 = R_2 = R_3 = H$
4 $R_1 = R_3 = Me, R_2 = H$
5 $R_1 = H, R_2 = R_3 = Me$
6 $R_1 = R_2 = H, R_3 = Me$



- 2** $R = Me$
3 $R = H$

4.50) and 2'-*N*-methyl singlet (δ 3.31) confirmed this *trans* relationship (18) as expected for a bisbenzylisoquinoline incorporating 7-8' and 11-12' ether linkages.

Finally, treatment of **2** with zinc powder and 10% HCl afforded **5**, which was identified as (+)-12-*O*-methylcoccoline by direct comparison (eims, 1H nmr, tlc) with an authentic sample.

The third new alkaloid was the monophenolic (+)-coccoline-2'- β -*N*-oxide [**3**], which showed an ms molecular ion 14 mass units less than for **2**, while the general fragmentation pattern was very close to that for **2** and **1**. The 1H -nmr spectrum of **3** was also close to that for **2**. The main difference was the absence of a second MeO group singlet at δ 3.90 in the spectrum of **3**. This indicated that C-12 in **3** bears a phenolic function rather than an MeO group. The 2'-*N*-methyl singlet at δ 3.22 and the H-1' multiplet at δ 4.50 argued in favor of the *trans* relationship between the *N*-oxide oxygen and H-1' as shown in **2** (7, 15-17). The reduction of (+)-coccoline-2'- β -*N*-oxide [**3**] by zinc powder and 10% HCl afforded **6**, which was identified as (+)-

coccoline by direct comparison (eims, 1H nmr, tlc) with an authentic sample (1,8,11,19).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ms was recorded at 70 eV with a VG Micromass 7070F apparatus. 1H -nmr spectra were recorded at 250 MHz on a Brücker WP250 spectrometer using TMS as internal standard. Uv spectra in MeOH were obtained on a Shimadzu UV-265FS spectrophotometer. Neutral Al_2O_3 (M. Woehlm, Eschwege, Germany) and Si gel 60 (230-400 mesh ASTM, E. Merck, Darmstadt, Germany) were used for cc. Preparative tlc (layer thickness 1.0 mm) was performed on Si gel 60 PF₂₅₄ (E. Merck, Darmstadt, Germany), and the alkaloids were detected under uv light (254 nm) and/or by potassium iodoplatinate and Dragendorff's reagents.

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

EXTRACTION AND ISOLATION.—Extraction and isolation were performed as described previously (1,2). The polar tertiary alkaloidal fraction from cc was subjected to preparative tlc with $CHCl_3$ -MeOH-Me₂CO-25% NH_4OH (30:4:3:0.5) and yielded the

TABLE 1. ¹H-nmr Data for Compounds 1–6 (250 MHz).^a

Proton	Compound					
	1	4 ^b	2	5 ^b	3	6 ^b
H-1	3.73 m	3.40 m	3.78 m	3.62 m	3.72 m	3.62 m
H-1'	4.37 m	4.04 m	4.42 m	4.01 m	4.45 m	3.95 m
H-5	6.64 s	6.66 s	6.65 s	6.63 s	6.69 s	6.62 s
H-5'	6.35 s	6.35 s	6.39 s	6.33 s	6.43 s	6.32
H-8	6.21 s	6.23 s	6.24 s	6.20 s	6.28 s	6.18 s
H-10	6.49 br s	6.54	6.57 d	6.63 s	6.50 br s	6.56 br s
H-10'	7.06 dd (8.3,2.5)	7.14 dd (8.3,2.0)	7.06 dd (8.3,2.0)	7.11 dd (8.2,2.0)	7.05 dd (8.3,2.0)	7.11 d (8.3,2.1)
H-11'	6.79 dd (8.3,2.5)	6.80 dd (8.3,2.5)	6.81 dd (8.2,2.5)	6.86 dd (8.5,2.6)	6.77 dd (8.5,2.5)	6.81 dd (6.6,2.5)
H-13	6.92 br s	6.94 br s	6.92 br s	6.90 br s	6.92 br s	6.90 br s
H-13'	7.17 dd (8.3,2.5)	7.22 dd (8.3,2.5)	7.20 dd (8.5,2.5)	7.22 dd (8.3,2.5)	7.20 dd (8.2,2.0)	7.18 dd (8.3,2.1)
H-14	6.92 br s	6.94 br s	6.92 br s	6.90 br s	6.92 br s	6.90 br s
H-14'	7.62 dd (8.3,1.9)	7.63 dd (7.6,1.8)	8.04 dd (7.5,1.8)	7.54 dd (8.4,2.0)	7.94 dd (8.4,1.9)	7.52 dd (8.3,2.0)
N-2Me		2.42				
N-2'Me		2.61	3.30	2.60	3.22	2.58
6'-OMe	3.85	3.87	3.88	3.86	3.89	3.86
12-OMe			3.95	3.96		

^aJ values are in parentheses and reported in Hz; chemical shifts are given in δ units (downfield TMS). Data for 1–3 were recorded in CDCl₃-CD₃OD (4:0.04); for 4–6 in CDCl₃.

^bAssignments for these compounds are from the literature (5, 12, 20–22).

new alkaloids **1** (12 mg), **2** (10 mg), and **3** (9 mg).

(+)-*Norcoccoline* [**1**].—Amorphous powder: uv λ max (MeOH) nm 287, 234; eims *m/z* (rel. int.) [M]⁺ 534 (73), [M-1]⁺ 533 (85), 322 (91), 321 (100), 307 (34), 161 (19); ¹H nmr see Table 1.

(+)-12-O-Methylcoccoline-2'- β -N-oxide [**2**].—Amorphous powder: uv λ max (MeOH) nm 283, 237; eims *m/z* (rel. int.) [M]⁺ 578 (29), [M-16]⁺ 563 (75), 349 (74), 335 (100), 321 (53), 175 (58), 168 (53); ¹H nmr see Table 1.

(+)-Coccoline-2'- β -N-oxide [**3**].—Amorphous powder: uv λ max (MeOH) nm 283, 235; eims *m/z* (rel. int.) [M]⁺ 564 (28), [M-16]⁺ 548 (72), 349 (82), 336 (35), 335 (100), 321 (44), 175 (76), 168 (80); ¹H nmr see Table 1.

N-METHYLATION OF (+)-NORCOCSOLINE [**1**].—The solution of **1** (6 mg) in MeOH (2 ml) added with HCO₂H (88%) (2 ml) and formaldehyde (37%) (1.0 ml) was heated under reflux for 24 h. Workup provided **4** (3 mg); spectroscopic data (uv, ¹H-nmr, eims, tlc) were in agreement with those recorded for coccoline (6–9). Uv λ max (MeOH) nm 284, 235; eims *m/z* (rel. int.) [M]⁺ 562, 350, 349, 336, 335, 175; ¹H nmr see Table 1.

REDUCTION OF (+)-12-O-METHYLCOCOSOLINE-2'- β -OXIDE [**2**].—Compound **2** (4 mg) was stirred at room temperature for 2 h with zinc powder (20 mg) in 10% HCl (5 ml). Workup afforded **5** identical to (+)-12-O-methylcoccoline (uv, ¹H-nmr, eims, tlc) previously isolated (1,6,12). Uv λ max (MeOH) nm 287, 235; eims *m/z* (rel. int.) [M]⁺ 562, 349, 336, 335, 321, 168; ¹H nmr see Table 1.

REDUCTION OF (+)-COCSOLINE-2'- β -N-OXIDE [**3**].—Compound **3** (4 mg) was treated as described above to afford **6** identical by direct comparison (uv, ¹H-nmr, eims, tlc) to authentic coccoline previously isolated (1,8,11,19). Uv λ max (MeOH) nm 287, 234; eims *m/z* (rel. int.) [M]⁺ 548, 349, 336, 335, 321, 168; ¹H nmr see Table 1.

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