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A new natural indole and three aporphine alkaloids from *Monodora bevipes* Benth. (Annonaceae)

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ABSTRACT
Four compounds were isolated from the leaves of *Monodora brevipes* Benth. (Annonaceae). Among them, one new natural indole named 5-formylindole (**1**) and three known aporphine alkaloids: (+)-roemeroline (**2**); (+)-corydine (**3**) and (+)-menispermine (**4**). They were isolated for the first time from this species. The structures of these compounds were established according to their spectral data (NMR, SM, IR and UV).

***Key Words*:** Annonaceae, *Monodora brevipes*, aporphine alkaloids, indole.

INTRODUCTION

The genus *Monodora* (Annonaceae) comprises 16 recognized species, all being small trees confining to tropical eastern and western Africa forests (Chatrou *et al.*, 2012; Couvreur *et al.*, 2011a; Couvreur *et al.*, 2011b; Thomas *et al.*, 2015; Li *et al.*, 2017). This genus is largely used in traditional medicine to treat various diseases. Among them, *Monodora myristica* is the most known and used. Its stem bark is used in the treatment of hemorrhoids, abdominal pain, febrile diseases, constipation, fever, headache and Buruli ulcer (Yemoa *et al.*, 2008). In Nigeria, the leaves of this species are used to stop bleeding (Udeala *et al.*, 1980; Iwu *et al.*, 1987; Okafor, 1987). In addition to their medicinal potential, several species of *Monodora* are used to build housing. *Monodora* genus is a reach source of bioactive compounds like alkaloids (Leboeuf *et al.*, 1982; Kablan *et al.*, 2013, Dade *et al.*, 2017), sesquiterpenes, monoterpenes, diterpenes (Etse *et al.*, 1989), indole (Etse *et al.*, 1989) and essential oils (Fournier *et al.*, 1999; Owokotomo *et al.*, 2012; Dje *et al.*, 2016).

Monodora brevipes Benth. is one of four *Monodora* species found in Côte d'Ivoire (Kablan *et al.*, 2013). It is a small tree distributed in the southern coastal humid zones of Côte d'Ivoire. There is no use for this species in traditional medicine in Côte d'Ivoire, but it is considered as endangered species. So it was important to investigate the chemistry of this species of *Monodora*.

We report here, the isolation and characterization of a new natural indole and three known aporphine alkaloids from the leaves of *Monodora brevipes* Benth.

MATERIALS AND METHODS

The NMR spectra were recorded on Brüker Advance-300 operating at 300 MHz, using TMS as internal standard. Chemical shifts were quoted in *d* ppm and coupling constant *J* was measured in Hertz (Hz). One-dimensional ^{1}H and ^{13}C spectra were acquired under standard conditions. Currently, ^{1}H–^{1}H homonuclear (COSY, NOESY) and ^{1}H–^{13}C heteronuclear (HSQC, HMBC) correlation techniques were routinely applied in field of constitutional analysis. These techniques were recorded on Brücker Avance-400 operating at 400 MHz. Column chromatography was performed on silica gel (Kieselgel 60, particle size 0.040–0.063 mm) and Sephadex®LH-20. TLC was run on silica gel precoated glass plates (Merck silica gel 60 F254). Spots were detected by spraying with Dragendorff's reagent or 50% H_2SO_4 and phosphomolibdic acid. This operation was followed by a heating.

ESIMS Mass spectra were obtained with ITQ 900 spectrometer using an Agilent DB-5HT (30 x0.32 x 0.1) column. Gas chromatography was performed on TRACE GC ULTRA Thermo Scientific instrument. HR-ESIMS were run

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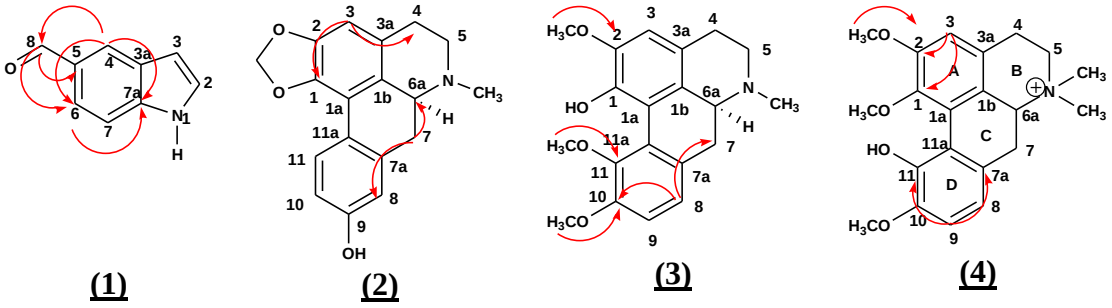

Figure 1: Structures of compounds **1**, **2**, **3** and **4**. ( ) HMBC correlation

on a TOF LCT Premier WATERS coupling with HPLC Alliance 2695 (Waters) and also with micrOTOFq Brüker. IR spectra were measured on Brüker Vector 22.

Polarimeter Optical rotations were recorded on an Optical Activity PolAAr 32. Polarimter using a sample concentration of 10 mg/ml, unless otherwise specified.

Plant material

The leaves of *Monodora brevipes* were collected in August 2010 in Diapodoumé (South of Côte d'Ivoire). They were identified by Pr. Aké Assi (Centre National de Floristique-Université Félix Houphouët Boigny de Cocody-Abidjan). A voucher specimen (n° MB-DADE-Diapodoumé2010-1) is deposited at the Herbarium of the Botanic Laboratory (Université Félix Houphouët Boigny de Cocody-Abidjan).

Isolation

Air-dried pulverized leaves of *M. brevipes* (2000 g) were three times defatted with petroleum ether and successively extracted with CH_2Cl_2 and MeOH. The collected extracts were evaporated under reduced pressure to yield 11.8 g of petroleum ether extract, 6.0 g of CH_2Cl_2 extract and 2.6 g of MeOH extract. The CH_2Cl_2 extract was chromatographed over silica gel column chromatography, eluting with cyclohexane-methanol gradient systems to give seven fractions (F-1 to F-7). Fraction F-3 was purified using repeated Sephadex® LH-20 and column chromatography on silica gel, to yield 7.4 mg of compound **1** (**Fig. 1**).

The MeOH extract was chromatographied on silica gel column chromatography, eluting with AcOEt-methanol gradient systems to give seven fractions (F-1′ to F-7′). Fraction F-6′ was purified on column chromatography of Sephadex® LH-20 [CH_2Cl_2/MeOH (2:1) and CH_2Cl_2/MeOH (1:1)] to yield 6.3 mg of compound **2**, 5.2 mg of compound **3** and 5.1 mg of compound **4**. The structures of these compounds (**Fig. 1**) were established according to their spectral data (NMR, IR and MS). Their stereochemistry was proposed on the basis of optical rotation measurement, in comparison with the literature (Hocquemiller *et al.*, 1981; Spiff *et al.*, 1984; Chang *et al.*, 1995; Slvaki al., 1996; Kablan *et al.*, 2013, Dade *et al.*, 2017).

Identification of compounds 1, 2, 3 and 4

5-formylindole (**1**): Amorphous whitish solid; ^1H and ^{13}C NMR (400 MHz) data in **table 1**; IR ($CHCl_3$): υ_{max} (cm^{-1}) = 3485, 3341, 2884, 2150, 772; UV (MeOH): λ_{max} (nm) = 252.9, 300.3; ESI-MS (*m/z*): 146 $[M+H]^+$ (molecular formula C_9H_7NO).

(+)-roemeroline (**2**): Amorphous brown solid ; ^1H and ^{13}C NMR (400 MHz) data in **table 2**; $[\alpha]_D^{21}$ (O) = +29.0; c 4.8 mg/ml in MeOH; IR ($CHCl_3$): υ_{max} (cm^{-1})=3315; 1588; 982 (cm^{-1}); UV (MeOH): λ_{max} (nm) = 214.4; 279.1; HR-ESI-MS (*m/z*): 296.1280 $[M+H]^+$ (molecular formula $C_{18}H_{18}NO_3$; calc. 296.1281 mDa = 0.1).

(+)-corydine (**3**) : Amorphous brown solid ; ^1H and ^{13}C NMR (400 MHz) data in **table** 2; $[\alpha]_D^{21}$ (O) = +11.0 ; c 0.37 mg/ml in MeOH ;546 nm; IR ($CHCl_3$): υ_{max} (cm^{-1})= 2959; 1609; 1124; 1049 ; 654; UV (MeOH): λ_{max} (nm) = 221,4 ; 265.0 ; 304.0 ; 366.8; HR-ESI-MS (*m/z*)= 342.1700 $[M+H]^+$ (molecular formula $C_{20}H_{24}NO_4$; calc. 342.1703, mDa = 0.3).

(+)-menispermine (**4**): Amorphous brown solid; ^1H and ^{13}C NMR (400 MHz) data in **table** 2, $[\alpha]_D^{21}$ (O) = +22.0; c 0.67 mg/ml in MeOH; 546 nm, IR ($CHCl_3$): υ_{max} (cm^{-1}) = 2839 ; 1604 ; 1277 ; 1105; 705; UV (MeOH): λ_{max} (nm) = 221.4; 265.0 ; 304.0; HR-ESI-MS (*m/z*) = 356.1862 $[M]^+$ (molecular formula $C_{21}H_{26}NO_4$; calc. 356.1864 mDa = 0,2), SMIE : *m/z* (%) 356 $[M]^+$(16%), 325$[M-OCH_3]^+$(5%), 311$[M-H-N(CH_3)_2]^+$(92%), 296$[M-CH_3-H-N(CH_3)_2]^+$(100%), 279$[M-CH_3-H-N(CH_3)_2 - OH]^+$(25%).

RESULTS AND DISCUSSION

Compound **1** was obtained as an amorphous whitish solid. The ESI-MS analyze gave the pseudo-molecular ion at *m/z* 146 $[M+H]^+$, corresponding to the molecular formula C_9H_7NO. The ^1H NMR spectrum (**Table 1**) exhibited characteristic signals of aromatic protons at δ_H 7.47 (1H, *d*, J = 8.4 Hz, H-7), 7.78 [(1H, *dd* (8.4, 1.6), H-6)] and 8.18 (1H, H-4). These attributions were done on the basis of its HSQC experiment data. The Analysis of its ^{13}C NMR (**Table 1**) and HSQC spectra revealed the presence of nine carbons resonances, comprising six methane and three quaternary carbon atoms, which was in agreement with the molecular formula proposed. The quaternary carbon signal at δ_C 192.4 ppm suggest the presence of an aldehyde group. The HMBC spectrum shows these C-H correlations: H-8 with

Table 1: ^1H and ^{13}C NMR spectral data of 5-formylindol (**1**)

Position	1	
	^{13}C	^1H
1	-	8.51 ; 1H ; *s*
2	126.1	7.29 ; 1H ; *m*
3	104.8	6.71 ; 1H ; *m*
3a	128.1	-
4	126.1	8.18 ; 1H ; *s*
5	130.4	-
6	122.7	7.78 ; 1H ; *dd* (*J* = 8.4 ; 1.6 Hz)
7	111.8	-
7a	139.7	7.47 ; 1H ; *d* (8.4 Hz)
8	192.4	10.05 ; 1H ; *s*

Table 2: ^{1}H and ^{13}C NMR spectral data of (+)-roemeroline (**2**), (+)-corydine (**3**) and (+)-menispermine (**4**).

Position	**2**		**3**		**4**	
	^{13}C	**^{1}H**	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**
1	142.0	-	142.5	-	144.8	-
1a	116.7	-	126.6	-	122.0	-
1b	126.5	-	128.1	-	121.2	-
2	147.1	-	149.4	-	151.9	-
3	106.9	7.08, 1H, *s*	111.1	6.69, 1H, *s*	112.0	7.00, 1H, *s*
3a	126.3	-	124.0	-	120.4	-
4	28.3	3.25, 1H$_\alpha$, *d* (*J* = 11.2 Hz)	29.1	2.68, 1H$_\alpha$, *dd* (*J* = 16.0, 3.9 Hz)	124.7	3.41, 1H$_\alpha$, *d* (*J* = 3.6 Hz)
		3.56, 1H$_\beta$, *d* (*J* = 11.2 Hz)		3.18, 1H$_\beta$, *dd* (*J* = 16.0, 3.9 Hz)		3.08, 1H$_\beta$, *d* (*J* = 3.6 Hz)
5	43.1	3.56, 1H$_\alpha$, *d* (*J* = 9.2 Hz)	52.9	2.55, 1H$_\alpha$, *m*	62.7	3.83, 1H$_\alpha$, *m*
		3.93, 1H$_\beta$, *d* (*J* = 9.2 Hz)		3.05, 1H$_\beta$, *m*		3.83, 1H$_\beta$, *m*
6a	53.4	4.49, 1H, *dd* (*J* = 11.2, 2.5 Hz)	62.9	2.97, 1H, *dd* (*J* = 13.7, 3.5 Hz)	70.6	3.08, 1H, *dd* (*J* = 12.7, 3.0 Hz)
7	36.8	3.31, 1H$_\alpha$, *dd* (*J* = 14.4, 4.8 Hz)	35.6	2.44, 1H$_\alpha$, *dd* (*J* = 12.8,3.5 Hz)	31.4	2.82, 1H$_\alpha$, *m*
		3.39, 1H$_\beta$, *dd* (*J* = 14.4,4.8 Hz)		3.05, 1H$_\beta$, *dd* (*J* = 12.8,3.5 Hz)		3.43, 1H$_\beta$, *m*
7a	136.7	-	130.9	-	127.4	-
8	114.2	7.31, 1H, *s*	124.5	7.08, 1H, *s*	125.7	7.27, 1H, *d* (*J* = 8.4 Hz)
9	156.7	-	111.5	6.88, 1H, *d* (*J* = 8.0 Hz)	125.7	7.12, 1H, *d* (*J* = 8.4 Hz)
10	115.1	7.37, 1H, *d* (*J* = 8.4 Hz)	152.0	-	154.2	-
11	128.7	8.52, 1H, *d* (*J* = 8.4 Hz)	144.0	-	146.0	-
11a	123.0	-	119.4	-	126.0	-
O-CH_2-O (1)	100.8	6.50, 1H, *s*	-	-	-	-
O-CH_2-O (2)	100.8	6.63, 1H, *s*	-	-	-	-
O-CH_3(C-1)	-	-	-	-	62.2	3.71, 3H, *s*
O-CH_3(C-2)	-	-	56.2	3.91, 3H, *s*	56.6	3.93, 3H, *s*
O-CH_3(C-10)	-	-	56.2	3.90, 3H, *s*	56.6	3.93, 3H, *s*
O-CH_3(C-11)	-	-	62.9	3.73, 3H, *s*	-	-
N-$(CH_3)_1$	42.7	2.56, 3H, s	44.0	2.55, 3H, *s*	43.9	3.05, 3H, *s*
N-$(CH_3)_2$	-	-	-	-	54.3	3.37, 3H, *s*

C-4; H-4 with C-7a/C-3; H-7 with C-5; H-6 with C-4/C-7a. These correlations confirmed the fixation of carbonyl function on the carbon C-5 of the aromatic ring. In addition to the aromatic ring, this observation was confirmed by the ^{1}H-^{1}H COSY spectrum (Fig.3), which showed correlations between H-2 (δ_H 7.29, 1H, *m*) and H-3 (δ_H 6.71 1H, *m*). These correlations confirmed the presence of aromatic ring in this molecule. Coupling between H-6 (δ_H 7.78, 1H, *dd* (8.4, 1.6)) and H-7 (δ_H 7.47, 1H, *d* (8.4)) showed that an aldehyde function was attached on the C-5 of the aromatic ring. The complete assignments of compound **1** were determined with the help of ^{1}H-^{1}H COSY, HSQC and HMBC experiments. This compound belongs to indole family and it was identified as 5-*formylindole* (**Fig. 1**). It is the first time that this molecule is isolated in a plant. For this, it can be considered as a new natural product.

Compound **2** was isolated as amorphous brown solid. Its HR-ESI-MS spectrum shown the pseudo-molecular ion fragment $[M+H]^+$ at *m*/*z* 296.1280. So, its molecular formula was deduced to be $C_{18}H_{17}NO_3$ (calc. 296.1281 mDa =0.1). The NMR spectra of **2** (**Table 2**) exhibited characteristic signals at δ_H 2.56 ppm (3H, *s*) and δ_C 42.7ppm, corresponding to an aporphine alkaloid, suchlike an *N*-methyl (Kablan *et al.*, 2013; Dade *et al.*, 2017). The combined analysis of its ^{13}C NMR and HSQC spectra revealed the presence of eighteen carbons: five methine, four methylene and eight quaternary carbon atoms. These data are in agreement with the proposed molecular formula. On the HMBC spectrum, the correlations between methylenedioxy unit (-O-CH_2-O-) and carbons C-1(δ_C 142.0) and C-2 (δ_C 147.1) established the linkage of (C-1)–O–CH_2–O–(C-2). The correlation between H-11 (δ_H 8.52,1H, *d* (8.4)) and C-9 (δ_C 156.7) indicated the attachment of the hydroxyl group to carbon C-9. Compound **2** was identified as **(+)-***roemeroline* (**Fig. 1**). Its physical and spectral data are consistent to those reported by literature (Slvaki and Slavikova, 1996).

Compound **3** was isolated as an amorphous brown solid. The UV spectrum of this compound showed maximum absorption bands at λ_{max}: 221.4 and 265.0 nm. Its HR-ESI-MS spectrum shown the pseudo-molecular ion fragment $[M+H]^+$ at (*m*/*z*) = 342.1700. So, its molecular formula was deduced to be $C_{20}H_{23}NO_4$ (calc. 342.1703 mDa = 0.3). Its ^{1}H NMR spectrum showed one singlet of aromatic proton at δ_H 6.69 ppm (H-3), two doublets of aromatic protons at δ_H 7.08 and 6.88 ppm, and three resonances corresponding to protons of aromatic methoxyl groups at δ_H 3.73, 3.90, and 3.91 ppm. The singlet at δ_H 7.08 ppm is attributable to an aromatic hydrogen. These data make it possible to suggest that this compound is an aporphine alkaloid. Correlations observed on its HMBC spectrum (between H-6a and C-5) and its NOE experiment indicated that **3** was an *N*-methyl derivative (Kablan *et al.*, 2013). According to its $[\alpha]_D$ value ($[\alpha]_D^{21}$ (O) = +11.0), absolute configuration of the asymmetric carbon C-6a was determined to be ***S*** form. The physical and spectral data of **3** are consistent to those of **(+)-***corydine* (Hocquemiller *et al.*, 1981; Spiff *et al.*, 1984; Chang *et al.*, 1995) (**Fig. 1**).

Compound **4** was isolated as an amorphous brown solid. Its UV spectrum showed identical maximum absorption bands like that of **3** (λ_{max}: 221.4 and 265.0 nm). Its ^{1}H NMR and ^{13}C NMR spectra (**Table** 2) were also similar to those of **3**. But, significant differences were observed on its carbons chemical shifts; precisely for C-1 (δ_C 144.8 ppm; 142.5 ppm for **4** and **3** respectively) and C-11 (δ_C 146.0 ppm; 144.0 ppm for **4** and **3** respectively). On the ^{1}H NMR spectrum, a difference was also observed for H-5 (δ_H 3.83/2.55 ppm; 3.08 ppm for **4** and **3** respectively) and H-6a (δ_H 3.08 ppm; 2.97 ppm for **4** and **3** respectively). An over different was the signals of *N,N* dimethyl at 43,9 ppm and 54,3 ppm. These observations suggested that structures of **4** and **3** were similar. The HMBC correlations confirmed the position of three methoxyl groups on the aromatic rings A and D; that of *N,N*-dimethyl on the ring B. So, compound **4** was identified as a 1,2,10,11-substituted aporphine alkaloid (Kablan *et al*., 2013); precisely a *N,N*-dimethyl aporphine alkaloid. The absolute configuration of asymmetric carbon C-6a was also determined according to its $[\alpha]_D$ value ($[\alpha]_D^{21}$ (O)= +22.0) to be ***S*** form. The compound **4** was identified as (+)-*menispermine* **(Fig. 1).** It was already isolated in *Xylopia parviflora* (Nishiyama *et al*., 2004), *Nandina domestica* (Iwasa *et al*., 2008) and *Anamirta cocculus* (Satya *et al*., 2012).

CONCLUSION

The phytochemical investigation of *Monodora brevipes's* leaves leaded to the isolation and identification of one indole derivative and three aporphines alkaloid derivatives. Their complete structures were established according to their spectroscopic (^{1}H and ^{13}C NMR, COSY, HSQC, HMBC, UV and IR) and spectrometric (ESI-MS) data. The indole derivative was identified as a new natural indole: 5-formylindole (**1**). The aporphines alkaloids were identified as three known alkaloids: (+)-roemeroline (**2**), (+)-corydine (**3**) and (+)-menispermine (**4**). Their structures are in agreement with those reported by literature.

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