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A novel anthraquinone from *Morinda lucida* Benth (Rubiaceae)

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Abstract
Morinda lucida (Rubiaceae) is a plant used in West African's traditional medicine for the treatment of various diseases. The Phytochemical investigation of its stem barks led to the isolation of eight anthraquinone derivatives. Among these compounds, one is a new structure: 2-acetyl-1-hydroxyanthraquinone (8). The others were known from this plant: damnacanthal (1), 3-hydroxy-2-carbaldehyde-anthraquinone (2), 1-hydroxy-2-methyl-anthraquinone (3), nordamnacanthal (4), rubiadin-1-methyl ether (5), morindone (6), tectoquinone (7). Their structures were established according to their spectral data (NMR 1D and 2D, MS).

Keywords: *Morinda lucida*, Rubiaceae, isolation, anthraquinone

Introduction
Morinda lucida Benth belongs to the family Rubiaceae. The genus consists of 90 species [1]. It is a medium-sized tree measuring approximately 15 m in height and widely used in Central and West Africa's traditional medicine. This species is used in the treatment of different types of fevers, cerebral congestion, dysentery, jaundice, hypertension, diabetes and gastric ulcer [2]. Previous studies had shown that the leaves [3, 4] and the roots [5] of *M. lucida* possess hypoglycemic and anti-diabetic activity. Phytochemical screening of this plant indicated the presence of important biological active compounds such as alkaloids, tannins, flavonoids, anthraquinols and anthraquinones [2, 6]. The anthraquinones have been reported to possess *in vitro* anti-*Plasmodium falciparum* activity [7]. They also possess trypanocidal [8] and antimalarial activities [9]. Twenty anthraquinones, were isolated from the roots, stem and stem barks [7, 10-12]. In this study, we report for the first time, the isolation and characterization of a new anthraquinone.

Materials and methods
General
^{1}H and ^{13}C NMR spectroscopic data were recorded at 303 K on an Avance III 500 MHz spectrometer (Bruker, www.bruker.com) fitted with a 5 mm i.d. $^{13}C/^{1}H$ cryoprobe carefully tuned to the recording frequencies of 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C. Chemical shifts are quoted in δ (ppm), and spectra are referenced to the solvent in which they were run (δ 7.26 for ^{1}H $C^{2}HCl_3$; δ 2.05 for ^{1}H $C^{2}H_3COC^{2}H_3$, δ 2.49 for ^{1}H $C^{2}H_3SOC^{2}H_3$). Electron impact and chemical ionization mass spectra were recorded on a DSQII mass spectrometer (Thermo-Fisher, www.thermofisher.com). MALDI TOF-TOF mass spectra were obtained on an Autoflex III mass spectrometer (Bruker) operating in positive ion mode using dihydoxybenzoic acid as matrix.
Column chromatography was performed with 0.063–0.200 mm, 70–230 mesh silica gel (Merck). Hydrophobic chromatography was carried out using Sephadex® LH20 gel. Analytical thin-layer chromatography (TLC) was conducted on TLC silica gel 60 F254 aluminum Plates 20 cm × 20 cm (Merck). Preparative normal phase TLC was conducted on 0.25 mm thick silica gel 60 F254 glass plates (Merck). Reverse-phase-C18 preparative TLC was performed using 0.25 mm thick silica gel 60-RP18 W F254 glass plates (Merck).

Plant Material
Stem barks of *Morinda lucida* were collected in May 2008 in Bobia, village in the west of Côte d'Ivoire (6°04'27.2"N 5°50'08.3"W).

Plant material was identified by Professor Ake Assi of the National Floristic Center of University Felix Houphouët-Boigny, Cocody-Abidjan, Department of Botany, Côte d'Ivoire, where the voucher specimen was deposited with number CNF-16259.

The stem barks were dried at ambient temperature in the dark and pulverized with a Retsch mill to give a powder that was of <0.5 mm diameter.

Extraction and isolation of phytochemicals

The dried, powdered stem barks of *M. lucida* (100 g) were macerated without agitation at room temperature for 72 h in, successively hexane (3 × 400 mL), CH_2Cl_2 (3 × 400 mL), EtOAc (3 × 400 mL), and MeOH (3 × 400 mL). After each maceration, the liquid phase was recovered by filtration (Whatman N8 1) and taken to dryness by rotary evaporation at reduced pressure to yield a residue. These were respectively hexane (M1, 400 mg), CH_2Cl_2 (M2, 410 mg), EtOAc (M3, 130 mg), and MeOH (M4, 1260 mg) crude extracts.

The EtOAc extract (M3, 130 mg) was fractionated on a normal-phase Si-gel column eluted with 100% CH_2Cl_2 to give two fractions (M3.1 and M3.2) then with hexane/ EtOAc (30:70) to give 20 fractions (M3.3 to M3.22). The pure fraction M3.2 (0.7 mg) is compound 8.

All other compounds already known in this plant were isolated by sequential chromatographic separation from the CH_2Cl_2 crude extract. The pure compounds 1 (2.1 mg), 2 (1.9 mg), 3 (1.6 mg), 4 (6.2 mg), 5 (1.0 mg), 6 (11.7 mg) and 7 (0.6 mg) were obtained.

3-Hydroxy-l-methoxy-2-carbaldehyde-anthraquinone or damnacanthal (1). Yellow needles. EI-MS *m/z* (rel.int.): 282 $[M]^+$ (55), 267 (35), 254 (100), 225 (33), 197 (24), 180 (31), 139 (41). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.13 (3H, *s*, 1-OCH_3), 7.69 (1H, *s*, H-4), 7.78-7.87 (2H, *m*, H-6 and H-7), 8.25 (1H, *m*, H-5), 8.32 (1H, *m*, H-8), 10.47 (1H, *s*, H-15), 12.31 (1H, *s*, 3-OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.1 (C-15), 181.9 (C-10), 180.8 (C-9), 165.6 (C-3), 164.3 (C-l), 139.2 (C-14), 135.6 (C-7), 134.3 (C-6), 134.1 (C-11), 132.5 (C-12), 128.1 (C-8), 127.5 (C-5), 61.5 (1-OCH_3), 110.4 (C-4), 117.5 (C-2), 118.7 (C-13).

3-Hydroxy-2-carbaldehyde-anthraquinone (2). Pale yellow solid. EI-MS *m/z* (rel. int.): 252 $[M]^+$ (100), 251 (55), 234 (10), 223 (7), 206 (8), 139 (16). ^{1}H NMR (500 MHz, $CDCl_3$): 7.82-7.86 (2H, *m*, H-6 and H-7), 7.84 (1H, *s*, H-4), 8.33-8.37 (2H, *m*, H-5 and H-8), 8.57 (lH, *s*, H-l), 10.49 (lH, *s*, H-15), 11.46 (1H, *s*, 3-OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 114.5 (C-4), 124.4 (C-13), 125.9 (C-2), 126.5 (C-5), 126.7 (C-8), 128.1 (C-1), 132.7 (C-12), 132.8 (C-l1), 134.2 (C-6), 134.5 (C-7), 138.7 (C-14), 165.2 (C-3), 180.6 (C-9), 181.8 (C-10), 190.1 (C-15).

1-Hydroxy-2-methyl-anthraquinone (3). Yellow needles. EI-MS *m/z* (rel. int.): 238 $[M]^+$ (100), 237 (24), 210 (23), 209 (10), 181 (17), 152 (12). ^{1}H NMR (500MHz, $CDCl_3$): δ 2.32 (3H, *s*, H-15), 7.47 (lH, *d*, J =7.4 Hz, H-4), 7.68 (IH, *d*, J =7.4 Hz, H-3), 7.71-7.74 (2H, *m*, H-5 and H-8), 8.19-8.22 (2H, *m*, H-6 and H-7), 12.87 (lH, *s*, 1-OH). ^{13}C NMR (125 MHz, $CDC1_3$): δ 16.2 (C-15), 116.1 (C-13), 119.3 (C-4), 126.9 (C-5), 127.4 (C-8), 131.6 (C-2), 133.2 (C-12), 133.8 (C-l1), 134.1 (C-6), 134.6 (C-7), 135.3 (C-14), 137.3 (C-3), 161.1 (C-1), 182.5 (C-10), 189.1 (C-9).

1,3-dihydroxy-2-carbaldehyde anthraquinone or nordamnacanthal (4). Orange–yellow needles. EI-MS m/z (rel. int.): 268 $[M]^+$ (70), 240 (100), 212 (34), 184 (32), 138 (12), 128 (21). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (1H, *s*, H-4), 7.81–7.85 (2H, *m*, H-6 and H-7), 8.28 (1H, *m*, H-5), 8.35 (2H, *m*, H-8), 10.51 (1H, *s*, H-15), 12.69 (1H, *s*, 3-OH), 14.07 (1H, *s*, 1-OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 109.2 (C-13), 109.5 (C-4), 112.9 (C-2), 126.8 (C-5), 127.8 (C-8), 133.4 (C-12), 133.7 (C-l1), 134.8 (C-6), 134.7 (C-7), 139.5 (C-14), 168.2 (C-1), 169.3 (C-3), 181.4 (C-10), 186.8 (C-9), 193.7 (C-15).

Rubiadin-1-methyl ether (5). Yellow needles. EI-MS *m/z* (rel. int.): 268 $[M]^+$ (100), 253 (40), 239 (25), 222 (12), 165 (13), 152 (22). ^{1}H-NMR (500 MHz, acetone-d_6): δ 2.18 (3H, *s*, H-15), 3.82 (1H, *s*, 1-OCH_3), 7.52 (1H, *s*, H-4), 7.85-7.89 (2H, *m*, H-6 and H-7), 8.10-8.13 (2H, *m*, H-5 and H-8). ^{13}C-NMR (125 MHz, acetone-d_6): δ 9.4 (C-15), 60.9 (1-OCH_3), 109.3 (C-4), 118.5 (C-13), 125.9 (C-5), 126.1 (C-2), 126.6 (C-8), 133.1 (C-11), 133.7 (C-6), 134.5 (C-7), 134.7 (C-14), 135.2 (C-12), 160.7 (C-1), 161.6 (C-3), 180.6 (C-9), 182.8 (C-10).

1,5,6-Trihydroxy-2-methyl-anthraquinone or morindone (6). Orange needles. EI-MS *m/z* (rel. int.): 270 $[M]^+$ (100), 253 (8), 242 (12), 213 (7), 139 (13), 135 (9). ^{1}H-NMR (500 MHz, acetone-d_6) δ 2.33 (3H, *s*, H-15), 7.14 (1H, *d*, J=8.2 Hz, H-7), 7.58 (1H, *d*, J=7.6 Hz, H-3), 7.75 (1H, *d*, J=7.6 Hz, H-4), 7.79 (1H, *d*, J=8.2 Hz, H-8). ^{13}C NMR (125 MHz, acetone-d_6): δ 15.7 (C-15), 115.1 (C-13), 116.1, (C-11), 117.9 (C-4), 120.7 (C-7), 122.4 (C-8), 123.8 (C-12), 130.6 (C-14), 134.8 (C-2), 135.5 (C-3), 151.2 (C-5), 153.9 (C-6), 160.1 (C-1), 186.8 (C-9), 187.9 (C-10).

2-Methyl-anthraquinone or Tectoquinone (7). Yellow amorphous powder. EI-MS m/z (rel. int.): 222 $[M]^+$ (25), 166 (49), 165 (100) 194 (31), 150 (7), 139 (21), 126 (11). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.46 (3H, *s*, H-15), 7.53 (1H, *d*, J = 7.8 Hz, H-3), 7.71–7.74 (2H, *m*, H-5 and H- 8) 8.04 (1H, *s*, H-1), 8.15 (1H, *d*, J = 7.8 Hz, H-4), 8.22–8.25 (2H, *m*, H-6, and H-7),. ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3 (C-15), 127.1 (C-8), 127.2 (C-5), 127.4 (C-4), 127.6 (C-1), 131.3 (C-14), 133.5 (C-11), 133.6 (C-12), 134.1 (C-7), 134.2 (C-6), 133.4 (C-13), 135.1 (C-3), 145.5 (C-2), 183.1 (C-10), 183.5 (C-9).

2-acetyl-1-hydroxyanthraquinone (8). Yellow powder. MALDI TOF-TOF *m/z* 305.0410 $[M+Na]^+$ (Calcd for $C_{16}H_{10}O_5Na$, 305.0426). EI-MS *m/z* (rel. int.): 282 $[M]^+$ (63), 252 (11), 251 (39), 250 (49), 224 (12), 223 (11), 222 (46), 194 (23), 167 (17), 166 (13), 140 (12), 139 (100), 138 (67), 137 (29), 43 (10). ^{1}H NMR (500 MHz, acetone-d_6,) data, see Table 1. ^{13}C NMR (125 MHz, acetone-d_6) data, see Table 1.

Results and Discussion

The dried powdered stem barks of *M. lucida* were sequentially washed with hexane, CH_2Cl_2, EtOAc then MeOH. Chromatography of the CH_2Cl_2 extract yielded damnacanthal (1) [7, 10, 12], 3-Hydroxy-2-carbaldehyde-anthraquinone (2) [12, 13], 1-Hydroxy-2-methyl-anthraquinone (3) [10, 12], nordamnacanthal (4) [12] Rubiadin-1-methyl ether (5) [10, 12], morindone (6) [12] and Tectoquinone (7) [12], while a further one compound, 8, was purified from the EtOAc extract. Compound 8 was obtained as a yellow powder soluble in acetone. The MALDI-TOF-TOF spectrum showed a pseudo molecular ion $[M+Na]^+$ at *m/z* 305.0410 corresponding to the molecular formula $C_{16}H_{10}O_5$. The ^{1}H NMR spectrum of 8 in showed a singlet signal at δ 13.37 (1H) attributed to a hydroxyl of a phenol group; two massifs at δ 8.29 and δ 8.37 each integrating for 1H attributable to protons H-5 and H-8 respectively of an unsubstituted A ring of anthraquinone nucleus; a further massif was observed at δ_H 7.97-8.03 (2H) that could be attributed to 2 equivalent aromatic protons H-6 and H-7 of the A ring. A doublet at δ 8.24 (J = 8.2 Hz, 1H) was attributed to H-3 of the C ring; a further doublet at δ 7.85 (J = 8.2 Hz, 1H) ortho-coupling with

H-3 was attributed to H-4 of the C ring and a singlet signal at δ 3.93 was characteristic of a methoxyl group.

The COSY spectrum confirms the correlations between H-3 and H-4, H-5 and H-6, and H-7 and H-8 (Fig. 1). The compound 8 is therefore a bisubstituted anthraquinone at positions 1 and 2 with the presence of hydroxyl (OH) and methylated carboxyl ($COOCH_3$) groups.

The study of the 2D-NMR spectrum HMBC allowed to position the two substituents of the C ring. This spectrum showed correlations between the proton of the hydroxyl group and the carbons at δ 118.1 (C-13) and δ 126.3 (C-2) in ^3J. These latter correlated in turn with the proton at δ 7.85 (H-4). In addition, the carbon of the CO of the carboxyl group at δ 165.8 (C-15) correlated with the proton at δ 8.24 (H-3) and with the three protons of the methoxyl group at δ 3.93. No correlation spots were observed between this carbon and the H-4 proton. Thus, compound 8 was determined as 2-acetyl-1-hydroxyanthraquinone. The main correlations observed in COSY and HMBC have been described in Figure 1.

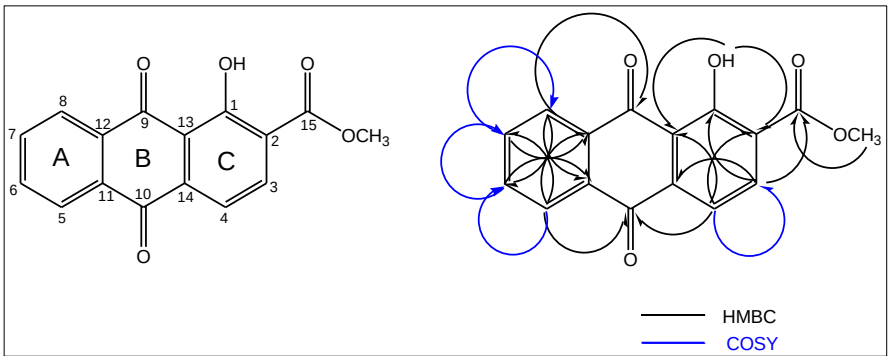

Fig 1: Compound 8: numbering and correlations deduced from the COSY and HMBC spectra

Table 1: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR assignments for 8 in acetone-d_6.

Position	δ_C	δ_H	HMBC
1	162.6	-	-
2	126.3	-	-
3	139.1	8.24 (*d*, *J* = 8.2 Hz)	C-1, C-14, C-15
4	118.7	7.85 (*d*, *J* = 8.2 Hz)	C-2, C-10, C-13
5	127.9	8.29 *m*	C-7, C-10, C-12
6	136.2	7.97-8.03 *m*	C-8, C-11
7	135.6	7.97-8.03 *m*	C-5, C-12
8	127.8	8.37 *m*	C-6, C-9, C-11
9	189.8	-	-
10	182.5	-	-
11	134.2	-	-
12	134.1	-	-
13	118.1	-	-
14	137.0	-	-
15	165.8	-	-
1-OH	-	13.37 *s*	C-2, C-13
15-OCH_3	52.7	3.93 *s*	C-15

Assignments are based on COSY, HSQC and HMBC experiments.

The compound 8 is a new anthraquinone of *M. lucida* and the genus Morinda. However, it has been isolated and identified from the methanol extract of the bark of *Rubia wallichiana* [14], a species belonging to another genus of the family Rubiaceae. The identification was carried out using MS, ^{1}H and ^{13}C-NMR, and NOESY spectra. In this study, we present for the first time the ^{13}C-NMR, HMBC and HSQC data of compound 8. In addition, the ^{1}H-NMR spectrum obtained in acetone-d_6 made it possible to differentiate the protons H-5 and H-8. Similarly, the HSQC and HMBC spectra allowed the differentiation of C-6 and C-7 carbons. This information could not be accessed in previous work.

Conclusion

The phytochemical investigation of the stem barks of *M. lucida* led to the isolation and identification of a new anthraquinone 2-acetyl-1-hydroxyanthraquinone (8) together with seven known anthraquinones damnacanthal (1), 3-hydroxy-2-carbaldehyde-anthraquinone (2), 1-hydroxy-2-methyl-anthraquinone (3), nordamnacanthal (4), rubiadin-1-methyl ether (5), morindone (6), tectoquinone (7) [10-12]. This study allowed, for the first time, to differentiate H-5 and H-8 protons, C-6 and C-7 carbons and to obtain ^{13}C-NMR, HMBC, HSQC data for 2-acetyl-1-hydroxyanthraquinone.

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