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A NEW ANTHRAQUINONE FROM *MORINDA LUCIDA* BENTH

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ABSTRACT
Morinda lucida (Rubiaceae) is a known medicinal plant used in traditional medicine in West Africa for the treatment of diseases and infections. The purpose of the present study was to investigate the chemical constituents of the stem barks *of M. lucida* from Côte d'Ivoire. The isolation of the compounds was carried out by a combination of silica gel column, sephadex gel filtration chromatography, preparative normal phase TLC and reverse-phase-C18 preparative TLC. The chemical structures were elucidated with the help of MS, 1D, 2D - ^{1}H and ^{13}C NMR spectroscopic analysis, as well as the comparison of spectra data with that reported in the literature. The present phytochemical investigation led to the isolation and characterization of one new anthraquinone, 1,5,15-trimethylmorindol (**8**) together with seven known anthraquinones, 3-hydroxy-2-hydroxymethyl-anthraquinone (**1**), damnacanthol (**2**), soranjidiol (**3**), rubiadin (**4**), damnacanthol-l-methyl ether (**5**), lucidin (**6**) and alizarin-1-methyl ether (**7**) from the stem barks of *M. lucida*.

KEYWORDS: *Morinda lucida*, Rubiaceae, stem bark, anthraquinone.

1. INTRODUCTION

The genus Morinda (Rubiaceae) is comprised of about 80 species and occurs throughout the tropical regions. In Africa, the five common species are *Morinda lucida, M. citrifolia, M. geminata, M. longiflora* and *M. Morindoides.*[1] *Morinda lucida* Benth is an important plant in traditional medicine in West Africa. Decoctions and infusions or plasters of roots, barks and leaves are recognized remedies for different types of ailments, including fever and malaria.[2-6] The plant is also used in cases of diabetes[2,7], high blood pressure[4,8,9] and amenorrhoea.[2] This species is cited in four African countries for its use against hepatitis.[10]

The traditional use of *M. lucida* in the cure of several diseases has led scientists to focus on the chemical constituents present in the extracts of this plant. Previous studies have made it possible to isolate twenty anthraquinones, two anthraquinols and two anthraquinones glycosides from the roots, stem and stem barks of *M. lucida*.[11-14] From leaves three tetracyclic spirolactone iridoids, two triterpenic acids[15,16] and a fatty acid[12] were isolated. It is easily observed that anthraquinones make up the majority of secondary metabolites isolated from *M. lucida*. These metabolites have been characterized by different spectroscopic methods including 1D NMR, Mass, UV, IR and by comparison with authentic specimens. These compounds exhibited interesting biological activities, such as antifungal[11,17] and antimalarial.[13]

In this paper, we described for the first time the isolation and characterization of one new chemical constituent obtained from the EtOAc extract of *M. lucida* stem barks.

2. MATERIALS AND METHODS

2.1 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

$C^2H_3SOC^2H_3$). Electron impact and chemical ionization mass spectra were recorded on a DSQII mass spectrometer (Thermo-Fisher, www.thermofisher.com).

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).

2.2 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.

2.3 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 compound **8** (1.4 mg) was obtained after treatment on a normal-phase Si-gel column eluted with 100% CH_2Cl_2 of the fraction M3.3 (6.4 mg).

All other compounds already known in this plant were isolated by sequential chromatographic separation from either the CH_2Cl_2 crude extract (**1**–**4**) or the EtOAc crude extract (**5**-**7**). The pure compounds **1** (1.4 mg), **2** (1.8 mg), **3** (5.3 mg), **4** (4.3 mg), **5** (2.5 mg), **6** (1.3 mg) and **7** (1.2 mg) were obtained.

3-Hydroxy-2-hydroxymethyl-anthraquinone (**1**). Yellow needles. EI-MS *m/z* (rel. int.): 254 $[M]^+$ (76), 236 (100), 208 (25), 180 (33), 152 (41), 139 (10). ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.61 (2H, *s*, H-15), 7.86-7.90 (2H, *m*, H-6 and H-7), 8.02 (lH, *s*, H-4), 8.15-8.18 (2H, *m*, H-5 and H-8), 8.25 (lH, *s*, H-1). ^{13}C NMR (125 MHz, DMSO-d_6): δ 60.1 (C-15), 114.0 (C-4), 125.3 (C-13), 126.1 (C-1), 126.5 (C-5), 126.7 (C-8), 133.3 (C-12), 133.5 (C-11), 133.9 (C-2), 134.2 (C-6), 134.4 (C-7), 134.6 (C-14), 160.1 (C-3), 180.8 (C-9), 182.7 (C-l0).

3-Hydroxy-1-methoxy-2-hydroxymethylanthraquinone or damnacanthol (**2**). Yellow needles. EI-MS *m/z* (rel. int.): 284 $[M]^+$ (26), 269 (100), 265 (39), 251 (36), 238 (18), 139 (22). ^{1}H NMR (500 MHz, DMSO-d_6,): δ 3.89 (3H, *s*, 1-OCH_3), 4.58 (2H, *s*, H-15), 7.56 (lH, *s*, H-4), 7.83 (1H, *m*, H-6), 7.90 (1H, *m*, H-7), 8.11 (1H, *m*, H-5), 8.18 (1H, *m*, H-8). ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.1 (C-15), 62.5 (1-OCH_3), 111.3 (C-4), 118.7 (C-13), 120.1 (C-2), 126.2 (C-5), 126.8 (C-8), 132.6 (C-11), 133.6 (C-6), 134.1 (C-7), 134.4 (C-12), 134.9 (C-14), 161.7 (C-1), 162.5 (C-3), 180.3 (C-9), 182.8 (C-10).

1,6-Dihydroxy-2-methylanthraquinone or soranjidiol (**3**). Yellow needles. EI-MS *m/z* (rel. int.): 254 $[M]^+$ (100), 226 (9), 197 (22), 152 (13), 128 (18), 115 (5). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.21 (3H, *s*, H-15), 7.18 (1H, *dd*, J = 8.5, 2.6 Hz, H-7), 7.42 (1H, *d*, J = 2.6 Hz, H-5), 7.51 (1H, *d*, J = 7.6 Hz, H-4), 7.57 (1H, *d*, J = 7.6 Hz, H-3), 8.06 (1H, *d*, J = 8.5 Hz, H-8), 11.21 (1H, br *s*, 6-OH), 13.05 (1H, *s*, 1-OH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.7 (C-15), 112.4 (C-5), 114.5 (C-13), 118.5 (C-4), 121.3 (C-7), 124.4 (C-12), 129.6 (C-8), 131.1 (C-14), 134.1 (C-2), 135.3 (C-11), 136.7 (C-3), 159.9 (C-1), 163.7 (C-6), 181.6 (C-10), 187.5 (C-9).

1,3-Dihydroxy-2-methylanthraquinone or rubiadin (**4**). Yellow needles. EI-MS *m/z* (rel. int.) 254 $[M]^+$ (100), 226 (10), 197 (9), 152 (9), 128 (21), 115 (9), 105 (11). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.03 (3H, *s*, H-15), 7.22 (1H, *s*, H-4), 7.83–7.87 (2H, *m*, H-6 and H-7), 8.09 (1H, *m*, H-5), 8.16 (1H, *m*, H-8), 13.06 (1H, *s*, 1-OH). ^{13}C-NMR (125 MHz, DMSO-d_6): δ 9.7 (C-15), 107.9 (C-2), 110.0 (C-13), 117.4 (C-4), 126.6 (C-5), 127.0 (C-8), 132.2 (C-14), 133.4 (C-11), 134.1 (C-12), 134.3 (C-6), 134.9 (C-7), 163.1 (C-3), 165.6 (C-1), 183.0 (C-9), 185.1 (C-10).

3-Hydroxy-l-methoxy-2-methoxymethylanthraquinone or damnacanthol-l-methylether (**5**). Yellow amorphous powder. EI-MS *m/z* (rel. int.) 298 $[M]^+$ (58), 283 (43), 266 (100), 265 (65), 251 (60), 138 (19). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.31 (3H, *s*, 15-OCH_3), 3.81 (3H, *s*, 1-OCH_3), 4.58 (2H, *s*, H-15), 7.53 (1H, *s*, H-4), 7.76 (1H, *m*, H-6), 7.84 (1H, *m*, H-7), 8.04 (1H, *m*, H-5), 8.11 (2H, *m*, H-8). ^{13}C NMR (125 MHz, DMSO-d_6): δ 61.2 (15-OCH_3), 62.4 (1-OCH_3), 69.8 (C-15), 109.9 (C-4), 117.5 (C-13), 125.2 (C-2), 125.9 (C-5), 126.6 (C-8), 132.0 (C-11), 133.2 (C-6), 133.9 (C-7), 134.5 (C-12), 136.8 (C-14), 162.3 (C-1), 162.9 (C-3), 179.8 (C-9), 182.5 (C-10).

1,3-Dihydroxy-2-(hydroxymethyl)-anthraquinone or lucidin (**6**). Yellow amorphous powder. EI-MS *m/z* (rel.

int.): 270 $[M]^+$ (18), 252 (100), 224 (20), 196 (38) 168 (22), 139 (30). ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.47 (2H, *s*, H-15), 7.26 (1H, *s*, H-4), 7.89-7.93 (2H, *m*, H-6 and H-7), 8.15 (1H, *m*, H-5), 8.22 (1H, *m*, H-8), 13.20 (1H, *s*, 1-OH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 51.3 (C-15), 62.1 (15-OCH_3), 62.4 (1-OCH_3), 109.8 (C-4), 118.1 (C-13), 126.3 (C-5), 126.5 (C-2), 126.9 (C-8), 132.2 (C-11), 133.7 (C-6), 134.5 (C-7), 134.9 (C-12), 135.3 (C-14), 161.3 (C-1), 162.6 (C-3), 180.4 (C-9), 183.1 (C-10).

1-Methoxy-2-hydroxy-anthraquinone or alizarin-1-methyl ether (**7**). Yellow crystals. EI-MS *m/z* (rel. int.): 254 $[M]^+$ (52), 236 (32), 208 (100), 183 (16), 139 (31), 127 (39). ^{1}H-NMR (500 MHz, acetone-d_6): δ 3.95 (3H, *s*, 1-OCH_3), 7.37 (1H, *d*, J = 8.4 Hz, H-3), 7.84-7.89 (2H, *m*, H-6 and H-7), 8.04 (1H, *d*, J = 8.4 Hz, H-4), 8.23-8.27 (2H, *m*, H-5 and H-8); 9.26 (1H, *s*, 2-OH). ^{13}C-NMR (125 MHz, acetone-d_6): δ 61.8 (1-OCH_3), 120.9 (C-3), 124.9(C-4), 126.2 (C-5), 126.6 (C-13), 126.7 (C-8), 127.0 (C-14), 133.0 (C-11), 133.6 (C-6), 133.8 (C-7), 134.8 (C-12), 148.3 (C-1), 157.3 (C-2), 181.5 (C-10), 183.7 (C-9).

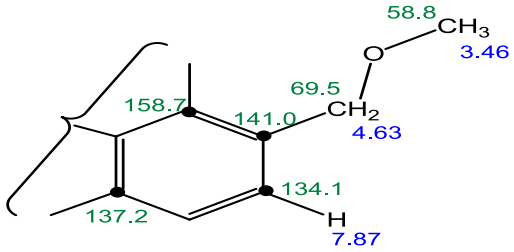
1,5,15-trimethylmorindol (**8**). Yellow needles. EI-MS *m/z* (rel. int.): 328 $[M]^+$ (60), 314 (19), 313 (100), 297 (18), 296 (29), 295 (25), 283 (27), 270 (15), 265 (26), 250 (21), 225 (17), 224 (15), 223 (19), 222 (52), 221 (17), 181 (19), 152 (18), 139 (24), 127 (16), 126 (15), 45 (23). ^{1}H NMR (500 MHz, acetone-d_6,) data, see Table 1. ^{13}C NMR (125 MHz, acetone-d_6) data, see Table 1.

3. RESULTS AND DISCUSSION

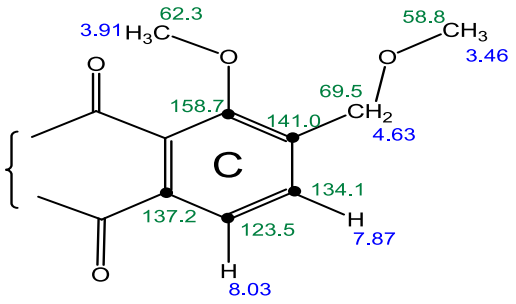
The dried powdered stem barks of *M. lucida* were sequentially washed with hexane, CH_2Cl_2, EtOAc then MeOH. Chromatography of the CH_2Cl_2 extract yielded 4 compounds, namely 3-Hydroxy-2-hydroxymethyl-anthraquinone (**1**)[11], damnacanthol (**2**)[11], soranjidiol (**3**)[12] and rubiadin (**4**)[12], while a further 4 compounds, damnacanthol-l-methylether (**5**)[14,18], lucidin (**6**)[15], 1-Methoxy-2-hydroxy-anthraquinone or alizarin-1-methyl ether (**7**)[11,12] and 1,5,15-trimethylmorindol (**8**), were purified from the EtOAc extract. Compound **8** soluble in acetone was obtained as yellow needles. The CI-MS of **8** gave an $[M+H]^+$ ion at *m/z* 329 and the EI spectrum indicated the molecular formula $C_{19}H_{20}O_5$ or $C_{18}H_{16}O_6$. The ^{13}C NMR spectrum (DEPT90 and DEPT135) showed 18 signals: 10 of these were due to quaternary carbons (of which 2 were carbonyl groups and 8 were aromatic), 4 to aromatic CH, 1 to CH_2 and 3 to CH_3 indicating the molecular formula $C_{18}H_{16}O_6$.

The ^{1}H NMR spectrum of **8** showed a broad singlet at δ 9.23 (1H) that could be attributed to the OH of a phenol group, four doublets at δ 8.03 (J = 8.0 Hz), 7.98 (J = 8.5 Hz), 7.87 (J = 8.0 Hz) and 7.36 (J = 8.5 Hz) each integrating for 1H and coupling in ortho were characteristic of the aromatic protons of a tetrasubstituted anthraquinone (two substituents on each ring A and C). A further singlet observed at δ 4.63 (2H) was attributed to CH_2O group. Additionally, 3 signals at δ 3.93, 3.91 and 3.46 were observed. These were attributed to the methoxyl groups. These preliminary results showed unambiguously that compound **8** was a bisubstituted anthraquinone on each ring A and C with the four aromatic protons ortho coupling two by two. The HSQC and HMBC spectra allowed to specify the structure of the molecule.

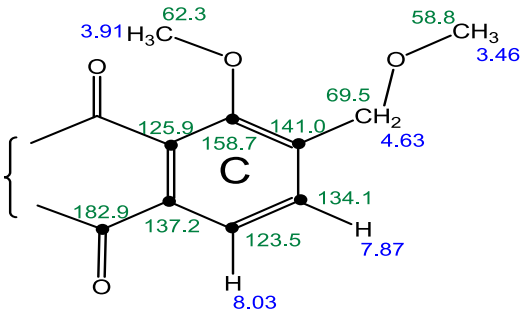
The 3H of OCH_3 at δ 3.46 correlated in ^3J with the carbon at δ 69.5 which carried the 2H at δ 4.63 of CH_2O. These two protons in turn correlated with the carbon at δ 134.1 carrying the proton at δ 7.87 and with the quaternary carbon at δ 158.7 in ^3J. They were also correlated with quaternary carbon at δ 141.0 in ^2J. The proton at δ 7.87 ppm correlated with carbon at δ_C 69.5 (CH_2O), with quaternary carbons at δ 137.2 and 158.7 in ^3J. Which gave the following motive:



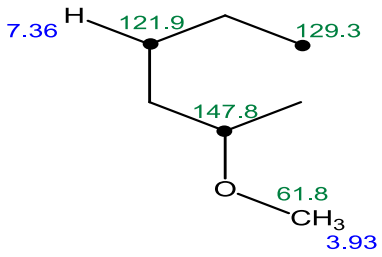
The quaternary carbon at δ 141.0 correlated with the proton at δ 8.03 carried by the carbon at δ 123.5 in ^3J. The carbon at δ 158.7 was correlated with the 3H of the methoxyl group at δ 3.91 carried by the carbon at δ 62.3. That gave ring C and its substituents.



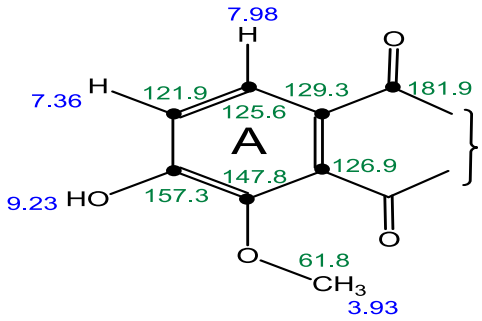
The proton at δ 8.03 correlated with the quaternary carbons at δ 125.9 and 141.0 and with the carbonyl carbon at δ 182.9 in ^3J.



The 3H of the methoxyl group at δ 3.93 carried by the carbon at δ 61.8 were correlated with the quaternary carbon at δ 147.8 in ^3J, which in turn correlated with the proton at δ 7.36 carried by the carbon at δ 121.9 in ^3J. This proton correlated in ^3J with quaternary carbon at δ 129.3.



The proton at δ 7.98 carried by the carbon at δ 125.6 correlated in ^3J with the quaternary carbons at δ 126.9 and 157.3 and then with the carbon of the carbonyl group at δ 181.9. The carbon at δ 157.3 was certainly the one carrying the hydroxyl group. Hence obtaining the ring A and its substituents:



Of all that preceded, compound **8** was determined as 1,5,15-trimethylmorindol. The main correlations observed in HMBC have been described in Figure 1.

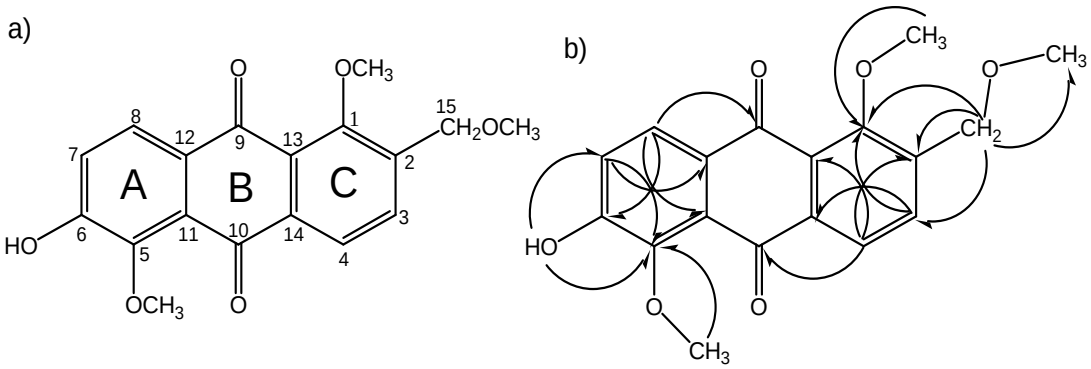


Fig. 1: Compound 8: (a) numbering and (b) correlations deduced from HMBC spectrum.

Table 1: 1H (500 MHz) and 13C (125 MHz) NMR assignments for 8 in acetone-d6.

Position	δ_C	δ_H	HMBC
1	158.7	-	-
2	141.0	-	-
3	134.1	7.87 (*d*, *J* = 8.0 Hz)	C-1, C-14, C-15
4	123.5	8.03 (*d*, *J* = 8.0 Hz)	C-2, C-10, C-13
5	147.8	-	-
6	157.3	-	-
7	121.9	7.36 (*d*, *J* = 8.5 Hz)	C-5, C-12
8	125.6	7.98 (*d*, *J* = 8.5 Hz)	C-6, C-9, C-11
9	181.9	-	-
10	182.9	-	-
11	126.9	-	-
12	129.3	-	-
13	125.9	-	-
14	137.2	-	-
15	69.5	4.63 *s*	C-1, C-2, C-3, 15-OCH_3
1-OCH_3	62.3	3.91 *s*	C-1
5-OCH_3	61.8	3.93 *s*	C-5
6-OH	-	9.23	C-5, C-7
15-OCH_3	58.8	3.46 *s*	C-15

Assignments are based on HSQC and HMBC experiments.

The compound 8 is a new anthraquinone from *M. lucida*. It has already been isolated from the leaves and fruits of *Morinda citrifolia*.[19,20] The studies of Takashima et al.[19] showed that 1,5,15-trimethylmorindol did not exhibit significant cytotoxic activity on cells of the human leukemia line T, Jurkat; but demonstrated significant cytotoxicity when combined with TRAIL protein (Tumor necrosis factor-related apoptosis-inducing ligand). These results suggested that the combined treatment of compound **8** with TRAIL protein may be a new strategy for the treatment of cancer.[21]

4. CONCLUSION

The phytochemical investigation of the stem barks of *M. lucida* led to the isolation and identification of one new anthraquinone 1,5,15-trimethylmorindol (**8**) together with seven known anthraquinones 3-hydroxy-2-hydroxymethyl-anthraquinone (**1**), damnacanthol (**2**), soranjidiol (**3**), rubiadin (**4**), damnacanthol-l-methylether (**5**), lucidin (**6**) and alizarin-1-methyl ether (**7**).[11,12,14,15] Anthraquinone 1,5,15-trimethylmorindol (compound **8**) demonstrating a cytotoxic activity on cancer cells of the human leukemia line T.[21] would justify the traditional use of barks against various inflammatory manifestations by the close link between inflammation and cancer.[22]

5. ACKNOWLEDGMENTS

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