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Cassane diterpenoids from the root bark of *Erythrophleum suaveolens* (Guill. & Perr.) Brenan (Fabaceae)

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Abstract

Cassane diterpenoids are among the major secondary metabolites of the genus *Erythrophleum suaveolens* and are well known for their diverse biological activities. In the present study, a phytochemical investigation was carried out on the root bark of *Erythrophleum ivorense* collected in Côte d'Ivoire. The methanolic extract was subjected to acid-base partitioning, followed by successive chromatographic separations including flash chromatography, Sephadex LH-20, silica gel column chromatography, and semi-preparative HPLC. This work led to the isolation of two cassane diterpenoid amines from the ethyl acetate fraction. Their structures were elucidated by detailed spectroscopic analyses, including IR, ^{1}H and ^{13}C NMR, HMBC, COSY, NOESY, and ESI-HRMS data. The isolated compounds were identified as 3*β*-hydroxy-*nor*-erythrosuamine (1) and 3*β*-hydroxy-*nor*-cassamidine (2). To the best of our knowledge, compounds 1 and 2 are reported here for the first time from the root bark of *Erythrophleum ivorense*. These findings contribute to the phytochemical knowledge of *Erythrophleum ivorense* and further support the chemical diversity of cassane diterpenoids in African medicinal plants.

Keywords: Erythrophleum suaveolens, erythrophleum ivorense, phytochemical investigation, spectroscopic analysis (NMR, HMBC, COSY, NOESY, HRMS)

Introduction

Erythrophleum alkaloids, also referred to as cassane alkaloids, are amide- or amine-type cassane diterpenoids that constitute the major metabolites found in the genus *Erythrophleum* [1–5]. These compounds are recognized for their diverse biological activities, particularly their effects on the cardiovascular system [6], as well as their cytotoxic activity against certain tumor cell lines [7]. A distinctive structural feature of these metabolites is the presence of amide or amine functional groups within their cassane skeletons [8–11].

Species belonging to the genus *Erythrophleum* are widely used in traditional African medicine [12]. Numerous phytochemical investigations have demonstrated that cassane-type diterpenoids represent one of the major classes of secondary metabolites in this genus [13–15]. Studies on Erythrophleum species have shown that both crude extracts and isolated secondary metabolites exhibit a broad spectrum of biological activities, including antioxidant [13], antibacterial [16], anti-inflammatory, anticancer [17], anti-angiogenic [18], cytotoxic [19], and cardiotonic effects [10].

Species belonging to the genus *Erythrophleum* are widely recognized for their numerous applications in traditional African medicine [12]. Various phytochemical investigations have demonstrated that cassane-type diterpenoids constitute one of the major classes of secondary metabolites in this genus [13-15]. Studies carried out on Erythrophleum species have revealed that both crude extracts and isolated compounds possess a broad spectrum of biological activities, including antioxidant [13], antibacterial [16], anti-inflammatory, anticancer [17], anti-angiogenic [18], cytotoxic [19], and cardiotonic effects [10]. Among these species, *Erythrophleum ivorense* is commonly used in traditional medicine in Côte d'Ivoire for the treatment of various ailments.

This large tree is native to tropical Africa [20] and is widely distributed in Côte d'Ivoire, Ghana, Congo, Cameroon, Gabon, Nigeria, and Liberia. In Sierra Leone, the seeds are traditionally used as analgesic, emetic, and laxative agents [21]. They have also been reported to exhibit broad-spectrum antimicrobial activity [22]. The stem bark is mainly employed in traditional medicine for the treatment of inflammation, parasitic diseases, smallpox, and convulsions [23,24]. However, both the seeds and bark are known to be toxic when ingested [25].

Despite the extensive use of *Erythrophleum ivorense* as a natural remedy for numerous ailments in Côte d'Ivoire, its chemical composition remains poorly documented. The present study was therefore undertaken to contribute to the characterization of the secondary metabolites of this species. Chemical investigation of the methanolic extract obtained from the root bark led to the isolation of two cassane diterpenoid, named 3β-hydroxy-nor-erythrosuamine (1) and 3β-hydroxy-nor-cassamidine (2). Their structures were elucidated on the basis of NMR and ESIMS spectral analyses.

Material and Methods

1. General Experimental Procedures

The samples were analyzed using an Agilent LC-MS system. This system includes an Agilent 1260 Infinity HPLC coupled to an Agilent 6530 QTOF-MS equipped with an ESI source operating with positive polarity. For preparative HPLC separations, we used a Sunfire C18 analytical column (150×2.1 mm ; inner diameter 3.5 µm) using a Waters Delta Prep equipped with a binary pump (Waters 2525) and a diode array UV-visible detector (190-600 nm, Waters 2996). For flash chromatography 120 g and 24 g silica Grace cartridges were used using an Armen Instrument flash liquid chromatography spot apparatus. Chemical solvents were purchased from Sigma-Aldrich. A Polar 32 polarimeter was used to measure optical rotations at 25 °C. IR spectra were recorded with a Bruker Vector 22. NMR spectra were recorded on a Bruker AM-400 NMR spectrometer (400 MHz), using CD_3OD as solvent.

2. Plant Material

The root barks from *E. ivorense* were collected in December 2014 in Agboville (Côte d'Ivoire) before being identified and authenticated by Pr. Joseph Ipou Ipou from National Flower Center of Félix HOUPHOUËT-BOIGNY University (Côte d'Ivoire). A voucher specimen **(**n°8 DIBI EI-2014) was deposited in the herbarium.

3. Extraction and isolation

The root barks of *E. ivorense* were dried and pulverized. The powder (500 g) was extracted with methanol (5L) to give 32.3 g of methanolic crude extract. Part of this methanolic extract (15.0 g) was dissolved in 50 mL MeOH, then alkalized with a few drops of NH_4OH (25%), and then supplemented with 50 mL CH_2Cl_2. To the obtained solution, 1% sulfuric acid was added and then it was counter-extracted with CH_2C1_2 (100 mL x 4) to give, after evaporation under reduced pressure, the dichloromethane extract (DME). The supernatant phase was first alkalized with NH_4OH at (pH = 10), then counter-extracted with distilled AcOEt (100 ml x 4) to give, after evaporation with a rotary evaporator, the ethyl acetate extract (ESA). This last extract was fractionated and purified using successively flash chromatography, Sephadex® LH-20, silica gel column chromatography and semi-prep HPLC. Purification by semi-prep HPLC was performed as follows : flow rate 250 µL/min, linear gradient from 5% B (A : H_2O + 0.1% formic acid, B : ACN) to 100% B over 30 min. These purifications resulted in two compounds : 1 (tR 9.41 min, 6.7 mg), 2 (tR 9.46 min, 6.6 mg).

4. Results and Discussion

The purification of the ethyl acetate fraction of the root barks of *E. ivoriense* led to the known compounds 3β-hydroxy-nor-erythrosuamine (1) [2, 4], and 3β-hydroxy-nor-cassamidine (2) [4, 19] (Figure 1).

Compound 1 was obtained as a colorless oil, soluble in methanol. Its IR spectrum, recorded in methanol, displayed two absorption bands at νmax 1765 and 1725 cm^{-1}, indicating the presence of two ester functionalities. An additional absorption band at ν_{max} 1704 cm^{-1} suggested the presence of a ketone group. The methyl (CH_3) and methylene (CH_2) groups were evidenced by absorption bands at νmax 2950, 2934, and 2853 cm^{-1}.

The ^{13}C NMR spectrum showed a carbonyl signal at δ_C 211.3 (C-7), confirming the presence of a ketone functionality. Two additional highly deshielded carbon signals at δ_C 167.1 (C-13) and 168.3 (C-16) suggested the occurrence of ester or lactone groups. The carbon resonance at δC 113.8 (C-15), bearing a singlet proton at δ_H 5.75, indicated the presence of a trisubstituted double bond or an olefinic carbon involved in an α,β-unsaturated system. Signals at δ_C 62.1 (C-21), 61.5 (C-22), and 48.6 (C-23), associated with protons H-21 at δ_H 4.22, H-22 at δH 2.83, and H-23 at δ_H 2.61, were characteristic of an epoxide ring or an oxygenated side chain. The methoxy group at δ_H 3.69 / δ_C 52.0 (C-24) showed an HMBC correlation with C-19 at δ_C 179.1, thereby confirming the presence of a methyl ester.

The proton H-6 at δ_H 4.76 (d, J = 12.5 Hz) correlated with C-5 and C-7 in the HMBC spectrum, indicating that C-6 bears an oxygenated substituent adjacent to the ketone carbonyl at C-7. Proton H-5 at δ_H 1.43 exhibited HMBC correlations with C-6, C-18, and C-20, confirming the ring junctions of the cassane skeleton. COSY correlations H-1/H-2/H-3 established the aliphatic sequence of ring A, whereas H-11/H-12 and H-14/H-17 correlations enabled the construction of the side-chain portion of ring D. Furthermore, HMBC correlations from H-14 to C-8 and C-15, together with those from H-17 to C-8 and C-13, confirmed the organization of the unsaturated system around C-13–C-16.

The relative stereochemistry was established from the NOESY spectrum. Correlations between H-5/H-9, H-5/H-17, and H-5/H-18 indicated that these protons are located on the same face of the molecule. In contrast, correlations H-6/H-20 and H-8/H-20 showed that H-6, H-8, and the methyl group at C-20 are oriented on the opposite face.

Overall, the spectroscopic data were fully consistent with an oxygenated cassane diterpenoid bearing a ketone function at C-7, a methyl ester group at C-19, a double bond at C-15, and an oxygenated side chain of epoxide type. Compared with previously reported cassane diterpenoids, compound 1 differs by the simultaneous presence of a hydroxyl group at C-6, a ketone function at C-7, and an oxygenated amine moiety within a nor-cassane framework. Accordingly, compound 1 was identified as 3*β*-hydroxy-*nor*-erythrosuamine. To the best of our knowledge, no similar structure has been reported in the literature. Therefore, this compound is described here for the first time from the root bark of *Erythrophleum ivorense*.

Compound 2 was isolated as a yellowish amorphous solid. Its IR spectrum, recorded in methanol, showed two absorption bands at ν_{max} 1720 and 1648 cm^{-1}, characteristic of carbonyl groups. A broad and intense absorption band at ν_{max} 3350 cm^{-1} indicated the presence of hydroxyl functionality. In addition, methyl (CH_3) and methylene (CH_2) groups were evidenced by absorption bands at ν_{max} 2989, 2969, and 2901 cm^{-1}.

The ^1H and ^{13}C NMR spectra of compound 2, recorded in $CDCl_3$, were very similar to those of compound 1. However, a notable difference was observed in the ^{13}C NMR spectrum, namely the absence of the ketone carbonyl signal at δ_C 211.3 (C-7), which was present in compound 1. Instead, a new oxygenated methine carbon appeared at δ_C 72.1, suggesting the reduction of the ketone group into a hydroxyl-bearing carbon.

The HMBC spectrum showed that the signal at δ_C 72.1 correlated in ^{2}JCH with H-6β (δ_H 1.75), H-6α (δ_H 2.17), and H-8 (δ_H 1.48), and in ^{3}JCH with H-5 (δ_H 1.18). These correlations clearly established that the hydroxyl group is attached to C-7. The NOESY spectrum revealed correlations between H-7 and both H-8 and H-20, indicating that H-7 is located on the same face as these protons. Consequently, the

hydroxyl group at C-7 was assigned to the opposite face of the molecule.

The molecular mass of compound 2 was determined by high-resolution electrospray ionization mass spectrometry (ESI-HRMS). The spectrum displayed a pseudo-molecular ion peak $[M+H]^+$ at *m/z* 438.2845, corresponding to a molecular weight of 437.2767 Da. The molecular formula was established as $C_{24}H_{39}NO_6$ (calcd. 437.2777). These data supported the proposed structure of compound 2 as 3β-hydroxy-nor-cassamidine.

Comparison of compounds 1 and 2 showed that both compounds share the same oxygenated nor-cassane diterpenoid framework. However, compound 1 possesses a ketone group at C-7, whereas compound 2 contains a hydroxylated methine carbon at the same position. This structural difference is clearly reflected by the disappearance of the carbonyl resonance at δC 211.3 and the appearance of the oxygenated carbon at δ_C 72.1 in compound 2. Such variation may significantly influence the polarity and biological activity of these molecules.

To confirm this structure, we proposed a fragmentation scheme based on the ESI-QTOF data (Figure 1). Thus, structures were proposed for the major fragment at m/z 452.2643; 392.2431; 361.2010; 343.1904; 301.1798; 283.1693 and 255.1743. Thus, the fragment observed at m/z 347 corresponds to the $[M+H-91]^+$ ion, which is specific to the loss of the 2-(hydroxy(methyl)amino)ethanol (HO-CH_2-CH_2-$NOHCH_3$) group attached to a cassane skeleton. This molecule is new, as no data has been found in the literature. The complete assignment of its chemical shifts is given in Table 1.

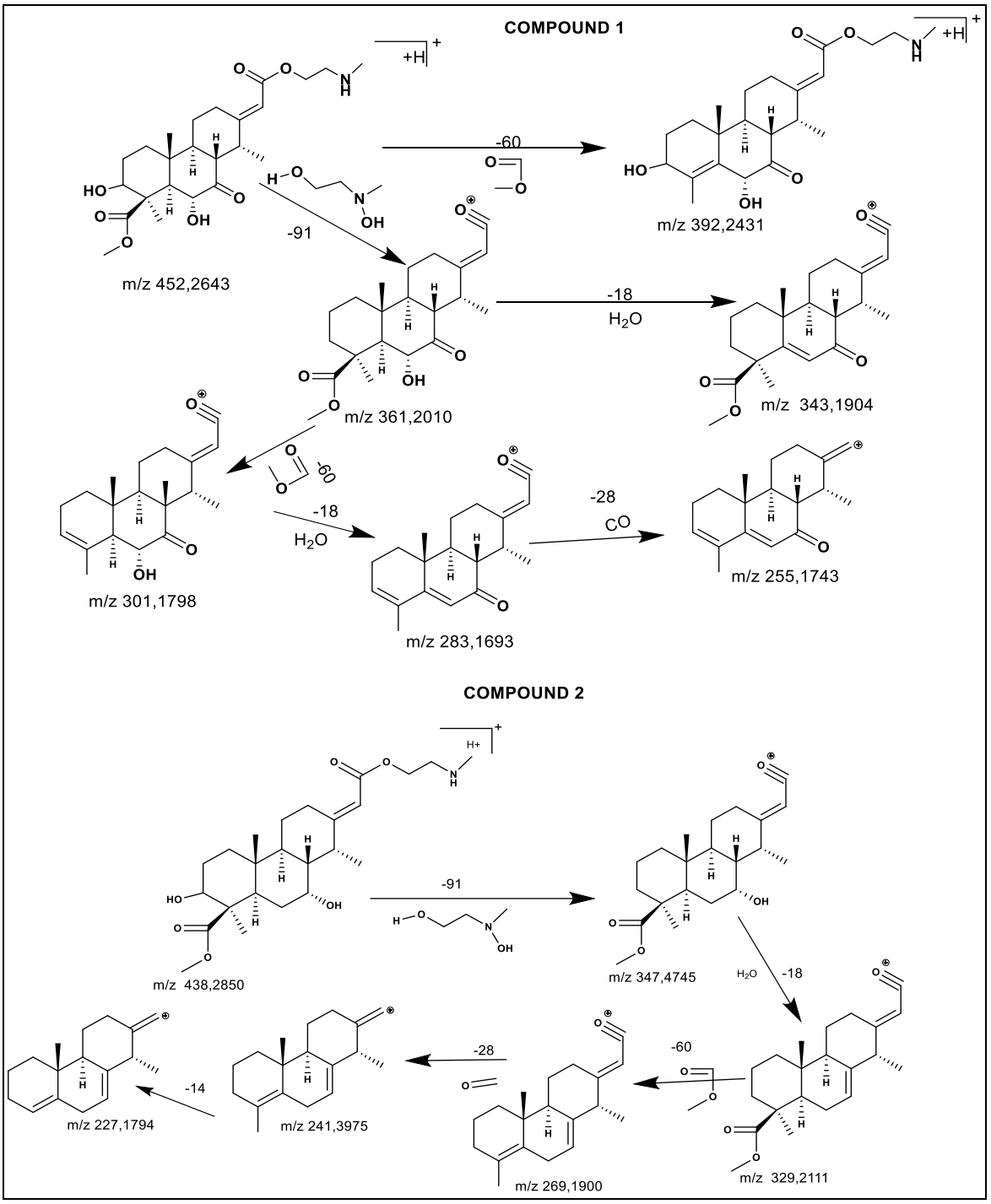

Fig 1: Fragmentation pathway of cassane diterpenoid amines

A full breakdown of its chemical movements is set out in Table 1.

Table 1: ^{1}H and ^{13}C NMR spectral data for compounds 1and 2 (in CD_3OD)

	Compound **1**		Compound **2**	
N°/ Position	**$\delta^{13}C$ (ppm)**	**$\delta^{1}H$ (ppm ; *m* ; *J*. Hz)**	**$\delta^{13}C$ (ppm)**	**$\delta^{1}H$ (ppm ; *m* ; *J*. Hz)**
1	41.0	1.26 (1H ; m) ; 1.88 (1H ; *m*)	40.7	1.30 (1H ; *m*) ; 1.80 (1H ; *m*)
2	20.4	1.51 (1H; m); 1.70 (1H ; *m*)	20.4	1.46 (1H; *m*); 1.80 (1H ; *m*)
3	39.9	1.67 (1H ; *m*) ; 2.11(1H ; *m*)	39.0	1.10 (1H ; *m*) ; 2.18 (1H ; *m*)
4	46.5	-	45.1	-
5	59.7	1.43 (1H ; *d* ; 12.5)	53.8	1.18 (1H ; *m*)
6	77.0	4.76 (1H ; *d* ; 12.5)	33.9	1.75 (1H; *m*); 2.17 (1H ; *m*)
7	211.3	-	72.1	3.41 (1H; *dd ;* 11.44; 4.69)
8	52.9	2.50 (1H ; *dd* ; 13.0 ; 3.0)	49.2	1.48 (1H ; *m*)
9	48.0	1.76 (1H ; *m*)	47.1	1.27 (1H ; *m*)
10	37.8	-	38.3	-
11	28.4	1.20 (1H ; *m*) ; 2.06 (1H ; *m*)	28.3	1.29 (1H ; *m*) ; 1.95 (1H ; *m*)
12	24.9	2.19 (1H ; *m*) ; 3.75 (1H ; *m*)	25.03	2.03 (1H ; *m*) ; 3.69 (1H ; *m*)
13	167.1	-	168.5	-
14	40.7	2.95 (1H ; *m*)	41.5	2.81 (1H ; *m*)
15	113.8	5.75 (1H ; *s*)	112.8	5.70 (1H ; *s*)
16	168.3	-	169.9	-
17	15.4	1.13 (3H ; *d* ; 6.8)	14.17	1.08 (3H ; *d* ; 6.89)
18	32.1	1.47 (3H ; *s*)	29.2	1.19 (3H ; *s*)
19	179.1	-	179.3	-
20	14.2	0.90 (3H ; *s*)	13.5	0.63 (3H ; *s*)
21	62.1	4.22 (2H ; *m*)	61.9	4.23 (2H ; *m*)
22	61.5	2.83 (2H ; *m*)	61.6	2.86 (2H ; *m)*
23	48.6	2.61 (3H ; *s*)	49.1	2.61 (3H ; *s*)
24	52.0	3.69 (3H ; *s*)	51.7	3.62 (3H ; *s*)

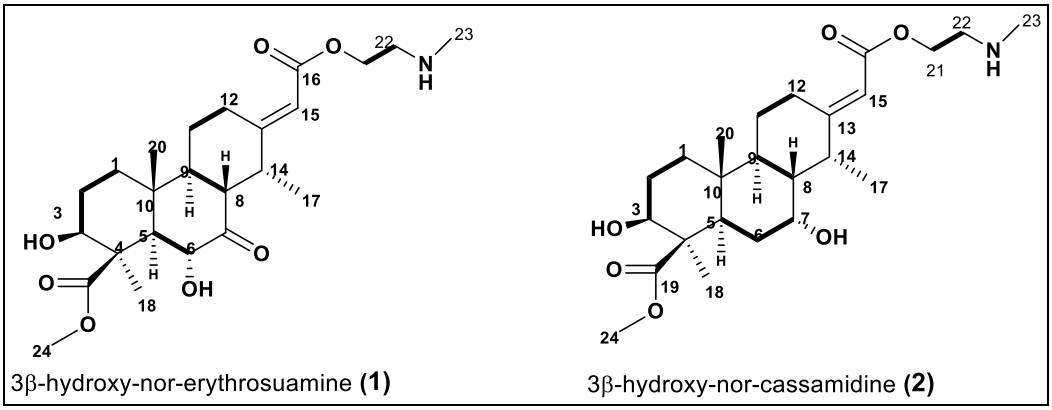

Fig 2: Cassane diterpenoid amines isolated from root bark of *Erythrophleum ivorense*

Introduction

The phytochemical investigation of the root bark of *Erythrophleum ivorense* A. Chev. (Fabaceae) led to the isolation and structural characterization of two cassane diterpenoid amines, identified as 3*β*-hydroxy-*nor*-erythrosuamine (compound 1) and 3*β*-hydroxy-*nor*-cassamidine (compound 2). Their structures were fully elucidated by a combination of spectroscopic methods, including IR, 1D and 2D NMR (HMBC, COSY, NOESY), and high-resolution ESI-MS analyses.

The two compounds share the same oxygenated *nor*-cassane diterpenoid framework, and their structural differentiation lies in the oxidation state at position C-7: compound 1 bears a ketone function at this position, whereas compound 2 possesses a secondary hydroxyl group, as confirmed by the disappearance of the carbonyl signal at δC 211.3 ppm and the appearance of an oxygenated methine carbon at δC 72.1 ppm. This structural variation may have significant implications for the polarity and the biological activities of these molecules.

Although both compounds had previously been described in related *Erythrophleum* species, notably *E. suaveolens* and *E. fordii*, the present study reports their first isolation from the root bark of *E. ivorense*. These findings broaden the known phytochemical profile of this species and further support the characteristic abundance of cassane-type diterpenoids in the genus *Erythrophleum*. Given the documented biological activities of related compounds — including cytotoxic, cardiotonic, anti-inflammatory, and anti-angiogenic effects — these newly isolated metabolites deserve further pharmacological investigation to assess their potential therapeutic relevance.

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