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# A chlorinated coumarinolignan from the African medicinal plant, *Mondia whitei*

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**Abstract**

The unusual chlorinated coumarinolignan, 5-chloropropacin, along with several other known compounds have been isolated from the roots of *Mondia whitei*. The structure of the chlorinated coumarinolignan was determined by NMR and mass spectroscopic analyses.


*Keywords:* *Mondia whitei*; Asclepidiaceae; Chlorinated coumarinolignan; Propacin, 5-Chloropropecin

## 1. Introduction

The roots of *Mondia whitei* are locally known as Mbombongazi (Swahili) in Tanzania and are used for gonorrhoea treatments (Kokwaro, 1976). It is also used to enhance male potency in folk medicine and aqueous roots extract was shown to possess androgenic property in male rats (Watcho et al., 2004). Despite its long use, there have been only a few studies about the isolation of bioactive compounds (Kubo and Kinst-Hori, 1999; Msonthi, 1991; Mukonyi and Ndiege, 2001) and pharmacological effects of extracts from this *Mondia* genus (Watcho et al., 2001). In this study, we have undertaken the chemical examination of roots of *M. whitei* and report the isolation and structural elucidation of an unusual chlorinated coumarinolignan 5-chloropropacin (**3**), along with eight known compounds including propacin (**1**) and its 5′-methoxylated analog (**2**).

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## 2. Results and discussion

The crude methanol extract of the roots of *M. whitei* was partitioned between hexane–$H_2O$, $CHCl_3$–$H_2O$, and *n*-BuOH–$H_2O$, respectively. The $CHCl_3$ extract was separately applied to silica gel column chromatography, followed by size exclusion chromatography over Sephadex LH-20, and preparative TLC, to afford 5-chloropropacin (**3**) and eight other known compounds including propacin (**1**) (see Fig. 1).

5-Chloropropacin (**3**) was obtained as an amorphous solid, analyzing for $C_{20}H_{17}ClO_7$ from HREIMS. The $^1$H NMR spectrum of **3** showed coumarin characteristic signals at 6.39 ppm (1H, *d*, $J = 9.9$ Hz) and 8.04 ppm (1H, *d*, $J = 9.9$ Hz), two aromatic *O*-methyl resonances at $\delta$ 3.89 ppm (3H, *s*) and 3.94 ppm (3H, *s*), one hydroxyl proton signal at $\delta$ 5.74 ppm (1H, *br s*) and 1,3,4-trisubstituted benzene resonances at $\delta$ 6.85 ppm (1H, *d*, $J = 1.8$ Hz), 6.90 ppm (1H, *dd*, $J = 1.8$, 8 Hz), and 6.99 ppm (1H, *d*, $J = 8$ Hz). In addition, it showed two methine proton signals at $\delta$ 4.14 ppm (1H, *m*) and 4.70 ppm (1H, *d*, $J = 7.7$ Hz) and one methyl doublet

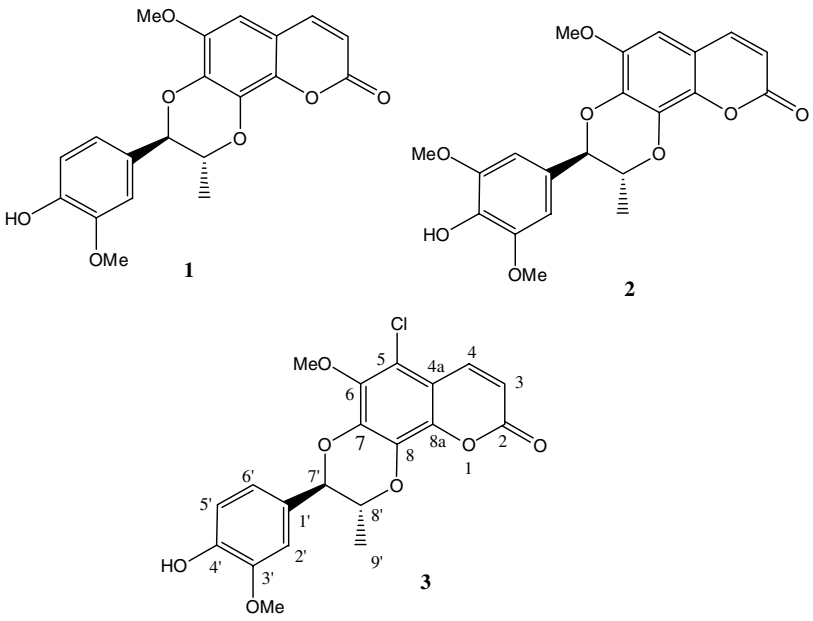



Fig. 1. Structures of the three coumarinolignans isolated from *M. whitei*.

at $\delta$ 1.31 ppm (3H, *d*, $J = 6.3$ Hz). The above spectroscopic data are similar to those of propacin (**1**) (Table 1) except for the absence of the H-5 signal in propacin at $\delta$ 6.52 ppm (1H, *s*). These assignments were supported by analogous $^{13}$C NMR spectroscopic data (Table 2). Because of insufficient amount of material, all the quaternary carbons could not be assigned. The $^{13}$C NMR spectrum of **3** showed C-3 and C-4 resonances at $\delta$ 114.6 ppm (*d*) and 140.4 ppm (*d*), three aromatic resonances at $\delta$ 109.5 ppm (*d*), 114.7 ppm (*d*), and 120.9 ppm (*d*), as well as two aromatic *O*-methyl signals at $\delta$ 56.0 ppm (*q*). In addition, it showed the two methine resonances at $\delta$ 74.5 ppm (*d*) and 81.6 ppm (*d*) and one methyl at $\delta$ 17.0 ppm (*q*). The foregoing NMR spectroscopic data indicated that **3** was a 5-substituted propacin. In addition to NMR data, the EIMS of **3** showed $[M + 1]^+$ and $[(M + 1) + 2]^+$ ions at *m*/*z* 405 (56) and 407 (24), characteristic of the presence of chlorine in **3**. The fragments at *m*/*z* 243 (53) and 245 (20) also further supported the presence of chlorine in coumarin fragments (Fig. 2). The presence of chlorine was further confirmed by HREIMS. From the foregoing data the structure of **3** was thus established as 5-chloropropacin.

In order to unambiguously attribute the presence of the chlorine atom in 5-chloropropacin from the natural source and not as an extraction artefact, we repeated the same extraction and isolation procedure with non-chlorinated solvents. The crude methanol extract of the roots of *M. whitei* was partitioned between toluene–$H_2O$, $Et_2O$–$H_2O$, and EtOAc–$H_2O$, respectively. The $Et_2O$ extract was fractionated by preparative TLC, and one fraction contained 5-chloropropacin (**3**)

Table 1
$^1$H NMR spectroscopic data of coumarinolignans (**1-3**) in $CDCl_3$ ($\delta$ ppm, $J$ in Hz)

| Protons | Compounds | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| 3 | 6.32 (1H, *d*, $J = 9.3$) | 6.32 (1H, *d*, $J = 9.6$) | 6.39 (1H, *d*, $J = 9.9$) |
| 4 | 7.63 (1H, *d*, $J = 9.3$ | 7.62 (1H, *d*, $J = 9.6$ | 8.04 (1H, *d*, $J = 9.9$) |
| 5 | 6.52 (1H, *s*) | 6.53 (1H, *s*) | – |
| 2′ | 6.84 (1H, *d*, $J = 1.8$) | 6.61 (1H, *s*) | 6.85 (1H, *d*, $J = 1.8$) |
| 5′ | 6.94 (1H, *d*, $J = 8$) | – | 6.99 (1H, *d*, $J = 8$) |
| 6′ | 6.88 (1H, *dd*, $J = 8,1.8$) | 6.61 (1H, *s*) | 6.90 (1H, *dd*, $J = 8$, 1.8) |
| 7′ | 4.67 (1H, *d*, $J = 8.0$) | 4.64 (1H, $J = 8.0$) | 4.70 (1H, *d*, $J = 7.7$) |
| 8′ | 4.22 (1H, *m*) | 4.22 (1H, *m*) | 4.14 (1H, *m*) |
| 9′ | 1.29 (3H, *d*, $J = 6.3$) | 1.30 (3H, *d*, $J = 6.3$) | 1.31 (3H, *d*, $J = 6.3$) |
| 6-OMe | 3.89 (3H, *s*) | 3.89 (3H, *s*) | 3.89 (3H, *s*) |
| 3′-OMe | 3.93 (3H, *s*) | 3.92 (3H, *s*) | 3.94 (3H, *s*) |
| 5′-OMe | – | 3.92 (3H, *s*) | – |
| 4′-OH | 5.72 (1H, *br s*) | 5.62 (1H, *br s*) | 5.74 (1H, *br s*) |

Table 2
$^{1}$C NMR spectroscopic data of coumarinolignans (**1**–**3**) ($\delta$ ppm)

| Carbon number | Compounds | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| 2 | 160.8 | 160.8 | |
| 3 | 114.0 | 114.1 | 114.6 |
| 4 | 145.8 | 145.8 | 140.4 |
| 4a | 111.5 | 111.6 | |
| 5 | 99.9 | 99.9 | |
| 6 | 143.7 | 143.7 | |
| 7 | 137.6 | 137.6 | |
| 8 | 132.3 | 132.3 | |
| 8a | 138.7 | 138.7 | |
| 1′ | 127.7 | 126.8 | 127.6 |
| 2′ | 109.7 | 104.5 | 109.5 |
| 3′ | 146.9 | 147.3 | 146.4 |
| 4′ | 146.6 | 135.6 | 146.2 |
| 5′ | 114.6 | 104.5 | 114.7 |
| 6′ | 121.2 | 126.1 | 120.9 |
| 7′ | 81.4 | 81.7 | 81.6 |
| 8′ | 74.3 | 74.3 | 74.5 |
| 9′ | 17.1 | 17.1 | 17.0 |
| 6-OMe | 56.0 | 56.2 | 56.0 |
| 3′-OMe | 56.3 | 56.4 | 56.0 |
| 5′-OMe | – | 56.4 | |

*Note*. Tertiary carbon signal at $\delta$ 110.5 ppm not assigned.

as evidenced by mass spectral analysis (ESI). Having established the original source of chlorine, we revert back to the extraction in chlorinated solvent because of the better yields obtained for it.

5-Chloropropacin (**3**) is the first chlorinated compound of the coumarinolignan family, and this is the first report of the isolation of coumarins and coumarinolignans (**1** and **2**) from the genus *Mondia*. Propacin (**1**) has been previously identified in *Protium opacum* (Zoghbi et al., 1981) and in *Jatropha gossypifolia* (Das and Venkataiah, 2001). Its structure has also been firmly established by chemical synthesis (Tanaka et al., 1988a,b), while compound **2** has been isolated from the root bark of *Hibiscus syriacus* and was shown to possess potent monoamine oxidase inhibitory activity (Yun et al., 2001). Natural propacin (**1**) is usually isolated in its racemic form (Das and Venkataiah, 2001; Zoghbi et al., 1981; Marques Marcia and Yoshida, 1990) and all known syntheses provided racemic mixtures (Lin and Cordell, 1984; Arnoldi et al., 1984; Tanaka et al., 1988a,b). From the absence of optical activities of both propacin (**1**) and 5-chloropopacin (**3**), we concluded that we also obtained racemic compounds. However, for compound **2**, the positive optical rotation value measured ($[\alpha]_D + 4.8°$) suggests that we isolated the enantiomer of the same coumarinolignan previously isolated from the root bark of *Hibiscus syriacus* (Yun et al., 2001). To our knowledge, no absolute stereochemistry has yet been assigned for propacin enantiomers.

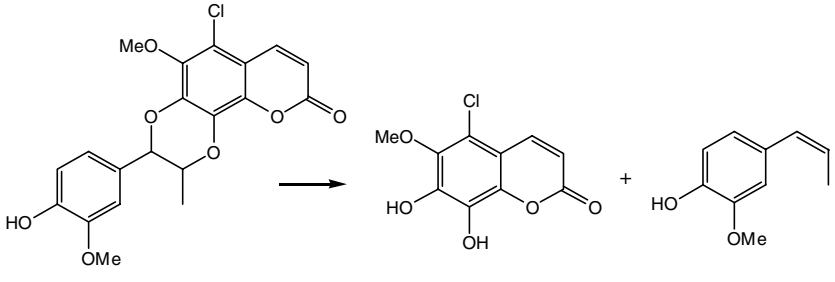
## 3. Experimental

### 3.1. General

Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. IR spectra were obtained with a Perkin–Elmer 681 spectrophotometer. NMR spectra were recorded on a Bruker AMX-500 spectrometer or Bruker AV-300 spectrometer. EIMS spectra were recorded on Kratos Concepts IIH mass spectrometer. Precoated silica gel plates (Merck, Kieselgel 60 F-254, 0.5 mm) were used for PTLC. Thin layer chromatography (TLC) was performed on silica gel $F_{254}$ (Merck) precoated aluminium sheets and spots were visualized under UV and by spraying with molybdenum solution and heating.

### 3.2. Plant material

The plant material was collected from AVE District in Togo (West Africa) in 2001, and identified by Professor K. Akpagana, Department of Botany, University of Lomé, Togo. A voucher specimen (No. 458) was deposited in the herbarium of the Department of Botany, University of Lomé, Togo. The outer cover of the roots was dried at room temperature and ground into a yellow powder. This material constitutes commercially available preparations in parts of west Africa.




*m/z* 404 *m/z* 242 *m/z* 164

Fig. 2. Mass fragmentation of 5-chloropopacin (**3**).

### 3.3. Extraction and isolation

The powder of *M. whitei* roots (693 g) was extracted with MeOH (3 × 3 L) at room temperature. The combined MeOH extracts were filtered, and the solvent was removed under reduced pressure to provide a brownish residue (51.5 g). The crude MeOH extract (50 g) was partitioned between *n*-hexane–$H_2O$, $CHCl_3$–$H_2O$, and *n*-BuOH–$H_2O$. The organic layers were concentrated under reduced pressure to yield an *n*-hexane extract (17.3 g), a $CHCl_3$ extract (23 g), and an *n*-BuOH extract (4.1 g), respectively.

The $CHCl_3$ extract (20 g) was subjected to silica gel column chromatography using solvents of increasing polarity from *n*-hexane to EtOAc as eluents, followed by gel filtration chromatography over Sephadex LH-20 using MeOH as eluent and by preparative TLC. This manipulation gave squalene (186 mg) (Grieco and Masaki, 1974), 2-hydroxy-4-methoxybenzaldehyde (26.5 mg), a known potent tyrosinase inhibitor (Kubo and Kinst-Hori, 1999), β-sitosterol (1.01 g) (Slomp and Mackellar, 1962), 3-methoxy-4-hydroxybenzaldehyde (856 mg) (Klinck and Stothers, 1962), 6-methoxy-7-hydroxycoumarin (68 mg) (Sankar et al., 1982), 6-methoxy-7,8-dihydroxycoumarin (15 mg) (Talapatra et al., 1975), propacin (**1**, $[\alpha]_D$ 0° ($CHCl_3$:MeOH (1:1), *c* 0.7) (8 mg) (Zoghbi et al., 1981; Das and Venkataiah, 2001; Tanaka et al., 1988a,b), coumarinolignan **2** ($[\alpha]_D$ + 4.8° ($CHCl_3$:MeOH (1:1), *c* 0.7) (4 mg) (Yun et al., 2001) and 5-chloropropacin (**3**, $[\alpha]_D$ 0° ($CHCl_3$:MeOH (1:1), *c* 0.7) (1 mg), respectively.

### 3.4. 5-Chloropropacin (*3*)

Amorphous solid; for the $^1H$ NMR ($CDCl_3$, 300 MHz) and $^{13}C$ NMR ($CDCl_3$, 75 MHz) spectroscopic data, see Tables 1 and 2, respectively; EIMS *m/z* 407 $[(M + 1) + 2]^+$ (24), 405 $[M + 1]^+$ (56), 404 $[M]^+$ (14), 369 (6), 341 (3), 313 (4), 283 (5), 245 (20), 243 (53), 209 (47), 165 (100), 137 (49), 123 (25), 85 (48); HREIMS *m/z* 404.0665 (calcd for $C_{20}H_{17}ClO_7$, 404.0663).

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