Trichotomol, a New Cadinenediol from Cordia trichotoma

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Um novo sesquiterpene, nomeado trichotomol e compostos conhecidos como cordiachrome C, α-cadinol, ácido oleanólico, oncocalyxona A, β-sitosterol, glicosídeo do β-sitosterol, alantoína e sacarose foram isolados a partir do extrato etanólico do cerne de Cordia trichotoma. Suas estruturas foram determinadas por análises espectroscópicas e comparação com dados publicados para compostos estruturalmente relacionados.

A new sesquiterpene, named trichotomol, and known compounds cordiachrome C, α-cadinol, oleanolic acid, oncocalyxone A, β-sitosterol, β-sitosterol-β-D-glucoside, allantoin and sucrose were isolated from the heart wood ethanol extract of Cordia trichotoma. Their structures were assigned unambiguously by spectroscopic analyses and comparison with the published data for structurally related compounds.

Keywords: Cordia trichotoma, Boraginaceae, sesquiterpene, trichotomol, cordiachrome C

Introduction

Cordia trichotoma Vell. (Boraginaceae) is a tropical tree, popularly known as “frei jorge” 1. According to a literature survey, several uses in traditional medicine such as cicatrizant, astringent, anti-inflammatory, antihelminthic, antimalarial, diuretic and to treat urinary infections, lung diseases and leprosy have been reported for several Cordia species 2-4. No medicinal use has been reported for C. trichotoma, but its wood is recognized for its durability in carpentry and construction 1. Previous phytochemical investigations of plants from this genus have described several natural products structurally related to terpenoid quinone and hydroquinones 5-7. In the last few years, several articles have been published on this kind of compounds, from Auxemma genus 8-10, belonging to the same family and formerly considered synonymous of Cordia. To the best of our knowledge, except for a publication in which the presence of eudesmol isomers from C. trichotoma wood 11 has been recorded, there have been no other reports of any similar chemical investigation in the literature. In this paper we describe the isolation and structure elucidation of the known compounds: β-sitosterol, sitosterol-β-D-glucoside 12, oleanolic acid 13, allantoin 14, sucrose 15, α-cadinol 16, oncocalyxone A 8, cordiachrome C 5, and a new sesquiterpene, trichotomol (1). Although cordiachrome C (2) had been previously isolated from C. millenii, only the partial 1H NMR data was provided but some doubt about its stereochemistry 5 has remained. Here the complete 1H and 13C spectral data and assignments for 2 are reported for the first time and used to corroborate the stereochemical aspects.

Results and Discussion

Compound 1 was obtained as colorless crystals, mp 159-160 °C and [α]589 = −17.1 (c 0.7, CHCl3, 23 °C). Its IR spectrum revealed hydroxyl (3353 cm⁻¹ and 1116 cm⁻¹ ) and olefinic (1657 cm⁻¹ ) absorptions.

The molecular formula C15H26O2, which indicates three double-bond equivalents, was deduced using EIMS, 13C NMR, and DEPT analyses. The 13C NMR (BB and DEPT) spectra displayed signals corresponding to four methyl, four methylene, four methine, and three non-hydrogenated carbons. Resonances due to two olefinic carbons at δC 134.3 (C) and 124.7 (CH) in the 13C NMR spectrum accounted for one double-bond equivalent,
suggesting that I as a bicyclic compound. Two of the nonhydrogenated saturated carbons, δC 74.2 and 72.1, were shifted to high frequency indicating they were attached to oxygen atoms. The EIMS spectrum did not present the molecular ion, but showed ions at m/z 220 (M - H2O) and 202 (M - 2H2O), in agreement with the presence of two hydroxyl groups for I. The 1H NMR spectrum indicated resonances corresponding to four methyl groups, three of which were attached to carbons bearing hydroxyl groups: δH 1.09 (s), 1.19 (s) and 1.20 (s), while the third one (δH 1.64, s) due to the high frequency chemical shift seemed to be attached to a double bond. The presence of just one olefinic hydrogen (δH 6.14 (br s), suggested the presence of a trisubstituted double bond which is in accordance with 13C NMR data.

These data were similar to those reported for α-cadinal16. Except for the observed differences, especially for the carbon atoms at δC 53.0 (C-7), 74.2 (C-11), 24.1 (C-12) and 32.1 (C-13), of I in respect to those of α-cadinal, what could be explained by the existence of an additional C-11 hydroxyl group in I. The slight difference between the chemical shift of methyls C-12 and C-13 (δC 24.1 and 32.1, respectively) revealed that there is no free rotation around the single bond C7-C11, as expected. From the NOESY data it was possible to assign unambiguously the chemical shift of both carbons through the dipolar interaction of H-6 (δH 1.93) with the slightly more protected H-12 (δH 1.19) and the equatorial H-8 (δH 1.75) with the other one H-13 (δH 1.20). HMQC data it was easy to assign both carbon chemical shifts.

The relative stereochemistry of I was determined by analysis of the NOESY spectrum. The observed nOes for H-1α, H-2α, H-9α and H-7α; for H-6β, H-2β and 3H-14β were consistent with a trans configuration of the A/B rings. These data also suggested that the configurations of HO-10 and HO(CH2)2-C7 groups were α and β, respectively (Figure 1). Based on these data, the structure of I was determined as the 10α,11-dihydroxy-4-cadinene, which is a new sesquiterpene.

Compound 2 was obtained as an orange oil, and its molecular formula, C16H18O2, was suggested by 13C NMR, DEPT, and EIMS (m/z 242, [M]+). The IR spectrum of 2 showed the presence of carbonyl (1680 cm⁻¹) and olefinic (1656 cm⁻¹) groups.

Comparative analysis of BB and DEPT – 13C NMR spectra revealed six sp3 carbons (two methyls, two methylenes, one methine and one quaternary), two carbonyl groups and eight sp² carbons (three non-hydrogenated, three methines and two methylenes). The presence of a 1,4-benzoquinone moiety was revealed by the chemical shifts for H-2 δH (6.70, d, J 9.2 Hz) and H-3 δH (6.68, d, J 9.2 Hz), and for the carbons atoms C-1 (δC 187.1) and C-4 (δC 186.9).

The 500 MHz 1H NMR spectrum presented information for all signals, including the homoallyl coupling of the methylene groups 2H-5 [δH 2.66 (H-5α), 2.24 (H-5β)], and 2H-8 [δH 2.60 (H-8β), 2.44 (H-8α)]. The signal at δH 2.18 (dd, J 11.1 and 5.0 Hz) was attributed to H-10a, whose coupling constant values correspond to vicinal spin-spin interaction between hydrogens H-10 and H-10a.

1H- and 13C-NMR spectra (DEPT and HMOC) also showed signals related to the methylene of a vinyl group – CH=CH2 δH [5.87 (dd, J 10.9 and 17.5 Hz, H-14), 4.98 (d, J 10.9 Hz, H-15α), 4.87 (d, J 17.7 Hz, H-15β)] and the methylene of an isopropenyl group –C(CH3)=CH2 δH [4.88 (s, H-12a), 4.74 (s, H-12b), 1.73 (s, 3H-13)]. The heteronuclear long-range interaction between the methyl carbon CH3-13 [δC 23.2; δH 1.73 (s)] and hydrogens 2H-12 δH [4.88 (s) and 4.74 (s)] and H-7 (δH 2.18, dd, J 11.1 and 5.0 Hz) observed in the HMBC spectrum, was also used to locate that methyl at carbon C-5 (δC 145.1).

The cis relative configuration for the double bond moieties was supported from the chemical shift at δ 1.11 corresponding to the angular methyl (CH3-16)5. The proposed stereochemistry was also supported by the NOESY experiment (Figure 2), that showed correlation between H-5β, 3H-16 and H-7. Thus, 2 was identified as 6-ethenyl-5,6,7,8-tetrahydro-6-methyl-7-(1-methyl-ethenyl)-1,4-naphthalenedione.
Figure 2. $^1$H - $^1$H dipolar correlations of 2 observed through NOESY experiments.

**Experimental**

**General experimental procedures**

Melting points were determined using a melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1000 FT-IR instrument. EIMS data were obtained using a VG-Auto Spec mass spectrometer. Optical rotations were measured in a Perkin-Elmer 341 digital polarimeter. The NMR spectra were recorded in a Bruker DRX 500 [500 MHz ($^1$H) and 125 MHz ($^{13}$C)] spectrometer. Chemical shifts were recorded in $\delta$(ppm) from TMS relative to the solvent absorption relative to TMS, CDCl$_3$.

**Plant material**

*Cordia trichotoma* was collected in March 1998, at the Meruoca mountain, State of Ceará, Brazil, and identified by A. S. Nogueira de Castro and E. P. Nunes, botanists of the Universidade Federal do Ceará. The voucher specimen is deposited (Herbarium Prisco Bezerra, N° 25.165).

**Extraction and Isolation**

The air-dried and pulverized heartwood (2.0 kg) was exhaustively extracted with EtOH at room temperature and then concentrated under vacuum to yield 124.0 g of a brown residue. The ethanol extract was first fractioned by CC with hexane, CHCl$_3$, EtOAc and MeOH. The hexane fraction was subjected to CC and eluted with mixtures of hexane and EtOAc of increasing polarities to give $\beta$-sitosterol (176.0 mg, mp 162-164 °C), oleanolic acid (25.0 mg, mp $>$300 °C), $\alpha$-cadinol (58.0 mg, mp 73-74 °C) and the new compound I (186.0 mg, mp 158-160 °C). Similarly, CC of the CHCl$_3$ fraction, eluting with an hexane-EtOAc gradient, yielded oncocalyxone A (73.0 mg, mp 208-209 °C) and cordiachrome C (2, 32.6 mg). The EtOAc fraction gave $\beta$-sitosterol-$\beta$-D-glucoside (287.0 mg, mp 289-292 °C), after repeated CC, using EtOAc-MeOH as eluent. From the MeOH fraction a precipitate was collected and was identified as sucrose (2.96 g, mp 185-186 °C). The residue from the supernatant MeOH fraction, after evaporation, was submitted to CC. Elution with increasing polarity with CHCl$_3$/EtOAc gave allantoin (630.0 mg, mp 230-232 °C).

**Compound I.** C$_{15}$H$_{26}$O$_2$, 10α,11-dihydroxy-4-cadinene. (185.6 mg, 1.49 %); colorless crystal, mp 159 – 160 °C (CHCl$_3$); $\lbrack 0\rbrack$_{350}$D$^2$ = -17.1 ($c$: 0.7, CHCl$_3$, 23 °C); IR $v_{\text{max}}$ (cm$^{-1}$) 3535, 2961, 2863, 1657, 1457, 1375, 1116 (KBr); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.26 (m, H-1), 1.99 (m, H-2α), 1.25 (m, H-2β), 1.98 (m, H-3β), 1.92 (m, H-3α), 6.14 (s, H-5), 1.93 (m, H-6), 1.21 (m, H-7), 1.75 (m, H-8α), 1.03 (m, H-8β), 1.46 (dq, J 3.4 and 12.5 Hz, H-9α), 1.78 (dq, J 3.4 and 12.5 Hz, H-9β), 1.19 (s, 3H-12), 1.20 (s, 3H-13), 1.09 (s, 3H-14), 1.64 (s, 3H-15); $^1$H NMR (DMSO-d$_6$, 500 MHz) $\delta$ 4.04 (s, HO-10), 4.11 (s, HO-11); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 49.8 (CH-1), 22.7 (CH$_2$-2), 30.6 (CH$_3$-3), 134.3 (C-4), 124.7 (CH-5), 40.8 (CH-6), 53.0 (CH-7), 134.3 (C-8), 127.8 (C-9), 134.3 (C-10), 74.2 (C-11), 24.1 (CH$_3$-12), 32.1 (CH$_3$-13), 20.7 (CH$_3$-14), 24.1 (CH$_3$-15); EIMS (70 eV) $m/z$ 220 (M – H$_2$O, 5), 202 (M – 2H$_2$O, 47), 43 (100).

**Compound 2.** C$_{16}$H$_{18}$O$_2$, 6-ethenyl-5,6,7,8-tetrahydro-6-methyl-7-(1-methyllethyl)-1,4-naphthalenedione. (32.6 mg, 0.026 %); orange oil; $\lbrack 0\rbrack$_{350}$D$^2$ = -11.1 (c: 0.27, CHCl$_3$, 23 °C); IR $v_{\text{max}}$ (cm$^{-1}$) 2920, 2851, 1680, 1656, 1464, 1376, 1278, 908, 725 (film); $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.69 (d, J 9.2 Hz, H-2), 6.67 (d, J 9.2 Hz, H-3), 6.66 (d, J 19.4 Hz, H-5α), 2.24 (ddd, J 19.4, 4.1 and 2.4 Hz, H-5β), 2.18 (dd, J 11.1 and 5.0 Hz, H-7), 2.60 (dd, J 19.9 and 2.6 Hz, H-8β), 2.44 (dddd, J 19.9, 11.1, 4.1 and 2.0 Hz, H-8α), 4.89 (s, H-12a), 4.74 (s, H-12b), 1.73 (s, Me-13), 5.87 (dd, J 17.5, and 10.9 Hz, H-14), 4.98 (d, J 17.5 Hz, H-15b), 1.11 (s, Me-16); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 186.9 (C-1), 136.3 (CH-2), 136.3 (CH-3), 187.1 (C-4), 36.2 (CH$_2$-5), 37.7 (C-6), 49.4 (CH-7), 26.5 (CH$_2$-8), 141.6 (C-9), 140.7(C-10), 145.0 (C-11), 113.8 (CH$_2$-12), 23.1 (CH$_3$-13), 141.3 (CH-14), 113.4 (CH$_2$-15), 26.1 (CH$_3$-16); EIMS (70 eV) $m/z$ 242 (M$^+$, 15), 227 (M – CH$_3$,100), 199 (19).

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