



ISOCAPNELL-9-EN-8-ONE AND 6α -HYDROXYISOCAPNELL-9-EN-8-ONE, SESQUITERPENES FROM *BUDDLEIA* SPECIES*

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Key Word Index—*Buddleia cordata*; *Buddleia sessiliflora*; Loganiaceae; sesquiterpenes; isocapnell-9-en-8-one; 6α -hydroxyisocapnell-9-en-8-one.

Abstract—The structures of the new sesquiterpenes, isocapnell-9-en-8-one and 6α -hydroxyisocapnell-9-en-8-one, isolated from two *Buddleia* species have been elucidated mainly on spectral grounds. The existence of a new carbon skeleton is described.

INTRODUCTION

The genus *Buddleia* comprises around 100 species, [1], natives of the tropical lands of America, Asia and Africa. These plants are used in traditional medicine of several parts of the world where they are indigenous. They are utilized as wound healing agents, as anti-inflammatory, diuretics and topical antiseptics among other uses [1].

The roots of some *Buddleia* species have been studied in the search for active principles. *Buddleia davidi* Franch afforded several bactericidal phenylethanoids [2] and piscicidal sesquiterpenes [3, 4]. A chemical study of the different organs of *Buddleia cordata* H. B. K. and *Buddleia sessiliflora* H. B. K. resulted in the isolation of some known compounds and the two new sesquiterpenes isocapnell-9-en-8-one (**1a**) and 6α -hydroxyisocapnell-9-en-8-one (**1c**) which belong to the new skeleton isocapnelene (**2**).

RESULTS

The bark of *B. cordata* afforded sucrose [5] and the known iridoids O-methyl catalpol [6] and aucubin [7]. The root bark afforded sitosterol, stigmasterol, the lignane sesamin [8] and the new compounds isocapnell-9-en-8-one (**1a**) and 6α -hydroxyisocapnell-9-en-8-one (**1c**). The root bark of *B. sessiliflora* gave aucubin, sesamin and **1a**.

Isocapnell-9-en-8-one (**1a**) presents a molecular ion at *m/z* 218, corresponding to $C_{15}H_{22}O$. Its IR and UV

spectra showed the presence of an α, β -unsaturated ketone, in agreement with the ^{13}C NMR spectrum (Table 1), which showed signals at δ 208.21, 140.32 and 176.34 assigned to C-8, C-9 and C-10 respectively. The 1H NMR spectrum (Table 2) exhibited two singlets at δ 1.02 and 1.25 assigned to the *gem*-methyls, and two doublets, one of the secondary methyl (δ 0.80, *J* = 7.0 Hz, C-13) and the other of the vinylic methyl (δ 1.73, *J* = 1.86 Hz, C-12). Owing to the instability of compound **1a**, its 2,4-dinitrophenylhydrazone was prepared [9]. The assignment of the signals of every C and H atom of compound **1b** was achieved by 1H NMR, ^{13}C NMR, DEPT, COSY, HETCOR, COLOC and NOESY experiments (Tables 1 and 2). Th NOESY experiments showed that H-5, H-6 and H-7 α were on the same side of the molecule and that H-4, H-11 and H-13 were on the oposite face, thus indicating a *cis*-fusion between the rings A and B (Fig. 1). The proximities of the NH hydrogen to H-7 and that of the aromatic proton H-6' to the vinylic methyl were indicative of an *E*-configuration for the imine (Fig. 1). The above data and the positive Cotton effect observed at 255 nm in the CD curve lead us to assign the structure **1b** for the hydrazone derivative and **1a** for the natural product isocapnell-9-en-8-one with the configurations 4S, 5S, 6S, 11R.

6α -Hydroxyisocapnell-9-en-8-one (**1c**), $C_{15}H_{22}O_2$ (MS) had UV, IR, 1H NMR and ^{13}C NMR spectral data (Tables 1 and 2) very similar to those of **1a**. The C-7 methylene appeared as an AB system (*2 d*, δ 2.83 and 2.49, *J* = 18.6 Hz) due to the presence of an alcohol at C-6. The alcohol function was shown by the band at 3500 cm^{-1} in the IR spectrum and by a singlet at δ 7.86 in the 1H NMR spectrum which interchanged with D_2O . The atom bearing the OH group appeared as a singlet at δ 92.93 in the ^{13}C NMR spectrum.

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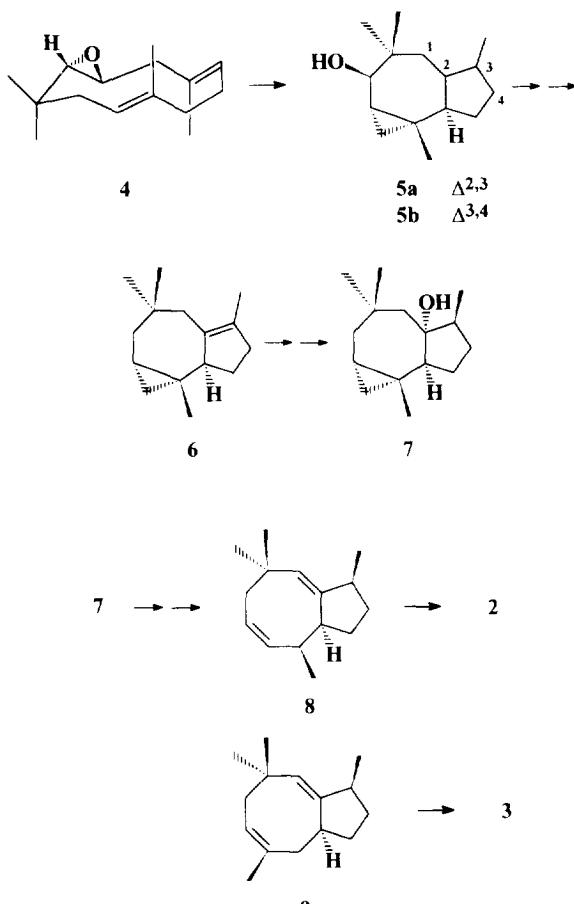
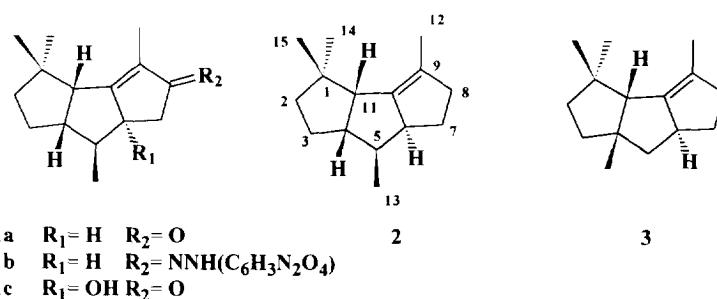


Table 1. ^{13}C NMR spectral data of compounds **1a–1c***

C	1a	1b	1c
1	25.9	25.1	22.6
2	32.5	32.0	30.9
3	21.1	21.2	25.9
4	32.3	27.7	27.1
5	42.5	32.1	45.7
6	29.5	45.5	92.9
7	40.2	31.5	45.0
8	208.2	161.8	206.6
9	140.3	136.7	144.4
10	176.3	161.8	169.3
11	31.7	31.3	26.4
12	8.2	9.5	9.7
13	17.4	17.7	18.7
14	28.5	16.6	17.8
15	16.5	29.2	28.4
1'		144.9	
2'		128.5	
3'		123.8	
4'		137.1	
5'		129.8	
6'		116.3	

*Run at 50 MHz, CDCl_3 , TMS as int. standard. Assignments were done using DEPT, HETCOR and COLOC experiments.

The NOESY experiments evidenced the proximity of $\text{H}-2\alpha$, $\text{H}-14$ and the OH . Interactions were also observed among $\text{H}-11$ with $\text{H}-12$ and $\text{H}-15$ and of $\text{H}-7\beta$ with $\text{H}-13$. These NOE effects were consistent with the stereochemistry depicted in **1c** ($4R, 5S, 6R, 11R$) for the sesquiterpene 6α -hydroxyisocapnell-9-en-8-one.

Compounds **1a** and **1c** present a novel sesquiterpene skeleton, isocapnellene (**2**). This sesquiterpene obeys the isoprene rule and differs from capnellene (**3**) [10, 11] in having a β -methyl group at C-5 instead of C-4. The isocapnellene (**2**) should be formed biogenetically from humulene oxide (**4**).

It was reported that humulen monoepoxide (**4**) reacts with $\text{CF}_3\text{SO}_3\text{Si}(\text{CH}_3)_3$ in the RSR-CT conformation

[12–14] to give the two africenol isomers **5a** and **5b**. The africen-10-ol (**5a**) is transformed into the natural products africene (**6**) and africanol (**7**). We propose that the sesquiterpene africanol (**7**) after dehydration and cyclopropane opening, affords the intermediary **8**, an isomer of **9**. Substance **9** has been proposed as precursor of capnellene (**3**). A transannular cyclization of **8** gives rise to isocapnellene (**2**).

EXPERIMENTAL

Plant material. *Buddleia cordata* H. B. K. was collected in the Valley of Mexico in September 1992 and March 1993. *Buddleia sessiliflora* H. B. K. was collected in Ozumba, Mexico in August 1993. Voucher specimens (25060 and 25064 respectively) are deposited in the Herbarium of Iztacala, U.N.A.M.

Table 2. ^1H NMR spectral data of compounds **1a–1c***

H	1a	1b	1c
2 α	1.7 <i>m</i>	1.5 <i>m</i>	1.74 <i>br t</i> (12.6)
2 β	1.5 <i>m</i>	1.65 <i>m</i>	1.49 <i>ddd</i> (12.6, 2, 0.8)
3 α	2.0 <i>m</i>	1.9 <i>m</i>	2.09 <i>br tdd</i> (13.9, 6, 1.4)
3 β	1.0 <i>m</i>		0.91 <i>br tdd</i> (14, 11.7, 0.9)
4	1.3 <i>m</i>	1.45 <i>m</i>	1.17 <i>ddd</i> (13.3, 9.3, 4.2, 2.8)
5	1.6 <i>m</i>	2.05 <i>qdd</i> (8.5, 4.2, 2.3)	1.54 <i>qd</i> (6.6, 2.7)
6	2.96 <i>m</i>	3.11 <i>br dd</i> (4.8, 2.3)	
7 α	2.5 <i>dd</i> (18.4, 6.4)	2.82 <i>dd</i> (17.4, 6.9)	2.83 <i>d</i> (18.6)
7 β	2.07 <i>br dd</i> (18.4, 2.3)	2.31 <i>dd</i> (17.4, 2.5)	2.49 <i>d</i> (18.6)
11	1.48 <i>d</i> (8.5)	1.2 <i>m</i>	1.37 <i>dd</i> (9.5, 1.7)
12	1.73 <i>d</i> (1.8)	1.92 <i>d</i> (1.5)	1.78 <i>d</i> (1.8)
13	0.8 <i>d</i> (7.0)	0.82 <i>d</i> (6.8)	1.09 <i>d</i> (6.8)
14	1.02 <i>s</i>	0.99 <i>s</i>	1.03 <i>s</i>
15	1.25 <i>s</i>	1.24 <i>s</i>	1.10 <i>s</i>
NH OH		10.95 <i>br s</i>	7.66 <i>br s</i>
3'		9.13 <i>d</i> (2.4)	
5'		8.28 <i>dd</i> (9.6, 2.5)	
6'		7.99 <i>d</i> (9.6)	

*Run at 200 MHz, CDCl_3 , TMS as int. standard. Values are in ppm. Values in parentheses are coupling constants in Hz. Assignments are based in COSY, COLOC and HECTOR experiments.

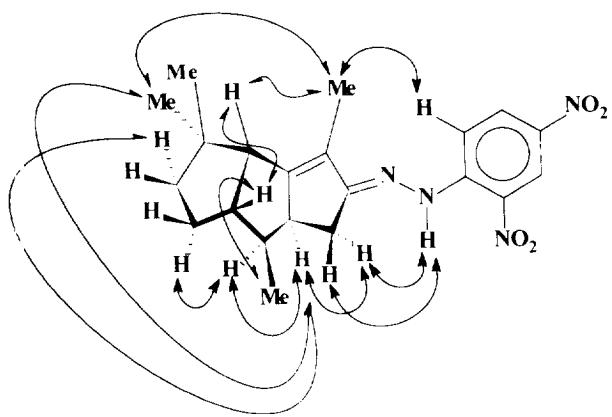


Fig. 1.

Extraction. *Buddleia cordata* bark was dried and the ground material (608 g) was extracted with MeOH. The extract (53 g) was washed with hexane and *n*-BuOH, leaving 44.12 g of methanolic residue. The extract after

successive CC over Kieselgel G and using as eluent different mixtures of CHCl_3 -MeOH, afforded *O*-methyl catalpol (851 mg) [6], aucubin (537.7 mg) [7] and sucrose (493.2 mg) [5].

Buddleia cordata root bark was dried and the ground material (1015 g) was extracted with hexane and MeOH. The hexane extract (14 g) was chromatographed over Kieselgel G (310 g) and eluted with a gradient of hexane-EtOAc. Frs 27–30 (1.62 g) eluted with hexane-EtOAc (4:1) were rechromatographed over Kieselgel G (40 g) and eluted with hexane-EtOAc (4:1). The less and the more polar frs were combined separately. The less polar residue afforded isocapnell-9-en-8-one (**1a**, 62.9 mg) after prep. TLC (hexane-EtOAc, 7:3). The more polar residue afforded 6 α -hydroxyisocapnell-9-en-8-one (**1c**, 113.9 mg) by crystallization. Frs 31–46 eluted with hexane-EtOAc (4:1) were purified by successive CC affording 9.6 mg of **1a**, 25.6 mg of sesamin [8] and 6.5 mg of a mixture of sitosterol and stigmastanol. The MeOH extract (81.3 g) was purified by CC (1 kg Kieselgel G), eluting with solvents mixture of increasing polarity

(CHCl₃, MeOH). After successive rechromatographing of the different fractions, sesamin (19.5 mg), **1a** (71.4 mg) and **1c** (36.5 mg) were separated.

Buddleia sessiliflora root bark was dried and the ground material (252.6 g) was extracted with hexane and MeOH. The hexane extract (2.01 g) after successive CC afforded **1a** (6.1 mg) and sesamin (11.1 mg). The MeOH extract (31.7 mg) afforded *O*-methyl catalpol (2.612 g) and aucubin (588 mg) after repeated CC.

Isocapnell-9-en-8-one (1a). Yellow pale gum, $[\alpha]_D + 149.5^\circ$ (CHCl₃; *c* 1.11). UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 260 (4.04). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1694, 1622. EIMS 70 eV *m/z* (rel. int.): 218 [M]⁺ (62), 203 [M - CH₃]⁺ (10), 175 [203 - CO]⁺ (39.6), 119 [175 - C₄H₈]⁺ (87.8), 105 [119 - CH₂]⁺ (92.7), 91 [105 - CH₂]⁺ (90.7), 77 [91 - CH₂]⁺ (68), 41 [C₃H₅]⁺ (100).

6 α -Hydroxyisocapnell-9-en-8-one (1c). Crystals from hexane-EtOAc, mp 151–155°. $[\alpha]_D + 140.9^\circ$ (CHCl₃; *c* 0.215). UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 245 (3.91). IR $\nu_{\text{max}}^{\text{MeOH}}$ cm⁻¹: 3527, 1698, 1636. FAB-MS (peg-nba) *m/z* (rel. int.): 233.1542 [M - 1, C₁₅H₂₁O₂]⁺ (100), 219 [M - CH₃]⁺ (57). FAB-MS (nba-CHCl₃) *m/z* (rel. int.): 217 [M - OH]⁺ (33.5), 191 [M - CH₃ - CO]⁺ (7.0), 173 [191 - H₂O]⁺ (5.6), 119 [173 - C₄H₆]⁺ (6.0), 105 [119 - CH₂]⁺ (8.5), 91 [105 - CH₂]⁺ (13), 77 [91 - CH₂]⁺ (11), 41 [C₃H₃]⁺ (15).

2,4-Dinitrophenylhydrazone of isocapnell-9-en-8-one (1b) [9]. To a soln of **1a** (51.4 mg) in EtOH (0.4 ml) was added 3 ml of the freshly prepared 2,4-dinitrophenylhydrazine soln (405 mg 2,4-DPH in 3 ml of H₂O, 2 ml H₂SO₄ and 10 ml EtOH). The reaction mixture was left for 12 hr at room temp. and filtered. The solid was chromatographed over Kieselgel G and eluted with hexane-EtOAc (97:3) given 18 mg of **1b** as red-orange crystals from CHCl₃-MeOH, mp 201–205°. CD $\Delta\epsilon_{255} + 27$ (MeOH; *c* 5.97 $\times 10^{-5}$). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3307, 1594, 1516, 1334. EIMS 70 eV *m/z* (rel. int.): 398 [M]⁺ (27.5), 383 [M-15]⁺ (5.0), 71 [C₅H₁₁]⁺ (67), 57 [C₄H₉]⁺ (67), 55 [C₄H₇]⁺ (67), 43 [C₃H₇]⁺ (100).

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