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SESQUITERPENOIDS FROM *LIPPIA INTEGRIFOLIA*—AFRICANONE, A TRICYCLIC SESQUITERPENE KETONE

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Key Word Index—*Lippia integrifolia*; Verbenaceae; α-humulene; α-himachalene; β-caryophyllene; spathulenol; bicyclohumulendione; tricyclic sesquiterpene ketone; africanone.

Abstract—The essential oil from the leaves of *Lippia integrifolia* afforded, besides the known α-humulene, α-himachalene, β-caryophyllene, spathulenol and the recently reported bicyclohumulendione, a new compound that was characterized as a tricyclic sesquiterpene ketone, named africanone, by means of spectroscopic methods.

In a continuation of our study of *Lippia integrifolia* (Griseb.) Hieron. [1], we have isolated from the essential oil of this plant α-humulene, α-himachalene, β-caryophyllene, spathulenol (**1**), bicyclohumulendione (**2**), and a new compound, $C_{15}H_{22}O$, for which structure **3** is proposed on the basis of the following properties. The molecular formula together with the IR bands at 1670 and 1590 cm^{-1} indicate the presence of a tricyclosesquiterpene ketone which gives no signals of olefinic protons in the 100 MHz ^1H NMR spectrum but presents signals of olefinic carbon-atoms at δ160.0 and 139.8 in the ^{13}C NMR spectrum. A double doublet at δ0.27 in the 360 MHz ^1H NMR spectrum (Table 1) and bands at 3060 and 1020 cm^{-1} in the IR spectrum point to a cyclopropane ring that is conjugated to the α,β-unsaturated carbonyl group; this assumption is confirmed by UV absorptions at 345 and 257 nm [2]. The proton at δ0.27 is coupled to two protons, one of them appearing at δ0.82 as a double doublet while the other resonates at δ1.01 as a four-fold doublet. In the 360 MHz ^1H NMR spectrum the first two signals show a coupling constant of 3.6 Hz with each other indicating a geminal coupling of the cyclopropane protons [3]. The coupling of these protons to the one appearing at δ1.01 are 4.1 and 7.8 Hz respectively indicating that the cyclopropane ring is *cis* oriented. It is interesting to note that in the bicyclohumulendione (**2**) isolated from the same plant the cyclopropane ring is in a *trans* configuration [1]. The proton resonating at δ1.01 is further coupled to two protons that appear at δ1.24 and δ1.85 both as double doublets; a similar situation has been described in the literature [4]. The ^1H NMR spectrum also shows three methyl singlets and one methyl doublet further confirmed by the fully decoupled and off resonance ^{13}C NMR spectra [5]. In the 360 MHz ^1H NMR spectrum taken in deutero-benzene and in that registered after addition of $Eu(fod)_3$ reagent, the deshielding observed for one of the methyl groups attached to C-7 and the same effect on the methyl group at C-4, indicate that the carbonyl group is located at C-6, and that the methyl group attached to C-4 is α-oriented. A hydroxy-humulene having the hydroxyl group at the same carbon as in compound **3** has been isolated from natural sources [6].

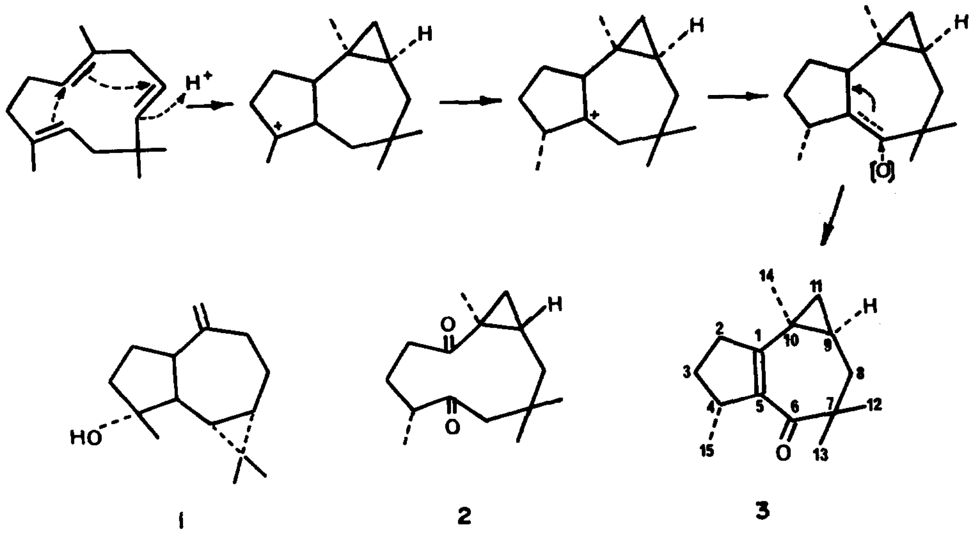
The formation of compound **3** from α-humulene could follow the pathway shown in Scheme 1. Most probably the humulene should adopt the CT conformation which has been demonstrated to be the energetically most stable and also the precursor of sesquiterpene derivatives having the configuration established for **3** [7, 8]. Scheme 1 is related to the one proposed for the formation of the sesquiterpenol africanol [4, 8, 9].

To the best of our knowledge, compound **3** is the first africanene derivative found in Verbenaceae and it is

Table 1. ^1H NMR spectral data of compound 3 (360 MHz, $CHCl_3$ as int. standard)

H	$CDCl_3$	C_6D_6	$\Delta\|C_6D_6 + Eu(fod)_3\|$
2α	2.33 *ddd*	1.93	0.08
2β	2.45 *ddd*	2.02	0.16
3α	1.50 *dddd*	1.21	0.18
3β	1.96 *dddd*	1.54	0.09
4β	2.18 *dd*	1.98	−0.30
8α	1.24 *dd*	1.08	0.12
8β	1.85 *dd*	1.78	0.09
9	1.01 *dddd*	0.84	0.09
11α	0.82 *dd*	0.58	0.03
11β	0.27 *dd*	0.10	0.08
12	1.17 *s*	0.92	0.03
13	1.18 *s*	1.46	0.31
14	1.18 *s*	1.37	0.18
15	1.11 *d*	1.15	0.27

J (Hz): 2α,2β = −17.7; 2α,3α = 4.9; 2α,3β = 3.6; 2β,3α = 11.6; 2β,3β = 4.5; 3α,3β = −12.7; 3α,4β = 11.6; 3β,4β = 5.0; 4β,15 = 6.9; 8α,8β = −13.5; 8α,9 = 5.5; 8β,9 = 7.7; 9,11α = 7.8; 9,11β = 4.1; 11α,11β = −3.9.



Scheme 1.

interesting to find the occurrence in this plant of compounds **2** and **3**, both structurally related to compounds obtained by transannular cyclizations of humulene-epoxide [8, 10].

EXPERIMENTAL

General. ^{1}H NMR: 100 and 360 MHz; ^{13}C NMR: 25.2 MHz; single focused MS at 70 eV.

Plant material. Leaves of *L. integrifolia* were collected in Tucumán Province and a voucher specimen was deposited in the Lillo Institute, Tucumán.

Isolation of sesquiterpenoids. The essential oil was obtained as previously described [1]. It was chromatographed on a silica gel (activity II) column affording α-himachalene, α-humulene and β-caryophyllene which were eluted with petrol and characterized by comparison (IR, MS) with known standards. Elution with petrol–Et_2O (6:1) gave an oily product that was purified further by prep. TLC (silica gel G, petrol–Et_2O, 3:1) giving compound **3** (200 mg) pure by GC (glass column, 2 m × 2 mm, packed with 2% OV-101 or 3% SE-30 on Chromosorb W-AW-DMCS; temp. program from 60 to 220° at a rate of 10°/min), $[\alpha]_D^{20}$ $-0.12°$ ($CHCl_3$; *c* 0.85); UV λ_{max}^{EtOH} nm (ε): 345 (57), 257 (10,000); IR ν_{max} cm^{-1}: 3060, 1020 (cyclopropane ring), 1670, 1590 (α,β-unsaturated ketone); ^{13}C NMR ($CDCl_3$-TMS): δ201.1 (C-6), 160.0 (C-1), 139.8 (C-5), 43.4 (C-7), 42.4 (C-9), 33.5 (C-4), 30.1 (C-3), 28.9 (C-2), 28.7 (C-8), 27.4 (C-12), 26.3 (C-13), 22.8 (C-14), 20.4 (C-10), 19.0 (C-11), 16.7 (C-15); MS *m/z* (rel. int.): 218 $[M]^+$ (81), 203 $[M-15]^+$ (74), 176 $[M-42]^+$ (17), 175 $[M-43]^+$ (14), 147 $[M-C_4H_7O]^+$ (12), 133 $[M-C_5H_9O]^+$ (100). The last chromatographic fractions were purified by prep. TLC (silica gel G, petrol–Et_2O, 2:1) and HPLC (RP-8, 10 μm, MeCN–H_2O, 1:1) affording spathulenol (**1**) and bicyclohumulendione (**2**) identified by comparison (IR, MS) with authentic samples.

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