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IBOZOL, A NEW DITERPENOID FROM *IBOZA RIPARIA**

RAYMOND ZELNIK†, EMA RABENHORST†, AMABILE K. MATIDA†§, HUGO E. GOTTLIEB‡, DAVID LAVIE‡ and SILVIO PANIZZA¶

†Department of Organic Chemistry, Institute Butantan, São Paulo, Brazil, ‡Department of Organic Chemistry, The Weizmann Institute of Science, Rehovoth, Israel; ¶Department of Botany, University of São Paulo, Brazil

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Key Word Index—*Iboza riparia*; Labiatae; new diterpenoid; ibozol; 7 α-hydroxyroyleanone.

In the course of a continuing phytochemical survey of Brazilian Labiatae, we have examined a sample of *Iboza riparia* N. E. Brown, a species originally from Southern Africa [1] and well adapted in Brazil (São Paulo). We now report the isolation of a new diterpenoid ibozol (**1a**) together with the known 7 α-hydroxyroyleanone (**2**) [2] and sitosterol.

The first compounds to be eluted from the chromatographic column of the acetone extract of the leaves were 7 α-hydroxyroyleanone (**2**) and sitosterol, identified by comparing their spectral properties with authentic samples. Further elutions yielded ibozol (**1a**), mp 146–150° whose molecular formula $C_{20}H_{34}O_2$ was established by elemental analyses and MS. The presence of a double bond, indicated first by its colour reaction with tetranitromethane, was confirmed by its IR absorption at 1650 cm^{-1}; also present was a band at 3450 cm^{-1} attributable to hydroxy groups. In the PMR spectrum signals for five methyl groups could be observed, three of which are singlets (δ 0.97, 0.97 and 1.17) and two appear at the same position as a 7 Hz doublet (δ 1.02) indicating an isopropyl group. A carbinol methine signal at δ 3.98 (*dd*, J = 8 and 4 Hz) accounted for a secondary hydroxyl group; no vinyl proton was present and therefore the double bond is tetrasubstituted. In the UV no major absorption above 210 nm could be observed. From these results as well as from the ^{13}C NMR and the reactions described in the sequel, an abietane skeleton was inferred and structure (**1a**) proposed for ibozol.

Acetylation of ibozol produced a secondary acetate (**1b**), mp 150–154°, which displayed a signal for one acetoxy group at δ 2.03 (3H, *s*) and the C<u>H</u>-OAc proton at δ 5.30 (*dd*, J = 8 and 4 Hz), as well as three tertiary methyls at δ 0.97, 0.97 and 1.19 together with the two superimposed doublets (6 H, δ 1.00, J = 7 Hz). The low field position of the proton in the acetate suggested that the C<u>H</u>OH proton in ibozol might be allylic [3] and from its coupling constants, an axial orientation could be assigned to this proton; consequently the acetoxy group is equatorial. Furthermore the multiplicity of the C<u>H</u>-OAc proton demonstrates that it is flanked by two hydrogens. In the IR the presence of the non-acylatable hydroxyl group gave rise to an absorption at 3600 cm^{-1}.

The interrelation between the secondary hydroxyl group and the ethylenic linkage was derived following Jones' oxidation of ibozol: the product, ibozone (**1c**), mp 119–121°, exhibited in the UV an absorption at λ_{max} 248 nm (ε 12 143) for an α,β-unsaturated ketone. The allylic position of the secondary OH in (**1a**) was thereby confirmed. The PMR spectrum of ibozone (**1c**) clearly indicated the presence of two secondary geminal methyl groups (isopropyl) at δ 0.92 and 0.99 (both *d*, J = 7 Hz) and three distinct tertiary methyls at δ 0.89, 0.95 and 1.13 (all *s*).

Reduction of ibozone (**1c**) with $NaBH_4$ afforded ibozol, confirming the equatorial orientation of the hydroxyl group [4].

From this evidence as well as biogenetic considerations, the tetrasubstituted double bond could be placed only at C-8, C-9 of the abietane skeleton whereas the secondary OH group remained to be located (either at C-7 or C-11). To this end ^{13}C NMR was utilized. Spectra of (**1a**) and (**1b**) were assigned by multiplicity information obtained from single-frequency off-resonance decoupled (sford) and from partially relaxed Fourier transform (PFRT) spectra as well as by comparison of the shift data of (**1a**) with that of sandaracopimaradiene (**3**) [5] (see Table 1). The ring A shifts are virtually identical for both compounds except for C-5 which is 2.4 ppm shielded in ibozol (**1a**). This is consistent only with an equatorial oxygenated substituent at C-7 [6]. Therefore in ibozol a 7 β-OH group is present, a fact which is also confirmed by the ring B carbon shifts.

The site of attachment of the tertiary OH group is indicated by analogy of the carbon shifts of ring C and of the isopropyl moiety with those of (4)-terpinenol (**4**)

Table 1. ^{13}C chemical shifts of diterpenoids **1a**, **1b** and **3***

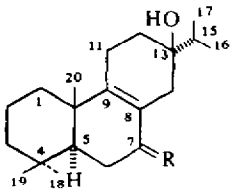
	1a	**1b**‡	**3**
C(1)	37.2	36.8	36.7
C(2)	18.9	18.8	19.0
C(3)	41.4	41.4	42.2†
C(4)	33.0	33.1	33.5
C(5)	49.6	49.5	52.0
C(6)	30.1	25.8	21.3
C(7)	71.4	74.7	32.6
C(8)	126.8	123.3	124.4
C(9)	141.7	144.3	134.4
C(10)	38.4	38.1	37.7
C(11)	20.9	21.4	19.0
C(12)	31.7	31.8	35.1
C(13)	72.3	71.9	35.1
C(14)	35.3	36.2	42.0†
C(15)	34.7	33.4	146.8
C(16)	16.7†	16.5†	111.2
C(17)	16.8†	16.6†	28.2
C(18)	33.0	33.0	33.5
C(19)	21.6	21.5	22.5
C(20)	20.2	19.9	19.7

* Values in ppm downfield from TMS; solvent: $CDCl_3$.
† Signals within any vertical column may be interchanged.
‡ δ ($OCOCH_3$) = 21.3 and 171.3 ppm.

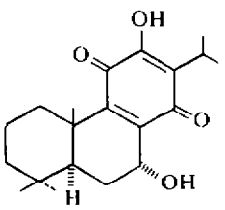
* Part 3 in a series "Chemistry of the Brazilian Labiatae". For part 2, see Zelnik, R., McMillan, J., Paul, I. C., Lavie, D., Toscano, V. G. and DaSilva, R. R. (1977) *J. Org. Chem.* **42**, 923.

§ On leave of absence from Institute Adolfo Lutz, São Paulo.

[7]. The configuration of the substituents at C-13 is based on the following arguments. It is known that conformation (**5**) is preferred not only for compound (**3**) where the 17-methyl group is equatorial but also for its C-13 epimer where the methyl is axial [5]. If ibozol



1a R = β-OH, H
1b R = β-OAc, H
1c R = O



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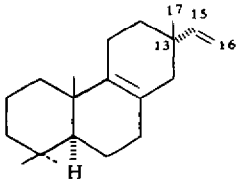

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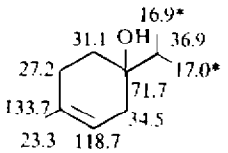
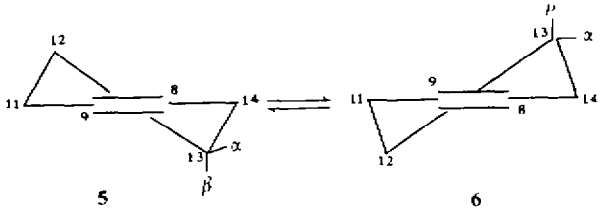


a α = OH, β = i-Pr
b α = i-Pr, β = OH
* Indicates a possible signal reversal.

4

(**1a**) had an α-OH, the expectedly large predominance of (**5a**) over (**6a**) would imply a fairly rigid ring C with an equatorial isopropyl side-chain. Instead, the methine of the latter is shielded by *ca* 2 ppm in ibozol (**1a**) relative to (**4**) (where the isopropyl group is assumed to be mostly equatorial) and appears even at higher field in acetate (**1b**). This together with the small variation in the rings B and C shifts on acetylation (**1a** vs **1b**) suggests a degree of conformational mobility that is best explained by an average ring C conformation between (**5b**) and (**6b**) for ibozol; thus the configuration as shown in (**1**).



5 **6**

Recent investigations of the genus *Solidago* (Compositae) have disclosed the occurrence of abietane diterpenoids such as missourienol B (3 β,13-dihydroxy-8(14)- abietene)[8] and junceanol Y (7 α,13-dihydroxy-8(14)-abietene) [9] but their stereochemistry at C-13 has not yet been definitely assigned. Other novel abietane diterpenoids are stemolide, a bis-epoxide isolated from *Stemodia maritima* (Scrophulariaceae) [10] and 7 α, 18-dihydroxy-8(14)-abietene from *Nepeta granatensis* (Labiatae) [11] and these were shown to possess an α-isopropyl moiety at C-13. Ibozol seems to be biosynthetically related to this group of substances.

EXPERIMENTAL

Mps are uncorrected. IR spectra were recorded using KBr pellets, UV spectra in 95% EtOH and PMR using $CDCl_3$. ^{13}C NMR spectra were measured on a Bruker WH-90 spectrometer operating at 22.6 MHz in the Fourier transform mode. MS are from Mr. Koichi Mizuta, Instituto de Pesquisas Tecnológicas, São Paulo, operating on a RMU-7 Hitachi instrument. Elemental analyses are from the Chemistry Department of the University of Illinois, Urbana, U.S.A.

Isolation procedure. The ground dried leaves of *Iboza riparia* (1100 g) were extracted with Me_2CO and concentrated under red. pres. to yield a viscous mass (103 g) which was chromatographed over Si gel. Hexane-C_6H_6 (1:1) fractions yielded 7 α-hydroxyroyleanone (**2**) (3.4 g), mp 169–171° (hexane), M^+ 332, λ_{max}^{EtOH} nm (log ε):275 (4.07); the spectrometric data (IR, PMR, CD) were compared with an authentic sample and found identical. Elutions with C_6H_6 furnished sitosterol (1.3 g), mp 140–145°, undepressed mmp and IR identical with an authentic sample. Further elutions with C_6H_6–Me_2CO (19:1) afforded ibozol (**1a**) (13.7 g), mp 146–150° (Me_2CO) (Found: C, 78.68; H, 11.26. $C_{20}H_{34}O_2$ requires: C, 78.37; H, 11.18%). M^+ 306; ν_{max} cm^{-1}: 3450, 1650, 1390 and 1240.

Ibozol acetate (**1b**). Ibozol (100 mg) was acetylated in the usual manner; recrystallization of the product from C_6H_6–hexane gave 90 mg of the acetate (**1b**), mp 150–152° (Found: C, 75.76; H, 10.47. $C_{22}H_{36}O_3$ requires: C, 75.81; H, 10.41%). ν_{max} cm^{-1}: 3600, 1720, 1660, 1470, 1380, 1260 and 1020.

Jones' oxidation of ibozol. To an ice-cooled soln of ibozol (400 mg) in Me_2CO (20 ml), 0.8 ml of Jones' reagent was added and the mixture stirred for 5 min. After the usual work-up the ppt. (317 mg) was recrystallized in hexane to yield ibozone (**1c**) (258 mg), mp 119–121° (Found: C, 78.96; H, 10.34. $C_{20}H_{32}O_2$ requires: C, 78.89; H, 10.59%). ν_{max} cm^{-1} 3500, 1660, 1610, 1380 and 1210.

$NaBH_4$ *reduction of ibozone.* To a soln of ibozone (32 mg) in MeOH (5 ml), $NaBH_4$ (20 mg) was added and the mixture stirred 30 min at room temp. After the usual work up the ppt. (28 mg) was chromatographed on a Si gel column. Elutions from $CHCl_3$ and $CHCl_3$–Me_2CO (19:1) afforded 16 mg of ibozol.

Biological activity. Anti-tumor tests of ibozol against lymphocytic leukemia P388 indicated no activity up to doses of 200 mg/kg [12].

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A NEW DIHYDRO-*TRANS*-CLERODANE DIACID FROM *HAPLOPAPPUS CILIATUS*

MAGALIS L. BITTNER, VOLKER ZABEL, WILLIAM B. SMITH and WILLIAM H. WATSON

FASTBIOS Laboratory, Department of Chemistry, Texas Christian University, Fort Worth, TX 76129, U.S.A.

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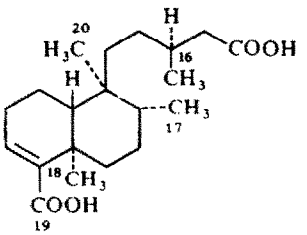
Key Word Index—*Haplopappus ciliatus*; Compositae; new *trans*-clerodane; diterpene; absolute configuration; haplociliatic acid.

A new dihydro-*trans*-clerodane diacid, haplociliatic acid (**1**), was isolated from *Haplopappus ciliatus* (Nutt.) DC. and the structure was determined [1] by X-ray diffraction techniques. The anomalous dispersion of the oxygen atoms was used to determine the absolute configuration. Haplociliatic acid is an isomer of the *cis*-clerodane cistodoic acid [2, 3].



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The diacid was converted to the dimethylester by reaction with CH_2N_2, and the ^{13}C NMR spectrum at 15.03 MHz was obtained using $CDCl_3$ as solvent. Line assignments were made using single frequency off-resonance decoupling, relaxation techniques and lanthanide induced chemical shifts. The assignments (ppm from TMS) and relative LIS are as follows: C-1, 17.4 (0.10); C-2, 29.4 (0.15); C-3, 136.8 (0.34); C-4, 142.5 (0.46); C-5, 37.6 (0.25); C-6, 35.9 (0.20); C-7, 27.2 (0.10); C-8, 36.1 (0.07); C-9; 38.5 (0.09); C-10, 46.4 (0.15); C-11, 27.2 (0.10); C-12, 35.5 (0.09); C-13, 31.0 (0.24); C-14, 41.6 (0.41); C-15, 173.6 (1.00); C-16, 20.0 (0.15)*; C-17, 15.9 (0.05)†; C-18, 20.7 (0.18)*; C-19, 168.3 (1.00); C-20, 18.5 (0.06)†; and two $-OCH_3$ resonances at 51.1 (0.38) and 51.4 (0.33). Assignments marked * and † are interchangeable.

EXPERIMENTAL

Dried, powdered leaves (4.22 kg) of *Haplopappus ciliatus* (Nutt.) DC. (*Prionopsis ciliata* (Nutt.)), collected around Fort Worth, Texas in September 1977, were extracted with petrol. A few mg of white solid pptd from the extract and were collected. The petrol extract was evapd. to yield 140 g of a gummy residue. This was disolved in a minimum amount of petrol leaving a small quantity of white solid. The combined white solids (50 mg) were recrystallized from EtOH yielding colourless crystals, mp 198–201° (uncorr), $[\alpha]_D^{25}$ −86° (*c* 2.5, EtOH). MS (probe), *m/e* (rel. int.): 336 (M^+; 1), 318 ($M^+ - 18$; 33), 285 (3), 271 (26), 203 (28), 174 (6), 151 (11), 137 (25), 125 ($C_7H_9O_2^+$; 100). $C_{20}H_{31}O_4$. λ_{max}^{EtOH} nm: 212 (ε 17800)(double bond); ν_{max}^{KBr} cm^{-1}; 3350 (acid OH), 2850, 1640 (strong C=O), 1400, 1360, 1260, 1200, 900. PMR, (90 MHz, $CDCl_3$): δ 0.71 (3H, *s*), *ca* 0.82–1.12 (6H, overlapping *d*), 1.24 (3H. *s*), *ca* 1.34–1.65 and 2.1–2.3 (complex *m*), 6.57 (H-3, *t*, $J = 4$ Hz).

The X-ray data were collected on a Syntex $P2_1$ diffractometer system. The crystals belong to space group $P2_12_12_1$ with unit cell dimensions $a = 12.946$ (3), $b = 14.408$ (3), $c = 10.254$ (2) Å and $V = 1917.7$ (7) Å^3.

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