

ISOLATION AND CHARACTERIZATION OF VICODIOL, A NEW
MONOTERPENEDIOL FROM *VICOA INDICA*SARADHA VASANTH, A.B. KUNDU,* K.K. PURUSHOTHAMAN,¹

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ABSTRACT.—The new monoterpene diol vicodiol isolated from *Vicoua indica* has been shown to be 2-hydroxy-1,7-dimethylbicyclo [2.2.1] heptane-7-methanol [1*S*-(endo, syn)] by a combination of spectroscopic data, chemical conversions, and X-ray crystallography.

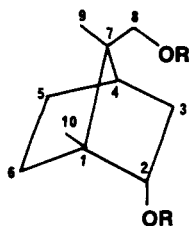
The plant *Vicoua indica* DC. (Compositae) is used by a tribal population in India (Bihar state) as a contraceptive agent in women (1). Four sesquiterpenoid lactones designated as vicolides A, B, C, and D were isolated from this plant (2,3). Vicolide B showed antifertility activity in female albino rats and was antiestrogenic in nature (4). It also exhibited abortifacient activity, but was neither progestational nor antiprogestational (5). During the process of isolation of large quantities of vicolide B for antifertility screening we isolated vicodiol, a new monoterpene diol, in low yield.

RESULTS AND DISCUSSION

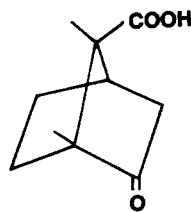
Vicodiol [**1**], C₁₀H₁₈O₂, [M]⁺ *m/z* 170, showed a prominent peak at *m/z* 139 corresponding to the loss of CH₂OH. The ¹H-nmr spectrum at 300.13 MHz in CD₃OD (Table 1) showed two methyl singlets located at δ 0.90 and 1.00, an AB quartet (*J* = 11 Hz) centered at 3.50 characteristic of a CH₂OH group, and a ddd at δ 4.05 indicative of a CHOH group. It formed a diacetate **2**, C₁₄H₂₂O₄, and a keto acid **3**, C₁₀H₁₄O₃.

The ¹³C- and DEPT ¹³C-nmr spectra indicated that **1** contained two methyl groups, four methylenes of which one was oxygenated, two methines of which one was oxygenated, and two quaternary carbons; **1** must be bicyclic.

The diacetate **2** showed a ddd at δ 4.95 (*J* = 10, 3, 5, 1.5 Hz) (Table 1) which is



1 R=H
2 R=Ac

**3**

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TABLE 1. ¹H-nmr and COSY Data of Vicodiol [1] and its Derivatives.

Proton	Compound			
	δ _H			COSY
	1 ^a (CD ₃ OD)	2 ^b	3 ^c	1
H-2β	4.05 ddd	4.95 ddd	—	3α, 3β, 6β
H-3α	0.95 dd	1.00 dd	2.00 d	2β, 3β
H-3β	2.20 dddd	2.32 dddd	2.40 dd	2β, 3α, 4, 5β
H-4	1.85 dd	1.90 dd	2.70 dd	3β, 5β
H-5α	1.20 mc	1.22 mc	1.40 mc	6α, 5β
H-5β	1.70 mc	1.65 mc	1.98 mc	6β, 5α, 4, 3β
H-6α	1.70 mc	1.68 mc	1.40 mc	6β, 5α
H-6β	1.90 ddd	1.90 ddd	1.68 mc	6α, 5β, 2β
H-8	3.65 d	4.15 d	—	8'
H-8'	3.45 d	3.95 d	—	—
H-9	1.00 s	1.00 s	1.18 s	—
H-10	0.90 s	0.90 s	1.15 s	—

quite reminiscent of a borneol type terpene (6). As the signal of H-4 was shifted downfield one of the methyls at the bridge was oxygenated. Eu(fod)₃-induced shifts led to the proposed position of the hydroxymethylene group, as H-2 was much less shifted than H-8 and H-3 showed a pronounced shift. Irradiation of the downfield doublet of the CH₂OH group gave an nOe 6.9% at the CHOH proton, and irradiation of the latter gave a 4.5% nOe of the downfield doublet of the CH₂OH group (δ 3.65). These experiments leave no doubt that the CH₂OH group is on the same side as the CHOH group.

Jones oxidation of **1** gave a keto acid **3** [δ_H ppm 10.55, δ_C ppm 215.95 (s), 181.05] (Tables 1 and 2). It exhibited almost the same mp and ¹H- and ¹³C-nmr spectral characteristics as *trans*-isoketopinic acid (7) but differed widely in the sign and magnitude of specific rotation; [α]_D of *trans*-isoketopinic acid is +4.5° (8).

All these data give conclusive proof for the assignment of **1** as 2-hydroxy-1,7-dimethylbicyclo [2.2.1] heptane-7-methanol [1*S*-(*endo*, *syn*)].

Structure **1** was further confirmed by X-ray crystallography.

9-Hydroxyborneol was isolated from the roots of South American *Ichthyothere terminalis* (9), 10-hydroxyborneol from *Artemisia rutifolia* and *Artemisia laciniata* of Mongolian origin (6), and 5-hydroxyborneol from the seeds of *Pleurospermum angelicoides* (10), but this is the first report of the occurrence of 8-hydroxyborneol in nature.

CRYSTAL STRUCTURE ANALYSIS OF **1**.—The molecular structure of **1** is illustrated in Figure 1, and the atomic coordinates of **1** are listed in Table 3. There are three

TABLE 2. ^{13}C -nmr Data of Vicodiol [1] and its Derivatives.

Carbon	Compound		
	1 (CD_3OD)	2	3
C-1 (s)	51.58	49.60	57.60
C-2 (d)	78.04	78.98	215.93 (s)
C-3 (t)	39.40	36.30	43.54
C-4 (d)	43.47	42.28	42.34
C-5 (t)	28.08	27.49	25.91
C-6 (t)	29.62	28.07	29.96
C-7 (s)	55.06	51.34	57.77
C-8 (t)	65.74	67.15	181.05 (s)
C-9 (q)	15.74	14.21	14.05
C-10 (q)	14.63	14.70	10.20
MeCO	—	171.10 (2)	—
MeCO	—	20.85	—
		21.15	

^aCoupling constants (Hz): $J_{2\beta,3\alpha}=3.5$, $J_{2\beta,3\beta}=10$, $J_{2\beta,6\beta}=1.5$, $J_{3\alpha,3\beta}=13.5$, $J_{3\beta,4}=4.5$, $J_{3\beta,5\beta}=3.5$, $J_{4,5\beta}=4.5$, $J_{5\alpha,5\beta}=J_{6\alpha,6\beta}=13$, $J_{5\beta,6\beta}=4$, $J_8=J_{8'}=11$.

^bCoupling constants (Hz): $J_{2\beta,3\alpha}=3.5$, $J_{2\beta,3\beta}=10$, $J_{2\beta,6\beta}=1.5$, $J_{3\alpha,3\beta}=14$, $J_{3\beta,4}=J_{4,5\beta}=4.5$, $J_8=J_{8'}=11$.

^cCoupling constants (Hz): $J_{3\alpha,3\beta}=18$, $J_{3\beta,4}=5$, $J_{3\beta,5\beta}=2.5$, $J_{4,5\beta}=4$.

molecules, A, B, C, in the asymmetric unit. The packing of the molecules is stabilized by six O-H-O hydrogen bonds. The hydroxyl group at position 2 is trans to the *gem*-dimethyl bridge. The torsion angle O-1-C-2-C-1-C-7 is $-161.2(4)^\circ$. The methyl substitution at C-1 is gauche to O-1, and O-1-C-2-C-1-C-10 torsion angle is $71.9(5)^\circ$. Bond lengths and bond angles agree with the standard values except for the C-6-C-5 distance of $1.48(2) \text{ \AA}$ in molecule B. This may be attributed to the large thermal vibration of the C-5 atom in molecule B. Average thermal vibrations of molecule C are greater than those of molecule B, and those of molecule B exceed those of molecule A. This is not unexpected as molecule C is disordered. For the same reason molecular dimensions in molecule C deviate significantly from the normal values, and the standard deviations are large (0.015 \AA). The angles at the *gem*-dimethyl bridge C-1-C-7-C-4 are 93.2° and 93.7° in molecules A and B, respectively. This is in agreement with the values observed in 2-bromo-2-nitrocamphane (11) and 10-bromo-2-chloro-2-nitrosocamphane (12).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps are uncorrected; Acme's Si gel was used for cc and tlc. The separation was monitored by tlc (Si gel G). ^1H -nmr spectra were recorded at 300.13 MHz and ^{13}C -nmr at 75.50 MHz on a Bruker instrument with TMS as internal standard in CDCl_3 as solvent unless otherwise stated. The ir spectra are for KBr pellets on a Perkin-Elmer 337 grating spectrophotometer; optical rotations were measured on a Carl-Zeiss polarimeter.

PLANT MATERIAL AND EXTRACTION.—*V. indica* (whole plant) was collected from Tambaram, Tamil Nadu, India, during February 1986, and was identified at the Department of Botany of Captain Srinivasa Murthi Drug Research Institute. A voucher specimen (No. 39/14) is deposited in this Institute's herbarium. The air-dried, powdered plant material (5 kg) was extracted with CHCl_3 (50 liters). The extract was concentrated in vacuo, charged on a column of Si gel in *n*-hexane, and eluted with C_6H_6 and increasing proportions of EtOAc in C_6H_6 followed by MeOH-EtOAc (1:4).

VICODIOL [1].—Elution with EtOAc yielded a crude mass which was rechromatographed on Si gel in C_6H_6 . C_6H_6 -EtOAc (3:1) eluates afforded a gum which after repeated chromatography and crystallization from CHCl_3 /*n*-hexane yielded vicodiol [1], mp $242\text{--}244^\circ$, $[\alpha]_D -17.0^\circ$ ($c=1\%$, CHCl_3); ir ν max

TABLE 3. Table of Positional Parameters and Their Estimated Standard Deviations.^a

Atom	x	y	z	B eq (Å ²)
O-1A	0.1119(7)	0.227	0.1068(2)	5.57(8)
O-2A	-0.1034(6)	0.2303(6)	0.3660(2)	5.8(1)
C-6A	0.0874(9)	0.4488(5)	0.1747(3)	4.8(1)
C-1A	-0.0530(7)	0.3450(5)	0.1858(2)	3.41(8)
C-2A	0.0514(7)	0.2285(5)	0.1730(2)	3.70(8)
C-3A	0.2218(8)	0.2233(6)	0.2345(3)	4.8(1)
C-4A	0.1866(8)	0.3351(7)	0.2773(3)	4.6(1)
C-5A	0.2459(9)	0.4439(7)	0.2390(4)	5.8(1)
C-7A	-0.0385(7)	0.3449(5)	0.2658(2)	3.75(9)
C-8A	-0.1422(8)	0.2372(7)	0.2922(3)	4.7(1)
C-9A	-0.117(1)	0.4597(7)	0.2953(3)	5.8(1)
C-10A	-0.2569(9)	0.3564(8)	0.1438(3)	5.7(1)
O-1B	0.8316(5)	0.4841(4)	0.9127(2)	4.78(8)
O-2B	0.1301(5)	0.3525(5)	0.9865(2)	5.48(9)
C-6B	0.566(1)	0.346(1)	0.8201(3)	8.2(2)
C-1B	0.5793(7)	0.3232(5)	0.8992(3)	4.4(1)
C-2B	0.6577(7)	0.4395(5)	0.9327(3)	3.81(9)
C-3B	0.4880(8)	0.5290(6)	0.9131(4)	5.7(1)
C-4B	0.3301(7)	0.4532(7)	0.8707(3)	5.1(1)
C-5B	0.397(1)	0.427(2)	0.8026(4)	9.9(4)
C-7B	0.3600(7)	0.3298(6)	0.9066(3)	4.3(1)
C-8B	0.3276(7)	0.3326(8)	0.9812(3)	5.5(1)
C-9B	0.233(1)	0.233(1)	0.8689(6)	11.3(2)
C-10B	0.694(1)	0.2134(7)	0.9289(5)	8.3(2)
O-1C	0.5933(6)	0.1962(5)	0.4375(2)	5.22(8)
O-1PC	0.7700(6)	0.6024(5)	0.5996(3)	6.5(1)
C-6C	0.686(1)	0.1647(7)	0.5829(4)	6.4(2)
C-1C	0.750(2)	0.2778(7)	0.5490(3)	7.9(2)
C-2C	0.615(1)	0.2982(8)	0.4821(3)	7.0(2)
C-3C ^b	0.468(2)	0.355(1)	0.5139(6)	5.0(2)
C-4C	0.504(1)	0.383(1)	0.6056(6)	15.8(3)
C-5C ^b	0.533(3)	0.220(2)	0.6116(8)	7.1(3)
C-6PC	0.855(1)	0.3753(9)	0.6617(3)	6.5(2)
C-1PC	0.712(2)	0.3874(8)	0.5955(3)	8.4(2)
C-2PC	0.765(1)	0.4975(7)	0.5585(3)	7.3(2)
C-3PC ^b	0.902(2)	0.443(1)	0.5222(6)	5.0(2)
C-4PC	0.959(1)	0.287(1)	0.5389(5)	17.4(3)
C-5PC ^b	1.002(2)	0.320(2)	0.6229(7)	6.0(3)

^aAnisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(4/3)[a^2*B(1,1)+b^2*B(2,2)+c^2*B(3,3)+ab(\cos \gamma)*B(1,2)+ac(\cos \beta)*B(1,3)+bc(\cos \alpha)*B(2,3)]$.

^bAtoms with half occupancy.

(KBr) 3350 cm⁻¹; eims (probe) 70 ev *m/z* [M]⁺ 170, 139, 121, 95, 68, 67, 53, 41; ¹H nmr see Table 1; ¹³C nmr see Table 2; COSY data see Table 1.

ACETYLATION OF VICODIOL [1].—Compound 1 (50 mg) was treated with pyridine (0.4 ml) and Ac₂O (0.5 ml) at room temperature overnight. The solvent was dried in vacuo and chromatographed through Si gel to yield the diacetate 2 as a gum.

OXIDATION OF VICODIOL [1].—Compound 1 (50 mg) was oxidized with Jones reagent (1 ml). After usual workup and chromatography it was recrystallized from Et₂O/hexane to yield shiny crystals of 3, mp 260–262°, [α]_D -94.14° (*c* = 0.657%, CHCl₃).

X-RAY DATA.²—Viciodiol [1] crystals are monoclinic, the space group is $P2_1$, $M_r = 170.3$, $Z = 6$, $a = 6.934(1)$, $b = 11.152(1)$, $c = 19.659(2)$ Å, $\beta = 98.75(5)^\circ$. The final R index = 0.094 for 2730 reflections with $I \geq 3\sigma(I)$, $V = 1502.4$ Å³, $D_c = 1.13$ g·cm⁻³, $\text{CuK}\alpha$ ($\lambda = 1.5418$ Å), $\mu = 5.7$ cm⁻¹, $F(000) = 564$. A colorless brick-like crystal of $\text{C}_{10}\text{H}_{18}\text{O}_2$, $0.5 \times 0.25 \times 0.15$ mm size from $\text{CHCl}_3 + \text{H}_2\text{O}$, three dimensional intensity data collected on an Enraf-Nonius CAD-4 automated diffractometer in the scan mode $W-2\theta$ with $2^\circ \leq 2\theta \leq 140^\circ$ with graphite monochromated $\text{CuK}\alpha$ radiation ($\lambda = 1.5418$ Å), data corrected for direct beam polarization and Lorentz effects and for absorption with a maximum and minimum transmission factor of 1.0 to 0.97 on I, 3012 measured, 2672 unique (agreement for reflection averaging on $I = 1.4\%$) and 2730 observed with $I > 3\sigma(I)$ cell constants from 23 reflections, $27^\circ < \theta < 35^\circ$, 3 standard reflections monitored every 100 reflections showed no variation in intensity, scan width = $(0.8 + 0.14 \tan \theta)^\circ$, aperture width = $(4 + 2 \tan \theta)$ mm, maximum time spent on any reflection was 45 sec, and the background count was half the scan time. Structure solution by direct methods, 33 out of 40 hydrogens were located from difference Fourier and refined isotropically, remaining hydrogens were geometrically fixed and not refined, while the nonhydrogens were refined anisotropically to a final $R(F) = 0.094$ and $W_R = 0.148$ (the alternative absolute structure also had the same R index) with individual weighting scheme based on counting statistics, where $W = 4(F_o)^2/\sigma^2(F_o^2)$, $\sigma^2(F_o^2) = [\sigma^2(I) + (0.051)^2]^{1/2}/\text{LP}$, all calculations on VAX 11/730 computing system using SDP package (13). Out of the three molecules in the asymmetric unit, molecule C exhibits an interesting disorder. The occupancy factors of four atoms which are not common to the two possible disordered orientations of the molecule were refined, but the lowest R index was obtained only for 0.5 occupancy. Some of the hydrogens of the disordered molecule were not included in the SF calculation. Final ΔF map had no peaks greater than 0.46 e/Å³. Table 3 gives the fractional coordinates. Figure 1 shows a stereoview of the molecule with atom numbering. Atomic scattering factors are from *International Tables for X-ray Crystallography* (14).

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²Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.