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STRUCTURE OF CYPERANIC ACID, A NEW SESQUITERPENE FROM *DITTRICHIA VISCOSA*

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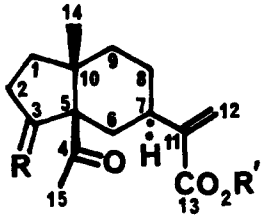
Dittrichia viscosa (L.) Greuter (Compositae), a widespread Mediterranean plant, has proven to be a rich source of sesquiterpenoid acids and lactones with eudesmane, guaiane, secoguaiane, and germacrane skeletons (1). We wish to report now the isolation and structure elucidation of a new cyperane-type sesquiterpene, cyperanic acid [**1**], which occurs as a minor constituent of this plant.

Chromatographic procedures applied to the Me_2CO extract of the air-dried aerial parts of *D. viscosa* provided cyperanic acid [**1**] as an oil, $[\alpha]_D$ +26.3°. The molecular formula, $C_{15}H_{22}O_4$, was deduced from elemental analysis and mass and ^{13}C-nmr spectra. In the ir spectrum three bands were in evidence, one at 1705 cm^{-1} due to the C-4 ketone, the others at 1685 and 1620 cm^{-1} representing the acrylate unit. The ^{1}H-nmr spectrum indicated the presence of a methyl (δ 0.96, s), an acyl (δ 2.16, s), a secondary hydroxyl group (δ 4.56, dd, J = 6, 9 Hz), and two geminal vinylic protons (δ 5.62, bs and 6.23, bs). The ^{13}C-nmr spectrum showed the presence of two methyls, six methylenes, two methynes including one methyne attached to an oxygen, three quaternary carbons, and two carbonyl carbons. Chemical shift values are listed in Table 1. The above data are accommodated most readily by a bicarbocyclic sesquiterpene structure related to the cyperane skeleton.

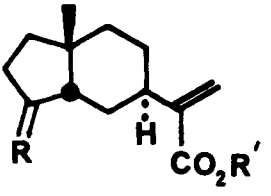
Treatment of **1** with CH_2N_2 afforded the monoester **2**, $C_{16}H_{24}O_4$, mp 62–64°, $[M]^+$ 280, ir 1720 cm^{-1}, whose ^{1}H-nmr spectrum differed significantly from that of the parent acid only in the absorption due to the protons related to the methyl ester (δ 3.80, s). Acetylation of **2** gave **3** as an oil, $C_{18}H_{26}O_5$, whose ^{1}H-nmr spectrum showed the oxymethine proton deshielded at δ 5.58 (dd, J = 6, 9 Hz). Oxidation of **1** with pyridinium chlorochromate afforded **4**, $C_{15}H_{20}O_4$, mp 58–60°, $[M]^+$ 264, whose ir absorption at 1685, 1705, and 1740 cm^{-1} (five-membered ring ketone) indicated the hydroxyl group of cyperanic acid [**1**] to be situated on a five-membered ring. Comparison of the ^{13}C-nmr spectra of **1** and **4** revealed a deshielding of C-2 and C-5 in the latter. This shift perturbation may be ascribed to the β effect of a neighboring carbonyl group. The secondary hydroxyl in cyperanic acid **1** must, therefore, be attached at C-3. Support for this assignment was obtained by hydrodeacylation of compound **4** into the corresponding *cis*-fused hydrindanone **7**, $C_{13}H_{18}O_3$, mp 107–109°, by treatment with base. The ^{13}C-nmr spectral analysis of this nor-derivative proved its structure to be **7**; comparison of its carbon shifts with those reported for hydrindanones (2) permitted both shift and structure assignment.

From these results and from biogenetic considerations, it was assumed that cyperanic acid has the structure **1**, excluding stereochemistry at C-3 and C-5. We assigned the *cis* relationship to the hydrindane skeleton on the basis of the ^{13}C-nmr shift of the methyl group at C-10. In *trans*- and *cis*-hydrindanones the angular methyl group should resonate around 18 (3) and 26 (2) ppm, respec-

tively. A γ effect of a substituent at C-5 would shield the methyl in the *cis* isomer to an extent of 5 ppm. The observed value of 21.6 ppm for **4** supports this assignment. Chemical shift perturbations of both methyl groups in **2** vs. **3** and **4** would be in agreement with a β configuration of the hydroxyl group at C-3. Because the preparation of the epimeric alcohol would facilitate the assignment at this site, **4** was subjected to reduction with $NaBH_4$: the expected α orientation of the C-3 hydroxyl group would correspond to the attack of the reagent from the least hindered convex β face of **4**. The carbonyl functions of this compound proved to be unexpectedly resistant to reduction. When the reaction was carried out at 50° and in the presence of excess reducing agent, only the nor-derivative **7** was produced (4). A model compound **5** with a 3α-hydroxy group was easily obtained by reduction of the ketoester **8**. The ^{13}C-nmr analysis of **5** was undertaken with use of derivatives **6** and **7** acting as models. Carbon 7 of **4**, whose equivalent site in **7** is unperturbed, was deshielded in the α alcohol **5** and shielded in **2**. The 1.8 ppm difference of the C-7 chemical shift in **2** vs. **5** is a reflection of the δ effect exerted by the α-oriented substituent at C-3. Furthermore, the hydroxy group in the natural cyperanic acid [**1**] possesses a β con-



1 R=β-OH, α-H; R′=H
2 R=β-OH, α-H; R′=Me
3 R=β-OAc, α-H; R′=Me
4 R=O; R′=H



5 R=α-OH, β-H; R′=Me
6 R=α-OAc, β-H; R′=Me
7 R=O; R′=H
8 R=O; R′=Me

TABLE 1. ^{13}C-nmr Data.[a]

Carbon	Compound						
	1	**2**	**3**	**4**	**5**	**6**	**7**
C-1	37.9[b]	37.7[c]	38.1[d]	35.7	39.2	39.3	35.0
C-2	31.6	31.5	27.7[e]	32.9	34.5	31.0	34.5
C-3	76.0	76.4	77.7	208.2	77.4	79.0	219.7
C-4	214.8	214.6	210.5	216.9	—	—	—
C-5	64.2	64.4	68.4	70.9	49.0	47.7	56.1
C-6	30.6	31.3	31.2	30.3	28.6	28.2	25.4
C-7	34.4	34.5	34.6	35.6	36.3	35.5	35.5
C-8	27.1	27.4	27.2[e]	27.0	26.9	27.1	27.6
C-9	37.6[b]	37.6[c]	38.7[d]	37.8	35.3	34.6	33.7
C-10	42.6	42.6	42.3	42.1	39.3	34.4	37.9
C-11	144.6	144.9	144.8	143.9	146.4	146.5	144.5
C-12	124.4	123.1	123.2	125.5	121.8	121.9	124.7
C-13	170.5	167.4	167.2	171.7	168.0	168.2	171.9
C-14	22.1	22.3	20.9	21.6	26.5	26.0	25.3
C-15	31.2	31.3	30.9	29.6	—	—	—
OMe	—	51.8	51.6	—	51.6	51.6	—
OAc	—	—	170.4–20.9	—	—	170.3–21.5	—

[a]The δ values are in parts per million downfield from TMS.
[b–e]Signals with the same superscripts within any vertical column may be reversed.

figuration. The *cis* relationship between the C-3 and C-5 substituents was further confirmed by the presence of an intramolecularly hydrogen-bonded hydroxyl band at 3570 cm^{-1} in the ir spectrum (CCl_4) of the ester **2**. The absolute stereochemistry of the natural compound was determined by comparing its optical rotation value with that of natural cyperolone (4).

Cyperanic acid [**1**] represents a rare example of a natural terpenoid bearing a cyperane skeleton. The co-occurence in *D. viscosa* of **1** with the well-known eudesmanes (1) reinforces the biogenetic hypothesis that cyperanes may be biosynthesized from a hydroxyeudesmane precursor (5,6).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were taken on a Reichert micro hot stage and are uncorrected. Elemental analyses were carried out on a Carlo Erba Model 1106 Elemental Analyzer. ^{1}H-nmr spectra were recorded at 90 MHz on a Varian EM390 instrument in $CDCl_3$ solutions using TMS as reference. ^{13}C-nmr spectra were recorded at 20.15 MHz on a Bruker WP80SY instrument, in the Fourier transform mode with proton decoupling throughout, in $CDCl_3$ solutions using TMS as reference. Ir spectra were obtained with a Perkin-Elmer 1320 spectrophotometer in $CHCl_3$ solutions unless otherwise specified. Mass spectra were recorded on a Varian MAT 311A at 70 eV. Cc was carried out on 0.063–0.200 mesh Merck Si gel. All extracts were dried over Na_2SO_4.

PLANT MATERIAL.—Plant material was collected in September 1986, near Perugia, Umbria, Italy, and voucher specimens were deposited in the Herbarium of the Dipartimento di Biologia Vegetale of the University of Perugia, Italy.

EXTRACTION AND ISOLATION OF THE COMPONENTS.—Dried and finely powdered *D. viscosa* aerial parts (1 kg) were extracted exhaustively with Me_2CO. The resulting extracts were concentrated at low temperature. The crude gum (50 g) was dissolved in $CHCl_3$ and extracted with a 5% solution of NaOH. The aqueous fraction was then treated with a 5% solution of H_2SO_4 and extracted with $CHCl_3$, and the organic fraction was dried and evaporated. The oily, colored acid fraction was chromatographed on Si gel; elution with $CHCl_3$-MeOH (95:5) gave, in addition to the previously reported compounds (1), 0.3 g (0.03%) of cyperanic acid [**1**]: $[\alpha]_D$ +26.3° (c = 0.004, $CHCl_3$), ir 1685, 1705 cm^{-1}, ms $[M]^+$ 266, ^{1}H nmr δ 0.96 (3H, s, 10-Me), 2.16 (3H, s, 4-Me), 4.56 (1H, dd, J = 6, 9 Hz, H-3), 5.62 (1H, bs, H-12), 6.23 (1H, bs, H-12); ^{13}C nmr see Table 1. *Anal.* calcd for $C_{15}H_{22}O_4$: C 67.65, H 8.33, found C 67.42, H 8.48.

CYPERANIC ACID METHYL ESTER **2**.—An ethereal solution of CH_2N_2 was added dropwise to a stirred solution of 0.2 g of acid **1** in 30 ml of Et_2O until the yellow color persisted, and stirring was continued for 5 min. A few drops of HOAc were added, and the solution was evaporated. Chromatography of the residue on Al_2O_3 (activity grade IV) and elution with $CHCl_3$ gave 0.2 g (95%) of the ester **2**: mp 62–64° (Et_2O); ir 1720 cm^{-1}; ms $[M]^+$ 280; ^{1}H nmr δ 1.01 (3H, s, 10-Me), 2.19 (3H, s, 4-Me), 3.80 (3H, s, CO_2Me), 4.56 (1H, dd, J = 6, 9 Hz, H-3), 5.63 (1H, bs, H-12), 6.20 (1H, bs, H-12); ^{13}C nmr see Table 1. *Anal.* calcd for $C_{16}H_{24}O_4$: C 68.55, H 8.63; found C 68.42, H 8.71.

ACETYLATION OF THE ESTER **2**.—A solution of 0.1 g of the ester **2** and 1 ml of Ac_2O in 3 ml of pyridine was kept at room temperature for 15 h. After the usual workup (7), the crude product was chromatographed. Elution with $CHCl_3$ gave 0.11 g (92%) of acetate **3** as an oil: ir 1720 cm^{-1}; ^{1}H nmr δ 0.98 (3H, s, 10-Me), 2.00 (3H, s, acetate), 2.15 (3H, s, 4-Me), 3.80 (3H, s, CO_2Me), 5.58 (1H, dd, J = 6, 9 Hz, H-3), 5.60 (1H, bs, H-12), 6.20 (1H, bs, H-12); ^{13}C nmr see Table 1. *Anal.* calcd for $C_{18}H_{26}O_5$: C 67.06, H 8.13; found C 66.85, H 8.29.

OXIDATION OF CYPERANIC ACID [**1**].—To a solution of the acid **1** (0.2 g) in 50 ml of anhydrous CH_2Cl_2, pyridinium chlorochromate (0.2 g) added under N_2. The suspension was stirred at room temperature for 2 h. The mixture was filtered and the filtrate evaporated. Chromatography of the residue and elution with $CHCl_3$-MeOH (95:5) gave 0.15 g (79%) of ketoacid **4**: mp 58–60° (Et_2O); ir 1685, 1705, 1740 cm^{-1}; ms $[M]^+$ 264; ^{1}H nmr δ 1.20 (3H, s, 10-Me), 2.14 (3H, s, 4-Me), 5.70 (1H, bs, H-12), 6.33 (1H, bs, H-12); ^{13}C nmr see Table 1. *Anal.* calcd for $C_{15}H_{20}O_4$: C 68.16, H 7.63; found C 67.91, H 7.81.

TREATMENT OF DIKETONE **4** WITH ALKALI.—A solution of 0.5 g of NaOH and 0.1 g of acid **4** in 10 ml of EtOH was refluxed under N_2 for 1 h. The cooled solution was poured into H_2O. The solution was brought to pH 2 with 10% H_2SO_4 solution and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. Chromatography of the residue and elution with $CHCl_3$-MeOH (95:5) gave 0.068 g (85%) of ketone **7**: mp 107–109° (Et_2O); ir 1685, 1740 cm^{-1}; ms $[M]^+$ 222; ^{1}H nmr δ 1.26 (3H, s, 10-Me), 5.60 (1H, bs, H-12), 6.23 (1H,

bs, H-12); ^{13}C nmr see Table 1. *Anal.* calcd for $C_{13}H_{18}O_3$: C 70.24, H 8.16; found C 70.01, H 8.36.

$NaBH_4$-INDUCED HYDRODEACYLATION OF **4**.—$NaBH_4$ (0.15 g) was added to a stirred solution of the acid **4** (0.15 g) in 10 ml of MeOH under N_2. The mixture was stirred at 50° for 4 h. After this period the reaction mixture was cooled to room temperature and was quenched with Me_2CO, diluted with H_2O, brought to pH 2 with 10% H_2SO_4 solution, and extracted with $CHCl_3$. The combined organic layers were washed with H_2O, dried, and evaporated. Chromatography of the residue and elution with $CHCl_3$-MeOH (95:5) gave 0.085 g (65%) of ketone **7**. For analytical and spectroscopical data see above.

ESTERIFICATION OF **7**.—Ketone **7** (0.05 g) was treated with an ethereal solution of CH_2N_2 as described above. Chromatography of the residue on Al_2O_3 (activity grade IV) and elution with $CHCl_3$ gave 0.045 g (90%) of ketoester **8** as an oil: ir 1710, 1740 cm^{-1}; ^1H nmr δ 1.31 (3H, s, 10-Me), 3.81 (3H, s, CO_2Me), 5.61 (1H, bs, H-12), 6.24 (1H, bs, H-12). *Anal.* calcd for $C_{14}H_{20}O_3$: C 71.16, H 8.53; found C 71.01, H 8.61.

REDUCTION OF THE ESTER **8**.—To a solution of 0.025 g of ester **8** in 15 ml of MeOH, $NaBH_4$ (0.020 g) was added under N_2. The solution was stirred at room temperature for 1 h. After this period the reaction was quenched with Me_2CO, diluted with H_2O, brought to pH 2 with 10% H_2SO_4 solution, and extracted with $CHCl_3$. The combined organic layers were washed with H_2O, dried, and evaporated. Chromatography of the residue and elution with $CHCl_3$-MeOH (95:5) gave 0.021 g (70%) of alcohol **5** as an oil: ir 1710 cm^{-1}; ^1H nmr δ 1.06 (3H, s, 10-Me), 3.78 (3H, s, CO_2Me), 4.40 (1H, m, H-3), 5.51 (1H, bs, H-12), 6.10 (1H, bs, H-12); ^{13}C nmr see Table 1. *Anal.* calcd for $C_{14}H_{22}O_3$: C 70.56, H 9.30; found C 70.39, H 9.42.

ACETYLATION OF ALCOHOL **5**.—A solution of 0.021 g of alcohol **5** and 0.5 ml of Ac_2O in 1 ml of pyridine was kept at room temperature for 12 h. After the usual workup (7), the residue was chromatographed. Elution with $CHCl_3$ gave 0.019 g (95%) of acetate **6** as an oil: ir 1715 cm^{-1}, ^1H nmr δ 1.06 (3H, s, 10-Me), 2.13 (3H, s, acetate), 3.76 (3H, s, CO_2Me), 5.36 (1H, m, H-3), 5.50 (1H, bs, H-12), 6.10 (1H, bs, H-12); ^{13}C nmr see Table 1. *Anal.* calcd for $C_{16}H_{24}O_4$: C 68.55, H 8.63; found C 68.42, H 8.78.

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