New Jaeschkeanadiol Derivatives from Ferula jaeschkeana

S. N. Garg, S. K. Agarwal, K. Fidelis, M. B. Hossain, and D. van der Helm

More About This Article

The permalink http://dx.doi.org/10.1021/np50094a014 provides access to:

- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

NEW JAESCHKEANADIOL DERIVATIVES FROM FERULA JAESCHKEANA

S.N. Garg, S.K. Agarwal,*

Central Institute of Medicinal and Aromatic Plants, Post Bag No. 1, R.S.M. Nagar, Lucknow 226016, India

K. Fidelis, M.B. Hossain, and D. van der Helm*

Department of Chemistry and Biochemistry, University of Oklahoma, Norman, Oklahoma 73019

ABSTRACT.—Two new jaeschkeanadiol derivatives have been isolated from Ferula jaeschkeana rhizomes. These have been identified as a dichloro compound, jaeschkenol [1], and $2\alpha,3\alpha$-dihydroxy-4-keto-5α-p-hydroxybenzoyl-jaeschkeanadiol [2], on the basis of spectral data and the X-ray analysis of the former.

The genus Ferula is chemically characterized by its production of coumarins and sesquiterpenes (1). Jaeschkeanadiol (2) and yeshferin (3) were obtained from Ferula jaeschkeana Vatke (Umbelliferae), a species found in the Himalayan range at an elevation of 2000–4000 m, from which we have reported several sesquiterpenes (4–8). We continue our studies on this species in the present communication and describe the isolation and structure elucidation of two new sesquiterpenes with the carotane skeleton.

RESULTS AND DISCUSSION

The petroleum ether and MeOH extract of F. jaeschkeana rhizomes, when chromatographed on SiO_2 columns and preparative layer, yielded two pure compounds tentatively named jaeschkenol [1] and $2\alpha,3\alpha$-dihydroxy-4-keto-5α-p-hydroxybenzoyl-jaeschkeanadiol [2].

Jaeschkenol [1] exhibited a strong absorption band in the ir at $3300\ cm^{-1}$, indicating the presence of hydroxy groups. Its hrms showed an $[M - H_2O]^+$ ion at m/z 302.120911, which analyzed for $C_{16}H_{24}OCl_2$. Other fragments $[M - C_3H_7]^+$ at 277.076385 ($C_{13}H_{19}O_2Cl_2$) and $[M - C_3H_7 - H_2O - HCl]^+$ at 223.089401, ($C_{13}H_{16}OCl$) were also present. The loss of an isopropyl group is typical in the carotane class of sesquiterpenes with a hydroxyl function at C-7 (2). The nature of the hydroxyl groups as one secondary and one tertiary was confirmed by the presence of ^{13}C-nmr signals at δ 68.20 (d) and δ 86.35 (s) and an oxymethine signal at δ 4.40 (ddd) in the ^1H-

1

2

3
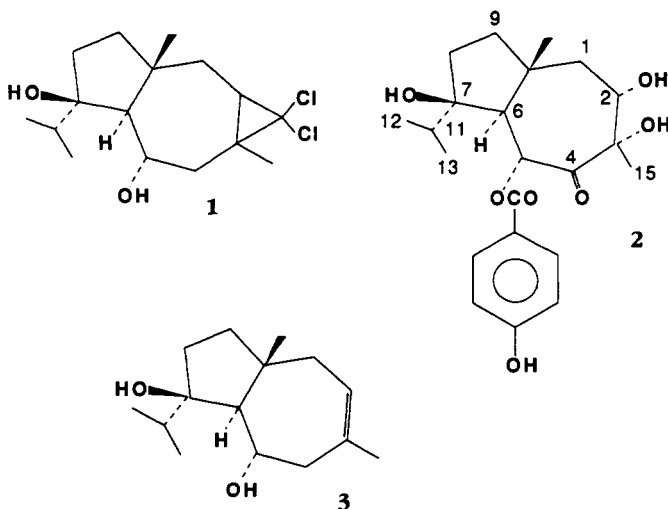
nmr spectrum (Table 1). By comparing ^{1}H- and ^{13}C-nmr chemical shifts of **1** with those of jaeschkeanadiol [**3**], it appears that **1** lacks a double bond and that it contains one more carbon atom. The C-16 at δ 73.70 (s) (^{13}C nmr) and one-proton signal at δ 1.03 (dd) (^{1}H nmr) together with three degrees of unsaturation indicated a cyclo-propane ring instead of a double bond as in **3**. In addition a methyl appeared at δ 1.57 which was assigned to the cyclopropane methyl at C-3. The *J* value between C-1a–C-2 and C-1b–C-2 was 8 Hz in its ^{1}H-nmr spectrum, and this indicated that the cyclo-propane ring methine C-2 is β. Thus, based on these facts the structure **1** was proposed for jaeschkenol.

To confirm our proposed structure **1** and to determine its absolute stereochemistry, its X-ray structure was determined. A perspective drawing of a single molecule of **1** is shown in Figure 1, which also shows the atom numbering and the absolute configura-tion as established by X-ray diffraction method. The cyclopentane ring is trans-fused with the cycloheptane ring. The C-10 methyl is β-oriented and is trans with respect to α-hydrogen at C-6. The configuration around the bridging atoms is opposite to that seen in hymenoratin (9) and related sesquiterpenes (10). The seven-membered ring is in a distorted chair conformation with the mirror symmetry passing through the atom C-6 and the midpoint of the bond C-2–C-3. The five-membered ring is in a half-chair con-formation. The two C–C distances are virtually equal. Both the hydroxyl groups form hydrogen bonds, and each acts as an acceptor as well as a donor. The O-2-H . . . O-1 geometry suggests an intramolecular hydrogen bond. The molecule forms a zigzag

TABLE 1.   Nmr Data of Compounds **1** and **2**.

Proton	Compound			Carbon	Compound
	1		**2**		**1**
	^{1}H nmr[a]		^{1}H nmr[a]		^{13}C nmr
	C_6D_6	$CDCl_3$	$CDCl_3$		
H$_a$-1	1.23, dd (14, 8)	1.51, dd (14, 8)	2.12, dd (14, 7)	C-1	37.14 (t)
H$_b$-1	1.81, dd (14, 8)	1.65, dd (14, 8)	—	C-2	32.38 (d)
H-2	1.08, dd (8, 8)	1.24, dd (8, 8)	4.35, brd (9)	C-3	28.75 (s)
H-3	—	—	—	C-4	37.74 (t)
H$_a$-4	1.66, dd (12, 8)	2.01, dd (12, 8)	—	C-5	68.20 (d)
H$_b$-4	1.97, dd (12, 3)	2.18, dd (12, 4)	—	C-6	63.17 (d)
H-5α . . .	3.88, tbr (10)	4.14, ddd (10, 8, 4)	5.85, d (10, 5)	C-7	86.35 (s)
H-6α . . .	1.34, d (10)	1.45, d (10)	2.20, d (10, 5)	C-8	43.54 (d)[b]
H-7	—	—	—	C-9	42.30 (t)[b]
H-8	1.1–1.8[c]	1.2–2.15[c]	1.2–1.7	C-10 . . .	41.36 (s)
H-9	—	—	—	C-11 . . .	38.20 (d)
H-10	—	—	—	C-12 . . .	18.40 (q)
H-11	2.33, dq (7)	2.16, dq (7)	1.70 Sep (7)	C-13 . . .	17.20 (q)
H-12	0.77, d (7)	0.90, d (7)	0.85, d (7)	C-14 . . .	27.20 (q)
H-13	0.97, d (7)	0.96, d (7)	0.90, d (7)	C-15 . . .	19.70 (q)
H-14	0.96, s	1.13, s	1.18, s	C-16 . . .	73.70 (s)
H-15	1.23, s	1.51, s	1.65, s		
H-2′, -6′ . .	—	—	6.9, d (9)		
H-3′, -6′ . .	—	—	7.95, d (9)		

[a]Chemical shifts in δ and *J* in Hz in parentheses.
[b]Assignments can be reversed.
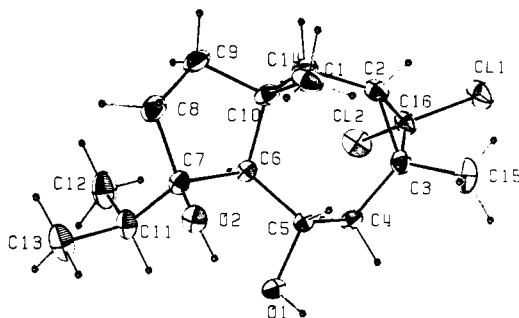[c]Marked with other signals.

FIGURE 1.   A perspective ORTEP plot of a single molecule of **1**. Numbering as followed in the text. Thermal ellipsoids drawn at the 30% probability level.

chain along the a-axis linked by an intermolecular hydrogen bond, O-1-H . . . O-2 [$-0.5 + x$, $-0.5 - y$, $1 - z$] = 2.792 (4) Å.

A new polar compound was assigned the structure of $2\alpha,3\alpha$-dihydroxy-4-keto-5α-p-hydroxybenzoyl-jaeschkeanadiol [**2**]. It analyzed for $C_{22}H_{30}O_7$, but in the mass spectrum a fragment lacking an H_2O molecule at m/z 388 was present. As in **1**, a fragment at m/z 345 $[M - H_2O - C_3H_7]^+$, due to typical loss of an isopropyl group, was also present (2). Its ir spectrum showed absorptions for an hydroxyl (3400 cm^{-1}), for a carbonyl (1710 cm^{-1}), and for an ester carbonyl (1690 cm^{-1}) group. The ^{1}H-nmr spectrum of **2** displayed signals characteristic for an isopropyl group, an angular methyl group, a quarternary methyl at a hydroxyl bearing carbon, an oxymethine, an ester oxymethine, and four aromatic ortho-coupled protons. Out of seven oxygens, three of the oxygens of **2** are part of an ester group, two oxygens are part of tertiary hydroxy groups, one oxygen is in the form of a carbonyl, and one is in the form of a secondary hydroxyl group (Table 1). On the basis of the chemical shifts of protons and ^{1}H-nmr decouplings, its structure was proposed as **2**. Further, the oxymethine signal at δ 4.35 was confirmed at C-2 in the molecule since it was downfield compared to those compounds having hydroxyl groups at C-1 (11) and C-9 (12). Further, **2** formed a monoacetonide of **2** when reacted with Me_2CO and anhydrous $CuSO_4$, indicating the vicinal nature of these hydroxyls. The ester moiety was characterized as p-hydroxybenzoic acid because of the two signals at δ 7.95 and δ 6.90 each for two protons in the ^{1}H-nmr, and because of the characteristic mass fragments at m/z 93 and 121. This moiety was further confirmed by alkaline hydrolysis of compound **2** resulting in p-hydroxybenzoic acid as one of the products, shown by comparison of mp, ir, and tlc with an authentic sample.

The stereochemistry of C-2 and C-5 oxymethines was fixed as β since their couplings were between 9 and 10.5 Hz in the ^{1}H-nmr spectrum. Further, formation of the acetonide between C-2 and C-3 hydroxyls also suggested that both the hydroxyls should be on the same face of the molecule (13). Thus, structure **2** was assigned to this compound.

EXPERIMENTAL

GENERAL PROCEDURE.—Mp's are uncorrected and measured on a Toshniwal apparatus. Optical rotations were measured on a Jasco Dip-181; ir spectra were obtained on a model 3998 Perkin Elmer; uv-vis spectra were taken on an SPB-100 Pye Unicam; ^{1}H nmr and ^{13}C nmr were taken on a Bruker 400 and Varian FT-80A in CDCl$_3$ with TMS as the internal standard. Assignments of ^{1}H nmr were based on spin-spin decoupling experiments. ^{13}C-nmr chemical shifts were made with the aid of resonance and noise-decoupled spectra. Eims were obtained on a Finnigan MAT model number 11020B.

ISOLATION OF SESQUITERPENES.—The compounds were obtained using the experimental procedure reported by Garg and co-workers (4,5). Compound 1, R_f 0.48 [petroleum ether-Me$_2$CO (85:15)] and compound 2, R_f 0.35 [CHCl$_3$-MeOH (95:5)] were isolated from petroleum ether and MeOH extracts, respectively, of *F. jaeschkeana*. These compounds 1 and 2 gave a red and violet color, respectively, when sprayed with 1% solution of vanillin in H$_2$SO$_4$ on heating at 110° for 10 min.

Jaeschkenol [1].—Compound 1 (20 mg): colorless needles (EtOH); mp 131°; [α]^{20}D +52.8 (*c*, CHCl$_3$, 1%), uv λ MeOH$_{max}$ 220 nm; ir (KBr) cm^{-1} 3300, 2960, 2920, 2860, 1460, 1440, 1370, 1350, 1320, 1290, 1190, 1150, 1080, 1040, 970, 840; molecular formula C$_{16}$H$_{26}$O$_2$Cl$_2$; hrms *m/z* [M − H$_2$O]$^+$ 302.120911 (C$_{16}$H$_{24}$OCl$_2$) (9), [M − C$_3$H$_7$]$^+$ 277.076385 (C$_{13}$H$_{19}$O$_2$Cl$_2$) (44), [M − H$_2$O − Cl]$^+$ 267 (7), [M − C$_3$H$_7$ − H$_2$O]$^+$ 259.065399 (12), [M − H$_2$O − Cl$_2$]$^+$ 232 (8), [M − C$_3$H$_7$ − H$_2$O − HCl]$^+$ 223.089401 (C$_{13}$H$_{16}$OCl) (42), [M − C$_3$H$_7$ − 2HCl]$^+$ 187 (26), 181 (22), 151 (base peak), 145 (14), 123 (55), 99 (24), 74 (54), 71 (96).

2α,3α-Dihydroxy-4-keto-5α-p-hydroxybenzoyl-jaeschkeanadiol [2].—Amorphous powder (50 mg): uv λ (MeOH) max 222, 255 nm; ir cm^{-1} (KBr) 3400, 2950, 2900, 1700, 1690, 1615, 1450, 1370, 1280, 1170, 1110, 1040, 930; ^{1}H nmr see Table 1; ms *m/z* (rel. int. %), [M − H$_2$O]$^+$ 388 (3.6), [M − H$_2$O − C$_3$H$_7$]$^+$ 345 (2), [M − H$_2$O − C$_3$H$_7$ − C$_6$H$_4$COOH]$^+$ 207 (15), 234 (6), 193 (20), 174 (25), 151 (18), 138 (40), 121 (base peak), 109 (20), 93 (30), 72 (13.5). Found C 65.89, H 7.33; C$_{22}$H$_{30}$O$_7$ requires C 65.02, H 7.38%.

HYDROLYSIS OF COMPOUND 2.—A mixture of 2 (15 mg) and aqueous methanolic KOH (4%, 2 ml) was refluxed for 3 h and worked up for the acidic and alcoholic fractions by the usual methods. The acidic fraction R_f 0.85 [C$_6$H$_6$-MeOH-HOAc (90:16:8)] showed one spot identical with an authentic sample of *p*-hydroxybenzoic acid, mp 210–212° (mp, mmp, ir). The alcoholic fraction, single spot R_f 0.51 [CHCl$_3$-MeOH (95:5)] as amorphous powder (7 mg): ir (KBr) 3420 (OH), 1695 (C=O) cm^{-1}; ^{1}H nmr (80 MHz, CDCl$_3$) δ 0.80, 0.93 (3H each, d, *J* = 7 Hz, 2 × Me), 1.12 and 1.60 (3H each, s, 2 × Me), 2.30 (1H, d, *J* = 10 Hz, -CH-), 4.57 (1H, d, *J* = 10 Hz, CHOH), 4.32 (1H, m, CHOH).

ACETONIDE OF COMPOUND 2.—Compound 2 (5 mg in dry Me$_2$CO, 5 ml) and freshly baked CuSO$_4$ (200 mg) were stirred at room temperature for 48 h and filtered. The filtrate was evaporated to obtain an amorphous powder. ^{1}H nmr (80 MHz, CDCl$_3$) δ 0.81, 0.95 (3H each, d, *J* = 7 Hz, 2 × Me), 1.12, 1.87, 1.46, 1.68 (3H each, s, 4 × Me), 2.32 (1H, d, *J* = 10 Hz), 5.8 (1H, d, *J* = 10 Hz, CHOR), 4.35 (1H, m, CHOH), 6.98 (2H, d, *J* = 9 Hz, ArH), 7.90 (2H, d, *J* = 9 Hz, ArH).

X-RAY CRYSTALLOGRAPHIC ANALYSIS OF 1[1].—A colorless crystal of compound 1, size 0.67 × 0.52 × 0.26 mm, was used for all X-ray measurements. The compound crystallizes in the orthorhombic system with the following crystal data: C$_{16}$H$_{26}$O$_2$Cl$_2$, M.W. = 321.3, orthorhombic, $P2_12_12_1$, *a* = 9.395 (2), *b* = 24.490 (4), *c* = 7.487 (1) Å, V = 1722.6 Å^3, Z = 4, Dx = 1.238 gm·cm^{-3} at 20°. The cell parameters were determined by a least-squares fit to ±2θ of 40 reflections.

Intensities of all unique reflections with 2θ<53° were measured using MoKα radiation (graphite monochromator) on an Enraf-Nonius CAD-4 diffractometer at 20°. The θ–2θ scan technique was used with a variable scan width of (0.80 + 0.20 tan θ)° and a variable horizontal aperture width of (3.00 + 0.86 tan θ) mm. Intensities of three monitor reflections were measured every 60 min of X-ray exposure, and appropriate scaling correction (maximum, 4%) was made to the intensity data. The intensities were corrected for Lorentz and polarization factors and also for absorption (14) (max./min. transmission factors (0.3979/0.2520). Of the total 2037 reflections, 1687 were considered observed on the basis of I>2σ (I), where σ (I) was obtained from counting statistics. The structure was determined by direct methods using the program MITHRIL (15) and refined by a full-matrix least-squares routine, SHELX76 (14). All hydrogen atoms were located from difference Fourier maps, and they were refined with isotropic thermal parameters. The refinement converged to a final R = 0.039, Rw = 0.045, S = 1.46, (Δ/δ)max = 0.015 for 1687 reflections

---

[1]Atomic coordinates for this compound have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

and 285 variables. The final difference map showed peaks of height ± 0.15 e/Å^3. The final atomic parameters of the non-hydrogen atoms are in Table 2.

The absolute configuration of **1** was determined by the Bijvoet method (16) using the anomalous dispersion of Cu radiation by chlorine and oxygen atoms. Intensities of 12 most enantiomer-sensitive Friedel pairs were measured repeatedly (15 times each) as low temperature ($-135°$) using CuKα radiation. The intensity differences of all 12 pairs are in agreement with the absolute configuration shown in this report.

TABLE 2.   Positional and Thermal Parameters of Non-Hydrogen Atoms (ESD in parentheses).

Atom	x	y	z	Ueq[a]
Cl-1	0.3362(1)	−0.00701(4)	0.6194(2)	0.0724(4)
Cl-2	0.4551(1)	−0.06337(4)	0.9213(1)	0.0622(3)
O-1	0.7030(3)	−0.23483(9)	0.6378(4)	0.0452(8)
O-2	0.9772(3)	−0.2173(1)	0.5474(3)	0.0441(8)
C-1	0.7528(4)	−0.0494(1)	0.7019(7)	0.047(1)
C-2	0.6125(4)	−0.0486(1)	0.6047(5)	0.043(1)
C-3	0.5179(3)	−0.0983(1)	0.5707(5)	0.041(1)
C-4	0.5546(3)	−0.1535(1)	0.6533(5)	0.039(1)
C-5	0.6993(3)	−0.1775(1)	0.5968(5)	0.0336(9)
C-6	0.8213(3)	−0.1505(1)	0.6955(5)	0.0325(9)
C-7	0.9656(3)	−0.1826(1)	0.7014(4)	0.037(1)
C-8	1.0816(4)	−0.1379(2)	0.6868(8)	0.054(1)
C-9	1.0048(4)	−0.0839(1)	0.7182(8)	0.060(2)
C-10	0.8585(3)	−0.0917(1)	0.6317(5)	0.041(1)
C-11	0.9806(4)	−0.2180(2)	0.8720(5)	0.050(1)
C-12	0.9812(7)	−0.1854(2)	1.0463(6)	0.076(2)
C-13	1.1159(6)	−0.2535(2)	0.8647(9)	0.074(2)
C-14	0.8735(5)	−0.873(2)	0.4300(7)	0.056(2)
C-15	0.4500(6)	−0.1030(3)	0.3878(7)	0.070(2)
C-16	0.4688(4)	−0.0525(1)	0.6903(5)	0.044(1)

[a]Ueq $= (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i \cdot a_j$.

LITERATURE CITED

1. A.I. Saidkhodzhaev, *Khim. Prir. Soedin.*, 437 (1979).
2. M.C. Sriraman, B.A. Nagasampagi, R.C. Pandey, and S. Dev, *Tetrahedron*, **29**, 985 (1973).
3. K.B. Bizanova, A.I. Saidkhodzhaev, and V.M. Malikov, *Khim. Prir. Soedin.*, 127 (1980).
4. S.N. Garg, L.N. Misra, S.K. Agarwal, V.P. Mahajan, and S.N. Rastogi, *Phytochemistry*, **26**, 449 (1987).
5. S.N. Garg and S.K. Agarwal, *Planta Med.*, **53**, 341 (1987).
6. S.N. Garg, S.K. Agarwal, V.P. Mahajan, and S.N. Rastogi, *J. Nat. Prod.*, **50**, 253 (1987).
7. S.N. Garg and S.K. Agarwal, *J. Nat. Prod.*, **51**, 771 (1988).
8. S.N. Garg, V.P. Mahajan, and S.N. Rastogi, *Phytochemistry*, **29**, 531 (1990).
9. P.W. Baures, K.-L. Sun, J.A. Chan, and D.S. Eggleston, *Acta Crystallogr.*, **C48**, 211 (1992).
10. W.H. Watson and R.P. Kashyap, *Acta Crystallogr.*, **C46**, 1524 (1990).
11. J.G. Diaz, B.M. Fraga, A.G. Gonzalez, P. Gonzalez, and M.G. Hernandez, *Phytochemistry*, **23**, 2541 (1984).
12. A.Sh. Kadyrov, A.I. Saidkhodzhaev, and G.K. Nikonov, *Khim. Prir. Soedin.*, 102 (1976).
13. B.M. Fraga, M.G. Hernandez, J.G. Diaz, A.G. Gonzalez, and P. Gonzalez, *Phytochemistry*, **25**, 2883 (1986).

14. G. Sheldrick, "SHELX76, Program for Crystal Structure Determination," University of Cambridge, England, 1984.
15. C.J. Gilmore, "MITHRIL, A Computer Program for Automatic Solution of Crystal Structure," University of Glasgow, Glasgow, Scotland, 1983.
16. D. van der Helm and M.B. Hossain, in: "Patterson and Pattersons." Ed. by J.P. Glusker, B.K. Patterson, and M. Rossi, Oxford University Press, New York, 1987, p. 482.

American Society of Pharmacognosy
Research Achievement Award

The American Society of Pharmacognosy Research Achievement Award is awarded annually, given candidates of sufficient merit. Candidates must be members of the American Society of Pharmacognosy and must have made distinguished contributions to natural product research. The award consists of a special honorarium of $2500 and travel expenses to present the award lecture at an annual meeting of the Society.

Nominations of candidates for this award are now being received for 1994. A nomination may be made by any member of the Society and must include a curriculum vitae of the nominee, a list of publications, and a statement emphasizing the nominee's accomplishments and their significance. Attachment of representative reprints may be helpful.

Nominations and inquiries should be received no later than June 1, 1993, and be directed to:

Kenneth L. Rinehart
Research Award Committee
454 Roger Adams Laboratory
University of Illinois
1209 W. California
Urbana, Illinois 61801
Phone (217) 333-0627
FAX (217) 244-3571