Hypertricone, a Constituent with a Novel Skeleton, Isolated from *Hypericum geminiflorum*

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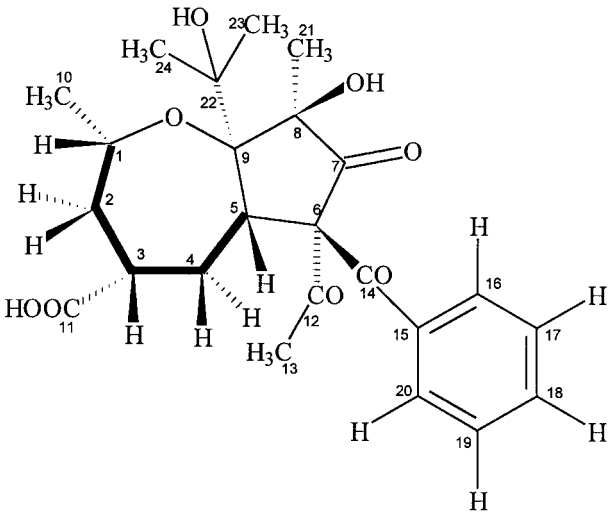
A novel compound containing an oxepane ring, hypertricone (**1**), was isolated from the leaves of *Hypericum geminiflorum*. Its structure, including the relative configuration, was elucidated from spectroscopic data and a computer-generated plot for the 3D structure.

1. Introduction. – Recently, the isolation and characterization of several constituents of the heartwood, root, and leaf of *Hypericum geminiflorum* HEMSL. (Guttiferae) has been reported [1–3]. A further search for structurally interesting and bioactive compounds from this plant resulted in the isolation of a novel constituent with an oxepane ring, hypertricone (**1**). In the present paper, the structure elucidation of **1** is reported.

2. Results and Discussion. – Compound **1**, an optically active colorless oil, possesses the molecular formula $C_{24}H_{30}O_8$, as determined by positive-mode DCI mass spectra ($[M+H]^+$ at m/z 447) and by signal counting in the ^{1}H- and ^{13}C-NMR spectra. The IR absorptions of **1** implied the presence of OH (3500 cm^{-1}), COOH (1760 cm^{-1}), and CO (1671 cm^{-1}) groups and of an aromatic-ring moiety (1615 cm^{-1}). The ^{1}H- and ^{13}C-NMR spectra (*Table*) revealed signals due to a monosubstituted benzene ring, two carbonyl, an acetyl, and one COOH group, two tertiary-alcohol moieties, three tertiary and a secondary Me, two CH_2, and one CH group, an O-bearing CH group, and four aliphatic quarternary C-atoms. Analysis of the COSY 90 and HMQC plots of **1** established the connectivities of a ^{1}H,^{1}H and ^{1}H,^{13}C spin system corresponding to partial structure shown in *Fig. 1* (bold lines).

The secondary Me(10) group of **1** is located at C(1), as established by HMBC correlation C(1)/Me(10). The HMBC correlations of C(9)/H–C(4), C(22)/H–C(5), Me(23), and Me(24), and C(23)/Me(24) confirm the connectivities of the partial structure of **1** (bold lines) and the 1-hydroxy-1-methylethyl group *via* the C(5)–C(9) and C(9)–C(22) bonds. The location at C(6) of the partial structure (bold lines), the acetyl group, and two carbonyl groups (C(7) and C(14)) is shown by the HMBC correlations C(6)/H–C(5), C(7)/H–C(5), C(14)/H–C(5), C(12)/Me(13), and C(6)/Me(13). The HMBC correlation C(14)/H–C(16) or H–C(20) establishes the connectivity between C(14) and C(15). In addition to the above evidence, the HMBC correlation C(9)/Me(21) and the presence of a tertiary oxygenated and two oxygenated quarternary C-signals at δ 92.8, 71.1, and 114.6 in the ^{13}C-NMR spectrum are compatible with the proposed structure **1**.



C,H-Correlations:
C(1)/H_α–C(2), CH_3(10)
C(2)/H–C(3), H_β–C(4)
C(3)/H_α–C(2), H_β–C(4)
C(4)/H–C(5)
C(5)/H–C(3), H_β–C(4)
C(6)/H_β–C(4), H–C(5), CH_3(13)
C(7)/H–C(5)
C(9)/H_α–C(4), CH_3(21)
C(11)/H_α–C(2), H_β–C(2), H–C(3), H_α–C(4)
C(12)/CH_3(13)
C(14)/H–C(5), H–C(16) or H–C(20)
C(22)/H–C(5), CH_3(23), CH_3(24)
C(23)/CH_3(24)

1

Fig. 1. *Structure and partial structure of* **1** (bold lines) *with some key HMBC correlations*. Bold lines represent ^{1}H,^{1}H and ^{1}H,^{13}C spin systems identified by ^{1}H,^{1}H-COSY, HMQC, and HMBC data. Arbitrary numbering.

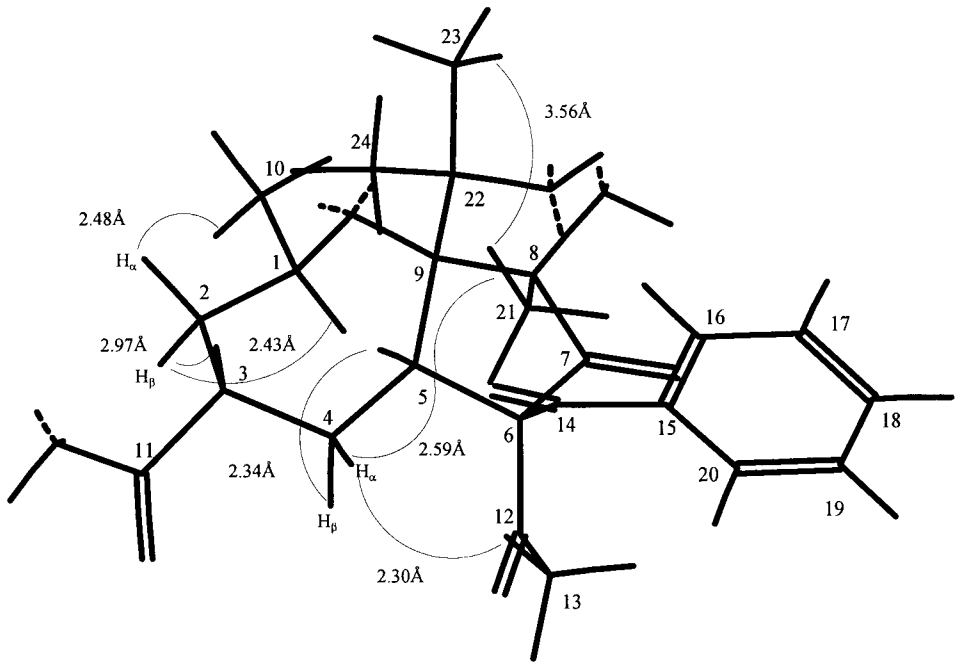


Fig. 2. *Selected NOESY correlations and relative configuration for hypertricone* (**1**)

Table. *^{1}H- and ^{13}C-NMR Data of* **1** *in CD_3OD.* Arbitrary numbering according to *Fig. 1*

	δ(H)(J [Hz])	δ (C)	HMBC (^{1}H)
H−C(1)	4.44 (*dd*, *J* = 11.0, 5.2)	92.8	1.03 (Me(10)), 1.91 (H_α−C(2))
H_α−C(2)	1.91 (*m*)	33.6	3.62 (2 H−C(3))
H_β−C(2)	2.46 (*ddd*, *J* = 12.4, 8.4, 5.2)		
2 H−C(3)	3.62 (*m*)	43.6	1.91 (H_α−C(2)), 2.35 (H_β−C(4))
H_α−C(4)	1.95 (*m*)	32.0	2.71 (H−C(5))
H_β−C(4)	2.35 (*ddd*, *J* = 13.0, 6.8, 2.0)		
H−C(5)	2.71 (*dd*, *J* = 12.3, 6.8)	55.9	3.62 (H−C(3))
C(6)		64.3	2.71 (H−C(5)), 1.82 (Me(13))
C(7)		197.5	2.71 (H−C(5))
C(8)		114.6	
C(9)		71.1	1.03 (Me(21)), 1.95 (H_α−C(4))
Me/C(10)	1.03 (*d*, *J* = 5.6)	25.5[a])	
C(11)		181.6	1.91 (H_α−C(2)), 2.46 (H_β−C(2)), 1.95 (H_α−C(4)), 2.35 (H_β−C(4)), 3.62 (H−C(3))
C(12)		176.9	1.82 (Me(13))
Me(13)	1.82 (*s*)	26.5	
C(14)		196.5	2.71 (H−C(5)), 7.83 (H−C(16) or H−C(20))
C(15)		138.9	
H−C(16)	7.83 (*m*)	130.1	
H−C(17)	7.48 (*m*)	129.8	
H−C(18)	7.60 (*m*)	134.6	
H−C(19)	7.48 (*m*)	129.8	
H−C(20)	7.83 (*m*)	130.1	
Me(21)	1.03 (*s*)	25.6[a])	
C(22)		85.9	2.71 (H−C(5)), 1.26 (Me(23)), 1.49 (Me(24))
Me(23)	1.26 (*s*)	24.0	1.49 (Me(24))
Me(24)	1.49 (*s*)	28.5	

[a]) Attributions may be interchanged.

The presence of characteristic peaks at *m*/*z* 430 ($[M+1-OH]^+$), 413 ($[430-OH]^+$), 388 ($[M+1-Me_2C(OH)]^+$), 371 ($[413-COMe]^+$), and 327 ($[371-COOH+H]^+$) in its positive-mode DCI-MS also support structure **1**.

The NOESY experiment of **1** reveals the cross-peaks represented in the computer-generated plot for the 3D structure of **1** (see below, *Fig. 2*). The relative configurations at C(1), C(3), C(5), C(6), C(8), and C(9) are deduced from the NOESY cross-peaks Me(10)/H_α−C(2), H_β−C(2)/H−C(3), H_β−C(4)/H−C(5), H_α−C(4)/Me(21), H_α−C(4)/Me(13), and Me(21)/Me(23), while Me(10), COOH at C(3), MeCO−C(6), Me(21), and $Me_2C(OH)$−C(9) are on the α-side, and H−C(1), H−C(3), H−C(5), PhCO−C(6), and OH−C(8) are on the β-side.

Based on the information from the ^{1}H-NMR, COSY, and NOESY experiments, a computer-generated plot for the 3D structure of **1** (*Fig. 2*) was obtained with the molecular-modeling program CS CHEM 3D V3.5.1 by MM2 force-field calculations for energy minimization. The calculated distances between Me(10)/H_α−C(2) (2.48 Å), H_β−C(2)/H−C(3) (2.97 Å), H−C(1)/H_β−C(2) (2.43 Å), H_β−C(4)/H−C(5) (2.34 Å), H_α−C(4)/Me(13) (2.30 Å), H_α−C(4)/Me(21) (2.59 Å), and Me(21)/Me(23) (3.56 Å) are all less than 4.00 Å, which is consistent with the well-defined NOEs observed for each of these proton pairs. Thus the structure of hypertricone (**1**) is that of 6-acetyl-6-benzoylhexahydro-8-hydroxy-8a-(1-hydroxy-1-methylethyl)-2,8-dimethyl-7-oxo-2*H*-cyclopent[*b*]oxepin-4-carboxylic acid.

Examination of the unusual C-skeleton of **1** suggested that biogenetically this compound might be derived from sesquiterterpenes.

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Experimental Part

General. M.p.: uncorrected. Optical rotations: *JASCO* model *DIP-370* digital polarimeter. IR Spectra: *Hitachi 260-30* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian-Unity 400* spectrometer; at 400 and 100 MHz, resp.; δ in ppm, J in Hz. MS: *JMS HX100* mass spectrometer; m/z (rel. %).

Plant Material. Whole plants of *H. geminiflorum* were collected at Ping Tung Hsieng, Taiwan, in July 1993, and a voucher specimen (9302) has been deposited at the Department of Medicinal Chemistry, School of Pharmacy, Kaohsiung Medical University.

Extraction and Isolation. The leaves (3 kg) of *H. geminiflorum* were chipped and extracted with MeOH at r.t. The extract (50 g) was subjected to column chromatography (silica gel, CH_2Cl_2/MeOH 4:1): **1** (10 mg).

Hypertricone (= *6-Acetyl-6-benzoylhexahydro-8-hydroxy-8a-(1-hydroxy-1-methylethyl)-2,8-dimethyl-7-oxo-2*H*-cyclopent[*b*]oxepin-4-carboxylic Acid*; **1**). Colorless oil (CH_2Cl_2/MeOH). $[\alpha]_D^{25} = +11$ ($c = 0.15$, MeOH). IR (KBr): 3500, 1760, 1671, 1615. ^1H-NMR (CD_3OD, 400 MHz; for numbering, see *Fig. 1*): *Table.* ^{13}C-NMR (CD_3OD, 100 MHz): *Table.* DCI-MS (65 Ev): 447 (85, $[M+H]^+$), 430 (90), 413 (63), 388 (10), 371 (35), 327 (5), 161 (6), 156 (6), 53 (100).

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