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Sinaicinone, a complex adamantanyl derivative from *Hypericum sinaicum*

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Abstract

The structure of sinaicinone, isolated from the aerial parts of the Egyptian medicinal plant *Hypericum sinaicum*, has been elucidated by means of spectroscopic data such as UV, IR, MS, 1D and 2D NMR spectra, and chemical degradation. It is a complex adamantanyl derivative with a unique skeleton and oxygenated side chains.

Keywords: *Hypericum sinaicum*; Guttiferae; Sinaicinone; Adamantanyl derivative; Sinai Peninsula (Egypt)

1. Introduction

The Guttiferae is a large family with more than 1000 species. The genus *Hypericum* has more than 400 species, which are accommodated in about 30 sections (Robson, 1990).

The species from the family Guttiferae have a strong tendency to accumulate phenolic compounds with the phloroglucinol substitution pattern. In the genus *Hypericum* many phloroglucinol derivatives have been isolated, some of which are polyisoprenylated phloroglucinol derivatives like the well-known hyperforin and adhyperforin isolated from *Hypericum perforatum* (Piovan et al., 2004; Klingauf et al., 2005).

Until recently, it was assumed that living organisms could not synthesize adamantane derivatives, whose origin was thus taken to be purely abiotic. This view was finally refuted in the second half of 1990s when adamantane derivatives were for the first time isolated and identified as biologically active compounds of plants from the Guttiferae family (Ciochina and Grossman, 2006).

Thus, a homoadamatane derivative, plukenetione A, has been isolated from *Clusia plukenetii* from Barbados (Henry et al., 1996). Further plukenetiones (B and C) were identified (Henry et al., 1999; Grossman and Jacobs, 2000) also in *C. plukenetii*. Extracts of the fruit of *C. havetiodes* var. *stenocarpa* from Jamaica have yielded two new prenylated benzophenone derivatives, 28,29-epoxyplukenetione A and 33-hydroperoxyisoplukenetione C (Christian et al., 2001). There is also a recent report of the isolation of the 17,18-dihydro derivative of plukenetione G from Cuban propolis collected in areas in which the main species foraged by the bees are *C. minor* and *C. rosea* (Rubio et al., 1999).

Six new prenylated phloroglucinol derivatives, hypersampsones A–F, were isolated from the aerial part of *H. sampsonii* from Taiwan, together with sampsoniones D and H (Hu and Sim, 1999a; Lin and Wu, 2003). Derivatives of homoadamantanes, e.g. sampsoniones A–H (Hu and Sim, 1998, 1999a, 2000) and sampsoniones I and J (Hu and Sim, 1999b) were isolated also from Chinese *H. sampsonii* and from different other sources.

The hexane extract of *C. obdeltifolia* trunk yielded three new homoadamantanes along with two known polyprenylated benzophenones, sampsonione B and sampsonione G (Cruz and Teixeira, 2004). Two new polyisoprenylated benzophenones along with the known compound 28,29-

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epoxyplukenetione A were isolated from the hexane extract of *C. obdeltifolia* (Teixeira and Cruz, 2005). One of the new benzophenones presented a novel 9-oxa-tetracyclic moiety arising from complex cyclizations of isopentenyl and lavandulyl substituents, the other presented an adamantyl skeleton.

Hyperibone K, a new polyprenylated benzophenone with adamantanyl skeleton, was isolated from the aerial parts of the Uzbekistan medicinal plant *H. scabrum* (Tanaka et al., 2004).

In the course of a search for biologically active compounds from medicinal plants (Dembitsky et al., 1992), we have examined the ethanolic extracts of the aerial parts *H. sinaicum*, a plant endemic to the Middle East, which occurs infrequently in Sinai Peninsula (Egypt), and succeeded in isolating a novel constituent named sinaicinone.

2. Results and discussion

A sample of 5.5 kg of *H. sinaicum* Hochst. & Steud. ex Boiss. was extracted with 95% ethanol and the ethanolic concentrate was partitioned between chloroform and water. The chloroform layer was analyzed by LC–MS/APCI (liquid chromatography atmospheric pressure chemical ionization mass spectrometry) and DAD (diode-array detector).

The chloroform-soluble portion of an extract of *H. sinaicum* was separated on a Sephadex LH-20 column with UV detection at 300–305 nm. The fraction having UV absorption in this range was further purified by RP-HPLC and the results showed one major and several minor peaks with a base peak at *m*/*z* 105. The major peak represented an adamantane derivative (**1**, 17.5 mg), which was identified by IR, UV, MS, and ^{1}H and ^{13}C NMR spectroscopic data and chemical degradation.

Sinaicinone (Fig. 1) was obtained as a colorless, waxy compound. The UV spectrum exhibited maxima at different wavelengths, see Section 4. IR spectrum showed several major bands corresponding to the absorption of carbonyl and double bond; for the data see also Section 4. High-resolution positive ion FAB mass spectroscopy gave a pseudo molecular ion at *m*/*z* 633.3561 $[M+Na]^{+}$, corresponding to a molecular formula of $C_{40}H_{50}O_5$. Electron impact mass spectrum had a base peak at *m*/*z* 105 which signifies the presence of an unsubstituted phenyl ketone in the molecule. This molecular formula was confirmed by the ^{13}C and DEPT NMR spectra (Table 1), which revealed 40 carbons comprised of 9 methyls, 4 methylenes, 14 methines, 12 quaternary carbons, and one aldehyde carbon. The ^{13}C NMR and DEPT spectra revealed signals due to three nonconjugated C=O at δ 202.5, 203.4, and 201.7 and two conjugated (at δ 193.4 and 193.2) C=O groups. The molecular formula

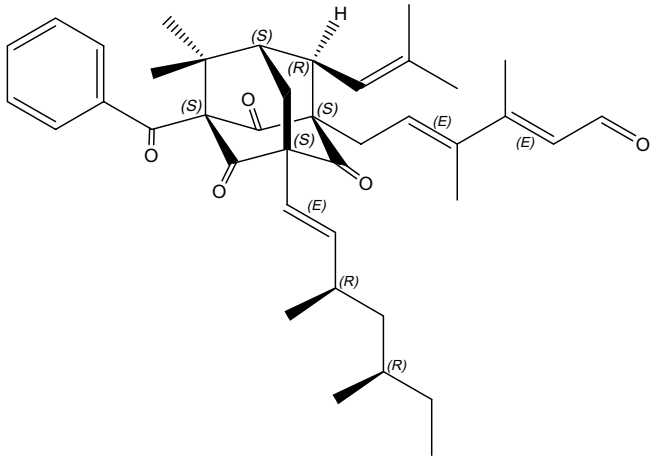

Fig. 1. Structure of sinaicinone (**1**), from *Hypericum sinaicum*.

Table 1
The ^{1}H (500.1 MHz) and ^{13}C (125.7 MHz) NMR data of sinaicinone (**1**) (in $CDCl_3$)

No.	δ_H (mult., *J*, Hz)	HMBC	δ_C
1	–	–	82.3 *s*
2	–	–	202.5 *s*
3	–	–	69.2 *s*
4	–	–	203.4 *s*
5	–	–	71.4 *s*
6	2.76 (*ddd*, 9.1, 2.9, 1.9)	4, 5, 7, 10, 20, 28, 29	51.6 *d*
7	1.89 (*ddd*, 2.9, 2.7, 2.6)	6, 10, 32, 33	48.6 *d*
8	–	–	54.9 *s*
9	–	–	201.7 *s*
10	2.47 (*ddd*, 13.7, 2.7, 1.9), 2.44 (*dd*, 13.7, 2.6)	2, 3, 6, 7, 8, 11	40.3 *t*
11	5.33 (*d*, 15.0)	2, 3, 4, 10, 13	128.4 *d*
12	5.22 (*dd*, 15.0, 8.0)	18	138.8 *d*
13	2.16 (*m*)	11, 18	35.8 *d*
14	1.22 (*ddd*, 14.0, 9.0, 4.0), 0.98 (*ddd*, 14.0, 9.0, 4.0)	18, 19	45.5 *t*
15	1.30 (*m*)	17, 19	33.2 *d*
16	1.28 (*m*), 1.12 (*m*)	17, 19	31.1 *t*
17	0.84 (*t*, 7.0)	15, 16	11.6 *q*
18	0.91 (*d*, 6.5)	12, 13, 14	22.3 *q*
19	0.82 (*d*, 6.5)	14, 15, 16	17.3 *q*
20	2.55 (*dd*, 15.0, 6.8), 2.36 (*dd*, 15.0, 6.8)	4, 5, 6, 9	33.5 *t*
21	5.38 (*t*, 6.8)	5, 26	136.1 *d*
22	–	–	147.5 *s*
23	–	–	136.8 *s*
24	6.17 (*d*, 7.1)	27	126.0 *d*
25	10.09 (*d*, 7.1)	–	193.2 *d*
26	2.17 (*s*)	21	14.9 *q*
27	2.04 (*s*)	24	14.3 *q*
28	5.10 (*dt*, 9.1, 1.4)	5, 6, 30, 31	119.5 *d*
29	–	–	136.8 *s*
30	1.68 (*d*, 1.4)	28, 29, 31	26.0 *q*
31	1.62 (*d*, 1.4)	28, 29, 30	18.1 *q*
32	1.47 (*s*)	1, 7, 8, 33	22.8 *q*
33	1.52 (*s*)	1, 7, 8, 32	23.4 *q*
34	–	–	193.4 *s*
35	–	–	134.8 *s*
36	7.18 (*d*, 8.3)	34, 38, 40	129.5 *d*
37	7.27 (*t*, 8.3)	35, 39	127.6 *d*
38	7.41 (*t*, 8.3)	36, 40	132.4 *d*
39	7.27 (*t*, 8.3)	35, 37	127.6 *d*
40	7.18 (*d*, 8.3)	34, 36, 38	129.5 *d*

^{1}H–^{1}H COSY: ^{4}J H-21–H-26, H-24–H-27, H-28–H-30, H-28–H-31, H-30–H-31; ^{5}J H-21–H-27, H-25–H-27, H-26–H-24.

corresponded to 16 double-bond equivalents, and by considering the ^{13}C NMR shifts and DEPT data, it was determined that sinaicinone contained three oxo groups tetrasubstituted at all α positions. These conclusions are based on ^{13}C NMR signals for the three nonconjugated carbonyls and the absence of the ^{1}H NMR peak (even in a spectral window of 20 ppm) attributable to a hydrogen-bonded enolic proton, a common feature in these systems.

On the basis of 1- and 2-D NMR spectra, the main side chains were (1) a benzoyl group on C-1, (2) an unsaturated branched side chain on C-3, (3) a *gem*-dimethyl group (C-32 and C-33) correlated by HMBC to each other and to C-8, (4) a methyl–propenyl chain (C-30 and C-31) correlated by HMBC to each other and to C-28 and C-29, and (5) an unsaturated aldehydic side chain on C-5.

The structure of the tricyclic core of the molecule was determined by tracing the connectivities shown in the HMBC spectra. Starting with the *gem*-dimethyls at C-8, cross peaks were observed between protons of both methyl groups and the quaternary carbon signal at δ 82.3 (C-1) which, from its deshielded position, had to be flanked by three carbonyl groups (shown as C-2, C-9, and C-34). Cross peaks between the quaternary carbon bearing the *gem*-dimethyl group, C-8 (δ 54.9), and the methylene protons at δ 2.44 and 2.47 necessitated their being in a 3-bond relationship, attached to C-10. Correlation of H_2-10 protons with the quaternary carbon signal at δ 69.2 (C-3) and with the two carbonyls established C-10 as the sixth carbon in the ring comprised of carbons 1, 2, 3, 7, 8, and 10 on the left-hand side of the tricycles. The methine proton at δ 2.76 which correlated with signals for two already assigned core carbons C-7 and C-10, one carbonyl (δ 203.4), and the α carbon at δ 71.4 was placed at the position designated C-6 of sinaicinone. Therefore, the carbons from C-1 to C-10 formed a tricyclic adamantanyl fragment.

Proof that the three protonated carbons in the core of compound **1** are contiguous was provided by the ^{1}H–^{1}H COSY spectrum which showed correlations between H-6 (δ 2.76) and H-7 (δ 1.89) and between H-7 and the H-10 methylene protons (δ 2.44, 2.47) (Fig. 2). In addition, H-6 shows a 4-bond W-coupling ($J = 1.9$ Hz) to the C-10 (δ 2.47) hydrogen. The stereochemistry at H-6 was determined by the W-coupling to H-10 and by the observation of a strong H-6/C-4 HMBC peak and the absence of H-6/C-9 peak indicating an *anti* arrangement of C-4 and H-6. In addition, NOE interaction of H-6 with the C-32 methyl protons and a similar interaction between the C-33 methyl and the W-coupled C-10 hydrogen were observed. These findings further confirmed the structure of sinaicinone.

The base peak at *m*/*z* 105 in the LREIMS and NMR resonances attributable to a phenyl group (Table 1) suggested an unsubstituted benzoyl moiety. The strong NOESY interaction (Fig. 3) of the proton signals at δ 7.18 (H-36 and H-40) with those at δ 5.33 (H-11) and 2.36 (H-20) suggested that the benzoyl moiety, C-3 and C-5 linked side chains have α-orientations.

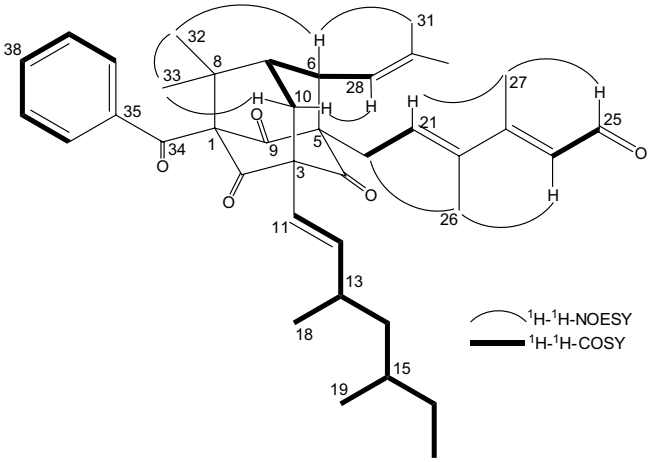

Fig. 2. The COSY and NOESY correlations of sinaicinone.

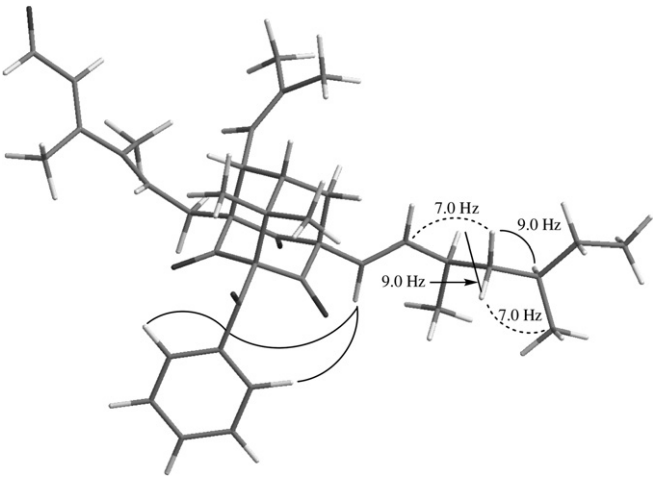

Fig. 3. The ^{1}H–^{1}H NOESY correlations and the ^{1}H–^{1}H and ^{1}H–^{13}C coupling constants of side chains of sinaicinone.

The C-6 methine proton is directly coupled ($J = 9.1$ Hz) to the C-28 vinyl proton, making C-6 the point of attachment of the 2-methylpropenyl group.

The relative stereochemistry of one side chain was analyzed by ^{1}H–^{1}H coupling constants. The geometry of disubstituted olefin at $\Delta^{11,12}$ was assigned as *E* by ^{1}H–^{1}H coupling constants ($J = 15.0$ Hz). Each *anti* orientation between H_a-14 and H-13, between H_b-14 and H-15, between H_a-14 and C-19, and between H_b-14 and C-18 was determined from large three bond couplings as shown in Fig. 3. ^{1}H–^{13}C long-range coupling constants were obtained by a *J*-resolved HMBC experiment (Furihata and Seto, 1999). These relationships assigned the relative stereochemistry of sinaicinone to (13*R**,15*R**) or (13*S**,15*S**).

To determine the absolute stereochemistry at C-13 and C-15, 2,4-dimethylhexanoic acid was prepared by ozonolysis and oxidation of degradation products. The appropriate compound displayed a negative optical rotation ($[\alpha]_D^{24}$ −29.8° (*c* 0.12, $CHCl_3$)) which is in agreement with the

literature value ($[\alpha]_D^{20}$ −30.6°) for (2*R*,4*R*)-2,4-dimethylhexanoic acid (White and Johnson, 1994). These results identified the absolute configurations of sianicinone as depicted in Fig. 1.

The *E*,*E* configuration of the conjugated double bonds in the aldehydic side chain was deduced from the NOESY data (Fig. 2). Key correlations were observed between the aldehyde proton and the C-27 methyl group, which in turn showed a strong correlation with the olefinic proton H-21. As further support, the C-26 methyl group showed a strong NOE correlation with H-24 and the allylic methylene protons H-20.

In ethanol extracts of *H. perforatum* collected in August 2004 about 30 km south of Prague, Czech Republic, LC–MS did not reveal any compound (detection limit 10^{-5}%) that would contain a benzoyl group (the major ion *m*/*z* 105 was completely missing) and simultaneously also the 1,3,5-trioxocyclohexane ring (UV absorption at 296–305 nm).

3. Conclusions

To our knowledge this is the first report of an adamantanyl derivative with the isoprenyl oxygenated side chain as a plant metabolite. Unfortunately, in the Central European *H. perforatum*, similar compounds with adamantanyl skeleton could not be detected up to the concentration of 10^{-5}%.

4. Experimental

4.1. General experimental procedures

UV–Vis spectra were measured in MeOH within the range of 220–550 nm in a Cary 118 (Varian) apparatus. A Perkin–Elmer (Perkin–Elmer, Norwalk, CT, USA) model 1310 IR spectrophotometer was used for scanning IR spectroscopy as neat films. NMR spectra were recorded on a Bruker AMX 500 spectrometer (Bruker Analytik, Karlsruhe, Germany) at 500.1 MHz (^{1}H), 125.7 MHz (^{13}C). High- and also low-resolution MS were recorded using a VG 7070E-HF spectrometer (70 eV). HRFABMS (positive and/or negative ion mode) were obtained with a PEG-400 matrix.

The LC–MS/APCI was realized as mentioned previously (Rezanka and Dembitsky, 2003), briefly: the HP 1090 series instrument (Hewlett–Packard, USA) was used with two columns in series (HIRPB-250AM 250 × 2.1 mm ID, 5 μm phase particle). A quadruple mass spectrometer system Navigator (Finnigan MAT, San Jose, CA, USA) was used: vaporizer temperature 400 °C, capillary heater temperature 220 °C, corona current 5 μA, sheath gas high-purity nitrogen, pressure ca. 380 kPa, and auxiliary gas (also nitrogen) flow rate 1500 ml/min. Ions with *m*/*z* 50–1500 were scanned with a scan time of 0.5 s, flow 0.37 ml/min. Compounds were separated using a solvent program with water–acetonitrile (50:50) for 10 min and linear gradient from 10 min to 40 min (100% acetonitrile). Agilent (HP) Model diode-array detector G1315B with a 0.5 μl flow cell (10 mm path length) and wavelength from 230 to 310 nm for diode-array detection (DAD) was used.

4.2. Plant material

The specimens of *H. sinaicum* Hochst. (Guttiferae) were collected in St. Katherine's Protectorate, the Sinai Peninsula, Egypt, in April 2004, while *Hypericum perforatum* L. was collected in August 2004 about 30 km south of Prague, Czech Republic. The plant material is deposited in the collection of the author.

4.3. Extraction, isolation and identification

The whole air-dried ground plants (5.5 kg) were extracted at room temperature with 95% ethanol for seven days, the extract was concentrated in vacuum and the residue partitioned between chloroform and water. The chloroform-soluble portion (74 g) was then separated into nine fractions by Sephadex LH-20 chromatography, eluted with different proportions of chloroform–ethanol. The fractions were rechromatographed on reversed phase and eluted with water–acetonitrile mixture (see above) to give pure sinaicinone (17.5 mg), i.e. 0.00034%.

4.4. Oxidative splitting

A stream of 4% ozone was passed through a solution of the given compound (~1 mg) in dichloromethane (2 ml) at −78 °C for 5 min. The solution was flushed with nitrogen and concentrated. The residue was dissolved in 90% HCOOH (0.7 ml) and 30% hydrogen peroxide (0.3 ml) was added. After gentle heating, the mixture was heated under reflux for 70 min (Kroft et al., 1981). The mixture was distilled and optical rotation of the distillate was measured $[\alpha]_D^{24}$ −29.8° (*c* 0.12, $CHCl_3$). HREIMS *m*/*z* 144.1150 $[M]^+$, calculated for $[C_8H_{16}O_2]^+$ 144.1150.

4.5. Sinaicinone

Yield 17.5 mg (0.00034%), colorless, waxy compound, $[\alpha]_D^{22}$ +37.5° (*c* 0.17, CH_2Cl_2); UV (MeOH) λ_{max} (log ε) 215 (3.95), 227 (3.70), 240 (3.80), 274 (3.15), 290 (2.95), and 305 (2.60) nm; IR (film) ν_{max} 1735, 1700, 1695, 1685, 1670 cm^{-1} (C=O) and 3060, 1590, 1575, 1495 cm^{-1} (C=C); LC–MS/APCI: *m*/*z* 611 $[M+H]^+$; HRFABMS *m*/*z* 633.3561 $C_{40}H_{50}O_5Na$ $[M+Na]^+$, calculated for $[M+Na]^+$ 633.3556; ^{1}H and ^{13}C NMR data, see Table 1.

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