PERGAMON

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Phytochemistry 63 (2003) 383–386

PHYTOCHEMISTRY

www.elsevier.com/locate/phytochem

Charminarone, a *seco*-pseudoguaianolide from *Parthenium hysterophorus*

B. Venkataiah, C. Ramesh, N. Ravindranath, Biswanath Das*

Organic Chemistry Division—I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 26 November 2002; received in revised form 20 February 2003

Abstract

A novel sesquiterpenoid, charminarone, the first *seco*-pseudoguaianolide, has been isolated along with several known compounds from the whole plant of *Parthenium hysterophorus*. The structure of the new compound has been settled as 1,10-*seco*-dihydroisoparthenin 1,10-dione from its spectral data as well as from its conversion by reductive coupling reaction with Zn/$TiCl_4$ reagent to the known compound, anhydrodihydroisoparthenin. The reagent Zn/$TiCl_4$ has been used here for the first time to construct the seven membered ring of a pseudoguaianolide sesquiterpenoid.

Keywords: *Parthenium hysterophorus*; Compositae; Charminarone; *seco*-Pseudoguaianolide; 1; 10-*seco*-Dihydroisoparthenin 1; 10-dione

1. Introduction

Parthenium hysterophorus Linn (Compositae) is an obnoxious weed (Towers et al., 1977). Its extract is used as folk remedy against skin diseases, ulcerated sores, facial neuralgia, fever and anemia (Herz et al., 1962). Its allelopathic effects on plants have also been reported (Kanchan, 1975; Patil and Hedge, 1988). The plant is a rich source of chemically complex sesquiterpenoids (Herz et al., 1962; Romo de Vivar et al., 1966; Shen et al., 1976; Pickman et al., 1980, 1982; Sethi et al., 1987; Das and Das, 1995; Dela Fuente et al., 1997). Parthenin (**1**) (Herz et al., 1962), the major constituent of the plant, exhibits significant medicinal activity including anticancer property (Kupchan et al., 1971; Mew et al., 1982). During our work on its constituents we have recently isolated a novel sesquiterpenoid, charminarone (**2**) which is the first *seco*-psedoguaianolide reported from nature. This paper describes its isolation, structure elucidation and chemical co-relation with parthenin (**1**).

2. Results and discussion

Charminarone (**2**) was obtained (yield 0.0005%) as a viscous mass from the CH_2Cl_2–MeOH (1:1) extract of the whole plant of *P. hysterophorus*. The compound was purified by column chromatography over silica gel using hexane–EtOAc (2:1) as eluent. Its molecular formula was assigned as $C_{15}H_{18}O_5$ from elemental analysis and mass spectrum, which showed a molecular ion peak at m/z 278 ($M^{+\cdot}$). The IR spectrum showed strong absorption at 1752 and 1720 cm^{-1} in accord with the presence of α,β-unsaturated-γ-lactone and ketone functionalities in the molecule. The structure of the new compound **2** has been established from its ^1H NMR spectrum, which was directly compared to that of the major constituent, parthenin (**1**). The comparison clearly showed that in the A-ring of **2** there is no olefinic double bond which is present in the A-ring of **1** but in both the compounds **1** and **2**, H-6 and Me-14 are present. It has also been observed that in the ^1H NMR spectrum of parthenin (**1**) Me-15 resonates as a doublet which is missing in the spectrum of **2** and instead a signal at δ 2.18 for a methyl group attached to a carbonyl function has appeared. This could be attributed to the presence of carbonyl group at C-10 indicating that the C_1–C_{10} bond of a common pseudoguaianolide has been

---

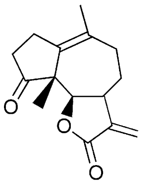
* Corresponding author. Tel.: +91-40-719-3434; fax: +91-40-716-0512.

E-mail address: biswanathdas@yahoo.com (B. Das).

0031-9422/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0031-9422(03)00147-X

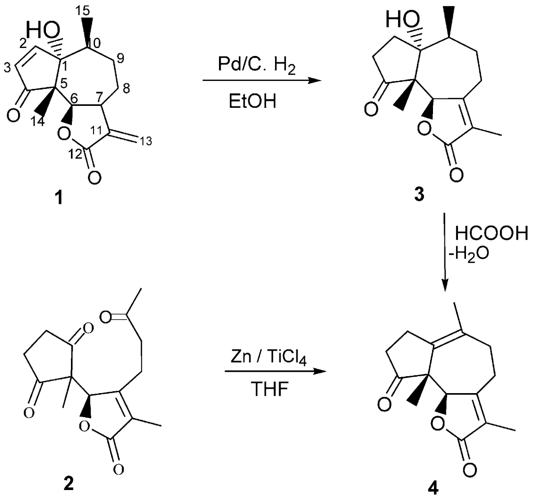
cleaved. Another methyl group resonating at δ 1.80 in **2** has reasonably been placed on the double bond at C-11 as H-7 is absent here. The four methylene groups of the new compound were observed as multiplet in the region δ 3.01–2.52.

The ^{13}C NMR spectrum of the compound (see Experimental) revealed the presence of 15 carbons including three ketone carbonyl groups (δ 212.6, 212.2, 205.7), one lactone carbonyl group (δ 172.3) and two olefinic carbons (δ 159.2 and 126.8). The assignment of the signal has been made by direct comparison of the spectrum with that of parthenin (**1**) as well as by comparison of the ^{13}C NMR values of the compound with those reported for the corresponding carbons of **1** (Sethi et al., 1987). Thus from the spectral properties the structure of charminarone (**2**) was derived as 1,10-*seco*-dihydroisoparthenin-1,10-dione.



5

As all the methylene protons of charminarone (**2**) appeared as a complex multiplet in the region δ 3.01–2.52 the 2D NMR spectra of the compound were not helpful for its structure elucidation. However the structure as well as stereochemistry of **2** was confirmed from its transformation to the known compound anhydrodihydroisoparthenin (**4**) (Herz et al., 1962) (Scheme 1) which was synthesized (by following the method reported by Herz et al., 1962) from parthenin (**1**) for direct comparison. Hydrogenation of **1** in the presence of 10% Pd/C in ethanolic solution gave the product, dihydroisoparthenin (**3**) and subsequent dehydration of the letter with formic acid afforded anhydrodihydroisoparthenin (**4**).



Scheme 1. Chemical co-relation between charminarone (**2**) and parthenin (**1**).

To achieve the synthesis of anhydrodihydroisoparthenin (**4**) from the new compound **2** the coupling of C-1 and C-10 carbonyls to form a C_1–C_{10} double bond is required. This coupling was made successful by treatment with Zn/TiCl$_4$ reagent in dry THF (McMurry, 1983; Mukaiyama et al., 1973). The compound **4** was isolated as the only reaction product but a compound with an alternative structure (that is C-5-epianhydrodihydroisopartenin) was not at all obtained. The molecular modeling experiment showed that the formation of the product **4** is energetically favored during the reductive coupling reaction of **2**. The reagent Zn/TiCl$_4$ has been utilized here for the first time to construct the seven membered ring of a pseudoguaianolide sesquiterpenoid (McMurry, 1983; Mukaiyama et al., 1973; Lenior, 1989).

Previously dihydroisoparthenin (**3**) (Pickman et al., 1982) and anhydroparthenin (**5**) (Das and Das, 1995) have been isolated from *P. hysterophorus*. The new compound **2** is possibly biogenetically formed from the former by dehydration followed by oxidation to generate two carbonyl groups at C-1 and C-10.

Along with parthenin (**1**) and charminarone (**2**) some other known compounds, coronopilin (Pickman et al., 1980), 2β-hydroxycoronopilin (Sethi et al., 1987), tetraneurin A (Pickman et al., 1980), quercetagetin-3,7-dimethylether (Pickman et al., 1982) and syringaresinol (Abe and Yamauchi, 1988) have also been isolated. These compounds were characterized by comparison of their physical and spectral data with those reported in the literature.

3. Experimental

3.1. General

Mps were measured in a Buchi-510 apparatus and are uncorr. Spectra were recorded with the following instruments: UV, Shimadzu 240 spectrophotometer; IR, Nicolet 740 FTIR spectrophotometer: ^{1}H and ^{13}C NMR, Varian Gemini 200 MHz and MS, VG Micromass 7070 H (70eV). The optical rotations were measured with a Jasco DIP 360 Digital polarimeter. Column chromatography was performed on silica gel (BDH, 100–200 mesh) and TLC with silica gel GF 254. The spots were detected under UV light and in an iodine chamber.

3.2. Plant material

Whole plants of *P. hysterophorus* L. were collected from campus in September 2000 and identified botanically. A voucher specimen (Ph-W) is preserved in our laboratory and another voucher specimen (IICP-090017) in IICT herbarium.

3.3. Extraction and isolation

The shade dried plant materials (4 kg) were powdered and extracted thrice with CH_2Cl_2–MeOH (1:1) at room temperature (each extraction was continued for 5 days using 4 l solvent). The total extract was concentrated under reduced pressure and kept in a freezer for 7 days. The major constituent parthenin (**1**) (7 g) crystallized out and was separated by filtration. The filtrate was purified by column chromatography over silica gel using the mixture of hexane and EtOAc. The eluents were collected in fractions of 50 ml each. Resolution of the components in the mixture was monitored by TLC. The following compounds were isolated according to the increasing order of polarity: syringaresinol (0.0001%), charminarone (**2**) (0.0005%), coronopilin (0.02%), parthenin (0.3%), 2β-hydroxycoronopilin (0.002%), tetraneurine A (0.001%) and quercetagetin-3,7-dimethylether (0.001%).

3.3.1. Charminarone (2)

Viscous mass, $[\alpha]_D^{25}$ −17.2 (*c* 0.25, $CHCl_3$), UV: λ_{max} (EtOH) 221 (3.99), 288 (1.48) nm, IR: υ_{max} (neat) 1752, 1720 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 4.98 (IH, *brs*, H-6), 3.01–2.52 (8H, *m*, H_2-2, H_2-3, H_2-8, H_2-9), 2.18 (3H, *s*, –COMe), 1.80 (3H, *s*, Me-13), 1.28 (3H, *s*, Me-14): ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.6 (C-1 or C-4), 212.8 (C-4 or C-1), 205.8 (C-10), 172.2 (C-12), 159.2 (C-7), 126.8 (C-8), 80.6 (C-6), 57.4 (C-5), 35.7 (C-2 or C-3), 35.2 (C-3 or C-2), 34.9 (C-9), 30.7 (C-8), 26.8 (Me-15), 21.8 (Me-13), 16.4 (Me-14); MS: *m*/*z* (rel. int) 278 (M+, 76), 235 (12), 220 (42), 167 (37), 139 (75), 95 (63). Anal. calc. for $C_{15}H_{18}O_5$. C, 64.75, H, 6.47), found, C, 64.81, H, 6.38.

4. Chemical co-relation between charminarone (2) and parthenin (1)

4.1. Conversion of parthenin (1) to dihydroisoparthenin (3)

A solution of parthenin (**1**) (200 mg) in ethanol (25 ml) was hydrogenated at room temperature and atmospheric pressure with 10% palladium on charcoal for 10 h. After completion of the reaction the mixture was filtered. The filtrate was concentrated and chromatographed over silica gel column to yield **3** (129.5 mg, 64%) as a white solid, m.p. 191 °C (MeOH): $[\alpha]_D^{25}$ +16.2 (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.36 (1H, *s*, H-6), 2.90–1.85 (8H, *m*, H_2-2, H_2-8, H_2-9, H_2-10), 1.80 (3H, *s*, Me-13), 1.08 (3H, *d*, J=7.0 Hz, Me-15), 0.82 (3H, *s*, Me-14). Anal. calc. for $C_{15}H_{20}O_4$ C: 68.18; H: 7.57%. Found C: 68.12; H: 7.65.

4.2. Conversion of dihydroisoparthenin (3) to anhydrodihydroisoparthenin (4)

A solution of dihydroisoparthenin (**3**) (100 mg) in formic acid (5 ml) was refluxed for 9 h. The reaction mixture was diluted with water (10 ml) and thoroughly extracted with chloroform (3×10 ml). On concentration the dried chloroform extract gave a residue which was chromatographed over silica gel column to give anhydrodihydroisoparthenin (**4**) (68 mg, 73%) as white solid, m.p. 148 °C ($CHCl_3$): $[\alpha]_D^{25}$ +7.1 (*c* 1.22, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.60 (^1H, *s*, H-6), 2.29–2.05 (8H, *m*, H_2-2, H_2-3, H_2-8, H_2-9), 1.85 (6H, *s*, Me-13 and Me-15), 1.00 (3H, *s*, Me-14); MS *m*/*z* (%): 246 (M^+, 64), 204 (8), 110 (100), 82 (76). Anal. calc. for $C_{15}H_{18}O_3$ C, 73.17; H, 7.32, found C, 73.08; H,7.35.

4.3. Conversion of charminarone (2) to anhydrodihydroisoparthenin (4)

Zn (33 mg, 0.505 mmol) was added in small portions to $TiCl_4$ (0.25 mmol, 0.25 ml of 1.0 M solution in CH_2Cl_2) in THF (5 ml) under N_2 atmosphere and the mixture was stirred for 30 min at room temperature. The substrate **2** (20 mg, 0.072 mmol) in THF (5 ml) was added at 0 °C. The mixture was warmed to room temperature and then refluxed for 4 h. After cooling the reaction was quenched with saturated K_2CO_3 solution (5 ml) and extracted with ether (3×20) ml). The extract was washed with water (3×30 ml), dried and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel to yield anhydrodihydoisoparthenin (**4**) (7.5 mg, 45%).

Acknowledgements

The authors thank UGC and CSIR, New Delhi for financial assistance.

References

Abe, F., Yamauchi, T., 1988. 9α-Hydroxypinoresinol, 9α-hydroxymedioresinol and related lignans from *Allamanda neriifolia*. Phytochemistry 27, 575–577.

Das, B., Das, R., 1995. Chemical investigation in *Parthenium hysterophorus*—an allelopathic plant. Allelopathy. J. 2, 99–104.

Dela Fuente, J.R., Novara, L., Alarcon, S.R., Diaz, O.J., Uribura, M.L., Sosa, V.E., 1997. Chemotaxonomy of parthenium: *P. hysterophorus–P. glomaratum*. Phytochemistry 45, 1185–1188.

Herz, W., Watanabe, H., Miyazaki, M., Kishida, Y., 1962. The structure of parthenin and ambrosin. J.Am. Chem. Soc. 84, 2601–2610.

Kanchan, D., 1975. Growth inhibitors from *P. hysterophorus*. L. Curr. Sci. 44, 358–359.

Kupchan, S.M., Eakia, M.A., Thomas, A.M., 1971. Tumour inhibitors 69: structure-cytotoxicity relation among the sesquiterpene lactones. J. Med. Chem. 14, 1147–1152.

Lenior, D., 1989. The application of low-valent titanium reagents in organic synthesis. Synthesis 883–897.

Mew, D., Blaza, F., Towers, G.H.N., Levy, J.G., 1982. Antitumour effects of sesquiterpene lactone parthenin. Planta Med. 45, 23.

McMurry, J.C., 1983. Titanium-induced dicarbonyl-coupling reactions. Acc. Chem. Res. 16, 405–411.

Mukaiyama, T., Sato, T., Hanna, J., 1973. Reductive coupling of carbonyl compounds to pinacols and olefins using titanium(IV) chloride and Zn. Chem. Lett 1041–1044.

Pickman, A.K., Towers, G.H.N., Subba Rao, P.V., 1980. Coronopilin—another major sesquiterpene lactone in *Parthenium hysterophorus*. Phytochemistry 19, 2206–2207.

Pickman, A.K., Blaza, F., Towers, G.H.N., 1982. Occurrence of hysterin and dihydroisoparthenin in *Parthenium hysterophorus*. Phytochemistry 21, 1801–1802.

Patil, T.M., Hedge, B.A., 1988. Isolation and purification of a sesquiterpene lactone from the leaves of *Parthenium hysterophorus*. L. Curr. Sci. 57, 1178–1181.

Romo de Vivar, A., Bradoeff, E.A., Rios, T., 1966. Structure of hysterin, a new sesquiterpene lactone. J. Org. Chem. 31, 673–677.

Sethi, V.K., Koul, S.K., Taneja, S.C., Dhar, K.L., 1987. Minor sesquiterpenes of flowers of *Parthenium hysterophotus*. Phytochemistry 26, 3359–3361.

Shen, M.C., Rodriguez, E., Kerr, K., Marby, T.J., 1976. Flavonoids of four species of Parthenium (compositae). Phytochemistry 15, 1045–1047.

Towers, G.H.N., Mitchel, J.C., Rodriguez, E., Bannet, D.F., Subba Rao, P.V., 1977. Biology and chemistry of *Parthenium hysterophorus* L., a problem weed in India. J. Sci. Ind. Res. 36, 672–684.