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AN UNUSUAL *m*-HYDROXYACETOPHENONE AND THREE NEW CHROMANONE DERIVATIVES FROM *CHRYSOTHAMNUS VISCIDIFLORUS*

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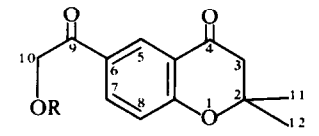
Key Word Index—*Chrysothamnus viscidiflorus*; Astereae; Compositae; *m*-hydroxyacetophenone; chroman-4-one derivatives.

Abstract—An unusual *m*-hydroxyacetophenone, named viscidone, and three new chroman-4-one derivatives were isolated from *Chrysothamnus viscidiflorus* ssp. *lanceolatus*, which also contained a known *p*-hydroxyacetophenone derivative. Their structures were determined by spectroscopic (^{1}H and ^{13}C NMR, UV, IR and MS) and chemical means.

INTRODUCTION

In a previous investigation we reported the isolation of two new *ent*-labdane derivatives, named viscidic acid A and B, from *Chrysothamnus viscidiflorus* [1]. We now describe the isolation and structure elucidation of an unusual *m*-substituted hydroxyacetophenone, named viscidone (**3**), and three new chromanone derivatives (**1**, **2** and **7**) from the polar fractions of the Et_2O–petrol extract, which also contained the known dihydrobenzofurane (**6**). It is noteworthy that dihydrobenzofurane and chromanone derivatives have not previously been isolated from *Chrysothamnus* species [1–4]. Remarkable also is the co-occurrence of the *p*- and *m*-hydroxyacetophenone derivatives (**6** and **3**) from the same plant source.



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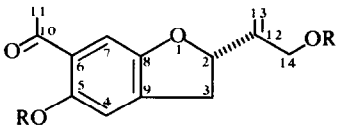
2 R = H



3 R = H
4 R = Ac

RESULTS AND DISCUSSION

The aerial parts of *C. viscidiflorus* afforded, in addition to the previously described viscidic acid A and B, elemicin, the *p*-hydroxyacetophenone and two bisabolene derivatives [1], five further compounds. Four of them are new. Their structures were established mainly by spectroscopic methods (^{1}H and ^{13}C NMR, UV, IR and MS) and some chemical transformations.

The ^{1}H NMR spectrum (in $CDCl_3$, Table 1) of the most apolar non-crystalline compound **1**, $C_{15}H_{16}O_5$ (high resolution MS) exhibited two chemically equivalent Me groups at δ 1.49 (6H) one two-proton singlet at δ 2.78 and three aromatic protons at 8.40 (*d*, J = 2.5 Hz), 8.12 (*dd*, J = 8.5 + 2.5 Hz) and 7.04 (*d*, J = 8.5 Hz) indicating one 1,2,4-trisubstituted benzene ring. These signals are characteristic of a chroman-4-one derivative [5]. In addition, two further singlets are present at δ 2.22 (*s*, 3H) and 5.31 (*s*, 2H) due to the presence of a CH_2OAc group.

Table 1. ^{1}H NMR data* of the chromanones **1**, **2**, **7** and **8**

Proton	1	2	7	8
3-H	2.78 *s*†	2.78 *s*†	2.75 *s*†	2.73 *s*†
5-H	8.40 *d*	8.35 *d*	8.61 *d*	8.54 *d*
7-H	8.12 *dd*‡	8.10 *dd*‡	8.14 *dd*‡	8.11 *dd*‡
8-H	7.04 *d*	7.02 *d*	6.97 *d*	6.94 *d*
10-H	5.31 *s*†	4.85 *s*†	—	—
11-H 12-H	1.49 *s*§	1.49 *s*§	1.47 *s*§	1.46 *s*§
OAc	2.22 *s*‖	—	—	—
OMe	—	—	—	3.88 *s*‖

* Spectra were run in $CDCl_3$, at 100 MHz (**1** and **2**) or at 80 MHz (**7** and **8**) and TMS was used as internal standard. Chemical shifts are in ppm relative to TMS. Signals correspond to one proton unless otherwise given.

† Intensity 2 protons.

‡ J (5–7) = 2.5 Hz; J (7–8) = 8.5 Hz.

§ Intensity 6 protons.

‖ Intensity 3 protons.

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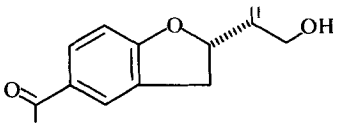
This was confirmed by the appearance of a $M^+ - 73$ peak at *m/e* 203 due to the loss of the CH_2OAc group from the M^+ at *m/e* 276. The relative downfield absorption of the CH_2OAc group suggested that this group must be attached to one carbonyl function, which in turn is attached to the benzene ring. On the basis of the chemical shifts of the aromatic protons, especially the one at δ 8.40 (*d*, J = 2.5 Hz), it was concluded that the $CO-CH_2OAc$ group must be attached to the benzene ring at C-6. The structure of compound **1** was thus established as 6-(2-acetoxyacetyl)-2,2'-dimethyl-chroman-4-one.

Compound **2**, $C_{13}H_{14}O_4$ (high resolution MS) which was more polar than **1**, exhibited an IR spectrum which indicated the presence of an OH group (3500 cm^{-1}). The ^1H NMR spectrum is very similar to that of **1**, the differences being only the absence of an acetate absorption at δ 2.22 (3H) and the shift of the two-proton singlet at δ 5.31 to 4.85 due to the CH_2OH group (Table 1). These data taken in combination with the empirical formula lead to the proposed structure **2**. Acetylation of **2** with acetic anhydride in pyridine gave an acetate which was identical with the natural product **1**. The structure of **2** is therefore 6-(2-hydroxyacetyl)-2,2'-dimethyl-chromanan-4-one.



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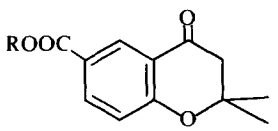


7 R = H
8 R = Me

The most polar compound (**7**) contained a carboxylic acid group which could be transformed to the Me ester **8** after addition of an ethereal diazomethane solution. The ^1H NMR of the ester **8** indicated the characteristic absorptions of a chroman-4-one derivative (Table 1), where the benzene ring is also trisubstituted. Based on the chemical shifts of the three aromatic protons [δ 8.54 (*d*, J = 2.5 Hz), 8.11 (*dd*, J = 8.5 + 2.5 Hz) and 6.94 (*d*, J = 8.5 Hz)], the ester or carboxylic acid group, respectively, must be located at C-6. The MS fragments are also consistent with the structure **8** (see Experimental). The structure of **7** is therefore 2,2'-dimethyl-6-carboxy-chroman-4-one.

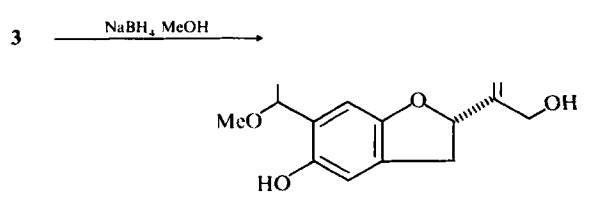
Compound **3**, $C_{13}H_{14}O_4$ (high resolution MS) is a diol (IR bands at 3630, 3480 cm^{-1}) which could be transformed to its diacetate **4** (two new Me singlets at δ 2.01 and 2.29, Table 2) after treatment with acetic anhydride in pyridine-4-pyrrolidinopyridine [6]. The ^1H NMR of **3** indicated the presence of one acetyl group (δ 2.55, *s*, 3H), one hydroxyisopropenyl group (δ 5.24, *br. s*, 2H and 4.23, *br. s*, 2H, which moved downfield to δ 4.66 in the diacetate **4**). In addition, two broadened doublets of doublets at δ 3.40 and 3.12 (J = 17 + 8.5 Hz) which coupled with one broadened triplet at δ 5.27 (J = 8.5 Hz) are characteristic of a 2,3-dihydro-benzofurane derivative, e.g. dihydro-ageratone [7]. Irradiation at the frequencies of the 3-H or 3'-H caused sharpening of one broadened singlet at δ 6.79, which could be assigned to the aromatic C-4 proton. Two other singlets are present, one is aromatic (δ 7.04) whereas the other is due to the hydrogen-bonded OH group (δ 12.18). The UV absorption at 364 nm and the NMR data of **3** suggested that it could not be a normal *p*-hydroxyacetophenone derivative (see dihydroageratone [7]). The similar chemical shifts of the two aromatic protons (δ 7.04, *s* and 6.79, *br. s*) and the presence of one hydrogen-bonded OH group (δ 12.18, *s*) must lead to the proposed structure **3** for viscidone. The ^1H NMR data of the diacetate **4** are also consistent with this structure (Table 2). The assignments of the ^{13}C NMR signals of **3** (micro sample, 1.7 mm, in $CDCl_3$) were made using single frequency off-resonance decoupling (SFORD) experiments and comparing to the known chemical shifts of the benzofuran derivatives [8]. The structure of viscidone was finally proved by conversion of **3** to the known reduction product **5** [9]. The first two

Table 2. ^1H NMR data* of viscidone **3** and its diacetate **4**

Proton	3	4
2-H	5.27 *br. t*† (8.5)	5.32 *br. t*† (8.5)
3-H	3.40 *br. dd* (17 + 8.5)	3.45 *br. dd* (17 + 8.5)
3-H	3.12 *br. dd* (17 + 8.5)	3.13 *br. dd* (17 + 8.5)
4-H	6.79 *br. s*	6.88 *br. s*
7-H	7.04 *s*	7.16 *s*
11-H	2.55 *s*	2.48 *s*
13-H	5.24 *br. s*	5.32 *br. s*
13-H		5.25 *br. s*
14-H	4.23 *br. s*	4.66 *br. s*
OH	12.18 *s*	—
OAc	—	2.29 *s*
		2.01 *s*

* Spectra were run in $CDCl_3$, at 100 MHz (**3**) or 80 MHz (**4**) and TMS was used as internal standard. Chemical shifts are in ppm relative to TMS. Signals are designated as described above. Figures in parentheses are coupling constants in Hz.

† Partly overlapped with 13-H.



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examples of this unusual type of compounds have been found in one *Baccharis* species [9]. We also isolated two further derivatives of this type from one *Leibnitzia* species [10].

The chemical findings within the genus *Chrysothamnus* are relatively diverse. *Matricaria* ester derivatives were found in *C. parryi* [2], labdane, bisabolene, germacrene and flavanone derivatives were isolated from *C. nauseousus* [3], whereas *C. viscidiflorus* afforded many flavanoids [4], *ent*-labdane, elemicin, bisabolene [1] chromanone derivatives, one *p*- and one *m*-substituted hydroxyacetophenone. For the first time chromanone and *m*-hydroxyacteophenone derivatives, which are very rare in nature, were found in one *Chrysothamnus* species. To determine whether these types of compounds are also of chemotaxonomic interest, and in order to shed light on the relationships within the genus and tribe, more chemical and botanical investigations are necessary. The chemical investigations of other *Chrysothamnus* species are in progress.

EXPERIMENTAL

UV spectra were recorded in Et_2O, IR in CCl_4 or $CHCl_3$. ^1H NMR spectra were obtained at 100 MHz or 80 MHz in $CDCl_3$, ^{13}C NMR in $CDCl_3$ tube size 1.7 mm (micro sample) and MS on a high resolution instrument at 70 eV using a direct probe. Optical rotations were determined in $CHCl_3$.

The air-dried plant material collected on 8 August 1973 in Colorado: Lake Co.: 1 mile from the junction of 82 and 24, along 82, road side (Urbatch No. 1302, voucher deposited at Louisiana State University Herbarium at Baton Rouge), was extracted with Et_2O–petrol (1:1) at room temp. The crude extract was first separated by column chromatography (Si gel, grade II activity), using petrol–Et_2O and Et_2O–MeOH mixtures as eluants and further purified by TLC (Si gel, GF 254) which was repeated several times using different solvent systems. The aerial part (490 g) of *C. viscidiflorus* ssp. *lanceolatus* afforded 30 mg **1** (two TLC systems: EtOAc–C_6H_6 (1:5) and MeOH–C_6H_6 (1:15), run twice), 15 mg **2** (EtOAc–CH_2Cl_2 (1:6), run ×3); 60 mg **3** (EtOAc–C_6H_6 (1:3), run ×3); 50 mg **6** and 20 mg **7** (Et_2O–CH_2Cl_2 (1:1), run twice).

6-(2-*Acetoxyacetyl*)-2,2′-*dimethyl-chroman*-4-*one* (**1**). Colourless crystals, mp 114° (Et_2O–petrol). UV (Et_2O) nm: 324 *sh*, 312, 268. IR (CCl_4) cm^{-1}: PhCO 1710, 1620; OAc 1715, 1210. MS *m/e* (rel. int.): 276.099 (M^+, 5.2) (calc. for $C_{15}H_{16}O_5$ 276.100); 203 ($M^+ - CH_2OAc$, 100); 147 (203 – $Me_2C{=}CH_2$, 69); 43 ($MeCO^+$, 29.5).

6-(2-*Hydroxyacetyl*)-2,2′-*dimethyl-chroman*-4-*one* (**2**). Colourless oil, UV (Et_2O) nm: 324 (*sh*), 312, 268. IR (CCl_4) cm^{-1}: OH 3500; PhCO 1700, 1620, 1500. MS *m/e* (rel. int.): 234.089 (M, 12.9) (calc. for $C_{13}H_{14}O_4$ 234.089); 203 ($M^+ - CH_2OH$, 90.7); 147 (203 – $Me_2C{=}CH_2$, 100); 43 ($MeCO^+$, 29.6).

Acetylation. **2** (5 mg) in 0.5 ml pyridine, 0.5 ml Ac_2O and 5 mg 4-pyrrolidinopyridine were stirred 18 hr at room temp. After usual work-up and TLC (EtOAc–C_6H_6 (1:5), run ×3) 4 mg **1** were obtained. ^1H NMR and MS were identical with the natural product **1**.

2,2′-*Dimethyl*-6-*carboxylic acid-chroman*-4-*one* (**7**). Colourless oil, IR (CCl_4) cm^{-1}: COOH 3480–2800, 1710. To 10 mg **7** in 2 ml Et_2O an excess of CH_2N_2–Et_2O soln was added. After 10 min the soln was evapd and the residue purified by TLC (CH_2Cl_2, run ×3) to give the Me-ester **8**, colourless crystals from petrol–Et_2O, mp 102°. UV (Et_2O) nm: 322 (*sh*), 314, 252. IR (CCl_4) cm^{-1}: PhCO 1700, 1720, 1620. MS *m/e* (rel. int.): 234.089 (M^+, 51.3) (calc. for $C_{13}H_{14}O_4$, 234.089); 219 (M^+ – Me, 100); 203 (M^+ – OMe, 11.8); 147 (203 – $Me_2C{=}CH_2$, 28.9).

Viscidone (**3**). Light yellow crystals from Et_2O–petrol, mp 77–78°. UV (Et_2O) nm: 364, 258. IR (CCl_4) cm^{-1}: OH 3630; H-bonded OH 3480; H-bonded PhCO 1650, 1640, 1600, 1490. MS *m/e* (rel. int.): 234.089 (M^+, 9.1) (calc. for $C_{13}H_{14}O_4$ 234.089); 216 ($M^+ - H_2O$, 13.6); 203 ($M^+ - CH_2OH$, 15.9); 201 (216 – Me, 12.5); 173 (201 – CO, 3.4) 176* (3); 161 (176 – Me 9); 43 ($MeCO^+$, 100).

$$[\alpha]_{24^\circ}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+26.7 \quad +30 \quad +35 \quad +91.7} (c = 0.6, CHCl_3).$$

^{13}C NMR, ppm relative to $CDCl_3$ (δ 77.0 downfield from TMS): C(2) *d* 83.0, C(3) *t* 35.5, C(4) *d* 107.8, C(5) *s* 157.6, C(6) *s* 117.6, C(7) *d* 114.2, C(8) *s* 151.4, C(9) *s* 137.4, C(10) *s* 203.6, C(11) *q* 26.4, C(12) *s* 146.9, C(13) *t* 111.6, C(14) *t* 62.2.

Acetylation. **3** (9 mg) acetylated as above, gave 8 mg **4**, colourless oil, UV (Et_2O) nm: 310, 246. IR (CCl_4) cm^{-1}: OAc 1740, PhCO 1690. MS *m/e* (rel. int.): 318.110 (M^+, 5.5) (calc. for $C_{17}H_{18}O_6$, 318.110); 276 ($M^+ - CH_2{=}C{=}O$, 66.8); 216 (276 – HOAc, 39.9); 201 (216 – Me, 16.2); 203 (216 – CH_2OAc, 18.2); 176* (33.2); 161 (176 – Me, 16.6); 43 ($MeCO^+$, 100).

Reduction. To 5 mg **3** in 1 ml MeOH an excess of $NaBH_4$ was added. After 5 min at room temp. the reaction product was acidified with 2 N H_2SO_4 and extracted ×3 with CH_2Cl_2. The combined CH_2Cl_2 phases were neutralized with $NaHCO_3$ soln, evapd and the residue purified by TLC to give 3 mg **5**, identical with the known reaction product (NMR, MS) [9].

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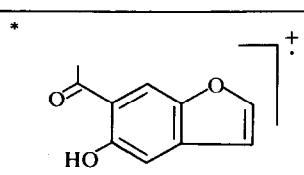

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REFERENCES

1. Le-Van, Ngo, and Pham, T. V. Cuong (1980) *Phytochemistry* **19**, 1971.
2. Bohlmann, F., Zdero, C., Robinson, H. and King, R. M. (1979) *Phytochemistry* **18**, 1519.
3. Bohlmann, F., Dutta, L., Robinson, H. and King, R. M. (1979) *Phytochemistry* **18**, 1889.
4. Urbatch, L. E., Bacon, J. D. and Mabry, T. J. (1975) *Phytochemistry* **14**, 2279.
5. Bohlmann, F., Zdero, C. and Lonitz, M. (1977) *Phytochemistry* **16**, 575.
6. Steglich, W. and Höfle, G. (1969) *Angew. Chem.* **81**, 1001.
7. Anthonsen, T. and Chantharasakul, S. (1970) *Acta Chem. Scand*, **24**, 721.
8. Platzer, N., Basselier, J. J. and Demerseman, P. (1974) *Bull. Soc. Chim. Fr.* 905.
9. Bohlmann, F. and Zdero, C. (1976) *Chem. Ber.* **109**, 1450.
10. Bohlmann, F., Zdero, C. and Le-Van, N. (1979) *Phytochemistry* **18**, 99.