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PRENYLATED PHTHALIDES FROM *ANAPHALIS ARANEOSA* AND *HELICHRYSUM PLATYPTERUM*

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Key Word Index—*Anaphalis araneosa*; *Helichrysum platypterum*; Compositae; phthalides.

Abstract—The aerial parts of *Anaphalis araneosa* afforded, in addition to known compounds, three new prenylated phthalides. A further compound of this type was isolated from the roots of *Helichrysum platypterum*. The structures were elucidated by high-field ^{1}H NMR and ^{13}C NMR spectroscopy.

INTRODUCTION

A few species of the genus *Anaphalis* (Compositae, tribe Inuleae, subtribe Gnaphaliinae) with about 60–100 species [1] have been studied chemically. In addition to flavanoids [2, 3], helipyrone [4], typical chloroacetylenic compounds with a dihydropyrane or furane ring [5] and two phthalides were reported [6]. Also *A. araneosa* DC. has been studied chemically [2, 3]. We have now re-investigated this species and also the roots of *Helichrysum platypterum*. The results are discussed in this paper.

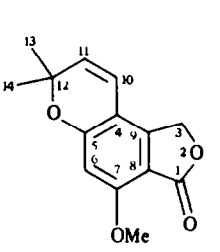
RESULTS AND DISCUSSION

The aerial parts of *A. araneosa* afforded 5,7-dimethoxyflavone, loliolide, sitosterol, stigmasterol and the phthalides **1**, **2** and **4**. The structure of **1** followed from the molecular formula ($C_{14}H_{14}O_4$) and the ^{1}H NMR spectral data (see Experimental). The presence of a 2,2-dimethylchromene derivative was deduced from the typical signals at δ1.48 *s* (6H), 6.16 and 5.61 *d* (each 1H, J = 10 Hz). The presence of an aromatic signal at δ6.36 *s* (1H), together with signals at δ5.16 *s* (2H) and 3.93 *s* (OMe), indicated the presence of three further substituents, one being a methoxyl group while the two remaining must form a γ-lactone ring, as followed from the molecular formula and the IR spectrum. The relative positions of the substituents were determined by NOE difference spectroscopy. Clear effects were obtained between H-3 and H-10 as well as between the methoxy protons and H-6. We have named compound **1** phthalidochromene.

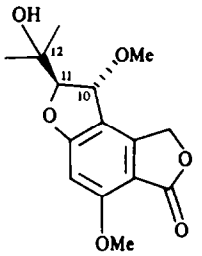
The ^{1}H NMR spectrum of **2** (see Experimental) indicated the presence of a dihydrofurane derivative combined with a phthalide. Comparison with the data of related compounds showed that the dihydrofurane was substituted with a methoxyl group which was in the *trans*-position to a hydroxyisopropyl group. Accordingly, the proposed structure for **2**, which we have named araneophthalide, was very likely.

Compound **4** showed an unclear ^{1}H NMR spectrum with highly broadened overlapped multiplets. However, after acetylation, a clear spectrum was obtained which showed the typical signals of a tetraacetate of a β-glucopyranoside (see Experimental). Singlets at δ2.73 (2H), 1.49 (3H) and 1.50 (3H) indicated the presence of a dimethyldihydrochromanone. The signal from the only aromatic proton was shifted downfield when compared with the chemical shift of H-6 in the spectrum of **1**, and the signal of H-3 was replaced by a pair of doublets at δ5.46 and 5.41. All data therefore agreed well with the proposed structure of **4a**, which was supported by the ^{13}C NMR spectrum (see Experimental). The ^{13}C NMR spectrum of the free glucoside **4** also showed broadened signals and therefore was much less useful. We have named the glucoside **4** aranochromanophthalide.

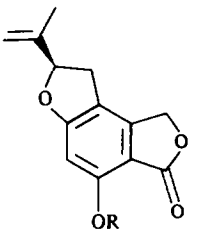
From the roots of *Helichrysum platypterum* DC. the phthalide **3** was isolated. The presence of a free hydroxyl group was shown by the formation of the methyl ether **3a**. The ^{1}H NMR spectra of **3** and **3a** (see Experimental) were close to that of **2**. However, the typical signals of an



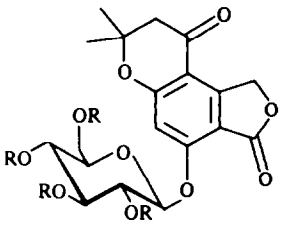
1



2



3 R = H
3a R = Me



4 R = H
4a R = Ac

isopropenyl group, a pair of double doublets and a broadened triplet indicated a dihydrobenzofurane derivative. All data therefore agreed with the proposed structure, which was further supported by the ^{13}C NMR spectrum of **3**, which we have named platypterophthalide.

The isolation of further phthalides may be of chemotaxonomic interest. So far, these relatively rare types of natural products have also been isolated from *Helichrysum* species [7–10] and from *Anaphalis contorta* [6]. Especially closely related to **14** are the prenylated phthalides from *Helichrysum arenarium* [7] and from the *Anaphalis* species [6]. The unusual polyynes with a dihydropyrane moiety are also present in several *Helichrysum* and *Anaphalis* species [5]. Further studies may show whether the prenylated phthalides are more widespread in the subtribe Gnaphaliinae.

EXPERIMENTAL

The air-dried plant material was extracted with Et_2O–MeOH–petrol (1:1:1) and the extracts obtained were separated as reported previously [11]. The extract of the aerial parts of *Anaphalis araneosa* (voucher 2729, deposited at the Herbarium of the Central Drug Research Institute of Lucknow, India, 10.36 g) was first separated by CC (SiO_2) into four fractions (1: Et_2O–petrol, 1:1; 2: Et_2O; 3: Et_2O–MeOH, 9:1; and 4: Et_2O–MeOH, 3:1). Prep. TLC of fraction 1 (Et_2O–petrol, 1:3) gave 50 mg sitosterol, 50 mg stigmasterol and 20 mg 5,7-dimethoxyflavone. HPLC (RP 8, MeOH–H_2O, 7:3, *ca* 100 bar) of fraction 2 gave two crude fractions (2/1 and 2/2). Prep. TLC ($CHCl_3$–MeOH, 20:1) of fraction 2/1 gave 5 mg loliolide and fraction 2/2 3.8 mg **1**. HPLC of fraction 3 (MeOH–H_2O, 13:7) gave 2 mg **2** and HPLC (MeOH–H_2O, 1:1) of fraction 4 afforded 18 mg **4**.

The extract of the roots (210 g) of *Helichrysum platypterum* (voucher 81/267, deposited at the National Botanic Research Institute, Pretoria, Republic of South Africa) gave on CC (silica gel) and prep TLC (Et_2O–petrol, 3:1) 2 mg **3**.

Phthalidochromene (**1**). Colourless gum; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1760 (γ-lactone); MS *m/z* (rel. int.): 246.089 $[M]^+$ (14) (calc. for $C_{14}H_{14}O_4$: 246.089), 231 $[M - Me]^+$ (100), 203 $[231 - CO]^+$ (8); CIMS *m/z* (rel. int.): 247 $[M + 1]^+$ (100); ^1H NMR ($CDCl_3$, always 400 MHz): δ5.16 (*s*, H-3), 6.36 (*s*, H-6), 6.16 (*d*, H-10, *J* = 10 Hz), 5.61 (*d*, H-11, *J* = 10 Hz), 1.48 (*s*, 6H, H-13, H-14), 3.93 (*s*, OMe).

Araneophthalide (**2**). Colourless gum; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1760 (γ-lactone); MS *m/z* (rel. int.): 294.110 $[M]^+$ (1.3) (calc. for $C_{15}H_{18}O_6$: 294.110), 262 $[M - MeOH]^+$ (4), 244 $[262 - H_2O]^+$ (24), 111 (100); ^1H NMR ($CDCl_3$): δ5.23 and 5.17 (*d*, H-3, *J* = 16 Hz), 6.44 (*s*, H-6), 5.06 (*d*, H-10, *J* = 3 Hz), 4.53 (*d*, H-11, *J* = 3 Hz), 1.33 (*s*, H-13), 1.32 (*s*, H-14), 3.96 and 3.35 (*s*, OMe).

Platypterophthalide (**3**). Colourless gum; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3590 (OH), 1760 (γ-lactone); MS *m/z* (rel. int.): 232.074 $[M]^+$ (72) (calc. for $C_{13}H_{12}O_4$: 232.074), 217 $[M - Me]^+$ (100); CIMS *m/z* (rel. int.): 233 $[M + 1]^+$ (100); ^1H NMR ($CDCl_3$): 5.20 (*s*, H-3), 6.40 (*s*, H-6), 3.35 (*dd*, H-10, *J* = 16, 9.5 Hz), 3.00 (*dd*, H-10′, *J* = 16, 8 Hz), 5.34 (*dd*, H-11, *J* = 8, 9.5 Hz), 5.08 and 4.94 [*s* (*br*), H-13], 1.76 [*s* (*br*), H-14], 7.76 (*s*, OH); ^{13}C NMR (C-1 and C-3–C-14): δ168.4 *s*, 70.2 *t*, 112.7 *s*, 153.0 *s*, 95.8 *d*, 164.4 *s*, 104.6 *s*, 143.0 *s*, 30.4 *t*, 88.3 *d*, 149.0 *s*, 112.8 *t*, 17.0 *q*.

Addition of CH_2N_2 in Et_2O gave **3a**, colourless gum; MS *m/z* (rel. int.): 246 $[M]^+$ (100), 231 $[M - Me]^+$ (81); ^1H NMR ($CDCl_3$): δ5.13 (*s*, H-3), 3.48 (*dd*, H-10, *J* = 16, 9.5 Hz), 3.11 (*dd*, H-10′, *J* = 16, 8 Hz), 5.30 (*dd*, H-11, *J* = 8, 9.5 Hz), 5.09 and 4.95 [*s* (*br*), H-13], 1.77 [*s* (*br*), H-14], 4.16 (*s*, OMe).

Aranochromanophthalide (**4**). Amorphous, colourless material; ^1H NMR ($CDCl_3$, 60°): δ5.28 [*s* (*br*), H-3], 6.58 [*s* (*br*), H-6], 2.70 and 2.64 [*d* (*br*), H-11], 1.46 [*s* (*br*), H-13], 1.44 [*s* (*br*), H-14], 5.09 [*d* (*br*), H-1′], 3.9–3.4 (*m*, H-2′–H-6′); ^{13}C NMR ($CDCl_3$): δ190.6 *s*, 168.9 *s*, 166.9 *s*, 161.0 *s*, 152.3 *s*, 110.1 *s*, 105.1 *d*, 101.3 *d*, 81.7 *s*, 76.7 *d*, 76.1 *d*, 73.1 *d*, 72.3 *d*, 70.8 *t*, 69.9 *d*, 61.7 *t*, 48.6 *t*, 26.8 *q*, 26.6 *q*. 8 mg **4** in 1 ml Ac_2O and 0.1 ml pyridine on standing for 12 hr gave, after usual work-up, 6 mg **4a**, colourless gum; ^1H NMR ($CDCl_3$): δ5.46 and 5.41 (*d*, H-3, *J* = 18 Hz), 6.70 (*s*, H-6), 2.73 (*s*, H-11), 1.50 (*s*, H-13), 1.49 (*s*, H-14), 5.25 (*d*, H-1′, *J* = 7.5 Hz), 5.39 (*dd*, H-2′, *J* = 7.5, 9.5 Hz), 5.31 (*dd*, H-3′, *J* = 9, 9.5 Hz), 5.14 (*dd*, H-4′, *J* = 9, 9.5 Hz), 3.96 (*ddd*, H-5′, *J* = 9.5, 6, 3 Hz), 4.26 (*dd*, H-$6'_1$, *J* = 12, 3 Hz), 4.21 (*dd*, H-$6'_2$, *J* = 12, 6 Hz); OAc: δ2.14, 2.08, 2.06 and 2.04 *s*; ^{13}C NMR ($CDCl_3$, C-1 and C-3–C-14): 166.6 *s*, 70.1 *t*, 110.5 *s*, 160.1 *s*, 105.8 *d*, 166.2 *s*, 109.2 *s*, 152.3 *s*, 190.5 *s*, 48.3 *t*, 81.5 *s*, 26.6 *q*, 26.7 *q*; C-1′–C-6′: 99.1 *d*, 70.3 *d*, 72.6 *d*, 68.3 *d*, 72.1 *d*, 62.0 *t*; OAc 170.4, 170.2, 169.3, 169.3 *s*, 20.6 *q*, 20.5 *q* (3 ×).

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