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HYPNOCRETENOLIDE DERIVATIVES FROM *HEDYPNOIS CRETICA*

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Key Word Index—*Hedypnois cretica*; Compositae; sesquiterpene lactones; guaian-5β-12-olides; glucosides.

Abstract—The aerial parts of *Hedypnois cretica* afforded four sesquiterpene lactones all closely related to hypnocretenolide. Two lactones were glucopyranosides which could only be separated as their tetraacetates. The structures were elucidated by high field NMR spectroscopy.

INTRODUCTION

Hedypnois (Compositae, tribe Lactuceae) is represented in Egypt by one species with five subspecies [1]. From two species, flavonoids have been isolated [2] but no further investigations are reported. We therefore have studied *H. cretica* (L.) Dum. Cours. ssp *rhagadioloides* (L.) F. W. Schmidt. The aerial parts afforded two mixtures. The less polar one could be separated by HPLC while the more polar fractions first had to be acetylated. The corresponding tetraacetates could then also be separated by HPLC. Finally the lactones **1**, **2** and the acetates of **3** and **4** (**3Ac** and **4Ac**) were obtained.

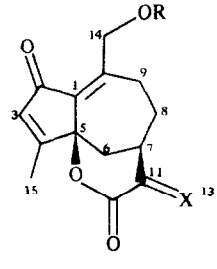
The structure of **1** followed from the molecular formula ($C_{15}H_{16}O_4$) and from the ^{1}H NMR spectrum (Table 1) which was very similar to that of hypocretenolide, a guaian-12,5β-olide from *Hypochoeris cretensis* [3]. However, one of the signals of the olefinic methyl groups was replaced by a pair of doublets at δ 4.68 and 4.43 Accordingly, as already followed from the molecular formula, an additional hydroxy group was at C-14 or C-15. As the H-3 signal was still a narrowly split quartet no function was at C-15. Thus the hydroxy group had to be placed at C-14. The ^{1}H NMR spectrum of **2** (Table 1) differed from that of **1** mainly by the replacement of the signals of the exomethylene protons by a double quartet at δ2.77 and a methyl doublet at δ1.38. Therefore the corresponding 11,13-dihydro derivative of lactone **1** was present. The configuration at C-11 followed from the observed couplings $J_{7,11}$. Inspection of a model indicated that the angles in the most preferred conformation agreed with the observed couplings.

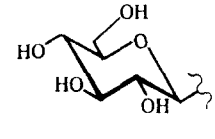
The ^{1}H NMR spectrum of the crude mixture of **3** and **4** indicated the presence of glycosides which could be separate after acetylation. The ^{1}H NMR spectra of **3Ac** and **4Ac** (Table 1) showed that the β-glucopyranoside tetraacetates of **1** and **2** were present. The nature of the sugar moiety could be deduced from the observed couplings which required a pyranoside where all protons were axial, only present in a β-glucopyranoside. Furthermore the chemical shifts were close to those reported in lit. for these glycosides. The ^{13}C NMR spectrum of **4Ac** (see Experimental) also agreed with the proposed structure.

The isolation of the so far very rare hypocretenolides supported the proposed relationship of *Hedypnois* to *Hypochoeris* which are both placed in one group or subtribe [4, 5]. However, the hypocretenolides are closely related to the corresponding guaian-12,6α-olides which are common in the whole tribe Lactuceae. Also glycosides are reported from several genera of this tribe.

EXPERIMENTAL

The fresh aerial parts (4 kg) were collected during the flowering stage from Borg El-Arag near Alexandria (voucher deposited in the Dept. of Pharmacognosy, Faculty of Pharmacy,



	1	2	3*	4*
X	CH_2	βMe,H	CH_2	βMe,H
R	H	H		

* **3Ac** and **4Ac** are the tetraacetates

Table 1. ^{1}H NMR spectral data of **1**, **2**, **4**, **3Ac** and **4Ac** (400 MHz, $CDCl_3$, δ-values)

H	1	2	4($CDCl_3$/MeOD)‡	3Ac*	4Ac†
3	6.22 *q*	6.21 *q*	6.05 *q*	6.17 *q*	6.15 *q*
6α	1.92 *dd*	1.93 *dd*	1.81 *dd*	1.86 *dd*	1.87 *dd*
6β	2.41 *br dd*	2.36 *ddd*	2.25 *m*	2.38 *br dd*	2.34 *dd*
7	3.29 *br s*	2.48 *br s*	2.37 *br s*	3.25 *br s*	2.44 *br s*
8α	2.41 *br d*	2.41 *ddd*	2.13 *br t*	2.38 *br dd*	2.21 *br t*
8β	1.96 *br dd*	1.71 *dddd*	1.59 *br t*	1.93 *m*	1.66 *br dd*
9α	2.03 *br d*	2.17 *br d*	2.00 *br d*	2.10 *m*	2.10 *m*
9β	2.75 *ddd*	2.54 *ddd*	2.65 *m*	2.67 *ddd*	2.66 *ddd*
11	—	2.77 *dq*	2.65 *dq*	—	2.75 *dq*
13	6.64 *d*	1.38 *d*	1.23 *d*	6.62 *d*	1.36 *d*
13′	5.74 *br s*			5.72 *br s*	
14	4.68 *d*	4.66 *d*	4.96 *d*	5.29 *d*	5.23 *d*
14′	4.43 *d*	4.39 *d*	4.71 *d*	4.71 *d*	4.71 *d*
15	2.10 *d*	2.12 *d*	1.97 *d*	2.07 *br s*	2.09 *d*

*H-1′ 4.58 *d*, H-2′ 5.01 *dd*, H-3′ 5.08 *t*, H-4′ 5.19 *t*, H-5′ 3.65 *ddd*, H-6′$_1$ 4.23 *dd*, H-6′$_2$ 4.08 *dd*; OAc 2.07, 2.02, 2.01, 1.99 *s*;

†H-1′ 4.56 *d*, H-2′ 5.01 *dd*, H-3′ 5.07 *t*, H-4′ 5.18 *t*, H-5′ 3.65 *ddd*, H-6′$_1$ 4.22, H-6′$_2$ 4.08 *dd*; OAc 2.07, 2.04, 2.01, 1.99 *s*;

‡H-1′ 4.18 *d*, H-2′–H-5′ 3.28 and 3.14 *m*, H-6′ 3.68 and 3.60 *dd*;

J [Hz]: 3, 15 = 1.5; 6α,6β = 13; 6α,7 = 2.5; 6β,7 = 3; 6β,8β = 1.5; 7,8α = 7,8β ~ 3; 8α,8β = 13; 8α,9α ≈ 5; 8α,9β = 12; 8β,9α = 2; 8β,9β = 3; 9α,9β = 15; 14,14′ = 14; compounds **1** and **3Ac**: 7,13 = 1.5; compounds **2** and **4Ac**: 7,11 = 7,13 = 7; compounds **3Ac** and **4Ac**: 1′,2′ = 8; 2′,3′ = 3′,4′ = 4′,5′ = 9.5; 5′,6′$_1$ = 4; 5′,6′$_2$ = 2; 6′$_1$, 6′$_2$ = 12.

Alexandria University) and exhaustively extracted with 95% EtOH. The extracts were concd to 500 ml, diluted with 500 ml H_2O and then extracted with hexane, $CHCl_3$, EtOH and *n*-BuOH. The $CHCl_3$ extract (1.4 g) was sepd by CC (sigel). The fractions obtained with $CHCl_3$–MeOH (19:1) (25 mg) were further separated by TLC [Si gel, PF 254, C_6H_6–Et_2O–CH_2Cl_2 (1:1:1) four developments) affording 10 mg **2** (R_f 0.70) and 3 mg **1** (R_f 0.75). The EtOAc extract (4.6 g) was separated by CC. The fraction obtained with $CHCl_3$–MeOH, 2:1 (60 mg) was further purified by TLC ($CHCl_3$–MeOH, 4:1, R_f 0.43) but was still a mixture (^{1}H NMR). After acetylation (Ac_2O, DMAP, $CHCl_3$, 1 hr, 70°). TLC (C_6H_6–Et_2O–CH_2Cl_2, 4:1:1, four developments) crude **4Ac** (R_f 0.75) and **3Ac** (R_f 0.85) were obtained. Purification by HPLC (RP 18, MeOH–H_2O, 3:1, *ca* 100 bar) gave 6 mg **4Ac** (R_t 6.0 min) and 2 mg **3Ac**.

14-*Hydroxyhypocretenolide* (**1**). Colourless oil; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3400 (OH), 1725 (δ-lactone), 1685, 1625 (C=CCOC=C); MS *m/z* (rel. int.): 260.105 $[M]^+$ (8) (calc. for $C_{15}H_{16}O_4$: 260.105), 231 $[M-CHO]^+$ (56), 213 (21), 189 (24), 162 (60), 97 (39), 69 (64), 61 (100).

14-*Hydroxy*-11,13-*dihydrohypocretenolide* (**2**). Colourless oil; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3400 (OH), 1725 (δ-lactone), 1685, 1625 (C=CCOC=C); MS *m/z* (rel. int.): 262.121 $[M]^+$ (32) (calc. for $C_{15}H_{18}O_4$: 262.121), 233 $[M-CHO]^+$ (37), 189 (32), 69 (58), 57 (100); $[\alpha]_D$ +5.4 ($CHCl_3$; *c* 0.56).

14-*Hydroxyhypocretenolide*-β-D-*glucopyranoside tetraacetate* (**3Ac**). Colourless oil; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 1750 (OAc), 1730 δ-lactone), 1690, 1625 (C=CCOC=C).

14-*Hydroxy*-11,13-*dihydrohypocretenoldi*-β-D-*glucopyranoside tetraacetate* (**4Ac**). Colourless oil; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 1750 (OAc), 1730 (δ-lactone), 1690, 1625 (C=CCOC=C); MS *m/z* (rel. int.): 262.121 $[M-sugar]^+$ (14) (calc. for $C_{15}H_{18}O_4$: 262.121), 73 (100); ^{13}C NMR ($CDCl_3$): δ 192.5 *s*, 173.5 *s*, 170.5 *s*, 170.0 *s*, 169.4 *s*, 169.3 *s*, 168.4 *s*, 151.0 *s*, 137.1 *s*, 134.8 *d*, 100.9 *d*, 88.7 *s*, 72.8 *d*, 71.7 *d*, 71.2 *d*, 60.2 *d*, 67.5 *t*, 61.7 *t*, 38.0 *d*, 34.8 *d*, 33.8 *t*, 25.2 *t*, 23.8 *t*, 20.6 (4×), 13.8 *q*, 12.7 *q*; $[\alpha]_D$ −10 ($CHCl_3$; *c* 0.45).

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