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COUMARINS OF *HERACLEUM THOMSONI* AND CLAISEN REARRANGEMENT OF LANATIN

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Key Word Index—*Heracleum thomsoni*; Umbelliferae; coumarins; furanocoumarins; 2H[1]benzopyran-2-one; 5-hydroxy-6-(1,1-dimethyl-2-propenyl)-2H-furo[2,3-H][1]benzopyran-2-one; 4-hydroxy-9-(1,1-dimethyl-2-propenyl)-7H-furo [3,2)g] [1]benzopyran-7-one; Claisen rearrangement of lanatin.

INTRODUCTION

The isolation of a large number of coumarins including four new coumarins from the roots of *Heracleum thomsoni* has been reported [1, 2]. One of the new coumarins, HT3 was assigned the structure **1** [2]. We now wish to report the revision of the structure of HT3 from **1** to **2**, isolation and characterization of one more coumarin with the structure **1** from the roots. We also describe an interesting Claisen rearrangement of lanatin (**3**), a major coumarin of *H. thomsoni* [1].

RESULTS AND DISCUSSION

The benzene extract of the hexane-extracted roots on repeated column chromatography afforded a polar coumarin, HT5. HT5 and HT3, assigned structures **1** and **2** respectively on the basis of chemical evidence and spectral data, had the same NMR pattern (Table 1).

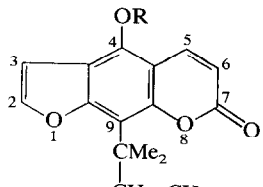
It may be noted that HT3 (**2**) was of very low polarity whereas HT5 was very polar. Even HT3 acetate (**5**) was more polar than **2**. The downfield value of the $=CH_2$ in **2** suggests some hydrogen bonding between $=CH_2$ and the OH group thereby explaining the low polarity of **2**. Like HT3, HT5 gave a positive $FeCl_3$ test (green colouration). Both compounds formed a methyl ether.

In an attempt to synthesize HT3 or HT5, lanatin (**3**) was subjected to Claisen rearrangement by heating it either alone or in *N,N*-dimethylaniline at 160–165° when the abnormal Claisen rearrangement product **4** (for proof of structure see Experimental) was obtained in good yield. However, when **3** was heated in a mixture of *N,N*-dimethylaniline and Ac_2O at the reflux temperature normal Claisen rearrangement took place and the product isolated in good yield was found to be identical with HT3 acetate (**5**) in all respects. Thus HT3 is identified as 5-hydroxy-6(1,1-dimethyl-2-propenyl)-2H-furo[2,3-h][1]benzopyran-2-one (**2**) and not by structure **1** as reported previously [2]. The earlier report on the formation of furopinnarin (**6**) from HT3 [2] was based on the fact that the HT3 used in that reaction was obviously impure.

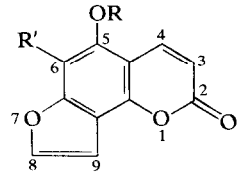
Table 1. ^1H NMR data of compounds **1** and **2** in DMSO-d_6 and $CDCl_3$ respectively*

Compound	H-6(in **1**) H-3(in **2**)	H-5(in **1**) H-4(in **2**)	Other groups
1	6.18 (9.5)	8.25 (9.5)	OH: 3.37 (*s*), exchangeable with D_2O; Chain at C-9: 1.77 (6H, *s*, Me's), 4.95 (*d*) and 4.97 (*d*) [1H each (11, 17.5),$=CH_2$], 6.37 [1H, *dd* (11, 17.5), $-\underline{CH}=CH_2$]; H-3: 7.22 [1H, *d* (2)]; H-2: 7.71 [1H, *d* (2)].
2	6.30 (9.5)	8.13 (9.5)	OH: 6.93 (*s*), exchangeable with D_2O; Chain at C-6: 1.72 (6H, *s*, Me's), 5.47 (*d*) and 5.54 (*d*) [1H each (11, 17),$=CH_2$], 6.44 [1H, *dd* (11, 17), $-\underline{CH}=CH_2$]; H-9: 7.02 [1H, *d* (2)]; H-8: 7.56 [1H, *d* (2)].

* 60 MHz. Chemical shifts are δ values; coupling constants (J in parentheses) are given by Hz.



1 R = H
6 R = Me



2 R = H, R′ = C(Me)$_2$—CH=CH$_2$
3 R = CH$_2$—CH=CMe$_2$, R′ = H
4 R = H, R′ = CH(Me)—C(Me)=CH$_2$
5 R = Ac, R′ = C(Me)$_2$—CH=CH$_2$
7 R = Me, R′ = C(Me)$_2$—CH=CH$_2$

having been recovered as a mixture from the alkaline hydrolysis (K_2CO_3) of HT3 acetate (**5**). An investigation into the hydrolysis of **5** indicated that a mixture of HT3 (**2**) and HT5 (**1**) was obtained rather than **2** alone when **5** was heated with aqueous MeOH K_2CO_3, compound **1** must obviously be produced by the opening of the lactone ring of **2** but this is followed by relactonization with the C-5 hydroxyl group. On refluxing **5** in aqueous MeOH K_2CO_3 for a longer time **1** was obtained as the major product. The hydrolysis product from **5** having been obtained in small amount during the course of earlier investigation [2] had been subjected to methylation as such without purification. Crystallization of the product yielded only **6**, HT3 methyl ether (**7**) presumably remaining in the mother liquor. Monitoring of **7** by TLC was difficult as **6** and **7** had very close R_f values. It may be noted that opening of the lactone ring in coumarin by K_2CO_3, which is not common, was responsible for assigning the linear structure **1** for HT3. During the present investigation HT3, isolated from the plant, was subjected to methylation with CH_2N_2 when only the methyl ether **7**, mp 90–91°, was obtained. No furopinnarin (**6**) was detected in the reaction mixture (TLC). Compound **5** on trans-methylation also gave **7** (cf. [4]).

HT5, which was reported to occur in *Peucedanum stenocarpum* [3], has the structure **1**, as it readily gives furopinnarin on methylation with CH_2N_2. Compound **1** can be synthesized in good yield by prolonged aqueous MeOH K_2CO_3 hydrolysis of **5**, obtained by refluxing **3** in a mixture of *N,N*-dimethylaniline and Ac_2O.

EXPERIMENTAL

Mps are uncorr. ^{1}H NMR spectra were recorded at 60 MHz in $CDCl_3$ unless otherwise stated. R_f values refer to TLC on Si gel using C_6H_6–Me_2CO (9:1) as solvent.

Extraction and isolation. Dried and ground roots of *H. thomsoni* (4 kg) were extracted successively with hexane and C_6H_6 (Soxhlet) for 48 hr. Chromatography of the hexane extract yielded HT3 (**2**) (130 mg), colourless needles from Me_2CO–hexane, mp 145–146°, R_f 0.70, dark yellow fluorescence in UV light [2]. C_6H_6 extraction of the hexane extracted roots yielded a dark brown residue (53 g) which was chromatographed over Si gel (1.5 kg) and the column eluted with solvents of increasing polarity. Elution with $CHCl_3$ gave successively isobergaptol (R_f 0.33), mp 257–259°, HT5 (R_f 0.28) and heratomol (R_f 0.20) [1, 2].

HT3. (**2**). UV λ_{max}^{MeOH} nm: 309, 267 (sh), 253, 223; IR ν_{max}^{KBr} cm^{-1}: 3396 (OH), 1721 (coumarin lactone CO), 1623 (3, 4-double bond in conjugation with CO), 1570, 1473, 1417, 999, 924 (—CH=CH$_2$), 876, 750.

HT5 (**1**). Light yellow plates from MeOH, mp 235–236°, yellow fluorescence in UV light. UV λ_{max}^{MeOH} nm: 317, 291, 273, 251, 226; IR ν_{max}^{KBr} cm^{-1}: 3118 (OH), 1683, 1610, 1475, 1422, 985, 910, 750.

Methylation of **2** *to form* **7**. Compound **2** (50 mg) in dry Et_2O (5 ml) was treated with an Et_2O soln of CH_2N_2. After 24 hr the soln was evapd to dryness and the residue crystallized from Me_2CO–hexane when HT3 methyl ether (**7**) (40 mg), mp 90–91°, R_f 0.71, was obtained as needles. ^{1}H NMR: δ1.77 (6H, *s*, Me's), 3.73 (3H, *s*, OMe), 4.95 (1H, *d*, *J* = 10 Hz, 1H of =CH$_2$), 5.02 (1H, *d*, *J* = 17.5 Hz, 1H of =CH$_2$), 5.10 (1H, *d*, *J* = 17 Hz, 1H of =CH$_2$), 6.32 (1H, *dd*, *J* = 11, 17 Hz, —CH=CH$_2$), 6.38 (1H, *d*, *J* = 9.5 Hz, H-3), (1H, *d*, *J* = 2 Hz, H-8), 7.88 (1H, *d*, *J* = 9.5 Hz, H-4).

Trans-methylation of **5**. Compound **5** (100 mg) in dry Me_2CO (10 ml) was refluxed with dry K_2CO_3 (500 mg) and 18-Crown-6 (20 mg) under N_2. After 1 hr MeI (1 ml) was added to this and the mixture refluxed for a further 8 hr adding three portions of MeI (1 ml each time) during the reflux. The mixture was cooled and the solid filtered off. The residue from the filtrate on separation by PLC gave **7** (50 mg), mp 90–91° (^{1}H NMR, mmp, TLC).

Acetylation of **2**. Compound **2** (60 mg) on treatment with Ac_2O–Py gave HT3 acetate (**5**) (50 mg), needles from MeOH, mp 128–129°, R_f 0.58. ^{1}H NMR: δ1.72 (6H, *s*, Me's), 2.38 (3H, *s*, OCOMe), 5.05 (1H, *d*, *J* = 11 Hz, 1H of =CH$_2$), 5.10 (1H, *d*, *J* = 17 Hz, 1H of =CH$_2$), 6.32 (1H, *dd*, *J* = 11, 17 Hz, —CH=CH$_2$), 6.38 (1H, *d*, *J* = 9.5 Hz, H-3), 7.13 (1H, *d*, *J* = 2 Hz, H-9), 7.58 (1H, *d*, *J* = 9.5 Hz, H-4), 7.72 (1H, *d*, *J* = 2 Hz, H-8).

Claisen rearrangement of lanatin (**3**) to form **4**. Lanatin (**3**) (1 g), mp 140–141°, R_f 0.75, isolated from the roots of *H. thomsoni* [1, 2] was heated at 160–165° for 2 hr. The product on crystallization from MeOH gave **4** as needles (830 mg), mp 155–156°, R_f 0.59. ^{1}H NMR: δ1.58 (3H, *d*, *J* = 7 Hz, Me—CH—), 1.86 (3H, *s*, Me—C=), 4.16 (1H, *q*, *J* = 7 Hz, Me—CH—), 5.40 (2H, *s*, =CH$_2$), 6.36 (1H, *d*, *J* = 9.5 Hz, H-3), 6.67 (1H, *s*, D_2O exchangeable, OH), 7.10 (1H, *d*, *J* = 2 Hz, H-9), 7.65 (1H, *d*, *J* = 2 Hz, H-8), 8.20 (1H, *d*, *J* = 9.5 Hz, H-4). **4** was also formed when **3** was heated in *N,N*-dimethylaniline at 160–165°.

Claisen rearrangement of **3** *in dimethylaniline–*Ac_2O *to form HT3 acetate* (**5**). Compound **3** (1 g) in a mixture of *N,N*-dimethylaniline (4 ml) and Ac_2O (4 ml) was refluxed for 2 hr. The mixture was cooled and poured in crushed ice and acidified with HCl (Congo red). The precipitated solid was extracted into $CHCl_3$ and the extract was washed with aq. $NaHCO_3$, H_2O and dried (Na_2SO_4). Evapn of $CHCl_3$ gave a solid which on crystallization from MeOH gave needles (910 mg), mp 128°. The product was found to be identical with the acetate (**5**) of HT3 on comparison of ^{1}H NMR, TLC mmp.

Hydrolysis of **5** *with aq.* MeOH–K_2CO_3 *to form* **1** *and* **2**. Compound **5** (300 mg) in MeOH (15 ml) was treated with aq. K_2CO_3 (10%, 5 ml) and the soln refluxed under N_2 for 20 min. After removal of MeOH *in vacuo*, H_2O (20 ml) was added and the soln acidified with dil H_2SO_4. The solid (2 spots on TLC) was filtered and separated by PLC. The polar product was identical with **1** (110 mg) in all respects. The upper band gave **2** (70 mg). Longer heating (1 hr) of **5** (300 mg) in MeOH (15 ml) with aq. K_2CO_3 (10%, 5 ml), afforded 160 mg of **1** and 20 mg of **2**.

Methylation of **1**. Compound **1** (50 mg) in MeOH (3 ml) was treated with an Et_2O soln of CH_2N_2. After 24 hr the soln was evapd to dryness and the residue crystallized from MeOH when furopinnarin (**6**) was obtained as needles (40 mg), mp 132–133° (lit. [3] mp 124–125°), R_f 0.68. ^{1}H NMR: δ1.90 (6H, s, Me's) 4.28 (3H, s, OMe), 5.08 (1H, *d*, J = 10.5 Hz, 1H of $=CH_2$), 5.10 (1H, *d*, J = 18 Hz, 1H of $=CH_2$), 6.35 (1H, *d*, J = 9.5 Hz, H-6), 6.50 (1H, *dd*, J = 10.5, 18 Hz, $-CH=CH_2$), 7.03 (1H, *d*, J = 2 Hz, H-3), 7.64 (1H, *d*, J = 2 Hz, H-2), 8.18 (1H, *d*, J = 9.5 Hz, H-5).

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TODDASIN, A NEW DIMERIC COUMARIN FROM *TODDALIA ASIATICA**

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Key Word Index—*Toddalia asiatica*; Rutaceae; roots; dimeric coumarin; toddasin; dihydrotoddasin; structural analysis; diuretic activity.

Abstract—A new dimeric coumarin, named toddasin and possessing a cyclohexene ring with a vinylic side-chain interposed between the two coumarin moieties has been isolated from the roots of *Toddalia asiatica*. It has been characterized as (*E*)-8,8′-[1″,4″-dimethyl-3″-cyclohexen-1″,2″-ylene vinylene]-bis-[5,7-dimethoxycoumarin] (**1**). The proposed structure is supported by the mass fragmentation of its dihydro derivative (**2**).

INTRODUCTION

Celebrated at one time in European medicine under the name of the 'Lopez root', *Toddalia asiatica* Lamk. (Rutaceae), a climbing shrub, found in northern, western and southern parts of India, has been claimed in the indigenous system of medicine to have cardiotonic, stimulant and antipyretic properties [1]. During a programme for systematic screening of Indian plants at this Institute, a 50% aqueous EtOH extract of its roots showed significant diuretic activity [2]. Subsequent studies led to the location of this activity in the EtOAc-soluble fraction. The present communication deals with the isolation and structural elucidation of a new coumarin, designated as toddasin from this fraction.

*CDRI Communication No. 2633.

RESULTS AND DISCUSSION

The EtOAc-soluble fraction on column chromatography over Si gel gave the dimeric coumarin, toddasin, in 0.01% yield.

Toddasin, mp 241°, $C_{32}H_{32}O_8$, M^+ *m/e* 544.2096, showed bands in its IR spectrum at ν_{max}^{KBr} 1725, 1620 (conjugated δ-lactone) and 1590 cm^{-1} (aromatic) indicative of a coumarin nucleus. Its UV absorption at λ_{max}^{EtOH} 228 (log ε 4.91), 263 (4.85), 285 (4.71) and 325 nm (4.84), and that of its dihydro derivative, suggested it to be a 5,7-dioxygenated dimeric coumarin system, though the possibility of an isomeric structure with a 7,8-dioxygenation pattern could not be ruled out at this stage. Its ^{1}H NMR spectrum revealed the presence of 4 OMe functions at δ 3.55, 3.82 and 3.88. Two pairs of complementary doublets at δ 6.0, 7.91