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TODDANOL AND TODDANONE, TWO COUMARINS FROM *TODDALIA ASIATICA**

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Key Word Index—*Toddalia asiatica*; Rutaceae; roots; coumarins; toddanol; toddanone; structural analysis.

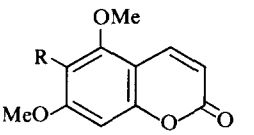
Abstract—Two new constituents isolated from the roots of *Toddalia asiatica* and designated as toddanol and toddanone have been characterized as 5,7-dimethoxy-6-(2-hydroxy-3-methylbut-3-enyl)coumarin (**1**) and 5,7-dimethoxy-6-(3-methyl-2-oxobutanyl)coumarin (**3**), respectively, by spectral analysis and interconversion experiments.

The conspicuous diuretic activity exhibited by the 50% aqueous EtOH extract of the roots of *Toddalia asiatica* Lamk. (Rutaceae) [1, 2], led to its chemical investigation. Accordingly, column chromatography of the Et_2O-soluble fraction of this extract on neutral Al_2O_3 furnished toddanol, mp 125°, $[\alpha]_D^{20}$ − 93.3° ($CHCl_3$; *c*, 3.0), $C_{16}H_{18}O_5$, M^+ *m/e* 290 (yield: 0.00057%). Toddanol displayed UV chromophores similar to toddaculin [3]. The usual resonances in the ^1H NMR spectrum at δ 3.94 and 3.96 (*s*, 3H each, 2 × OMe) and at 6.24 and 7.94 for pyran-ring protons (*d*, 1H each, J = 10 Hz), confirmed a coumarin nucleus with a 5,7-dioxygenated pattern. The chemical shift at δ 6.69 attributed to C-8H suggested that the side-chain (C_5H_9O) was linked to the C-6 of the coumarin nucleus [3]. The side-chain contained one vinylic methyl (δ 1.80), two vinylidene protons (δ 4.89, *d*, J = 12 Hz; ν_{max} cm^{-1}: 895) and two benzylic protons (δ 2.88, *d*, J = 7 Hz). The latter protons were coupled to a methine (δ 4.36, *m*) bearing an oxygen function. This was confirmed by double resonance experiments. Catalytic hydrogenation of toddanol to dihydrotoddanol (**2**) resulted in replacement of the vinylidene group by an isopropyl function δ 0.91 (*d*, 6H, 2 × Me); 2.0 (*m*, 1H, CH), thereby leading to the identification of the side-chain as 2-hydroxy-3-methylbut-3-enyl and the characterization of toddanol as **1**.

The EtOAc-soluble fraction of the EtOH extract on chromatography over Si gel afforded toddanone in 0.0075% yield, mp 116°, $C_{16}H_{18}O_5$, M^+ *m/e* 290. Correspondence with UV spectral features of **1** together with the presence of an intense carbonyl band (ν_{max} cm^{-1}: 1715) and the absence of an OH function suggested that it was an isomer of **1** with a carbonyl group in the side-chain. Salient features of its ^1H NMR spectrum were the presence of a singlet at δ 3.80 for benzylic protons (obscured under OMe signals and discernible in the C_6H_6-induced solvent shift) and an isopropyl function δ 1.19 (*d*, 6H, 2 × Me), 2.80 (*m*, 1H, CH) attached to a carbonyl group. Assigning the C-8 position to the lone aromatic proton resonating at δ 6.63, the side-chain, 3-methyl-2-oxobutanyl, was attached to C-6 of the coumarin nucleus, leading to the characterization of toddanone as **3**, which is a known conversion product of toddalolactone (**4**) [4]. A structural relationship between the two was evidenced by transformation of **1** on acid-catalysed isomerization to **3**.

It is interesting to note that the allylic alcohol and ketone corresponding to toddanol and toddanone, but with the side-chain at C-8 have recently been isolated from *Seseli tortuosum* (Umbelliferae) [5] and *Severinia buxifolia* (Rutaceae) [6], respectively.

The presence of **4**, pimpinellin, isopimpinellin, aculeatin hydrate and 5,7-dimethoxy-6-(3-chloro-2-hydroxy-3-methylbutyl)coumarin (**5**) was confirmed in the plant by direct comparison with authentic samples. The presence of **5** as evidenced by direct isolation from the crude EtOH extract by preparative TLC, where the involvement of HCl has been denied, reflects its natural origin, and the claim is being further substantiated by the occurrences of this chain in natural products [7].



1 R = $-CH_2CHC(OH)=CH_2$ (Me)

2 R = $CH_2CHOHCHMe_2$

3 R = $CH_2COCHMe_2$

4 R = $CH_2CHOHCMe_2$ (OH)

5 R = $CH_2CHClCMe_2$ (OH)

*CDRI communication No. 2706.

Compounds **3**, **4**, **5**, pimpinellin, isopimpinellin and aculeatin hydrate when tested at 125 mg/kg in rats exhibited 62, 87, 77, 71, 84 and 79% diuretic activity respectively compared to chlorothiazide (100%) at the same dose level.

EXPERIMENTAL

All mps are uncorr. The ^{1}H NMR spectra were recorded at 90 MHz using HMDS as int. standard. The MS were recorded on a mass spectrometer fitted with a direct inlet system.

Isolation of constituents. The air-dried roots of *T. asiatica* (6 kg) were percolated with 95% EtOH (3 × 7 l.) and the solvent removed. The residue (800 g) was suspended in H_2O and defatted with hexane (4 × 200 ml). It was then treated with 2 N HCl (4 × 700 ml) and extracted successively with Et_2O (4 × 300 ml) and EtOAc (4 × 600 ml). The Et_2O extract afforded a residue (8.81 g) which was chromatographed on a column of neutral Al_2O_3 (580 g) in hexane and eluted with increasing proportions of C_6H_6 followed by EtOAc (9:1) to furnish toddanol (80 mg) and aculeatin hydrate (500 mg).

Toddanol (**1**). Mp 125° (CH_2Cl_2–Et_2O); $[\alpha]_D^{20}$ −93.3° ($CHCl_3$; *c*, 3.0); UV λ_{max}^{EtOH} nm: 233 (log ε 4.90), 246 (4.68), 255 (4.57) and 329 (4.99); IR ν_{max}^{KBr} cm^{-1}: 3450, 1700 (δ-lactone), 1560, 1440 and 830; ^{1}H NMR ($CDCl_3$): δ 1.80 (*s*, 3H, Me), 2.57 (*br. s*, 1H, OH), 2.88 (*d*, *J* = 7 Hz, 2H, CH_2), 3.94 (*s*, 3H, OMe), 3.96 (*s*, 3H, OMe), 4.36 (*m*, 1H, CH), 4.89 (*d*, *J* = 12 Hz, 2H, $=CH_2$), 6.24 (*d*, *J* = 10 Hz, 1H, C-3H), 6.69 (*s*, 1H, C-8H) and 7.94 (*d*, *J* = 10 Hz, 1H, C-4H); MS *m/e* (rel. int.): M$^+$ 290 (8), 272 (4), 259 (3), 241 (6), 220 (93), 219 (100), 205 (11), 189 (8), 176 (10) and 161 (42).

Dihydrotoddanol (**2**). A soln of **1** (15 mg) in $CHCl_3$ (10 ml) and PtO_2 (5 mg) was shaken in an atmosphere of H_2 for 5 hr. The filtrate was concd to afford **2** (12 mg), mp 85° (CH_2Cl_2–Et_2O); UV λ_{max}^{MeOH} nm: 232, 247, 256 and 330; ^{1}H NMR ($CDCl_3$): δ 0.91 (*d*, *J* = 7 Hz, 3H each, 2 × Me), 2.62 (*d*, *J* = 7 Hz, 2H, CH_2), 3.42 (*m*, 1H, CH), 3.76 (*s*, 3H, OMe), 3.82 (*s*, 3H, OMe), 5.94 (*d*, *J* = 10 Hz, 1H, C-3H), 6.44 (*s*, 1H, C-8H) and 7.60 (*d*, *J* = 10 Hz, 1H, C-4H); MS *m/e* (rel. int.): M$^+$ 292 (13), 249 (8), 220 (100) and 219 (48).

Part (25 g) of the EtOAc-soluble residue (160 g) was chromatographed on a column of Si gel (1 kg) in C_6H_6 and eluted with increasing proportions of EtOAc to yield **3** (100 mg), **4** (2.5 g), pimpinellin (800 mg), isopimpinellin (400 mg) and **5** (80 mg). **5** was also isolated directly from the crude EtOH extract by prep. TLC (Si gel, EtOAc–C_6H_6, 3:47).

Toddanone (**3**). Mp 116° (CH_2Cl_2–Et_2O); UV λ_{max}^{EtOH} nm: 231 (log ε 5.25), 245 (4.87), 254 (4.76) and 325 (5.19); IR ν_{max}^{KBr} cm^{-1}: 1715, 1600, 1555 and 1450; ^{1}H NMR ($CDCl_3$): δ 1.19 (*d*, *J* = 7 Hz, 3H each, 2 × Me), 2.80 (*m*, 1H, CH), 3.78 (*s*, 3H, OMe), 3.80 (*s*, 2H, CH_2), 3.83 (*s*, 3H, OMe), 6.24 (*d*, *J* = 9 Hz, 1H, C-3H), 6.63 (*s*, 1H, C-8H) and 7.85 (*d*, *J* = 9 Hz, 1H, C-4H); MS *m/e* (rel. int.): M$^+$ 290 (26), 220 (38), 219 (100) and 161 (36).

Isomerization of **1** *to* **3**. A mixture of **1** (30 mg), *p*-toluenesulphonic acid (4 mg) and dry toluene (1.5 ml) was heated at 100° in a sealed tube under an atmosphere of N_2 for 7 hr. It was concd, diluted with H_2O and extracted with $CHCl_3$ (4 × 5 ml). The combined organic layer, after removal of the solvent, afforded a residue, which on crystallization from CH_2Cl_2–Et_2O furnished **3** (15 mg), identical in all respects with the natural product.

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