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

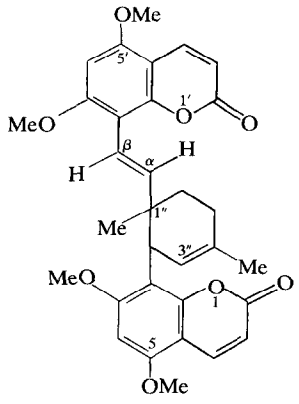
Celebrated at one time in European medicine under the name of the 'Lopez root', *Toddalia asiatica* Lamk. (Rutaceae), a climbing shrub, found in northern, western and southern parts of India, has been claimed in the indigenous system of medicine to have cardiotonic, stimulant and antipyretic properties [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.

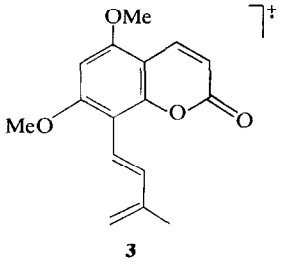
RESULTS AND DISCUSSION

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



1
2 α,β-Dihydro



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and 5.66, 7.7 (each 1H, $J = 10$ Hz) were attributed to C-3H, C-4H and C-3′H, C-4′H respectively to the pyran rings and confirmed by decoupling techniques. Another singlet at δ 6.22 was assigned to two aromatic protons, the upfield value of which lends support for the preference of a 5,7-dioxygenation system to the 7,8-isomer. The remaining C_{10} fragment interposed between the two coumarin units contained one allylic Me at δ 1.21, one vinylic Me at δ 1.76 and two *trans* olefinic protons at δ 6.18 and 6.24 (each *d*, $J = 18$ Hz). In addition to these, there were signals for one vinylic proton at δ 5.31 (*bs*), one methine proton at δ 3.41 (*m*) and for a methylene envelope *ca* δ 2.55 accounting for 4 protons.

The preceding evidence together with the bisectral cleavage of toddasin under electron impact involving a retro-Diels–Alder process into the only fragment ion (**3**), ($C_{16}H_{16}O_4$) constituting the base peak, permitted the identification of the monoterpene part, $C_{10}H_{14}$, as a cyclohexene ring with a vinylic side chain. The chemical shift values of the C-6H in 8-alkylated-5,7-dioxygenated monomeric coumarins range from δ 6.28 to 6.45, whereas the C-8H in the 6-alkylated isomers, for example in toddaculine, [3] resonates at *ca* δ 6.62. The bridging of the monoterpene part with the coumarin nuclei through C-8 and C-8′ was, therefore, favoured in this case by observing the chemical shift values of the two aromatic protons at δ 6.22 in toddasin and δ 6.11 and 6.2 in its dihydro derivative.

Catalytic hydrogenation of toddasin under controlled conditions gave the dihydro derivative, mp 235°, M^+ *m/e* 546, ($C_{32}H_{34}O_8$) showing UV absorption at λ_{max}^{MeOH}: 220, 263 and 330 nm. Retention of the olefinic proton of the cyclohexene ring (δ 5.05, *bs*) and the presence of the doublets of the pyran ring protons at δ 5.94, 7.82 and 5.90, 7.78, indicated that the reduction had occurred at the site of the *trans* olefinic bond only. This was further confirmed by the appearence in its MS of the tropylium ion at *m/e* 219 caused by the fission of the molecule at a point β—to one of the coumarin nuclei. The rest of the fragmentation pattern showed the usual losses of elements of formaldehyde and carbon monoxide from the ion *m/e* 219.

The above evidence led to the formulation of toddasin as (*E*)-8,8′-[1″,4″-dimethyl-3″-cyclohexen-1″,2″-ylene vinylene]-bis-5,7-dimethoxycoumarin] (**1**) and its dihydro derivative as (**2**).

Toddasin, thus represents the third example of a dimeric coumarin incorporating identical cyclohexene nuclei [4, 5].

In a preliminary evaluation, toddasin possessed diuretic activity (71%) at a dose of 21 mg/kg in rats when compared with chlorothiazide (125 mg/kg, 100%) [6].

EXPERIMENTAL

All mps are uncorr. ^{1}H NMR spectra were recorded at 90 MHz using TMS as int. standard. MS were recorded using a direct inlet system.

Isolation of toddasin. Powdered roots of *T. asiatica* (6 kg) were percolated with 95% EtOH (3 × 7 l.). The residue (800 g) obtained after removal of solvent was diluted with H_2O and defatted with hexane (4 × 500 ml). The defatted material was treated with 2M HCl (1.4 l.) and extracted with Et_2O (4 × 300 ml) followed by EtOAc (4 × 600 ml). The latter extract on concn left a residue (160 g), part of which (25 g) was chromatographed on a column of Si gel (1 kg) in C_6H_6 and eluted with increasing proportions of EtOAc followed by MeOH.

Toddasin (**1**). The compound (100 mg) was eluted with C_6H_6–EtOAc (9 : 1) and had mp 241° (CH_2Cl_2–Et_2O); $[\alpha]_D^{27°}$ 0° (C_5H_5N, *c* 1.24); UV λ_{max}^{EtOH} nm: 228 (log ε 4.91), 263 (4.85), 285 (4.77) and 325 (4.84); IR ν_{max}^{KBr} cm^{-1}: 1725, 1620 and 1590; ^{1}H NMR ($CDCl_3$): δ 1.21 (*s*, 3H, C$\underline{H}_3$), 176 (*bs*, 3H, C$\underline{H}_3$), 3.41 (*m*, 1H, C-2″$\underline{H}$), 3.55 (*s*, 3H, OC$\underline{H}_3$), 3.82 (*s*, 3H, OC$\underline{H}_3$), 3.88 (*s*, 6H, 2 × OC$\underline{H}_3$), 5.31 (*bs*, 1H, $W_{1/2} = 10$ Hz, C-3″$\underline{H}$), 5.66 (*d*, 1H, $J = 10$ Hz, C-3′$\underline{H}$), 6.0 (*d*, 1H, $J = 10$ Hz, C-3H), 6.18 (*d*, 1H, $J = 18$ HzCα-$\underline{H}$), 6.22 (*s*, 2H, C-6H and C-6′H), 6.24 (*d*, 1H, $J = 18$ Hz, Cβ-$\underline{H}$), 7.7 (*d*, 1H, $J = 10$ Hz, C-4′$\underline{H}$) and 7.91 (*d*, 1H, $J = 10$ Hz, C-4H); MS: *m/e* M^+, 544.2096 (40%), ($C_{32}H_{32}O_8$), 273.1099 (18) ($C_{16}H_{17}O_4$), 272.1081 (100) ($C_{16}H_{16}O_4$), 257.0844 (5) $C_{15}H_{13}O_4$), 241.0872 (22) ($C_{15}H_{13}O_3$), 219 (10), 213 (8), 189 (21) and 161 (12).

Dihydrotoddasin (**2**). A soln of **1** (30 mg) in $CHCl_3$ (10 ml) was shaken with Pd–C (10%, 5 mg) in an atmosphere of H_2 until the UV absorption at λ_{max} 285 nm disappeared (*ca* 20 min). The residue obtained on concn of the filtrate was chromatographed over a column of Si gel in C_6H_6 and eluted with increasing proportions of EtOAc to afford dihydrotod-

dasin (11 mg), mp 235°; UV λ_{max}^{MeOH} nm: 220, 263 and 330; IR ν_{max}^{KBr} cm^{-1}: 1730, 1605 and 1590; ^1H NMR ($CDCl_3$): δ 0.99 (*s*, 3H, CH_3), 1.64 (*bs*, 3H, CH_3), 1.89–2.76 (*m*, 8H, $4\times CH_2$), 3.47 (*s*, 1H, C-2″H), 3.79 (*s*, 12H, $4\times OCH_3$), 5.05 (*bs*, 1H, C-3″H), 5.9 (*d*, 1H, $J = 10$ Hz, C-3′H), 5.94 (*d*, 1H, $J = 10$ Hz, C-3H), 6.11 (*s*, 1H, C-6′H), 6.2 (*s*, 1H, C-6H), 7.78 (*d*, 1H, $J = 10$ Hz, C-4′H) and 7.82 (*d*, 1H, $J = 10$ Hz, C-4H); MS: *m/e* M^+ 546, 273, 272, 257, 241, 233, 219, 189, 161, 159 and 131.

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A NEW NEOLIGNAN AND OTHER PHENOLIC CONSTITUENTS FROM *CEDRUS DEODARA**

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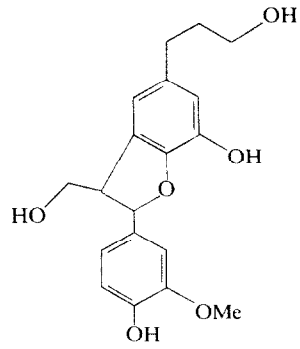
Key Word Index—*Cedrus deodara*; Pinaceae; 2-(3′-methoxy-4′-hydroxyphenyl)-3-hydroxymethyl-2,3-dihydro-7-hydroxybenzofuran-5-*n*-propanol; cedrusin; dihydrobenzofuran neolignans; tetrahydrofuran lignan; phenyl tetralin lignan; dihydroflavonol glucoside.

In a previous communication the characterization of dihydroflavonols from *Cedrus deodara* was described [1]. The present paper reports the identification of a further seven substances from the same plant, including four neolignans; dihydrodehydrodiconiferyl alcohol and its 4′-glucoside, cedrusin **1** and its 4′-glucoside. Cedrusin has not been reported prevously as a natural product, although the 4′-glucoside has been described recently from *Pinus sylvestris* [2] and *P. contorta* [3]. The other known compounds characterized in the present study include the lignans, lariciresinol and isolariciresionol and the dihydroflavonol, taxifolin 3′-glucoside.

Cedrusin, $C_{19}H_{22}O_6$, M^+ *m/e* 346. The UV maxima indicated the presence of a 2-aryl-3,5-dialkyl-7-hydroxybenzofuran chromophore in the molecule. ^1H NMR revealed the presence of an arylmethoxyl, a methylol group and an oxymonobenzylic proton (δ5.43, *d*) in addition to 5 aryl protons. Other signals at δ1.85, 2.54 and 3.55 indicated the presence of an *n*-propanol side-chain. The formation of a dimethyl ether sustaining two methol groups was borne out by ^1H NMR and MS of the dimethyl diacetyl and tetraacetyl derivatives. Thus, the structure of cedrusin



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was assigned as **1**, 2-(3′-methoxy-4′-hydroxyphenyl)-3-hydroxymethyl-2,3-dihydro-7-hydroxybenzofuran-5-*n*-propanol.

*CDRI Communication No. 2580.

EXPERIMENTAL

Isolation procedure. The filtrate, obtained on $Pb(OAc)_2$ pptn of the BuOH-soluble fraction of the plant extract was saturated with H_2S, filtered and evapd to a brown viscous mass (43.2 g), which was chromatographed on cellulose and 9 fractions collected (Table 1).