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SYNTHESIS OF 4-PHENYLCOUMARINS FROM *DALBERGIA VOLUBILIS* AND *EXOSTEMA CARIBAEUM*

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Key Word Index—*Dalbergia volubilis*; Leguminosae; *Exostema caribaeum*; Rubiaceae; neoflavonoids; 4-phenylcoumarins; seshadrin; synthesis.

Abstract—Two isomeric 4-phenyl coumarins, 3′,7-dihydroxy-4′,5-dimethoxy-4-phenylcoumarin (seshadrin) from *Dalbergia volubilis* and 3′,5-dihydroxy-4′,7-dimethoxy-4-phenylcoumarin from *Exostema caribaeum* have been synthesized. However, the spectral properties of the former were not in conformity with those reported for the natural product, seshadrin.

INTRODUCTION

In continuation of our work [1] on 4-phenylcoumarins we undertook the synthesis of the two naturally reported coumarins, 3′,7-dihydroxy-4′,5-dimethoxy-4-phenylcoumarin (seshadrin) and 3′,5-dihydroxy-4′,7-dimethoxy-4-phenylcoumarin. This is the first report of the synthesis of these two coumarins.

RESULTS AND DISCUSSION

3,4-Dimethoxyacetophenone (**1**) was treated with concentrated sulphuric acid at 65° for 24 hr under nitrogen. It afforded 3-hydroxy-4-methoxyacetophenone (**2**) [2]. The latter, on treatment with benzyl bromide in the presence of potassium hydroxide produced 3-benzyloxy-4-methoxyacetophenone (**3**). Ethyl-3-benzyloxy-4-methoxybenzoyl acetate (**4**) was prepared from **3** by treatment with diethyl carbonate in the presence of sodium hydride in dry ether. von Pechmann condensation of **4** with 5-methoxyresorcinol (**5**) in the presence of dry hydrogen chloride in dry ethanol yielded two isomeric 4-phenylcoumarins: 3′,7-dihydroxy-4′,5-dimethoxy-4-phenylcoumarin (**6**) and 3′,5-dihydroxy-4′,7-dimethoxy-4-phenylcoumarin (**7**). In order to achieve total debenzylation the concentration of acid was increased as our earlier work [1] had revealed that at low concentrations partial debenzylation occurred.

Literature data [3] of the naturally occurring compound **7** was identical with that of the synthetic product. However, the literature data on seshadrin [4] differed considerably from the data of the synthetic product (**6**). The synthetic compound (**6**) showed the presence of three aromatic protons (C-2′, C-5′ and C-6′) at δ6.70–7.0, 3H, *m*, and two aromatic protons (C-8 and C-6) at δ6.42, 1H, *d* and 6.32, 1H, *d*. It also confirmed the presence of the C-3 proton at δ5.78 (1H, *s*) and two methoxy groups at (C-4′) δ3.82 (3H, *s*) and (C-5) 3.46 (3H, *s*). The reported [4] ^{1}H NMR data of seshadrin for the C-5 and C-4 methoxy groups were at δ3.80 (6H, *s*) and for the C-8 and C-6 protons at δ7.40 (1H, *d*) and 7.30 (1H, *d*), respectively. The appearance of the C-5 methoxy at δ3.80 is not possible due to the deshielding effect of ring B [1, 5, 6]. The relatively downfield chemical shifts of the C-6 and C-8 protons were also equally unusual. Hence, the structure of seshadrin as reported [4] needs correction.

EXPERIMENTAL

Mps: uncorr. UV: MeOH. IR: KBr. ^{1}H NMR: 100 MHz using TMS as an int. standard. MS: 70 eV.

3-Hydroxy-4-methoxyacetophenone. 3,4-Dimethoxyacetophenone (15 g) was dissolved in conc H_2SO_4 (75 ml) at room temp. under N_2. The soln was stirred at 65° for 20 hr under N_2, then

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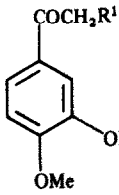
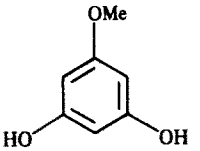


	R^1	R^2
1	H	Me
2	H	H
3	H	CH_2Ar
4	CO_2Et	CH_2Ar



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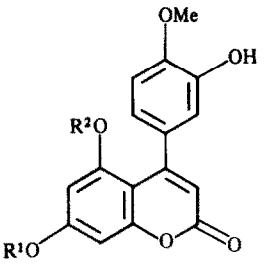

	R^1	R^2
6	H	Me
7	Me	H

cooled and poured onto ice (500 g). After stirring for 15 min, the mixt. was filtered and the filter cake washed with H_2O (35 ml). The filtrate, including washings, was extracted with CH_2Cl_2 (4 × 40 ml). The combined CH_2Cl_2 extracts, the filter cake obtained above and 1 M NaOH (85 ml) were shaken in a separating funnel. The CH_2Cl_2 layer was washed with 1 M NaOH (25 ml) and H_2O (25 ml). The combined aq. phases were washed with CH_2Cl_2 and then acidified with conc HCl (10 ml). The mixt. was cooled at 0°, filtered, washed with H_2O (2 × 15 ml) and dried *in vacuo* at 30° to give product **2** (yield 60%). $C_9H_{10}O_3$ ($[M]^+$ *m/z* 166). Mp 88–89° (lit. [2] 92–93°).

3-Benzyloxy-4-methoxyacetophenone. Compound **2** (4.5 g), KOH (1.25 g) and benzyl bromide (7 ml) were mixed thoroughly and refluxed for 4 hr. After cooling, the mixt. was poured into chilled H_2O (75 ml) and then extracted with $CHCl_3$ (3 × 75 ml). The organic layer was washed several times with H_2O, concd and passed through a silica gel column. The product **3**, $C_{16}H_{16}O_3$, was obtained from the petrol–C_6H_6 (5:1) eluate (68% yield). Mp 75–76°. IR ν_{max}^{KBr} cm^{-1}: 1660, 1585, 1575, 1500. ^1H NMR ($CDCl_3$): δ6.84–7.64 (8H, *m*, H-2, H-5, H-6), 5.20 (2H, *s*, $-OCH_2Ar$), 3.96 (3H, *s*, –OMe), 2.53 (3H, *s*, –Ac). MS *m/z* 256 $[M]^+$, 241, 228, 214.

Ethyl 3-benzyloxy-4-methoxybenzoyl acetate. To a vigorously stirred suspension of NaH (3.5 g) in dry Et_2O (60 ml) containing diethyl carbonate (4 ml), a soln of **3** (2.2 g) in dry Et_2O (30 ml) was added at room temp. The mixt. was stirred and refluxed for 24 hr, cooled, treated with ice and acidified with conc HCl. The Et_2O layer was sepd, washed with aq. $NaHCO_3$ soln, dried and concd. The residual oil was heated under red. pres. at 100° to remove excess diethyl carbonate. The reddish viscous oil solidified when dried *in vacuo* to give product **4**, $C_{19}H_{20}O_5$ (yield 75%). Mp 48–49°. IR ν_{max}^{neat} cm^{-1}: 1725, 1670, 1590, 1575, 1500. ^1H NMR ($CDCl_3$): δ6.88–7.65 (8H, *m*, H-2, H-5, H-6 and $-OCH_2Ar$), 5.20 (2H, *s*, $-OCH_2Ar$), 4.20 (2H, *q*, J=8.0 Hz, $-CO_2CH_2Me$), 3.96 (3H, *s*, –OMe), 3.91 (2H, *s*, $-COCH_2CO-$), 1.24 (3H, *t*, J=8.0 Hz, $-CO_2CH_2Me$). MS *m/z* 328 $[M]^+$, 311, 282, 251, 241.

3′,7-Dihydroxy-4′,5-dimethoxy-4-phenylcoumarin (**6**) *and 3′,5-dihydroxy-4′,7-dimethoxy-4-phenylcoumarin* (**7**). A cooled soln of **4** (1 g) and 5-methoxyresorcinol (350 mg) in EtOH (12 ml) was satd with dry HCl gas. After 48 hr, the mixt. was poured into H_2O and concd *in vacuo*. It was then extracted with $CHCl_3$ (5 × 100 ml), made acid free and dried. The extract was then concd and subjected to CC with solvents of increasing polarity.

Compound **7**, $C_{17}H_{14}O_6$, was isolated from the C_6H_6–EtOAc (8:1) eluate (yield 14%). Mp 221–222° (MeOH), (lit. [3] mp 225–226°). UV λ_{max}^{MeOH} nm (log ε): 328 (4.22), 258 (4.15) 214 (4.57). IR ν_{max}^{KBr} cm^{-1}: 3480, 3310, 1690, 1620, 1600 and 1510. ^1H NMR (DMSO-d_6): δ9.08 (1H, *br s*, –OH), 6.78–7.02 (3H, *m*, H-2′, H-5′, H-6′), 6.56 (1H, *d*, J=2.5 Hz, H-8), 6.28 (1H, *d*, J=2.5 Hz, H-6), 5.84 (1H, *s*, H-3), 3.84 (6H, *s*, 2 × –OMe). MS *m/z* 314 $[M]^+$, 297, 286, 271.

Compound **6**, $C_{17}H_{14}O_6$, was isolated from the C_6H_6–EtOAc (6:1) eluate (yield 14%). Mp 256–257° (MeOH). UV λ_{max}^{MeOH} nm (log ε): 330 (4.21), 257 (4.13) and 214 (4.55). IR ν_{max}^{KBr} cm^{-1}: 3490, 3200, 1695, 1615, 1580 and 1505. ^1H NMR (DMSO-d_6): δ6.70–7.0 (3H, *m*, H-2′, H-5′, H-6′), 6.42 (1H, *d*, J=2.5 Hz, H-8), 6.32 (1H, *d*, J=2.5 Hz, H-6), 5.78 (1H, *s*, H-3), 3.82 (3H, *s*, 4′-OMe), 3.46 (3H, *s*, 5-OMe). MS *m/z* 314 $[M]^+$, 299, 287, 286, 273, 272, 271.

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