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COUMARINS AND RELATED COMPOUNDS —VII[1]

A DIRECT SYNTHESIS OF DIHYDROLAPACHENOLE

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Abstract—A direct synthesis of dihydrolapachenole (IIa) is described. 6-Methoxy-7,8-benzocoumarin (Id), an intermediate for the synthesis of lapachenole (Ia) has been prepared by Elbs persulphate oxidation of 7,8-benzocoumarin and subsequent methylation.

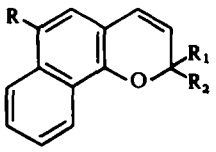
IN CONTINUATION of our studies[1-2] on the synthesis of coumarin derivatives, we report the synthesis of dihydrolapachenole (IIa) and lapachenole (Ia), two naturally occurring compounds from the heartwood of *Paratecoma peroba*.[3,4] Starting point for the synthesis of the former is 3,4-dihydro-7,8-benzocoumarin, (IIb) obtained by the condensation of α-naphthol with methyl acrylate[5] in the presence of anhydrous aluminium chloride, which on oxidation with potassium persulphate[6] in alkaline medium gave 6-hydroxy-3,4-dihydro-7,8-benzocoumarin (IIc). Methylation of IIc yielded 6-methoxy-3,4-dihydro-7,8-benzocoumarin (IId) as light yellow flakes. Reaction of IId with excess of methyl magnesium iodide did not furnish directly dihydrolapachenole but 1-hydroxy-4-methoxy-2-(3-hydroxy-3-methylbutyl)naphthalene (IIId) which, however, underwent smooth cyclization to the former in the presence of *p*-toluenesulphonic acid.

Livingstone *et al.*[7] have described a synthesis of lapachenole by the Grignard reaction of 6-methoxy-7,8-benzocoumarin (Id), the latter being prepared by the Perkin reaction of 1-hydroxy-4-methoxy-2-naphthaldehyde (IIIb) which was obtained in a very poor yield (3%) either by the reduction of the acid IIIc with sodium amalgam or through the Reimer–Tiemann reaction of IIIa (2%). Reduction of the acid IIIc with LAH followed by Oppenauer oxidation, however gave the desired aldehyde (IIIb) in a better yield (22%). 6-Methoxy-7,8-benzocoumarin (Id) has been prepared by us in a more elegant manner. Elbs oxidation of 7,8-benzocoumarin (Ib)[5,8] gave 6-hydroxy-7,8-benzocoumarin (Ic) which on methylation with dimethyl sulphate yielded 6-methoxy-7,8-benzocoumarin (Id). Grignard reaction on Id with excess methyl magnesium iodide by the method of Livingstone *et al.*[7] lead to the formation of lapachenole.

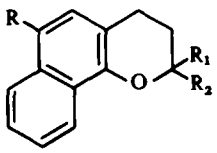
EXPERIMENTAL

UV spectra were measured in a EtOH soln on a Hilger automatic recording spectrophotometer. Unless otherwise stated, IR spectra were determined as Nujol mulls. TLC were prepared with Silica Gel G (Merck) and eluted in benzene–dioxan–acetic acid (90:25:4).

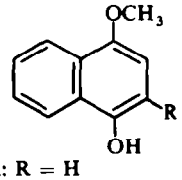
6-Hydroxy-3,4-dihydro-7,8-benzocoumarin [IIc]. 3,4-Dihydro-7,8-benzocoumarin[5] (4·5 g) was dissolved in 10% KOH aq (70ml) and oxidized by the slow addition (6 hr) of an aqueous soln of potassium



Ia: R = OCH_3, $R_1 = R_2 = CH_3$
b: R = H, R_1R_2 = O
c: R = OH, R_1R_2 = O
d: R = OCH_3, R_1R_2 = O



IIa: R = OCH_3, $R_1 = R_2 = CH_3$
b: R =H, $R_1 R_2$ = O
c: R = OH, R_1R_2 = O
d: R = OCH_3, R_1R_2 = O



IIIa: R = H
b: R = CHO
c: R = COOH
d: R = CH_2—CH_2—C(OH)(CH_3)(CH_3)

persulphate (6%; 116 ml) and left overnight. The reaction mixture was stirred vigorously during the addition and the temp was maintained below 10°. It was then acidified with dil HCl (congo-red), and the separated solid filtered (2 g). The filtrate was treated with excess HCl and heated on a steam bath for 1 hr. The separated solid (2 g) was purified by chromatography over silica gel and finally crystallized from EtOAc to 6-*hydroxy*-3,4-*dihydro*-7,8-*benzocoumarin* (IIc) (1·2 g: 41%), (on the basis of recovered dihydro coumarin) as light yellow needles, m.p. 233–234° (Found: C, 73·2; H, 4·9. $C_{13}H_{10}O_3$ requires: C, 72·9; H, 4·7%); R_F 0·40, IR bands at 3280 (OH), 1724 (lactone), 880, 770 (substituted aromatic) cm^{-1}.

6-*Methoxy*-3,4-*dihydro*-7,8-*benzocoumarin* IId). A soln of 6-*hydroxy*-3,4-*dihydro*-7,8-*enzocoumarin* (IIc, 1·0 g) in dry acetone as methylated with Me_2SO_4 (2·5 ml) in presence of anhyd K_2CO_3 (8 g) by refluxing for 3 hr. After the removal of solvent, the residual solid was washed with water and sublimed (130–160%·8 mm). Crystallization from EtOH gave 6-*methoxy*-3,4-*dihydro*-7,8-*benzocoumarin* (1·0 g; 93%), m.p. 95–96° (Found: C, 73·4; H, 5·3, $C_{14}H_{12}O_3$ requires: C, 73·6; H, 5·3%); R_f 0·63, IR bands at 1754 (lactone), 860, 830 and 770 (substituted aromatic) cm^{-1}.

6-*Hydroxy*-7,8-*benzocoumarin* (Ic). 7,8-Benzocoumarin (5·8 g) on oxidation by Elbs persulphate method gave 6-*hydroxy*-7,8-*benzocoumarin* (Ic; 1·2 g; 66%), m.p. 240–245° (on the basis of recovered coumarin). The analytical sample was crystallized from EtOH as light yellow needles, m.p. 249–250°. (Found: C, 73·7; H, 3·9. $C_{13}H_8O_3$ requires: C, 73·6; H, 3·8%); R_f 0·33, IR bands at 3448 (OH), 1695 (α,β-unsaturated lactone), 1630 (olefinic strech), 852, 770 (substituted phl) cm^{-1}, UV maxima at 226, 278, 288, 317, 390 mμ (log ε = 4·5, 4·4, 4·4, 3·8, 3·7).

6-*Methoxy*-7,8-*benzocoumarin* (Id). Methylation of Ic (0·6 g) with Me_2SO_4 (1·8 ml) and K_2CO_3 (3·75 g) in dry acetone afforded 6-methoxy-7,8-benzocoumarin (1 g; 94%) m.p. 140° (from MeOH) (lit[7]., m.p. 132–134°), identical with an authentic specimen* (mixed m.p. and IR) prepared by Livingstone *et al.* (Found: C, 74·5; H, 4·3. Calc. for $C_{14}H_{10}O_3$; C, 74·3; H, 4·4%); R_f 0·54, IR ($CHCl_3$) bands at 1733, 1705 (α,β-unsaturated lactone), 1600 (olefinic stretch), 885, 840 (substituted phenyl) cm^{-1}, UV maxima at 223, 274, 285, 318, 327 (sh), 380 mμ (log ε = 4·6, 4·4, 4·5, 3·7, 3·5, 3·7). On reduction with Pd–C in THF it gave 6-*methoxy*-3,4-*dihydro*-7,8-*benzocoumarin* (IId; 70%) m.p. 96–97° undepressed on admixture with the authentic sample (loc. cit.).

1-*Hydroxy*-4-*methoxy*-2-(3-*hydroxy*-3-*methylbutyl*)-*naphthalene* (IIId) Compound IId (2·2 g) in dry THF (40 ml) was added slowly in cold to a Grignard reagent [prepared from MeI (4·3 g) and Mg (0·70

*We are indebted to Prof. R. Livingstone, Huddersfield College of Technology for kindly comparing the identity of 6-methoxy-7,8-benzocoumarin and dihydrolapachenole with his authentic samples.

g)]. in ether. The soln was refluxed for 1 hr and then decomposed with sat NH_4Cl aq (25 ml) and extracted with ether. The residual oil after removal of the ether was evaporatively distilled (180–200°/1 mm) to a greenish brown viscous liquid (1·7 g) which rapidly darkened on exposure to air, was triturated with pet ether (60–80°) to a solid (700 mg) m.p. 94–95°. Two crystallizations from the same solvent gave tiny needles m.p. 96–97° which on admixture with IId melted at 71–72°. From the analytical data and IR spectra the compound has been proved to be 1-*hydroxy*-4-*methoxy*-2-(3-*hydroxy*-3-*methylbutyl*]-*naphthalene* (IIId). (Found: C, 74·4; H, 7·2. $C_{16}H_{20}O_3$ requires: C, 73·8; H, 7·7%); R_f 0·46, IR bands at 3380 (OH), 1630 (olefinic strech), 1385, 1210 (gem dimethyl) cm^{-1}.

Dihydrolapachenole (IIa). Compound IIId (100 mg) in super dry benzene was refluxed to boiling with *p*-toluenesulphonic acid (20 mg) for 2 hr. The benzene layer was washed with water, dried and evaporated to dryness to a solid (80 mg) m.p. 74–76°. Crystallization from MeOH gave IIa as needles m.p. 75–76° (lit[3]., m.p. 78°), identical with an authentic specimen* (mixed m.p. and IR). (Found: C, 78·9; H, 7·2. Calc. for $C_{16}H_{18}O_2$: C, 79·3; H, 7·5%); R_f, 0·78, IR bands at 1630 (olefinic stretch), 1390, 1210, 1195 (gem dimethyl), 1130 (C—O—C) cm^{-1}; picrate, violet needles m.p. 140°. Dihydrolapachenole gave a light violet fluorescence in EtOH solution.

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