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A NOVEL SYNTHESIS OF 4-PHENYL COUMARINS HAVING A FREE HYDROXYL GROUP IN THE PHENYL RING : SYNTHESIS OF MELANETTIN AND STEVENIN

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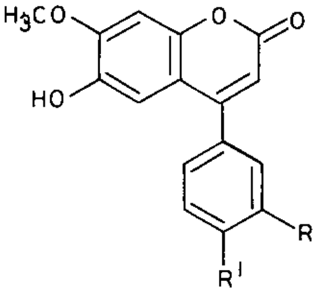
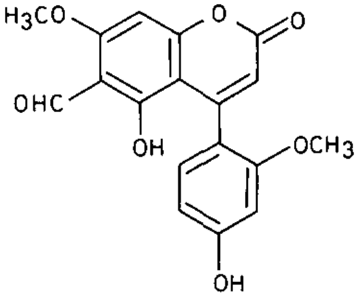
Abstract - Melanettin (1) and stevenin (2), two naturally occurring 4-phenyl coumarins have been synthesised in good yield using a novel method.

Melanettin[1] (1), stevenin[2] (2), melannein[3] (3) and sisafolin[4] (4) are the only examples of naturally occurring 4-phenyl coumarins having a free hydroxyl group in the phenyl ring. The structures of the above coumarins were assigned on the basis of their spectral data and confirmed (except sisafolin) by their synthesis[5-7] involving partial methylation of the corresponding hydroxy coumarins or their acetates. The desired products could be obtained only in small amounts from a complex mixture of the partial methyl ethers. These coumarins have also been prepared[1,2] in poor yield by the Perkin cyclisation of the corresponding benzophenones.



(1 - 3)

	R	R'
1	H	OH
2	OH	H
3	OH	OCH_3



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In this communication, we describe a novel synthesis of two such coumarins viz., melanettin [6-hydroxy-7-methoxy-4-(p-hydroxyphenyl)coumarin, 1] and stevenin [6-hydroxy-7-methoxy-4-(m-hydroxyphenyl) coumarin, 2] . The special feature of this method is the synthesis of appropriately substituted ethyl benzoyl acetate. The usual method of preparation of these esters consists in the reaction of methoxy acetophenones with diethyl carbonate in presence of sodium hydride. This method cannot be used for the preparation of ethyl benzoyl acetates having a free hydroxyl group. It has been found useful to protect the hydroxyl groups of ketones by benzylation. The subsequent steps involve the reaction of benzyloxy acetophenones with diethyl carbonate in presence of sodium hydride followed by condensation of the formed ester with appropriate phenol. Complete debenzylation occurred during the condensation yielding the required coumarin with free hydroxyl group in the phenyl ring. Thus, melanettin (1) was prepared in good yield as described below : Condensation of p-benzyloxyacetophenone (9 gm) with diethyl carbonate (8.1 gm, 2 moles) in dry ether in presence of sodium hydride (3.8 gm, 4 moles) afforded ethyl p-benzyloxy benzoyl acetate, m.p.60-61^{o} in 60% yield. Its structure was in agreement with its NMR spectral data which showed the following absorptions: δ(CDCl$_3$) 1.26(3H, t, J = 7.5 Hz), 3.98(2H, s), 4.25(2H, q, J = 7.5 Hz), 5.16(2H, s), 7.02(2H, d, J = 10 Hz), 7.42(5H, s) and 7.94(2H, d, J = 10 Hz) .

Ethyl p-benzyloxy benzoyl acetate on condensation with O-methoxyhydroquinone[8] in absolute alcohol in presence of dry hydrogen chloride gas yielded melanettin (1) in 50% yield, m.p.236-37^{o} (acetate, m.p.151-52^{o}), identical with authentic sample[5].

Similarly, the ethyl m-benzyloxy benzoyl acetate on condensation with O-methoxyhydroquinone afforded stevenin (2) in 50% yield, m.p.252-53^{o}, identical with an authentic sample[6].

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