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A NOVEL SYNTHESIS OF 3-PHENYL-4-HYDROXYCOUMARINS*

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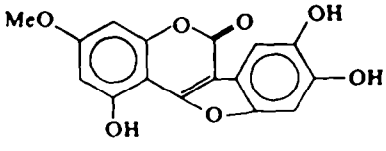
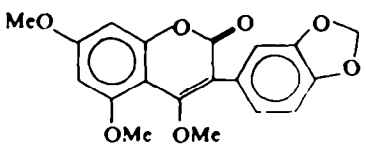
Abstract—Several 2α-hydroxybenzyl-2,4,6-trimethoxycoumaran-3-ones which are substituted in the benzyl part have been found to undergo transformation in the presence of BF_3-etherate into the corresponding 3-phenyl-4-hydroxy-coumarins. Since these coumaranones are in turn readily obtainable from α-methoxychalkones, this constitutes a novel and useful synthesis of 3-phenyl-4-hydroxy-coumarins. It involves an acid catalysed rearrangement and suggests an alternative route of biogenesis of these natural products from the corresponding chalkones.

ALTHOUGH 3-phenyl-4-hydroxycoumarins have been discovered only during the last few years as nonrotenoids of *Derris* spp.; the derived compounds now called coumestanes[1] were known earlier. The eleven coumestanes recognized to date are: wedelolactone (I), desmethyl wedelolactone, coumestrol, erosnin, psoralidin,[2] trifoliol,[1] medicagol[3,4] 4'-methyl coumestrol,[5] lucernol,[6] sativol and 7-hydroxy-11,12-dimethoxycoumestane.[7] The seven nonrotenoids occurring in the roots of *D.scandens* and *D.robusta* have been identified as 3-phenyl-4-hydroxycoumarins; they are scandenin, lonchocarpic acid,[8-10] robustic acid,[11,12] methyl robustate[12] D.R.-5(II), D.R.-8 and D.R.-9.[13] Two more compounds viz. chandanin and nallanin isolated from the Indian sample of *Derris scandens* are also considered to belong to



I



II

* For preliminary communication, see *Tetrahedron Letters* No. 24, 2701 (1966).

[1] A. L. Livingston, *Tetrahedron* **20**, 1963 (1964).
[2] N. R. Krishnaswami and T. R. Seshadri, *Chemistry of Natural and Synthetic Colouring Matters and Related Fields*. (Edited by T. S. Gore, B. S. Joshi *et al.*) p. 235. Academic Press, New York (1962).
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[4] L. Jurd, *J. Pharm. Sci* **54**, 1221 (1965).
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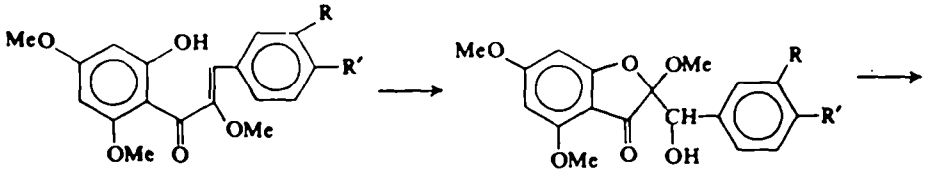
this group.[14] 3-Phenyl-4-hydroxycoumarins are tautomeric with 2-hydroxyisoflavones. In fact, if a 5-OH is free, the latter tautomer predominates.[12]

A number of methods have been described in the literature for the synthesis of 3-phenyl-4-hydroxycoumarins. They can broadly be divided into two groups.

(1) An aryl group is introduced in 4-hydroxycoumarin by the Meerwein reaction[15,16] Earlier, this method had been used for introducing a 3-phenyl group in simple coumarins[17] and 4-alkyl coumarins[18] and yields of 10–50% were reported. Though the reactivity in 3 position is greater in 4-hydroxycoumarins, the application of this reaction has been only to the synthesis of alkyl and nitro substituted 3-phenyl-4-hydroxycoumarins. 3-Unsubstituted 4-hydroxycoumarins have successfully been converted into coumestanes by condensation with phenols like catechol under dehydrogenating conditions.[19,20]

(2) The coumarin ring is formed at the final stage.[15] For oxygenated compounds, those methods are the best which start from 2-hydroxydesoxybenzoins. When all hydroxyls except the 2-hydroxyl group are protected by alkylation, ethyl carbonate in the presence of sodium is satisfactory for building up the α-pyrone ring.[21] But with polyhydroxydesoxybenzoin, refluxing with methyl chloroformate in the presence of potassium carbonate and acetone followed by alkaline hydrolysis is found to give better yields.[22] Thus a number of 3-phenyl-4-hydroxycoumarins oxygenated in the various positions had been synthesized.

During a recent study of the products obtained by the oxidation of 2′-hydroxy-α-methoxychalkones with alkaline hydrogen peroxide,[23,24] an important reaction has been noted which affords 3-phenyl-4-hydroxycoumarins in very good yields. Thus when 2-(α-hydroxy-4-methoxybenzyl)2,4,6-trimethoxycoumaran-3-one (IVa) obtained by oxidation of 2′-hydroxy-α-4,4′,6′-tetramethoxychalkone (IIIa) with alkaline hydrogen peroxide,[23,24] was treated with BF_3-etherate in benzene, the product was 3-(4-methoxyphenyl)4-hydroxy-5,7-dimethoxycoumarin (Va), identical in m.p., UV and IR bands with the sample obtained by the desoxybenzoin method.[22]



III IV

[14] N. V. Subba Rao *Advancing Frontiers in the Chemistry of Natural Products* p. 110. Hindustan Publishing Corp., Delhi (1965).
[15] B. van Zanten, U. A. Th. Brinkman and W. Th. Nauta, *Recueil* **79**, 1223 (1960).
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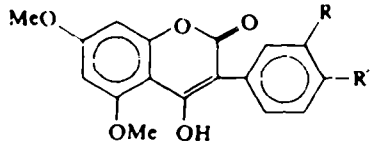
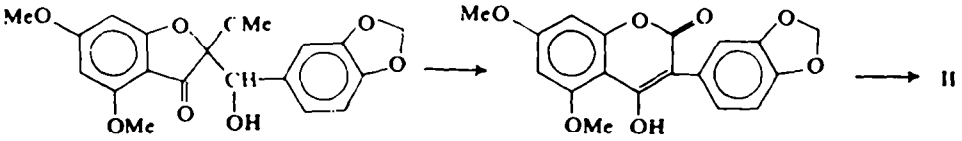
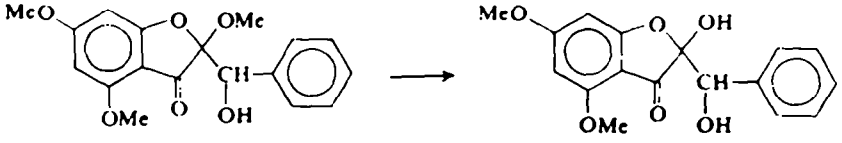


a, R = H; R′ = OMe
b, R = R′ = OMe

V

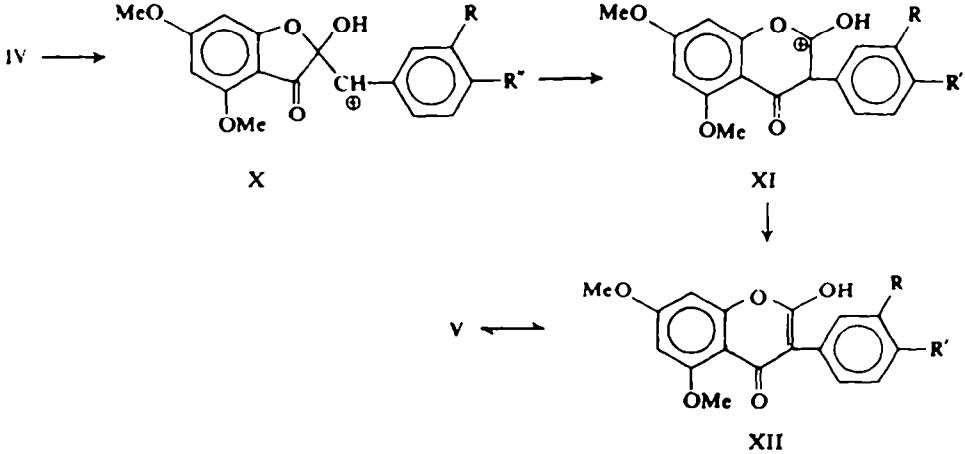


VI VII II



VIII IX

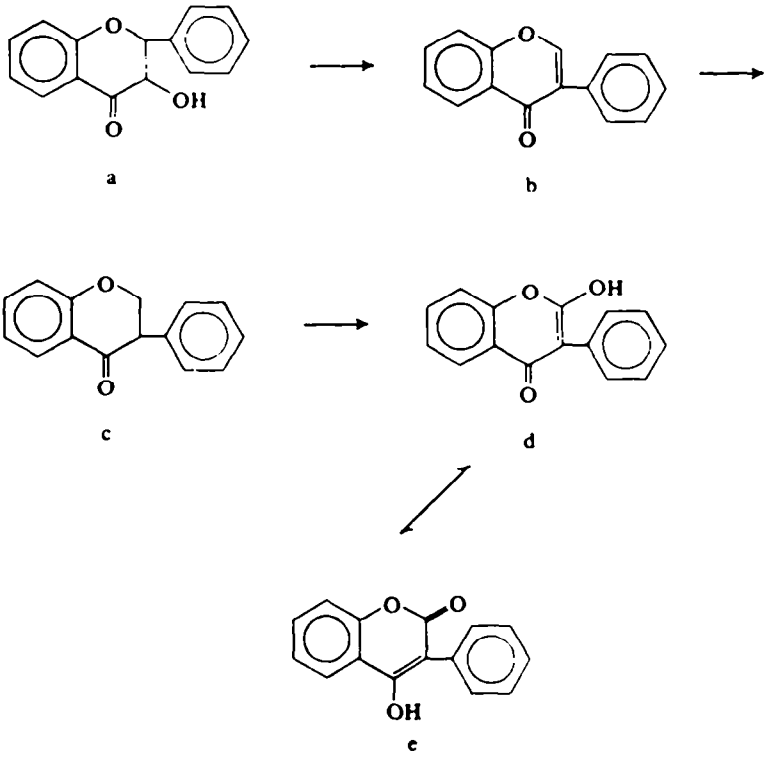
A parallel series of experiments were carried out with three more 2-α-hydroxybenzyl-2-methoxycoumaran-3-ones, viz. IVb, VI and VIII.[23,24] The first two gave the corresponding 3-phenyl-4-hydroxycoumarins Vb and VII respectively. But VIII which had no substituent in the side phenyl did not undergo any rearrangement; it gave only the demethylated product, 2-α-hydroxybenzyl-2-hydroxy-4,6-dimethoxycoumaran-3-one (IX). These results are similar to those observed in the rearrangement of 2′-benzyloxychalkone epoxides with the same reagent,[25] in which rearrangement does not occur when there are no substituents in the Ring B. Hence the following mechanism could be suggested for the formation of 3-phenyl-4-hydroxycoumarins. First the 2-methoxy-2-α-hydroxybenzyl coumaran-3-one (VIII) being a ketal, undergoes demethylation in the presence of Lewis acid to give a compound of type IX. This, being a benzylic



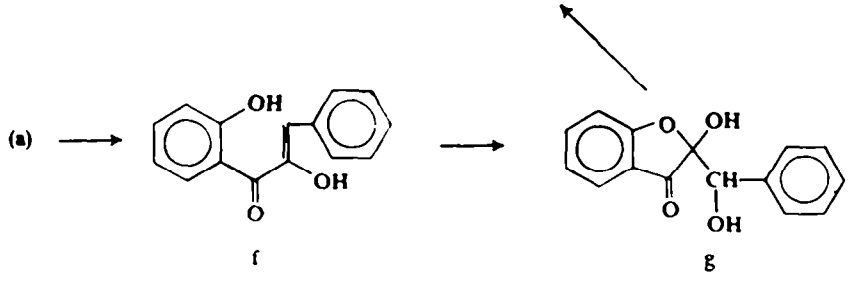
X XI XII V

[25] S. C. Bhrara, A. C. Jain and T. R. Seshadri, *Tetrahedron* **20**, 1141 (1964).

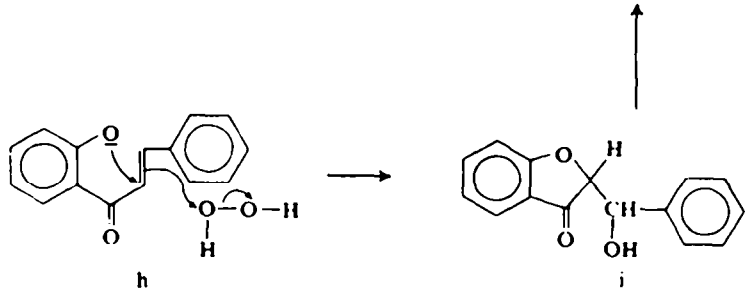
SCHEME I



SCHEME II



SCHEME III



alcohol loses OH anion in favourable cases giving a carbonium ion X. Subsequently, rearrangement takes place to give XI followed by deprotonation to the isoflavonol structure XII which is tautomeric with 3-phenyl-4-hydroxycoumarin (V).

3-(3,4-Methylenedioxyphenyl)4-hydroxy-5,7-dimethoxycoumarin (VII) has been methylated to II which is the structure proposed for one of the natural substances called DR-5 isolated from *D robusta*.[13]

The above rearrangement thus affords a novel synthesis of 3-phenyl-4-hydroxycoumarins starting from α-methoxychalkones. The advantage over the desoxybenzoin method is that the desired starting materials for the chalkone method are easily available; whereas phenyl acetonitriles or phenyl acetyl chlorides required for the desoxybenzoin method require lengthy preparation. The only limitation is that the ring B should be substituted by alkoxy groups as mentioned above.

The new synthesis emphasizes the central role of chalkones in the biogenesis of other natural products besides flavonoids and isoflavonoids.[26] They could also be the precursors of 3-phenyl-4-hydroxycoumarins in Nature. One route (scheme I) for this evolution has been discussed.[27] The present work would suggest an alternative route starting from the common dihydroflavonol which is equivalent to α-hydroxychalkone and can give on oxidation (hydrogen peroxide model) 2-hydroxy-2-α-hydroxybenzylcoumaran-3-one. This can be followed by the acid catalysed isomeric change giving rise to 3-phenyl-4-hydroxycoumarins, as indicated in scheme II. Still another possibility exists for the formation of the intermediate (g) in the above scheme; 2-α-hydroxybenzylcoumaran-3-one postulated as the intermediate for aurones[28] could also undergo hydroxylation in the 2 position (Scheme III). In this connection, the co-occurrence of the following pairs in plant sources may be significant: (a) chalkones, flavonones and isoflavones,[29-33] (b) chalkones and aurones[32-34] (c) chalkones, aurones and isoflavones,[35] (d) isoflavones and 3-phenyl-4-hydroxycoumarins,[13] (e) isoflavones and coumestanes.[36]

EXPERIMENTAL

3-(4-Methoxyphenyl) 4-hydroxy-5,7-dimethoxycoumarin (Va). Compound IVa,[19] (100 mg) was dissolved in dry benzene (200 ml) and treated with BF_3-etherate (0·1 ml). After shaking for 20 min, the resulting complex was decomposed by the addition of water. The organic layer was washed several times with water, dried and the residue crystallized from EtOH. The coumarin Va (40 mg) separated as colourless needles, m.p. 241–243° alone or when mixed with the synthetic sample,[19] λ_{max} (MeOH): 320 mμ (log ε 4·15); $\lambda_{inflex.}$ 237–240 mμ (log ε 4·19); ν_{max} (Nujol): 5·82 with shoulders at 5·78 and 5·90 μ (C=O). (Found: C, 65·9; H, 5·5. Calc. for $C_{19}H_{16}O_6$: C, 65·8; H, 4·9%.)

3-(3,4-Dimethoxyphenyl) 4-hydroxy-5,7-dimethoxycoumarin (Vb). Compound IVb,[19] (100 mg)

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[34] B. Puri and T. R. Seshadri., *J. Chem. Soc.* 1589 (1955).
[35] E. Wong, *Phytochem.* **5**, 463 (1966).
[36] H. Grisebach and W. Bay, *Z. Naturforsch.* **18B**, 466 (1963).

was reacted with BF_3-etherate (0·1 ml) in benzene (200 ml). The resulting Vb (45 mg) crystallized from EtOH as colourless long needles, mp. 201°. (Lit.[18] 200–202°), λ_{max} (MeOH): 320 mμ (log ε 4·36); λ_{inflex} 236–240 mμ (log ε 4·40). (Found: C, 63·3; H, 4·7. Calc. for $C_{18}H_{16}O_7$: C, 63·7; H, 5·1%.)

3-(3,4-*Methylenedioxyphenyl*) 4-*hydroxy*-5,7-*dimethoxycoumarin* (VII). Compound VI[24] (500 mg) was dissolved in benzene (1·1 l.) by warming and was treated with BF_3-etherate (0·6 ml). The product (300 mg) crystallized from glacial AcOH as clusters of colourless needles, m.p. 231–232° (lit.[22] 234–235°), λ_{max} (MeOH): 317 mμ (log ε 4·34); λ_{inflex} 233–239 mμ (log ε 4·17). (Found: C, 63·5; H, 4·2. Calc. for $C_{18}H_{14}O_7$: C, 63·2; H, 4·1.%)

3-(3,4-*Methylenedioxyphenyl*) 4,5,7-*trimethoxycoumarin* (DR-5, II). The above VII (300 mg) was suspended in a mixture of ether (300 ml) and MeOH (100 ml) and cooled in ice-salt mixture. Excess of diazomethane in ether was added in 3 lots during 1 hr and stirred till the suspended compound dissolved. It was left in the refrigerator for 20 hr. The solvent was removed and the product (250 mg) crystallized from MeOH as colourless needles, m.p. 179–180°, λ_{max} (MeOH): 327 mμ (log ε 4·2). (Found C, 63·4; H, 4·6%. $C_{19}H_{16}O_7$ requires: C, 64·0; H, 4·5%.)

2-*Hydroxy*-2-(α-*hydroxy*)*benzyl*-4,6-*dimethoxycoumaran*-3-*one* (IX). Compound VIII (300 mg) was dissolved in dry benzene (150 ml) and treated with BF_3-etherate (0·3 ml). The product (150 mg) crystallized from benzene as colourless prisms, m.p. 206–207°, λ_{max} (MeOH) 290 mμ (log ε 4·34). (Found C, 64·8; H, 5·6. $C_{17}H_{16}O_6$ requires: C, 64·5; H, 5·1%.)

Note added in proof—A synthetic sample of DR-5 has been compared with the natural sample and they are found to be identical by mixed m.p., and comparative IR spectra. Our thanks are due to Prof. W. D. Ollis for this comparison.