SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part XX. Synthesis of Some 3-Phenyl-4. Hydroxy Coumarins

By V. R. Lalitha and N. V. Subba Rao

(*Department of Chemistry, Osmania University, Hyderabad-7*)

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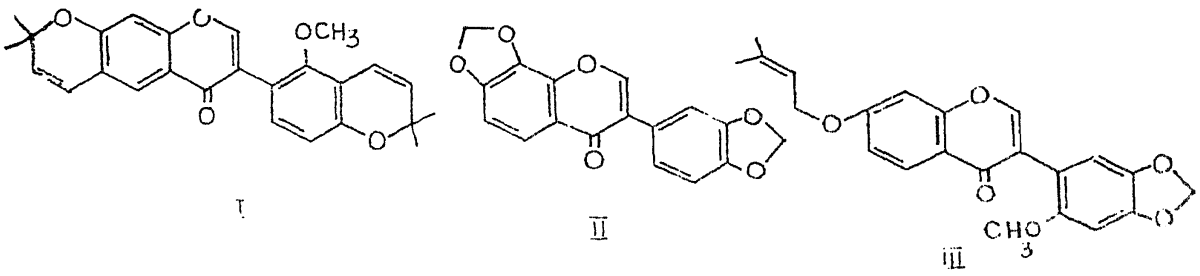
3-Aryl-4-hydroxy coumarins as well as isoflavones have been isolated from the roots of *D. scandens*[1] and *D. robusta*.[2] The pods of *T. purpurea maxima*[3] and roots of *M. suberosa*[4] also contain isoflavones. The occurrence of 3-aryl-4-hydroxy coumarins and isoflavones in the same plant is of bio-genetic significance.

It was therefore considered desirable to synthesise a number of 3-phenyl-4-hydroxy coumarins from the intermediate deoxybenzoins obtained by the alkali degradation of the isoflavones isolated from *T. purpurea* var. *maxima* and *M. suberosa* and evaluate their fish toxicity. In addition, a number of 3-aryl-4-hydroxy coumarins having resorcinol and phloroglucinol system in ring 'A' and their methyl and allyl ethers have also been synthesised as model compounds for spectral comparison with the naturally occurring compounds—scandenin, lonchocarpic acid, robustic acid and other compounds isolated from *D. scandens* and *D. robusta*.

Of the various methods available[5-9] for the synthesis of 3-phenyl-4-hydroxy coumarins, the method due to Boyd and Robertson,[8] using diethyl carbonate and that due to Gilbert, McGookin and Robertson[9] using ethyl chloroformate gave good yields of the 3-phenyl-4-hydroxy coumarins from the corresponding hydroxylated deoxybenzoins. The intermediate deoxybenzoins required have all been prepared by condensing phenyl acetonitrile, *p*-methoxy,[10] *o*-methcxy[11] and homoveratroyl[12] acetonitriles with either resorcinol or phloroglucinol giving rise to 2 : 4-dihydroxy,[13] 2 : 4-dihydroxy-4′-methoxy[11], 2 : 4-dihydroxy-2′-methoxy,[14] 2 : 4 : 6-trihydroxy,[15] 2 : 4 . 6-trihydroxy-4′-methoxy[16] and 2 : 4 : 6-trihydroxy-3′ : 4′-dimethoxy[15] deoxybenzoins adopting Hoesch procedure. The deoxybenzoins were then condensed with either ethyl carbonate in the presence of sodium, or ethyl chloroformate and potassium carbonate in acetone medium, depending upon whether the hydroxyls are fully protected or not. In particular, the later method gave good yields of the 3-phenyl-4-hydroxy coumarins, having a phloroglucinol system with unprotected hydroxyls. Similarly, the deoxy-

benzoins obtained from the natural products munetone (I), purpuranin-B (II) and maximin[3] (III) by alkali degradation were condensed with ethyl carbonate and sodium to give the corresponding 3-phenyl-4-hydroxy coumarins.

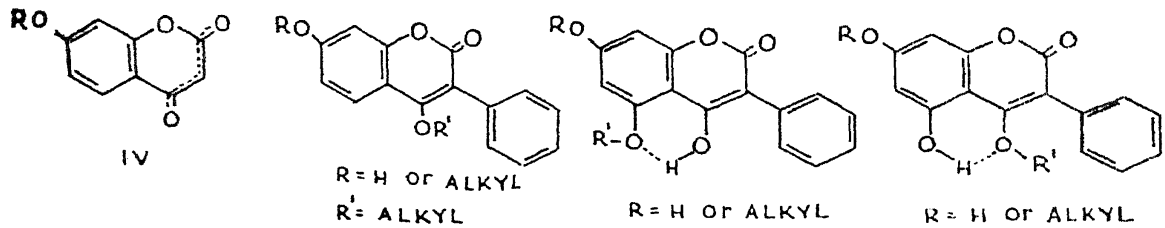
CHART I



I II III

Most of the 3-aryl-4-hydroxy coumarins synthesised absorb in the UV at 240–280 nm with high intensity and at 320–340 nm with comparatively low intensity (Table III). The IR spectra of 3-aryl-4-hydroxy coumarins derived from resorcinol nucleus exhibit the C =O frequency between 1630 and 1660 cm^{-1}, whereas on methylation or allylation of the 4-hydroxyl the C =O frequency rose to 1724 cm^{-1}. In the case of those derived from phloroglucinol nucleus, the carbonyl frequency was observed at 1700 cm^{-1}, irrespective of whether the 4-hydroxyl was free or alkylated. The difference in behaviour of 3-aryl-4-hydroxy coumarins with and without 5-hydroxyl in IR spectra, can be explained by considering 4 : 7-dihydroxy or 7-methoxy-4-hydroxy-3-aryl coumarins existing in dianion state (IV). On alkylation of the 4-hydroxyl (V) the carbonyl got stabilised and its frequency reverted to its original position, *i.e.*, 1720 cm^{-1}. However, in the phloroglucinol series a weak hydrogen bonding between 4-hydroxy group and 5-hydroxyl (VI) or methoxyl (VII) could be envisaged which prevented the dianion formation and consequently the carbonyl frequency was unaffected.

CHART II



IV V VI VII

The compounds synthesised are given in Table I, with their physical and analytical data in the experimental section.

TABLE I

Sl. No.	3-Aryl coumarin	m.p. °C	Solvent for crystallisation	Crystalline shape	Molecular formula	Analysis			
						Found		Required	
						C	H	C	H
1	4 : 7-Dihydroxy-4′-methoxy ..	192	Alcohol	Colourless needles	$C_{16}H_{12}O_5$	67·4	4·5	67·6	4·2
2	4 : 7-Diallyloxy ..	78–79	Pet.ether ethyl acetate	Colourless prisms	$C_{21}H_{18}O_4$	75·4	5·4	75·5	5·4
3	4 : 7 : 4′-Trimethoxy ..	142	Methanol	Square plates	$C_{18}H_{16}O_5$	69·5	5·0	69·2	5·1
4	4 : 7-Dihydroxy-2′-methoxy ..	225	Benzene	Colourless stout prisms	$C_{16}H_{12}O_5$	67·3	4·4	67·6	4·2
5	4-Hydroxy-7-allyloxy ..	202–204	Alcohol	Colourless needles	$C_{18}H_{14}O_4$	73·6	5·0	73·4	4·7
6	4-Hydroxy-7-allyloxy-2′-methoxy ..	154	Methanol benzene	Rods	$C_{19}H_{16}O_5$	70·5	5·2	70·3	4·9
7	4-Allyloxy-5 : 7 : 4′-trimethoxy ..	129–130	Pet.ether benzene	Plates	$C_{21}H_{20}O_6$	68·3	5·6	68·5	5·4
8	4-Hydroxy-2′-methoxy(6 : 7 : 4′: 5′-di-2, 2-dimethyl pyrene	209–210	Dilute alcohol	Rods	$C_{26}H_{24}O_6$	72·0	5·7	72·2	5·5
9	4-Hydroxy-7-dimethylallyloxy-2′ methoxy-4′ : 5′-methylenedioxy	196–198	Alcohol	Prisms	$C_{22}H_{20}O_7$	66·5	5·2	66·7	5·1
10	4-Hydroxy-(7 : 8 : 3′:4′) dimethylenedioxy	273–275	Methanol	Colourless prisms	$C_{17}H_{10}O_7$	62·9	3·2	62·6	3·1

The UV and IR data of these compounds is presented in Tables II and III. None of the compounds showed appreciable toxicity to fish.

EXPERIMENTAL

1. *General Procedure for the Ethyl Chloroformate Method*

A solution of the deoxybenzoin (2 moles) in dry acetone (85 ml) was treated with excess of ethyl chloroformate (4 ml) and anhydrous potassium carbonate (6 g) and the mixture was refluxed on a water-bath for 6 hours. The excess ethyl chloroformate and acetone was distilled off and the residue treated with aqueous sodium hydroxide solution (2%, 25 ml) and boiled on a water-bath for an hour. The alkali solution on cooling and acidifying, yielded crude solid which was crystallised from appropriate solvent.

2. *General Procedure for the Diethyl Carbonate Method*

The deoxybenzoin (0·4 mole), ethyl carbonate (10 ml) and pulverised sodium (0·3 g) were kept together at room temperature for 14 hours. Methyl

TABLE II

UV DATA

Sl. No.	3-Aryl coumarin	UV ABSORPTION max in m	log
1.	4 : 7-Dimethoxy ..	332	4·2
2.	4 : 5 : 7-Trihydroxy-4′-methoxy ..	270	3·99
		322	4·43
3.	4-Hydroxy-5 : 7-dimethoxy ..	247	4·34
		322	4·18
4.	4 : 5 : 7-Trimethoxy ..	333	4·29
5.	4-Hydroxy-5 : 7 : 4′-trimethoxy ..	252	3·78
		329	4·15
6.	4 : 5-Dihydroxy-7-methoxy	246	4·30
	..	333	3·79
7.	4-Hydroxy-2′-methoxy (6 : 7, 4′ : 5′)-di-5, 2-dimethyl pyrene	259	4·43
		340	4·08
8.	4-Hydroxy (7 : 8, 3 : 4)-dimethylene dioxy ..	324	4·08
9.	4-Hydroxy-7-dimethylallyloxy-2′-methoxy-4′ : 5′- ..... methylene dioxy	286	4·93
		317	4·19

TABLE III

IR DATA

Sl. No.	3-Aryl coumarin	C=O	—OH
1.	4 : 7-Dihydroxy ..	1639 cm^{-1}	3571 cm^{-1}
2.	4-Hydroxy-7-methoxy ..	1653 cm^{-1}	..
3.	4-Hydroxy-7-allyloxy ..	1653 cm^{-1}	..
4.	4 : 7-Dimethoxy ..	1724 cm^{-1}	..
5.	4 : 7-Diallyloxy ..	1709 cm^{-1}	..
6.	4-Hydroxy-5 : 7 dimethoxy ..	1704 cm^{-1}	3509 cm^{-1}
7.	4 : 5 : 7-Trimethoxy ..	1709 cm^{-1}	..
8.	4-Hydroxy-5 : 7 : 4′-trimethoxy ..	1659 cm^{-1}	3509 cm^{-1}
9.	4-Allyloxy-5 : 7 : 4′-trimethoxy ..	1695 cm^{-1}	..

alcohol was added to destroy excess of sodium. The solution was diluted with water and extracted with ether. The aqueous solution was acidified with hydrochloric acid and the corresponding 3-phenyl-4-hydroxy coumarin precipitated was filtered, washed and recrystallised from appropriate solvent.

3. *General Procedure for Alkylation or Allylation*

A mixture of the 4 : 7-dihydroxy or 4 : 5 : 7-trihydroxy 3-phenyl coumarin (0·5 g), dry acetone (20 to 40 ml), dimethyl sulphate (0·5 ml) or allyl bromide (0·3 ml) and anhydrous potassium carbonate (1·5 g) was refluxed on a water-bath for 16–20 hours. The acetone was distilled off and water was added to the residue. The solid that separated was filtered and crystallised from methanol or a mixture of ethyl acetate and petroleum ether.

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