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IODINE, A PROTECTING GROUP FOR THE SYNTHESIS OF PSORALEN DERIVATIVES OXYGENATED IN PYRONE RING

SYNTHESIS OF 4,5-DIMETHOXYPSORALEN AND 3,4,5-TRIMETHOXYPSORALEN (HALFORDIN)

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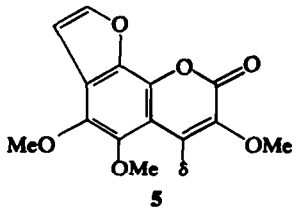
Abstract—A convenient synthesis of psoralen derivatives oxygenated in pyrone ring, *viz* 4,5-dimethoxy-7-oxo-7H-furo [3, 2-g] [1] benzopyran (4,5-dimethoxypsoralen) and 4,5,6-trimethoxy-7-oxo-7H-furo [3, 2-g] [1] benzopyran (halfordin) (3,4,5-trimethoxypsoralen) is described by blocking the 8-position with iodine, Claisen migration followed by cyclisation.

Halfordin[1] (**1**) and isohalfordin[1] (**2**), the chief components of the bark of *Halfordia scleroxyla* are known examples of 3,4-dimethoxyfuranocoumarins in nature. These compounds have also been isolated[2] from the related plant *H. kendack*, which also contains halkendin[3] (**3**) and halfordinin[4] (**4**), which have an α,α-dimethyl ether linkage at 4-position. Hegarty and Lahey[1] first proposed a 3-methoxyfuranocoumarin structure (**5** or **6**) for halfordin on the basis of chemical degradation but later the structure was revised[2] to **1**, based on its ^{1}H NMR spectrum and confirmed by synthesis.[5] However the ^{1}H NMR signal of synthetic halfordin showed[5] downfield displacement for OMe groups. Hence it was considered of interest to develop a convenient method for its synthesis and other similar psoralen derivatives.

The psoralen derivatives were earlier synthesised[6-11] by tedious methods involving a number of steps with very poor yields. It has been found[12] that Claisen rearrangement of 7-allyloxycoumarin derivatives gives exclusively 8-allyl isomers but if the 8-position is blocked[13] or the 3,4-double bond is reduced,[14] the Claisen migration yields 6-allyl isomers. A number of 4-methyl[13]- and 4-phenyl-[15] psoralen derivatives have been synthesised by blocking the 8-position with a bromide group. These intermediates were obtained by the condensation of 2-bromoresorcinol with ethylacetoacetate and ethylbenzoyl acetate respectively. This method could not be effected for the synthesis of psoralen derivatives oxygenated in the pyrone ring. However, these psoralen derivatives have been synthesised by very tedious methods[2,5,16,17] involving the use of the corresponding *o*-hydroxy-(ω-methoxyacetyl)benzopyran or *o*-hydroxy-(ω-methoxyacetyl)benzocoumaran as starting materials, both of which are difficult to prepare. A convenient method has now been developed for the synthesis of such compounds by blocking the 8-position with an easily introduceable and removable group like iodide. The required intermediates, i.e. 8-iodocoumarin derivatives were prepared by direct iodination of the corresponding 7-hydroxycoumarins with iodine and periodic acid or starting from 2-hydroxy-3-iodoacetophenone derivatives, which can be obtained by iodination of corresponding ketones.



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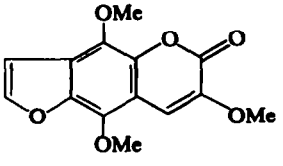

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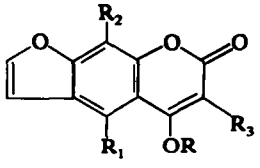
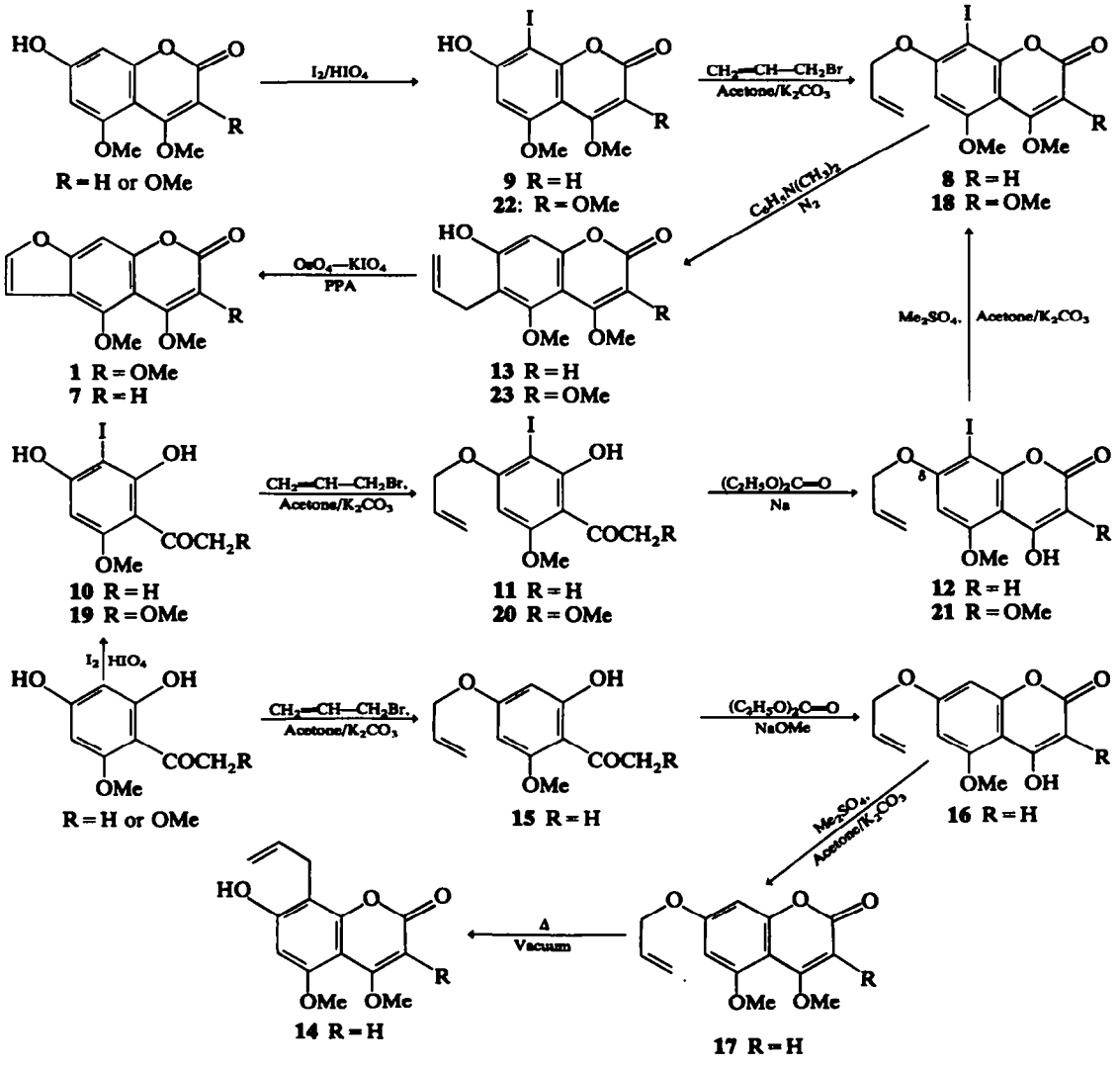


	R	R_1	R_2	R_3
1	Me	OMe	H	OMe
2	Me	H	OMe	OMe
3	Me	H	H	OMe
4	$-CMe_2-CH=CH_2$	OMe	H	OMe
7	Me	OMe	H	H

As a test case, 4,5-dimethoxy-7-oxo-7H-furo [3, 2-g] [1] benzopyran (**7**) was synthesised starting from 7-allyloxy-8-iodo-4,5-dimethoxycoumarin (**8**), obtained by iodination of 7-hydroxy-4,5-dimethoxycoumarin,[18] followed by allylation of the formed 7-hydroxy-8-iodo-4,5-dimethoxycoumarin (**9**). The structure of **8** was confirmed by comparison with a sample prepared as follows: Iodination of 2,4-dihydroxy-6-methoxyacetophenone[19] gave 2,4-dihydroxy-3-iodo-6-methoxyacetophenone (**10**) which on allylation afforded 4-allyloxy-2-hydroxy-3-iodo-6-methoxyacetophenone (**11**). Cyclisation of **11** afforded 7-allyloxyl-4-hydroxy-8-iodo-5-methoxycoumarin (**12**), which on methylation yielded the required coumarin (**8**). Claisen migration of **8** gave an alkali soluble product, which showed the absence of iodine indicating that iodine was eliminated in the above reaction and was assigned the structure, 6-allyl-7-hydroxy-4,5-dimethoxycoumarin (**13**). Further evidence that the iodine was eliminated and that the allyl group entered the 6-position was provided by its ^{1}H NMR spectral data and its non-identity with 8-allyl-7-hydroxy-4,5-dimethoxycoumarin (**14**) prepared as follows: Cyclisation of 4-allyloxy-2-hydroxy-6-methoxyacetophenone (**15**) and methylation of the formed 7-allyloxy-4-hydroxy-5-methoxycoumarin (**16**) gave 7-allyloxy-4,5-dimethoxycoumarin (**17**), which on Claisen migration afforded **14**. Further support was also given by IR spectra of these isomers, which differed in the aromatic region. Oxidation of **13** with OsO_4-KIO_4, followed by cyclodehydration of the intermediate phenylacetaldehyde yielded the required **7**.

Using the above method, halfordin (**1**) was synthesised starting from 7-allyloxy-8-iodo-3,4,5-trimethoxycoumarin (**18**), which was prepared as follows: Iodination of 2,4-dihydroxy-ω,6-dimethoxyacetophenone[20] gave 2,4-dihydroxy-3-iodo-ω,6-dimethoxyacetophenone (**19**). Cyclisation of its partial allyl ether, *viz* 4-allyloxy-2-hydroxy-3-iodo-ω,6-dimethoxyacetophenone (**20**) gave 7-allyloxy-4-hydroxy-8-iodo-3,5-dimethoxycoumarin (**21**), which on methylation yielded the methyl ether (**18**). Compound **18** could also be prepared by allylation of 7-hydroxy-8-iodo-3,4,5-trimethoxycoumarin (**22**), which was obtained by direct iodination of 7-hydroxy-3,4,5-trimethoxycoumarin.[21]



Claisen migration of **18** gave alkali soluble product i.e. 6-allyl-7-hydroxy-3,4,5-trimethoxycoumarin (**23**). Its structure was confirmed by its ^{1}H NMR spectral data and non identity with 8-allyl-7-hydroxy-3,4,5-trimethoxycoumarin.[20] Oxidation of **23** followed by cyclisation of the formed phenyl acetaldehyde with PPA gave the required **1**, identical with the synthetic sample obtained earlier.[5]

EXPERIMENTAL

M.ps were determined in a H_2SO_4 bath, IR spectra were recorded on a Perkin–Elmer infracord. ^{1}H NMR spectra were recorded on a Varian A-60 or on a Perkin–Elmer 90 MHz spectrometer using TMS as an internal standard.

4,5-Dimethoxy-7-oxo-7H-furo [3,2-g] [1] *benzopyran* (**7**)

(a) *7-Allyloxy-8-iodo-4,5-dimethoxycoumarin* (**8**)—*Method* (*A*). (i) *7-Hydroxy-8-iodo-4,5-dimethoxycoumarin* (**9**). 7-Hydroxy-4,5-dimethoxycoumarin[18] (1 g) was dissolved in the minimum amount of alcohol and to this soln, I_2 (0.45 g) and periodic acid (0.16 g) in water were added. The mixture was stirred for 2 hr at room temp and then diluted with water to give **9** (1.1 g). It crystallised from alcohol as colourless needles, m.p. 248–50°. (Found: C, 38.1; H, 2.7. $C_{11}H_9IO_5$ Requires: C, 37.9; H, 2.6%). Acetate (Ac_2O—C_5H_5N), m.p. 129–30°. NMR($CDCl_3$): δ 2.39 (s, 3H, 7-OAc); 3.88 and 3.93 (each s, each 3H, 4- and 5- OMe), 5.58 (s, 1H, H3) and 6.61 (s, 1H, H6).

(ii) *7-Allyloxy-8-iodo-4,5-dimethoxycoumarin* (**8**). Compound **9** (1 g) in dry acetone (75 ml) was refluxed for 4–5 hr with allyl bromide (0.3 ml) in presence of anhyd K_2CO_3 (3 g). After filtration and evaporation, the residue was treated with crushed ice to give solid **8** (0.8 g), which crystallised from MeOH as colourless needles, m.p. 215–7° (Found: C, 43.1; H, 3.4. $C_{14}H_{13}IO_5$ Requires: C, 43.3; H, 3.4%). NMR(DMSO-d_6): δ 3.37 and 3.98 (each s, each 3H, 4- and 5-OMe); 4.97 (d, 2H, J = 4.5 Hz, —OCH_2—CH=CH_2); 5.47 (m, 2H, —OCH_2—CH=CH_2); 5.85 (s, 1H, H3); 6.16 (m, 1H, —OCH_2—CH=CH_2) and 6.93 (s, 1H, H6).

Method (*B*). (i) *2,4-dihydroxy-3-iodo-6-methoxyacetophenone* (**10**). 2,4-Dihydroxy-6-methoxyacetophenone[19] (2 g) was dissolved in the minimum amount of alcohol and to this soln I_2 (1.2 g) and periodic acid (0.4 g in water) were added. The mixture was stirred for 2 hr at 60–70° and then diluted with water to give **10** (2.5 g). This crystallised from AcOH as light yellow needles, m.p. 193–5°. (Found: C, 35.2; H, 3.0. $C_9H_9IO_4$ Requires: C, 35.0; H, 2.9%). Diacetate (Ac_2O–C_5H_5N), m.p. 107–8°. NMR($CDCl_3$); δ 2.26 (s, 3H, —$COCH_3$); 2.34 and 2.45 (each s, each 3H, 2- and 4-OAc); 3.82 (s, 3H, 6-OMe) and 6.71 (s, 1H, H5).

(ii) *4-Allyloxy-2-hydroxy-3-iodo-6-methoxyacetophenone* (**11**). Compound **10** (2 g) in dry acetone (60 ml) was refluxed for 4–5 hr with allyl bromide (0.6 ml) in presence of anhyd K_2CO_3 (6 g). After filtering and evaporation, the residue was dissolved in EtOAc and the soln extracted with 10% NaOHaq (200 ml). Acidification of the clear alkaline soln yielded **11** (1.3 g), which crystallised from MeOH–Me_2CO as pale yellow shining needles, m.p. 162–4°. (Found: C, 41.5; H, 3.6. $C_{12}H_{13}IO_4$ Requires: C, 41.4; H, 3.7%). NMR($CDCl_3$): δ 2.58 (s, 3H, —$COCH_3$); 3.88 (s, 3H, 6-OMe); 4.63 (d, 2H, J = 5 Hz, —OCH_2—CH=CH_2); 5.41 (m, 2H, —OCH_2—CH=CH_2); 5.93 (s, 1H, H5); 6.01 (m, 1H, —OCH_2—CH=CH_2) and 15.13 (s, 1H, —OH, exchangeable with D_2O).

(iii) *7-Allyloxy-4-hydroxy-8-iodo-5-methoxycoumarin* (**12**). A soln of **11** (1 g) in diethyl carbonate (15 ml) was heated with pulverised Na (0.5 g) for 4 hr on a boiling water bath. The mixture was cooled and diluted with water. Ether was added in excess and the aqueous layer separated. Acidification of this layer yielded **12** (0.7 g), which crystallised from EtOAc–benzene as yellow shining prisms, m.p. 154–6°. (Found: C, 41.6; H, 3.1. $C_{13}H_{11}IO_5$ Requires: C, 41.7; H, 2.9%). Acetate (Ac_2O—C_5H_5N), m.p. 183–4°. NMR($CDCl_3$): δ 2.28 (s, 3H, 4-OAc); 3.87 (s, 3H, 5-OMe); 4.67 (d, 2H, J = 4.5 Hz, —OCH_2—CH=CH_2); 5.44 (m, 2H, —OCH_2—CH=CH_2); 5.86 (s, 1H, H3); 5.94 (m, 1H, —OCH_2—CH=CH_2) and 6.30 (s, 1H, H6).

(iv) *7-Allyloxy-8-iodo-4,5-dimethoxycoumarin* (**8**). The above **12** (1 g) in dry Me_2CO (75 ml) was methylated with Me_2SO_4 (0.3 ml) to give **8** (0.7 g). It crystallised from MeOH as colourless needles, m.p. 215–7° (Found: C, 43.0; H, 3.5. $C_{14}H_{13}IO_5$ Requires: C, 43.3; H, 3.4%).

(b) *6-Allyl-7-hydroxy-4,5-dimethoxycoumarin* (**13**). Compound **8** (1 g) was refluxed for 6 hr with N,N-dimethyl aniline (8 ml) under N_2. The mixture was cooled and poured into ice cold HCl. The separated solid was treated with dil. NaOHaq and the soln filtered. The filtrate on acidification yielded **13** (0.5 g), which crystallised from MeOH as colourless needles, m.p. 227–9° (Found: C, 67.8; H, 4.6. $C_{14}H_{14}O_5$ Requires: C, 67.6; H, 4.8%). NMR(CD_3COCD_3): δ 3.77 (d, 2H, J = 7 Hz, —CH_2—CH=CH_2); 3.92 and 4.02 (each s, each 3H, 4- and 5-OMe); 5.15 (m, 2H, —CH_2—CH=CH_2); 5.91 (m, 1H, —CH_2—CH=CH_2); 6.16 (s, 1H, H3) and 6.58 (s, 1H, H8).

(c) *4,5-Dimethoxy-7-oxo-7H-furo* [3,2-g] [1] *benzopyran* (**7**). The above **13** (200 mg) in EtOAc (80 ml) and an equal amount of water was oxidised with OsO_4 (60 mg) and the mixture stirred for 1½ hr. During this period KIO_4 (2 g) was added in small portions. The above mixture was stirred for a further 2 hr, the EtOAc layer separated and the aqueous soln extracted with more EtOAc. The combined EtOAc extract was washed with water, dried (Na_2SO_4) and distilled. The residue was heated on a boiling water bath with polyphosphoric acid (10 ml) for 30 min and then poured over cruched ice. The separated solid was taken up in ether; the ether extract washed successively with Na_2CO_3 aq (5%, 50 ml) and water, dried (Na_2SO_4) and distilled. The residue was crystallised from benzene–petroleum ether (60–80°) to give **7** (100 mg) as colourless needles, m.p. 144–6°. (Found: C, 63.1; H, 4.4. $C_{13}H_{10}O_5$ Requires: C, 63.4; H, 4.1%). NMR($CDCl_3$): δ 3.93 and 4.02 (each s, each 3H, 4- and 5-OMe); 5.60 (s, 1H, H6); 6.92 (dd, 1H, $J_{\beta,\alpha}$ = 2.5 Hz, $J_{\beta,9}$ = 1 Hz, Hβ); 7.21 (d, 1H, $J_{9,\beta}$ = 1 Hz, H9) and 7.57 (d, 1H, $J_{\alpha,\beta}$ = 2.5 Hz, Hα). IR: ν_{max}^{KBr} (cm^{-1}) 1715 (>C=O), 1600 (>C=C<), 1100 and 810 (furan ring).

8-Allyl-7-hydroxy-4,5-dimethoxycoumarin (**14**)

(a) *4-Allyloxy-2-hydroxy-6-methoxyacetophenone* (**15**). 2,4-Dihydroxy-6-methoxyacetophenone[19] (2 g) in dry Me_2CO (100 ml) was refluxed for 5 hr with allyl bromide (1.04 ml) in presence of anhyd K_2CO_3 (6 g). Working up of the mixture gave **15** (1.5 g). It crystallised from MeOH as colourless shining needles, m.p. 74–6° (Found: C, 64.7; H, 6.4. $C_{12}H_{14}O_4$ Requires: C, 64.9; H, 6.3%). NMR($CDCl_3$): δ 2.57 (s, 1H, —$COCH_3$); 3.83 (s, 3H, 6-OMe); 4.51 (d, 2H, J = 5 Hz, —OCH_2—CH=CH_2); 5.44 (m, 2H, —OCH_2—CH=CH_2); 5.90 (m, 1H, —OCH_2—CH=CH_2); 5.94 and 6.01 (each d, each 1H, J = 2.5 Hz each, H3 and H5) and 15.10 (s, 1H, —OH, exchangeable with D_2O).

(b) *7-Allyloxy-4-hydroxy-5-methoxycoumarin* (**16**). A soln of above **15** (1 g) in Et_2CO_3 (10 ml) was added to a suspension of NaOMe (prepared from 0.2 g Na) in Et_2CO_3 (10 ml). The mixture was heated for 4 hr on a boiling water bath. Work up gave **16** (0.8 g). It crystallised from EtOAc–benzene as colourless prisms, m.p. 228–30°. (Found: C, 63.1; H, 4.6. $C_{13}H_{12}O_5$ Requires: C, 62.9; H, 4.8%).

(c) 7-*Allyloxy*-4,5-*dimethoxycoumarin* (**17**). Methylation of **16** (1 g) in Me_2CO (50 ml) with Me_2SO_4 (0.45 ml) in presence of anhyd K_2CO_3 yielded **17** (0.85 g). It crystallised from MeOH as colourless needles, m.p. 147–9°. (Found: C, 67.4; H, 4.9. $C_{14}H_{14}O_5$ Requires: C, 67.6; H, 4.8%). NMR($CDCl_3$): 3.87 and 3.92 (each s, each 3H, 4- and 5-OMe); 4.47 (d, 2H, J = 4.5 Hz, —OCH_2—CH=CH_2); 5.38 (m, 2H, —OCH_2—CH=CH_2); 5.46 (s, 1H, H3); 5.94 (m, 1H, —OCH_2—C**H**=CH_2) and 6.31 and 6.40 (each d, each 1H, J = 2.5 Hz, H6 and H8).

(d) 8-*Allyl*-7-*hydroxy*-4,5-*dimethoxycoumarin* (**14**). The above **17** (0.5 g) was heated in an oil bath at 190–5° for 2 hr under reduced pressure. The cooled product was dissolved in ether and extracted with NaOH soln (1%, 20 ml). Acidification of the clear alkaline soln yielded **14** (0.2 g). It crystallised from MeOH as colourless needles, m.p. 220–2°. (Found: C, 67.3; H, 4.7. $C_{14}H_{14}O_5$ Requires: C, 67.6; H, 4.8%). NMR (CD_3COCD_3): δ 3.67 (d, 2H, J = 7 Hz, —CH_2—CH=CH_2); 3.83 and 3.93 (each s, each 3H, 4- and 5-OMe); 5.10 (m, 2H, —CH_2—CH=CH_2); 5.86 (m, 1H, —CH_2—C**H**=CH_2); 6.37 (s, 1H, H3) and 6.56 (s, 1H, H6).

4,5,6-*Trimethoxy*-7-*oxo*-7*H*-*furo* [3,2-g] [1] *benzopyran* (*halfordin*) (**1**)

(a) 7-*Allyloxy*-8-*iodo*-3,4,5-*trimethoxycoumarin* (**18**). *Method* (*A*). (I) 2,4-*dihydroxy*-3-*iodo*-ω,6-*dimethoxyacetophenone* (**19**). Iodination of 2,4-dihydroxy-ω,6-dimethoxyacetophenone[20] (2 g) with I_2 (1 g) and periodic acid (0.35 g) yielded **18** (2.5 g). It crystallised from AcOH as colourless needles, m.p. 191–3°. (Found: C, 35.6; H, 3.1. $C_{10}H_{11}IO_5$ Requires: C, 35.5; H, 3.3%). Diacetate (Ac_2O–C_5H_5N), m.p. 112–4°. NMR($CDCl_3$): δ 2.28 and 2.35 (each s, each 3H, 2- and 4-OAc); 3.43 (s, 3H, —$COCH_2OCH_3$); 3.81 (s, 3H, 6-OMe); 4.40 (s, 2H, —$COCH_2OCH_3$) and 6.70 (s. 1H, H5).

(ii) 4-*Allyloxy*-2-*hydroxy*-3-*iodo*-ω,6-*dimethoxyacetophenone* (**20**). Compound **19** (2 g) in dry Me_2CO (60 ml) was refluxed for 4–5 hr with allyl bromide (0.65 ml) in presence of anhyd K_2CO_3 (6 g). Working up of the mixture gave **20** (1.2 g). It crystallised from MeOH–Me_2CO as colourless shining needles, m.p. 167–8°. (Found: C, 41.5; H, 4.2. $C_{13}H_{15}IO_5$ Requires: C, 41.3; H, 4.0%). NMR($CDCl_3$): δ 3.48 (s, 3H, —$COCH_2OCH_3$); 3.90 (s, 3H, 6-OMe); 4.53 (s, 2H, —$COCH_2OCH_3$); 4.64 (d, 2H, J = 5 Hz, —OCH_2—CH=CH_2); 5.44 (m, 2H, —OCH_2—CH=CH_2); 5.90 (s, 1H, H5); 6.25 (m, 1H, —OCH_2—C**H**=CH_2) and 14.44 (s, 1H, —OH, exchangeable with D_2O).

(iii) 7-*Allyloxy*-4-*hydroxy*-8-*iodo*-3,5-*dimethoxycoumarin* (**21**). A soln of **20** (1 g) in Et_2CO_3 (15 ml) was heated with pulverised Na (0.5 g) for 4 hr on a boiling water bath. Working up of the mixture yielded **21** (0.7 g). It crystallised from EtOAc–benzene as light yellow prisms, m.p. 225–7°. (Found: C, 41.3; H, 3.3. $C_{14}H_{13}IO_6$ Requires: C, 41.6; H, 3.2%). Acetate (Ac_2O—C_5H_5N), m.p. 211–3°. NMR($CDCl_3$): δ 2.25 (s, 3H, 4-OAc); 3.80 and 3.90 (each s, each 3H, 3- and 5-OMe); 4.61 (d, 2H, J = 4.5 Hz, —OCH_2—CH=CH_2); 5.41 (m, 2H, —OCH_2—CH=CH_2); 5.91 (m, 1H, —OCH_2—C**H**=CH_2); and 6.10 (s, 1H, H6).

(iv) 7-*Allyloxy*-8-*iodo*-3,4,5-*trimethoxycoumarin* (**18**). The above **21** (1 g) in dry Me_2CO (75 ml) was methylated with Me_2SO_4 (0.25 ml) in presence of K_2CO_3 (3 g) to give **18** (0.7 g). It crystallised from MeOH as colourless shining needles, m.p. 138–40°. (Found: C, 42.9; H, 3.5. $C_{15}H_{15}IO_6$ Requires: C, 43.1; H, 3.6%). NMR($CDCl_3$): δ 3.71 and 3.75 (each s, each 3H, 4- and 5-OMe); 4.05 (s, 3H, 3-OMe); 4.63 (d, 2H, J = 4.5 Hz, —OCH_2—CH=CH_2); 5.41 (m, 2H, —OCH_2—CH=CH_2); 5.94 (m, 1H, —OCH_2—C**H**=CH_2) and 6.31 (s, 1H, H6).

Method (*B*). (I) 7-*Hydroxy*-8-*iodo*-3,4,5-*trimethoxycoumarin* (**22**). Iodination of 7-hydroxy-3,4,5-trimethoxycoumarin[21] (1 g) with I_2 (0.45 g) and periodic acid (0.15 g) yielded **22** (1.1 g). It crystallised from alcohol as colourless shining needles, m.p. 212–4°. (Found: C, 38.0; H, 2.7. $C_{12}H_{11}IO_6$ Requires: C, 38.1; H, 2.9%). Acetate (AC_2O—C_5H_5N), m.p. 180–2°. NMR($CDCl_3$): δ 2.37 (s, 3H, 7-OAc); 3.78 (s, 6H, 4- and 5-OMe); 4.08 (s, 3H, 3-OMe) and 6.60 (s, 1H, H6).

(ii) 7-*Allyloxy*-8-*iodo*-3,4,5-*trimethoxycoumarin* (**18**). Compound **22** (1 g) in dry Me_2CO (50 ml) was refluxed for 4–5 hr with allyl bromide (0.26 ml) in presence of anhyd K_2CO_3 (3 g). Work up gave **18** (0.7 g), which crystallised from MeOH as shining needles, m.p. 138–40°. (Found: C, 43.2; H, 3.7. $C_{15}H_{15}IO_6$ Requires: C, 43.1; H, 3.6%).

(b) 6-*Allyl*-7-*hydroxy*-3,4,5-*trimethoxycoumarin* (**23**). Compound **18** (1 g) was refluxed for 6 hr with N,N-dimethylaniline (7 ml) under N_2. Working up of the mixture yielded **23** (0.4 g). It crystallised from MeOH as colourless needles, m.p. 224–6°. (Found: C, 61.7; H, 5.3. $C_{15}H_{16}O_6$ Requires: C, 61.6; H, 5.5%). NMR(CD_3COCD_3): δ 3.58 (d, 2H, J = 7 Hz, —CH_2—CH=CH_2); 3.70 and 3.74 (each s, each 3H, 4- and 5-OMe); 4.03 (s, 3H, 3-OMe); 5.13 (m, 2H, —CH_2—CH=CH_2); 5.95 (m, 1H, —CH_2—C**H**=CH_2) and 6.57 (s, 1H, H8).

(c) 4,5,6-*Trimethoxy*-7-*oxo*-7*H*-*furo* [3,2-g] [1] *benzopyran* (*halfordin*) (**1**). The above **23** (100 mg) in EtOAc (40 ml) and an equal amount of water was oxidised with OsO_4 (30 mg) and KIO_4 (1 g). Work up yielded the intermediate phenylacetaldehyde, which cyclised with PPA (5 ml) to give **1** (50 mg). It crystallised from benzene–petroleum ether as colourless needles, m.p. 136–8°. (lit.[5] m.p. 136–7°) (Found: C, 60.7; H, 4.1. $C_{14}H_{12}O_6$ Requires: C, 60.9; H, 4.4%). NMR($CDCl_3$): δ 3.92 and 4.03 (each s, each 3H, 4- and 5-OMe); 4.21 (s, 3H, 6-OMe); 6.94 (dd, 1H, $J_{\beta,\alpha}$ = 2.5 Hz, $J_{\beta,9}$ = 1 Hz, Hβ); 7.23 (d, 1H, $J_{9,\beta}$ = 1 Hz, H9) and 7.62 (d, 1H, $J_{\alpha,\beta}$ = 2.5 Hz, Hα). IR: ν_{max}^{KBr} (cm^{-1}) 1720 (>C=O), 1610 (>C=C<), 1080 and 770 (furan ring).

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