Synthesis of Linear 3-Phenylpyranocoumarins: Synthesis of Robustin, Robustic Acid, and their Methyl Ethers

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The linear 3-phenylpyranocoumarins, *viz.*, robustin (5b; R^4 = H), its methyl ether (5b; R^4 = Me), robustic acid (5c; R^4 = H), its methyl ether (5c; R^4 = Me), 4-methoxy-3-phenylxanthyletin (5a; R^4 = H), and its methyl ether (5a; R^4 = Me), have been synthesised starting from the corresponding 7-(1,1-dimethylprop-2-ynyloxy)-coumarin derivatives having the 8-position blocked with an easily introduceable and removable group like iodine. The subsequent step consists of heating the prop-2-ynyl ethers in *NN*-dimethylaniline, which resulted in cyclization to linear pyranocoumarins, accompanied by the removal of iodine and also partial demethylation of the methoxy-group at the 4-position. The compounds obtained were identical with the natural samples and were different from authentic samples of the corresponding angular isomers.

A NUMBER of 3-aryl-4-hydroxycoumarin derivatives having a C_5 unit either in the form of side-chain or as a 2,2-dimethylpyran ring, *viz.*, robustic acid,[1-4] robustin,[4] their methyl ethers,[4] lonchocarpic acid,[3,5-7] lonchocarpin,[7] and scandenin,[3,7] have been found to occur in nature. The few known syntheses of such systems [8-12] are multi-staged and give poor overall yields. Here we report a convenient route for the synthesis of such compounds.

Robustin (5b; R^4 = H), its methyl ether (5b; R^4 = Me), robustic acid (5c; R^4 = H), and its methyl ether (5c; R^4 = Me) were isolated from roots of *Derris robusta*.[1-4] Their structures were determined [4,7,13,14] on the basis of spectral data, chemical degradations, and partial synthesis. Later, these structures were supported by their total synthesis.[8,12]

Jain and Jain [8] reported the first total synthesis of (5c; R^4 = H), starting from corresponding 5-C-prenyldeoxybenzoin which was cyclodehydrogenated with dichlorodicyanobenzoquinone and finally cyclized with ethyl chloroformate. The intermediate 5-C-prenyldeoxybenzoin was prepared in low yield by prenylation of 2,4-dihydroxy-6,4'-dimethoxydeoxybenzoin with 2-methylbut-3-en-2-ol in the presence of BF_3–Et_2O, which resulted in the formation of 3-C-, 5-C- and 3,5-di-C-prenyl compounds. Recently, Pathare and Shah [12] have reported the synthesis of (5b; R^4 = Me), (5c; R^4 = H), and (5c; R^4 = Me) starting from 5,7-dihydroxy-2,2-dimethylchroman, which was converted into the required deoxybenzoins in poor yield. The final step involved the dehydrogenation with *N*-bromosuccinimide–collidine.

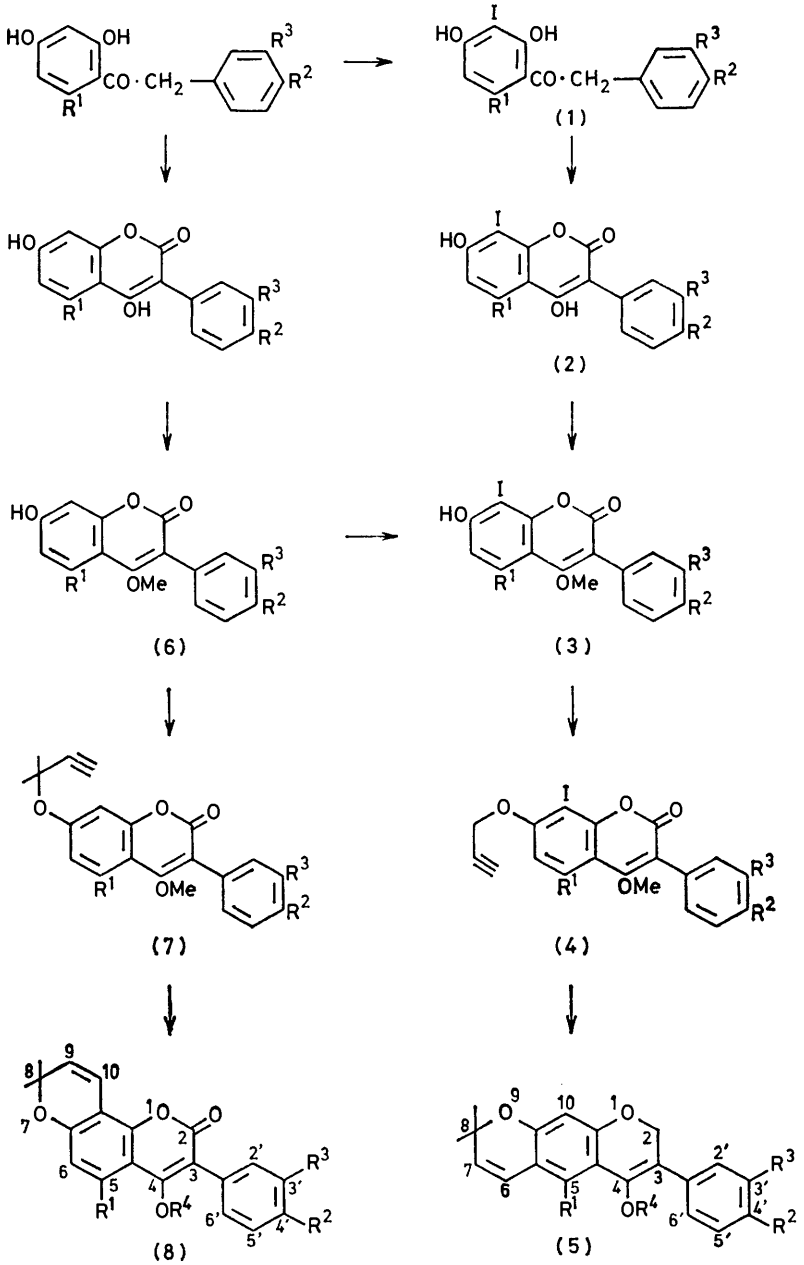
Further, in the above methods the α-pyranone ring was built up on the pre-formed 2,2-dimethylbenzopyran nucleus. The synthesis, which involves the formation of a 2,2-dimethylpyran ring on a pre-formed benzopyranone nucleus and which may be closer to the biosynthetic process in plants, has not been reported so far. In fact, Jain and Jain [15] failed in an attempted synthesis by the latter route, since prenylation of 4,5,7-trihydroxy-3-phenylcoumarins resulted in the formation of tri-C- and tetra-C-prenyl compounds.

It has been observed [10,16,17] that the 7-(1,1-dimethylprop-2-ynyl) ethers of coumarins, when heated in *NN*-dimethylaniline, result in the formation of angular pyranocoumarins, cyclization taking place at the more reactive 8-position. If the 8-position is substituted,[9,10] however, the corresponding 8-substituted linear pyranocoumarins are obtained. In the present method the 8-position is blocked with iodine, a substituent easily introduced and removed. Thus, 7-hydroxy-8-iodocoumarins on prenylation with 3-chloro-3-methylbut-1-yne in acetone in the presence of potassium carbonate and potassium iodide, followed by heating in *NN*-dimethylaniline resulted in the formation of linear pyranocoumarins in quantitative yield, the iodine being removed during the thermal rearrangement.

The synthesis of 4-hydroxy-8,8-dimethyl-3-phenyl-2*H*,8*H*-benzo[1,2-*b*:5,4-*b*']dipyran-2-one (4-hydroxy-3-phenylxanthyletin) (5a; R^4 = H) and its methyl ether (5a; R^4 = Me) was effected as a test case. Thus, 2,4-dihydroxydeoxybenzoin [18] on iodination with iodine–periodic acid in alcohol gave 2,4-dihydroxy-3-iododeoxybenzoin (1a), which on treatment with ethyl chloroformate in acetone in the presence of potassium carbonate, followed by alkaline hydrolysis, yielded 4,7-dihydroxy-8-iodo-3-phenylcoumarin (2a). The dihydroxy-coumarin (2a) on partial methylation with 1.1 mol equiv. of dimethyl sulphate in acetone in the presence of sodium hydrogencarbonate gave 7-hydroxy-8-iodo-4-methoxy-3-phenylcoumarin (3a), which was also prepared by direct iodination of 7-hydroxy-4-methoxy-3-phenylcoumarin [19] with iodine–periodic acid. Prenylation of the coumarin (3a) with 3-chloro-3-methylbut-1-yne gave 8-iodo-4-methoxy-3-phenyl-7-(1,1-dimethylprop-2-ynyloxy)coumarin (4a), which when heated in *NN*-dimethylaniline resulted in the formation of (5a; R^4 = H) and (5a; R^4 = Me), the former presumably being formed by the demethylation of the latter; the structures were supported by spectral results. ^{1}H N.m.r. spectral data of (5a; R^4 = Me) showed two singlets at δ 7.61 and δ 6.77 corresponding to 5-H and 10-H, indicating that the cyclization had taken place at the 6-position with elimination of iodine. Further, (5a; R^4 = H) and (5a; R^4 = Me) were different from authentic samples of the corresponding angular isomers, *viz.*, 4-

hydroxy-8,8-dimethyl-3-phenyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-2-one (4-hydroxy-3-phenylsesselin) (8a; R^4 = H) and its methyl ether (8a; R^4 = Me), respectively, which were prepared by prenylation of 7-hydroxy-4-methoxy-3-phenylcoumarin [19] with 3-chloro-3-methylbut-1-yne, followed by heating in *NN*-dimethylaniline of the 4-methoxy-3-phenyl-7-(1,1-dimethylprop-2-ynyloxy)coumarin (7a) formed. ^{1}H N.m.r. spectral data of (8a; R^4 = Me) showed the two doublets at δ 7.45 and 6.72 (*J* 10 Hz) corresponding to *o*-coupled 5-H and 6-H, respectively.

In a precisely analogous way, the natural products, robustin (5b; R^4 = H), its methyl ether (5b; R^4 = Me), robustic acid (5c; R^4 = H) and its methyl ether (5c; R^4 = Me) were prepared and were shown to be different from the corresponding angular isomers (8b; R^4 = H and Me) and (8c: R^4 = H and Me) (see Scheme).



	R^1	R^2	R^3
a;	H	H	H
b;	OMe	OCH_2O	
c;	OMe	OMe	H

SCHEME

EXPERIMENTAL

A sulphuric acid-bath was used to record the m.p.s which are uncorrected. ^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R-32 (90 MHz) instrument for solutions in deuteriochloroform–acetone or –dimethyl sulphoxide with $SiMe_4$ as an internal standard; J in Hz.

4-Hydroxy-8,8-dimethyl-3-phenyl-2H,8H-benzo[1,2-b:5,4-b′]*dipyran-2-one* (*4-Methoxy-3-phenylxanthyletin*) (5a; R^4 = H) *its Methyl Ether* (5a; R^4 = Me).

7-Hydroxy-8-iodo-4-methoxy-3-phenylcoumarin (3a).—*Method I.* *2,4-Dihydroxy-3-iododeoxybenzoin* (1a). 2,4-Dihydroxydeoxybenzoin [18] (1 g) was dissolved in the minimum amount of ethanol, and iodine (0.48 g) and periodic acid (0.14 g; in water) were added; the mixture was then stirred for 2 h at 60—70 °C. The mixture was cooled and diluted with water to give compound (1a) as needles (1 g), m.p. 205—207 °C (from methanol), δ[$(CD_3)_2SO$] 8.22 (1 H. s, 4-OH), 7.99 (1 H, d, J 10, 6-H), 7.28 (5 H, s, $COCH_2C_6H_5$), 6.63 (1 H, d, J 10, 5-H), 4.27 (2 H, s, $COCH_2C_6H_5$), and 13.81 (1 H, s, 2-OH) (Found: C, 47.3; H, 3.2. Calc. for $C_{14}H_{11}IO_3$: C, 47.4; H, 3.1%).

4,7-Dihydroxy-8-iodo-3-phenylcoumarin (2a). The above deoxybenzoin (3 g) was refluxed for 5 h with ethyl chloroformate (2.28 ml) in dry acetone (75 ml) in the presence of anhydrous potassium carbonate (6 g). The reaction mixture was filtered whilst hot and the inorganic residue washed with hot acetone; the combined filtrates were distilled. The residual oil was hydrolysed by heating it with aqueous sodium hydroxide (1N; 75 ml) for 2 h in a boiling water-bath. Acidification of the cold mixture yielded compound (2a) as needles (2 g), m.p. 289—291 °C (from methanol). The dimethyl ether had m.p. 202—203 °C, δ($CDCl_3$) 7.71 (1 H, d, J 10, 5-H), 7.30 (5 H, s, Ph), 6.72 (1 H, d, J 10, 6-H), 3.91 and 3.46 (each s, each 3 H, 7- and 4-OMe respectively) (Found: C, 49.8; H, 3.1. Calc. for $C_{17}H_{13}IO_4$: C, 50.0; H, 3.2%).

7-Hydroxy-8-iodo-4-methoxy-3-phenylcoumarin (3a). The dihydroxycoumarin (2a) (1 g) was refluxed for 6 h with dimethyl sulphate (0.3 ml) in dry acetone (100 ml) in the presence of anhydrous sodium hydrogencarbonate (5 g). The reaction mixture was worked up and ethyl acetate (75 ml) was added to the residue. Extraction of the ethyl acetate layer with sodium hydroxide (2%; 3 × 10 ml), followed by cold acidification of the aqueous layer gave the coumarin (3a) as needles (0.8 g), m.p. 219—221 °C (from methanol) (Found: C, 48.7; H, 2.9. $C_{16}H_{11}IO_4$ requires C, 48.8; H, 2.8%). The methyl ether of (3a) had m.p. 202—203 °C and was identical (m.p., mixed m.p., and i.r.) with the 8-iodo-4,7-dimethoxy-3-phenylcoumarin prepared above.

Method II. 7-Hydroxy-4-methoxy-3-phenylcoumarin [19] (1 g) was dissolved in the minimum amount of ethanol and iodine (0.41 g) and periodic acid (0.13 g; in water) were added; the mixture was stirred for 2 h at 60—70 °C. Work-up of the reaction mixture gave compound (3a) as needles, m.p. 219—221 °C (from methanol), identical in all respects with the compound prepared by Method I.

8-Iodo-4-methoxy-3-phenyl-7-(1,1-dimethylprop-2-ynyloxy)-coumarin (4a).—7-Hydroxy-8-iodo-4-methoxy-3-phenylcoumarin (3a) (1 g), 3-chloro-3-methylbut-1-yne (4 ml), anhydrous potassium carbonate (4 g), anhydrous potassium iodide (0.5 g), and anhydrous acetone (100 ml) were refluxed for 30 h. Work-up of the reaction mixture yielded (4a) as prisms (0.9 g), m.p. 152—153 °C [from benzene–light petroleum (b.p. 60—80 °C)], δ($CDCl_3$) 7.78 (1 H, d, J 10, 5-H), 7.59 (1 H, d, J_o 10, 6-H), 7.41 (5 H, s, Ph), 3.53 (3 H, s, OMe), 2.66 (1 H, s, C≡CH), and 1.78 (6 H, s, CMe_2) (Found: C, 54.6; H, 3.8. $C_{21}H_{17}IO_4$ requires C, 54.8; H, 3.7%).

4-Hydroxy-8,8-dimethyl-3-phenyl-2H,8H-benzo[1,2-b:5,4-b′]*dipyran-2-one* (*4-Hydroxy-3-phenylxanthyletin*) (5a; R^4 = H) *and its Methyl Ether* (5a; R^4 = Me).—The preceding prop-2-ynyl ether (4a) (1 g) was refluxed for 6 h in *NN*-dimethylaniline (6 ml). Ethyl acetate was added to the cooled mixture which was then washed successively with cold hydrochloric acid (5%; 3 × 25 ml), brine, and water; it was then extracted with aqueous sodium carbonate (10%; 3 × 10 ml). Acidification in the cold of the aqueous layer gave (5a; R^4 = H) as needles (0.4 g), m.p. 228—230 °C (lit.,[15] m.p. 228—229 °C) (from methanol), δ[$(CD_3)_2$CO] 10.04 (1 H, s, OH), 7.60 (1 H, s, 5-H); 7.36 (5 H, s, Ph), 6.72 (1 H, s, 10-H), 6.57 (1 H, d, $J_{6,7}$ 10, 6-H), 5.87 (1 H, d, $J_{7,6}$ 10, 7-H), and 1.47 (s, 6 H, CMe_2) (Found: C, 75.2; H, 5.1. Calc. for $C_{20}H_{16}O_4$: C, 75.0; H, 5.0%). The ethyl acetate layer was dried ($MgSO_4$) and distilled to give (5a; R^4 = Me), m.p. 202—204 °C [from benzene–light petroleum (b.p. 60—80 °C)], δ($CDCl_3$) 7.61 (1 H, d, 5H), 7.45 (5 H, s, Ph), 6.77 (1 H, s, 10-H), 6.43 (1 H, d, $J_{6,7}$ 10, 6-H), 5.74 (1 H, d, $J_{7,6}$ 10, 7-H), 3.58 (3 H, s, OMe), and 1.52 [6 H, s, CMe_2]. Further methylation of (5a; R^4 = H) gave a compound identical in all respect with (5a; R^4 = Me).

4-Hydroxy-8,8-dimethyl-3-phenyl-2H,6H-benzo[1,2-b:1,2-b′]*dipyran-2-one* (*4-Hydroxy-3-phenylsesselin*) (8a; R^4 = H) *and its Methyl Ether* (8a; R^4 = Me).

4-Methoxy-3-phenyl-7-(1,1-dimethylprop-2-ynyloxy)-coumarin (7a).—A mixture of 7-hydroxy-4-methoxy-3-phenylcoumarin [19] (1 g), 3-chloro-3-methylbut-1-yne (4 ml), anhydrous potassium carbonate (4 g), and anhydrous potassium iodide (0.5 g) were refluxed for 30 h in anhydrous acetone (100 ml). Work-up of the reaction mixture gave (7a) as hexagonal crystals (0.9 g), m.p. 102—104 °C [from benzene–light petroleum (b.p. 60—80 °C)], δ($CDCl_3$) 7.81 (1 H, d, J_o, 10, 5-H), 7.47 (5 H, s, Ph), 7.39 (1 H, d, J_m 2.5, 8-H), 7.12 (1 H, dd, J_o 10, J_m 2.5, 6-H), 3.58 (3 H, s, OMe), 2.71 (1 H, s, C≡CH), and 1.76 (6 H, s, CMe_2) (Found: C, 75.2; H, 5.5. $C_{21}H_{18}O_4$ requires C, 75.4; H, 5.4%).

Formation of Compounds (8a; R^4 = H *and* Me).—The preceding prop-2-ynyl ether (7a) (1 g) was refluxed for 6 h in *NN*-dimethylaniline (10 ml). Work-up of the reaction mixture [as for compound (5a)] gave (8a; R^4 = H) as needles (0.7 g), m.p. 222—223 °C (lit.,[15] m.p. 223 °C) (from methanol), δ[$(CD_3)_2$CO] 10.01 (1 H, s, OH), 7.72 (1 H, d, J_o 10, 5-H), 7.31 (5 H, s, Ph), 6.93 (1 H, d, $J_{10,9}$ 10, 10-H), 6.78 (1 H, d, J_o 10, 6-H), 5.77 (1 H, d, $J_{9,10}$ 10, 9-H), and 1.54 [6 H, s, CMe_2) (Found: C, 74.9; H, 5.0. Calc. for $C_{20}H_{16}O_4$: C, 75.0; H, 5.0%) and (8a; R^4 = Me) as prisms (0.25 g), m.p. 208—209 °C [from benzene–light petroleum (b.p. 60—80 °C)], δ($CDCl_3$) 7.45 (1 H, d, J_o 10, 5-H), 7.27 (5 H, s, Ph), 6.80 (1 H, d, $J_{10,9}$ 10, 10-H), 6.72 (1 H, d, J_o 10, 6-H), 5.55 (1 H, d, $J_{9,10}$ 10, 9-H), 3.36 (3 H, s, OMe), and 1.32 [6 H, s, CMe_2). Finally, the methyl ether of (8a; R^4 = H) was identical with a specimen of (8a; R^4 = Me).

Robustin (5b; R^4 = H) *and its Methyl Ether* (5b; R^4 = Me).—*7-Hydroxy-8-iodo-4,5-dimethoxy-3-(3′,4′-methylenedioxyphenyl)coumarin* (3b). *Method I.* *2,4-Dihydroxy-3-iodo-6-methoxy-3′,4′-methylenedioxydeoxybenzoin* (1b). 2,4-Dihydroxy-6-methoxy-3′,4′-methylenedioxydeoxybenzoin [20] (1 g) was dissolved in the minimum amount of

ethanol, and iodine (0.31 g) and periodic acid (0.11 g; in water) were added; the mixture was stirred for 2 h at 60—70 °C. Work-up of the reaction mixture gave compound (1b) as creamish needles (1.1 g), m.p. 158—159 °C (from methanol), δ[$(CD_3)_2SO$] 8.19 (1 H, s, 4-OH), 6.64—6.87 (3 H, m, ABX system of 2′-, 5′-, and 6′-H), 6.22 (1 H, s, 5-H), 5.95 (2 H, s, OCH_2O), 4.22 [2 H, s, $COCH_2 \cdot C_6H_3(O_2CH_2)$], 3.85 (3 H, s, OCH_3), and 13.80 (1 H, s, 2-OH) (Found: C, 44.5; H, 3.2. Calc. for $C_{16}H_{13}IO_6$: C, 44.6; H, 3.0%).

4,7-Dihydroxy-8-iodo-5-methoxy-3-(3′,4′-methylenedioxyphenyl)coumarin (2b). The deoxybenzoin (1b) (3 g) was refluxed for 4 h with ethyl chloroformate (1.9 ml) in dry acetone (75 ml) in the presence of potassium carbonate (6 g). Work-up of the reaction mixture followed by hydrolysis with sodium hydroxide (1N; 75 ml) gave compound (2b) as needles (2.3 g), m.p. 264—265 °C (from methanol) (Found: C, 45.1; H, 2.6. Calc. for $C_{17}H_{11}IO_7$: C, 45.2; H, 2.4%). The dimethyl ether had m.p. 151—152 °C, δ($CDCl_3$) 7.45—7.25 (3 H, m, ABX system of 2′-, 5′-, and 6′-H), 6.65 (1 H, s, 6-H), 5.98 (2 H, s, OCH_2O), and 3.97, 3.85, and 3.52 (each 3 H, each s, 4-, 5-, and 7-OMe).

7-Hydroxy-8-iodo-4,5-dimethoxy-3-(3′,4′-methylenedioxyphenyl)coumarin (3b). The preceding dihydroxycoumarin (2b) (1 g) was refluxed for 6 h in anhydrous acetone (100 ml) with dimethyl sulphate (0.23 ml) in the presence of anhydrous sodium hydrogencarbonate (5 g). Work-up of the reaction mixture [as for compound (3a)] yielded compound (3b) as needles (0.7 g), m.p. 194—195 °C (from methanol) (Found: C, 46.1; H, 2.9. Calc. for $C_{18}H_{13}IO_7$: C, 46.2; H, 2.8%); its methyl ether had m.p. 152—153 °C and was identical (m.p., mixed m.p. and i.r.) with the 8-iodo-4,5,7-trimethoxy-3-(3′,4′-methylenedioxyphenyl)coumarin prepared above.

Method II. *7-Hydroxy-4,5-dimethoxy-3-(3′,4′-methylenedioxyphenyl)coumarin* (6b). 4,7-Dihydroxy-5-methoxy-3-(3′,4′-methylenedioxyphenyl)coumarin [20] (1 g) was refluxed for 6 h with dimethyl sulphate (0.3 ml) in acetone (100 ml) in the presence of sodium hydrogencarbonate (5 g). Work-up of the reaction mixture [as for compound (3a)] gave (6b) as needles (0.8 g), m.p. 221—222 °C (from methanol) (Found: C, 63.2; H, 4.2. $C_{18}H_{14}O_7$ requires C, 63.2; H, 4.1%); its methyl ether, m.p. 185—187 °C, was identical (m.p. and ^1H n.m.r.) with derrusnin [4,5,7-trimethoxy-3-(3′,4′-methylenedioxyphenyl) coumarin] isolated from *Derris robusta* [4] (lit.,[4] m.p. 187 °C).

7-Hydroxy-8-iodo-4,5-dimethoxy-3-(3′,4′-methylenedioxyphenyl)coumarin (3b). The above dihydroxycoumarin (6b) (1 g) was dissolved in the minimum amount of alcohol and iodine (0.33 g) and periodic acid (0.1 g; in water) were added; the mixture was stirred for 2 h at 60—70 °C. Work-up of the reaction mixture gave (3a), m.p. 194—196 °C, identical in all respects with the compound prepared by Method I.

8-Iodo-4,5-dimethoxy-3-(3′4′-methylenedioxyphenyl)-7-(1,1-dimethylprop-2-ynyloxy)coumarin (4b). 7-Hydroxy-8-iodocoumarin (3b) (1 g), 3-chloro-3-methylbut-1-yne (4 ml), anhydrous potassium carbonate (3 g), anhydrous potassium iodide (0.5 g), and anhydrous acetone (100 ml) were refluxed for 30 h. Work-up of the reaction mixture gave (4b) as needles (0.85 g), m.p. 142—144 °C [from benzene–light petroleum (b.p. 60—80 °C)], δ($CDCl_3$) 7.22—7.41 (3 H, m, ABX system of 2′-, 5′-, and 6′-H); 6.75 (1 H, s, 6-H), 5.99 (2 H, s, OCH_2O), 3.94 and 3.51 (each 3 H, each s, 4- and 5-OMe), 2.62 (1 H, s, C:CH), and 1.74 (6 H, s, CMe_2) (Found: C, 51.8; H, 3.8. Calc. for $C_{23}H_{19}IO_7$: C, 51.7; H, 3.6%).

Robustin (5b; R^4 = H) *and its methyl ether* (5b; R^4 = Me). The above prop-2-ynyl ether (4b) (1 g) was refluxed for 6 h in *NN*-dimethylaniline (10 ml). Work-up of the reaction mixture [as for compound (5a)] gave (5b; R^4 = H) as needles (0.45 g), m.p. 204—206 °C (from methanol) (lit.,[4] m.p. 207 °C), δ[$(CD_3)_2CO$] 10.12 (1 H, s, OH), 7.21—6.90 (3 H, m, ABX system of 2′-, 5′-, and 6′-H), 6.60 (1 H, s, 10-H), 6.05 (2 H, s, OCH_2O), 6.62 and 5.82 (1 H, each d, $J_{7,6}$ 10, 6- and 7-H, respectively), 4.05 (3 H, s, OMe), and 1.52 (6 H, s, CMe_2); and (5b; R^4 = Me) as needles (0.12 g) m.p. 208—209 °C (from methanol) (lit.,[4] m.p. 211 °C), δ($CDCl_3$) 7.26—7.10 (3 H, s, ABX system of 2′-, 5′-, and 6′-H), 6.73 (1 H, s, 10-H), 6.0 (2 H, s, OCH_2O), 6.65 and 5.78 (each 1 H, each d, $J_{7,6}$ 10, 6- and 7-H respectively), 3.78 and 3.52 (each 3 H, each s, 4- and 5-OMe), and 1.48 [6 H, s, CMe_2).

4-Hydroxy-5-methoxy-8,8-dimethyl-3-(3′,4′-methylenedioxyphenyl)-2H,8H-benzo[1,2-b:3,4-b′]dipyran-2-one [4,5-*Dimethoxy-3-(3′,4′-methylenedioxyphenyl)sesselin*] (8a; R^4 = H) *and its Methyl Ether* (8b; R^4 = Me).—*4,5-Dimethoxy-3-(3′,4′-methylenedioxyphenyl)-7-(1,1-dimethylprop-2-ynyloxy)coumarin* (7b). 7-Hydroxy-4,5-dimethoxycoumarin (6b) (1 g) was refluxed for 30 h with 3-chloro-3-methylbut-1-yne (4 ml) in anhydrous acetone (100 ml) in the presence of anhydrous potassium carbonate (3 g) and anhydrous potassium iodide (0.5 g). Work-up of the reaction mixture yielded compound (6b), as pale yellow prisms (0.9 g), m.p. 98—99 °C [from benzene–light petroleum (60—80 °C)], δ($CDCl_3$) 7.29—7.08 (3 H, m, ABX system of 2′-, 5′-, and 6′-H), 6.76 and 6.67 (each 1 H, each d, J_m 2.5, 6- and 8-H), 6.01 (2 H, s, OCH_2O), 4.01 and 3.57 (each 3 H, each s, 4- and 5-OMe), 2.58 (1 H, s, C:CH), and 1.72 (6 H, s, CMe_2) (Found: C, 67.5; H, 4.8. Calc. for $C_{23}H_{20}O_7$: C, 67.6; H, 4.9%).

Formation of (8a; R^4 = H) *and* (8b; R^4 = Me). The preceding prop-2-ynyl ether (7b) (1 g) was refluxed for 6 h in *NN*-dimethylaniline (10 ml). Work-up of the reaction mixture [as for compound (5a)] gave compound (8a; R^4 = H) as needles (0.7 g), m.p. 218—220 °C (from methanol), δ[$(CD_3)_2CO$] 10.1 (1 H, s, OH), 7.19—6.83 (3 H, m, ABX system of 2′-, 5′-, and 6′-H), 6.61 (1 H, s, 6-H), 6.08 (2 H, s, OCH_2O), 6.50 and 5.84 (each 1 H, each d, $J_{7,6}$ 10, 10- and 9-H, respectively), 4.03 (3 H, s, OMe), and 1.51 (6 H, s, CMe_2) (Found: C, 67.1; H, 5.0. Calc. for $C_{22}H_{18}O_7$: C, 67.0; H, 4.8%); and (8b; R^4 = Me) as needles (0.20 g), m.p. 207—208 °C (from methanol), δ($CDCl_3$) 7.17—6.87 (3 H, m, ABX system of 2′-, 5′-, and 6′-H); 6.69 (1 H, s, 6-H), 6.00 (2 H, s, OCH_2O), 6.58 and 5.86 (each 1 H, each d, $J_{7,6}$ 10, 10- and 9-H, respectively), 3.88 and 3.51 (each 3 H, each s, 4- and 5-OMe), 1.49 (6 H, s, CMe_2) (Found: C, 67.5; H, 5.1. Calc. for $C_{23}H_{20}O_7$: C, 67.6; H, 4.9%).

Robustic Acid (5c; R^4 = H) *and its Methyl Ether* (5c; R^4 = Me).—*7-Hydroxy-8-iodo-4,5-dimethoxy-3-(4′-methoxyphenyl)coumarin* (3c). *Method I.* *2,4-Dihydroxy-3-iodo-6,4′-dimethoxydeoxybenzoin* (1c).—2,4-Dihydroxy-6,4′-dimethoxydeoxybenzoin [20] (1 g) was dissolved in the minimum amount of ethanol and iodine (0.38 g) and periodic acid (0.11 g; in water) were added; the mixture was then stirred for 2 h at 60—70 °C. Work-up of the reaction mixture gave compound (1c) as creamish needles (1.1 g), m.p. 215—216 °C (from methanol), δ[$(CD_3)_2SO$] 8.10 (1 H, s, 4-OH), 7.12 and 6.85 (each 2 H, J_{AX} 9.5, A_2X_2 system of 2′-, 6′- and 3′-, 5′-H), 6.01 (1 H, s, 5-H), 4.17 (2 H, s, $COCH_2C_6H_4OCH_3$-p), 3.78 (6 H, s, 4- and 6-OMe), and 13.8

(1 H, s, 2-OH) (Found: C, 46.4; H, 3.5. Calc. for $C_{16}H_{15}IO_5$: C, 46.4; H, 3.6%).

4,7-Dihydroxy-8-iodo-5-methoxy-3-(4'-methoxyphenyl)-coumarin (2c). The preceding deoxybenzoin (1c) (3 g) was refluxed for 4 h with ethyl chloroformate (2.0 ml) in anhydrous acetone (100 ml) in the presence of potassium carbonate (5 g). Work-up of the reaction mixture followed by hydrolysis with aqueous sodium hydroxide (1N; 75 ml) gave compound (2c) as needles (2.2 g), m.p. 293—294 °C (from methanol) (Found: C, 46.3; H, 3.1. Calc. for $C_{17}H_{13}IO_6$: C, 46.4; H, 2.9%). The dimethyl ether had m.p. 215—216 °C, δ($CDCl_3$) 7.43 and 7.03 (each 2 H, each d, J 10, A_2X_2 system of 2'-, 6'- and 3'-, 5'-H), 6.42 (1 H, s, 6-H), and 3.94, 3.80, and 3.45 (3 H, 6 H and 3 H respectively, each s, 4-, 5'-, 7-, and 4'-H, OMe).

7-Hydroxy-8-iodo-4,5-dimethoxy-3-(4'-methoxyphenyl)-coumarin (3c). The above dihydroxycoumarin (2c) (1 g) was refluxed for 6 h with dimethyl sulphate (0.24 ml) in dry acetone (100 ml) in the presence of sodium hydrogencarbonate (5 g). Work-up of the reaction mixture [as for compound (3a)] gave compound (3c) as needles (0.7 g), m.p. 212—213 °C (from methanol) (Found: C, 47.7; H, 3.3. Calc. for $C_{18}H_{15}IO_6$: C, 47.6; H, 3.3%); the methyl ether was identical with the 8-iodo-4,5,7-trimethoxy-3-(4'-methoxyphenyl)coumarin prepared above.

Method II. *7-Hydroxy-4,5-dimethoxy-3-(4'-methoxyphenyl)coumarin* (6c). 4,7-Dihydroxy-5-methoxy-3-(4'-methoxyphenyl)coumarin [20] (1 g) was refluxed for 6 h in anhydrous acetone (100 ml) with dimethyl sulphate (0.34 ml) in the presence of sodium hydrogencarbonate (5 g). Work-up of the reaction mixture [as for compound (3a)] gave compound (6c) as needles (0.75 g), m.p. 241—243 °C (from methanol) (Found: C, 65.8; H, 4.8. Calc. for $C_{18}H_{16}O_6$: C, 65.9; H, 4.8%); its methyl ether had m.p. 181—182 °C, δ($CDCl_3$) 7.22 and 6.84 (each 2 H, each d, J_{AX} 10, A_2X_2 system of 2'-, 6'- and 3'-, 5'-H), 6.39 and 6.31 (each 1 H, each d, J_m 2.5, 6- and 8-H), 3.79, 3.74, and 3.43 (6 H, 3 H, and 3 H respectively, each s, 4-, 5-, 7- and 4'-OMe).

7-Hydroxy-8-iodo-4,5-dimethoxy-3-(4'-methoxyphenyl)-coumarin (3c).—The preceding coumarin (6c) (1 g) was dissolved in the minimum amount of ethanol and iodine (0.33 g) and periodic acid (0.1 g; in water) were added; the mixture was then stirred for 6 h at 60—70 °C. Work-up of the reaction mixture gave compound (3c), m.p. 212—213 °C. It was found to be identical in all respects with the compound prepared by method I.

8-Iodo-4,5-dimethoxy-3-(4'-methoxyphenyl)-7-(1,1-dimethylprop-2-ynyloxy)coumarin (4c).—The above 7-hydroxy-8-iodocoumarin (6c) (1 g) was refluxed for 30 h with 3-chloro-3-methylbut-1-yne (4 ml) in anhydrous acetone (100 ml) in the presence of potassium carbonate (3 g) and potassium iodide (0.5 g). Work-up of the reaction mixture gave (4c) as prisms, m.p. 161—162 °C [from benzene–light petroleum (b.p. 60—80 °C)], δ($CDCl_3$) 7.39 and 7.09 (each 2 H, each d, J_{AX} 10, A_2X_2 system of 2'-, 6'- and 3'-, 5'-H), 6.57 (1 H, s, 6-H), 3.95, 3.84, and 3.51 (each 3 H, each s, 4-, 5-, and 4'-MeO), 2.64 (1 H, s, C≡CH), and 1.75 (6 H, s, CMe_2) (Found: C, 53.2; H, 4.2. Calc. for $C_{23}H_{21}IO_6$: C, 53.1; H, 4.0%).

Robustic Acid (5c; R^4 = H) *and its Methyl Ether* (5c; R^4 = Me).—The above prop-2-ynyl ether (4c) (1 g) was refluxed for 6 h in *NN*-dimethylaniline (10 ml). Work-up of the reaction mixture [as for compound (5a)] gave (5c; R^4 = H) as needles (0.40 g), m.p. 207—208 °C (lit.,[14] m.p. 208—210 °C) (from methanol), δ[$(CD_3)_2CO$] 10.01 (1 H, s, OH), 7.53 and 6.98 (each 2 H, each d, J_{AX} 9.5, A_2X_2 system of 2'-, 6'- and 3'-, 5'-H), 6.64 (1 H, s, 10-H), 6.57 and 5.74 (each 1 H, each d, $J_{7,6}$ 10, 6- and 7-H respectively), 3.94 and 3.79 (each 3 H, each s, 5- and 6-OMe), 1.43 [6 H, s, CMe_2); and (5c; R^4 = Me) as needles (0.20 g), m.p. 194—196 °C (lit.,[4] m.p. 195—196 °C, 198—200 °C); δ($CDCl_3$) 7.31 and 6.78 (each 2 H, each d, J_{AX} 9.5, A_2X_2 system of 2'-, 6'- and 3'-, 5'-H), 6.65 (1 H, s, 10-H), 6.57 and 5.71 (each 1 H, each d, $J_{7,6}$ 10, 6- and 7-H respectively), 3.83, 3.79 and 3.53 (each 3 H, each s, 5-, 4-, and 4'-OMe), and 1.43 (6 H, s, CMe_2).

4-Hydroxy-5-methoxy-8,8-dimethyl-3-(4'-methoxyphenyl)-2H,8H-benzo[1,2-b:3,4-b']dipyran-2-one [*4,5-Dimethoxy-3-(4'-methoxyphenyl)sesselin* (8c; R^4 = H)] *and its Methyl Ether* (8c; R^4 = Me).—*4,5-Dimethoxy-3-(4'-methoxyphenyl)-7-(1,1-dimethylprop-2-ynyloxy)coumarin* (7c). 7-Hydroxy-4,5-dimethoxy-3-(4'-methoxyphenyl)coumarin (prepared above) (6c) (1 g) was refluxed for 30 h with 3-chloro-3-methylbut-1-yne (4 ml) in anhydrous acetone (100 ml) in the presence of anhydrous potassium carbonate (3 g) and anhydrous potassium iodide (0.5 g). Work-up of the reaction mixture gave compound (7c) as plates (0.9 g), m.p. 113—114 °C [from benzene–light petroleum (b.p. 60—80 °C)], δ($CDCl_3$) 7.27 and 6.95 (each 2 H, each d, J_{AX} 9.5, A_2X_2 system of 2'-, 6'- and 3'-, 5'-H), 6.61 and 6.58 (each 1 H, each d, J_m 2.5, 6- and 8-H), 4.0, 3.87 and 3.53 (each 3 H, each s, 4-, 5-, and 4'-OMe), 2.61 (1 H, s, C≡CH), and 1.77 (6 H, s, CMe) (Found: C, 70.1; H, 5.7. Calc. for $C_{23}H_{22}O_6$: C, 70.0; H, 5.6%).

Formation of Compounds (8c; R^4 = H *and* Me).—The prop-2-ynyl ether (7c) (1 g) was refluxed for 6 h in *NN*-dimethylaniline (10 ml). Work-up of the reaction mixture as for compound (5a), gave compound (8c; R^4 = H) as needles (0.72 g), m.p. 221—222 °C (lit.,[8] m.p. 220—221 °C) (from methanol), δ[$(CD_3)_2CO$] 10.02 (1 H, s, OH), 7.62 and 7.09 (each 2 H, each d, J_{AX} 9.5, A_2X_2! system of 2'-, 6'- and 3'-, 5'-H), 6.57 (1 H, s, 6-H), 6.63 and 5.68 (each 1 H, each d, $J_{7,8}$ 10, 10- and 9-H, respectively), 3.82 and 3.79 (each 3 H, each s, 4- and 5-OMe), 1.45 (6 H, s, CMe_2) and (8c; R^4 = Me) as needles (0.2 g), m.p. 205—206 °C (from methanol), δ($CDCl_3$) 7.33 and 6.91 (each 2 H, each d, J_{AX} 9.5, A_2X_2 system of 2'-, 6'- and 3'-, 5'-H), 6.40 (1 H, s, 6-H), 6.59 and 5.65 (each 1 H, each d, $J_{9,10}$ 10, 10- and 9-H respectively), 3.80, 3.78, and 3.53 (each 3 H, each s, 4-, 5- and 4'-OMe), 1.45 (6 H, s, CMe_2) (Found: C, 69.9; H, 5.7. Calc. for $C_{23}H_{22}O_6$: C, 70.0; H, 5.6%).

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