A Facile Synthesis of Isopongaflavone, Atalantoflavone Dimethylether, Racemoflavone Dimethylether and their Analogues

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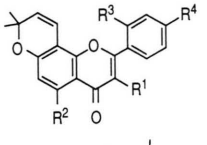
2-Aryl-8,8-dimethyl-6,7-dihydro-4H,8H-benzo[1,2-b:5,4-b']dipyran-4-ones,
2-Aryl-9-methoxy-6,6-dimethyl-7,8-dihydro-4H,6H-benzo[1,2-b:3,4-b']dipyran-4-ones,
2-Aryl-5-methoxy-8,8-dimethyl-9,10-dihydro-4H,8H-benzo[1,2-b:3,4-b']dipyran-4-ones,
Natural Pyranoflavones

A convenient route to pyranoflavones (natural and synthetic) from acetyl hydroxy chromans *via* the corresponding dihydro analogues by the use of Claisen condensation in the key step is reported.

Flavones possessing prenyl substituents occur quite frequently in nature, so do those with 2,2-dimethylpyran ring system [1, 2]. Many of such pyranoflavones exhibit interesting biological activities. A health food, designed to prevent diseases, consisted of extracts of *Morbus bombycis* or related plants (containing morusin (**1**) and/or its hydrate) [3]. Isopongaflavone (**2**) – otherwise known as candidin [4] – was very much active against *Maruca testualis* and *Eldana saccharina* and hence was effective as an antifeedant [5]. Atalantoflavone dimethylether (**3**) displayed significant insecticidal activity [6].



1 R^1 =  , $R^2 = R^3 = R^4 = OH$

2 $R^1 = R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$

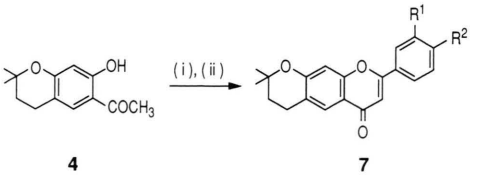
3 $R^1 = R^3 = H$, $R^2 = R^4 = OCH_3$

In many of the reported procedures, the starting point was the simple flavone moiety on which the pyrano ring was fashioned. Later Banerji and Goomer [7] and Prasad *et al.* [8] constructed the titled system from chromenes and chromans respectively. Our approach was intended to prepare such compounds starting with the chroman part.

We wish to report here a convenient method for the construction of pyranoflavones with Claisen condensation [9] as a tool. Hansley [10, 11] had shown that sodium hydride which is available commercially produced better yields than other common reagents like sodium ethoxide, sodium *etc.*, in acylations of certain ketones. Sodium hydride produced fewer side reaction products, when compared to sodium amide which was regarded as one of the best reagents for the purpose [12]. Due to these advantages, sodium hydride was chosen as the base for our condensation.

In the Claisen condensation method, 6-acetyl-7-hydroxy-2,2-dimethylchroman (**4**) [13] was condensed with ethyl 3,4-dimethoxybenzoate in the presence of sodium hydride in ether as a solvent. This was followed by acid-catalysed cyclisation *in situ* to give a single product as evidenced by TLC. Its IR absorption spectrum revealed a band at 1630 cm^{-1} indicating the presence of an α,β-unsaturated carbonyl function. Based on the PMR, mass and elemental analysis data (Tables I and II), the structure of 2-(3',4'-dimethoxyphenyl)-8,8-dimethyl-6,7-dihydro-4H,8H-benzo[1,2-b:5,4-b']dipyran-4-one (**7c**) was assigned for the product. This structure was further attested by the ^{13}C NMR data (Table II).

When the acetyl hydroxy chroman **4** was treated with ethyl benzoate, ethyl 4-methoxybenzoate and



4 **7**

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Table I. Elemental analysis, mass and IR spectral data of compound **7–16.**

Compound	Overall yield (%)	M.p. (°C)[a] (Lit. m.p.)	Molecular formula[b]	Mass M^+ (*m/e*)	IR(KBr) ν (cm^{-1})
7a	55	145–46 (145–46 [15])	$C_{20}H_{18}O_3$ (306.36)	306	1635
7b	54	160–61 (161–62 [8])	$C_{21}H_{20}O_4$ (336.39)	336	1630
7c	57	165–66	$C_{22}H_{22}O_5$ (366.42)	366	1630
7d	60	222–23 (222–23 [8])	$C_{21}H_{18}O_5$ (350.37)	350	1640
8a	51	206–7	$C_{21}H_{20}O_4$ (336.39)	336	1635
8b	55	203–4 (203–4 [8])	$C_{22}H_{22}O_5$ (366.42)	366	1640
8c	58	210–12	$C_{23}H_{24}O_6$ (396.44)	396	1630
8d	55	222–23 (222–23 [8])	$C_{22}H_{20}O_6$ (380.40)	380	1630
9a	59	205–6	$C_{21}H_{20}O_4$ (336.39)	336	1640
9b	56	219–20	$C_{22}H_{22}O_5$ (366.42)	366	1635
9c	55	255–56	$C_{23}H_{24}O_6$ (396.44)	396	1630
9d	57	279–80	$C_{22}H_{20}O_6$ (380.40)	380	1635
10	68	154–55 (156 [16]) (150–51 [15])	$C_{20}H_{16}O_3$ (304.35)	304	1660
11	65	168–70	$C_{21}H_{18}O_4$ (334.38)	334	1650
12	67	211–12	$C_{21}H_{16}O_5$ (348.36)	348	1660
13	63	205–6	$C_{22}H_{20}O_5$ (364.40)	364	1665
14	65	224–25	$C_{22}H_{18}O_6$ (378.39)	378	1665
2	66	213–14 (215–16 [17, 18] 204–5 [19])	$C_{21}H_{18}O_4$ (334.38)	334	1650
3	63	208–9 (207–9 [20])	$C_{22}H_{20}O_5$ (364.40)	364	1660
15	68	194–95 (194–96 [20])	$C_{23}H_{22}O_6$ (394.43)	394	1660
16	61	240–41 (242–44 [17, 21])	$C_{22}H_{18}O_6$ (378.39)	378	1655

[a] Uncorrected, measured using mettler FP5 apparatus and a Boetius microheating table; [b] satisfactory microanalyses obtained: C ± 0.23, H ± 0.11.

Table II. PMR spectral data of newly derived dihydropyranoflavones.

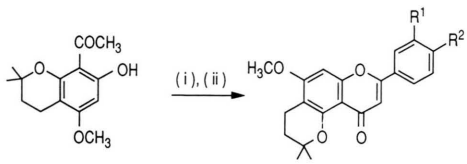
Compound	$C(CH_3)_2$ (s)	Methylene protons (2t, J = 7 Hz)	H-3 (s)	Aromatic protons (J in Hz)	Other protons
7c*	1.40	1.88, 2.90	6.64	6.90 (s, 1H, H-10), 7.30 (m, 3H, H-2′, H-5′ and H-6′), 7.90 (s, 1H, H-5)	3.96 (s, 6H, 3′-OCH_3 and 4′-OCH_3)
8a	1.44	1.83, 2.66	6.65	6.50 (s, 1H, H-10), 7.49 (m, 3H, H-3′, H-4′ and H-5′), 7.88 (m, 2H, H-2′ and H-6′)	3.93 (s, 3H, 9-OCH_3)
8c*	1.40	1.78, 2.60	6.40	6.38 (s, 1H, H-10), 6.82 (d, 1H, H-5′, J = 10), 7.24 (s, 1H, H-2′), 7.40 (d, 1H, H-6, J = 10)	3.88 (s, 9H, 9-OCH_3, 3′-OCH_3 and 4′-OCH_3)
9a*	1.43	1.94, 2.97	6.73	6.33 (s, 1H, H-6), 7.53 (m, 3H, H-3′, H-4′ and H-5′), 7.90 (m, 2H, H-2′ and H-6′)	3.95 (s, 3H, 5-OCH_3)
9b	1.35	1.85, 2.90	6.54	6.23 (s, 1H, H-6), 6.93 (d, 2H, H-3′ and H-5′, J = 9), 7.75 (d, 2H, H-2′ and H-6′, J = 9)	3.82, 3.88 (2s, 6H, 5-OCH_3 and 4′-OCH_3)
9c	1.30	1.80, 2.82	6.50	6.20 (s, 1H, H-6), 6.85 (d, 1H, H-5′, J = 10), 7.25 (s, 1H, H-2′), 7.40 (d, 1H, H-6′, J = 10)	3.85 (s, 9H, 5-OCH_3, 3′-OCH_3 and 4′-OCH_3)
9d	1.50	1.93, 2.95	6.60	6.35 (s, 1H, H-6), 6.90 (d, 1H, H-5′, J = 10) 7.35 (s, 1H, H-2′), 7.50 (d, 1H, H-6′, J = 10)	3.95 (s, 3H, 5-OCH_3), 6.10 (s, 2H, OCH_2O)

* ^{13}C NMR spectral data

7c δ 22.434 (C-6), 27.353 (8-$(CH_3)_2$), 32.849 (C-7), 56.400 and 56.452 (2×-OCH_3), 76.387 (C-8), 104.751 (C-5a), 106.306 (C-3), 109.085 (C-5′), 111.501 (C-2′), 117.472 (C-4a), 120.115 (C-6′), 120.568 (C-10), 124.967 (C-1′), 126.615 (C-5), 149.571 (C-3′), 152.169 (C-4′), 156.500 (C-2), 159.608 (C-10a), 163.263 (C-9a) and 178.465 (C_4 = 0) ppm.

8c δ 16.644 (C-8), 26.018 (6-$(CH_3)_2$), 30.833 (C-7), 55.329, 55.555, 55.644 (9-OCH_3, 3′-OCH_3, and 4′-OCH_3), 74.928 (C-6), 89.838 (C-10), 106.239 (C-3), 107.600 (C-2′), 108.085 (C-5′), 108.663 (C-4a), 110.526 (C-8a), 118.893 (C-6′), 123.955 (C-1′), 148.643 (C-3′), 150.940 (C-4′), 154.271 (C-2), 157.603 (C-4b), 159.608 (C-10a), 160.805 (C-9) and 177.042 (C_4 = 0) ppm.

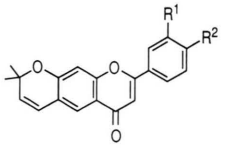
9a δ 16.686 (C-10), 26.639 (8-$(CH_3)_2$), 31.873 (C-9), 56.259 (-OCH_3), 75.993 (C-8), 96.982 (C-6), 101.380 (C-4a), 108.833 (C-3 and C-10a), 125.781 (C-2′ and C-6′), 128.951 (C-3′ and C-5′), 131.071 (C-4′), 131.824 (C-1′), 159.300 (C-2), 159.625 (C-6a), 159.996 (C-5, C-10b) and 177.947 (C_4 = 0) ppm.



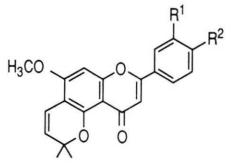
ethyl 3,4-methylenedioxybenzoate, under identical conditions, the dihydropyranoflavones **7a, 7b** and **7d** respectively were formed. Similarly derived were the dihydropyranoflavones **8a–d** and **9a–d** from the condensation of the acetyl chromans **5** and **6** respectively with suitable aryl esters. It is worth to mention here that the present method of synthesizing the dihydro analogues of pyranoflavones is superior to the one involving Baker-Venkataraman method [8], because in the former considerable yield is obtained with lesser number of steps.

The dihydropyranoflavone **7b** on dehydrogenation with DDQ in dioxan yielded the pyranoflavone **11**; spectral studies being the supportive evi-

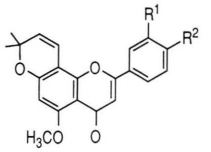
dences. The olefinic protons on C-6 and C-7 of **11** appeared as a clear AB system in the PMR, each with a coupling constant of 10 Hz, characteristic of the *'cis'* protons on olefinic carbon atoms. The 'benzalic' protons – appeared substantially downfield at δ 6.48 and the other olefinic proton at δ 5.86 ppm. These signals are calculated to appear at δ 6.50 and 5.60 ppm respectively by the rule of additivity of olefinic protons [14].



10 $R^1 = R^2 = H$
11 $R^1 = H$, $R^2 = OCH_3$
12 $R^1, R^2 = OCH_2O$



13 $R^1 = H$, $R^2 = OCH_3$
14 $R^1, R^2 = OCH_2O$



2 $R^1 = R^2 = H$
3 $R^1 = H$, $R^2 = OCH_3$
15 $R^1 = R^2 = OCH_3$
16 $R^1, R^2 = OCH_2O$

The dihydropyranoflavones **9a, 9b, 9c** and **9d** were similarly transformed to the natural pyranoflavones, namely, isopongaflavone (**2**), atalantoflavone dimethylether (**3**), racemoflavone dimethylether (**15**) and 2-(3′,4′-methylenedioxyphenyl)-5-methoxy-8,8-dimethyl-4H,8H-benzo[1,2-b:3,4-b′]dipyran-4-one (**16**). The analogous pyranoflavones **10, 12, 13** and **14** were derived similarly.

Experimental

Synthesis of dihydropyranoflavones by Claisen condensation method. General procedure

The acetyl hydroxy chroman (2 mmol) in ether (15 ml) was added in portions to a stirred mixture

Table III. PMR data of the pyranoflavones.

Compound	$C(CH_3)_2$ (s)	Olefinic protons (d, J = 10, 11 Hz)	H-3 (s)	Aromatic protons (J in Hz)	Other protons
10	1.50	5.74, 6.46	6.76	6.89 (s, 1H, H-10), 7.51 (m, 3H, H-3′, H-4′ and H-5′), 7.88 (m, 3H, H-2′, H-6′ and H-5)	–
11	1.46	5.86, 6.48	6.70	6.78 (s, 1H, H-10), 7.06 (d, 2H, H-3′ and H-5′, J = 9), 7.88 (d, 2H, H-2′, and H-6′, J = 9), 8.28 (s, 1H, H-5)	3.98 (s, 3H, 4′-OCH_3)
12	1.44	5.84, 6.54	6.62	6.88 (s, 1H, H-10), 7.44 (d, 1H, H-5′, J = 9), 7.52 (s, 1H, H-2′), 7.88 (d, 1H, H-6′, J = 9), 8.08 (s, 1H, H-5)	6.08 (s, 2H, OCH_2O)
13	1.42	5.56, 6.64	6.48	6.38 (s, 1H, H-10), 6.96 (d, 2H, H-3′ and H-5′ J = 9), 7.72 (d, 2H, H-2′ and H-6′, J = 9)	3.88, 3.96 (2s, 6H, 4′-OCH_3 and 9-OCH_3)
14	1.45	5.62, 6.80	6.40	6.52 (s, 1H, H-10), 6.80 (d, 1H, H-5′, J = 9), 7.55 (s, 1H, H-2′), 7.84 (d, 1H, H-6′, J = 9)	3.98 (s, 3H, 9-OCH_3), 6.03 (s, 2H, OCH_2O)
2	1.56	5.70, 7.00	6.45	6.85 (s, 1H, H-6), 7.60 (m, 3H, H-3′, H-4′ and H-5′), 8.30 (m, 2H, H-2′ and H-6′)	4.00 (s, 3H, 5-OCH_3)
3	1.50	5.62, 6.84	6.58	6.32 (s, 1H, H-6), 7.01 (d, 2H, H-3′ and H-5′, J = 9), 7.81 (d, 2H, H-2′ and H-6′, J = 9)	3.88 and 3.95 (2s, 6H, 4′-OCH_3 and 5-OCH_3)
15	1.52	5.63, 6.83	6.60	6.34 (s, 1H, H-6), 6.98 (d, 1H, H-5′, J = 9), 7.32 (s, 1H, H-2′), 7.51 (d, 1H, H-6′, J = 9)	3.97, 3.98 (2s, 9H, 3′-OCH_3, 4′-OCH_3, 5-OCH_3)
16	1.55	5.60, 6.80	6.50	6.25 (s, 1H, H-6), 7.25 (m, 3H, arom)	3.95 (s, 3H, 5-OCH_3), 6.05 (s, 2H, OCH_2O)

of sodium hydride (2.0 g 50% dispersion in mineral oil), dry ether (10 ml) and the ester (4 mmol). The temperature was maintained at 40–50 °C during the addition. A drop of absolute ethanol was added to start the reaction. Stirring was continued at room temperature for 20 h after which the contents were poured onto crushed ice, neutralised with glacial acetic acid, and extracted with chloroform. The dried extract was concentrated and the residue refluxed for 2 h in absolute ethanol (20 ml) containing a few drops of concentrated sulfuric acid. The excess ethanol was then removed and the residue was poured onto crushed ice with stirring. The product was taken as chloroform extract, dried and evaporated to give a crude product which was purified by passing through a column of silica gel and eluting with ethyl acetate-pet ether (1 : 4) mixture.

Dehydrogenation of dihydropyranoflavones
General procedure

A solution of the dihydropyranoflavone (1 mmol) in dioxan (20 ml) containing DDQ (1 mmol) was refluxed on an oil bath for 5 h, cooled and filtered to remove the hydroquinone. After stripping off the solvent, the residue obtained was purified by column chromatography over silica gel. The pyranoflavones resulted by eluting with ethyl acetate-pet ether (3 : 17) mixture. The analytical data of the pyranoflavones thus derived are tabulated (Table I and III).

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