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# FURO[2,3-*h*]CHROMONES AND PYRANO[2′,3′:5,6]CHROMENO [4,3-*b*]PYRIDINES BASED ON NATURAL ISOFLAVONES

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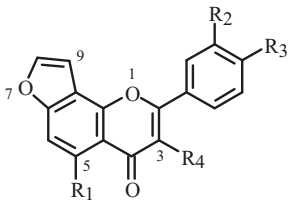
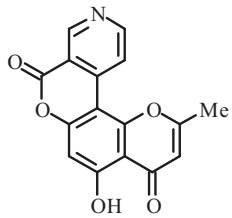
*Furo[2,3-*h*]chromone and pyrano[2′,3′:5,6]chromeno[4,3-*b*]pyridine derivatives were synthesized from 7-hydroxy-8-formylisoflavones, which were prepared from natural isoflavones using a Duff reaction, via reactions with bromoacetophenones and ethyl 3-aminocrotonate, respectively.*

**Keywords:** 7-hydroxy-8-formylisoflavones, furo[2,3-*h*]chromones, pyrano[2′,3′:5,6]chromeno[4,3-*b*]pyridines.

Angular hetarenochromones provide a template for a broad spectrum of natural flavonoids and a few alkaloids. Furo[2,3-*h*]flavones **1a**–**d** were isolated from plants of the genus *Pongamia* (Fabaceae) and possessed antibacterial, antifungal, and cytotoxic activity [1, 2]. Pyridine alkaloids were represented by schumanniophytine (**2**) from plants of the genus *Schumanniophyton* [3].




**1a - d**




**2**

**a:** $R_1 = R_2 = R_3 = R_4 = H$ (lanceolatin B)
**b:** $R_1 = OH$, $R_2 = R_3 = R_4 = H$ (pongaglabol)
**c:** $R_1 = R_4 = H$, $R_2 + R_3 = -O-CH_2-O-$ (pongaglabrone)
**d:** $R_1 = R_2 = R_3 = H$, $R_4 = OMe$ (karanjin)

Two reported approaches to the synthesis of chromones annelated by heterocycles at the C(7)–C(8) bond involve annelation of a heterocycle to a chromone core and annelation of a γ-pyrone ring to a benzohetarene [4]. 7-Hydroxy-8-formylchromones are convenient synthons for synthesizing angular hetarenochromones by the first approach [5]. Previously, 8-formylformononetin (**3a**) was used by us to synthesize α-pyrono[2,3-*f*]isoflavones [6].

The goal of the present work was to annelate furan and α-pyronopyridine rings to natural isoflavone cores. The starting materials were 8-formylformononetin (**3a**) and 7-hydroxy-8-formylisoflavone (**3b**) and its 2-methyl derivative (**3c**), which were prepared by a Duff reaction from natural isoflavones **4b** (isolated from *Echinops echinatus* [7]) and **4c** (from roots of *Glycyrrhiza glabra* [8]).

The Hantzsch reaction was a convenient one-step method for annelation of α-pyrone and pyridine rings to a chromone [9]. Use of this reaction of 7-hydroxy-8-formylisoflavones **3a**–**c** and ethyl 3-aminocrotonate in AcOH afforded 5*H*,9*H*-pyrano[2′,3′:5,6]chromeno[4,3-*b*]pyridine-5,9-diones **5a**–**c**. Their IR spectra showed strong bands at 1742–1723 $cm^{-1}$ that were characteristic of ethoxycarbonyl and α-pyrone C=O stretching vibrations and bands at 1653–1644 $cm^{-1}$ that corresponded to γ-pyrone. PMR spectra of **5a**–**c** were characterized by two methyl singlets at 2.69–2.72 ppm and $CO_2Et$

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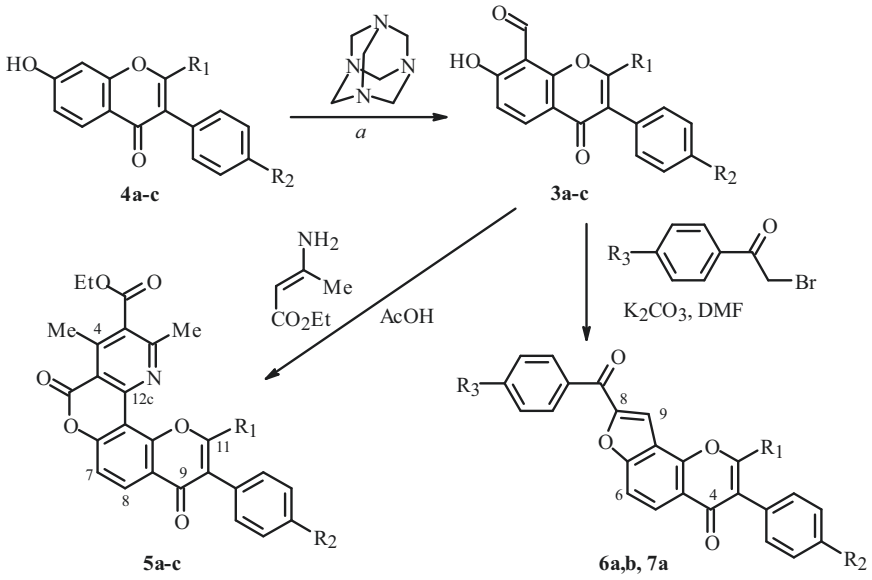
proton resonances and were missing weak-field singlets at 10.5 and 12.2 ppm for CHO and OH protons of starting 7-hydroxy-8-formylisoflavones **3a**–**c**. The structures of **5a**–**c** differed from those of the classical Hantzsch reaction by the position of the Py N atom. The proposed mechanism of the transformation [9] included attack of the 7-hydroxy-8-formylchromone formyls at the *N*-nucleophilic center of aminocrotonate to form Schiff bases that then added a second aminocrotonate molecule whereas *ortho*-unsubstituted benzaldehydes were attacked by the aminocrotonate *C*-nucleophilic center [10]. X-ray structure studies confirmed that type **5** compounds and not the isomers with the schumanniophytine skeleton formed [11]. The yields of **5a** and **5b**, which were unsubstituted in the 11-position, were much less (18–23%) than those of 11-methyl derivative **5c** (56%) and other previously reported 11-methyl-5*H*,9*H*-pyrano[2′,3′:5,6]chromeno[4,3-*b*]pyridine-5,9-diones [9, 11] regardless of the heating and stirring time (up to 20 h).




**3a–7a:** $R_1$ = H, $R_2$ = OMe, **7a:** $R_3$ = $NO_2$; **3b–6b:** $R_1$ = $R_2$ = H; **6a,b:** $R_3$ = OMe; **3c–5c:** $R_1$ = Me, $R_2$ = H
*a*. 1. AcOH, 100°C, 6–8 h; 2. HCl, $H_2O$

Previously, a furan ring was annelated to the chromone core of 7-hydroxy-8-formylisoflavones using bromoacetic [12] or bromomalonic ester [13–16]. Condensation of 8-benzoyl-7-hydroxy-2-methylchromone with various *para*-substituted phenacylbromides in $Me_2CO$ in the presence of potash synthesized 8-benzoyl-2-methyl-9-phenylfuro[2,3-*h*]chromones [17]. We adapted this method to the synthesis of 8-benzoylfuro[2,3-*h*]isoflavones **6a**, **6b**, and **7a**. Reaction of 7-hydroxy-8-formylisoflavones **3a** and **3b** and 4-methoxy- or 4-nitrobromoacetophenones with a two-fold excess of potash with heating in DMF gave high yields (78–93%) of **6a**, **6b**, and **7a**. PMR spectra of these compounds in the aromatic region showed characteristic doublets for protons of a *para*-substituted phenyl and a singlet for 9-H at 7.94–7.96 ppm (**6a** and **6b**) and 8.10 ppm (**7a**). IR spectra contained benzoyl and γ-pyrone C=O stretching bands at 1645 and 1631 $cm^{-1}$, respectively.

Thus, 7-hydroxy-8-formylisoflavones, which were prepared by Duff reactions of natural isoflavones, were used to synthesize furo[2,3-*h*]chromone and pyrano[2′,3′:5,6]chromeno[4,3-*b*]pyridine derivatives.

## EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck 60 $F_{254}$ plates using $CHCl_3$–MeOH (9:1). Melting points were measured on a Kofler apparatus. PMR spectra were recorded in DMSO-$d_6$–$CCl_4$ (1:1) with TMS internal standard; $^{13}C$ NMR spectra, in DMSO-$d_6$ and $CF_3CO_2D$ on a Varian Mercury-400 spectrometer. Elemental analyses were obtained using a Vario micro Cube analyzer and agreed with those calculated. Compound **3a** was prepared and characterized by us earlier [6].

**7-Hydroxy-4-oxo-3-phenyl-4*H*-8-chromenecarbaldehyde (3b).** $C_{16}H_{10}O_4$, prepared analogously to **3a**, yield 69%, mp 194–195°C (lit. [13]: mp 197–198°C). IR spectrum (KBr, ν, $cm^{-1}$): 3423 (OH), 1639 (C=O). $^1H$ NMR spectrum (δ, ppm, J/Hz): 7.06 (1H, d, J = 9.2, H-6), 7.36–7.54 (3H, m, H-3′, 4′, 5′), 7.56 (2H, d, J = 9.2, H-2′, 6′), 8.29 (1H, d, J = 9.2, H-5), 8.38 (1H, s, H-2), 10.55 (1H, s, CHO), 12.26 (1H, s, OH). $^{13}C$ NMR spectrum (DMSO-$d_6$–$CCl_4$, δ, ppm): 109.67, 116.44, 123.49, 125.61, 128.47, 128.59, 129.30, 131.85, 134.79, 153.44, 161.70, 167.02, 173.94, 191.42.

**7-Hydroxy-2-methyl-4-oxo-3-phenyl-4*H*-8-chromenecarbaldehyde (3c).** $C_{17}H_{12}O_4$, prepared analogously to **3a**, yield 69%, mp 165–166°C (lit. [12]: mp 164–165°C). IR spectrum (KBr, ν, $cm^{-1}$): 3417 (OH), 1634 (C=O). $^1H$ NMR spectrum (δ, ppm, J/Hz): 2.35 (3H, s, $CH_3$), 7.01 (1H, d, J = 9.2, H-6), 7.24 (2H, d, J = 7.2, H-2′, 6′), 7.35–7.44 (3H, m, H-3′, 4′, 5′), 8.17 (1H, d, J = 9.2, H-5), 10.56 (1H, s, CHO), 12.23 (1H, s, OH). $^{13}C$ NMR spectrum (DMSO-$d_6$, δ, ppm): 19.34, 109.92, 115.98, 116.18, 123.66, 128.34, 128.77, 131.08, 133.28, 134.17, 157.10, 163.41, 166.30, 174.61, 191.09.

**Ethyl 10-Aryl-2,4-dimethyl-5,9-dioxo-5*H*,9*H*-pyrano[2′,3′:5,6]chromeno[4,3-*b*]pyridine-3-carboxylates (5a–c) (general method).** A solution of **3a–c** (1 mmol) in AcOH (5 mL) was treated with ethyl 3-aminocrotonate (0.52 g, 4 mmol) and stirred vigorously with heating for 18–20 h. The resulting precipitate was filtered off and rinsed with alcohol.

**Ethyl 2,4-Dimethyl-5,9-dioxo-10-(4-methoxyphenyl)-5*H*,9*H*-pyrano[2′,3′:5,6]chromeno[4,3-*b*]pyridine-3-carboxylate (5a).** $C_{27}H_{21}NO_7$, yield 0.11 g (23%), mp 177–178°C. IR spectrum (KBr, ν, $cm^{-1}$): 1723 ($C=O_{ester+\alpha}$), 1645 ($C=O_\gamma$). $^1H$ NMR spectrum (δ, ppm, J/Hz): 1.44 (3H, t, J = 7.2, $\underline{CH_3}CH_2CO_2$-3), 2.69 (3H, s, $CH_3$-2), 2.71 (3H, s, $CH_3$-4), 3.84 (3H, s, $CH_3O$), 4.47 (2H, q, J = 7.2, $CH_3\underline{CH_2}CO_2$-3), 6.96 (2H, d, J = 8.0, H-3′, 5′), 7.42 (1H, d, J = 8.8, H-7), 7.56 (2H, d, J = 8.0, H-2′, 6′), 8.36 (1H, d, J = 8.8, H-8), 8.44 (1H, s, H-11). $^{13}C$ NMR spectrum (DMSO-$d_6$, δ, ppm): 14.59, 19.74, 24.21, 62.71, 108.34, 114.40, 115.37, 121.62, 124.65, 128.70, 128.82, 129.73, 131.27, 131.88, 148.92, 151.61, 154.02, 155.02, 156.39, 158.55, 159.80, 167.55, 174.37.

**Ethyl 2,4-Dimethyl-5,9-dioxo-10-phenyl-5*H*,9*H*-pyrano[2′,3′:5,6]chromeno[4,3-*b*]pyridine-3-carboxylate (5b).** $C_{26}H_{19}NO_6$, yield 0.08 g (18%), mp 217–218°C. IR spectrum (KBr, ν, $cm^{-1}$): 1742 ($C=O_{ester}$), 1734 ($C=O_\alpha$), 1653 ($C=O_\gamma$). $^1H$ NMR spectrum (δ, ppm, J/Hz): 1.43 (3H, t, J = 7.2, $\underline{CH_3}CH_2CO_2$-3), 2.70 (3H, s, $CH_3$-2), 2.72 (3H, s, $CH_3$-4), 4.47 (2H, q, J = 7.2, $CH_3\underline{CH_2}CO_2$-3), 7.39–7.47 (4H, m, H-7, 3′, 4′, 5′), 7.64 (2H, d, J = 6.8, H-2′, 6′), 8.40 (1H, d, J = 8.0, H-8), 8.54 (1H, s, H-11). $^{13}C$ NMR spectrum (DMSO-$d_6$, δ, ppm): 14.59, 19.74, 24.21, 62.71, 108.34, 114.40, 115.37, 121.62, 124.65, 128.70, 128.82, 129.73, 131.27, 131.88, 148.92, 151.61, 154.02, 155.02, 156.39, 158.55, 159.80, 167.55, 174.37.

**Ethyl 2,4,11-Trimethyl-5,9-dioxo-10-phenyl-5*H*,9*H*-pyrano[2′,3′:5,6]chromeno[4,3-*b*]pyridine-3-carboxylate (5c).** $C_{27}H_{21}NO_6$, yield 0.26 g (56%), mp 246–247°C. IR spectrum (KBr, ν, $cm^{-1}$): 1723 ($C=O_{ester+\alpha}$), 1645 ($C=O_\gamma$). $^1H$ NMR spectrum (δ, ppm, J/Hz): 1.44 (3H, t, J = 7.2, $\underline{CH_3}CH_2CO_2$-3), 2.45 (3H, s, $CH_3$-11), 2.68 (3H, s, $CH_3$-2), 2.72 (3H, s, $CH_3$-4), 4.47 (2H, q, J = 7.2, $CH_3\underline{CH_2}CO_2$-3), 7.39–7.47 (4H, m, H-7, 3′, 4′, 5′), 7.64 (2H, d, J = 6.8, H-2′, 6′), 8.40 (1H, d, J = 8.0, H-8), 8.54 (1H, s, H-11). $^{13}C$ NMR spectrum (DMSO-$d_6$ + $CCl_4$, δ, ppm): 14.61, 19.69, 19.73, 24.16, 62.50, 107.96, 114.34, 114.74, 120.75, 123.74, 128.26, 128.71, 129.91, 130.98, 131.29, 133.05, 149.14, 151.74, 153.75, 156.37, 158.34, 159.82, 164.06, 167.37, 174.76.

**3-Aryl-8-(4-$R^3$-benzoyl)-4*H*-furo[2,3-*h*]chromen-4-ones (6a, 6b, 7a) (general method).** A solution of **3a** or **3b** (1 mmol) and 4-methoxy- or 4-nitrobromoacetophenone (1 mmol) in DMF (5 mL) was treated with $K_2CO_3$ (0.28 g, 2 mmol), stirred vigorously with heating for 20 h, cooled, diluted with $H_2O$, and neutralized with HCl. The precipitate was filtered off and recrystallized from DMF.

**8-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-4*H*-furo[2,3-*h*]chromen-4-one (6a).** $C_{26}H_{18}O_6$, yield 0.40 g (93%), mp 241–242°C (DMF). IR spectrum (KBr, ν, $cm^{-1}$): 1645 (C=O), 1631 ($C=O_\gamma$). $^1H$ NMR spectrum (δ, ppm, J/Hz): 3.68 (3H, s, $CH_3O$-4′), 3.93 (3H, s, $CH_3O$-4″), 6.97 (2H, d, J = 8.0, H-3′, 5′), 7.10 (2H, d, J = 8.0, H-3″, 5″), 7.54 (2H, d, J = 8.0, H-2′, 6′), 7.79 (1H, d, J = 8.8, H-6), 7.94 (1H, s, H-9), 8.10 (2H, d, J = 8.0, H-2″, 6″), 8.28 (1H, d, J = 8.8, H-5), 8.45 (1H, s, H-2). $^{13}C$ NMR spectrum ($CF_3CO_2D$, δ, ppm): 57.14, 57.40, 115.00, 116.63, 117.14, 119.40, 120.29, 124.77, 124.82, 128.07, 128.41, 130.06, 133.27, 135.13, 155.06, 155.69, 159.21, 161.38, 162.61, 167.42, 181.36, 187.92.

**8-(4-Methoxybenzoyl)-3-phenyl-4*H*-furo[2,3-*h*]chromen-4-one (6b).** $C_{25}H_{16}O_5$, yield 0.31 g (78%), mp 248–249°C (DMF). IR spectrum (KBr, ν, $cm^{-1}$): 1645 (C=O), 1631 ($C=O_\gamma$). $^1H$ NMR spectrum (δ, ppm, J/Hz): 3.93 (3H, s, $CH_3O$), 7.10 (2H, d, J = 8.0, H-3″, 5″), 7.44–7.59 (3H, m, H-3′, 4′, 5′), 7.59 (2H, d, J = 8.0, H-2′, 6′), 7.81 (1H, d, J = 8.8, H-6), 7.96 (1H, s, H-9), 8.11 (2H, d, J = 8.0, H-2″, 6″), 8.29 (1H, d, J = 8.8, H-5), 8.51 (1H, s, H-2). $^{13}C$ NMR spectrum ($CF_3CO_2D$, δ, ppm): 57.14, 115.18, 117.10, 119.39, 120.25, 128.35, 128.67, 130.01, 131.17, 131.45, 131.94, 135.13, 155.07, 155.70, 159.47, 162.60, 167.46, 181.13, 187.79.

**3-(4-Methoxyphenyl)-8-(4-nitrobenzoyl)-4*H*-furo[2,3-*h*]chromen-4-one (7a).** $C_{25}H_{15}NO_7$, yield 0.38 g (86%), mp 287–288°C (DMF). IR spectrum (KBr, ν, $cm^{-1}$): 1645 (C=O), 1631 ($C=O_\gamma$).$^1H$ NMR spectrum (δ, ppm, J/Hz): 3.85 (3H, s, $CH_3O$), 6.98 (2H, d, J = 6.8, H-3′, 5′), 7.56 (2H, d, J = 6.8, H-2′, 6′), 7.80 (1H, d, J = 8.4, H-6), 8.10 (1H, s, H-9), 8.32–8.43 (6H, m, H-2″, 3″, 5″, 6″, 5, 2). $^{13}C$ NMR spectrum ($CF_3CO_2D$, δ, ppm): 57.19, 114.59, 116.82, 118.23, 119.07, 119.18, 124.74, 125.92, 126.53, 128.22, 129.22, 132.61, 132.93, 142.70, 152.61, 155.55, 158.88, 161.17, 169.67, 181.31, 187.16.

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