Synthesis and Structure Elucidation of 3,4-Dihydroxy-2-quinolin-2-ylpyrido[3,2,1-*jk*]carbazol-6-ones

Hoai V. Dang, Nargues S. Habib, Thomas Kappe, Klaus Zangger and Wolfgang Stadlbauer*

Department of Chemistry, Organic and Bioorganic Chemistry, Karl-Franzens University of Graz
Heinrichstrasse 28, A-8010 Graz, Austria/Europe
wolfgang.stadlbauer@uni-graz.at

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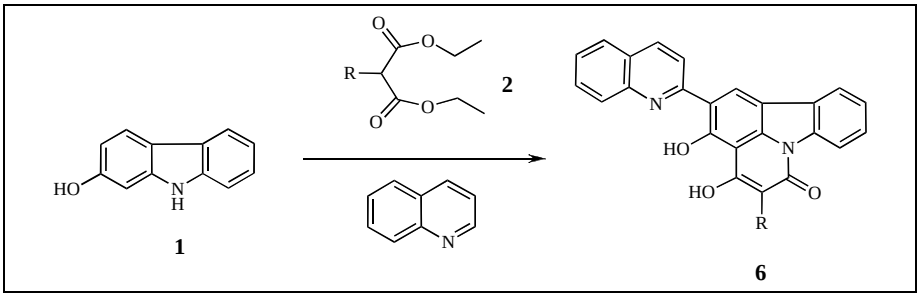

3,4-Dihydroxy-2-quinolin-2-ylpyrido[3,2,1-*jk*]carbazol-6-ones **6** were obtained by cyclocondensation of carbazole **1** with malonates **2** in the presence of quinoline. The assignment of the structures of **6** was performed by NMR experiments such as 1D ^{1}H, ^{13}C and DEPT, as well as 2D COSY, HSQC, HMBC and 1,1-ADEQUATE spectra.

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INTRODUCTION

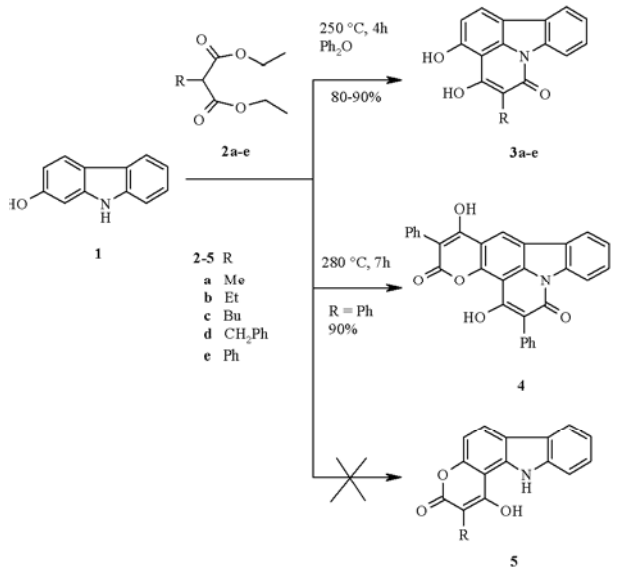
Pyrido[3,2,1-*jk*]carbazol-6-one is part of the heterocyclic skeleton of many natural products (*e.g.* strychnos alkaloids and related structures [1-3]) and contains the biologically interesting moieties of both an indole structure as well as a 2-pyridone. Some derivatives have also found industrial interest [4,5]. Recently we have described the synthesis and some reactions of 4-hydroxypyrido[3,2,1-*jk*]carbazol-6-ones [6,7]. In this contribution we want to report about some results in the synthesis of 3,4-dihydroxypyrido[3,2,1-*jk*]carbazol-6-ones.

RESULTS AND DISCUSSION

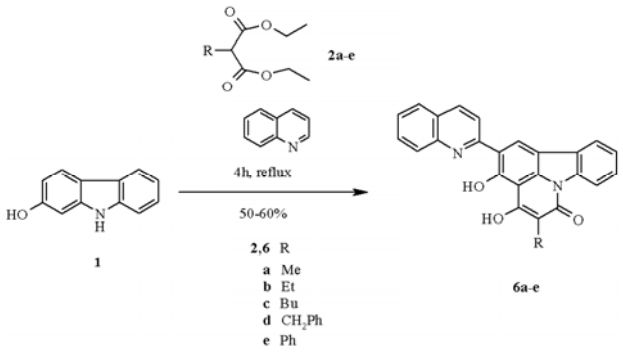
When 2-hydroxycarbazole **1** was brought to reaction with malonates **2a-e** at 250 °C in a 1:1 reaction for 1-4 hours, we expected from similar reactions with 2-naphthols [8] a competitive attack of malonates **2** both at the nitrogen of the heterocycle and at the 2-hydroxy group of carbazole **1**. The cyclocondensation should form *via* intermediate carbazolyl-esters or amides the isomeric pyridocarbazoles **3** and indolocoumarins **5**. Indolocoumarins **5** were desired products for the study of thermal rearrangement reactions at temperatures above 300 °C *via* α-oxo-ketene intermediates [8]. However, already at temperatures of 250 °C exclusively as the only products pyridocarbazoles **3** were formed in excellent yields of 81-95% as reported previously [6]. Lower temperatures gave no cyclization products. This fact could be observed with methyl- and ethylmalonates **2a,b**, which needed diphenyl ether as the solvent to raise the reaction temperature from about 200 to 250 °C to obtain the pyridocarbazoles **3a,b** in about 95% yield.

On the other hand, with phenylmalonate **2e** having a boiling point of 280 °C, again diphenyl ether had to be used to maintain the reaction temperature to 250 °C, which gave **3e** in 81% yield. Without such a temperature control, however, the reaction temperature reaches more than 280 °C, and a mixture of two products, **3e** as by-product and **4** as main product, was formed. The ir signals of **4** at 1736 and 1712 cm^{-1} indicated lactone carbonyl signals; ^{1}H NMR spectra show a single aryl-H signal at 8.94 ppm besides the signals of the 10 phenyl protons and 4 aryl protons; only one single hydroxy signal at 10.34 ppm is visible, probably because of hydrogen bonding. Mass spectra and elemental analysis confirm the structure of **4** as the sodium salt. The formation of this bis-adduct **4** can be explained by esterification at the 3-hydroxy group of the primarily formed pyrido[3,2,1-*jk*]carbazol-6-one **3e** by a second molecule of phenylmalonate **2e** at elevated temperatures above 260 °C, followed by a subsequent cyclocondensation at position 2 to a pyrono ring. As a result, a 2:1 cyclocondensation of two molecules of **2e** and one molecule of carbazole **1** takes place.

Attempts to use highly reactive bis(2,4,6-trichlorophenyl)malonates with short reaction times of 15 min at 210 °C to favor a kinetically controlled reaction of **1** to **5**, resulted again in the formation of pyrido[3,2,1-*jk*]-carbazol-6-one derivatives **3** as we have described previously [6]. As an attempt to raise the reactivity of the



hydroxy group of **1** and to direct the reaction to the formation of **5**, we added quinoline both as basic catalyst and as the solvent to the reaction mixture of **1** and **2**. Surprisingly, we obtained quinoline-substituted pyrido-[3,2,1-*jk*]carbazol-6-ones **6a-e** in excellent yields as bright orange-red crystals after a reaction time of 2 hours at 260 °C. From simple spectral and analytical data it was not possible to assign unequivocally the structure of **6**. The ir spectra reveal only amide carbonyl signals; therefore a substitution at C-5, the CH-acidic moiety of pyrido-carbazoles **3** in their tautomeric dioxo form, can be excluded. A simple quinoline salt was not likely because we obtained a mass spectrum of **6e** showing a 100 % mass peak of a quinoline-substituted pyridocarbazolone; also the elemental analyses gave the correct values for all samples of **6**.



Finally, NMR experiments on a Bruker Avance DRX 500 MHz NMR spectrometer at 25 °C allowed the assignment of the structure. The assignments were obtained using 1D ^{1}H, ^{13}C and DEPT, as well as 2D COSY, HSQC [12a], HMBC [12b] and 1,1-ADEQUATE [12c] spectra. Between 5 and 20 mg of sample were dissolved in 600 µl of DMSO-d_6 (**3a**) or TFA-d (**6a,e**). For the 1,1-ADEQUATE experiment of **6e**, 200 mg were used. Due to the low number of protons in these heteronuclear systems the assignment relied on the acquisition of HMBC as well as 1,1-ADEQUATE spectra. The latter helps in identifying H_a-C_a-C_b-H_b fragments by correlating the double-quantum frequency C_a-C_b (=(C_a)+(C_b)) with the frequencies of the protons H_a and H_b. Since for each proton the frequency of the attached carbon can be extracted from an HSQC experiment, the 1,1-ADEQUATE spectrum essentially gives a correlation between proton H_a and C_b, as well as H_b to C_a.

The correlations used for the assignment of **6e** are shown in Figure 1, where HMBC and 1,1-ADEQUATE connectivities are represented by dotted and full lines, respectively. The complete assignment is shown in Table 1 for ^{1}H and in Table 2 for ^{13}C resonances. Carbons 4 and 6 could not be differentiated by any of the applied experiments due to the absence of proton nuclei close by (up to 3 bonds).

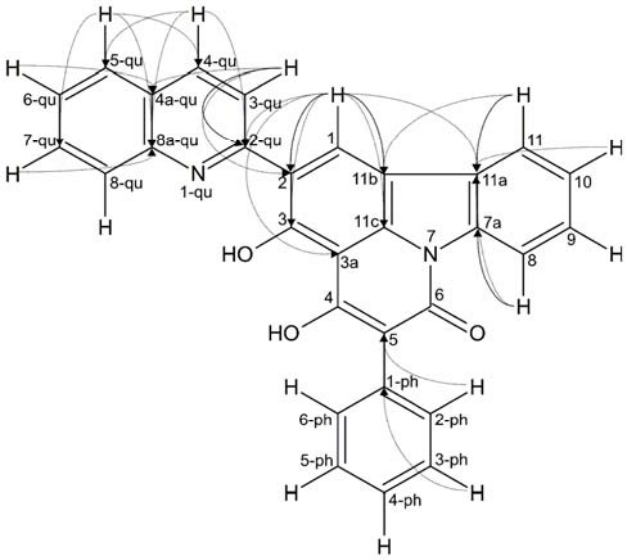


Figure 1. HMBC (dotted lines) and 1,1-ADEQUATE (full lines) connectivities of **6e**.

A literature survey showed, that the direct introduction of quinoline or pyridyl substituents in aromatic or heteroaromatic structures is a reaction that is nearly unknown. Most reaction sequences use appropriate substituted quinolines or pyridines, which are introduced by cyclocondensation as substituents, *e.g.* ref. [9]. A direct introduction of pyridinium acetate or bromide into the 3-position of 4-hydroxycoumarin derivatives was described; in this way 3-pyridylbenzopyranones [10,11] were obtained. We repeated the reaction sequence described in ref. [10] starting from 4-hydroxycoumarin

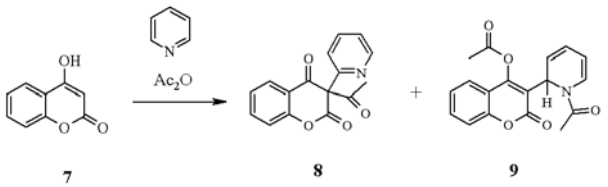
Table 1

^{1}H NMR Chemical shifts of 3,4-Dihydroxy-5-methylpyrido[3,2,1-*jk*]carbazol-6-one (**3a**) and 3,4-Dihydroxy-2-quinolin-2-ylpyrido[3,2,1-*jk*]carbazol-6-ones **6a**, **6e** (as the solvent CF_3COOD was used)

Assignment	**6e**	**6a**	**3a**
1-H	9.11 (s)	8.27 (s)	8.13 (d, J=8.2 Hz)
2-H	-----	-----	6.99 (d, J=8.2 Hz)
8-H	8.75 (d, J=7.7 Hz)	8.07 (d, J=7.3 Hz)	8.55 (d, J=7.7 Hz)
9-H	7.85 (t, J=7.6 Hz)	7.13 [a]	7.47 (t, J=7.6 Hz)
10-H	7.91 (t, J=7.6 Hz)	7.13 [a]	7.43 (t, J=7.6 Hz)
11-H	8.45 (d, J=7.7 Hz)	7.66 [a]	8.11 (d, J=7.6 Hz)
2- and 6-H of phenyl	7.90 [a]	-----	-----
2- and 6-H of phenyl	7.90 [a]	-----	-----
3- and 5-H of phenyl	7.85 [a]	-----	-----
4-H of phenyl	7.96 [a]	-----	-----
-CH_3	-----	1.97 (s)	2.07 (s)
3-H of quinoline	8.92 (d, J=8.9 Hz)	8.12 (d, J=9.2 Hz)	-----
4-H of quinoline	9.51 (d, J=8.9 Hz)	8.73 (d, J=9.2 Hz)	-----
5-H of quinoline	8.71 (d, J=8.3 Hz)	7.95 (d, J=8.5 Hz)	-----
6-H of quinoline	8.61 [a]	7.70 [a]	-----
7-H of quinoline	8.61 [a]	7.90 [a]	-----
8-H of quinoline	8.45 [a]	7.90 [a]	-----

[a] overlapping did not allow the determination of coupling.

(**7**) and obtained a mixture of the new 3-acetyl-3-pyridinylchromandione **8** together with 3-(1-acetyl-dihydropyridin-2-yl)-2-oxochromen-4-yl acetate **9** which was described in ref. [10]. However, we failed to direct this reaction to the similar 4-hydroxyquinolones, 4-hydroxypyridocarbazolones and 3,4-dihydroxypyrido-carbazolones **3**.



Conclusion

This work shows that it is possible to introduce directly quinoline and pyridine as substituents in heterocyclic systems at electron rich positions to obtain *e.g.* compounds **6**, **8** and **9**. However, the reaction is strongly dependent on the particular heterocyclic system and could not be generalized.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus, Mod. MFB-595 in open capillary tubes. The ^{1}H NMR spectra were recorded on a Bruker AMX 360 instrument (360 MHz ^{1}H frequency) or on a Bruker Avance DRX NMR spectrometer (500 MHz ^{1}H frequency). The ^{13}C NMR spectra were recorded on a Bruker AMX 360 instrument (90 MHz ^{13}C frequency) or on a Bruker Avance DRX 500 NMR spectrometer (125 MHz ^{13}C frequency) at 25 °C. Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ-units. The solvent for NMR spectra was deuteriodimethyl sulfoxide unless otherwise stated. Infrared spectra were taken on a Galaxy Series FTIR 7000 in potassium bromide pellets. Elemental analyses (values are within ±0.4 of the theoretical percentages) were performed either on a Fisons elemental analyzer Mod. EA 1108, or at the Microanalytical Laboratory at the Faculty of Chemistry at the University of Vienna. Mass

Table 2: ^{13}C NMR Chemical shifts of 3,4-Dihydroxy-5-methylpyrido-[3,2,1-*jk*]carbazol-6-one (**3a**) and 3,4-Dihydroxy-2-quinolin-2-ylpyrido-[3,2,1-*jk*]carbazol-6-ones **6a**, **6e** (as the solvent CF_3COOD was used).

Assignment	**6e**	**6a**	**3a**
1-C	128.5	126.9	124.7
2-C	115.4	114.5	111.1
3-C	157.6	157.5	154.6
3a-C	105.0	104.8	101.5
4-C	165.8	165.8	162.2
5-C	129.6	127.7	106.8
6-C	163.4	162.3	159.0
7a-C	141.6	141.1	138.2
8-C	119.8	119.4	116.3
9-C	131.4	131.3	126.6
10-C	129.6	127.0	124.7
11-C	123.6	123.3	120.9
11a-C	128.0	127.7	126.2
11b-C	121.9	121.2	115.3
11c-C	140.3	139.1	134.7
2-C of quinoline	154.9	154.6	-----
3-C of quinoline	124.0	122.7	-----
4-C of quinoline	149.8	149.1	-----
4a-C of quinoline	130.2	129.8	-----
5-C of quinoline	131.8	131.4	-----
6-C of quinoline	133.6	133.1	-----
7-C of quinoline	138.7	138.6	-----
8-C of quinoline	122.7	122.2	-----
8a-C of quinoline	139.8	139.5	-----
1-C of phenyl	117.5	-----	-----
2- and 6-C of phenyl	132.6	-----	-----
3- and 5-C of phenyl	133.7	-----	-----
4-C of phenyl	133.9	-----	-----
-CH_3	-----	9.7	9.2

spectra were obtained by using atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) techniques on a HP 1100 LC/MSD mass spectral instrument, performed with nitrogen and 50-200 eV collision energy. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using uv light (254 and 366 nm) for detection.

Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

3,4-Dihydroxy-5-methyl-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (3a). A mixture of 2-hydroxycarbazole (**1**) (1.83 g, 10 mmol) and diethyl methylmalonate (**2a**) (3.40 mL, 20 mmol) in diphenyl ether (5 mL) was heated for 1 hour under reflux. The reaction mixture was cooled to room temperature and methanol (5 mL) was added. The solid was filtered by suction and washed with methanol (10 mL). The yield was 2.50 g (94%), yellow powder, mp 274 °C (dimethylformamide); lit. mp 274 °C [6]; ir: 3380 -2700 w, 1655 s, 1620 s, 1600 s, 1580 s cm^{-1}; ^{1}H nmr: see Table 1. ^{13}C nmr: see Table 2.

3,4-Dihydroxy-6*H*-pyrido[3,2,1-*jk*]carbazol-6-ones **3b-d** were prepared according to the procedure described previously in ref. [6].

3,4-Dihydroxy-5-phenyl-6*H*-pyrido[3,2,1-*jk*]carbazol-6-one (3e). A mixture of 2-hydroxycarbazole (**1**) (0.50 g, 2.73 mmol) and diethyl phenylmalonate (**2e**) (2.50 mL, 12 mmol) in diphenyl ether (3 mL) was heated for 6 hours under reflux. The reaction mixture was cooled to room temperature and methanol (5 mL) added. The solid was collected by suction filtration and washed with methanol. The yield was 0.72 g (81%), yellow powder, mp 312 °C (dimethylformamide); lit. mp 312 °C [6]; ir: 3380-2700 w, 1655 s, 1620 s, 1600 s, 1580 s cm^{-1}; ^{1}H nmr: δ 7.04 (d, J= 8.0 Hz, 1 H, H of Ph), 7.35 (t, J= 6.4 Hz, 1 H, H of Ph), 7.41-7.48 (m, 6 H, ArH), 8.16 (d, J= 7.1 Hz, 1 H, 1-H), 8.22 (d, J= 8.2 Hz, 1 H, 11-H), 8.55 (d, J= 7.8 Hz, 1 H, 8-H).

3,7-Dihydroxy-2,6-diphenyl-1*H*,5*H*-pyrano[2,3-*b*]pyrido-[1,2,3-*lm*]carbazol-1,5-dione (4). A mixture of 2-hydroxycarbazol (**1**) (0.25 g, 1.4 mmol) and diethyl phenylmalonate (**2e**) (5.0 mL, 21 mmol) was heated without solvent under reflux at 280 °C bath temperature for 7 hours. After cooling to room temperature, a precipitate was formed. Methanol (20 mL) was added, the crushed solid was collected by suction filtration and washed with cold methanol (10 mL). The solid product was dissolved in aqueous sodium hydroxide (0.25 *M*, 1000 mL) and filtered from insoluble products. The filtrate was extracted with toluene (2x 250 mL) and cleared with charcoal (about 1 g) and neutralized with diluted hydrochloric acid (50 mL); the precipitate was collected by filtration, washed several times with water, recrystallized from methanol and dried at 80-100 °C. The yield was 0.64 g (93%) of the mono-sodium salt of **4**, yellowish crystals, mp 340 °C dec. (methanol); ir: 3489 s, 1736 s, 1712 s, 1653 s, 1621 s, 1605 s, 1580 cm^{-1}; ^{1}H nmr: δ 7.38-7.42 (m, 2 H, H of Ph), 7.43-7.54 (m, 9 H, 8 H of Ph, ArH), 7.62 (t, J= 7.8 Hz, 1 H, ArH), 8.39 (d, J= 7.6 Hz, 1 H, ArH), 8.56 (d, J= 8.0 Hz, 1 H, ArH), 8.94 (s, 1 H, 8-H), 10.34 (s, 1 H, OH); MS (APCI): m/z (%) = 500 (15), 499 (50), 472 (32, M+1), 471 (100, M of free OH-compound), 399 (15, M-71). *Anal.* Calcd. for $C_{30}H_{16}NNaO_5$ (493.46): C, 73.02; H, 3.27; N, 2.84. Found: C, 72.65; H, 3.59; N, 3.02.

3,4-Dihydroxy-5-methyl-2-quinolin-2-yl-6*H*-pyrido[3,2,1-*jk*]-carbazol-6-one (6a). A mixture of 2-hydroxycarbazole (**1**) (1.00 g, 5.46 mmol), diethyl methylmalonate (**2a**) (5.00 mL, 29.4 mmol) and quinoline (3.00 mL, 25 mmol) was heated under reflux for 4 hours. After cooling, hexane (90 mL) was added and the solid was collected by filtration and washed with hexane. The yield was 1.00 g (47%), yellow-orange powder, mp 264 °C (dimethylformamide); ir: 3500-3405 m, 1668 s, 1609 s, 1591 s, 1556 s cm^{-1}; ^{1}H nmr (CF_3COOD): see Table 1. ^{13}C nmr (CF_3COOD): see Table 2. *Anal.* Calcd. for $C_{25}H_{16}N_2O_3$ (392.42): C, 76.52; H, 4.11; N, 7.14. Found: C, 76.77; H, 3.87; N, 7.09.

5-Ethyl-3,4-dihydroxy-2-quinolin-2-yl-6*H*-pyrido[3,2,1-*jk*]-carbazol-6-one (6b). This compound was obtained from 2-hydroxycarbazole (**1**) (0.91 g, 5 mmol), diethyl ethylmalonate (**2b**) (1.9 g, 10 mmol) and quinoline (3.00 mL, 25 mmol) according to the procedure and workup described for **6a**; the yield was 1.05 g (52%) orange needles, mp 276 °C (dimethyl-formamide); ir: 3100-2800 w, 1675 m, 1645 s, 1625 s, 1610 s, 1600 m, 1590 m cm^{-1}; ^{1}H nmr (CF_3COOH): δ 1.21 (t, J = 7.3 Hz, 3 H, Me), 2.72 (q, J = 7.1 Hz, 2 H, CH_2), 7.05-7.30 (m, 2 H, ArH), 7.35-7.70 (m, 7 H, ArH), 8.05 (d, J = 8 Hz, 1 H, ArH), 8.30 (d, J = 8.2 Hz, 1 H, 8-H). *Anal.* Calcd. for $C_{26}H_{18}N_2O_3$ (406.44): C, 76.83; H 4.46; N, 6.89. Found: C, 77.07; H, 4.57; N, 7.24.

5-Butyl-3,4-dihydroxy-2-quinolin-2-yl-6*H*-pyrido[3,2,1-*jk*]-carbazol-6-one (6c). This compound was obtained from 2-hydroxycarbazole (**1**) (0.91 g, 5 mmol), diethyl butylmalonate (**2c**) (2.2 g, 10 mmol) and quinoline (3.00 mL, 25 mmol) according to the procedure and workup described for **6a**; the yield was 1.00 g (46%), orange fine prisms, mp 254 °C (dimethylformamide); ir: 3100-2800 w, 1665 m, 1640 m, 1620 s, 1605 s, 1570 w cm^{-1}; ^{1}H nmr (CF_3COOH): δ 0.98 (t, J = 7.3 Hz, Me), 1.30-1.90 (m, 2 H, CH_2), 2.60-2.90 (m, 2 H, CH_2), 7.05-7.30 (m, 2 H, ArH), 7.40-7.75 (m, 7 H, ArH), 8.10 (d, J = 8 Hz, 1 H, ArH), 8.30 (d, J = 8.1 Hz, 1 H, 8-H). *Anal.* Calcd. for $C_{28}H_{22}N_2O_3$ (434.50): C, 77.40; H, 5.10; N, 6.45. Found: C, 77.03; H, 5.15; N, 6.54.

5-Benzyl-3,4-dihydroxy-2-quinolin-2-yl-6*H*-pyrido[3,2,1-*jk*]-carbazol-6-one (6d). This compound was obtained from 2-hydroxycarbazole (**1**) (0.91 g, 5 mmol), diethyl benzylmalonate (**2d**) (2.5 g, 10 mmol) and quinoline (3.00 mL, 25 mmol) according to the procedure and workup described for **6a**; the yield was 1.30 g (56%) orange needles, mp 340 °C (dimethylformamide or 1,2-dichlorobenzene); ir: 3100-2800 w, 1670 m, 1640 s, 1620 m, 1585 s cm^{-1}; ^{1}H nmr (CF_3COOH): δ 4.30 (s, 2 H, CH_2), 7.10-7.30 (m, 5 H, ArH), 7.40-7.80 (m, 9 H, ArH), 8.10 (d, J = 8 Hz, 1 H, ArH), 8.35 (d, J = 8 Hz, 1 H, 8-H). *Anal.* Calcd. for $C_{31}H_{20}N_2O_3$ (468.52): C, 79.47; H, 4.30; N, 5.98. Found: C, 79.79; H, 4.32; N, 6.15.

3,4-Dihydroxy-5-phenyl-2-quinolin-2-yl-6*H*-pyrido[3,2,1-*jk*]-carbazol-6-one (6e). This compound was obtained from 2-hydroxycarbazole (**1**) (1.00 g, 5.4 mmol) and diethyl phenylmalonate (**2e**) (5.00 g, 21 mmol) according to the procedure and workup described for **6a**; the yield was 1.50 g (61%), orange needles, mp >360 °C (dimethylformamide); ir: 3500 - 3405 m, 1640 s, 1584 s, 1568 s cm^{-1}; ^{1}H nmr (CF_3COOD): see Table 1; ^{13}C nmr (CF_3COOD): see Table 2; MS (APCI): m/z (%) = 453 (100, M - 1). *Anal.* Calcd. for $C_{30}H_{18}N_2O_3$ (454.49): C, 79.28; H, 3.99; N, 6.16. Found: C, 78.90; H, 3.85; N, 6.12.

3-Acetyl-3-pyridin-2-yl-2*H*,4*H*-chromane-2,4-dione (8). A solution of 4-hydroxycoumarin (**7**) (3.50 g, 22 mmol) in pyridine (8.5 g, 110 mmol) and acetic anhydride (160 mL) was stirred at room temperature for 24 hours. The formed precipitate was collected by suction filtration and washed with pyridine (5 mL).

The yield was 1.10 g (18%), yellow prisms, mp 230 °C (pyridine); ir: 1770 s, 1680 s, 1620sh, 1610s, 1570s, 1505 sh, 1495 s cm^{-1}; ^1H nmr: δ 1.95 (s, 3 H, Me), 7.05-7.60 (m, 4 H, 3 ArH, 1 pyridine-H), 8.05 (m, 1 H, ArH), 8.35 (m, 2 H, pyridine-H), 9.21 (dd, J = 2 and 7 Hz, 1 H, α-pyridine-H). MS (APCI): 281 (12), 240 (8), 239 (44), 238 (10), 195 (8), 162 (10), 149 (40), 121 (36), 120 (28), 58 (60). 56 (40), 44 (36), 43 (100), 42 (41), 41 (90). *Anal*. Calcd. for $C_{16}H_{11}NO_4$ (281.27): C, 68.33; H, 3.94; N, 4.98. Found: C, 67.97; H, 3.84; N, 5.03.

3-(1-Acetyl-1,2-dihydropyridin-2-yl)-2-oxo-2*H*-chromen-4-yl acetate (9). The mother liquor obtained from the filtrate in the separation of **8** was kept for 24 hours at room temperature then the red solution was poured onto ice/water. The resulting oil was allowed to crystallize, was collected by suction filtration, washed with diluted hydrochloric acid and crystallized from methanol/water. The yield was 2.50 g (40%) colorless prisms, mp 172-173 °C (methanol/water); lit. mp 177-178 °C [10]; spectral data are identical with literature data. [10].

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