# SYNTHESIS OF 6-, 7-, 8- OR 9-SUBSTITUTED 1*H*-PYRANO[4,3-*b*]-QUINOLINE DERIVATIVES BY THE CYCLIZATION OF 3-ACETYL-4-ARYLAMINO-2*H*-PYRAN-2-ONE DERIVATIVES

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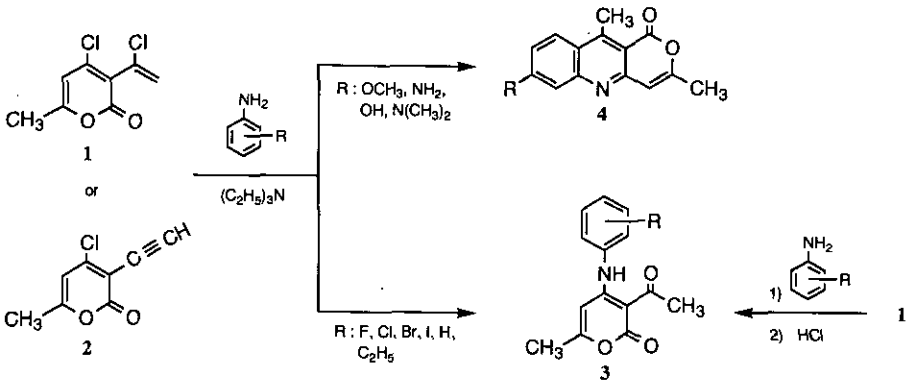
***Abstract-*** Heating of 3-acetyl-4-arylamino-6-methyl-2*H*-pyran-2-one derivatives in concd $H_2SO_4$ gave 6-, 7-, 8- or 9-substituted 3,10-dimethyl-1*H*-pyrano[4,3-*b*]quinoline derivatives.

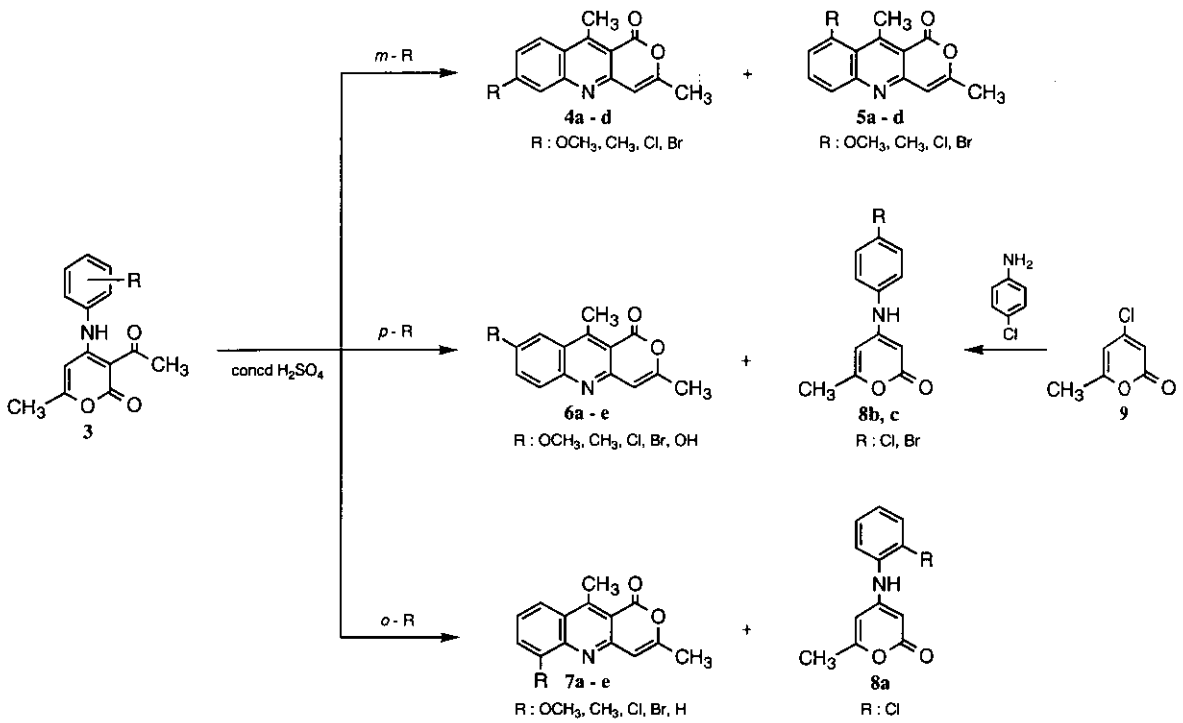
Recently, it has been reported that the activity of 1*H*-pyrano[4,3-*b*]quinoline derivatives was investigated as memory-enhancing agents for the treatment of Alzheimer's disease.[1] Although pyrano[4,3-*b*]quinolines are certainly expected to possess pharmacological activities, there are few reports on their synthesis.[2] In the course of a study on the reactivity of 4-chloro-3-(1-chlorovinyl)-6-methyl-2*H*-pyran-2-one (**1**) and 4-chloro-3-ethynyl-6-methyl-2*H*-pyran-2-one (**2**), we found that the reaction of **1** and **2** with anilines yields pyrano[4,3-*b*]quinoline derivatives.[3] However, this method has a limitation in that the substituent at the 3-position of aniline must have a strong electron-donating effect such as $NH_2$, $N(CH_3)_2$, and $OCH_3$. If the substituent has little or no such effect, the reaction yields 3-acetyl-4-arylaminopyrones (**3**) without pyranoquinolines (**4**). On the other hand, 3-acetyl-4-arylaminopyrones (**3**) are considered to be an acylacetoanilide or alkyl $\beta$-anilinocrotonate analog which is a starting material in the Knorr or Combes synthesis, because **3** has a $\beta$-anilinocarbonyl structure. Therefore this suggests that **3** can be readily converted to pyranoquinoline (**4**) with sulfuric acid. Furthermore, 3-acetyl-4-arylaminopyrones (**3**) are easily obtained by the reaction of **1** with anilines in good yields.[4] In this paper, we report the synthesis of 1*H*-pyrano[4,3-*b*]quinoline derivatives by the cyclization of **3** in sulfuric acid.

A mixture of 3-acetyl-4-(*m*-anisidino)pyrone (**3a**) and 98 % sulfuric acid was heated for 5 min at 130 ℃ to give two products, (**4a**) and (**5a**), in 87 % and 5 % yields, respectively. These products have the same molecular formula of $C_{15}H_{13}NO_3$, and their $^1$H-NMR spectra show many similar features. The structure of **4a** as 7-methoxy-3,10-dimethyl-1*H*-pyrano[4,3-*b*]quinolin-1-one was determined using an authentic sample obtained from the reaction of **2** with *m*-anisidine.

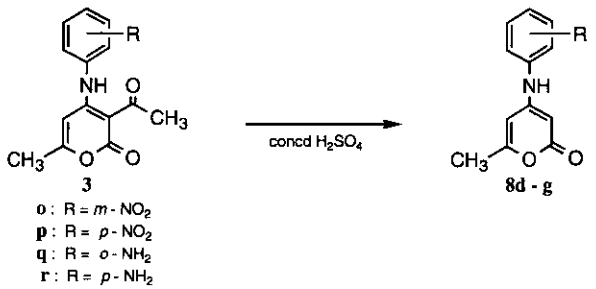



Scheme 1

Irradiation of the methyl proton at the 10-position on the pyrano[4,3-*b*]quinoline ring gave NOE on the *ortho*-coupled proton at 8.06 ppm of **4a** but did not give it on any ring proton of **5a**. These data support the belief that **5a** is 9-methoxy-3,10-dimethyl-1*H*-pyrano[4,3-*b*]quinolin-1-one. The reaction of 3-acetyl-4-(*p*-anisidino)pyrone (**3b**) and 3-acetyl-4-(*o*-anisidino)pyrone (**3c**) under similar conditions gave the respective products (**6a**) and (**7a**), of which the molecular formulas and $^1$H-NMR spectra corresponded closely to those of **4a**. Especially, irradiation of the methyl proton at the 10-position on the pyrano[4,3-*b*]quinoline ring gave NOE on the *meta*-coupled proton of **6a** and on the *ortho*- and *meta*-coupled proton of **7a**. These data are consistent with the structures of **6a** and **7a** as 8- and 6-substituted pyrano[4,3-*b*]quinoline derivatives, respectively. Analogously, the cyclization of various 3-acetyl-4-arylaminopyrones (**3**) having $CH_3$, OH, Cl or Br instead of $OCH_3$ in sulfuric acid gave the corresponding 6-, 7-, 8-, and 9-substituted pyrano-[4,3-*b*]quinoline derivatives as shown in Table 1. However, in the reactions of **3h**, **3i**, and **3k**, 4-arylamino-6-methyl-2*H*-pyrones (**8**) were obtained as a subproduct along with the pyrano-quinolines. The structure of **8b** was determined with an authentic sample prepared from 4-chloro-6-methyl-2*H*-pyran-2-one (**9**)[5] and *p*-chloroaniline. As a reason of the formation of **8** by deacetylation, it seems that the electron-donating character of the substituent on the benzene ring is weaker and/or does not clearly show on the carbon which attacks the carbonyl carbon at the acetyl group. In the reaction of 3-acetyl-4-nitroanilinopyrones (**3o**, **p**) and 3-acetyl-4-aminoanilino-pyrones (**3q**, **r**), a similar deacetylation was also carried out to give the corresponding 4-nitro-anilinopyrones (**8d**, **e**) and 4-aminoanilinopyrones (**8f**, **g**) without the pyranoquinolines (Scheme 3). The formation of **8d-g** is caused by the decrease in the electron density of the benzene ring due to a nitro group or ammonium ion being formed by protonation of the amino group. The yields of the 9-substituted pyranoquinolines (**5**) were lower than those of the other pyranoquinolines



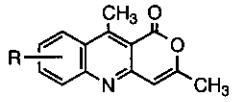

Scheme 2




Scheme 3

due to the steric hindrance between the 9-substituent and the methyl group at the 10-position. Furthermore, the use of 90 % instead of 98 % sulfuric acid resulted in a decrease in the yield to afford pyrano[4,3-*b*]quinolines because of the inhibition of the cyclization accompanying dehydration. The structures of these products were determined by the spectral and analytical characteristics. A probable route of the cyclization of 3-acetyl-4-arylaminopyrone (**3**) using sulfuric acid may be postulated as shown in Scheme 4.

Table 1. Spectral and Analytical Data for **4**, **5**, **6**, and **7**



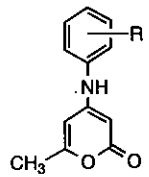

| Starting material | | Product | Yield (%) | mp (℃) | Recryst. solvent | Formula (*m/z* $M^+$) | Analysis (%) Calcd (Found) | | | IR[KBr] ($cm^{-1}$) | $^1$H-NMR $\delta$ (ppm) [$CDCl_3$][a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. | R | | | | | | C | H | N | | |
| **3a** | *m* - $OCH_3$ | **4a** | 87 | 196 - 197[b] | EtOH | $C_{15}H_{13}NO_3$ (255) | 70.58 (70.75 | 5.13 5.07 | 5.49 5.50) | 1725, 1680 | 2.31 (3H, s, 3-$CH_3$), 3.16 (3H, s, 10-$CH_3$), 3.97 (3H, s, $OCH_3$), 6.42 (1H, s, 4-H), 7.16 (1H, dd, *J* = 9.0 and 2.5 Hz, 8-H), 7.25 (1H, d, *J* = 2.5 Hz, 6-H), 8.06 (1H, d, *J* = 9.0 Hz, 9-H) |
| **3a** | *m* - $OCH_3$ | **5a** | 5 | 198 - 199 | EtOH | $C_{15}H_{13}NO_3$ (255) | 70.58 (70.42 | 5.13 5.32 | 5.49 5.51) | 1725, 1675 | 2.31 (3H, s, 3-$CH_3$), 3.42 (3H, s, 10-$CH_3$), 4.00 (3H, s, $OCH_3$), 6.47 (1H, s, 4-H), 6.86 (1H, dd, *J* = 7.7 and 1.1 Hz, 8-H), 7.59 (1H, dd, *J* = 8.4 and 1.1 Hz, 6-H), 7.69 (1H, dd, *J* = 7.7 and 8.4 Hz, 7-H) |
| **3b** | *p* - $OCH_3$ | **6a** | 35 | 189 - 190 | MeOH | $C_{15}H_{13}NO_3$ (255) | 70.58 (70.39 | 5.13 5.04 | 5.49 5.32) | 1735, 1680 | 2.32 (3H, s, 3-$CH_3$), 3.20 (3H, s, 10-$CH_3$), 3.98 (3H, s, $OCH_3$), 6.49 (1H, s, 4-H), 7.37 (1H, d, *J* = 2.6 Hz, 9-H), 7.48 (1H, dd, *J* = 9.2 and 2.6 Hz, 7-H), 7.93 (1H, d, *J* = 9.2 Hz, 6-H) |
| **3c** | *o* - $OCH_3$ | **7a** | 21 | 228 - 229 | MeOH | $C_{15}H_{13}NO_3$ (255) | 70.58 (70.76 | 5.13 5.21 | 5.49 5.53) | 1725, 1670 | 2.32 (3H, s, 3-$CH_3$), 3.24 (3H, s, 10-$CH_3$), 4.11 (3H, s, $OCH_3$), 6.70 (1H, s, 4-H), 7.16 (1H, dd, *J* = 7.8 and 1.0 Hz, 7-H), 7.49 (1H, dd, *J* = 7.8 and 8.7 Hz, 8-H), 7.80 (1H, dd, *J* = 8.7 and 1.0 Hz, 9-H) |
| **3d** | *m* - $CH_3$ | **4b** | 73 | 174 | EtOH | $C_{15}H_{13}NO_2$ (239) | 75.30 (75.13 | 5.48 5.44 | 5.85 5.70) | 1730, 1680 | 2.31 (3H, s, 3-$CH_3$), 2.55 (3H, s, 7-$CH_3$), 3.14 (3H, s, 10-$CH_3$), 6.44 (1H, s, 4-H), 7.32 (1H, dd, *J* = 9.0 and 2.0 Hz, 8-H), 7.73 (1H, d, *J* = 2.0 Hz, 6-H), 8.03 (1H, d, *J* = 9.0 Hz, 9-H) |
| **3d** | *m* - $CH_3$ | **5b** | 10 | 171 | EtOH | $C_{15}H_{13}NO_2$ (239) | 75.30 (75.53 | 5.48 5.37 | 5.85 5.72) | 1725, 1675 | 2.33 (3H, s, 3-$CH_3$), 2.92 (3H, s, 9-$CH_3$), 3.31 (3H, s, 10-$CH_3$), 6.50 (1H, s, 4-H), 7.34 - 7.86 (3H, m, 6-, 7-, 8-H) |
| **3e** | *p* - $CH_3$ | **6b** | 75 | 196 - 197 | MeOH | $C_{15}H_{13}NO_2$ (239) | 75.30 (75.51 | 5.48 5.54 | 5.85 5.75) | 1725, 1670 | 2.32 (3H, s, 3-$CH_3$), 2.58 (3H, s, 8-$CH_3$), 3.22 (3H, s, 10-$CH_3$), 6.49 (1H, s, 4-H), 7.64 (1H, dd, *J* = 8.7 and 1.7 Hz, 7-H), 7.91 (1H, d, *J* = 8.7 Hz, 6-H), 7.97 (1H, d, *J* = 1.7 Hz, 9-H) |
| **3f** | *o* - $CH_3$ | **7b** | 85 | 209 | EtOH | $C_{15}H_{13}NO_2$ (239) | 75.30 (75.40 | 5.48 5.57 | 5.85 5.57) | 1730, 1675 | 2.31 (3H, s, 3-$CH_3$), 2.77 (3H, s, 6-$CH_3$), 3.22 (3H, s, 10-$CH_3$), 6.54 (1H, s, 4-H), 7.43 (1H, dd, *J* = 6.9 and 8.6 Hz, 8-H), 7.64 (1H, dd, *J* = 6.9 and 1.2 Hz, 7-H), 8.05 (1H, dd, *J* = 8.6 and 1.2 Hz, 9-H) |

Table 1: Continued

| Starting material | | Product | Yield (%) | mp (℃) | Recryst. solvent | Formula (*m/z* $M^+$) | Analysis (%) Calcd (Found) | | | IR[KBr] ($cm^{-1}$) | $^1$H-NMR δ (ppm) [CDCl3][a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. | R | | | | | | C | H | N | | |
| **3g** | *m* - Cl | **4c** | 70 | 168 | EtOH | $C_{14}H_{10}NO_2Cl$ (259) | 64.75 (64.49 | 3.88 4.10 | 5.39 5.44) | 1740, 1675 | 2.33 (3H, s, 3-$CH_3$), 3.19 (3H, s, 10-$CH_3$), 6.45 (1H, s, 4-H), 7.47 (1H, dd, *J* = 9.2 and 2.0 Hz, 8-H), 7.94 (1H, d, *J* = 2.0 Hz, 6-H), 8.10 (1H, d, *J* = 9.2 Hz, 9-H) |
| **3g** | *m* - Cl | **5c** | 17 | 183 - 184 | EtOH | $C_{14}H_{10}NO_2Cl$ (259) | 64.75 (64.92 | 3.88 4.04 | 5.39 5.38) | 1730, 1680 | 2.34 (3H, s, 3-$CH_3$), 3.48 (3H, s, 10-$CH_3$), 6.50 (1H, s, 4-H), 7.59 - 7.70 (2H, m, 7-, 8-H), 7.93 (1H, dd, *J* = 7.4 and 2.3 Hz, 6-H) |
| **3h** | *p* - Cl | **6c** | 58 | 220 - 221 | EtOH | $C_{14}H_{10}NO_2Cl$ (259) | 64.75 (64.76 | 3.88 3.87 | 5.39 5.23) | 1735, 1670 | 2.34 (3H, s, 3-$CH_3$), 3.22 (3H, s, 10-$CH_3$), 6.51 (1H, s, 4-H), 7.72 (1H, dd, *J* = 9.0 and 2.0 Hz, 7-H), 7.98 (1H, d, *J* = 9.0 Hz, 6-H), 8.19 (1H, d, *J* = 2.0 Hz, 9-H) |
| **3i** | *o* - Cl | **7c** | 45 | 247 | EtOH | $C_{14}H_{10}NO_2Cl$ (259) | 64.75 (64.54 | 3.88 3.94 | 5.39 5.24) | 1735, 1670 | 2.34 (3H, s, 3-$CH_3$), 3.27 (3H, s, 10-$CH_3$), 6.67 (1H, s, 4-H), 7.48 (1H, dd, *J* = 7.4 and 8.7 Hz, 8-H), 7.94 (1H, dd, *J* = 7.4 and 1.3 Hz, 7-H), 8.17 (1H, dd, *J* = 8.7 and 1.3 Hz, 9-H) |
| **3j** | *m* - Br | **4d** | 83 | 187 - 188 | $Et_2O$ | $C_{14}H_{10}NO_2Br$ (302) | 55.29 (55.31 | 3.31 3.22 | 4.61 4.54) | 1740, 1670 | 2.35 (3H, s, 3-$CH_3$), 3.20 (3H, s, 10-$CH_3$), 6.49 (1H, s, 4-H), 7.62 (1H, dd, *J* = 9.6 and 1.8 Hz, 8-H), 8.08 (1H, d, *J* = 9.6 Hz, 9-H), 8.18 (1H, d, *J* = 1.8 Hz, 6-H) |
| **3j** | *m* - Br | **5d** | 10 | 186 - 187 | EtOH | $C_{14}H_{10}NO_2Br$ (302) | 55.29 (55.48 | 3.31 3.43 | 4.61 4.47) | 1725, 1670 | 2.34 (3H, s, 3-$CH_3$), 3.47 (3H, s, 10-$CH_3$), 6.49 (1H, s, 4-H), 7.54 (1H, dd, *J* = 7.6 and 8.6 Hz, 7-H), 7.88 (1H, dd, *J* = 7.6 and 1.3 Hz, 8-H), 7.95 (1H, dd, *J* = 8.6 and 1.3 Hz, 6-H) |
| **3k** | *p* - Br | **6d** | 45 | 217 | EtOH | $C_{14}H_{10}NO_2Br$ (302) | 55.29 (55.40 | 3.31 3.55 | 4.61 4.53) | 1730, 1670 | 2.33 (3H, s, 3-$CH_3$), 3.22 (3H, s, 10-$CH_3$), 6.51 (1H, s, 4-H), 7.84 - 7.91 (2H, m, 6-, 7-H), 8.35 - 8.40 (1H, m, 9-H) |
| **3l** | *o* - Br | **7d** | 63 | 256 (decomp) | EtOH | $C_{14}H_{10}NO_2Br$ (302) | 55.29 (55.26 | 3.31 3.47 | 4.61 4.57) | 1740, 1670 | 2.34 (3H, s, 3-$CH_3$), 3.27 (3H, s, 10-$CH_3$), 6.69 (1H, s, 4-H), 7.42 (1H, dd, *J* = 7.4 and 8.6 Hz, 8-H), 8.17 (1H, dd, *J* = 7.4 and 1.2 Hz, 7-H), 8.23 (1H, dd, *J* = 8.6 and 1.2 Hz, 9-H) |
| **3m** | *p* - OH | **6e** | 42 | 303 - 304 (decomp) | MeOH | $C_{14}H_{11}NO_3$ (241) | 69.70 (69.42 | 4.60 4.86 | 5.81 5.81) | 3350, 1710, 1680 | 2.27 (3H, s, 3-$CH_3$), 3.06 (3H, s, 10-$CH_3$), 6.55 (1H, s, 4-H), 7.44 - 7.53 (2H, m, 7-, 9-H), 7.87 (1H, d, *J* = 8.6 Hz, 6-H), 10.27 (1H, br, OH) |
| **3n** | H | **7e** | 80 | 165 | $Et_2O$ | $C_{14}H_{11}NO_2$ (225) | 74.65 (74.69 | 4.92 4.88 | 6.22 6.08) | 1730, 1670 | 2.31 (3H, s, 3-$CH_3$), 3.22 (3H, s, 10-$CH_3$), 6.46 (1H, s, 4-H), 7.33 - 8.30 (4H, m, Ar-H), |

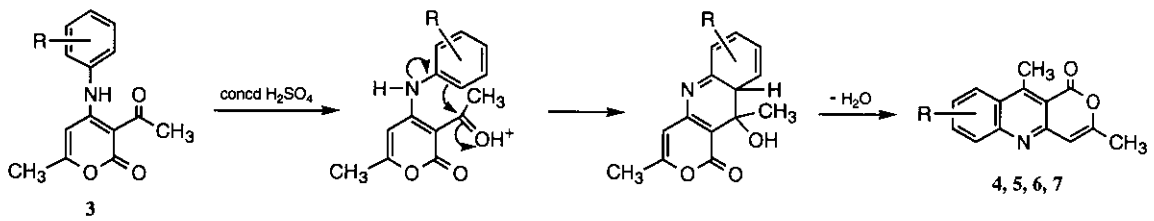
*a*) **6e** in DMSO. *b*) lit.,[2] mp 196 - 197 ℃.

Table 2. Spectral and Analytical Data for **8**




| Compd. No. | R | Yield (%) | mp (℃) | Recryst. solvent | Formula (*m/z* $M^+$) | Analysis (%) Calcd (Found) C | H | N | IR[KBr] ($cm^{-1}$) | $^1$H-NMR $\delta$ (ppm) [$CDCl_3$ - DMSO][a] |
|---|---|---|---|---|---|---|---|---|---|---|
| **8a** | *o* - Cl | 30 | 171 | $Et_2O$ | $C_{12}H_{10}NO_2Cl$ (235) | 61.16 (61.28 | 4.28 4.18 | 5.94 6.06) | 1680, 1645 | 2.13 (3H, s, $CH_3$), 5.31 (1H, s, 3-H), 5.90 (1H, s, 5-H), 6.96 - 7.63 (5H, m, Ar-H, NH) |
| **8b** | *p* - Cl | 26 | 216 - 217 | EtOH | $C_{12}H_{10}NO_2Cl$ (235) | 61.16 (61.08 | 4.28 4.31 | 5.94 5.92) | 1670, 1635 | 2.18 (3H, s, $CH_3$), 5.26 (1H, s, 3-H), 6.00 (1H, s, 5-H), 7.17 - 7.60 (4H, m, Ar-H), 9.25 (1H, br s, NH) |
| **8c** | *p* - Br | 25 | 220 - 221 | EtOH | $C_{12}H_{10}NO_2Br$ (279) | 51.45 (51.58 | 3.60 3.86 | 5.00 4.80) | 1680, 1640 | 2.22 (3H, s, $CH_3$), 5.33 (1H, s, 3-H), 5.98 (1H, s, 5-H), 7.15, 7.51 (2H×2, d, *J* = 9 Hz, Ar-H), 9.09 (1H, br s, NH) |
| **8d** | *m* - $NO_2$ | 92 | 237 | EtOH | $C_{12}H_{10}N_2O_4$ (246) | 58.54 (58.81 | 4.09 4.24 | 11.38 11.37) | 1680, 1645 | 2.22 (3H, s, $CH_3$), 5.42 (1H, s, 3-H), 6.04 (1H, s, 5-H), 7.59 - 8.28 (4H, m, Ar-H), 9.55 (1H, br, NH) |
| **8e** | *p* - $NO_2$ | 87 | 283 - 284 (decomp) | EtOH | $C_{12}H_{10}N_2O_4$ (246) | 58.54 (58.59 | 4.09 4.36 | 11.38 11.28) | 1725, 1680, 1615 | 2.22 (3H, s, $CH_3$), 5.61 (1H, s, 3-H), 6.09 (1H, s, 5-H), 7.42, 8.26 (2H×2, d, *J* = 9 Hz, Ar-H), 9.76 (1H, br s, NH) |
| **8f** | *o* - $NH_2$ | 89 | 161 - 162 | AcOEt | $C_{12}H_{12}N_2O_2$ (216) | 66.65 (66.66 | 5.59 5.51 | 12.95 12.90) | 1680, 1625 | 2.11 (3H, s, $CH_3$), 4.02 (2H, br s, $NH_2$), 4.99 (1H, s, 3-H), 5.88 (1H, s, 5-H), 6.53 - 7.27 (4H, m, Ar-H), 7.90 (1H, br s, NH) |
| **8g** | *p* - $NH_2$ | 67 | 224 (decomp) | AcOEt | $C_{12}H_{12}N_2O_2$ (216) | 66.65 (66.55 | 5.59 5.74 | 12.95 12.86) | 1670, 1630 | 2.14 (3H, s, $CH_3$), 4.73 (2H, br s, $NH_2$), 4.98 (1H, s, 3-H), 5.87 (1H, s, 5-H), 6.62, 6.90 (2H×2, d, *J* = 9 Hz, Ar-H), 8.61 (1H, br s, NH) |

*a*) **8a** in $CDCl_3$, **8c** in DMSO.




Scheme 4

## EXPERIMENTAL

All melting points are uncorrected. IR spectra were taken with a Hitachi Model 260-30 spectrophotometer. MS spectra were measured using a JEOL JMS-DX303/JMA-DA5000 instrument. $^1$H-NMR spectra were recorded using JEOL JNM-GSX400 and JNM-PMX60SI spectrometers. Chemical shifts are reported in parts per million ($\delta$) downfield from tetramethylsilane as the internal standard.

**Reaction of 3-acetyl-4-arylaminopyrones (3) with sulfuric acid; General procedure:** A mixture of **3** (0.5 g) in 98 % sulfuric acid (7 mL) was heated for 5 min at 130 ℃. The resulting mixture was slowly poured into ice-water. The precipitates formed were collected by filtration and purified by recrystallization. When there was little or no precipitate, the aqueous solution was extracted with $CHCl_3$. The organic layer was washed with water and dried over anhydrous $Na_2SO_4$. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$ and recrystallized from the solvent which is shown in Tables 1 and 2. In the reaction of the 3-acetyl-4-aminoanilinopyrones (**3q**, **r**), the resulting mixture after heating was poured into ice-water, and then the aqueous solution was made alkaline with $Na_2CO_3$. The treatment was continued using the same procedure as already described. The physical, spectra, and analytical data of the products are shown in Tables 1 and 2.

**Reaction of 4-chloro-6-methyl-2*H*-pyran-2-one with 4-chloroaniline:** A mixture of **9** (0.5 g, 3.5 mmol), 4-chloroaniline (0.5 g, 3.9 mmol), and $Et_3N$ (0.5 g, 5.0 mmol) in EtOH (50 mL) was heated under reflux for 5 h. The solvent was removed *in vacuo*. To the residue was added $CHCl_3$ (70 mL). After washing with water, the solution was dried over anhydrous $Na_2SO_4$. The solvent was removed *in vacuo* to give a solid, which was recrystallized from EtOH to give **8b** (mp 217 - 217.5 ℃) in 25 % (0.2 g) yield.

## REFERENCES AND NOTES

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