

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

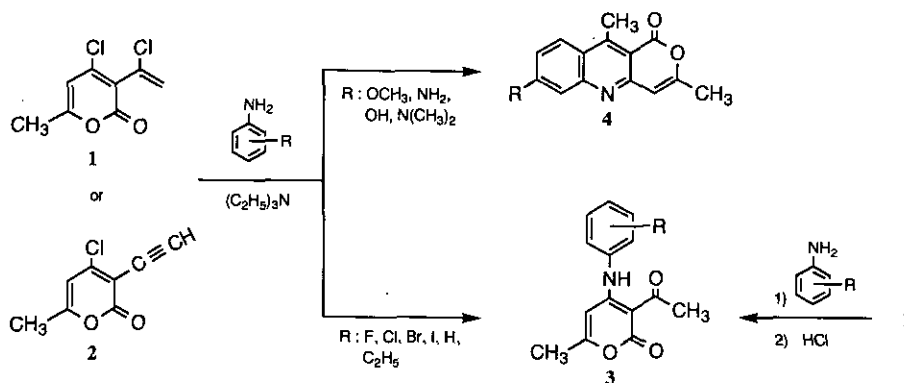
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Abstract- Heating of 3-acetyl-4-arylamino-6-methyl-2*H*-pyran-2-one derivatives in concd H₂SO₄ gave 6-, 7-, 8- or 9-substituted 3,10-dimethyl-1*H*-pyrano[4,3-*b*]quinoline derivatives.

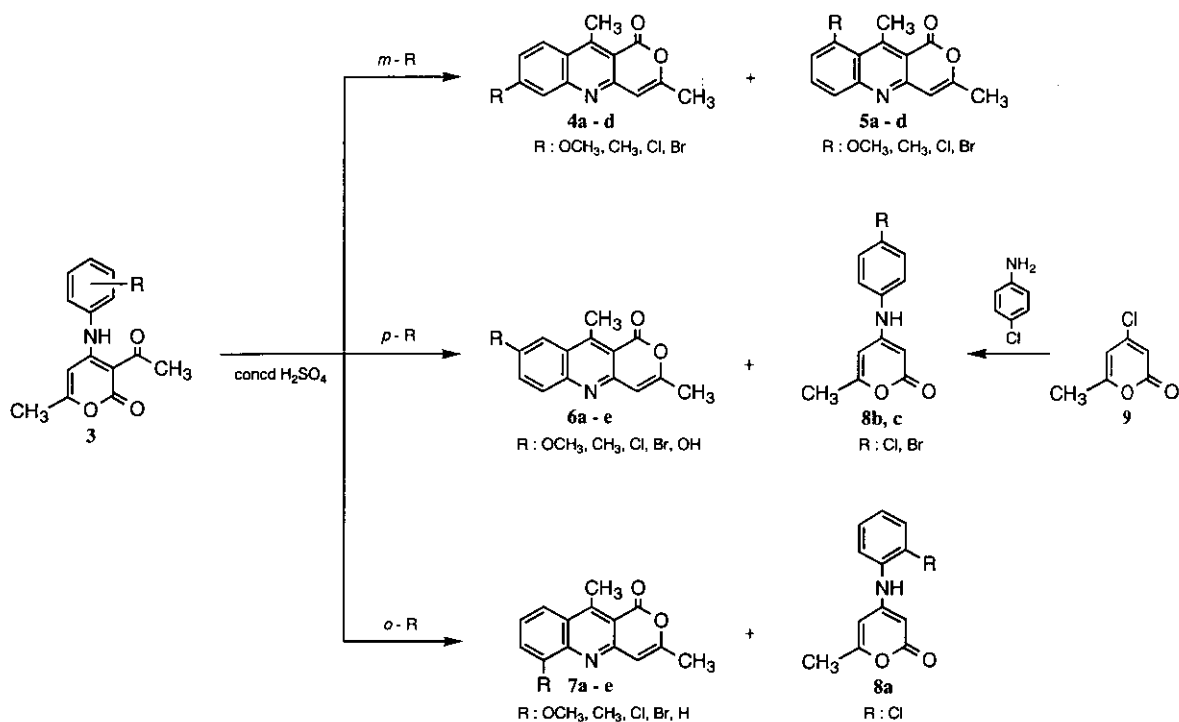
Recently, it has been reported that the activity of 1*H*-pyrano[4,3-*b*]quinoline derivatives was investigated as memory-enhancing agents for the treatment of Alzheimer's disease.¹ Although pyrano[4,3-*b*]quinolines are certainly expected to possess pharmacological activities, there are few reports on 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 NH₂, N(CH₃)₂, and OCH₃. If the substituent has little or no such effect, the reaction yields 3-acetyl-4-arylamino-6-methyl-2*H*-pyran-2-one (**3**) without pyranoquinolines (**4**). On the other hand, 3-acetyl-4-arylamino-6-methyl-2*H*-pyran-2-one (**3**) are considered to be an acylacetoanilide or alkyl β-anilinocrotonate analog which is a starting material in the Knorr or Combes synthesis, because **3** has a β-anilinocarbonyl structure. Therefore this suggests that **3** can be readily converted to pyranoquinoline (**4**) with sulfuric acid. Furthermore, 3-acetyl-4-arylamino-6-methyl-2*H*-pyran-2-one (**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 °C to give two products, (**4a**) and (**5a**), in 87 % and 5 % yields, respectively. These products have the same molecular formula of C₁₅H₁₃NO₃, and their ¹H-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.

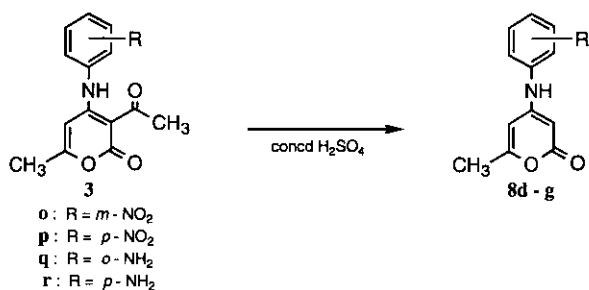


Scheme 1

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 ¹H-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-arylamino-pyrones (**3**) having CH₃, OH, Cl or Br instead of OCH₃ 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 pyranoquinolines. 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-aminoanilinopyrones (**3q**, **r**), a similar deacetylation was also carried out to give the corresponding 4-nitroanilinopyrones (**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-arylamino-2-pyrone (**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 (°C)	Recryst. solvent	Formula (m/z M ⁺)	Analysis (%)			IR[KBr] (cm ⁻¹)	¹ H-NMR δ (ppm) [CDCl ₃] ^a
						Calcd (Found)	C	H		
3a <i>m</i> -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, <i>J</i> = 9.0 and 2.5 Hz, 8-H), 7.25 (1H, d, <i>J</i> = 2.5 Hz, 6-H), 8.06 (1H, d, <i>J</i> = 9.0 Hz, 9-H)
3a <i>m</i> -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, <i>J</i> = 7.7 and 1.1 Hz, 8-H), 7.59 (1H, dd, <i>J</i> = 8.4 and 1.1 Hz, 6-H), 7.69 (1H, dd, <i>J</i> = 7.7 and 8.4 Hz, 7-H)
3b <i>p</i> -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, <i>J</i> = 2.6 Hz, 9-H), 7.48 (1H, dd, <i>J</i> = 9.2 and 2.6 Hz, 7-H), 7.93 (1H, d, <i>J</i> = 9.2 Hz, 6-H)
3c <i>o</i> -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, <i>J</i> = 7.8 and 1.0 Hz, 7-H), 7.49 (1H, dd, <i>J</i> = 7.8 and 8.7 Hz, 8-H), 7.80 (1H, dd, <i>J</i> = 8.7 and 1.0 Hz, 9-H)
3d <i>m</i> -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, <i>J</i> = 9.0 and 2.0 Hz, 8-H), 7.73 (1H, d, <i>J</i> = 2.0 Hz, 6-H), 8.03 (1H, d, <i>J</i> = 9.0 Hz, 9-H)
3d <i>m</i> -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 <i>p</i> -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, <i>J</i> = 8.7 and 1.7 Hz, 7-H), 7.91 (1H, d, <i>J</i> = 8.7 Hz, 6-H), 7.97 (1H, d, <i>J</i> = 1.7 Hz, 9-H)
3f <i>o</i> -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, <i>J</i> = 6.9 and 8.6 Hz, 8-H), 7.64 (1H, dd, <i>J</i> = 6.9 and 1.2 Hz, 7-H), 8.05 (1H, dd, <i>J</i> = 8.6 and 1.2 Hz, 9-H)

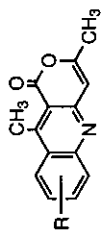


Table 1: Continued

Starting material No.	Product R	Yield (%)	mp (°C)	Recryst. solvent	Formula (<i>m/z</i> M ⁺)	Analysis (%)			IR[KBr] (cm ⁻¹)	¹ H-NMR δ (ppm) [CDCl ₃] ^{a)}	
						Calcd (Found)					
						C	H	N			
3g	<i>m</i> -Cl	4c	70	168	EtOH	C ₁₄ H ₁₀ NO ₂ Cl (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, <i>J</i> = 9.2 and 2.0 Hz, 8-H), 7.94 (1H, d, <i>J</i> = 2.0 Hz, 6-H), 8.10 (1H, d, <i>J</i> = 9.2 Hz, 9-H)
3g	<i>m</i> -Cl	5c	17	183 - 184	EtOH	C ₁₄ H ₁₀ NO ₂ Cl (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, <i>J</i> = 7.4 and 2.3 Hz, 6-H)
3h	<i>p</i> -Cl	6c	58	220 - 221	EtOH	C ₁₄ H ₁₀ NO ₂ Cl (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, <i>J</i> = 9.0 and 2.0 Hz, 7-H), 7.98 (1H, d, <i>J</i> = 9.0 Hz, 6-H), 8.19 (1H, d, <i>J</i> = 2.0 Hz, 9-H)
3i	<i>o</i> -Cl	7c	45	247	EtOH	C ₁₄ H ₁₀ NO ₂ Cl (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, <i>J</i> = 7.4 and 8.7 Hz, 8-H), 7.94 (1H, dd, <i>J</i> = 7.4 and 1.3 Hz, 7-H), 8.17 (1H, dd, <i>J</i> = 8.7 and 1.3 Hz, 9-H)
3j	<i>m</i> -Br	4d	83	187 - 188	Et ₂ O	C ₁₄ H ₁₀ NO ₂ Br (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, <i>J</i> = 9.6 and 1.8 Hz, 8-H), 8.08 (1H, d, <i>J</i> = 9.6 Hz, 9-H), 8.18 (1H, d, <i>J</i> = 1.8 Hz, 6-H)
3j	<i>m</i> -Br	5d	10	186 - 187	EtOH	C ₁₄ H ₁₀ NO ₂ Br (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, <i>J</i> = 7.6 and 8.6 Hz, 7-H), 7.88 (1H, dd, <i>J</i> = 7.6 and 1.3 Hz, 8-H), 7.95 (1H, dd, <i>J</i> = 8.6 and 1.3 Hz, 6-H)
3k	<i>p</i> -Br	6d	45	217	EtOH	C ₁₄ H ₁₀ NO ₂ Br (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	<i>o</i> -Br	7d	63	256 (decomp)	EtOH	C ₁₄ H ₁₀ NO ₂ Br (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, <i>J</i> = 7.4 and 8.6 Hz, 8-H), 8.17 (1H, dd, <i>J</i> = 7.4 and 1.2 Hz, 7-H), 8.23 (1H, dd, <i>J</i> = 8.6 and 1.2 Hz, 9-H)
3m	<i>p</i> -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, <i>J</i> = 8.6 Hz, 6-H), 10.27 (1H, br, OH)
3n	H	7e	80	165	Et ₂ O	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 °C.

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

Compd. No.	R	Yield (%)	mp (°C)	Recryst. solvent	Formula (m/z M ⁺)	Analysis (%)			IR [KBr] (cm ⁻¹)	¹ H-NMR δ (ppm) [CDCl ₃ - DMSO] ^{a)}
						Calcd	Found			
						C	H	N		
8a	<i>o</i> -Cl	30	171	Et ₂ O	C ₁₂ H ₁₀ NO ₂ Cl (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	<i>p</i> -Cl	26	216 - 217	EtOH	C ₁₂ H ₁₀ NO ₂ Cl (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	<i>p</i> -Br	25	220 - 221	EtOH	C ₁₂ H ₁₀ NO ₂ Br (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	<i>m</i> -NO ₂	92	237	EtOH	C ₁₂ H ₁₀ N ₂ O 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	<i>p</i> -NO ₂	87	283 - 284 (decomp)	EtOH	C ₁₂ H ₁₀ N ₂ O 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	<i>o</i> -NH ₂	89	161 - 162	AcOEt	C ₁₂ H ₁₂ N ₂ O 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	<i>p</i> -NH ₂	67	224 (decomp)	AcOEt	C ₁₂ H ₁₂ N ₂ O 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 CDCl₃, **8c** in DMSO.

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 3. Y. Azuma, A. Sato, and M. Morone, *Heterocycles*, 1993, **35**, 599; *idem, ibid.*, 1994, **38**, 1573.
 4. Y. Azuma, A. Sato, and M. Morone, *Yakugaku Zasshi*, in press: Preparation of **3**: A solution of **1** (5.0 g, 24 mmol), 2.2 molar eq. of anilines, and Et₃N (7.3 g, 72 mmol) in EtOH (200 mL) was heated under reflux for 5 h. To the reaction mixture was added 10 % HCl (50 mL), and the mixture was stirred for 2 h at rt. The precipitates formed were separated by filtration and purified by recrystallization. The filtrate was concentrated *in vacuo*. To the residue was added CHCl₃ (200 mL). The solution was washed with water and dried over anhydrous Na₂SO₄. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel with CHCl₃.
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