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SYNTHESIS OF PYRIDOPYRANOQUINOLINES BY THE SKRAUP REACTION OF AMINO-5*H*-BENZOPYRANO[2,3-*b*]PYRIDIN-5-ONES

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Abstract - 7-, 8- and 9-amino-5*H*-[1]benzopyrano[2,3-*b*]-pyridin-5-ones were synthesized. Skraup reaction of 6-amino-, 7-amino-, 8-amino- and 9-amino-5*H*-[1]benzo-pyrano[2,3-*b*]pyridin-5-ones in the presence of glycerol, fuming sulfuric acid, nitrobenzene, iron(II) sulfate and boric acid gave 12*H*-pyrido[3′,2′:5,6]pyrano[2,3-*h*]-quinolin-12-one, 12*H*-pyrido[3′,2′:5,6]pyrano[3,2-*f*]-quinolin-12-one, 7*H*-pyrido[3′,2′:5,6]pyrano[2,3-*f*]quin-olin-7-one and 7*H*-pyrido[3′,2′:5,6]pyrano[3,2-*h*]quino-lin-7-one, respectively.

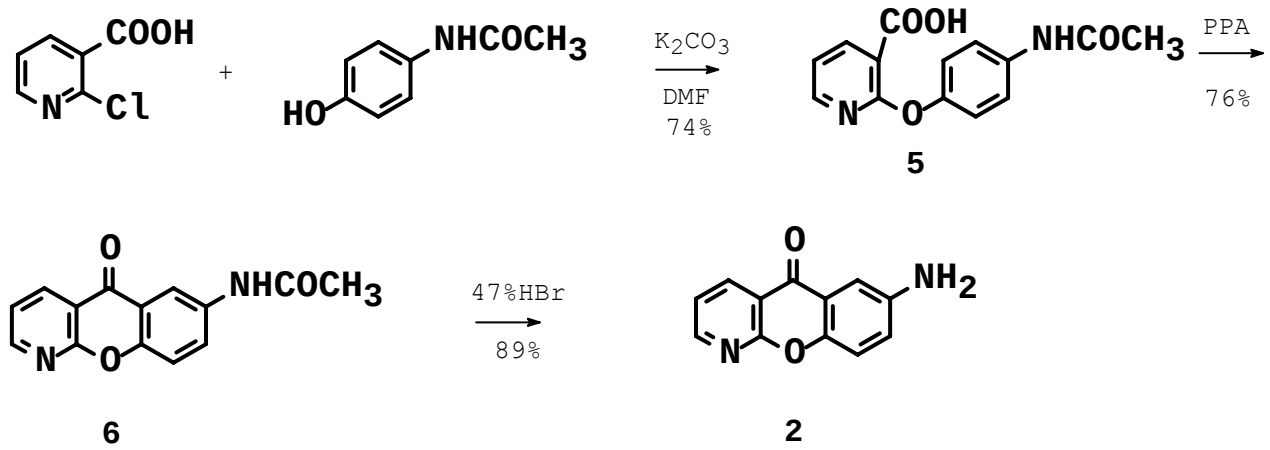
INTRODUCTION

In recent years, a number of heteroaromatic antitumor compounds have been prepared with the hope of increasing their pharmacological effects or to find new derivatives with reduced side effects.[1-3] DNA intercalating agents, which are a very important classes of antitumor drugs, usually possess planar aromatic and heteroaromatic polycyclic systems. Some thioxanthene derivatives are effective against tumors.[4-6] As an extension of our synthetic studies of xanthene derivatives, we prepared xanthene analogues consisting of a tetracyclic system containing two pyridine rings.[7-9] In this note we describe the synthesis of 12*H*-pyrido[3′,2′:5,6]pyrano[2,3-*h*]quinolin-12-one(**10**), 12*H*-pyrido[3‘,2′:5,6]pyrano[3′2-*f*]-quinolin-12-one(**11**), 7*H*-pyrido[3′,2′:5,6]pyrano[2,3-*f*]quinolin-7-one (**12**), and 7*H*-pyrido[3′,2′:5,6]pyrano[3,2-*h*]quinolin-7-one(**13**) by the Skraup reaction[10,11] of amino-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ones.

RESULTS AND DISCUSSION

The synthesis of 6-amino-5*H*-benzopyrano[2,3-*b*]pyridin-5-one(**1**) was described previously.[12]

The synthetic route of 7-amino-5*H*-benzopyrano[2,3-*b*]pyridin-5-one(**2**) is summarized in Scheme 1.

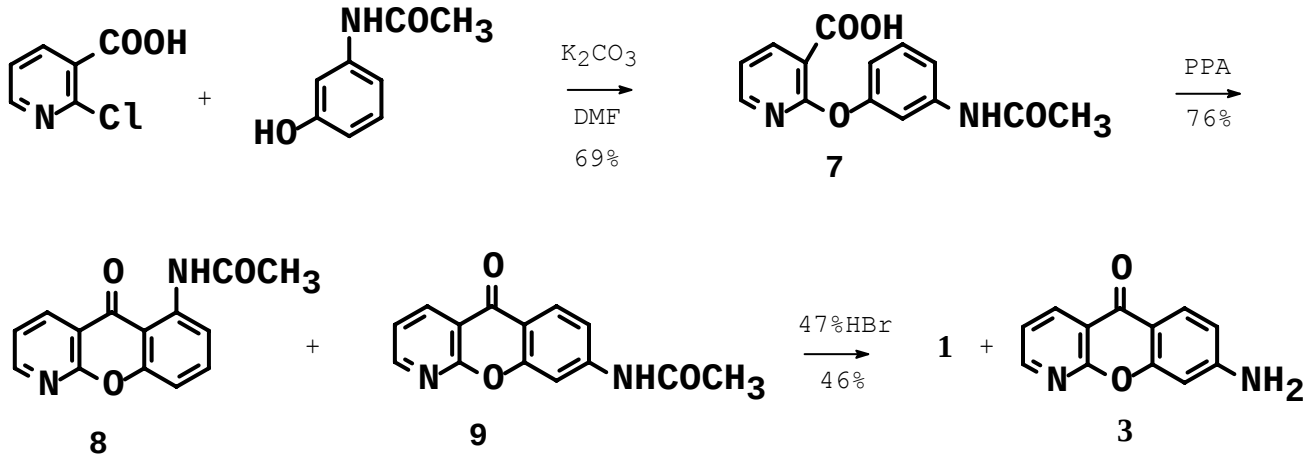


Scheme 1

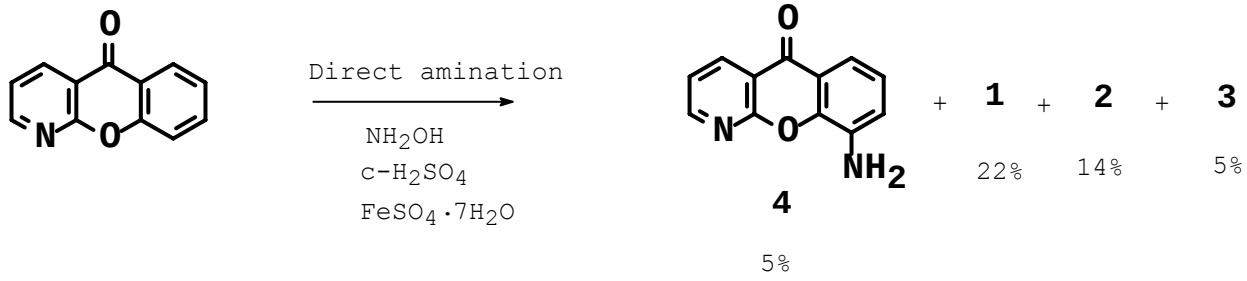
The Ullmann reaction of 2-chloronicotinic acid with 4-hydroxyacetanilide in the presence of K_2CO_3 in DMF under reflux for 2 h gave 2-(4-acetaminophenoxy)nicotinic acid (**5**)(yield 74%). This acid (**5**) was heated with PPA at 120°C for 3 h and then hydrolyzed with hydrobromic acid in the presence of phenol for 1 h to give 7-amino-5*H*-benzopyrano[2,3-*b*]pyridin-5-one (**2**)(yield 68% from **5**). In a similar way, the reaction of 2-chloronicotinic acid with 3-hydroxyacetanilide afforded 2-(3-acetaminophenoxy)-nicotinic acid (**7**) (yield 69%), which was cyclized with PPA and then hydrolyzed with hydrobromic acid to give a mixture of 6- (**1**) and 8-amino-5*H*-benzopyrano[2,3-*b*]pyridin-5-ones (**3**) (Scheme 2).

The mixture was separated by column chromatography to give **3** (yield 35% from **7**).

Although the Ullmann reaction of 2-chloronicotinic acid with *o*-hydroxyacetanilide or *o*-nitrophenol was attempted, it failed. One of synthetic method of amino-9*H*-xanthen-9-ones is direct amination using sulfuric acid and hydroxylamine.[13] Thus, this direct amination method was similarly applied to the amination of 5*H*-benzopyrano[2,3-*b*]pyridin-5-one to afford a mixture of 6-amino- (**1**)(yield 22%),7-amino- (**2**)(yield 14%), 8-amino- (**3**) (yield 5%) and 9-amino-5*H*-benzopyrano[2,3-*b*]pyridin-5-ones (**4**)(yield 5%) (Scheme 3).



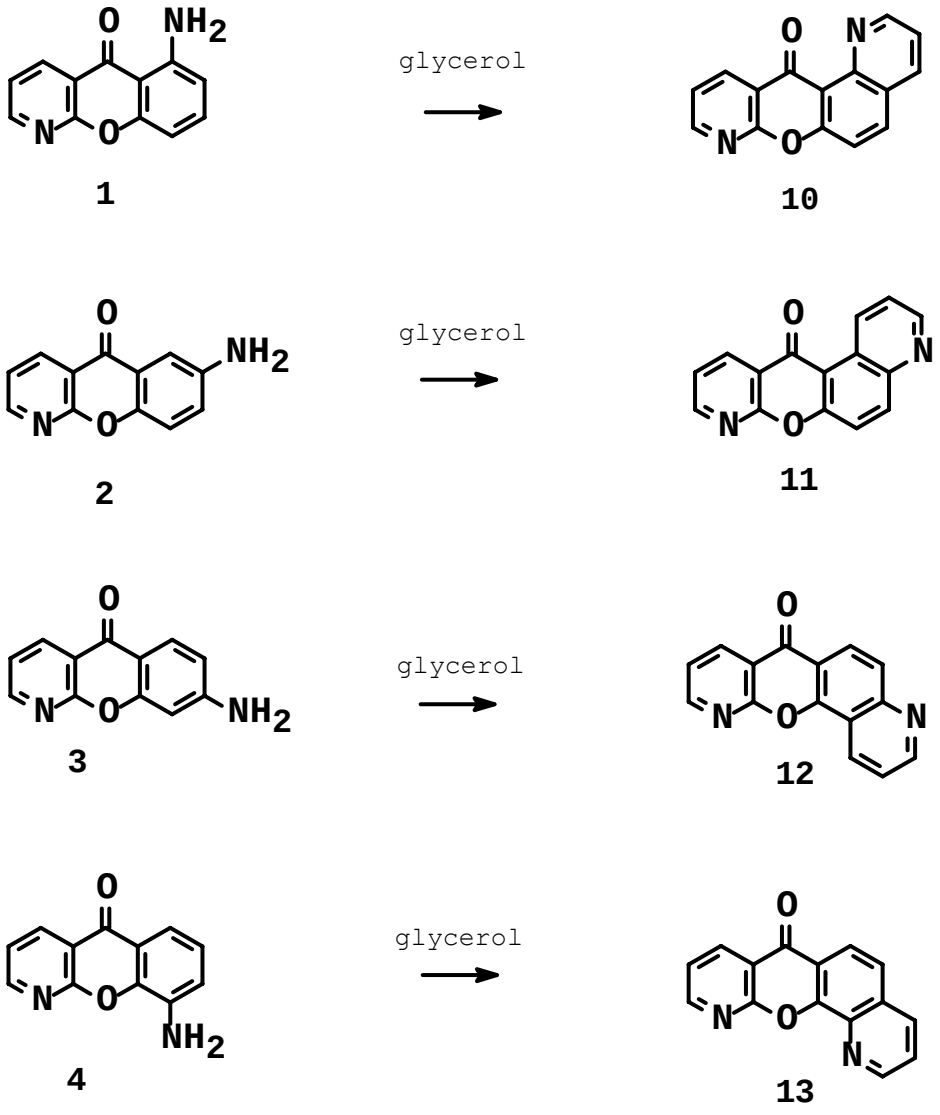
Scheme 2



Scheme 3

Skraup reactions of amino-5*H*-benzopyrano[2,3-*b*]pyridin-5-ones (**1**-**4**) with glycerol, fuming sulfuric acid, and nitrobenzene were conducted in the presence of iron(II) sulfate and boric acid, and all obtained products were found to have the molecular formula $C_{15}H_8N_2O_2$ based on the elemental analytical data and the MS spectra [*m/z* 248 ($M^{+\cdot}$)]. The Skraup reaction products are summarized in Scheme 4. The Skraup reaction of **1** gave 12*H*-pyrido[3′,2′:5,6]pyrano[2,3-*h*]quinolin-12-one (**10**) in 71 % yield. The structure of **10** was determined by ^{1}H-NMR. The ^{1}H-NMR showed proton signals of the new pyridine ring at δ 7.56 (dd, *J*=4.4, 8.3 Hz, 3-H), 8.25 (dd, *J*=1.9, 8.3 Hz, 4-H) and 9.29 (dd, *J*=1.9, 4.4 Hz, 2-H), and proton signals of the 5*H*-benzopyrano[2,3-*b*]pyridin-5-one skeleton at δ 7.79 (d, *J*=8.3 Hz, 6-H) and 8.16 (d, *J*=8.3 Hz, 5-H). The Skraup reaction of **2** afforded only 12*H*-pyrido[3′,2′:5,6]pyrano[3,2-*f*]quinolin-12-one (**11**) in 82% yield. The ^{1}H-NMR spectrum of **11** demonstrated a new pyridine ring and two doublet proton signals of the 5*H*-benzopyrano[2,3-*b*]pyridin-5-one skeleton as in the case of **2**.

Similarly, the Skraup reaction of **3** produced one product, 7*H*-pyrido [3′, 2′:5,6]pyrano[2,3-*f*]quinolin-7-one (**12**), in 75 % yield, and the structure of **12** was confirmed by ^{1}H-NMR spectrum as in the case of **11**. Based on the present results, the Skraup reaction of **3** affored the corresponding angular-type product (**12**) without the linear-type product. Skraup reaction of **4** gave 7*H*-pyrido[3′,2′:5,6]pyrano[3,2-*h*]quinolin-7-one (**13**) in 84 % yield.



1 **10**

2 **11**

3 **12**

4 **13**

Scheme 4

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 260-10

spectrophotometer. ^{1}H-NMR spectra were measured on a JEOL FX-400 instrument using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. MS were taken with a Hitachi M-2500 spectrometer.

2-(4-Acetamidophenoxy)nicotinic acid (5)

A mixture of 2-chloronicotinic acid (7.85 g, 50 mmol), 4-acetamidophenol (7.55 g, 50 mmol), potassium carbonate (13.8 g, 100 mmol), copper (0.7 g), cuprous iodide (0.7 g) and DMF (120 mL) was stirred under reflux for 2 h, cooled and filtered. The filtrate was concentrated. The residue was mixed with hot water, filtered, and the filtrate was acidified with 10% hydrochloric acid. The resulting precipitate was collected. The residue was purified by recrystallization from methanol to give **5** (10.0 g, 74%) as colorless needles. mp 241-242 °C. Anal. Calcd for $C_{14}H_{12}N_2O_4$: C,61.76; H,4.44; N, 10.29. Found: C, 61.68; H, 4.65; N, 10.13. ^{1}H-NMR(DMSO-d_6) δ: 7.03(1H, dd, J=2.0, 8.8 Hz, 2′-H), 7.20(1H, dd, J=4.9, 7.3 Hz, 3-H), 7.59 (1H, dd, J=2.0, 8.8 Hz, 3′-H), 8.22 (1H, dd, J=2.0, 7.3 Hz, 4-H), 8.30 (1H, dd, J=2.0, 4.9 Hz, 2-H), 9.96 (1H, s, NH). MS: ***m/z*** 272 ($M^{+\cdot}$).

7-Acetamido-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (6)

2-(4-Acetamidophenoxy)benzoic acid (10 g, 40 mmol) was heated with PPA (300 g) at 130°C for 8 h. The hot reaction solution was poured into water, and the resulting precipitate was collected, washed and recrystallized from methanol to give **6** (7.2 g, 76%). mp 225-226 °C. Anal. Calcd For $C_{14}H_{10}N_2O_3$: C, 66.13, H, 3.96, N, 11.02. Found: C, 65.89, H, 4.26, N, 11.03. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, CH_3), 7.63 (1H, dd, ***J***=4.4, 7.8 Hz, 3-H),7.72 (1H, d, ***J***=8.8 Hz, 9-H), 8.03 (1H, dd, ***J***=2.9, 8.8 Hz, 8-H), 8.48 (1H, d, ***J***=2.9 Hz, 6-H), 8.64 (1H, dd, ***J***=2.0, 7.8 Hz, 4-H), 8.82 (1H, dd, ***J***=2.0, 4.4 Hz, 2-H). MS: ***m/z*** 254 ($M^{+\cdot}$).

7-Amino-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (2)

Compound (**6**, 7.2 g, 30 mmol) heated with 47% hydrobromic acid (100 mL) and phenol (5.6 g, 60 mmol) under reflux for 2 h. After cooling, the mixture was basified with 10% aqueous sodium hydroxide to give a yellow solid which was recrystallized from methanol to afford **2** (4.97 g, 89%) as yellow needles, mp 253-254 °C. ***Anal.*** Calcd for $C_{12}H_8N_2O_2$: C, 67.91; H, 3.80;

N, 13.21. Found: C, 67.83; H, 3.89; N, 13.19. IR (KBr): 1600, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.16 (1H, dd, ***J***=3.0, 8.7 Hz, 8-H), 7.41 (1H, dd, ***J***=4.7, 7.8 Hz, 3-H), 7.47 (1H, d, ***J***=8.3 Hz, 9-H), 7.50 (1H, d, ***J***=3.0, 6-H), 8.71 (1H, dd, ***J***=2.0, Hz, 4-H), 8.73 (1H, dd, ***J***=2.0, 4.7 Hz, 2-H). MS: ***m/z*** 212 ($M^{+\cdot}$).

2-(3-Acetamidophenoxy)nicotinic acid (7)

A mixture of 2-chloronicotinic acid (7.85 g, 50 mmol), 3-acetamidophenol (7.55 g, 50 mmol), potassium carbonate (13.8 g, 100 mmol), copper powder (0.7 g), cuprous iodide (0.7 g) and DMF (120 mL) was stirred under reflux for 2 h, then cooled and filtered. The filtrate was concentrated. The residue was mixed with hot water, filtered, and acidified with 10% hydrochloric acid. The resulting precipitate was collected by filtration and recrystallized from methanol to give **7** (9.33 g, 69%) as colorless needles. mp 283-284 °C. Anal. Calcd for $C_{14}H_{12}N_2O_4$: C,61.76; H,4.44; N, 10.29. Found: C, 61.92; H, 4.59; N, 10.32. ^{1}H-NMR (DMSO-d_6) δ: 2.03 (3H, s, CH_3), 6.77 (1H, dd, ***J***=2.0, 7.3 Hz, 6‘-H), 7.24 (1H, dd, ***J***=4.9, 7.3 Hz, 3-H), 7.27-7.88 (2H, m, 4’-H, 5‘-H), 7.44 (1H, s, 2’-H), 8.25 (1H, dd, ***J***=2.0, 7.3 Hz, 4-H), 8.28 (1H, dd, ***J***=2.0, 4.9 Hz, 2-H), 9.96 (1H, s, NH). MS: ***m/z*** 272 ($M^{+\cdot}$).

8-Amino-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (3)

Compound (**7**, 9.33 g, 40 mmol) was heated with PPA (500 g) at 130°C for 6 h. The hot solution was poured into ice-water. The resulting precipitate was collected (a mixture of **8** and **9** , 6.60 g, 77%), and then heated with 47% hydrobromic acid (120 mL) and phenol (7.5 g, 80 mmol) under reflux for 2 h. After cooling, the mixture was alkalinized with 10% aqueous sodium hydroxide to give a mixture of **1** and **3** as a yellow solid. This mixture was separated by silica gel column chromatography ($CHCl_3$) to afford **1** (1.07 g, 14 %) and **3** (1.27 g, 16%). Compound (**3**) : Pale yellow needles (from MeOH); mp 272-273 °C. ***Anal***. Calcd for $C_{12}H_8N_2O_2$: C, 67.91; H, 3.80; N, 13.21. Found: C, 67.95; H, 3.96; N, 13.15. IR (KBr): 1585, 1620 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 6.69 (1H, dd, ***J***= 2.0, 8.3 Hz, 7-H), 6.70 (1H, d, ***J***=2.0 Hz, 9-H), 7.39 (1H, dd, ***J***=4.8, 7.3 Hz, 3-H), 8.11 (1H, d, ***J***=8.3 Hz, 6-H), 8.66 (1H, dd, ***J***=1.9, 4.8 Hz, 2-H), 8.68 (1H, dd, ***J***=1.9, 7.3 Hz, 4-H). MS: m/z

212 ($M^{+\cdot}$).

9-Amino-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (4)

A mixture of 5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (19.7 g, 100 mmol), hydroxylamine sulfate (10 g, 50 mmol), ferrous sulfate (37 g,) and 94 % sulfuric acid (400 g) was stirred at 140-150 °C for 7 h. The reaction mixture was poured into water and then filtered. To the filtrate was added potassium hydrogen tartrate and the mixture was basified with 25% ammonium hydroxide. The resulting precipitate was collected by filtration and dried (13.17 g). The products were purified with silica gel (solvent: benzene) and alumina column chromatography (solvent: chloroform) to give 6-amino- (**1**) (4.57 g, 22%), 7-amino- (**2**) (2.88 g, 14 %), 8-amino- (**3**) (1.10 g, 5%) and 9-amino-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one(**4**)(1.04 g, 5%).

Compound (**4**): Yellow needles (from methanol), mp 212-213 °C. *Anal*. Calcd for $C_{12}H_8N_2O_2$: C, 67.91; H, 3.80; N, 13.21. Found: C, 68.01; H, 3.86; N, 13.32. IR (KBr): 1580, 1650 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ : 7.12 (1H, dd, *J*= 1.5, 7.8 Hz, 8-H), 7.21 (1H, t, *J*=7.8 Hz, 7-H), 7.44 (1H, dd, *J*=3.5, 5.4 Hz, 3-H), 7.66 (1H, dd, *J*=1.5, 7.8 Hz, 6-H), 8.72 (1H, dd, *J*=1.5, 3.5 Hz, 2-H), 8.73 (1H, dd, *J*=1.5, 5.4 Hz, 4-H). MS: m/z 212 ($M^{+\cdot}$).

General procedure for the Skraup reaction of amino-5*H*-benzopyrano[2,3-*b*]-pyridin-5-ones (1-4)

A mixture of $H_2SO_4 \cdot SO_3$ (6.0 g, 50 mmol), nitrobenzene (1.23 g, 10 mmol), $FeSO_4 \cdot 7H_2O$ (0.28 g, 1.0 mmol) and H_3BO_3 (0.31 g, 5.0 mmol) was chilled to 0-5 °C, and then glycerol (1.84 g, 20 mmol), amino-5*H*-benzopyrano[2,3-*b*]-pyridin-5-one (1.06 g, 5 mmol) and water (2.5 mL) were successively added. The mixture was heated at 130°C for 5 h. The reaction mixture was basified with 28 % NH_4OH, the resulting precipitate was collected by filtration, and the precipitate was dissolved in $CHCl_3$. The extract was dried over Na_2SO_4, the solvent was evaporated and the residue was recrystallized from MeOH to give the corresponding pyrido[3′,2′:5,6]-pyranoquinoline derivative.

12*H*-Pyrido[3′,2′:5,6]pyrano[2,3-*h*]quinolin-12-one(10)

Colorless needles, mp 237-238 °C. Yield 71 %. ***Anal***. Calcd for $C_{15}H_8N_2O_2$: C,72.56; H, 3.25; N, 11.29. Found: C, 72.60; H, 3.07; N, 11.26. IR (KBr): 1580, 1600, 1640 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 7.51 (1H, dd, ***J***=4.4, 7.8 Hz, 10-H), 7.56 (1H, dd, ***J***=4.4, 8.3 Hz, 3-H), 7.79 (1H, d, ***J***=8.8 Hz, 6-H), 8.14 (1H, d, ***J***=8.8 Hz, 5-H), 8.25 (1H, dd, ***J***=2.0, 8.3 Hz, 4-H), 8.75 (1H, dd, ***J***=2.0, 4.4 Hz, 9-H), 8.85 (1H, dd, ***J***=2.0, 7.8 Hz, 11-H), 9.29 (1H, dd, ***J***=2.0, 4.4 Hz, 2-H). MS: m/z 248 ($M^{+\cdot}$).

12*H*-Pyrido[3′,2′:5,6]pyrano[3,2-*f*]quinolin-12-one(11)

Colorless needles, mp 190-191 °C. Yield 82 %. ***Anal***. Calcd for $C_{15}H_8N_2O_2$: C, 72.56; H, 3.25; N, 11.29. Found: C, 72.72; H, 3.33; N, 11.41. IR (KBr): 1580, 1600, 1620 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 7.69 (1H, dd, ***J***=4.4, 7.8 Hz, 10-H), 7.79 (1H, dd, ***J***=4.4, 8.7 Hz, 2-H), 8.04 (1H, d, ***J***=9.3 Hz, 6-H), 8.49 (1H, d, ***J***=9.3 Hz, 5-H), 8.79 (1H, dd, ***J***=2.0, 7.8 Hz, 11-H), 8.87 (1H, dd, ***J***=2.0, 4.4 Hz, 9-H), 9.02 (1H, dd, ***J***=1.0, 8.7 Hz, 3-H), 10.27 (1H, dd, ***J***=1.0, 8.7 Hz, 1-H). MS: m/z 248 ($M^{+\cdot}$).

7*H*-Pyrido[3′,2′:5,6]pyrano[2,3-*f*]quinolin-7-one (12)

Colorless needles, mp 218-219 °C. Yield 75 %. ***Anal***. Calcd for $C_{15}H_8N_2O_2$: C, 72.56; H, 3.25; N, 11.29. Found: C,72.39; H, 3.33; N, 11.22. IR (KBr): 1580, 1600, 1640 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 7.54 (1H, dd, ***J***=4.4, 7.8 Hz, 9-H), 7.64 (1H, dd, ***J***=4.4, 8.3 Hz, 2-H), 8.03 (1H, d, ***J***=8.8 Hz, 5-H), 8.45 (1H, d, ***J***=8.8 Hz, 6-H), 8.78 (1H, dd, ***J***=1.9, 7.8 Hz, 8-H), 8.81 (1H, dd, ***J***=1.9, 4.4 Hz, 10-H), 9.08 (1H, dd, ***J***=2.0, 8.3 Hz, 1-H), 9.11 (1H, dd, ***J***=2.0, 4.4 Hz, 3-H). MS: m/z 248 ($M^{+\cdot}$).

7*H*-Pyrido[3′,2′:5,6]pyrano[3,2-*h*]quinolin-7-one (13)

Colorless needles, mp 291-292 °C. Yield 84 %. ***Anal***. Calcd for $C_{15}H_8N_2O_2$: C, 72.56; H, 3.25; N, 11.29. Found: C,72.72; H,3.25; N, 11.39. IR (KBr): 1580, 1600, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.54 (1H, dd, ***J***=4.4, 7.8 Hz, 9-H), 7.69 (1H, dd, ***J***=4.4, 8.3 Hz, 3-H), 7.80 (1H, d, ***J***=8.8 Hz, 5-H), 8.30 (1H, dd, ***J***=1.5, 8.3 Hz, 4-H), 8.36 (1H, d, ***J***=8.8 Hz, 6-H), 8.80 (1H, dd, ***J***=2.0, 7.8 Hz, 8-H), 8.87 (1H, dd, ***J***=2.0, 4.4 Hz, 10-H), 9.20 (1H, dd, ***J***=1.5, 4.4 Hz, 2-H). MS:m/z 248 (M^+).

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REFERENCES

1. W. A. Denny, B. F. Cain, G. J. Atwell, C. Hansch, A. Panthananickal, and A. Leo, ***J. Med. Chem.***, 1982, **25**, 276.
2. I. Antonini and S. Martelli, ***J. Heterocycl. Chem.***, 1992**, 29,** 471.
3. W. M. Cholody, S. Martelli, and J. Konopa, ***J. Med. Chem.***, 1992, **35,** 378.
4. S. Archer, L. Pica-Mattoccia, D. Cioli, A. Seyed-Mozaffari, and A.-H. Zayed**, *J. Med. Chem.*,** 1988, **31**, 254.
5. H. D. H. Showalter, M. M. Angelo, E. M. Berman, G. D. Kanter, D. F. Ortwine, S. G. Ross-Kesten, A. D. Sercel, W. R. Turner, L. M. Werbel, D. F. Worth, E. F. Elslager, W. R. Leopold, and J. L. Shillis*, J. Med. Chem., 1988, **31**, 1527.*
6. S. Archer, K. J. miller, R. Rej, C. Periana, and L. Fricker, ***J. Med. Chem.***, 1982, **25**, 220.
7. H. Fujiwara and I. Okabayashi, ***Heterocycles***, 1993, **36**, 1105.
8. H. Fujiwara and I. Okabayashi, ***Chem. Pharm. Bull.***, 1993, **41**, 1163.
9. H. Fujiwara, ***Heterocycles***, 1997, **45**, 119.
10. I. Takeuchi, Y. Hamada, and K. Okamura, ***Heterocycles***, 1989, **29**, 2109.
11. I. Takeuchi and Y. Hamada, ***Chem. Pharm. Bull.***, 1976, **24**, 1813.
12. H. Fujiwara and I. Okabayashi, ***Heterocycles***, 1993, **36**, 1105.
13. J. F. de Turski, Ger. Pat. 287756, 1914(***Chem. Abstr.***, 1916, **10**, 2128).