# PREPARATION OF PYRIDO[3′,2′:5,6]THIOPYRANO[4,3,2-*de*]-QUINOLINE

Hidetoshi Fujiwara* and Ichizo Okabayashi

Niigata College of Pharmacy, 5-13-2 Kamishin'ei-cho, Niigata, 950-21, Japan

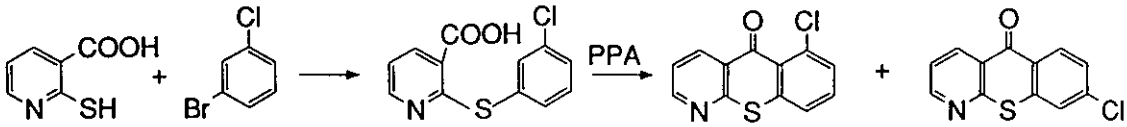
*Abstract* —— New tetracyclic compound, pyrido[3′,2′:5,6]thiopyrano[4,3,2-*de*]quinoline (**1**) was synthesized from 6-amino-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (**2**) in a ten step sequence.

One of the most important classes of antitumor drugs, the DNA intercalating agents, usually possess a planar aromatic or heteroaromatic polycyclic system with one or two flexible cationic side chains in the appropriate position. Among them acridines represent one of the groups early and most thoroughly investigated.[1-5]

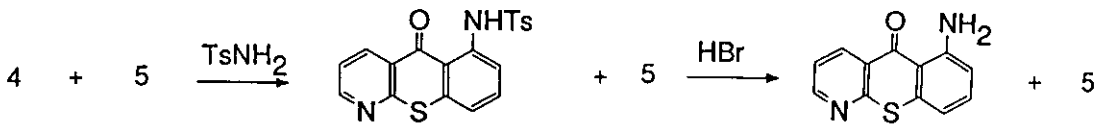
The search of new heterocyclic ring was stimulated by the recent reports that the polyheterocyclic compounds from marine products showed antitumor activity.[6-13]

Tetracyclic compounds, 2-dimethylamino[1]benzopyrano[4,3,2-*de*]quinoline,[14] 10-chloro-*N*,*N*-dimethyl[1]benzothiopyrano[4,3,2-*de*]cinnoline-1-ethanamine,[15] and 1-amino-6-methyl[1]benzothiopyrano[4,3,2-*de*]quinolin-2(3*H*)-one,[16] derived from 1-amino-9*H*-xanthen-9-one and 1-amino-9*H*-thioxanthen-9-one were already synthesized and reported to have analgesic and psychopharmacological activities.

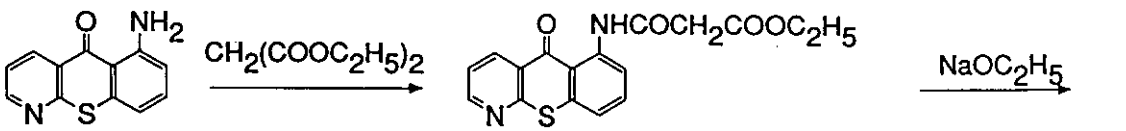
In this paper, we report the synthesis of new tetracyclic compound,




3 4 5

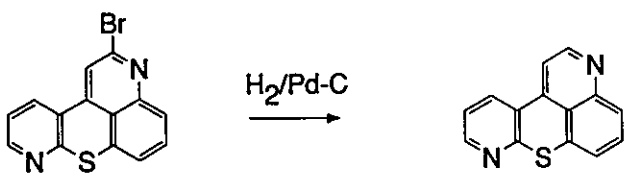



6 2




2 7


8 9 10




11 1

pyrido[3',2':5,6]thiopyrano[4,3,2-*de*]quinoline (**1**) from 6-amino-5*H*-[1]-benzothiopyrano[2,3-*b*]pyridin-5-one (**2**).

## RESULTS AND DISCUSSION

The Ullmann reaction of 2-mercaptonicotinic acid with *m*-bromochlorobenzene in dimethylformamide (DMF) under reflux gave 2-[(3-chlorophenyl)thio]-nicotinic acid (**3**) in 84% yield. Compound (**3**) was treated with polyphosphoric acid (PPA) to give a mixture (1:1) of 6-chloro-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (**4**) and 8-chloro-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (**5**) in 90% yield. These compounds were not separated with column chromatography. The reaction of the mixture with *p*-toluenesulfonamide ($TsNH_2$) in DMF gave a mixture of 6-(*p*-toluenesulfonamido)-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (**6**) and **5**. The mixture was treated successively with 47% HBr in the presence of phenol to give **2** in 36% yield (from the mixture of **4** and **5**) and **5**. The ir spectrum of **2** showed the absoption due to the amino group at 3430 $cm^{-1}$ and its nmr spectrum gave the signal of the amino group at $\delta$ 7.00. The product was sufficiently pure for use in the next reaction. This method is effective to obtain a large amount of **2**. By refluxing crude **2** with diethyl malonate, 6-carbethoxyacetamido-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (**7**) was obtained in 85% yield. The ir spectrum of **7** showed the absorptions due to the ester carbonyl group at 1730 $cm^{-1}$ and the amido carbonyl group at 1680 $cm^{-1}$, and its nmr spectrum showed signals due to the hydrogens of the ethyl group at $\delta$ 1.34 and 4.32 and methylene group at $\delta$ 3.60. Compound (**7**) was refluxed with sodium ethoxide in ethanol to give ethyl 2-hydroxypyrido[3',2':5,6]thiopyrano-[4,3,2-*de*]quinoline-1-carboxylate (**8**) in 80% yield. The nmr spectrum of **8** gave no signal due to hydrogens of methylene group and its mass spectrum showed a molecular ion peak at *m/z* 324. Hydrolysis of the ester (**8**) with an aqueous sodium hydroxide solution gave the corresponding carboxylic acid (**9**) in 92% yield. The carboxylic acid (**9**) was decarboxylated by

heating at 300°C to give 2-hydroxypyrido[3',2':5,6]thiopyrano[4,3,2-*de*]-quinoline (**10**) in 90% yield. The nmr spectrum of **10** showed the signal (1H, s) due to a $C_1$-H at δ 7.12. A mixture of **10** and phosphorus pentabromide was heated at 130°C to give 2-bromopyrido[3',2':5,6]thiopyrano-[4,3,2-*de*]quinoline (**11**) in 88% yield. The Beilstein test of compound (**11**) showed positive, and its mass spectrum showed molecular ion peaks of the same intensities at *m/z* 314 and 316. These data supported the presence of a bromine atom. The compound (**11**) was reduced with hydrogen and 5% Pd-C at 60°C in acetic acid under one atmospheric pressure to afford pyrido[3',2':5,6]thiopyrano[4,3,2-*de*]quinoline (**1**) in 85% yield. The reduction did not proceed at room temperature.

## EXPERIMENTAL

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Ir spectra were measured with a Hitachi 260-10 spectrophotometer. $^1$HNmr spectra were obtained on JEOL FX-200 (200 MHz) and JEOL JNM-A400 (400 MHz) spectrometers in chloroform-*d* unless otherwise noted, with tetramethylsilane as an internal standard. Ms and high resolution ms (HRms) were recorded on a Hitachi RMU-7MG mass spectrometer with a direct inlet system and $M^{+\cdot}$ are indicated as *m/z*. Column chromatography was performed on Wakogel C-200 (silica gel). Thin layer chromatography (tlc) performed on precoated Kieselgel 60 $PF_{254}$ (Merck).

**6-Chloro- (4) and 8-Chloro-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-ones (5)**

A mixture of 2-mercaptonicotinic acid (15.5 g, 100 mmol), *m*-bromochlorobenzene (21.0 g, 110 mmol), anhydrous potassium carbonate (30.0 g, 220 mmol), copper powder (1.4 g, 20 mmol), and copper iodide (1.4 g, 7 mmol), in DMF (240 ml) was stirred under reflux for 12 h. The cooled mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was treated with hot water and then acidified with 5% HCl. The precipitate was collected and dried to give **3** (22.3 g, 84 %).

A mixture of the above acid **3** (11.6 g, 40 mmol) and PPA(500 g) was heated at 120°C with stirring for 3 h, then cooled, poured into water, and filtered. The filtered cake was washed with water, 10% sodium hydrogen carbonate solution, and again with water. The mixture (1:1) of **4** and **5** weighed 8.9 g (90 %). The mixture of **4** and **5** was separated by preparative tlc (silica gel, $CHCl_3$).

**4**: colorless needles (from MeOH). mp 189-190°C. Anal. Calcd for $C_{12}H_6ClNOS$: C, 58.30; H, 2.45; N, 5.67. Found: C, 58.51; H, 2.32; N, 5.47. Ir (KBr): 1730(CO), 1670, 1600, 1595 $cm^{-1}$. $^1$HNmr δ:7.42 (1H, dd, *J*=5, 8 Hz, 3-H), 7.50-7.60 (3H, m, 7-H, 8-H, 9-H), 8.70 (1H, d, *J*=8 Hz, 4-H), 8.74 (1H, d, *J*=5 Hz, 2-H). HRms *m/z*: Calcd for $C_{12}H_6ClNOS$: 246.9858. Found: 246.9868 ($M^{+\cdot}$).

**5**: colorless needles (from MeOH). mp 209-210°C. Anal. Calcd for $C_{12}H_6ClNOS$: C, 58.30; H, 2.44; N, 5.67. Found: C, 58.27; H, 2.55; n,5.34. Ir (KBr): 1730(CO), 1665, 1600, 1595 $cm^{-1}$. $^1$HNmr δ: 7.44 (1H, dd, *J*=5, 8 Hz, 3-H), 7.46 (1H, d, *J*=8 Hz, 7-H), 7.64 (1H, s, 9-H), 8.50 (1H, d, *J*=8 Hz, 6-H), 8.78 (1H, d, *J*=8 Hz, 4-H), 8.80 (1H, d, *J*=5 Hz, 2-H). HRms *m/z*: Calcd for $C_{12}H_6ClNOS$: 246.9858. Found: 246.9845 ($M^{+\cdot}$).

As it is difficult to separate **4** and **5** by column chromatography, a mixture of **4** and **5** was used in next reaction without separation.

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

The mixture (12.4 g, 50 mmol) of **4** and **5**, $TsNH_2$ (17.1 g, 100 mmol), anhydrous sodium acetate (8.2 g, 100 mmol), and copper (II) acetate monohydrate (1.0 g, 5 mmol) were mixed in *n*-amyl alcohol (160 ml), and the whole was stirred under reflux for 8 h in an oil bath at 160-170°C. After cooling, the resulting solid was filtered, dried to give 13.4 g as a mixture of **5** and 6-(*p*-toluenesulfonamido)-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (**6**). A mixture (13.4 g) of **5** and **6**, phenol (14.1 g, 150 mmol), and 47% HBr (150 ml) were stirred and heated under reflux for 8 h. After cooling, the acidic solution was extracted with chloroform. The acidic

layer was poured into 30% sodium hydroxide solution. The precipitate was filtered to give **2** (3.3 g, 36 %) as yellow needles (from MeOH). mp 181-182°C. Ir (KBr): 3430($NH_2$), 3300, 1600, 1560 $cm^{-1}$. $^1$HNmr δ : 6.56 (1H, d, *J*=8 Hz, 9-H), 6.78 (1H, d, *J*=8 Hz, 7-H), 7.00 (2H, br s, $NH_2$), 7.22 (1H, t, *J*=8 Hz, 8-H), 7.32 (1H, dd, *J*=5, 8 Hz, 3-H), 8.66 (1H, d, *J*=8 Hz, 4-H), 8.68 (1H, d, *J*=5 Hz, 2-H). HRms *m/z*: Calcd for $C_{12}H_8N_2OS$: 228.0356. Found: 228.0355.

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

A solution of **2** (7.0 g, 30 mmol) in diethyl malonate (60 ml, 368 mmol) was boiled for 20 min, then an excess of diethyl malonate was removed by evaporation. The residue was purified by columm chromatography on silica gel ($CHCl_3$) to give **7** (8.9 g, 85 %) as pale yellow needles. mp 146-147°C (MeOH). Anal. Calcd for $C_{17}H_{14}N_2O_4S$: C, 59.64; H, 4.12; N, 8.19. Found: C, 59.62; H, 4.34; N, 8.15. Ir (KBr): 3450(CONH), 1730 ($COOC_2H_5$), 1680(CONH), 1600, 1590 $cm^{-1}$. $^1$HNmr δ: 1.34 (3H, t, *J*=8 Hz, $CH_3$), 3.60 (2H, s, $CH_2$), 4.32 (2H, q, *J*=8 Hz, $CH_2CH_3$), 7.34 (1H, d, *J*=8 Hz, 9-H), 7.40-7.50 (2H, m, 3-H, 7-H), 7.60 (1H, t, *J*=8 Hz, 8-H), 8.76 (1H, d, *J*=5 Hz, 2-H), 8.80 (1H, d, *J*=8 Hz, 4-H). HRms *m/z*: Calcd for $C_{17}H_{14}N_2O_4S$: 342.0673. Found: 342.0681 ($M^{+\cdot}$).

**Ethyl 2-Hydroxypyrido[3′,2′,:5,6]thiopyrano[4,3,2-*de*]quinoline-1-carboxylate (8)**

A solution of sodium ethoxide in ethanol, prepared from sodium (1.0 g, 40 mmol) and ethanol (30 ml), was added to a boiling suspension of **7** (3.4 g, 10 mmol) in ethanol (90 ml). The mixture was boiled for 15 min and then cooled. The solid product was stirred for several times with dilute HCl, then washed and dried, giving **8** (2.6 g, 80 %) as yellow powder (from acetic acid). mp 256-257°C. Anal. Calcd for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64. Found: C, 62.83; H, 3.81; N, 8.65. Ir (KBr): 3400 (CONH), 1745 ($COOC_2H_5$), 1660 (CONH), 1640, 1610, 1590 $cm^{-1}$. $^1$HNmr δ : 1.36 (3H, t, *J*=8 Hz, $CH_3$), 4.46 (2H, q, *J*=8 Hz, $CH_2$), 7.10-7.30 (3H, m, 4-H, 6-H, 10-H),

7.46 (1H, t, *J*=8 Hz, 5-H), 8.20 ( 1H, d, *J*=8 Hz, 11-H), 8.48 (1H, d, *J*=5 Hz, 9-H). HRms *m/z*: Calcd for $C_{17}H_{12}N_2O_3S$: 324.0568. Found: 324.0586 ($M^{+\cdot}$).

**2-Hydroxypyrido[3′,2′:5,6]thiopyrano[4,3,2-*de*]quinoline-1-carboxylic acid (9)**

The ester **(8)** (2.4 g, 7 mmol) was saponified by boiling for 6 h with excess 5% aqueous sodium hydroxide. The solution was then poured into excess hot dilute HCl and the product was crystallized from acetic acid, giving **9** (1.9 g, 92 %) as yellow powder. mp >300°C. Anal. Calcd for $C_{15}H_8N_2O_3S$: C, 60.81; H, 2.72; N, 9.46. Found: C, 60.64; H, 2.94; N, 9.51. Ir (KBr): 3430(CONH), 1720 (COOH), 1630, 1570 $cm^{-1}$. $^1$HNmr δ (DMSO-$d_6$): 7.17 (1H, d, *J*=8 Hz, 6-H), 7.25 (1H, d, *J*=8 Hz, 4-H), 7.43 (1H, dd, *J*=5, 8 Hz, 10-H), 7.52 (1H, t, *J*=8 Hz, 5-H), 8.36 (1H, d, *J*=8 Hz, 11-H), 8.57 (1H, d, *J*=5 Hz, 9-H). HRms *m/z*: Calcd for $C_{15}H_8N_2O_3S$: 296.0255. Found: 296.0239 ($M^{+\cdot}$).

**2-Hydroxypyrido[3′,2′:5,6]thiopyrano[4,3,2-*de*]quinoline (10)**

The acid **(9)** (1.5 g, 5 mmol) left a residue of nearly pure decarboxylation product **10** (1.2 g, 90 %) when it was heated at 300°C. Sublimation (300°C) gave yellow needles. mp >300°C. Ir (KBr): 3450(CONH), 1640(CONH), 1560 $cm^{-1}$. $^1$HNmr δ (DMSO-$d_6$): 7.11 (1H, d, *J*=8 Hz, 6-H), 7.12 (1H, s, 1-H), 7.13 (1H, d, *J*=8 Hz, 4-H), 7.38 (1H, dd, *J*=5, 8 Hz, 10-H), 7.45 (1H, t, *J*=8 Hz, 5-H), 8.63 (1H, d, *J*=5 Hz, 9-H), 8.65 (1H, d, *J*=8 Hz, 11-H). HRms *m/z*: Calcd for $C_{14}H_8N_2OS$: 252.0357. Found: 252.0382.

**2-Bromopyrido[3′,2′:5,6]thiopyrano[4,3,2-*de*]quinoline (11)**

A mixture of **10** (1.3 g, 5 mmol) and phosphorus pentabromide (2.55 g, 6 mmol) was heated in an oil bath at 130°C for 1 h, then cooled and poured on ice. The resulting product was filtered, then washed with 5% aqueous sodium hydrogen carbonate and water, and dried, giving **11** (1.4 g, 88 %) as yellow crystals. mp 213-214°C. Anal. Calcd for $C_{14}H_7BrN_2S$: C, 53.51; H, 2.25; N, 8.92. Found: C, 52.49; H, 2.37; N, 8.54. Ir (KBr): 1630, 1595 $cm^{-1}$. $^1$HNmr δ: 7.20 (1H, dd, *J*=5, 8 Hz, 10-H), 7.30 (1H, d, *J*=8 Hz, 6-H),

7.54 (1H, t, *J*=8 Hz, 5-H), 7.64 (1H, s, 1-H), 7.68 (1H, d, *J*=8 Hz, 4-H), 8.16 (1H, d, *J*=8 Hz, 11-H), 8.46 (1H, d, *J*=5 Hz, 9-H). HRms *m/z*: Calcd for $C_{14}H_7BrN_2S$: 313.9514. Found: 313.9519 ($M^{+\cdot}$).

**Pyrido[3',2':5,6]thiopyrano[4,3,2-de]quinoline (1)**

A solution of **11** (1.6 g, 5 mmol) and anhydrous sodium acetate (0.5 g, 6 mmol) in acetic acid (50 ml) was stirred with 5% Pd-C (0.05 g) and hydrogen under one atmospheric presure at 60°C for 1 h. The mixture was filterd and then evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$:MeOH =50:1) to give **1** (1.0 g, 85 %) as yellow needles (from MeOH). mp 186-187°C. Anal. Calcd for $C_{14}H_8N_2S$: C, 71.17; H, 3.42; N, 11.86. Found: C, 71.03; H, 3.13; N, 11.57. Ir (KBr): 1630, 1600, 1580 $cm^{-1}$. $^1$HNmr δ: 7.16 (1H, dd, *J*=5, 8 Hz, 10-H), 7.28 (1H, d, *J*=8 Hz, 6-H), 7.52 (1H, t, *J*=8 Hz, 5-H), 7.54 (1H, d, *J*=8 Hz, 1-H), 7.74 (1H, d, *J*=8 Hz, 4-H), 8.18 (1H, d, *J*=8 Hz, 11-H), 8.42 (1H, d, *J*=5 Hz, 9-H), 8.74 (1H, d, *J*=8 Hz, 2-H). HRms m/z: Calcd for $C_{14}H_8N_2S$: 236.0407. Found: 236.0401 ($M^{+\cdot}$).

**ACKNOWLEDGMENT**

The authors are grateful to the members of the Analysis Center of Kyoto University for elemental analyses.

**REFERENCES**

1. W. A. Denny, B. C. Baguley, B. F. Cain, and M. J. Waring," Molecular Aspects of Anticancer Drug Action", ed. by S. Neidle and M. H. Waring, Verlag Chemie, Weinheim, 1983, pp. 1-34.
2. D. B. Capps, European Patent Appl. EP 145,226 (1985) (*Chem. Abstr.*, 1985, **103**, 215182s).
3. G. J. Atwell, B. F. Cain, B. C. Baguley, G. J. Finlay, and W. A. Denny, *J. Med. Chem.*, 1984, **27**, 1481.
4. L. P. G. Wakelin, G. J. Atwell, G. W. Rewcastle, and W. A. Denny, *J.*

*Med. Chem.*, 1987, **30**, 855.

5. W. A. Denny, G. J. Atwell, R. F. Anderson, and W. R. Wilson, *J. Med. Chem.*, 1990, **33**, 1288.
6. G. A. Charyulu, T. C. McKee, and C. M. Ireland, *Tetrahedron Lett.*, 1989, **30**, 4201.
7. J. Kobayashi, J.-f. Cheng, M. R. Walchli, H. Nakamura, Y. Hirata, T. Sasaki, and Y. Ohizumi, *J. Org. Chem.*, 1988, **53**, 1800.
8. M. A. Ciufolini and N. E. Byrne, *J. Am. Chem. Soc.*, 1991, **113**, 8016.
9. A. R. Carroll, N. M. Cooray, A. Poiner, and P. J. Scheuer, *J. Org. Chem.*, 1989, **54**, 4231.
10. A. Rudi and Y. Kashman, *J. Org. Chem.*, 1989, **54**, 5331.
11. A. R. Carroll and P. J. Scheuer, *J. Org. Chem.*, 1990, **55**, 4426.
12. F. J. Schmitz, F. S. DeGuzman, M. B. Hossain, and D. van der Helm, *J. Org. Chem.*, 1991, **56**, 804.
13. G. Cimino, A. Crispino, S. de Rosa, S. de Stefano, M. Gavagnin, and G. Sodano, *Tetrahedron*, **43**, 1987, 4023.
14. F. Eiden and K. Berndl, *Arch. Pharm.*, 1986, **319**, 347.
15. B. S. Ross and R. A. Wiley, *J. Med. Chem.*, 1985, **28**, 870.
16. F. Eiden and J. Dusemund, *Arch. Pharm. Ber. Deut. Pharm. Ges.*, 1972, **305**, 324.

Received, 10th November, 1992