Synthesis of Pyrido[3′,2′:5,6]pyrano[4,3,2-*de*]quinoline

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Pyrido[3′,2′:5,6]pyrano[4,3,2-*de*]quinoline (1), which can be regarded as a combined structure of a xanthene analog and quinoline, was synthesized starting from 6-amino-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (2).

Keywords heterocyclic compound; xanthene analog; quinoline

One of the most important classes of antitumor drugs is the DNA intercalating agents, which 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 most thoroughly investigated groups.[1-5]

The search for new heterocyclic ring has been stimulated by recent reports that the polyheterocyclic marine products show 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 thioxantheno-1,4-diazepine,[16] derived from 1-aminoxanthone and 1-aminothioxanthone have already been synthesized and reported to have analgetic and psychopharmacological activity.

In this paper, we report the synthesis of a new tetracyclic compound, pyrido[3′,2′:5,6]pyrano[4,3,2-*de*]quinoline (**1**), which can be regarded as a combined structure of a xanthene analog and quinoline, starting from 6-amino-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (**2**).

Results and Discussion

The synthetic route to **1** is summarized in Chart 1. The Ullmann reaction of 2-chloronicotinic acid with *m*-chlorophenol in dimethylformamide (DMF) under reflux for 3—4 h gave the corresponding carboxylic acid, 2-(3-chlorophenoxy)nicotinic acid (**3**) in 71% yield. Compound **3** was heated with polyphosphoric acid (PPA) at 120 °C for 3 h to give, in 87% yield, a mixture (1 : 1) of 6-chloro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (**4**) and 8-chloro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (**5**) which could not be separated on a column-chromatographical scale. The above mixture with *p*-toluenesulfonamide in *n*-amyl alcohol gave 6-(*p*-toluenesulfonamido)-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (**6**) and **5**, which were treated, without separation, with 47% HBr in the presence of phenol to give **2** (32%). The structure of **2** was determined by spectroscopy. The IR spectrum showed a peak due to

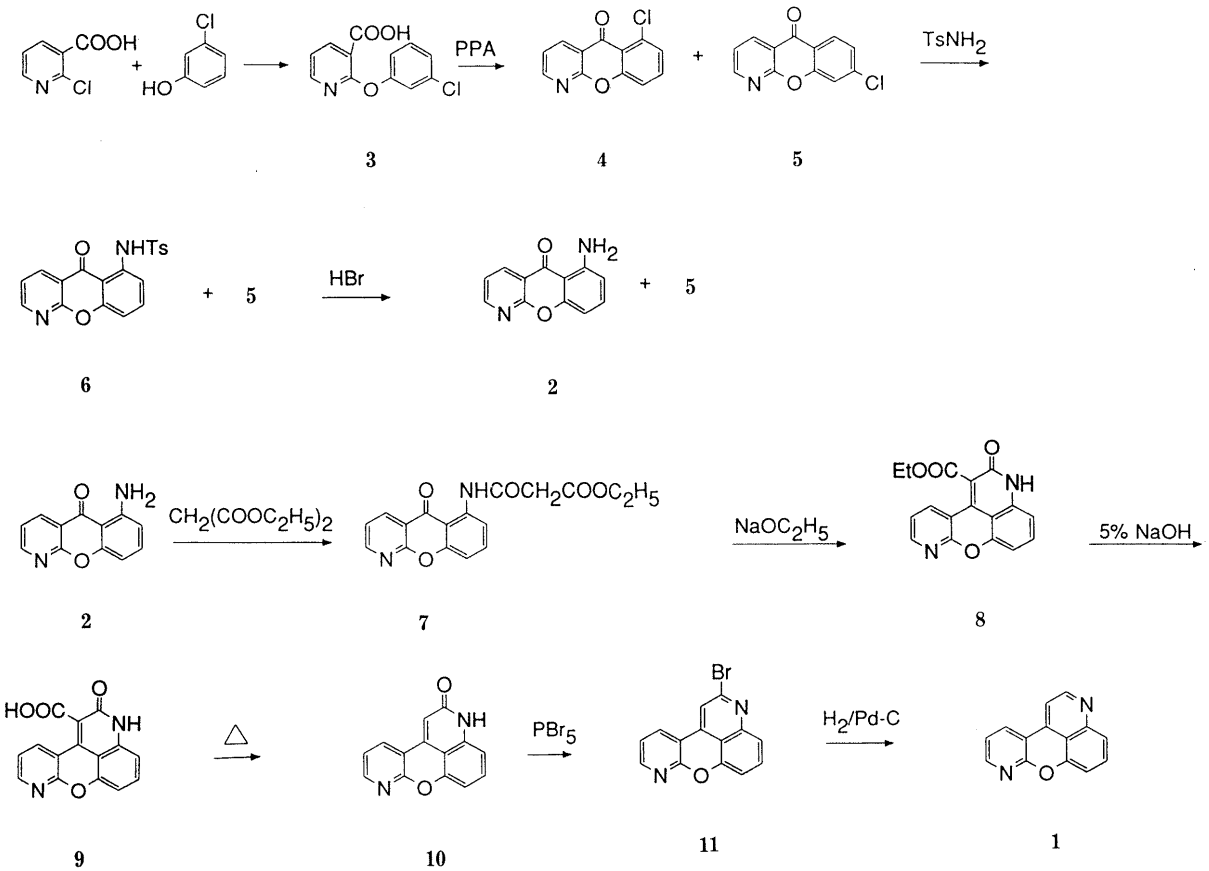

Chart 1

an amino group at 3420 cm^{-1} and the ^{1}H-NMR spectrum exhibited the absorption of an amino group at 6.70 ppm. This method is effective to obtain a large amount of **2**. Refluxing of the crude **2** with diethyl malonate gave 6-carbethoxyacetamido-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (**7**) in 90% yield; this was refluxed with sodium ethoxide in ethanol to give ethyl pyrido[3′,2′:5,6]pyrano-[4,3,2-*de*]quinolin-2(3*H*)-one-1-carboxylate (**8**) in 89% yield. The structure of **8** was determined on the basis of spectroscopy; in the MS, a molecular ion peak at *m/z* 308 was observed. Furthermore, hydrolysis of the ester **8** with aqueous sodium hydroxide solution gave the corresponding carboxylic acid (**9**) in 95% yield. The carboxylic acid **9** was decarboxylated by heating at 300 °C to give pyrido-[3′,2′:5,6]pyrano[4,3,2-*de*]quinolin-2(3*H*)-one (**10**) in 89% yield. The ^{1}H-NMR spectrum of **10** showed a peak (1H, s) at 6.95 ppm due to a hydrogen at the 1-position. A mixture of **10** and phosphorus pentabromide was heated at 130 °C to give 2-bromopyrido[3′,2′:5,6]pyrano[4,3,2-*de*]quinoline (**11**) in 94% yield. It was Beilstein test-positive. In the MS, peaks of equal intensity at *m/z* 298 and 300 showed the presence of a bromine atom. Finally, compound **11** was reduced with 5% palladium carbon and hydrogen at 60 °C in acetic acid under one atmosphere pressure to afford pyrido[3′,2′:5,6]pyrano[4,3,2-*de*]quinoline (**1**) in 91% yield.

Experimental

Melting points were determined on a Yanagimoto micro-hot stage melting point apparatus and are uncorrected. IR spectra were taken in KBr disks and data are given in cm^{-1}. ^{1}H-NMR spectra were obtained on a JEOL FX-200 (200 MHz) spectrometer in chloroform-*d* unless otherwise noted, and the chemical shifts are given in ppm 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 $M^{+\cdot}$ and/or major peaks are indicated as *m/z*. Column chromatography was performed on Wakogel C-200 (silica gel). Thin layer chromatography was performed on precoated Kieselgel 60 PF_{254} plates and spots were monitored by exposure to UV radiation (254 nm).

6-Chloro- (4) and 8-Chloro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ones (5) A mixture of 15.8 g of 2-chloronicotinic acid, 15.4 g of *m*-chlorophenol, 30.0 g of K_2CO_3, 1.4 g of copper powder, and 1.4 g of copper(I) iodide in 240 ml of DMF was stirred under reflux for 3 h. After cooling, the precipitate was collected by filtration and the filtrate was concentrated under reduced pressure. The collected solid and the residue were washed with hot water. The filtrate was acidified with 5% HCl. The resulting precipitate was collected, washed with water and dried to give **3** (17.7 g, 71%).

The above acid **3** (11.6 g) was added in one portion to 500 g of PPA preheated at 120 °C. The mixture was stirred at the same temperature for 3 h, then cooled to room temperature, poured into water, and filtered. The filter cake was washed with water, 10% $NaHCO_3$ solution, and again with water. The dried mixture weighed 9.4 g (87%). This mixture of **4** and **5** was separated by preparative TLC ($CHCl_3$).

6-Chloro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (**4**): Colorless needles, mp 134—135 °C (from MeOH). IR: 1730 (CO), 1670, 1600, 1595 cm^{-1}. ^{1}H-NMR δ: 7.42 (1H, d, J=8 Hz, 9-H), 7.45 (1H, dd, J=4, 8 Hz, 3-H), 7.53 (1H, d, J=8 Hz, 7-H), 7.62 (1H, d, J=8 Hz, 8-H), 8.67 (1H, d, J=8 Hz, 4-H), 8.73 (1H, d, J=4 Hz, 2-H). HRMS *m/z*: Calcd for $C_{12}H_6ClNO_2$: 231.0087. Found: 231.0063.

8-Chloro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (**5**): Colorless needles, mp 200—201 °C (from MeOH). IR: 1730 (CO), 1665, 1600, 1595 cm^{-1}. ^{1}H-NMR δ: 7.38 (1H, d, J=8 Hz, 7-H), 7.46 (1H, dd, J=4, 8 Hz, 3-H), 7.60 (1H, s, 9-H), 8.20 (1H, d, J=8 Hz, 6-H), 8.68 (1H, d, J=8 Hz, 4-H), 8.72 (1H, d, J=4 Hz, 2-H). HRMS *m/z*: Calcd for $C_{12}H_6ClNO_2$: 231.0087. Found: 231.0060.

It is difficult to separate **4** and **5** by column chromatography. Thus, the mixture of **4** and **5** was used in the next reaction without separation.

6-Amino-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (2) A mixture of **4** and **5** (12.4 g), 17.1 g of *p*-toluenesulfonamide, 8.2 g of sodium acetate, and 1.0 g of copper(II) acetate monohydrate in 160 ml of *n*-amyl alcohol was stirred under reflux for 8 h in an oil bath at 160—170 °C. After cooling, the resulting precipitate was collected by filtration and dried to give 13.4 g of a yellow product. A mixture of the crude product (13.4 g), 14.1 g of phenol, and 150 ml of 47% HBr was refluxed with stirring for 8 h. After cooling, the acidic solution was extracted with $CHCl_3$. The acidic layer was poured into 30% NaOH solution. The resulting material was filtered to give **2** (3.7 g, 32%) as yellow needles, mp 217—218 °C (from MeOH). IR: 3420 (NH_2), 3320, 1630, 1590 cm^{-1}. ^{1}H-NMR δ: 6.48 (1H, d, J=8 Hz, 7-H), 6.70 (2H, br s, NH_2), 6.74 (1H, d, J=8 Hz, 9-H), 7.36 (1H, dd, J=4, 8 Hz, 3-H), 7.40 (1H, t, J=8 Hz, 8-H), 8.60 (1H, d, J=8 Hz, 4-H), 8.66 (1H, d, J=4 Hz, 2-H). HRMS *m/z*: Calcd for $C_{12}H_8N_2O_2$: 212.0585. Found: 212.0544.

6-Carbethoxyacetamido-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (7) A solution of 6.4 g of **2** in 60 ml of diethyl malonate was boiled for 20 min, then most of the ester was removed by evaporation. The residue was purified by column chromatography using $CHCl_3$ as an eluent to afford **7** (8.9 g, 90%) as a pale yellow powder. mp 150—151 °C (from MeOH). IR: 3450 (CONH), 3180 (CONH), 3080 (CONH), 1740 ($COOC_2H_5$), 1690 (CONH), 1630, 1590 cm^{-1}. ^{1}H-NMR δ: 1.33 (3H, t, J=8 Hz, CH_3), 3.60 (2H, s, CH_2), 4.30 (2H, q, J=8 Hz, CH_2–CH_3), 7.30 (1H, d, J=8 Hz, 7-H), 7.46 (1H, dd, J=4, 8 Hz, 3-H), 7.46 (1H, d, J=8 Hz, 9-H), 7.74 (1H, t, J=8 Hz, 8-H), 8.68 (1H, d, J=8 Hz, 4-H), 8.76 (1H, d, J=4 Hz, 2-H). HRMS *m/z*: Calcd for $C_{17}H_{14}N_2O_5$: 326.0902. Found: 326.0914.

Ethyl Pyrido[3′,2′:5,6]pyrano[4,3,2-*de*]quinolin-2(3*H*)-one-1-carboxylate (8) A solution of NaOEt (prepared from 1.0 g of Na in 30 ml of EtOH) was added to a boiling suspension of 3.2 g of **7** in 90 ml of EtOH. The mixture was boiled for 15 min and then cooled. The solid product was stirred for 30 min with 10% HCl, then washed and dried, giving **8** (2.7 g, 89%) as a yellow powder (from AcOH). mp > 300 °C. IR: 3400 (CONH), 1745 ($COOC_2H_5$), 1660, 1640, 1610, 1590 cm^{-1}. ^{1}H-NMR δ: 1.44 (3H, t, J=8 Hz, CH_3), 4.55 (2H, q, J=8 Hz, CH_2), 7.00 (1H, d, J=8 Hz, 4-H), 7.05 (1H, d, J=8 Hz, 6-H), 7.26 (1H, dd, J=4, 8 Hz, 10-H), 7.57 (1H, t, J=8 Hz, 5-H), 8.15 (1H, d, J=8 Hz, 11-H), 8.48 (1H, d, J=4 Hz, 9-H). HRMS *m/z*: Calcd for $C_{17}H_{12}N_2O_4$: 308.0791. Found: 308.0800.

Pyrido[3′,2′:5,6]pyrano[4,3,2-*de*]quinolin-2(3*H*)-one-1-carboxylic Acid (9) The ester **8** (2.4 g) was saponified by boiling for 6 h with 5% aqueous NaOH (50 ml). The solution was then poured into an excess of hot 10% HCl and the product was crystallized from AcOH, giving 2.1 g (95%) of a yellow powder, mp > 300 °C. IR: 3350 (CONH), 1710 (COOH), 1640, 1600, 1580 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.12 (1H, d, J=8 Hz, 6-H), 7.26 (1H, d, J=8 Hz, 4-H), 7.44 (1H, dd, J=4, 8 Hz, 10-H), 7.58 (1H, t, J=8 Hz, 5-H), 8.30 (1H, d, J=8 Hz, 11-H), 8.52 (1H, d, J=4 Hz, 9-H). HRMS *m/z*: Calcd for $C_{15}H_8N_2O_4$: 280.0484. Found: 280.0451.

Pyrido[3′,2′:5,6]pyrano[4,3,2-*de*]quinolin-2(3*H*)-one (10) The acid **9** (2.0 g) was heated at 300 °C to give nearly pure decarboxylation product **10** (1.5 g, 89%). Sublimation gave yellow needles, mp > 300 °C. IR: 3450 (CONH), 1640 (CONH), 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.94 (1H, s, 1-H), 6.95 (1H, d, J=8 Hz, 6-H), 7.00 (1H, d, J=8 Hz, 4-H), 7.40 (1H, dd, J=4, 8 Hz, 10-H), 7.53 (1H, t, J=8 Hz, 5-H), 8.48 (1H, d, J=4 Hz, 9-H), 8.65 (1H, d, J=8 Hz, 11-H). HRMS *m/z*: Calcd for $C_{14}H_8N_2O_2$: 236.0584. Found: 236.0537.

2-Bromopyrido[3′,2′:5,6]pyrano[4,3,2-*de*]quinoline (11) A mixture of 1.4 g of **10** and 2.55 g of PBr_5 was heated in an oil bath at 130 °C for 1 h, then cooled and poured onto ice. The resulting product was collected by filtration, then washed with 5% aqueous $NaHCO_3$ and water, and dried, giving 1.7 g (94%) of **11** as yellow crystals. mp 233—234 °C (from MeOH). IR: 1630, 1595 cm^{-1}. ^{1}H-NMR δ: 7.24—7.28 (2H, m, 6-H, 10-H), 7.56 (1H, s, 1-H), 7.65 (1H, d, J=8 Hz, 4-H), 7.72 (1H, t, J=8 Hz, 5-H), 8.22 (1H, d, J=8 Hz, 11-H), 8.46 (1H, d, J=4 Hz, 9-H). HRMS *m/z*: Calcd for $C_{14}H_7BrN_2O$: 297.9741. Found: 297.9755.

Pyrido[3′,2′:5,6]pyrano[4,3,2-*de*]quinoline (1) A solution of 3.0 g of **10** and 1 g of NaOAc in 100 ml of AcOH was stirred with 0.1 g of 5% Pd–C and hydrogen at 1 atmosphere pressure and 60 °C for 1 h. The mixture was filtered and the filtrate was evaporated. The residue was subjected to silica gel chromatography using $CHCl_3$–MeOH (50 : 1, v/v) to give 2.0 g (91%) of **1** as yellow needles. mp 181—182 °C (from MeOH). IR: 1630, 1600, 1580 cm^{-1}. ^{1}H-NMR δ: 7.16 (1H, d, J=8 Hz, 6-H), 7.20 (1H, dd, J=4, 8 Hz, 10-H), 7.39 (1H, d, J=4 Hz, 1-H), 7.65 (1H, t, J=8 Hz, 5-H), 7.69 (1H, d, J=8 Hz, 4-H), 8.12 (1H, d, J=8 Hz, 11-H), 8.34 (1H, d, J=4 Hz, 9-H), 8.72 (1H, d, J=4 Hz, 2-H). HRMS

m/z: Calcd for $C_{14}H_8N_2O$: 220.0635. Found: 220.0607.

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