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Studies on Quinoline and Isoquinoline Derivatives. IX.[1] Synthesis of Pyrrolo[1,2-*b*]isoquinolines from 3-Bromoisoquinoline Derivatives

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The reaction of 3-bromo-1-methoxyisoquinoline with propargyl alcohol in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide gave 3-(1-methoxy-3-isoquinolyl)propargyl alcohol in good yield. Cyclization of 3-(1-methoxy-3-isoquinolyl)propanol obtained by the catalytic reduction of the propargyl alcohol, afforded a 1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline derivative. The synthesis of a pyrrolo[3,2,1-*de*]phenanthridine derivative was accomplished by the introduction of an acrylic acid moiety into the pyrrolo[1,2-*b*]isoquinoline and subsequent reduction and cyclization of the resulting ethyl pyrrolo[1,2-*b*]isoquinoline-10-acrylate.

Keywords——palladium-catalyzed reaction; dichlorobis(triphenylphosphine)palladium; carbon–carbon bond formation; cyclization reaction; bromination; intramolecular Grignard reaction; pyrrolo[1,2-*b*]isoquinoline; pyrrolo[3,2,1-*de*]phenanthridine; 1,3-dibromoisoquinoline

During our investigation on the palladium-catalyzed reaction of haloisoquinolines with terminal olefins or acetylenes,[2,3] this type of reaction was found to be a practical method for the synthesis of isoquinoline derivatives having a carbon substituent at the 3-position. As an application of the above-mentioned findings, this paper deals with the synthesis of pyrrolo[1,2-*b*]isoquinoline and pyrrolo[3,2,1-*de*]phenanthridine derivatives from 3-bromoisoquinolines using such palladium-catalyzed reactions and subsequent cyclizations.

First, the synthesis of 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline (**10**) was investigated. When 1,3-dibromoisoquinoline (**1**)[4] was treated with propargyl alcohol in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide in triethylamine,[5] colorless needles (**2**) of mp 134—135 °C were obtained in good yield. The spectral data and elemental analysis of the product showed the compound to contain a 3-hydroxypropynyl group and a bromine atom. Catalytic reduction of the product (**2**) gave 3-(1-isoquinolyl)-propanol (**3**), which was identical with an authentic specimen prepared from 3-(1-isoquinoyl)-propargyl alcohol.[2]

Similarly, **1** reacted with ethyl acrylate in the presence of palladium acetate and triphenylphosphine in triethylamine[6] to give colorless needles of mp 112—113.5 °C, although in this case a considerable amount (63%) of the starting material was recovered. Catalytic reduction of ethyl 3-bromo-1-isoquinolyl-*trans*-acrylate (**4**) thus obtained afforded ethyl 1-isoquinolylpropanonate (**5**), whose structure was determined by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy. These results demonstrated that in the 1,3-dibromoisoquinoline system, the reaction occurred at the 1-position rather than the 3-position.

Thus, in order to introduce the necessary substituent into the 3-position, **1** was transformed into 3-bromo-1-methoxyisoquinoline (**6**) prior to the palladium-catalyzed reaction with propargyl alcohol. The reaction of **6** and propargyl alcohol under similar conditions to the above gave 3-(1-methoxy-3-isoquinolyl)propargyl alcohol (**7**), as expected. On treatment with phosphorus tribromide in chloroform, 3-(1-methoxy-3-isoquinolyl)-

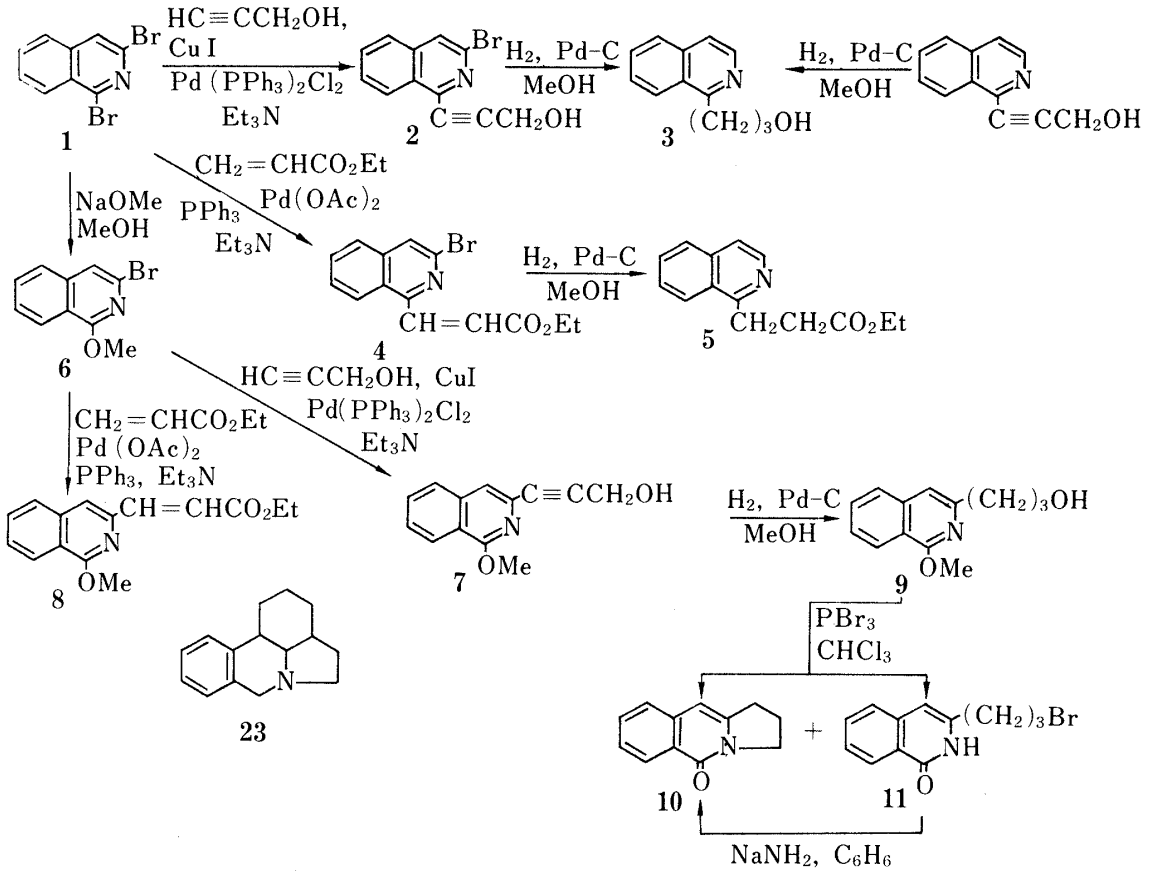

Chart 1

propanol (**9**), which was obtained by the catalytic reduction of **7** over palladium charcoal, was readily cyclized to the pyrrolo[1,2-*b*]isoquinoline (**10**), together with a small amount of 3-(3-bromopropyl)-1-isoquinolone (**11**). Compound **11** was dehydrobrominated with sodium amide in benzene to give **10** in good yield. In addition, the reaction of **6** with ethyl acrylate in the presence of palladium (II) acetate and triphenylphosphine gave the ethyl 1-methoxy-3-isoquinoline-*trans*-acrylate (**8**), in which the geometry of the side chain was determined by ^{1}H-NMR spectrometry.

Next, the transformation of **10** into a derivative of pyrrolo[3,2,1-*de*]phenanthridine (**22**) was examined as follows. When **10** was brominated with a limited amount of *N*-bromosuccinimide (NBS) in carbon tetrachloride, a monobromide (**12**) was obtained as a sole product. The subsequent bromination of **12** with the same reagent gave the dibromide (**13**). On the other hand, the oxidation of **10** with selenium dioxide gave the 1-hydroxypyrrolo[1,2-*b*]isoquinoline (**14**), which on treatment with phosphorus tribromide was converted to the positional isomer (**15**) of the bromide (**12**).

Then, the reaction of these bromides (**12**, **13**, and **15**) with ethyl acrylate were tested to find a suitable route for the construction of the pyrrolo[3,2,1-*de*]phenanthridine ring. Although the reaction of **13** and that of **15** both failed to give the desired products, the reaction of **12** with ethyl acrylate was successfully achieved to give compound **16** under similar conditions to the case of **6**. In order to synthesize **18** by intramolecular condensation, **16** was reduced to the saturated compound (**17**), but **17** was unchanged by treatment with sodium amide, and **18** was not obtained. Thus, before the reduction of the acrylate moiety in **16**, compound **16** was oxidized with selenium dioxide to give the hydroxy-ester (**19**). The hydroxy-ester (**19**) was reduced to the saturated hydroxy-ester (**20**) by catalytic reduction over palladium-charcoal catalyst.

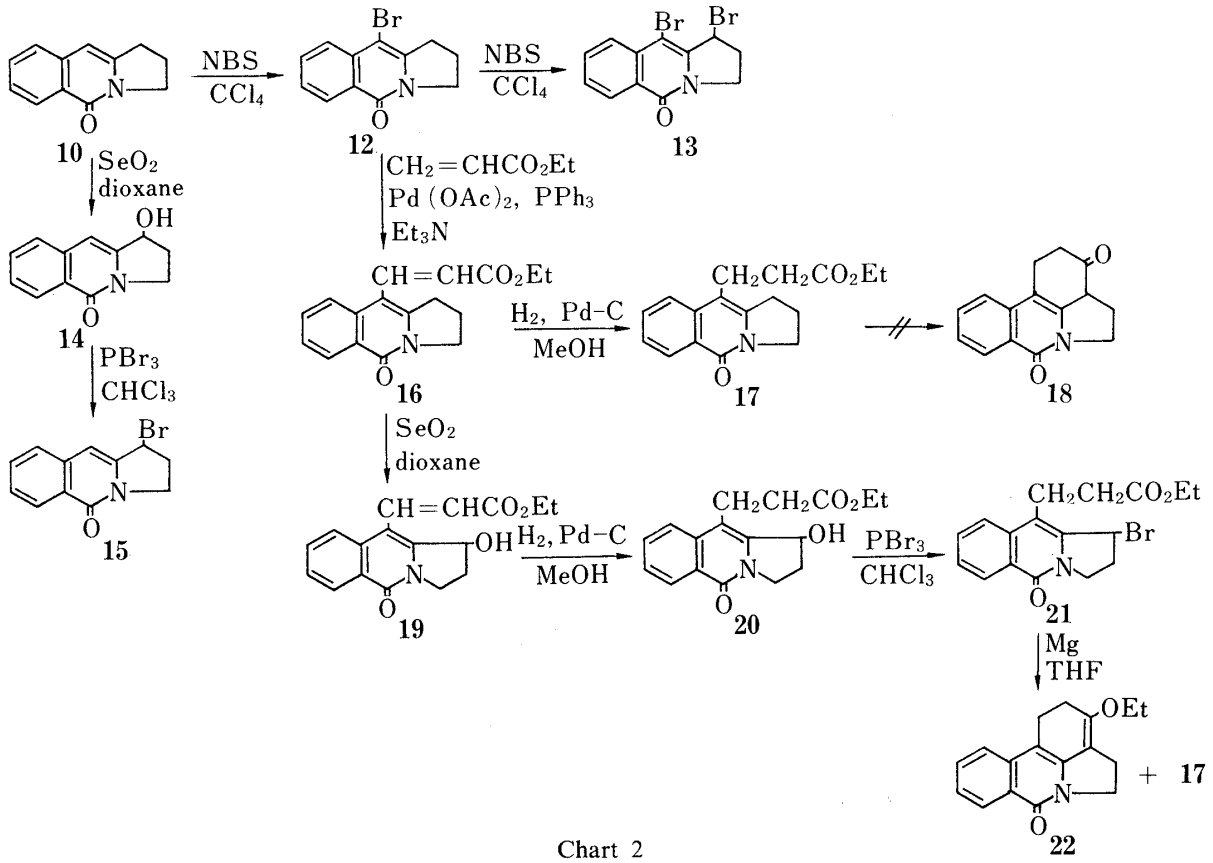

Chart 2

Finally, the synthesis of the pyrrolo[3,2,1-*de*]phenanthridine (**21**) was accomplished by intramolecular Grignard reaction. Namely, **20** was brominated by treatment with phosphorus tribromide, and the resultant bromo-ester (**21**) was allowed to react with magnesium foil in tetrahydrofuran. The usual work-up of the reaction mixture afforded 3-ethoxy-7-oxo-2,4,5,7-tetrahydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (**22**) as a main product, together with a small amount of **17**.

The structures of all the products described above were supported by the spectral data and the satisfactory elemental analyses.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. ^{1}H-NMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ value. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, m=multiplet, br=broad, and br s=broad singlet. Mass spectra (MS) were taken on a Hitachi M-52G spectrometer.

3-(3-Bromo-1-isoquinolyl)propargyl Alcohol (2)——A mixture of 1,3-dibromoisoquinoline (**1**) (800 mg, 2.8 mmol), propargyl alcohol (170 mg, 3 mmol), $Pd(PPh_3)_2Cl_2$ (50 mg), CuI (25 mg), and Et_3N (20 ml) was stirred for 13.5 h at room temperature. After removal of the resulting precipitate by filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. Recrystallization from acetone–hexane gave colorless needles, mp 134—135 °C. Yield 650 mg (89%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620, 2240. ^{1}H-NMR ($CDCl_3$): 3.97 (1H, s), 4.45 (2H, s), 7.35—8.00 (4H, m), 8.15—8.40 (1H, m). *Anal.* Calcd for $C_{12}H_8BrNO$: C, 54.99; H, 3.08; Br, 30.49; N, 5.35. Found: C, 54.88; H, 3.07; Br, 30.14; N, 5.31.

3-(1-Isoquinolyl)propanol (3)——i) Catalytic Reduction of **2**: A mixture of **2** (120 mg, 0.46 mmol), 10% Pd-C (400 mg), and MeOH (20 ml) was shaken in an H_2 stream at room temperature. After absorption of H_2 had ceased (44 ml), the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure. The residue was passed through a short Al_2O_3 column using $CHCl_3$ as an eluent. The residual oil was distilled under reduced pressure to give a colorless liquid, bp 191—198 °C (1 mmHg). Yield 65 mg (76%), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640.

^{1}H-NMR ($CDCl_3$): 2.14 (2H, quint, J=6.0 Hz), 3.47 (2H, t, J=6.0 Hz), 3.76 (2H, t, J=6.0 Hz), 4.88 (1H, s), 7.35—7.93 (4H, m), 7.93—8.50 (1H, m), 8.35 (1H, d, J=6.0 Hz). *Anal.* Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.85; H, 7.07; N, 7.62.

ii) Catalytic Reduction of 3-(1-Isoquinolyl)propargyl Alcohol: A mixture of 3-(1-isoquinolyl)propargyl alcohol (900 mg, 5 mmol), 10% Pd-C (2.0 g), and MeOH (20 ml) was shaken in an H_2 stream at room temperature. After absorption of H_2 had ceased (230 ml), the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to give a colorless liquid, which was distilled under reduced pressure. Yield 650 mg (71%).

Ethyl 3-Bromo-1-isoquinoline-*trans*-acrylate (4)——A mixture of **1** (800 mg, 2.8 mmol), ethyl acrylate (330 mg, 3.3 mmol), $Pd(OAc)_2$ (25 mg), PPh_3 (50 mg), and Et_3N (5 ml) was heated in a sealed tube at 120 °C for 20 h. After removal of the resulting precipitate by filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by SiO_2 column chromatography using C_6H_6 as an eluent. The first fraction gave the starting material (500 mg, 63%) and the second fraction afforded colorless needles (**4**) (110 mg, 13%), which were recrystallized from acetone–hexane. mp 112—113.5 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 970. ^{1}H-NMR ($CDCl_3$): 1.25 (3H, t, J=7.0 Hz), 4.66 (2H, q, J=7.0 Hz), 7.13 (1H, d, J=16.0 Hz), 7.30—7.90 (4H, m), 7.90—8.30 (1H, m), 8.20 (1H, d, J=16 Hz). *Anal.* Calcd for $C_{14}H_{12}BrNO$: C, 54.92; H, 3.95; Br, 26.10; N, 4.58. Found: C, 54.76; H, 4.00; Br, 26.05; N, 4.63.

Ethyl 1-Isoquinolinepropanoate (5)——A mixture of **4** (70 mg, 0.23 mmol), 10% Pd-C (0.2 g), and MeOH (10 ml) was shaken in an H_2 stream at room temperature. After absorption of H_2 had ceased (20 ml), the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure. The residue was passed through a short Al_2O_3 column using $CHCl_3$ as an eluent. The residual oil was distilled under reduced pressure to give a colorless liquid, bp 145—150 °C (2 mmHg). Yield 30 mg (57%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR ($CDCl_3$): 1.23 (3H, t, J=7.0 Hz), 2.70—3.13 (2H, m), 3.34—3.80 (2H, m), 4.12 (2H, q, J=7.0 Hz), 7.40—8.00 (4H, m), 8.00—8.40 (1H, m), 8.45 (1H, d, J=6.0 Hz). *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.34; H, 6.62; N, 6.01.

3-Bromo-1-methoxyisoquinoline (6)——A solution of **1** (10.5 g, 36 mmol) in dioxane (70 ml) was added to a solution of NaOMe–MeOH [prepared from Na (1.2 g, 50 mmol) and dry MeOH (60 ml)], and the mixture was refluxed for 1.5 h, then concentrated to dryness under reduced pressure. H_2O (80 ml) was added to the residue, and the aqueous layer was extracted with $CHCl_3$. Removal of the solvent gave the residue, which was purified by Al_2O_3 column chromatography using C_6H_6 as an eluent. Recrystallization from acetone–hexane gave colorless needles, mp 73—74 °C. Yield 8.0 g (92%). ^{1}H-NMR ($CDCl_3$): 4.06 (3H, s), 7.20—7.88 (4H, m), 7.97—8.30 (1H, m). *Anal.* Calcd for $C_{10}H_8BrNO$: C, 50.44; H, 3.39; Br, 33.56; N, 5.88. Found: C, 50.64; H, 3.33; Br, 33.22; N, 5.87.

3-(1-Methoxy-3-isoquinolyl)propargyl Alcohol (7)——A mixture of **6** (4.92 g, 20 mmol), propargyl alcohol (1.80 g, 34 mmol), $Pd(PPh_3)_2Cl_2$ (300 mg), CuI (150 mg), and Et_3N (80 ml) was refluxed for 16 h. After removal of the precipitate by filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by Al_2O_3 column chromatography using $CHCl_3$ as an eluent. Recrystallization from hexane–acetone gave pale yellow needles, mp 94—95 °C. Yield 3.9 g (89%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3635. ^{1}H-NMR ($CDCl_3$): 3.00—3.56 (1H, br), 4.12 (3H, s), 4.60 (2H, s), 7.06—7.85 (4H, m), 7.85—8.28 (1H, m). *Anal.* Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 72.93; H, 5.19; N, 6.39.

Ethyl 1-Methoxy-3-isoquinoline-*trans*-acrylate (8)——A mixture of **6** (450 mg, 1.9 mmol), ethyl acrylate (380 mg, 3.8 mmol), $Pd(OAc)_2$ (30 mg), PPh_3 (60 mg), and Et_3N (3.0 ml) was heated in a sealed tube at 120 °C for 22 h. The precipitate was filtered off, and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. Recrystallization from hexane–ether gave colorless needles, mp 84—85 °C. Yield 410 mg (84%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710, 985. ^{1}H-NMR ($CDCl_3$): 1.37 (3H, t, J=7.0 Hz), 4.06 (3H, s), 4.21 (2H, q, J=7.0 Hz), 6.98 (1H, d, J=17.0 Hz), 7.12 (1H, s), 7.20—7.90 (4H, m), 7.90—8.30 (1H, m). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.07; H, 6.12; N, 5.49.

3-(1-Methoxy-3-isoquinolyl)propanol (9)——A mixture of **7** (5.60 g, 26.3 mmol), 10% Pd-C, and MeOH (60 ml) was shaken in a stream of H_2 at room temperature. After absorption of H_2 (1400 ml) had ceased the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure. The residue was purified by Al_2O_3 column chromatography using $CHCl_3$ as an eluent. The residual oil was distilled under reduced pressure to give a colorless viscous liquid, bp 170—172 °C (1 mmHg). Yield 5.18 g (92%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600. ^{1}H-NMR ($CDCl_3$): 2.00 (2H, quint, J=6.0 Hz), 2.90 (2H, t, J=6.0 Hz), 3.73 (2H, t, J=6.0 Hz), 3.70—4.05 (1H, br), 4.07 (3H, s), 6.96 (1H, s), 7.23—7.70 (3H, m), 7.96—8.35 (1H, m). *Anal.* Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.11; H, 6.88; N, 6.44.

Reaction of 9 with Phosphorus Tribromide——Phosphorus tribromide (5.2 g, 19 mmol) was slowly added to a solution of **9** (3.40 g, 16 mmol) in $CHCl_3$ (40 ml) with stirring at 0—5 °C, and the mixture was refluxed for 20 h. After concentration to dryness under reduced pressure, a small amount of ice was added to the residue. The aqueous layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. Removal of the $CHCl_3$ gave the crude product, which was purified by Al_2O_3 column chromatography using C_6H_6 and C_6H_6–$CHCl_3$ (10:1). The C_6H_6 fraction gave 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline (**10**) as colorless needles, which were recrystallized from hexane–acetone. mp 123—124 °C. Yield 1.98 g (68%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. ^{1}H-NMR ($CDCl_3$): 2.15 (2H, quint, J=7.0 Hz), 3.03 (2H, t, J=7.0 Hz), 4.12 (2H, t, J=7.0 Hz), 6.31 (1H, s), 7.20—7.80 (3H, m), 8.25—8.53 (1H, m). *Anal.* Calcd for

$C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.59; H, 5.95; N, 7.65.

The C_6H_6–$CHCl_3$ (10:1) fraction afforded colorless needles, 3-(3-bromopropyl)isoquinolin-1(2*H*)-one (**11**), which were recrystallized from hexane–acetone. mp 184.5—185 °C. Yield 0.32 g (8%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1660. ^{1}H-NMR ($CDCl_3$): 2.20—2.67 (2H, m), 2.89 (2H, t, J=7.0 Hz), 3.15 (2H, t, J=7.0 Hz), 6.40 (1H, s), 7.05—8.08 (3H, m), 8.40 (1H, d, J=8.0 Hz), 12.00—12.85 (1H, br). *Anal.* Calcd for $C_{12}H_{12}BrNO$: C, 54.15; H, 4.51; N, 5.26; Br, 30.02. Found: C, 54.62; H, 4.57; N, 5.28; Br, 29.62.

5-Oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline from 11——A solution of **11** (1.5 g, 5.6 mmol) in C_6H_6 (10 ml) was added to a suspension of $NaNH_2$ (0.65 g, 17 mmol) in C_6H_6 (20 ml) with stirring at room temperature and the mixture was sitrred for 24 h, then concentrated to dryness under reduced pressure. A small amount of ice was added to the residue, and the aqueous layer was extracted with $CHCl_3$. Removal of the $CHCl_3$ gave the crude product, which was purified by Al_2O_3 column chromatography using C_6H_6–$CHCl_3$ (2:1) as an eluent. Recrystallization from acetone–hexane gave colorless needles. mp 123—124 °C. Yield 0.96 g (92%).

10-Bromo-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline (12)——*N*-Bromosuccinimide (0.95 g, 5.3 mmol) was added to a solution of **10** (0.9 g, 5 mmol) in CCl_4 (15 ml) during 2 h under refluxing, and the mixture was refluxed for 1 h, then concentrated to dryness under reduced pressure. H_2O (20 ml) was added to the residue, and the aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ extract was passed through a short column of Al_2O_3 using $CHCl_3$ as an eluent. Recrystallization from acetone–hexane gave colorless needles, mp 141—142 °C. Yield 1.15 g (90%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650. ^{1}H-NMR ($CDCl_3$): 2.17 (2H, quint, J=7.0 Hz), 3.12 (2H, t J=7.0 Hz), 4.21 (2H, t, J=7.0 Hz), 7.05—7.90 (3H, m), 8.06—8.50 (1H, m). *Anal.* Calcd for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.78; Br, 30.25; N, 5.30. Found: C, 54.56; H, 3.73; Br, 30.06; N, 5.29.

1,10-Dibromo-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline (13)——*N*-Bromosuccinimide (660 mg, 3.7 mmol) was added to a solution of **12** (900 mg, 3.4 mmol) in CCl_4 (15 ml), and the mixture was refluxed for 2 h. After removal of the solvent under reduced pressure, H_2O (20 ml) was added to the residue, and the aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ extract was passed through a short column of Al_2O_3 using $CHCl_3$ as an eluent. Recrystallization from acetone–hexane gave colorless needles, mp 170 °C (dec.). Yield 1.53 g (92%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650. ^{1}H-NMR ($CDCl_3$): 2.30—2.88 (2H, m), 3.97—4.83 (2H, m), 5.35—5.70 (1H, m), 7.28—8.07 (3H, m), 8.15—8.57 (1H, m). *Anal.* Calcd for $C_{12}H_9Br_2NO$: C, 42.01; H, 2.64; Br, 46.59; N, 4.08. Found: C, 42.23; H, 2.64; Br, 46.76; N, 4.14.

1-Hydroxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline (14)——Selenium dioxide (124 mg, 1 mmol) was added to a solution of **10** (400 mg, 2 mmol) in dioxane (20 ml), and the mixture was refluxed for 1 h. After filtration of the precipitated Se, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by SiO_2 column chromatography using ether as an eluent. The ethereal fraction gave pale yellow needles, mp 170—171 °C, which were used without further purification in the next experiment. Yield 360 mg (38%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1660. ^{1}H-NMR ($CDCl_3$) 1.80—2.97 (2H, m), 3.50—4.50 (2H, m), 4.80—5.53 (1H, m), 5.05 (1H, br s), 6.50 (1H, s), 7.07—7.87 (3H, m), 8.02—8.46 (1H, m).

1-Bromo-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline (15)——Phosphorus tribromide (500 mg, 1.8 mmol) was slowly added to a solution of **14** (140 mg, 0.7 mmol) in $CHCl_3$ with stirring at 0—5 °C, and the mixture was refluxed for 1.5 h. After removal of the solvent, a small amount of ice was added to the residue. The aqueous layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was passed through a short column of SiO_2 using $CHCl_3$ as an eluent. The $CHCl_3$ fraction gave pale yellow needles, mp 142—145 °C, which were used without further purification in the next step. Yield 160 mg (87%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660. ^{1}H-NMR ($CDCl_3$): 2.10—2.87 (2H, m), 3.86—4.78 (2H, m), 5.38 (1H, t, J=3.0 Hz), 6.64 (1H, s), 7.25—7.93 (3H, m), 8.16—8.70 (1H, m).

Ethyl 5-Oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline-10-*trans*-acrylate (16)——A mixture of **12** (250 mg, 0.9 mmol), ethyl acrylate (250 mg, 2.5 mmol), $Pd(OAc)_2$ (20 mg), PPh_3 (40 mg), and Et_3N (10 ml) was heated in a sealed tube at 130 °C for 16 h. After removal of the precipitate by filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was passed through a short column of Al_2O_3 using $CHCl_3$ as an eluent. Recrystallization from acetone–hexane gave pale yellow needles, mp 215—216 °C. Yield 220 mg (82%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1660, 985. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, t, J=7.0 Hz), 2.19 (2H, quint, J=7.0 Hz), 3.23 (2H, t, J=7.0 Hz), 4.20 (2H, t, J=7.0 Hz), 4.28 (2H, q, J=7.0 Hz), 6.13 (1H, d, J=16.0 Hz), 7.13—8.00 (3H, m), 7.85 (1H, d, J=16.0 Hz), 8.20—8.63 (1H, m). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.88; H, 6.02; N, 4.93.

Ethyl 5-Oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinolinepropanoate (17)——A mixture of **16** (170 mg, 0.6 mmol) and 10% Pd-C (0.68 g) in MeOH (10 ml) was shaken in a stream of H_2 at room temperature. After absorption of H_2 (21 ml) had ceased, the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure. The residue was passed through a short column of Al_2O_3 using $CHCl_3$ as an eluent. The $CHCl_3$ fraction gave a colorless viscous liquid which was used without further purification in the next step. Yield 150 mg (88%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1660. ^{1}H-NMR ($CDCl_3$): 1.22 (3H, t, J=7.0 Hz), 1.83—2.78 (4H, m), 2.78—3.55 (4H, m), 4.10 (2H, q, J=7.0 Hz), 4.17 (2H, t, J=7.0 Hz), 7.18—7.86 (3H, m), 8.15—8.60 (1H, m).

Ethyl 1-Hydroxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline-10-*trans*-acrylate (19)——Selenium dioxide (210 mg, 1.6 mmol) was added to a soluiton of **16** (800 mg, 2.8 mmol) in dioxane (30 ml) and the mixture was refluxed

for 44 h. After removal of the precipitated Se by filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by Al_2O_3 column chromatography using $CHCl_3$ as an eluent. The crude product obtained from the $CHCl_3$ fraction was treated with active charcoal in MeOH. Recrystallization from acetone–hexane gave pale yellow needles, mp >230 °C. Yield 0.80 g (94%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3310, 1710. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, t, J=7.0 Hz), 2.00—2.73 (2H, m), 4.06—4.70 (2H, m), 4.28 (2H, q, J=7.0 Hz), 4.76—5.50 (2H, m), 6.62 (1H, d, J=16.0 Hz), 7.03—7.53 (3H, m), 7.68 (1H, d, J=16.0 Hz), 7.85—8.33 (1H, m). *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.02; H, 5.50; N, 4.45.

Ethyl 1-Hydroxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline-10-propanoate (20)——A mixture of **19** (800 mg, 2.7 mmol) and 10% Pd-C (2.0 g) in MeOH (20 ml) was shaken in a stream of H_2 at room temperature. After absorption of H_2 (88 ml) had ceased, the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure to give a residue, which was passed through a short column of Al_2O_3 using $CHCl_3$ as an eluent. Removal of the solvent gave a colorless viscous liquid which was used without further purification in the next step. Yield 620 mg (77%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1710. ^{1}H-NMR ($CDCl_3$): 1.16 (3H, t, J=7.0 Hz), 1.80—2.47 (2H, m), 2.47—2.92 (2H, m), 2.92—3.50 (2H, m), 3.85—4.50 (2H, m), 4.08 (2H, q, J=7.0 Hz), 4.70—5.23 (1H, br), 5.38 (1H, t, J=4.0 Hz), 7.10—7.90 (3H, m), 8.07—8.54 (1H, m).

Ethyl 1-Bromo-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinoline-10-propanoate (21)——Phosphorus tribromide (560 mg, 2 mmol) was slowly added to a solution of **20** (270 mg, 0.9 mmol) in $CHCl_3$ with stirring at 0—5 °C, and the mixture was refluxed for 4 h. After removal of the solvent, a small amount of ice was added to the residue. The aqueous layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was passed through a short column of SiO_2 using $CHCl_3$ as an eluent. Removal of the solvent gave a colorless viscous liquid, which was used without further purification in the next step. Yield 310 mg (95%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$): 1.21 (3H, t, J=7.0 Hz), 2.34—2.90 (4H, m), 2.90—3.47 (2H, m), 3.80—4.80 (2H, m), 4.11 (2H, q, J=7.0 Hz), 5.77 (1H, t, J=2.0 Hz), 7.20—7.88 (3H, m), 8.27—8.60 (1H, m).

3-Ethoxy-7-oxo-2,4,5,7-tetrahydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine (22)——Magnesium (40 mg, 1.7 mmol) and a small amount of I_2 were added to a solution of **21** (300 mg, 0.83 mmol) in tetrahydrofuran (THF) (20 ml), and the mixture was refluxed for 7 h with stirring. After removal of the solvent under reduced pressure, H_2O (30 ml) was added to the residue. The aqueous layer was treated with NH_4Cl, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography using ether and acetone as eluents. The ether fraction gave a colorless viscous liquid (20 mg, 9%) which was identical with **17** obtained in the above experiment. The acetone fraction afforded pale yellow needles, which were recrystallized from acetone–hexane after treatment with active charcoal in MeOH. mp 216—218 °C. Yield 110 mg (50%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. MS *m/z*: 267 (M^+). ^{1}H-NMR ($CDCl_3$): 1.15 (3H, t, J=7.0 Hz), 1.85—3.05 (6H, m), 4.05 (2H, q, J=7.0 Hz), 3.45—4.75 (2H, m), 7.15—7.90 (3H, m), 8.25—8.70 (1H, m). *Anal.* Calcd for $C_{17}H_{17}NO_2$: C, 76.32; H, 6.41; N, 5.24. Found: C, 76.13; H, 6.22; N, 5.03.

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