New Strategy for Indole Synthesis from Ethyl Pyrrole-2-carboxylate (Synthetic Studies on Indoles and Related Compounds. XXXIX[1])

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As a synthetic application of the previously reported C_4-acylation of ethyl pyrrole-2-carboxylate (1), a new strategy for indole synthesis was developed. Ethyl pyrrole-2-carboxylate (1) was allowed to react with succinic anhydride or 3-methoxycarbonylpropionyl chloride to give, in good yield, a C_4-succinyl derivative of 1, which was converted into ethyl 7-oxo-4,5,6,7-tetrahydroindole-2-carboxylate (6) as a key intermediate for indole synthesis. Starting from 6, several indoles functionalized on the benzene moiety were synthesized.

Key words pyrrole; β-acylation; cyclization; indole; bromination; dehydrobromination

Well-established methods for preparation of the indole nucleus mainly involve elaboration of substituted benzene derivatives.[2] One such method is Fischer indolization.[3] A method starting from pyrrole derivatives has been studied recently[4]; *N*-protected pyrrole derivatives are substituted at the 2- (α-) or 3- (β-) position, and the elaboration of the substituent leads to indole derivatives. A distinctive feature of this method is its availability for the synthesis of various 4-substituted indoles[5] from 2- (α-) substituted pyrroles. These indoles have required longer preparative sequences in classical methodology. In the previous report[1] we presented an advantageous method for preparation of β-acylpyrroles, using ethyl pyrrole-2-carboxylate (**1**). As little work has been done on the preparation of indole derivatives using 4-acyl pyrroles, or on the synthesis of 7-substituted indoles from pyrrole derivatives, we started to develop a new route from pyrrole to indoles variously substituted on the benzene ring. As an application of this strategy we have reported a new synthesis of benz[*f*]indole derivatives.[6] We now report the syntheses of usual indole derivatives *via* the same strategy.

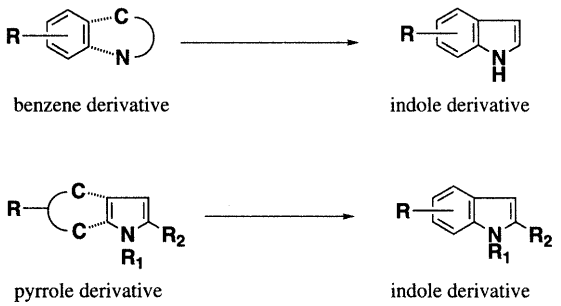

Chart 1

We first aimed to prepare the 4,5,6,7-tetrahydroindolic ketone (**6**) as a key compound, as shown in Chart 2. The Friedel–Crafts acylation of ethyl pyrrole-2-carboxylate (**1**) with 3-methoxycarbonylpropionyl chloride in the presence of aluminum chloride (4 eq) gave the corresponding 4-acylpyrrole (**2a**) as a single product in excellent yield. The reduction of **2a** with triethylsilane in trifluoroacetic acid gave the 4-alkylpyrrole (**3**) in good yield. Cyclization of **3** with polyphosphoric acid (PPA), however, gave the cyclic ketone (**6**) in very low yield. Thus, the ester (**3**) was

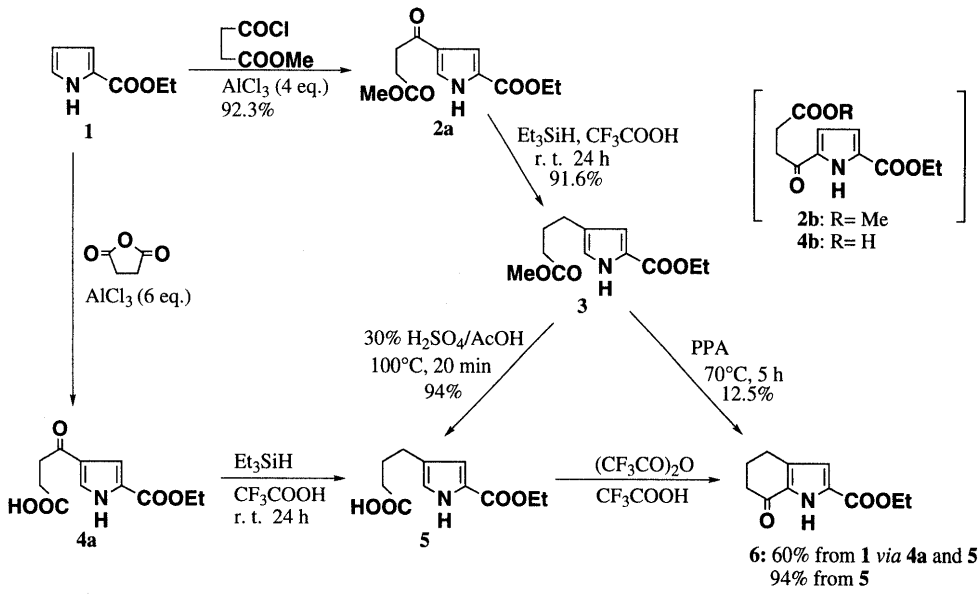

Chart 2

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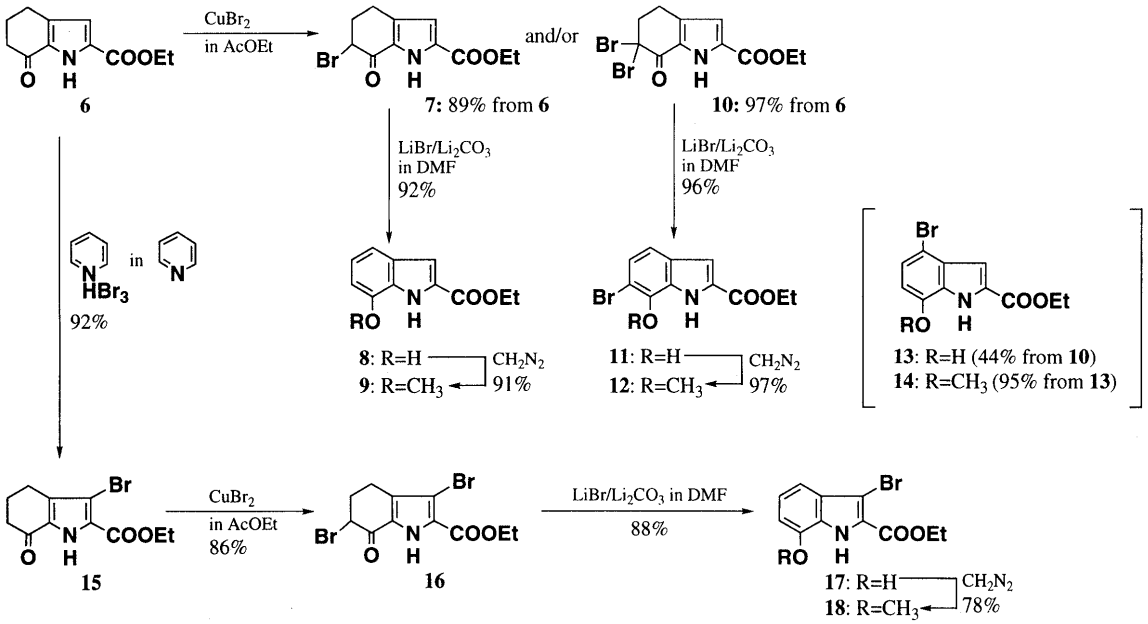

Chart 3

selectively hydrolyzed to the carboxylic acid (**5**), which was successfully cyclized with trifluoroacetic anhydride to the target ketone (**6**) in good yield. In order to shorten the sequence, **1** was treated with succinic anhydride in the presence of aluminum chloride (6 eq). The resulting keto-carboxylic acid (**4a**) was reduced with triethylsilane to **5** without purification, and then cyclized as above to give the target ketone (**6**) in good total yield (60% from **1**). The use of a smaller ratio of aluminum chloride (2 eq) in the Friedel–Crafts acylation with both 3-methoxycarbonylpropionyl chloride and succinic anhydride proceeded with lower regioselectivity to give the 4-acylpyrrole (**2a** or **4a**) and the 5-acyl isomer (**2b**, **4b**). In addition, the acylation of **1** with 3-methoxycarbonylpropionic acid by using the mixed anhydride method[7] gave the 4-acylpyrrole (**2a**) and its 5-acyl isomer (**2b**) in 74% and 26% yields, respectively. These data supported the hypothesis in the previous paper[1] that coordination of carbonyl oxygen of **1** with aluminum chloride deactivates the reactivity of the C_5-position of the pyrrole (**1**), thus directing the acylation toward the C_4-position.

In order to elaborate the ketone (**6**) to various indoles functionalized on the benzene moiety, we first attempted to convert **6** into ethyl 7-hydroxyindole-2-carboxylate (**8**). However, treatment with selenium oxide or Pd–C failed to give the desired compound (**8**). Thus, **6** was treated with 2 molar eq of cupric bromide,[5e] which is the theoretical amount required to introduce one bromine atom at the α-position of the ketone, in ethyl acetate to give the monobromoketone (**7**) in good yield (89%). Dehydrobromination with lithium bromide/lithium carbonate in *N*,*N*-dimethylformamide (DMF)[8] gave rise to aromatization to afford the 7-hydroxyindole (**8**), which was converted into the 7-methoxyindole (**9**) by methylation with diazomethane in 84% yield from **7**. The overall yield of **9** from the pyrrole (**1**) was 45%, which is comparable to that in the reported preparation of 7-methoxyindole-2-carboxylic acid (47%)[9] by means of the Reissert reaction starting from 3-methoxy-2-nitrotoluene. Bromination of **6** with 4 molar eq of cupric bromide in ethyl acetate gave the dibromoketone (**10**) in 51% and the monobromoketone (**7**) in 15% yield. Attempts to increase the yield of **10** revealed that the same reaction with 6 molar eq of cupric bromide in ethyl acetate gave **10** as a sole product in 97% yield. The dehydrobromination of **10** in the same manner as that of **7** at 105 °C for 40 min, followed by methylation with diazomethane, gave the 6-bromo-7-methoxyindole (**12**) in 93% yield from **10**. On the other hand, it is interesting to note that dehydrobromination at higher temperature and with a longer reaction time, 145 °C for 5 h, gave the 6-bromo-7-hydroxyindole (**11**) in only 12% yield and the 4-bromo-7-hydroxyindole (**13**) in 44% yield *via* rearrangement of the bromine atom. The mechanism of this rearrangement can be explained as follows: in the previous paper,[10] we reported the conversion of ethyl 3-bromo-7-methoxyindole-2-carboxylate (**18**) to the corresponding 4-bromo-7-methoxyindole (**14**) in the presence of bromide ion in acidic media, as shown in Chart 4. This conversion was caused by initial protonation, followed by removal of the bromine atom at the C_3-position and irreversible reattack on the benzene moiety of the indole nucleus. In the case of the 6-bromo-7-hydroxyindole (**11**), a similar mechanism could be applied. In basic media, **11** could be transformed into a keto-form (**20**), where bromide ion would attack the bromine atom in the same manner as in **18** to yield the phenolate ion (**21**) and bromine (Br_2). The bromine thus formed could attack the C_4-position of **21**, followed by protonation to yield the 4-bromo-7-hydroxyindole (**13**), which was finally transformed to the bromine-rearranged product (**14**) by methylation with diazomethane.

Bromination of the ketone (**6**) with pyridinium bromide perbromide unexpectedly gave the 3-bromoketone (**15**) in good yield (Chart 3), whereas the bromination of **6** with cupric bromide gave **7**. The structure of **15** was initially determined from the ^{1}H-NMR and mass spectra and finally confirmed by chemical means as follows: the 3-bromoketone (**15**) was brominated with cupric

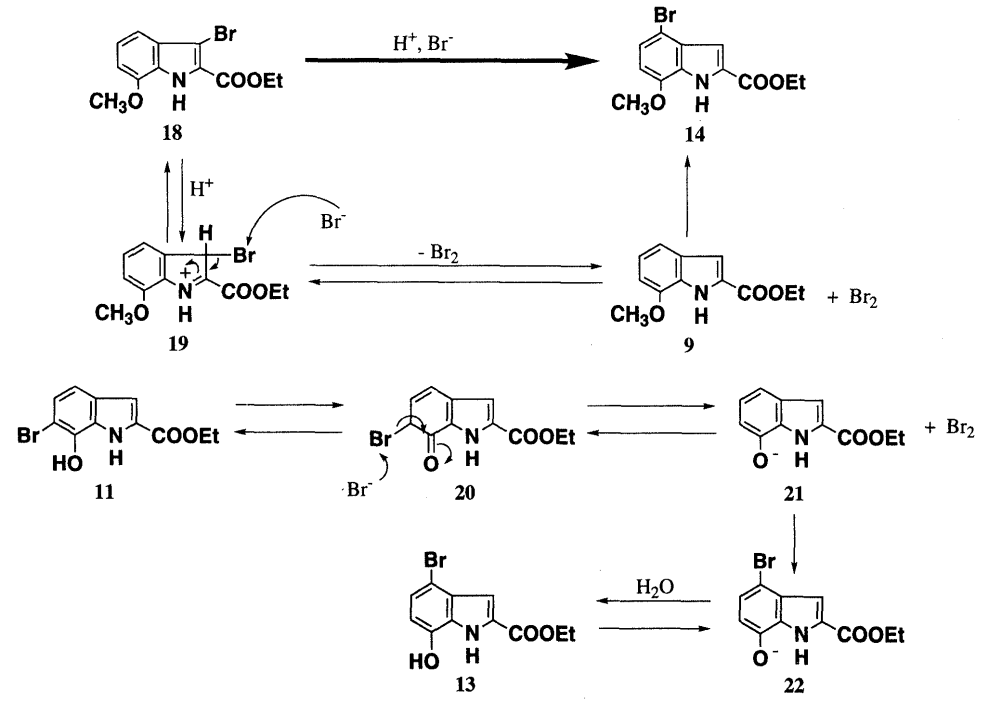

Chart 4

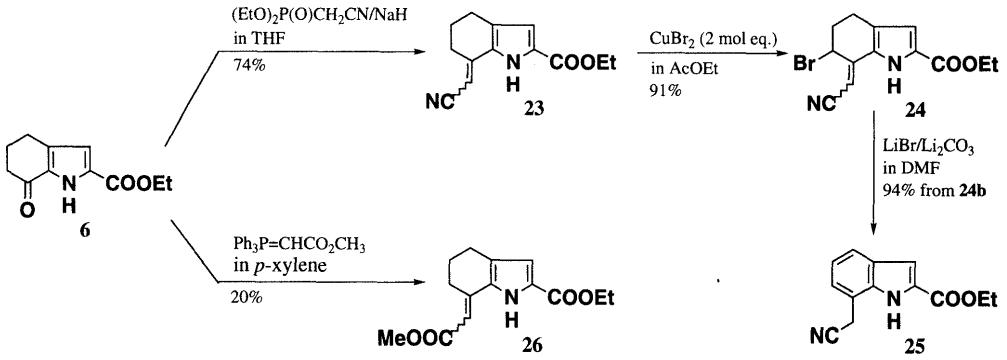

Chart 5

bromide, aromatized to **17** by dehydrobromination, and then converted to the known 3-bromo-7-methoxyindole (**18**).[10]

Next, we focused our attention on the synthesis of 7-alkylindoles from **6**. The reaction of the cyclic ketone **6** with diethyl cyanomethylphosphonate proceeded to give 74% yield of the desired olefin (**23**) as a mixture of *Z*- and *E*-form after refluxing for 15 h (Chart 5). These isomers (**23a, b**) were easily separated by column chromatography on silica gel. The reaction with methyl (triphenylphosphoranylidene)acetate, however, gave the corresponding olefin [**26a** (*Z*-isomer) and **26b** (*E*-isomer)] in only a poor yield (13% and 7%, respectively). Other reagents did not give the corresponding olefin in appreciable yield.

The *Z*- and *E*-mixture of the conjugated olefin (**23**) was then brominated with cupric bromide to yield **24**, as in the case of the ketone (**6**). The *Z*-isomer (**24b**) was then allowed to react under dehydrobromination conditions to yield the 7-functionalized alkylindole (**25**). Dibromination at the α-position of the olefin in **23** was unsuccessful, whereas the bromination of the cyclic ketone (**6**) with an excess of cupric bromide (6 eq) gave the dibromoketone (**10**). As shown in Fig. 1, the *E*- and *Z*-form of **23**, **24** and **26** were determined by observing signal enhancements in nuclear Overhauser effect (NOE) experiments, after separation of the isomers.

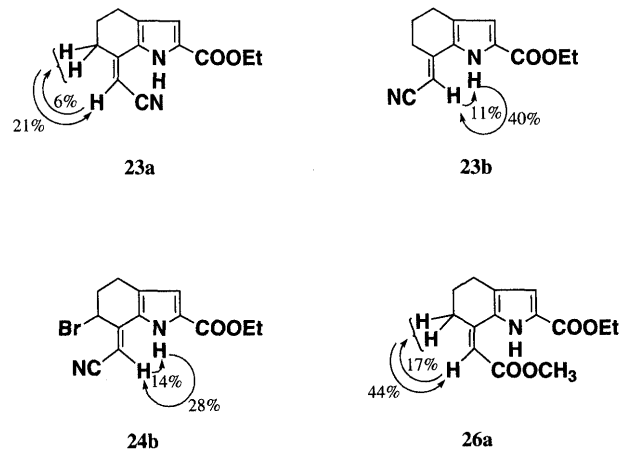

Fig. 1. NOE Correlations Observed in **23a, b**, **24b**, and **26a**

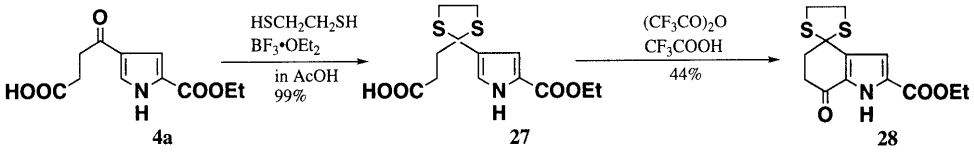

Chart 6

Finally we prepared the C_4-functionalized cyclic ketone (**28**) (Chart 6). The keto-carboxylic acid (**4a**) was converted into the dithioketal derivative (**27**), which was successfully cyclized with trifluoroacetic anhydride to give the dithioketal ketone (**28**) in moderate yield, after examination of a variety of cyclization conditions. The ketone (**28**) should be useful as another key intermediate for the synthesis of indoles with a more highly functionalized benzene moiety.

The present methodology should be valuable for preparing benzene-ring-functionalized indoles.

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-300 or on a Shimadzu IR-400 spectrometer (in Nujol, unless otherwise stated). ^{1}H-NMR spectra were measured on a Hitachi R-24B (60 MHz) spectrometer unless otherwise stated, or on a JEOL GX-400 (400 MHz). Deuteriochloroform was used as the solvent with tetramethylsilane as an internal reference, unless otherwise stated. The assignments of NH signals were confirmed by disappearance of the signals after addition of deuterium oxide. Mass spectra (MS) were measured on JEOL JMS-01-SG-2, JEOL JMS-D300, and JEOL JMS-DX303 spectrometers with a direct inlet system. For column chromatography, Silica gel 60 (70—230 mesh ASTM, Merck, unless otherwise stated), and for thin layer chromatography (TLC), Silica gel $60F_{254}$ (Merck) were used. All identifications of products were done by analysis of MS, IR spectra, and especially NMR spectra. When the products were difficult to separate, the ratios of the products were measured by comparison of the signal intensities of each compound in the 400 MHz ^{1}H-NMR spectrum. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; ddd, double double doublet; t, triplet; q, quartet; m, multiplet; br, broad; dif., diffused; arom., aromatic; BP, base peak.

Acylation of Ethyl Pyrrole-2-carboxylate (1) Method A (Friedel–Crafts Acylation of **1** with 3-Carbomethoxypropionyl Chloride): A solution of **1** (209 mg, 1.5 mmol) in 1,2-dichloroethane (4 ml) was added dropwise to a solution of aluminum chloride (800 mg, 6 mmol) and 3-methoxycarbonylpropionyl chloride (390 μl, 3 mmol) in 1,2-dichloroethane (4 ml) under an argon atmosphere, and the reaction mixture was stirred for 1 h at room temperature. Then it was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel with benzene–ethyl acetate gave ethyl 4-(3-methoxycarbonylpropionyl)pyrrole-2-carboxylate (**2a**) (351 mg, 92.3%).

Method B (Mixed Anhydride Method with 3-Methoxycarbonylpropionic Acid): A solution of **1** (209 mg, 1.5 mmol) in CH_3CN (4 ml) was added to a solution of H_3PO_4 (85%, 49 mg, 0.5 mmol), $(CF_3CO)_2O$ (636 μl, 4.5 mmol) and 3-methoxycarbonylpropionic acid (95%, 606 μl, 4.4 mmol) in CH_3CN (4 ml) at 0 °C under an argon atmosphere, and the mixture was stirred for 5 h at room temperature, then poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give the C_4-acylated compound (**2a**) (283 mg, 74%) and the C_5-acylated one (**2b**) (97 mg, 26%).

Ethyl 4-(3-Methoxycarbonylpropionyl)pyrrole-2-carboxylate (**2a**): Colorless needles from benzene, mp 113—114 °C. *Anal.* Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 57.16; H, 6.07; N, 5.66. IR ν_{max} cm^{-1}: 3260 (NH), 1710, 1660 (CO). ^{1}H-NMR δ: 1.37 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.74 (2H, dif. s, $COC\underline{H}_2CH_2COO$ or $COCH_2C\underline{H}_2COO$), 3.13 (2H, dif. s, $COCH_2C\underline{H}_2COO$ or $COC\underline{H}_2CH_2COO$), 3.69 (3H, s, $OC\underline{H}_3$), 4.34 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.29 (1H, m, C_3-H), 7.54 (1H, m, C_5-H), 10.20 (1H, br s, NH). MS *m/z*: 253 (M^+, 38% of BP), 166 (BP).

Ethyl 5-(3-Methoxycarbonylpropionyl)pyrrole-2-carboxylate (**2b**): Pale yellow plates from hexane, mp 89.5—91 °C. *Anal.* Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.76; H, 5.94; N, 5.39. IR ν_{max} cm^{-1}: 3270 (NH), 1740, 1705, 1680 (CO). ^{1}H-NMR δ: 1.35 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.55—2.95 and 3.00—3.50 (each 2H, m, $COC\underline{H}_2C\underline{H}_2CO$), 3.65 (3H, s, $OC\underline{H}_3$), 4.32 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.86 (2H, d, J=2 Hz, arom.-H), 9.95 (1H, br s, NH). MS *m/z*: 253 (M^+, 51% of BP), 120 (BP).

Ethyl 4-(3-Methoxycarbonylpropyl)pyrrole-2-carboxylate (3) Triethylsilane (4.3 ml, 27 mmol) was added to a solution of **2a** (1.755 g, 6.9 mmol) in 28 ml of trifluoroacetic acid, and the reaction mixture was stirred for 24 h at room temperature. After the removal of trifluoroacetic acid by distillation under reduced pressure, the residue was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel with a hexane to benzene–ethyl acetate gradient to give **3** (1.519 g, 91.6%). Recrystallization of a part of the compound **3** from hexane gave pure sample of **3** as colorless prisms, mp 34.5—35 °C. *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.93; H, 7.22; N, 5.75. IR ν_{max} cm^{-1}: 3360 (NH), 1720, 1680 (CO). ^{1}H-NMR δ: 1.30 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.65—2.75 (6H, m, $ArC\underline{H}_2C\underline{H}_2C\underline{H}_2CO$), 3.61 (3H, s, $OC\underline{H}_3$), 4.27 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.68 (2H, d, J=3 Hz, arom.-H), 9.45 (1H, br s, NH). MS *m/z*: 239 (M^+, 71% of BP), 106 (BP).

4-(2-Ethoxycarbonylpyrrol-4-yl)butyric Acid (5) A mixture of **3** (1.0 g, 4.2 mmol), acetic acid (4 ml), and 30% H_2SO_4 (2 ml) was stirred for 20 min at 100 °C and then poured into ice-water. The whole was made alkaline by adding K_2CO_3 and extracted with ethyl acetate. The alkaline aqueous layer was acidified with concentrated HCl, and extracted with ethyl acetate. The latter organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give **5** (888 mg, 94%). Recrystallization from benzene gave a pure sample of **5** as colorless needles, mp 86—87 °C. *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.72; H, 6.76; N, 6.14. IR ν_{max} cm^{-1}: 3450—2400 (OH), 3300 (NH), 1705, 1675 (CO). ^{1}H-NMR δ: 1.32 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.70—2.20 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.20—2.80 (4H, m, arom.-$C\underline{H}_2CH_2C\underline{H}_2CO$), 4.29 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.73 (2H, d, J=3 Hz, arom.-H), 9.60 (1H, br s, OH or NH), 10.31 (1H, br s, NH or OH). MS *m/z*: 225 (M^+, 82% of BP), 152 (BP).

Ethyl 7-Oxo-4,5,6,7-tetrahydroindole-2-carboxylate (6) Method A: A mixture of **3** (120 mg, 0.5 mmol) and polyphosphoric acid (1.2 g) was stirred for 5 h at 70 °C, and the reaction mixture was poured into water, then extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give an oily residue. The residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give **6** (13 mg, 12.5%). This product was identical with a sample of **6** obtained by method B.

Method B: A solution of **1** (2 g, 14.4 mmol) in 1,2-dichloroethane (20 ml) was added to a suspension of aluminum chloride (11.2 g, 84 mmol) and succinic anhydride (2.8 g, 28 mmol) in 1,2-dichloroethane (20 ml) under an argon atmosphere, and the reaction mixture was stirred for 2 h at room temperature. Then the mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue (crude **4a**).

Triethylsilane (8 ml, 50 mmol) was added dropwise to a solution of the residue in trifluoroacetic acid (28 ml) and the mixture was stirred for 25 h at room temperature. Removal of the trifluoroacetic acid by distillation under reduced pressure gave an oily residue, which was

extracted with ethyl acetate. The organic solution was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to give crude **5**.

Trifluoroacetic anhydride (3 ml, 21 mmol) was added to a solution of the crude product in trifluoroacetic acid (28 ml), and the mixture was stirred for 1 h at room temperature. After the removal of trifluoroacetic acid by distillation under reduced pressure, the residue was extracted with ethyl acetate. The organic layer was washed with saturated K_2CO_3 and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give a residue. The residue was chromatographed on silica gel with a hexane to benzene–ethyl acetate gradient to give **6** (1.8 g, 60% from **1**). Recrystallization from benzene gave a pure sample of **6** as colorless needles, mp 92.5—93 °C. *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.52; H, 6.26; N, 6.80. IR ν_{max} cm^{-1}: 3275 (NH), 1710, 1675 (CO). ^{1}H-NMR δ: 1.36 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.85—2.38 (2H, m, C_5-H), 2.38—2.94 (4H, m, C_4-, C_6-H), 4.35 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.69 (1H, d, J=2.5 Hz, arom.-H), 9.90 (1H, br s, NH). MS *m/z*: 207 (M^+, BP).

In the same way as described above, **4a** was prepared in 87% yield from **1**, and characterized as follows. Colorless needles from hot water, mp 167—168.5 °C. *Anal.* Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.00; H, 5.49; N, 5.79. IR ν_{max} cm^{-1}: 3370—2450 (OH), 3230 (NH), 1718, 1650 (CO). ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.15—3.20 (4H, m, $COC\underline{H}_2C\underline{H}_2CO$), 4.22 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.09 (1H, dd, J=4, 2 Hz, C_3-H), 7.62 (1H, dd, J=4, 2.5 Hz, C_5-H), 11.90 (1H, br s, OH or NH), 12.29 (1H, br s, NH or OH). MS *m/z*: 239 (M^+, 24% of BP), 166 (BP).

Ethyl 6-Bromo-7-oxo-4,5,6,7-tetrahydroindole-2-carboxylate (7) A mixture of **6** (104 mg, 0.5 mmol) and cupric bromide (223 mg, 1 mmol) in ethyl acetate (2 ml) was stirred for 1 h at reflux temperature under an argon atmosphere, and then the reaction mixture was filtered with suction. The residue was washed with hot ethyl acetate, and the combined organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give a residue. The residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give a product **7** (128 mg, 89%) and the starting material **6** (5 mg, 5% recovery) in order of elution. Recrystallization of **7** from benzene–hexane gave a pure sample as colorless needles, mp 112—113 °C. *Anal.* Calcd for $C_{11}H_{12}BrNO_3$: C, 46.18; H, 4.23; N, 4.90. Found: C, 46.05; H, 4.14; N, 4.76. IR ν_{max} cm^{-1}: 3240 (NH), 1700, 1660 (CO). ^{1}H-NMR δ: 1.38 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.25–3.40 (4H, m, C_4-, C_5-H), 4.37 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.61 (1H, t, J=4 Hz, C_6-H), 6.70 (1H, d, J=2 Hz, arom.-H), 10.00 (1H, br s, NH). MS *m/z*: 287 (M^++2, 84% of BP), 285 (M^+, 87% of BP), 160 (BP).

Ethyl 7-Hydroxyindole-2-carboxylate (8) A mixture of **7** (858 mg, 3 mmol), lithium carbonate (233 mg, 3.2 mmol), and lithium bromide (274 mg, 3.2 mmol) in DMF (30 ml) was stirred for 40 min at 150 °C under an argon atmosphere. After cooling, the reaction mixture was poured into saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to give a residue. The residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give **8** (565 mg, 92%). Recrystallization from benzene gave a pure sample of **8** as colorless plates, mp 202.5—203.5 °C. *Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.10; H, 5.31; N, 6.79. IR ν_{max} cm^{-1}: 3370 (NH or OH), 3325 (OH or NH), 1658 (CO). ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.41 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.39 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.50—7.35 (4H, m, arom.-H), 10.65 (1H, br s, NH). MS *m/z*: 205 (M^+, 82% of BP), 159 (BP).

Ethyl 7-Methoxyindole-2-carboxylate (9) An ether (10 ml) solution of diazomethane, prepared from *N*-nitrosomethylurea (3.5 g, 34 mmol) and KOH (85%, 1.9 g, 28.8 mmol), was added to a solution of **8** (346 mg, 1.7 mmol) in diethyl ether (2 ml), and the mixture was stirred at room temperature overnight. It was then evaporated to dryness *in vacuo* to give a residue. The residue was chromatographed on silica gel with benzene to give **9** (335 mg, 91%). Recrystallization of a part of **9** from benzene gave a pure sample as colorless needles, mp 114—115 °C (lit.,[9] mp 114 °C from EtOH). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.82; H, 5.94; N, 6.40. IR ν_{max} cm^{-1}: 3325 (NH), 1700 (CO). ^{1}H-NMR δ: 1.39 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.93 (3H, s, $OC\underline{H}_3$), 4.38 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.5—7.43 (4H, m, arom.-H), 9.01 (1H, br s, NH). MS *m/z*: 219 (M^+, BP).

Ethyl 6,6-Dibromo-7-oxo-4,5,6,7-tetrahydroindole-2-carboxylate (10) A mixture of **6** (1.0 g, 4.8 mmol) and cupric bromide (6.8 g, 30 mmol) in ethyl acetate (20 ml) was stirred at reflux temperature for 5 h under an argon atmosphere, and the reaction mixture was worked up as described above to give a residue. The residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give **10** (1.7 g, 97%). Recrystallization from benzene–hexane gave a pure sample of **10** as colorless needles, mp 162.5—164.5 °C. *Anal.* Calcd for $C_{11}H_{11}Br_2NO_3$: C, 36.19; H, 3.04; N, 3.84. Found: C, 36.20; H, 3.00; N, 3.85. IR ν_{max} cm^{-1}: 3240 (NH), 1710, 1683 (CO). ^{1}H-NMR δ: 1.37 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.70—3.25 (4H, m, C_4-, C_5-H), 4.37 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.69 (1H, d, J=2.5 Hz, arom.-H), 9.90 (1H, br s, NH). MS *m/z*: 367 (M^++4, 55% of BP), 365 (M^++2, BP), 363 (M^+, 57%).

Ethyl 6-Bromo-7-hydroxyindole-2-carboxylate (11) A mixture of **10** (365 mg, 1 mmol), lithium carbonate (79 mg, 1.1 mmol), and lithium bromide (92 mg, 1.1 mmol) in DMF (4.5 ml) was stirred for 40 min at 104—108 °C under an argon atmosphere. After cooling, the mixture was worked up as described above, and subjected to column chromatography on silica gel with benzene–ethyl acetate to give **11** (273 mg, 96%). Recrystallization from ethyl acetate–hexane gave a pure sample of **11** as colorless needles, mp 214—218 °C. *Anal.* Calcd for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.44; H, 3.48; N, 4.81. IR ν_{max} cm^{-1}: 3345 (NH), 1675 (CO). ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.32 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.32 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.08 (3H, dif. s, arom.-H), 9.80 (1H, br s, OH or NH), 11.20 (1H, br s, NH or OH). MS *m/z*: 285 (M^++2, 46% of BP), 283 (M^+, 46% of BP), 237 (BP).

Ethyl 6-Bromo-7-methoxyindole-2-carboxylate (12) An ether solution (20 ml) of diazomethane, prepared from *N*-nitrosomethylurea (1.1 g, 10.7 mmol) and KOH (85%, 1.4 g, 21.2 mmol), was added to a solution of **11** (149 mg, 0.5 mmol) in ethyl acetate (20 ml), and the reaction mixture was stirred for 25 min at 0 °C. The mixture was worked up as described above, and subjected to column chromatography on silica gel with benzene to give **12** (151 mg, 97%). Recrystallization from benzene–hexane gave a pure sample of **12** as colorless plates, mp 100—102.5 °C. *Anal.* Calcd for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.28; H, 4.02; N, 4.63. IR ν_{max} cm^{-1}: 3300 (NH), 1695 (CO). ^{1}H-NMR δ: 1.40 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.99 (3H, s, $OC\underline{H}_3$), 4.41 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.14 (1H, d, J=2 Hz, C_3-H), 7.22 (2H, s, C_4-, C_5-H), 9.19 (1H, br s, NH). MS *m/z*: 299 (M^++2, 95% of BP), 297 (M^+, BP).

Ethyl 4-Bromo-7-hydroxyindole-2-carboxylate (13) A mixture of **10** (166 mg, 0.45 mmol), lithium carbonate (35.6 mg, 0.48 mmol), and lithium bromide (41.8 mg, 0.48 mmol) in DMF (2.3 ml) was stirred at 145 °C (bath temperature) for 5 h under an argon atmosphere. After cooling, the reaction mixture was worked up as described above, and the residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give **11** (15 mg, 12%) and the C_4-brominated product (**13**) (57 mg, 44%) in order of elution. The former product (**11**) was identical with a sample of **11** obtained by the above method, based on comparison of TLC behavior and IR and ^{1}H-NMR spectra. Recrystallization of **13** from ethyl acetate–hexane gave a pure sample as colorless needles, mp 218—222 °C. High-resolution MS: Calcd for $C_{11}H_{10}BrNO_3$: 282.9843. Found: 282.9858. IR ν_{max} cm^{-1}: 3325 (NH), 1665 (CO). ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.34 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 4.32 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.55 (1H, d, J=8.5 Hz, C_6-H), 6.92 (1H, dif. s, C_3-H), 7.08 (1H, d, J=8.5 Hz, C_5-H), 9.72 (1H, br s, OH or NH), 11.70 (1H, br s, NH or OH). MS *m/z*: 285 (M^++2, 51% of BP), 283 (M^+, 52% of BP), 237 (BP).

Ethyl 4-Bromo-7-methoxyindole-2-carboxylate (14) An ether solution (4 ml) of diazomethane, prepared from *N*-nitrosomethylurea (207 mg, 2 mmol) and KOH (85%, 278 mg, 4.2 mmol), was added to a solution of **13** (29 mg, 0.1 mmol) in ethyl acetate (4 ml), and the reaction mixture was stirred for 30 min at 0 °C. The mixture was worked up as described above, and subjected to column chromatography on silica gel with benzene–ethyl acetate to give **14** (29 mg, 95%). Recrystallization from hexane–benzene gave a pure sample of **14** as colorless needles, mp 137—138.5 °C. *Anal.* Calcd for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.20; H, 3.98; N, 4.67. IR ν_{max} cm^{-1}: 3300 (NH), 1705 (CO). ^{1}H-NMR δ: 1.40 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 3.90 (3H, s, $OC\underline{H}_3$), 4.39 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.50 (1H, d, J=8 Hz, C_6-H), 7.13 (1H, d, J=8 Hz, C_5-H), 7.15 (1H, d, J=2.5 Hz, C_3-H), 9.19 (1H, br s, NH). MS *m/z*: 299 (M^++2, 98% of BP), 297 (M^+, 97% of BP), 253 (BP).

Ethyl 3-Bromo-7-oxo-4,5,6,7-tetrahydroindole-2-carboxylate (15) A solution of pyridinium bromide perbromide (90%, 110 mg, 0.3 mmol) in pyridine (1.3 ml) was added dropwise to a solution of **6** (62 mg, 0.3 mmol) in pyridine (1.3 ml), and the mixture was stirred for 24 min

at 0 °C, poured into ice-water, acidified by adding 10% HCl, and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to give nearly pure **15** (80 mg). This product was subjected to column chromatography on silica gel with benzene–ethyl acetate to give **15** (79 mg, 92%). Recrystallization from ethyl acetate–hexane gave a pure sample of **15** as colorless needles, mp 126—127.5 °C. *Anal.* Calcd for $C_{11}H_{12}BrNO_3$: C, 46.18; H, 4.23; N, 4.89. Found: C, 46.37; H, 4.21; N, 4.97. IR ν_{max} cm^{-1}: 3230 (NH), 1693, 1675 (CO). ^{1}H-NMR δ: 1.39 (3H, t, J=8 Hz, $CH_2\underline{CH}_3$), 1.90—2.90 (6H, m, C_4-, C_5-, C_6-H), 4.38 (2H, q, J=8 Hz, $OC\underline{H}_2CH_3$), 9.90 (1H, br s, NH). MS m/z: 287 (M^++2, 98% of BP), 285 (M^+, BP).

Ethyl 3,6-Dibromo-7-oxo-4,5,6,7-tetrahydroindole-2-carboxylate (16) A mixture of **15** (273 mg, 0.95 mmol) and cupric bromide (427 mg, 1.9 mmol) in ethyl acetate (7 ml) was stirred at reflux temperature for 80 min under an argon atmosphere. The reaction mixture was worked up as described above, and subjected to column chromatography on silica gel with benzene–ethyl acetate to give the product (**16**) (299 mg, 86%) and starting material (**15**) (8 mg, 3% recovery). Recrystallization of **16** from benzene–hexane gave a pure sample as colorless needles, mp 154—157 °C. *Anal.* Calcd for $C_{11}H_{11}Br_2NO_3$: C, 36.19; H, 3.04; N, 3.84. Found: C, 36.07; H, 3.02; N, 3.78. IR ν_{max} cm^{-1}: 3230 (NH), 1700, 1661 (CO). ^{1}H-NMR δ: 1.40 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 2.30—3.00 (4H, m, C_4-, C_5-H), 4.41 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.62 (1H, m, C_6-H), 10.00 (1H, br s, NH). MS m/z: 367 (M^++4, 49% of BP), 365 (M^++2, BP), 363 (M^+, 50% of BP).

Ethyl 3-Bromo-7-hydroxyindole-2-carboxylate (17) A mixture of **16** (211 mg, 0.6 mmol), lithium carbonate (45 mg, 0.6 mmol), and lithium bromide (54 mg, 0.6 mmol) in DMF (2.5 ml) was stirred at 100—120 °C for 1.5 h under an argon atmosphere. After cooling, the reaction mixture was worked up as described above to give the product (**17**) (145 mg, 88%). Recrystallization from ethyl acetate–benzene gave a pure sample of **17** as colorless needles, mp 196—198 °C. *Anal.* Calcd for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.62; H, 3.50; N, 4.62. IR ν_{max} cm^{-1}: 3450—3100 (OH), 3351 (NH), 1658 (CO). ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.36 (3H, t, J=8 Hz, $CH_2\underline{CH}_3$), 4.34 (2H, q, J=8 Hz, $OC\underline{H}_2CH_3$), 6.58—7.10 (3H, m, arom.-H), 9.67 (1H, br s, OH or NH), 11.64 (1H, br s, NH or OH). MS m/z: 285 (M^++2, 42% of BP), 283 (M^+, 42% of BP), 237 (BP).

Ethyl 3-Bromo-7-methoxyindole-2-carboxylate (18) An ether solution (7 ml) of diazomethane, prepared from *N*-nitrosomethylurea (314 mg, 3 mmol) and KOH (85%, 350 mg, 5.3 mmol), was added to a solution of **17** (43 mg, 0.15 mmol) in ethyl acetate (7 ml), and the mixture was stirred at 0 °C for 25 min, then for 1 h at room temperature. The mixture was worked up as described above, and the residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give **18** (35 mg, 78%). Recrystallization from benzene–hexane gave a pure sample of **18** as colorless needles, mp 119—120.5 °C. *Anal.* Calcd for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.35; H, 4.04; N, 4.59. IR ν_{max} cm^{-1}: 3300 (NH), 1695 (CO). ^{1}H-NMR δ: 1.41 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 3.92 (3H, s, $O\underline{CH}_3$), 4.42 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.68 (1H, dd, J=8, 2 Hz, C_6- or C_4-H), 7.04 (1H, t, J=8 Hz, C_5-H), 7.21 (1H, dd, J=8, 2 Hz, C_4- or C_6-H), 9.10 (1H, br s, NH). MS m/z: 299 (M^++2, 87% of BP), 297 (M^+, 88% of BP), 251 (BP).

The Reaction of 6 with Diethyl Cyanomethylphosphonate A solution of **6** (508 mg, 2.5 mmol) in tetrahydrofuran (15 ml) was added to an ice-cooled suspension of sodium hydride (60%, 375 mg, 9.4 mmol) in tetrahydrofuran (140 ml) under an argon atmosphere, and the mixture was stirred at 0 °C for 1 h. Then diethyl cyanomethylphosphonate (1.6 ml, 9.7 mmol) was added dropwise, and the whole was stirred under reflux for 15 h, poured into ice-water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give (*Z*)-ethyl 7-cyanomethylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**23a**) (232 mg, 41%), (*E*)-ethyl 7-cyanomethylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**23b**) (186 mg, 33%), and the starting material (**6**) (126 mg, 25% recovery) in order of elution. Recrystallization of **23a** and **23b** gave pure samples, respectively.

(*Z*)-Ethyl 7-Cyanomethylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**23a**): Colorless needles from hexane–chloroform, mp 59.0—60.0 °C. *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.68; H, 6.14; N, 12.10. IR ν_{max} cm^{-1}: 3430 (NH), 2210 (CN), 1710 (CO). ^{1}H-NMR (400 MHz) δ: 1.37 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 1.89 (2H, m, C_5-H), 2.56 (2H, ddd, J=7.5, 4.5, 1.5 Hz, C_6-H), 2.67 (2H, dif. t, J=6 Hz, C_4-H), 4.35 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.94 (1H, t, J=1.5 Hz, olefinic-H), 6.73 (1H, d, J=2.5 Hz, C_3-H), 10.09 (1H, br s, NH). Difference NOE: irradiation of olefinic proton (4.94 ppm), 6% enhancement of C_6-H (2.56 ppm); irradiation of C_6-H (2.56 ppm), 21% enhancement of olefinic proton (4.94 ppm). MS m/z: 230 (M^+, 90% of BP), 184 (BP).

(*E*)-Ethyl 7-Cyanomethylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**23b**): Colorless needles from hexane–ethyl acetate, mp 200.0—201.0 °C. *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.92; H, 6.13; N, 12.21. IR ν_{max} cm^{-1}: 3320 (NH), 2215 (CN), 1683 (CO). ^{1}H-NMR δ: 1.37 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 1.64—2.20 (2H, m, C_5-H), 2.50—2.95 (4H, m, C_4-, C_6-H), 4.32 (2H, q, J=7 Hz, OCH_2CH_3), 5.74 (1H, dif. s, olefinic-H), 6.68 (1H, d, J=2 Hz, C_3-H), 10.22 (1H, br s, NH). Difference NOE: irradiation of olefinic proton (5.74 ppm), 11% enhancement of NH proton (10.22 ppm); irradiation of NH proton (10.22 ppm), 40% enhancement of olefinic proton (5.74 ppm). MS m/z: 230 (M^+, BP).

Bromination of Ethyl 7-Cyanomethylidene-4,5,6,7-tetrahydroindole-2-carboxylate (23) with Cupric Bromide A mixture of **23** (125 mg, 0.54 mmol; the ratio of **23a** : **23b** was approximately 2 : 3) and cupric bromide (250 mg, 1 mmol) in ethyl acetate (10 ml) was stirred at reflux temperature for 7 h under an argon atmosphere. After cooling, the reaction mixture was worked up as described above, and the residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give (*E*)-ethyl 6-bromo-7-cyanomethylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**24a**) (25 mg, 15%) and (*Z*)-ethyl 6-bromo-7-cyanomethylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**24b**) (127 mg, 76%) in order of elution. Recrystallization of **24a** and **24b** gave pure samples, respectively.

(*E*)-Ethyl 6-Bromo-7-cyanomethylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**24a**): Colorless needles from hexane–ethyl acetate, mp 127—132 °C. High-resolution MS: Calcd for $C_{13}H_{13}BrN_2O_2$: 308.0160. Found: 308.0164. IR ν_{max}^{KBr} cm^{-1}: 3440 (NH), 2200 (CN), 1715 (CO). ^{1}H-NMR δ: 1.34 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 1.90—2.35 and 2.69—3.05 (each 2H, m, C_4-, C_5-H), 4.31 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.91 (1H, dif. t, J=3 Hz, C_6-H), 5.16 (1H, s, olefinic-H), 6.70 (1H, d, J=2.5 Hz, C_3-H), 10.00 (1H, br s, NH). MS m/z: 310 (M^++2, 49% of BP), 308 (M^+, 50% of BP), 183 (BP).

(*Z*)-Ethyl 6-Bromo-7-cyanomethylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**24b**): Colorless needles from ethyl acetate–hexane, mp 181—185 °C. *Anal.* Calcd for $C_{13}H_{13}BrN_2O_2$: C, 50.51; H, 4.24; N, 9.06. Found: C, 50.64; H, 4.27; N, 9.04. IR ν_{max} cm^{-1}: 3320 (NH), 2225 (CN), 1680 (CO). ^{1}H-NMR (400 MHz) δ: 1.41 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 2.12 and 2.37 (each 1H, m, C_5-H), 2.73 and 3.00 (each 1H, m, C_4-H), 4.37 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.43 (1H, t, J=3 Hz, C_6-H), 5.73 (1H, s, olefinic-H), 6.78 (1H, d, J=2 Hz, C_3-H), 10.11 (1H, br s, NH). Difference NOE: irradiation of NH proton (10.11 ppm), 28% enhancement of olefinic proton (5.73 ppm); irradiation of olefinic proton (5.73 ppm), 14% enhancement of NH proton (10.11 ppm). MS m/z: 310 (M^++2, 63% of BP), 308 (M^+, 64% of BP), 183 (BP).

Ethyl 7-Cyanomethylindole-2-carboxylate (25) A mixture of **24b** (85 mg, 0.27 mmol), lithium carbonate (22 mg, 0.3 mmol), and lithium bromide (26 mg, 0.3 mmol) in DMF (2 ml) was stirred at 100 °C for 2.4 h under an argon atmosphere, then the mixture was poured into saturated NH_4Cl, and extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to give a residue. The residue was subjected to column chromatography on silica gel with benzene–ethyl acetate to give **25** (59 mg, 94%). Recrystallization from ethyl acetate–hexane gave a pure sample of **25** as colorless needles, mp 185—186 °C. *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.31; H, 5.31; N, 12.16. IR ν_{max} cm^{-1}: 3325 (NH), 2250 (CN), 1675 (CO). ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.33 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 4.28 (2H, s, arom.-$C\underline{H}_2CN$), 4.34 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.89—7.75 (4H, m, arom.-H), 11.84 (1H, br s, NH). MS m/z: 228 (M^+, 69.3% of BP), 182 (BP).

Reaction of 6 with Methyl (Triphenylphosphoranylidene)acetate A mixture of **6** (258 mg, 1.24 mmol) and methyl (triphenylphosphoranylidene)acetate (98%, 1.62 g, 4.7 mmol) in *p*-xylene (4 ml) was stirred at reflux temperature for 5.5 h under an argon atmosphere. The reaction mixture was poured into ice-water, and extracted with methylene chloride. The organic solution was washed with saturated NaCl, dried over $MgSO_4$, and then evaporated to give a residue. The residue was subjected to column chromatography on silica gel with hexane-ethyl acetate to

give (*Z*)-ethyl 7-methoxycarbonylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**26a**) (41 mg, 13%), (*E*)-ethyl 7-methoxycarbonylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**26b**) (23 mg, 7%) and the starting material (**6**) (169 mg, 66% recovery) in order of elution.

(*Z*)-Ethyl 7-Methoxycarbonylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**26a**): Colorless needles from hexane–ethyl acetate, mp 73—77.5 °C. *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.97; H, 6.59; N, 5.24. IR ν_{max} cm^{-1}: 3195 (NH), 1713, 1685 (CO). ^{1}H-NMR (400 MHz) δ: 1.38 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.88 (2H, dif. quintet, J=6 Hz, C_5-H), 2.56 (2H, m, C_6-H), 2.67 (2H, t, J=6 Hz, C_4-H), 3.77 (3H, s, $OC\underline{H}_3$), 4.36 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.59 (1H, dif. t, J=1 Hz, olefinic-H), 6.71 (1H, d, J=2.5 Hz, arom.-H), 12.84 (1H, br s, NH). Difference NOE: irradiation of C_6-H (2.56 ppm), 44% enhancement of olefinic proton (5.59 ppm); irradiation of olefinic proton (5.59 ppm), 17% enhancement of C_6-H (2.56 ppm). MS *m/z*: 263 (M^+, BP).

(*E*)-Ethyl 7-Methoxycarbonylidene-4,5,6,7-tetrahydroindole-2-carboxylate (**26b**): Colorless needles from hexane–ethyl acetate, mp 157—162 °C. *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.83; H, 6.55; N, 5.26. IR ν_{max} cm^{-1}: 3300 (NH), 1693, 1679 (CO). ^{1}H-NMR (400 MHz) δ: 1.36 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.87 (2H, quintet, J=6 Hz, C_5-H), 2.62 (2H, t, J=6 Hz, C_4- or C_6-H), 3.12 (2H, m, C_6- or C_4-H), 3.73 (3H, s, $OC\underline{H}_3$), 4.35 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.96 (1H, dif. s, olefinic-H), 6.70 (1H, d, J=2 Hz, C_3-H), 9.34 (1H, br s, NH). MS *m/z*: 263 (M^+, BP).

4-[2-(1,3-Dithiolanyl)]-4-(2-ethoxycarbonylpyrrol-4-yl)butyric Acid (27) Boron trifluoride diethyl etherate (1.5 ml of 47% solution, 12 mmol) and 1,2-ethanedithiol (1.4 ml, 17 mmol) were added successively to a solution of 4-(2-ethoxycarbonylpyrrol-4-yl)-4-oxobutyric acid (**4a**) (2.0 g, 8.4 mmol) in acetic acid (95 ml) under an argon atmosphere, and the mixture was stirred at room temperature for 8 d. Then it was poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give a residue. The residue was subjected to column chromatography on silica gel with hexane–ethyl acetate to afford a product (**27**) (2.6 g, 99%). Recrystallization from hexane–ethyl acetate gave a pure sample of **27** as colorless needles, mp 157—158 °C. *Anal.* Calcd for $C_{13}H_{17}NO_4S_2$: C, 49.51; H, 5.43; N, 4.44. Found: C, 49.38; H, 5.43; N, 4.43. IR ν_{max} cm^{-1}: 3380 (NH), 3200—2450 (OH), 1700 (CO). ^{1}H-NMR δ: 1.32 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.53 (4H, s, $SC\underline{H}_2C\underline{H}_2S$ or $CC\underline{H}_2C\underline{H}_2CO$), 3.42 (4H, s, $CC\underline{H}_2C\underline{H}_2CO$ or $SC\underline{H}_2C\underline{H}_2S$), 4.28 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.88 (1H, m, arom.-H), 7.00 (1H, m, arom.-H), 8.22 (1H, br s, NH or OH), 9.68 (1H, br s, OH or NH). MS *m/z*: 315 (M^+, 10% of BP), 242 (BP).

Ethyl 4-[2-(1,3-Dithiolanyl)]-7-oxo-4,5,6,7-tetrahydroindole-2-carboxylate (28) Trifluoroacetic anhydride (274 μl, 1.9 mmol) was added dropwise to an ice-cooled solution of **27** (204 mg, 0.7 mmol) in trifluoroacetic acid (12 ml) under an argon atmosphere, and the mixture was stirred at room temperature for 3.7 h. It was poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give a residue. The residue was subjected to column chromatography on silica gel with hexane–ethyl acetate to afford a product (**28**) (85 mg, 44%). Recrystallization from hexane–ethyl acetate gave a pure sample of **28** as colorless needles, mp 151—152 °C. *Anal.* Calcd for $C_{13}H_{15}NO_3S_2$: C, 52.50; H, 5.08; N, 4.71. Found: C, 52.27; H, 5.08; N, 4.83. IR ν_{max} cm^{-1}: 3250 (NH), 1705, 1670 (CO). ^{1}H-NMR δ: 1.35 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.72 (4H, dif. s, $SC\underline{H}_2C\underline{H}_2S$ or $CC\underline{H}_2C\underline{H}_2CO$), 3.47 (4H, dif. s, $CC\underline{H}_2C\underline{H}_2CO$ or $SC\underline{H}_2C\underline{H}_2S$), 4.30 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.90 (1H, d, J=3 Hz, arom.-H), 9.80 (1H, br s, NH). MS *m/z*: 297 (M^+, 54.5% of BP), 237 (BP).

References and Notes

1) A part of this paper was reported as a preliminary communication: Murakami Y., Tani M., Nishiyama C., Watanabe T., Yokoyama Y., *Heterocycles*, **27**, 1855—1860 (1988). Part XXXVIII: Tani M., Ariyasu T., Nishiyama C., Watanabe T., Yokoyama Y., Murakami Y., *Chem. Pharm. Bull.*, **44**, 48—54 (1996).
2) *a*) Brown R. K., "The Chemistry of Heterocyclic Compounds, Indoles Part 1," ed. by Houlihan W. J., Wiley-Interscience, John Wiley & Sons, Inc. New York, 1972, pp. 227—558; *b*) Sundberg R. J., "Comprehensive Heterocyclic Chemistry," Vol. 4, ed. by Katritzky A. R., Rees C. W., Pergamon Press, Oxford, 1984, pp. 313—376.
3) Robinson B., "The Fischer Indole Synthesis," A Wiley Interscience Publication, John Wiley & Sons, Chichester, 1982.
4) Ref. 2*b*, pp. 348—370.
5) *a*) Yamashita A., Scahill T. A., Toy A., *Tetrahedron Lett.*, **26**, 2969—2972 (1985); *b*) Trost B. M., Reiffen M., Crimmin M., *J. Am. Chem. Soc.*, **101**, 257—259 (1979); *c*) Natsume M., Muratake H., *Tetrahedron Lett.*, **1979**, 3477—3480; *d*) Fujii M., Muratake H., Natsume M., *Chem. Pharm. Bull.*, **40**, 2344—2352 (1992); *e*) Matsumoto M., Ishida Y., Watanabe N., *Heterocycles*, **23**, 165—170 (1985) and their subsequent papers.
6) *a*) Murakami Y., Watanabe T., Ishii H., *J. Chem. Soc., Perkin Trans. 1*, **1988**, 3005—3012; *b*) Watanabe T., Miyagi C., Murakami Y., *J. Heterocycl. Chem.*, **30**, 217—224 (1993).
7) Murakami Y., Tani M., Suzuki M., Sudoh K., Uesato M., Tanaka K., Yokoyama Y., *Chem. Pharm. Bull.*, **33**, 4707—4716 (1985).
8) Kastri T. R., Arunachalam T., *Can. J. Chem.*, **46**, 3625—3629 (1968).
9) Blaikie K. G., Perkin W. H., Jr., *J. Chem. Soc. Abstr.*, **125**, 296—335 (1924).
10) Tani M., Ikegami H., Tashiro M., Hiura T., Tsukioka H., Kaneko C., Notoya T., Shimizu M., Uchida M., Aida Y., Yokoyama Y., Murakami Y., *Heterocycles*, **34**, 2349—2362 (1992).