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Cyclic Tautomers of Tryptophans and Tryptamines. VI.[1] Preparation of N_a-Alkyl-, 5-Chloro-, and 5-Nitrotryptophan Derivatives[2]

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Selective N_a-alkylation, 5-chlorination, 5-bromination, and 5-nitration of tryptophan derivatives were achieved. The alkylation of the cyclic tautomer **2** of N_b-methoxycarbonyl-DL-tryptophan methyl ester (**1**) with alkyl halides in acetone-K_2CO_3 gave the N_a-alkyl derivatives (**3a** and **4**) in excellent yields. The chlorination of the cyclic tautomer **3b** with NCS–AcOH gave the 5-chloro derivative (**5b**) in 89% yield, and this was readily converted to the 5-chlorotryptophan derivatives (**7a**, **7b**, **9**). The similar chlorination of **12** gave the 5-chloro derivatives (**13a**, **15a**) and the 3a-chloropyrroloindole derivative (**17**). On the other hand the bromination of **12** with NBS–AcOH gave the 5-bromo derivative (**13b**) in good yield, and this was readily converted to **15d** and further to **15c**. The nitration of **3b** and **12** with fuming nitric acid also gave the 5-nitro derivatives (**5c**, **7c**, **13c**, **15e**) in excellent yields.

Keywords——tryptophan derivatives; cyclic tautomer of N_b-acyltryptophans; chlorination; bromination; nitration; *N*-alkylation; 5-substituted tryptophan derivatives; *N*-chlorosuccinimide; *N*-bromosuccinimide

Tryptophan derivatives carrying a substituent at the benzene moiety of the indole ring have usually been prepared from the substituted benzene derivatives *via* the indole ring closure. For example, 5-nitro-[3] and 5-chlorotryptophan[4] derivatives have been prepared from *p*-nitro and *p*-chlorophenylhydrazines and the appropriate ketone by Fischer indolization followed by appropriate elaboration. Direct electrophilic substitution of 3-substituted indole derivatives usually gives 2,3-disubstituted indoles or the oxindole derivatives and not 3-substituted indoles carrying a substituent at the benzene ring.[5] However, 3-acylindole derivatives gave 5- or 6-substituted 3-acylindoles on the halogenation,[6] nitration,[7] and acetylation.[8] As an exception, 6-nitrotryptophan was obtained by the nitration of tryptophan nitrate.[9] These results depend upon the fact that the electrophilic substitution of 3-substituted indoles in general yield the 2-substituted derivatives *via* the 3,3-disubstituted indolenine form due to the strong enamine character of the pyrrole moiety.[5]

In our previous paper[1,2,10] we described a simple synthesis of the cyclic tautomer of N_b-acyltryptophan esters (**1**). The cyclic tautomer (**2**) obtained by acid treatment of acyltryptophan esters loses the enamine character which is specific to the open chain tautomer (**1**), and the benzene ring of **2** gains aniline reactivity. Therefore the electrophilic substitution of the cyclic tautomer (**2**, **3**) may give the 5-substituted derivatives (**5**) which may easily be converted to 5-substituted tryptophan derivatives (**7**). Furthermore, N_a-alkylation of **2** may occur more easily than in the case of the open chain tautomer (**1**) where N_b-alkylation might also occur.

We now describe the N_a-alkylation, chlorination, bromination and nitration of the cyclic tautomer (**2**, **3**) to prepare substituted tryptophan derivatives.

When the cyclic tautomer (**2**)[10] obtained from N_b-methoxycarbonyl-DL-tryptophan methyl ester (**1**) by 85% phosphoric acid treatment was treated with methyl iodide–potassium carbonate–acetone at room temperature for 60 h, the N_a-methyl derivative (**3a**) was obtained in 69% yield. This compound (**3a**) was readily converted to **4a** quantitatively by dissolving **3a** in acetic acid at room temperature. Compound **4a** mp 74—76°C, was identical with an authentic sample prepared from N_a-methyl-DL-tryptophan. On the other hand, dimethylallylation of **2** with dimethylallyl bromide–potassium carbonate–acetone for 5.5 h at room

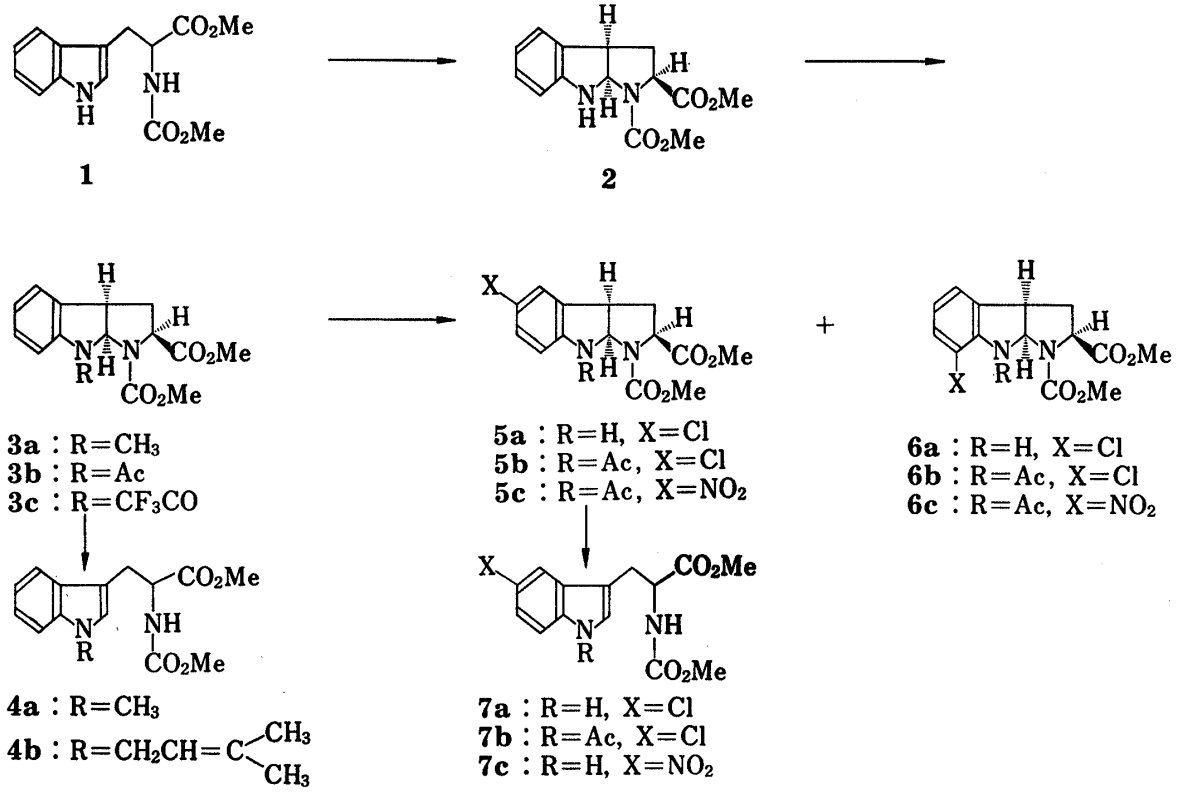


Chart 1

temperature gave **4b** directly in 92% yield. These alkylations are much easier than that of open chain tautomer (**1**), for which a strong base such as sodium amide in liq. ammonia[11] is required. This alkylation is especially useful in the N_a-alkylatin of N_b-acyltryptophan derivatives.

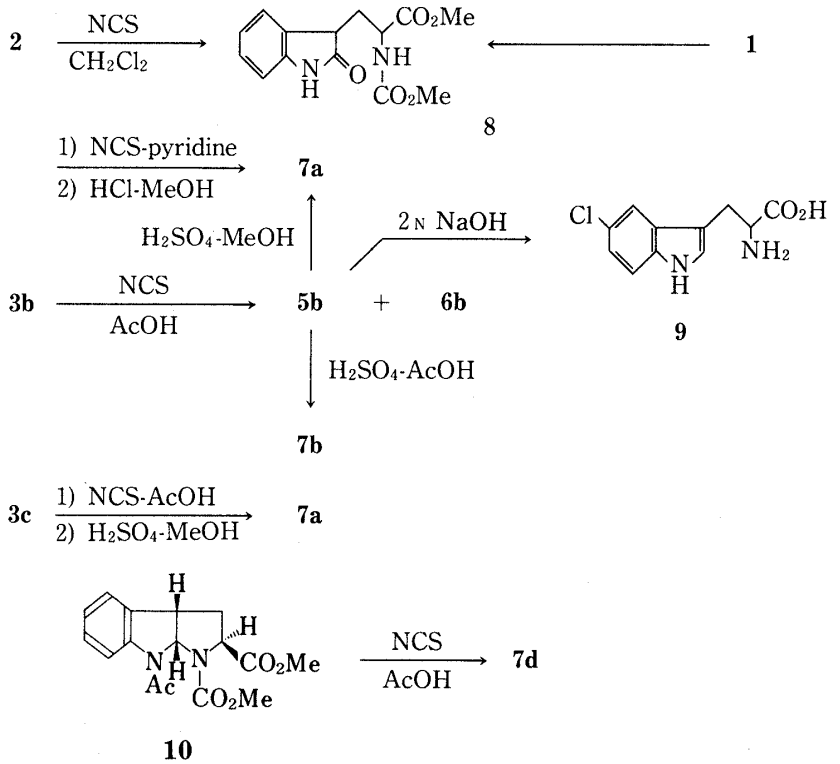


Chart 2

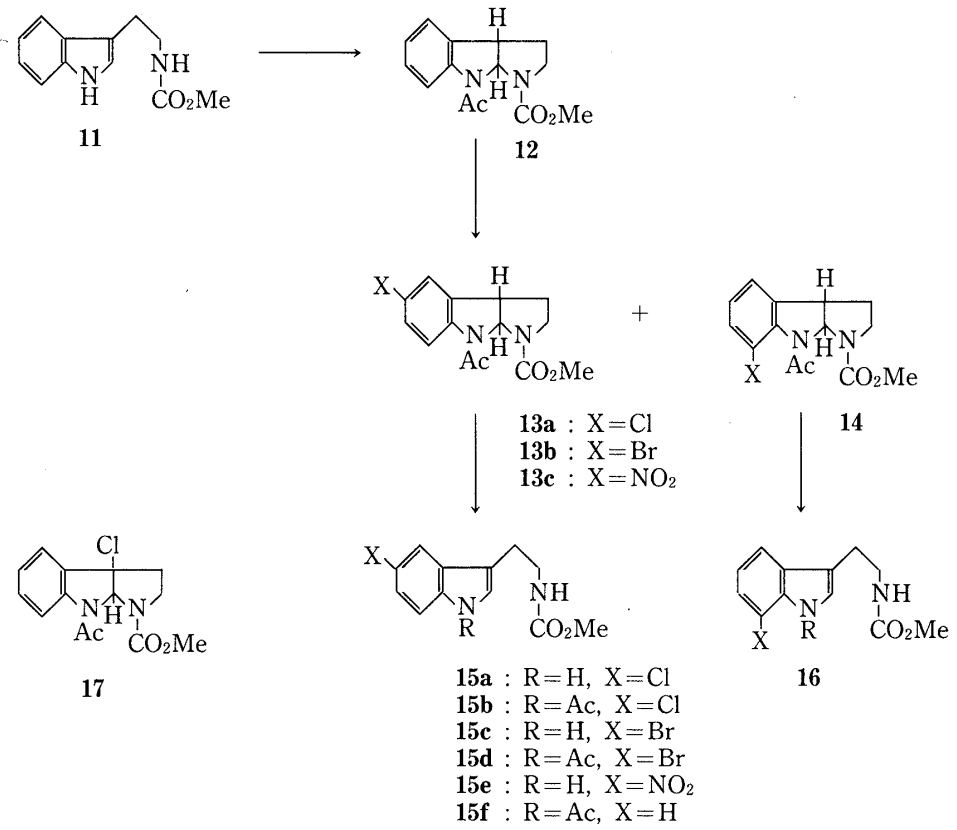
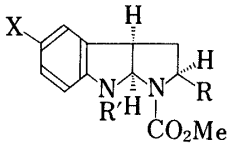


Chart 3

We next carried out the chlorination of the cyclic tautomers. As 2 reverts to the open chain tautomer in acetic acid, the chlorination of **2** with *N*-chlorosuccinimide (NCS) was carried out in methylene chloride. However, the product isolated was the corresponding oxindole derivative (**8**), which was also obtained from **1** with NCS–methylene chloride. A trace of an acid produced during the reaction favored the open chain tautomer in methylene chloride. However, the 5-chlorotryptophan derivative (**7a**) was obtained in 40% yield when **2** was chlorinated with NCS in pyridine at room temperature followed by ring opening with HCl–methanol. In order to find a more selective chlorination, we next carried out the chlorination of the N_a-acetyl cyclic tautomer (**3b**), which is stable in acetic acid. The chlorination of **3b** with NCS in acetic acid for 24 h at room temperature gave the 5-chloro derivative (**5b**), mp 157.5—159.5°C, in 89% yield along with a trace amount of the 7-chloro derivative (**6b**). Compound **5b** was converted to **7a** in 98% yield on treatment with 10% H_2SO_4–methanol at room temperature, while **7b** was obtained with H_2SO_4–acetic acid. Furthermore, hydrolysis of **5b** with 2 N NaOH at 100°C gave 5-chlorotryptophan (**9**), whose melting point and nuclear magnetic resonance (NMR) spectrum were identical with reported values.[4] Attempted chlorination of the N_a-trifluoroacetyl derivative (**3c**) which has a more electronegative substituent failed to give the 6-chloro isomer, but gave the 5-chloro derivative (**7a**) in 74% yield. On the other hand, the chlorination of a stereoisomer **10**[10] with NCS in acetic acid gave **7b** as the main product, indicating facile ring opening of the chlorinated cyclic tautomer under the reaction conditions used.

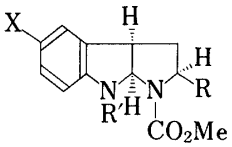
Similar chlorination of the N_a-acetyl cyclic tautomer of tryptamine (**12**),[10] prepared from N_b-methoxycarbonyltryptamine (**11**), with NCS in acetic acid gave the 5-chloro-N_a-acetyltryptamine (**15b**) in 39% yield along with **13a** (2.5%), **17** (21%), and N_a-acetyl-N_b-methoxycarbonyltryptamine (**15f**) (16%). In this case, partial ring opening of **12** did occur and chlorination at the 3-position of the indolic form followed by ring closure gave the **3a**-chloro derivative (**17**). The structure **17** was once proposed as an intermediate in the biosynthesis

TABLE I. Spectral Data for Cyclic Tautomers



Compd. No.	R	R′	X	λ_{max}(EtOH) nm ($\epsilon\times10^{-3}$)	Mass *m/z* (rel. intens.)	ν_{max}(KBr) cm^{-1}
5b	CO_2Me	Ac	Cl	252 (15.5), 286 (2.0), 294[s](1.8)	354 (M+2, 7), 352(M^+, 19) 312 (32), 310 (100), 164 (85)	1743, 1714, 1672
5c	CO_2Me	Ac	NO_2	226 (10.2), 323 (11.9)	363 (M^+, 10), 321 (88), 262 (35), 230 (31), 175 (100)	1760, 1730, 1680 (CO) 1515, 1330 (NO_2)
13a	H	Ac	Cl	252, 287, 293.5	296 (M+2, 1), 294(M^+,3)	
13b	H	Ac	Br	254, 286.5, 294[s]	338 (M^+, 24), 340 (M+2, 27), 298 (100), 296 (91)	1700, 1662 (CO)
13c	H	Ac	NO_2	226 (10.7), 324.5 (12.4)	305 (M^+, 12), 263 (100), 176 (36), 175 (15), 159 (48)	1720, 1687 (CO), 1515, 1370, 1350, 1330 1310

TABLE II. NMR Data for Cyclic Tautomers (ppm in $CDCl_3$)

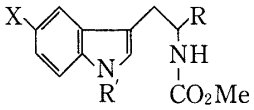


Compd. No.	R	R′	X	CO_2Me	2-H	3-H	3a-H	8a-H	4-H	6-H	7-H	N-Ac
5b	CO_2Me	Ac	Cl	3.23[s] 3.73[s]	4.62[dd] (*J*=2,6)	2.4—2.8[m]	4.04[t] (*J*=6)	6.24[d] (*J*=6)	7.10[d] (*J*=2)	7.20[dd] (*J*=8,2)	7.90[d] (*J*=8)	2.57[s]
5c	CO_2Me	Ac	NO_2	3.23[s] 3.76[s]	4.68[dd] (*J*=6,3)	2.45—2.85[m]	4.04—4.28[m]	6.36[d] (*J*=6)	8.00[bs]	8.14[bs]		2.65[s]
13b	H	Ac	Br	3.72[s]	2.72—3.06[m] 3.60—4.00[m]	2.0—2.26[m]	4.04[m]	6.20[d] (*J*=7)	7.18—7.40[m]		7.92[d] (*J*=8)	2.51[s]
13c	H	Ac	NO_2	3.72[s]	2.92[m] 3.90[m]	2.22[m]	4.13[m]	6.33[d] (*J*=6)	8.12[bs]	8.00[bs]	8.12[bs]	2.56[s]

of pyrrolnitrin from tryptophan,[12] but **17** has not been prepared previously. In contrast to the chlorination, the bromination of **12** with *N*-bromosuccinimide in acetic acid for 3.5 h at room temperature gave 5-bromo derivative (**13b**) as the main product. Treatment of the 5-brominated product (**13b**) with 10% H_2SO_4 in methanol gave the 5-bromo-1-acetyltryptamine (**15d**) which was easily converted to 5-bromo-N_b-methoxycarbonyltryptamine (**15c**) by treatment with triethylamine in methanol. Starting from **12**, the 5-bromotryptamine (**15c**) was obtained in 85% yield by bromination, ring opening ,and deacetylation without purification of the intermediates.

As the selective 5-chlorination of **3b** to **5b** was successful, we next carried out the nitration of **3b**. The nitration of **3b** with HNO_3–H_2SO_4 for 30 min at 10°C gave the 5-nitro derivative (**5c**) in 76% yield. A better result was obtained when **3b** was nitrated with fuming nitric acid at −12——5°C for 45 min; **5c** was isolated in 83% yield together with a small amount of the 7-isomer (**6c**) (2%). Compound **5c** was easily converted to the 5-nitrotryptophan derivative (**7c**) in 93% yield on treatment with 10% H_2SO_4–methanol. Similar nitration of **12** gave the 5-nitro cyclic tautomer (**13c**) in 91% yield, in contrast to the chlorination. The 5-nitrotryptamine (**15e**) was obtained in 94% yield from **13c** on treatment with H_2SO_4 in methanol. The position of the nitro group was confirmed by the coupling pattern of the proton at the 7-position in the NMR spectra of **5c** and **13c**. To confirm the preparative value of this nitration we carried

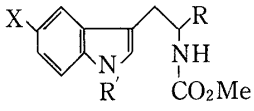
TABLE III. Spectral Data for Tryptophan Derivatives



Compd. No.	R	R′	X	λ_{max}(EtOH) nm ($\epsilon\times10^{-3}$)	Mass *m/z* (rel. intens)	ν_{max}(KBr) cm^{-1}
7a	CO_2Me	H	Cl	227.5 (36.5), 283 (5.4), 290 (5.6), 300 (4.4)	312 (M+2,3), 310 (M^+,6) 166 (40), 164 (100)	3370, 3290, 1749, 1705
7b	CO_2Me	Ac	Cl	243.5 (22.8), 267 (8.5), 296 (6.5), 305.5 (7.3)	354 (M+2, 2), 352 (M^+,5) 166 (37), 164 (100)	3350, 1748, 1720^s, 1715^s, 1703
7c	CO_2Me	H	NO_2	257^s (14.4), 271 (17.4), 326 (8.2)	321 (M^+,7), 246 (15), 175 (100)	3350, 3260, 1745, 1700, 1545, 1520, 1335
7d	CO_2Me	Ac	NO_2	229.5 (9.3), 258^s (21.8), 268 (23.8), 302 (8.8)[a]	363 (M^+, 32), 288 (35), 175 (100)	3345, 1743, 1723, 1698, 1550, 1540, 1530, 1448, 1337
15b	H	Ac	Cl	245, 268^s, 298, 307	296 (M+2, 6) 294 (M^+, 33) 219 (46), 177 (44), 164 (100)	
15c	H	H	Br	228.5, 285^s, 291.5, 301^s	298 (M+2, 31), 296 (M^+, 26), 210 (100), 208 (100)	3290, 1660, 1545
15d	H	Ac	Br	246, 276^s, 297.5, 306.5	340 (M+2, 28), 338 (M^+, 33), 210 (100), 208 (100)	3400, 1728, 1700, 1540
15e	H	H	NO_2	260^s (14.6), 274 (18.0), 329 (8.4)	263 (M^+,41), 245 (39), 188 (100), 175 (75)	3375, 3240,1703,1580, 1540, 1328

a) In acetonitrile.

TABLE IV. NMR Data for Tryptophan Derivatives (ppm in $CDCl_3$)



Compd. No.	R	R′	X	β-CH_2	α-CH	CO_2Me	NH	2-H	4-H	6-H	7-H	NH or Ac
7a	CO_2Me	H	Cl	3.24^d (J=6)	4.64^m	3.66^s 3.68^s	5.2^m	6.96^d (J=2)	7.46^d (J=2)	7.1^{dd} (J=8, 2)	7.2^d (J=8)	8.32^{bs}
7b	CO_2Me	Ac	Cl	3.20^m	4.70^m	3.69^s 3.72^s	5.4^m	7.0—7.5^m			8.32^d (J=9)	2.57^s
7c DMSO-d_6	CO_2Me	H	NO_2	3.24^m	4.33^m	3.51^s 3.64^s	7.60^{bs}	7.46$^{d,a)}$ (J=2)	8.52^d (J=2)	7.98^{dd} (J=8, 2)	7.52^d (J=8)	11.64$^{bs,b)}$
7d DMSO-d_6	CO_2Me	Ac	NO_2	3.10^m	4.42^m	3.51^s 3.65^s	7.72$^{d,b)}$ (J=8)	7.96^s	8.50^d (J=2)	8.17^{dd} (J=8, 2)	8.44^d (J=8)	2.68^s
15b	H	Ac	Cl	2.87^t (J=7)	3.52^q (J=7)	3.68^s	4.99^{bs}	7.1— 7.4^m	7.45^d (J=2)	7.1— 7.4^m	8.30^d (J=8)	2.55^s
15c	H	H	Br	2.86^m	3.43^m	3.64^s	4.73$^{bs,b)}$	6.88$^{d,a)}$ (J=2)	7.60^s	7.15^s		8.30$^{bs,b)}$
15e DMSO-d_6	H	H	NO_2	2.91^t (J=7)	3.20— 3.40^m	3.54^s	7.20$^{bs,b)}$	7.41$^{d,a)}$ (J=2)	8.51^d (J=2)	7.98^{dd} (J=10, 2)	7.50^d (J=10)	11.56$^{bs,b)}$

a) The signal became a singlet after the addition of D_2O.
b) The signal disappeared on addition of D_2O.

out a series of reactions from **1** and **11** without purification of the intermediates. The 5-ntiro derivative (**7c**) was obtained in 66% yield in the tryptophan series, while the compound **15e** was obtained in 55% yield from **11**.

The nitro group in **7c** and **5c** can be readily reduced to the corresponding amino group by catalytic hydrogenation to form **18a** and **19**. As the 5-amino derivative (**18a**) was rather unstable compared to **19**, which was easily purified, **18a** was converted to the *N*-acetyl derivative (**18b**) by treatment with acetic anhydride in pyridine.

In conclusion we have succeeded in developing the first practical procedures for the

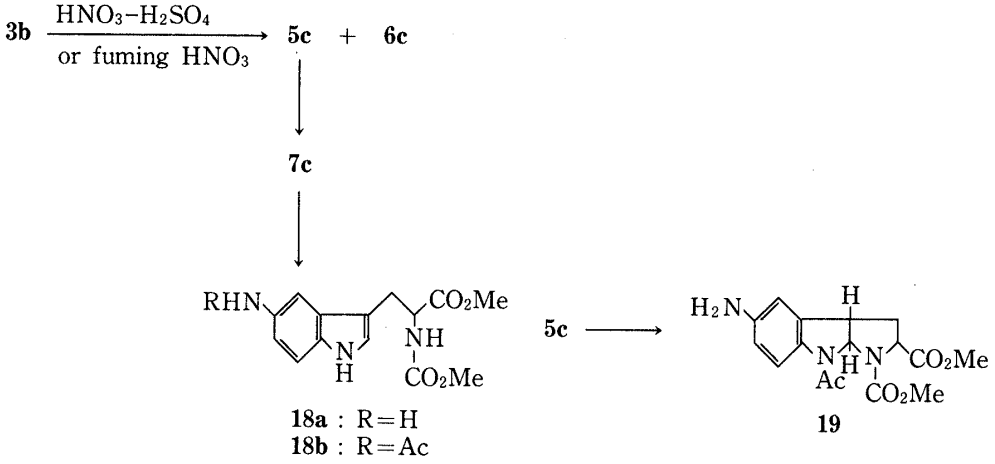


Chart 4

5-chlorination, bromination, and nitration of tryptophan derivatives. The cyclic tautomers (**2**, **3**, and **12**) should thus serve as convenient intermediates to prepare other 5-substituted tryptophan derivatives.

Experimental

All melting points are uncorrected. The ultraviolet (UV) spectra were taken with Hitachi 323 and 340 spectrophotometers, and infrared (IR) spectra with Hitachi IR-295 and 215 spectrometers. The NMR spectra were recorded on a JEOL MH-100 spectrometer and mass spectra (MS) on Hitachi RMU-6 and M-60 instruments.

(2*S, 3a*R**, 8a*R**)-1,2-Bis(methoxycarbonyl)-8-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (3a)**——A mixture of **2**[10] (276 mg, 1 mmol), methyl iodide (0.71 g, 5 mmol) and K_2CO_3 (1.38 g, 10 mmol) in acetone (5 ml) was stirred for 60 h at room temperature. The mixture was concentrated *in vacuo* and the residue was extracted with CH_2Cl_2. The extract was filtered, then the filtrate was washed with sat. aq. $NaHCO_3$ and brine, and dried over anhyd. Na_2SO_4. The solvent was evaporated off to leave a pale yellow oil (236 mg) which was purified by silica gel column chromatography (10 g, CH_2Cl_2) to give **3a** (201 mg, 69%) as a colorless oil. The NMR spectrum was identical with that of the sample obtained below.

A solution of N_a-methyl-N_b-methoxycarbonyl-DL-tryptophan methyl ester (**4a**) (200 mg, 0.69 mmol) in 85% H_3PO_4 (2 ml) was stirred for 3 h at room temperature. The mixture was poured into 10% Na_2CO_3 (40 ml) and extracted with benzene. The benzene layer was washed with brine and dried. The solvent was evaporated off *in vacuo* to leave a residue, which was separated by preparative thin layer chromatography (TLC) (silica gel, benzene–acetone 30 : 1—10 : 1) to give **3a** (84 mg, 42%) as a colorless oil and **4a** (72 mg, 36%). **3a**: λ_{max} (EtOH) 254.5, 300 nm; MS *m/z*: 290 ((M+, 35), 144 (100); NMR ($CDCl_3$) δ: 2.48 (2H, m, 3-CH_2), 2.99 (3H, s, NMe), 3.24 (3H, s, OMe), 3.72 (3H, s, OMe), 3.8 (1H, m, 3a-H), 4.67 (1H, m, 2-H), 5.71 (1H, m, 8a-H), 6.29 (1H, d, J=7 Hz, arom. H), 6.56 (1H, t, J=7 Hz, arom. H), 7.0 (2H, m, arom. H).

***N*b-Methoxycarbonyl-1-methyl-DL-tryptophan Methyl Ester (4a)**——A mixture of **2** (276 mg, 1 mmol), methyl iodide (1.42 g, 10 mmol), and K_2CO_3 (2.76 g, 20 mmol) in acetone (5 ml) was stirred for 15 h at 30°C and the mixture was worked up as above. The crude oil of **3a** (164 mg) was dissolved in AcOH (1 ml) and the solution was kept for 1 h at room temperature, then the solvent was evaporated off. The residue showed a single spot of **4a** on TLC. Recrystallization of the residue from benzene–hexane gave colorless prisms, mp 74—76°C, (54 mg) which were identical with an authentic sample prepared from 1-methyl-DL-tryptophan (mp and IR spectra).

***N*b-Methoxycarbonyl-1-(3-methyl-2-buten-1-yl)-DL-tryptophan Methyl Ester (4b)**——A mixture of **2** (1.38 g, 5 mmol), dimethylallyl bromide (1.49 g, 10 mmol) and K_2CO_3 (6.91 g, 50 mmol) in acetone (30 ml) was stirred for 5.5 h at room temperature. The mixture was concentrated *in vacuo* and the residue was extracted with CH_2Cl_2. The extract was filtered, and removal of the solvent by evaporation gave a residue, which was purified by silica gel column chromatography (30 g, benzene–acetone (25 : 1)) to give **4b** as an oil (1.59 g, 92%). **4b**: λ_{max} (EtOH) 226, 281s, 289.5s, 297s nm. MS *m/z*: 344 (M+, 12), 198 (50), 130 (100). NMR ($CDCl_3$) δ: 1.75, 1.79 (6H, two s, Me), 3.26 (2H, d, β-CH_2), 3.67 (6H, s, 2×MeO), 4.61 (3H, m, allylic CH_2+α-CH), 5.3 (2H, m, NH+olefinic H), 6.87 (1H, s, 2-H), 7.0—7.6 (4H, m, arom. H).

Chlorination of 2 with NCS in CH_2Cl_2——A solution of **2** (55 mg, 0.2 mmol) and NCS (27 mg, 0.2 mmol) in CH_2Cl_2 (5 ml) was stirred for 14 h at room temperature. Although the KI–starch test was still positive, the mixture was washed with water, dried and concentrated to leave a residue which was separated by preparative

TLC (silica gel, CH_2Cl_2–acetone (10 : 1)) to give **8** (35 mg, oil, 60%) as a mixture of diastereoisomers and **1** (17 mg, 31%). **8**: λ_{max} (EtOH): 251.5, 280^s, nm. MS *m/z*: 292 (M^+, 12), 146 (100). NMR ($CDCl_3$) δ: 2.2—2.6 (2H, m, β-CH_2), 3.6 (1H, m, 3-H), 3.7 (6H, s, 2×OMe), 4.4—4.9 (1H, m, α-CH), 5.9—6.4 (1H, m, NH), 6.8—7.6 (1H, m, arom. H), 9.05 (1H, bs, oxindolic NH).

5-Chloro-N_b-methoxycarbonyl-DL-tryptophan Methyl Ester (**7a**)——i) From **2** with NCS–Pyridine: Compound **1** (1.38 g, 5 mmol) was dissolved in 85% H_3PO_4 (10 ml) at room temperature. The mixture was kept for 2 h, then poured into 10% Na_2CO_3 (200 ml) and extracted with benzene. The organic layer was washed with brine and dried. The solvent was evaporated off to leave crude **2** as an oil. The residue was dissolved in pyridine (30 ml) and NCS (1.00 g, 7.5 mmol) was added to the stirred solution in small portions. After being stirred for 1.5 h at room temperature, the mixture was concentrated *in vacuo* to leave a residue which was extracted with benzene. The benzene extracts were washed with 5% HCl, sat. $NaHCO_3$ solution and brine, and dried. Removal of the solvent by evaporation left a solid, which was dissolved in MeOH, and several drops of 10% HCl were added to the solution. The mixture was left standing for several min then concentrated *in vacuo* to give a residue, which was dissolved in benzene. The benzene solution was washed with sat. $NaHCO_3$ solution and brine, and dried. Removal of the solvent by evaporation gave a residue, which was separated by silica gel column chromatography to give **7a** (620 mg, 40%). Recrystallization of **7a** from acetone–hexane gave colorless prisms, mp 144.5—146.5°C. *Anal.* Calcd for $C_{14}H_{15}ClN_2O_4$: C, 54.11; H, 4.87; Cl, 11.41; N, 9.02. Found: C, 54.25; H, 4.76; Cl, 11.53; N, 9.16. Spectral data: see Tables III and IV.

ii) From **5b**: Compound **5b** (353 mg, 1 mmol) was added to 10% H_2SO_4 in MeOH (20 ml) and the solution was stirred for 3 h at room temperature. The solution was poured into water (150 ml) and extracted with CH_2Cl_2. The extracts were washed with sat. $NaHCO_3$ and brine, and dried. Removal of the solvent by evaporation left a white solid which was recrystallized from acetone–hexane to give **7a** (282 mg). After evaporation of the mother liquor, the residue was separated by preparative TLC (silica gel, AcOEt–hexane (2 : 1)) to afford further **7a** (22 mg, total 304 mg, 98%). Further recrystallization of **7a** from the same solvent gave colorless prisms, mp 144.5—146.5°C.

(2*S, 3a*R**, 8a*R**)-8-Acetyl-5-chloro-1,2-bis(methoxycarbonyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]-indole** (**5b**)——*N*-Chlorosuccinimide (264 mg, 2 mmol) was added to a solution of **3b** (478 mg, 1.5 mmol) in AcOH (15 ml) and the mixture was stirred for 24 h at room temperature. After evaporation of AcOH *in vacuo*, the residue was dissolved in benzene, washed with sat. $NaHCO_3$ and water, and dried. The solvent was evaporated of to leave a residue, which was recrystallized from acetone–hexane to yield **5b** (404 mg) as colorless needles. Further **5b** (67 mg, total 471 mg, 89%) was obtained from the mother liquor by preparative TLC. The 7-chloro isomer (**6b**) (16 mg, 3%) was also obtained as a minor product. Recrystallizations of **5b** from acetone–hexane gave colorless crystals, mp 157.5—159.5°C. *Anal.* Calcd for $C_{16}H_{17}O_5N_2Cl$: C, 54.48; H, 4.86; Cl, 10.05; N, 7.94. Found: C, 54.22; H, 4.80; Cl, 10.33; N, 7.82. Spectral data: see Table II. **6b** (caramel): λ_{max} (EtOH): 215, 245.5, 278.5, 286 nm. MS *m/z*: 354 ($M+2$, 2), 352 (M^+, 4), 312 (35), 310 (100). NMR ($CDCl_3$) δ: 2.1—2.8 (2H, m, 3-CH_2), 3.13 (3H, s, OMe), 3.72 (3H, bs, OMe), 4.1 (1H, m, 3a-H), 4.5 (1H, m, 2-CH), 6.20 (1H, d, J=6 Hz, 8a-H), 6.9—7.4 (3H, m, arom. H).

1-Acetyl-5-chloro-N_b-methoxycarbonyl-DL-tryptophan Methyl Ester (**7b**)——A solution of **5b** (353 mg, 1 mmol) in 10% H_2SO_4 in AcOH (10 ml) was stirred for 3 h at room temperature. The mixture was poured into water (150 ml) and extracted with CH_2Cl_2. The extracts were washed with sat. $NaHCO_3$ and brine, and dried. Removal of the solvent by evaporation gave a residue which was recrystallized from acetone–iso-Pr_2O to give **7b** (311 mg) as colorless needles. From the mother liquor, further **7b** (13 mg, total 324 mg, 92%) was isolated by preparative TLC (silica gel, AcOEt–hexane (2 : 1)). Recrystallization of **7b** from acetone gave colorless needles, mp 173—174.5°C. *Anal.* Calcd for $C_{16}H_{17}ClN_2O_5$: C, 54.48; H, 4.86; N, 7.94. Found: C, 54.41; H, 4.89; N, 7.95. Spectral data: see Tables III and IV.

5-Chloro-DL-tryptophan (**9**)——Crude **5b** obtained from **3b** (476 mg, 1.5 mmol) was heated with 2 N NaOH (10 ml) for 4 h at 100°C. The solution was acidified to pH 5 with 10% HCl, filtered and concentrated *in vacuo* to precipitate a pale brown solid which was filtered, washed with water, and dried to give crude **9** (288 mg, 80%). Recrystallizations of **9** from water gave a white solid, mp 253—257°C (reported mp[4] 254—256°C). Its NMR spectrum was identical with that reported.

Chlorination of the N_a-trifluoroacetyl Derivative (**3c**)——*N*-Chlorosuccinimide (233 mg, 1.74 mmol) was added to a solution of **3c** (500 mg, 1.34 mmol) in AcOH (10 ml) at room temperature. The mixture was stirred for 24 h at 45°C. After evaporation of the AcOH, the residue was dissolved in benzene and the solution was washed with water and dried. Removal of the solvent by evaporation gave a residue, which was dissolved in 10% H_2SO_4–MeOH (20 ml) and the solution was stirred for 7 h at room temperature. The mixture was poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with sat. $NaHCO_3$, brine, and dried. Removal of the solvent by evaporation gave a residue, which was crystallized from acetone–hexane to give **7a** (264 mg) as colorless prisms, mp 138—142.5°C, whose IR spectrum was identical with that of **7a** obtained above. Separation of the mother liquor by preparative TLC (silica gel, AcOEt–hexane (2 : 1)) gave further **7a** (146 mg, total 310 mg, 74%).

Chlorination of Less Stable N_a-acetyl Cyclic Tautomer (**10**)——*N*-Chlorosuccinimide (54 mg, 0.40 mmol) was added to a solution of **10** (100 mg, 0.31 mmol) in AcOH (1 ml) and the mixture was stirred for 7 h at

room temperature. The solution was diluted with benzene, washed with water, and dried. Removal of the solvent by evaporation gave a residue which was separated by preparative TLC (silica gel, AcOEt–hexane (2 : 1)) to yield crude **7b** (87 mg) containing a small amount of 1-acetyl **1**. Recrystallizations from acetone–hexane gave pure **7b** (31 mg) which was identical with the sample obtained above.

Chlorination of 12——*N*-Chlorosuccinimide (200 mg, 1.5 mmol) was added to a solution of **12** (300 mg, 1.15 mmol) in AcOH (10 ml) and the mixture was stirred for 4.5 h at room temperature. Evaporation of AcOH *in vacuo* gave a residue, which was dissolved in benzene (50 ml). The benzene solution was washed with water and dried. Removal of the solvent by evaporation gave a residue which was separated by silica gel column chromatography and preparative TLC. The following compounds were obtained; **13a** (8.5 mg, 2.5%), **15b** (133 mg, 39%), **17** (70 mg, 20.5%) and **15f** (48 mg, 16%). **13a** (caramel): λ_{max} (EtOH) 252, 287, 293.5 nm. MS *m/z*: 296 (M^++2,1), 294 (M^+, 3). **15b**: mp 128.5—130°C (from acetone–hexane). Spectral data: see Tables II and III. **17**: (caramel): λ_{max} (EtOH): 213, 246, 288 nm. MS *m/z*: 296 (M+2, 5), 294 (M^+, 15), 254 (29), 252 (88), 217 (62), 215 (100). NMR ($CDCl_3$) δ: 2.58 ((3H, s, Ac), 2.6—3.1 (3H, m, 3-CH_2+2-CH), 3.72 (3H, s, OMe), 3.76 (1H, m, 2-CH), 6.08 (1H, s, 8a-H), 7.0—7.5 (3H, m, arom. H), 8.03 (1H, d, J=8 Hz, 7-H). **15f**: mp 95—96°C (from acetone–hexane) λ_{max} (EtOH): 241, 262.5, 271^s, 292.5, 301 nm. MS *m/z*: 260 (M^+, 30), 189 (29), 130 (100). NMR ($CDCl_3$) δ: 2.54 (3H, s, Ac), 2.90 (2H, t, J=7 Hz, β-CH_2), 3.52 (2H, q, J=7 Hz, α-CH_2), 3.66 (3H, s, OMe), 4.93 (1H, bs, NH), 7.0—7.7 (3H, m, arom. H), 8.38 (1H, m, 7-H).

5-Bromo-N_b-methoxycarbonyltryptamine (15c). Bromination of 12——The cyclic tautomer **12** (500 mg, 1.92 mmol) was added to a solution of NBS (445 mg, 2.50 mmol) in AcOH (15 ml) and the mixture was stirred for 3 h at room temperature, then poured into water (100 ml) and extracted with benzene. The extracts were washed with 5% NaOH, brine, and water, and dried. Removal of the solvent by evaporation gave crude **13b** (765 mg). Recrystallization of **13b** from MeOH gave colorless needles, mp 175—178°C. Spectral data: see Table III. The crude **13b** (765 mg) was dissolved in 10% H_2SO_4–MeOH (15 ml) and the mixture was stirred for 30 min at room temperature, then poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine and dried. Evaporation of the solvent gave crude **15d** (664 mg). Recrystallization of **15d** from MeOH gave colorless needles, mp 130—132°C. Spectral data: see Table III. The crude **15d** (664 mg) was dissolved in MeOH (20 ml) containing a few drops of triethylamine. The mixture was stirred for 10 min and concentrated *in vacuo* to leave a residue which was purified through a silica gel column to give **15c** (555 mg, 85% from **12**). Recrystallization of **15c** from CH_2Cl_2 gave colorless needles, mp 80—83°C. Spectral data: see Tables III and IV.

(2*S, 3a*R**, 8a*R**)-8-Acetyl-1,2-bis(methoxycarbonyl)-5-nitro-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (5c)**——i) With HNO_3–H_2SO_4: The cyclic tautomer **3b** (954 mg, 3 mmol) was added to a solution of HNO_3 (d=1.38, 485 mg) and conc H_2SO_4 (5 ml) in small portions and the mixture was stirred for 30 min at 10—14°C, then poured into water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried. Evaporation of the solvent gave a residue, which was recrystallized from MeOH to give **5c** (831 mg, 76%), mp 152.5—153.5°C, as pale yellow needles. *Anal.* for $C_{16}H_{17}N_3O_7$: C, 52.89; H, 4.72; N, 11.57. Found: C, 52.75; H, 4.66; N, 11.66. Spectral data: see Tables I and II.

ii) With Fuming HNO_3: The cyclic tautomer **3b** (1.00 g, 3.14 mmol) was added to chilled fuming HNO_3 (d=1.50, 10 ml) in small portions at −12°C. The mixture was stirred for 45 min at −12——5°C, then poured into ice-water and extracted with CH_2Cl_2. The organic layer was washed with 10% Na_2CO_3 and brine, and dried. Removal of the solvent by evaporation gave a residue, which was recrystallized from MeOH to yield **5c** (940 mg, 83%), mp 153—157°C. From the mother liquor, the 7-nitro isomer (**6c**) (26 mg, 2%), mp 216.5—217°C (from MeOH), was obtained. *Anal.* Calcd for $C_{16}H_{17}N_3O_7$: C, 52.89; H, 4.72; N, 11.57. Found: C, 52.82; H, 4.76; N, 11.42. UV λ_{max} (EtOH) 234.5 (ε=16100), 324 (ε=2300) nm. IR ν_{max} (KBr) 1753, 1695 (CO), 1537, 1370 (NO_2) cm^{-1}. NMR (pyridine-d_5) δ: 2.65 (2H, m, 3-CH_2), 2.85 (3H, s, Ac), 3.12 (3H, s, OMe), 3.57 (3H, bs, OMe), 4.16 (1H, m, 3a-H), 4.78 (2-H, overlapped with the signal of H_2O), 6.48 (1H, d, J=6 Hz, 8a-H), 7.13 (1H, t, J=8 Hz, 5-H, overlapped with β-proton of pyridine), 7.46 (1H, d, J=8 Hz, 4-H, overlapped with γ-proton of pyridine), 7.84 (1H, d, J=8 Hz, 6-H); in DMSO-d_6 δ: 2.30—2.80 (3-CH_2+Ac, overlapped with DMSO protons), 3.04 (3H, s, OMe), 3.63, 3.68 (3H, s, N-CO_2Me), 4.24 (1H, m, 3a-H), 4.58 (1H, m, 2-H), 6.33 (1H, d, J=6 Hz, 8a-H), 7.28 (1H, t, J=8 Hz, 5-H), 7.64 (1H, d, J=8 Hz, 4-H), 7.72 (1H, d, J=8 Hz, 6-H). Ms *m/z*: 363 (M^+, 2), 321 (100), 262 (80), 175 (20).

N_a-Acetyl-N_b-methoxycarbonyl-5-nitro-DL-tryptophan Methyl Ester (7d)——i) From **3b** with HNO_3–H_2SO_4: The cyclic tautomer **3b** (954 mg, 3 mmol) was added to a solution of HNO_3 (d=1.38, 441 mg)–H_2SO_4 (5 ml) in small portions and the mixture was stirred for 5 h at 20°C. Work-up as above left a residue which was crystallized from acetone to give **7d** (415 mg, 38%), mp 204—205°C, as colorless needles. *Anal.* Calcd for $C_{16}H_{17}N_3O_7$: C, 52.89; H, 4.72; N, 11.57. Found: C, 53.00; H, 4.70; N, 11.35. Spectral data: see Table III.

ii) From **5c**: A solution of **5c** (104 mg, 0.29 mmol) in H_2SO_4 (1 ml) and AcOH (10 ml) was stirred for 3 h at room temperature, then the mixture was poured into ice water, and extracted with CH_2Cl_2. The organic layer was washed with 5% Na_2CO_3 and brine, and dried. Removal of the solvent by evaporation gave a residue, which was crystallized from acetone to give **7d** (77 mg, 74%), mp 213—214.5°C.

N_b-Methoxycarbonyl-5-nitro-DL-tryptophan Methyl Ester (7c)——i) From **7d**: A solution of **7d** (111 mg, 0.31 mmol) in MeOH (50 ml) was refluxed for 30 min. The mixture was concentrated to leave a residue,

which recrystallized from MeOH to give **7c** (95 mg, 95%), mp 174—175.5°C, as yellow prisms. *Anal.* Calcd for $C_{14}H_{15}N_3O_6$: C, 52.33; H, 4.71; N, 13.08. Found: C, 52.30; H, 4.73; N, 12.92. Spectral data: see Tables III and IV.

ii) From **5c**: A solution of **5c** (100 mg, 0.28 mmol) in 10% H_2SO_4–MeOH (5 ml) was stirred for 1 h at room temperature, then poured into ice water (20 ml) and extracted with CH_2Cl_2. The extracts were washed with 10% Na_2CO_3 and water, and dried. Removal of the solvent by evaporation left a residue, which was recrystallized from MeOH to give **7c** (79 mg). Further **7c** (3 mg, total 82 mg, 93%) was isolated by preparative TLC of the mother liquor.

8-Acetyl-1-methoxycarbonyl-5-nitro-1,2,3,3a,8a-hexahydropyrrolo[2,3-*b*]indole (13c)——The cyclic tautomer **14** (1.00 g, 3.8 mmol) was added to chilled fuming HNO_3 (d=1.5, 15 ml) and the mixture was stirred for 25 min at −13——5°C, then poured into ice water and extracted with CH_2Cl_2. The extracts were washed with 10% Na_2CO_3 and brine, and dried. Removal of the solvent by evaporation gave a residue, which was recrystallized from MeOH to yield **13c** (940 mg, 80%). Preparative TLC of the mother liquor gave further **13c** (79 mg, total 1.02 g, 87%) and **15e** (55 mg, 5%). Further recrystalization of **13c** from MeOH gave pale yellow needles, mp 165—166.5°C. *Anal.* Calcd for $C_{13}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.77. Found: C : 55.03; H, 4.90; N, 13.81. Spectral data: see Tables I and II.

***N*$_b$-Methoxycarbonyl-5-nitrotryptamine (15e)**——A solution of **13c** (1.00 g, 3.3 mmol) in 10% H_2SO_4–MeOH (40 ml) was stirred for 2.3 h at room temperature, then poured into ice water and extracted with CH_2Cl_2. The extracts were washed with 10% Na_2CO_3 and water, and dried. Removal of the solvent by evaporation left a residue which was crystallized from MeOH to give **15e** (788 mg). Separation of the mother liquor by preparative TCL (silica gel, CH_2Cl_2–acetone (10: 1)) gave further **15e** (26 mg, total 814 mg, 91%). Repeated recrystallizations of **15e** from MeOH gave yellow needles, mp 184—185°C. *Anal.* Calcd for $C_{12}H_{13}N_3O_4$: 1/3 MeOH: C, 54.08; H, 5.27; N, 15.34. Found: C, 54.02; H, 5.06; N, 15.40. Spectral data: see Tables III and IV.

7c from 1 without Purification of Intermediates——Compound **1** (4.00 g, 14.5 mmol) was dissolved in 85% H_3PO_4 (30 ml) at room temperature. The mixture was stirred for 7.5 h at room temperature, then poured into 10% Na_2CO_3 (400 ml), and extracted with benzene. The benzene solution was washed with water, and dried. Removal of the solvent by evaporation left a residue, which was dissolved in Ac_2O (20 ml)–pyridine (40 ml). The mixture was stirred for 13.5 h at room temperature and concentrated *in vacuo*. Benzene was added to the mixture, which was then washed with 5% HCl, 10% Na_2CO_3, and water, and dried. Evaporation of the solvent left a residue (crude **3b**), which was added to chilled fuming HNO_3 (d=1.5, 15 ml). The mixture was stirred for 35 min at −12——5°C, poured into ice water (100 ml) and extracted with CH_2Cl_2. The extracts were washed with 10% Na_2CO_3 and water, and dried. Evaporation of the solvent gave a residue which was dissolved in 10% H_2SO_4–MeOH (40 ml). The mixture was stirred for 2.5 h at room temperature, poured into ice water (100 ml), and extracted with CH_2Cl_2. The organic layer was washed with 10% Na_2CO_3 and water, and dried. Removal of the solvent by evaporation gave a residue, which was recrystallized from MeOH to give **7c** (2.65 g). Separation of the mother liquor by silica gel column chromatography (AcOEt–hexane (2 : 1)) gave further **7c** (400 mg, total 3.05 g, 66%)

15e from 11 without Purification of Intermediates——Compound **11** (2.00 g, 9.16 mmol) was dissolved in 85% H_3PO_4 (20 ml) at room temperature, and the mixture was stirred for 7 min, then poured into 10% Na_2CO_3 (500 ml) and extracted with benzene. The extracts were washed with water and dried. Removal of the solvent by evaporation gave a residue, which was dissolved in Ac_2O (3 ml)–pyridine (14 ml). The mixture was stirred for 18 h at room temperature, then poured into water (50 ml), acidified to pH 4 with 5% HCl, and extracted with benzene. The benzene layer was washed with 5% NaOH and brine, and dried. Removal of the solvent by evaporation left a residue (crude **14**) which was added to chilled fuming HNO_3 (10 ml). The mixture was stirred for 30 min under ice cooling, poured into ice water and extracted with CH_2Cl_2. The extracts were washed with 10% Na_2CO_3 and brine, and dried. Removal of the solvent by evaporation left a residue, which was purified by filtration through a short silica gel and alumina column. The crude **13c** obtained was dissolved in 10% H_2SO_4–MeOH (100 ml) and the mixture was stirred for 3 h at room temperature, then poured into ice water (100 ml) to precipitate a yellow solid, which was collected and recrystallized from MeOH to give **15e** (1.43 g, 56% from 11), mp 185—191°C.

5-Acetamido-*N*$_b$-methoxycarbonyl-DL-tryptophan Methyl Ester (18b)——A solution of **7c** (500 mg, 1.56 mmol) in MeOH (100 ml) was hydrogenated with 5% Pd–C (100 mg), and hydrogen for 12 h. After removal of the catalyst, the filtrate was concentrated to leave a residue, which was dissolved in Ac_2O (1.5 ml)–pyridine (5 ml). The mixture was stirred for 1.5 h at room temperature, poured into water (50 ml) and extracted with CH_2Cl_2. The organic layer was washed with 5% Na_2CO_3 and water, and dried. Evaporation of the solvent left a residue, which was recrystallized from MeOH–iso-Pr_2O to give **18b** (432 mg, 83%), mp 87—91°C. UV λ_{max} (EtOH) 241, 300^s, 312^s nm. NMR ($CDCl_3$) δ: 2.09 (3H, s, Ac), 3.14 (2H, d, J=5 Hz, β-CH_2), 3.61, 3.64 (each s, 6H, 2×OMe), 4.58 (1H, m, α-CH), 5.43 (1H, m, N_b-H, exchangeable), 6.85 (1H, s, 2-H), 7.09 (2H, bs, arom. H), 7.65 (1H, bs, arom. H), 7.95 (1H, bs, NH, exchangeable), 8.82 (1H, bs, N_a-H, exchangeble). MS m/z: 333 (M^+, 44), 257 (12), 188 (53), 187 (100).

(2*S, 3a*R**, 8a*R**)-8-Acetyl-5-amino-1,2-bis(methoxycarbonyl)-1,2,3,3a,8,8a,-hexahydropyrrolo[2,3-*b*]-indole (19)**——A solution of **5c** (500 mg, 1.38 mmol) in MeOH (100 ml) was hydrogenated with Pd-C (5%, 100

mg) under hydrogen for 2.5 h. After removal of the catalyst, the filtrate was concentrated to leave a residue, which was recrystallized from MeOH to give **19** (376 mg, 82%), mp 209—212°C. Separation of the mother liquor by preparative TLC (silica gel AcOEt) afforded further **19** (10 mg, total 386 mg, 84%). Further recrystallization of **19** from MeOH gave pale yellow granucles, mp 210—211°C. UV λ_{max} (EtOH) 267, 315[s] nm. IR ν_{max} (KBr): 3440, 3345, 3220, 1715, 1700 cm^{-1}. NMR (DMSO-d_6) δ: 2.41 (3H, s, Ac), 3.14 (3H, s, OMe), 3.59 (3H, s, OMe), 3.91 (1H, m, 3a-H), 4.50 (1H, m, 2-H), 4.81 (1H, bs, NH_2), 6.11 (1H, d, J=6 Hz, 8a-H), 6.16—6.55 (2H, m, 4,6-H), 7.38 (1H, d, J=9 Hz, 7-H). The signal of 3-CH_2 was not observed, probably due to overlapping with the signal of DMSO. MS m/z: 333 (M^+, 61), 291 (79), 232 (26), 145 (100).

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