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Cyclic Tautomers of Tryptophans and Tryptamines. VIII.[1] Cyclic Tautomers of *cyclo*-L-Prolyl-L-tryptophyl and Related Compounds[2]

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Two diastereomers (**6** and **7**) of the cyclic tautomer of *cyclo*-L-propyl-L-tryptophyl (**5**) have been prepared by dissolving **5** in 85% phosphoric acid or trifluoroacetic acid. The stable isomer (**6**) was obtained in 89% yield on the acid treatment of **5** at room temperature. Cyclic tautomers (**15** and **17**) of the related 2,5-piperazinediones (**14** and **16**) have also been prepared. Hydroxylation of the *N*-acetyl cyclic tautomers (**8** and **9**) with lead tetraacetate in trifluoroacetic acid followed by methylation gave the 8- and 9-methoxy derivatives (**18**, **19**, **21**, and **22**) in moderate yields. The 9-methoxy derivative (**22**) was the major product of the oxidation of **9**. On the other hand, oxidation of **5** in trifluoroacetic acid with lead tetraacetate followed by reduction with zinc gave the 8-hydroxy derivative (**28**) selectively in good yield *via* the cyclic tautomer (**26**) and the quinoneimine (**27**).

Keywords——cyclic tautomer; 2,5-piperazinedione; tryptophan; hydroxylation; oxidation; lead tetraacetate; *cyclo*-L-prolyl-methoxy-L-tryptophyl; *cyclo*-L-prolyl-8-hydroxy-L-tryptophyl

We have reported facile formation of the cyclic tautomer (**2**) of the N_b-acyltryptophans (**1**) which have a pyrrolo[2,3-*b*]indole ring system and indoline character, and we also developed a new method to introduce a substituent onto the benzene ring by utilizing this cyclic tautomer (formation of **3** and **4**).[2]

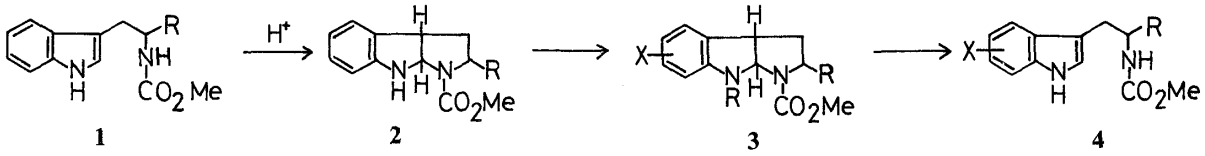

Chart 1

As an extension of this work we examined the formation of the cyclic tautomer (**6**, **7**) of *cyclo*-L-prolyl-L-tryptophyl (**5**), whose derivatives are found in fungal metabolites such as brevianamides[3] and fumitremorgins.[4] The 2,5-piperazinediones derived from tryptophan are the derivatives of N_b-acyltryptophan and could be candidates to form cyclic tautomers with acid. When *cyclo*-L-prolyl-L-tryptophyl (**5**) was dissolved in 85% phosphoric acid at room temperature, a cyclic tautomer (**6**) was obtained in 89% yield. The melting point (188—200 °C) of this compound was rather broad, but its nuclear magnetic resonance (NMR) spectrum showed the presence of a single isomer. *N*-Acetylation of the crude cyclic tautomer also gave a single isomer (**8**), and the other diastereoisomer (**9**) of **8** was not isolated. However, the diastereoisomer (**7**) of **6** was isolated as the major product when **5** was dissolved in trifluoroacetic acid at −10 °C for 1—2 min. The composition of the cyclic tautomers formed at low temperature was found to be **6**:**7**=1:1.75 from the NMR spectrum of the crude

mixture. The diastereoisomer (**7**) reverted to **5** on a silica gel or alumina column, and was isolated by fractional recrystallization (40—50%). In the case of N_b-acyltryptophan derivatives (**1**), only one isomer was isolated as the N_a-H cyclic tautomer (**2**) because of the instability of the other isomer, and two diastereoisomers were obtained after N_a-acetylation.[5] Compound **7** was found to be the thermodynamically less stable cyclic tautomer, as **7** was immediately converted to **6** on dissolving it in trifluoroacetic acid at room temperature. The less stable isomer (**7**) was readily converted to the open-chain tautomer (**5**) in a few min by dissolution in methanol containing a small amount of dilute hydrochloric acid, while the stable isomer (**6**) was converted to **5** in 2.5 h under similar conditions. Another difference in reactivity between the two isomers (**6** and **7**) was observed in the acetylation: acetylation of **6** with acetic anhydride-pyridine to give **8** was completed within 3 h, while the similar acetylation of **7** gave **9** in only 59% yield even after 18 h. These results suggested that the less stable isomer (**7**) is sterically crowded around the N_a-atom, and ring-opened readily. Spectral data for **6**—**9** are summarized in Table I. From these spectral data it is difficult to assign the stereochemistry of these compounds. Circular dichroism (CD) spectra of **8** and **9** were compared with those of **10** (the less stable isomer) and **11** (stable isomer) in the tryptophan series for which the stereochemistry is established.[2b]

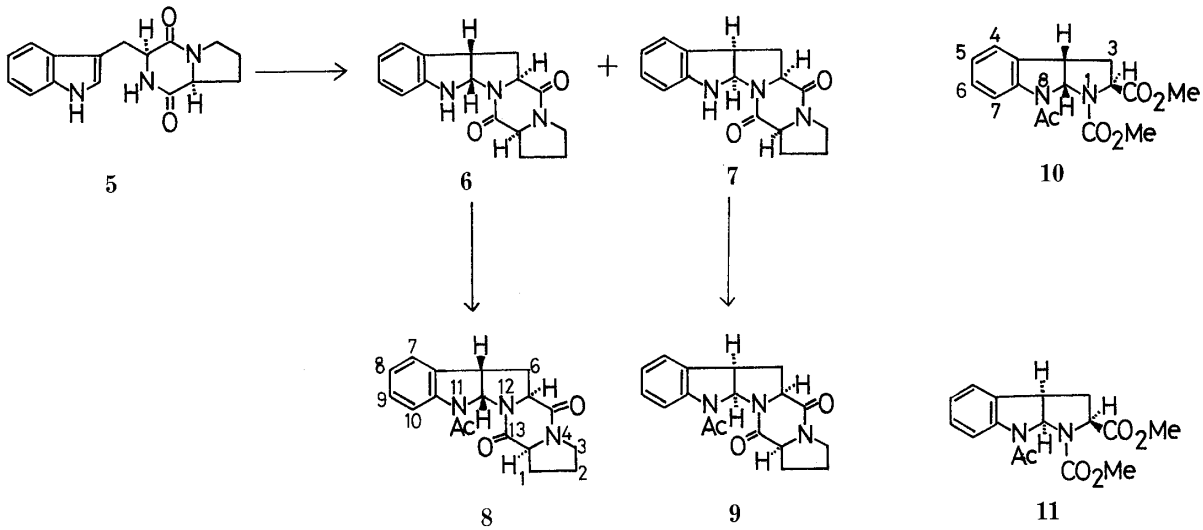

Chart 2

TABLE I. Spectral Data for the Cyclic Tautomers

	6	**7**	**8**	**9**
UV λ_{max}^{EtOH} nm (ε)	242.5 (7600), 297.5 (2600)	240 (7500), 293.5 (2500)	244 (11300), 275 (1850), 283 (1600)	245 (10200), 275.5 (1800), 284 (1600)
MS m/z (%)	283 (M^+, 74), 153 (71), 130 (100)	283 (M^+, 75), 153 (40), 130 (100)	325 (M^+, 27), 283 (100), 130 (79)	325 (M^+, 8), 283 (100), 130 (40)
^{1}H-NMR ($CDCl_3$)				
3-H_2	3.52 (t, J=7 Hz)	3.48 (t, J=7 Hz)	3.53 (t, J=7 Hz)	3.0—3.6 (m)
N-Ac	—	—	2.66 (s)	2.56 (s)
N_a-H	5.21 (s)	5.28 (d, J=2 Hz)	—	—
11$_a$-H	5.64 (d, J=7 Hz)	5.75 (dd, J=8, 2 Hz)	6.23 (d, J=6 Hz)	6.05 (d, J=6 Hz)
Arom-H	6.5—7.2 (m)	6.5—7.2 (m)	6.9—7.5 (m), 7.96 (d, J=8 Hz, 10-H)	7.0—7.4 (m), 7.87 (dd, J=7, 2 Hz, 10-H)
Other protons	1.6—2.8 (m), 3.8—4.25 (m)	1.6—2.9 (m), 3.75—4.45 (m)	1.6—2.8 (m), 3.8—4.2 (m)	1.6—2.9 (m), 3.9—4.4 (m)

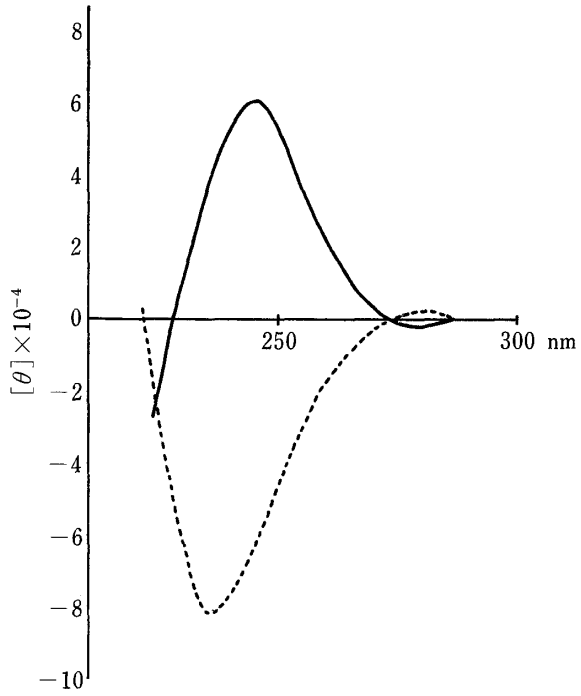

Fig. 1. CD Spectra of the Cyclic Tautomers (**8** and **9**) in Ethanol
——, **8**; ----, **9**.

The CD spectra of the *N*-acetyl stable isomer (**8**) showed a large positive Cotton effect at around 240 nm, is similar to that of **10**. The CD spectrum of **9**, which showed a negative Cotton effect, was similar to that of **11**. From these results, the stereochemistry of **8** and **9** can be assigned as depicted. However, in the tryptophan series **11** was the stable form, while the **9** was the less stable form in the 2,5-piperazinedione series, though the stereochemistry around the pyrrolo[2,3-*b*]indole ring system is the same. After our preliminary publication on the cyclic tautomer (**6**),[2a] Sammes' group reported[5] a cyclic tautomer of **5**, mp 187—188 °C, $[\alpha]_D$ −44 °, which was obtained by treatment with trifluoro-acetic acid at room temperature and differed from both **6** and **7** in $[\alpha]_D$ value; they proposed the structure **7**. We repeated their procedure and obtained **6** as a sole product. For further confirmation of the stereochemistry

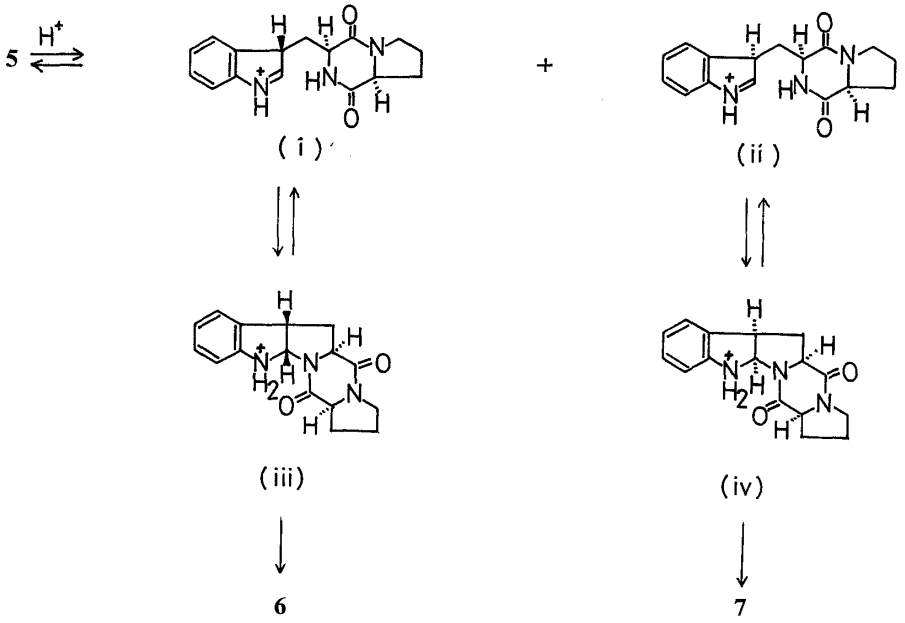

Chart 3

of **8** and **9**, X-ray analysis was carried out on **8** and the stereochemistry of **8** was proved to be as depicted.[1] Subsequently the stereochemistry of **6** and **7** was also established.

Formation of the cyclic tautomers (**6**, **7**) from **5** can be rationalized as shown in Chart 3. As in the case of N_b-acyltryptophans,[6] protonation may occur both from above and below the indole ring to form (i) and (ii) at nearly equal rates. In contrast to the tryptophan series, however, (ii) cyclized more smoothly to (iv) than (i) did to (iii), probably due to some steric factor which was not clear from a model study. The protonated less stable isomer (iv) may be gradually converted to the stable form (iii) through equilibration between iv⇄ii⇄**5**⇄i⇄iii. Evidence for the equilibrium between **5** and the protonated cyclic tautomer (iii) was obtained from the NMR spectrum of **6** in deuterotrifluoroacetic acid, which showed rapid deuterium exchange at 6_a-H and 11_a-H. The formation of the cyclic tautomer (**6**) can be readily seen in the NMR spectrum of **5** in CF_3COOH; new peaks appeared at 6.50 ppm due to 11_a-H.

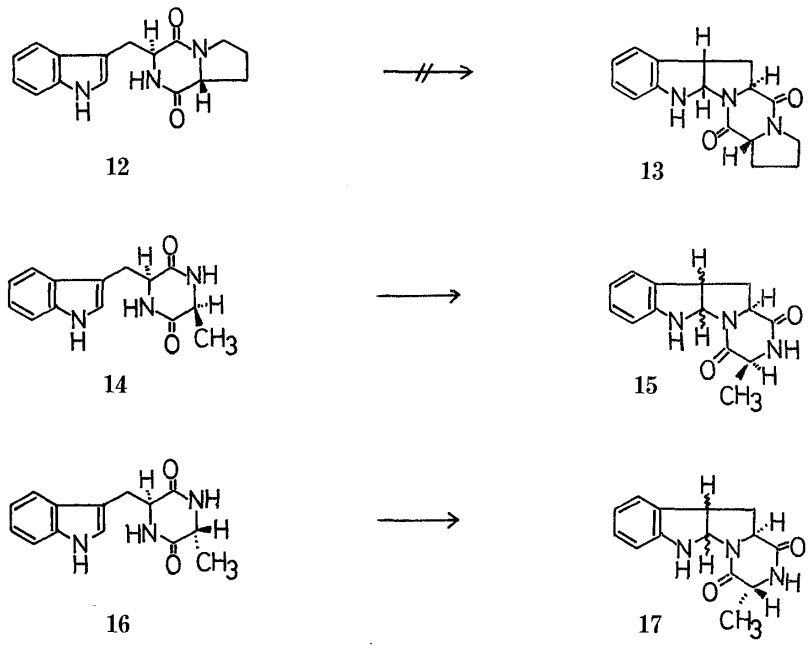

Chart 4

We then examined this cyclization with other 2,5-piperazinediones. Contrary to our expectation, *cyclo*-D-prolyl-L-tryptophyl (*trans*) (**12**) and *cyclo*-*N*-methyl-L-phenylalanyl-L-tryptophyl did not cyclize to the corresponding cyclic tautomers in CF_3COOH, while *cyclo*-*N*-methyl-D-phenylalanyl-L-tryptophyl smoothly cyclized to the cyclic tautomer.[7] However, both *cyclo*-L-alanyl-L-tryptophyl (**14**) and *cyclo*-D-alanyl-L-tryptophyl (**16**) cyclized moderately well to the cyclic tautomers (**15** and **17**) in trifluoroacetic acid. Both cyclic tautomers (**15** and **17**) were obtained as single isomers, but the stereochemistry was not determined. We can not yet explain these results, though the precise stereochemical features seem to be important for the cyclization.

We next examined the hydroxylation of the cyclic tautomers (**8** and **9**) with lead tetraacetate in trifluoroacetic acid, with which the cyclic tautomer (**10** and **11**) of N_b-acyltryptophan gave 5- and 6-hydroxy derivatives. When the stable isomer (**8**) was treated with lead tetraacetate in trifluoroacetic acid at -2— -3 °C followed by methylation, the 8-methoxy derivative (**18**, 38%), the 9-methoxy derivative (**19**, 26%), the 10-methoxy derivative (**20**, R=CH_3, 11%), and the 10-hydroxy derivative (**20**, R=H, 3%) were obtained. On the other hand the less stable isomer (**9**) gave the 8-methoxy derivative (**21**, 25%), 9-methoxy derivative (**22**, 34%), and the 10-hydroxy derivative (**23**, 4%) under similar conditions.

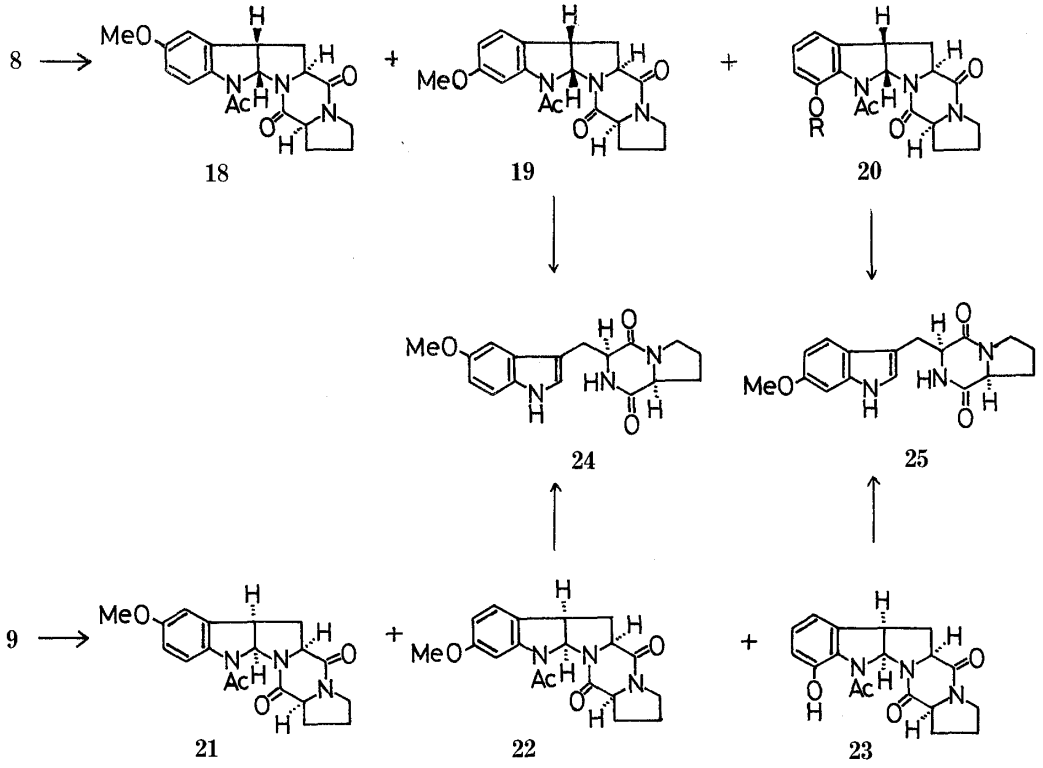

Chart 5

TABLE II. Spectral Data for the Methoxylated Cyclic Tautomer

	18	**19**	**20** (R = Me)
UV λ_{max}^{EtOH} nm (ε)	251 (13300), 292.5 (3100), 299 (s, 2800)	213.5 (29400), 246 (9400), 288 (4700), 293.5 (4500)	211 (35300), 244.5 (8000), 278 (2100), 285.5 (2100)
MS *m/z* (%)	355 (M^+, 38), 313 (100), 160 (57)	355 (M^+, 31), 313 (100), 160 (53)	355 (M^+, 17), 313 (100), 160 (65)
^{1}H-NMR ($CDCl_3$) δ (ppm)			
1-H_2, 2-H_2, 6-H_2	1.6—2.9 (m)	1.8—2.9 (m)	1.7—2.9 (m)
N-Ac	2.63 (s)	2.65 (s)	2.54 (s)
3-H_2	3.52 (t, J = 6 Hz)	3.53 (t, J = 6 Hz)	3.3—3.7 (m)
OCH_3	3.79 (s)	3.79 (s)	3.87 (s)
5_a-H, 6_a-H, 13_a-H	3.9—4.3 (m)	3.9—4.3 (m)	4.0—4.3 (m)
11_a-H	6.21 (d, J = 6 Hz)	6.21 (d, J = 6 Hz)	6.35 (d, J = 6 Hz)
Arom-H	6.6—6.9 (m, 7-H, 9-H)	6.65 (dd, J = 8, 2 Hz, 8-H)	6.88 (d, 7-, 8-H)
	7.86 (d, J = 9 Hz, 10-H)	7.10 (d, J = 8 Hz, 7-H)	7.22 (dd, J = 9, 2 Hz, 9-H)
		7.63 (d, J = 2 Hz, 10-H)	

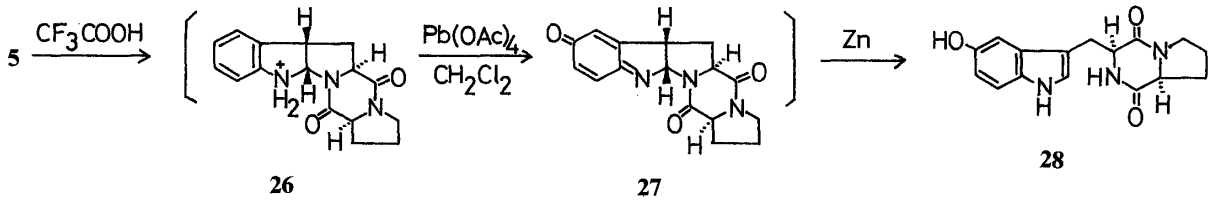

Chart 6

These results were similar to those for the tryptophan series[2c,f]; the *cis* isomer (**10**) gave the 5-methoxy derivative as the major product, while the 6-methoxy derivative was obtained as the major product with the *trans* isomer (**11**). The position of the methoxy group was confirmed by the coupling patterns of the 10-proton signal in the NMR spectra (see Table). These methoxylated cyclic tautomers were readily converted to the *cyclo*-L-prolyl-5- and 6-methoxy-L-tryptophyl (**24**, **25**) on treatment with 10% H_2SO_4–MeOH.

Selective 8-hydroxylation of **5** was also successful under conditions similar to those applied to the tryptophan series.[2e] *cyclo*-L-Prolyl-L-tryptophyl (**5**) was dissolved in trifluoroacetic acid in which the cyclic tautomer (**26**) was formed. The solution was added to two equivalents of lead tetraacetate in methylene chloride to form the quinoneimine (**27**), which was reduced and ring-opened with zinc to give the 8-hydroxy derivative (**28**, 73% from **5**). Although no derivative of **28** has yet been found as a natural product, this hydroxylation method may be applicable to a biomimetic synthesis of fumitremorgins, which are derivatives of **25**.

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 a Hitachi M-60 instrument.

Cyclic Tautomer of *cyclo*-L-Prolyl-L-tryptophyl (Stable Form 6)——*cyclo*-L-Prolyl-L-tryptophyl (**5**, 567 mg, 2 mmol) was added to 85% H_3PO_4 (10 ml) at room temperature, and the mixture was stirred for 40 min, then poured into chilled 10% Na_2CO_3 (200 ml) under cooling, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with sat. NaCl and dried. Removal of the solvent by evaporation gave a residue, which was recrystallized from acetone–hexane to give the cyclic tautomer (**6**, 433 mg). The mother liquor was evaporated to give a residue, which was separated by preparative thin layer chromatography (TLC) to give **6** (72 mg, total 505 mg, 89%) and the starting material (**5**, 34 mg, 6%). Repeated recrystallization of the cyclic tautomer from acetone gave colorless scales, mp 188—200 °C (dec.). *Anal.* Calcd for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.81; H, 6.00; N, 14.73. Spectral data: See Table I. $[\alpha]_D$ −498° (c=0.2, EtOH).

The Less Stable Isomer of the Cyclic Tautomer (7)——1) *cyclo*-L-Prolyl-L-tryptophyl (**5**, 500 mg, 1.77 mmol) was added to CF_3COOH (10 ml) at −10 °C under stirring. After complete dissolution (1—2 min), the mixture was poured into 10% Na_2CO_3 (120 ml) under cooling and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with sat. NaCl solution and dried. Removal of the solvent by evaporation gave a residue, which was separated by fractional recrystallization from CH_2Cl_2–acetone–ether to give the less stable isomer (**7**, 257 mg, 51%) and the stable isomer (**6**, 114 mg). Separation of the mother liquor by preparative TLC (CH_2Cl_2–acetone 5:1) gave **6** (49 mg, total 163 mg, 33%) and the starting material (**5**, 41 mg, 8%). Repeated recrystallization of the less stable isomer from CH_2Cl_2–acetone–ether gave colorless needles, mp 165—178 °C. *Anal.* Calcd for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.93. Found: C, 67.64; H, 5.99; N, 14.87. Spectral data: See Table I. $[\alpha]_D$ = +212° (c=0.2, EtOH).

2) NMR: *cyclo*-L-Prolyl-L-tryptophyl (**5**, 50 mg) was dissolved in CF_3COOH (2 ml) at −10 °C, and the mixture was immediately poured into 10% Na_2CO_3 as above. The NMR spectrum of the crude mixture in $CDCl_3$ showed that the ratio of **7**:**6** was 1.7:1, based on the integrated signals of the 11_a-H of both isomers.

Conversion of the Less Stable Isomer (7) to the Stable Isomer (6)——The less stable isomer (**7**, 100 mg, 0.35 mmol) was dissolved in CF_3COOH (1 ml) at room temperature. After 10 min, the mixture was poured into 10% Na_2CO_3 (30 ml) and treated as above to give the stable isomer (**6**, 85 mg), which was identical with the sample obtained above (IR comparison).

Ring Opening of the Cyclic Tautomer (6)——A solution of the stable cyclic tautomer (**6**, 40 mg, 0.14 mmol) in MeOH (2 ml) containing a few drops of 10% HCl was stirred for 3 h at room temperature. The mixture was poured into sat. $NaHCO_3$ (20 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with sat. NaCl solution and dried. Evaporation of the solvent gave a residue (36 mg) which was recrystallized from acetone–hexane to give *cyclo*-L-prolyl-L-tryptophyl (**5**, 23 mg).

N_a-Acetyl Derivative of the Stable Tautomer (8)——1) From the Cyclic Tautomer (6): A solution of the cyclic tautomer (**6**, 2.00 g, 7.1 mmol) in Ac_2O (7.5 ml) and pyridine (25 ml) was stirred for 3 h at room temperature. The mixture was concentrated to a small volume *in vacuo* and diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O and dried. The solvent was evaporated off *in vacuo* to give a residue, which was crystallized from MeOH to give the acetyl derivative (**8**, 2.04 g) as colorless prisms. Separation of the mother liquor on a silica gel column gave further **8** (83 mg, total 2.12 g, 92%). Recrystallization from MeOH gave colorless prisms, mp 257—259 °C. *Anal.* Calcd for

$C_{18}H_{19}N_3O_3$: C, 66.44; H. 5.86; N, 12.92. Found: C, 66.41; H, 5.87; N, 12.93. Spectral data: See Table I. $[\alpha]_D$ −215° (c=0.106, $CHCl_3$).

2) From *cyclo*-L-Prolyl-L-tryptophyl (**5**): *cyclo*-L-Prolyl-L-tryptophyl (**5**, 2.00 g, 7.1 mmol) was added to 85% H_3PO_4 (20 ml) and the mixture was stirred for 50 min at room temperature, then treated as above to give the crude cyclic tautomer (**6**), which was dissolved in Ac_2O (7 ml) and pyridine (24 ml). The mixture was stirred overnight at room temperature, and then treated as above to give **8** (2.01 g, 87%) and **5** (212 mg, 11%).

N_a-Acetyl Derivative of the Less Stable Isomer (9)——A solution of the less stable isomer (**7**, 223 mg, 0.79 mmol) in Ac_2O (5 ml) was stirred for 2 h at room temperature. The mixture was evaporated *in vacuo* to give a residue, which was separated by preparative TLC (silica gel, AcOEt–acetone 5 : 1) to give the acetyl derivative (**9**, 128 mg, 50%) and **5** (117 mg, 52%). Recrystallization of the *N*-Ac derivative from acetone–ether gave colorless needles, mp 231—236 °C (dec.). Acetylation of the cyclic tautomer (**7**) with Ac_2O–pyridine for 18 h at room temperature gave the *N*-Ac derivative in 59% yield. *Anal.* Calcd for $C_{18}H_{19}N_3O_3$: C, 66.44; H, 5.89; N, 12.92. Found: C, 66.38; H, 5.89; N, 12.89. Spectral data: See Table I. $[\alpha]_D$ = −107° (c=0.138, $CHCl_3$).

Cyclic Tautomer (15) of *cyclo*-L-Alanyl-L-tryptophyl——*cyclo*-L-Alanyl-L-tryptophyl (**14**, 500 mg, 1.94 mmol) was dissolved in CF_3COOH (5 ml), and the solution was kept at room temperature for 15 min, then poured into 10% Na_2CO_3 (100 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O and dried. The solvent was removed by evaporation to give a white solid (322 mg), which was recrystallized from MeOH–ether to give the cyclic tautomer as colorless needles (**15**, 255 mg, 51%). Repeated recrystallization from MeOH gave a pure sample, mp 250—251 °C. The other diastereoisomer was not detected. UV λ_{max}^{EtOH} nm (ε): 242 (7500), 297 (2450). IR (KBr) cm^{-1}: 3390, 3318, 1682, 1660. MS m/z (%): 257 (M^+, 90), 131 (36), 130 (100), 77 (29). NMR (DMSO-d_6) δ: 1.24 (3H, d, J=7 Hz, Me), 2.1—2.6 (2H, m, 5-H_2), 3.8—4.2 (3H, m, 2-H, 5$_a$-H, 4$_a$-H), 5.61 (1H, d, J=7 Hz, 10$_a$-H), 6.4 (10-H), 6.4—7.2 (4H, m, arom H), 8.09 (s, amide NH). *Anal.* Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.24; H, 5.86; N, 16.31. A similar reaction at −10 °C for 15 min gave the cyclic tautomer in 76% yield.

Cyclic Tautomer (17) of *cyclo*-D-Alanyl-L-tryptophyl——*cyclo*-D-Alanyl-L-tryptophyl (**16**, 500 mg, 1.94 mmol) was dissolved in CF_3COOH (5 ml) and kept at room temperature for 15 min. The mixture was poured into 10% Na_2CO_3 (100 ml) and extracted with CH_2Cl_2. Insoluble material (**16**, 146 mg) was filtered off and the CH_2Cl_2 solution was washed with H_2O and dried. Removal of the solvent by evaporation gave a residue, which was recrystallized from MeOH to give the cyclic tautomer (**17**, 160 mg, 32%). Recrystallization from MeOH gave colorless needles, mp 231—233 °C. UV λ_{max}^{EtOH} nm (ε): 243 (7600), 298 (2500). IR (KBr) cm^{-1}: 3300, 3240, 1675, 1630. MS m/z (%): 257 (M^+, 100), 130 (90), 117 (65). NMR (DMSO-d_6) δ: 1.25 (3H, d, J=7 Hz, Me), 2.0—2.6 (2H, m, 5-H_2). 3.6—4.0 (3H, m, 2-H, 4$_a$-H, 5$_a$-H), 5.67 (1H, d, J=8 Hz, 10$_a$-H), 6.4—7.2 (5H, m, arom H, NH), 8.14 (NH). *Anal.* Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.63; H, 5.90; N, 16.35.

Oxidation of the *N*-Ac Cyclic Tautomer (8) with Pb $(OAc)_4$-CF_3COOH——Lead tetraacetate (1.60 g, 3.7 mmol) in CF_3COOH (5 ml) was added to a solution of *N*-Ac cyclic tautomer (**8**, 975 mg, 3 mmol) in CF_3COOH (25 ml) during 20 min at −2— −3 °C. The mixture was stirred for 2.5 h and then poured into ice-water (20 ml). The mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with $NaHCO_3$ solution and H_2O, and dried. Removal of the solvent by evaporation gave a brown residue, which was dissolved in acetone (35 ml). Methyl iodide (2.56 g, 18 mmol) and K_2CO_3 (2.49 g, 18 mmol) were added to the solution, and the mixture was refluxed for 8 h. Removal of the solvent by evaporation gave a residue, which was dissolved in CH_2Cl_2 (30 ml). After removal of the insoluble material, the CH_2Cl_2 solution was concentrated to a small volume and chromatographed on a silica gel column (80 g, benzene–hexane–acetone 4 : 2 : 1) to give the 10-OH derivative (**20** (R = H), 30 mg, 3%) from the first fraction. The 9-MeO derivative (**19**, 272 mg, 26%), the 8-MeO derivative (**18**, 399 mg, 38%), and the 7-MeO derivative (**20** (R = CH_3), 113 mg, 11%) were eluted successively.

Recrystallization of **19** from MeOH gave colorless needles, mp 281—283 °C. *Anal.* Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.24; H, 5.97; N, 11.83. $[\alpha]_D$ = −226° (c=0.072, $CHCl_3$).

Recrystallization of **18** from benzene–hexane gave colorless prisms, mp 168.5—170 °C. *Anal.* Calcd for $C_{19}H_{21}N_3O_4 \cdot 1/2H_2O$: C, 62.62; H, 6.09; N, 11.54. Found: C, 62.85; H, 5.88; N, 11.62. $[\alpha]_D$ = −209° (c=0.098, $CHCl_3$).

Recrystallization of the 10-MeO derivative (**20**, R = CH_3) from MeOH gave colorless prisms, mp 296—301 °C (dec.). *Anal.* Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.11; H, 5.97; N, 11.82. Spectral data for these compounds are listed in Table II. 10-OH derivative (**20**, R = H): UV λ_{max}^{EtOH} nm (ε): 251, 189. IR (KBr) cm^{-1}: 3430, 1660. MS m/z (%): 341 (M^+, 31), 299 (75), 146 (100). NMR (DMSO-d_6) δ: 1.5—2.4 (m, 1-H_2, 2-H_2, 6-H_2), 2.69 (s, Ac), 3.34 (t, J=6 Hz, 3-H_2), 3.8—4.5 (m, 5$_a$-H, 6$_a$-H, 12$_a$-H), 6.21 (d, J=6 Hz, 11$_a$-H), 6.7—7.3 (m, 7-H, 8-H, 9-H), 10.33 (s, OH).

Oxidation of the *N*-Acetyl Cyclic Tautomer (Less Stable Form, 9) with Pb $(OAc)_4$-CF_3COOH——Pb $(OAc)_4$ (1.06 g, 2.4 mmol) in CF_3COOH (5 ml) was added to a solution of **9** (650 mg, 2 mmol) in CF_3COOH (10 ml) during 30 min at 2 °C under ice cooling. The mixture was stirred for 30 min and the excess Pb $(OAc)_4$ was destroyed by the addition of Zn powder (0.5 g). The mixture was poured into H_2O (30 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with sat. $NaHCO_3$ solution and H_2O, and dried. Removal of the solvent by evaporation gave a residue, which was methylated with CH_3I (2.84 g, 20 mmol) and K_2CO_3 (2.76 g, 20 mmol) in acetone (20 ml) as above.

Work-up as above gave a mixture, which was separated on a silica gel column (30 g, CH_2Cl_2–acetone 4 : 1—3 : 1) and by preparative TLC (silica gel, CH_2Cl_2–acetone 3 : 1) to give the 8-MeO (**21**, 176 mg, 25%), the 9-MeO (**22**, 240 mg, 34%), and the 10-OH (**23**, 30 mg, 4%), derivatives.

Recrystallization of **21** from MeOH gave colorless prisms, mp 264—266 °C (dec.). *Anal.* Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 63.94; H, 5.99; N, 11.69. UV λ_{max}^{EtOH} nm (ε): 253 (12400), 292.5 (3000), 301.5^{s} (2400). IR (KBr) cm^{-1}: 1670. MS *m/z*(%): 355 (M^+, 18), 313 (86), 305 (29), 160 (100), 159 (27), 147 (28). NMR ($CDCl_3$) δ: 1.5—2.8 (5H, m), 2.51 (1H, s, $COCH_3$), 2.9—3.5 (3H, m, 3-H_2, 1-H), 3.75 (3H, s, OCH_3), 3.8—4.4 (3H, m, 5_a-, 6_a-, 13_a-H), 6.01 (1H, d, J=6 Hz, 11_a-H), 6.7 (2H, m, 7-H, 9-H), 7.73 (1H, d, J=8 Hz, 10-H).

Recrystallization of **22** from MeOH gave colorless scales, mp 262—265 °C (dec.). *Anal.* Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.20; H, 5.96; N, 11.82. UV λ_{max}^{EtOH} nm (ε): 215.5 (26200), 246.5 (8400), 288 (4700), 294 (4500). IR (KBr) cm^{-1}: 1700, 1686, 1667. MS *m/z* (%): 355 (M^+, 29), 313 (77), 305 (48), 160 (100), 159 (47), 147 (34). NMR ($CDCl_3$): 1.5—2.8 (5H, m), 2.53 (3H, s, $COCH_3$), 2.9—3.5 (3H, m, 3-H_2, 1-H), 3.75 (3H, s, OCH_3), 3.8—4.4 (3H, m, 5_a-, 6_a-, 13_a-H), 6.00 (1H, d, J=6 Hz, 11_a-H), 6.58 (1H, dd, J=8, 2 Hz, 8-H), 7.10 (1H, d, J=8 Hz, 7-H), 7.50 (1H, d, J=2 Hz, 10-H).

Recrystallization of **23** from MeOH gave colorless scales, mp 258—260 °C (dec.). *Anal.* Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.21; H, 5.64; N, 12.61. UV λ_{max}^{EtOH} nm (ε): 250.5 (6100), 289 (2600). IR (KBr) cm^{-1}: 3460, 3100—2500, 1685, 1630. MS *m/z* (%): 341 (M^+, 13), 299 (44), 146 (100). NMR ($CDCl_3$) δ: 1.5—2.7 (5H, m), 2.6 (3H, s, $COCH_3$), 3.0—3.5 (3H, m, 3-H_2, 1-H), 3.9—4.4 (3H, m, 5_a-, 6_a-, 13_a-H), 5.94 (1H, d, J=6 Hz, 11_a-H), 6.78 (2H, m, 7-H, 9-H), 7.06 (1H, dd, J=8, 6 Hz, 8-H), 10.20 (1H, s, OH).

***cyclo*-L-Prolyl-5-methoxy-L-tryptophyl (24)**——1) From **18**: A solution of **18** (355 mg, 1 mmol) in 10% H_2SO_4–MeOH (20 ml) was stirred for 5 h at room temperature, then poured into H_2O (150 ml) and extracted with CH_2Cl_2. The extracts were washed with sat. $NaHCO_3$ solution and sat. NaCl solution, and dried. Evaporation of the solvent *in vacuo* gave a residue, which was recrystallized from MeOH to give **24** (236 mg). The mother liquor was chromatographed on a silica gel column and subjected to preparative TLC to give further **24** (9 mg, total 245 mg, 80%). Recrystallizations from MeOH gave colorless prisms, mp 211—212 °C. *Anal.* Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.11; H, 6.09; N, 13.48. $[\alpha]_D = -186°$ (c=0.07, $CHCl_3$). UV λ_{max}^{EtOH} nm (ε): 219^{sh} (27200), 276 (6200), 296.5 (4800), 308^{sh} (3500). IR (KBr) cm^{-1}: 3280, 1680, 1665. MS *m/z* (%): 313 (M^+, 18), 160 (100). NMR (DMSO-d_6) δ: 1.2—2.2 (4H, m, 13-H_2, 14-H_2), 2.9—3.6 (4H, m, 8-H_2, 15-H_2), 3.76 (3H, s, OCH_3), 4.04 (1H, t, 12-H), 4.28 (1H, t, 9-H), 6.67 (1H, dd, J=8, 2 Hz, 6-H), 7.0—7.3 (3H, m, 2-, 4-, 7-H), 7.59 (1H, s, amide NH), 10.63 (1H, s, indole NH).

2) From **21**: A solution of **21** (50 mg, 0.14 mmol) in 10% H_2SO_4–MeOH (2 ml) was stirred for 8 h at room temperature. The solution was treated as above to give **24** (40 mg, 91%). Recrystallization from MeOH gave colorless prisms, mp 202—206 °C, which were identical with the above sample (mp, mmp, IR).

***cyclo*-L-Prolyl-6-methoxyl-L-tryptophyl (25)**——1) From **19**: A solution of 19 (300 mg, 0.85 mmol) in 10% H_2SO_4–MeOH (17 ml) was stirred for 7 h at room temperature, then poured into H_2O (120 ml) and extracted with CH_2Cl_2. The extracts were washed with sat. $NaHCO_3$ solution and sat. NaCl solution, and dried. Evaporation of the solvent *in vacuo* gave a residue, which was recrystallized from MeOH to give **25** (169 mg). Further **25** (38 mg, total 207 mg, 78%) was obtained by preparative TLC of the mother liquor.

Recrystallization of **25** from MeOH gave colorless prisms, mp 170—171 °C. *Anal.* Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.13; H, 6.10; N, 13.41. $[\alpha]_D = -158°$ (c=0.086, $CHCl_3$). UV λ_{max}^{EtOH} nm (ε): 222.5 (32900), 264 (4000), 273 (4400), 292 (5000), 299.5^{sh} (4100). IR (KBr) cm^{-1}: 3460, 1680, 1655. MS *m/z* (%): 313 (M^+, 17), 160 (100). NMR ($CDCl_3$) δ: 1.6—2.5 (4H, m, 13-H_2, 14-H_2), 2.94 (1, dd, J=10, 15 Hz, 8-H), 3.4—3.7 (3H, m, 8-H, 15-H_2), 3.80 (3H, s, OCH_3), 4.04 (1H, t, 12-H), 4.31 (1H, m, 9-H), 5.95 (1H, s, amide NH), 6.7—7.0 (3H, m, 2-, 5-, 7-H), 7.45 (1H, d, J=8 Hz, 4-H), 8.68 (1H, s, indole NH).

2) From **22**: A solution of **22** (50 mg, 0.14 mmol) in 10% H_2SO_4–MeOH (2 ml) was stirred for 8 h at room temperature. The solution was treated as above to give **25** (39 mg, 87%), which was identical with the above sample (mp, mmp, IR).

Hydroxylation of 5 with $Pb(OAc)_4$——Compound **5** (566 mg, 2 mmol) was dissolved in CF_3COOH (6 ml) and kept for 50 min at room temperature. The solution was then added to a solution of $Pb(OAc)_4$ (1.98 g, 4 mmol) in CH_2Cl_2 (44 ml) at 10 °C, and the mixture was stirred for 30 min at the same temperature to give a reddish brown mixture. Zinc powder (1.1 g) was added to the mixture at 10 °C and the whole was stirred for 30 min to give a clean solution. After removal of the zinc, the solvent was removed *in vacuo* to give a brown residue (3.6 g), which was separated on a silica gel column to give the 5-hydroxy derivative (**28**, 437 mg, 73%) and the starting material (35 mg, 6%). Recrystallization of **28** from MeOH gave colorless scales, mp 227—231 °C (dec.). UV λ_{max}^{EtOH} nm (ε): 276.5 (6100), 300.5 (4500). IR (KBr) cm^{-1}: 3482, 3300, 1680, 1628. MS *m/z* (%): 299 (M^+, 18), 146 (100). NMR (DMSO-d_6) δ: 1.2—2.2 (4H, m, 13-H_2, 14-H_2), 2.7—3.9 (4H, m, 8-H_2, 15-H_2, MeOH), 3.9—4.4 (2H, m, 9-H, 12-H), 6.57 (1H, dd, J=8, 2 Hz, 6-H), 7.0—7.2 (2H, m, 2-H, 7-H), 7.57 (1H, s, amide NH), 8.5 (1H, br s, OH), 10.48 (1H, s, indole NH). *Anal.* Calcd for $C_{16}H_{17}N_3O_3 \cdot 1/2$MeOH: C, 62.84; H, 6.07; N, 13.33. Found: C, 62.81; H, 6.07; N, 13.40.

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References and Notes

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