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Formation and Reactions of the Cyclic Tautomers of Tryptophans and Tryptamines. VII.[1] Hydroxylation of Tryptophans and Tryptamines[2]

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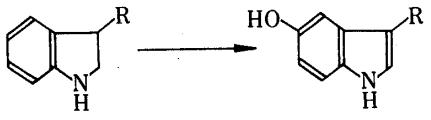
The 5-hydroxytryptophan derivative **12** was prepared in 60% yield from the tryptophan derivative **8** by selective oxidation of the cyclic tautomer **9** with Fremy's salt or $Pb(OAc)_4$–CF_3COOH to the *p*-quinoneimine **10**, followed by reduction and ring-opening. By analogous oxidation, serotonin was prepared from tryptamine. On the other hand, the oxidation of the N_a-acetyl-cyclic tautomers (**16** and **22**) with $Pb(OAc)_4$–CF_3COOH followed by methylation gave the 5- and 6-methoxy derivatives (**17**, **18**, **23**, and **24**) in 20—40% yields. These compounds were readily converted to the 5- and 6-methoxytryptophan derivatives (**20**, **21**) by acid treatment. These methods are the first practical hydroxylation procedures to be reported for tryptophans.

Keywords——5-hydroxytryptophan; methoxytryptophan; cyclic tautomer; tryptophan; oxidation; hydroxylation; lead tetraacetate; Fremy's salt

The hydroxylation of tryptophan at the 5-position is a well-known biological oxidation catalyzed by monooxygenase. The indole ring system hydroxylated at the 5-position as well as at other positions is found in various indole alkaloids and other natural products. However, the chemical hydroxylation of tryptophan and related indole derivatives has not been established from a practical view point, although the hydroxylation of tryptamines, tryptophan and other simple indole derivatives with Udenfriend's system or the Fenton-type system has been reported to give various hydroxylated indoles in poor yields.[3] For the preparation of hydroxylated tryptamines and tryptophans, protected hydroxyindoles were prepared from the hydroxybenzene derivatives by an indolization procedure such as Fischer cyclization, Reissert reduction, Nenitzescu synthesis or Gassman's method, and converted to the desired hydroxytryptamines and tryptophans.[3] Another approach to 5-hydroxytryptamines from the 5-bromo derivatives by the substitution reaction with NaOMe–MeOH–DMF–CuI was reported.[4] Oxidation of the indoline derivatives (**1**) with Fremy's salt was reported to give the 5-hydroxyindole derivatives (**2**).[5] On the other hand, similar oxidation of the pyrroloindole (**3**), which is an indoline, but which could not be aromatized to the indole by oxidation, gave the *p*-quinoneimine (**4**) in good yield.[6]

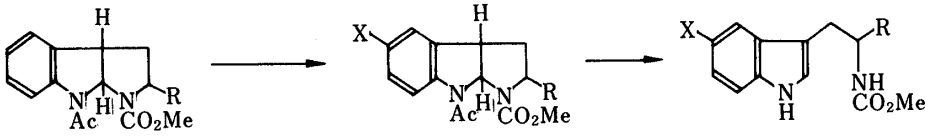
In our previous papers[1,7] we have reported a simple preparation of the cyclic tautomer (**5**) of N_b-acyltryptamines and tryptophans, and the chlorination and nitration of these cyclic tautomers (**5**) to give the 5-substituted derivatives (**6** and **7**). In this paper we describe the preparation of 5- and 6-hydroxytryptamines and -tryptophans by oxidation of the cyclic tautomers with Fremy's salt or lead tetraacetate in trifluoroacetic acid.

When a solution of the cyclic tautomer (**9**) of N_b-methoxycarbonyl-DL-tryptophan methyl ester (**8**)[8] in methanol was oxidized with four equivalents of Fremy's salt in phosphate buffer (pH 7) at room temperature for 5 min, the expected *p*-quinoneimine (**10**) was obtained in 50% yield. This compound was not stable enough to be purified, but the structure was confirmed by its ultraviolet (UV) spectrum, λ_{max} (EtOH) 266.5 nm, which is similar to that of



1 2

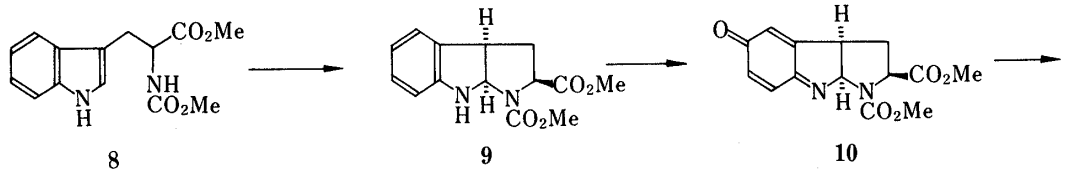
3 4



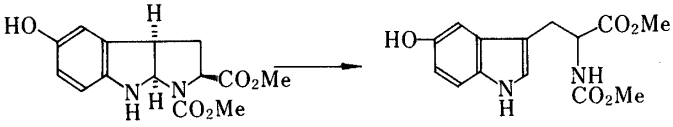
5 6 7

R=H, CO_2Me X=Cl, NO_2, Br

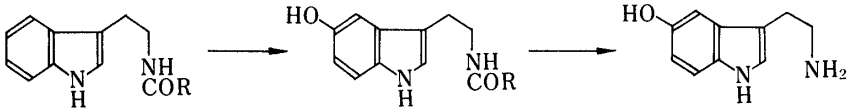
Chart 1



8 9 10



11 12



13 14 15

a : R=OCH_3
b : R=OCH_2Ph

Chart 2

4,[5] and the nuclear magnetic resonance (NMR) spectrum excluded the *o*-quinoneimine structure because of the coupling pattern of the aromatic protons: 6.38 ppm (1H, d, $J=2$ Hz, 4-H); 6.61 (1H, dd, $J=10$ and 2 Hz, 6-H); 7.49 (1H, d, $J=10$ Hz, 7-H). The quinoneimine (**10**) was reduced with $NaBH_4$ in methanol followed by the addition of acetic acid to give the 5-hydroxytryptophan derivative (**12**), mp 123—125 °C, *via* **11**. The yield of **12** from **8** was 44%

without purification of **10** and **11**.

This method was improved in terms of the yield and procedure by using lead tetraacetate in trifluoroacetic acid, which has been reported as a hydroxylating agent for various benzene derivatives.[9] N_b-Methoxycarbonyl-DL-tryptophan methyl ester (**8**) was dissolved in trifluoroacetic acid at room temperature to form the cyclic tautomer (**9**) (in protonated form). The solution was added to a solution of lead tetraacetate in methylene chloride at 10 °C to afford the quinoneimine (**10**). The quinoneimine (**10**) was converted to the 5-hydroxy derivative (**12**) in 46% yield by reduction with $NaBH_4$ in methanol followed by the addition of acetic acid. When $NaBH_4$ was replaced by zinc powder, isolation of the quinoneimine (**10**) was not required; all the procedures could be carried out in one pot and the yield of the 5-hydroxy derivative (**12**) from **8** increased to 60%. This procedure was also applied to N_b-methoxycarbonyl-(**13a**) and N_b-benzyloxycarbonyl-tryptamine (**13b**) to give the 5-hydroxytryptamine derivatives (**14a** and **14b**) in 44 and 67% yields, respectively. The N_b-benzyloxycarbonyl derivative (**14b**) was converted to serotonin (**15**) in 57% yield by catalytic hydrogenation. These results are the first practical example of the selective 5-hydroxylation of tryptophan and tryptamine derivatives.

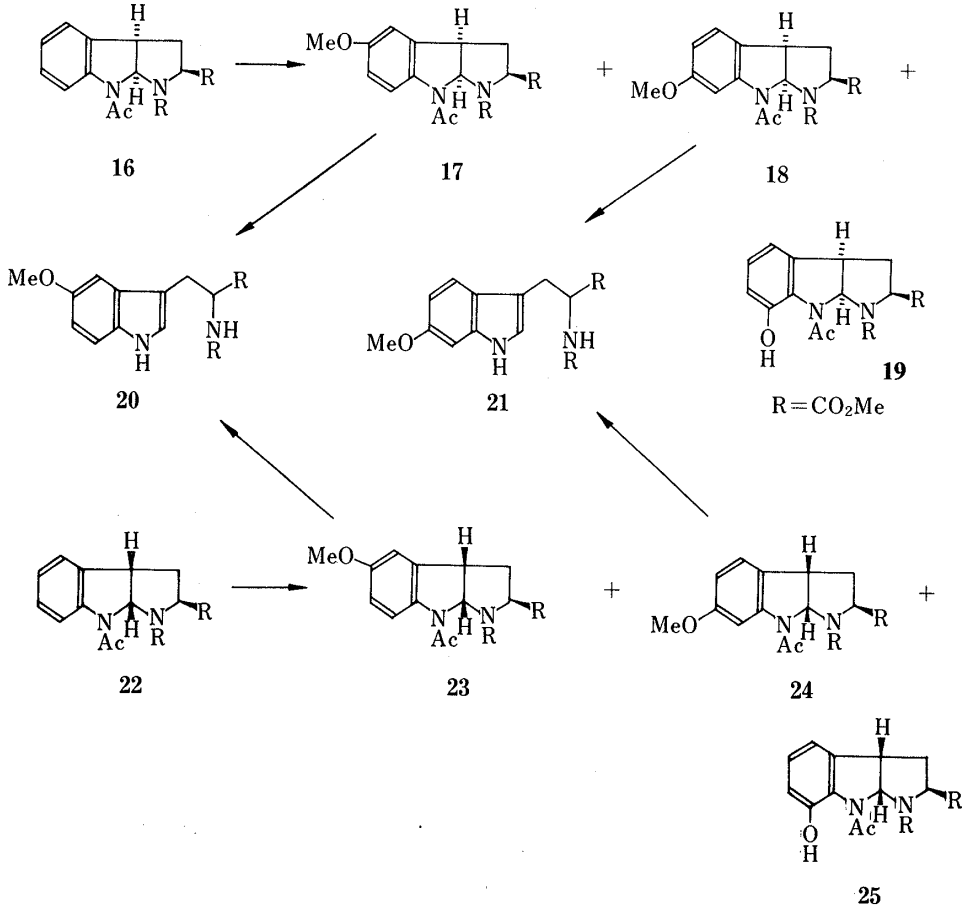
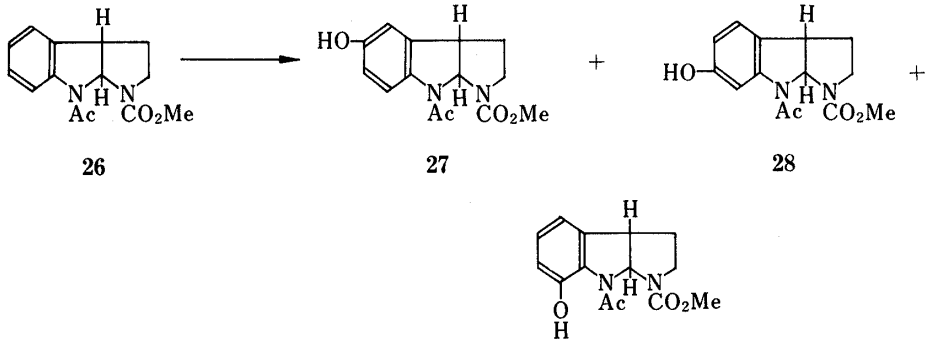


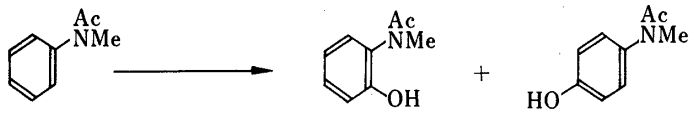
Chart 3

We next examined the oxidation of the N_a-acetyl cyclic tautomers (**16** and **26**)[7b] with lead tetraacetate in trifluoroacetic acid and found that it gave different results from those described above. When a solution of the N_a-acetyl cyclic tautomer **16**, the stable isomer, in trifluoroacetic acid was treated with lead tetraacetate at 1—2 °C for 2 h, a mixture of hydroxylated products was obtained, but was difficult to separate owing to its insolubility in organic solvents. The mixture was methylated with CH_3I–K_2CO_3–acetone at room tempera-

ture and separated to give the 5-methoxy derivative (**17**, 17%), mp 191—193 °C, the 6-methoxy derivative (**18**, 42%), mp 137.5—139.5 °C, and the 7-hydroxy derivative (**19**, 4%). The 5- and 6-methoxy derivatives were readily converted to the corresponding tryptophan derivatives (**21** and **20**) by treatment with 10% H_2SO_4–methanol at room temperature. The position of the methoxy group was confirmed by their spectral data and further by direct comparison of the 5-methoxy derivative (**20**) with a sample obtained from 5-hydroxy-DL-



26 **27** **28** **29**



30 **31** **32**

Chart 4

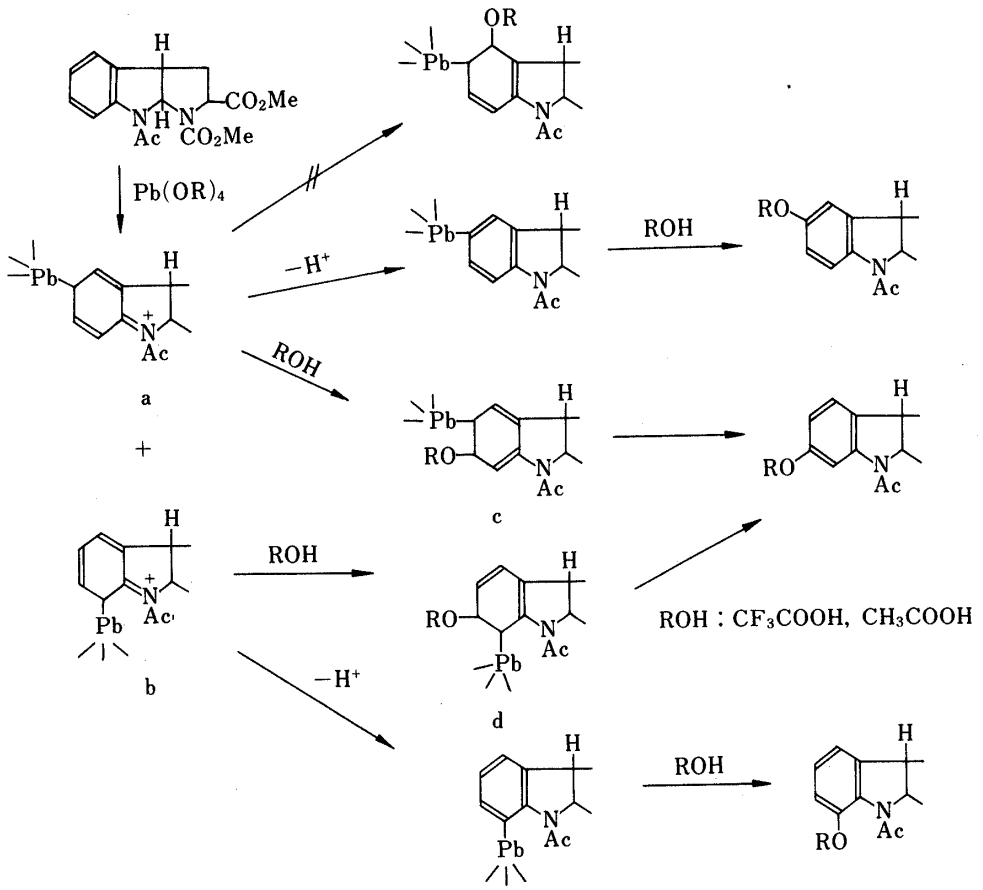


Chart 5

tryptophan. Selectivity of the oxidation was not high, but the oxidation did occur preferentially at the *meta*-position to the acetamido group, which is not easily accessible. Similar oxidation was then carried out on the less stable isomer (**22**) to give the 5-methoxy derivative (**23**, 30%), the 6-methoxy derivative (**24**, 25%), and the 7-hydroxy derivative (**25**, 5%). Furthermore, oxidation of the cyclic tautomer of the tryptamine derivative (**26**) under similar conditions gave the 5-hydroxy derivative (**27**, 30%), the 6-hydroxy derivative (**28**, 22%), and the 7-hydroxy derivative (**29**, 6%). These results indicate that the stereochemistry of the cyclic tautomers affects the ratio of the 5- and 6-methoxy derivatives, but the 6-isomer was always obtained.

To extend this oxidation procedure to simple acetanilides we examined the oxidation of *N*-methylacetanilide. Contrary to our expectation, this oxidation proceeded slowly and gave the *ortho*- and *para*-hydroxylated derivatives in poor yields.

Although no direct evidence is available, a plausible mechanism is depicted in Chart 5. Plumbation would occur at the 5- and 7-positions to form a and b. Trifluoroacetic acid may attack the 6-position to form c and d before deprotonation to form the aromatic lead derivative, which could be converted to the hydroxy derivative by loss of a lead compound.

The oxidation of the cyclic tautomer of tryptophans to form the 5-hydroxy derivatives selectively suggests that the biological oxidation of tryptophan to 5-hydroxytryptophan might proceed *via* the cyclic tautomer on the enzyme.

Experimental

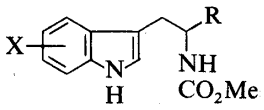
All melting points are uncorrected. The UV spectra were taken with Hitachi 323 and 340 spectrophotometers, and infrared (IR) spectra with Hitachi IR-295 and -215 spectrometers. The NMR spectra were recorded on a JEOL MH-100 spectrometer and mass spectra (MS) on a Hitachi M-60 instrument.

Oxidation of the Cyclic Tautomer (9) with Fremy's Salt: Formation of the Quinoneimine 10——A solution of DL-**9** (100 mg, 0.36 mmol) in MeOH (10 ml) was added to a solution of Fremy's salt ($ON(SO_3K)_2$, 0.4 g, 1.5 mmol) in phosphate buffer (1/15 M Na_2HPO_4 (24 ml) + 1/15 M KH_2PO_4 (16 ml), pH 7) under ice-cooling. The mixture was stirred for 5 min and then extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O and dried over Na_2SO_4. Removal of the solvent by evaporation left a residue (92 mg), which was separated by preparative thin-layer chromatography (TLC) (silica gel/CH_2Cl_2–acetone (5 : 1)) to give the quinoneimine (**10**, 53 mg, 50%) and a mixture of **8** and **9** (19 mg, 19%). The quinoneimine (**10**) decomposed during further purification. **10**: UV λ_{max} (EtOH): 266.5 nm. MS *m/z*: 292 (M+2, 15), 290 (M^+, 4), 231 (100), NMR ($CDCl_3$) δ: 2.0—3.0 (2H, m, 3-H_2), 3.56 (3H, s, CO_2Me), 3.7 (1H, m, 3a-H), 3.86 (3H, s, NCO_2Me), 4.66 (1H, m, 2-H), 6.38 (2H, d, J=2 Hz, 4-H overlapped with 8a-H), 6.4 (m, impurities), 6.61 (1H, dd, J=10 and 2 Hz, 6-H), 7.49 (1H, d, J=10 Hz, 7-H). When three mol of Fremy's salt was used in the reaction, the yield of **10** was less satisfactory.

Preparation of 5-Hydroxy-N_b-methoxycarbonyl-DL-tryptophan Methyl Ester (12) from 8——1) Oxidation with Fremy's Salt: A solution of **8** (500 mg, 1.81 mmol) in 85% H_3PO_4 (3 ml) was stirred for 2 h at room temperature and poured into 10% Na_2CO_3 (80 ml). The mixture was extracted with benzene, and the extracts were washed with H_2O, and dried. The solvent was removed by evaporation to leave a residue (crude **9**), which was dissolved in MeOH (20 ml). The methanolic solution was added to a solution of Fremy's salt (2.46 g, 9.2 mmol) in phosphate buffer (200 ml, pH 7). The mixture was stirred for 5 min and then extracted with CH_2Cl_2. The extracts were dried and concentrated by evaporation to leave a residue (crude **9**), which was dissolved in MeOH (20 ml). $NaBH_4$ (200 mg) was added to the methanolic solution at room temperature and the mixture was stirred for 50 min (formation of **11**). Acetic acid (10 ml) was added to the mixture, and the whole was stirred for 5 h. The solvent was removed by evaporation to leave a residue, which was extracted with CH_2Cl_2. The extracts were washed with H_2O and dried. Removal of the solvent by evaporation left a brown caramel (326 mg) which was chromatographed over silica gel (CH_2Cl_2–acetone (20 : 1)) to give **12** (231 mg, 44%). Recrystallizations of **12** from MeOH–benzene gave colorless prisms, mp 123.5—125 °C. *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.40; H, 5.53; N, 9.44. Spectral data for **12**: see Tables. The product (**12**) was methylated with CH_3I–K_2CO_3–acetone to give the 5-methoxy derivative (**20**), mp 86—89 °C, which was identical (mixed mp, IR) with an authentic sample prepared from commercial 5-hydroxytryptophan.

2) Oxidation with $Pb(OAc)_4$–CF_3COOH: a) Reduction with $NaBH_4$: Compound **8** (276 mg, 1 mmol) was dissolved in CF_3COOH (5 ml) at room temperature and the solution was allowed to stand for 1.5 h, then added to a solution of $Pb(OAc)_4$ (0.79 g, 1.8 mmol) in CH_2Cl_2 (20 ml) at 10 °C. After 15 min, water (50 ml) was added to the

TABLE I. Spectral Data for Substituted Tryptophans



Compd. No.	R	X	UV λ_{max}^{MeOH} nm ($\varepsilon \times 10^{-3}$)	MS *m/z* (Rel. intensity)	IR (KBr) cm^{-1}
12	CO_2Me	5-OH	220[s] (23.3), 277 (6.1) 300 (4.6)	292 (M^+, 13) 146 (100)	3460, 3345, 1740, 1685
14	H	5-OH	223.5 (21.6), 278.5 (6.1) 300.5 (4.6)	234 (M^+, 33) 146 (100)	3420, 3380, 3345, 1730
20	CO_2Me	5-MeO	220.5 (26.2), 277 (6.3) 297 (5.0), 309 (3.7)	306 (M^+, 11) 160 (100)	3420[s], 3360, 1747[s], 1739, 1710
21	CO_2Me	6-MeO	223 (34.2), 273 (4.5) 293 (5.2)	306 (M^+, 15) 160 (100)	3380, 3305, 1750, 1710

mixture and the whole was extracted with CH_2Cl_2. The extracts were washed with H_2O, sat. $NaHCO_3$ solution, and H_2O, and then dried. Removal of the solvent by evaporation gave a residue (crude **10**), which was dissolved in MeOH (20 ml). $NaBH_4$ (100 mg) was added to the stirred solution until the solution became colorless. The mixture was stirred for a further 30 min then AcOH (10 ml) was added. The reaction mixture was left overnight at room temperature and the solvent was removed by evaporation to leave a residue, which was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with sat. $NaHCO_3$ and H_2O, and dried. Removal of the solvent by evaporation gave a brown caramel (230 mg), which was chromatographed over a silica gel column (10 g, CH_2Cl_2–acetone (20 : 1)). The 5-hydroxy derivative **12** (135 mg, 46%) and recovered **8** (8.5 mg, 3%) were obtained.

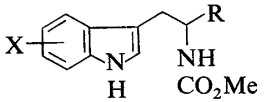
b) Reduction with Zn: A Simple Method. Compound **8** (500 mg, 1.8 mmol) was dissolved in CF_3COOH (5 ml) at room temperature and left to stand for 2.5 h, then a solution of $Pb(OAc)_4$ (1.77 g, 4 mmol) in CH_2Cl_2 (40 ml) was added at 10 °C during 10 min. The dark brown mixture was stirred for 5 min, then Zn powder (1.0 g) was added at 10 °C. The mixture became pale yellow after stirring for 15 min. Water (50 ml) was added to the mixture and the aqueous solution was extracted with CH_2Cl_2. The combined extracts were washed with H_2O and dried. Removal of the solvent by evaporation gave a brown caramel (509 mg), which was chromatographed over a silica gel column (15 g, AcOEt–hexane (1 : 2—1 : 1)) to afford **12** (317 mg, 60%) and **8** (42 mg, 8%).

5-Hydroxy-N_b-methoxycarbonyltryptamine (14a)——Compound **13a** (500 mg, 2.3 mmol) was dissolved in CF_3COOH (5 ml) and the solution was added to $Pb(OAc)_4$ (2.23 g, 5 mmol) in CH_2Cl_2 (40 ml). The mixture was reduced with Zn (1 g) and treated as above [2(b)] to give **14a** (237 mg, 44%) and **13a** (23 mg, 5%). Recrystallizations of **14a** from acetone–hexane gave colorless prisms, mp 115—117 °C. *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.49; H, 6.01; N, 11.86. Spectral data: see Tables.

Preparation of Serotonin (15) from 13b——Compound **13b** (1.00 g) was dissolved in CF_3COOH (10 ml) at room temperature. The mixture was treated with $Pb(OAc)_4$ (3.32 g, 7.5 mmol) in CH_2Cl_2 (80 ml) followed by Zn powder (2.0 g) as above to give **14b** (702 mg, 67%) as a caramel (λ_{max} (EtOH) 224, 280, 302.5, and 313 nm). The crude **14b** (700 mg, 2.25 mmol) was hydrogenated in MeOH (13 ml) in the presence of 5% Pd–C. After removal of the catalyst by filtration, the solvent was removed by evaporation to give a residue, which was dissolved in a solution of creatinine sulfate (364 mg) in H_2O (3 ml) on warming. On cooling, **15** creatinine sulfate (521 mg, 57% from **14b**), mp 216—218 °C (reported mp 215 °C[10]), was obtained. The sample was identical with authentic serotonin creatinine sulfate (mixed mp, IR).

Oxidation of the N_a-Acetyl Cyclic Tautomer (16, Stable Form) with $Pb(OAc)_4$–CF_3COOH——A solution of $Pb(OAc)_4$ (3.34 g, 7.54 mmol) in CF_3COOH (10 ml) was added to a solution of **16** (2.00 g, 6.28 mmol) in CF_3COOH (50 ml) at 1—2 °C during 30 min. The mixture was stirred for 1.5 h at the same temperature and then poured into ice-water (500 ml). The mixture was extracted with CH_2Cl_2 and the extract was washed with sat. $NaHCO_3$ and NaCl solution, then dried. Removal of the solvent by evaporation left a dark green solid (2.0 g), which was dissolved in acetone (50 ml). Methyl iodide (4.46 g, 31.4 mmol) and K_2CO_3 (4.34 g, 31.4 mmol) were added to the solution and the mixture was stirred for 3 h at room temperature. Removal of the solvent by evaporation left a residue, which was dissolved in CH_2Cl_2. Insoluble materials were filtered off and the filtrate was evaporated *in vacuo* to leave a brown caramel (1.92 g), which was chromatographed over a silica gel column (80 g, AcOEt–hexane 3 : 2–AcOEt). The 7-hydroxy derivative **19** (82 mg, 4%) was eluted first. The 6-methoxy derivative **18** (929 mg, 42%) and 5-methoxy derivative **17** (377 mg, 17%) were eluted next. Further elution gave the 6-hydroxy derivative (37 mg, 2%) and the 5-hydroxy derivative (38 mg, 2%). Recrystallization of **19** from benzene gave colorless prisms, mp 177—178.5 °C.

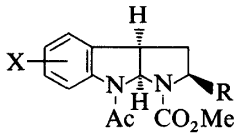
TABLE II. NMR Data for Substituted Tryptophans



Compd. No.	R	X	β-CH_2	α-CH α-CH_2	OMe	N_b-H	2-H	4-H	5-H	6-H	7-H	N_a-H	OH
12	CO_2Me	5-OH	2.7—3.2^m	4.25^m	3.48^s	7.48$^{d,b)}$	7.03$^{d,a)}$	6.79^d	—	6.58^{dd}	7.12^d	10.48$^{s,b)}$	8.55$^{bs,b)}$
DMSO-d_6					3.60^s	(J=8)	(J=2)	(J=2)		(J=9, 2)	(J=9)		
14	H	5-OH	2.6—2.9^m	3.1—3.5^m	3.54^s	7.1$^{bs,b)}$	7.00$^{d,a)}$	6.80^d	—	6.57^{dd}	7.10^d	10.42$^{s,b)}$	8.51$^{bs,b)}$
DMSO-d_6							(J=2)	(J=2)		(J=9, 2)	(J=9)		
20	CO_2Me	5-MeO	3.25^d	4.7^m	3.64^s	5.3^{bs}	6.90^d (J=2)		—	6.82^{dd}	7.20^d	8.25^s	—
$CDCl_3$			(J=6)		3.66^s		6.97^d (J=2)			(J=9, 2)	(J=9)		
					3.84^s								
21	CO_2Me	6-MeO	3.22^d	4.6^m	3.62^s	5.3$^{bs,b)}$	6.8^m	7.36^d	6.8^m	—	6.8^m	8.32$^{bs,b)}$	—
$CDCl_3$			(J=6)		3.65^s			(J=9)					
					3.79^s								

a) Became a singlet on addition of D_2O.
b) Disappeared on addition of D_2O.

TABLE III. Spectral Data for Substituted Cyclic Tautomers



Compd. No.	R	X	UV λ_{max}^{MeOH} nm ($\varepsilon \times 10^{-3}$)	MS *m/z* (Rel. intensity)	IR (KBr) cm^{-1}
17	CO_2Me	5-MeO	252.5 (14.1) 294.5 (2.9)	348 (M^+, 23), 306 (33) 247 (15), 160 (100)	1740, 1700, 1670
18	CO_2Me	6-MeO	218 (24.6), 248 (10.2) 288.5 (4.5), 294.5 (4.5)	348 (M^+, 29), 306 (61) 247 (26), 160 (100)	1769, 1745^s, 1720 1666
19	CO_2Me	7-OH	217 (23.4), 249 (6.3) 289 (2.6)	334 (M^+, 26), 292 (53) 233 (24), 146 (100)	3100—2500, 1739, 1714
27	H	5-OH	251.5 (13.8) 294.5 (3.3)	276 (M^+, 13), 234 (48) 147 (33), 146 (100)	3293, 1730, 1637 1620, 1375
28	H	6-OH	215 (25.0) 246.5 (9.8) 290 (5.0)	276 (M^+, 36), 234 (100) 147 (21), 146 (58)	3175, 1712, 1645, 1452
29	H	7-OH	215 (25.6) 248 (6.6) 285.5 (2.6)	276 (M^+, 44), 234 (100) 147 (27), 146 (69)	3450^{br}, 3200—2500 1710, 1640, 1610

Anal. Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.40; H, 5.40; N, 8.24. Recrystallization of **18** from acetone gave colorless prisms, mp 137.5—139.5 °C. *Anal.* Calcd for $C_{17}H_{20}N_2O_6$: C, 58.51; H, 5.79; N, 8.04. Found: C, 58.52; H, 5.77; N, 8.06. Recrystallization of **17** from acetone–hexane gave colorless prisms, mp 191—193 °C. *Anal.* Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.61; H, 5.83; N, 7.89. Spectral data for these compounds: see Tables.

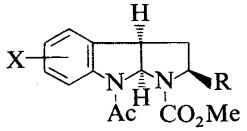
5-Methoxy-N_b-methoxycarbonyl-DL-tryptophan Methyl Ester (20)——1) From **17**: A solution of **17** (100 mg, 0.29 mmol) in 10% H_2SO_4–MeOH (3 ml) was stirred for 5 h at room temperature and then poured into water (30 ml). The mixture was extracted with CH_2Cl_2. The extracts were washed with sat. $NaHCO_3$ and sat. NaCl solutions, then dried. Removal of the solvent by evaporation gave **20** (92 mg), which was recrystallized from acetone–iso-Pr_2O–hexane to give colorless prisms, mp 84—86 °C. The sample was identical with an authentic sample prepared from 5-hydroxy-DL-tryptophan (mp, IR, NMR).

2) From 5-Hydroxy-DL-tryptophan: 5-Hydroxy-DL-tryptophan (100 mg, 0.45 mmol) was esterified with MeOH–HCl followed by treatment with methyl chloroformate as in the case of tryptophan to give crude 5-hydroxy-N_b-methoxycarbonyl-DL-tryptophan methyl ester. The crude ester carbamate was dissolved in acetone (3 ml). Methyl iodide (730 mg, 5.1 mmol) and K_2CO_3 (710 mg, 5.1 mmol) were added to the solution and the mixture was refluxed for 4 h. Removal of the solvent by evaporation gave a residue, which was dissolved in H_2O (20 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with H_2O and dried. The solvent was removed by evaporation to give a residue, which was purified by preparative TLC (silica gel, CH_2Cl_2–acetone (10 : 1)) to give **20** (75 mg, 54% from 5-hydroxytryptophan). Recrystallization from acetone–hexane gave colorless prisms, mp 87—89 °C. *Anal.* Calcd for $C_{15}H_{18}N_2O_5$: C, 58.81; H, 5.92; N, 9.15. Found: C, 58.80; H, 5.86; N, 9.04.

6-Methoxy-N_b-methoxycarbonyl-DL-tryptophan Methyl Ester (21)——Compound **18** (500 mg, 1.44 mmol) was dissolved in 10% H_2SO_4–MeOH (20 ml) and the mixture was stirred for 4 h at room temperature, then poured into H_2O (150 ml) and extracted with CH_2Cl_2. The extracts were washed with sat. $NaHCO_3$ and sat. NaCl, and dried. Removal of the solvent by evaporation gave a residue, which was purified on a silica gel column to give **21** (432 mg, 98%) as a colorless caramel. Recrystallizations from MeOH–iso-Pr_2O gave colorless needles, mp 72—74 °C. *Anal.* Calcd for $C_{15}H_{18}N_2O_5$: C, 58.81; H, 5.92; N, 9.15. Found: C, 58.75; H, 5.93; N, 9.02. Spectral data: see Tables.

Oxidation of N_a-Acetyl Cyclic Tautomer (22, Less Stable Form) with $Pb(OAc)_4$–CF_3COOH——Lead tetraacetate (0.50 g, 1.1 mmol) in CF_3COOH (2 ml) was added to a solution of **22** (280 mg, 0.88 mmol) in CF_3COOH (8 ml) at 2 °C during 5 min. The mixture was stirred for 25 min and excess $Pb(OAc)_4$ was quenched by the addition of Zn (0.5 g). Water (30 ml) was added to the mixture and the whole was extracted with CH_2Cl_2. The extracts were washed with sat. $NaHCO_3$, and H_2O, and dried. Removal of the solvent by evaporation gave a residue, which was dissolved

TABLE IV. NMR Data for Substituted Cyclic Tautomers (in $CDCl_3$)



Compd. No.	R	X	CH_3CO	3-CH_2	2-CH 2-CH_2	OMe	3a-H	8a-H	4-H	5-H	6-H	7-H
17	CO_2Me	5-MeO	2.58^s	2.2—2.8^m	4.58^{dd} (J=8, 2)	3.17^s 3.72^s 3.77^s	4.00^t (J=7)	6.20^d (J=6)	6.68^d (J=2)	—	6.76^{dd} (J=8, 2)	7.81^d (J=8)
18	CO_2Me	6-MeO	2.61^s	2.2—2.8^m	4.58^{dd} (J=8, 2)	3.18^s 3.72^s 3.79^s	3.98^t (J=6)	6.20^d (J=6)	6.98^d (J=8)	6.55^{dd} (J=8, 2)	—	7.60^d (J=2)
19	CO_2Me	7-OH[a]	2.2—2.9^m		4.51^d (J=8)	3.15^s 3.72^s	4.05^t (J=7)	6.10^d (J=6)		6.6—7.2^m		—
27 DMSO-d_6	H	5-OH[b]	2.40^s	1.9—2.3^m	2.75^m 4.0^m	3.60^s	4.0^m	6.10^d (J=6)	6.68^d (J=2)	—	6.57^{dd} (J=9, 2)	7.60^d (J=9)
28 DMSO-d_6	H	6-OH[c]	2.42^s	1.9—2.2^m	2.75^m 3.7^m	3.60^s	3.97^m	6.13^d (J=6)	7.04^d (J=9)	6.45^{dd} (J=9, 2)	—	7.36^d (J=2)
29	H	7-OH[d]	2.70^s	2.0—2.4^m	2.8^m 3.7^m	3.70^s	4.06^m	6.01^d (J=6)		6.6—7.3^m		—

a) A hydroxy signal was observed at 10.08 ppm.
b) A hydroxy signal was observed at 9.17 ppm and a signal due to methanol was observed.
c) A hydroxy signal was observed at 9.25 ppm.
d) A hydroxy signal was observed at 10.29 ppm.

in acetone (10 ml). Methyl iodide (1.42 g, 10 mmol) and K_2CO_3 (1.38 g, 10 mmol) were added to the solution and the mixture was refluxed for 4 h. The mixture was treated as in the case of the oxidation of **16**. The 7-hydroxy derivative (**25**, 16 mg, 5%), the 6-methoxy derivative (**24**, 77 mg, 25%), and the 5-methoxy derivative (**23**, 93 mg, 30%) were obtained. Recrystallization of **25** from MeOH–ether gave colorless needles, mp 183—186 °C. *Anal.* Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.49; H, 5.48; N, 8.22. IR (KBr): 3450, 3100—2500, 1767, 1725 cm^{-1}. UV λ_{max} (MeOH) nm (ε): 215 (26000), 248 (6400), 286.5 (2700). MS *m/z* (rel. intens.) 292 ($M^+ - Ac$, 100), 233 (52), 201 (29), 146 (64). NMR ($CDCl_3$) δ: 2.0—2.8 (5H, m, C_3–H_2, Ac), 3.65, 3.74 (each 3H, s, 2 × OCH_3), 4.0 (2H, m, C_2–H, C_{3a}–H), 6.08 (1H, d, J=6 Hz, C_{8a}–H), 6.6—7.3 (3H, m, 4, 5,6-Hs), 10:13 (1H, bs, OH). Recrystallization of **24** from MeOH gave colorless needles, mp 200—201 °C. *Anal.* Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.61; H, 5.75; N, 8.01. IR (KBr) cm^{-1}: 1762, 1731, 1678. UV λ_{max} (MeOH) nm (ε): 216 (9000), 245 (9900), 287 (4600), 293 (4400). MS *m/z* (rel. intens.): 348 (M^+, 44), 306 (100), 247 (41), 215 (27), 160 (80). NMR ($CDCl_3$) δ: 2.0—2.8 (2H, m, C_3–H_2), 2.53 (3H, s, Ac), 3.64, 3.74, 3.80 (each 3H, s, 3 × OMe), 4.0 (2H, m, C_2–H, C_{3a}–H), 6.13 (1H, d, J=5 Hz, C_{8a}–H), 6.64 (1H, dd, J=8, 2 Hz, C_5–H), 7.06 (1H, d, J=8 Hz, C_4–H), 7.60 (1H, d, J=2 Hz, C_7–H). Recrystallization of **23** from MeOH gave colorless needles, mp 202—204 °C. *Anal.* Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.85; H, 5.77; N, 8.03. IR (KBr) cm^{-1}: 1768, 1734, 1676. UV λ_{max} (MeOH) nm (ε): 250.5 (14400), 292 (3200) 299^s(2800). MS *m/z* (rel. intens.): 348 (M^+, 41), 306 (100), 247 (38), 215 (16), 160 (46). NMR ($CDCl_3$) δ: 2.0—2.8 (2H, m, C_3–H_2), 2.50 (3H, s, Ac), 3.64, 3.73, 3.78 (each 3H, s, 3 × OMe), 4.0 (2H, m, C_2–H, C_{3a}–H), 6.13 (1H, d, J=6 Hz, C_{8a}–H), 6.6—6.9 (2H, m, C_4–H, C_6–H), 7.83 (1H, d, J=8 Hz, C_7–H).

Oxidation of 8-Acetyl-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (26) with $Pb(OAc)_4$–CF_3COOH——Lead tetraacetate (530 mg, 1.2 mmol) in CF_3COOH (2 ml) was added to a solution of **26** (260 mg, 1 mmol) in CF_3COOH (5 ml) at 2 °C during 7 min. The mixture was stirred for 1 h, and then water (30 ml) was added. The reaction mixture was extracted with CH_2Cl_2 and the extracts were washed with $NaHCO_3$, and H_2O, then dried. Removal of the solvent by evaporation gave a residue which was chromatographed over a silica gel column (20 g, AcOEt–hexane (1 : 1—2 : 1)). The 7-hydroxy derivative (**29**, 15 mg, 5%), the starting meterial (**26**, 11 mg, 6%), the 6-hydroxy derivative (**28**, 61 mg, 22%), and the 5-hydroxy derivative **27**, 83 mg, 30%) were obtained. Recrystallization of **29** from MeOH–ether gave colorless prisms, mp 133.5—135 °C. *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.98; H, 5.88; N, 10.08. Recrystallization of **28** from MeOH gave colorless prisms, mp 215—217 °C. *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.66; H, 5.85; N, 10.01. Recrystallization of **27** from MeOH gave colorless prisms, mp 220—222 °C. *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.89; H, 5.82; N, 10.07. Spectral data for **27**—**29** are shown in the Tables.

Oxidation of *N*-Methylacetanilide (30) with $Pb(OAc)_4$–CF_3COOH——Lead tetraacetate (4.46 g, 10.1 mmol) in CF_3COOH (10 ml) was added to a solution of *N*-methylacetanilide (1.00 g, 6.7 mmol) in CF_3COOH (25 ml) under ice cooling during 30 min. The mixture was stirred for 1 h under ice cooling and for 3.6 h at room temperature. The solvent was removed by evaporation to leave a residue, which was dissolved in CH_2Cl_2 (200 ml). The mixture was washed with H_2O, 5% NaOH and H_2O. The CH_2Cl_2 solution was dried and concentrated by evaporation to give the starting material (254 mg, 25%).

The NaOH solution was acidified with 5% HCl 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 purified by silica gel column chromatography and preparative TLC. The *o*-hydroxy derivative **31** (214 mg, 19%) and the *p*-hydroxy derivative **32** (164 mg, 14%) were isolated. *o*-Hydroxy-*N*-methylacetanilide (**31**), mp 153—154.5 °C (dec.) (reported[11] mp 150 °C). UV λ_{max} (EtOH) nm (ε): 277.5 (3000), 282^s. NMR (DMSO-d_6) δ: 1.67 (3H, s, Ac), 3.02 (3H, s, NMe), 6.70—7.35 (4H, m, arom H), 9.73 (br s, OH). *p*-Hydroxy derivative (**32**), mp 239.5—243.5 °C (dec.) (reported[12] mp 240—241 °C). UV λ_{max} (EtOH) nm (ε): 230 (11000), 280 (1700), 285^s. NMR (DMSO-d_6) δ: 1.72 (3H, s, Ac), 3.20 (3H, s, NMe), 6.78 (2H, d, J=5 Hz, arom H), 7.10 (2H, d, J=5 Hz, arom H), 9.56 (1H, br s, OH).

Both compounds were methylated to give their methoxy derivatives, *N*-methyl-*o*-acetaniside[13] and *N*-methyl-*p*-aniside,[14] which were identical with authentic samples prepared from *o*- and *p*-anisidine, respectively (mp, mixed mp, IR).

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