Formation and Reactions of the Cyclic Tautomers of Tryptophans and Tryptamines. VII.¹ Hydroxylation of Tryptophans and Tryptamines²

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(Received October 19, 1983)

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-CF₃COOH 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 N₅-acetyl-cyclic tautomers (16 and 22) with Pb(OAc)₄-CF₃COOH 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 monoxygenase. 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 papers¹,⁷ we have reported a simple preparation of the cyclic tautomer (5) of N₅-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 N₅-methoxy carbonyl-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, λₘₐₓ (EtOH) 266.5 nm, which is similar to that of
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 NaBH₄ 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) \( N_5 \)-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 \( N_6 \)-methoxycarbonyl-(13a) and \( N_6 \)-benzyloxycarbonyl-tryptamine (13b) to give the 5-hydroxytryptamine derivatives (14a and 14b) in 44 and 67% yields, respectively. The \( N_6 \)-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 \( N_5 \)-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 \( N_5 \)-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\(_3\)I-K\(_2\)CO\(_3\)-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% H₂SO₄—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-
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 acetonilides 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 Freny'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 Freny's salt (ON(SO_{3}K), 0.4 g, 1.5 mmol) in phosphate buffer (1/15 M Na_{2}HPO_{4} (24 ml)+1/15 M KH_{2}PO_{4} (16 ml), pH 7) under ice-cooling. The mixture was stirred for 5 min and then extracted with CH_{2}Cl_{2}. The CH_{2}Cl_{2} solution was washed with H_{2}O and dried over Na_{2}SO_{4}. Removal of the solvent by evaporation left a residue (92 mg), which was separated by preparative thin-layer chromatography (TLC) (silica gel/CH_{2}Cl_{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), 3.56 (3H, s, CO_{2}Me), 3.7 (1H, m, 3a-H), 3.86 (3H, s, NCO_{2}Me), 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 Freny's salt was used in the reaction, the yield of 10 was less satisfactory.

Preparation of 5-Hydroxy-\textit{N}_{\text{O}}-methoxycarbonyl-DL-tryptophan Methyl Ester (12) from 8—1 Oxidation with Freny's Salt: A solution of 8 (500 mg, 1.81 mmol) in 85% H_{3}PO_{4} (3 ml) was stirred for 2 h at room temperature and poured into 10% Na_{2}CO_{3} (80 ml). The mixture was extracted with benzene, and the extracts were washed with H_{2}O, 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 Freny'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_{2}Cl_{2}. The extracts were dried by 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_{2}Cl_{2}. The extracts were washed with H_{2}O and dried. Removal of the solvent by evaporation left a brown caramel (326 mg) which was chromatographed over silica gel (CH_{2}Cl_{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_{16}H_{16}N_{2}O_{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_{3}I−K_{2}CO_{3}−acetone to give the 5-methoxy derivative (20), mp 86−89 °C, which was identical (mixed mp, 1R) with an authentic sample prepared from commercial 5-hydroxytryptophan.

2) Oxidation with Pb(OAc)_{4}−CF_{3}COOH: a) Reduction with NaBH_{4}: Compound 8 (276 mg, 1 mmol) was dissolved in CF_{3}COOH (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_{2}Cl_{2} (20 ml) at 10°C. After 15 min, water (50 ml) was added to the
mixture and the whole was extracted with CH₂Cl₂. The extracts were washed with H₂O, sat. NaHCO₃ solution, and H₂O, and then dried. Removal of the solvent by evaporation gave a residue (crude 10), which was dissolved in MeOH (20 ml). NaBH₄ (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 CH₂Cl₂. The CH₂Cl₂ solution was washed with sat. NaHCO₃ and H₂O, and dried. Removal of the solvent by evaporation gave a brown caramel (230 mg), which was chromatographed over a silica gel column (10 g, CH₂Cl₂-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 CF₃COOH (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 CH₂Cl₂ (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 CH₂Cl₂. The combined extracts were washed with H₂O 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-N⁶-methoxy carbonyl tryptamine (14a)— Compound 13a (500 mg, 2.3 mmol) was dissolved in CF₃COOH (5 ml) and the solution was added to Pb(OAc)₄ (2.23 g, 5 mmol) in CH₂Cl₂ (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 C₁₂H₁₄N₂O₃: 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 CF₃COOH (10 ml) at room temperature. The mixture was treated with Pb(OAc)₄ (3.32 g, 7.5 mmol) in CH₂Cl₂ (80 ml) followed by Zn powder (2.0 g) as above to give 14b (702 mg, 67%) as a caramel (λmax (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 H₂O (3 ml) on warming. On cooling, 15 creatinine sulfate (521 mg, 57% from 14b), mp 216–218 °C (reported mp 215 °C[49]), was obtained. The sample was identical with authentic serotonin creatinine sulfate (mixed mp, IR).

Oxidation of the N₂-Acetyl Cyclic Tautomer (16, Stable Form) with Pb(OAc)₄–CF₃COOH—A solution of Pb(OAc)₄ (3.34 g, 7.54 mmol) in CF₃COOH (10 ml) was added to a solution of 16 (2.00 g, 6.28 mmol) in CF₃COOH (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 CH₂Cl₂ and the extract was washed with sat. NaHCO₃ 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 K₂CO₃ (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 CH₂Cl₂. 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>
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<th>Compd. No.</th>
<th>R</th>
<th>X</th>
<th>$\beta$-CH$_2$</th>
<th>$\alpha$-CH$_2$</th>
<th>OMe</th>
<th>$N_\alpha$-H</th>
<th>2-H</th>
<th>4-H</th>
<th>5-H</th>
<th>6-H</th>
<th>7-H</th>
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<td>5-OH</td>
<td>2.7—3.2$^m$</td>
<td>4.25$^m$</td>
<td>3.48$^a$</td>
<td>7.48$^{d,b}$</td>
<td>7.03$^{d,a}$</td>
<td>6.79$^d$</td>
<td>—</td>
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<td>7.12$^d$</td>
<td>10.48$^{b,b}$</td>
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<td>(J=2)</td>
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<td>14</td>
<td>H</td>
<td>5-OH</td>
<td>2.6—2.9$^m$</td>
<td>3.1—3.5$^m$</td>
<td>3.54$^a$</td>
<td>7.1$^{b,n,b}$</td>
<td>7.00$^{d,a}$</td>
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<td>10.42$^{b,b}$</td>
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$a$) Became a singlet on addition of D$_2$O.

$b$) Disappeared on addition of D$_2$O.
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<th>Compd. No.</th>
<th>R</th>
<th>X</th>
<th>UV λ&lt;sub&gt;max&lt;/sub&gt; MeOH (nm) (ε × 10&lt;sup&gt;-3&lt;/sup&gt;)</th>
<th>MS m/z (Rel. intensity)</th>
<th>IR (KBr) cm&lt;sup&gt;-1&lt;/sup&gt;</th>
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<tr>
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<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>5-MeO</td>
<td>252.5 (14.1) 294.5 (2.9)</td>
<td>348 (M&lt;sup&gt;+&lt;/sup&gt;, 23), 306 (33)</td>
<td>1740, 1700, 1670</td>
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<td>18</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>6-MeO</td>
<td>218 (24.6), 248 (10.2), 288.5 (4.5), 294.5 (4.5)</td>
<td>348 (M&lt;sup&gt;+&lt;/sup&gt;, 29), 306 (61)</td>
<td>1769, 1745, 1720</td>
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<td>19</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>7-OH</td>
<td>217 (23.4), 249 (6.3) 289 (2.6)</td>
<td>334 (M&lt;sup&gt;+&lt;/sup&gt;, 26), 292 (53)</td>
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<td>27</td>
<td>H</td>
<td>5-OH</td>
<td>251.5 (13.8) 294.5 (3.3)</td>
<td>276 (M&lt;sup&gt;+&lt;/sup&gt;, 13), 234 (48)</td>
<td>3293, 1730, 1637</td>
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<td>28</td>
<td>H</td>
<td>6-OH</td>
<td>215 (25.0) 246.5 (9.8) 290 (5.0)</td>
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<td>29</td>
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<td>3450&lt;sup&gt;nr&lt;/sup&gt;, 3200—2500</td>
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*Anal.* Caled for C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>O<sub>6</sub>: 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.* Caled for C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>O<sub>6</sub>: 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.* Caled for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>: 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<sub>2</sub>-methoxy carbonyl-dl-tryptophan Methyl Ester (20) (1)*** From 17: A solution of 17 (100 mg, 0.29 mmol) in 10% H<sub>2</sub>SO<sub>4</sub>—MeOH (3 ml) was stirred for 5 h at room temperature and then poured into water (30 ml). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were washed with sat. NaHCO<sub>3</sub> and sat. NaCl solutions, then dried. Removal of the solvent by evaporation gave 20 (92 mg), which was recrystallized from acetone–isopropyl ether–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 chlorofomate as in the case of tryptophan to give crude 5-hydroxy-N<sub>2</sub>-methoxy carbonyl-dl-tryptophan methyl ester. The crude ester carboxamide was dissolved in acetone (3 ml). Methyl iodide (730 mg, 5.1 mmol) and K<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>O (20 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> extract was washed with H<sub>2</sub>O and dried. The solvent was removed by evaporation to give a residue, which was purified by preparative TLC (silica gel, CH<sub>2</sub>Cl<sub>2</sub>–acetone 10:1) to give 20 (75 mg, 54% from 5-hydroxytryptophan). Recrystallization from acetone–hexane gave colorless prisms, mp 87—89°C. *Anal.* Caled for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>: C, 58.80; H, 5.86; N, 9.04.

**6-Methoxy-N<sub>2</sub>-methoxy carbonyl-dl-tryptophan Methyl Ester (21)*** Compound 18 (500 mg, 1.44 mmol) was dissolved in 10% H<sub>2</sub>SO<sub>4</sub>—MeOH (20 ml) and the mixture was stirred for 4 h at room temperature, then poured into H<sub>2</sub>O (150 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were washed with sat. NaHCO<sub>3</sub> 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–isopropyl ether gave colorless needles, mp 72—74°C. *Anal.* Caled for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>: 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<sub>2</sub>-Acetyl Cyclic Taurom (22, Less Stable Form) with Pb(OAc)<sub>4</sub>—CF<sub>3</sub>COOH*** Lead tetraacetate (0.50 g, 1.1 mmol) in CF<sub>3</sub>COOH (2 ml) was added to a solution of 22 (280 mg, 0.88 mmol) in CF<sub>3</sub>COOH (8 ml) at 2°C during 5 min. The mixture was stirred for 25 min and excess Pb(OAc)<sub>4</sub> 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<sub>2</sub>Cl<sub>2</sub>. The extracts were washed with sat. NaHCO<sub>3</sub>, and H<sub>2</sub>O, and dried. Removal of the solvent by evaporation gave a residue, which was dissolved
### Table IV. NMR Data for Substituted Cyclic Tautomers (in CDCl<sub>3</sub>)

![Chemical Structure](image)

<table>
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<th>Compd. No.</th>
<th>R</th>
<th>X</th>
<th>CH₃CO</th>
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<sup>a</sup> A hydroxy signal was observed at 10.08 ppm.
<sup>b</sup> A hydroxy signal was observed at 9.17 ppm and a signal due to methanol was observed.
<sup>c</sup> A hydroxy signal was observed at 9.25 ppm.
<sup>d</sup> A hydroxy signal was observed at 10.29 ppm.
in acetonitrile (10 ml). Methyl iodide (1.42 g, 10 mmol) and K₂CO₃ (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. Caled for C₉H₁₈N₂O₇: 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 (48000), 268 (2700). MS m/z (rel. intens.): 292 (M⁺—Ac, 100), 233 (52), 201 (29), 146 (64). NMR (CDCl₃): δ: 2.0—2.8 (5H, m, C₂—H₂, Ac), 3.65, 3.74 (each 3H, s, 2 × OCH₃), 4.0 (2H, m, C₂—H, C₃—H), 6.08 (1H, d, J = 6 Hz, C₃—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. Caled for C₁₃H₂₀N₂O₇: 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⁺, 41), 306 (100), 247 (41), 215 (27), 160 (80). NMR (CDCl₃): δ: 2.0—2.8 (2H, m, C₂—H₂), 2.53 (3H, s, Ac), 3.64, 3.74, 3.80 (each 3H, s, 3 × OMe), 4.0 (2H, m, C₂—H, C₃—H), 6.13 (1H, d, J = 5 Hz, C₃—H), 6.64 (1H, dd, J = 8, 2 Hz, C₅—H), 7.06 (1H, d, J = 8 Hz, C₆—H), 7.60 (1H, d, J = 2 Hz, C₇—H). Recrystallization of 23 from MeOH gave colorless needles, mp 202—204°C. Anal. Caled for C₁₃H₂₀N₂O₇: 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 (2800). MS m/z (rel. intens.): 348 (M⁺, 41), 306 (100), 247 (38), 215 (16), 160 (46). NMR (CDCl₃): δ: 2.0—2.8 (2H, m, C₂—H₂), 2.50 (3H, s, Ac), 3.64, 3.73, 3.78 (each 3H, s, 3 × OMe), 4.0 (2H, m, C₂—H, C₃—H), 6.13 (1H, d, J = 6 Hz, C₃—H), 6.6—6.9 (2H, m, C₅—H, C₆—H), 7.83 (1H, d, J = 8 Hz, C₇—H). Oxidation of 8-Acetyl-1-methoxy carbonyl-1,2,3,2a,8a,8-hexahydropyrrolo[2,3-b]indole (26) with Ph(OAc)₂—CF₃COOH—CF₃COOH—Lead tetraacetate (530 mg, 1.2 mmol) in CF₃COOH (2 ml) was added to a solution of 26 (260 mg, 1 mmol) in CF₃COOH (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 CH₂Cl₂ and the extracts were washed with NaHCO₃ and H₂O, 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 (25, 15 mg, 5%), the starting material (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. Caled for C₁₉H₂₄N₂O₇: 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. Caled for C₁₉H₂₄N₂O₇: 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. Caled for C₁₉H₂₄N₂O₇: C, 60.86; H, 5.84; N, 10.07. Spectral data for 27—29 are shown in the Tables. Oxidation of N-Methylacetanilide (30) with Ph(OAc)₂—CF₃COOH—Lead tetraacetate (4.46 g, 10.1 mmol) in CF₃COOH (10 ml) was added to a solution of N-methylacetanilide (1.00 g, 6.7 mmol) in CF₃COOH (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 CH₂Cl₂ (200 ml). The mixture was washed with H₂O, 5% NaOH and H₂O. The CH₂Cl₂ 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 CH₂Cl₂. The CH₂Cl₂ 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 a-hydroxy derivative (31) (214 mg, 19%) and the p-hydroxy derivative (32) (164 mg, 14%) were isolated. a-Hydroxy-N-methylacetanilide (31), mp 153—154.5°C (dec.) (reported13) mp 150°C. UV λ_max (EtOH) nm (ε): 277.5 (3000), 282. NMR (DMSO-d₆): 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—245.5°C (dec.) (reported12) mp 240—241°C. UV λ_max (EtOH) nm (ε): 230 (11000), 280 (17000), 285. NMR (DMSO-d₆): 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-acetaniside13 and N-methyl-p-aniside,14 which were identical with authentic samples prepared from a- and p-anisidine, respectively (mp, mixed mp, IR).

Acknowledgements We are grateful to Mrs. H. Seki, Miss S. Nakajima, and Mr. T. Kuramochi in the Analytical Center of our University for measurements of spectral data (MS and NMR) and microanalytical data. Financial support from the Ministry of Education, Science and Culture is gratefully acknowledged.

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