CYCLIC TAUTOMERS OF TRYPTOPHANS AND TRYPTAMINES. III.[1] SELECTIVE 5-HYDROXYLATION OF TRYPTOPHAN AND TRYPTAMINE DERIVATIVES.

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Abstract — The oxidation of the cyclic tautomer (5) of tryptophan derivatives with Fremy's salt or lead tetraacetate gave p-quinoneimine derivative (6) selectively which was readily converted to 5-hydroxytryptophan derivatives on the reduction and the ring-opening.

5-Hydroxytryptophan and its derivatives have been prepared usually from a protected 5-hydroxyindole by stepwise method, as the direct and practical hydroxylation of tryptophan and indole derivatives has not been known. On the other hand, the 5-hydroxylation of indoline derivatives with Fremy's salt[2,3] and the methoxylation of 5-chloroindoline derivatives via the chromium complex have been reported[4].

In our previous paper[1] we have reported that hydroxylation of N_a-acetylated cyclic tautomer (1) of tryptophan derivative with lead tetraacetate in trifluoroacetic acid gave 6-hydroxy derivative (2) as the major product and 5-hydroxy derivative (2) as the minor product. We now report a selective 5-hydroxylation of the cyclic tautomer and simple preparation of 5-hydroxy-tryptophans from tryptophan derivatives.

When the cyclic tautomer (5) was treated with 4 moles equivalents of Fremy's salt, $ON(SO_3K)_2$, in phosphate buffer (pH 7.0) and methanol at 0°, a quinoneimine derivative (6) was obtained in 50% yield which was not crystallized due to partial decomposition during the purification. However, the structure of 6 was supported by the following spectral data. The UV spectrum in ethanol showed an intense maximum at 266.5 nm which is corresponding to the known

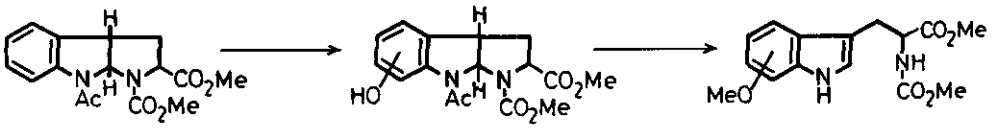
quinoneimine chromophor[2]. The nmr spectrum in deuterochloroform showed a fine doublet (J=2 Hz) at 6.38 ppm for H_a proton, a quartet (J=10 and 2 Hz) at 6.61 ppm for H_b proton and a doublet (J=10 Hz) at 7.49 ppm for H_c proton. Reduction of the quinoneimine (6) with sodium borohydride in methanol gave the 5-hydroxy derivative (7) which was readily converted to 5-hydroxytryptophan derivative (8), mp 123.5-125°, in acetic acid. The structure of 8 was confirmed by methylation to the 5-methoxy derivative (3) which was identical with an authentic sample[1]. 5-Hydroxytryptophan derivative (8) was obtained in 44% yield from N_b-methoxycarbonyl-DL-tryptophan methyl ester by a series of reactions; the cyclization, oxidation, reduction, and ring opening, without purification of the intermediates.

Furthermore, more simplified procedure was established as the oxidation of the cyclic tautomer (5) with two equivalents of lead tetraacetate in trifluoroacetic acid was also shown to give the corresponding quinoneimine (6). N_b-Methoxycarbonyl-DL-tryptophan methyl ester (4) was dissolved in trifluoroacetic acid at room temperature and the solution was added to the solution of two moles of lead tetraacetate in methylene chloride at 10°, and then zinc powder was added to the solution at the room temperature. Usual work-up gave N_b-methoxycarbonyl-5-hydroxy-DL-tryptophan methyl ester (8) in 60% yield from the ester carbamate (4). *The ester carbamate (4) was converted to the cyclic* tautomer (5) when dissolved in trifluoroacetic acid. The quinoneimine (6) obtained by the oxidation with lead tetrakistrifluoroacetate was reduced to the 5-hydroxy cyclic tautomer (7) with zinc, which was converted to 5-hydroxytryptophan derivative (8) with aqueous acid during work-up.

By the similar procedure, N_b-methoxycarbonyl-5-hydroxytryptamine (10a), mp 115-117°, was obtained in 44% yield. 10a: λ_{max}^{EtOH} nm(ε); 223.5(21600), 278.5(6090), 300.5(4600). Mass m/e; 234(M^+, 33), 159(26), 146(100). Nmr (DMSO-d_6) δ; 6.57(dd, J=9 and 2 Hz, 6-H), 6.80(d, J=2 Hz, 4-H), 7.00(d, J=2 Hz, 2-H), 7.10(d, J=9 Hz, 7-H), 7.1(br. s, amide NH), 8.51(br. s, OH), 10.42(br. s, indole NH).

N_b-Benzyloxycarbonyltryptamine (9b) similarly gave 5-hydroxy derivative (10b) in 67% yield which was further converted to 5-hydroxytryptamine creatinine sulfate in 57% yield by subsequent hydrogenolysis.

This oxidation procedure provides a new selective hydroxylation at 5-position of tryptophan and tryptamine derivatives, and the other hydroxylated



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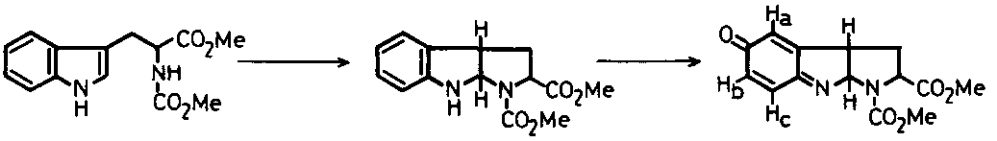

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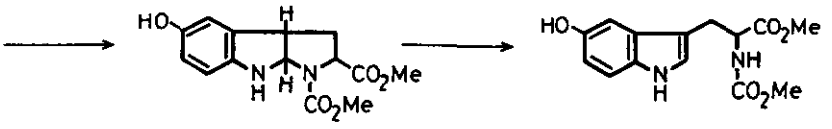

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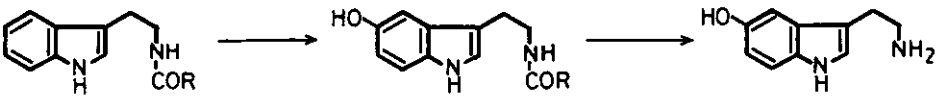

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a : R = OMe
b : R = OCH_2Ph

products were not isolated.

Further application of this procedure is now in progress.

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REFERENCES

1. T. Hino and M. Taniguchi, J. Am. Chem. Soc., 100, 5564 (1978); T. Hino M. Taniguchi, A. Gonsho and M. Nakagawa, Heterocycles, 12, 1027 (1979).

2. H.-J. Teuber and G. Staiger, Chem. Ber., 89, 489 (1956); H.-J. Teuber and O. Glosauer, ibid., 98, 2939 (1965).

3. Y. Mori and M. Sato, Japan 74 32,532 (C.A. 82, 98391u (1975)).

4. T. Oishi, M. Fukui and Y. Endo, Heterocycles, 7, 947 (1977); K. Saito and Y. Kikugawa, J. Heterocyclic Chem., 16, 1325 (1979).

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