CYCLIC TAUTOMERS OF TRYPTOPHANS AND TRYPTAMINES II[1]. SYNTHESIS OF 5-NITRO-, 5-METHOXY-, AND 6-METHOXY-TRYPTOPHAN DERIVATIVES.

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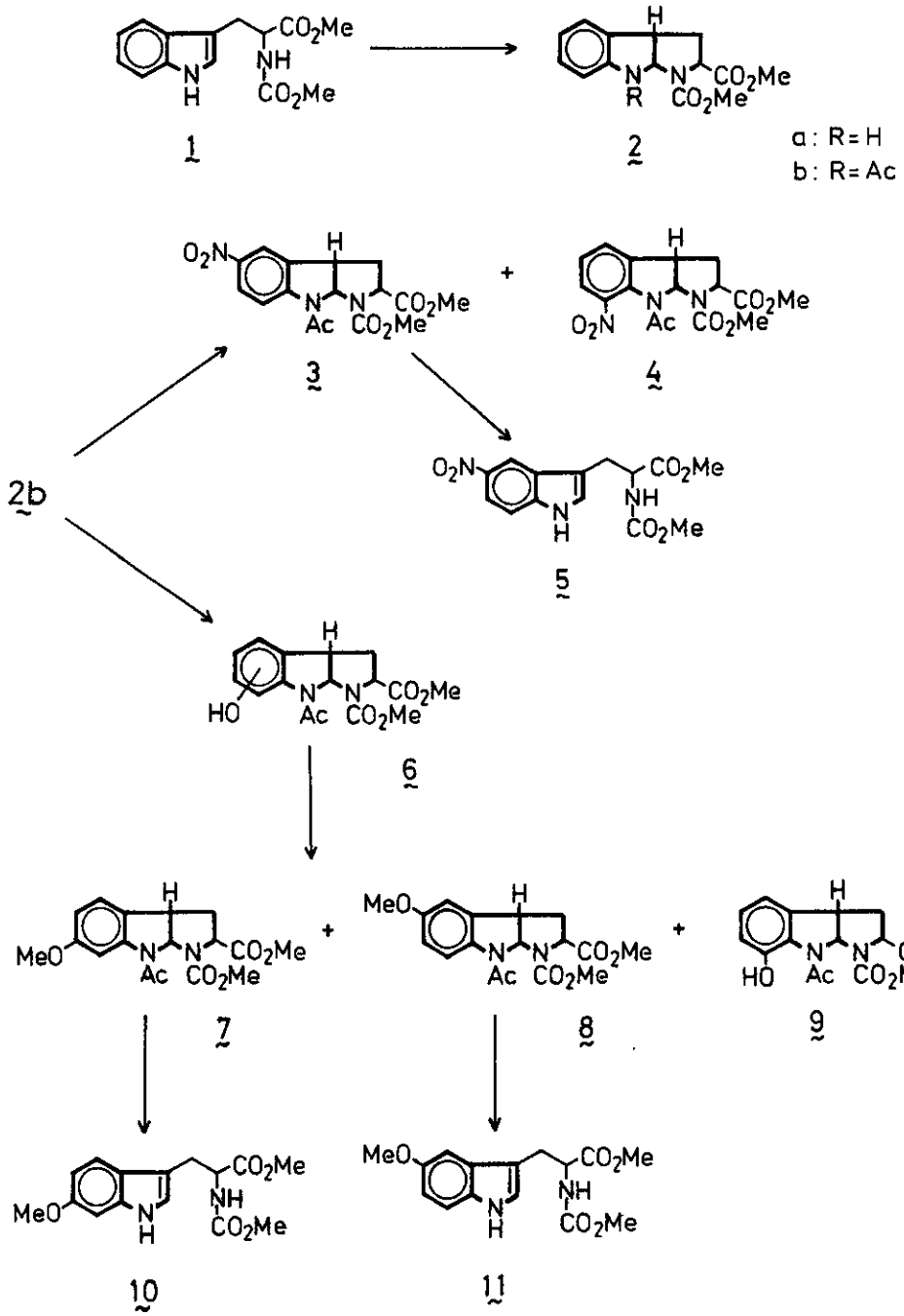
Abstract —— Nitration of the cyclic tautomer (2b) of N_b-methoxycarbonyl-DL-tryptophan methyl ester with fuming nitric acid followed by treatment with sulfuric acid in methanol gave 5-nitro-N_b-methoxycarbonyl-DL-tryptophan methyl ester (5) in excellent yield. The reaction of 2b with lead tetraacetate in trifluoroacetic acid followed by methylation provided 6-methoxy- (major) and 5-methoxy- (minor) derivatives (7 and 8) which were readily converted to 6- and 5-methoxytryptophan derivatives (10 and 11).

In our previous paper we have described a convenient synthesis of cyclic tautomers (2a) of tryptophans and the chlorination of Na-acetylated cyclic tautomer (2b) was found to give 5-chloropyrroloindole derivative in excellent yield which was readily converted to 5-chloro-N_b-methoxycarbonyltryptophan methyl ester.

We report here a facile synthesis of 5-nitro-, 6-methoxy-, and 5-methoxy-N_b-methoxycarbonyltryptophan methyl esters from the cyclic tautomer (2b). The direct nitration of tryptophan has been reported to give 6-nitro derivative[2], whereas 5-nitrotryptophan has been prepared by stepwise method from 5-nitroindole[3]. Likewise, 5-methoxy- and 6-methoxy-tryptophans has been prepared from methoxyindoles[4]. No simple method to prepare methoxytryptophans has been known. Furthermore, direct hydroxylation of indole derivatives has not been successful.

The nitration of Na-acetylated cyclic tautomer (2b) prepared from N_b-methoxycarbonyl-DL-tryptophan methyl ester (1) by fuming nitric acid at -12 - -5° gave 5-nitro derivative (3), mp 152-153.5°, in 83% yield accompanied by 7-nitro derivative (4), mp 214-215°[5], in 2% yield. Treatment of 3 with 10% sulfuric acid in methanol provided 5-nitrotryptophan derivative (5), mp 174-175°[5], in 93% yield. A series of reactions from 1 without purification of the intermediates gave 5-nitrotryptophan derivative (5) in 66% yield besides a trace amount of 7-isomer. Position of 5-nitro group was confirmed by comparison of the nmr spectrum of 5


1
2
a: R=H
b: R=Ac
3
4
5
2b
6
7
8
9
10
11

with that of 6-nitro-N_b-methoxycarbonyltryptophan methyl ester prepared from 6-nitrotryptophan[2].

Lead tetratrifluoroacetate was known to trifluoroacetoxylate less reactive aromatics such as benzene or chlorobenzene which was innert towards oxidation with lead tetraacetate, although trifluoroacetoxylation of acetanilide derivatives by this reagent has not been described[6]. The reaction of 2b with lead tetraacetate in trifluoroacetic acid at 1-2° for 2 hr gave a mixture of hydroxylated products (6)[7] which were methylated with methyl iodide in acetone in the presence of potassium carbonate to give 6-methoxy derivative (7, 42%), mp 137.5-139.5°, 5-methoxy derivative (8, 17%), mp 191-193°, and 7-hydroxy derivative(9, 4%), mp 177-178.5°[5]. 7: λ_{max}^{MeOH} nm(ε); 218(24600), 248(10200), 288.5(4530), 294.5(4460). Mass m/e; 348(29, M^+), 306(61, M-CH_2CO), 247(26), 160(100). Nmr (in $CDCl_3$) δ: 2.2-2.8(m, 3-CH_2), 2.6(s, Ac), 3.18(s, OMe), 3.72(s, OMe), 3.79(s, OMe), 3.98(t, J=6Hz, 3a-H), 4.58(dd, J=2 and 8 Hz, 2-H), 6.20(d, J=6Hz, 8a-H), 6.55(dd, J=2 and 8Hz, 5-H), 6.98(d, J=8Hz, 4-H),7.60(d, J=2 Hz, 7-H). 8: λ_{max}^{MeOH}nm(ε) ; 252.5(14100), 294.5(2880). Mass m/e ; 348(23, M^+), 306(33), 247(15), 160(100). Nmr (in $CDCl_3$) δ: 2.2-2.8(m, 3-CH_2), 2.56(s, Ac), 3.17(s, OMe), 3.72(s, OMe), 3.77(s, OMe), 4.00(t, J=7 Hz, 3a-H), 4.58(dd, J=2 and 8 Hz, 2-H), 6.20(d, J=6 Hz, 8a-H), 6.7(m, 4-H and 6-H), 7.81(d, J= 8 Hz, 7-H). On treatment with 10% sulfuric acid in methanol 8 gave 5-methoxy-N_b-methoxycarbonyl-DL-tryptophan methyl ester (11), mp 87-89°, which was identical with a standard sample prepared from 5-hydroxy-DL-tryptophan. Similarly 7 gave 6-methoxytryptophan derivative (10, oil) in good yield.

In contrast with chlorination and nitration the reaction of 2b with lead tetraacetate afforded not only the 6-derivative (major), but also the 5-derivative (minor). Although the high regiospecific hydroxylation has not occurred in the above reactions, this method may serve as a new and simple preparation of 6-hydroxytryptophans as well as 5-derivatives.

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7. 6-Hydroxy derivative (6, 6-OH), mp 250-255° (decomp), was isolated from the mixture.

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