INTRODUCTION OF A HYDROXY GROUP ONTO 5- AND 6-POSITION OF INDOLE NUCLEUS BY FRIEDEL-CRAFTS ACYLATION AND SUBSEQUENT BAEYER-VILLIGER OXIDATION

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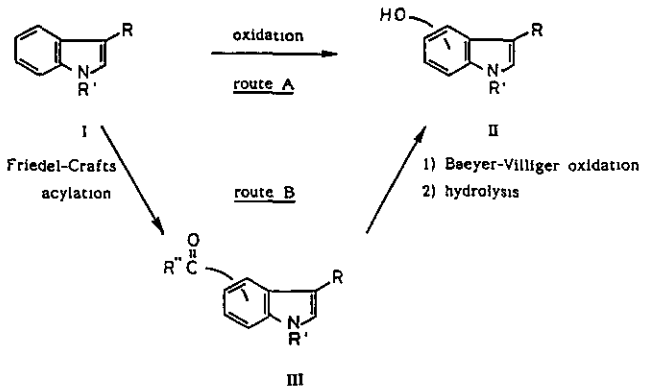
Abstract —— A hydroxy group was efficiently introduced onto 5- and 6-position of methyl 1-methylindole-3-carboxylate 1 and methyl indole-3-carboxylate 11.

Although there are many indole alkaloids containing oxygen function(s) at the benzene part of the indole nucleus, no efficient method for introduction of such function(s) has been reported except a few limited cases.[1,2] Oxidation of indole derivatives with peracid[3], singlet oxygen[4], $MoO_5 \cdot HMPA$,[5] etc. has always occurred at the pyrrole part. Much higher nucleophilicity of the pyrrole ring than that of the benzene ring would prevent the direct introduction of oxygen function(s) on the benzene part [route A]. Recently, we have found novel methods[6-9] for introduction of substituents onto the benzene part (4- and 7-position) of the indole derivatives having a strongly electron-drawing group at 3-position (for example, I, R=CO_2CH_3). Now, we report an efficient method to introduce an oxygen function



onto 5- and 6-position of the indole nucleus of III derived from I by Baeyer-Villiger oxidation followed by hydrolysis (route B).

We chose methyl 1-methylindole-3-carboxylate 1 as a starting material because whose pyrrole part was stabilized by conjugation with ester carbonyl group. 5- And 6-acetylindole derivatives,[9] 2 and 3, were obtained in good yield by Friedel-Crafts acylation of 1. To examine the effectiveness of Baeyer-Villiger oxidation, 3 was treated with m-chloroperbenzoic acid (m-CPBA) in chloroform at 60 °C for 1.5 h in the presence of radical inhibitor[10] (Sumilizer WXR). After chromatography, a desired product 4[11] was obtained but the yield was extremely low (-3%). In this reaction condition, the oxidized products at the pyrrole part were also produced.

On the purpose of activation of the acyl carbonyl toward peracid, we chose chloroacetyl derivatives, 5 and 6, in which the carbonyl group connected to 5,6-position would be much more reactive than those of 2 and 3.

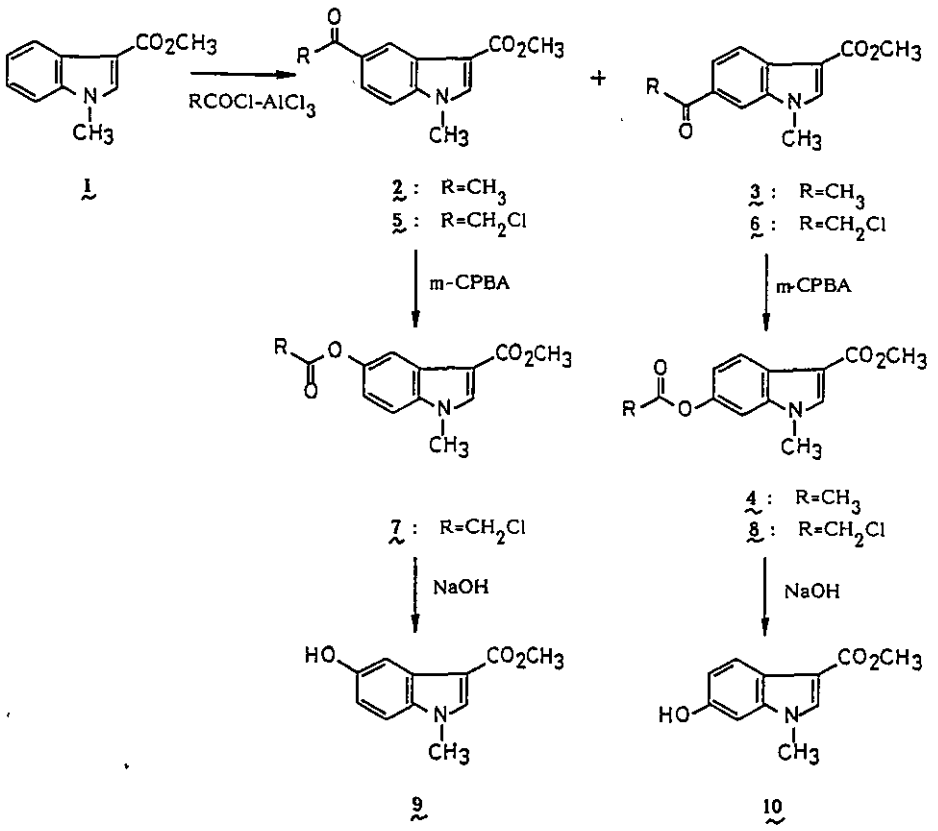
The chloroacetylindoles, 5 and 6, were easily obtained by Friedel-Crafts acylation of 1 with chloroacetyl chloride in methylene chloride in the presence of $AlCl_3$. Compound 5 and 6 could be separeted on silica gel TLC but the mixture was employed for the next Baeyer-Villiger oxidation without separation.

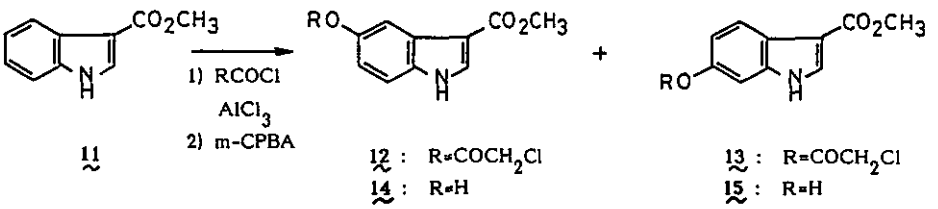
The mixture was treated with 1.5 eq. m-CPBA in chloroform in the presence of Na_2HPO_4 at 20 °C for 8 h to afford a mixture of 5- and 6-chloroacetoxy derivatives, 7 (66%; mp 148-148.5°C) and 8 (22%; oil) which were separated on TLC plate. Hydrolysis of the chloroacetoxy group of 7 and 8 with 1N NaOH in methanol afforded 5- and 6-hydroxy derivatives, 9[12] and 10,[13] in quantitative yields respectively.

We have further examined to apply our method to methyl indole-3-carboxylate 11, in which 1-position of the indole nucleus contains no substituent.

Compound 11 was chloroacetylated with chloroacetyl chloride-$AlCl_3$ (53%) followed by m-CPBA oxidation to afford a mixture which was separated to the 5- and 6-chloroacetoxy derivatives, 12 (56%) and 13 (23%). Hydrolysis of the chloroacetoxy group of 12 and 13 with 1N NaOH in methanol gave methyl 5- and 6-hydroxyindole-3-carboxylate, 14[14] (60%) and 15[15] (65%), respectively.

Thus, we have succeeded in the introduction of a hydroxy group onto 5- and 6-position of indole nucleus starting from the conjugated indole derivatives, 1 and 11. Our new method seems to be very efficient for the synthesis of indole derivatives containing an oxygen function at the position. Further synthetic studies on related indole alkaloids are now in progress.





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11. 4: MS m/z 247(M^+); ^{1}H-NMR ($CDCl_3$) δ: ppm 2.34(3H,s), 3.79(3H,s), 3.90(3H,s), 7.00(1H,dd,J=8.5 and 2Hz), 7.11(1H,d,J=2Hz), 7.78(1H,s), 8.13(1H,d,J=8.5Hz).
12. 9: MS m/z 205(M^+); ^{1}H-NMR ($CDCl_3$-CD_3OD) δ: ppm 3.78(3H,s), 3.87(3H,s), 6.86(1H,dd,J=8.5 and 2Hz), 7.20(1H,d,J=8.5Hz), 7.52(1H,d,J=2Hz), 7.71(1H,s).
13. 10: MS m/z 205(M^+); ^{1}H-NMR ($CDCl_3$-CD_3OD) δ: ppm 3.71(3H,s), 3.87(3H,s), 6.77(1H,br.s), 6.82(1H,br.d,J=8.5Hz), 7.64(1H,s), 7.87(1H,d,J=8.5Hz).
14. 14: MS m/z 191(M^+); ^{1}H-NMR ($CDCl_3$-CD_3OD) δ: ppm 3.89(3H,s), 6.83(1H,dd,J=8.5 and 2Hz), 7.30(1H,d,J=8.5Hz), 7.55(1H,d,J=2Hz), 7.87(1H,s).
15. 15: MS m/z 191(M^+); ^{1}H-NMR ($CDCl_3$-CD_3OD) δ: ppm 3.90(3H,s), 6.84(1H,br.d,J=8.5 Hz), 6.88(1H,br.s), 7.80(1H,s), 7.95(1H,d,J=8.5Hz).

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