REGIOSPECIFIC CYCLIZATION OF 3-CARBOMETHOXYINDOLE-1-PROPANOIC ACID ONTO 7-POSITION OF THE INDOLE NUCLEUS

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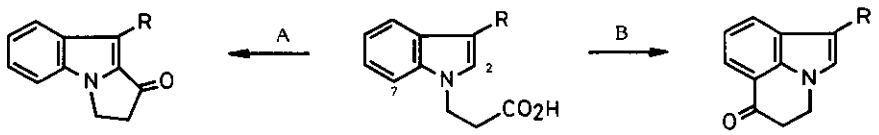
Abstract– Intramolecular cyclization of 3-carbomethoxyindole-1-propanoic acid (3) occurred not onto 2-position but onto 7-position to afford pyrrolo[3,2,1-ij]quinoline derivative 5.

For the synthesis of indole alkaloids containing alkyl or acyl substituent(s) on the benzene part of the indole nucleus, direct introduction of the substituent(s) on the desired position(s) should be one of the most important steps, but only a few limited cases[1-4] have so far been reported because 1-, 2- and 3-positions are much more reactive than 4-7 positions of an indole nucleus. Hoechst et al.[5] reported a cyclization reaction of 3-methylindole-1-propanoic acid Ia ($R=CH_3$) to give only II, which was the cyclization product onto 2-position of the indole nucleus (route A). Recently, we have found a unique intramolecular cyclization[6,7] of dehydrotryptophan derivatives onto 4-position of the indole nucleus, in which 4-position seemed to be more reactive than 2-position. Now we wish to report an unusual cyclization of Ib, whose pyrrole part is stabilized by conjugation with the carbonyl group at 3-position, onto 7-position of the indole nucleus to give III (route B).



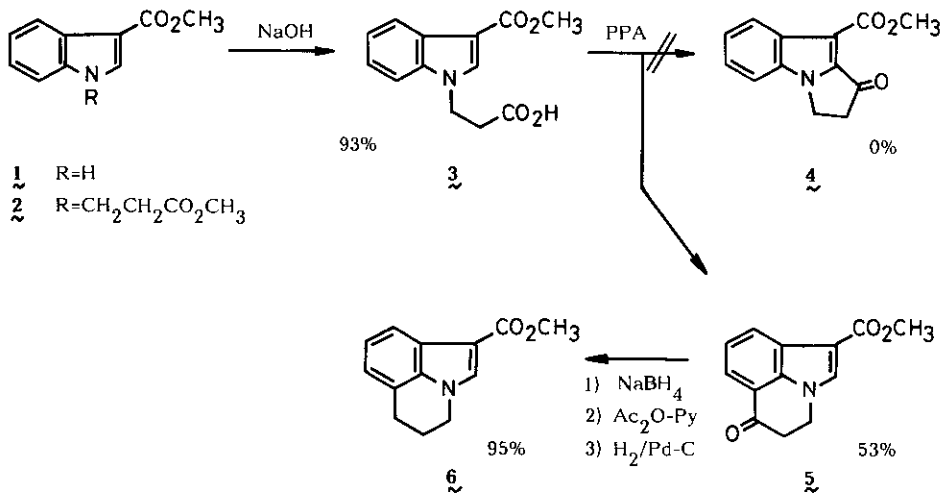
II

Ia R=alkyl
Ib R=COR'

III

As the starting material, we chose 3-carbomethoxyindole-1-propanoic acid (3) [mp 157-158°C; ^{1}H-NMR δ ($CDCl_3$-CD_3OD) ppm 2.83(2H, t, J=7 Hz), 3.88(3H, s), 4.50(2H, t, J=7 Hz), 7.16-7.60(3H, m), 7.97(1H, s), 8.10(1H, m)], which was easily obtained in 93% yield by conjugate addition of methyl indole-3-carboxylate (1) to methyl acrylate in the presence of K_2CO_3 in dimethylformamide and the product 2 [oil, ^{1}H-NMR δ ($CDCl_3$) ppm 2.86(2H, t, J=7 Hz), 3,69(3H, s), 3.93(3H, s), 4.50(2H, t, J=7 Hz), 7.20-7.56(3H, m), 7.88(1H, s), 8.23(1H, m)] was selectively hydrolyzed with NaOH.

The carboxylic acid 3 was treated with polyphosphoric acid (PPA) at 60°C for 1.5 h. After addition of



water, the reaction mixture was extracted with dichloromethane and the extract was dried with Na_2SO_4. Only a single cyclization product **5** [mp 152-153°C; MS m/z 229(M^+); ^{1}H-NMR δ($CDCl_3$) 3.10(2H, t, J=7 Hz), 3.90(3H, s), 4.56(2H, t, J=7 Hz), 7.37(1H, t, J=8 Hz), 7.58(1H, d, J=8 Hz), 7.91(1H, s), 8.32(1H, d, J=8 Hz)] was obtained by silica gel column chromatography in 53% yield. The structure was deduced from the spectroscopic data to be pyrrolo[3,2,1-ij]quinoline derivative **5** produced by cyclization onto 7-position of the indole nucleus. In this reaction, the alternate cyclization product **4** was not detected. The tricyclic ketone **5** was further derived to **6** [mp 30-40°C; MS m/z 215(M^+); ^{1}H-NMR δ($CDCl_3$) 2.24(2H, m), 2.98(2H, t, J=5 Hz), 3.92(3H, s), 4.16(2H, t, J=5 Hz), 7.00(1H, d, J=8 Hz), 7.20(1H, t, J=8 Hz), 7.77(1H, s), 7.92(1H, d, J=8 Hz)] by (1) $NaBH_4$ reduction, (2), acetylation with Ac_2O/Py, and (3) hydrogenolysis with H_2/Pd-C in 95% overall yield.

Thus we succeeded in introduction of an acyl or alkyl substituent onto 7-position of the indole nucleus via intramolecular cyclization of a stabilized indole-1-propanoic acid. This procedure may have a broad applicability for synthesis of indole derivatives. Further application of this regiospecific cyclization is now in progress.

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