THE CHEMISTRY OF 4-SUBSTITUTED INDOLES

Masanori Somei, Yoshio Karasawa, Shoichi Tokutake, Toshiya Shoda,
Fumio Yamada, and Chikara Kaneko
Faculty of Pharmaceutical Sciences, Kanazawa University
13-1 Takara-machi, Kanazawa, Ishikawa, Japan

I. A convenient route to 5-substituted isocoumarins and its application for the synthesis of methyl indole-4-carboxylate.

One step synthesis of 5-nitroisocoumarin (1) and 3,4-dihydro-3-methoxy-5-nitroisocoumarin (2) was achieved by the reaction of 2-methyl-3-nitrobenzoic acid with dimethylformamide dimethyl acetal (DMFDMA). Reduction of 1 or 2 with aqueous titanium (III) chloride ($TiCl_3$) afforded 5-aminoisocoumarin (3) or 5-amino-3,4-dihydro-3-methoxyisocoumarin (4) in high yields, respectively. Subsequent nucleophilic addition reaction using sodium methoxide converted both compounds, (3) and (4), into methyl indole-4-carboxylate in excellent yields. The reaction of 3 and 4 with various carbon nucleophiles is in progress.

II. The syntheses of 4-substituted 1-hydroxyindoles.

2-Nitrotoluene carrying nitro, methoxycarbonyl, or benzyloxy groups at the 6 position were converted successfully to the corresponding 6-substituted trans-β-dimethylamino-2-nitrostyrenes by the reaction with DMFDMA. Controlled reduction of these enamines with either aqueous $TiCl_3$ or zinc-ammonium chloride produced the corresponding 4-substituted 1-hydroxyindoles and 4-substituted indoles in varied yields depending upon the kind of solvents and ratio of the reducing agents. The stability of 4-substituted 1-hydroxyindoles was decreased in the following order: 4-nitro- $\gg$ 4-methoxycarbonyl- $>$ 4-benzyloxy-1-hydroxyindole. This fact clearly shows that 4-substituent plays an important role in the stability of 1-hydroxyindole structure.

It was also found that 4-hydroxyindole and 4-benzyloxyindole were readily accessible by the reduction of 6-benzyloxy-2-nitrophenylacetaldehyde, which was obtained through the hydrolysis of 6-benzyloxy-trans-β-dimethylamino-2-nitrostyrene.