ON THE EFFECT OF THE STERIC ENVIRONMENT OF THE STARTING PHENYLHYDRAZONE TO THE FISCHER INDOLIZATION

Hisashi Ishii, Takao Hagiwara, Tsutomu Ishikawa, Nisaburo Ikeda, and Yasuoki Murakami

Faculty of Pharmaceutical Sciences, Chiba University

Yayoi-cho, Chiba 280

Treatment of ethyl pyruvate N_A-methyl 2-chlorophenylhydrazone with HCl·EtOH gave ethyl 7-chloro-1-methylindole-2-carboxylate as a main product, while Fischer indolization of ethyl pyruvate 2-chlorophenylhydrazone did not take place under the same condition. These evidences indicate that the replacement by a methyl group at an N_A-nitrogen of a phenylhydrazone facilitates the Fischer indolization. On the other hand, treatment of ethyl pyruvate 2,6-dichlorophenylhydrazone with anhydrous $ZnCl_2$ in AcOH afforded ethyl 5,7-dichloroindole-2-carboxylate, a product of ortho-C_5 abnormal Fischer indolization, in 82.3 % yield, but not the N_A-methyl derivative of the phenylhydrazone under the same condition.

An electrophilic cyclization of Fischer indolization could be clearly indicated from the facts that ethyl pyruvate N_A-(4-methoxyphenyl)- and N_A-(3,5-dimethoxyphenyl)- phenylhydrazones were preferably cyclized to the benzene ring bearing the methoxy group, while ethyl pyruvate N_A-(4-carboethoxyphenyl)phenylhydrazone to the unsubstituted benzene ring. However, treatment of ethyl pyruvate N_A-(2-methoxyphenyl)phenylhydrazone with HCl·EtOH gave ethyl 1-(o-methoxyphenyl)indole-2-carboxylate as a main product.

The inspection of the structure of the intermediate expected from Robinson mechanism on a model discloses the facts that, on ethyl pyruvate N_A-methyl 2,6-dichlorophenylhydrazone, the arrangement of their atoms concerned to cyclization on a plane is not allowed by the steric hindrance between the two chlorine atoms located on both ortho positions of the same phenyl ring and the N_A-methyl group and that the same factor forces the enehydrazine form of ethyl pyruvate N_A-(2-methoxyphenyl)phenylhydrazone to place the unsubstituted phenyl and enehydrazine groups on the same plane. These considerations allow us to conclude that the 3,3-sigmatropic mechanism is of importance on Fischer indolization even under an acidic condition.