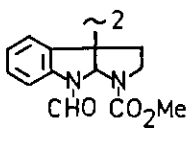
OXIDATIVE DIMERIZATION OF TRYPTOPHAN DERIVATIVES TOTAL SYNTHESIS OF DITRYPTOPHENALINE AND FOLICANTHINE

Masako Nakagawa, Hiroyuki Sugumi, Shinichi Kodato, and Tohru Hino

Faculty of Pharmaceutical Sciences, Chiba University

1-33 Yayoi-cho, Chiba-shi, 260, Japan

When Nb-methoxycarbonyltryptamine 1 in thoroughly O_2-saturated formic acid was irradiated with a halogen lamp for 1 hr in the presence of an acridine dye such as proflavine, acridine orange (AO), acriflavine, oxidative dimeric compounds 2 (17-23%) and 3 (38-40%) were obtained as a mixture of two diastereoisomers along with Na-formyl-3a-hydroxypyrrolindole (13-27%) and oxidative 2,3-bond cleavage compounds were not obtained. Stereoisomeric mixture of 2 was separated into racemi- and meso-isomers (2a, mp 255-256° ; 2b, mp 282-284°) which were readily converted to racemi- and meso-folicanthine (4a, mp 167.5-168.5° ; 4b, mp 174-175°) by $LiAlH_4$ reduction.[1] On the other hand, the similar reaction without light or in a solvent like MeOH or F_3CCO_2H did not give 2. Using methylene blue or toluidine blue gave only traces of 2 and 3 under similar conditions. However, the reaction in HCO_2H-dicyanoanthrathene (DCA) or chloranil provided 2, suggestive of the indolyl radical cation intermediate by electron transfer mechanism. In fact, 1 quenches the fluorescence of AO at 575 nm in HCO_2H. Furthermore, the oxidation of 1 with thallium (III) trifluoroacetate (TTFA) in acetonitril gave the deformylated 2. In light of these results, we intended to synthesize ditryptophenaline 5 by analogous oxidative coupling of cyclo-L-N-methylphenylalanyl-L-tryptophanyl 6. Irradiation of 6 in HCO_2H with proflavine, chloranil, DCA under a variety of conditions did not give the corresponding dimeric compounds. However, an alternate reagent, TTFA was employed successfully to produce the desired dimer, ditryptophenaline 5 in 5% yield which was readily crystallized from CH_2Cl_2-MeOH to give mp 196-203° (Lit. mp 204-205°) identical through spectral (IR, UV, NMR, $[\alpha]_D^{33}$ -318.1, high resolution mass) and chromatographic comparison with authentic sample of the natural material. Since relative configuration of 5 has been reported, our total synthesis established the absolute configuration of 5 as shown below.[2]



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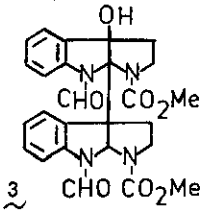

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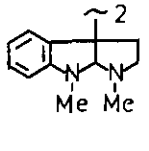

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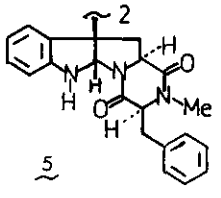

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1) T. Hino, S. Kodato, K. Takahashi, H. Yamaguchi, and M. Nakagawa, Tetrahedron Lett., 4913 (1978)

2) M. Nakagawa, H. Sugumi, S. Kodato, and T. Hino, ibid., 22, 5323 (1981)