Benzimidazole Condensed Ring Systems, III [1].
Synthesis of Some Substituted 2,3-Dihydrocyclopenta-1H-[4',5': 2,3]pyrido[1,2-a]benzimidazole-11-carbonitriles

El-Sayed A. M. Badawey¹, Samia M. Rida¹, Farid S. G. Soliman¹, and Thomas Kappe²,*

¹ Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, A. R. Egypt
² Institute of Organic Chemistry, Karl-Franzens-University Graz, A-8010 Graz, Austria

Summary. The synthesis of compound 3 by condensing 1H-benzimidazole-2-acetonitrile (1) with ethyl cyclopentanone-2-carboxylate (2) in the presence of ammonium acetate is described. Methylation of 3 with trimethyl phosphate yielded the N-methyl derivative 4. Methods for converting 3 to some of its related derivatives in which the carbonyl function was replaced by Cl, N₃, and amines are also reported.

Keywords. 1H-Benzimidazole-2-acetonitrile; Ethyl cyclopentanone-2-carboxylate; Tetracyclic pyrido[1,2-a]benzimidazoles.

In the preceeding publication [1] the authors described a facile onestep synthesis of 3-substituted and 2,3-disubstituted-1-oxo-1H,5H-pyrido[1,2-a]benzimidazole-4-carbonitriles by fusing 1H-benzimidazole-2-acetonitrile (1) with some β-keto esters in presence of ammonium acetate. We have now extended this cyclocondensation to the synthesis of the titled tetracyclic system as a part of continuing interest in benzimidazole condensed ring systems of potential biological significance [2, 3].

Thus, fusing 1 with ethyl cyclopentanone-2-carboxylate (2) in the presence of ammonium acetate afforded 2,3-dihydro-4-oxo-1H,4H,10H-cyclopenta [4',5':2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (3) in high yield. The reaction followed the same pattern as that discussed before [1]. Methylation of 3 with trimethyl phosphate in the presence of potassium carbonate resulted in its 10-methyl derivative 4. Chlorination of 3 with phosphorus oxychloride yielded 4-
chloro-2,3-dihydro-1H-cyclopenta[4',5':2,3]pyrido[1,2-a]benzimidazole-11-carbonitrile (5). Displacement of the 4-chloro atom in the latter with sodium azide gave the 4-azido derivative 6 which was converted to the 4-amino compound 8 through acid hydrolysis of the 4-triphenylphosphoranylideneamino intermediate 7. Whereas, displacement of this chloro atom with morpholine afforded the 4-morpholino derivative 9 (Scheme 1). The fact that this tetracyclic system comprises a cyclopentane residue within its structure may be of value for the bioactivity, if any, of these compounds.

Compounds 3, 5, and 9 were screened against P-388 lymphocytic leukemia in mice according to a standard protocol [4] and were inactive. Compounds 5 and 6 were screened for in vitro activity against three Staphylococcus aureas strains (S14, S17 and S18) and two Escherichia coli strains (E21 and E41) and one Candida albicans strain (M 1) using a disc method [5], however, they were inactive.