Introduction

The Furo-, pyrrolo- and pyridazino[4,5-c]quinolines 2, 3 and 4 can be synthesized from ethyl methyl 2,3-dihydro-2-hydroxy-5-methyl-3-(2-nitrophenyl) furan-2,4-dicarboxylate (1; R¹ = COOEt, R² = Me) [1,2]. Cyclic hydroxamic acids with this framework are of pharmaceutical interest with regard to lipoygenase inhibitors, while lactams are suitable educts foraza analogues of the antimalarial drug halofantrine.

Now we report the synthesis of the isomeric furo[2,3-c]- and pyrrolo[2,3-c]quinolines 5 [3] and 6 from the 4-t-butyl ester 1a as well as the isomeric pyridazino[4,5-c]quinolines 7 from the 4-mono-ethyl ester 1b.

2-Hydroxy-2,3-dihydro-2,4-furandicarboxylates

The t-butyl ethyl 1,3-dithiolancarboxylate 9 is formed by Michael addition of t-butyl (2-nitrobenzylidene)acetoacetate 8 to lithium 2-carbethoxy-1,3-dithiolan. Cleavage of the dithiocacetal with NBS leads to the 4-t-butyl 2-ethyl 2-hydroxy-2,3-dihydro-2,4-furandicarboxylate 1a, whose structure is confirmed by X-ray crystal structure analysis. Compound 1a represents the educt for the synthesis of the furo[2,3-c]- and pyrrolo[2,3-c]quinolines 5 and 6.
Furo[2,3-c]quinolines

Dehydration of the 2-hydroxy-2,3-dihydrofuran 1a with CaH₂ / DMF yields the 4-t-butyl-2-ethyl-2,4-furandicarboxylate 10. Compound 10 is converted selectively into the ethoxycarbonyl-furan-carboxylic acid 11 by heating in diphenylether / p-TosOH. The t-butylester is completely eliminated to yield 12 by using 1a under the same conditions. Reduction of the nitro group of 12 with Fe / AcOH, followed by ring closure of the obtained amine with the ester function forms the lactam 5a [3]. Treating 12 with Zn / AcOH (pH = 4.6) forms the hydroxamic acid 5b by intramolecular cyclization of the intermediate hydroxylamine.

Pyrrolo[2,3-c]quinolines

The 4-t-butyl-2-ethyl-2,3-dihydro-2,4-pyrrololicarboxylate 13 is obtained from the reaction of the furan 1a with NH₂OAc. The halfaminale 13 easily loses water to give the pyrrole 14. The carboxylic acid 15 is released from the selective cleavage of the t-butylester by reaction with TFA. The decarboxylation of 15 by heating in diphenylether / p-TosOH gives only low yield of 16. Much better results are achieved by an alternative way of reaction. After removing the t-butylester of 1a with TFA, the resulting tricarboxyl compound 17 is cyclized with NH₂OAc to yield the pyrrole 16. Reduction of the nitro group with Fe / AcOH or Zn / AcOH at pH = 4.6 and subsequent ring closure affords the lactam 6a or the hydroxamic acid 6b, respectively.
Pyridazino[4,5-c]quinolines

Michael addition of the ethyl (2-nitrobenzylidene)acetacetate 18 with the (methylsulfonyl) (methylsulfanyl)methan leads to the 1,4-adduct 19 as the main product and the 1,2-adduct 20 as the by-product. Cleavage of the dithioacetate 19 with HClO₄ yields the ethyl 5-hydroxy-4,5-dihydro-3-furan carboxylate 1b. The configuration of compound 1b is elucidated by X-ray crystal structure analysis. Reaction of 1b with hydrazine forms the 1,4-dihydropyridazine 21, which can be dehydrogenated by CAN to achieve the pyridazine 22. Reductive cyclization of 22 under the conditions described previously yields the lactam 7a or the hydroxamic acid 7b, respectively.

Acknowledgement

The authors thank Prof. Dr. P. G. Jones, Institute of Inorganic and Analytical Chemistry, Technical University of Braunschweig, for X-ray crystal structure analyses.

References