REACTIONS OF AMINOQUINONES, SYNTHETIC APPROACHES TO MITOMYCINS

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In our synthetic approach to the mitomycins, a one step synthesis of pyrrolo[1,2-a]indoloquinone by the thermolysis of acetyl-aminoquinone tosylhydrazones(1) has been reported. To investigate the mechanism of this reaction, the carefully controlled thermolysis and photolysis of 1 were examined.

Refluxing 2-acetyl-3-pyrrolidino-5-methyl-1,4-benzoquinone tosylhydrazone(1a) in benzene gave 5-acetyl-1,2,3,9a-tetrahydro-8-methylpyrrolo[2,1-b]benzoxazol-6-ol tosylhydrazone(2a) in good yield. The same compound(2a) was also obtained by the photolysis of 1a in benzene. 2a was decomposed on heating in chlorobenzene to form 2,3,6,7-tetrahydro-6,9-dimethyl-5,8-dioxo-1H-pyrrolo[1,2-a]indole(3a) in 19% yield. Furthermore, the oxazoline(2a) and dihydroindoloquinone(3a) were also refluxed in DMF to convert pyrrolo[1,2-a]indoloquinone(4a) quantitatively. These facts suggest that the oxazoline may be an intermediate in the reaction course of indoloquinone synthesis.

The thermolysis and photolysis of 1 were also examined in various solvents. From the results of the solvent effects, the thermal reaction using DMF as the solvent appeared to be more versatile than the photochemical reaction for the indoloquinone formation.

Subsequently, the application of this improved reaction to newly prepared aziridinoaminoquinone tosylhydrazone(5) was carried out as an approach to synthesis of the mitomycins. The photo-induced reaction of 2-acetyl-3-[2-(4-bromophenyl)-2,3,4,7-tetraazabicyclo[3.3.0]oct-3-en-7-yl]-5-methyl-1,4-benzoquinone tosylhydrazone(5a) or 2-acetyl-3-[6-(4-bromophenyl)-3,6-diazabicyclo[3.1.0]hex-3-yl]-5-methyl-1,4-benzoquinone tosylhydrazone(5b) gave the hydroxyquinols(6a and b), which were converted to 1-(4-bromophenylimino)-6,9-dimethyl-5,8-dioxo-1H-pyrrolo[1,2-a]indole(7), 1-(4-bromophenylimino)-2,3-dihydro-6,9-dimethyl-5,8-dioxo-1H-pyrrolo[1,2-a]indole(8), 2-(4-bromophenylamino)-2,3-dihydro-6,9-dimethyl-5,8-dioxo-1H-pyrrolo[1,2-a]indole(9), and 1,2-disubstituted pyrrolo[1,2-a]indoloquinone(10) via the oxazolines(11). These compounds, 8, 9, and 10, were also prepared in a one step synthesis by the thermal decomposition reaction of 5a.

Therefore, the aziridinopyrrolo[1,2-a]indoloquinone(13), as model mitomycins, was photosynthesized from 2-bisethoxycarbonylmethyl-3-[6-(4-bromophenyl)-3,6-diazabicyclo[3.1.0]hex-3-yl]-5,6-dimethyl-1,4-benzoquinone(12) having a more efficient nucleophilic substituent than the tosylhydrazone function in a one-pot sequence.