A SYNTHETIC APPROACH TO THE MITOMYCINS

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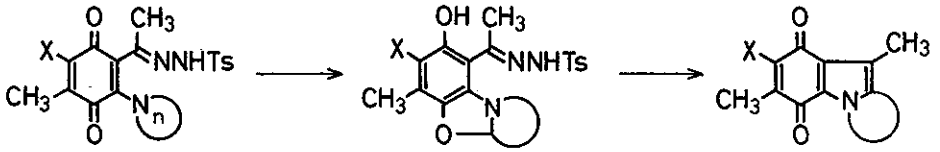
The photo-induced reaction of 2-acetyl-3-[2-(4-bromophenyl)-2,3,4,7-tetraazabicyclo[3.3.0]oct-3-en-7-yl]-5-methyl-1,4-benzoquinone tosylhydrazone (1b) or 2-acetyl-3-[6-(4-bromophenyl)-3,6-diazabicyclo[3.1.0]hex-3-yl]-5-methyl-1,4-benzoquinone tosylhydrazone (1c) gave the hydroxyquinols (2a and b), which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

The mitomycins, naturally occurring anticancer antibiotics, contain a unique pyrroloindoloquinone skeleton. Since Webb, et al.[1] determined their structures in 1962, many attempts[2] toward their synthesis have been reported. More recently, the first brilliant total synthesis of some of the mitomycins has been reported by Kishi, et al.[3] During our synthetic studies on the mitomycins, it has been observed that the thermolysis and photolysis of acetylaminoquinone tosylhydrazones followed by the degradation of the resulting unstable oxazoline afforded the indoloquinones[4] (Scheme 1). In this communication we wish to describe the application of this improved photo-induced and

thermal decomposition reaction to newly prepared acetyl-aziridinoaminoquinone tosylhydrazones as an approach to synthesis of the mitomycins.



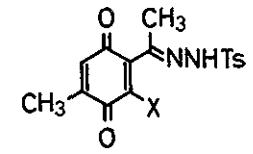
X=H, or amino groups
n=5, or 6

Scheme 1

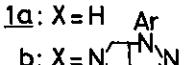
A solution of the aminoquinone 1b[5], mp 122-124°(decomp.), in ethanol, prepared by the reaction of acetyltoluquinone tosylhydrazone 1a with 2-(4-bromophenyl)-2,3,4,7-tetraazabicyclo[3.3.0]oct-3-ene[6], was irradiated with a high pressure mercury lamp through Pyrex glass for 20 min. After evaporation of the solvent, the hydroxyquinols 2a and 2b were obtained as an inseparable mixture of trans- and cis-stereoisomers in 37% yield. A similar photolysis of the aminoquinone 1c[5], mp 137°(decomp.), prepared from 1a and 6-(4-bromophenyl)-3,6-diazabicyclo[3.1.0]hexane[6], gave the trans-isomer 2a (52%), mp 163°(decomp.), and an oxidized product 3b (5.5%), a violet-red oil derived from 2b.

2a was oxidized with potassium nitrosodisulfonate in water-ethanol affording the stereoisomer 3a, mp 172°(decomp.), of 3b in 53% yield. A similar oxidation of the mixture of 2a and 2b gave 3a and 3b in a ratio of 1 : 1 after chromatography on silica gel. The NMR and IR spectra of 3a and 3b were similar to each other except for the following observations. The more polar isomer, 3b, having the characteristic coupling constants of 2.0 Hz at δ 5.88 ppm, was assigned as the cis isomer, while the less polar isomer, 3a, was assigned as the trans isomer because of the absence of the coupling constant.

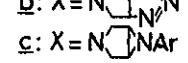
The compounds 2 and 3 seem to be convenient intermediates[7] for the total synthesis of mitomycins. Consequently, many attempts were made to cyclize 2



1a: X=H

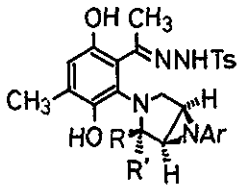


b: X=



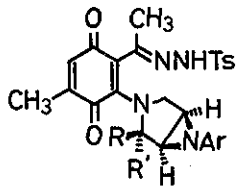
c: X=

(Ar = -C_6H_4Br-p)



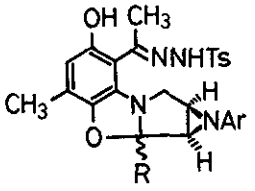
2a: R=H, R'=OH

b: R=OH, R'=H



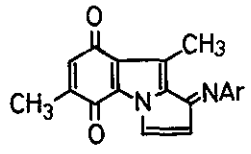
3a: R=H, R'=OH

b: R=OH, R'=H



4a: R= -H

b: R= ···H



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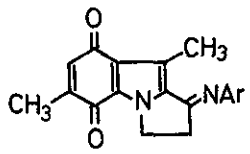

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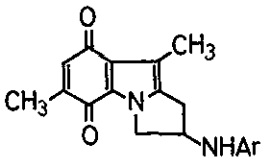

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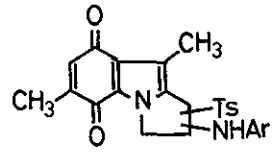

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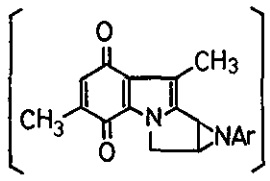


9

or 3 to the aziridinopyrroloindoloquinone 9 under various reaction conditions.

Heating 2a in chlorobenzene, a yellow oil was obtained in 34% yield. The structure of this compound was characterized as the oxazoline 4b by the appearance of doublets (J = 2.0 Hz) at δ 5.97 ppm in its NMR spectrum assigned to the proton attached to the oxazoline ring and by the similarity of its UV spectrum with that of 2a. When 4b was refluxed in pyridine, 1,2-disubstituted pyrroloindoloquinone 8[8], 2-aminopyrroloindoloquinone 7[9], and 1-iminopyrroloindoloquinone 6 were obtained. The first compound was a major one and others minor.

The structures of these compounds were confirmed by the following spectral data: [6, mp 204-206°; IR (KBr) 1650, 1640 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 7.48 (2H, d, J = 8.0 Hz, Ar-H), 6.80 (2H, d, J = 8.0 Hz, Ar-H), 6.46 (1H, q, J = 1.0 Hz, CH=C-CH_3), 4.43 (2H, t, J = 6.5 Hz, CH_2), 3.09 (2H, t, J = 6.5 Hz, CH_2), 2.60 (3H, s, CH_3), 2.08 (3H, d, J = 1.0 Hz, CH_3); MS. m/e 382, 384 (M^+). 7, mp 201° ; IR (KBr) 3340 (NH), 1630 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 7.3 (2H, d, J = 8.0 Hz, Ar-H), 6.54 (2H, d, J = 8.0 Hz, Ar-H), 6.30 (1H, q, J = 1.0 Hz, CH=C-CH_3), 4.7 (1H, broad, NH, disappeared with D_2O), 4.5 (1H, dd, J = 12.0, J = 6.0 Hz, -N-CH), 4.2 (1H, m, -NH-CH), 4.1 (1H, dd, J = 12.0, J = 2.5 Hz, -N-CH), 3.2 (1H, dd, J = 16.0, J = 6.0 Hz, C=C-CH), 2.8 (1H, dd, J = 16.0, J = 2.5 Hz, C=C-CH), 2.22 (3H, s, CH_3), 2.01 (3H, d, J = 1.0 Hz, CH=C-CH_3); MS. m/e 384, 386 (M^+). 8, mp 267°(decomp.); IR (KBr) 3280 (NH), 1640 (C=O) cm^{-1}; NMR (pyridine-d_5) δ 7.98 (2H, d, J = 8.0 Hz, Ar-H), 7.32 (4H, d, J = 8.0 Hz, Ar-H), 6.75 (2H, d, J = 8.0 Hz, Ar-H), 6.36 (1H, q, J = 1.0 Hz, CH=C-CH_3), 4.5 (2H, m, CH), 2.26 (3H, s, CH_3), 2.08 (3H, s, CH_3), 1.82 (3H, d, J = 1.0 Hz, CH=C-CH_3); MS. m/e 538, 540 (M^+)].

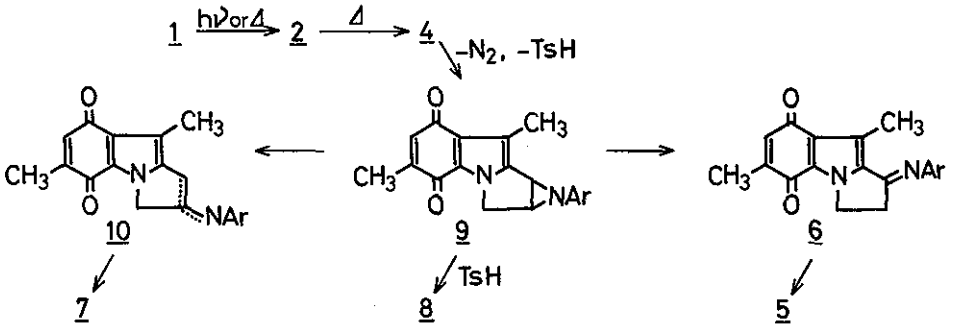
The cyclized products 8, 7, and 6 were also obtained directly by the thermolysis of 2a in pyridine. Therefore, the pyrroloindoloquinones may be formed via the oxazoline 4b in the thermal reaction course of the quinol.

The thermolysis of the mixture of the stereoisomers 2a and 2b in chlorobenzene afforded 4b (53%) and a small amount of the unstable dehydroiminoquinone 5, mp 207°(decomp.); IR (KBr) 1655 (C=O), 1615 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 7.86 (1H, d, J = 4 Hz, N-CH=CH), 7.50 (2H, d, J = 8.0 Hz, Ar-H), 6.88 (2H, d, J = 8.0 Hz, Ar-H), 6.45 (1H, q, J = 1.0 Hz, CH=C-CH_3), 6.06 (1H, d, J = 4.0 Hz, N-CH=CH), 2.60 (3H, s, CH_3), 2.09 (3H, d, J = 1.0 Hz, CH=C-CH_3); MS. m/e 380, 382 (M^+). This fact suggests that 2b may cyclize to 4a followed by isomerization to 4b via a zwitter ion intermediate[4]. To shorten the syn-

thetic route, the direct thermolysis of 1b in dimethylformamide was attempted to give 6 (5%), 7 (11%), and 8 (2%) which were also obtained by the thermolysis of the mixture of 2a and 2b in the same solvent.

On the other hand, the thermolysis of the quinone 3a and 3b afforded an intractable reaction mixture, and the expected cyclized products were not isolated.

To explain the above results, we propose the following mechanism:



Scheme 2

The thermal decomposition of the oxazoline 4 gave the aziridinopyrroloindoloquinone intermediate 9, which undergoes further attack of the sulfinic acid and thermal isomerization to form 8, 6, and 10 followed by intermolecular disproportionation to afford 5 and 7 as shown in Scheme 2. These investigations point to the formation of the substituted pyrroloindoloquinones via the aziridinopyrroloindoloquinone.

Therefore, the photolysis and thermolysis of the aminoquinones having a more efficient nucleophilic substituent than the tosylhydrazone function would provide a versatile pathway to the mitomycins.

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References and Notes

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5 Its structure was supported by spectral (UV, IR, and NMR) data.

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8 Elucidation of the complete structure of this compound is carried out.

9 The results from a 100 MHz NMR spectrum of 7, together with those from double irradiation experiment permitted assignment of all of the proton signals and determination of proton-proton coupling constants.

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