A SIMPLE PHOTOSYNTHESIS OF PYRROLOINDOLOQUINONES

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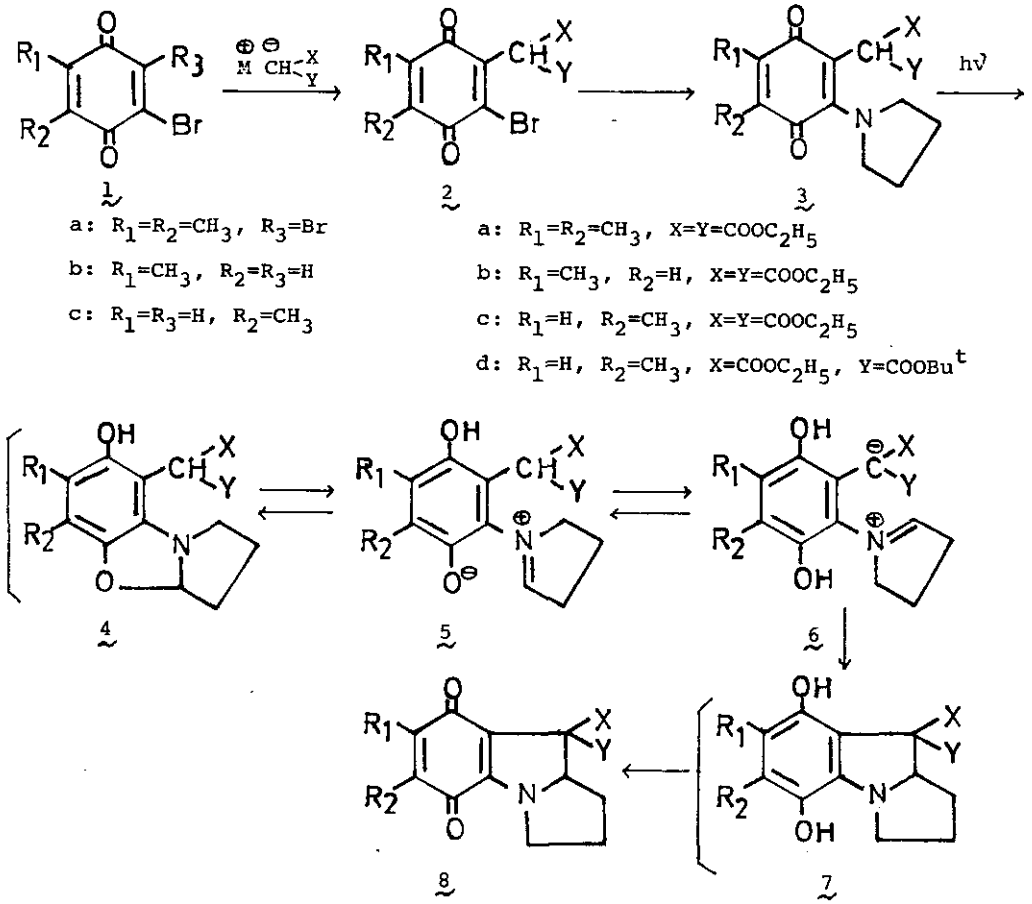
Abstract --- The improved photoreaction of pyrrolidino-1,4-benzoquinones having the active methylene groups afforded a simple and preparative route to the synthesis of pyrroloindoloquinones, which were the mother framework of mitomycins.

The pyrroloindoloquinone[1] has the basic structure of mitomycins and very important for their biological activities[2]. Recently we have reported that the photolysis of amino-1,4-naphthoquinones having the active methylene groups at the 2-position provided a preparative route to the heterocyclic quinones[3]. In this paper we wish to describe the improvement and application of this photo-induced reaction to newly prepared pyrrolidinobenzoquinones for the simple synthesis of pyrroloindoloquinones.

The synthetic process can be represented as shown in Scheme I. The benzoquinone 2a[4] was prepared easily from the substitution reaction of the dibromoquinone 1a with ethyl sodium malonate. However, 2b-d were not obtained from the corresponding quinones 1b-c under the same condition. Since it is possible for the active methylene anion to react with 1b-c at three positions (C_2, C_3, and C_5 or C_6) or four positions (C_2, C_3, C_5 or C_6, and methyl group[5]), the reaction resulted in an intractable mixture. Using the thallium malonates[6], the regioselective Michael addition of these to 1b-c followed by oxidation gave the corresponding quinones 2b-d in moderate yields. On treatment with 2 equimolar amounts of pyrrolidine in chloroform, 2b-d afforded the corresponding aminoquinones 3b-d in good yields, respectively. The structures of 2 and 3, oily products, were confirmed by the analytical and spectroscopic data (IR, NMR, and MS).

The photo-induced reaction of pyrrolidinoquinones 3 was carried out as follows. A solution of 3a-c in ethanol was irradiated with a high pressure mercury lamp

through Pyrex glass. After allowing the irradiated solution 3a-c to stand for more than 3 days at room temperature, the pyrroloindoloquinones 8a-c were obtained in 47-51% yields (Method A). Secondly, an attempt to increase the yield of 8 was examined under the mild condition. The irradiated solution of 3a-c in ethanol was retained on a silica gel column for a few days, and then eluated with ethyl acetate to give 8a-c in 60-68% yields (Method B). The similar photolysis of 3d afforded the stereoisomers, 8d-(i) and 8d-(ii), due to the different substituents in a ratio of 5 : 4 after chromatography on silica gel. The stereochemistry of these isomers has not been clarified yet. The structural assignments for 8a-d were based on their analytical and spectral properties, which were in good agreement with their formulations. The results are summarized in Table I.



1
a: $R_1=R_2=CH_3$, $R_3=Br$
b: $R_1=CH_3$, $R_2=R_3=H$
c: $R_1=R_3=H$, $R_2=CH_3$

2

3
a: $R_1=R_2=CH_3$, $X=Y=COOC_2H_5$
b: $R_1=CH_3$, $R_2=H$, $X=Y=COOC_2H_5$
c: $R_1=H$, $R_2=CH_3$, $X=Y=COOC_2H_5$
d: $R_1=H$, $R_2=CH_3$, $X=COOC_2H_5$, $Y=COOBu^t$

4

5

6

7

8

Scheme I

Table I. Photoreaction of Pyrrolidinoquinones 3

Compound 8[a]	Mp (°C)	Yield (%)		IR ν cm^{-1}	NMR δ(CDCl$_3$) ppm	Mass
		Method A	Method B	ester C=O	bridgehead CH[b]	M$^+$ (m/z)
a	137	49	65	1740, 1715	4.81	361
b	86-88	47	60	1745, 1730	4.80	347
c	90-91	51	68	1740, 1718	4.70	347
d-(i)	109	--	34	1740, 1717	4.71	375
d-(ii)	oil	--	27	1740, 1718	4.72	375

a Recrystallized from hexane

b 1H, double doublet

This photoreaction may proceed through the following sequence: photo-insertion, ring degradation, intramolecular cyclization, and oxidation (4, 5, 6, 7, and 8) as reported previously[3]. Silica gel in this reaction sequence may be considered to act as acid and make promotion of 4 to dissociate to 5 and 6. Although the closure of 6 to 7 is "5-endo-trig"[7], it also involves a fully conjugated 6π electron system and this can also be viewed as a thermally allowed disrotatory electrocyclization of the Woodward-Hoffmann classification π6s→π4s+62s[8].

The compounds, 8c and 8d, will be a key intermediate of the mitosene synthesis. Therefore, these conversion to mitosene are being carried out and will be reported elsewhere.

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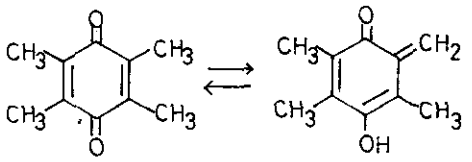

(I)

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