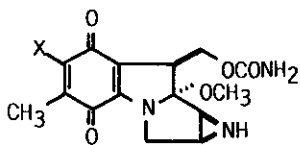


## EFFICIENT SYNTHESIS OF INDOLOQUINONE DERIVATIVE BY SEVERAL OXIDATIVE DERIVATIONS OF 6-METHYLINDOLE

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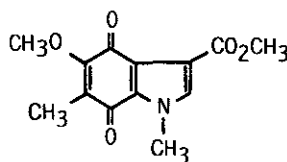
**Abstract**— Indoloquinone **3** was efficiently synthesized from simple 6-methylindole by several oxidation steps.

Although many synthetic studies<sup>3-5</sup> on mitomycin<sup>1,2</sup> derivatives have been reported over twenty years, no method for the synthesis of indoloquinone system by direct oxidative functionalization of benzene part of simple indole was appeared except from 5-hydroxy<sup>4-1</sup> or 5-methoxyindole derivative.<sup>6, 4-2</sup> Recently, we have found several methods to introduce alkyl,<sup>7,8</sup> acyl,<sup>9</sup> and heteroatoms<sup>10</sup> directly onto the benzene part of stabilized indole derivatives. Now, we report a new method for the synthesis of indoloquinone **3** which contains the same quinone system with mitomycin A (**1**).



mitomycin A : X=OCH<sub>3</sub> (**1**)

mitomycin C : X=NH<sub>2</sub> (**2**)



**3**

6-Methylindole **4** was derived to methyl 1,6-dimethylindole-3-carboxylate **5** by (1) NaH/CH<sub>3</sub>I, (2) (COCl)<sub>2</sub>, (3) 120 °C, (4) MeOH in 60% overall yield [MS m/z 203(M<sup>+</sup>); <sup>1</sup>H-NMR δ(CDCl<sub>3</sub>) ppm 2.50(3H, br.s), 3.78(3H, s), 3.89(3H, s), 7.09(1H, br.d, J=8.5 Hz), 7.12(1H, br.s), 7.70(1H, s), 8.02(1H, d, J=8.5 Hz)].

Friedel-Crafts acylation<sup>11</sup> of **5** with chloroacetylchloride-AlCl<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C

for 1.3 h afforded single chloroacetyl derivative [MS m/z 280(M<sup>+</sup>); <sup>1</sup>H-NMR δ(CDCl<sub>3</sub>) ppm 2.66(3H, br.s), 3.81(3H, s), 3.90(3H, s), 4.81(2H, s), 7.18(1H, br.s), 7.75(1H, s), 8.49(1H, s)] in quantitative yield. The acylated position was determined by its <sup>1</sup>H-NMR spectra.

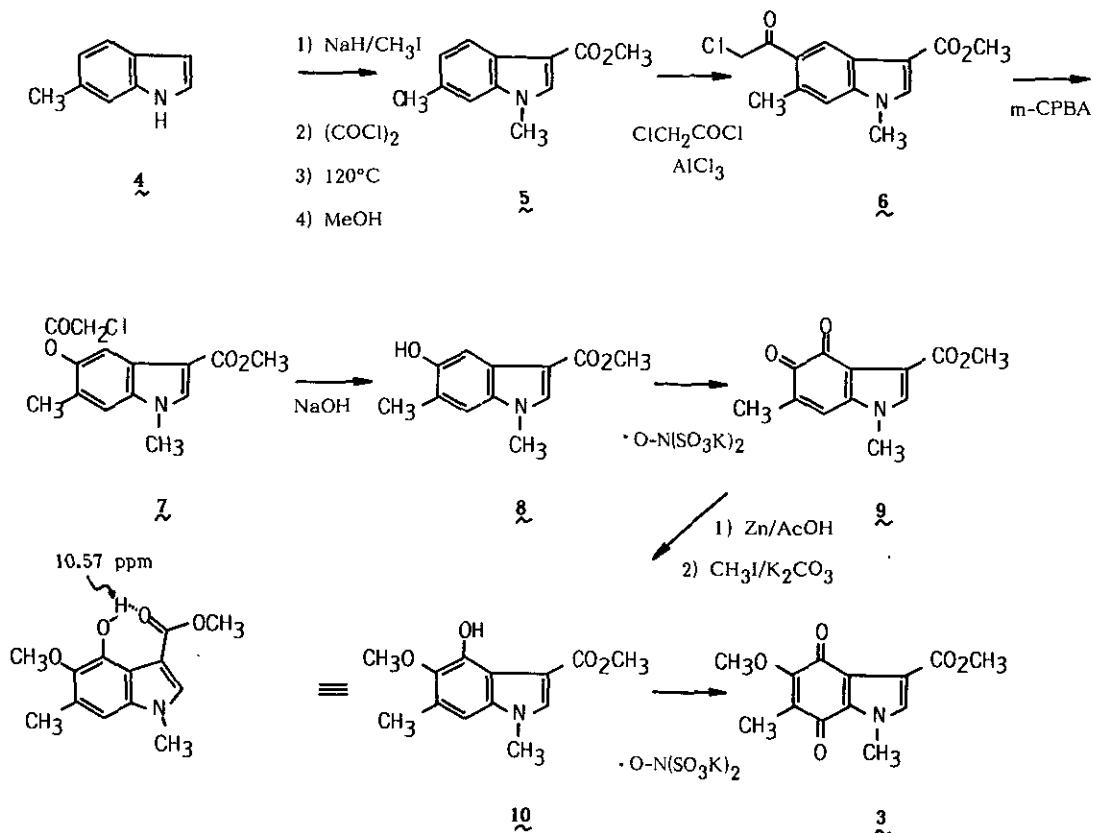
Baeyer-Villiger oxidation<sup>11,12</sup> of 6 with m-chloroperbenzoic acid in the presence of powdered Na<sub>2</sub>HPO<sub>4</sub> in chloroform at 25°C for 6 h afforded desired 6-chloroacetoxy derivative 7 in 59% yield [MS m/z 296(M<sup>+</sup>); <sup>1</sup>H-NMR δ(CDCl<sub>3</sub>) ppm 2.32(3H, br.s), 3.80(3H, s), 3.88(3H, s), 4.36(2H, s), 7.18(1H, br.s), 7.73(1H, s), 7.78(1H, s)]. Hydrolysis of chloroacetyl group of 7 was achieved by treatment with 1N NaOH in MeOH at 25 °C to afford 6-hydroxy derivative 8 in quantitative yield [MS m/z 219 (M<sup>+</sup>); <sup>1</sup>H-NMR δ(CDCl<sub>3</sub>) ppm 2.39(3H, br.s), 3.75(3H, s), 3.88(3H, s), 7.06(1H, br.s), 7.61(1H, s), 7.63(1H, s)].

Compound 8 was oxidized with Fremy's salt [·ON(SO<sub>3</sub>K)<sub>2</sub>] in acetone-H<sub>2</sub>O(1:2) at 25 °C for 10 min to give orthoquinone 9 in quantitative yield [MS m/z 233(M<sup>+</sup>); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) ppm 1.97(3H, br.s), 3.66(3H, s), 3.84(3H, s), 6.94(1H, br.s), 7.20(1H, s)].

Unfortunately, treatment of 9 with Ac<sub>2</sub>O-BF<sub>3</sub>OEt<sub>2</sub><sup>4-1</sup> afforded no desired triacetoxo derivative. So, we planned to reoxidize reduced hydroquinone derivative such as 10. After reduction of 9 with Zn/AcOH to hydroquinone, selective methylation was achieved with CH<sub>3</sub>I/K<sub>2</sub>CO<sub>3</sub> in DMF at 25°C for 45 min to give 5-methoxy derivative 10 in 54% yield [10: MS m/z 249(M<sup>+</sup>); <sup>1</sup>H-NMR δ(CDCl<sub>3</sub>) ppm 2.39(3H, br.s), 3.71(3H, s), 3.87(3H, s), 3.89(3H, s), 6.59(1H, br.s), 7.53(1H, s), 10.57(1H, s)]. We assume that the hydroxy group at 4-position of indole nucleus is less reactive because its stabilization by hydrogen bond with ester carbonyl group at 3-position.

In fact, a chemical shift of 4-OH in <sup>1</sup>H-NMR spectrum of 10 was appeared at low field (10.57 ppm). Reoxidation of 10 with Fremy's salt in acetone-phosphate buffer(pH 7) at 40°C for 2.5 h afforded desired indoloquinone 3, which contains the same quinone part with mitomycin A (1) [3: MS m/z 263(M<sup>+</sup>); <sup>1</sup>H-NMRδ(CDCl<sub>3</sub>) ppm 1.96(3H, s), 3.87(3H, s), 3.98(3H, s), 4.07(3H, s), 7.36(1H, s)] in 65% yield.

Thus three oxygen functions at 4, 5, and 7-positions of indole nucleus could be introduced directly onto the benzene part of indole derivative and compound 3 was synthesized from simple 6-methylindole 4. These new method seems to be very usefull for the synthesis of mitomycins and related compounds. Further synthetic studies are now in progress.



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