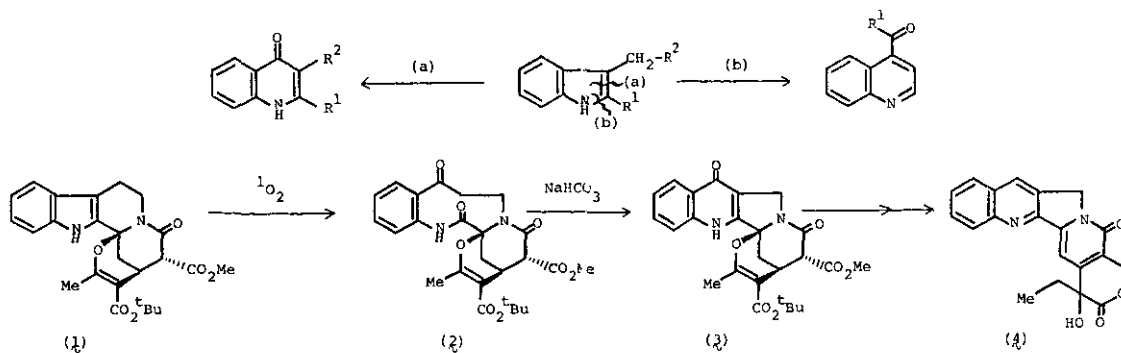


PHOTO-OXYGENATION OF INDOLE-3-ACETIC ACIDS AND INDOLE-3-ACET-ALDEHYDES: BIOMIMETIC CONVERSION OF INDOLES INTO QUINOLINES VIA  $N_1-C_2$  FISSION

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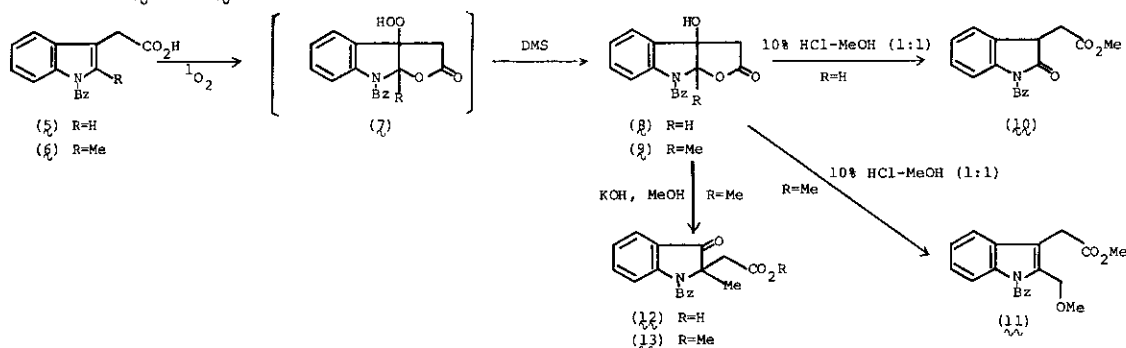
**Abstract** — New conversion of indoles to quinolines via the  $N_1-C_2$  fission using singlet oxygen reaction was investigated starting from indole-3-acetic acids and indole-3-acetaldehydes. Dye-induced photo-oxidation of indole-3-acetaldehyde derivatives (**17** and **18**) followed by treatments with dimethyl sulfide and then acetic acid produced 4-formyl- and 4-acetylquinolines (**19** and **20**), respectively.

Some quinoline alkaloids are known to be biosynthesized from indole alkaloids. Namely camptothecin is derived through the fission of  $C_2-C_3$  bond of indole alkaloids<sup>1</sup> [type (a) fission], while the cleavage of the  $N_1-C_2$  bond [type (b) fission] leads quinine alkaloids.<sup>2</sup> Suggestion of the important role of molecular oxygen in the above oxidative cleavage had promoted extensive studies of the reaction of indoles, including tryptophan, with molecular oxygen.<sup>3,4</sup> Thus quinoline derivatives were prepared from indoles by the type (a) fission using oxygen molecule.<sup>4</sup> Recently we synthesized ( $\pm$ )-camptothecin (**4**) via the photo-oxygenation of the indole derivative (**1**), followed by the basic treatment of the resulting keto-amide (**2**) to the quinolone (**3**).<sup>5</sup> On the other hand the formation of quinolines through the type (b) fission with molecular oxygen has not been reported.<sup>6</sup> Intending a duplication of the hypothesis in the biogenesis of quinine<sup>2</sup>, we examined photo-oxygenation of indole-3-acetic acid and indole-3-acetaldehyde derivatives.



When *N*-benzylindole-3-acetic acid (**5**), mp 152 - 153°C (lit.<sup>7</sup> mp 148°C), prepared in 98 % yield by the reaction of indole-3-acetic acid<sup>8</sup> with benzyl bromide in the presence of two equivalent of sodium hydride in dimethylformamide, was irradiated at 0°C for 3 h with 200 W halogen lamp in the presence of 1 mM Rose Bengal in methanol under oxygen atmosphere, a formation of single product was observed on tlc analysis. The product, which was assumed to be the tricyclic hydroperoxide (**7**; R = H), was treated, without isolation, with dimethyl sulfide for 2 h to give the hydroxy-lactone (**8**)<sup>9</sup> in 96.2 % yield from **5** after purification using silica gel column chromatography. Similarly, *N*-benzyl-2-methylindole-3-acetic acid (**6**), mp 174 - 176°C, prepared from 2-methylindole-3-acetic acid<sup>10</sup> was converted into the corresponding lactone (**9**)<sup>11</sup>, mp 157 - 158°C, in quantitative yield.

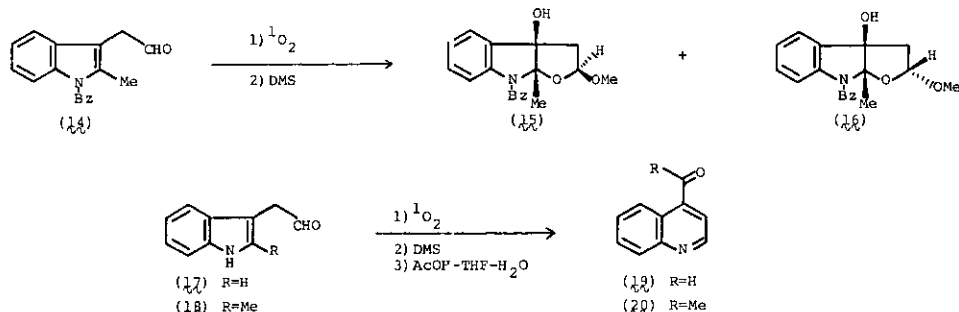
Reaction of the lactone (**8**) with a mixture of 10 % hydrochloric acid and methanol (1 : 1 v/v) at room temperature for 10 h produced in 68.3 % yield the ester (**10**)<sup>12</sup>, whose UV spectrum (MeOH),  $\lambda_{\text{max}}$  nm ( $\epsilon$ ) 249 (9,338) and 286 (2,886), indicated the 2-oxindole structure<sup>13</sup>. This compound would be formed by methanolysis of **8** and dehydration. On the other hand, the same treatment of **9** for 12 h afforded the methyl ether (**11**)<sup>14</sup> in 71.3 % yield, which would be gained by methanolysis, dehydration and a successive S<sub>N</sub>2' type reaction. Reaction of **9** with 10 % methanolic potassium hydroxide at room temperature for 12 h caused the hydrolysis of the lactone and successive rearrangement<sup>4a</sup> giving the carboxylic acid (**12**)<sup>15</sup> in 96.7 % yield. The UV spectrum (MeOH) of the corresponding methyl ester (**13**)<sup>16</sup> derived from **12**,  $\lambda_{\text{max}}$  nm ( $\epsilon$ ) 233 (21,443), 258 (6,495) and 400 (3,090), clearly suggested the 3-oxindole structure.<sup>13</sup> All attempts for the conversion of the tricyclic lactones (**8** and **9**) to quinoline derivatives resulted in failure.



The photo-oxidation was then tested on indole-3-acetaldehydes (**14**, **17** and **18**), which were obtained from the corresponding acids by reduction with diisobutylaluminum hydride at -78°C in 90.8, 75.0 and 83.9 % yield, respectively. On the dye-induced photo-oxidation followed by the reaction with dimethyl sulfide, *N*-benzyl-2-methylindole-3-acetaldehyde (**14**) furnished the separable 1 : 1 mixture of two epimers (**15**)<sup>17</sup> and (**16**)<sup>18</sup> in 81.5 % yield. Acidic treatment of the lactols (**15** and **16**) gave intractable polar products. Finally the desired transformation of indole derivatives to quinolines by the N<sub>1</sub>-C<sub>1</sub> fission was achieved starting from the *N*-unsubstituted aldehydes (**17** and **18**).

The aldehydes (**17** and **18**) were subjected to the photo-oxygenation for 3 h followed by treatment with dimethyl sulfide for 2 h. After evaporation of the solvent and reagents, the crude products were reacted, respectively, with a mixture of acetic

acid - tetrahydrofuran-water (3 : 2 : 2 v/v) at room temperature for 10 h. 4-Formylquinoline (19) and 4-acetylquinoline (20) were obtained in 16.3 % and 62.6 % yield, respectively. The latter product (20) was characterized as picrate, mp 165 - 170°C (decomp.) [lit.<sup>19</sup> mp 165 - 170°C (decomp.)].



Application of the above biomimetic conversion to the synthesis of quinine alkaloids is the next subject.

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- 9) IR (CHCl<sub>3</sub>) 3550 (OH), 1770 cm<sup>-1</sup> (C=O); NMR (CDCl<sub>3</sub>) δ 3.03 (2H, s, CH<sub>2</sub>), 4.47 (2H, s, NCH<sub>2</sub>Ph), 5.53 (1H, s, NCHO); MS m/e 281 (M<sup>+</sup>).
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- 11) IR (CHCl<sub>3</sub>) 3570 (OH), 1760 cm<sup>-1</sup> (C=O); NMR (CDCl<sub>3</sub>) δ 1.63 (3H, s, CH<sub>3</sub>), 2.96 (2H, s, CH<sub>2</sub>), 4.23 and 4.63 (each 1H, each d, J = 17 Hz, NCH<sub>2</sub>Ph); MS m/e 295 (M<sup>+</sup>).
- 12) IR (CHCl<sub>3</sub>) 1725 and 1700 cm<sup>-1</sup> (C=O); NMR (CDCl<sub>3</sub>) δ 2.77 (1H, dd, J = 8 and 17 Hz, CHHCO<sub>2</sub>Me), 3.17 (1H, dd, J = 5 and 17 Hz, CHHCO<sub>2</sub>Me), 3.61 (3H, s, CO<sub>2</sub>Me), 3.84 (1H, dd, J = 5 and 8 Hz, >CHCO), 4.87 (2H, s, NCH<sub>2</sub>Ph); MS m/e 295 (M<sup>+</sup>).
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- 14) IR (CHCl<sub>3</sub>) 1720 cm<sup>-1</sup> (C=O); NMR (CDCl<sub>3</sub>) δ 3.23 (3H, s, OMe), 3.60 (3H, s, CO<sub>2</sub>Me), 3.77 (2H, s, CH<sub>2</sub>CO<sub>2</sub>Me), 4.50 (2H, s, CH<sub>2</sub>OMe), 5.36 (2H, s, NCH<sub>2</sub>Ph); MS m/e 323 (M<sup>+</sup>).
- 15) IR (CHCl<sub>3</sub>) 1710 and 1690 cm<sup>-1</sup> (C=O); NMR δ 1.26 (3H, s, CH<sub>3</sub>), 2.56 and 2.97 (each 1H, each d, J = 16 Hz, CH<sub>2</sub>CO<sub>2</sub>H), 4.50 (2H, s, NCH<sub>2</sub>Ph), 7.60 (1H, d, J = 8 Hz, 4-ArH), 8.30 (1H, br s, CO<sub>2</sub>H); MS m/e 295 (M<sup>+</sup>).
- 16) IR (CHCl<sub>3</sub>) 1730 and 1690 cm<sup>-1</sup> (C=O); NMR 1.27 (3H, s, CH<sub>3</sub>), 2.60 and 2.96 (each 1H, each d, J = 16 Hz, CH<sub>2</sub>CO<sub>2</sub>Me), 3.36 (3H, s, CO<sub>2</sub>Me), 4.53 (2H, s, NCH<sub>2</sub>Ph), 7.62 (1H, d, J = 8 Hz, 4-ArH); MS m/e 309 (M<sup>+</sup>).
- 17) IR (CHCl<sub>3</sub>) 3550 cm<sup>-1</sup> (OH); NMR (CDCl<sub>3</sub>) δ 1.53 (3H, s, CH<sub>3</sub>), 2.53 (2H, d, J = 4.2 Hz, >CH<sub>2</sub>), 3.33 (3H, s, OMe), 4.43 (2H, s, NCH<sub>2</sub>Ph), 4.83 (1H, t, J = 4.2 Hz, >CH), 6.13 (1H, d, J = 8 Hz, ArH); MS m/e 311 (M<sup>+</sup>).
- 18) IR (CHCl<sub>3</sub>) 3580 cm<sup>-1</sup> (OH); NMR (CDCl<sub>3</sub>) δ 1.47 (3H, s, CH<sub>3</sub>), 2.52 (2H, d, J = 3 Hz, >CH<sub>2</sub>), 3.04 (3H, s, OMe), 4.18 and 4.70 (each 1H, each d, J = 17 Hz, NCH<sub>2</sub>Ph), 4.90 (1H, t, J = 3 Hz, >CH), 6.13 (1H, d, J = 8 Hz, ArH).
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