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

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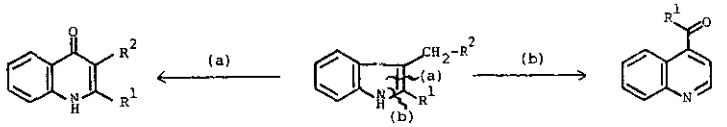
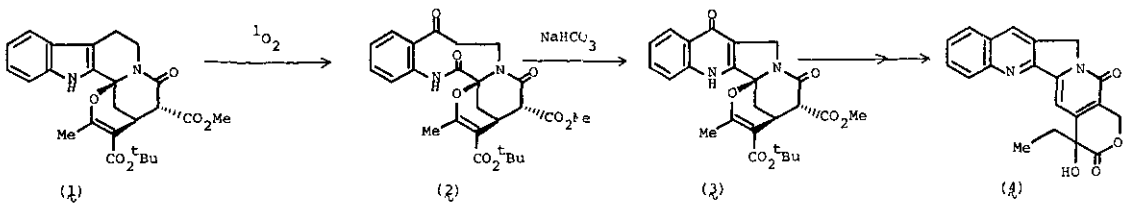
Abstract —— New conversion of indoles to quinolines via the N_1-C_2 fission using singlet oxygen reaction was investigated starting from indole-3-acetic acids and indole-3-acetaldehydes. Dye-induced photo-oxidation of indole-3-acetaldehyde derivatives (17 and 18) followed by treatments with dimethyl 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[1] [type (a) fission], while the cleavage of the N_1-C_2 bond [type (b) fission] leads quinine alkaloids.[2] 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.[3,4] Thus quinoline derivatives were prepared from indoles by the type (a) fission using oxygen molecule.[4] Recently we synthesized (±)-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).[5] On the other hand the formation of quinolines through the type (b) fission with molecular oxygen has not been reported.[6] Intending a duplication of the hypothesis in the biogenesis of quinine[2], we examined photo-oxygenation of indole-3-acetic acid and indole-3-acetaldehyde derivatives.

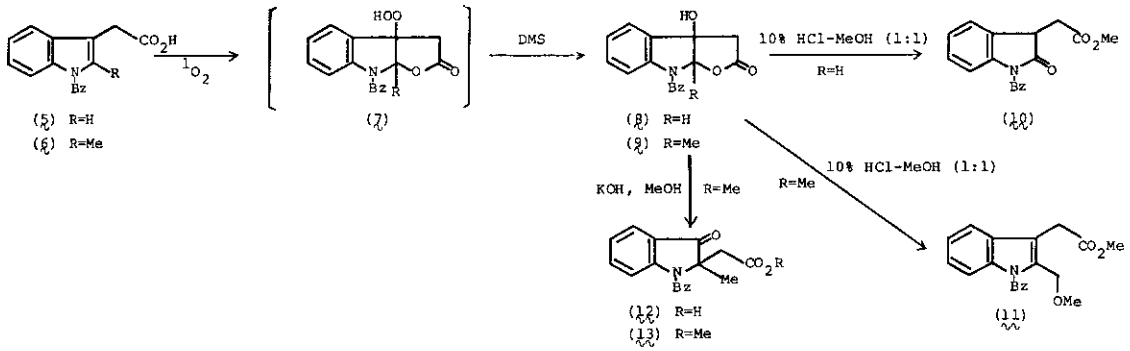




(1) (2) (3) (4)

When N-benzylindole-3-acetic acid (5), mp 152 - 153°C (lit.[7] mp 148°C), prepared in 98 % yield by the reaction of indole-3-acetic acid[8] 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 anaylsis. 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)[9] 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[10] was converted into the corresponding lactone (9)[11], 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)[12], whose UV spectrum (MeOH), λ_{max} nm (ε) 249 (9,338) and 286 (2,886), indicated the 2-oxindole structure[13]. 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 methy ether (11)[14] in 71.3 % yield, which would be gained by methanolysis, dehydration and a successive S_N2' 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[4a] giving the carboxylic acid (12)[15] in 96.7 % yield. The UV spectrum (MeOH) of the corresponding methyl ester (13)[16] derived from 12, λ_{max} nm (ε) 233 (21,443), 258 (6,495) and 400 (3,090), cleanly suggested the 3-oxindole structure.[13] All attempts for the conversion of the tricyclic lactones (8 and 9) to quinoline derivatives resulted in failure.

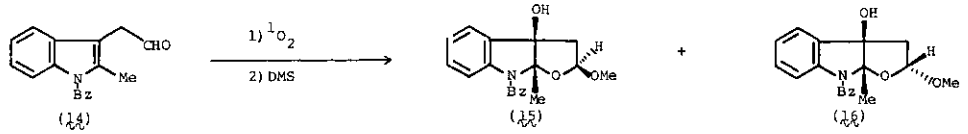


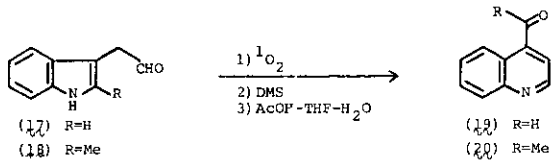
(5) R=H
(6) R=Me
(7)
(8) R=H
(9) R=Me
(10)
(12) R=H
(13) R=Me
(11)

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 diemthyl sulfide, N-benzyl-2-methylindole-3-acetaldehyde (14) furnished the separable 1 : 1 mixture of two epimers (15)[17] and (16)[18] 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_1-C_1 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.[19] 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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7) M. Julia and G. Tchernoff, Bull. Soc. chim. France, 1960, 741.

8) Photo-oxygenation of indole-3-acetic acid followed by treatments with dimethyl sulfide and then 10 % hydrochloric acid afforded 7.5 % yield 3-formylindole, verified by the direct comparison with the authentic sample.

9) IR ($CHCl_3$) 3550 (OH), 1770 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.03 (2H, s, CH_2), 4.47 (2H, s, $NC\underline{H}_2Ph$), 5.53 (1H, s, NCHO); MS m/e 281 (M^+).

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11) IR ($CHCl_3$) 3570 (OH), 1760 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.63 (3H, s, CH_3), 2.96 (2H, s, CH_2), 4.23 and 4.63 (each 1H, each d, J = 17 Hz, $NC\underline{H}_2Ph$); MS m/e 295 (M^+).

12) IR ($CHCl_3$) 1725 and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.77 (1H, dd, J = 8 and 17 Hz, $C\underline{H}HCO_2Me$), 3.17 (1H, dd, J = 5 and 17 Hz, $CH\underline{H}CO_2Me$), 3.61 (3H, s, CO_2Me), 3.84 (1H, dd, J = 5 and 8 Hz, $\rangle CHCO$), 4.87 (2H, s, $NC\underline{H}_2Ph$); MS m/e 295 (M^+).

13) A. I. Scott, "Interpretation of Ultraviolet Spectra of Natural Products", Pergamon Press, Oxford, 1964, p. 172.

14) IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.23 (3H, s, OMe), 3.60 (3H, s, CO_2Me), 3.77 (2H, s, $C\underline{H}_2CO_2Me$), 4.50 (2H, s, $C\underline{H}_2OMe$), 5.36 (2H, s, $NC\underline{H}_2Ph$); MS m/e 323 (M^+).

15) IR ($CHCl_3$) 1710 and 1690 cm^{-1} (C=O); NMR δ 1.26 (3H, s, CH_3), 2.56 and 2.97 (each 1H, each d, J = 16 Hz, $C\underline{H}_2CO_2H$), 4.50 (2H, s, $NC\underline{H}_2Ph$), 7.60 (1H, d, J = 8Hz, 4-ArH), 8.30 (1H, br s, CO_2H); MS m/e 295 (M^+).

16) IR ($CHCl_3$) 1730 and 1690 cm^{-1} (C=O); NMR 1.27 (3H, s, CH_3), 2.60 and 2.96 (each 1H, each d, J = 16 Hz, $C\underline{H}_2CO_2Me$), 3.36 (3H, s, CO_2Me), 4.53 (2H, s, $NC\underline{H}_2Ph$), 7.62 (1H, d, J = 8 Hz, 4-ArH); MS m/e 309 (M^+).

17) IR ($CHCl_3$) 3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.53 (3H, s, CH_3), 2.53 (2H, d, J = 4.2 Hz, $\rangle CH_2$), 3.33 (3H, s, OMe), 4.43 (2H, s, $NC\underline{H}_2Ph$), 4.83 (1H, t, J = 4.2 Hz, $\rangle CH$), 6.13 (1H, d, J = 8 Hz, ArH); MS m/e 311 (M^+).

18) IR ($CHCl_3$) 3580 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.47 (3H, s, CH_3), 2.52 (2H, d, J = 3 Hz, $\rangle CH_2$), 3.04 (3H, s, OMe), 4.18 and 4.70 (each 1H, each d, J = 17 Hz, $NC\underline{H}_2Ph$), 4.90 (1H, t, J = 3 Hz, $\rangle CH$), 6.13 (1H, d, J = 8 Hz, ArH).

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