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

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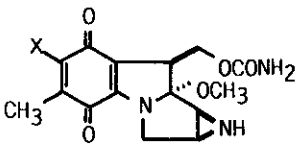
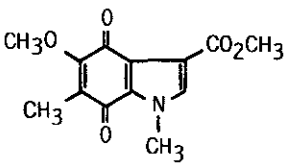
Abstract— Indoloquinone 3 was efficiently synthesized from simple 6-methyindole by several oxidation steps.

Although many synthetic studies[3-5] on mitomycin[1,2] 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[4-1] or 5-methoxyindole derivative.[6, 4-2] Recently, we have found several methods to introduce alkyl,[7,8] acyl,[9] and heteroatoms[10] 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_3 (1)
mitomycin C : X=NH_2 (2)



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6-Methylindole 4 was derived to methyl 1,6-dimethylindole-3-carboxylate 5 by (1) NaH/CH_3I, (2) $(COCl)_2$, (3) 120°C, (4) MeOH in 60% overall yield [MS m/z 203(M^+); ^{1}H-NMR δ($CDCl_3$) 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[11] of 5 with chloroacetylchloride-$AlCl_3$ in CH_2Cl_2 at 25 °C

for 1.3 h afforded single chloroacetyl derivative [MS m/z 280(M^+); ^{1}H-NMR δ ($CDCl_3$) 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 ^{1}H-NMR spectra.

Baeyer-Villiger oxidation[11,12] of 6 with m-chloroperbenzoic acid in the presence of powdered Na_2HPO_4 in chloroform at 25°C for 6 h afforded desired 6-chloroacetoxy derivative 7 in 59% yield [MS m/z 296(M^+); ^{1}H-NMR δ($CDCl_3$) 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)].

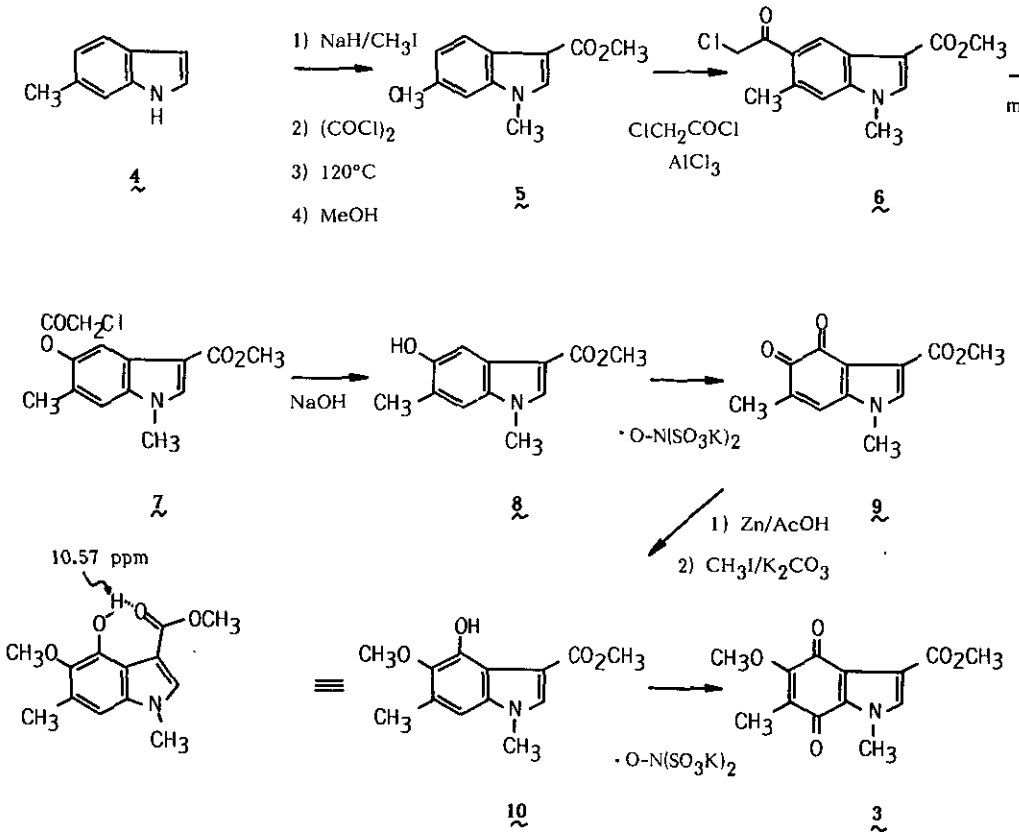
Hydrolysis of chloroacetyl group of 7 was achieved by treatment with 1N NaOH in MeOH at 25 °C to afford 6-hydroxy derivative 8 in quantitative yield [MS m/z 219 (M^+);^{1}H-NMR δ($CDCl_3$) ppm 2.39(3H, br.s), 3.75(3H, s), 3.88(3H, s), 7.06(1H, br.s), 7.61(1H, s), 7.63(1H, s)].

Compound 8 was oxidized with Fremy's salt [$\cdot ON(SO_3K)_2$] in acetone-H_2O(1:2) at 25 °C for 10 min to give orthoquinone 9 in quantitative yield [MS m/z 233(M^+); ^{1}H-NMR ($CDCl_3$) 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_2O-BF_3OEt_2 [4-1] afforded no desired triacetoxy 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_3I/K_2CO_3 in DMF at 25°C for 45 min to give 5-methoxy derivative 10 in 54% yield [10: MS m/z 249(M^+); ^{1}H-NMR δ($CDCl_3$) 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 ^{1}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^+); ^{1}H-NMRδ($CDCl_3$) 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.



REFERENCES

1. 1) T. Hata, Y. Sano, R. Sugiura, A. Matsumae, K. Kanamori, Y. Shima, and T. Hoshi, J. Antibiotics, 1956, 9, 141 and 146. 2) S. Sawaki, K. Marumo, G. Tomioka, E. Shimazu, H. Kato, H. Kamata, S. Kudo, Y. Fujimoto, Antibiotics and Chemotherapy, 1958, 8, 228.

2. 1) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broshard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, J. Amer. Chem. Soc., 1962, 84, 3185. 2) A. Tulinsky, ibid, 1962, 84, 3188.

Recently the absolute configulation of mitomycins have been revised.

1) K. Shirahata, and N. Hirayama, J. Amer. Chem. Soc., 1983, 105, 7199. 2) U. Hornemann and M. J. Heins, J. Org. Chem., 1985, 50, 1301.

3. Y. Kishi, J. Natul. Prod., 1979, 42, 549 and references cited therein.

4. Syntheses of mitosene and mitosane derivative.
1) G. R. Allen, J. F. Poletto, and M. J. Weiss, J. Amer. Chem. Soc., 1964, 86, 3877. Idem, J. Org. Chem., 1965, 30, 2897. 2) T. Kametani, T. Takahashi, M. Ihara, and K. Fukumoto, J.C.S. Perkin Trans. I, 1976, 389. 3) R. M. Coats and P. A. MacManus, J. Org. Chem., 1982, 47, 4822. 4) M. Akiba, S. Ikuta, and T. Takada, J.C.S. Chem. Commun., 1983, 817. 5) J. R. Luly and H. Rapoport, J. Amer. Chem. Soc., 1983, 105, 2859. 6) Y. Naruta, N. Nagai, and K. Maruyama, Chemistry Lett., 1983, 1383. 7) J. Rebek, Jr., S. H. Shaber, Youe-Kong Shue, J-C. Gehret, and S. Zimmerman, J. Org. Chem., 1984, 49, 5164. 8) S. Danishefsky, E. M. Berman, M. Ciufolini, S. J. Etheredge, and B. E. Segmuller, J. Amer. Chem. Soc., 1985, 107, 3891. 9) K. J. Shaw, J. R. Luly, and H. Rapoport, J. Org. Chem., 1985, 50, 4515.

5. The other synthetic studies. For instance, see: 1) T. Hirata, Y. Yamada, and M. Matsui, Tetrahedron Lett., 1969, 4107. 2) J. W. Lown and T. Itoh, Can. J. Chem., 1975, 53, 960. 3) K. Takahashi and T. Kametani, Heterocycles, 1979, 13 411. 4) R. M. Cory and B. M. Ritchie, J.C.S. Chem. Commun., 1983, 1244. 5) K. Oda, T. Ohnuma, and Y. Ban, J. Org. Chem., 1984, 49, 953. 6) W. Sucrow, R. Brockmann, H. -J. Haupt, and H. Preut, Liebigs Ann. Chem., 1984, 1711. 7) M. Dartmann, W. Flitsch, B. Krebs, and P. Russkamp, ibid., 1985, 1437. 8) W. C. Dijksman, W. Verboon, R. J. M. Egberrink, and D. N. Reinhoudt, J. Org. Chem., 1985, 50, 3791. 9) Y. Naruta, N. Nagai, T. Yokota, and K. Maruyama, Chemistry Lett., 1986, 1185.

6. G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, J. Amer. Chem. Soc., 1964, 86, 3879.

7. S. Nakatsuka, H. Miyazaki, and T. Goto, Tetrahedron Lett., 1980, 21, 2817.

8. S. Nakatsuka, H. Miyazaki, and T. Goto, Chemistry Lett., 1981, 407.

9. S. Nakatsuka, O. Asano, and T. Goto, Heterocycles, 1986, 24, 2109.

10. S. Nakatsuka, T. Masuda, O. Asano, T. Teramae, and T. Goto, Tetrahedron Lett., 1986, 27, 4327.

11. Similar Friedel-Crafts acetylation of stabilized indole derivatives was reported [T. Hino, Y. Torisawa, and M. Nakagawa, Chem. Pharm. Bull., 1982, 30, 2349]]. But such acetyl derivative afforded mainly oxidized products of the pyrrole part by m-CPBA oxidation.

12. Methyl indole-3-carboxylate was also derived to corresponding 5- and 6-hydroxy derivatives by the same method.

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