A SYNTHESIS OF 6-METHYLINDOLE DERIVATIVES BY METHYLTHIOMETHYLATION AT 6-POSITION IN INDOLE NUCLEUS

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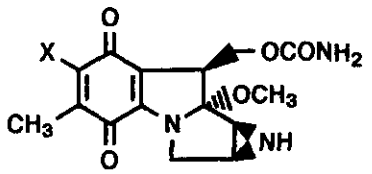
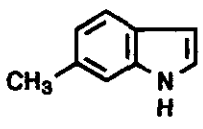
Abstract- 6-Methylindole derivatives were synthesized by introduction of methylthiomethyl group onto the 6-position of indole nucleus and subsequent desulfurization.

Introduction of substituents on the benzene part (4~7 position) of indole ring is one of the most difficult problems in the organic syntheses.[1] We have developed several useful methods to resolve the problem and applied those to the syntheses of some natural products.[2~4] Mitomycin[5] is one of the most complicated natural products containing modified indole nucleus. All attempts toward total syntheses[6] of mitomycins or its common structure: mitosenes[4d, e, 7] started from substituted aniline and no synthetic route toward mitomycins from simple indole have been appeared.



Mitomycin **A** X=OCH_3 **(1)**
C X=NH_2 **(2)**



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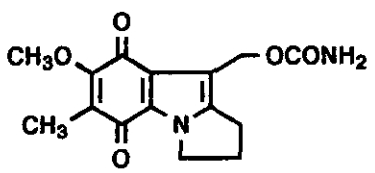

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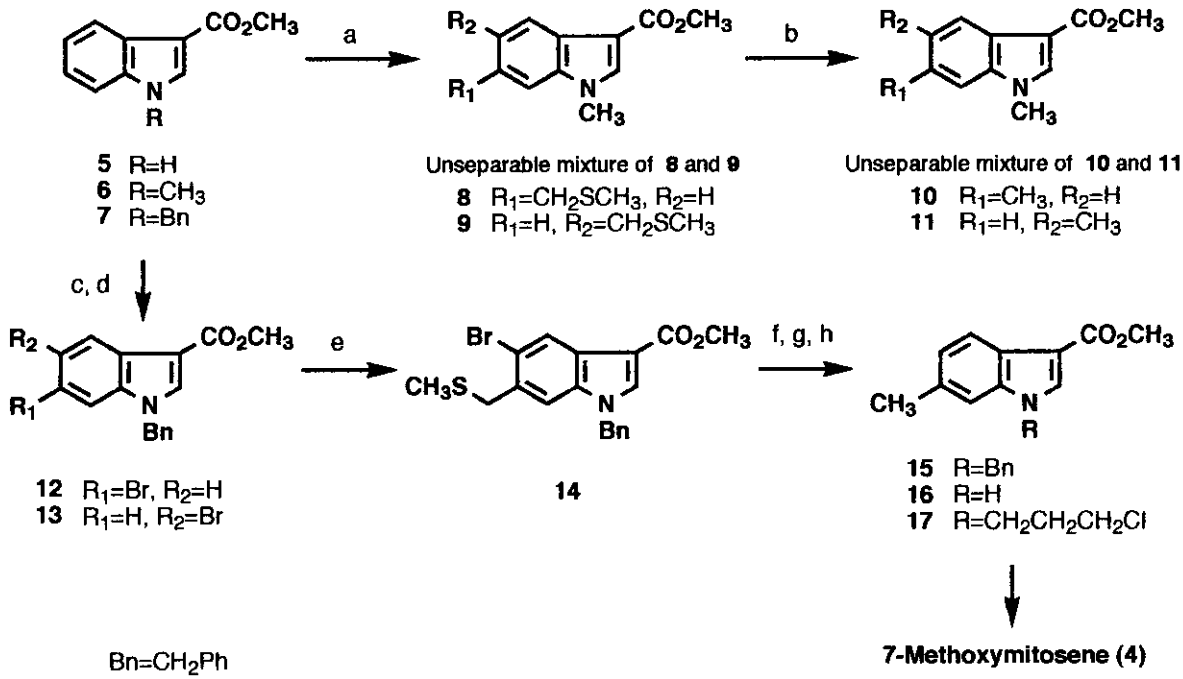
We have been reported efficient methods for the synthesis of indoloquinone[4a~c] and applied them for the synthesis of 7-methoxymitosene (**4**) starting from 6-methylindole (**3**).[4d, e] In this paper, we report a novel method for the synthesis of 6-methylindole derivative by methylation at 6-position of indole nucleus.

Although Friedel-Crafts acylation[4b, c, 8] of methyl indole-3-carboxylate (**5**) afforded corresponding 5- and 6-monoacyl derivatives in reasonable yields, Friedel-Crafts alkylation of **5** gave only small amount of 5- and 6-alkylated products. For the synthesis of mitomycin, we tried methylation of methyl 1-methylindole-3-carboxylate (**6**) by $CH_3Br/AlCl_3$, $(CH_3)_2SO_4/AlCl_3$ *etc.*, but no desired methylated product was obtained.

On the other hands, Friedel-Crafts alkylation of **6** using stabilized alkylating agent: chloromethyl methyl sulfide (5 eq. $ClCH_2SCH_3$)/5 eq. $AlCl_3$ at 25°C for 1 h gave desired monoalkylated products (**8** and **9**) as unseparable mixture in 28% yield(1:1). **8**; ^{1}H-nmr ($CDCl_3$) δ(ppm) 2.02 (3H, br s), 3.82 (3H, s), 3.83 (2H, s), 3.90 (3H, s), 7.23 (1H, br d, J=8.2 Hz), 7.26 (1H, s), 7.78 (1H, s), 8.09 (1H, d, J=8.2 Hz). **9**; ^{1}H-nmr ($CDCl_3$) δ(ppm) 2.00 (3H, s), 3.82 (3H, s), 3.84 (2H, s), 3.91 (3H, s), 7.29~7.34 (2H, m), 7.76 (1H, s), 8.04 (1H, s). Desulfurization of **8** and **9** was achieved with Raney Ni to give 5- and 6-methyl derivatives (**10** and **11**) in 90% yield but those were also unseparable on silica gel tlc or column chromatography.

N-Benzyl derivative (**7**)[9] was obtained by benzylation of **5** with $BnBr/K_2CO_3$ in DMF in 96% yield. Bromination of **7** with 1.5 eq. Br_2 at 0°C for 2 h afforded 5-bromo derivative (**13**,[11] 31%) with its 6-bromo isomer (**12**,[10] 61%). Those were easily separated on silica gel column chromatography. The brominated positions of **12** and **13** were easily determined by ^{1}H-nmr spectra [H-4 proton signal. **12**; 8.05 ppm (1H, d, J=8.6 Hz), **13**; 8.33 ppm (1H, d, J=1.8 Hz)].[4a~c, 8] Methylthiomethylation of **13** with 1.2 eq. $ClCH_2SCH_3$/5 eq. $AlCl_3$ in CH_2Cl_2 at -20°C for 30 min was very clean and 6-methylthiomethyl derivative (**14**)[12] was obtained in 91% yield after short column chromatography using silica gel. We understand that bromine atom at the 5-position of **13** accelerated the reactivity of the 6-position and alkylating yield was very high.

Not only desulfurization but also debromination of **14** with Raney Ni in methanol at 25°C for 10 min gave desired 6-methylindole derivative (**15**,[13] 76%). Removal of *N*-benzyl group of **15** was achieved with $AlCl_3$ in CH_2Cl_2 at 25°C to give methyl 6-methylindole-3-carboxylate (**16**,[14] 87%). Consequently, methyl group was introduced at the 6-position of indole nucleus by (1) bromination, (2) methylthiomethylation, (3)



Reagents: a) $ClCH_2SCH_3$, $AlCl_3$ (28%); b) Raney Ni (90%); c) BnBr, K_2CO_3 (96%); d) Br_2 (**12**; 61%, **13**; 31%); e) $ClCH_2SCH_3$, $AlCl_3$ (91%); f) Raney Ni (76%); g) $AlCl_3$ (87%); h) $BrCH_2CH_2CH_2Cl$, K_2CO_3 (94%).

reduction with Raney Ni in 21% over all yield (**7**→**15**).

Then, 6-methylindole derivative (**16**) was treated with $Br(CH_2)_3Cl/K_2CO_3$ in DMF to afford *N*-chloropropyl derivative (**17**) in 94% yield.[4e] Since we reported a synthetic route toward 7-methoxymitosene (**4**) from **17** as a key intermidiate, we could establish an improved route to **4**.

By combination of those results and the previous publication, we could introduce all functional groups found in 7-methoxymitosene (**4**) in a simple indole (**5**). Further synthetic studies toward mitomycins are now in progress.

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9. **7**; mp 69.5~70°C, ^{1}H-nmr ($CDCl_3$) δ(ppm) 3.91 (3H, s), 5.34 (2H, s), 7.14~7.33 (8H, m), 7.84 (1H, s), 8.20 (1H, m).

10. **12**; mp 113.5~114°C, ^{1}H-nmr ($CDCl_3$) δ(ppm) 3.89 (3H, s), 5.28 (2H, s), 7.12~7.38 (6H, m), 7.46 (1H, d, J=1.5 Hz), 7.78(1H, s), 8.05 (1H, d, J=8.6 Hz).

11. **13**; mp 118°C, ^{1}H-nmr ($CDCl_3$) δ(ppm) 3.91 (3H, s), 5.30 (2H, s), 7.11~7.17 (3H, m), 7.30~7.33 (4H, m), 7.83 (1H, s), 8.33 (1H, d, J=1.8 Hz).

12. **14**; mp 131°C, ^{1}H-nmr ($CDCl_3$) δ(ppm) 1.92 (3H, s), 3.88 (2H, s), 3.91 (3H, s), 5.32 (2H, s), 7.12~7.15 (2H, m), 7.27~7.34 (3H, m), 7.83 (1H, s), 8.39 (1H, s).

13. **15**; mp 81°C, ^{1}H-nmr ($CDCl_3$) δ(ppm) 2.44 (3H, s), 3.89 (3H, s), 5.28 (2H, s), 7.09~7.15 (4H, m), 7.30~7.36 (3H, m), 7.76 (1H, s), 8.38 (1H, d, J=8.6 Hz).

14. **16**; mp 155°C, ^{1}H-nmr ($CDCl_3$) δ(ppm) 2.46 (3H, s), 3.92 (3H, s), 7.11 (1H, br d, J=8.2 Hz), 7.20 (1H, br s), 7.84 (1H, d, J=3.1 Hz), 8.05 (1H, d, J=8.2 Hz), 8.56 (1H, br s).

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