NOVEL DIMERIZATION PRODUCTS OF *N*-ACYLINDOLES WITH $AlCl_3$

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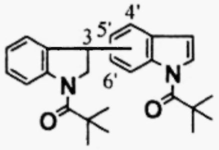
Abstract : The reactivity of *N*-methoxycarbonylindole **2** in the presence of aluminum chloride was studied and the structures of the products were determined to be dimers **3a-c**, **4a-c**, **5** and **6**.

Although many indole alkaloids containing functional groups on the benzene part of indole nucleus had been appeared. introduction of the functional groups at the specific positions was difficult except a few cases (1). We have developed novel methods (2) introducing various functional groups on the benzene part of stabilized indoles and applied them for total synthesis of Teleocidin B (3) and efficient synthesis of the Mitomycin skeleton (4). In the study of chemical reactivity of *N*-pivaloylindole, we found novel dimerization of *N*-pivaloylindole in presence of $AlCl_3$ to give **1a-c** (Fig. 1.) (5). These were completely different from polymerization products (6) of indole itself in acidic conditions. In this publication we report novel dimerization products of *N*-methoxycarbonylindole **2**.



1a-c (**a**: 3-4', **b**: 3-5', **c**: 3-6')

Fig. 1. Dimers of *N*-pivaloylindole

First of all, we examined polymerization of *N*-acetyl and *N*-benzoylindoles in the presence of 5 eq. $AlCl_3$ and the results were very similar with *N*-pivaloylindole to give dimers corresponding to **1a-c**.

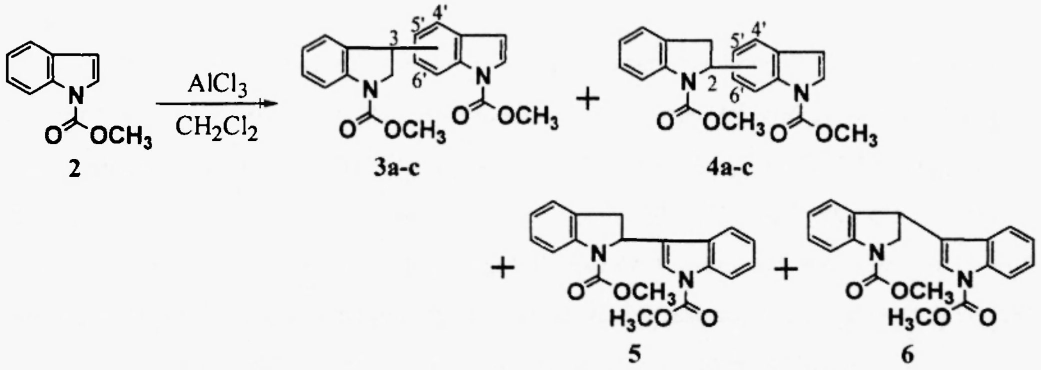
N-Methoxycarbonylindole **2** (7) was treated with $AlCl_3$ under various conditions, we isolated eight dimers. Two types of dimers of **2** were observed. One of them was produced by condensation between a pyrrole part and a benzene part of each indole moiety (dimers **3a-c** and **4a-c**) and the other one was between both pyrrole parts (**5** and **6**) (Scheme 1).

When the reaction was carried out with 1.0 eq. $AlCl_3$ in CH_2Cl_2 at 25℃ for 120 min, major product was 2,3'-dimer **5** in 70% yield (entry 1 in Table). It is considered that the dimer **5** was formed by condensation between coordinated **2** with $AlCl_3$ at the pyrrole part (electrophile) and $AlCl_3$-free **2** (nucleophile).

When the reaction was carried out with 5.0 eq. $AlCl_3$ in CH_2Cl_2 at 25℃ (entry 2), **3a-c** were obtained as a major component in 24% (**a**:**b**:**c** = 1:1:4), and **4a-c** were obtained in 6% (**a**:**b**:**c** = 1:1:8). When the reaction was carried out at -20℃ (entry 3), 2,4'~6'-dimers **4a-c** were obtained as a major component in 18% (**a**:**b**:**c** = 1:1:9). At low temperature, the selectivity of electrophilic addition at 2-position was increased. Purification of dimer **3-6** was carried out by HPLC using reversed-phase column (solvent : 75% MeOH, 1% AcOH in H_2O) to give a mixture of **4a-c**. Further purification of **4a-c** by normal phase HPLC (solvent : 7% EtOAc in hexane) gave **4c** (8) and **4ab**. Since separation of **4ab** was difficult, a mixture of **4ab** was hydrolyzed with 1N NaOH in MeOH at 25℃ for 10 min. **7a** and **7b** (9, 10) were isolated by reversed-phase HPLC (solvent : 55% MeOH, 1% AcOH in H_2O). In the same way, a mixture of **3a-c** and **6** were also hydrolyzed with 1N NaOH in MeOH at 50℃ for 15 min and it has succeeded in refining each component by HPLC. Structures of each isolated compounds were determined by ^{1}H-NMR *etc.*

Dimerization mechanism for the reaction of 2 to dimer **4c** was shown in Scheme 2. Though $AlCl_3$ coordinated at N-position for *N*-pivaloylindole, the nucleophilicity of pyrrole part is lost by the coordination of **2** with $AlCl_3$ (I) at the 3-position and electrophilic 2-position was attacked with a benzene part of the other I to give 2,6'-dimer **4c**.

Thus obtained **4a-c** were novel dimers of simple indole. Reactivity of *N*-acylindole and application of these reaction is now in progress.



	$AlCl_3$	temp.	time	3a-c	4a-c	5	6
entry 1	1.0 eq.	25℃	120min	—	—	70%	—
entry 2	5.0 eq.	25℃	2min	24%	6%	1%	5%
entry 3	5.0 eq.	-20℃	30min	10%	18%	1%	2%

Scheme 1. Dimerization of *N*-methoxycarbonylindole

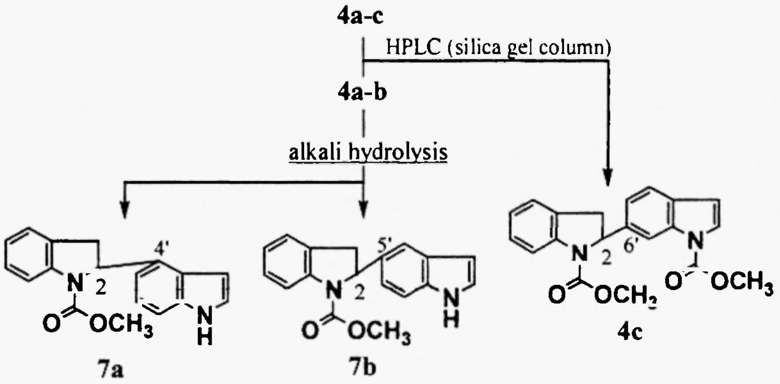
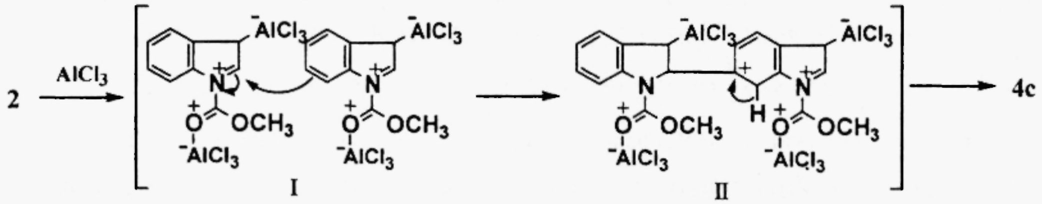


Fig. 2. Purification of a mixture of dimers **4a-c**



Scheme 2. Dimerization mechanism of *N*-methoxycarbonylindole

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8) **4c** : m.p. 137-138℃; ^{1}H-NMR δppm (500MHz, d_6-Aceton) : 3.00 (1H, dd, *J*=3, 16Hz), 3.64 (3H, br.s), 3.82 (1H, dd, *J*=11, 16Hz), 3.99 (3H, s), 5.65 (1H, dd, *J*=3, 11Hz), 6.62 (1H, br.d, *J*=4Hz), 7.01 (1H, br.t, *J*=8Hz), 7.08 (1H, br.d, *J*=8Hz), 7.19 (1H, d, *J*=8Hz), 7.25 (1H, t, *J*=8Hz), 7.51 (1H, d, *J*=8Hz), 7.61 (1H, d, *J*=4Hz), 7.88 (1H, br.s), 8.07 (1H, s); EI-MS *m/z* : 350 (M^+).

9) **7a** : amorphous solid; ^{1}H-NMR δppm (400MHz, 10% CD_3OD in $CDCl_3$) : 3.12 (1H, dd, *J*=3, 16Hz), 3.38 (3H, br.s), 3.80 (1H, dd, *J*=10, 16Hz), 5.87 (1H, dd, *J*=3, 10Hz), 6.37 (1H, br.s), 6.85 (1H, br.d, *J*=8Hz), 7.01 (1H, t, *J*=8Hz), 7.05 (1H, t, *J*=8Hz), 7.13 (1H, d, *J*=8Hz), 7.21 (1H, br.s), 7.27 (1H, t, *J*=8Hz), 7.31 (1H, d, *J*=8Hz), 7.96 (1H, br.s), 9.57 (1H, br.s); EI-MS *m/z* : 292 (M^+).

10) **7b** : amorphous solid; ^{1}H-NMR δppm (500MHz, d_6-Aceton) : 3.00 (1H, dd, *J*=3, 16Hz), 3.63 (3H, s), 3.77 (1H, dd, *J*=10, 16Hz), 5.58 (1H, dd, *J*=3, 10Hz), 6.38~6.39 (1H, m), 6.95 (1H, d, *J*=8Hz), 6.99 (1H, t, *J*=7Hz), 7.18 (1H, d, *J*=7Hz), 7.23 (1H, t, *J*=7Hz), 7.27 (1H, t, *J*=3Hz), 7.32 (1H, d, *J*=8Hz), 7.38 (1H, s), 7.86 (1H, br.s), 10.15 (1H, br.s); EI-MS *m/z* : 292 (M^-).

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