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Structures of dimers and trimers of 1-trimethylacetylindole produced in presence of aluminum chloride

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Abstract

The reactivity of 1-trimethylacetylindole **3** in the presence of aluminum chloride was studied and the structures of the products were determined as its dimers **4a–c** and trimers **5c**, etc. © 2000 Elsevier Science Ltd. All rights reserved.

Many important indole alkaloids such as tumor promoter: teleocidins **3**,[1] mitomycins[2] etc., contain several substituent(s) at the benzene part of their indole nucleus. But, introduction of such substituents on the indole nucleus is one of the most difficult problems for their chemical synthesis.[3]

We have reported unique methods[4] for direct introduction of substituent at the benzene part of simple indole derivatives and applied them for the synthesis of indole alkaloids.[5] Recently, we have developed novel synthetic method[6] of Uhle's ketone and 6-acylindole derivatives by intra and intermolecular acylation of 4 or 6-position of indole nucleus.[7] In this publication, we describe the reactivity of **3** in the presence of protonic or Lewis acid and unique structures of its dimers and trimers produced in the presence of aluminum chloride.

Dimerization of simple indole in concd hydrochloric acid was first studied by Schimitz-Dumont[8] and the proposed structure was revised by Smith[9] as shown in Scheme 1. The mechanism producing **2** was realized as follows; (i) protonation at 3-position of indole gives intermediate [**I**], (ii) nucleophilic attack at 2-position of [**I**] with most reactive 3-position as nucleophilic center of the other indole molecule.

Friedel–Crafts type acylation of **3** with various acyl chloride or alkyl halide in presence of aluminum chloride were studied for the synthesis of substituted indoles. But, very similar products were always obtained in the different reaction. Therefore, polymerization of **3** in the presence of aluminum chloride was expected in these reactions.

By treatment of **3** with 5 equiv. aluminum chloride in dichloromethane at 25°C for 30 min the starting material **3** completely disappeared and more polar compounds were detected on silica gel TLC plate. Aqueous potassium sodium tartrate solution was added to the reaction mixture and the solution was

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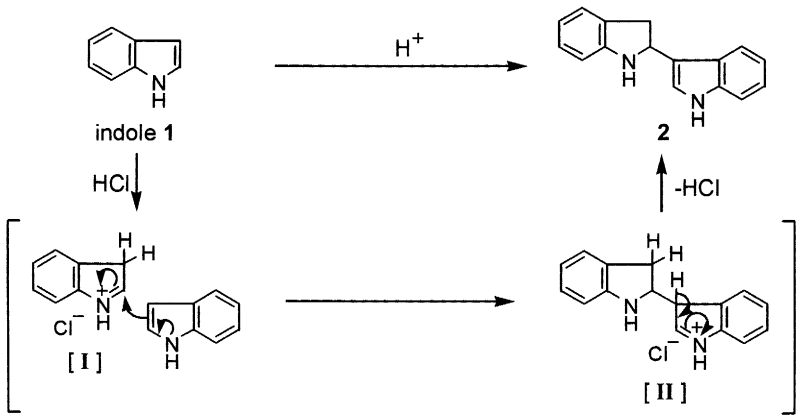
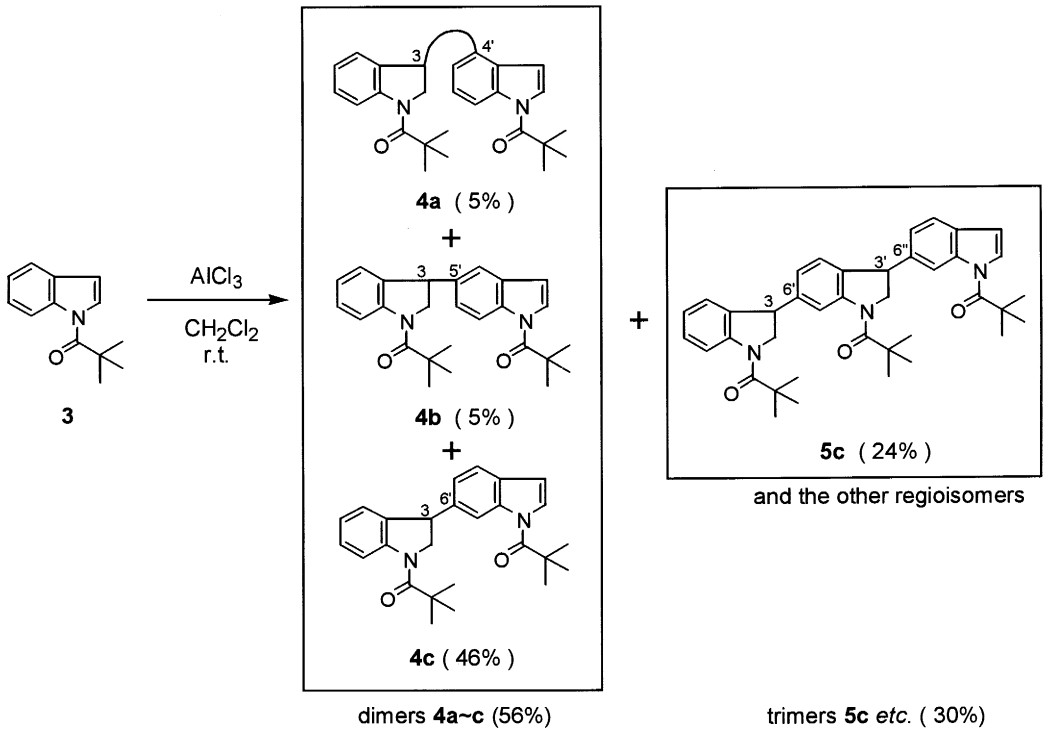


Scheme 1. Dimerization of indole in the presence of protonic acid [Hodson and Smith (1957)[9b]]

extracted with dichloromethane. Major two groups were separated on preparative silica gel TLC plate [20% EtOAc in hexane to give group A (56%) and group B (30%), respectively].

Since ^{1}H NMR spectra of non-polar group A suggested that group A was a mixture of three isomers (ratio=10:1:1), we tried isolation of these three isomers by combination of normal phase silica gel HPLC column (solvent: 2% EtOAc in hexane or 0.5% CH_3CN in hexane) and obtained three dimers **4a** (5%), **4b** (5%) and **4c** (46%). MS and ^{1}H NMR spectra of those compounds indicated the structures were dimer of **3**. These structures were determined by their H–H cosy spectra to be (3–4′)-dimer **4a**,[10] (3–5′)-dimer **4b**[11] and (3–6′)-dimer **4c**,[12] respectively.

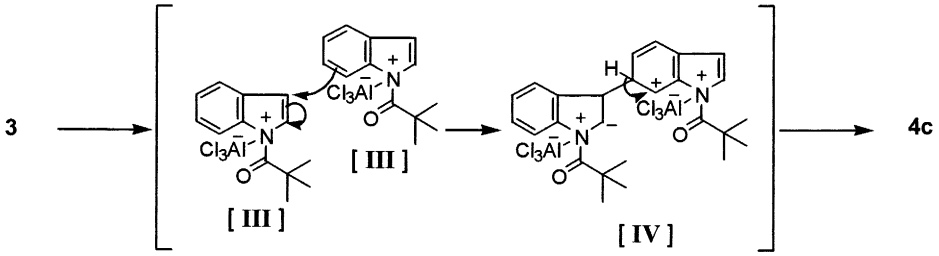
Since group B consisted of four or more components by analysis with HPLC, the most component **5c**



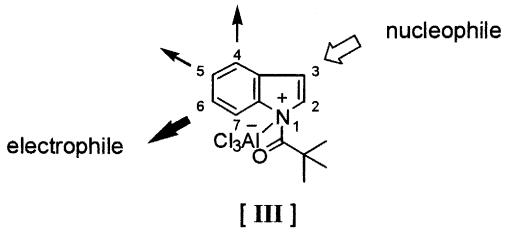
Scheme 2.

was purified with HPLC (solvent: 10% EtOAc in hexane). MS and ^{1}H NMR spectra of **5c** indicated the structure was (3-6′)-(3′-6′′)-trimer **5c**[13] as shown in the structure (Scheme 2).

Reaction mechanism producing these dimers and trimers were realised to be (i) formation of $AlCl_3$-**3** complex [**III**], (ii) intermolecular nucleophilic attack at 3-position of [**III**] by 6-position (or 5- or 4-position) of the other complex [**III**] (Scheme 3). From such regio-selectivity to produce dimers **4a**–**c** and trimers **5c** etc., we understand that (i) 2- and 3-position of **3** completely lost the reactivity as a nucleophile by formation of $AlCl_3$ complex [**III**] and the 3-position became the most electron deficient position and attacked by nucleophile and (ii) benzene part (6≫5≒4) of [**III**] is relatively electron rich center toward electrophile (Scheme 4).



Scheme 3. Dimerization mechanism of **3**



Scheme 4. Reactivity of $AlCl_3$–**3** complex [**III**] with electrophile and nucleophile

We believe that the polymerization of 1-trimethylacetylindole **3** indicates the typical reactivity of indole nucleus. Further mechanistic study and application of these selectivities for the synthesis of natural products are now in progress.

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10. Compound **4a**: MS: *m/z* 402. ^{1}H NMR ($CDCl_3$): δ ppm 1.34 (9H, s), 1.51 (9H, s), 4.24 (1H, d.d., J=8, 10 Hz), 4.72 (1H, br.t, J=10 Hz), 4.92 (1H, br.t, J=8 Hz), 6.38 (1H, br.d, J=4 Hz), 6.97 (1H, br.d, J=8 Hz), 7.00 (lH, br.t, J=8 Hz), 7.09 (1H, br.d, J=8 Hz), 7.27 (1H, br.t, J=8 Hz), 7.30 (1H, t, J=8 Hz), 7.70 (1H, d, J=4 Hz), 8.34 (1H, br.d, J=8 Hz), 8.47 (lH, br.d, J=8 Hz).
11. Compound **4b**: MS: *m/z* 402. ^{1}H NMR ($CDCl_3$): δ ppm 1.34 (9H, s), 1.51 (9H, s), 4.16 (1H, m), 4.65 (2H, m), 6.56 (1H, d, J=4 Hz), 6.99 (1H, br.d, J=8 Hz), 7.02 (1H, br.t, J=8 Hz), 7.21 (1H, br.d, J=8 Hz), 7.26 (1H, br.t, J=8 Hz), 7.34 (1H, br.s), 7.74 (1H, d, J=4 Hz), 8.31 (1H, br.d, J=8 Hz), 8.47 (1H, d, J=8 Hz).
12. Compound **4c**: MS: *m/z* 402. ^{1}H NMR ($CDCl_3$): δ ppm 1.35 (9H, s), 1.53 (9H, s), 4.16 (1H, d.d., J=11, 14 Hz), 4.68 (2H, m), 6.61 (lH, d, J=4 Hz), 6.97 (1H, br.d, J=8 Hz), 7.00 (1H, br.t, J=8 Hz), 7.04 (1H, br.d, J=8 Hz), 7.24 (1H, br.t, J=8 Hz), 7.49 (1H, d, J=8 Hz), 7.74 (1H, d, J=4 Hz), 8.30 (1H, br.d, J=8 Hz), 8.52 (1H, br.s).
13. Compound **5c**: MS: *m/z* 603. The ^{1}H NMR spectrum was very complicated. We assume **5c** might be a mixture of two diastereomers.