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Dimerization of indole derivatives with hypervalent iodines(III): a new entry for the concise total synthesis of *rac*- and *meso*-chimonanthines

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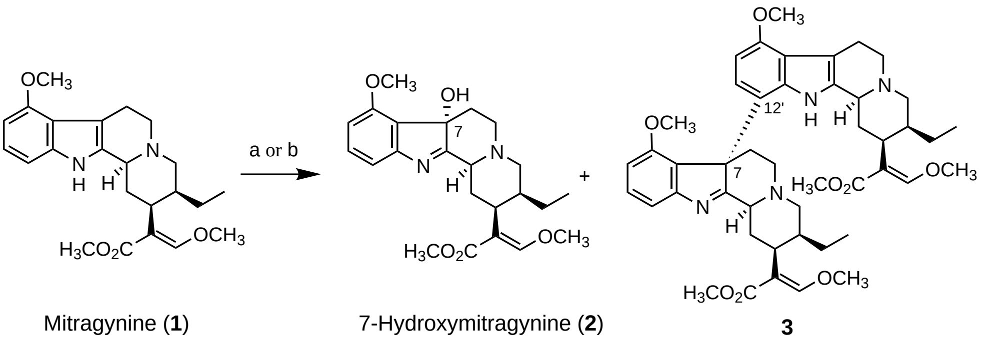
Abstract—Hypervalent iodine(III)-induced dimerization of indole derivatives, mitragynine, tetrahydrocarbazole, and N_b-carbomethoxytryptamine, was investigated. By applying this procedure, the concise total synthesis of *rac*- and *meso*-chimonanthines was accomplished. © 2002 Elsevier Science Ltd. All rights reserved.

In our recent chemical[1] and pharmacological[2] studies on the opioid agonistic indole alkaloid, mitragynine (**1**), we investigated the preparation of several kinds of oxidative derivatives of **1**.[3] During this study, we discovered an unusual dimerization reaction when **1** was treated with phenyliodine (III) bis(trifluoroacetate) (PIFA). This finding prompted us to investigate the dimerization reaction of indole derivatives using hypervalent iodines.[4] By applying the reaction conditions developed in the present study, we accomplished the concise total synthesis of *meso*- and *rac*-chimonanthines (**9** and **10**). In this communication, we describe these novel and significant findings on the dimerization of indole derivatives with hypervalent iodines.

In order to prepare 7-hydroxymitragynine (**2**), which was found to exhibit strong opioid agonistic activity,[3a] we first exposed mitragynine (**1**) to a hypervalent iodine(III) reagent, PIFA, according to the reported method[5] with slight modification. In the previous procedure,[5a] methanol, which was used as solvent, was introduced at the β position of the indole ring as a methoxy group. Accordingly, we changed the solvent to aqueous CH_3CN expecting the introduction of a hydroxyl group at C-7, and obtained the desired product **2** in 50% yield (Scheme 1). Investigation of the minor products in the residue led to the isolation of a novel dimeric compound (**3**) in 6% yield. The structure of **3** was determined by spectroscopic analysis, in par-



Scheme 1. *Reagents and conditions*: (a) 1.0 equiv. PIFA, aq. CH_3CN, 0°C, **2** (50%), **3** (6%); (b) 1.0 equiv. PIFA, dry CH_2Cl_2, 0°C, **2** (39%), **3** (10%).

Keywords: alkaloids; natural products; indole; dimerization; hypervalent iodines; chimonanthine.

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ticular, by using the following characteristic observations in the NMR spectra measured at −50°C: the presence of a set of *ortho*-coupled protons at δ 7.34 (1H, d, $J=7.7$ Hz, H-11′) and 6.50 (1H, d, $J=7.7$ Hz, H-10′), HMBC correlation between H-6 and C-12′, and NOE correlation between H-11′ and H-3 (Fig. 1). When the solvent in the above reaction was replaced with dry CH_2Cl_2, the same products **2** and **3** were obtained in 39% and 10% yields, respectively, indicating that the origin of the hydroxyl group in **2** would be the trifluoroacetoxy function in PIFA.

To examine the generality of the dimerization of indoles with hypervalent iodines(III), we chose a simple indole derivative, 1,2,3,4-tetrahydrocarbazole (THC, **4**), as substrate (Scheme 2). Oxidation of **4** with 0.5 equiv. of PIFA in dry CH_2Cl_2 gave a dimeric compound (**5**),[6] having a C–C bond between the β position of an indolenine unit and the C-7 position of an indole nucleus, in 77% yield, together with trace amounts of two different types of dimers (**6a** and **6b**). Quite interestingly, these dimeric compounds, which have a linkage between the β-β′ positions of two indolenine units, were obtained as major products in 42% total yield, when phenyliodine(III) diacetate (PIDA) was used as a reagent instead of PIFA. These two dimeric compounds, i.e. *meso* (**6a**, less polar) and *racemic* (**6b**, more polar), could be separated by SiO_2 chromatography, and the structure of **6b** was determined by X-ray analysis.[7]

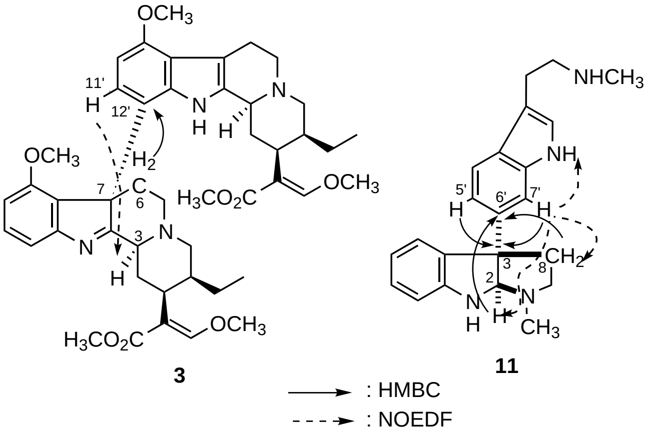
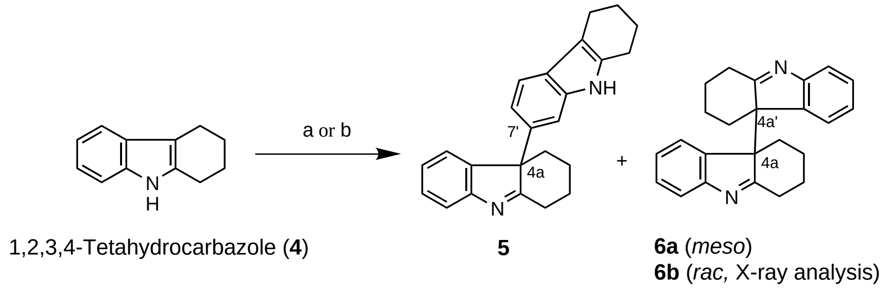
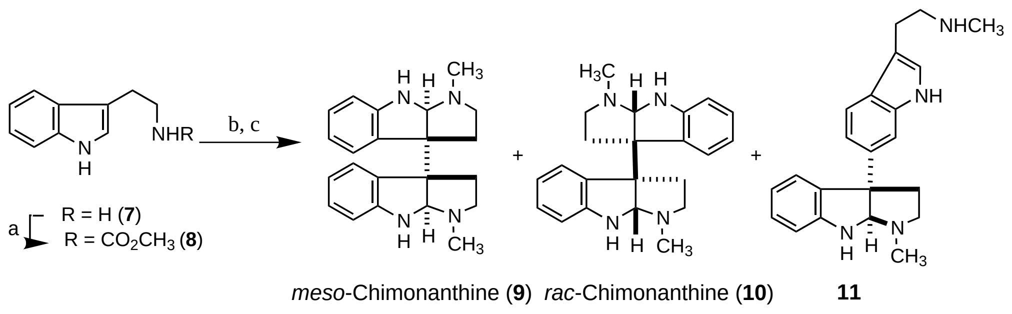


Figure 1.

Using this new synthetic procedure, we attempted the total synthesis of chimonanthines, which are dimeric pyrrolidinoindoline alkaloids isolated from plants belonging to Calycanthaceae,[8] Idiospermaceae,[9] and Rubiaceae,[10] as well as from dendrobatid frog.[11] The syntheses of these alkaloids have been accomplished so far by using the direct coupling reaction of tryptamine derivatives under various conditions[8b,12] as well as by employing a multistep procedure via an elegant strategy.[13] Initially, we treated N_b-carbomethoxytryptamine (**8**) with PIDA under the conditions developed above; however, this resulted mainly in the recovery of the starting material. After several attempts under various conditions, i.e. combinations of reagents (PIDA or PIFA), solvents (CH_2Cl_2 or CF_3CH_2OH), and various temperatures, we succeeded in the preparation of the desired dimeric compounds in good yield (Scheme 3). Thus, compound **8** was treated with 0.5 equiv. of PIFA in CF_3CH_2OH at −30°C and the resultant residual



Scheme 2. *Reagents and conditions*: (a) 0.5 equiv. PIFA, dry CH_2Cl_2, **5** (77%), **6** (trace); (b) 0.5 equiv. PIDA, dry CH_2Cl_2, rt, **5** (12%), **6a** (22%), **6b** (20%).



Scheme 3. *Reagents and conditions*: (a) $ClCO_2CH_3$, $NaOH/H_2O$, CH_2Cl_2, 0°C, quant.; (b) 0.5 equiv. PIFA, CF_3CH_2OH, −30°C; (c) Red-Al, toluene, reflux, **9** (30%), **10** (13%), **11** (23%), N_b-methyltryptamine (9%).

mixture of carbamates, without purification, was reduced with Red-Al in toluene to afford *meso*-chimonanthine (**9**, 30% yield) and *rac*-chimonanthine (**10**, 13% yield), together with a dimeric compound (**11**, 23% yield) and N_b-methyltryptamine (9% yield). The synthetic *rac*-chimonanthine (**10**, mp 178–180°C) was directly compared with the natural product that was isolated from *Calycanthus praecox* in our laboratory. The spectral data of synthetic **9** (mp 199–202°C) agreed with those in the literature.[13a] The structure of dimer **11** (mp 119–123°C) was inferred from spectral data, particularly, by observations of HMBC correlations and NOEs as shown in Fig. 1.

Further application of this type of reaction to the synthesis of natural indole alkaloids is in progress.

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7. Crystal data for **6b** (mp 149–155°C). Data were acquired with a CCD diffractometer with Mo–Kα radiation ($\lambda=0.71069$ Å), graphite monochromated, monoclinic, $C_{24}H_{24}N_2$ (Mw: 340.47), space group $P2_1/n$ with $a=12.056$ (2) Å, $b=12.466$ (2) Å, $c=12.073$ (2) Å, $\beta=102.487$ (2) °, $V=1771.6$ (4) Å^3, $Z=4$, and $D_{calc}=1.276$ g/cm^3. The final R value was 0.039 ($R_w=0.048$) for 2521 reflections ($I>3\sigma(I)$).
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