# A New Approach to Pyrrolophenanthridone Alkaloids *via* Intramolecular Radical Cyclization

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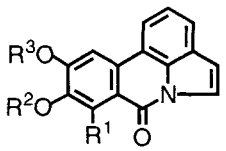
A new approach to the synthesis of pyrrolophenanthridone class of alkaloids is described. The method is based on intramolecular radical cyclization of easily accessible 1-aroyl-7-bromoindoles with $Bu_3SnH$ and AIBN.

Hippadine (**Ia**), pratosinine (**Ib**), pratorimine (**Ic**), and pratorinine (**Id**) are representative members of the pyrrolophenanthridone alkaloids isolated from various *Crinum* species (Amerillidacea).[1] Since of their discovery, several of these alkaloids have been shown to possess significant biological activity. It has been demonstrated, for example, that hippadine (**Ia**) reversibly inhibits fertility in male rates[2] and kalbretorine (**Ie**) exhibits antitumor activity.[3]



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**a**: $R^1$=H, $R^2R^3$=-$(CH_2)$-
**b**: $R^1$=H, $R^2$=$R^3$=$CH_3$
**c**: $R^1$=$R^2$=H, $R^3$=$CH_3$
**d**: $R^1$=$R^3$=H, $R^2$=$CH_3$
**e**: $R^1$=OH, $R^2R^3$=-$(CH_2)$-

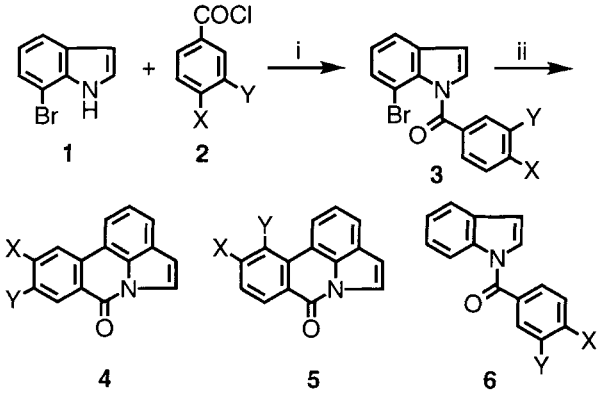
Pyrrolophenanthridones have previously prepared *via* a variety of synthetic strategies[4] involving formation of an aryl aryl bond through an inter or intramolecular coupling reaction starting from indoline derivatives. Examples of this include DDQ-dehydrogenation of dihydropyrrolophenanthridones prepared *via* oxazoline-mediated process,[4a] intramolecular aryne cyclo-addition,[4b] palladium catalyzed coupling,[4c,e] and modified Suzuki coupling.[4g]

On the other hand, free radical cyclizations now constitute a major tactic in the synthesis of mono-, bi-, and polycyclic ring systems.[5] Indeed, several examples of synthesis of 1,2-fused indoles by radical cyclization have been demonstrated.[6-9] To the best of our knowledge, however, attempts to prepare 1,7-fused indoles by intramolecular radical strategy have not heretofore been reported. Intramolecular radical cyclization of 1-aroyl-7-bromoindoles seems to provide a promising route to pyrrolophenanthridones. In fact this strategy offered a new concise synthetic route to pyrrolophenanthridones including hippadine (**Ia**) and pratosinine (**Ib**). In this connection intramolecular radical cyclization of 1-(2-bromobenzoyl)-3-methylindole is also described.

1-Aroyl-7-bromoindoles (**3**) were prepared by the reaction of 7-bromoindole (**1**)[10] with the corresponding aroyl chlorides (**2**) as shown in Scheme 1. Thus aroylation of the indole **1** using NaH in THF furnished the corresponding aroylindoles (**3**) in good yield, respectively.

Treatment of **3** (1.0 mmol) with $Bu_3SnH$ (1.5 mmol) in the presence of azobisisobutyronitrile (AIBN) (0.25 mmol) in boiling benzene (150 ml) for 10 h resulted in radical cyclization with oxidation to give regioisomeric pyrrolophenanthridones (**4**) and (**5**) along with reduction product (**6**).[11] The result stands in a striking contrast to the palladium catalyzed cyclization in which 1-piperonylindole gave a mixture of two regioisomeric 1,2-fused indoles.[4c]

The results are shown in Scheme 1 and Table 1.



**a**: X=Y=H; **b**: X=OMe, Y=H;
**c**: X=Y=OMe; **d**: XY=$OCH_2O$

Reagents and conditions: i, NaH, rt, THF, 15 h
ii, $Bu_3SnH$, AIBN, reflux, $C_6H_6$.

**Scheme 1.**

**Table 1.** *N*-Aroylation of **1** and radical cyclization of aroylindoles **3**[a]

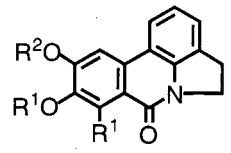
| Aroylation of **1**[b] | | | Radical cyclization of **3**[c] | | | | | |
|---|---|---|---|---|---|---|---|---|
| Aroylindoles **3** | | | Pyrrolophenanthridones | | | | | |
| | | | **4** | | | **5** | | |
| | Mp/°C | Yield/% | | Mp/°C | Yield/% | | Mp/°C | Yield/% |
| **3a** | 68-69 | 84 | **4a** | 145-147 | 48 | | | |
| **3b** | 99 | 75 | **4b** | 187-188 | 52 | | | |
| **3c** | 177 | 82 | **4c** | 238-239 | 42 | **5c** | 201-202 | 26 |
| **4d** | 107-108 | 78 | **4d** | 218-219 | 29 | **5d** | 226-227 | 20 |

[a]Isolated yield are shown. [b]In all aroylations, the corresponding 1,3-diaroylindoles were formed in small amounts. [c] Reduction products **6a**, **6b**, **6c** and **6d** were also isolated in 21, 8, 2, and 20% yields, respectively.

On the basis of their spectral data **4c** and **4d** were assigned to pratosinine (**Ib**) and hippadine (**Ia**), respectively.[12] Since **Ia** has previously been converted into pratorinine (**Id**),[13] this work also constitutes a formal synthesis of **Id**.

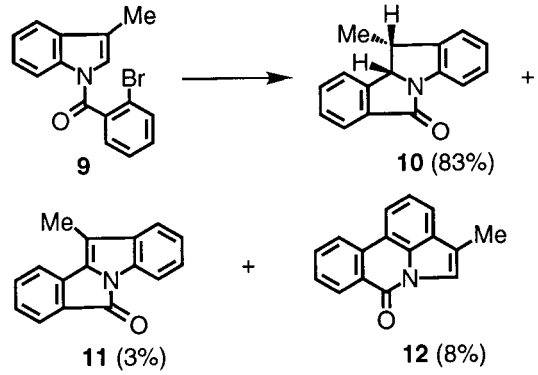
In addition, **4c** and **4d** were quantitatively converted into oxoassoarine (**7**) (mp 269 °C, lit.[4a] mp 268-269 °C) and

anhydrolycoyin-7-one (**8**) (mp 233 °C, lit.[13] mp 228-230 °C), respectively, by formic acid-catalytic transfer hydrogenation.[14]



**7**: $R^1$=$R^2$=Me
**8**: $R^1R^2$=-$(CH_2)$-

In connection with the above work, we became interested in the radical cyclization of 1-(2-bromobenzoyl) substituted indole. Thus, the similar radical cyclization of 1-(2-bromobenzoyl)-3-methylindole (**9**)[15] with $Bu_3SnH$ and AIBN in refluxing benzene for 3 h was investigated. Interestingly, 1,7-fused pyrrolophenanthridone (**12**) was obtained,[16] besides 1,2-fused cis-10b,11-dihydro-6*H*-11-methylisoindolo[2,1-*a*]indol-6-one (**10**) and its dehydrogenated derivative (**11**) (Scheme 2).



**9** **10** (83%) **11** (3%) **12** (8%)

**Scheme 2.**

In conclusion, intramolecular radical cyclization of 1-aroyl-7-bromoindoles offered a versatile route to pyrrolophenanthridones: The synthesis of hippadine (**Ia**) and pratosinine (**Ib**) has been achieved in 23 and 34% overall yields respectively by a short, convenient and potentially general route which competes favorably with previous syntheses[4] of this group of Amaryllidaceae alkaloids.

## References and Notes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11 All the new compounds gave satisfactory analytical and spectroscopic data.

12 **4c**: pale yellow needles ($CH_3CN$), mp 238-239 °C (lit.[4a] mp 234-235 °C); $^1H$ NMR ($CDCl_3$) δ 4.03, 4.10 (each 3H, s), 6.87 (1H, d, J=3.6 Hz, H-4), 7.43 (1H, t, J=7.6 Hz, H-2), 7.58 (1H, s, H-11), 7.60-7.91 (2H, m, H-1, H-3), 7.94 (1H, s, H-8), 8.02 (1H, s, H-5); $^{13}C$ NMR ($CDCl_3$) δ 56.20, 56.24, 103.69, 110.09, 110.61, 116.60, 117.98, 120.79, 122.32, 123.49, 123.86, 128.47, 129.44, 131.11, 149.65, 153.67, 158.30. **4d**: colorless needles (EtOH), mp 218-219 °C (lit.[4a] mp 217-218 °C); $^1H$ NMR ($CDCl_3$) δ 6.15 (2H, s), 6.88 (1H, d, J=3.6 Hz, H-4), 7.44 (1H, t, J=7.6 Hz, H-2), 7.62 (1H, s, H-11), 7.70-7.90 (2H, m, H-1, H-3), 7.96 (1H, s, H-8), 8.03 (1H, d, J=3.6 Hz, H-5); $^{13}C$ NMR ($CDCl_3$) δ 101.62, 1002.27, 107.94, 110.73 (2), 116.63, 118.31, 122.55, 123.47 (2), 123.92, 128.35, 131.56, 148.46, 152.52, 158.06.

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15 The compound **9** (mp 111 °C) was obtained in 94% yield by the reaction of 3-methylindole with 2-bromobenzoyl chloride in the presence of NaH in dry THF.

16 **12**:Yellow needles (hexane), mp 184-185 °C; $^1H$ NMR ($CDCl_3$) δ 2.41 (3H, d, J=1.3 Hz), 7.21-7.70 (3H, m), 7.76 (1H, d, J=1.3 Hz), 7.80-8.71 (3H, m); $^{13}C$ NMR ($CDCl_3$) δ 10.16, 116.51, 118.50, 120.32, 121.04, 121.43, 122.59, 123.70, 127.34, 128.01, 129.41, 129.66, 1331.78, 132.77, 134.29, 158.22; MS *m/z* 233 ($M^+$). Dehydrogenation of **10** (mp 124 °C) with 5% Pd-C in decalin (reflux, 20 h) gave **11** (mp174-175 °C) in 65% yield.