A Convenient Divergent Approach to the Alkaloids Isaindigotone and Luotonin A

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Abstract: Deoxyvasicinone has been used as the key intermediate to prepare the alkaloids isaindigotone and luotonin A. This intermediate is directly converted into isaindigotone by condensation with 4-acetoxy-3,5-dimethoxybenzaldehyde; alternatively oxidation with SeO_2 afforded the pyrrolo[2,1-*b*]quinazoline-3,9-dione, a putative precursor of the luotonin A.

Key words: alkaloids, condensation, oxidations, isaindigotone, luotonin A, deoxyvasicinone, *o*-azidobenzoyl chloride

Isatis indigotica Fort is a biennial herbaceous plant distributed widely in the Changjiang River valley. The purified extracts of its root named "Ban-Lan-Gen" in Chinese are popularly used in clinical practice for treatment of influenza, epidemic hepatitis, epidemic encephalitis B, carbunde, erypsipelas, etc.[1] Recently, the new alkaloid isaindigotone (**1**) has been isolated from the chloroform/butanol fraction of the ethanol extracts of the roots, which was found to be effective for antiendotoxic test using limulus amebocyte lysate (LAL).[2] No synthesis of **1** has been previously reported to the best of our knowledge.

Luotonin A (**2**), the first known natural product to possess the heteroaromatic pyrroloquinazolinoquinoline ring system, was isolated in 1997 from the aerial parts of the *Peganum nigellastrum* Bunge, a plant indigenous to northwest China, which showed cytotoxic activity against mouse leukemia P-388 cells.[3] The pentacyclic ring system presents in luotonin A (**2**) is strikingly reminiscent of camptothecin, an inhibitor of topoisomerase I, derivatives of which are clinically useful anticancer agents.[4] The biological activity of luotonin A (**2**) and the possibility of obtaining camptothecin-like analogs has focused considerable attention on its synthesis. Three syntheses have been previously reported. The first one[5] (Ganesan synthesis) is based on the coupling reaction of 3-oxopyrroloquinoline with 2-sulfinylaminobenzoyl chloride in the presence of $LiN(TMS)_2$. In the two others, vasicinone, prepared in five steps from anthranilic acid and 2-pyrrolidinone,[6] is converted into **2** either by reaction with anthranyl aldehyde[7] (Nomura synthesis) or by oxidation with Jones reagent followed by Friedländer condensation of the resulting dione with 2-aminobenzaldehyde[8] (Kelly synthesis).

We have devised and improved a reliable divergent approach to isaindigotone (**1**) and luotonin A (**2**) which is based on the suitable use of the readily available deoxyvasicinone (**3**) as a key common intermediate in which the methylene group at position 2 of the pyrimidine ring is able to undergo functionalization either by condensation with aldehydes[9] or by oxidation.[10]

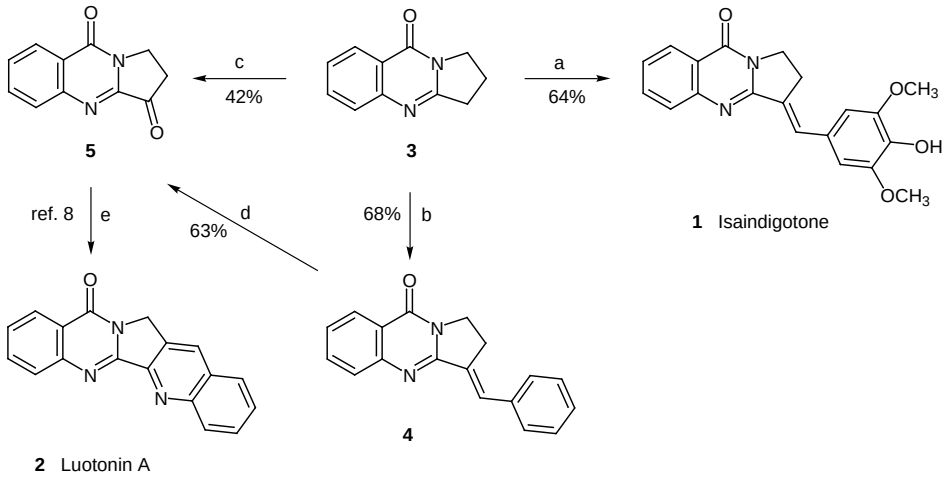
The first synthesis of isaindigotone (**1**) begins with deoxyvasicinone (**3**) prepared in two steps and 74% overall yield from *o*-azidobenzoyl chloride and pyrrolidone.[11] Direct conversion of **3** into **1** is accomplished in 64% yield by condensation with 4-acetoxy-3,5-dimethoxybenzaldehyde in acetic acid at reflux temperature followed by basic treatment with ethanolic NaOH. Spectra of synthetic **1** are identical to those of the natural product (Scheme). This two-steps synthesis of isaindigotone (**1**) from the readily available deoxyvasicione (**3**) provides a convenient access to **1** and, potentially, its analogs.

On the other hand, it has been reported that the oxidation reaction of deoxyvasicinone (**3**) employing (1*S*)-10-camphorsulfonyloxaziridine (Davis reagent) gave vasicinone in 55% yield,[7] which by the conventional oxidation ways did not give the expected pyrrolo[2,1-*b*]quinazoline-3,9-dione (**5**), a significant precursor leading to luotonin A (**2**) in the Kelly synthesis. However, compound **5** has been prepared in 56% yield by oxidation of the vasicinone using Jones reagent.[8]

We have found that deoxyvasicinone (**3**) does convert into the pyrrolo[2,1-*b*]quinazoline-3,9-dione (**5**) in 42% yield by oxidation with SeO_2 in dioxane at reflux temperature. An alternative way for the conversion of **3** into **5** involves the following two-steps sequence: a) condensation of **3** with benzaldehyde in the presence of acetic acid to give **4** in 68% yield and b) ozonolysis of **4** and subsequent addition of Me_2S leading to **5** in 63% yield (Scheme). This constitutes a formal total synthesis of luotonin A (**2**) since **5**, now available by a shorter route (3 steps) and higher overall yield (31%) than the reported in the previously mentioned methods, is the quinazolinone derivative of the Kelly synthesis of luotonin A (**2**) and may be converted into the target molecule in a straighforward manner.

In conclusion, we have achieved for the first time the synthesis of the isaindigotone (**1**) from deoxyvasicinone (**3**), which in turn can be directly converted into the pyrrolo[2,1-*b*]quinazoline-3,9-dione (**5**), a putative precursor of the luotonin A (**2**).

All reagents were of commercial quality used from freshly opened containers. Solvent were dried and purified by conventional methods prior to use. Preparative column chromatography: Merck



Reagents and conditions: a) i: 4-acetoxy-3,5-dimethoxybenzaldehyde/Ac_2O/reflux, ii: NaOH/EtOH, reflux; b) PhCHO/Ac_2O, reflux; c) SeO_2/dioxane, reflux; d) $O_3/CH_2Cl_2/Me_2S$; e) *o*-aminobenzaldehyde/Triton B/EtOH, reflux

Scheme

silica gel 60, particle size 0.040−0.063 mm (230−400 mesh, flash). Analytical TLC: silica gel 60 F_{254} plates, Merck, Darmstadt. All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as nujol emulsions or films on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Brucker AC-200 (200 MHz) or a Varian Unity 300 (300 MHz). Mass spectra were recorded on a Hewlett-Packard 5993C spectrometer or a Fisons Autospec 500 VG. Microanalyses were performed on a Perkin-Elmer 240 C instrument.

Isaindigotone (1)

To a solution of deoxyvasicinone (**3**; 90 mg, 0.48 mmol) in Ac_2O (11 mL) was added 4-acetoxy-3,5-dimethoxybenzaldehyde (739 mg, 3.3 mmol) and the resultant mixture was heated under reflux for 24 h. After cooling, the solvent was removed under reduced pressure and the crude product was dissolved in 10% NaOH in EtOH (15 mL). The solution was heated at reflux temperature for 1 h and, after cooling, was neutralized with 1 N HCl and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (20 mL), H_2O (20 mL) and dried ($MgSO_4$). After filtration, the solution was concentrated under vacuum and the resulting crude product was purified by column chromatography on silica gel using EtOAc/hexane (2:1) as eluent to give **1** (107 mg); yield: 64%; mp 249−250 °C (Lit.[2] mp 247−248 °C). Spectroscopic data are identical to those reported for the natural product.

3-Benzylidenepyrrolo[2,1-*b*]quinazoline-9-one (4)

A mixture of deoxyvasicinone (**3**; 200 mg, 1.07 mmol), benzaldehyde (910 mg, 8.56 mmol) and Ac_2O (10 mL) was heated at reflux temperature for 24 h. After cooling, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel using EtOAc/hexane (2:1) as eluent to give **4** (199 mg); yield: 68%; mp 175−176 °C.

IR (nujol): ν = 1680, 1590, 1345, 769, 688 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$/TMS): δ = 3.27 (td, 2 H, *J* = 7.8 Hz, *J* = 2.0 Hz), 4.26 (t, 2 H, *J* = 7.8 Hz), 7.35−7.48 (m, 4 H), 7.56 (d, 1 H, *J* = 8.0 Hz), 7.55 (d, 1 H, *J* = 8.0 Hz), 7.72 (m, 2 H), 7.83 (t, 1 H, *J* = 2.0 Hz), 8.27 (d, 1 H, *J* = 8.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$/TMS): δ = 25.5 (C-2), 44.0 (C-1), 120.8 (C-8a), 126.1 (C-8), 126.3 (C-7), 127.2 (C-5), 128.8 (C-3'), 128.9 (C-7'), 129.7 (C-2'), 130.6 (C-4'), 131.5 (C-3), 134.2 (C-6), 135.4 (C-1'), 149.6 (C-4a), 155.5 (C-3a), 161.2 (C-9, C=O)

MS (EI, 70 eV): *m*/*z* (%) = 274 (M^+, 100), 228 (19), 185 (18), 128 (23), 115 (51).

Anal. calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.63; H, 5.27; N, 10.12.

Pyrrolo[2,1-*b*]quinazoline-3,9-dione (5)

Method A: To a solution of SeO_2 (120 mg, 1.07 mmol) in H_2O (5 mL), was added a solution of deoxyvasicinone (**3**; 200 mg, 1.07 mmol) in dioxane (10 mL) and the mixture was heated under reflux temperature for 12 h. After cooling, the solid was removed by filtration and the filtrate was concentrated under vacuum. The residue was slurried with Et_2O (30 mL) and the resulting brown solid was recrystallized from acetone to give **5** (90 mg); yield: 42%; mp 165−170 °C (darkens without melting), (Lit.[8] mp 165−170 °C), 205 °C (chars without melting). Spectroscopic data are identical to those previously reported.[8]

Method B: A stream of O_3 was passed throught a solution of compound **4** (500 mg, 1.8 mmol) in CH_2Cl_2 (100 mL) for 3 min, whereupon Me_2S (0.4 mL) was added. The solution was stirred at r.t. for 30 min and the solvent was removed under reduced pressure. The resulting crude product was slurried with Et_2O (40 mL) and the brown solid obtained was crystallized as above to give **5** (225 mg); yield: 63%.

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