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A new synthesis of the cytotoxic alkaloid Luotonine A

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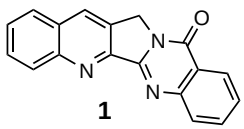
Abstract—A convenient synthesis of the cytotoxic alkaloid Luotonine A has been achieved using cheap and readily accessible reagents. The key intermediate in the synthesis is the tricyclic compound 2,3-dihydro[1*H*]-pyrrolo[3,4-*b*]quinolin-3-one (**5**).

Luotonine A (**1**) is a cytotoxic alkaloid of natural origin isolated for the first time in 1997 from the aerial parts of *Peganum nigellastrum Bunge*, a plant distributed over Asia which was employed in traditional medicine for rheumatism, abscess and inflammation.[1] It was found to be active in vitro against murine leukemia P-388 cells at a concentration of 1.8 μg/mL.[1]



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The structure of Luotonine is strikingly reminiscent of the cytotoxic alkaloid camptothecine, whose derivatives are clinically useful anticancer agents.

This similarity has stimulated much activity directed toward the synthesis of the alkaloid and four multistep syntheses of such a compound have been reported. The first two syntheses started by building the pyrroloquinazoline ring-system and used as a key intermediate vasicinone, prepared by a multistep sequence.[2,3] A Friedländer condensation with *o*-aminobenzaldehyde then gave the desired product. Recently Molina and co-workers proposed a new oxidation method of desoxyvasicinone to vasicinone using selenium dioxide.[4]

On the contrary, the third approach was based on the synthesis of 3-oxopyrroloquinoline, which was then coupled with 2-sulfinylaminobenzoylchloride to give **1**.[5]

Our particular interest was in the possibility of synthesizing camptothecine-like analogues in order to obtain cytotoxic compounds and to clarify the structure–activity relationships connected with these molecules. The absence of labile functions such as the lactone moiety of camptothecine made Luotonine A appealing from a synthetic point of view, so we focused our attention on an alternative approach to the synthesis of **1**. In this note we describe a new straightforward synthetic method to obtain Luotonine A and analogues which uses only simple reagents.

We envisaged the synthesis of **1** via a D/E ring-closing acylation/reduction reaction and a Friedländer condensation as key steps. Thus, the tricyclic compound 2,3-dihydro[1*H*]-pyrrolo[3,4-*b*]quinolin-3-one **5** (Scheme 1) can be seen as the precursor of Luotonine A; it can in turn be obtained by condensation of *o*-aminobenzaldehyde with pyrrolidine-2,3-dione.

Being the *N*-unsubstituted pyrrolidine-2,3-dione of limited stability,[6] we have investigated the synthesis of derivatives with potentially removable protecting groups in position 1, easily obtainable by condensation of ethyl oxalate with *N*-substituted β-aminopropionic esters (*N*-benzyl, *N*-*p*-methoxyphenyl, *N*-α-methoxybenzyl, *N*-allyl).

After several attempts the *N*-allyl derivative was chosen for the easiness of removal of the protecting group.

1-Allylpyrrolidine-2,3-dione (**3**) was prepared by hydrolysis and decarboxylation of the corresponding ester **2**, which in turn was synthesized by a slight modification of the original Sundberg method[6] with a one-step reaction from ethyl acrylate, allylamine and ethyl oxalate (Scheme 1).[7]

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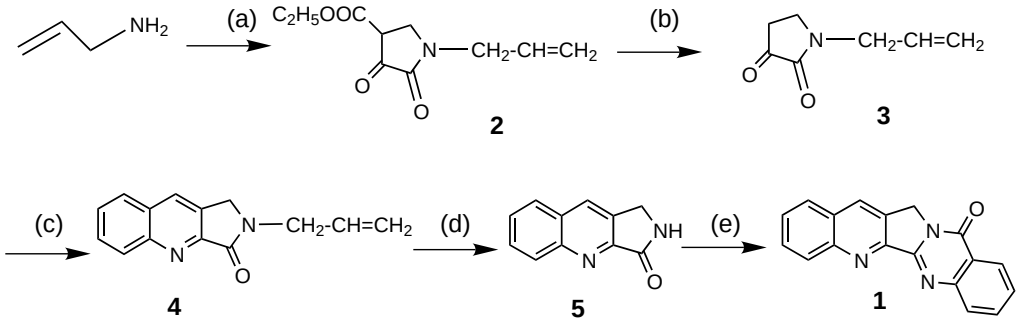

Scheme 1. Synthesis of **1**. *Reagents and conditions*: (a) CH_2=CH–COOEt, EtOH, rt 48 h; then $NaOC_2H_5$, H_5C_2OOC–$COOC_2H_5$, reflux 15 h, 70%; (b) HCl 10%, reflux 2 h, 61%; (c) 2-aminobenzaldehyde, toluene, *p*TsOH, reflux, 50%; (d) i. PPh_3, $PdCl_2$, DMF/H_2O 8/2, reflux 4 h, 100%; ii. HCl 6N reflux 2 h, 98%; (e) NaH, THF, 60°C 1 h; then 2-nitrobenzoylchloride 50°C 1 h; then Fe, AcOH/EtOH 1/1, reflux 2 h, 38%.

Condensation of 1-allylpyrrolidine-2,3-dione with *o*-aminobenzaldehyde was carried out under Friedländer conditions to obtain the pyrroloquinoline compound **4**.[8] The allylic protective group was then easily isomerized with $PdCl_2$ to an enamide function and then quantitatively removed through acidic hydrolysis.[9] A one-pot sequence of acylation of **5** with 2-nitrobenzoylchloride, reduction of the nitro group and subsequent ring-closure led to Luotonine A (**1**).[10]

In summary we have devised an improved and new synthesis of Luotonine A. The friendly reaction conditions, the cheap and readily available reagents make this method suitable for large-scale production; moreover it offers the possibility of obtaining camptothecine-like analogues in which the lactone moiety can be easily replaced by a variously substituted benzene ring. The synthesis and testing of such analogues for antitumor activity is in progress.

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7. Experimental procedure for the synthesis of **3**. To a solution of 15.5 g (0.175 mol) of freshly distilled ethyl acrylate in 100 mL of absolute ethanol 10 g (0.175 mol) of allylamine was dropped. The mixture was allowed to stand at room temperature for 48 h. In a separate flask an ethanolic sodium ethoxide solution was prepared by dissolving 4 g (0.175 mol) of metallic sodium in 100 mL of absolute ethanol. To this solution 23.7 mL (0.175 mol) of ethyl oxalate were added, followed by the previously prepared solution of ethyl β-allylaminopropionate. The mixture was refluxed for 1.5 h and the solvent was then removed by distillation. The residual slurry was added to 300 mL of warm water and acidified with HCl 6N. The mixture was then cooled and allowed to stand for some time to complete the precipitation. The product was filtered out and recrystallized from ethanol to obtain 26 g of **2** in the form of white needles. Yield 70%, mp 82°C, ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, J=7.3 Hz, 3H), 3.95 (s, 2H), 4.10 (d, J=6.2 Hz, 2H), 4.31 (q, J=7.3 Hz, 2H), 5.14–5.28 (m, 2H), 5.70–5.90 (m, 1H), 8.83 (brs, 1H). 10 g (0.047 mol) of **2** were refluxed 2 h in 530 mL of HCl 10%. The aqueous solution was then extracted with CH_2Cl_2 (300 mL×3) and with ethyl acetate (300 mL×3). The combined organic layers were dried and evaporated to give 4 g of 1-allyl-pyrrolidine-2,3-dione (**3**) as a yellow oil. Yield 61%. ^{1}H NMR ($CDCl_3$) δ: 2.72 (t, J=5.9 Hz, 2H), 3.63 (t, J=5.9 Hz, 2H), 4.13 (d, J=6.6 Hz, 2H), 5.29–5.33 (m, 2H), 5.77 (m, 1H).
8. Synthesis of **4**. 517 mg (4.28 mmol) of 2-aminobenzaldehyde was dissolved in 25 mL of toluene. To this solution 594 mg (4.28 mmol) of **3** was added together with a catalytic amount of *p*-toluenesulfonic acid (0.4 mmol). The reaction flask was fitted with a Dean–Stark apparatus for the distillation of water and the reaction was refluxed until no more water was collected. The largest part of the solvent was removed under reduced pressure. The residue was triturated with ether and filtered to give **4** as a brownish solid. Yield 50%, mp 153–155°C, ^{1}H NMR ($CDCl_3$) δ: 4.40 (dd, J=1.1 and 6.2 Hz, 2H), 4.55 (s, 2H), 5.26–5.40 (m, 2H), 5.83–6.03 (m, 1H), 7.65–7.90 (m, 2H), 7.93 (d, J=9.2 Hz, 1H), 8.26 (s, 1H), 8.42 (d, J=9.2 Hz, 1H).
9. Synthesis of **5**: 200 mg (0.89 mmol) of **4** were dissolved in 2.3 mL of DMF/H_2O 8/2 (v/v). After adding 38 mg (0.18 mmol) of triphenylphosphine and 8 mg (0.045 mmol) of $PdCl_2$, the mixture was refluxed for 4 h and 165 mg of a pale-gray solid were obtained by filtration. The resulting solution was diluted with 20 mL of water and extracted

with dichloromethane (×3). The organic layer was washed with water, dried and evaporated to afford further 35 mg (overall yield 100%) of 2-propenyl-1,2-dihydro[1*H*]pyrrolo[3,4-*b*]quinolin-3-one, mp 167–168°C, ^{1}H NMR ($CDCl_3$) δ: 1.86 (dd, $J=7.0$ and 1.8 Hz, 3H), 4.69 (s, 2H), 5.38 (m, 1H), 7.34 (d, $J=14.3$ Hz, 1H), 7.67 (ddd, $J=8.5$, 8.5 and 1.5 Hz, 1H), 7.81 (ddd, $J=8.5$, 8.5 and 1.5 Hz, 1H), 7.92 (dd, $J=8.5$ and 1.5 Hz, 1H), 8.27 (s, 1H), 8.40 (dd, $J=8.5$ and 1.5 Hz, 1H). 2-Propenyl-1,2-dihydro[1*H*]pyrrolo[3,4-*b*]quinolin-3-one (160 mg, 0.72 mmol) was refluxed in 5.6 mL of HCl 6N for 2 h. The solution was then neutralized with K_2CO_3 and extracted fivefold with ethyl acetate. The combined organic layers were dried and evaporated. Purification by flash chromatography (ethyl acetate:methanol 7:3) afforded 130 mg of **5** as a white solid, Yield 98%, mp>270°C (dec.), ^{1}H NMR (DMSO-d_6) δ: 4.53 (s, 2H), 7.69 (ddd, $J=8.5$, 8.5 and 1.47 Hz, 1H), 7.82 (ddd, $J=8.5$, 8.5 and 1.47 Hz, 1H), 8.09 (dd, $J=8.5$ and 1.5 Hz, 1H), 8.16 (dd, $J=8.5$ and 1.5 Hz, 1H), 8.55 (s, 1H), 9.21 (brs, 1H).

10. Synthesis of Luotonine A. To a suspension of 40 mg (0.22 mmol) of **5** in 2 mL of THF 15 mg (0.62 mmol), NaH (60% in mineral oil, previously washed with hexane) was added with cooling in one portion. The mixture was heated at 60°C until the evolution of gas ceased (ca. 1 h). It was then ice-cooled and 32 μl (0.24 mmol) of 2-nitrobenzoylchloride was added. After heating at 50°C for an additional hour the solvent was evaporated. The resulting solid was suspended in 5 mL of a mixture of acetic acid:absolute ethanol 1:1 and 73 mg (1.3 mmol) of Fe was added. After refluxing for 2 h the iron was removed by filtration and the filter was carefully washed with ethanol, ethyl acetate and chloroform. The combined organic layers were washed with a saturated solution of sodium bicarbonate and then with water. After drying and removal of the solvent the product was purified by flash chromatography (from ethyl acetate:hexane 9:1 to ethyl acetate). Yield 38%. Synthetic **1** matched the spectroscopic data reported in literature.[1]