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Short Note

9-Aminoquino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one

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Abstract: Chemoselective reduction of the corresponding 9-nitro precursor by catalytic transfer hydrogenation afforded the title compound, a new 9-amino derivative of the antitumor alkaloid Luotonin A, in good yield. The structure of the compound was established by means of 1D and 2D ^{1}H-NMR and ^{13}C-NMR spectroscopy as well as by EI-MS and high-resolution ESI-MS.

Keywords: Luotonin A; nitro group reduction; catalytic transfer hydrogenation

1. Introduction

Luotonin A (Figure 1), a pentacyclic natural product with the systematic name quino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one, was first isolated from the plant *Peganum nigellastrum* Bunge (Zygophyllaceae) in 1997 by Ma et al. [1]. Due to its cytotoxic activity, which is based on an interaction with the Topoisomerase I enzyme in its complexed form with DNA [2], the alkaloid has become the subject of several investigations aiming at its total synthesis and/or its structural modification, as summarized in a review article by Liang et al. [3]. Among the various known Luotonin A derivatives, bearing substituents mainly at ring A or at ring E, there have been only a few examples with a primary amino group at these locations. Our group has recently published the synthesis of four isomeric A-ring amino derivatives [4], and previously two E-ring amino derivatives had been reported: the 7-amino compound was described by Nacro et al. [5] and the 8-amino derivative was reported by Cagir et al. [6]. In 2004, Dallavalle et al. published the synthesis of 9-nitro-Luotonin A [7] (among other Luotonin A derivatives) from 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline [8] and a nitroisatoic anhydride building block (Scheme 1). However, an attempt to reduce the nitro group to the amino function by catalytic hydrogenation on palladium/carbon in acetic acid was found to lead to concomitant partial reduction of ring B [7] (Scheme 1).

In the course of our group's investigations of substituted Luotonin A derivatives as potential anticancer agents [4,9–12], we have frequently encountered severe solubility problems with these compounds. Thus, we became interested in the amino group, also as a solubility enhancing substituent. Herein, we want to report the convenient preparation of the hitherto unknown 9-amino derivative of Luotonin A by reduction of the known 9-nitro precursor [7] under mild conditions.

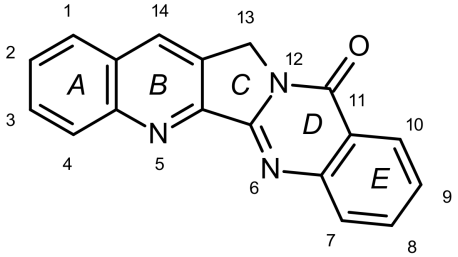
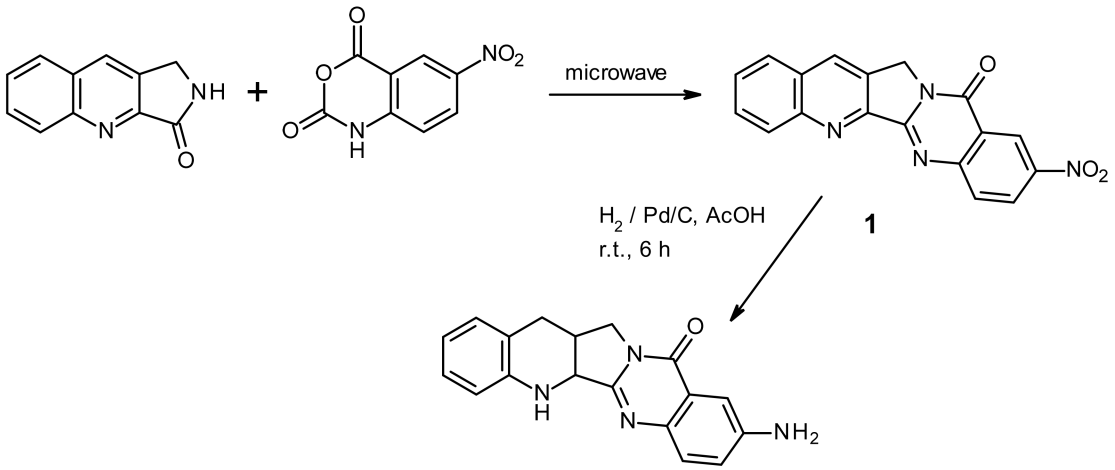


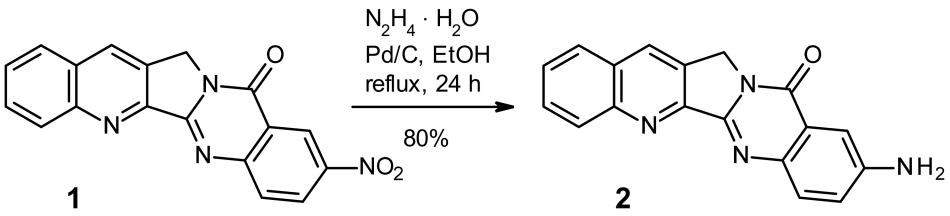
Figure 1. Structure of Luotonin A (IUPAC-conformant numbering scheme).



Scheme 1. Synthesis of 9-nitro-Luotonin A (**1**) and its attempted catalytic hydrogenation [7].

2. Results and Discussion

Replacement of gaseous hydrogen with liquid or solid hydrogen sources in catalytic hydrogenation reactions is generally referred to as catalytic transfer hydrogenation [13] and it offers some advantages in terms of safety, as well as easier reaction monitoring and (in some cases) easier work-up. We previously made positive experiences with the selective reduction of a nitrocarbazolediester by catalytic transfer hydrogenation [14], employing Deady's protocol [15]. Recently, we successfully employed this technique also to the synthesis of A-ring amino derivatives of Luotonin A [4]. In this work, we have applied analogous conditions (hydrazine hydrate as hydrogen source, Pd/C as catalyst, alcoholic solution/suspension at reflux temperature) in an attempt to reduce the NO_2 group in 9-nitro-Luotonin A (**1**) while leaving ring B intact. Indeed, we have found that the desired selective reduction takes place very cleanly under these conditions (Scheme 2), despite the extremely low solubility of the substrate (**1**) in ethanol requires prolonged refluxing (24 h) of the suspension in order to complete the transformation.



Scheme 2. Synthesis of the title compound (**2**) by catalytic transfer hydrogenation.

The amino compound (**2**) is thus obtained in 80% yield after separation of the catalyst. Its structure is in full agreement with the mass spectrum showing a prominent M^+ peak at m/z = 300 and with the high-resolution ESI-TOF-MS data obtained for the $[M + Na]^+$ ion (see below). As expected, the presence of an amino group instead of a nitro group at ring E is reflected by a marked upfield shift for the proton signals of this substructure in the ^{1}H-NMR spectrum: the doublet of 7-H is shifted from 8.15 ppm to 7.66 ppm, the doublet of doublets of 8-H from 8.66 ppm to 7.20 ppm and the doublet of 10-H from 8.97 ppm to 7.36 ppm. An additional broad singulet at 5.86 ppm is clearly associated with the newly introduced amino group. While the lack of ^{13}C-NMR data for the nitro compound (**1**) (which is practically insoluble in all common NMR solvents) did not permit to carry out a comparison of ^{13}C chemical shifts with those of the amino compound (**2**), all carbon signals of the latter could be assigned by means of HSQC and HMBC experiments, and they also fully support the postulated structure. The title compound is scheduled for an in-vitro cytotoxicity assay, the results will be reported elsewhere.

3. Materials and Methods

3.1. General Information

The melting point (uncorrected) was determined on a Kofler hot-stage microscope (Leica GmbH, Wetzlar, Germany). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance III 400 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) at 400 MHz and 100 MHz, respectively; chemical shifts (ppm) were referenced to residual amounts of undeuterated solvent. The mass spectrum (EI) was obtained on a Shimadzu QP5050A DI 50 instrument (Shimadzu Corp., Kyoto, Japan); the high-resolution mass spectrum (ESI-TOF) was recorded on a Bruker maXis HD spectrometer (Bruker Daltonics GmbH, Bremen, Germany). Thin layer chromatography was done on Merck aluminium sheets pre-coated with Kieselgel 60 F_{254} (Merck, Darmstadt, Germany). 9-Nitroquino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one [7] (**1**) was prepared in three steps starting from ethyl 6-nitro-4-oxo-3,4-dihydroquinazoline-2-carboxylate [16,17] by adaptation of a previously described route [9] that involves an intramolecular cycloaddition reaction (for details, see Supplementary Material).

3.2. Synthesis of 9-Aminoquino[2′,3′:3,4]pyrrolo[2,1-b]quinazolin-11(13H)-one (**2**)

A suspension of 9-nitroquino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazolin-11(13*H*)-one (**1**) (165 mg, 0.5 mmol) in EtOH (50 mL) was flushed with argon. After the addition of 80% hydrazine hydrate (438 mg, 7 mmol) and 10% Pd/C (30 mg), the mixture was refluxed under an argon atmosphere for 24 h. The solvent was evaporated under reduced pressure and the residue was taken up in DMF (20 mL) and stirred at 60 °C for 15 min. The mixture was filtered while hot to remove the catalyst. The filter cake was again taken up in DMF (20 mL) and stirred at 60 °C for 15 min. After filtration, this procedure was repeated two more times. The combined DMF solutions (4 × 20 mL) were concentrated under reduced pressure to a volume of approximately 10 mL. Water (10 mL) was added and the mixture was kept in the refrigerator for 24 h. The precipitate was collected by filtration and it was washed with cold water and dried in vacuo to give the title compound (121 mg, 80%) as orange-colored crystals, m.p. > 350 °C (decomposition). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.69 (s, 1H, 14-H), 8.22 (d, *J* = 8.2 Hz, 1H, 4-H), 8.13 (d, *J* = 8.0 Hz, 1H, 1-H), 7.88 (t, *J* = 7.2 Hz, 1H, 3-H), 7.73 (t, *J* = 7.3 Hz, 1H, 2-H), 7.66 (d, *J* = 8.7 Hz, 1H, 7-H), 7.36 (d, *J* = 2.5 Hz, 1H, 10-H), 7.20 (dd, *J* = 8.8, 2.5 Hz, 1H, 8-H), 5.86 (br s, 2H, NH_2), 5.27 (s, 2H, 13-CH_2) ppm. ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 159.4 (11-C), 152.0 (5a-C), 148.7 (9-C), 148.3 (5b-C or 4a-C), 148.2 (4a-C or 5b-C), 139.7 (6a-C), 131.5 (14-C), 130.5 (13a-C), 130.2 (3-C), 129.5 (4-C), 129.1 (7-C), 128.4 (1-C), 128.1 (14a-C), 127.7 (2-C), 122.4 (10a-C), 122.3 (8-C), 106.1 (10-C), 47.2 (13-C) ppm. MS (EI, 70 eV): *m/z* (rel.int.) = 301 (18%), 300 (M^+, 72), 239 (18), 97 (36), 95 (37), 83 (44), 71 (55), 69 (47), 57 (100), 55 (58). HRMS (ESI-TOF) calculated for $C_{18}H_{12}N_4NaO$ ([M + Na]$^+$): 323.0903. Found: 323.0901.

Supplementary Materials: The following are available online at http://www.mdpi.com/1422-8599/2019/1/M1050/s1, experimental procedures for the synthesis of the nitro compound (**1**); 1D and 2D NMR spectra and EI-MS spectra of the amino compound (**2**).

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Conflicts of Interest: The authors declare no conflict of interest.

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