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(*Z*)-Ethyl 2-phenyl-1-(2-vinylphenyl)vinylcarbamates. Part 1: Synthesis and preliminary studies on their divergent transformation into benzo[*c*]phenanthridines and 2-phenyl-1,4-naphthoquinones

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ABSTRACT

Treatment of *N*-carbethoxy-1-benzylideneisoquinolines with LDA gives *N*-ethoxycarbonyl-1-amino-1-(2-vinylphenyl)-2-phenylethylenes, which can easily be transformed into *N*-carbethoxy-1-amino-2-phenylnaphthalenes. Bischler–Napieralski reaction of these latter compounds affords the corresponding benzo[*c*]phenanthridines, while their hydrolysis and subsequent oxidation constitutes a novel route to 2-phenyl-1,4-naphthoquinones.

1. Introduction

1-Benzylisoquinolines have received considerable attention both as synthetic and biogenetic precursors of a wide variety of natural compounds of pharmacological interest, including morphines, aporphines, protoberberines and benzo[*c*]phenanthridines (**1**).[1] These four families of isoquinoline alkaloids have a widespread occurrence in nature and a broad range of biological activities,[2,3] but only protoberberines and benzo[*c*]phenanthridines exhibit antineoplastic activity. In fact, nitidine (**1a**) and benzo[*c*]phenanthridine analogues, such as fagaronine (**1b**), exhibit potent antitumour activity by inhibition of DNA topoisomerase I,[3a,4] a property that has been related to their structural similarity with carcinogenic polycyclic aromatic hydrocarbons, such as chrysene and dimethylbenzanthracene. This behaviour has been attributed to the presence in their structures of a conformationally rigid embedded 2-phenylnaphthalene subunit, because other polycyclic aromatic hydrocarbons where this subunit is not present, such as triphenylene, do not show carcinogenic properties.[5] The antineoplastic properties of benzo[*c*]phenanthridines have been attributed to the fact that their tetracyclic framework includes the 2-phenylnaphthalene structural pattern present in chrysene, although in this case it is formed not only by carbon atoms. The presence of a nitrogen atom in these alkaloids modifies the electronic distribution of the annular system and, furthermore, the presence of alkoxy substituents at strategic positions of this annular system interferes with the epoxidation–hydroxylation processes involved in the carcinogenesis mechanism.

The range of 2-phenylnaphthalene-based compounds that show antineoplastic activity also includes several types of antibiotics with antitumour activity, such as 5*H*-benzo[*b*]carbazole-6,11-diones **2**[6] and ellipticine quinones **4**,[7] which retain a close structural relationship with ellipticine **3**,[8] a naturally occurring 6*H*-pyrido[4,3-*b*]carbazole alkaloid with powerful antitumour activity. The embedded 2-phenylnaphthalene subunits present in **2** and **4** are a 2-phenyl-1,4-naphthoquinone and a 6-phenylisoquinoline-5,8-dione, respectively (Fig. 1).

As a result of these important pharmacological properties, a variety of methods have been used for the synthesis of targets **1**,[9,10] **2**[11] and **4**,[12] and particularly attractive are those in which the key step is the annelation of an appropriate 2-phenylnaphthalene

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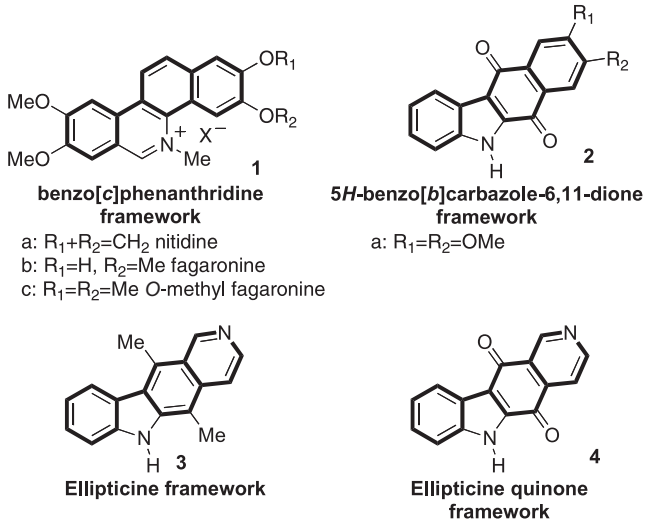


Fig. 1. Frameworks for benzo[*c*]phenanthridines, 5*H*-benzo[*b*]carbazole-6,11-diones, ellipticines and ellipticine quinones.

precursor. Accordingly, different approaches for the synthesis of 2-phenylnaphthalenes have been developed. These include recent approaches based on a key step consisting of the construction of their biarylic bond, a process, that is, usually very sensitive to steric hindrance.[13] The search for new and efficient approaches to 2-phenylnaphthalenes is therefore of current interest.

2. Results and discussion

In a previous communication[14] we reported preliminary results on a novel access to 2-phenylnaphthalenes **7** (Scheme 1) from 1-benzylideneisoquinolines **9** via the novel (*Z*)-alkyl 2-phenyl-1-(2-vinylphenyl)vinylcarbamates **8**, and their divergent transformation into benzo[*c*]phenanthridin-1-ones **5** and 2-phenyl-1,4-naphthoquinones **6**. The present article includes a full description of this chemistry, together with the following unpublished related results: (a) the novel photochemically induced transformation of compound **8b** into the complex compound **12** (Scheme 2); (b) a novel formal synthesis of *O*-methyl fagaronine (**1e**) (Scheme 2) and (c) the novel rearrangement of *N*-carbethoxy 1-(2-nitrobenzylide-ne) isoquinoline **9c** to 5-nitroisoquinolin-1(2*H*)-one **19**, which, in turn, rearranges to the novel 2-(2-methylamino-carbonyl)isoquinolin-1(2*H*)-one **21** via its derivative **20** (Scheme 5).

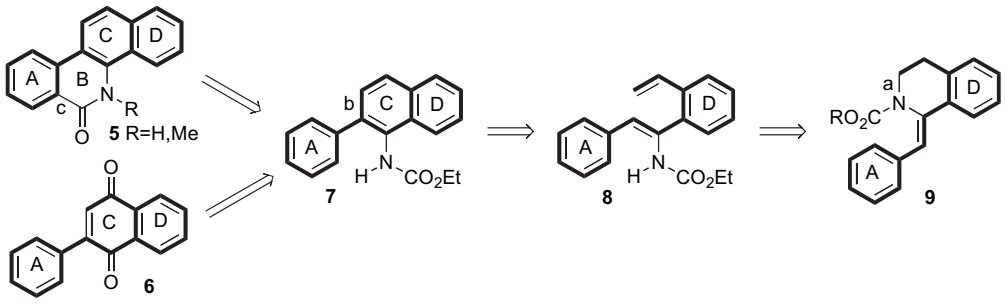
Our synthetic plan for benzo[*c*]phenanthridines **5** is based on the three key steps depicted in Scheme 1. We reasoned that disconnection of the strategic bond **a** in isoquinolines **9** should allow access to the novel stilbene-like compounds **8**, which have the required carbon skeleton and a suitable functionality for the sequential construction of the central C and B rings of our targets **5**. Ring C should result from an electrocyclic cyclization, allowing the transformation of stilbene compounds **8** into the corresponding 2-phenylnaphthalenes **7**. In addition, ring B should result from a previously described Bischler–Napieralski cyclization of 2-phenylnaphthalenes **7**.

According to our synthetic plan, treatment of the known 1-benzylideneisoquinoline **9a**[15] with LDA at 0 °C provided the styrylurethane **8a** resulting from the expected cleavage of its C_3–N bond (Scheme 2).[14]

The structure of compound **8a** was unambiguously established from its analytical data and by 1D and 2D NMR studies, including heteronuclear multiple-bond correlations (HMBC). A ^{1}H NMR NOE experiment on **8a** established a Z configuration for its stilbenic double bond. This conclusion was based on the observation that irradiation of its H_2, $H_{6'}$ and N–H protons results in a large increase in the peak intensities of the protons indicated in Fig. 2.

Continuing with our plan, when a solution of compound **8a** in *o*-xylene containing 10% Pd/C was refluxed for 3 days, the desired 2-phenylnaphthalene derivative **7a** was obtained in only a 35% yield,[16] as a result of the generation of its C ring by a thermically induced electrocyclic cyclization, as it was easily established from analytical and spectroscopic data. In fact, its mass spectrum showed the molecular weight expected for this compound (*m*/*z*=351, M^+, 100) and its ^{1}H NMR spectrum includes signals for nine aromatic protons (two less than **8a**). After, compound **7a** was easily converted into its *N*-methyl derivative **11a** by treatment with MeI in a basic medium. Finally, following the designed plan for the sequential construction of rings B and C of our targets **5**, the formation of the B ring of benzo[*c*]phenanthridine target **5a** was easily achieved in a 57% yield by subjecting its precursor **11a** to the well known Bischler–Napieralski protocol for the synthesis of isoquinolines,[17] by refluxing a solution of **11a** and P_2O_5 in $POCl_3$ during 1.5 h. The successful outcome of these reaction was easily stated from analytic and spectroscopical data of **5a**. Thus, its mass spectrum allowed to establish its molecular weight of 319 (46 mass units fewer than those of **11a**). In addition, its ^{1}H NMR spectrum includes signals for eight aromatic protons (a proton less than its precursor **11a**). A similar sequence led to the tetrasubstituted benzo[*c*]phenanthridine **5b** from the known 1-benzylideneisoquinoline **9b**,[15] via compounds **8b**, **7b** and **11b**.

Attempts to transform 2-phenylnaphthalene derivatives **7a** and **7b** into their respective *N*-unsubstituted benzo[*c*]phenanthridine-1-ones **5d** and **5e** were partially satisfactory (Scheme 2). Thus



Scheme 1.

2-phenylnaphthalene **7b** remained unaltered when subjected to the same Bischler–Napieralski cyclization conditions as for **11a**, but satisfactory results were achieved when harsher reaction conditions (triflic anhydride and DMAP) were used.[18] Under these