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Unexpected 5,6,7,8,9,10-Hexahydro-6,6-pentamethylenephenanthridines and 2,3,4,5-Tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]quinolines from Skraup–Doebner–Von Miller Quinoline Synthesis and Their Implications for the Mechanism of That Reaction

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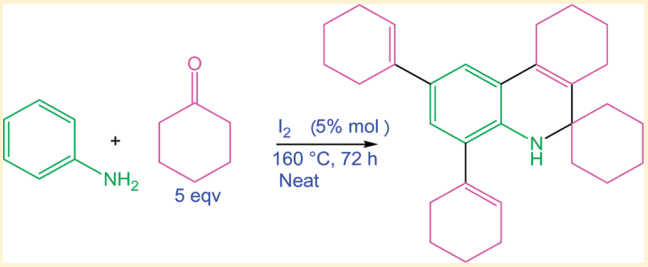
Supporting Information

ABSTRACT: The real mechanism of the Skraup–Doebner–Von Miller quinoline synthesis remains controversial and not well understood despite several mechanistic studies reported on the matter. A series of unexpected and unusual 5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridines and 2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]quinolines have been obtained through the Skraup–Doebner–Von Miller quinoline synthesis. On the basis of these unexpected results and in agreement with some of the previously reported quinoline syntheses, an alternative mechanistic pathway is proposed for this variant of the reaction. It involves the formation of a Schiff base through a reaction between the ketone and the aniline derivative in the first step, followed by a cycloalkenylation at the *ortho*-position to the amine functional group of the aniline derivative, and an annulation in the final step to close the quinoline ring, leading to a dihydroquinoline derivative. To the best of our knowledge, this is the first report of such a mechanistic pathway being proposed for any variant of the Skraup–Doebner–Von Miller quinoline synthesis.



INTRODUCTION

Quinolines and dihydroquinolines are found as important components of naturally occurring and synthetic compounds clinically used for the treatment of infectious diseases and in synthetic dyes. In fact, quinolines such as quinine and chloroquines are well-known for their antimalarial activity,[1] while dihydroquinolines are known to display, among other biological activities, antioxidant,[2,3] anti-inflammatory,[4] and hormone receptor modulating[5] properties. Furthermore, ethoxyquin (6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline) is an FDA-approved antioxidant commonly used as a preservative in the food processing industry.[6] We have recently discovered that some dihydroquinolines also display outstanding anti-trypanosomal activities.[7]

In view of their numerous applications, several methods of synthesis enabling an easy access to this family of compounds have been developed over the years. Around 1880, Skraup reported in a series of papers[8] that heating a mixture of nitroethane, aniline, and glycerol in the presence of concentrated sulfuric acid resulted in the formation of quinoline in a very low yield. Doebner and Von Miller later reported that the use of aniline and an α,β-unsaturated ketone (mesityl oxide) or 2 equiv of acetone in the presence of a catalytic amount of iodine or acid resulted in 1,2-dihydro-2,2,4-trimethylquinoline.[9] Since then, several modifications and optimizations of the Skraup reaction using varieties of catalysts have been reported.[10] Despite the intensive research in the area, the detailed mechanism of this family of reactions remains controversial. Skraup first proposed that the reaction goes through an aldehyde anil intermediate, which undergoes acid-catalyzed annualation to quinoline.[8a] It was later shown that anils cannot undergo direct closure,[11] and the mechanism was dismissed. Today's most accepted mechanisms involve a series

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of fragmentations and recombinations,[12] in which aldehyde anils must first undergo a rearrangement through 1,3-diazetidinium ions. However, Denmark and Venkatraman,[13] when investigating these mechanistic pathways using ^{13}C-labeled ketones in crossover experiments, found that none of these mechanisms were complete on their own. They concluded that this family of reactions follows a complex mechanistic pathway.[13] More importantly, they suggested that the mechanism of these reactions may actually change depending upon the starting material used, and that substituted ketones such as pulegone may not actually follow the "scrambling" mechanism.[13]

As part of our continuing effort to optimize the antitrypanosomal activity of dihydroquinolines,[7] a series of closely related 5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridines (**1**; Figure 1) were designed, and in an attempt to

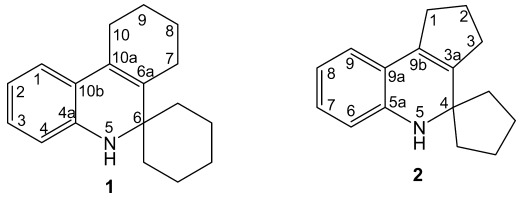

Figure 1. Basic structure of 5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridines (**1**) and 2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]quinolines (**2**), with the numbering used in the naming of prepared derivatives.

prepare these compounds through the Skraup–Doebner–Von Miller reaction, some rather unexpected cycloalkenylated derivatives of the target molecules were obtained. These compounds appeared to be systematically cycloalkenylated at either the 2 or the 4 positions or at both positions. These unexpected results prompted us to extend the investigation to 2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]-quinolines (**2**; Figure 1). In light of these new and unexpected results, we proposed an alternative and straightforward mechanistic pathway for the Skraup–Doebner–Von Miller quinoline synthesis, at least as far as cyclic ketones are concerned.

RESULTS AND DISCUSSION

In 1985, Mammen et al.[14] reported that they were able to prepare a series of 5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridines by heating a mixture of aniline derivatives and 2 equiv of cyclohexanone in the presence of 12 equiv of iodine. These compounds can be considered as close derivatives of 1,2-dihydroquinolines with the only difference that instead of using an open-chain ketone in their Skraup–Doebner–Von Miller quinoline synthesis, they used cyclohexanone. Thus, as part of our investigation on the optimization of the antitrypanosomal activity of 1,2-dihydroquinolines,[7] we designed some of these derivatives. When following the same reaction conditions as Mammen et al.[14] using 4-chloroaniline as the starting material, we obtained mainly a clear sticky oil that was characterized as 2-cyclohexenylcyclohexanone (**3**), the starting material (4-chloroaniline), and a trace of an unknown material for which GC–MS data did not match the expected quinoline derivative. Curious about the origin of 2-cyclohexenylcyclohexanone, we decided to heat up a mixture of cyclohexanone or cyclopentanone in the presence of a catalytic amount of iodine (5% mol). Under these conditions, these two compounds proved to polymerize very quickly, generating oligomers (di-, tri-, and tetramers) as observed when monitoring the reaction by GC–MS for two hours. As a consequence, 2-cyclohexenylcyclohexanone (**3**; Figure 2) was always present in appreciable amount

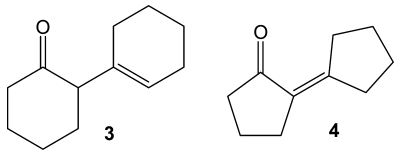

Figure 2. Structure of 2-cyclohexenylcyclohexanone (**3**) and 2-cyclopentylidenecyclopentanone (**4**) obtained from iodine-catalyzed polymerization of cyclohexanone and cyclopentanone, respectively.

each time cyclohexanone was used as starting material, while 2-cyclopentylidenecyclopentanone (**4**; Figure 2) was produced each time cyclopentanone was used as a starting material throughout this entire investigation. The trimers and tetramers were present only in a very limited amount (about 5–10%), as observed in the GC–MS spectra. It is important to notice that cyclopentanone dimerizes to yield predominantly an *α,β*-unsaturated ketone, while cycloclohexanone dimerizes to produce mainly a *β,γ*-unsaturated ketone. The difference in the geometry of these two starting materials may be the key factor behind the observed difference in reactivity.

Considering our unsuccessful attempt, and with the fact that cyclohexanone and cyclopentanone have proven to polymerize very quickly when heated in the presence of iodine, and since in our previous studies 0.05 equiv of iodine as catalyst was found to be the optimal conditions for the preparation of dihydroquinolines through the Skraup–Doebner–Von Miller reaction,[7] we decided to modify Mammen et al.'s[14] reaction conditions. In addition to using just a catalytic amount of iodine instead of 12 equiv, an excess (5 equiv) of ketones was also used in order to make up for the self-polymerization. In these conditions, 4-chloroaniline, 4-ethoxyaniline, or aniline in the presence of 5 equiv of cyclohexanone or cyclopentanone at 165 °C for 72 h did not produce the expected products. Instead, surprising cycloakenylated derivatives of the expected compounds were systematically obtained in a good yield (Scheme 1).

In fact, 4-chloroaniline in the presence of cyclohexanone in these conditions yielded 2-chloro-4-cyclohexenyl-5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridine (**5a**, 59%), while in the presence of cyclopentanone, it yielded 8-chloro-6-cyclopentenyl-2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]quinoline (**6a**, 58%). In the same conditions, 4-ethoxyaniline in the presence of cyclohexanone yielded 4-cyclohexenyl-2-ethoxy-5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridine (**5b**, 53%), while aniline in the presence of cyclopentanone, yielded 6-cyclopentenyl-2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]quinoline (**6b**, 46%). More interestingly, aniline in the presence of cyclohexanone yielded 2,4-dicyclohexenyl-5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridine (**7**, 63%), a derivative with cyclohexenyl groups at the *ortho* and *para* positions to the nitrogen atom of the dihydroquinoline ring system (Scheme 2). In all these cases, an increase in the amount of ketones did not have any impact on the yield of the reaction. Nevertheless, the increase in the amount of iodine appeared to exacerbate the polymerization of these cyclic ketones as observed in the GC–MS spectra.

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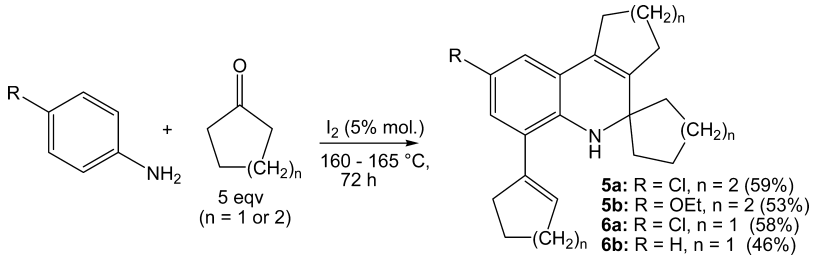
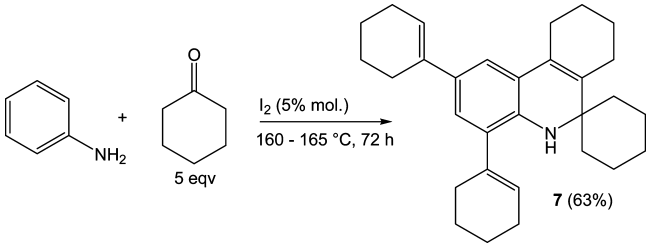
Scheme 1. Reactions between 4-Chloroaniline, 4-Ethoxyaniline, or Aniline and Cyclohexanone or Cyclopentanone

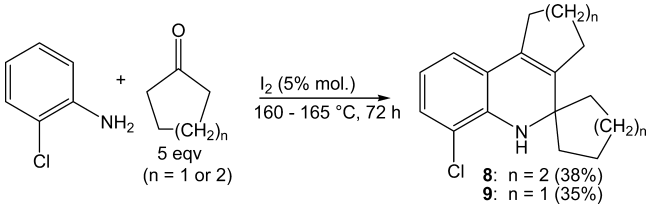


Scheme 2. Reaction between Aniline and Cyclohexanone



Furthermore, 2-chloroaniline in which one of the *ortho*-positions to the nitrogen atom is already substituted, in the same conditions, yielded mainly the noncycloalkenylated derivative (Scheme 3), although some traces of the *para*-

Scheme 3. Reaction between 2-Chloroaniline and Cyclohexanone or Cyclopentanone

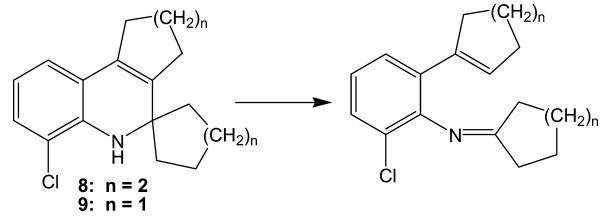


cycloalkenylated (*para* to the nitrogen atom) derivatives were detected in the GC–MS spectra.[15]

In fact, 2-chloroaniline in the presence of cyclohexanone yielded mainly 4-chloro-5,6,7,8,9,10-hexahydro-6,6-pentamethylene-phenanthridine (**8**, 38%), while in the presence of cyclopentanone, it yielded mainly 6-chloro-2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]quinolines (**9**, 35%). All these compounds were characterized based on their NMR (^{1}H, ^{13}C, COSY, gHSQC, and HMBC) and HRESI-MS spectra. The structures of compounds **5a**, **5b**, and **7** were unambiguously determined by single crystal X-ray diffraction, and the obtained molecular structures of these compounds are shown in the Supporting Information.

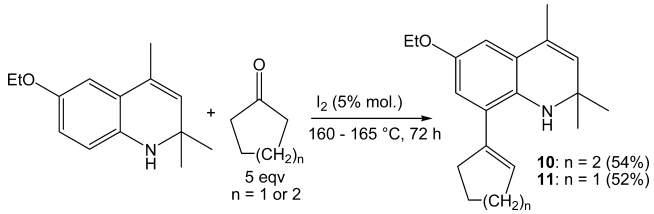
At this stage of the investigation, it was obvious that in addition to the usual Skraup–Doebner–Von Miller quinoline synthesis, a regioselective (*ortho*/*para* to the amine of the dihydroquinoline ring) cycloalkanylation was taking place. More importantly, this latter reaction sequence seems to be playing an important role in the Skraup–Doebner–Von Miller reaction since, by simple retrosynthesis (Scheme 4), it could be observed that at least one of the *ortho*-positions to the amino function of the aniline derivative used as starting material appeared to be cycloalkenylated at some point during the course of the reaction, even in compounds **8** and **9**, which did not display an apparent cycloalkenyl substitution.

Scheme 4. Retrosynthesis of Compounds 8 and 9



While investigating whether iodine can actually catalyze a cycloalkenylation on an aromatic ring system, ethoxyquin (6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline) was submitted to the same reaction conditions. In fact, ethoxyquin reacts with cyclohexanone and cyclopentanone in the presence of a catalytic amount of iodine to yield 8-cyclohexenyl-6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (**10**, 54%) and 8-cyclopentenyl-6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (**11**, 52%), respectively, as shown in Scheme 5.

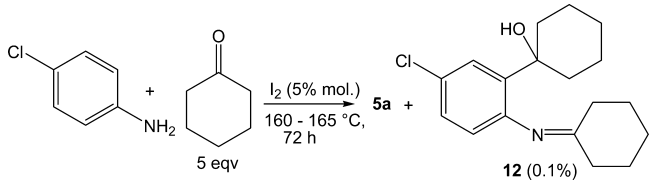
Scheme 5. Reaction between Ethoxyquin and Cyclohexanone or Cyclopentanone



Furthermore, during the preparation of **5a**, 1-(5-chloro-2-(cyclohexylideneamino)phenyl)cyclohexanol (**12**, 0.1%) was also isolated as a key reaction intermediate (Scheme 6). This is the only case in which the isolation of such an intermediate was successfully (mainly luckily) achieved. Several other attempts to isolate such an intermediate during other reactions were proven unsuccessful.

On the basis of the data collected throughout this study, we hypothesized that the Skraup–Doebner–Von Miller reaction

Scheme 6. 1-(5-Chloro-2-(cyclohexylideneamino)phenyl)cyclohexanol (12) Isolated as a Side Product during the Synthesis of 5a



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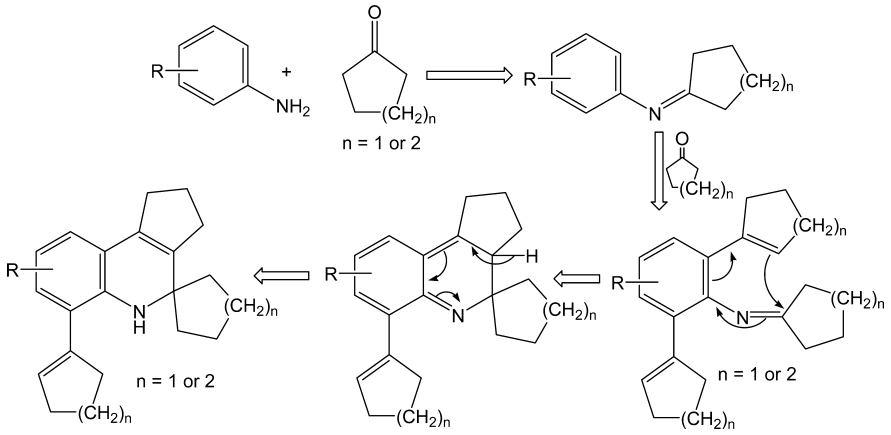
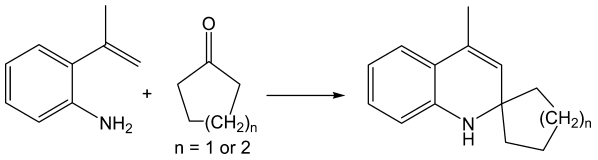
Scheme 7. Proposed Mechanistic Pathway for Skraup–Doebner–Von Miller Quinoline Synthesis Involving Cyclic Ketones



involved in the synthesis of the above-listed cycloalkenylated 5,6,7,8,9,10-hexahydro-6,6-pentamethylene-phenanthridines and 2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]-quinolines may be proceeding through three basic sequences: (1) the formation of a Schiff base through a reaction between the ketone and the aniline derivative in the first step, followed by (2) a cycloalkenylation at the *ortho*-position to the amine functional group of the aniline derivative, and (3) an annulation in the final step to close the quinoline ring, leading to a dihydroquinoline derivative as described in Scheme 7.

The formation of a Schiff base as the initial step in the mechanism of the Skraup–Doebner–Von Miller quinoline synthesis is well accepted.[12,13] Furthermore, Edwards et al.[16] have previously reported that *o*-aminostyrenes can easily react with ketones/cyclic ketones in the presence of a catalytic amount of iodine to yield the corresponding *spiro*-dihydroquinoline derivatives as shown in Scheme 8. These findings were recently confirmed by Denmark and Venkatraman.[13]

Scheme 8. Reaction between *o*-Aminostyrenes and Cyclic Ketones According to Edwards et al.[16]



Since this study shows that iodine can effectively catalyze an *ortho*-cycloalkanylation on arylamines, in addition to the fact that Edwards et al.[16] have already proven that *o*-aminostyrenes can easily react with ketones/cyclic ketones in the very same conditions to yield the corresponding *spiro*-dihydroquinoline derivatives, the mechanistic pathway proposed in this report is viable and fully supported by strong data. More importantly, the final step of this mechanism consists in a typical 6π-electrocyclization of 2-azahexa-1,3,5-triene (electrocyclic closure),[17] followed by a sigmatropic rearrangement ([1,5]-H shift) resulting in a dihydroquinoline ring.

The fact that cyclohexanone and cyclopentanone were found to quickly polymerize through self-condensation (cf. compounds **2** and **3**) is an indication that the pathway involving the fragmentation and recombination (cf. ref 12) cannot be completely excluded. Nevertheless, the high yield of the cycloalkenylation reaction on one hand, and the Edwards et al.[16] *spiro*-dihydroquinoline synthesis on the other, are clear indications that the mechanism proposed in this study is definitely the preferred pathway for this variant of the Skraup–Doebner–Von Miller quinoline synthesis. However, since the iodine-catalyzed *ortho*-vinylation of arylamines through a direct reaction with open-chain ketones produced only traces of the expected products during this study, this mechanism might not apply to open-chain ketones. This is an additional proof that the Skraup–Doebner–Von Miller quinoline synthesis follows complex mechanistic pathways that might be dependent upon the starting material, as previously suggested by Denmark and Venkatraman.[13]

CONCLUSION

A series of unexpected and unusual 5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridines and 2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]quinolines have been obtained through the Skraup–Doebner–Von Miller quinoline synthesis. These data have led to the development of an alternative and straightforward mechanistic pathway for the Skraup–Doebner–Von Miller quinoline synthesis, at least as far as cyclic ketones are concerned. More importantly, this report provides an easy method for direct access to regioselective cycloalkenylated dihydroquinoline derivatives through a single-pot Skraup–Doebner–Von Miller quinoline synthesis. This study also suggests that iodine can catalyze a one-pot regioselective cycloalkenylation on aromatic rings (at least as far as arylamines are concerned). Additional studies to determine the full scope of such a one-pot regioselective cycloalkenylation reaction on aromatic rings are already underway in our lab, and the obtained results will be part of future reports.

EXPERIMENTAL SECTION

General Methods. NMR data were collected on two different spectrometers, one operating at 600 MHz for ^{1}H and 150 MHz for ^{13}C and on another at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts were referenced to the solvent ($CDCl_3$ δH observed at 7.25 ppm and δC observed at 77.2 ppm). These data were recorded at 27 °C, and all two-dimensional spectra were recorded with 2048 data points for *x*-domain and 256 for *y*-domain. The edited g-HSQC and g-HMBC spectra were optimized for 8 and 140 Hz, respectively. It is important to mention that because of the complexity of the structure of these molecules, and the succession and overlap of CH_2 signals in the ^{1}H NMR spectra, it was difficult to accurately integrate these protons in some cases. Thus, a special sequence known as DEPT-HMQC was used for accurate integration of protons attached on each carbon in these cases. Crystal structure analyses of **5a**, **5b**, and **7** were

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based on data collected at low temperature on either a Nonius KappaCCD diffractometer equipped with MoKα radiation or a Bruker Kappa Apex-II CCD diffractometer with CuKα radiation. Melting points were measured on a digital capillary melting point apparatus calibrated with benzoic acid (≥99.5%) [mp 122.38 °C (lit), obtained 122.4−122.6 °C]. Reaction mixtures were monitored using a 200-MS GC−MS ion trap mass spectrometer or by TLC silica gel 60 F254 plates. Gravity and flash column chromatography were performed using type 60A silica gel (60−230 mesh). All the compounds were further purified using silica gel GF preparative 1000 or 1500 μm UV254 plates or recrystallized from a mixture of hexanes and ethyl acetate (for compounds **5a**, **5b**, and **7**).

Materials. All chemicals and solvents were purchased from major chemical suppliers and were used without further purification unless stated otherwise.

Preparation and Characterization of Compounds. All reactions were performed at 160−165 °C for 72 h in the presence of 0.05 equiv of iodine and 5 equiv of ketones.

2-Cyclohexenylcyclohexanone (3). This clear sticky oil was present throughout the entire investigation each time cyclohexanone was used as a starting material, but it was isolated only once for characterization through a purification on a silica gel column using hexanes−ethyl acetate (95:5) as eluent: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.51−1.69 (6H, m), 1.75−2.01 (8H, m), 2.15−2.39 (2H, m), 2.85−2.87 (1H, m), 5.40 (1H, m); it is important to mention that the fact that two protons from the same carbon appear at very different chemical shift makes it difficult to accurately integrate these protons; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.5, 22.9, 24.9, 25.3, 27.3, 27.7, 31.9, 42.2, 58.8, 123.7, 135.9, 211.8; HRESI-MS $[M + H]^+$ m/z 179.1426 (calcd. 179.143042 for $C_{12}H_{19}O$).

2-Cyclopentylidenecyclopentanone (4). This clear sticky oil was present throughout the entire investigation each time cyclopentanone was used as a starting material. It was also isolated only once for characterization through a purification on a silica gel column using hexanes−ethyl acetate (95:5) as eluent: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.61−1.65 (4H, m), 1.83−1.85 (2H, m), 2.21−2.24 (4H, m), 2.46−2.47 (2H, m), 2.70−2.71 (2H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.1, 25.3, 27.0, 29.6, 32.6, 34.3, 39.8, 127.9, 158.6, 207.4; HRESI-MS $[M + H]^+$ m/z 151.1118 (calcd. 151.111742 for $C_{10}H_{15}O$).

2-Chloro-4-cyclohexenyl-5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridine (5a). This compound was obtained by reacting 4-chloroaniline (5 g, 39 mmol) and cyclohexanone (19.3 g, 196 mmol) in the presence of a catalytic amount of iodine (498 mg, 1.96 mmol). After purification on a silica gel column using hexanes−ethyl acetate (9:1), compound **5a** was obtained as a yellowish needles (8.4 g, 59%): mp 127.9−128.7 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.11−1.13 (2H, m), 1.27−1.29 (2H, m), 1.42−1.46 (2H, m), 1.58−1.59 (2H, m), 1.66−1.71 (8H, m), 1.77−1.78 (2H, m), 2.10- 2.11 (2H, m), 2.20−2.22 (4H, m), 2.31−2.33 (2H, m), 5.00 (1H, brs, NH), 5.83 (1H, m), 6.80 (1H, d, J = 2.0 Hz), 6.93 (1H, d, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.5, 22.3, 23.0, 23.4, 24.9, 25.4, 25.6, 25.7, 30.1, 32.5, 54.8, 120.6, 122.0, 125.0, 125.9, 126.0, 128.0, 130.5, 135.0, 137.1, 137.4. The *spiro*-quaternary carbon (C-6) appears at 54.8 ppm, while the g-HSQC and g-HMBC sequences enable us to find the key correlation between the protons at δ 5.83 ppm (the proton on the cyclohexenyl double bond carried by the carbon at 125.9 ppm) and the quaternary aromatic carbon (C-4) at δ 126.0 ppm. HRESI-MS: $[M + H]^+$ m/z 368.2140 (calcd. 368.213954 for $C_{24}H_{31}NCl$). The structure of this compound was unambiguously determined by single crystal X-ray diffraction. Crystal data: $C_{24}H_{30}ClN$, M_r = 367.94, triclinic space group $P\bar{1}$, a = 8.1800(10), b = 9.9875(13), c = 13.2073(15) Å, α = 97.344(6), β = 98.122(8), γ = 111.627(8)°, V = 973.8(2) Å^3, T = 95 K, Z = 2, D_x = 1.255 Mg m^{-3}, θ_{max} = 33.1°(MoKα), R = 0.044 for 7378 data and 257 refined parameters. This structure has some disorder involving alternate conformations of six-membered rings. The crystal structure data are deposited in the Cambridge database (CCDC 845943).

4-Cyclohexenyl-2-ethoxy-5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridine (5b). This compound was obtained by reacting 4-ethoxyaniline, also known as *p*-phenitidine (5 g, 36 mmol), and cyclohexanone (17.9 g, 182 mmol) in the presence of a catalytic amount of iodine (463 mg, 1.82 mmol). After purification on a silica gel column using hexanes−ethyl acetate (9:1), compound **5b** was obtained as a yellowish needles (7.3 g, 53%): mp 106.4−107.3 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.09−1.13 (2H, m), 1.26−1.31 (2H, m), 1.35 (3H, t, J = 6.8 Hz), 1.40−1.42 (2H, m), 1.56−1.58 (2H, m), 1.65−1.72 (8H, m), 1.75−1.79 (2H, m), 2.10−2.13 (2H, m), 2.21−2.25 (4H, m), 2.36−2.38 (2H, m), 3.96 (2H, q, J = 6.8 Hz), 4.84 (1H, brs, NH), 5.83 (1H, m), 6.46 (1H, d, J = 2.8 Hz), 6.62 (1H, d, J = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 15.2, 21.6, 22.4, 22.5, 23.1, 23.5, 24.9, 25.5, 25.6, 25.8, 30.3, 32.1, 54.7, 64.0, 108.1, 112.6, 125.7, 125.8, 127.2, 129.9, 132.4, 135.9, 137.2, 151.1. The *spiro*-quaternary carbon (C-6) appears at 54.7 ppm, while the g-HSQC and g-HMBC sequences enable us to find the key correlation between the protons at δ 5.83 ppm (the proton on the cyclohexenyl double bond carried by the carbon at 125.7 ppm) and the quaternary aromatic carbon (C-4) at δ 125.8 ppm. HRESI-MS: $[M + H]^+$ m/z 378.2806 (calcd. 378.279142 for $C_{26}H_{36}NO$). The structure of this compound was unambiguously determined by single crystal X-ray diffraction. Crystal data: $C_{26}H_{35}NO$, M_r = 377.55, monoclinic space group $P2_1/c$, a = 18.545(3), b = 10.021(2), c = 11.5921(15) Å, β = 92.327(10)°, V = 2152.5(6) Å^3, T = 95 K, Z = 4, D_x = 1.165 Mg m^{-3}, θ_{max} = 27.9°(MoKα), R = 0.050 for 5106 data and 287 refined parameters. This structure has some disorder involving alternate conformations of six-membered rings. The crystal structure data are deposited in the Cambridge database (CCDC 845945).

8-Chloro-6-cyclopentenyl-2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]quinoline (6a). This compound was obtained by reacting 4-chloroaniline (5 g, 39 mmol) and cyclopentanone (16.5 g, 196 mmol) in the presence of a catalytic amount of iodine (498 mg, 1.96 mmol). After purification on a silica gel column using hexanes−ethyl acetate (9:1), compound **6a** was obtained as yellowish oil (7.4 g, 58%). This compound, like some other derivatives obtained from cyclopentanone, showed some signs of auto-oxidation, as it turned dark-greenish upon standing, a phenomenon previously observed with dihydroquinolines in general[7] and more importantly with cylopentyl-*spiro*-derivatives of dihydroquinoline as reported by Edwards et al.[16] Nevertheless, this oxidation was not as dramatic as previously reported,[18] as indicated by the ^{13}C NMR and HRESI-MS spectra: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.67−1.70 (6H, m), 1.83−1.85 (2H, m), 1.95−2.03 (4H, m), 2.49−2.52 (2H, m), 2.54−2.56 (2H, m), 2.60−2.65 (4H, m), 4.64 (1H, brs, NH), 5.90 (1H, m), 6.73 (1H, d, J = 2.0 Hz), 6.84 (1H, d J = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.4, 23.3, 23.8, 31.4, 32.2, 33.9, 36.7, 39.6, 65.1, 121.1, 121.7, 122.0, 122.8, 125.9, 128.4, 132.0, 138.3, 140.1, 140.7. In this case, the *spiro*-quaternary carbon (C-4) appears at 65.1 ppm, while the g-HSQC and g-HMBC sequences enable us to find the key correlation between the protons at δ 5.90 ppm (the proton on the cyclopentenyl double bond carried by the carbon at 125.9 ppm) and the quaternary aromatic carbon (C-6) at δ 122.8 ppm. HRESI-MS: $[M + H]^+$ m/z 326.1669 (calcd. 326.167004 for $C_{21}H_{25}NCl$).

6-Cyclopentenyl-2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]quinoline (6b). This compound was obtained by reacting aniline (5 g, 53.7 mmol) and cyclopentanone (22.6 g, 268 mmol) in the presence of a catalytic amount of iodine (682 mg, 2.68 mmol). After purification on a silica gel column using hexanes−ethyl acetate (95:5), compound **6b** was obtained as yellowish oil (7.2 g, 46%). This compound displayed better stability than its counterpart **6a** as indicated by the ^{1}H and ^{13}C NMR spectra: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.70−1.72 (6H, m), 1.85−1.90 (2H, m), 2.00−2.03 (4H, m), 2.50−2.52 (2H, m), 2.54−2.60 (2H, m), 2.66−2.68 (4H, m), 4.64 (1H, brs, NH), 5.91 (1H, m), 6.59 (1H, t, J = 7.6 Hz), 6.80 (1H, dd, J = 7.7 and 1.4 Hz), 6.90 (1H, dd, J = 7.6 and 1.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.5, 23.4, 23.8, 31.5, 32.2, 33.9, 36.8, 39.6, 65.0, 116.3, 120.5, 121.5, 122.2, 126.6, 127.3, 132.8, 138.5, 139.7, 141.8. In this case, the *spiro*-quaternary carbon (C-4) appears at 65.0 ppm, while the g-HSQC and g-HMBC sequences enable us to find the key correlation between the proton at δ 5.91 ppm (the proton on the cyclopentenyl double bond carried by the carbon at 126.6 ppm) and

the quaternary aromatic carbon (C-6) at δ 121.5 ppm. HRESI-MS: $[M + H]^+$ m/z 292.2060 (calcd. 292.205976 for $C_{21}H_{26}N$).

2,4-Dicyclohexenyl-5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridine (7). This compound was obtained by reacting aniline (5 g, 53.7 mmol) and cyclohexanone (26.3 g, 268 mmol) in the presence of a catalytic amount of iodine (682 mg, 2.68 mmol). After purification on a silica gel column using hexanes−ethyl acetate (95:5), compound **7** was obtained as a transparent needles (14.0 g, 63%): mp 146.5 −147.9 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.11−1.14 (2H, m), 1.28−1.32 (2H, m), 1.42−1.48 (2H, m), 1.56−1.59 (2H, m), 1.63−1.79 (14H, m), 2.10−2.13 (2H, m), 2.17−2.18 (2H, m), 2.19−2.23 (2H, m), 2.25−2.28 (2H, m), 2.38−2.40 (2H, m), 2.41−2.43 (2H, m), 5.03 (1H, brs, NH), 5.83 (1H, m), 6.00 (1H, m), 6.91 (1H, d, J = 2.1 Hz), 7.05 (1H, d, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.5, 22.5, 22.6, 22.7, 23.4, 23.5, 24.9, 25.5, 26.0, 27.6, 30.4, 32.4, 54.7, 117.3, 121.4, 123.1, 124.0, 125.9, 127.2, 129.2, 131.3, 135.9, 136.2, 136.7, 137.2. The *spiro*-quaternary carbon (C-6) appears at 54.7 ppm, while the g-HSQC and g-HMBC sequences enable us to find key correlations between the protons at δ 5.83 ppm (the proton on the *ortho*-cyclohexenyl double bond carried by the carbon at 127.2 ppm) and the quaternary aromatic carbon (C-4) which also appears at δ 129.2 ppm, and between the proton at 6.00 ppm (the proton on the *para*-cyclohexenyl double bond carried by the carbon at 121.4 ppm) and the quaternary aromatic carbon (C-2) at δ 131.3 ppm. HRESI-MS: $[M + H]^+$ m/z 414.3157 (calcd. 414.315527 for $C_{30}H_{40}N$). The structure of this compound was unambiguously determined by single crystal X-ray diffraction. Crystal data: $C_{30}H_{39}N$, M_r = 413.62, orthorhombic space group *Pbca*, a = 9.7385(4), b = 11.6917(6), c = 41.5907(19) Å, V = 4735.5(4) Å^3, T = 90 K, Z = 8, D_x = 1.160 Mg m^{-3}, θ_{max} = 59.3°(CuKα), R = 0.053 for 3376 data and 293 refined parameters. This structure has some disorder involving alternate conformations of six-membered rings. The crystal structure data are deposited in the Cambridge database (CCDC 845944).

4-Chloro-5,6,7,8,9,10-hexahydro-6,6-pentamethylenephenanthridine (8). This compound was obtained by reacting 2-chloroaniline (5 g, 39.2 mmol) and cyclohexanone (19.2 g, 196 mmol) in the presence of a catalytic amount of iodine (498 mg, 1.96 mmol). After purification on a silica gel column using hexanes−ethyl acetate (97.5:2.5), compound **8** was obtained as yellowish oil (4.3 g, 38%). This compound also showed some signs of decomposition as observed on the ^{1}H NMR spectrum: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.50−1.53 (2H, m), 1.58−1.61 (2H, m), 1.65−1.73 (8H, m), 2.13−2.14 (2H, m), 2.35−2.36 (2H, m), 5.04 (1H, brs, NH), 6.59 (1H, dd, J = 7.8, and 8.2 Hz), 6.97 (1H, d,d J = 8.2 and 2.4 Hz), 7.05 (1H, dd, J = 7.8 and 2.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.2, 22.5, 23.0, 25.0, 25.3, 25.6, 32.8, 55.1, 117.5, 118.2, 120.6, 125.0, 125.6, 127.0, 136.9, 138.5; the *spiro*-quaternary carbon (C-6) appears at 55.1 ppm; HRESI-MS $[M + H]^+$ m/z 288.1507 (calcd. 288.151354 for $C_{18}H_{23}NCl$).

6-Chloro-2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*]quinolines (9). This compound was obtained by reacting 2-chloroaniline (5 g, 39.2 mmol) and cyclopentanone (16.5 g, 196 mmol) in the presence of a catalytic amount of iodine (498 mg, 1.96 mmol). After purification on a silica gel column using hexanes−ethyl acetate (95:5), compound **9** was obtained as yellowish oil (3.54 g, 35%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.69−1.72 (2H, m), 1.78−1.81 (4H, m), 1.89−1.91 (2H, m), 2.01−2.04 (2H, m), 2.51−2.52 (2H, m), 2.63−2.65 (2H, m), 4.53 (1H, brs, NH), 6.51 (1H, dd, J = 8.3 and 7.6 Hz), 6.77 (1H, dd, J = 7.6 and 2.3 Hz), 7.01 (1H, dd, J = 8.3 and 2.3 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.6, 23.9, 31.3, 32.3, 40.4, 65.3, 116.5, 116.8, 121.6, 121.7, 127.4, 131.9, 138.9, 139.7; in this case, the *spiro*-quaternary carbon (C-4) appears at 65.3 ppm; HRESI-MS $[M + H]^+$ m/z 260.1206 (calcd. 260.120054 for $C_{16}H_{19}NCl$).

8-Cyclohexenyl-6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (10). This compound was obtained by reacting ethoxyquin (1.5 g, 6.9 mmol) and cyclohexanone (3.4 g, 34.5 mmol) in the presence of a catalytic amount of iodine (88 mg, 0.35 mmol). After purification on a silica gel column using hexanes−ethyl acetate (9:1), compound **10** was obtained as yellowish oil (1.11 g, 54%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.22 (6H, s), 1.36 (3H, t, J = 6.9 Hz), 1.68−1.69 (2H, m), 1.75−1.76 (2H, m), 1.98 (3H, s), 2.16−2.18 (4H, m), 3.42 (1H, brs, NH), 3.96 (2H, q, J = 6.9 Hz), 5.37 (1H, s), 5.71 (1H, m), 6.46 (1H, d, J = 2.8 Hz), 6.62 (1H, d, J = 2.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 15.2, 18.9, 22.2, 23.3, 25.5, 29.8, 30.0, 50.8, 51.5, 64.2, 109.5, 114.1, 123.4, 127.2, 129.1, 129.9, 134.0, 136.0, 150.7. The g-HSQC and g-HMBC sequences enable us to find the key correlation between the proton at δ 5.71 ppm (the proton on the cyclohexenyl double bond carried by the carbon at 127.2 ppm) and the quaternary aromatic carbon (C-6) at δ 129.1 ppm. HRESI-MS: $[M + H]^+$ m/z 298.2158 (calcd. 298.216541 for $C_{20}H_{28}NO$).

8-Cyclopentenyl-6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (11). This compound was obtained by reacting ethoxyquin (2.02 g, 9.3 mmol) and cyclopentanone (3.9 g, 46.5 mmol) in the presence of a catalytic amount of iodine (118 mg, 0.46 mmol). After purification on a silica gel column using hexanes−ethyl acetate (9:1), compound **11** was obtained as yellowish oil (1.37 g, 52%). This compound, as for some other derivatives obtained from cyclopentanone, showed some signs of auto-oxidation, as it turned dark-greenish upon standing. However, this oxidation was not very dramatic as indicated by the ^{13}C NMR and HRESI-MS spectra:[18] ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.25 (6H, s), 1.38 (3H, t, J = 6.9 Hz), 1.99−2.00 (2H, m), 2.00 (3H, s), 2.57−2.58 (2H, m), 2.66−2.67 (2H, m), 3.96 (2H, q, J = 6.9 Hz), 4.20 (1H, brs, NH), 5.40 (1H, s), 5.90 (1H, m), 6.58 (1H, d, J = 2.8 Hz), 6.64 (1H, d, J = 2.8 Hz) ; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 15.2, 19.1, 23.3, 30.3, 33.9, 36.8, 51.6, 64.2, 110.0, 113.6, 123.2, 128.4, 129.1, 129.8, 134.9, 141.2, 150.4. The g-HSQC and g-HMBC sequences enable us to find the key correlation between the proton at δ 5.90 ppm (the proton on the cyclopentenyl double bond carried by the carbon at 129.1 ppm) and the quaternary aromatic carbon (C-6) at δ 123.2 ppm. HRESI-MS: $[M + H]^+$ m/z 284.2009 (calcd. 284.200891 for $C_{19}H_{26}NO$).

1-(5-Chloro-2-(cyclohexylideneamino)phenyl)cyclohexanol (12). This compound was obtained as a side product during the preparation of **5a**, in which 4-chloroaniline (5 g, 39 mmol) and cyclohexanone (19.3 g, 196 mmol) were allowed to react in the presence of a catalytic amount of iodine (498 mg, 1.96 mmol). After purification on a silica gel column using hexanes−ethyl acetate (85:15), compound **12** was obtained as white solid (12 mg, 0.1%): mp 103.4 −103.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.65−1.71 (3H, m), 1.90−1.99 (3H, m), 2.27−2.37 (3H, m), 3.01−3.13 (3H, m), 3.16−3.20 (3H, m), 3.23−3.28 (3H, m), 4.15−4.19 (2H, m), 4.16 (1H, brs, OH) (this OH proton is hidden by the 2H around 4.15−4.19, and that explains the broad base observed for those protons and the fact that the integral shows 3H instead of 2H), 7.55 (1H, dd, J = 9.3 and 1.8 Hz), 7.73 (1H, d, J = 1.8 Hz), 7.88 (1H, d, J = 9.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 23.8, 24.2, 25.3, 31.2, 31.3, 34.9, 78.3, 123.0, 125.6, 129.3, 129.4, 131.4, 144.5, 152.3, 158.9; HRESI-MS $[M + H]^+$ m/z 306.1429 ($C_{18}H_{25}ClNO$), with the base peak $[M - H_2O + H]^+$ m/z 288.1518 (calcd. 288.151354 for $C_{18}H_{23}NCl$).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR of **3**, **4**, **5a**, **5b**, **6a**, **6b**, **7**, **8**, **9**, **10**, **11**, and **12**; the molecular structures obtained from single crystal X-ray diffraction as well as the single crystal X-ray diffraction data (CIF files) for compounds **5a**, **5b**, and **7**; the HRESI-MS spectra of **6a**, **8**, and **11** that showed some signs of decomposition in their ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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