METALLATION OF METHOXY-2(1*H*)-QUINOLINONES

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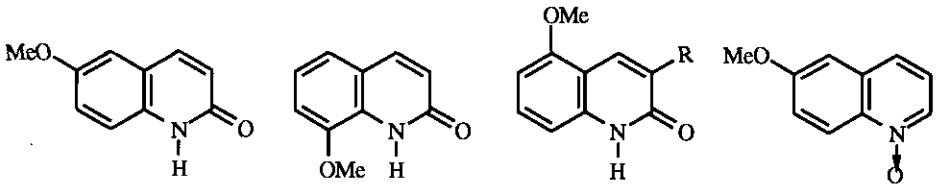
Abstract-Methoxy group at 5- or 6-position of 2(1*H*)-quinolinones is compatible with the regioselective electrophilic substitution and chain enlargement at the 3-position imposed by the *ortho*-directed effect of the quinolinone lithium salt. The coordination effect of a methoxy group at the 8- position changes the reaction course, precluding the *ortho*-directed metallation and enhancing the conjugate addition at the 4- position.

INTRODUCTION

We have shown the synthetic utility of the directed *ortho*-metallation (DoM) in 2(1*H*)-quinolinone and 3-methyl-2(1*H*)-quinolinone to obtain 3-substituted[1,2] or chain enlargement[3] compounds, respectively. These reactions are performed through the *ortho*-directed effect of the lithium quinoline- or 3-methylquinoline-2-oxides to give *C,O*-dilithiated species, which are quenched by electrophiles. The tandem nucleophile-electrophile addition to the C_3=C_4 conjugated bond, in contrast to what is known to occur in open-chain analogues such as *N*-alkylcinnamamides,[4] was in those substrates a minor reaction. This one-pot procedure works with a wide range of electrophiles and, although the yields are dependent on the nature of these reagents and vary from 40 to 90 %, it permits the synthesis of otherwise inaccessible compounds and competes in many cases with alternative multi-step processes.

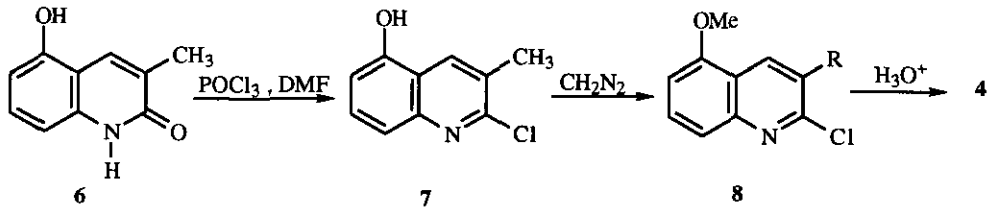
Taking into account that methoxy groups are considered to be much stronger *ortho*-directors than phenoxide anions,[5] we investigated this methodology in methoxyquinolinones, in order to study the scope of the method. In these derivatives it is important to determine the effect of these substituents and the competition as *ortho*-directors between the quinoline-2-oxide anions and the additional methoxy groups present in the benzene ring of

these systems. In this way, we have used compounds (**1**-**4**) as model substrates and methyl iodide and trimethylsilyl chloride as model electrophiles. The substrates were selected either by their accessibility or to permit further transformations to carbostyrilquinones used as dienophiles in the synthesis of diazaquinomicin A analogues.[3,6]



RESULTS

Compound (**1**) has been previously obtained from 5-methoxy-2-aminocinnamic acid[7] and from 6-methoxyquinoline through its conversion to the *N*-oxide (**5**).[8] We have used the latter procedure, but due to the discrepancies observed in the melting points and the absence of spectroscopic data for compounds (**5**) and (**1**), they have been here described in full. The same strategy[9] was used in the synthesis of **2**. Synthesis of compound (**3**) has been previously reported[10] and compound (**4**) has been obtained in a similar way from 3-methyl-1,2,3,4,5,6,7,8-octahydroquinoline-2,5-dione, prepared by reaction of 3-aminocyclohexenone and methyl methacrylate,[11] followed by dehydrogenation and subsequent *O*-methylation according to our previous experience with 5-hydroxy-2(1*H*)-quinolinone[10] (compounds (**6**-**8**), Scheme 1). The alternative route to obtain **4** through metallation of **3** and quenching with methyl iodide is discussed below.

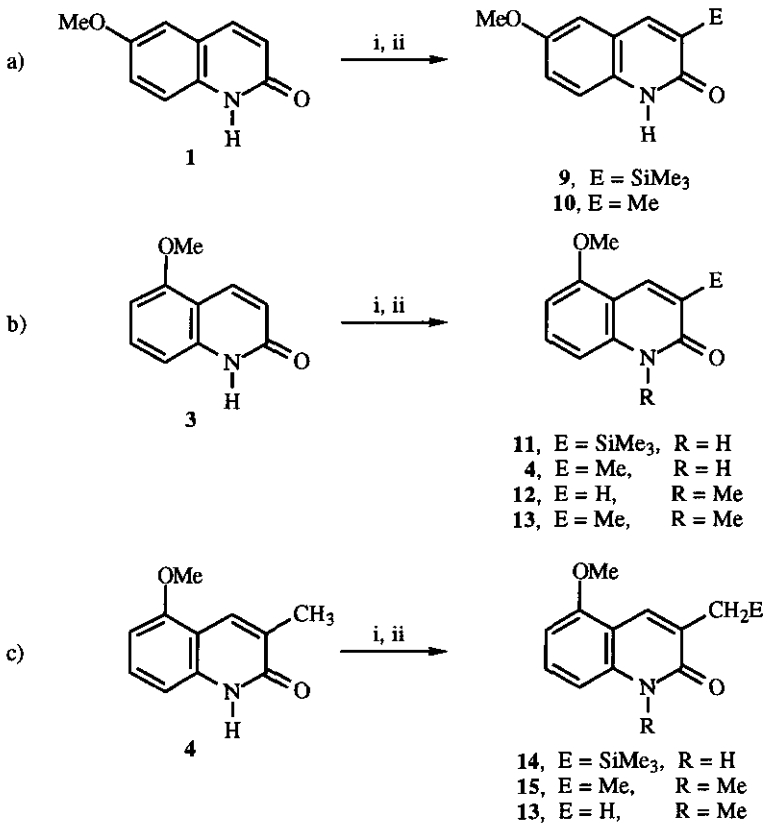


Scheme 1

Schemes 2 and 4 summarize the reaction products obtained with compounds (**1**-**4**) after treatment with 2.3 equivalents of *n*-BuLi in THF/ TMEDA at -78 °C, followed by addition of the corresponding electrophile. In none of these reactions did the methoxy substituent compete as a director group, since substitution at benzene ring was not observed.

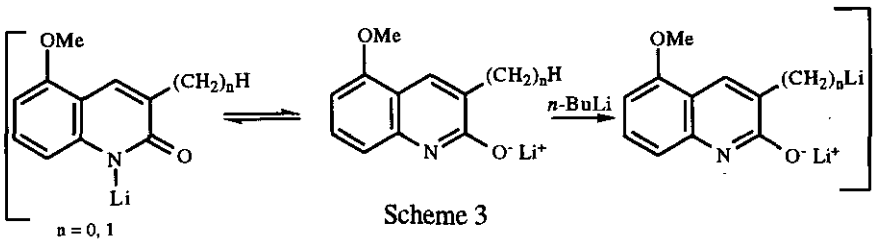
The 6-methoxy derivative (**1**) gave compounds (**9**) (38%) and (**10**) (47%) exclusively (Scheme 2a). The C_6-methoxy group is compatible with the regioselective electrophilic substitution, although it lowered the yield with

2b and 2c) gave with trimethylsilyl chloride the expected 3-substituted products (**11**) (25%) and (**14**) (30%) respectively, but in the case of methyl iodide high amounts of *N*-methyl derivatives (**12**, 20% from **3** and **13**, 28% from **4**) and 3,*N*-dimethyl derivatives (**13**, 15% from **3** and **15**, 57% from **4**) were obtained, together with the 3-substituted compound (**4**) (from **3**, 25%).



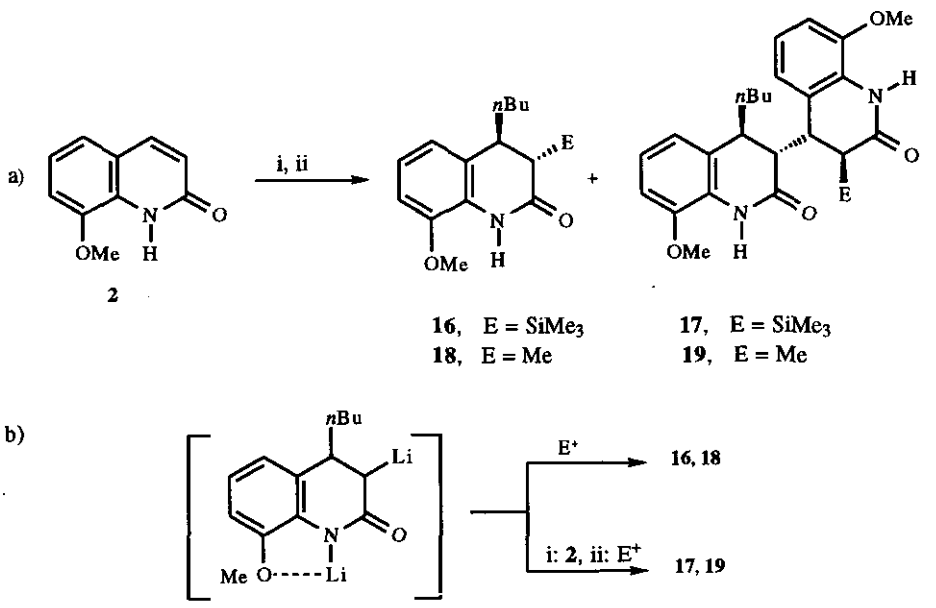
Scheme 2

These results show that a C_5-methoxy substituent does not compete as an *ortho*-directing group under these conditions, and confirm our previous interpretation about the regioselective C_3-electrophilic substitution, which is due to the capability of the oxygen atom of lithium phenoxide to coordinate an organolithium reagent.[1] Thus, because of the conjugation of methoxy and carbonyl groups at 5- and 2-positions, the equilibrium between the *N*- and *O*-monolithiated forms is altered, with a more important contribution of the former. In consequence, the amount of *O*,3-dilithium species is lowered and *N*-substituted compounds are formed (Scheme 3). Obviously these products are not observed in the case of the reaction with trimethylsilyl chloride due to their unstability in the workup of the reactions.



Scheme 3

The results with compound (**2**) (Scheme 4a) were very interesting since no C_3-substitution was here observed. Instead, the tandem conjugate addition-α-alkylation reactions to C_4=C_3 bond afforded compounds (**16**) (32%) and (**18**) (52%) together with compounds (**17**) (39%) and (**19**) (44%) respectively. These results can be understood if the C_8-methoxy substituent stabilizes the *N*-lithium salt by coordination. Thus the *O*-lithiated species are absent and the *ortho*-direction to the 3-position is precluded.Tandem nucleophile-electrophile addition to C_4=C_3 bond takes place instead, giving compounds (**16**) and (**18**). Compounds (**17**) and (**19**) come from nucleophilic attack of the anion at the 3-position to **2** folloved by electrophile trapping (Scheme 4b). All these products were isolated as single *trans*-diastereoisomers. The analysis of the vicinal $J_{3,4}$ coupling constant and NOE experiments, when it was possible, showed an axial axial conformation. For instance, $J_{3,4}$ in the DMSO-d_6 ^{1}H-*nmr* spectrum of **18** is 1.86 Hz, and irradiation of the H-4 proton produced significant enhancement of the H-3 and H-5 resonances. The stereochemistry of this reaction has been previously discussed in reference 3.

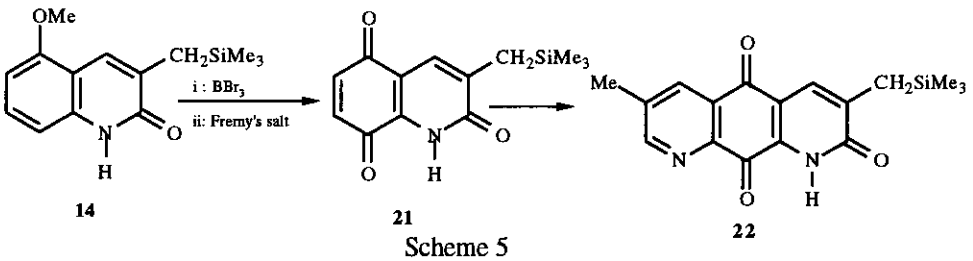


i. *n*-BuLi, TMEDA, -78 °C
ii. E^+

Scheme 4

In conclusion, methoxy groups at 5- and 6-positions are compatible with the C_3 regioselective electrophilic substitution while a C_8-OMe group changes the reaction course to give conjugate addition at the 4-position. All these results confirm the previously proposed reaction mechanisms[1-3] based on the *ortho*-directing effect of lithium quinoline-2-oxides.

In order to obtain new Diazaquinomycin A analogues, compound (**14**) was demethylated to **20** and oxidized to the carbostyrilquinone derivative (**21**), which after heterocyclization with methacrolein dimethylhydrazone[6,12] gave the 1,8-diazaanthracene-2,9,10-trione (**22**) (Scheme 5).



Scheme 5

EXPERIMENTAL

Nmr spectra were obtained on Bruker AC-250 (250 MHz for ^{1}H, 63 MHz for ^{13}C) and Varian VXR-300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometers; DMSO-d_6 was used as solvent, unless otherwise noted, and TMS was added in all cases as an internal standard. Elemental analyses of new compounds were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyser. Mass spectra were recorded on a Hewlett-Packard 5993C (EI, 70 eV) Melting points were measured in open capillary tubes using a Büchi immersion apparatus, and are uncorrected. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Scharlau Cf 530). Separations by chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh, and Scharlau Ge 048). All reagents were of commercial quality (Aldrich, Fluka, Merck, SDS, Probus) and were purified following standard procedures. The expression "petroleum ether" refers to the fraction boiling at 40-60 °C. For compounds reported in the literature, only new spectral data are included.

6-Methoxyquinoline-*N*-oxide (**5**). mp 80-82 °C (acetic anhydride), (lit.,[13] 110-112 °C).^{1}H-Nmr ($CDCl_3$) δ: 8.65 (d, 1H, J= 9.55 Hz, H-8); 8.41 (d, 1H, J= 6.01 Hz, H-2); 7.65 (d, 1H, J= 8.44 Hz, H-4); 7.39 (dd, 1H, J= 9.56 and 2.58 Hz, H-7); 7.29 (dd, 1H, J= 8.44 and 6.01 Hz, H-3); 7.11 (d, 1H, J= 2.54 Hz, H-5) and 3.94 (s, 3H, OCH_3) ppm. ^{13}C-Nmr ($CDCl_3$) δ: 159.46 (C-6); 136.87 (C-8a); 133.92 (C-2); 131.98 (C-4a); 125.35 and 122.94 (C-8 and C-4); 121.50 and 121.45 (C-3 and C-7); 105.73 (C-5); and 55.73 (OCH_3) ppm.

6-Methoxy-2(1*H*)-quinolinone (1). mp 207-208 °C (ethyl acetate/hexane), (lit.,[7] 208-210 °C; lit.,[8] 215-217 °C).^{1}H-Nmr ($CDCl_3$) δ: 12.4 (s, 1H, NH); 7.80 (d, 1H, J= 9.48 Hz, H-4); 7.40 (d, 1H, J= 8.9 Hz, H-8); 7.15 (dd, 1H, J= 8.9 and 2.7 Hz, H-7); 7.00 (d, 1H, J= 2.7 Hz, H-5); 6.68 (d, 1H, J= 9.48 Hz, H-3) and 3.90 (s, 3H, OCH_3) ppm. ^{13}C-Nmr ($CDCl_3$) δ: 164.01 (C-2); 151.21 (C-6); 140.56 (C-4); 133.02 (C-8a); 121.74 (C-3); 120.48 (C-4a); 120.24 (C-7); 117.43 (C-8); 108.8 (C-5) and 55.69 (OCH_3) ppm.

5-Hydroxy-3-methyl-2(1*H*)-quinolinone (6). A solution of 3-methyl-1,2,3,4,5,6,7,8-octahydro-quinoline-2,5-dione[11] (3 g, 16.7 mmol) in decalin (50 ml) containing 10% Pd-C (2.5 g) was refluxed for 4 days. After cooling the solution was filtered and the solvent was removed under reduced pressure. Both filtrate and residue were extracted with MeOH and the extract was concentrated to give **6** (2.9 g, 100 %) as a solid. mp > 300 °C (MeOH). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.17; N, 7.99. Found: C, 68.66; H, 4.85; N, 7.64. ^{1}H-Nmr δ: 11.58 (s, 1H, NH); 10.19 (s, 1H, OH); 7.88 (s, 1H, H-4); 7.18 (m, 1H, H-7); 6.70 (d, 1H, J= 8.18 Hz, H-8); 6.54 (dd, 1H, J= 7.92 and 0.82 Hz, H-6) and 2.07 (s, 3H, CH_3) ppm. ^{13}C-Nmr δ: 162.85 (C-2); 153.74 (C-5); 139.51 (C-8a); 131.19 (C-4); 130.07 (C-7); 127.69 (C-3); 109.36 (C-4a); 106.7 (C-8); 105.83 (C-6) and 16.94 (CH_3) ppm.

2-Chloro-3-methylquinolin-5-ol (7). A solution of **6** (2.5 g, 13.8 mmol) in DMF (1.59 ml) and phosphorus oxychloride (9.2 ml, 100 mmol) was allowed to stand for 12 h. After subsequent heating at 115 °C for 2 h, the reaction mixture was poured onto ice. The precipitate was filtered and extracted with acetone. The acetone solution concentrated *in vacuo* gave quantitatively compound (**7**), mp 196-197 °C. An analytical sample was obtained by column chromatography (silica gel, ethyl acetate). Anal. Calcd for $C_{10}H_8NOCl$: C, 62.03; H, 4.16; N, 7.23. Found: C, 62.11; H, 4.29; N, 6.99. ^{1}H-Nmr δ: 10.65 (s, 1H, OH); 8.44 (s, 1H, H-4); 7.55 (m, 1H, H-7); 7.37 (d, 1H, J= 8.4 Hz, H-8) and 6.96 (d, 1H, J= 7.21 Hz, H-6) ppm, (CH_3, was overlapped with DMSO). ^{13}C-Nmr δ: 153.23(C-5); 151.43 (C-2); 147.22 (C-8a); 133.55 (C-4); 130.59 (C-7); 128.38 (C-3); 119.13 (C-4a); 118.07 (C-8); 109.34 (C-6) and 19.75 (CH_3) ppm.

2-Chloro-5-methoxy-3-methylquinoline (8). To a solution of **7** (2.6 g, 13.42 mmol) in MeOH (100 ml) a 0.35 *N* solution of diazomethane in ether (220 ml, 758 mmol) was added dropwise. The solution was stirred at room temperature for 12 h. After addition of water, the precipitate was filtered to give **8**. The crude product was purified by silica gel column chromatography using CH_2Cl_2 as eluent. Yield: 70%. mp 200 °C (decomp.). Anal. Calcd for $C_{11}H_{10}NOCl$: C, 63.62; H, 4.84; N, 6.74. Found: C, 63.40; H, 4.74; N, 6.48. ^{1}H-Nmr δ: 8.46 (s, 1H, H-4); 7.67 (m, 1H, H-7); 7.49 (d, 1H, J= 8.49 Hz, H-8); 7.09 (d, 1H, J= 7.78 Hz, H-6); 3.99 (s, 3H, OCH_3) and 2.50 (s, 3H, CH_3 and DMSO were overlapped) ppm. ^{13}C-Nmr δ: 154.5 (C-5); 151.63 (C-2);

146.80 (C-8a); 132.95 (C-4); 130.37 (C-7); 129.12 (C-3); 119.39 (C-4a); 119.65 (C-8); 105.73 (C-6); 56.12 (OCH_3) and 19.72 (CH_3) ppm.

3-Methyl-5-methoxy-2(1*H*)-quinolinone (4). A solution of **8** (1.7 g, 8.186 mmol) in acetic acid (24 ml) and water (8 ml) was refluxed for 5 h and poured onto ice. The filtered precipitate yielded **4**, 1.4 g (90 %). mp 242-43 °C (MeOH). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.85; N, 7.40. Found: C, 69.54; H, 5.85; N, 7.05. ^{1}H-Nmr δ:11.72 (s, 1H, NH); 7.9 (s, 1H, H-4); 7.34 (m, 1H, H-7); 6.86 (d, 1H, J= 8.2 Hz, H-8); 6.70 (d, 1H, J= 7.98 Hz, H-6); 3.88 (s, 3H, OCH_3) and 2.08 (s, 3H, CH_3) ppm. ^{13}C-Nmr δ: 162.36 (C-2); 154.82 (C-5); 138.95 (C-8a); 130.19 (C-4); 129.88 (C-7); 128.42 (C-3); 109.43 (C-4a); 107.43 (C-8); 102.46 (C-6); 55.64 (OCH_3) and 16.65 (CH_3) ppm.

Lithiation of methoxy-2(1H)quinolinones. General procedure.

A solution of *n*-BuLi (9.8 ml of 1.6 M solution in hexane, 15.7 mmol) and TMEDA (3.4 ml, 22.5 mmol) in dry THF (25 ml) prepared at -70 °C and warmed to 0 °C was added in small portions *via* syringe to a stirred suspension of methoxy-2(1*H*)-quinolinone (**1-4**) (6.9 mmol) in THF (25 ml) kept at -70 °C in a nitrogen atmosphere. When the addition was complete, the reaction mixture was warmed to room temperature over 2 h. The resulting red solution was quenched with the electrophile (8-10 mmol) and stirred at room temperature for 15-30 min. The reaction mixture was diluted with chloroform, washed sequentially with 6 *N* hydrochloric acid, aqueous sodium bicarbonate (9%) and sodium chloride (30%) solutions, dried over sodium sulfate and the solvent was evaporated.

3-Trimethylsilyl-6-methoxy-2(1*H*)-quinolinone (9). It was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether 9:1). Yield 37 %. mp 220 °C (MeOH). Anal. Calcd for $C_{13}H_{17}NO_2Si$: C, 63.12; H, 6.92; N, 5.66. Found: C, 63.03; H, 6.64; N, 5.74. ^{1}H-Nmr ($CDCl_3$) δ: 12.30 (s, 1H, NH); 7.85 (s, 1H, H-4); 7.30 (d, 1H, J= 8.9 Hz, H-8); 7.15 (dd, 1H, J= 8.9 and 2.7 Hz, H-7); 7.00 (d, 1H, J= 2.7 Hz, H-5); 3.80 (s, 3H, OCH_3) and 0.40 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C-Nmr ($CDCl_3$) δ: 166.64 (C-2); 154.75 (C-6); 146.67 (C-4); 134.26 and 134.13 (C-8a and C-3); 120.61 (C-4a); 120.08 and 116.98 (C-7 and C-8); 108.66 (C-5); 55.66 (OCH_3) and -1.54 ($Si(CH_3)_3$) ppm.

3-Methyl-6-methoxy-2(1*H*)-quinolinone (10). It was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether 9:1). Yield 47%. mp. 247-248 °C (MeOH). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.85; N, 7.40. Found: C, 69.45; H, 5.69; N, 7.10. ^{1}H-Nmr δ: 11.80 (s, 1H, NH); 7.85 (s, 1H, H-4); 7.40 (d, 1H, J= 8.9 Hz, H-8); 7.25 (m, 2H, H-7 and H-5); 3.95 (s, 3H, OCH_3) and 2.20 (s, 3H, CH_3)

ppm. ^{13}C-Nmr δ: 161.93 (C-2); 154.0 (C-6); 136.01 (C-4); 132.21 and 130.18 (C-8a and C-3); 120.0 (C-4a); 115.94 and 118.02 (C-7 and C-8); 108.51 (C-5); 55.31 (OCH_3) and 16.61 (CH_3) ppm.

3-Trimethylsilyl-5-methoxy-2(1*H*)-quinolinone (11). Yield 50%, mp 240 °C (ethyl acetate). It was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 7:3). Anal. Calcd for $C_{13}H_{17}NO_2Si$: C, 63.12; H, 6.92; N, 5.66. Found: C, 63.33; H, 6.90; N, 5.59. ^{1}H-Nmr δ: 11.54 (s, 1H, NH); 8.1 (s, 1H, H-4); 7.40 (m, 1H, H-7); 6.85 (d, 1H, J= 8.25 Hz, H-8); 6.70 (d, 1H, J= 8.05 Hz, H-6); 3.89 (s, 3H, OCH_3) and 0.23 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C-Nmr δ: 164.61 (C-2); 155.67 (C-5); 140.22 and 141.04 (C-8a and C-4); 131.83 (C-7); 131.93 (C-3); 109.56 (C-4a); 107.76 (C-8); 102.68 (C-6); 55.99 (OCH_3) and -1.35 ($Si(CH_3)_3$) ppm.

3-Methyl-5-methoxy-2(1*H*)-quinolinone (4). Yield 26 % (from **3**).

***N*-Methyl-5-methoxy-2(1*H*)-quinolinone (12)**. Yield 23 %, mp 129-130 °C (lit.,[14] 129-130 °C).

3,*N*-Dimethyl-5-methoxy-2(1*H*)-quinolinone (13). Yield 16 % (from **3**) or 28 % (from **4**), mp 112 °C (MeOH/ether). It was purified by column chromatography (silica gel, ethyl acetate/ CH_2Cl_2 8:2). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.44; N, 6.89. Found: C, 70.86; H, 6.54; N, 6.93. ^{1}H-Nmr δ: 7.96 (s, 1H, H-4); 7.49 (m, 1H, H-7); 7.08 (d, 1H, J= 8.6 Hz, H-8); 6.84 (d, 1H, J= 8.12 Hz, H-6); 3.91 (s, 3H, OCH_3); 3.78 (s, 3H, N-CH_3) and 2.12 (s, 3H, CH_3) ppm. ^{13}C-Nmr δ: 161.62 (C-2); 155.09 (C-5); 139.82 (C-8a); 130.28 (C-4); 129.06 (C-7); 127.41 (C-3); 109.84 (C-4a); 107.02 (C-8); 103.2 (C-6); 55.83 (OCH_3); 30.04 (N-CH_3) and 17.89 (CH_3) ppm.

3-Trimethylsilylmethyl-5-methoxy-2(1*H*)-quinolinone (14) Yield 48%, mp 112-113 °C (MeOH). It was purified by column chromatography (silica gel, ethyl acetate/petroleum ether 7:3). Anal. Calcd for $C_{14}H_{17}NO_2Si$: C, 64.33; H, 7.32; N, 5.36. Found: C, 63.93; H, 7.13; N, 5.23. ^{1}H-Nmr δ: 11.66 (s, 1H, NH); 7.68 (s, 1H, H-4); 7.30 (m, 1H, H-7); 6.84 (d, 1H, J= 8.2 Hz, H-8); 6.68 (d, 1H, J= 7.7 Hz, H-6); 3.87 (s, 3H, OCH_3); 2.06 (s, 2H, CH_2) and -0.01 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C-Nmr δ: 162.21 (C-2); 150.70 (C-5); 138.39 (C-8a); 131.80 (C-4); 129.25 (C-7); 127.24 (C-3); 110.04 (C-4a); 107.64 (C-8); 102.62 (C-6); 55.88 (OCH_3); 20.41 (CH_2) and -1.20 ($Si(CH_3)_3$) ppm.

3-Ethyl-*N*-methyl-5-methoxy-2(1*H*)-quinolinone (15). Yield 57 %, mp 90 °C (EtOH/ether). It was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 7:3). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.95; N, 6.44. Found: C, 71.48; H, 6.95; N, 6.28. ^{1}H-Nmr δ: 7.87 (s, 1H, H-4); 7.47 (m, 1H, H-7); 7.05 (d, 1H, J= 8.48 Hz, H-8); 6.83 (d, 1H, J= 8.03 Hz, H-6); 3.90 (s, 3H, OCH_3); 3.60 (s, 3H, N-CH_3) and 1.13 (t, 3H, J= 7.31 Hz, $C\underline{H}_3$-CH_2) (CH_2 and DMSO were overlapped) ppm. ^{13}C-Nmr δ: 161.17

(C-2); 155.46 (C-5); 140.0 (C-8a); 133.06 (C-4); 130.63 (C-7); 127.64 (C-3); 110.08 (C-4a); 107.24 (C-8); 103.43 (C-6); 56.10 (OCH_3); 29.93 (N-CH_3); 24.13 (CH_2) and 13.02(CH_3) ppm.

4-*n*-Butyl-3-trimethylsilyl-8-methoxy-1,2,3,4-tetrahydroquinolin-2-one (16). Yield 32 %. It was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether 9:1), mp 50 °C (petroleum ether). Anal. Calcd for $C_{17}H_{27}NO_2Si$: C, 66.83; H, 8.91; N, 4.56. Found: C, 66.40; H, 8.26; N, 4.52. ^{1}H-Nmr ($CDCl_3$) δ: 7.85 (s, 1H, NH); 6.80 (m, 1H, H-6); 6.40 (m, 2H, H-5 and H-7); 3.85 (s, 3H, OCH_3); 2.85 (m, 1H, H-4); 1.60-0.80 (m, 10H, *n*-Bu and H-3) and 0.05 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C-Nmr ($CDCl_3$) δ: 172.13 (C-2); 145.66 (C-8); 127.46 (C-8a); 126.00 (C-4a); 122.34 (C-6); 120.36 (C-5); 108.82 (C-7); 55.68 (OCH_3); 40.09 (C-4); 38.92, 37.32, 28.97 and 22.58 (C-3 and CH_2); 14.01 (CH_3) and -2.40 ($Si(CH_3)_3$) ppm.

4-*n*-Butyl-3-methyl-8-methoxy-1,2,3,4-tetrahydroquinolin-2-one (18). Yield 52%. Oil purified by column chromatography (silica gel, ethyl acetate/ petroleum ether 9:1). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.55; N, 5.66. Found: C, 72.41; H, 8.69; N, 5.39. ^{1}H-Nmr δ: 9.02 (s, 1H, NH); 6.95-6.84 (m, 2H, H-5 and H-6); 6.72 (dd, 1H, J= 10.06 and 1.43 Hz, H-7); 3.78 (s, 3H, OCH_3); 2.57 (td, 1H, J= 7.83 and 1.86 Hz, H-4); 2.45 (qd, 1H, J= 6.07, and 1.86 Hz, H-3); 1.45-1.07 (m, 6H, CH_2-CH_2-CH_2 and H-4); 0.95 (d, 3H, J= 7.29 Hz, CH_3) and 0.75 (t, 3H, J= 6.83 Hz, CH_2-$C\underline{H}_3$). ^{1}H-Nmr ($CDCl_3$) δ: 7.70 (s, 1H, NH); 6.85 (m, 1H, H-6); 6.63 (m, 2H, H-5 and H-7); 3.69 (s, 3H, OCH_3); 2.45 (m, 1H, H-3); 1.45 -1.20 (m, 7H, CH_2-CH_2-CH_2 and H-4); 1.05 (d, 3H, J= 7.08 Hz, CH_3) and 0.75 (t, 3H, J= 6.83 Hz, CH_2-$C\underline{H}_3$) ppm. ^{13}C-Nmr ($CDCl_3$) δ: 173.38 (C-2); 145.87 (C-8); 126.56 (C-8a); 124.50 (C-4a); 122.56 (C-6); 121.44 (C-5); 108.80 (C-7); 55.65 (OCH_3); 44.36, 41.17 (C-3 and C-4); 34.58, 29.71, 22.70 (CH_2) and 16.82 and 11.35 (CH_3) ppm.

4-*n*-Butyl-3-(3-trimethylsilyl-8-methoxy-2-oxo-1,2,3,4-tetrahydro-4-quinolyl)-8-methoxy-1,2,3,4-tetrahydroquinolin-2-one (17). Yield 39 %. It was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether 9:1). mp 200-201 °C (chloroform/petroleum ether). ^{1}H-Nmr ($CDCl_3$) δ: 7.82 and 7.76 (s, 2H, NH); 6.70-6.64 (m, 4H, H-6, H-6', H-5 and H-5'); 6.04 (m, 2H, H-7 and H-7'); 3.82 (s, 6H, OCH_3); 2.95 (m, 1H, H-3); 2.84-2.65 (m, 2H, H-4 and H-4'); 1.97 (m, 1H, H-3'); 1.50-1.13 (m, 6H, $(CH_2)_3$); 0.83 (t, 3H, J= 6.72 Hz, CH_3) and 0.06 (s, 9H, $(CH_3)_3$) ppm. ^{13}C-Nmr ($CDCl_3$) δ: 171.84 and 169.07 (C-2 and C-2'); 145.74 and 145.36 (C-8 and C-8'); 125.87, 125.15, 125.00, 123.56, 122.29, 122.24, 122.24, 122.11, 120.85, 109.27 and 109.21 (aromatic carbon atoms); 55.79 and 55.70 (OCH_3); 44.32, 43.63 and 40.01 (C-3, C-4 and C-4'); 33.51 (C-3'); 30.86, 29.16 and 22.41 ($(CH_2)_3$); 13.87 (CH_3) and 1.94 ($Si(CH_3)_3$) ppm. Ms: 480 (M^+, v.w.); 248 (27 %); 232 (80 %) ; 176 (100 %).

4-*n*-Butyl-3-(3-methyl-8-methoxy-2-oxo-1,2,3,4-tetrahydro-4-quinolyl)-8-methoxy-1,2,3,4-tetrahydroquinolin-2-one (19). Yield 44 %. It was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether 9:1). mp 194-195 °C (chloroform/petroleum ether). ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 7.80 (s, 2H, NH); 6.70-6.56 (m, 4H, H-6, H-6', H-5 and H-5'); 5.92 (m, 2H, H-7 and H-7'); 3.84 (s, 6H, OCH_3); 2.91 (m, 1H, H-3'); 2.84-2.66 (m, 3H, H-3, H-4 and H-4'); 1.40-1.20 (m, 6H, $(CH_2)_3$); 1.11 (d, 3H, J= 7.34 Hz, CH_3) and 0.82 (t, 3H, J= 6.95 Hz, $\underline{CH_3}$-CH_2) ppm. ^{13}C-Nmr (75 MHz, $CDCl_3$) δ: 172.42 and 171.83 (C-2 and C-2'); 145.15 (C-8 and C-8'); 124.61, 124.53, 123.53, 123.25, 122.41, 122.18, 121.96 and 108.94 (aromatic carbon atoms); 55.60 and 55.48 (OCH_3); 47.08 and 45.04 (C-3 and C-3'); 44.06 and 38.54 (C-4 and C-4'); 30.39, 29.04 and 22.23 ($(CH_2)_3$); 16.85 (C_3-$\underline{CH_3}$) and 13.72 ($\underline{CH_3}$-CH_2) ppm. Ms: 422 (M^+, 3%); 232 (100 %); 190 (93 %); 176 (58 %).

5-Hydroxy-3-trimethylsilylmethyl-2(1*H*)-quinolinone (20). To the ice-cooled solution of **14** (0.1 g, 3.81 mmol) in dry dichloromethane (10 ml) was added dropwise boron tribromide (1.15 ml of 1 M solution in CH_2Cl_2, 10.88 mmol). The reaction mixture was stirred at room temperature for 3 h. Water (5 ml) was then added and the mixture was extracted with ether (3 x 15 ml). The ether extract was dried over magnesium sulfate and concentrated to give **20** (0.090 g, 96 %), mp 250 °C (MeOH). Anal. Calcd for $C_{13}H_{17}NO_2Si$: C, 63.12; H, 6.92; N, 5.66. Found: C, 62.98; H, 6.82; N, 5.38. ^{1}H-Nmr δ: 11.52 (s, 1H, NH); 10.10 (s, 1H, OH); 7.66 (s, 1H, H-4); 7.13 (m, 1H, H-7); 6.68 (d, 1H, J= 8.07 Hz, H-8); 6.52 (d, 1H, J= 7.86 Hz, H-6); 2.04 (s, 2H, CH_2) and -0.01 (s, 9H, CH_3) ppm. ^{13}C-Nmr δ: 162.35 (C-2); 153.22 (C-5); 138.69 (C-4); 130.71 (C-7); 129.16 (C-8a); 127.94 (C-3); 109.64 (C-8); 106.67 (C-4a); 105.76 (C-6); 20.22 (CH_2) and -1.21 (CH_3) ppm.

3-Trimethylsilylmethyl-2,5,8(1*H*)-quinolinetrione (21). Potassium nitrosodisulfonate (Fremy's salt) (0.24 g, 0.89 mmol) and aqueous sodium acetate (20 M, 10 ml) were dissolved in water (25 ml) and added dropwise to a cooled solution of **20** (0.09 g, 0.36 mmol) in $CHCl_3$ (8 ml). The reaction mixture was stirred at room temperature for 3 h and extracted with $CHCl_3$. The extract was dried over magnesium sulfate and concentrated, the residue was purified by column chromatography (silica gel, ethyl acetate/ hexane 7:4). Yield 50%, mp 170 °C (decomp.) (ethyl acetate). Anal. Calcd for $C_{13}H_{15}NO_3Si$: C, 59.74; H, 5.78; N, 5.35. Found: C, 59.44; H, 5.41; N, 5.10. ^{1}H-Nmr δ: 11.94 (s, 1H, NH); 7.5 (s, 1H, H-4); 6.92 (d, 1H, J= 10.29 Hz, H-6); 6.85 (d, 1H, J= 10.29 Hz, H-7); 2.14 (s, 2H, CH_2) and -0.009 (s, 9H, CH_3) ppm.

6-Methyl-3-trimethylsilylmethyl-1,8-diaza-2,9,10-anthracenetrione (22).

To a solution of **21** (0.062 g, 0.237 mmol) in dry THF (10 ml) was added 3-methyl-1-dimethylamino-1-azabuta-1,3-diene[12] (0.053 g, 0.474 mmol) and the mixture was stirred at room temperature for 12 h. After

evaporation of the solvent at reduced pressure, the residue was purified by column chromatography (silica gel, ethyl ether) to give **22** (0.077 g, 90 %), mp 225 °C (CH_2Cl_2/petroleum ether). Anal. Calcd for $C_{17}H_{18}N_2O_3Si$: C, 62.55; H, 5.55; N, 8.58. Found: C, 62.86; H, 5.84; N, 8.39. ^{1}H-Nmr δ: 12.09 (s, 1H, NH); 8.84 (s,1H, H-7); 8.24 (s, 1H, H-5); 7.69 (s, 1H, H-4); 2.20 (s, 2H, CH_2) and -0.02 (s, 9H, $Si(CH_3)_3$), (CH_3 and DMSO were overlapped) ppm. ^{13}C-Nmr δ: 180.80 (C-9); 176.20 (C-10); 162.05 (C-2); 154.63 (C-7); 145.56 (C-8a); 140.54 and 138.21 (C-6 and C-9a); 139.26 (C-5); 134.03 (C-4); 128.92 and 128.48 (C-3 and C-10a); 115.55 (C-4a); 21.68 (CH_2); 18.50 (CH_3) and -1.17 ($Si(CH_3)_3$) ppm.

ACKNOWLEDGEMENTS

Financial support from CICYT (projects FAR-553-90 and PTR-93-0028) is gratefully acknowledged.

REFERENCES

1. R. González, M. T. Ramos, E. de la Cuesta, and C. Avendaño, *Heterocycles*, 1993, **36**, 315.

2. M. Fernández, E. de la Cuesta, and C.Avendaño, *Synthesis* , 1995, 1362.

3. O. Martín, E. de la Cuesta, and C. Avendaño, *Tetrahedron* , 1995, **51**, 7547.

4. J. E. Baldwin and W. A. Dupont, *Tetrahedron Lett.*, 1980, **21**, 1881.

5. G. H. Posner and K. A. Canella, *J. Am. Chem. Soc.*, 1985, **107**, 2571 and references therein.

6. a) C. Gesto, E. de la Cuesta, and C. Avendaño, *Tetrahedron* , 1989, **45**, 4477. b) C. Gesto, E. de la Cuesta C. Avendaño, and F. Emling, *J. Pharm. Sci.*, 1992, **81**, 815. c) B. Ocaña, M. Espada, and C. Avendaño,*Tetrahedron* , 1994, **50**, 9505. d) C. Avendaño, M. A. Alonso, M. Espada, D. García-Grávalos, J. C. Menéndez, B. Ocaña, and J. M. Pérez, EP 0574195 A1, 1993 (*Chem. Abstr.*, 1994, **120**, P270358e). e) J.M. Pérez , C. Avendaño, and J. C. Menéndez, *Tetrahedron* , 1995, **51**, 6573.

7. G. H. Jones, M. C.Venuti, R. Alvarez, J. J. Bruno, A. H. Berks, and A. Prince, *J. Med. Chem.*, 1987, **30**, 295.

8. J. DeRuiter, A. N. Brubaker, W. L.Whitmer, and J. L. Stein Jr., *J. Med. Chem.*, 1986, **29**, 2024.

9. a) G. R. Pettit and M. V. Kalnins, *J. Org. Chem.*, 1968, **33**, 1089. b) S. Yoshizaki, K. Tanimura, S. Tamada, Y. Yabuuchi, and K. Nakagawa, *J. Med. Chem.*, 1976, **19**, 1138.

10. M. Fernández, E. de la Cuesta, and C. Avendaño, *Heterocycles*, 1994, **38**, 2615.

11. T. Shono, Y. Matsumura, and S. Kashimura, *J. Org. Chem.*, 1981, **46**, 3719.

12. B. W. Ioffe and K. N. Zelenin, *Dokl. Akad. Nauk SSRR,* 1961, **141**, 1369 (*Chem. Abstr.*, 1962, **56**, 14038b).

13. M. J. Dimsdale, *J. Heterocycl. Chem.,* 1979, **16**, 1209.

14. S. A. Glover and A. Goosen, *J. Chem. Soc., Perkin Trans.I* , 1977, 1348.

Received, 8th December, 1995