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Electrophilic Substitution in 3- and 4-Methyl-2(1*H*)quinolinone through Metallated Species

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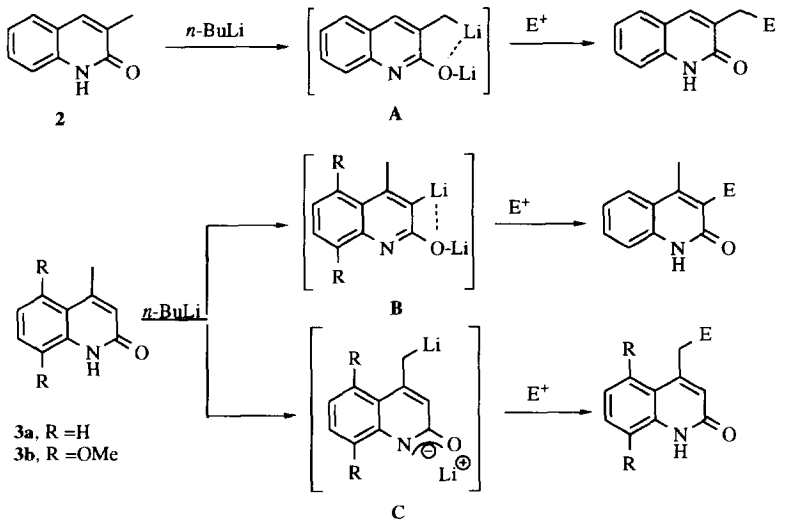
Abstract: *Unprotected 3- (**2**) and 4-methyl-2(1H)quinolinones (**3a**) and 4-methyl-5,8-dimethoxy-2(1H)quinolinone (**3b**) undergo through regioselective lithiation chain enlargement with different electrophiles.*

The scarcity of methods to prepare 3- and/or 4-substituted (1*H*)2,5,8-quinolinetriones is a limitation in the synthesis, through Diels-Alder cycloadditions, of antitumour analogues of the natural antifolate antibiotic Diazaquinomycin A.[1] These dienophiles are currently obtained by oxidative demethylation of 5,8-dimethoxy-2(1*H*)quinolinones, which have been prepared by applying Knorr,[2,3] Friedländer[4] and Vilsmeier-Haack[5,6] reactions. All of them include the substituents in the aliphatic chain, which is lately submitted to cyclization. It is well known that acid catalysed electrophilic substitution in 2(1*H*)-quinolinone (**1**) is directed to C-6.[7] Taking into account that alkyllithium reagents and pyridone[8] or cynnamic amides[9] give nucleophile-electrophile additions it would be expected that a similar addition to the C_3=C_4 bond of **1** could be a competitive reaction in the metallation of **1** to give *C,O*-dilithiated species, intermediates in the electrophilic substitution in basic media.

Until 1983 lithiations directed by hydroxy, amino and carboxylic groups were not considered of synthetic utility,[10] but in 1985 Posner and coworkers showed that lithium phenoxide can coordinate an organolithium reagent and/or stabilize other lithium atom at the *ortho* position. This *C,O*-dianion has an acceptable stability and permits the *ortho* electrophilic substitution in moderate yields.[11] However extension of this *ortho* directed effect to 2(1*H*)-pyridone lithium salt to get regioselective C_3-lithiation was not considered, because protection of the NH group was thought necessary to achieve directed metallation.[12] In this context, we showed that 2(1*H*)-quinolinone lithium salt can be regioselectively lithiated at the *ortho* position, opening a new entry to C-3 electrophilic substitution of this system.[13]

The utility of directed metallations at benzylic positions/*ortho* to certain directing groups to achieve regioselective electrophilic substitutions has been shown with tertiary and secondary amides,[14,15] oxazolines,[16] α-aminoalcoxides[17] and esters.[18] We here study its application to **2**, through the *C,O*-dilithiated species **A**, and the competition between the *ortho*-directed metallation at the 3-position and the deprotonation at the 4-methyl group in **3a** and **3b** through **B** and **C**, respectively (Scheme 1).

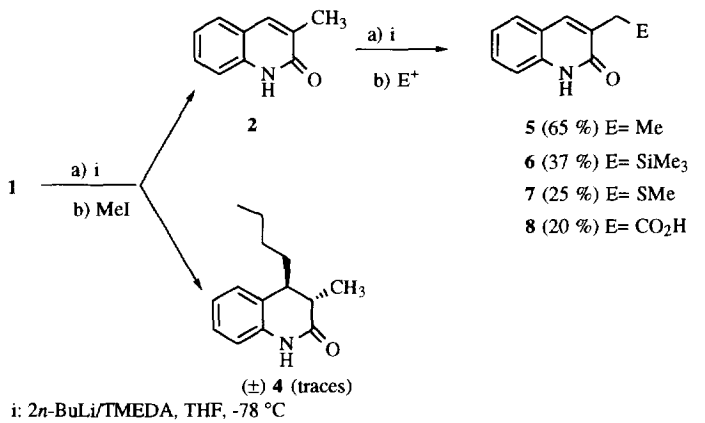
Compound **2** was obtained by methylation of **1**[13] together with traces of a previously unidentified compound **4**, produced by tandem nucleophile-electrophile addition.



Scheme 1

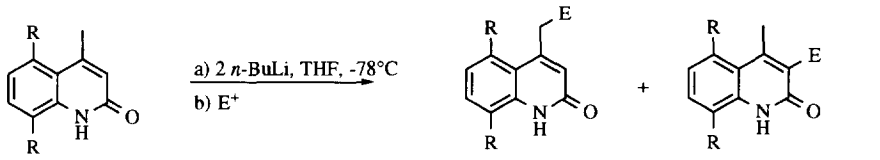
The value of the vicinal $J_{3,4}$ coupling constant (1.5 Hz) in the ^1H NMR spectrum of **4** is compatible with both *trans*-axial-axial and *cis*-equatorial-axial conformations, produced through the corresponding intermediate with an axial or equatorial butyl group. Irradiation of the H-3 proton (2.43 ppm, DMSO-d_6) in a NOE difference experiment produced significant enhancement of the H-4 (2.58 ppm) and CH_3 (0.97 ppm) resonances supporting the absence of a possible eq.-eq. conformation. On the other hand, irradiation of H-4 produced NOE in H-3 and H-5, being the latter more significant. Although these experiments are compatible with both stereoisomers, the magnitude of the NOE observed in H-5 when H-4 is irradiated points to a *trans*-axial-axial conformer. Semiempirical calculations also support the given stereochemistry, since both *cis*- and *trans* -adducts with prefixed equatorial methyl group show similar energies.

As expected, the *ortho*-directed effect of the lithium salt derived from **2** permitted the regioselective substitution with different electrophiles giving **5-8** (Scheme 2).



Scheme 2

When commercial compound **3a** was lithiated (2eq. *n*-BuLi/THF/TMEDA/-78°C) and the reaction was quenched with methyl iodide as an electrophile, 4-ethyl-2(1*H*)-quinolinone (**9a**) was obtained. The reaction was nearly quantitative (98% yield) in absence of TMEDA. On this basis we performed the lithiation of **3a** and **3b**[2] obtaining the corresponding derivatives substituted on the 4-methyl group (compounds **9a-12a** and **9b-12b**, Scheme 5). Compound **9b** could not be completely separated from the unreacted starting reagent but it was unequivocally identified by comparison with the same product obtained through an alternative procedure.[19]



3a, R=H
3b, R=OMe

	R	E	% Yield		R	E	% Yield
9a	H	Me	98[a,b]	**13a**	H	SMe	9[c]
10a	H	$SiMe_3$	61[a]	**13b**	OMe	SMe	16[c]
11a	H	SMe	62[c]				
12a	H	CO_2H	34[a]				
9b	OMe	Me	30[a]				
10b	OMe	$SiMe_3$	40[a]				
11b	OMe	SMe	63[c]				
12b	OMe	CO_2H	42[a]				

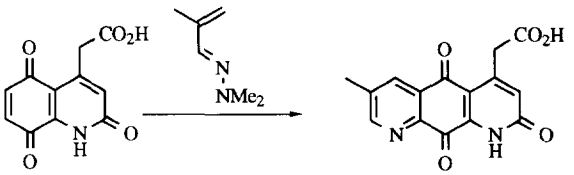
[a]The reaction time was 20 min
[b]60% in the presence of TMEDA
[c]The reaction time was 20 h

Scheme 3

In the experiments with dimethyldisulfide a competitive *ortho*-directed electrophilic substitution at *C*-3 occurred (compounds **13a** and **13b**). These results can be interpreted, according to previous studies about the regioselectivity in *N,N*-diethyl 4-methylbenzamide lithiations,[20] if **B** is the kinetically controlled metallated product which by acid-base interchange with **3** gives **C**, thermodynamically favoured. Being **B** softer than **C** as a *C*-nucleophile, the reaction on **B** is observed only with the softer electrophile (Schemes 1 and 3).

This work confirms the synthetic potential of the electrophilic substitutions in 2(1*H*)-quinolinone dianions. It has to be remarked that, although the yields are moderate in some instances, 3-, or 4-substituted derivatives that would be inaccessible by other strategies are thus possible.

Compounds **11b** and **12b** were oxidatively demethylated with cerium ammonium nitrate (CAN) to give quinones **14** and **15**. Heterocyclization of **14** with methacrolein-*N,N*-dimethyl-hydrazone[21] gave **16** in 75% yield (Scheme 4) while the reaction with **15** gave a mixture of compounds that could not be resolved. The regiochemistry of the cycloaddition was assumed to be the same found with other 1*H*-quinoline-2,5,8-triones, for which the reaction is governed by the more electronically deficient C_8=O group.



14 **16**

Scheme 4

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Infrared spectra were recorded on Perkin-Elmer 577 and Beckmann Acculab 4 spectrophotometers, with all compounds compressed into KBr pellets. 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; $CDCl_3$ was used as solvent, 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. 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 flash 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.

***Trans*-4-butyl-3-methyl-3,4-dihydro-2(1*H*)-quinolinone (4)**.To a stirred suspension of **1** (1g, 6.88 mmol) in dry THF (25 ml) under a nitrogen atmosphere at -78 °C, was slowly injected *n*-BuLi (9.89 ml of 1.6M solution in hexane, 15.8 mmol) and TMEDA (3.42 ml, 22.70 mmol). When the addition was complete, the reaction mixture was warmed to room temperature for 2 h, treated with methyl iodide (0.64 ml, 10.32 mmol) at 0° C and stirred at room temperature for 30 min. The mixture was cooled to 0 °C, treated with 10 ml of 2*N* HCl acid and extracted with $CHCl_3$ (3 x 30 ml). The organic layer was separated and washed sequentially with aqueous sodium bicarbonate (10%) and sodium chloride (30 %), dried over sodium sulphate and concentrated *in vacuo*.The residue was purified by column chromatography on silicagel eluting with a mixture of ethyl acetate/ hexane 7:3, yielding **2**[13] and **4** (3%). Mp 93-94 °C. IR, υ_{max} (KBr): 3100-2960 (NH), 1670 (CO) cm^{-1}. ^{1}H-NMR (250 MHz, DMSO-d_6) δ: 10.00 (s, 1H, NH); 7.16-7.09 (m, 2H, H-5 and H-7); 6.95-6.82 (m, 2H, H-8 and H-6); 2.58 (dt, 1H, *J*= 6.8 and 1.5 Hz, H-4); 2.43 (dq, 1H, *J*= 7.2 and 1.5 Hz, H-3); 1.46-1.07 (m, 6H, CH_2); 0.97 (d, 3H, *J*= 7.2 Hz, CH_3) and 0.81 (t, 3H, *J*= 6.8 Hz, CH_3) ppm.^{1}H-NMR (250 MHz, $CDCl_3$) δ: 10.34 (s, 1H, NH); 7.18-7.09 (m, 2H, H-5 and H-7); 7.00-6.97 (m, 2H, H-6 and H-8); 2.67 (q, 1H, *J*= 7.2 Hz, H-3); 2.58 (t, 1H, *J*= 7.1 Hz, H-4); 1.54-1.22 (m, 6H, CH_2); 1.15 (d, 3H, *J*= 7.2 Hz, CH_3) and 0.84 (t, 3H, *J*= 6.6 Hz, CH_3) ppm. Analysis calc. for $C_{14}H_{19}NO$: C, 77.37; H, 8.81; N, 6.44. Found: C, 77.63; H, 8.65; N, 6.18.

Lithiation of 3-methyl-2(1*H*)-quinolinone (2). General Procedure.

To a stirred suspension of **2** (1g, 6.28 mmol) in dry THF (25 ml) under nitrogen atmosphere at -78 °C, was slowly injected *n*-BuLi (8.63 ml of 1.6M solution in hexane, 13.81 mmol) and TMEDA (3.11 ml, 20.7 mmol). When the addition was complete, the reaction mixture was warmed to room temperature for 2 h, treated with the electrophilic reagent (8-10 mmol) at 0 °C and stirred at room temperature for 15-30 min. The mixture was cooled to 0° C and 10 ml of 2*N* HCl acid was added, and extracted with $CHCl_3$ (3 x 30 ml). The organic layer was separated and washed sequentially with aqueous sodium bicarbonate (10%) and sodium chloride (30%), dried over sodium sulphate and concentrated *in vacuo* and the residue was conveniently purified.

3-Ethyl-2(1*H*)-quinolinone (5). Yield 66 % after chromatography eluting with ethyl acetate/hexane 8:2. Mp 158-59 °C. IR, υ_{max} (KBr): 3000-2700 (NH), 1650 (CO). ^{1}H-NMR (250 MHz, DMSO-d_6) δ: 11.74 (s, 1H, NH); 7.72 (s, 1H, H-4); 7.61 (d, 1H, *J*= 7.7 Hz, H-5); 7.43 (m, 1H, H-7); 7.28 (d, 1H, *J*= 7.9 Hz, H-8); 7.14 (m, 1H, H-6); 1.16 (t, 3H, *J*= 7.4 Hz, CH_3); 2.5 (CH_2, overlapped with the solvent) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ: 161.89 (CO); 137.59 and 135.16 (C-8a and C-3); 134.63 (C-4); 129.00 (C-7); 127.05 (C-5); 121.49 (C-6); 119.36 (C-4a); 114.54 (C-8); 22.78 (CH_2) and 12.59(CH_3) ppm. Analysis calc. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.08. Found: C, 75.77; H, 6.55; N, 7.82.

3-Trimethylsilylmethyl-2-(1*H*)-quinolinone (6). Yield 37% after chromatography eluting with ethyl acetate/hexane 7:3. Mp 161-62 °C (methanol). IR, υ_{max} (KBr): 3100-2600 (NH), 1670 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 11.69 (s, 1H, NH); 7.55-7.53 (m, 2H, H-4 and H-5); 7.37 (m, 1H, H-7); 7.25 (d, 1H, *J*= 7.8 Hz, H-8); 7.11 (m, 1H, H-6); 2.05 (s, 2H, CH_2); 0.05 (s, 9H, CH_3) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ: 161.96 (C-2); 137.03 and 132.89 (C-8a and C-3); 133.09 (C-4); 128.20 (C-7); 126.38 (C-5); 121.48 (C-6); 119.77 (C-4a); 114.53 (C-8); 20.00 (CH_2) and -1.41 (CH_3) ppm. Analysis calc. for $C_{13}H_{17}NOSi$: C, 67.48; H, 7.40; N, 6.05. Found: C, 67.17; H, 7.17; N, 6.07.

3-Methylthiomethyl-2-(1*H*)-quinolinone (7). Stirred at room temperature with the electrophilic reagent overnight . Yield 25% after chromatography eluting with ethyl acetate/hexane 5:5. Mp 134-35 °C (methanol). IR, υ_{max} (KBr): 3650-3331 (NH), 1650 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 11.85 (s, 1H, NH); 7.83 (s, 1H, H-4); 7.65 (d, 1H, *J*= 7.8, H-5); 7.46 (m, 1H, H-7); 7.29 (d, 1H, *J*= 8.1, H-8); 7.17 (m, 1H, H-6); 3.5 (s, 2H, CH_2); 2.03 (s, 3H, CH_3) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ: 161.24 (C-2); 138.07 (C-8a); 136.40 (C-4); 129.69 (C-3 and C-7); 127.52 (C-5); 121.78 (C-6); 118.98 (C-4a); 114.77 (C-8); 31.97 (CH_2) and 14.82 (CH_3) ppm. Analysis calc. for $C_{11}H_{11}NOS$: C, 64.36; H, 5.39; N, 6.82. Found: C, 64.16; H, 5.19; N, 6.67.

2-Oxo-1*H*-3-quinolinylacetic acid (8). Yield 40% after purification by acid-base interchange. Mp 195-96 °C. IR, υ_{max} (KBr): 3500-2700 (OH and NH), 1720 and 1650 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 12.1 (s, 1H, COOH); 11.85 (s, 1H, NH); 7.84 (s, 1H, H-4); 7.63 (d, 1H, *J*= 7.8 Hz, H-5); 7.45 (m, 1H, H-7); 7.31 (d, 1H, *J*= 8.1 Hz, H-8); 7.18 (m, 1H, H-6); CH_2 (H_2O overlapped signal) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ: 172.0 (COOH); 161.76 (C-2); 138.14 (C-8a); 127.80 (C-3); 138.25 (C-4); 129.69 (C-7); 127.38 (C-5); 121.79 (C-6); 119.12 (C-4a); 114.81 (C-8) and 35.62 (CH2) ppm. Analysis calc. for $C_{11}H_9NO_3.1/2\ H_2O$: C, 58.53; H, 4.90; N, 6.20. Found: C, 58.31; H, 4.81; N, 6.27.

Lithiation of 4-Methyl-2(1*H*)-quinolinone (3a) and 4-Methyl-5,8-dimethoxy-2(1*H*)-quinolinone (3b). General Procedure.

To a stirred suspension of **3** (6.28 mmol) in dry THF (25 ml) under a nitrogen atmosphere at -78 °C, was slowly injected *n*-BuLi (8.63 ml of 1.6M solution in hexane, 13.81 mmol). When the addition was complete, the

reaction mixture was warmed to room temperature for 2h , treated with the electrophilic reagent (8-10 mmol) at 0° C and stirred at room temperature for 15-30 min. The mixture was cooled to 0 °C, treated with 10 ml of 2*N* HCl acid, and extracted with $CHCl_3$ (3 x 30 ml). The organic layer was separated and washed sequentially with aqueous sodium bicarbonate (10%) and sodium chloride (30 %), dried over sodium sulphate and concentrated *in vacuo* and the residue conveniently purified.

4-Ethyl-2(1*H*)-quinolinone (9a). Yield 98% . Mp 191-92 °C (ethyl acetate). IR, υ_{max} (KBr): 3500-2600 (NH), 1660 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 11.61 (s, 1H, NH); 7.73 (d, 1H, *J*= 8.0 Hz, H-5); 7.47 (m, 1H, H-7); 7.30 (d, 1H, *J*= 8.1 Hz, H-8); 7.17 (m, 1H, H-6); 6.34 (s, 1H, H-3); 2.80 (q, 2H, *J*= 7.4 Hz, CH_2) and 1.21 (t, 3H, *J*= 7.4 Hz, CH_3) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ: 161.73 (C-2); 152.93 (C-4); 138.80 (C-8a); 130.08 (C-7); 124.18 (C-5); 121.60 (C-6); 118.84 (C-3); 118.64 (C-4a); 115.58 (C-8); 24.20 (CH_2) and 12.96 (CH_3) ppm. Analysis calc. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.08. Found: C, 75.96; H, 6.38; N, 8.05.

4-Trimethylsilylmethyl-2(1*H*)-quinolinone (10a). Yield 61% after chromatography eluting with ethyl acetate/hexane 8:2. Mp 131-32 °C (dec). IR, υ_{max} (KBr): 3500-2600 (NH), 1662 (CO) cm^{-1}.^{1}H-NMR (250 MHz, $CDCl_3$) δ: 12.9 (s, 1H, NH); 7.58 (d, 1H, *J*= 8.0 Hz, H-5); 7.44 (m, 2H, H-7 and H-8); 7.15 (m, 1H, H-6); 6.39 (s,1H, H-3); 2.36 (s, 2H, CH_2) and 0.04 (s, 9H, CH_3) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 164.55 (C-2); 153.14 (C-4); 138.75 (C-8a); 130.47 (C-7); 125.02 (C-5); 122.04 (C-6); 120.07 (C-3); 117.78 (C-4a); 117.05 (C-8); 24.02 (CH_2) and -1.10 (CH_3) ppm. Analysis calc. for $C_{13}H_{17}NOSi$: C, 66.34; H, 7.28; N, 5.95. Found: C, 65.98; H, 7.07; N, 5.75.

4-Methylthiomethyl-2(1*H*)-quinolinone (11a). Yield 62% after chromatography eluting with ethyl acetate/hexane 5:4. Mp 160-61 °C (methanol). IR, υ_{max} (KBr): 3500-2600 (NH), 1680 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 11.72 (s,1H NH); 7.80 (d, 1H, *J*= 7.4 Hz, H-5); 7.48 (m, 1H, H-7); 7.31 (d, 1H, *J*= 7.3 Hz, H-8); 7.17 (m, 1H, H-6); 6.45 (s,1H, H-3); 3.90 (s, 2H, CH_2) and 1.99 (s, 3H, CH_3) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ: 161.25 (C-2); 146.64 (C-4); 139.24 (C-8a); 130.22 (C-7); 125.01 (C-5); 121.39 (C-6); 120.97 (C-3); 117.72 (C-4a); 115.61 (C-8); 33.45 (CH_2) and 14.69 (CH_3) ppm. Analysis calc. for $C_{11}H_{11}NOS$: C, 64.36; H, 5.39; N, 6.82. Found: C, 64.67; H, 5.50; N, 6.72.

4-Methyl-3-methylthio-2(1*H*)-quinolinone (13a). Yield 9%. Mp 196-97 °C. IR, υ_{max} (KBr): 3650-3320 (NH),1651 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 11.82 (s, 1H, NH); 7.76 (d, 1H, *J*= 8.1 Hz, H-5); 7.48 (m, 1H, H-7); 7.30 (d, 1H, *J*= 8.1 Hz, H-8); 7.20 (m, 1H, H-6); 2.72 (s, 3H, C-CH_3) and 2.38 (s, 3H, S-CH_3) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ: 159.89 (C-2); 149.17 (C-4); 137.51 (C-8a); 130.15 (C-7); 127.40 (C-3); 125.43 (C-5); 121.83 (C-6); 119.40 (C-4a); 115.15 (C-8); 17.47 (CH_3) and 16.42 (S-CH_3) ppm. Analysis calc. for $C_{11}H_{11}NOS$: C, 64.36; H, 5.39; N, 6.82. Found: C, 63.98; H, 5.68; N, 6.80.

2-Oxo-1*H*-4-quinolinylacetic acid (12a). Yield 34% after purification by acid-base interchange. Mp 189-90 °C (methanol). IR, υ_{max} (KBr): 3500-2600 (OH and NH), 1680 and 1600 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 11.60 (s,1H NH); 7.69 (d, 1H, *J*= 7.9 Hz, H-5); 7.45 (m, 1H, H-7); 7.29 (d, 1H, *J*= 8.0 Hz, H-8); 7.13 (m, 1H, H-6); 6.38 (s, 1H, H-3) and 3.70 (s, 2H, CH_2) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ: 171.50 (COOH); 161.66 (C-2); 146.99 (C-4); 138.64 (C-8a); 129.84 (C-7); 125.03 (C-5); 121.83 (C-6); 121.35 (C-3); 119.41 (C-4a); 115.26 (C-8); 2.5 (CH_2 overlapped with the solvent) ppm. Analysis calc. for $C_{11}H_9NO_3$.3/4 H_2O: C, 60.90; H, 5.11; N, 6.46. Found: C, 60.67; H, 4.92; N, 6.46.

4-Trimethylsilylmethyl-5,8-dimethoxy-2(1*H*)-quinolinone (10b). Yield 40% after

chromatography eluting with ethyl acetate/hexane 9:1. Mp 60-61 °C (dec).^{1}H-NMR (250 MHz, DMSO-d_6) δ: 10.00 (s, 1H, NH); 7.05 (d, 1H, *J*= 8.9 Hz, H-7); 6.62 (d, 1H, H-6); 6.26 (s, 1H, H-3); 3.82 and 3.78 (s, 6H, OCH_3), 2.62 (s, 2H, CH_2) and 0.3 (s, 9H, CH_3) ppm. Analysis calc. for $C_{15}H_{21}NO_3Si$: C, 61.82; H, 7.25; N, 4.80. Found: C, 61.61; H, 7.14; N, 4.45.

4-Methylthiomethyl-5,8-dimethoxy-2(1*H*)-quinolinone (11b). Yield 63% after chromatography eluting with ethyl acetate/hexane 7:3. Mp 199-200 °C. IR, υ_{max} (KBr): 3500-2600 (NH), 1680 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 10.4 (s, 1H NH); 7.04 (d, 1H, *J*= 8.8 Hz, H-7); 6.63 (d, 1H, *J*=8.8 Hz, H-6); 6.24 (s, 1H, H-3); 3.90 (s, 2H, CH_2); 3.79 and 3.75 (s, 6H, OCH_3) and 1.90 (s, 3H, SCH_3) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ: 160.26 (C-2); 150.98 (C-5); 147.42 (C-8); 140.00 (C-4); 130.88 (C-8a); 121.06 (C-3); 111.50 (C-4a); 108.80 (C-7); 103.02 (C-6); 56,41 and 55.96 (OCH_3) and 13.70 (SCH_3) ppm. Analysis calc. for $C_{13}H_{14}NO_3S$: C, 58.85; H, 5.69; N, 5.27. Found: C, 58.56; H, 5.58; N, 4.98.

4-Methyl-3-methylthio-5,8-dimethoxy-2(1*H*)-quinolinone (13b).Yield 16%. Mp 216-17 °C. IR, υ_{max} (KBr): 3675-3400 (NH),1651 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 10.51 (s, 1H NH); 7.06 (d, 1H, *J*= 8.8 Hz, H-7); 6.66 (d, 1H, *J*= 8.8 Hz, H-6); 3.90 and 3.79 (s, 6H, OCH_3); 2.88 (s, 3H, C-CH_3) and 1.97(s, 3H, S-CH_3) ppm. Analysis calc. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.69; N, 5.27. Found: C, 58.58; H, 5.59; N, 4.80

5,8-Dimethoxy-2-oxo-1*H*-4-quinolinylacetic acid (12b).Yield 42% after purification by acid-base interchange. Mp 105-6 °C. IR, υ_{max} (KBr): 3510 -2600 (OH and NH), 1725 and 1680 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 12.29 and 10.52 (2H, ws, COOH and NH); 7.06 (d, 1H, *J*= 8.8 Hz, H-7); 6.63 (d, 1H, *J*= 8.8 Hz, H-6); 6.36 (s, 1H, H-3); 3.79 (s, 6H, OCH_3) and 3.68 (s, 2H, CH_2) ppm. ^{13}C-NMR (63 MHz, DMSO-d_6) δ: 171.73 (COOH); 160.62 (C-2); 150.67 (C-5); 145.07 (C-8); 140.0 (C-4); 130.25 (C-8a); 123.90 (C-3); 111.41 (C-4a); 110.16 (C-7); 102.69 (C-6); 56.45 and 55.5 (OCH_3) and 42.24 (CH_2) ppm. Analysis calc. for $C_{13}H_{13}NO_5.H_2O$: C, 55.42; H, 5.18; N, 4.79. Found: C, 55.51; H, 5.37; N, 4.98.

Oxidative demethylation in 11b and 12b. General procedure.

To a solution of the suitable dimethoxy derivative (1,89 mmol) in H_2O (5 ml) and MeCN (12.5 ml), was added CAN (3.76 g, 6.76 mmol), and the mixture was stirred at room temperature for 1h. Water was then added (50 ml) and the mixture was extracted with $CHCl_3$ (3 x 50 ml). The combined organic layers were dried, and the solvent was removed to give the respective 1*H*-quinoline-2,5,8-triones.

2,5,8-Trioxo-1*H*-4-quinolinylacetic acid (14).Yield 45% after purification by acid-base interchange. Mp 110-11 °C (dec). IR, υ_{max} (KBr): 3510 -3000 (OH and NH), 1645 and 1600 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 11.92 (s, 1H, COOH); 6.97 (d, 1H, *J*= 10.1 Hz, H-6); 6.84 (d, 1H, *J*= 10.1 Hz, H-7); 6.67 (s, 1H, H-3) and 2.46 (s, 2H, CH_2) ppm. Analysis calc. for $C_{11}H_7NO_5$: C, 56.66; H, 3.02; N, 6.00. Found: C, 56.86; H, 3.43; N, 5.65.

4-Methylthiomethyl-2,5,8(1*H*)-quinolinetrione (15). Yield 20% after chromatography eluting with ethyl acetate/petroleum ether 7:3. Mp 152-53 °C. IR, υ_{max} (KBr): 3700-3250 (NH), 1710-1700 (CO) cm^{-1}.^{1}H-NMR (250 MHz, DMSO-d_6) δ: 10.5 (s, 1H, NH); 6.97 (d, 1H, *J*=10.2 Hz, H-6); 6.83 (d, 1H, *J*= 10.2 Hz, H-7); 6.50 (s,1H, H-3); 3.91 (s, 2H, CH_2) and 1.95 (s, 3H, CH_3) ppm. Analysis calc. for $C_{11}H_9NO_3S$: C, 56.14; H, 3.84; N, 5.97. Found: C, 55.94; H, 4.06; N, 5.98.

6-Methyl-2,9,10-trioxo-(1*H*)1,8-diaza-4-anthrylacetic acid (16).

To a stirred solution of **14** (0.12 g, 0.51 mmol) in dry $CHCl_3$ (40 ml), was added 3-methyl-1-dimethylamino-1-azabuta-1,3-diene[22] (0.056 g, 0.51 mmol) and the mixture was stirred at room temperature for

20 h. Evaporation of the solvent at reduced pressure afforded **16**. Yield 75% after chromatography eluting with athyl acetate. Mp 210 °C (dec). ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.8 (s, 1H, NH); 8.87 (s, 1H, H-7); 8.83 (s, 1H, H-5); 6.71 (s, 1H, H-3); 2.70 (s, 2H, CH_2) and 2.58 (s, 3H, CH_3) ; Analysis calc. for $C_{15}H_{10}N_2O_5$: C, 56.14; H, 3.84; N, 5.97. Found: C, 55.94; H, 4.06; N, 5.98.

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