A FRIEDLÄNDER APPROACH TO 3-SUBSTITUTED 2,5,8-(1*H*)-QUINOLINETRIONES

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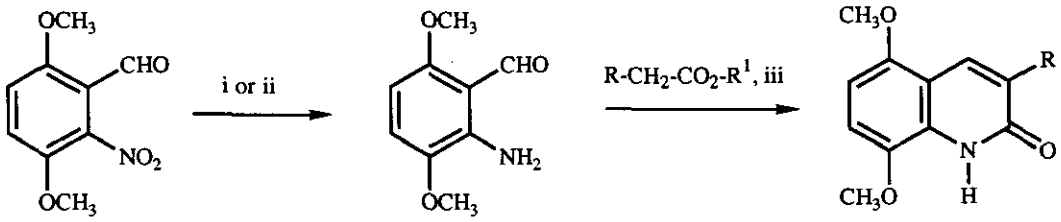
Abstract- An efficient method is proposed for the preparation of 3-substituted carbostyrilquinone derivatives, based on Friedländer synthesis of the 5,8-dialkoxyquinolines followed by cerium ammonium nitrate oxidative demethylation.

Derivatives of 2,5,8-(1*H*)-quinolinetrione ("carbostyrilquinone") have been used as dienophiles in an hetero Diels-Alder approach to analogues of the antibiotic Diazaquinomycin A,[1] an inhibitor of thymidilate synthase that shows great promise as a new lead compound in the field of antitumor agents.[1b,2,3] The main limitation in this strategy lies in the scarcity of literature references to the preparation of carbostyrilquinones,[4] in spite of recent efforts.[5] Indeed, some derivatives of this system, such as 3-substituted carbostyrilquinones, are unknown.

In this paper we report an efficient synthesis of carbostyrilquinones bearing electron-withdrawing groups at C_3, based on the use of the Friedländer quinoline synthesis,[6,7], a reaction that continues to attract the attention of synthetic chemists.[8,9] Its main drawback, namely the tendency to self-condensation and hence the low stability of *o*-aminobenzaldehydes required as starting materials, was not an unsurmountable difficulty in our case. Thus, 2-amino-3,6-dimethoxy-benzaldehyde (**1**), a suitable starting compound for our proposed synthesis, could be obtained from the corresponding nitro

precursor[10] by catalytic hydrogenation over Pd-C (78 % yield), or, alternatively, by means of Heck's triethylammonium formate/Pd-C reagent (58 % yield).[11] Treatment of **1** with several acetates bearing electron-withdrawing substituents in the α position in a refluxing mixture of ethanol and piperidine for 15 min to 10 h afforded the desired 3-substituted 5,8-dimethoxy-2-(1*H*)-quinolinones (**2a-2d**) in good yields, generally as colored (yellow to orange) crystalline solids that precipitated from the reaction medium (Scheme 1). In contrast, an attempted reaction with ethyl 2-phenylacetate gave a poor yield (17 %, after 24 h) of an impure product that could not be properly characterized.



1 **2**

	R	R^1	Yield, %
a	$CO_2C_2H_5$	C_2H_5	86
b	CN	C_2H_5	80
c	NO_2	C_2H_5	78
d	CO_2H	H	73

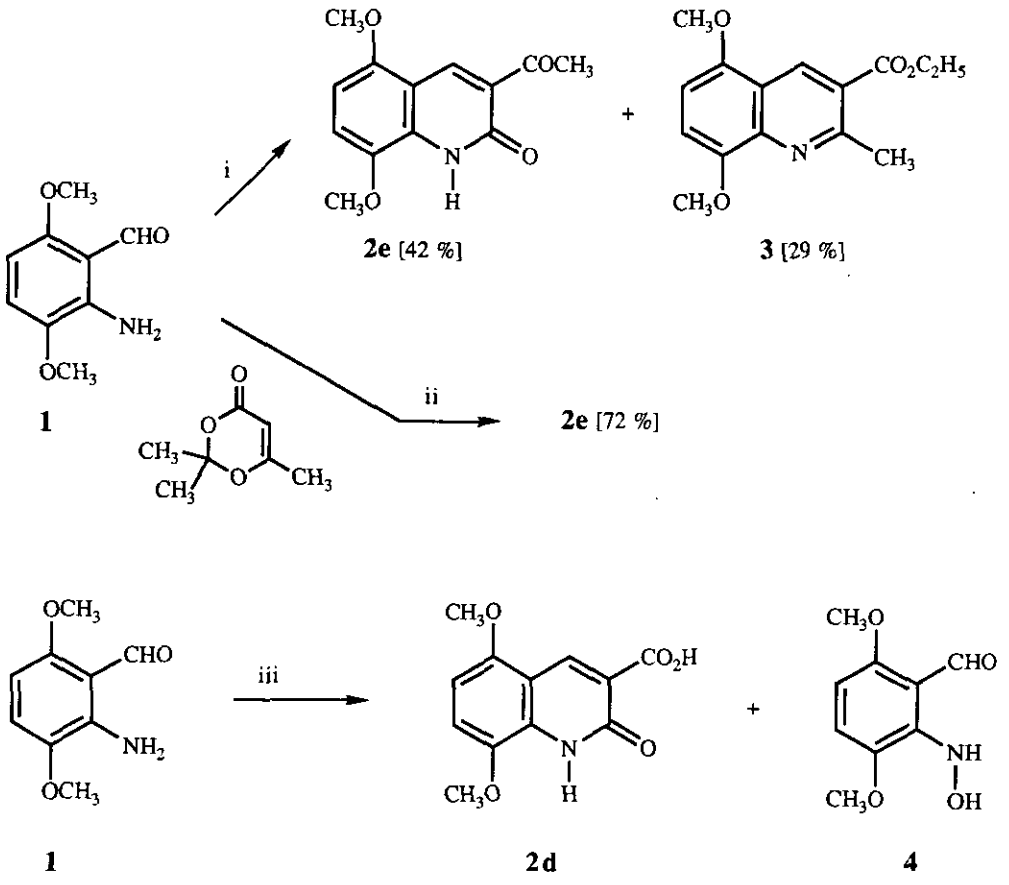
Reagents and conditions: i. H_2, 10% Pd-C, 35 psi, room temperature, 6 h ii. HCO_2^- $(C_2H_5)_3NH^+$, 10 % Pd-C, DMF, 140 °C, 6 h iii. Piperidine, C_2H_5OH, 100 to 180 °C, 15 min to 10 h

Scheme 1

Compound (**2e**, R = $COCH_3$), however, was obtained in only moderate yields, as a consequence of the low chemoselectivity of the reaction between **1** and ethyl acetoacetate, even under conditions that have been described to promote formation of 2-quinolinones,[12] leading to formation of the quinoline derivative (**3**) in 29 % yield, together with the expected **2e** (42 %). In order to improve this result, the β-oxo ester was replaced by 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one,[13] an alternative acetoacetylating reagent, affording **2e** in 72 % yield (Scheme 2).

It is worth mentioning that reaction between **1** and malonic acid gave, together with the expected quinolinone (**2d**), varying amounts (6 % in the optimized reaction) of compound (**4**), depending on

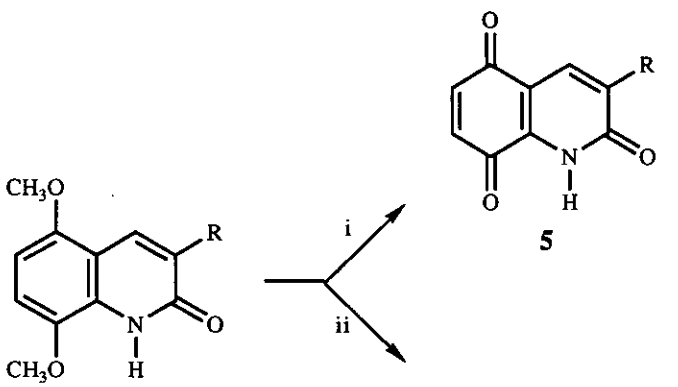
reaction conditions (Scheme 2). Compound (**4**) was apparently formed by partial oxidation of **1**, and its structure was confirmed by spectral techniques, by alternative synthesis through partial hydrogenation of 3,6-dimethoxy-2-nitrobenzaldehyde, and by reduction of **4** to **1**. We have no knowledge of a previous reference to a similar oxidation.



Scheme 2

Finally, oxidative demethylation of compounds (**2**) with cerium ammonium nitrate (CAN)[14] in acetonitrile-water gave quinones (**5**) in good yields. In an effort to simplify the purification protocol of

these rather unstable compounds by retaining cerium species, this reaction was also attempted with a silica gel-supported cerium ammonium nitrate reagent that has been reported to allow the extremely efficient oxidation of a variety of hydroquinones to quinones.[15] However, nitration of the benzenic ring was observed instead of oxidation in the examples studied, giving compounds (**6a** and **6c**). In order to test the generality of such nitration, the reaction was also carried out on a 2-quinolinone derivative bearing an electron-releasing group on C_3, namely 5,8-dimethoxy-3-methyl-(1*H*)-quinolin-2-one (**2f**), which was prepared through Vilsmeier-Haack formylation[16] of *N*-(2,5-dimethoxy)propianilide, using a procedure whose full details will be revealed in a forthcoming paper. Treatment of **2f** with the silica gel-supported reagent also gave the corresponding 6-nitro derivative (**6f**) (Scheme 3). A literature search revealed that a similar supported CAN reagent has been described to nitrate 1-hydroxynaphthalene.[17]



	R	Yield, %
a	$CO_2C_2H_5$	98
b	CN	96
c	NO_2	75
d	CO_2H	74
e	$COCH_3$	95

	R	Yield, %
a	$CO_2C_2H_5$	19
c	NO_2	57
f	CH_3	57

Reagents and conditions: i. $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, room temperature, 20-35 min
ii. 20 % $(NH_4)_2Ce(NO_3)_6/SiO_2$, CH_2Cl_2 or CH_3CN, room temperature, 20 min-6 h.

Scheme 3

EXPERIMENTAL

Ir spectra were recorded on Perkin-Elmer 577 and Buck Scientific 500 spectrophotometers, with all compounds compressed into KBr pellets. Nmr spectra were obtained on the following instruments:

Hitachi-Perkin Elmer R 24B (60 MHz), Bruker AC-250 (250 MHz for ^{1}H, 63 MHz for ^{13}C) and Varian VXR-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C); $CDCl_3$, DMSO-d_6, pyridine-d_5 and acetone-d_6 were used as solvents, and TMS was added in all cases as an internal standard. The low resolution mass spectrum of compound (**6**) was obtained on a Hitachi Perkin-Elmer RMV-6M spectrometer at 75 eV, using the DIP mode for the introduction of the samples. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer. Catalytic hydrogenations were carried out on a Parr 3920 reactor. Melting points were measured in open capillary tubes, using a Büchi inmersion 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, Merck, SDS, Probus) and were used as received. Solvents were purified and dried using standard procedures. The expression "petroleum ether" refers to the fraction boiling at 40-60 °C.

2-Amino-3,6-dimethoxybenzaldehyde (**1**). Method A. A solution of 3,5-dimethoxy-2-nitrobenzaldehyde (300 mg, 1.42 mmol) in methanol (350 ml) was hydrogenated at room temperature and 35 psi of pressure for 6 h, in the presence of 50 mg of 10% Pd-C. The suspension was filtered through celite, which was washed with dichloromethane (3 x 20 ml). The combined organic phases were evaporated and the oily residue was purified by flash chromatography on silicagel, eluting with chloroform-petroleum ether (3:1), to yield 200 mg (78 %) of **1**. mp 53 °C (petroleum ether). A similar result was obtained when compound (**4**) was used as the starting material. Ir (KBr): 3460, 3340 (NH), 1650 (C=O), 1270 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 10.30 (s, 1H, CHO); 6.76 (d, 1H, J = 8.7 Hz, C_4-H); 6.68 (br s, 2H, NH_2); 5.98 (d, 1H, J = 8.7 Hz, C_4-H); 3.81 (s, 6H, 2 OCH_3) ppm. ^{13}C-Nmr (63 MHz, $CDCl_3$) δ: 191.69 (CHO); 156.59 (C_6); 142.37 (C_3); 140.62 (C_2); 114.65 (C_4); 108.23 (C_1); 94.41 (C_5); 55.88 and 55.40 (OCH_3). *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.11; N, 7.73. Found: C, 60.03 ; H, 6.00; N, 7.85.

Method B. To a solution of 3,6-dimethoxy-2-nitrobenzaldehyde (422 mg, 2 mmol) in freshly distilled DMF (2 ml), prepared by heating the initial suspension at 140 °C for 10 min, was added 10% Pd-C (10 mg) and dry triethylamine (1.80 ml, 12.9 mmol). Formic acid (0.36 ml, 9.60 mmol) was then dropwise added, with external cooling. The suspension thus obtained was heated in an oil bath at 140 °C for 4 h, while it was magnetically stirred, and was then diluted with dichloromethane (10 ml) and filtered through celite, which was washed with dichloromethane (3 x 10 ml). The filtrates were combined and evaporated,

and the residue was purified by flash column chromatography, eluting with chloroform-petreoleum ether (1:1), to yield 211 mg (58 %) of **1**.

Friedländer Synthesis of compounds **2a-d**. General Method A solution of **1** in ethanol (2 ml per mmol of **1**) and piperidine (0.5 equivalents) was treated with the appropriate ester or acid (3 equivalents). The reaction mixture was heated under the conditions described in each case, in a system protected from moisture by a calcium chloride guard tube. The solution was cooled, and the precipitate was filtered, washed with a small amount of ethanol and recrystallized from the appropriate solvent.

Ethyl 5,8-Dimethoxy-2-oxo-(1*H*)-quinoline-3-carboxylate (**2a**). Starting from 155 mg (0.85 mmol) of **1**, and heating the reactants at 130 °C for 10 h, a precipitate of 200 mg (86 %) of yellow plates of **2a** was obtained. mp 189 °C (ethanol). Ir (KBr): 3300-2800 (NH), 1740 (CO_2Et), 1650 (C=O), 1280 and 1260 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.89 (s, 1H, C_4-H); 6.93 (d, 1H, *J* = 8.6 Hz, C_7-H); 6.47 (d, 1H, J = 8.6 Hz, C_6-H); 4.41 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3); 3.91 and 3.90 (2 s, 6H, 2 OCH_3); 1.41 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3) ppm. ^{13}C-Nmr (75 MHz, $CDCl_3$) δ: 164.46 ($CO_2C_2H_5$); 158.74 (C_2); 150.59 (C_5); 145.02 (C_8); 140.50 (C_4); 139.05 (C_{8a}); 121.51 (C_3); 112.71 (C_7); 109.68 (C_{4a}); 101.16 (C_6); 61.31 (CH_2CH_3); 56.19 and 55.77 (2 OCH_3); 14.30 (CH_2CH_3) ppm. *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.40 ; H, 5.37; N, 5.01.

5,8-Dimethoxy-2-oxo-(1*H*)-quinoline-3-carbonitrile (**2b**). Starting from 240 mg (1.32 mmol) of **1**, and heating the reactants at 100 °C for 15 min, a precipitate of 242 mg (80 %) of yellow needles of **2b** was obtained. mp 296 °C (ethanol-dichloromethane, 1:1). Ir (KBr): 3200-2700 (NH), 2200 (CN), 1655 (C=O), 1250 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.70 (s, 1H, C_4-H); 7.07 (d, 1H, *J* = 8.1 Hz, C_7-H); 6.58 (d, 1H, *J* = 8.1 Hz, C_6-H); 3.80 (s, 6H, 2 OCH_3) ppm. *Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.37; N, 12.16. Found: C, 62.89 ; H, 4.24; N, 11.99.

5,8-Dimethoxy-3-nitro-(1*H*)-quinolin-2-one (**2c**). Starting from 350 mg (1.93 mmol) of **1**, and heating the reactants at 100 °C for 8 h, a precipitate of 375 mg (78 %) of orange needles of **2c** was obtained. mp 291 °C (acetone-dichloromethane). Ir (KBr): 3200-2800 (NH), 1675 (C=O), 1620 and 1475 (NO_2), 1255 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, pyridine-d_5) δ: 8.88 (s, 1H, C_4-H); 7.09 (d, 1H, *J* = 8.0 Hz, C_7-H); 6.57 (d, 1H, *J* = 8.0 Hz, C_6-H); 3.79 and 3.77 (2 s, 6H, 2 OCH_3) ppm. ^{13}C-Nmr (75 MHz, pyridine-d_5) δ: 155.00 (C_2); 140.80 (C_{8a}); 140.60 (C_4); 133.20 (C_3); 115.00 (C_7); 108.20 (C_{4a}); 102.30 (C_6); 56.65 and 56.05 (2 OCH_3) ppm. Signals due to C_5 and C_8 were hidden by resonances from the solvent. *Anal.* Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.02; N, 11.90. Found: C, 52.42 ; H, 4.03; N, 11.70.

5,8-Dimethoxy-2-oxo-(1*H*)-quinoline-3-carboxylic acid (**2d**). Starting from 127 mg (0.70 mmol) of **1**, and heating the reactants at 150 °C for 3 h, a precipitate of 120 mg of yellow plates of **2d** was obtained. After evaporation of the filtrate and purification by column chromatography on silica gel, eluting with ether, additional 30 mg of **2d** were obtained, together with 8 mg (6 %) of compound (**4**) (see below). Overall yield, 130 mg (75 %) of **2d**. mp 297 °C (methanol). Ir (KBr): 3280-2780 (OH and NH), 1740 (CO_2H), 1635 (C=O), 1260 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, pyridine-d_5) δ: 9.49 (s, 1H, C_4-H); 7.16 (d, 1H, J = 9.0 Hz, C_7-H); 6.65 (d, 1H, J = 9.0 Hz, C_6-H); 3.83 and 3.77 (2 s, 6H, 2 OCH_3) ppm. *Anal.* Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 4.45. Found: C, 57.55 ; H, 4.63; N, 4.42.

3-Acetyl-5,8-Dimethoxy-(1*H*)-quinolin-2-one (**2e**). Method A. A solution of **1** (242 mg, 1.33 mmol) in ethyl acetoacetate (0.26 ml, 1.6 mmol) was refluxed for 25 min in a bath at 180 °C, while protected with a calcium chloride guard tube. After addition of 0.1 ml (0.6 mmol) of ethyl acetoacetate and heating for further 10 min, the reaction mixture was cooled and the precipitate was filtered, washed with a small amount of petroleum ether, and chromatographed on silica gel, eluting with petroleum ether-chloroform (2:1), yielding 30 mg of recovered **1**, 121 mg (42 %) of **2e** and 98 mg (29 %) of **3** (yields are calculated on unrecovered **1**).

Data for **2e**: mp 232 °C (acetone). Ir (KBr): 3240-2800 (NH), 1680 ($COCH_3$), 1650 (C=O), 1260 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.13 (s, 1H, NH); 8.89 (s, 1H, C_4-H); 6.96 (d, 1H, J = 8.7 Hz, C_7-H); 6.49 (d, 1H, J = 8.7 Hz, C_6-H); 3.94 and 3.91 (2 s, 6H, 2 OCH_3); 2.76 (s, 3H, $COCH_3$) ppm. ^{13}C-Nmr (75 MHz, $CDCl_3$) δ: 197.53 ($\underline{C}OCH_3$); 160.38 (C_2); 151.49 (C_5); 145.10 (C_8); 139.60 (C_4); 139.11 (C_{8a}); 128.21 (C_3); 113.05 (C_7); 110.34 (C_{4a}); 101.35 (C_6); 56.31 and 55.84 (2 OCH_3); 30.95 ($CO\underline{C}H_3$) ppm. *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.26; N, 5.66. Found: C, 63.33 ; H, 5.26; N, 5.36.

Data for Ethyl 2-Methyl-5,8-dimethoxyquinoline-3-carboxylate (**3**). mp 128 °C (petroleum ether-dichloromethane, 1:1). Ir (KBr): 1710 (CO_2Et); 1270 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.12 (s, 1H, C_4-H); 7.04 (d, 1H, J = 8.5 Hz, C_7-H); 6.77 (d, 1H, J = 8.5 Hz, C_6-H); 4.47 (q, 2H, J= 7.1 Hz, $C\underline{H}_2CH_3$) 3.98 and 3.90 (2 s, 6H, 2 OCH_3); 3.06 (s, 3H, C_2-CH_3); 1.49 (t, 3H, CH_2-$C\underline{H}_3$) ppm.^{13}C-Nmr (63 MHz, $CDCl_3$) δ: 166.52 ($CO_2C_2H_5$); 158.21 (C_2); 149.03 (C_8); 148.53 (C_5); 134.80 (C_4); 123.47 (C_{8a}); 119.13 (C_{4a}); 109.26 (C_7); 103.49 (C_6); 61.32 (C_2-CH_3); 56.14 and 55.74 (OCH_3). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.18; N, 5.09. Found: C, 65.22 ; H, 6.46; N, 4.84.

Method B. A solution of **1** (368 mg, 2.0 mmol) in xylene (5 ml) at 120 °C was treated with 2,2,6-

trimethyl-4*H*-1,3-dioxin-4-one (2.8 g, 20 mmol). A precipitate was immediately formed. The reaction mixture was heated at 120 °C for further 5 min and, after cooling, was filtered to yield 360 mg (72 %) of **2e**.

3,6-Dimethoxy-2-hydroxylaminobenzaldehyde (**4**). A solution of 3,6-dimethoxy-2-nitrobenzaldehyde (1 g, 4.73 mmol) in methanol (500 ml) was hydrogenated at room temperature and 35 psi of pressure for 3 h, in the presence of 70 mg of 10% Pd-C. The suspension was filtered through celite, which was washed with dichloromethane (3 x 30 ml). The residue from the evaporation of the organic phases was shown to be a 1.5:1 mixture of compound (**4**) and the amine (**1**), which could be completely transformed into the latter by further hydrogenation for 6 h under the same conditions. An analytical sample of **4** was obtained by column chromatography of the mixture on silica gel, eluting with a gradient of chloroform-petroleum ether (3:1) to net chloroform, and was identical to the compound obtained as a secondary product during the synthesis of **2d**. mp 87 °C (hexane). Ir (KBr): 3560-3280 (NHOH); 1650 (CHO) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.09 (s, 1H, CHO); 6.36 (d, 1H, J = 7.8 Hz, C_4-H); 6.02 (d, 1H, J = 7.8 Hz, C_4-H); 5.40 (br s, 1H, NH); 3.95 and 3.87 (2 s, 6H, 2 OCH_3) ppm. ^{13}C-Nmr (75 MHz, $CDCl_3$) δ: 191,73 (CHO); 153.51 (C_6); 145.98 (C_3); 141.98 (C_2); 115.42 (C_1); 106.36 (C_4); 98.89 (C_5); 56.01 and 55.40 (OCH_3). Ms, m/z (%): 179 (100, M-18), 164 (63), 150 (84), 136 (100), 121 (60), 108 (53), 93 (45), 76 (51). *Anal.* Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.58; N, 7.11. Found: C, 54.58 ; H, 5.23; N, 7.17.

3-Substituted 2,5,8-(1*H*)-Quinolinetriones (**5**). General Synthesis. Cerium ammonium nitrate (2.2 equivalents) was added portionwise to a suspension of the suitable compound(**2**)in water (2 ml) and acetonitrile (5 ml). The orange solution thus obtained was stirred at room temperature for the time indicated in each case, and was then diluted with water (50 ml) and extracted with chloroform (4 x 50 ml). The extracts were dried (sodium sulfate) and evaporated, and the residue was usually purified by rapid chromatography on silica gel.

Ethyl 2,5,8-Trioxo-(1*H*)quinoline-3-carboxylate (**5a**). The reaction was performed on 46 mg (0.17 mmol) of **2a** and 435 mg (0.51 mmol) of cerium ammonium nitrate for 20 min. Yield, 40 mg (98 %) of **5a** after chromatography, eluting with a gradient of ethyl acetate-1:1 ethyl acetate/ethanol. mp 158 °C (dec.). Ir (KBr): 1760 ($CO_2C_2H_5$); 1665, 1655 and 1650 (C=O) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.67 (s, 1H, C_4-H); 7.01 (m, 2H, C_6-H and C_7-H); 4.44 (q, 2H, J = 7.2 Hz, $C\underline{H}_2CH_3$); 1.42 (t, 3H, J = 7.1 Hz, CH_2-$C\underline{H}_3$) ppm.^{13}C-Nmr (75 MHz, $CDCl_3$) δ: 181.21 (C_8); 178.93 (C_5); 163.25 ($\underline{C}O_2CH_2CH_3$); 158.39 (C_2); 140.02 (C_4); 138.82 (C_6); 135.49 (C_{8a}); 135.37 (C_7); 124.42 (C_3);

114.27 (C_{4a}); 62.17 ($CO_2\underline{C}H_2CH_3$); 11.16 ($CO_2CH_2\underline{C}H_3$) ppm. *Anal.* Calcd for $C_{12}H_9NO_5$: C, 58.29; H, 3.64; N, 5.69. Found: C, 58.35 ; H, 3.75; N, 5.87.

2,5,8-Trioxo-(1*H*)quinoline-3-carbonitrile (**5b**). The reaction was performed on 55 mg (0.24 mmol) of **2b** and 401 mg (0.47 mmol) of cerium ammonium nitrate for 20 min. Yield, 46 mg (96 %) of **5b** after chromatography, eluting with a gradient of ethyl acetate-1:1 ethyl acetate/ethanol. mp 154 °C (decomp.). Ir (KBr): 2225 (CN); 1660 (C=O) cm^{-1}. ^{1}H-Nmr (250 MHz, acetone-d_6) δ: 8.33 (s, 1H, C_4-H); 6.92 (d, 1H, J = 10.2 Hz, C_7-H); 6.84 (d, 1H, J = 10.2 Hz, C_6-H) ppm. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.41 (s, 1H, C_4-H); 7.05 (s, 2H, C_7-H and C_8-H) ^{13}C-Nmr (63 MHz, acetone-d_6) δ: 191.62 (C_8); 189.63 (C_5); 168.69 (C_2); 154.52 (C_6); 148.71 (C_7); 146.57 (C_4); 124.84 (C_3); 121.49 (C_{4a}); 116.45 (CN) ppm. *Anal.* Calcd for $C_{10}H_4N_2O_5$: C, 60.00; H, 2.00; N, 14.00. Found: C, 59.70 ; H, 1.97; N, 13.95.

3-Nitro-(1*H*)quinoline-2,5,8-trione (**5c**). The reaction was performed on 50 mg (0.20 mmol) of **2c** and 225 mg (0.26 mmol) of cerium ammonium nitrate for 30 min. Yield, 30 mg (75 %) of **5c** . Its unstability in solution precluded further purification by crystallization or chromatography. Ir (KBr): 1660 (C=O) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.35 (s, 1H, C_4-H); 7.28 (d, 1H, J = 8.4, C_7-H); 6.75 (d, 1H, J = 8.4, C_6-H). ^{13}C-Nmr (63 MHz, acetone-d_6) δ: 191.72 (C_8); 189.20 (C_5); 163.68 (C_2); 149.06 (C_6); 148.91 (C_3); 146.65 (C_7); 146.31 (C_{8a}); 143.16 (C_4) ppm.

2,5,8-Trioxo-(1*H*)quinoline-3-carboxylic acid (**5d**). The reaction was performed on 40 mg (0.16 mmol) of **2d** and 274 mg (0.32 mmol) of cerium ammonium nitrate for 10 min. Yield, 26 mg (74 %) of **5d**. mp 173 °C (decomp.). Ir (KBr): 3500-3100 (OH); 1740 (CO_2H); 1650 (C=O) cm^{-1}. ^{1}H-Nmr (250 MHz, acetone-d_6) δ: 8.71 (s, 1H, C_4-H); 7.07 (d, 1H, J = 10.4 Hz, C_7-H); 6.99 (d, 1H, J = 10.4 Hz, C_6-H) ppm. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.15 (s, 1H, C_4-H); 7.12 (s, 2H, C_7-H and C_8-H). ^{13}C-Nmr (63 MHz, acetone-d_6) δ: 192.13 (C_8); 189.46 (C_5); 175.24 ($\underline{C}O_2H$); 173.48 (C_2); 151.70 (C_6); 148.89 (C_7); 146.86 (C_4); 139.29 (C_{8a}); 133.34 (C_3); 126.13 (C_{4a}) ppm. *Anal.* Calcd for $C_{10}H_5NO_5$: C, 54.75; H, 2.28; N, 6.39. Found: C, 54.54 ; H, 2.58; N, 6.27.

3-Acetyl-(1*H*)quinoline-2,5,8-trione (**5e**). The reaction was performed on 47.5 mg (0.19 mmol) of **2e** and 220 mg (0.25 mmol) of cerium ammonium nitrate for 25 min. Yield, 35 mg (95 %) of **5e**. mp 168 °C (decomp.). Ir (KBr): 1680 ($COCH_3$); 1655 (C_2=O, C_5=O, C_8=O) cm^{-1}. ^{1}H-Nmr (250 MHz, acetone-d_6) δ: 8.34 (s, 1H, C_4-H); 7.03 (d, 1H, J = 10.2 Hz, C_6-H); 6.94 (d, 1H, J = 10.2 Hz, C_7-H); 2.54 (s, 3H, $COCH_3$) ppm. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.64 (s, 1H, C_4-H); 7.00 (s, 2H, C_7-H and C_8-H); 2.74 (s, 3H, $COCH_3$). *Anal.* Calcd for $C_{11}H_6N_2O_6$: C, 60.82; H, 3.22; N, 6.45. Found: C, 60.55;

H, 3.18; N, 6.25.

5,8-Dimethoxy-6-nitro-(1*H*)quinoline-2,5,8-triones (**6**). To a solution of the suitable compound (**2**) in dry acetonitrile (40 ml) or dichloromethane (15 ml) was portionwise added the 20 % cerium ammonium nitrate-silica gel reagent[15] (3 equivalents of CAN). The yellow suspension was stirred at room temperature for 20 min to 6 h, and was then filtered. The silica gel layer was washed with dichloromethane (2 x 25 ml), and the combined organic layers were evaporated and the residue was purified by column chromatography on silica gel.

Ethyl 5,8-Dimethoxy-6-nitro-2-oxo-(1*H*)-quinoline-3-carboxylate (**6a**). Starting from 70 mg (0.25 mmol) of compound (**2a**) in 15 ml of dichloromethane and 2 g of the CAN-silica gel reagent (0.3 mmol of CAN), 16 mg (19 %) of **6a** were obtained after 6 h of reaction and purification by chromatography on silicagel, eluting with ethyl acetate. mp 240 °C. Ir (KBr): 1760 (CO_2Et), 1660 (C=O), 1530, 1330 (NO_2), 1260 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.78 (s, 1H, C_4-H); 7.64 (s, 1H, C_7-H); 4.46 (q, 2H, J = 7.2 Hz, $C\underline{H}_2$-CH_3); 4.08 and 4.07 (2 s, 6H, 2 OCH_3); 1.45 (t, 3H, J = 7.2 Hz, CH_2-$C\underline{H}_3$) ppm. *Anal.* Calcd for $C_{14}H_{14}N_2O_7$: C, 52.17; H, 4.35; N, 8.69. Found: C, 51.96; H, 4.21; N, 8.53.

5,8-Dimethoxy-3,6-dinitro-(1*H*)-quinolin-2-one (**6c**). Starting from 124.5 mg (0.5 mmol) of compound (**2c**) in 40 ml of acetonitrile and 3.5 g of the CAN-silica gel reagent (1.05 mmol of CAN), 84 mg (57 %) of **6c** were obtained after 45 min of reaction and purification by chromatography on silica gel, eluting with dichloromethane-methanol (3:1). mp 310 °C (methanol-acetone). Ir (KBr): 1700 (C=O), 1520, 1390 (NO_2), 1260 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, pyridine-d_5) δ: 9.03 (s, 1H, C_4-H); 7.81 (s, 1H, C_7-H); 4.06 and 3.99 (2 s, 6H, 2 OCH_3) ppm. *Anal.* Calcd for $C_{11}H_9N_3O_7$: C, 44.74; H, 3.05; N, 14.23. Found: C, 44.59; H, 3.21; N, 13.74.

3-Methyl-5,8-dimethoxy-6-nitro(1*H*)-quinolin-2-one (**6f**). Starting from 109.5 mg (0.5 mmol) of compound (**2f**)[16] in 7.5 ml of dichloromethane and 3.5 g of the CAN-silica gel reagent (3.5 mmol of CAN), 71 mg (57 %) of **6f** were obtained after 20 min of reaction and purification by chromatography on silica gel, eluting with dichloromethane. mp 285 °C (acetone). Ir (KBr): 1680 (C=O), 1550, 1350 and 1320 (NO_2), 1270 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, pyridine-d_5) δ: 8.04 (s, 1H, C_4-H); 7.68 (s, 1H, C_7-H); 3.82 and 3.65 (2 s, 6H, 2 OCH_3); 2.00 (s, 3H, CH_3) ppm. ^{13}C-Nmr (75 MHz, pyridine-d_5) δ: 162.76 (C_2); 145.52 (C_5); 141.85 (C_8); 133.76 (C_{8a}*); 133.20 (C_3*); 130.51 (C_4); 114.77 (C_{4a}); 105.03 (C_7); 63.35 (C_5-$O\underline{C}H_3$); 56.08 (C_8-$O\underline{C}H_3$); 16.92 (C_3-$\underline{C}H_3$) ppm. Assignments marked with * can be interchanged. The signal due to C_6 was hidden by resonances from the solvent. *Anal.* Calcd for

$C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.54; N, 10.60. Found: C, 54.25; H, 4.54; N, 10.30.

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