# 8-Fluoro-4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*]quinoline-1,6(2*H*)-dione: synthesis and reactivity



Dolorès Edmont and Jacques Chenault*

Institut de Chimie Organique et Analytique, Université d'Orléans, B. P. 6759, 45067 Orléans cedex 2, France

Received March 5, 2003

A simple and versatile methodology to synthesise 4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*]quinoline-1,6(2*H*)-dione from methyl 6-fluoro-4-oxo-1,4-dihydro-2-quinolinecarboxylate has been developed. It involves carbohydrazide formation followed by a condensation with triphosgene to form the fused [1,2,4]triazino ring. In addition, the reactivity of the [1,2,4]triazino ring has been studied.

*J. Heterocyclic Chem.*, **40**, 789 (2003).

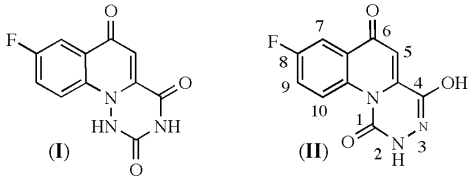
Recently, we reported the *in vivo* activities of some quinolinoylguanidines as hypoglycaemic agents [1], and encouraged by these promising results, we therefore decided to investigate the structure/activity relationships of the *N*-[(2-quinolin) carbonyl]guanidines [2]. This prompted us to investigate the selective introduction of a functional group at the nitrogen atom of 4-oxo-1,4-dihydro-2-quinoline carboxylic acid.

We have been particularly interested for some time in the synthesis of novel fused tricyclic quinolones that are non carboxylic at the C3 position, and containing a four-atom bridge connecting the N1 and C2 positions which incorporates a [1,2,4]triazino ring.

The 8-fluoro-1*H*-[1,2,4]triazino[1,6-*a*]quinoline - 2,4,6(3*H*)-trione **I** (Scheme 1), the first molecule of this class, was obtained from methyl 6-fluoro-4-oxo-1,4-dihydro-2-quinolinecarboxylate by an *N*-amination followed by a condensation of an aroyl isocyanate to form an alpha semicarbazido- carboxylate that readily cyclizes to give a fused [1,2,4] triazino ring upon treatment with ammonia/ethanol solution as described previously [3].

In order to perform some structural modifications within the framework of our SAR studies, we have been interested in preparing the 8-fluoro-4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*] quinoline-1,6(2*H*)-dione **II** (Scheme 1) and in studying the reactivity of the new [1,2,4]triazino ring.

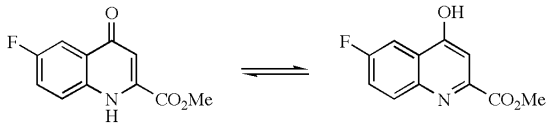
Scheme 1




A competitive alkylation takes place between the nitrogen atom and the oxygen atom of quinoline-2-carboxylic acids, due to tautomerism (Scheme 2).

However we have selectively alkylated the nitrogen atom *via* the ring opening of the 8-fluoro-1,2-dihydro[1,4]oxazino[4,3-*a*]quinoline-4,6-dione [2], which has been achieved from an intramolecular cyclization of the 2-chloroethyl 6-fluoro-4-oxo-1,4-dihydro-2-quinoline carboxylate.

Scheme 2




A suitable synthetic route to these 4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*]quinoline-1,6(2*H*)-dione structures therefore lies in the intramolecular cyclization of the 6-fluoro-4-oxo-1,4-dihydro-2-quinoline carbohydrazide using triphosgene.

The starting compound **1** was obtained by condensation of dimethyl acetylene dicarboxylate with 4-fluoroaniline, followed by a cyclization in diphenylether at reflux as described previously [1]. The subsequent reaction of **1** with hydrazine gave the carbohydrazide **2**, which reacts with triphosgene to give the desired tricyclic quinolone **II** (Scheme 3).

In order to assess the reactivity of the [1,2,4]triazino moiety, a number of different reactions were investigated. Chlorination [4] using phosphorus oxychloride as reagent and solvent, readily gives compound **3** in 97% yield (Scheme 3).

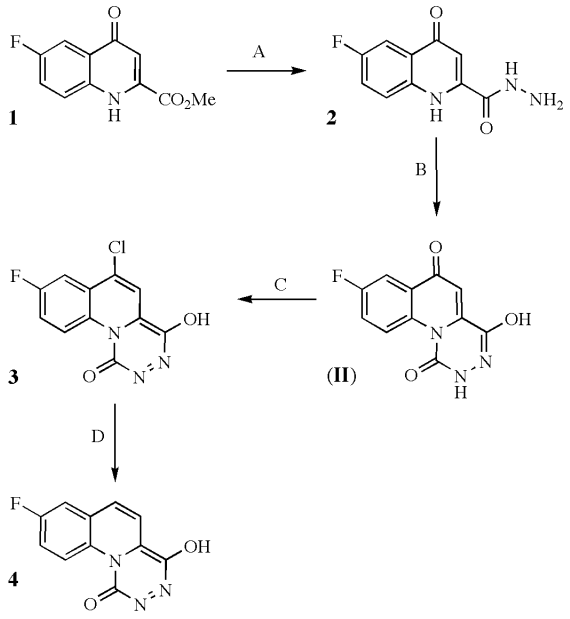
The presence of only one chloro substituent in the resulting compound (**3**) was corroborated by the mass spectrum with peaks m/z 266 $[M]^+$ (100%) and m/z 268 $[M+2]^+$ (30%). In addition, the proton NMR spectrum displayed a shift of the H5 signal to low field (6.94 ppm to 8.14 ppm), consistent with the introduction of an electronegative chlorine.

In order to ascertain the position of the chloro substituent, compound **3** was subsequently reduced using catalytic hydrogenation under pressure. The 8-fluoro-4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*] quinolin-1-one **4** was obtained with 71% yield. The structure was confirmed by proton NMR: A coupling of 8 Hz between H5 and H6 characteristic of ethylenic protons in quinolines and by

NOESY experiment in which a significant NOE between H6 and H7 was observed. The structure of compound **4** provides further support for the location of the chloro substituent at the 6 position of the 1*H*-[1,2,4]triazino[4,5-*a*]quinolin-1-one skeleton.

This result may be explained by delocalisation of the

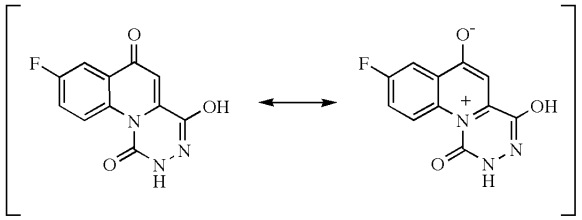
Scheme 3



A) $NH_2$-$NH_2$, 1,5 $H_2O$, reflux, 69%; B) pyridine, $CH_2Cl_2$, triphosgene, 0°C to 25°C, 77%; C) $POCl_3$, reflux, 97%; D) DMF, $H_2$, Pd-C (10%), 71%.

lone pair on the nitrogen at the ring junction onto the oxygen atom at position-6, as in the mesomeric representation (Scheme 4) which is comparable to the electronic structure of 4-pyridone [5].

Scheme 4



A calculation of the charge and the electron density of compound **I** and **II** was performed. The two compounds were modeled and optimized with SYBYL (v.6.4) [6] *via* MOPAC [7], using AM1.

The results in Tables 1 and 2 show without ambiguity, that the ring junction nitrogen atom of compound **II** is more electronegative than the ring junction nitrogen atom of compound **I**.

Table 1

Charge and Atom Electron Density of Compound **I**

| ATOM NO. | TYPE | CHARGE | ATOM ELECTRON DENSITY |
|---|---|---|---|
| 1 | C | -0.1150 | 4.1150 |
| 2 | C | 0.0683 | 3.9317 |
| 3 | C | -0.0900 | 4.0900 |
| 4 | C | -0.1457 | 4.1457 |
| 5 | C | 0.672 | 3.9328 |
| 6 | C | -0.1423 | 4.1423 |
| 7 | C | 0.2967 | 3.7033 |
| 8 | C | -0.1840 | 4.1840 |
| 9 | C | -0.0140 | 4.0140 |
| 10 | N | -0.0907 | 5.0907 |
| 11 | N | -0.2299 | 5.2299 |
| 12 | C | 0.3746 | 3.6254 |
| 13 | N | -0.3636 | 5.3636 |
| 14 | C | 0.3534 | 3.6466 |
| 15 | O | -0.2774 | 6.2774 |
| 16 | O | -0.2930 | 6.2930 |
| 17 | O | -0.3252 | 6.3252 |
| 18 | H | 0.1590 | 0.8410 |
| 19 | F | -0.0939 | 7.0939 |
| 20 | H | 0.1804 | 0.8196 |
| 21 | H | 0.1511 | 0.8489 |
| 22 | H | 0.1948 | 0.8052 |
| 23 | H | 0.2418 | 0.7582 |
| 24 | H | 0.2775 | 0.7225 |

Scheme 5

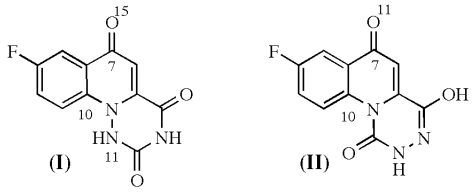


Table 2

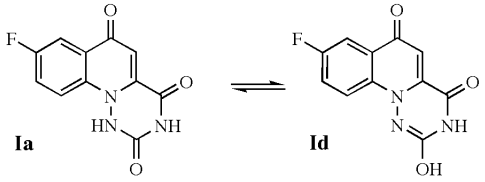
Charge and Atom Electron Density of Compound **II**

| ATOM NO. | TYPE | CHARGE | ATOM ELECTRON DENSITY |
|---|---|---|---|
| 1 | C | -0.1201 | 4.1201 |
| 2 | C | 0.0696 | 3.9304 |
| 3 | C | -0.0975 | 4.0975 |
| 4 | C | -0.1477 | 4.1477 |
| 5 | C | 0.0890 | 3.9110 |
| 6 | C | -0.1330 | 4.1330 |
| 7 | C | 0.3027 | 3.6973 |
| 8 | C | -0.2524 | 4.2524 |
| 9 | C | -0.0632 | 3.9368 |
| 10 | N | -0.1978 | 5.1978 |
| 11 | O | -0.2936 | 6.2936 |
| 12 | F | -0.962 | 7.0962 |
| 13 | C | 0.3917 | 3.6083 |
| 14 | O | -0.3294 | 6.3294 |
| 15 | N | -0.2924 | 5.2924 |
| 16 | N | 0.0182 | 4.9818 |
| 17 | C | 0.0105 | 3.9895 |
| 18 | O | -0.2156 | 6.2156 |
| 19 | H | 0.1595 | 0.8405 |
| 20 | H | 0.1797 | 0.8203 |
| 21 | H | 0.1813 | 0.8187 |
| 22 | H | 0.1769 | 0.8231 |
| 23 | H | 0.3008 | 0.6992 |
| 24 | H | 0.2329 | 0.7671 |

It is therefore likely that the nitrogen atom at the ring junction in compound **II** could share its lone pair of electrons and thus carry a positive charge. Whereas for compound **I**, the lone pair on the nitrogen cannot be

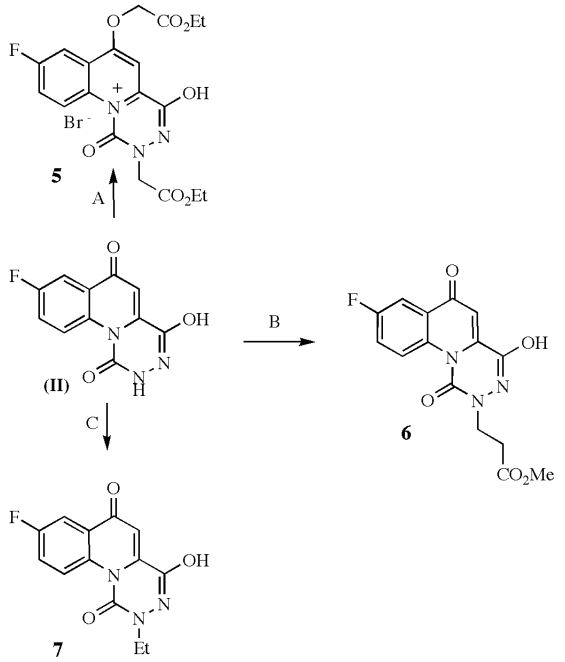
delocalised onto the oxygen atom at position-6 making it unreactive, due to conjugation of this lone pair with the π-bond of the hydrazone moiety of the tautomeric form **Id** (scheme 6), as described previously [3].

Scheme 6




Alkylation of **II** with two equivalents of potassium carbonate and ethyl bromoacetate at 50 °C results in double alkylation without any trace of monoalkylated compounds to give the *N*- and *O*-alkylated 6-(2-ethoxy-2-oxoethoxy)-2-(2-ethoxy-2-oxoethyl)-8-fluoro-4-hydroxy-1-oxo-1*H*,2*H*-[1,2,4] triazino[4,5-*a*]quinolin-11-ium **5** in 87% yield (Scheme 7). The structure of compound (**5**) was determined by proton and carbon NMR. The NOESY and HMBC (inverse mode) experiments indicate that the ethyl-2-oxyacetate group is attached at the 6 position because of the proximity in space observed between the proton H5 or the proton H7 with $OCH_2$ protons, and because of the correlation between carbons and protons H5-C5-C6-O-$CH_2$.

Scheme 7



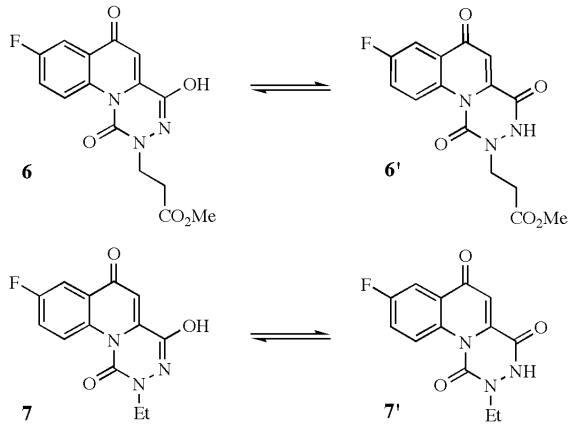

A) DMF, $K_2CO_3$, $BrCH_2CO_2Et$, 50°C, 87%; B) DMF, $Et_3N$, methyl acrylate, 100°C, 93%; C) DMF, NaH, EtI, 53%.

In contrast, a Michael addition [8a-b] with methyl acrylate in presence of triton B at 100 °C led to the selective introduction of a methyl propanoate group onto the nitrogen atom N2 in 56% yield after 4 hours (Scheme 7). However, when triethylamine was used as base, but in a stoichiometric amount, the time of the reaction was halfed and the desired product was obtained in greatly improved yield of 93%.

In the proton NMR spectrum at room temperature of the resulting compound **6**, the signals of the OH proton and H5 were not well-defined: a broad singlet was observed for the exchangeable hydrogen atom of the hydroxyl group and the signal for H5 was split into two, indicating that compound **6** in DMSO was in equilibrium with its tautomer **6'** (Scheme 8).

A regioselective alkylation onto the nitrogen atom N2 was also obtained upon reaction with ethyl iodide employing sodium hydride as base [9]. However, the reaction was slow and incomplete (53 % yield) despite the use of the reactive iodide. The proton NMR spectrum at room temperature showed that compound **7** in DMSO was probably in equilibrium with its tautomer **7'** (Scheme 8).

Scheme 8




In summary, we have synthesized a new class of fused tricyclic quinolones that contain a four-atom bridge connecting the N1 with the C2 forming a triazino ring. The route requires 4 steps from commercially available 4-fluoroaniline with an overall yield of 44%. The nitrogen atom N2 can be selectively alkylated by a Michael addition and by a reaction with sodium hydride whereas a standard alkylation with potassium carbonate gave an *N*- and *O*-alkylated product (double alkylation). The structural modification within the triazino ring level in comparison with the 8-fluoro-1*H*-[1,2,4]triazino[1,6-*a*]quinoline-2,4,6(3*H*)-trione **I** considerably alters the reactivity of the molecule toward the phosphorus oxychloride: in the case of the

8≠fluoro-1*H*-[1,2,4]triazino[1,6-*a*]quinoline-2,4,6(3*H*)-trione **I**, chlorination readily gave the dichloro compound [3], whereas for 8-fluoro-4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*]quinoline-1,6 (2*H*)-dione **II**, the chlorination occurred selectively at the more reactive carbonyl group at the 6-position. This result may be explained by extensive delocalisation of the lone pair from the nitrogen at the ring junction onto the oxygen atom in 6 position in case of compound **II**, which cannot occur in case of the 8-fluoro-1*H*-[1,2,4]triazino[1,6-*a*]quinoline-2,4,6(3*H*)-trione **I** because of the presence of the ring junction nitrogen atom within a hydrazino group.

The study of the reactivity of these compounds now offers routes to a wide variety of further analogues in order to perform some structural modifications within the framework of our SAR studies. Further work including the biological activity and other reactions of these compounds are currently underway in our laboratory.

## EXPERIMENTAL

The name of each product was obtained with ACD/IUPAC Name pro software (3.5 for Microsoft Windows). All reagents were purchased from commercial suppliers and used without purification. Melting points (uncorrected) were determined on a Köfler apparatus. Infrared (ir) spectra were recorded on a Perkin-Elmer Paragon FT-IR 1000 spectrophotometer with 4 $cm^{-1}$ resolution, only the most significant ir absorptions are given. Nuclear Magnetic Resonance (NMR) spectra were run on a Bruker Avance DPX250 spectrometer. $^1H$ spectra were run at 250 MHz and $^{13}C$ spectra were run at 62.89 MHz. All chemical shifts are quoted in δ relative to tetramethylsilane as an external standart and expressed in parts per million (ppm). All coupling constants are quoted in Hertz. Mass spectra were recorded on a Perkin-Elmer SCIEZ API 3000 spectrometer (ion spray).

6-Fluoro-4-oxo-1,4-dihydro-2-quinolinecarbohydrazide (**2**).

Compound **1** (8 g, 36.19 mmol) in 80 mL of hydrazine hydrate was heated under reflux during four hours. After evaporation under reduced pressure, the crude product was poured into 500 mL of ice cold water. The precipitate formed was then collected by filtration, washed with water until pH 6, dried under vacuum to afford a white solid (69%), mp > 264 °C; ir (KBr) 3325 and 3188 (NH), 1703 and 1626 (C=O) $cm^{-1}$; $^1H$ nmr (250 MHz, DMSO-$d_6$): δ 4.65 (s, 2, $NH_2$), 6.62 (s, 1, H3), 7.49 (ddd, 1, $J_{7,5}$ = 3.0 Hz, $J_{7,F}$ = 10.0 Hz, $J_{7,8}$ = 9.0 Hz, H7), 7.67 (dd, 1, $J_{5,7}$ = 3.0 Hz, $J_{5,F}$ = 9.0 Hz, H5), 8.02 (dd, 1, $J_{8,7}$ = 9.0 Hz, $J_{8,F}$ = 5.0 Hz, H8), 10.33 (s, 1, NH), 11.98 (s, 1, NH).

8-Fluoro-4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*]quinoline-1,6(2*H*)-dione (**II**).

To a suspension of **2** (4 g, 18.1 mmol) in 225 mL of dichloromethane, was added dropwise a solution of triphosgene (7.2 g, 1.3 eq, 23.53 mmol) dissolved in 225 mL of dichloromethane, at 0 °C, over three hours. After twelve hours at room temperature, the resulting precipitate was then collected by filtration, washed with water until pH 6 and dried under vacuum to afford a white solid (77%). The compound can be purified from acid-base precipitation (35% to 42 %), mp > 264°C; ir (KBr) 3486 (NH), 1777 and 1608 (C=O) $cm^{-1}$; uv: (ethanol): λ max 279 nm (ε 15849-19952); λ max 355 nm (ε 7943-10000); m/z = 248 $[M+H]^+$ (100%); $^1H$ nmr (250 MHz, DMSO-$d_6$): δ 6.61 (s, 1, OH), 6.94 (s, 1, H5), 7.65 (ddd, 1, $J_{9,7}$ = 3.02 Hz, $J_{9,F}$ = 9.5 Hz, $J_{9,10}$ = 9.35 Hz, H9), 7.73 (dd, 1, $J_{7,9}$ = 3.02 Hz, $J_{7,F}$ = 9.02 Hz, H7), 8.00 (dd, 1, $J_{10,9}$ = 9.0 Hz, $J_{10,F}$ = 5.0 Hz, H10), 13.13 (s, 1, NH); $^{13}C$ nmr (62.89 MHz, DMSO-$d_6$): δ 105.17 (C5), 108.92 (d, $J_{C,F}$ = 23.27 Hz, C7), 123.10 (d, $J_{C,F}$ = 26.41 Hz, C9), 126.74 (d, $J_{C,F}$ = 8.17 Hz, C10), 138.73 (Cq), 140.95 (Cq), 151.64 (Cq), 155.20 (C4), 160.61 (d, $J_{C,F}$ = 245.27 Hz, C8), 172.06 (C=O), 176.10 (C=O).

*Anal.* Calcd. for $C_{11}H_6N_3O_3F$: C, 53.45; H, 2.44; N, 16.99. Found: C, 53.23; H, 2.42; N, 17.28.

6-Chloro-8-fluoro-4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*]quinolin-1-one (**3**).

Compound **II** (3.4 g, 13.76 mmol) in 46 mL of phosphorus oxychloride was heated under reflux during four hours. After evaporation, the crude product was poured into 500 mL of ice cold water. The precipitate formed was then collected by filtration, washed with water until pH 6, and dried under vacuum to afford a yellow solid (93%), mp > 264 °C. The compound can be recrystallised from *N*,*N*-dimethyl formamide; ir (KBr): 3101 (OH), 1826 (C=O), 1773 (C=C), 1426 (N=N) $cm^{-1}$; uv: (ethanol): λ max 279 nm (ε 15849); λ max 334 nm (ε 5012-6309); λ max 349 nm (ε = 5012-6309); m/z = 266 $[M]^+$ (100%); 268 $[M+2]^+$ (30%); $^1H$ nmr (250 MHz, DMSO-$d_6$): δ 7.86 (ddd, 1, $J_{9,10}$ = 9.0 Hz, $J_{9,F}$ = 8.0 Hz, $J_{9,7}$ = 3.0 Hz, H9), 7.93 (dd, 1, $J_{7,9}$ = 3.0 Hz, $J_{7,F}$ = 10.0 Hz, H7), 8.14 (s, 1, H5), 8.24 (dd, 1, $J_{10,9}$ = 9.0 Hz, $J_{10,F}$ = 5.0 Hz, H10), 13.00 (s, 1, OH); $^{13}C$ nmr (62.89 MHz, DMSO-$d_6$): δ 108.44 (d, $J_{C,F}$ = 25.15 Hz, C7), 119.17 (C5), 122.67 (d, $J_{C,F}$ = 26.41 Hz, C9), 127.50 (d, $J_{C,F}$ = 10.69 Hz, C10), 133.86 (Cq), 142.42 (Cq), 143.20 (Cq), 145.44 (Cq), 152.89 (Cq), 154.83 (C=O), 162.05 (d, $J_{C,F}$ = 257.85 Hz, C8). hrms ($Fab^+$) 266.013258 ($MH^+$); calc. for $C_{11}H_6N_3O_2FCl$, 266.012652).

*Anal.* Calcd. for $C_{11}H_5N_3O_2FCl$: C, 49.73; H, 1.89; N, 15.81; Cl, 13.34. Found: C, 49.48; H, 1.89; N, 15.82; Cl, 13.11.

8-Fluoro-4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*]quinolin-1-one (**4**).

A solution of **3** (2 g, 7.53 mmol) in 200 mL of *N*,*N*-dimethylformamide was hydrogenated, under pressure (58 psi) with a catalytic amount of 10% palladium on carbon overnight. After filtration on Celite, the filtrate was evaporated under reduced pressure to afford a white solid (71%), mp 262-264 °C. The compound can be recrystallised from *N*,*N*-dimethylformamide; ir (KBr): 3073 (OH), 1824 (C=O), 1779 (C=C), 1424 (N=N) $cm^{-1}$; uv: (ethanol): λ max 275 nm (ε 31623); λ max 331 nm (ε 12589); λ max 346 nm (ε = 10000-12589); m/z = 232 $[M+H]^+$ (100%); $^1H$ nmr (250 MHz, DMSO-$d_6$): δ 7.75 (ddd, 1, $J_{9,10}$ = 9.5 Hz, $J_{9,F}$ = 9.0 Hz, $J_{9,7}$ = 3.0 Hz, H9), 7.87 (dd, 1, $J_{7,9}$ = 3.0 Hz, $J_{7,F}$ = 9.0 Hz, H7), 8.03 (d, 1, $J_{5,6}$ = 8.0 Hz, H5), 8.16 (dd, 1, $J_{10,9}$ = 9.05 Hz, $J_{10,F}$ = 5.0 Hz, H10), 8.5 (d, 1, $J_{6,5}$ = 8.0 Hz, H6), 12.85 (s, 1, OH); $^{13}C$ nmr (62.89 MHz, DMSO-$d_6$): δ 112.38 (d, $J_{C,F}$ = 25.01 Hz, C7), 119.76 (C5), 121.92 (d, $J_{C,F}$ = 25.78 Hz, C9), 130.15 (Cq), 133.23 (d, $J_{C,F}$ = 8.80 Hz, C10), 138.24 (C6), 143.64 (Cq), 145.21 (Cq), 154.32 (Cq), 155.58 (C=O), 161.59 (d, $J_{C,F}$ = 248.16 Hz, C8).

*Anal.* Calcd. for $C_{11}H_6N_3O_2F$: C, 57.14; H, 2.61; N, 18.17. Found: C, 56.91 ; H, 2.59; N, 18.11.

6-(2-Ethoxy-2-oxoethoxy)-2-(2-ethoxy-2-oxoethyl)-8-fluoro-4-hydroxy-1-oxo-1*H*,2*H*-[1,2,4]triazino[4,5-*a*]quinolin-11-ium (**5**).

To a solution of **II** (8 g, 32.39 mmol) in 65 mL of *N*,*N*-dimethylformamide and potassium carbonate (9.39 g, 2.1 eq) stirred for one hour at room temperature, was added ethyl bromoacetate (7.7 mL, 2.1 eq). The reaction mixture was then heated at 50 °C during four hours. After evaporation under reduced pressure, the crude product was poured into 500 mL of ice cold water. The precipitate formed was then filtered, washed with water until pH 6, washed with diethyl ether, and dried under vacuum to afford a white solid (84%), mp 140-142 °C; ir (KBr): 1789 (C=N), 1760 (C=O) $cm^{-1}$; m/z = 420 $[M]^+$ (100%); $^1H$ nmr (250 MHz, DMSO-$d_6$): δ 1.19 (t, 6, *J* = 7.0 Hz, $OCH_2CH_3$), 4.15-4.19 (m, 4, $OCH_2CH_3$), 4.79 (s, 2, $NCH_2$), 5.23 (s, 2, $OCH_2$), 7.37 (s, 1, H5), 7.73-7.81 (m, 2, H7 and H9), 8.13 (dd, 1, $J_{10,9}$ = 9.5 Hz, $J_{10,F}$ = 5.0 Hz, H10); $^{13}C$ nmr (62.89 MHz, DMSO-$d_6$): δ 13.33 (2, $OCH_2CH_3$), 46.41 ($NCH_2$), 60.42 ($OCH_2CH_3$), 61.02 ($OCH_2CH_3$), 64.87 ($OCH_2$), 98.44 (C5), 106.41 (d, $J_{C,F}$ = 23.90 Hz, C7), 120.45 (Cq), 122.18 (d, $J_{C,F}$ = 25.78 Hz, C9), 133.20 (d, $J_{C,F}$ = 9.40 Hz, C10), 142.16 (Cq), 144.62 (Cq), 151.20 (Cq), 152.35 (Cq), 161.89 (d, $J_{C,F}$ = 246.53 Hz, C8), 161.89 (Cq), 166.36 (C=O), 166.95 (C=O).

*Anal.* Calcd. for $[C_{19}H_{19}N_3O_7F]^+$ $Br^-$: C, 45.61; H, 3.82; N, 8.39; Br, 15.97. Found: C, 45.38; H, 3.80; N, 8.34; Br, 15.69.

Methyl 3-[8-Fluoro-4-hydroxy-1,6-dioxo-1*H*-[1,2,4]triazino[4,5-*a*]quinolin-2(6*H*)-yl]propanoate (**6**).

A solution of **II** (8 g, 32.39 mmol) in 65 mL of *N*,*N*-dimethylformamide, methyl acrylate (5.8 mL, 2 eq), and triethylamine (5.4 mL) stirred one hour at room temperature, was heated at 110 °C during two hours. After evaporation under reduced pressure, the crude product was poured into 500 mL of ice cold water. The precipitate formed was then filtered, washed with water until pH 6, washed with diethyl ether, and dried under vacuum to afford a yellow solid (93%), mp 140-142 °C; ir (KBr): 1778, 1738, 1606 (C=O) $cm^{-1}$; m/z = 334 $[M+H]^+$ (100%); $^1H$ nmr (250 MHz, DMSO-$d_6$): δ 2.83 (t, 2, *J* = 7.0 Hz, $CH_2$), 3.59 (s, 3, $OCH_3$), 4.00 (q, 2, *J* = 7.0 Hz, $NCH_2$), 6.40 (s, 0.5, H5), 7.29 (s, 0.5, H5), 7.64 (ddd, 1, $J_{9,10}$ = 9.0 Hz, $J_{9,F}$ = 9.0 Hz, $J_{9,7}$ = 3.0 Hz, H9), 7.73 (dd, 1, $J_{7,9}$ = 3.0 Hz, $J_{7,F}$ = 10.5 Hz, H7), 7.99 (dd, 1, $J_{10,9}$ = 9.0 Hz, $J_{10,F}$ = 5.0 Hz, H10), 12.24 (sl, 1, OH or NH); $^{13}C$ nmr, *DEPT* 135 (62.89 MHz, DMSO-$d_6$): δ 32.67 ($CH_2$), 42.42 ($NCH_2$), 52.54 ($OCH_3$).

*Anal.* Calcd. for $C_{15}H_{12}N_3O_5F$: C, 54.06; H, 3.62; N, 12.60. Found: C, 53.81; H, 3.62; N, 12.63.

2-Ethyl-8-fluoro-4-hydroxy-1*H*-[1,2,4]triazino[4,5-*a*]quinoline-1,6(2*H*)-dione (**7**).

To a solution of **II** (300 mg, 1.21 mmol) in 17.3 mL of freshly distilled *N*,*N*-dimethylformamide was added sodium hydride 60% in oil (49 mg, 1 eq). When hydrogen evolution ceased, 0.12 mL of ethyl iodide was added dropwise. After 24 hours at room temperature, the reaction mixture was neutralized with aqueous ammonium chloride and evaporated under vacuum. The residue was adsorbed on silica gel and chromatographed by eluting with 9:1 $CH_2Cl_2$/MeOH to give a white solid (53%), mp 260-262 °C; ir (KBr): 1789, 1620 (C=O) $cm^{-1}$; m/z = 276 $[M+H]^+$ (100%); $^1H$ nmr (250 MHz, DMSO-$d_6$): δ 1.29 (t, 3, *J* = 7.0 Hz, $NCH_2CH_2$), 3.80 (q, 2, *J* = 7.0 Hz, $NCH_2CH_3$), 6.41 (sl, 0.5, H5), 7.32 (sl, 0.5, H5), 7.65-7.74 (m, 2, H7, H9), 7.96 (dd, 1, $J_{10,9}$ = 9.0 Hz, $J_{10,F}$ = 5.0 Hz, H10), 12.31 (sl, 1, OH or NH); $^{13}C$ nmr, *DEPT* 135 (62.89 MHz, DMSO-$d_6$): δ 13.10 ($NCH_2CH_3$), 40.84 ($NCH_2CH_3$).

*Anal.* Calcd. for $C_{13}H_{10}N_3O_3F$: C, 56.72; H, 3.66; N, 15.26. Found: C, 56.49; H, 3.64; N, 15.19.

Acknowledgements.

We are grateful to Dr Christophe Marot from the laboratory of molecular modeling at the University of Orléans for the calculation of the charge and the electron density.

REFERENCES AND NOTES

[1] D. Edmont, R. Rocher, Ch. Plisson, J. Chenault, *Bioorg. Med. Chem. Lett.* **10**, 1831 (2000).

[2] D. Edmont and J. Chenault, *Synlett*, **6**, 833 (2001).

[3] D. Edmont, Ch. Marot and J. Chenault, *J. Heterocyclic Chem*., **39**, 1161 (2002).

[4] J. Hasmukh, and U. Paresh, *J. Indian Chem. Soc*., **67** (9), 779 (1990).

[5] Aromatic Heterocyclic Chemistry, Oxford Chemistry Primers, David T. Davies, Oxford Science Publications 2, Series sponsor Zeneca, 1992, chap 5, 39-40.

[6] SYBYL 6,6, Tripos Associates, Inc., 1699 South Hanley Road, St. Louis, MO 63144.

[7] J. J. P. Stewart; MOPAC: A Semi-Empirical Molecular Orbital Program, *J. Comput-Aided. Mol. Des.*, **4**, 1-103,

[8a] H. Feuer and R. Harmetz, *J. Am. Chem. Soc*., **80**, 5877 (1958); [b] F. C. Whitmore, H. S. Mosher, R. R. Adams and E. C. Chapin, *J. Am. Chem. Soc*., **66**, 725 (1944).

[9] S. D. Cho, J. W. Chung, W. Y. Choi, S. K. Kim and Y. J. Yoon, *J. Heterocyclic Chem.*, **31**, 1199 (1994).