REARRANGEMENT OF AN *N*-ARYL-2-VINYLTETRAHYDRO-4-OXOQUINOLINE TO AN ACRIDINE DERIVATIVE

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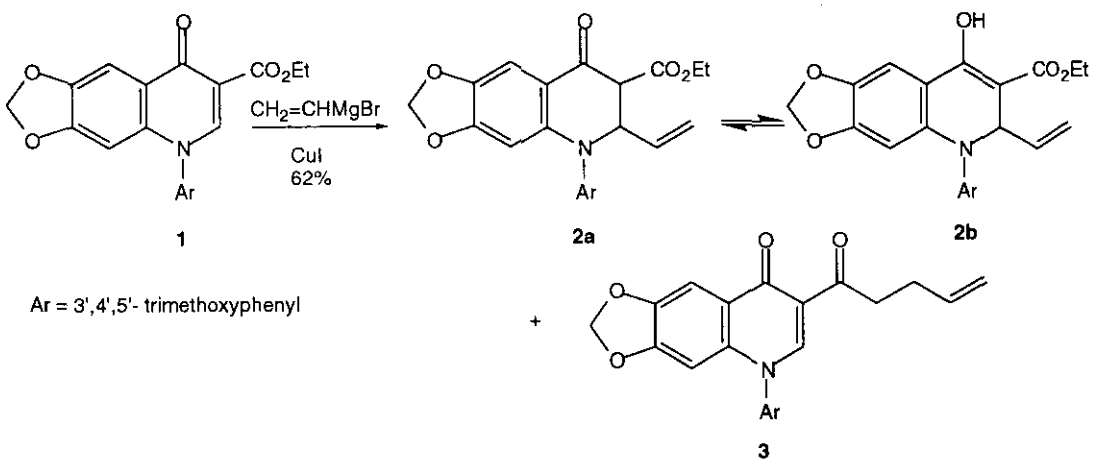
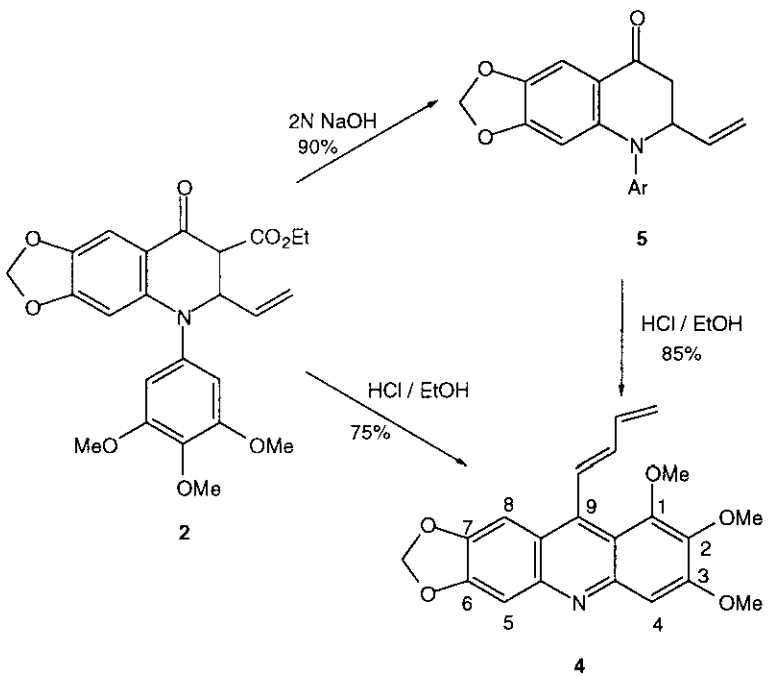
Abstract - Acridine (**4**) has been obtained by acidic rearrangement of *N*-aryl-2-vinyltetrahydro-4-oxoquinoline (**2**). The mechanism involved a retro-Michael process followed by the attack of the electron rich aromatic ring onto the keto group.

During a study dealing with the preparation of *N*-arylquinolones annelated to either a 5-membered or a 6-membered lactone,[1] we prepared compound (**2**) by conjugate addition of vinyl cuprate to quinolone (**1**)[2] as previously described in the quinolone series[3] (Scheme 1). Alkylated product was obtained in 62% yield as a tautomeric equilibrium of keto ester (**2a**) and enol ester (**2b**) in $CDCl_3$ solution along with **3** (24%), an unexpected product resulting from 1,2-addition of vinylmagnesium bromide to the ester group followed by a 1,4-addition of vinylcuprate to the resulting vinyl ketone.



Scheme 1

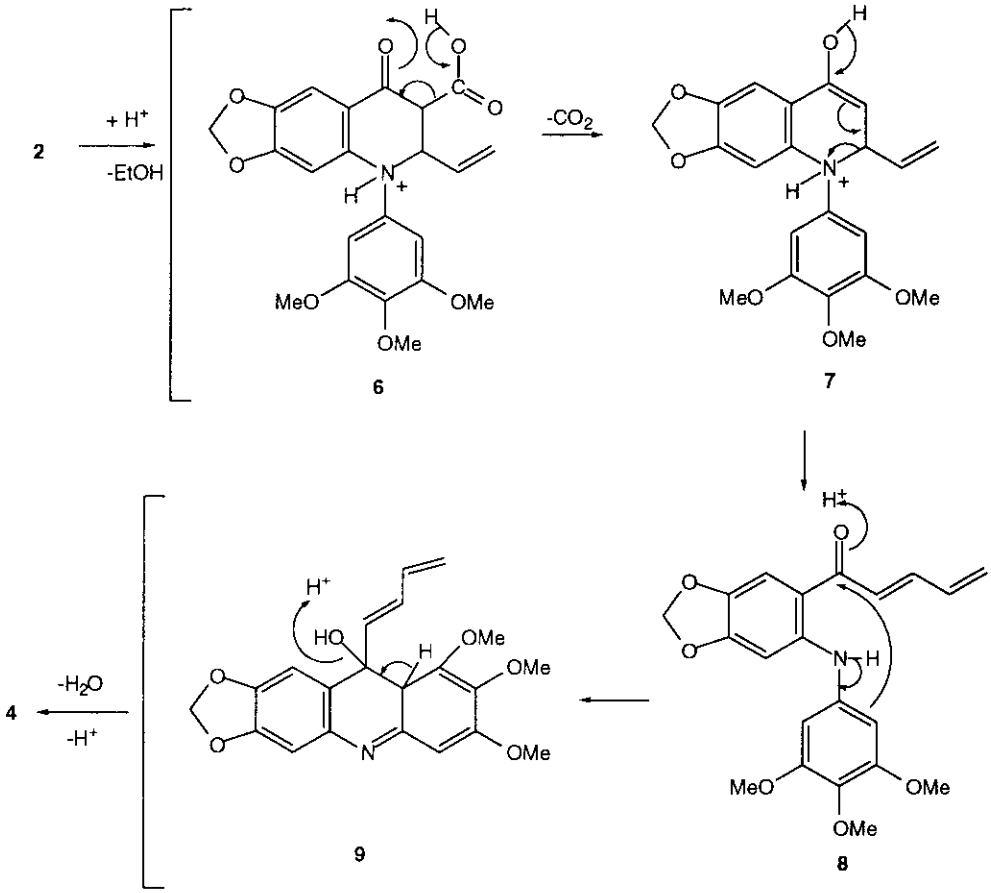
In an attempt to hydrolyse the ethyl ester of **2** in acidic medium, we observed the formation of acridine (**4**) in 75% yield (Scheme 2). This compound was obtained as a yellow crystalline product characterized by MS, showing a molecular peak at m/z : 365. The presence of a butadiene chain was deduced from the ^1H NMR spectrum by a characteristic series of signals [δ : 5.40 (m, 2H), 6.37 (dd, J = 15.8, 10.4 Hz, 1H), 6.70 (td, J = 16.9, 10.4 Hz, 1H) and 7.46 (d, J = 15.8 Hz, 1H)]. Three aromatic singlets were observed at δ : 7.52, 8.02 and 8.14 ppm, indicating a new substitution in one of the two benzene rings. The non-equivalence of the methoxy groups (δ : 3.80, 3.91 and 4.08 ppm) led us to assume substitution of the trimethoxy aromatic ring.



Scheme 2

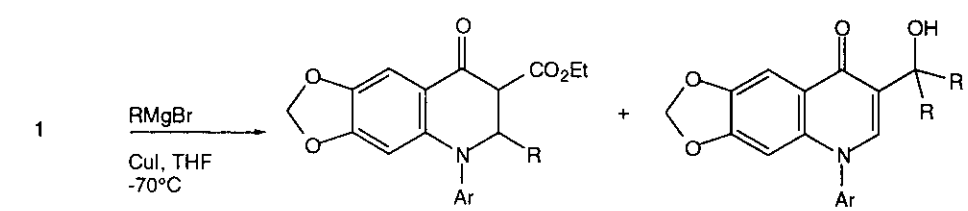
In order to understand the formation of compound (**4**) lacking the ester function, we were interested in studying the rearrangement of decarboxylated product (**5**) obtained in 90% yield by basic treatment of keto ester (**2**). When **5** was treated with HCl in refluxing ethanol, the same acridine (**4**) was isolated in 85% yield, indicating that **5** was probably an intermediate during the rearrangement of **2** (Scheme 2).

Thus the formation of **4** can be explained as follows (Scheme 3) : (i) decarboxylation of acid (**6**) into **7** ; (ii) retro-Michael reaction on intermediate (**7**) leading to butadienone (**8**) ; (iii) nucleophilic attack of the trimethoxy aromatic ring on the carbonyl group to give dihydroacridine (**9**) ; (iv) dehydration of the tricyclic system to result in an aromatic nucleus.



Scheme 3

In an attempt to widen this strategy with a view toward the preparation of different substituted acridines, the same treatment was applied to quinolones (**10**) and (**11**). They were obtained as described for **2** but in low yields along with compounds (**12**) and (**13**) resulting from a double attack of Grignard reagents on the ester function of **1** (Scheme 4).

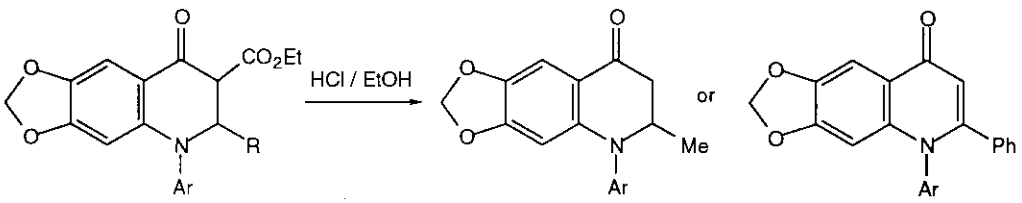


10 : R = Me (54%)
11 : R = Ph (10%)

12 : R = Me (29%)
13 : R = Ph (68%)

Scheme 4

Surprisingly, whatever the conditions were, none of compounds (**10**) or (**11**) furnished the expected acridines. The only products isolated were the tetrahydro-4-oxoquinoline (**14**) from **10** and the dihydro-4-oxoquinoline (**15**) from **11** (Scheme 5). The reasons for the observed differences of reactivity between **2** and **10**-**11** are not clear. It is likely that the presence of the vinyl group favored the ring opening by stabilizing the formation of the conjugated ketone. One could imagine that a phenyl group would have the same influence. The non rearrangement of **11** could be due to a special orientation of this substituent because of a strong interaction with the trimethoxy aromatic substituent preventing ring opening.



Scheme 5

In conclusion, we described in this paper a new rearrangement of a *N*-aryltetrahydro-4-oxoquinoline into an acridine skeleton. To our knowledge, this is the first report of such a reaction and compound (**4**) is the first 9-[1-(buta-1,3-dienyl)]acridine described in the literature.

EXPERIMENTAL

All melting points were determinated on a Maquenne apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Bristol-Myers Squibb Analytical Department. IR spectra were recorded on a Perkin-Elmer 1600 infrared spectrophotometer. CI, EI MS measurements were made on a Nermag R 10-10 mass spectrometer a quadripole instrument. NMR spectra were recorded on a Bruker AC-300 or AC-500 spectrometer ; chemical shift values are given in ppm (δ), tetramethylsilane being used as internal standard. Flash columm chromatographies were performed using Merck silica gel 60, 70-230 mesh ASTM.

Ethyl 2-ethenyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline-3-carboxylate (2) and 1,4-dihydro-6,7-methylenedioxy-3-(1-oxo-4-pentenyl)-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline (3). To a slurry composed of **1** (2 g, 4.68 mmol) and CuI (1.78 g, 10 mmol) in 100 mL of dry THF at -70°C, 14 mL of a 1.0 M solution of vinylmagnesium bromide in THF (14 mmol) was added under N_2 atmosphere. After stirring for 1.5 h at -70°C, another 14 mL of vinylmagnesium bromide (14 mmol) was added and then a third amount (14 mL, 14 mmol) after 45 min. The temperature was allowed to raise to -40°C and the reaction was quenched with a saturated aqueous solution of NH_4Cl. THF was removed in vacuo and the aqueous residue extracted with

CH_2Cl_2 (3x60 mL). The combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and evaporated to yield a yellow residue (2.05 g). Chromatographic purification (ligroin / AcOEt 80 : 20 to 30 : 70) afforded 1.3 g (62%) of **2**, 0.59 g (24%) of **3** and 0.1 g (5%) of starting material **1**.
2 : mp 152°C (EtOH). IR υ_{max} (KBr) cm^{-1} : 3445, 3080, 1699, 1633, 1593, 1508. MS (EI) : *m/z* 455 $(M)^{+\cdot}$. Anal. Calcd for $C_{24}H_{25}NO_8$: C, 63.29; H, 5.53; N, 3.08. Found : C, 62.96; H, 5.60; N, 3.01. **2** exists in two tautomeric forms **2a** : **2b** (16 : 84) in $CDCl_3$ solution. ^1H NMR (500 MHz) ($CDCl_3$) for **2a** : δ 1.22 (t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 3.52 (d, *J* = 4.6 Hz, H-3), 3.85 (s, 2 OMe), 3.91 (s, OMe), 4.34 (m, $OC\underline{H}_2CH_3$), 4.75 (m, H-2), 5.25 (m, $CH{=}C\underline{H}_2$), 5.90 (m, OCH_2O), 5.91 (m, $C\underline{H}{=}CH_2$), 6.45 (s, H-2' and H-6'), 6.55 (s, H-5 or H-8), 7.36 (s, H-5 or H-8). ^1H NMR (500 MHz) ($CDCl_3$) for **2b** : δ 1.41 (t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 1.53 (s, OH), 3.75 (s, 2 OMe), 3.81 (s, OMe), 4.22 (m, $OC\underline{H}_2CH_3$), 5.05 (dt, *J* = 1.4, 10 Hz, $CH{=}C\underline{H}_2$), 5.11 (d, *J* = 6 Hz, H-2), 5.15 (dt, *J* = 1.4, 19 Hz, $CH{=}C\underline{H}_2$), 5.92 (m, OCH_2O), 5.95 (m, $C\underline{H}{=}CH_2$), 6.41 (s, H-5 or H-8), 6.55 (s, H-2' and H-6'), 7.15 (s, H-8 or H-5).
3 : mp 248°C (EtOH); IR υ_{max} (KBr) cm^{-1} : 3432, 3080, 2945, 2941, 1739, 1667, 1629, 1599, 1519. MS (CI) : m/z 438 $(MH)^+$. Anal. Calcd for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.30; N, 3.20. Found : C, 65.65; H, 5.27; N, 3.20. ^1H NMR (500 MHz) ($CDCl_3$): δ 2.50 (m, CH_2), 3.41 (m, CH_2), 3.85 (s, 2 OMe), 3.95 (s, OMe), 4.94 (dd, *J* = 1.3, 10 Hz, $CH{=}C\underline{H}_2$), 5.12 (dd, *J* = 1.3, 17 Hz, $CH{=}C\underline{H}_2$), 5.90 (m, $C\underline{H}{=}CH_2$), 6.10 (s, OCH_2O), 6.41 (s, H-8 or H-5), 6.61 (s, H-2' and H-6'), 7.85 (s, H-5 or H-8), 8.40 (s, H-2).

9-[1-(Buta-1,3-dienyl)]-6,7-methylenedioxy-1,2,3-trimethoxyacridine (4) : To a solution of compound (**2**) (50 mg, 0.11 mmol) in EtOH (4 mL) was added a 6N aqueous solution of HCl (0.5 mL). The reaction mixture was heated at reflux for 7 h, then solvent was evaporated. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with water (2x4 mL). The organic layer was dried over Na_2SO_4 then evaporated to furnish a yellow residue which was recrystallized from CH_2Cl_2 leading to **4** (30 mg, 75 %) as yellow crystals. mp 179°C (CH_2Cl_2). IR υ_{max} (KBr) cm^{-1} : 3005, 2977, 2908, 2363, 1615, 1541, 1463. MS (CI) : *m/z* : 366 $(MH)^+$. Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found : C, 68.92; H, 5.20; N, 3.82. ^1H NMR (300 MHz) ($CDCl_3$) : δ 3.80, 3.91 and 4.08 (3 s, 3 OMe), 5.40 (m, $CH{=}C\underline{H}_2$), 6.18 (s, OCH_2O), 6.37 (dd, *J* = 10.4, 15.8 Hz, $CH{=}C\underline{H}{-}CH{=}CH_2$), 6.70 (td, *J* = 16.9, 10.4 Hz, $CH{=}CH{-}C\underline{H}{=}CH_2$), 7.46 (d, *J* = 15.8 Hz, $C\underline{H}{=}CH{-}CH{=}CH_2$), 7.52 (s, Ar), 8.02 (s, Ar), 8.14 (s, Ar). ^{13}C NMR (75 MHz) ($CDCl_3$) : δ 57.37 (OMe), 61.48 (OMe), 61.50 (OMe), 89.52 ($\underline{C}H{=}CH{-}CH{=}CH_2$), 95.77 (Ar), 97.18 (Ar), 98.22 ($CH{=}\underline{C}H{-}CH{=}CH_2$), 100.22 ($OCH_2O$), 101.31 ($CH{=}CH{-}\underline{C}H{=}CH_2$), 102.14 (Ar), 103.55 ($CH{=}CH{-}CH{=}\underline{C}H_2$), 120.32, 121.55, 128.69, 135.99, 137.33, 139.65, 148.94, 149.57, 149.82, 154.23 (Cq).

2-Ethenyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline (5) : To a solution of compound (**2**) (60 mg, 0.14 mmol) in EtOH (1 mL) was added a 2N aqueous solution of NaOH (0.15 mL). The reaction mixture was heated at reflux for 6 h, then water (1 mL) was added and the aqueous residue was extracted with CH_2Cl_2 (4x2 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and evaporated to yield a yellow oil which

recrystallized from a ligroin / AcOEt mixture leading to **5** (49 mg, 90%) as yellow crystals. mp 198°C (ligroin / AcOEt 50 : 50). IR υ_{max} (KBr) cm^{-1} : 2929, 1660, 1629, 1590, 1466. MS (CI) : *m/z* 384 $(MH)^+$. Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found : C, 65.89; H, 5.32; N, 3.42. ^1H NMR (300 MHz) ($CDCl_3$) : δ 2.67 (dd, *J* = 5, 16 Hz, H-3), 2.96 (dd, *J* = 6, 16 Hz, H-3), 3.70 (s, 2 OMe), 3.78 (s, OMe), 4.31 (m, H-2), 5.15 (m, CH=C$\underline{H}_2$), 5.83 (m, OCH_2O), 5.94 (m, C$\underline{H}$=CH_2), 6.04 (s, H-5 or H-8), 6.40 (s, H-2' and H-6'), 7.25 (s, H-5 or H-8).

Ethyl 2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline-3-carboxylate (10) and 1,4-dihydro-3-[2-(2-hydroxy)propyl]-6,7-methylenedioxy-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline (12) : The procedure was exactly the same as described for **2** using quinolone (**1**) (1 g, 2.35 mmol), CuI (984 mg, 5.17 mmol) and a 3.0 M solution of methylmagnesium bromide in THF (3x2.3 mL, 3x7.0 mmol). The crude product (1.10 g) was purified by columm chromatography (ligroin / AcOEt 80 : 20 to 30 : 70) to afford 560 mg (54%) of **10**, 280 mg (29%) of **12** and 50 mg (5%) of starting material **1**.

10 : mp 160°C (EtOH). IR υ_{max} (KBr) cm^{-1} : 2966, 2924, 1745, 1642, 1629,1593, 1507. MS (EI) : *m/z* 443 $(M)^+$. Anal. Calcd for $C_{23}H_{25}NO_8$: C, 62.30; H, 5.68; N, 3.16. Found : C, 62.19; H, 5.65; N, 2.98. **10** exists in two tautomeric forms ketone **10a** : enol **10b** (25 : 75) in $CDCl_3$ solution. ^1H NMR (300 MHz) ($CDCl_3$) for **10a** : δ 1.21 (t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 1.42 (d, *J* = 6 Hz, Me-2), 3.40 (d, *J* = 6 Hz, H-3), 3.87 (s, 2 OMe), 3.91 (s, OMe), 4.35 (m, $OC\underline{H}_2CH_3$), 4.78 (m, H-2), 5.96 (m, OCH_2O), 6.40 (s, H-5 or H-8), 6.48 (s, H-2' and H-6'), 7.36 (s, H-5 or H-8). ^1H NMR (300 MHz) ($CDCl_3$) for **10b** : δ 1.28 (t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 1.33 (d, *J* = 6 Hz, Me-2), 3.86 (s, 2 OMe), 3.88 (s, OMe), 4.22 (m, $OC\underline{H}_2CH_3$), 4.28 (d, *J* = 6 Hz, H-2), 5.92 (m, OCH_2O), 6.46 (s, H-2' and H-6'), 6.49 (s, H-5 or H-8), 7.29 (s, H-5 or H-8).

12 : mp 114°C. IR υ_{max} (KBr) cm^{-1} : 3517, 2996, 2972, 1633, 1600, 1464, 1503. MS (CI) : *m/z* 414 $(MH)^+$. Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.61; N, 3.39. Found : C, 63.98; H, 5.62; N, 3.22. ^1H NMR (300 MHz) ($CDCl_3$) : δ 1.56 (s, 2 Me), 1.97 (s, OH), 3.82 (s, 2 OMe), 3.88 (s, OMe), 5.96 (s, OCH_2O), 6.36 (s, H-5 or H-8), 6.50 (s, H-2' and H-6'), 7.45 (s, H-5 or H-8), 7.71 (s, H-2).

Ethyl 6,7-methylenedioxy-2-phenyl-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline-3-carboxylate (11) and 1,4-dihydro-6,7-methylenedioxy-3-diphenylhydroxymethyl-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline (13) : The procedure was exactly the same as described for **2** using quinolone **1** (1 g, 2.35 mmol), CuI (984 mg, 5.17 mmol) and a 2.0 M solution of phenylmagnesium bromide in THF (3x3.5 mL, 3x7.0 mmol). The crude product (1.15 g) was purified by columm chromatography (ligroin / AcOEt 90 : 10 to 40 : 60) to afford 850 mg (68%) of **13** as white solid, and 120 mg (10%) of **11** as yellow solid.

13 : mp 162-170°C (ether). IR υ_{max} (KBr) cm^{-1} : 3330, 3005, 2936, 2833, 1628, 1592, 1562, 1497. MS (CI) : *m/z* 538 $(MH)^+$. Anal. Calcd for $C_{32}H_{27}NO_7$: C, 71.50; H, 5.06; N, 2.61. Found : C, 71.13; H, 4.99; N, 2.60. ^1H NMR (300 MHz) ($CDCl_3$) : δ 3.76 (s, 2 OMe), 3.84 (s, OMe), 5.97 (s, OCH_2O), 6.39 (s, H-5 or H-8), 6.41 (s, H-2' and H-6'), 6.84 (s, H-5 or H-8), 7.18-7.35 (m, 2 Ar), 7.72 (s, H-2).

11 : mp 138°C (cyclohexane / ether). IR υ_{max} (KBr) cm^{-1} : 3005, 2925, 2892, 1720, 1610, 1592, 1502. MS (CI) : *m/z* 506 $(MH)^+$. Anal. Calcd for $C_{28}H_{27}NO_8$: C, 66.53; H, 5.38; N, 2.77. Found : C, 66.12; H, 5.22; N, 2.73. Only the enol form exists in $CDCl_3$ solution. ^1H NMR (300 MHz) ($CDCl_3$) : δ 1.20 (t, *J* = 7 Hz, $OCH_2C\underline{H}_3$), 3.61 (s, 2 OMe), 3.77 (s, OMe), 4.17 (q, *J* = 7 Hz, $OC\underline{H}_2CH_3$), 5.53 (s, H-2), 5.87 (m, OCH_2O), 6.17 (s, H-5 or H-8), 6.80 (s, H-2' and H-6'), 7.12 (s, H-5 or H-8), 7.20-7.35 (m, Ar).

2-Methyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline (14) : The compound (**14**) was prepared from **10** (50 mg, 0.11 mmol) by using the procedure described for the conversion of **2** into **4**. The crude product was recrystallized from EtOH to yield 30 mg (73%) of **14**. mp 124°C (EtOH). IR υ_{max} (KBr) cm^{-1} : 2972, 2938, 2842, 1658, 1629, 1594, 1503. MS (CI) : *m/z* 372 $(MH)^+$. Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found : C, 64.28; H, 5.68; N, 3.71. ^1H NMR (300 MHz) ($CDCl_3$) : δ 1.15 (d, *J* = 6.5 Hz, Me), 2.53 (dd, *J* = 8.5, 16 Hz, H-3), 2.85 (dd, *J* = 4.6, 16 Hz, H-3), 3.78 (s, 2 OMe), 3.83 (s, OMe), 3.90 (m, H-2), 5.86 (s, OCH_2O), 5.90 (s, H-5 or H-8), 6.40 (s, H-2' and H-6'), 7.27 (s, H-5 or H-8).

1,4-Dihydro-6,7-methylenedioxy-2-phenyl-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline (15) : The compound (**15**) was prepared from **11** (20 mg, 0.04 mmol) by using the procedure described for the conversion of **2** into **4**. The crude product was purified by columm chromatography (ligroin / AcOEt 80 : 20) to yield 10 mg (59%) of **15** as colorless oil. IR υ_{max} (KBr) cm^{-1} : 3221, 3015, 2950, 2898, 1610, 1598, 1550. MS (CI) : *m/z* 432 $(MH)^+$. Anal. Calcd for $C_{25}H_{21}NO_6$: C, 69.60; H, 4.91; N, 3.25. Found : C, 69.22; H, 4.84; N, 3.22. ^1H NMR (300 MHz) ($CDCl_3$) : δ 3.64 (s, 2 OMe), 3.76 (s, OMe), 5.26 (s, H-3), 6.00 (s, OCH_2O), 6.28 (s, H-2' and H-6'), 6.31 (s, H-5 or H-8), 6.40 (s, H-5 or H-8), 7.10 (m, Ar).

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