

## SYNTHESIS AND BEHAVIOUR OF FURO[2,3,4-*k,l*]ACRIDINES AND FURO[2,3,4-*k,l*]PYRANO[3,2-*h*]ACRIDINES

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**Abstract** - From noracronycine and 1-hydroxy-3-methoxy-10-methylacridone, a [2,3,4-*k,l*] fused furan ring bearing an ethoxycarbonyl group was built up. Amidification of this ester function with *N,N*-dimethylaminoalkylamines allowed us to prepare watersoluble furo[2,3,4-*k,l*]pyrano[3,2-*h*]acridine and furo[2,3,4-*k,l*]acridine derivatives. In the course of attempts to saponify the ester function under aqueous sodium hydroxide basic conditions and to reduce it upon aluminium hydride, an abnormal ring opening reaction of the ethoxycarbonylated furan was ascertained.

For several years, acronycine (1) or noracronycine derivatives such as *O*-dimethylaminoethylnoracronycine (2) have elicited interest for their cytotoxic and antitumor properties.<sup>1</sup> Recently, several analogues bearing a fused heterocycle on the acridine nucleus have been synthesized<sup>2-8</sup> which display various biological properties. So, diazepino[7,6,5-*k,l*]acridones (3),<sup>2-3</sup> diazepino[7,6,5-*k,l*]imidazo[1,5,4-*f,g*]acridones (4)<sup>2</sup> are potential reverse transcriptase inhibitors,<sup>4</sup> and imidazo[4,5,1-*c,d*]acridones (5)<sup>5</sup> shows a significant *in vivo* activity in the P388 murin model.<sup>6</sup> The triazolo[4,5,1-*k,l*]acridines (6)<sup>7</sup> and pyrazolo[5,4,3-*k,l*]acridines (7),<sup>8</sup> the two most studied series, have been shown to intercalate into DNA for compounds (7) and the two series displayed important antitumor activities (Figure 1).

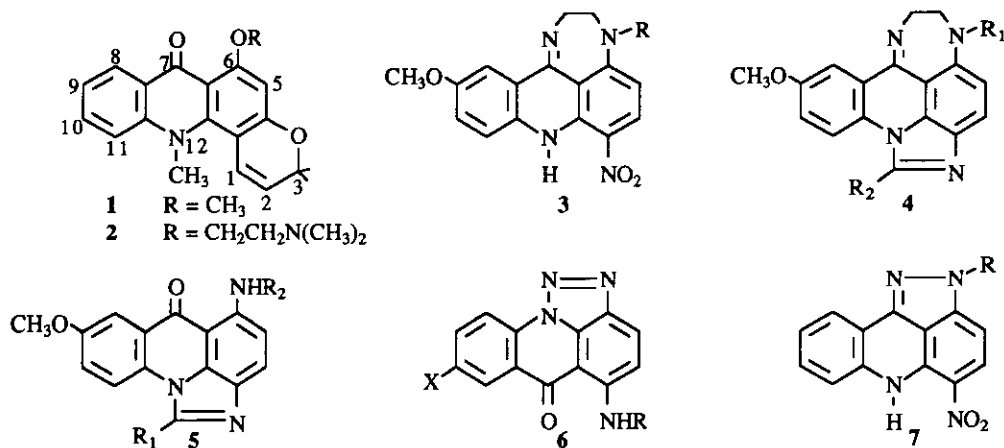


Figure 1

In the course of our search of new watersoluble acronycine derivatives and analogues<sup>9-10</sup> and taking into account these various results, we designed furo[2,3,4-*k,l*]acridines (**8**) and furo[2,3,4-*k,l*]pyrano[3,2-*h*]acridines (**9**) which correspond to the acridine and the pyrano[2,3-*c*]acridine skeletons with a [2,3,4-*k,l*] fused furan ring as new target molecules (Figure 2).

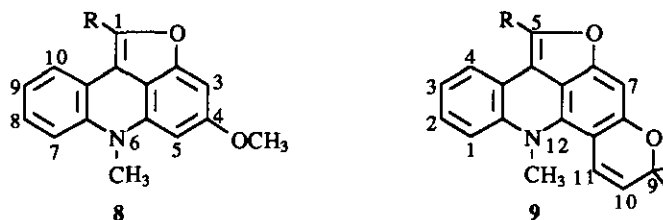
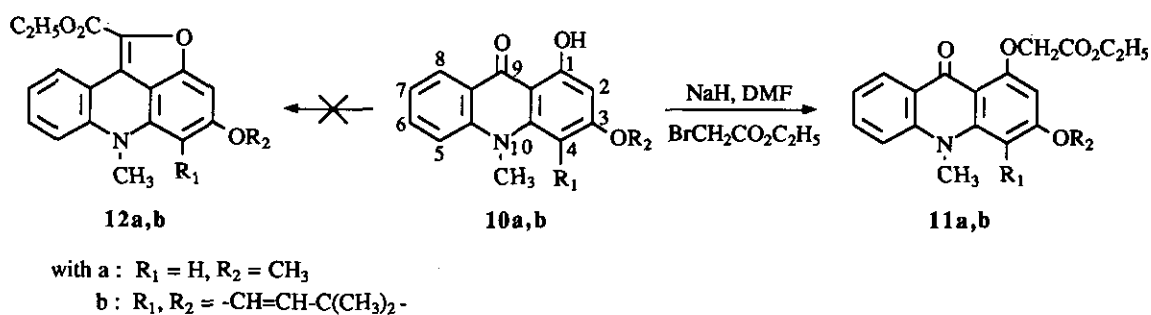


Figure 2

## RESULTS AND DISCUSSION

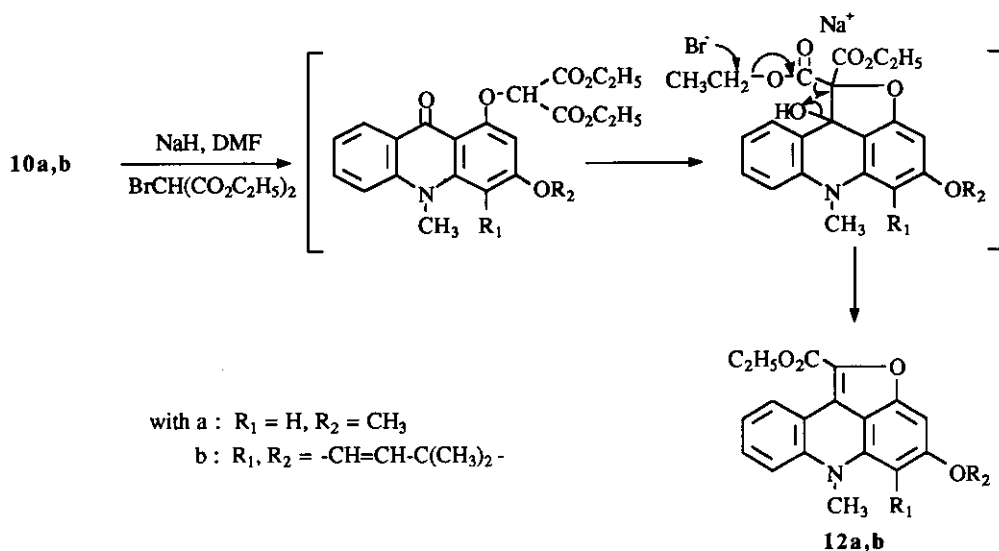
From *o*-hydroxy-aryl aldehydes and ketones, a common route to introduce a 2-carbomethoxylated furan ring was to use the condensation reaction with ethyl bromoacetate or chloroacetate.<sup>11</sup> For example, condensation of 5-chloro-2-hydroxybenzophenone with ethyl bromoacetate in the presence of sodium hydride led to 2-ethoxycarbonyl-3-phenyl-5-chlorobenzofuran in 23 % yield.<sup>12</sup>

However, our attempts to apply the same reaction to hydroxyacridone (**10a**) or to noracronycine (**10b**) in DMF with ethyl bromoacetate only led to corresponding aryloxyacetates (**11a**) and (**11b**), 80% and 66% yields, respectively and no traces of the expected ethoxycarbonylfuro[2,3,4-*k,l*]acridines (**12a-b**) (Scheme 1). Compound (**11b**) was previously obtained by such a reaction<sup>1</sup> but using THF as solvent and in 30% yield.



Scheme 1

In order to obtain the target furo[2,3,4-*k,l*]acridine (**12**), we then replaced ethyl bromoacetate by the far 2*H*-more acidic diethyl bromomalonate. This new reagent provided the desired compounds : ethyl (4-methoxy-6-methyl-6*H*-furo[2,3,4-*k,l*]acridin-1-yl)carboxylate (**12a**) and ethyl (9,9,12-trimethyl-9,12-dihydrofuro[2,3,4-*k,l*]pyrano[3,2-*h*]acridin-5-yl)carboxylate (**12b**) in 17% and 18% yields respectively, beside the unreacted starting compounds (29-59%) and without characterization of other possible intermediates (Scheme 2).

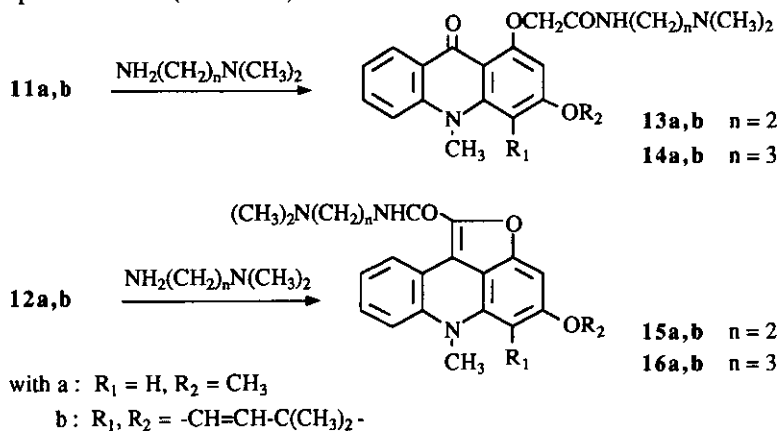


Scheme 2

Probably, the reaction at first proceeds through alkylation of the phenol to produce aryloxymalonate derivative whose condensation on the carbonyl function led to the intermediate. A deethoxycarbonylation followed by dehydration then occurred to yield **12a** and **12b**. Such a reaction proceeding by a nucleophilic bromine anion attack of the ethoxy group which triggered the decarboxylation followed by a concerted elimination has already been described by Krapcho.<sup>13</sup> Our results are fully consistent with these reported observations (Scheme 2).

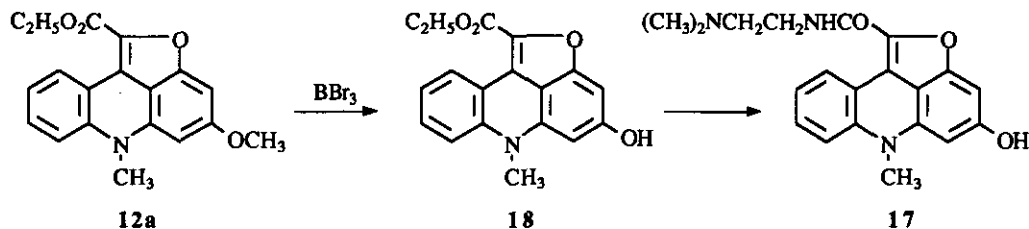
Since so far the most active acronycine derivative is the *O*-dimethylaminoethylnoracronycine (**2**),<sup>1</sup> we then prepared the related aryloxyacetamide compounds (**13a-b**) and (**14a-b**) from the corresponding aryloxyacetate derivatives (**11a-b**) by reaction with *N,N*-dimethylethylenediamine and 3-dimethylamino-propylamine respectively.

The carboxamido derivatives (**15a-b**) and (**16a-b**) were also prepared from esters (**12a,b**) by treatment with the boiling required amines (Scheme 3).



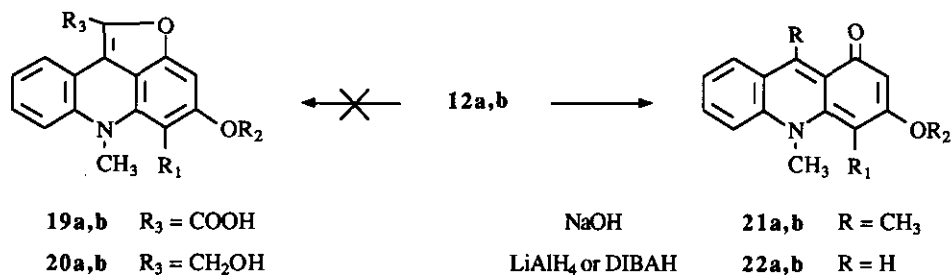
Scheme 3

To obtain the carboxamido derivative (**17**) with the *N,N*-dimethylethylenediamine chain and bearing an hydroxyl group at the 4 position, the 4-methoxy group of **12a** was cleaved with boron tribromide to yield **18**. The aminated chain was then introduced by reaction of **18** with the corresponding amine at 80°C (Scheme 4).



Scheme 4

To obtain other watersoluble acronycine derivatives without aminated chain, we then tried to obtain acids (**19a-b**) and alcohols (**20a-b**) from **12a-b**. Surprisingly, reaction of **12a-b** with sodium hydroxide in aqueous ethanol provided low yields (18-21%) of compounds (**21a-b**), bearing a quinonemethide system instead of the expected carboxylated derivatives (**19a-b**). In the same way, reaction of **12a-b** with lithium aluminium hydride or DIBAH gave no alcohols (**20a-b**) but compounds (**22a-b**) bearing the unsubstituted quinonemethide system in 20-21% yield (Scheme 5).



Scheme 5

It must be pointed out that the elucidation of these phenomena was established by comparison of the resulting compounds with those recently described.<sup>9</sup> Indeed, compounds (**21b**) and (**22b**) were unambiguously obtained by treatment of noracronycine (**10b**) with methyl lithium and lithium aluminium hydride, respectively.

To the best of our knowledge, such an ethoxycarbonylfuran ring opening and degradation(s) are unprecedented. The reaction proceeds with quite a lot of bond hydrolysis or "hydrogenolysis" and subsequent transformations. They could be specific to the furo[2,3,4-*k,l*]acridine and furo[2,3,4-*k,l*]pyrano[3,2-*h*]acridine ring systems behaviour and we do not find a convenient and satisfactory explanation to these fully established findings.

Several compounds were tested *in vitro* against L1210 murine lymphocytic leukemia cells. Cytostatic activities are shown in Table 1. Generally, a moderate cytotoxicity against L1210 murine lymphocytic leukemia cells was observed.

Products	1	10b	11a	12a	13a	13b	14a	14b	15a	15b	16a	16b	17
IC50 ( $\mu$ M)	22	60	10	9	2.5	6	6	13	7	5.5	11	8	2.5

Table 1 : *In vitro* activities against L1210 murine lymphocytic leukemia cells

In conclusion, this work allowed us to built up [2,3,4-*k,l*] fused ethoxycarbonylated furo ring to acridine and pyrano[2,3-*c*]acridine heterocycles. This was achieved by the use of diethyl bromomalonate and the study of the resulting compounds illustrated the particular and unexpected behaviour of the furo[2,3,4-*k,l*]acridine and furo[2,3,4-*k,l*]pyrano[3,2-*h*]acridine ring systems toward aqueous sodium hydroxide hydrolysis and aluminium hydride reduction. On the biological point of view, the additional fused furo ring seems to weakly increase the pyrano[2,3-*c*]acridine cytostatic activity but has no effect on the acridine derivative properties. Furthermore, the observed cytostatic activities of 2-dimethylaminoethylcarboxamides were generally more significant than those of their 3-dimethylaminopropyl related compounds.

## EXPERIMENTAL

Melting points were measured with Electrothermal apparatus using capillary tubes and are uncorrected.  $^1\text{H}$  Nmr spectra were obtained in  $\text{CDCl}_3$  or  $\text{DMSO-d}_6$  using an AC-200 MHz Bruker spectrometer. Chemical shifts are reported in ppm relative to deuteriated solvent as internal standard and all coupling constants ( $J$ ) are given in Hz. The mass spectra were recorded on AEI.MS-50 (MS-EI) spectrometer and, as elemental analyses, they were performed in ICSN/CNRS, Gif sur Yvette, France.

### 1-Hydroxy-3-methoxy-10-methylacridone (10a)

This compound was prepared according to our described procedure<sup>9</sup> and recrystallized from ethyl acetate as yellow needles, mp 164-165°C (lit.,<sup>9</sup> 164-165°C).

### Noracronycine (10b)

This compound was prepared according to a described procedure<sup>14</sup> and recrystallized from ethyl acetate as yellow needles, mp 201-203°C (lit.,<sup>14</sup> 200-201°C).

### Procedure for preparation of ethyl (3-methoxy-10-methyl-9-oxo-9,10-dihydro-acridin-1-yl)oxyacetate (11a) and ethyl (3,3,12-trimethyl-7-oxo-7,12-dihydro-3H-pyrano[2,3-*c*]acridin-1-yl)oxyacetate (11b)

Under nitrogen, to a solution containing 10a or 10b (1 mmol) in dry DMF (10 ml), sodium hydride (60% in oil, 44 mg, 1.1 mmol) was added. The mixture was stirred at room temperature for 1 h and ethyl bromoacetate (0.12 ml, 1.08 mmol) was added. Another equivalent of each reagent was added from times to times until there was no more evolution (tlc monitoring). The mixture was poured onto a saturated aqueous ammonium chloride solution and extracted with methylene chloride. The organic layer was then dried ( $\text{MgSO}_4$ ) and concentrated. The crude product was purified on a silica gel column with methylene chloride-ethanol (95:5) as eluent.

**Ethyl (3-methoxy-10-methyl-9-oxo-9,10-dihydro-acridin-1-yl)oxyacetate (11a)**

Product (11a) was obtained in 80% yield as yellow needles;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  8.44 (dd, 1H,  $J=8$ , 1.5 Hz, H-8), 7.59 (td, 1H,  $J=8$ , 1.5 Hz, H-6), 7.35 (dd, 1H,  $J=8$ , 1.5 Hz, H-5), 7.20 (td, 1H,  $J=8$ , 1.5 Hz, H-7), 6.45 (d, 1H,  $J=2$  Hz, H-4), 6.32 (d, 1H,  $J=2$  Hz, H-2), 4.71 (s, 2H,  $\text{OCH}_2$ ), 4.23 (q, 2H,  $J=7.2$  Hz,  $\text{CH}_2$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 3.73 (s, 3H,  $\text{NCH}_3$ ), 1.26 (t, 3H,  $J=7.2$  Hz,  $\text{CH}_3$ ).

**Ethyl (3,3,12-trimethyl-7-oxo-7,12-dihydro-3H-pyrano[2,3-c]acridin-1-yl)oxyacetate (11b)**

Product (11b) was obtained (66%) as yellow needles, mp 97-97.5°C (lit.,<sup>1</sup> 98-100°C).

**Procedure for preparation of ethyl (4-methoxy-6-methyl-6H-furo[2,3,4-k,l]acridin-1-yl)carboxylate (12a) and ethyl (9,9,12-trimethyl-9,12-dihydrofuro[2,3,4-k,l]pyrano[3,2-h]acridin-5-yl)carboxylate (12b)**

Under nitrogen, to a solution containing 10a or 10b (1 mmol) in dry DMF (15 ml), sodium hydride (60% in oil, 46 mg, 1.15 mmol) was added. After stirring at 100°C for 2 h, ethyl bromomalonate (215  $\mu\text{l}$ , 1.26 mmol) was added. The mixture was stirred at 100°C until there was no more evolution (tlc monitoring). The mixture was then cooled, poured onto a saturated aqueous ammonium chloride solution (60 ml) and extracted with methylene chloride. The organic layer was then dried ( $\text{MgSO}_4$ ) and concentrated. The crude product was purified on a silica gel column.

**Ethyl (4-methoxy-6-methyl-6H-furo[2,3,4-k,l]acridin-1-yl)carboxylate (12a)**

Eluent used for chromatography was a methylene chloride-ethanol (98:2) mixture. Recrystallization from ethyl acetate gave the expected product (12a) (17 %) as yellow crystals, mp 214-215°C beside the unreacted acridone (10a) (29 %);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  7.81 (dd, 1H,  $J=8.3$ , 1.2 Hz, H-10), 7.59 (td, 1H,  $J=8.3$ , 1.2 Hz, H-8), 7.33 (dd, 1H,  $J=8.3$ , 1.2 Hz, H-7), 7.12 (td, 1H,  $J=8.3$ , 1.2 Hz, H-9), 6.54 (d, 1H,  $J=2.2$  Hz, H-5), 6.44 (d, 1H,  $J=2.2$  Hz, H-3), 4.42 (q, 2H,  $J=7.1$  Hz,  $\text{OCH}_2$ ), 3.89 (s, 3H,  $\text{OCH}_3$ ), 3.66 (s, 3H,  $\text{NCH}_3$ ), 1.34 (t, 3H,  $J=7.1$  Hz,  $\text{CH}_3$ ); Anal. Calcd for  $\text{C}_{19}\text{H}_{17}\text{NO}_4 \cdot 0.5 \text{H}_2\text{O}$ : C, 68.66; H, 5.46; N, 4.21. Found: C, 68.48; H, 5.18; N, 3.97.

**Ethyl (9,9,12-trimethyl-9,12-dihydrofuro[2,3,4-k,l]pyrano[3,2-h]acridin-5-yl)carboxylate (12b)**

Eluent used for chromatography was heptane-ethyl acetate (1:1). After precipitation from heptane, the expected product (12b) (18 %) was obtained as yellow crystals, mp 245-246°C beside the unreacted noracronycine (10b) (59 %);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  7.76 (dd, 1H,  $J=8.2$ , 1.4 Hz, H-4), 7.61 (td, 1H,  $J=8.2$ , 1.4 Hz, H-2), 7.33 (dd, 1H,  $J=8.2$ , 1.4 Hz, H-1), 7.15 (td, 1H,  $J=8.2$ , 1.4 Hz, H-3), 6.55 (s, 1H, H-7), 6.52 (d, 1H,  $J=9.7$  Hz, H-11), 5.61 (d, 1H,  $J=9.7$  Hz, H-10), 4.41 (q, 2H,  $J=7.2$  Hz,  $\text{OCH}_2$ ), 3.80 (s, 3H,  $\text{NCH}_3$ ), 1.52 (s, 6H, 9-Me<sub>2</sub>), 1.32 (t, 3H,  $J=7.2$  Hz,  $\text{CH}_3$ ); Anal. Calcd for  $\text{C}_{23}\text{H}_{21}\text{NO}_4$ : C, 73.59; H, 5.64; N, 3.73. Found: C, 73.83; H, 5.67; N, 3.72.

**N-(2-Dimethylaminoethyl)-3,3,12-trimethyl-7-oxo-7,12-dihydro-3H-pyrano[2,3-c]-acridine-1-oxyacetamide (13b)**

A solution containing the aryloxyacetate (11b) (50 mg, 0.13 mmol) in *N,N*-dimethylethylenediamine (1.5 ml, 13.7 mmol) was stirred at 50°C for 1 h. After being cooled, the solid was filtered, washed with pentane to obtain compound (13b) (42 mg, 76 %) as yellow crystals, mp 220-221°C;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )

$\delta$  9.80 (m, 1H, NH), 8.37 (dd, 1H,  $J=8, 1.5$  Hz, H-8), 7.67 (td, 1H,  $J=8, 1.5$  Hz, H-10), 7.39 (dd, 1H,  $J=8, 1.5$  Hz, H-11), 7.29 (td, 1H,  $J=8, 1.5$  Hz, H-9), 6.52 (d, 1H,  $J=9.7$  Hz, H-1), 6.19 (s, 1H, H-5), 5.52 (d, 1H,  $J=9.7$  Hz, H-2), 4.59 (s, 2H, OCH<sub>2</sub>), 3.85 (s, 3H, NCH<sub>3</sub>), 3.77 (m, 2H,  $\alpha$ -CH<sub>2</sub>), 3.04 (m, 2H,  $\beta$ -CH<sub>2</sub>), 2.65 (s, 6H, NMe<sub>2</sub>), 1.59 (s, 6H, 3-Me<sub>2</sub>); Anal. Calcd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub> : C, 68.95; H, 6.71; N, 9.65. Found : C, 68.96; H, 6.65; N, 9.58.

***N*-(2-Dimethylaminopropyl)-3,3,12-trimethyl-7-oxo-7,12-dihydro-3*H*-pyrano[2,3-*c*]-acridine-1-oxyacetamide (14b)**

A solution containing the aryloxyacetate (11b) (54 mg, 0.14 mmol) in 3-dimethylaminopropylamine (1.5 ml, 11.9 mmol) was stirred at 50°C for 1.5 h. The amine was then evaporated, ice-water was added and the mixture was extracted with methylene chloride. The organic layer was then dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was then washed with ether to give compound (14b) (46 mg, 74 %) as yellow crystals, mp 151-152°C; <sup>1</sup>H nmr (CDCl<sub>3</sub>)  $\delta$  9.58 (t, 1H,  $J=6.1$  Hz, NH), 8.32 (dd, 1H,  $J=8.1, 1.4$  Hz, H-8), 7.68 (td, 1H,  $J=8.1, 1.4$  Hz, H-10), 7.40 (dd, 1H,  $J=8.1, 1.4$  Hz, H-11), 7.29 (td, 1H,  $J=8.1, 1.4$  Hz, H-9), 6.52 (d, 1H,  $J=9.6$  Hz, H-1), 6.20 (s, 1H, H-5), 5.52 (d, 1H,  $J=9.6$  Hz, H-2), 4.57 (s, 2H, OCH<sub>2</sub>), 3.86 (s, 3H, NCH<sub>3</sub>), 3.54 (q, 2H,  $J=6.1$  Hz,  $\alpha$ -CH<sub>2</sub>), 3.11 (t, 2H,  $J=6.1$  Hz,  $\gamma$ -CH<sub>2</sub>), 2.69 (s, 6H, NMe<sub>2</sub>), 2.20 (m, 2H,  $\beta$ -CH<sub>2</sub>), 1.59 (s, 6H, 3-Me<sub>2</sub>); Anal. Calcd for C<sub>26</sub>H<sub>31</sub>N<sub>3</sub>O<sub>4</sub>·0.25 H<sub>2</sub>O : C, 68.78; H, 6.99; N, 9.25. Found : C, 68.81; H, 6.87; N, 9.15.

**General procedure for preparation of oxyacetamides (13a-14a) and carboxamides (15a-b) and (16a-b)**

A solution containing the aryloxyacetate (11a) or furoacridines (12a or 12b) (1 mmol) in *N,N*-dimethylethylene diamine or 3-dimethylaminopropylamine (5 ml) was stirred at 50-80°C until the reaction was complete (tlc monitoring). The amine was then evaporated, ice-water was added and the mixture was extracted with methylene chloride. The organic layer was then dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified on neutral alumina column with methylene chloride-ethanol (98:2) as eluent.

***N*-(2-Dimethylaminoethyl)-3-methoxy-10-methyl-9-oxo-9,10-dihydroacridine-1-oxyacetamide (13a)**

After recrystallization from ethanol, the product (13a) was obtained (66 %) as yellow crystals, mp 199°C; <sup>1</sup>H nmr (CDCl<sub>3</sub>)  $\delta$  10.07 (m, 1H, NH), 8.47 (dd, 1H,  $J=8, 1.6$  Hz, H-8), 7.68 (td, 1H,  $J=8, 1.6$  Hz, H-6), 7.45 (dd, 1H,  $J=8, 1.6$  Hz, H-5), 7.29 (td, 1H,  $J=8, 1.6$  Hz, H-7), 6.47 (d, 1H,  $J=2.1$  Hz, H-4), 6.20 (d, 1H,  $J=2.1$  Hz, H-2), 4.65 (s, 2H, OCH<sub>2</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 3.82 (s, 3H, NCH<sub>3</sub>), 3.81 (m, 2H,  $\alpha$ -CH<sub>2</sub>), 3.19 (m, 2H,  $\beta$ -CH<sub>2</sub>), 2.76 (s, 6H, NMe<sub>2</sub>); Anal. Calcd for C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>·0.25 H<sub>2</sub>O : C, 65.02; H, 6.63; N, 10.83. Found : C, 65.27; H, 6.51; N, 10.76.

***N*-(3-Dimethylaminopropyl)-3-methoxy-10-methyl-9-oxo-9,10-dihydroacridine-1-oxyacetamide (14a)**

After recrystallization from ethanol, the product (14a) was obtained (58 %) as yellow crystals, mp 146-147°C; <sup>1</sup>H nmr (CDCl<sub>3</sub>)  $\delta$  9.63 (t, 1H,  $J=6.2$  Hz, NH), 8.43 (dd, 1H,  $J=8, 1.4$  Hz, H-8), 7.68 (td, 1H,  $J=8, 1.4$  Hz, H-6), 7.46 (dd, 1H,  $J=8, 1.4$  Hz, H-5), 7.28 (td, 1H,  $J=8, 1.4$  Hz, H-7), 6.47 (d, 1H,  $J=2$  Hz, H-4), 6.21 (d, 1H,  $J=2$  Hz, H-2), 4.61 (s, 2H, OCH<sub>2</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 3.82 (s, 3H, NCH<sub>3</sub>),

3.54 (q, 2H,  $J=6.2$  Hz,  $\alpha$ -CH<sub>2</sub>), 2.97 (t, 2H,  $J=6.2$  Hz,  $\gamma$ -CH<sub>2</sub>), 2.60 (s, 6H, NMe<sub>2</sub>), 2.15 (qn, 2H,  $J=6.2$  Hz,  $\beta$ -CH<sub>2</sub>); Anal. Calcd for C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>·0.33 H<sub>2</sub>O : C, 65.50; H, 6.91; N, 10.42. Found : C, 65.74; H, 6.83; N, 10.22.

***N*-(2-Dimethylaminoethyl)-4-methoxy-6-methyl-6*H*-furo[2,3,4-*k,l*]acridine-1-carboxamide (15a)**

After recrystallization from acetonitrile, the product (15a) was obtained (49 %) as orange crystals, mp 174-176°C; <sup>1</sup>H nmr (CDCl<sub>3</sub>)  $\delta$  15.75 (br s, 1H, NH), 8.14 (dd, 1H,  $J=8.4, 1.2$  Hz, H-10), 7.60 (td, 1H,  $J=8.4, 1.2$  Hz, H-8), 7.35 (dd, 1H,  $J=8.4, 1.2$  Hz, H-7), 7.12 (td, 1H,  $J=8.4, 1.2$  Hz, H-9), 6.10 (d, 1H,  $J=2.3$  Hz, H-5), 5.78 (d, 1H,  $J=2.3$  Hz, H-3), 4.01 (q, 2H,  $J=6.7$  Hz,  $\alpha$ -CH<sub>2</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 3.64 (s, 3H, NCH<sub>3</sub>), 2.74 (t, 2H,  $J=6.7$  Hz,  $\beta$ -CH<sub>2</sub>), 2.33 (s, 6H, NMe<sub>2</sub>); Anal. Calcd for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>·0.25 CH<sub>3</sub>CN : C, 68.74; H, 6.37; N, 12.12. Found : C, 69.24; H, 6.52; N, 12.61.

***N*-(2-Dimethylaminoethyl)-9,9,12-trimethyl-9,12-dihydrofuro[2,3,4-*k,l*]pyrano[3,2-*h*]acridine-1-carboxamide (15b)**

After being washed with pentane, the product (15b) was obtained (61 %) as an orange solid, mp 85-91°C; <sup>1</sup>H nmr (CDCl<sub>3</sub>)  $\delta$  8.06 (dd, 1H,  $J=8.3, 1.3$  Hz, H-4), 7.62 (td, 1H,  $J=8.3, 1.3$  Hz, H-2), 7.37 (dd, 1H,  $J=8.3, 1.3$  Hz, H-1), 7.16 (td, 1H,  $J=8.3, 1.3$  Hz, H-3), 6.42 (d, 1H,  $J=9.7$  Hz, H-11), 6.10 (s, 1H, H-7), 5.39 (d, 1H,  $J=9.7$  Hz, H-10), 4.00 (q, 2H,  $J=6.7$  Hz,  $\alpha$ -CH<sub>2</sub>), 3.78 (s, 3H, NCH<sub>3</sub>), 2.71 (t, 2H,  $J=6.7$  Hz,  $\beta$ -CH<sub>2</sub>), 2.32 (s, 6H, NMe<sub>2</sub>), 1.47 (s, 6H, 9-Me<sub>2</sub>); Anal. Calcd for C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>·2 H<sub>2</sub>O : C, 66.21; H, 6.89; N, 9.27. Found : C, 66.28; H, 6.82; N, 8.95.

***N*-(3-Dimethylaminopropyl)-4-methoxy-6-methyl-6*H*-furo[2,3,4-*k,l*]acridine-1-carboxamide (16a)**

After being washed with pentane, the product (16a) was obtained (50 %) as an orange solid, mp 189-197°C; <sup>1</sup>H nmr (CDCl<sub>3</sub>)  $\delta$  8.15 (dd, 1H,  $J=8, 1.1$  Hz, H-10), 7.60 (td, 1H,  $J=8, 1.1$  Hz, H-8), 7.35 (dd, 1H,  $J=8, 1.1$  Hz, H-7), 7.12 (td, 1H,  $J=8, 1.1$  Hz, H-9), 6.12 (d, 1H,  $J=2.2$  Hz, H-5), 5.80 (d, 1H,  $J=2.2$  Hz, H-3), 3.95 (m, 2H,  $\alpha$ -CH<sub>2</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 3.64 (s, 3H, NCH<sub>3</sub>), 2.48 (t, 2H,  $J=7$  Hz,  $\gamma$ -CH<sub>2</sub>), 2.23 (s, 6H, NMe<sub>2</sub>), 2.00 (qn, 2H,  $J=7$  Hz,  $\beta$ -CH<sub>2</sub>); Anal. Calcd for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub>·4 H<sub>2</sub>O : C, 58.52; H, 7.37; N, 9.31. Found : C, 58.81; H, 7.10; N, 9.16.

***N*-(3-Dimethylaminopropyl)-9,9,12-trimethyl-9,12-dihydrofuro[2,3,4-*k,l*]pyrano[3,2-*h*]acridine-1-carboxamide (16b)**

After being washed with pentane, the product (16b) was obtained (71 %) as an orange solid, mp 106-117°C; <sup>1</sup>H nmr (CDCl<sub>3</sub>)  $\delta$  8.08 (dd, 1H,  $J=8.3, 1.3$  Hz, H-4), 7.62 (td, 1H,  $J=8.3, 1.3$  Hz, H-2), 7.37 (dd, 1H,  $J=8.3, 1.3$  Hz, H-1), 7.17 (td, 1H,  $J=8.3, 1.3$  Hz, H-3), 6.41 (d, 1H,  $J=9.6$  Hz, H-11), 6.10 (s, 1H, H-7), 5.39 (d, 1H,  $J=9.6$  Hz, H-10), 3.95 (q, 2H,  $J=6.9$  Hz,  $\alpha$ -CH<sub>2</sub>), 3.79 (s, 3H, NCH<sub>3</sub>), 2.48 (t, 2H,  $J=6.9$  Hz,  $\gamma$ -CH<sub>2</sub>), 2.23 (s, 6H, NMe<sub>2</sub>), 1.99 (qn, 2H,  $J=6.9$  Hz,  $\beta$ -CH<sub>2</sub>), 1.47 (s, 6H, 9-Me<sub>2</sub>); Anal. Calcd for C<sub>26</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>·0.5 C<sub>5</sub>H<sub>12</sub> : C, 73.20; H, 7.54; N, 8.99. Found : C, 72.95; H, 7.23; N, 8.82.



***N*-(2-Dimethylaminoethyl)-4-hydroxy-6-methyl-6*H*-furo[2,3,4-*k,l*]acridine-1-carboxamide (17)**

A solution containing furoacridine (18) (50 mg, 0.16 mmol) in *N,N*-dimethylethylenediamine (2 ml, 18.2 mmol) was stirred at 80°C for 19 h. The amine was then evaporated, ice-water was added and extracted with methylene chloride. The organic layer was washed with water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified on a silica gel column with initially methylene chloride-ethanol (95:5) and finally methylene chloride-ethanol (85:15) as eluent. The expected product (17) (10 mg, 18 %) was obtained as an orange solid, mp 159-161°C; <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ 14.89 (br s, 1H, NH), 13.17 (s, 1H, OH), 8.09 (dd, 1H, J=8.3, 1.1 Hz, H-10), 7.57 (td, 1H, J=8.3, 1.1 Hz, H-8), 7.33 (dd, 1H, J=8.3, 1.1 Hz, H-7), 7.08 (td, 1H, J=8.3, 1.1 Hz, H-9), 6.04 (m, 2H, H-5 and H-3), 3.98 (q, 2H, J=6.7 Hz, α-CH<sub>2</sub>), 3.63 (s, 3H, NCH<sub>3</sub>), 2.76 (t, 2H, J=6.7 Hz, β-CH<sub>2</sub>), 2.37 (s, 6H, NMe<sub>2</sub>); Anal. Calcd for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>·2 H<sub>2</sub>O : C, 68.36; H, 6.02; N, 11.96; O, 13.66. Found : C, 68.00; H, 5.93; N, 12.44; O, 13.63.

**Ethyl (4-hydroxy-6-methyl-6*H*-furo[2,3,4-*k,l*]acridin-1-yl)carboxylate (18)**

To a solution of 12a (150 mg, 0.46 mmol) in dry methylene chloride (18 ml), cooled at -20°C, boron tribromide (1M in methylene chloride; 4.6 ml, 4.6 mmol) was added dropwise. After being stirred at room temperature for 48 h, the mixture was poured onto ice-water (200 ml) and basified with 28% ammonia. Ethanol (10 ml) was added, the solution was stirred for 14 h and after evaporation of ethanol, the precipitate was filtered. It was purified on an alumina column with initially methylene chloride-ethanol (95:5) and finally methylene chloride-ethanol-triethylamine (68:28:5) to obtain compound (18) (69 mg, 48 %) as brown crystals, beside the unreacted substrate (12a) (40 mg, 27 %); <sup>1</sup>H nmr (DMSO) δ 10.87 (br s, 1H, OH), 7.74 (m, 3H, H-10, H-8 and H-7), 7.30 (td, 1H, J=8.1, 1 Hz, H-9), 6.67 (d, 1H, J=1.5 Hz, H-5), 6.52 (d, 1H, J=1.5 Hz, H-3), 4.35 (q, 2H, J=7 Hz, CH<sub>2</sub>), 3.74 (s, 3H, NCH<sub>3</sub>), 1.28 (t, 3H, J=7 Hz, CH<sub>3</sub>).

**3-Methoxy-9,10-dimethyl-1,10-dihydro-acridin-1-one (21a)**

A solution containing the furoacridine (12a) (50 mg, 0.15 mmol) in ethanol (2 ml) and 1M aqueous sodium hydroxide (2 ml) was stirred at 65°C for 4 h. Ethanol was evaporated and the aqueous layer was extracted with methylene chloride. The organic layer was washed with water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified on a silica gel column with methylene chloride-ethanol (95:5) to obtain, after recrystallization from acetonitrile, the product (21a) (8 mg, 21 %) as a blue solid, mp 124-132°C; <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ 8.11 (dd, 1H, J=8.3, 1.3 Hz, H-8), 7.63 (td, 1H, J=8.3, 1.3 Hz, H-6), 7.43 (dd, 1H, J=8.3, 1.3 Hz, H-5), 7.26 (td, 1H, J=8.3, 1.3 Hz, H-7), 6.01 (d, 1H, J=2.1 Hz, H-4), 5.62 (d, 1H, J=2.1 Hz, H-2), 3.81 (s, 3H, OCH<sub>3</sub>), 3.72 (s, 3H, NCH<sub>3</sub>), 3.23 (s, 3H, 9-CH<sub>3</sub>); EIms (m/z) : 253 (M<sup>+</sup>, 100%).

**3,3,7,12-Tetramethyl-6,12-dihydro-3*H*-pyrano[2,3-*c*]acridin-6-one<sup>9</sup> (21b)**

A solution containing the furoacridine (12b) (100 mg, 0.27 mmol) in ethanol (4 ml) and 1M aqueous sodium hydroxide (4 ml) was stirred at 65°C for 1 h. Ethanol was evaporated and, after neutralization by acetic acid, the aqueous layer was extracted with methylene chloride. The organic layer was then washed with water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified on a

silica gel column with methylene chloride-ethanol (98:2) to obtain the product (**21b**) (15 mg, 18 %) as a blue solid, mp 134-143°C; This spectrum is in all respects identical to that of the same compound prepared by a specific reaction.<sup>9</sup>

### 3-Methoxy-10-methyl-1,10-dihydro-acridin-1-one (**22a**)

To a solution containing **12a** (100 mg, 0.31 mmol) in toluene (30 ml), DIBAH (1M in toluene; 1.86 ml, 1.86 mmol) was added dropwise under argon, at -78°C. After being stirred at room temperature for 24 h, 6M aqueous hydrochloric acid was added. The mixture was extracted with methylene chloride after addition of a saturated aqueous sodium hydrogen carbonate solution. The organic layer was then washed with water, dried (MgSO<sub>4</sub>) and concentrated. The crude product was purified on an alumina column with initially pure methylene chloride and finally methylene chloride-ethanol (98:2) as eluent. The product (**22a**) (15 mg, 20 %) was obtained as a blue solid, mp 195-206°C, beside the recovered material (**12a**) (49 mg, 49 %); <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ 9.01 (s, 1H, H-9), 7.86 (dd, 1H, J=7.9, 1.5 Hz, H-8), 7.73 (td, 1H, J=7.9, 1.5 Hz, H-6), 7.53 (dd, 1H, J=7.9, 1.5 Hz, H-5), 7.31 (td, 1H, J=7.9, 1.5 Hz, H-7), 6.04 (d, 1H, J=1.8 Hz, H-4), 5.70 (d, 1H, J=1.8 Hz, H-2), 3.87 (s, 3H, OCH<sub>3</sub>), 3.82 (s, 3H, NCH<sub>3</sub>); EIms (m/z) : 239 (M<sup>+</sup>, 100%).

### 3,3,12-Trimethyl-6,12-dihydro-3H-pyrano[2,3-c]acridin-6-one<sup>9</sup> (**22b**)

Under argon, at -78°C, to a solution containing **12b** (55 mg, 0.15 mmol) in toluene (5 ml), DIBAH (1M in toluene; 0.9 ml, 0.9 mmol) was added dropwise. After being stirred at room temperature for 4 days, 6M aqueous hydrochloric acid was added. The mixture was extracted with methylene chloride after addition of a saturated aqueous sodium hydrogen carbonate solution. The organic layer was then washed with water, dried (MgSO<sub>4</sub>) and concentrated. The crude product was purified on a silica gel column with methylene chloride-ethanol (95:5) as eluent. Product (**22b**) (9 mg, 21 %) was obtained as a blue solid, mp 208-215°C, beside unreacted substrate (**12b**) (13 mg, 24 %); This spectrum is in all respects identical to that of the same compound prepared by a specific reaction.<sup>9</sup>

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