Pergamon

Tetrahedron 56 (2000) 3703–3708

TETRAHEDRON

# Preparation of New Pyridoacridine Derivatives and Formal Synthesis of 11-Hydroxyascididemine

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Received 3 February 2000; accepted 27 March 2000

**Abstract**—The preparation of pyrido[2,3,4-*kl*]acridin-6-ones substituted at position 4 following our previous methodology is described. A new synthetic route for the preparation of aminopyridoacridone **16**, used before for the synthesis of the 11-hydroxyascididemine, is described. The cytotoxic activity of pyridoacridones **19** and **20** in four cell lines is reported. © 2000 Elsevier Science Ltd. All rights reserved.

Ascididemine (**1**),[1] bromoleptoclidinone (**2**),[2] and 11-hydroxyascididemine (**3**)[3] are marine alkaloids of the pyridoacridine group, isolated from sea invertebrates. The important cytotoxic activity of these alkaloids, amongst other pharmacological activities, has encouraged several research groups to develop synthetic strategies for the preparation of the natural products and related compounds.[4]

We have described a simple and effective strategy[5] for the synthesis of a diazaphenalene (**4**) which contains the B, C and E rings of these alkaloids by addition of the 'top' pyridine ring to a bicyclic precursor and have applied the same methodology to the synthesis of a pyrido[2,3,4-*k,l*]acridin-6-one (**5**), which was then used in a total synthesis of ascididemine (Fig. 1).[6]

In this paper we describe the results of studies aimed at the preparation of the linear pyridoacridone **6** from the 1,4-dimethoxyacridone **7**, with the ultimate goal of utilising our methodology for the addition of the 'top' pyridine ring. We also describe here the synthesis of pyrido[2,3,4-*k,l*]acridin-6-ones substituted at position 4, following the previously described method[5,6] for construction of the 'top' pyridine ring, from the acridone **9**. The introduction of a substituent at position 4 of the pyridoacridone **5** could produce a modification of the pharmacological activity and when that substituent is an amino group, this would result in a potentially very useful synthetic intermediate for the preparation of alkaloids like kuanoniamines[7] or shermilamines[8] which contain condensed heterocycles, other than pyridines.

The dimethoxyacridone **7** was obtained in 71% yield following the procedure described by Ionescu,[9] from 2-chlorobenzoic acid and 2,5-dimethoxyaniline. Nitration of **7** with fuming $HNO_3$ at −40°C for only three minutes

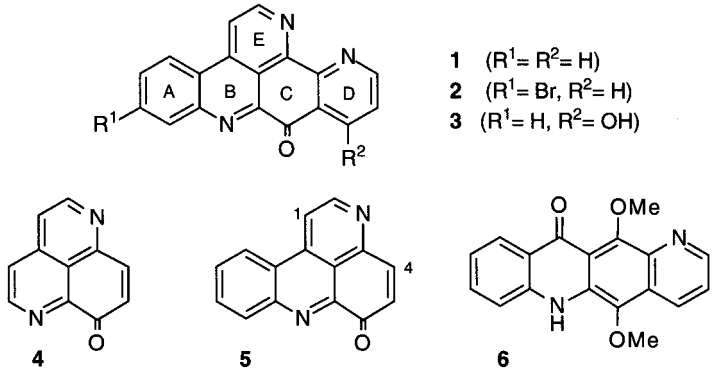


**Figure 1.**

*Keywords*: marine alkaloids; pyridoacridines; cytotoxic compounds.
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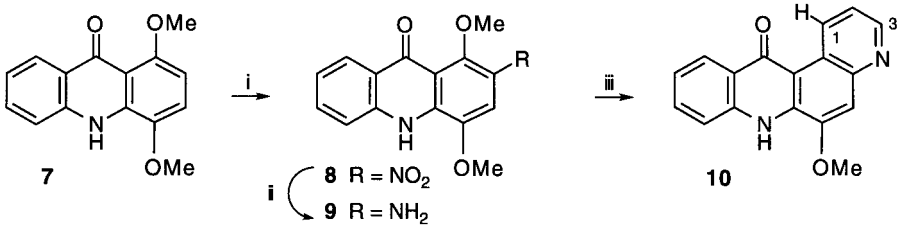
PII: S0040-4020(00)00251-9




**Scheme 1.** *Reagents:* (i) conc. $HNO_3$, conc. $H_2SO_4$, −20°C (94%); (ii) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, rt (78%); (iii) glycerol, $FeSO_4{\cdot}7H_2O$, conc. $H_2SO_4$, $C_6H_5NO_2$, $H_2O$, 0°C→130°C (40%).

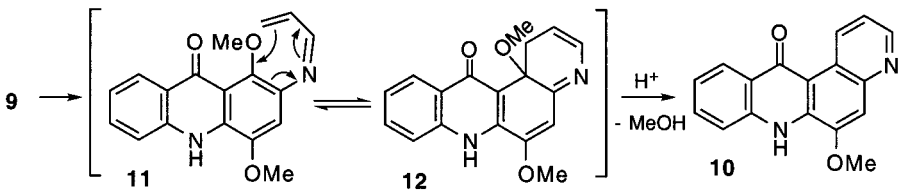
gave a 2,7-dinitro-derivative in 63% yield. However, with milder conditions, using conc. $HNO_3$ and a catalytic quantity of conc. $H_2SO_4$ the desired nitro-compound **8** was isolated in excellent yield (Scheme 1). That substitution had taken place in the more activated carbocyclic ring was proved by the singlet in the $^1$H NMR spectrum at **8** at 7.53 ppm corresponding to the 3-H, and by the presence of an ABCD coupling system, as in the precursor **7**, appropriate for the four protons of the *ortho* disubstituted benzene ring. That nitration had occurred at C-2 and not C-3 is consistent with electron release from the *para* related nitrogen; final experimental verification for the regiochemistry of nitration was provided later (see below) when the amine **16**, derived from **8**, was also prepared by displacement of bromine in **17**.[6]

Reduction of the nitro group in **8** with $NiCl_2$ and $NaBH_4$ in MeOH afforded in good yield the very polar and unstable aminoacridone **9**. We anticipated that this amino group could be made the basis for the fusion of a pyridine ring to the tricycle, as required for the pyridoacridine alkaloids. Formation of pyridine ring from **9** under Skraup conditions[10] using as reagents acrolein, and ferric chloride or sodium *m*-nitrobenzenesulfonate for the oxidation, afforded a solid material which was impossible to purify sufficiently for proper characterisation. When glycerol was used for the generation of acrolein in situ an unexpected pyridoacridone **10** was obtained in 40% yield. The structure of acridone **10** in which the cyclisation has taken place to position 1 with displacement of the methoxy group was established by spectroscopic data and a high resolution mass measurement of the molecular ion. The $^1$H NMR spectrum of **10** showed a singlet at 4.04 ppm for only one methoxy group and a singlet at 7.51 ppm from H-5 as signals indicative of cyclisation to position 1; the signals of the newly formed pyridine ring are a double doublet at 7.50 ppm for H-2 and two doublets at 8.77 and 10.48 ppm for H-3 and H-1, respectively, the assignments resting on the typically smaller coupling constant ($J$=4.4 Hz) between the pyridine α and β protons than that ($J$=8.5 Hz) between the β and γ protons. The exceptionally low field shift of H-1 must be related to its proximity to the carbonyl group.

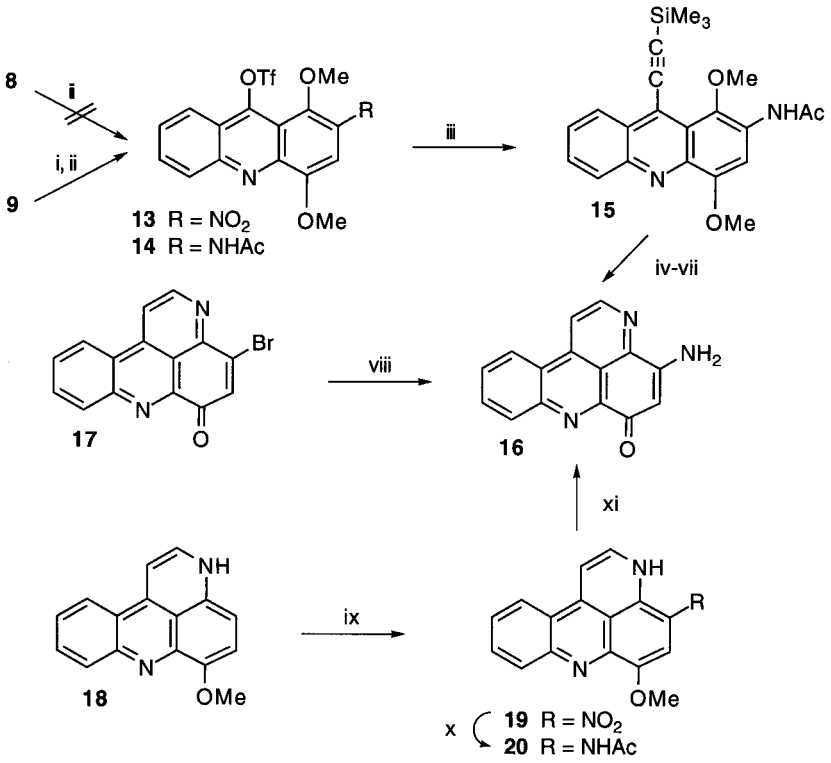
A possible explanation for the formation of the pyridoacridone **10** is shown in Scheme 2: formation the imine **11** by condensation of acrolein with **9** then a reversible electrocyclisation to **12** and irreversible loss of methanol, catalysed by the acid present in the reaction. We have recently described a somewhat similar pyridine ring formation by an electrocyclisation with substitution of a methoxy group from position 1 of a 9-substituted acridine with formation of a pyrido[2,3,4-*k,l*]acridine.[6]

The utilisation of nitroacridone **8** as starting material for the preparation of a 4-nitropyrido[2,3,4-*kl*]acridone following methodology described[6] earlier, was prevented because the formation of the *O*-triflate **13** by reaction of the acridone **8** and $Tf_2O$ in several conditions, failed, possibly because the nucleophilic character of the carbonyl oxygen is substantially reduced by inductive withdrawal by nitro group. However, the amine **9** could be converted into a triflate **14**, in two steps, by protection of the amino group as an acetyl derivative and then triflate formation. Clearly, the presence of an activating acetylamino group at position 2 increases the reactivity of the acridone in comparison with the nitroacridone **8**. The $^{13}$C spectrum of the triflate **14** had the usual quartet at 119.0 ppm due to the trifluoromethyl group.

Coupling between **14** and trimethylsilylacetylene (TMSA) was tested under several different conditions and different palladium catalysts, the best yield of **15** being obtained with $Pd_2(dba)_3{\cdot}CHCl_3$ in THF with diisopropylethylamine (DEA) as base. The introduction of the trimethylsilylethynyl substituent was verified by the nine-hydrogen singlet at 0.43 ppm due to the $SiMe_3$ in the $^1$H NMR spectrum of the product. Elimination of the silicon was achieved in excellent yield by treatment with KF in MeOH. Addition of sodium diformamide[5,6] in DMF followed by oxidation with cerium(IV) ammonium nitrate (CAN) and TFA cyclisation afforded the aminopyridoacridone **16**. The spectroscopic data of **16** agree with those in work described by Kubo[11] in which this compound was utilised in a synthesis of 11-hydroxyascididemine. The instabilities of the




**Scheme 2.**

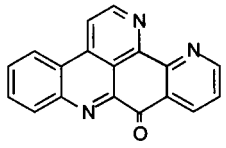
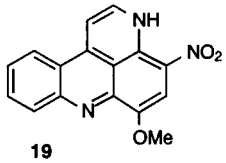
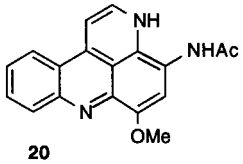



**Scheme 3.** *Reagents:* (i) $Ac_2O$, reflux (69%); (ii) $Tf_2O$, DMAP, 2,6-lutidine, $CH_2Cl_2$ (60%); (iii) TMSA, $Pd_2(dba)_2{\cdot}CHCl_3$, DEA, THF, reflux (70%); (iv) KF, MeOH, reflux (92%); (v), $NaN(CHO)_2$, DMF, reflux, (42%); (vi) CAN, $CH_3CN$, $H_2O$; (vii), TFA, MeOH (24% two step); (viii) $NH_4OH$, *i*-PrOH, 80°C (31%); (ix) $Cu(NO_3)_2$, $Ac_2O$, AcOH, 0°C (51%); (x), $SnCl_2$, MeOH, reflux, then $Ac_2O$ (55%); (xi) CAN, $CH_3CN$, $H_2O$ then HCl, MeOH (60%).

synthetic intermediates in this sequence made impossible a complete characterisation of each of them (see Experimental). The amino-quinone **16** was also obtained from the bromopyridoacridone **17**[6] by substitution of the bromine using $NH_4OH$ in *i*-PrOH, thus verifying the location of the amino group in **16**.

Nitration of pyridoacridine **18**[6] with copper(II) nitrate in $Ac_2O$[12] gave the nitro-derivative **19** in 51% yield, other nitrating agents such as nitric acid in $Ac_2O$ or higher reaction temperatures gave a mixture of nitrated compounds. The nitro-compound **19** was also obtained as a minor product in 20% yield in the oxidation of **18** with

**Table 1.** Antitumor activity $IC_{50}$ (μM) of compounds **1**, **19** and **20**

| Compound | P-388D | A-549 | HT-29 | SK-MEL-28 |
|---|---|---|---|---|
|  ascididemine **1** | 0.35 | 0.02 | 0.35 | 0.004 |
|  **19** | 0.34 | 0.03 | 0.34 | 0.03 |
|  **20** | 1.64 | 0.03 | 1.64 | 0.03 |

CAN when we were studying the preparation of **5**. The electrophilic substitution in the ring C and on the position 4 of the pyridoacridine **18** was previously established during the preparation of **17**. The pyridoacridine **19** showed in its $^1$H NMR spectrum the AB coupling system for the two protons of the pyridine ring, the ABCD system for the four protons of the *ortho* disubstituted benzene ring and finally a singlet at $\delta$ 6.40 ppm for H-5. A nuclear Overhauser experiment on **19** showed a positive effect between the H-5 and the methoxy group at $\delta$ 4.12 ppm and also between H-1 at $\delta$ 8.51 ppm and H-11 at $\delta$ 8.56 ppm. The chemical shift observed for H-5, at higher field than that usual for a proton *ortho* to a nitro group, can be explained by an anisotropic effect due to the nitro group which may have restricted mobility because of formation of a hydrogen bond with the NH. Reduction of the nitro group with tin(II) chloride and acylation of the unstable amino-derivative gave **20** which by CAN oxidation yielded the aminoquinone **16** (Scheme 3).

In summary, we have developed three alternative routes for the preparation of the aminopyridoacridone **16**, used for a synthesis of 11-hydroxyascididemine[11] and of potential for the synthesis of other alkaloids in this group. Although the yields from **17** or **18** are similar, the easier manipulation of the synthetic intermediates through the bromoiminoquinone **17**[6] and the smaller number of steps make the route more favourable.

## Biological Results

The cytotoxic activity of ascididemine and substituted pyridoacridines **16** and **17** was tested in murine lymphoma (P388D), human cell lung carcinoma (A549), human colon carcinoma (HT-29), and human melanoma (SK-MEL-28) cell lines and the results are detailed in Table 1. The nitropyridoacridine **16** presented a potent cytotoxic activity similar to ascididemine, and **17** displayed a similar activity on human lung carcinoma and melanoma cell lines but less in murine lymphoma and human colon carcinoma cells.

## Experimental

### General

Melting points were determined in a capillary tube and are uncorrected. TLC was carried on $SiO_2$ (silica Gel 60 $F_{254}$, Merck 0.063–0.200 mm) and spots were located with UV light. Column chromatography was carried out on $SiO_2$ (silica Gel 60 SDS 0.060–0.2 mm). Flash chromatography was carried out on $SiO_2$ (silica Gel 60 A CC, Merck). Organic extracts were dried with anhydrous $Na_2SO_4$, and solutions were evaporated under reduced pressure with a rotary evaporator. IR spectra was performed with a Nicolet 205 FT-IR. NMR spectra were measured with Varian Gemini-200 (200 MHz), Varian Gemini-300 (300 MHz) and Varian VXR-500 (500 MHz) spectrometers; data are given in $\delta$ referenced to TMS. Mass spectra were measured in the electron impact (EI) or chemical ionisation (CI) mode with a Hewlett–Packard model 5989A. High resolution mass spectra were performed with an Autospec/VG by the Departament de Química Orgànica Biològica (C.S.I.C.) Barcelona. Elemental analyses were performed with a C.E. Instruments EA-1108 in the Serveis Científico-Tècnics de Universitat de Barcelona.

**1,4-Dimethoxy-2,7-dinitroacridone.** 1,4-Dimethoxyacridone (0.1 g, 0.4 mmol) was slowly added to fuming $HNO_3$ (0.6 ml) cooled to −40°C and the resulting mixture was stirred at that temperature for 3 min. After this time the mixture was basified with NaOH and saturated $NaHCO_3$. The solid residue was collected by filtration and dried to give 1,4-dimethoxy-2,7-dinitroacridone (87 mg, 63%). IR (KBr) $\nu$ 3580, 1623, 1607, 1334 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 3.92 (s, 3H, $OCH_3$); 4.09 (s, 3H, $OCH_3$); 7.81 (s, 1H, H-3); 8.09 (d, $J$=8.0 Hz, 1H, H-5); 8.49 (d, $J$=8.0 Hz, 1H, H-6); 8.91 (s, 1H, H-8). $^{13}$C NMR (DMSO-$d_6$, 75.4 MHz) $\delta$ 57.4 (q, $OCH_3$); 63.6 (q, $OCH_3$); 108.6 (d, C-3); 109.1 (s, C-9a); 115.1 (s, C-2); 120.4 (d, C-5); 121.6 (s, C-8a); 122.9 (d, C-8); 127.8 (d, C-6); 131.9 (s, C-4a); 137.5 (s, C-10a); 142.3 (s, C-4); 143.8 (s, C-1); 144.1 (s, C-7); 175.4 (s, C=O). MS (EI): 345 ($M^+$, 4); 315 (100); 285 (44); 239 (45).

**1,4-Dimethoxy-2-nitroacridone (8).** 1,4-Dimethoxyacridone (2 g, 7.8 mmol) was added in portions to a cooled (−20°C) solution of conc. $HNO_3$ (12 ml) and catalytic amount of conc. $H_2SO_4$ and the reaction mixture was stirred at that temperature for 1 h. After this time the cooled solution was basified with conc. NaOH and then with saturated $NaHCO_3$. The solid material was filtered and dried under vacuum to give **8** (2.2 g, 94%) as a yellow solid. Mp 206–208°C ($CH_2Cl_2$); IR (KBr) $\nu$ 3400, 1641, 1618, 1332 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 4.08 (s, 3H, $OCH_3$); 4.12 (s, 3H, $OCH_3$); 7.33 (dd, $J$=8.1 and 7.7 Hz, 1H, H-7); 7.33 (d, $J$=7.8 Hz, 1H, H-5); 7.53 (s, 1H, H-3); 7.68 (dd, $J$=7.8 and 7.7 Hz, 1H, H-6); 8.38 (d, $J$=8.1 Hz, 1H, H-8); 8.79 (br, 1H, NH). $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 56.6 (q, $OCH_3$); 63.7 (q, $OCH_3$); 107.2 (d, C-3); 116.7 (d, C-5); 123.5 (d, C-7); 127.2 (d, C-8); 133.9 (d, C-6). MS (EI) 300 ($M^+$, 7); 270 (100); 240 (45). Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.97; H, 4.03; N, 9.16.

**2-Amino-1,4-dimethoxyacridone (9).** $NiCl_2{\cdot}6H_2O$ (0.8 g, 3.3 mmol) was added to a solution of **8** (1 g, 3.3 mmol) in MeOH (15 ml) and the mixture was stirred for 15 min at room temperature. After this time $NaBH_4$ (0.5 g, 13.3 mmol) was added in portions and the reaction mixture was stirred at room temperature for 5 min. $H_2O$ (50 ml) was added and the solution extracted with $CH_2Cl_2$. The organic solution was dried and evaporated to give **9** (0.7 g, 78%) as an orange solid. Mp 206–210°C ($CH_2Cl_2$): IR (KBr) $\nu$ 3400, 3308, 1599 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 3.69 (s, 3H, $OCH_3$); 3.93 (s, 3H, $OCH_3$); 4.81 (br, 2H, $NH_2$); 6.89 (s, 1H, H-3); 7.10 (dd, $J$=6.9 and 7.7 Hz, 1H, H-7); 7.55 (dd, $J$=6.9 and 8.6 Hz, 1H, H-6); 7.78 (d, $J$=8.6 Hz, 1H, H-5); 8.11 (d, $J$=7.7 Hz, 1H, H-8); 10.66 (br, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75.4 MHz) $\delta$ 56.2 (q, $OCH_3$); 60.2 (q, $OCH_3$); 104.2 (d, C-3); 116.2 (s, C-9a); 117.8 (d, C-5); 120.3 (d, C-7); 121.1 (s, C-2); 124.9 (s, C-8a); 126.0 (d, C-8); 132.2 (d, C-6); 134.8 (s, C-10a); 135.7 (s, C-4a); 139.8 (s, C-4); 144.0 (s, C-1), 175.9 (s, C=O). MS (EI) 270 ($M^+$, 75); 255 (100); 227 (39). HRMS Calculated for $C_{15}H_{14}N_2O_3$, 270.1004. Found 270.0999.

**6-Methoxy-7*H*-pyrido[3,2-*a*]acridin-12-one (10).** To a stirred mixture of $FeSO_4 \cdot 7H_2O$ (41 mg, 0.1 mmol), conc. $H_2SO_4$ (0.4 ml, 7.4 mmol) and $C_6H_5NO_2$ (0.15 ml, 1.5 mmol) cooled at 0°C were successively added **9** (200 mg, 0.7 mmol), glycerol (0.22 ml, 3 mmol) and $H_2O$ (0.4 ml). The mixture was warmed to 130°C and stirred at that temperature for 5 h. After this time the mixture was basified with saturated $NaHCO_3$ and filtered. The solid residue was dried in vacuum and purified by column chromatography. Elution with $CH_2Cl_2$/MeOH (9:1) afforded **10** (80 mg, 40%). Mp 196–201°C ($CH_2Cl_2$): IR (KBr) $\nu$ 3397, 1622, 1539, 1318 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 4.04 (s, 3H, $OCH_3$); 7.37 (dd, $J$=7.5 and 8.2 Hz, 1H, H-10); 7.45 (d, $J$=8.2 Hz, 1H, H-8); 7.50 (dd, $J$=4.4 and 8.5 Hz, 1H, H-2); 7.51 (s, 1H, H-5); 7.67 (dd, $J$=7.5 and 8.2 Hz, 1H, H-9); 8.52 (d, $J$=8.2 Hz, 1H, H-11); 8.77 (d, $J$=4.4 Hz, 1H, H-3); 9.23 (br, 1H, NH); 10.48 (d, $J$=8.5 Hz, 1H, H-1). $^{13}C$ NMR ($CDCl_3$ 75.4 MHz) $\delta$ 56.0 (q, $OCH_3$); 110.2 (d, C-5); 112.2 (s, C-12a); 116.9 (d, C-8); 121.0 (d, C-2); 122.7 (s, C-12b); 122.8 (d, C-10); 123.5 (s, C-11a); 126.4 (d, C-11); 132.6 (d, C-9); 134.1 (s, C-7a); 134.3 (d, C-1); 137.4 (s, C-6a); 144.6 (s, C-6); 147.7 (d, C-3); 148.3 (s, C-4a); 178.6 (s, C=O). MS (EI) 277 (M+1, 20); 276 ($M^+$, 100); 261 (55). HRMS Calculated for $C_{17}H_{12}N_2O_2$, 276.0899. Found 276.0899.

**2-Acetylamino-1,4-dimethoxyacridone.** A solution of **9** (2.3 g, 8.5 mmol) in $Ac_2O$ (40 ml) was stirred at 60°C for 1 h. The reaction mixture was poured over crushed ice, basified with saturated $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic solution was dried and evaporated giving a yellow solid which was purified by column chromatography. Elution with $CH_2Cl_2$/MeOH (99:1) afforded the title compound (1.8 g, 69%). Mp 215–218°C ($CH_2Cl_2$): IR (Film) $\nu$ 3310, 1627, 1605, 1537 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.27 (s, 3H, $COCH_3$); 3.97 (s, 3H, $OCH_3$); 4.05 (s, 3H, $OCH_3$); 7.25 (ddd, $J$=8.6, 7.6 and 1.2 Hz, 1H, H-7); 7.32 (dd, $J$=9.2 and 1.2 Hz, 1H, H-5); 7.63 (ddd, $J$=9.2, 7.6 and 1.4 Hz, 1H, H-6); 8.01 (brs, 1H, NH); 8.40 (s, 1H, H-3); 8.43 (dd, $J$=8.6 and 1.4 Hz, 1H, H-8); 8.58 (brs, 1H, NH). $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 24.9 (q, $CH_3$); 56.2 (q, $OCH_3$); 62.1 (q, $OCH_3$); 106.0 (d, C-3); 114.6 (s, C-2); 116.4 (d, C-5); 121.6 (d, C-8); 122.1 (s, C-9a); 124.6 (s, C-8a); 126.9 (d, C-7); 129.1 (s, C-4a); 133.1 (d, C-6); 138.8 (s, C-10a); 140.4 (s, C-4); 142.6 (s, C-1); 168.6 (s, C=O); 176.9 (s, C=O). MS (EI): 313 (M+1, 8); 312 ($M^+$, 34); 283 (100); 255 (29). Anal. Calcd for $C_{17}H_{16}N_2O_4 \cdot 0.5CH_2Cl_2$: C, 59.24; H, 4.83; N, 7.90. Found: C, 59.04; H, 5.20; N, 7.97.

**2-Acetylamino-1,4-dimethoxy-9-(trifluoromethylsulfonyloxy)acridine (14).** To a solution of 2-acetylamino-1,4-dimethoxyacridone (0.5 g, 1.6 mmol) in $CH_2Cl_2$ (15 ml) under nitrogen was successively added DMAP (39 mg, 0.3 mmol), 2,6-lutidine (0.3 ml, 2.2 mmol), and $Tf_2O$ (0.3 ml, 1.9 mmol). The mixture was stirred for 2 h at 0°C and 1 h at room temperature. The organic solution was washed with $H_2O$, dried and evaporated. The residue was purified by column chromatography, elution with hexane–$CH_2Cl_2$ (3:7) gave **14** (426 mg, 60%). IR (KBr) $\nu$ 3308, 1630, 1242, 1021 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.35 (s, 3H, $CH_3$); 3.84 (s, 3H, $OCH_3$); 4.20 (s, 3H, $OCH_3$); 7.68 (dd, $J$=9.2 and 6.8 Hz, 1H, H-7); 7.81 (dd, $J$=8.0 and 6.8 Hz, 1H, H-6); 8.17 (d, $J$=9.2 Hz, 1H, H-8); 8.39 (d, $J$=8.0 Hz, 1H, H-5); 8.42 (s, 1H, H-3). $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 25.0 (q, $CH_3$); 56.6 (q, $OCH_3$); 61.8 (q, $OCH_3$); 102.8 (d, C-3); 114.4 (s, C-2); 119.0 (q, $CF_3$); 119.5 (s, C-9a); 120.0 (d, C-6); 129.4 (d, C-8); 130.4 (s, C-4a); 130.6 (d, C-5); 140.1 (s, C-10a); 146.9 (s, C-1); 147.3 (s, C-4); 151.6 (s, C-9); 169.2 (s, C=O). MS (EI): 444 ($M^+$, 0.003); 312 (20).

**2-Acetylamino-1,4-dimethoxy-9-(trimethylsilylethynyl)-acridine (15).** To solution of **14** (0.4 g, 0.9 mmol) in 10 ml of dry THF (10 ml) was added under nitrogen $Pd_2(dba)_3 \cdot CHCl_3$ (0.2 g, 0.2 mmol), $PPh_3$ (0.4 g, 1.5 mmol), DEA (0.5 ml, 2.7 mmol) and TMSA (0.4 ml, 2.7 mmol) and the mixture was refluxed for 24 h. The solvent was evaporated and the residue was dissolved in $CH_2Cl_2$ and washed with $H_2O$. The organic solution was dried and evaporated to give a crude material which was purified by column chromatography. Elution with $CH_2Cl_2$ gave the alkyne **15** (248 mg, 70%). $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.43 (s, 9H, $SiMe_3$); 2.33 (s, 3H, $COCH_3$); 3.90 (s, 3H, $OCH_3$); 4.17 (s, 3H, $OCH_3$);7.60–7.80 (m, 2H, H-6, H-7); 8.08 (bs, 1H, NH); 8.30 (s, 1H, H-3); 8.34 (d, $J$=7.5 Hz, 1H, H-5), 8.57 (d, $J$=8.0 Hz, 1H, H-8). $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ −0.1 (q, $Si(CH_3)_3$); 25.3 (q, $COCH_3$); 56.5 (q, $OCH_3$); 62.4 (q, $OCH_3$); 101.6 (d, C-3); 110.0 (s); 125.8 (d, C-7), 127.7 (d, C-6); 129.6 (d, C-5), 130.7 (d, C-8); 146.2 (s); 152.9 (s); 169.0 (s).

**4-Amino-6*H*-pyrido[2,3,4-*kl*]acridin-6-one (16).** *Method A*: A solution of trimethylsilylacridine **15** (0.5 g, 1.3 mmol) in MeOH (30 ml) with KF (0.2 g, 3.9 mmol) was refluxed for 1 h. The solvent was evaporated and the residue was dissolved in $CH_2Cl_2$ and washed with $H_2O$. The organic solution was dried and evaporated giving the free acetylene (375 mg, 92%). $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.32 (s, 3H, $COCH_3$); 3.91 (s, 3H, $OCH_3$); 4.17 (s, 3H, $OCH_3$); 4.18 (s, 1H, C≡CH); 7.60–7.80 (m, 2H, H-6, H-7); 8.10 (bs, 1H, NH); 8.32 (s, 1H, H-3); 8.36 (d, $J$=7.5 Hz, 1H, H-5), 8.62 (d, $J$=8.5 Hz, 1H, H-8). $NaN(CHO)_2$ (190 mg, 3.6 mmol) was added to a solution of the acetylene (400 mg, 1.2 mmol) in dry DMF (10 ml). The mixture was refluxed for 30 min and the solvent was evaporated. The residue was dissolved in $CH_2Cl_2$ and washed with $H_2O$. The organic solution was dried and evaporated producing crude product which was purified by column chromatography. Elution with $CH_2Cl_2$/MeOH (99:1) gave a bisformylenamide (200 mg, 42%). A solution of CAN (557 mg, 1.0 mmol) in $H_2O$ (1 ml) was added to a solution of bisformylenamide (200 mg, 0.5 mmol) in MeCN (3 ml) and the mixture was stirred for 10 min at room temperature. After this time, $H_2O$ (5 ml) was added and the crude was extracted with $CH_2Cl_2$. The organic solution was dried and evaporated leaving a residue which was dissolved in dry MeOH (5 ml). Argon was bubbled through the methanol solution for 3 min, then TFA (0.04 ml, 0.6 mmol) was added and solution was refluxed for 30 min. To the cooled solution, saturated $NaHCO_3$ was added, the organic layer was removed and the residual aqueous layer was re-extracted with $CH_2Cl_2$. The combined organic extracts were dried and evaporated leaving a residue which was purified by column chromatography. Elution with $CH_2Cl_2$/MeOH (98:2) afforded aminopyridoacridone **16** (30 mg, 24%). IR (KBr) $\nu$ 3280,

1584 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 200 MHz) $\delta$ 5.97 (s, 1H, H-5); 7.64 (bs, 2H, $NH_2$); 7.91 (t, $J$=7.9 Hz, 1H, H-9); 8.00 (t, $J$=7.9 Hz, 1H, H-10); 8.32 (d, $J$=7.9 Hz, 1H, H-8); 8.87 (d, $J$=5.6 Hz, 1H, H-1); 8.90 (d, $J$=7.9 Hz, 1H, H-11); 9.02 (d, $J$=5.6 Hz, 1H, H-2). MS (EI): 249 (M+2, 14); 248 (M+1, 31); 247 ($M^+$, 82); 219 (100).

*Method B*: $NH_4OH$ (20%, 7 ml) was added to a solution of 4-bromopyridoacridone **17** (44 mg, 0.1 mmol) in *i*-PrOH (7 ml) and the mixture was heated at a 80°C for 2 h. After this time the solvent was evaporated at reduced pressure and the residue was purified by column chromatography. Elution with $CH_2Cl_2$/MeOH (98:2) gave **16** (11 mg, 31%).

*Method C*: A solution of CAN (106 mg, 0.2 mmol) in $H_2O$ (1 ml) was added to a solution of **20** (60 mg, 0.2 mmol) in MeCN (3 ml) and the mixture was stirred for 10 min at room temperature. After this time $H_2O$ (5 ml) was added and crude material was extracted into $CH_2Cl_2$. The organic solution was dried and evaporated. The residue was dissolved in MeOH with a catalytic amount of HCl and the solution was stirred for 2 h. After this time saturated $NaHCO_3$ was added and the MeOH was removed under vacuum, the aqueous solution was extracted with $CH_2Cl_2$. The organic solution was dried and evaporated. The residue was purified by column chromatography. Elution with $CH_2Cl_2$/MeOH (98:2) gave **16** (30 mg, 60%).

**6-Methoxy-4-nitro-3*H*-pyrido[2,3,4-*kl*]acridine (19).** A solution of $Cu(NO_3)_2$ (144 mg, 0.6 mmol) in $Ac_2O$ (6 ml) was added to a solution of **18**[6] (100 mg, 0.4 mmol) in $Ac_2O$ (3 ml) cooled to 0°C and mixture was stirred for 3 h at this temperature. Aqueous NaOH 50% was added until basic and the mixture was extracted with $CH_2Cl_2$. The organic solution was dried and evaporated to give a crude product which was purified by column chromatography. Elution with $CH_2Cl_2$/MeOH (99:1) afforded the nitro-derivative **19** (60 mg, 51%), mp 220–223°C ($CH_2Cl_2$): IR (KBr) $\nu$ 3390, 1609, 1578, 1263 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 4.12 (s, 3H, $OCH_3$); 6.40 (s, 1H, H-5); 7.83 (ddd, $J$=7.7, 7.5 and 0.5 Hz, 1H, H-10); 7.92 (ddd, $J$=7.7, 7.5 and 0.5 Hz, 1H, H-9); 8.40 (dd, $J$=7.7 and 0.5 Hz, 1H, H-8); 8.51 (d, $J$=5.5 Hz, 1H, H-1); 8.56 (dd, $J$=7.7 and 0.5 Hz, 1H, H-11); 9.19 (d, $J$=5.5 Hz, 1H, H-2); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 57.0 (q, $OCH_3$); 108.1 (d, C-5); 118.5 (s, C-11c); 118.8 (d, C-1); 122.3 (s, C-11a); 122.9 (d, C-11); 130.0 (d, C-10); 131.7 (d, C-9); 132.0 (d, C-8); 137.1 (s, C-11b); 145.1 (s, C-7a); 146.6 (s, C-3a); 149.8 (d, C-2); 164.4 (s, C-6); 183.3 (s, C-6a). MS(EI) 293 ($M^+$, 4); 262 (42); 233 (52); 205 (100) HRMS Calculated for $C_{16}H_{11}N_3O_3$, 293.0800. Found 293.0798.

**4-Acetylamino-6-methoxy-3*H*-pyrido[2,3,4-*kl*]acridine (20).** A solution of **19** (136 mg, 0.5 mmol) and $SnCl_2$ (0.5 g, 2.0 mmol) in MeOH (5 ml) was refluxed for 2 h. The solvent was evaporated under vacuum, the residue was dissolved in $Ac_2O$ (10 ml) and the resulting solution was refluxed for 30 min The excess of $Ac_2O$ was evaporated under vacuum, the residue was dissolved in $CH_2Cl_2$ and the organic solution was washed with saturated $NaHCO_3$. The organic layer was dried and evaporated giving **20** (78 mg, 55%). Mp 128–132°C ($CH_2Cl_2$): IR (KBr) $\nu$ 2939, 1764 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 2.50 (s, 3H, $CH_3$); 3.95 (s, 3H, $OCH_3$); 6.91 (dd, $J$=8.6 and 1.0 Hz, 1H, H-8); 7.00 (ddd, $J$=8.2, 7.6 and 1.0 Hz, 1H, H-10); 7.09 (d, $J$=5.1 Hz, 1H, H-1); 7.18 (s, 1H, H-5); 7.34 (ddd, $J$=8.6, 17.6, and 1.4 Hz, 1H, H-9); 7.76 (dd, $J$=8.2 and 1.4 Hz, 1H, H-11); 8.48 (d, $J$=5.1 Hz, 1H, H-2). $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 21.0 (q, $CH_3$); 56.4 (q, $OCH_3$); 106.5 (d, C-5); 109.1 (d, C-1); 115.8 (d, C-8); 116.7 (s, C-11a); 118.9 (s, C-11c); 121.2 (d, C-10); 123.6 (s, C-4); 123.8 (d, C-11); 129.9 (s, C-6); 131.7 (d, C-9); 135.7 (s, C-3a); 136.2 (s, C-6a); 139.6 (s, C-7a); 150.4 (d, C-2); 170.2 (s, C=O); MS (EI) 306 (M+1, 15); 305 ($M^+$, 1); 264 (71); 249 (100); HRMS calculated for $C_{18}H_{16}N_3O_2$, 306.1242. Found 306.1255.

## Acknowledgements

We acknowledge the financial support from the Ministerio de Educación y Cultura (PB97-0871 and 2FD97-0486) and the Comissionat per a Universitats i Recerca (Generalitat de Catalunya) (Grant 97-SGR00075 and 98XT-0049). We also thank the CIRIT for a fellowship for one of us (L. F.) and INSTITUTO BIOMAR S.A. (Dr J. L. Fernández Puentes, Dr J. A. de la Fuente and Dra. M. D. Garcia-Grávalos) for carrying out the biological tests.

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