Reaction of *ortho*-lithiated protected anilines with *o*-hydroxycarbonyl compounds: formation of quino- and pyranoquino-acridines

Catherine Jolivet,[a] Christian Rivalle,[a] Christiane Huel[b] and Emile Bisagni*,[a]
[a] *URA 1387 CNRS, Institut Curie, Section de Biologie, Bat 110, Centre Universitaire, 91405 Orsay, France*
[b] *U 350 INSERM, Institut Curie, Section de Biologie, Bat 110, Centre Universitaire, 91405 Orsay, France*

Reaction of *N-tert*-butoxycarbonyl-2-lithioaniline and *p*-anisidine with 1-hydroxy-3-methoxy-10-methylacridone and noracronycine gave quino[2,3,4-*kl*]acridines and pyrano[3,2-*b*]quino[4,3,2-*mn*]acridines respectively, which are related to biologically active compounds recently isolated from various marine animals.

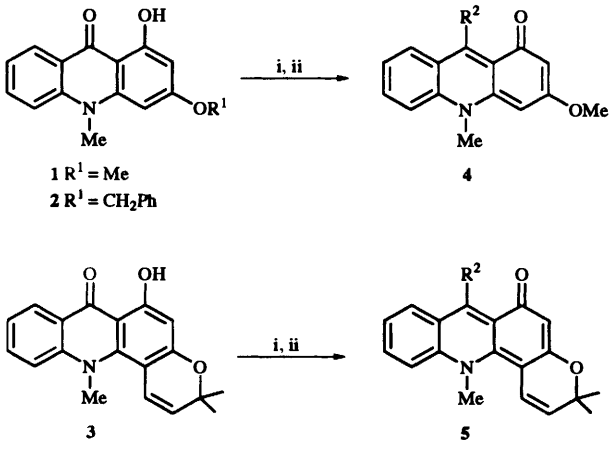
Introduction

Over the past decade, a wide variety of marine alkaloids [1] have been isolated from several marine animals such as tunicates,[2–6] ascidians,[3,7,8] sponges[9,10] and sea anemones.[11] Many of these natural substances contain a pyrido[*kl*]acridine ring system in their structure and display diverse biological activities: Ca^{2+} releasing,[5] anti-HIV,[12] antimicrobial,[6] cytotoxicity toward L1210[4] and P388[8,10] murine leukaemia cells, topoisomerase II[8] inhibition and antitumour[12,13] properties.

In this paper, the synthesis of the first representatives of the quino[2,3,4-*kl*]acridines and pyrano[3,2-*b*]quino[4,3,2-*mn*]-acridines ring systems is described. Considering also that for related heterocycles (ellipticines,[14] γ-carbolines[15] and benzo analogues[16]) the phenolic forms are more cytotoxic than their O-methoxylated counterparts, the O-demethyl derivatives of these heterocycles were also prepared. Compared with various pyrido[*kl*]acridines recently described, these new compounds include an additional fused benzo ring. Their synthesis was achieved starting from acridones **1** or **2** and noracronycine **3**.

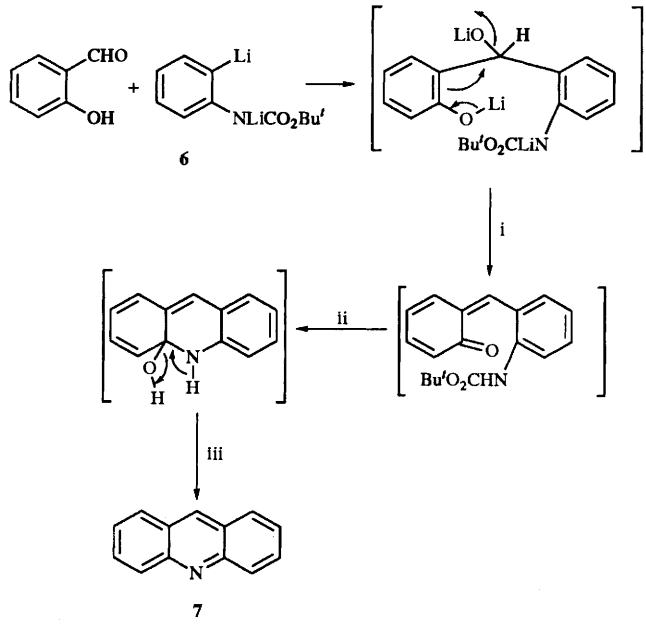
Results and discussion

In a previous paper,[17] we showed that the reaction of compounds **1** and **3** with alkyl- or aryl-lithium reagents provides the corresponding carbonyl derivatives **4** and **5** (Scheme 1).



Scheme 1 *Reagents and conditions:* i, R^2Li, THF; ii, water

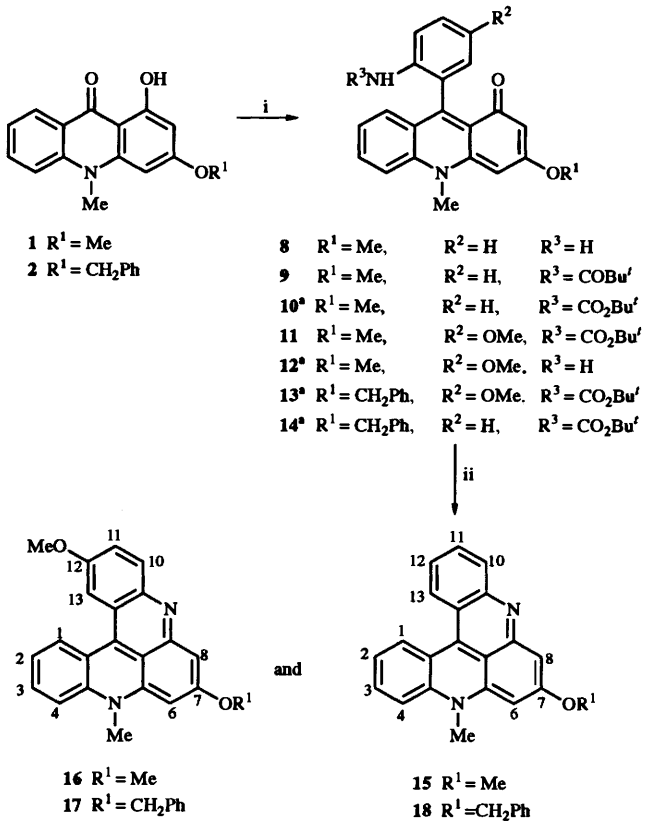
Replacement of these alkyllithiums by *ortho*-lithiated *N-tert*-butoxycarbonylanilines could theoretically afford cyclic products after deprotection of the amino group. Indeed this was illustrated by reaction of *N-tert*-butoxycarbonyl-2-lithioaniline **6** with salicylaldehyde to provide a new access to acridine **7** in a rather low yield (13%) (Scheme 2).



Scheme 2 *Reagents and conditions:* i, water; ii, HCl, THF; iii, water, then NaOH

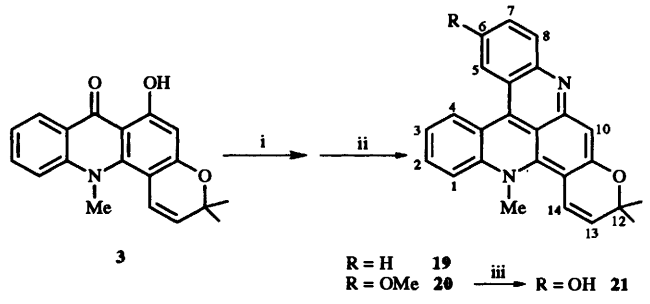
Application of this strategy to the preparation of quino[2,3,4-*kl*]acridines **15–18** involved treatment of acridones **1** and **2** with the anion generated from *N-tert*-butoxycarbonyl-[18] or 2-bromo-*N*-pivaloyl-anilines[19] and *N-tert*-butoxycarbonyl-*p*-anisidine[18] by lithium–hydrogen exchange [*tert*-butyllithium in tetrahydrofuran (THF) at −78 °C]. Reactions of these carbanions with acridones **1** and **2** at room temperature gave, after extractive work-up, the expected blue coloured intermediates **8–14** containing an *N-tert*-butoxycarbonyl group or the corresponding deprotected amine (Scheme 3). Interestingly, varying quantities of cyclized compounds **15–18** were also obtained under these conditions. To drive the formation of these red coloured quino[2,3,4-*kl*]acridines **15–18** to completion, the crude product mixture from the anion condensation step was generally treated with THF–HCl (6 mol dm^{-3}; 1:1) at 80 °C. In this way compounds **15–18** were obtained in 25–42% overall yield.

Using the same protocol, pyrano[3,2-*b*]quino[4,3,2-*mn*]-



Scheme 3 *Reagents and conditions:* i, ArLi, THF; ii, HCl, THF. [a] Products not isolated and characterized.

acridines **19** and **20** were also prepared from noracronycine **3** in four steps in 32–45% overall yield (Scheme 4).

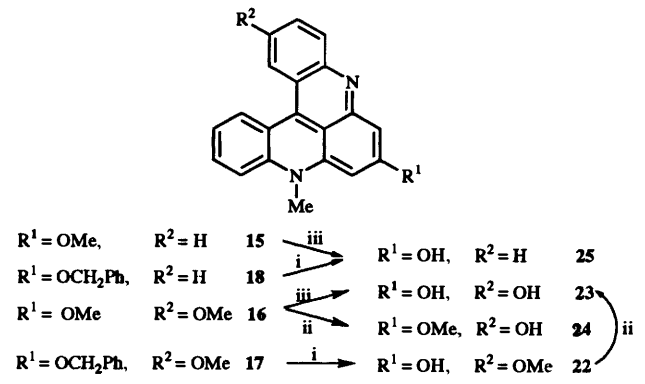


Scheme 4 *Reagents and conditions:* i, ArLi, THF; ii, HCl, THF; iii, BBr_3, CH_2Cl_2

To access the corresponding free hydroxy derivatives of these quino- and pyrano-acridines **15–20**, the O-methyl group was cleaved by using boron tribromide in methylene dichloride or with hydrobromic acid at reflux. For the O-benzyl compounds **17** and **18** hydrogenolysis conditions were used to obtain the quinoacridines **22** and **25** (Scheme 5).

The monohydroxylated product **22**, obtained by hydrogenation from compound **17**, was subsequently treated with boron tribromide in methylene dichloride for 24 h to give the dihydroxylated derivative **23**. This compound was also obtained from compound **16** by using 47% boiling hydrobromic acid for 7 h.

On the other hand, when hydrobromic acid was replaced by boron tribromide, only the 12-methoxy group in compound **16** was cleaved, to give compound **24**. Thus, it appears that the 12-methoxy group *para* to the electron-rich nitrogen atom at



Scheme 5 *Reagents and conditions:* i, H_2, Pd–C, EtOH; ii, BBr_3, CH_2Cl_2; iii, HBr 47%, 100 °C

position 5 is more sensitive to cleavage than is the 7-methoxy substituent.

Consequently, in order to obtain the 7-hydroxy derivative **25**, it was necessary to use either boiling 47% hydrobromic acid to demethylate compound **15** or catalytic hydrogenation to cleave the benzyl group in compound **18**.

With the preceding results in mind, hydroxypyranoquinoacridine **21**, (Scheme 4) was obtained by treatment of the O-methoxy derivative **20** with boron tribromide (19% yield).

Structure elucidation and complete assignments of ^1H signals for all compounds described in this paper were achieved with the help of ^1H–^1H homonuclear chemical-shift correlation spectroscopy (COSY) and ^1H–^1H nuclear Overhauser enhancement spectroscopy (NOESY) experiments.

Thus it was shown that reaction of *N*-protected-*o*-lithioanilines with appropriately substituted *o*-hydroxyaryl ketones leads to intermediate ketones which are easily cyclized to give quino- and pyranoquino-acridines. Therefore, this work provides an access to many heterocycles possessing an acridine nucleus.

Experimental

Mps were measured with an Electrothermal apparatus using capillary tubes and are uncorrected. ^1H NMR spectra were obtained in $CDCl_3$ or $(CD_3)_2SO$ ([$^2H_6$]DMSO) on 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. UV spectra were obtained on a Varian DMS 200 spectrophotometer. Mass spectra were recorded on AEI.MS-50 (MS-EI) or AEI.MS-9 (MS-CI) spectrometers and, as elemental analyses, they were performed in ICSN/CNRS, Gif sur Yvette, France.

1-Hydroxy-3-methoxy-10-methylacridone 1

This compound, prepared as described,[17] was recrystallized from ethyl acetate as yellow needles, mp 164–165 °C.

3-Benzyloxy-1-hydroxy-10-methylacridone 2

To a solution containing 1,3-dihydroxy-10-methylacridone[20] (3 g, 12.4 mmol) in acetone (125 cm^3) were added potassium carbonate (1.89 g, 13.7 mmol) and benzyl bromide (1.63 cm^3, 13.7 mmol). The mixture was stirred at reflux for 20 h, cooled, filtered, and evaporated under reduced pressure. The crude product was dissolved in methylene dichloride, and washed successively with 1 mol dm^{-3} aq. sodium hydroxide, brine and water. The organic layer was then dried ($MgSO_4$) and concentrated. The expected product was recrystallized from ethyl acetate to obtain *title compound* **2** (1.7 g, 41%) as yellow needles, mp 167–168 °C (Found: C, 75.8; H, 5.55; N, 4.25.

$C_{21}H_{17}NO_3$ requires C, 76.1; H, 5.2; N, 4.25%); $\delta_H([^2H_6]$-DMSO) 14.92 (1 H, s, 1-OH), 8.35 (1 H, dd, *J* 7.9 and 1.4, 8-H), 8.0–7.15 (8 H, m, ArH), 6.75 (1 H, d, *J* 1.8, 4-H), 6.43 (1 H, d, *J* 1.8, 2-H), 5.34 (2 H, s, OCH_2) and 3.91 (3 H, s, NMe).

Noracronycine 3

This compound was prepared according to the described procedure[20] and recrystallized from ethyl acetate as yellow needles, mp 201–203 °C (lit.,[20] 200–201 °C).

Acridine 7

Under nitrogen, *N*-(*tert*-butoxycarbonyl)aniline[18] (2.37 g, 12.26 mmol) was dissolved in THF (30 cm^3) at −78 °C. *tert*-Butyllithium (1.7 mol dm^{-3} solution in pentane; 17.3 cm^3, 29.4 mmol) was then added at such a rate that the temperature did not rise over −60 °C. After 15 min at −78 °C and 3.5 h at −20 °C, the mixture was added to a solution containing salicylaldehyde (250 mg, 2.05 mmol) in THF (30 cm^3). After 5 h at reflux, the cooled mixture was poured onto ice–water (50 cm^3) and extracted with methylene dichloride. The organic layer was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was then cyclized by heating it in a THF (30 cm^3) solution containing HCl (6 mol dm^{-3}; 30 cm^3) at 80 °C for 1.5 days. The cooled mixture was extracted with methylene dichloride at neutral pH, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified on a silica gel column with, initially, methylene dichloride–ethanol (95:5) and finally methylene dichloride–ethanol (90:10) as eluent. After recrystallization from ethanol–water, the expected acridine **7** was obtained (47 mg, 13% without optimization of conditions), mp 111–112 °C (lit.,[21] 110–111 °C).

Procedure for the preparation of compounds 8 and 11

Under argon, *N*-(*tert*-butoxycarbonyl)aniline[18] or *N*-(*tert*-butoxycarbonyl)anisidine[18] (6 mmol) was dissolved in dry THF (15 cm^3) and the solution was stirred at −78 °C. *tert*-Butyllithium (1.7 mol dm^{-3} solution in pentane; 14.5 mmol) was added through a dropping funnel at such a rate that the temperature did not rise over −60 °C. After complete addition, the mixture was stirred for 15 min at −78 °C and for 3.5 h at −20 °C. The preceding mixture was then added to a solution of the acridone **1** (1 mmol) in THF (15 cm^3). After complete reaction at room temp. (TLC monotoring), the mixture was poured onto ice–water (35 cm^3) (neutralized for **11**) and extracted with methylene dichloride. The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column.

9-(2-Aminophenyl)-3-methoxy-10-methyl-1,10-dihydroacridin-1-one 8. This product was prepared by the above mentioned procedure from *N*-(*tert*-butoxycarbonyl)aniline and the acridone **1**. Chromatography eluent on a silica gel column was heptane–ethyl acetate–triethylamine (20:75:5). Recrystallization from acetonitrile gave the expected *product* **8** [R_f 0.18 on silica gel plates with heptane–ethyl acetate–triethylamine (20:75:5) as solvent; 170 mg, 14%] as blue crystals, mp 269 °C (Found: C, 75.65; H, 5.6; N, 8.5; O, 10.3. $C_{21}H_{18}N_2O_2 \cdot 0.25H_2O$ requires C, 75.3; H, 5.6; N, 8.4; O, 10.7%); λ_{max}(EtOH)/nm 575 (5710) and 308 (35 500); $\delta_H(CDCl_3)$ 7.86 (2 H, m, ArH), 7.15 (3 H, m, ArH), 6.76 (1 H, d, *J* 8, ArH), 6.65 (2 H, m, ArH), 5.80 (1 H, d, *J* 2.2, 2-H), 5.67 (1 H, d, *J* 2.2, 4-H), 4.38 (2 H, s, NH_2) and 3.80 (6 H, s, OMe and NMe).

***tert*-Butyl 4-methoxy-2-(3-methoxy-10-methyl-1-oxo-1,10-dihydroacridin-9-yl)phenylcarbamate 11.** This product was prepared from *N*-(*tert*-butoxycarbonyl)-*p*-anisidine and acridone **1**. Chromatography eluent on a silica gel column was initially heptane–ethyl acetate (1:4) and finally heptane–ethyl acetate–triethylamine (20:75:5). Recrystallization from acetonitrile gave the expected *product* **11** (245 mg, 10%) as blue crystals, mp 198–200 °C (Found: C, 69.3; H, 6.05; N, 6.25; O, 18.45. $C_{27}H_{28}N_2O_5 \cdot 0.5H_2O$ requires C, 69.05; H, 6.25; N, 5.95; O, 18.75%); λ_{max}(EtOH)/nm 579 (5210) and 309 (33 800); $\delta_H([^2H_6]$DMSO) 9.23 (1 H, s, NH), 7.86 (1 H, dd, *J* 8.6 and 1.6, 8-H), 7.76 (1 H, td, *J* 8.6 and 1.6, 6-H), 7.45 (1 H, dd, *J* 9 and 2.5, 5′-H), 7.20 (1 H, td, *J* 8.6 and 1.6, 7-H), 7.13 (1 H, dd, *J* 8.6 and 1.6, 5-H), 7.05 (1 H, d, *J* 2.5, 3′-H), 7.02 (1 H, d, *J* 9, 6′-H), 5.81 (1 H, d, *J* 2.2, 4-H), 5.54 (1 H, d, *J* 2.2, 2-H), 3.87 (3 H, s, 4-OMe), 3.81 (3 H, s, 3′-OMe), 3.56 (3 H, s, NMe) and 1.47 (9 H, s, CMe_3).

***N*-[2-(3-Methoxy-10-methyl-1-oxo-1,10-dihydroacridin-9-yl)-phenyl]-2,2-dimethylpropionamide 9**

Under argon, 2-bromo-*N*-pivaloylaniline[19] (5.74 g, 23.5 mmol) was dissolved in dry THF (232 cm^3) and the mixture was stirred at −78 °C. Methyllithium (1.6 mol dm^{-3} solution in hexane; 14.5 cm^3, 23.2 mmol) and, after 15 min, *tert*-butyllithium (1.7 mol dm^{-3} solution in pentane; 31.4 cm^3, 56.5 mmol) were then added using a dropping funnel. After being stirred at −78 °C for 1.5 h, the mixture was added to a solution of the acridone **1** (1 g, 3.9 mmol) in THF (50 cm^3). After 3 h at reflux, the cooled mixture was poured onto ice–water (200 cm^3) and extracted with methylene dichloride. The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with, initially, heptane–ethyl acetate (1:4) and, finally, heptane–ethyl acetate–triethylamine (20:75:5) as eluent. Recrystallization from ethyl acetate gave the expected *product* **9** (746 mg, 46%), mp 214–215 °C (Found: C, 75.15; H, 6.25; N, 6.75. $C_{26}H_{26}N_2O_3$ requires C, 75.3; H, 6.3; N, 6.6%); λ_{max}(EtOH)/nm 580 (5865) and 309 (36 800); $\delta_H([^2H_6]$DMSO) 8.05 (1 H, s, NH), 7.89 (1 H, dd, *J* 8.3 and 1.1, 3′-H), 7.78 (1 H, dd, *J* 7.8 and 1.2, 8-H), 7.67 (1 H, dd, *J* 8.3 and 1.1, 6′-H), 7.45 (1 H, td, *J* 8.3 and 1.1, 5′-H), 7.26 (1 H, td, *J* 7.8 and 1.2, 6-H), 7.16 (1 H, td, *J* 8.3 and 1.1, 4′-H), 7.01 (1 H, dd, *J* 7.8 and 1.2, 5-H), 6.99 (1 H, td, *J* 7.8 and 1.2, 7-H), 5.90 (1 H, d, *J* 1.8, 4-H), 5.70 (1 H, d, *J* 1.8, 2-H), 3.92 (3 H, s, NMe), 3.84 (3 H, s, OMe) and 0.78 (9 H, s, CMe_3).

General procedure for the synthesis of quinoacridines 15–20

Under nitrogen, *N*-(*tert*-butoxycarbonyl)aniline[18] or *N*-(*tert*-butoxycarbonyl)-*p*-anisidine[18] (6 mmol) was dissolved in dry THF (15 cm^3) at −78 °C. *tert*-Butyllithium (1.7 mol dm^{-3} solution in pentane; 14.5 mmol) was then added *via* a dropping funnel at such a rate that the temperature did not rise over −60 °C. After complete addition, the mixture was stirred for 15 min at −78 °C and for 3–4 h at −20 °C. The mixture was then added by a cannula to a solution of the substrate (1 mmol) in THF (15 cm^3). After the reaction was complete at room temp. (TLC monitoring), the cooled mixture was poured onto ice–water (35 cm^3) and extracted with methylene dichloride. The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure, and the crude product was purified on a silica gel column. The residue (except for compound **17**) was then dissolved in 6 mol dm^{-3} hydrochloric acid (80 cm^3)–THF (80 cm^3) and the solution was stirred at 80 °C for 5.5–24 h. The cooled mixture was basified with 5 mol dm^{-3} aq. sodium hydroxide and extracted with methylene dichloride. The organic layer was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on a silica gel column.

7-Methoxy-5-methyl-5*H*-quino[2,3,4-*kl*]acridine 15. To compound **9** (250 mg, 0.6 mmol) were added THF (7.5 cm^3) and 6 mol dm^{-3} hydrochloric acid (7.5 cm^3). The mixture was then stirred at 80 °C for 3 days. The cooled mixture was basified with 1 mol dm^{-3} aq. sodium hydroxide and extracted with methylene dichloride. The organic layer was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on a silica gel column with heptane–ethyl acetate–triethylamine

(20:75:5) as eluent. After recrystallization from acetonitrile, the expected *product* **15** (142 mg, 75%) was obtained as a red solid, mp 163–164 °C (Found: C, 80.4; H, 5.3; N, 9.05. $C_{21}H_{16}N_2O$ requires C, 80.75; H, 5.15; N, 9.0%); λ_{max}(EtOH)/nm 518 (7970), 295 (43 000) and 237 (43 400); δ_H($CDCl_3$) 8.50 (1 H, dd, *J* 8.6 and 1.1, 13-H), 8.33 (1 H, dd, *J* 8.3 and 1.4, 1-H), 8.01 (1 H, dd, *J* 8.6 and 1.1, 10-H), 7.66 (1 H, td, *J* 8.6 and 1.1, 11-H), 7.50 (1 H, td, *J* 8.3 and 1.4, 3-H), 7.36 (1 H, td, *J* 8.6 and 1.1, 12-H), 7.25 (1 H, dd, *J* 8.3 and 1.4, 4-H), 7.16 (1 H, td, *J* 8.3 and 1.4, 2-H), 6.93 (1 H, d, *J* 2.2, 8-H), 6.20 (1 H, d, *J* 2.2, 6-H), 3.96 (3 H, s, OMe) and 3.55 (3 H, s, NMe); *m/z* 312 (M^+, 100%) and 297 (M − CH_3, 14). This product was also prepared by the described general procedure from *N*-(*tert*-butoxycarbonyl)aniline and the acridone **1**. The reaction mixture was stirred for 5 h, and the chromatography eluent was heptane–ethyl acetate–triethylamine (20:75:5). The cyclization required 24 h and the chromatography eluent was initially heptane–ethyl acetate (1:4) and finally heptane–ethyl acetate–triethylamine (20:75:5) to obtain, after recrystallization from acetonitrile, the product **15** in 25% yield.

7,12-Dimethoxy-5-methyl-5*H*-quino[2,3,4-*kl*]acridine 16. Compound **11** (415 mg, 0.9 mmol) was dissolved in a mixture of THF (15 cm^3) and 6 mol dm^{-3} hydrochloric acid (15 cm^3). The mixture was stirred at 80 °C for 24 h, cooled, basified with 1 mol dm^{-3} aq. sodium hydroxide, and extracted with methylene dichloride. The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The desired product was then recrystallized from acetonitrile to provide *compound* **16** (216 mg, 70%) as a red solid, mp 195–196 °C (Found: C, 77.0; H, 5.6; N, 8.35. $C_{22}H_{18}N_2O_2$ requires C, 77.15; H, 5.3; N, 8.2%); λ_{max}(EtOH)/nm 516 (8530), 297 (36 900) and 248 (49 500); δ_H($CDCl_3$) 8.40 (1 H, dd, *J* 8.3 and 1.3, 1-H), 7.94 (1 H, d, *J* 9.3, 10-H), 7.85 (1 H, d, *J* 2.6, 13-H), 7.49 (1 H, td, *J* 8.3 and 1.3, 3-H), 7.39 (1 H, dd, *J* 2.6 and 9.3, 11-H), 7.22 (1 H, dd, *J* 8.3 and 1.3, 4-H), 7.14 (1 H, td, *J* 8.3 and 1.3, 2-H), 6.89 (1 H, d, *J* 2.1, 8-H), 6.18 (1 H, d, *J* 2.1, 6-H), 3.95 (3 H, s, 12-OMe), 3.94 (3 H, s, 7-OMe) and 3.53 (3 H, s, NMe); *m/z* 342 (M^+, 100%) and 327 (M − CH_3, 79). This product was also prepared from *N*-(*tert*-butoxycarbonyl)-*p*-anisidine and the acridone **1**. The reaction mixture was stirred for 2 h 15 min and chromatography eluent was heptane–ethyl acetate–triethylamine (20:75:5). The cyclization required 14 h and the chromatography eluent was, initially, heptane–ethyl acetate (1:4) and, finally, heptane–ethyl acetate–triethylamine (20:75:5) to obtain, after recrystallization from acetonitrile, the product **16** in 38% yield.

7-Benzyloxy-12-methoxy-5-methyl-5*H*-quino[2,3,4-*kl*]acridine 17. This product was prepared from *N*-(*tert*-butoxycarbonyl)-*p*-anisidine and the acridone **2**. The reaction mixture was stirred for 17 h and chromatography eluent was methylene dichloride–ethanol (95:5). The time of cyclization was 5.5 h and the chromatography eluent was methylene dichloride–ethanol (95:5) to obtain, after recrystallization from ethanol, the *product* **17** in 42% yield, mp 135–137 °C (Found: C, 75.2; H, 6.0; N, 6.5; O, 12.3. $C_{28}H_{22}N_2O_2 \cdot 1.5H_2O$ requires C, 75.5; H, 5.65; N, 6.3; O, 12.55%); λ_{max}(EtOH)/nm 516 (6840), 297 (35 800) and 249 (47 000); δ_H($CDCl_3$) 8.36 (1 H, dd, *J* 8.2 and 1.3, 1-H), 7.97 (1 H, d, *J* 9, 10-H), 7.81 (1 H, d, *J* 2.5, 13-H), 7.49 (1 H, td, *J* 8.2 and 1.3, 3-H), 7.39 (1 H, dd, *J* 9 and 2.5, 11-H), 7.21 (1 H, dd, *J* 8.2 and 1.3, 4-H), 7.13 (1 H, td, *J* 8.2 and 1.3, 2-H), 7.09 (1 H, d, *J* 1.8, 8-H), 7.55–7.30 (5 H, m, *Ph*CH_2), 6.25 (1 H, d, *J* 1.8, 6-H), 5.19 (2 H, s, OCH_2), 3.92 (3 H, s, 12-OMe) and 3.49 (3 H, s, NMe).

7-Benzyloxy-5-methyl-5*H*-quino[2,3,4-*kl*]acridine 18. This product was prepared from *N*-(*tert*-butoxycarbonyl)aniline and the acridone **2**. The reaction mixture was stirred for 16 h and chromatography eluent was methylene dichloride–ethanol (95:5) to obtain, after crystallization in hexane, the *product* **18** in 39% yield, as an amorphous solid, mp 116–128 °C (Found: C, 74.15; H, 6.25; N, 6.45. $C_{27}H_{20}N_2O \cdot 2.75H_2O$ requires C, 74.05; H, 5.9; N, 6.4%); λ_{max}(EtOH)/nm 518 (4150), 295 (29 700) and 238 (37 500); δ_H($CDCl_3$) 8.40 (1 H, dd, *J* 8.5 and 1.2, 13-H), 8.27 (1 H, dd, *J* 8.3 and 1.3, 1-H), 8.04 (1 H, dd, *J* 8.5 and 1.2, 10-H), 7.64 (1 H, td, *J* 8.5 and 1.2, 11-H), 7.56 (1 H, td, *J* 8.3 and 1.3, 3-H), 7.33 (1 H, td, *J* 8.5 and 1.2, 12-H), 7.29 (1 H, dd, *J* 8.3 and 1.3, 4-H), 7.19 (1 H, td, *J* 8.3 and 1.3, 2-H), 7.58–6.9 (5 H, m, *Ph*CH_2), 7.11 (1 H, d, *J* 2, 8-H), 6.60 (1 H, d, *J* 2, 6-H), 5.17 (2 H, s, OCH_2) and 3.55 (3 H, s, NMe); *m/z* 388 (M^+, 100%) and 373 (M − CH_3, 11).

12,12,15-Trimethyl-12,15-dihydropyrano[3,2-*b*]quino[4,3,2-*mn*]acridine 19. This product was prepared from *N*-(*tert*-butoxycarbonyl)aniline and noracronycine **3**. The reaction mixture was stirred for 4 h and chromatography eluent was heptane–ethyl acetate–triethylamine (20:75:5). The cyclization required 24 h and the chromatography eluent was heptane–ethyl acetate (1:4) to obtain, after crystallization in hexane, the *product* **19** in 45% yield, mp 120–129 °C (Found: C, 80.5; H, 6.0; N, 7.1; O, 6.4. $C_{25}H_{20}N_2O \cdot 0.5H_2O$ requires C, 80.4; H, 5.7; N, 7.5; O, 6.4%); λ_{max}(EtOH)/nm 541 (6065), 324 (42 200), 261 (30 200) and 236 (28 500); δ_H($CDCl_3$) 8.43 (1 H, dd, *J* 8.4 and 1.3, 5-H), 8.24 (1 H, dd, *J* 8.3 and 1.4, 4-H), 8.02 (1 H, dd, *J* 8.4 and 1.3, 8-H), 7.63 (1 H, td, *J* 8.4 and 1.3, 7-H), 7.53 (1 H, td, *J* 8.3 and 1.4, 2-H), 7.34 (1 H, td, *J* 8.4 and 1.3, 6-H), 7.30 (1 H, dd, *J* 8.3 and 1.4, 1-H), 7.20 (1 H, td, *J* 8.3 and 1.4, 3-H), 7.07 (1 H, s, 10-H), 6.63 (1 H, d, *J* 9.8, 14-H), 5.76 (1 H, d, *J* 9.8, 13-H), 3.82 (3 H, s, NMe) and 1.53 (6 H, s, 12-Me_2); *m/z* 364 (M^+, 100%) and 349 (M − CH_3, 57).

6-Methoxy-12,12,15-trimethyl-12,15-dihydropyrano[3,2-*b*]quino[4,3,2-*mn*]acridine 20. This product was prepared from *N*-(*tert*-butoxycarbonyl)-*p*-anisidine and noracronycine **3**. The reaction mixture was stirred for 15 h and chromatography eluent was heptane–ethyl acetate–triethylamine (20:75:5). The cyclization required 13 h and the chromatography eluent was heptane–ethyl acetate–triethylamine (20:75:5) to obtain, after crystallization in hexane, the *product* **20** in 32% yield, as an amorphous solid, mp 120–133 °C (Found: C, 77.45; H, 5.9; N, 6.9; O, 9.7. $C_{26}H_{22}N_2O_2 \cdot 0.5H_2O$ requires C, 77.4; H, 5.75; N, 6.95; O, 9.9%); λ_{max}(EtOH)/nm 538 (7050), 328 (42 000) and 259 (37 600); δ_H($CDCl_3$) 8.33 (1 H, dd, *J* 8.3 and 1.3, 4-H), 7.95 (1 H, d, *J* 9.3, 8-H), 7.81 (1 H, d, *J* 2.6, 5-H), 7.52 (1 H, td, *J* 8.3 and 1.3, 2-H), 7.37 (1 H, dd, *J* 2.6 and 9.3, 7-H), 7.30 (1 H, dd, *J* 8.3 and 1.3, 1-H), 7.21 (1 H, td, *J* 8.3 and 1.3, 3-H), 7.03 (1 H, s, 10-H), 6.64 (1 H, d, *J* 9.9, 14-H), 5.77 (1 H, d, *J* 9.9, 13-H), 3.92 (3 H, s, OMe), 3.79 (3 H, s, NMe) and 1.52 (6 H, s, 12-Me_2); *m/z* 394 (M^+, 100%) and 379 (M − CH_3, 19).

12-Methoxy-5-methyl-5*H*-quino[2,3,4-*kl*]acridin-7-ol 22

A mixture of compound **17** (500 mg, 1.12 mmol), 10% palladized charcoal (250 mg) and ethanol (50 cm^3) was stirred under hydrogen at 50 °C at normal pressure for 19 h. The cooled mixture was then filtered, the palladium was washed with ethanol, and the mixture was evaporated under reduced pressure. The expected product was recrystallized from acetonitrile to obtain the *alcohol* **22** (249 mg, 60%) as a red solid, mp 192–194 °C (Found: C, 72.8; H, 5.4; N, 7.55. $C_{21}H_{16}N_2O_2 \cdot H_2O$ requires C, 72.8; H, 5.25; N, 8.1%); λ_{max}(EtOH)/nm 559 (4015), 467 (5530) and 270 (38 400); δ_H($CDCl_3$) 8.51 (1 H, dd, *J* 8.2 and 1.2, 1-H), 7.84 (1 H, d, *J* 1, 13-H), 7.82 (1 H, d, *J* 8.9, 10-H), 7.67 (2 H, m, 3- and 11-H), 7.51 (1 H, dd, *J* 8.2 and 1.2, 4-H), 7.36 (1 H, td, *J* 8.2 and 1.2, 2-H), 6.73 (1 H, d, *J* 1.6, 8-H), 6.43 (1 H, d, *J* 1.6, 6-H), 3.96 (3 H, s, OMe), 3.75 (1 H, br s, 7-OH) and 3.68 (3 H, s, NMe).

5-Methyl-5*H*-quino[2,3,4-*kl*]acridine-7-12-diol 23

Method A. Under nitrogen, hydrobromic acid (47%; 1.5 cm^3) was added to compound **16** (30 mg, 0.088 mmol). The mixture was refluxed for 7 h and the cooled mixture was poured onto

ice–water and basified with ammonia. The precipitate was filtered off to provide compound **23** (19 mg, 59%).

Method B. Under argon, boron tribromide (1 mol dm^{-3} in methylene dichloride; 6 cm^3, 6 mmol) was added to a solution of compound **22** (100 mg, 0.3 mmol) in dry methylene dichloride (12 cm^3) at −20 °C. After being stirred at room temp. for 24 h, the mixture was poured onto ice-water (5 cm^3) and basified with ammonia. Ethanol (20 cm^3) was added to the mixture and the resulting homogeneous solution was stirred for 5 h. After evaporation off of ethanol, the solid product was filtered off, washed with water and air dried to give *product* **23** (88 mg, 85%), mp > 400 °C (Found: C, 70.55; H, 4.95; N, 8.0; O, 16.5. $C_{20}H_{14}N_2O_2 \cdot 1.5H_2O$ requires, C, 70.4; H, 5.0; N, 8.2; O, 16.4%); λ_{max}(EtOH)/nm 566 (3285), 468 (4645) and 270 (28 300); δ_H([$^2H_6$]DMSO) 9.87 (1 H, s, 12-OH), 8.37 (1 H, dd, *J* 8.1 and 1.2, 1-H), 7.84 (1 H, d, *J* 1, 13-H), 7.77 (1 H, d, *J* 9, 10-H), 7.64 (1 H, d, *J* 9 and 1, 11-H), 7.58 (1 H, td, *J* 8.1 and 1.2, 3-H), 7.37 (1 H, dd, *J* 8.1 and 1.2, 4-H), 7.29 (1 H, td, *J* 8.1 and 1.2, 2-H), 6.65 (1 H, d, *J* 1.5, 8-H), 6.32 (1 H, d, *J* 1.5, 6-H), 3.65 (1 H, br s, 7-OH) and 3.61 (3 H, s, NMe).

7-Methoxy-5-methyl-5*H*-quino[2,3,4-*kl*]acridin-12-ol 24

Under argon, compound **16** (60 mg, 0.18 mmol) was dissolved in dry methylene dichloride (7.5 cm^3) and boron tribromide (1 mol dm^{-3} in methylene dichloride; 4 cm^3, 4 mmol) was added dropwise. The mixture was stirred at room temp. for 3 days and then was poured onto ice–water (20 cm^3) and basified with 1 mol dm^{-3} aq. sodium hydroxide. Ethanol (20 cm^3) was added to give an homogeneous solution, which was stirred for a 12 h period. After evaporation, 6 mol dm^{-3} hydrochloric acid was added (to pH 6–7) and the product was filtered off to give the *alcohol* **24** (15 mg, 20%), mp > 400 °C (Found: C, 65.45; H, 5.25; N, 6.95; O, 13.8. $C_{21}H_{16}N_2O_2 \cdot HCl \cdot 1.25H_2O$ requires C, 65.15; H, 5.1; N, 7.25; O, 13.4%); λ_{max}(EtOH)/nm 522 (6490), 299 (30 000) and 247 (44 400); δ_H([$^2H_6$]DMSO) 9.93 (1 H, br s, 12-OH), 8.36 (1 H, dd, *J* 8.1 and 1.2, 1-H), 7.88 (1 H, d, *J* 1.1, 13-H), 7.85 (1 H, d, *J* 9, 10-H), 7.61 (1 H, td, *J* 8.1 and 1.2, 3-H), 7.49 (1 H, d, *J* 9 and 1.1, 11-H), 7.39 (1 H, dd, *J* 8.1 and 1.2, 4-H), 7.26 (1 H, td, *J* 8.1 and 1.2, 2-H), 6.81 (1 H, d, *J* 1.8, 8-H), 6.66 (1 H, d, *J* 1.8, 6-H), 3.94 (3 H, s, OMe) and 3.57 (3 H, s, NMe); *m/z* 328 (M^+, 100%) and 313 (M − CH_3, 17).

5-Methyl-5*H*-quino[2,3,4-*kl*]acridin-7-ol 25

Method A. Compound **18** (50 mg, 0.13 mmol), 10% palladized charcoal (23 mg) and ethanol (5 cm^3) were stirred under hydrogen at 50 °C at normal pressure for 3 h. The cooled mixture was then filtered, the palladium was washed with ethanol, and the mixture was evaporated under reduced pressure. The expected product **25** was then obtained (20 mg, 52%).

Method B. The quinoacridine **15** (50 mg, 0.16 mmol) was dissolved in hydrobromic acid (47%; 2.6 cm^3) and the solution was refluxed for 24 h. The cooled mixture was poured onto ice–water and basified with ammonia. The precipitate was filtered off and dissolved in ethanol, and the solution was evaporated to obtain the *product* **25** (32 mg, 55%) as an amorphous solid, mp > 400 °C (Found: C, 65.95; H, 5.0; N, 7.6; O, 10.95; Br, 10.45. $C_{20}H_{14}N_2O \cdot 1.5H_2O \cdot 0.5HBr$ requires C, 65.7; H, 4.8; N, 7.65; O, 10.9; Br, 10.9%); λ_{max}(EtOH)/nm 545 (6025), 462 (9560) and 273 (54 800); δ_H($CDCl_3$) 8.45 (1 H, dd, *J* 8.3 and 1.1, 13-H), 8.35 (1 H, dd, *J* 8.2 and 1.1, 1-H), 7.77 (4 H, m, ArH), 7.58–7.34 (2 H, m, ArH), 6.66 (1 H, d, *J* 1.8, 8-H), 6.37 (1 H, d, *J* 1.8, 6-H), 3.72 (1 H, s, 7-OH) and 3.68 (3 H, s, NMe); *m/z* 298 (M^+, 100%) and 283 (M − CH_3, 39).

12,12,15-Trimethyl-12,15-dihydropyrano[3,2-*b*]quino[4,3,2-*mn*]acridin-6-ol 21

To a solution containing **20** (100 mg, 0.25 mmol) in dry methylene dichloride (12 cm^3) under argon was added boron tribromide (1 mol dm^{-3} in methylene dichloride; 5 cm^3, 5 mmol) dropwise. After being stirred at −20 °C for 6 h, the mixture was poured onto ice–water (20 cm^3) and basified with ammonia. Ethanol was added, the solution was stirred for 7 h and, after evaporation off of ethanol, the residue was extracted with methylene dichloride. The organic layer was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give compound **21** (20 mg, 19%), mp > 400 °C (Found: C, 76.4; H, 6.2; N, 8.05. $C_{25}H_{20}N_2O_2 \cdot 0.5CH_3CN \cdot 0.5C_2H_5OH$ requires C, 76.5; H, 5.8; N, 8.25%); λ_{max}(EtOH)/nm 543 (6300), 327 (35 000) and 253 (33 200); δ_H($CDCl_3$) 9.91 (1 H, s, 6-OH), 8.31 (1 H, dd, *J* 8.3 and 1.1, 4-H), 7.86 (1 H, d, *J* 8.5, 8-H), 7.85 (1 H, d, *J* 1.1, 5-H), 7.64 (1 H, dd, *J* 8.3 and 1.1, 1-H), 7.54 (1 H, td, *J* 8.3 and 1.1, 2-H), 7.38 (1 H, d, *J* 8.5 and 1.1, 7-H), 7.34 (1 H, td, *J* 8.3 and 1.1, 3-H), 6.86 (1 H, s, 10-H), 6.79 (1 H, d, *J* 9.9, 14-H), 5.91 (1 H, d, *J* 9.9, 13-H), 3.81 (3 H, s, NMe) and 1.52 (6 H, s, 12-Me_2); *m/z* 380 (M^+, 100%) and 365 (M − CH_3, 42).

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