Reaction of Noracronycine and 1-Hydroxy-3-methoxy-10-methylacridone with Alkyl- and Aryl-lithiums: Formation of Quinone Methides

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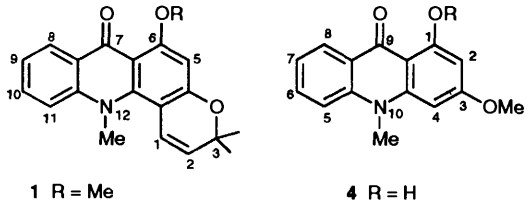
Alkyl- and aryl-lithiums reacted with noracronycine and 1-hydroxy-3-methoxy-10-methylacridone in a one-step addition–dehydration transformation to provide the corresponding 7- and 9-substituted derivatives having a quinone methide function and, therefore, potential alkylating antitumour properties.

Acronycine **1** (6-methoxy-3,3,12-trimethyl-3,12-dihydro-7*H*-pyrano[2,3-*c*]acridin-7-one), isolated from *Acronychia baueri*, an Australian scrub ash from the family of Rutacees [1] is a broad spectrum antitumour agent,[2-3] although its poor solubility in aqueous media has hindered its development as a clinical agent. As a way of solving this problem, various water-soluble acronycine analogues have been prepared of which only *O*-dimethylaminoethyl noracronycine **2**,[4] displayed good antitumour activity. This compound is cytotoxic against some multi drug resistant (MDR) cells [3] as is acronycine **1** itself.

Through our continuing interest in the search for new antitumour drugs with improved biological properties and bioavailability, we have synthesized new derivatives of **1** although structural modifications to the model compound were limited by the need to retain antitumour activity and by the numerous analogues and derivatives already prepared.[4-6]

Our approach was to substitute the acronycine ring system with hydrophilic side-chains. Here we describe our studies of the reactivity of acronycine **1**, noracronycine **3** and the tricyclic model compounds **4**, **5** (Scheme 1) in the presence of alkyl-, aryl-, aminoalkyl- and aminoaryl-lithium derivatives.



1 R = Me
2 R = $CH_2CH_2NMe_2$
3 R = H
4 R = H
5 R = Me

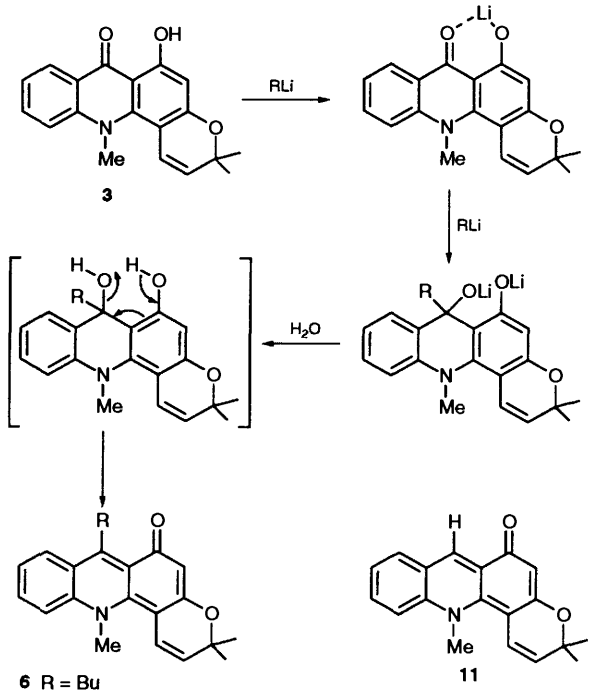
Scheme 1

Results and Discussion

We thought that introduction of the hydrophilic aminoalkyl or *N*-aminoalkylcarboxamido substituents [7] could be achieved *via* the corresponding formyl- or carboxy-substituted compounds.

Since the two *ortho*-directing ether groups in **1** were likely to lead to lithiation at the 5-position we attempted such a reaction with lithium diisopropylamide (LDA). ^{1}H NMR monitoring of CH_3OD-quenched samples showed the absence of lithiation between −78 and −20 °C. We then attempted hydrogen–deuterium exchange using *tert*-butyl-, butyl- and methyl-lithium in various solvents (tetrahydrofuran or diethyl ether) at different temperatures (−78, −20 and 0 °C, reflux) and with crown ether 12C4 or tetramethylethylenediamine (TMEDA). Our results with acronycine **1**, even in the presence of TMEDA (for decomplexation of alkyllithium reagent), show that, as reported for acridone,[6] there is no exchange with alkyllithium reagents. For acronycine **1** this may be explicable in terms of steric hindrance near the position 5. Thus, when noracronycine **3** was allowed to react with butyllithium in diethyl ether at room temperature for 1 h and the reaction mixture then treated with CH_3OD, ^{1}H NMR analysis showed the appearance of new signals in the 1–2 and 7–8.5 ppm regions, a 0.4 ppm shielding for the 5-H signal (without decrease of its intensity), a 0.2 ppm shielding for 1-H and 2-H, and the disappearance of the 6-OH peak. Further, thin layer chromatography showed the presence of a new product, characterized by a blue colour, the mass spectrum (CI, isobutane) of which had a peak at *m/z* 348 (M + 1) corresponding to butyllithium addition and subsequent dehydration. ^{1}H NMR spectral analysis together with an elemental analysis supported identification of the product as compound **6**.

Addition of butyllithium to the 7-carbonyl group followed by dehydration (see Scheme 2) accounts for the observed



6 R = Bu
7 R = Me
8 R = Ph
9 R = $C_6H_4NMe_2$-4
10 R = $CH_2CH_2CH_2NMe_2$
11

Scheme 2

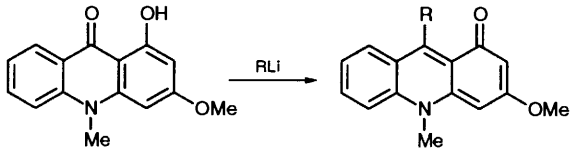
transformation. This mechanism is in agreement with those involved in the reduction of quinizarin by an excess of sodium borohydride to give 1,4-anthraquinone.[8]

Reactivity differences observed for the carbonyl groups of acronycine **1** and noracronycine **3** may be explained in terms of activation of this group by the lithium atom bound to the oxygen atom in the *peri* position. Attempted verification of this failed, since there was no reaction when the tricyclic model compound **5** was treated under similar conditions in the presence of $LiClO_4$, a Lewis acid carbonyl-activating compound.[9]

The blue colour of compound **6** (and analogues) may result from conjugation similar to that found in azulenes; thus comparison of the UV spectra of noracronycine **3** (410 cm^{-1}) and compound **6** (614 cm^{-1}) is characterized by a blue shift.

Extending our work to the functionalization of the 7-position, we allowed noracronycine **3** to react with methyl-, phenyl-, *p*-dimethylaminophenyl- and 3-dimethylaminopropyl-lithium to give the corresponding compounds **7**–**10**. Methyllithium gave the by-product **11** in addition to the expected condensation product **7**, a compound also prepared in low yield by lithium aluminium hydride reduction of noracronycine **3**. Formation of **11** with the methyllithium reaction probably resulted from a reduction involving an unknown source of hydrogen.

The addition of organolithium reagents to other carbonyl compounds having a *peri* hydroxy group was extended by treating the tricyclic compound **4** with butyl-, *p*-dimethylaminophenyl- and 3-dimethylaminopropyllithium (Scheme 3) to give compounds **12**, **13**, **14**, respectively.



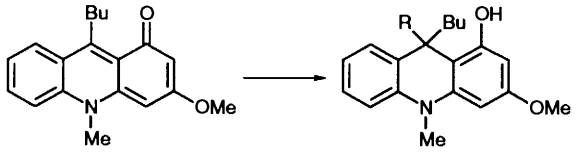
4

12 R = $C_6H_4NMe_2$-4
13 R = Bu
14 R = $CH_2CH_2CH_2NMe_2$

Scheme 3

In order to optimize yields (61–68%) in this work, 3 equiv. at least of the organolithium reagents were required: it was also possible to use 1 equiv. of methyllithium and 2 equiv. of another alkyl- or aryl-lithium derivative.

To demonstrate the reactivity of the quinone methides prepared, **13** was treated with a nucleophile (methyllithium) and a reducing agent (lithium aluminium hydride) to give compounds **15** and **16** respectively (Scheme 4); this probably resulted from a 1,4- **15** and a 1,2-addition followed by a tautomerization **16**, respectively.



13

15 R = Me
16 R = H

Scheme 4

Experimental

Melting points were measured with an Electrothermal apparatus using capillary tubes and are uncorrected and with a Reichert microscope for compounds **6**, **7**, **8**, **11**. ^1H NMR spectra were obtained in $CDCl_3$ or [$^2H_6$]-DMSO using an AC-200MHz 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. The mass spectra were recorded on AEI.MS-50 (MS-EI) or AEI.MS-9 (MS-CI) spectrometers and, as for the elemental analyses, they were performed in ICSN/CNRS, Gif sur Yvette, France.

Acronycine **1**.—This compound, prepared by a literature[10] synthesis, was recrystallized from ethanol to give yellow needles, mp 173–175 °C (lit.,[10] 175–176 °C); δ_H([$^2H_6$]-DMSO) 8.13 (1 H, dd, *J* 8 and 1.5, 8-H), 7.77 (1 H, td, *J* 8 and 1.5, 9-H), 7.60 (1 H, dd, *J* 8 and 1.5, 11-H), 7.31 (1 H, td, *J* 8 and 1.5, 10-H), 6.75 (1 H, d, *J* 9.7, 1-H), 6.43 (1 H, s, 5-H), 5.67 (1 H, d, *J* 9.7, 2-H), 3.88 (3 H, s, NMe), 3.86 (3 H, s, OMe) and 1.55 (6 H, s, 3-Me_2).

Noracronycine **3**.—This compound, prepared by a literature[10] synthesis, recrystallized from ethyl acetate as yellow needles, mp 201–203 °C (lit.,[10] 200–201 °C); λ_{max}(EtOH)/nm 410 (4290), 285 (38 700) and 256 (23 100); δ_H([$^2H_6$]-DMSO) 14.95 (1 H, s, 6-OH), 8.27 (1 H, dd, *J* 8 and 1.4, 8-H), 7.91 (1 H, td, *J* 8 and 1.4, 9-H), 7.75 (1 H, dd, *J* 8 and 1.4, 11-H), 7.43 (1 H, td, *J* 8 and 1.4, 10-H), 6.80 (1 H, d, *J* 9.7, 1-H), 6.20 (1 H, s, 5-H), 5.66 (1 H, d, *J* 9.7, 2-H), 3.96 (3 H, s, NMe) and 1.53 (6 H, s, 3-Me_2).

1-*Hydroxy*-3-*methoxy*-10-*methylacridone* **4**.—To a solution of 1,3-dihydroxy-10-methylacridone[10] (2.95 g, 12.2 mmol) in acetone (122 cm^3), potassium carbonate (1.85 g, 13.4 mmol) and iodomethane (0.84 cm^3, 13.5 mmol) were added. The mixture was stirred at reflux for 15 h, cooled, filtered and evaporated under reduced pressure. The crude oil was extracted with methylene dichloride and the extract washed with 1 mol dm^{-3} aqueous sodium hydroxide, brine and water, dried ($MgSO_4$) and concentrated. The residue was recrystallized from ethyl acetate to give the pure *product* **4** (2.4 g, 77%) as yellow needles, mp 164–165 °C (Found: C, 70.3; H, 5.3; N, 5.6; O, 18.8. $C_{15}H_{13}NO_3$ requires C, 70.6; H, 5.1; N, 5.5; O, 18.8%); λ_{max}(EtOH)/nm 391 (3540), 271 (28 900) and 263 (25 700); δ_H($CDCl_3$) 8.44 (1 H, dd, *J* 8 and 1.6, 8-H), 7.69 (1 H, td, *J* 8 and 1.6, 6-H), 7.46 (1 H, dd, *J* 8 and 1.6, 5-H), 7.27 (1 H, td, *J* 8 and 1.6, 7-H), 6.29 (2 H, s, 2-H and 4-H), 3.88 (3 H, s, OMe) and 3.77 (3 H, s, NMe); δ_H[$^2H_6$]-DMSO 14.90 (1 H, s, 1-OH).

1,3-*Dimethoxy*-10-*methylacridone* **5**.—Under argon, sodium hydride (352 mg, 8.8 mmol) was added to a solution of 1,3-dihydroxy-10-methylacridone[10] (513 mg, 2.2 mmol) in dried *N*,*N*-dimethylformamide (8 cm^3). After 15 min, dimethyl sulfate (1.3 cm^3, 13.2 mmol) was added to the mixture which was then stirred for 15 h. After this it was poured onto water and extracted with methylene dichloride and the extract dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Chromatography of the residue on a silica gel column, eluting with a heptane–ethyl acetate gradient (1:1 to 1:4), gave the pure *title product* **5** (254 mg, 42%) as yellow crystals, mp 167–168 °C (lit.,[10] 163–165 °C); δ_H($CDCl_3$) 8.46 (1 H, dd, *J* 8 and 1.6, 8-H), 7.63 (1 H, td, *J* 8 and 1.6, 6-H), 7.41 (1 H, dd, *J* 8 and 1.6, 5-H), 7.24 (1 H, td, *J* 8 and 1.6, 7-H), 6.44 (1 H, d, *J* 1.8, 4-H), 6.29 (1 H, d, *J* 1.8, 2-H), 3.99 (3 H, s, OMe), 3.95 (3 H, s, OMe) and 3.81 (3 H, s, NMe).

7-*Butyl*-3,3,12-*trimethyl*-3,12-*dihydro*-6H-*pyrano*[2,3-c]-*acridin*-6-*one* **6**.—To a solution of noracronycine **3** (311 mg, 1.01 mmol) in dry diethyl ether (50 cm^3) was added butyllithium (1.6 mol dm^{-3} solution in hexane; 3.1 cm^3, 4.96 mmol) under argon. After 1 h at room temperature, the mixture was poured onto ice–water (100 cm^3) and extracted with methylene dichloride. The extract was washed with water, dried ($MgSO_4$) and evaporated on a rotatory evaporator. The residue was chromatographed on a silica gel column with heptane–ethyl

acetate (1:2) as eluent. Evaporation of the solvent and trituration of the residue with hexane provided **6** (179 mg, 50%) as an amorphous solid, mp 153–161 °C (Found: C, 79.3; H, 7.2; N, 3.95; O, 9.55. $C_{23}H_{25}NO_2$ requires C, 79.5; H, 7.25; N, 4.05; O, 9.2%); λ_{max}(EtOH)/nm 614 (3690) and 315 (36 800); δ_H($CDCl_3$) 8.41 (1 H, dd, *J* 8 and 1.3, 8-H), 8.05 (1 H, td, *J* 8 and 1.3, 10-H), 7.92 (1 H, dd, *J* 8 and 1.3, 11-H), 7.76 (1 H, s, 5-H), 7.69 (1 H, td, *J* 8 and 1.3, 9-H), 6.57 (1 H, d, *J* 9.8, 1-H), 5.61 (1 H, d, *J* 9.8, 2-H), 4.32 (3 H, s, NMe), 3.92 (2 H, m, α-CH_2), 1.90–1.62 (4 H, m, β,γ-CH_2), 1.56 (6 H, s, 3-Me_2) and 0.99 (3 H, t, *J* 6.8, Me); *m*/*z* 348 (MH^+).

3,3,7,12-*Tetramethyl*-3,12-*dihydro*-6H-*pyrano*[2,3-c]*acridin*-6-*one* **7**.—Under argon, methyllithium (1.6 mol dm^{-3} solution in diethyl ether; 3.1 cm^3, 5 mmol) was added to a solution of noracronycine **3** (308 mg, 1 mmol) in dry diethyl ether (50 cm^3). The mixture was refluxed for 2 h after which the cooled solution was poured onto ice–water (100 cm^3). The resulting blue aqueous layer was quickly separated and extracted with methylene dichloride. The combined ether layer and extract were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residue on a silica gel column with methylene dichloride and then methylene dichloride–ethanol (96:4) as eluent gave, after precipitation in hexane, the expected *compound* **7** (210 mg, 69%) as a blue amorphous solid, mp 134–143 °C (Found: C, 77.5; H, 6.6; N, 4.25; O, 11.65. $C_{20}H_{19}NO_2$·0.25H_2O requires C, 77.55; H, 6.35; N, 4.5; O, 11.6%); λ_{max}(EtOH)/nm 612 (3510), 316 (28 500) and 240 (15 300); δ_H($CDCl_3$) 8.09 (1 H, dd, *J* 8.3 and 1.2, 8-H), 7.66 (1 H, td, *J* 8.3 and 1.2, 10-H), 7.41 (1 H, dd, *J* 8.3 and 1.2, 11-H), 7.31 (1 H, td, *J* 8.3 and 1.2, 9-H), 6.40 (1 H, d, *J* 9.9, 1-H), 6.05 (1 H, s, 5-H), 5.55 (1 H, d, *J* 9.9, 2-H), 3.90 (3 H, s, NMe), 3.20 (3 H, s, 7-Me) and 1.48 (6 H, s, 3-Me_2); *m*/*z* 306 (MH^+). Continuing elution gave the by-product **11** (11 mg, 4%) described below.

3,3,12-*Trimethyl*-7-*phenyl*-3,12-*dihydro*-6H-*pyrano*[2,3-c]-*acridin*-6-*one* **8**.—To a solution of noracronycine **3** (310 mg, 1.01 mmol) dissolved in dry diethyl ether (50 cm^3), phenyllithium (2 mol dm^{-3} solution in cyclohexane–diethyl ether; 2.5 cm^3, 5 mmol) was added. After 1.5 h at reflux, the cooled mixture was poured onto ice–water (100 cm^3) and extracted with diethyl ether. After work-up, the crude product was crystallized from hexane to give **8** (316 mg, 75%) as a blue amorphous solid, mp 214–221 °C (Found: C, 81.45; H, 6.2; N, 3.45; O, 8.9. $C_{25}H_{21}NO_2$ requires C, 81.75; H, 5.75; N, 3.8; O, 8.7%); λ_{max}(EtOH)/nm 632 (3940), 317 (32 000) and 309 (28 400); δ_H($CDCl_3$) 7.64 (1 H, td, *J* 1.5 and 8.4, 10-H), 7.50–7.05 (8 H, m, Ar-H), 6.49 (1 H, d, *J* 9.8, 1-H), 5.78 (1 H, s, 5-H), 5.61 (1 H, d, *J* 9.8, 2-H), 3.99 (3 H, s, NMe) and 1.50 (6 H, s, 3-Me_2); *m*/*z* 367 (M^+, 100%) and 352 (73, M − CH_3).

4-*Dimethylaminophenyllithium*.[11]—To a solution of *p*-bromo-*N*,*N*-dimethylaniline (1 g, 5 mmol) in dry diethyl ether (30 cm^3), lithium cut into pieces (1.52 g, 220 mmol) was added under argon. Gentle heating was necessary to start the reaction after which the remaining *p*-bromo-*N*,*N*-dimethylaniline (22.5 g, 113 mmol) dissolved in dry diethyl ether (50 cm^3) was added dropwise so that a gentle reflux was maintained. After 5 h at reflux, the mixture was cooled and kept under argon in the reaction flask. Titration of the solution[12] showed that its concentration was 0.9 mol dm^{-3}.

7-(4-*Dimethylaminophenyl*)-3,3,12-*trimethyl*-3,12-*dihydro*-6H-*pyrano*[2,3-c]*acridin*-6-*one* **9**.—To a solution of noracronycine **3** (321 mg, 1.04 mmol) in dry diethyl ether (50 cm^3), 4-dimethylaminophenyllithium (0.9 mol dm^{-3} solution in diethyl ether; 3.5 cm^3, 3.15 mmol) was added. The mixture was stirred at reflux for 2 h and then poured onto ice–water (100 cm^3). The aqueous layer was quickly separated and extracted with diethyl ether. The combined ether layer and extract were washed with water, dried ($MgSO_4$) and then evaporated under reduced pressure to give **9** which crystallized from diethyl ether as blue crystals (345 mg, 75%), mp 255 °C (Found: C, 79.0; H, 6.55; N, 6.7; O, 7.75. $C_{27}H_{26}N_2O_2$ requires C, 79.0; H, 6.4; N, 6.8; O, 7.8%); λ_{max}(EtOH)/nm 622 (4320), 317 (37 600) and 309 (33 800); δ_H($CDCl_3$) 7.65 (1 H, td, *J* 8.3 and 1.3, 10-H), 7.50 (1 H, dd, *J* 8.3 and 1.3, 8-H), 7.44 (1 H, dd, *J* 8.3 and 1.3, 11-H), 7.14 (1 H, td, *J* 8.3 and 1.3, 9-H), 7.05 (2 H, d, *J* 8.6, 3′-H), 6.80 (2 H, d, *J* 8.6, 2′-H), 6.48 (1 H, d, *J* 9.8, 1-H), 5.98 (1 H, s, 5-H), 5.59 (1 H, d, *J* 9.8, 2-H), 3.99 (3 H, s, NMe), 3.00 (6 H, s, NMe_2) and 1.50 (6 H, s, 3-Me_2); *m*/*z* 410 (M^+, 100%), 409 (91, M − H) and 395 (40, M − CH_3).

3-*Dimethylaminopropyllithium*.[13]—To a mixture of granular lithium (3 g, 0.43 mol) and dry diethyl ether (40 cm^3) under argon, freshly distilled 3-dimethylaminopropyl chloride (22 g, 0.15 mol) was added by way of a dropping funnel. After a gentle heating to initiate the reaction, the reagent was added dropwise so that a reflux was maintained. After complete addition, stirring was continued for 1 h. The resulting cooled mixture was used for the reactions described below.

7-(3-*Dimethylaminopropyl*)-3,3,12-*trimethyl*-3,12-*dihydro*-12H-*pyrano*[2,3-c]*acridin*-6-*one* **10**.—To a solution of noracronycine **3** (1 g, 3.3 mmol) in dry diethyl ether (160 cm^3) under argon, the above mentioned solution of 3-dimethylaminopropyllithium (20 cm^3) was added. The mixture was heated at reflux for 18 h and then poured onto ice-cooled brine. The organic layer was separated and the aqueous solution was extracted with diethyl ether. The combined ether layer and extract were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with initially methylene dichloride–ethanol (95:5) as eluent and then finally the same mixture plus triethylamine (91:4.5:4.5). After evaporation of the solvent, the residue was taken up in hexane to obtain the expected *product* **10** (290 mg, 20%) as blue crystals, mp 108–109 °C (Found: C, 75.5; H, 8.25; N, 7.4; O, 8.85. $C_{24}H_{28}N_2O_2$·0.3$C_4H_{10}O$ requires C, 75.9; H, 7.85; N, 7.05; O, 9.25%); λ_{max}(EtOH)/nm 618 (3740) and 316 (32 700); δ_H($CDCl_3$) 8.16 (1 H, dd, *J* 8.1 and 1.3, 8-H), 7.70 (1 H, td, *J* 8.1 and 1.3, 10-H), 7.42 (1 H, dd, *J* 8.1 and 1.3, 11-H), 7.37 (1 H, td, *J* 8.1 and 1.3, 9-H), 6.41 (1 H, d, *J* 9.9, 1-H), 5.97 (1 H, s, 5-H), 5.58 (1 H, d, *J* 9.9, 2-H), 3.91 (3 H, s, NMe), 3.71 (2 H, m, α-CH_2), 3.10 (2 H, t, *J* 7.1, γ-CH_2), 2.64 (6 H, s, NMe_2), 2.13 (2 H, qn, *J* 7.1, β-CH_2) and 1.50 (6 H, s, 3-Me_2); *m*/*z* 376 (M^+, 11%) and 318 [100, M − CH_2=$N^+(CH_3)_2$].

3,3,12-*Trimethyl*-3,12-*dihydro*-6H-*pyrano*[2,3-c]*acridin*-6-*one* **11**.—To a solution of noracronycine **3** (311 mg, 1.01 mmol) in dry diethyl ether (50 cm^3), lithium aluminium hydride (190 mg, 5 mmol) was added under argon. After being stirred at room temperature for 1 h, the mixture was poured onto ice–water (100 cm^3), acidified with 1 mol dm^{-3} hydrochloric acid and extracted with diethyl ether. The combined ether layer and extract were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The crude blue product was purified on a silica gel column with methylene dichloride and then methylene dichloride–ethanol (95:5) as eluent to provide the expected *product* **11** (27 mg, 9%) as blue amorphous solid, mp 208–215 °C (Found: C, 78.85; H, 6.3; N, 4.65. $C_{19}H_{17}NO_2$ requires C, 78.35; H, 5.9; N, 4.8%); λ_{max}(EtOH)/nm 619 (4270), 315 (34 200), 309 (33 400) and 239 (13 600); δ_H([$^2H_6$]-DMSO) 8.90 (1 H, s, 7-H), 8.14 (1 H, dd, *J* 8 and 1.2, 8-H), 7.91 (1 H, td, *J* 8 and 1.2, 10-H), 7.78 (1 H, dd, *J* 8 and 1.2, 11-H), 7.49 (1 H, td, *J* 8 and 1.2, 9-H), 6.80 (1 H, d, *J* 9.7, 1-H), 5.68 (1 H, s, 5-H), 5.69 (1 H, d, *J*

9.7, 2-H), 4.08 (3 H, s, NMe) and 1.52 (6 H, s, 3-Me_2); *m/z* 292 (MH^+).

9-(4-*Dimethylaminophenyl*)-3-*methoxy*-10-*methyl*-1H-*acridin*-1-*one* **12**.—To a solution of 1-hydroxy-3-methoxy-10-methylacridone **4** (1 g, 3.9 mmol) in dry diethyl ether (115 cm^3), 4-dimethylaminophenyllithium (0.9 mol dm^{-3} solution in diethyl ether; 13 cm^3, 11.7 mmol) was added under argon. After 1 h at reflux, the mixture was poured onto ice–water (300 cm^3) and extracted with diethyl ether. The combined ether layer and extract were washed with water, dried ($MgSO_4$) and evaporated to dryness to provide *compound* **12** which was crystallized from diethyl ether (1.27 g, 90%) to give purple crystals, mp 274–275 °C (Found: C, 77.35; H, 6.45; N, 7.8. $C_{23}H_{22}N_2O_2$ requires C, 77.05; H, 6.2; N, 7.8%); λ_{max}(EtOH)/nm 563 (6360), 308 (34 600) and 258 (25 700); δ_H($CDCl_3$) 7.61 (1 H, td, *J* 8.4 and 1.3, 6-H), 7.52 (1 H, dd, *J* 8.4 and 1.3, 8-H), 7.46 (1 H, dd, *J* 8.4 and 1.3, 5-H), 7.08 (1 H, td, *J* 8.4 and 1.3, 7-H), 7.04 (2 H, d, *J* 8.8, 3'-H), 6.83 (2 H, d, *J* 8.8, 2'-H), 5.83 (1 H, d, *J* 1, 4-H), 5.67 (1 H, d, *J* 1, 2-H), 3.80 (3 H, s, NMe), 3.78 (3 H, s, OMe) and 3.00 (6 H, s, NMe_2); *m/z* 358 (M^+, 52%) and 357 (100, M − H).

9-*Butyl*-3-*methoxy*-10-*methyl*-1H-*acridin*-1-*one* **13**.—To a solution of 1-hydroxy-3-methoxy-10-methylacridone **4** (263 mg, 1.03 mmol) in dry diethyl ether (30 cm^3), butyllithium (1.6 mol dm^{-3} solution in hexane; 3.2 cm^3, 5.12 mmol) was added under argon and the mixture was stirred at reflux for 1 h. The cooled mixture was then poured onto ice–water (100 cm^3) and the aqueous layer, quickly separated and extracted with diethyl ether. The combined ether layer and extract were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with heptane–ethyl acetate (1:4) as eluent. After recrystallization from ethyl acetate, the pure *product* **13** (200 mg, 66%) was obtained as purple crystals, mp 157 °C (Found: C, 77.55; H, 7.05; N, 4.65; O, 10.75. $C_{19}H_{21}NO_2$ requires C, 77.25; H, 7.15; N, 4.75; O, 10.85%); λ_{max}(EtOH)/nm 562 (6460) and 306 (38 800); δ_H($CDCl_3$) 8.18 (1 H, dd, *J* 8.5 and 1.2, 8-H), 7.71 (1 H, td, *J* 8.5 and 1.2, 6-H), 7.52 (1 H, dd, *J* 8.5 and 1.2, 5-H), 7.34 (1 H, td, *J* 8.5 and 1.2, 7-H), 6.21 (1 H, d, *J* 1.5, 2-H), 5.75 (1 H, d, *J* 1.5, 4-H), 3.85 (3 H, s, OMe), 3.83 (2 H, m, α-CH_2), 3.82 (3 H, s, NMe), 1.69 (4 H, m, β, γ-CH_2) and 1.03 (3 H, t, *J* 6.9, Me); *m/z* 295 (M^+, 46%) and 266 (100, M − CH_2CH_3).

9-(3-*Dimethylaminopropyl*)-3-*methoxy*-10-*methyl*-1H-*acridin*-1-*one* **14**.—To a solution of 1-hydroxy-3-methoxy-10-methylacridone **4** (1 g, 3.9 mmol) in diethyl ether (110 cm^3), the above mentioned solution of 3-dimethylaminopropyllithium (20 cm^3) was added under argon. After 5 h under reflux, the mixture was poured onto ice-cooled brine. The aqueous layer was extracted with diethyl ether and the combined ether layer and extract were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Crystallization of the residue from diethyl ether provided the desired *product* **14** (312 mg, 25%) as purple needles, mp 132–133 °C (Found: C, 73.65; H, 7.55; N, 8.75; O, 10.05. $C_{20}H_{24}N_2O_2$ requires C, 74.05; H, 7.45; N, 8.65; O, 9.85%); λ_{max}(EtOH)/nm 565 (5670) and 306 (36 700); δ_H($CDCl_3$) 8.19 (1 H, dd, *J* 1.2 and 8.4, 8-H), 7.66 (1 H, td, *J* 1.2 and 8.4, 6-H), 7.45 (1 H, dd, *J* 1.2 and 8.4, 5-H), 7.29 (1 H, td, *J* 1.2 and 8.4, 7-H), 5.97 (1 H, d, *J* 2.3, 2-H), 5.64 (1 H, d, *J* 2.3, 4-H), 3.84 (2 H, t, *J* 7.2, α-CH_2), 3.83 (3 H, s, NMe), 3.74 (3 H, s, OMe), 2.71 (2 H, t, *J* 7.2, γ-CH_2), 2.38 (6 H, s, NMe_2) and 1.97 (2 H, qn, *J* 7.2, β-CH_2); *m/z* 324 (M^+, 7%) and 266 [100, M − $CH_2{=}N^+(CH_3)_2$].

9-*Butyl*-1-*hydroxy*-3-*methoxy*-9,10-*dimethyl*-9,10-*dihydroacridine* **15**.—To a solution of **13** (255 mg, 0.86 mmol) in diethyl ether (20 cm^3), methyllithium (1.6 mol dm^{-3} solution in hexane; 4.85 cm^3, 7.75 mmol) was added dropwise under nitrogen. After being stirred at room temperature for 30 h, the mixture was poured onto ice–water and extracted with methylene dichloride. The organic layer was then washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified on a silica gel column with heptane–ethyl acetate (1:1) as eluent. After recrystallization from hexane, the *product* **15** (130 mg, 60%) was obtained as white crystals, mp 131–132 °C (Found: C, 77.0; H, 7.9; N, 4.85; O, 10.25. $C_{20}H_{25}NO_2$ requires C, 77.15; H, 8.1; N, 4.5; O, 10.3%); δ_H($CDCl_3$) 7.35 (1 H, dd, *J* 8 and 1.5, 8-H), 7.13 (1 H, td, *J* 8 and 1.5, 6-H), 6.88 (1 H, td, *J* 8 and 1.5, 7-H), 6.78 (1 H, dd, *J* 8 and 1.5, 5-H), 6.03 (1 H, d, *J* 2.4, 2-H), 5.84 (1 H, d, *J* 2.4, 4-H), 3.77 (3 H, s, OMe), 3.32 (3 H, s, NMe), 2.43 (1 H, m, α-CH), 1.78 (3 H, s, 9-Me), 1.70 (1 H, m, α-CH), 1.11 (2 H, m, γ-CH_2), 0.91 (2 H, m, β-CH_2) and 0.71 (3 H, t, *J* 7, Me).

9-*Butyl*-1-*hydroxy*-3-*methoxy*-10-*methyl*-9,10-*dihydroacridine* **16**.—Compound **13** (170 mg, 0.58 mmol) dissolved in dry tetrahydrofuran was added dropwise to a solution containing lithium aluminium hydride (35 mg, 0.92 mmol) in dry tetrahydrofuran (5 cm^3). The mixture was stirred at room temperature for 22 h after which it was quenched by the addition of ethyl acetate (2 cm^3) and then water (1 cm^3) and evaporated under reduced pressure. The residue was then extracted with methylene dichloride and the extract was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with heptane–ethyl acetate (1:1) as eluent to provide *compound* **16** which was crystallized from acetonitrile (127 mg, 74%) as white crystals, mp 188–189 °C (Found: C, 76.9; H, 7.55; N, 4.9; O, 10.65. $C_{19}H_{23}NO_2$ requires C, 76.75; H, 7.8; N, 4.7; O, 10.75%); δ_H($CDCl_3$) 7.18 (1 H, td, *J* 8 and 1.4, 6-H), 7.12 (1 H, dd, *J* 8 and 1.4, 8-H), 6.91 (1 H, td, *J* 8 and 1.4, 7-H), 6.87 (1 H, dd, *J* 8 and 1.4, 5-H), 6.09 (1 H, d, *J* 2.2, 2-H), 6.04 (1 H, d, *J* 2.2, 4-H), 4.08 (1 H, t, *J* 6.9, 9-H), 3.77 (3 H, s, OMe), 3.32 (3 H, s, NMe), 1.48 (2 H, m, α-CH_2), 1.21 (4 H, m, β,γ-CH_2) and 0.79 (3 H, t, *J* 6.9, Me).

References

1 G. K. Hughes, F. N. Lahey, J. R. Price and L. J. Webb, *Nature*, 1948, **162**, 223; F. N. Lahey and W. C. Thomas, *Aust. J. Sci. Res., Ser. A*, 1949, **2**, 423.

2 G. H. Svoboda, *Lloydia*, 1966, **29**, 206; H. L. Shieh, J. M. Pezzuto and G. A. Cordell, *Chem. Biol. Interaction*, 1992, **81**, 35.

3 R. T. Dorr, J. D. Liddil, D. D. Von Hoff, M. Soble and C. K. Osborne, *Cancer Research*, 1989, **49**, 340.

4 J. Schneider, E. L. Evans, E. Grunberg and R. I. Fryer, *J. Med. Chem.*, 1972, **15**(3), 26.

5 Chan Soo Oh and C. V. Greco, *J. Heterocycl. Chem.*, 1970, **7**(2), 261; L. J. Drummond and F. N. Lahey, *Aust. J. Sci. Res., Ser. A*, 1949, **2**, 630; S. Mitaku, A. L. Skaltsounis, F. Tillequin and M. Koch, *Planta Medica*, 1988, 24; R. R. Smolders, J. Hanuise, R. Coomans, V. Proietto, N. Voglet and A. Waefelaer, *Synthesis*, 1982, 493; J. R. Dimmock, A. J. Repta and J. Kaminski, *J. Pharm. Sci.*, 1979, **68**(1), 36; J. Reisch and A. Wickramasinghe, *Monatsh. Chem.*, 1990, **121**, 709; J. Reisch, P. Dziemba, M. La Mura and A. R. Ram Rao, *J. Heterocycl. Chem.*, 1993, **30**, 981; R. R. Smolders, J. Hanuise, T. Lepoint, N. Voglet, B. Tinant, J. P. Declercq and M. Van Meerssche, *Tetrahedron*, 1984, **40**(24), 5181; G. M. Coppola, *J. Heterocycl. Chem.*, 1984, **21**, 913; A. Elomri, S. Michel, F. Tillequin and M. Koch, *Heterocycles*, 1992, **34**(4), 799; J. Reisch, I. Mester and S. M. El-Moghazy Aly, *J. Chem. Soc., Perkin Trans. 1*, 1983, 219; S. Blechert, K. E. Fichter and E. Winterfeldt, *Chem. Ber.*, 1978, **111**, 439; S. Blechert, K. E. Fichter, J. Lindner and E. Winterfeldt, *Liebigs Ann. Chem.*, 1980, 503; K. Ramesh and R. S. Kapil, *Indian J. Chem., Sect. B*, 1989, **25**, 684; J. H. Adams, P. J. Bruce and J. R. Lewis, *Lloydia*, 1976, **39**(6), 399; R. R. Smolders, A. Waefelaer, R. Coomans, D. Francart, J. Hanuise and N. Voglet, *Bull. Soc. Chim. Belg.*, 1982, **91**, 33; J. Reisch and P. Dziemba, *Arch. Pharm. (Weinheim)*, 1991, **324**, 67; J. Reisch and W. Probst, *Arch. Pharm. (Weinheim)*, 1989, **322**, 31; J. Reisch and P. Dziemba, *J. Heterocycl.*

Chem., 1992, **29**, 1293; R. D. Brown, L. J. Drummond, F. N. Lahey and W. C. Thomas, *Aust. J. Sci. Res., Ser. A*, 1949, **2**, 622.
6 J. R. Beck, R. Kwok, R. N. Booher, A. C. Brown, L. E. Patterson, P. Pranc, B. Rockey and A. Pohland, *J. Am. Chem. Soc.*, 1968, **90**(17), 4706.
7 T. Sugaya, Y. Mimura, Y. Osawa, I. Matsukuma, S. Ikeda, S. Akinaga, M. Morimoto, T. Ashizawa, M. Okabe, H. Ohno, K. Gomi and M. Kasai, *J. Med. Chem.*, 1994, **37**, 1028; P. Cherubim, L. W. Deady, M. Dorkos, N. H. Quazi, B. C. Baguley and W. A. Denny, *Anticancer Drug Design*, 1993, **8**, 423.
8 A. Etienne and Y. Lepage, *C. R. Rech., IRSiA*, 1955, **240**, 1233; D. N. Gupta, P. Hodge and N. Kahn, *J. Chem. Soc., Perkin Trans. 1*, 1981, 689.
9 A. Loupy and B. Tchoubar, *Effets de sels en chimie organique et organometallique*, Dunod Université, Paris, 1988, p. 67.
10 J. Hlubucek, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, 1970, **23**, 1881.
11 H. Gilman, E. A. Zoellner and W. M. Selby, *J. Am. Chem. Soc.*, 1933, **55**, 1252.
12 E. Juaristi, A. Martinez-Richa, A. Garcia-Rivera and J. S. Cruz-Sanchez, *J. Org. Chem.*, 1983, **48**, 2603.
13 K. H. Von Thiele, E. Langguth and G. E. Muller, *Z. Anorg. Allg. Chem.*, 1980, **462**, 152.

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