# Regiospecific Syntheses of Glycocitrine-II and Acronycine

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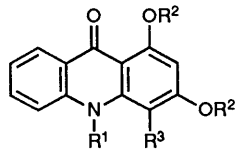
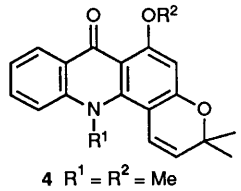
Regiospecific syntheses of glycocitrine-II and acronycine have been achieved from 3-acetyl-4-chloro-2-cyanomethylquinoline which, in turn, has been prepared by two different routes, from the aniline and anthranilic acid derivatives methyl 3-anilino-2-cyano-3-(methylthio)prop-2-enoate and methyl *N*-(1-methyl-3-oxobut-1-enyl)anthranilate.

Glycocitrine-II, a prenylated acridone alkaloid, was isolated from *Glycosmis citrifolia* (Willd) Lind by Furukawa and co-workers[1] and has been assigned structure **1** on the basis of spectroscopic studies and its chemical reactions. Prior to its isolation it was prepared as an intermediate by Ritchie and co-workers.[2] However, the m.p. and spectral data recorded for the synthetic sample are not in good agreement with the values reported for the natural product. Therefore we have devised an unambiguous synthesis of the alkaloid to confirm its structure. An intermediate in this scheme has also been elaborated to give acronycine **4**, a 2,2-dimethylpyranoacridone alkaloid,[3] isolated from *Acronycia baueri* and *Vepris amphody*. In view of the biological activity of this natural product, many synthetic investigations have been carried out on acronycine and its analogues.[4] The syntheses reported either have circuitous routes[5a,5d] or give a mixture of angular and linear isomers in different proportions;[5b,5c,5e] however, the synthesis by Watanabe *et al.*[5f] has been described as being regioselective. The present route, in addition to being regiospecific, is also flexible,[6] allowing for the preparation of analogues of acronycine.



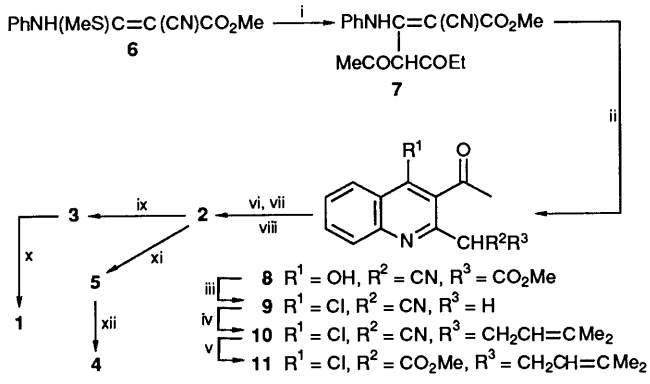
**1** $R^1$ = Me, $R^2$ = H, $R^3$ = $CH_2CH{=}CMe_2$
**2** $R^1$ = $R^2$ = H, $R^3$ = $CH_2CH{=}CMe_2$
**3** $R^1$ = H, $R^2$ = Ac, $R^3$ = $CH_2CH{=}CMe_2$



**4** $R^1$ = $R^2$ = Me
**5** $R^1$ = $R^2$ = H

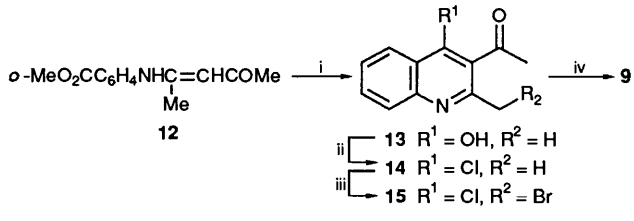
## Results and Discussion

The key intermediate, 3-acetyl-4-chloro-2-cyanomethylquinoline **9**, was prepared by two routes. The first involved substitution of the methylthio group in the ketene *S,N*-ketal **6** by the carbanion of ethyl acetoacetate, in refluxing isopropyl alcohol with $Pr^iONa$ as the base, to give the keto ester **7** in 71% yield. In order to effect cyclization of the ethoxycarbonyl group onto the *N*-phenyl ring, the ester **7** was refluxed in *o*-dichlorobenzene, when a mixture of products, *viz.* compound **8**, demethoxycarbonylated **8**, and the starting compound **7** was obtained. It was found that the proportions of this mixture were dependent upon refluxing time, and when the duration was limited to 2 h the cyclized product **8** was obtained predominantly, in 55% yield. The 4-OH compound **8** was transformed into the 4-chloro derivative by treatment with $POCl_3$ on a steam-bath in 20% yield. Prolonged reaction did not improve the yield. However, when the temperature was raised to 120–125 °C for 5 h, the only compound isolated was the nitrile **9**, *i.e.* demethoxycarbonylation also took place under the reaction conditions (see Scheme 1).




**Scheme 1** *Reagents and conditions:* i, $MeCOCH_2CO_2Et$, $Me_2CHONa$, $Me_2CHOH$, heat; ii, *o*-$ClC_6H_4Cl$, heat; iii, $POCl_3$, 120–125 °C; iv, $K_2CO_3$, DMF, $Me_2C{=}CHCH_2Br$; v, MeOH, HCl; vi, NaH–THF; vii, PhOH, 100 °C; viii, 2 mol $dm^{-3}$ HCl, MeOH, heat; ix, $Ac_2O$, NaOAc, heat; x, NaH, DMF, MeI; xi, DDQ, PhMe, heat; xii, NaH, DMF, MeI

In the second route the ethoxy group in the ethyl enol ether of acetylacetone (4-ethoxypent-3-en-2-one) was substituted by heating it with methyl anthranilate in refluxing *o*-dichlorobenzene to afford the enaminone **12**. NaOMe-catalysed cyclization of compound **12** was smoothly carried out in methanol to provide the 3-acetylquinoline **13** as the only product, in 87% yield. The 2-methyl group, in the corresponding 4-chloro derivative **14**, obtained by refluxing of compound **13** with $POCl_3$, was functionalized by bromination with *N*-bromosuccinimide (NBS) in $CCl_4$, The bromo derivative **15** was obtained in 73% yield as crystalline needles (Scheme 2). In view




**Scheme 2** *Reagents and conditions:* i, NaOMe, MeOH; ii, $POCl_3$, 100 °C; iii, NBS, $CCl_4$; iv, NaCN, DMF, −5 °C

of the tendency of the bromoquinoline **15** to turn yellow and finally dark on storage, it was freshly crystallized for the next reaction. When the bromoquinoline **15** was stirred with NaCN in dimethyl sulphoxide (DMSO) crystalline product was obtained which showed signals in the $^1H$ NMR spectrum at $\delta$ 3.03 and 4.1, in addition to the expected signals at $\delta$ 2.6, 3.7 and 7.75 corresponding to the nitrile **9**. The unexpected

signals probably arose from alkylation of DMSO by the bromo compound **15**. In view of the significant intensity of these peaks, no attempt was made to purify the desired compound **9** from the reaction product. However, when the reaction was carried out in dimethylformamide (DMF) at −5 °C, the desired nitrile **9** was isolated in modest yield (42%). The alkylation of the methylene moiety of the cyanomethyl in compound **9** with 1-bromo-3-methylbut-2-ene was attempted with NaH in a number of solvents; however, the best results were obtained using $K_2CO_3$ in DMF. Methanolysis of the resulting nitrile **10** was accomplished with methanol saturated with HCl gas to give the corresponding ester **11**. Cyclization of this keto ester was carried out by refluxing it with NaH in tetrahydrofuran (THF) to afford a thick reddish oil. This was not purified but was directly heated with phenol at 100 °C and the crude product obtained on work-up was refluxed with HCl in methanol to provide norglycocitrine-II **2** (47%). The hydroxy groups in this acridone were protected by acetylation with acetic anhydride in the presence of NaOAc to furnish the corresponding diacetate **3** in nearly quantitative (84%) yield. This compound was then methylated with MeI in DMF with NaH as the base. The crude product obtained after work-up was refluxed with $K_2CO_3$ in methanol to yield an orange solid. Purification of this product finally gave glycocitrine-II **1** (52%) as orange needles having m.p., UV, IR and NMR data well in accord with those reported for the natural product.[1]

For the synthesis of acronycine, the acridone **2** was refluxed with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in toluene to afford dinoracronycine **5** (52%), which, with MeI in DMF with NaH as the base, gave acronycine **4** (85%). The IR, UV and NMR spectral data and the m.p. of the synthetic sample were in good agreement with the values reported for the natural product.[7]

## Experimental

M.p.s (measured in capillary tubes on an ADCO melting point apparatus) and b.p.s are uncorrected. Silica gel (60–120 mesh, Qualigen) was used for column chromatography. Silica gel G (Qualigen) with 13% $CaSO_4$ as the binder was employed for TLC and $R_f$-values were recorded after TLC on 0.25 mm thick plates. IR spectra were recorded on a BIO–RAD Digilab Div FTS-40 or a Nicolet SDX FTIR instrument for samples as liquid films or KBr pellets. UV spectra were recorded in methanol on a Perkin-Elmer Lambda 38 UV/VIS spectrophotometer, usng a 1 $cm^3$ quartz cell. $^1H$ NMR spectra were recorded on a 100 MHz JNM-FX100 FT JEOL spectrometer. Chemical shifts are given in ppm ($\delta$) from $SiMe_4$ as internal standard, and $CDCl_3$ was used as the solvent unless specified otherwise. *J*-Values are given in Hz.

*Methyl* 3-*Anilino*-2-*cyano*-3-*methylthioprop*-2-*enoate* **6**.—The carbanion of ethyl cyanoacetate (5.2 g, 0.052 mol), generated from Na (1.2 g, 0.052 mol) and methanol (100 $cm^3$) was treated with phenyl isothiocyanate (7.02 g, 0.052 mol) and this was followed by the addition of a solution of MeI (7.4 g, 0.052 mol) in methanol (10 $cm^3$). The methanol was removed under reduced pressure, cold water (150 $cm^3$) was added to the residue, and the solid was crystallized from n-hexane–$Et_2O$ (3:1) to give the *ketene* S,N-*ketal* **6** (10.83 g, 84%), m.p. 76–78 °C (Found: C, 57.8; H, 5.1, N, 11.3. $C_{12}H_{12}N_2O_2S$ requires C, 58.1; H, 4.9; N, 11.3%); $\nu_{max}/cm^{-1}$ 3290 (NH), 2255 (CN) and 1680 ($CO_2Me$); $\delta$ 2.4 (3 H, s, SMe), 3.98 (3 H, s, $CO_2Me$), 4.16 (1 H, br, NH, $D_2O$ exchangeable) and 7.2–7.6 (5 H, m, Ph).

5-*Ethyl* 1-*Methyl* 4-*Acetyl*-3-*anilino*-2-*cyanopent*-2-*enedioate* **7**.—To the Na salt of ethyl acetoacetate (2.6 g, 0.02 mol), prepared from a solution of Na (0.46 g, 0.02 mol) in isopropyl alcohol (100 $cm^3$), was added a solution of the ketene *S,N*-ketal **6** (5.0 g, 0.02 mol) in isopropyl alcohol (25 $cm^3$) and the mixture was refluxed for 24 h. Removal of the solvent under reduced pressure, followed by addition of cold water (250 $cm^3$) and acidification with AcOH, gave a solid, which was filtered off and crystallized from benzene–EtOAc to give the crystalline *title compound* **7** (4.72 g, 71%), m.p. 91–93 °C; $R_f$ 0.29 ($C_6H_6$) (Found: C, 61.7; H, 5.6; N, 8.7. $C_{17}H_{18}N_2O_5$ requires C, 61.8; H, 5.5; N, 8.5%); $\nu_{max}/cm^{-1}$ 3096–2991 (NH), 2214 (CN), 1748 ($CO_2Et$) and 1715–1680 (Ac and $CO_2Me$); $\delta$ 1.68 (3 H, t, *J* 7, $CO_2CH_2\mathit{Me}$), 2.2 (3 H, s, COMe), 3.9 (3 H, s, $CO_2Me$), 4.24 (2 H, q, *J* 7, $CO_2C\mathit{H}_2Me$), 4.82 (1 H, br, CH), 7.1 (2 H, m, ArH), 7.4 (3 H, m, ArH) and 10.8 (1 H, br NH, $D_2O$ exchangeable).

*Methyl* (3-*Acetyl*-4-*hydroxyquinolin*-2-*yl*)*cyanoacetate* **8**.—A solution of the keto ester **7** (0.66 g, 0.002 mol) in *o*-dichlorobenzene (15 $cm^3$) was refluxed for 2 h. Removal of the solvent, followed by trituration with n-hexane, gave a solid, which was crystallized from diethyl ether to furnish the crystalline *title compound* **8** (2.5 g, 55%), m.p. 138–140 °C; $R_f$ 0.54 [benzene–EtOAc (5:1)] (Found: C, 63.4; H, 2.7; N, 9.5. $C_{15}H_{12}N_2O_4$ requires C, 63.4; H, 2.5; N, 9.9%); $\nu_{max}/cm^{-1}$ 3280–2851 (OH), 2215 (CN), 1740 ($CO_2Me$) and 1675 (Ac); $\delta$ 2.8 (3 H, s, COMe), 4.05 (3 H, s, $CO_2Me$), 4.9 (1 H, s, CH), 7.5–7.9 (4 H, m, ArH) and 13.8 (1 H, br, OH, $D_2O$ exchangeable); *m/z* 284 ($M^+$, 100%), 253 (25), 224 (75), 209 (10) and 77 (57.5).

(3-*Acetyl*-4-*chloroquinolin*-2-*yl*)*acetonitrile* **9**.—A mixture of the hydroxyquinoline **8** (5.7 g, 0.02 mol) and $POCl_3$ (40 $cm^3$) was heated on an oil-bath at 120–125 °C for 5 h. The product was poured onto ice-cold water (250 $cm^3$), basified with $NH_4OH$, and extracted with $CHCl_3$ (30 $cm^3$ × 3). The combined extracts were washed with water (30 $cm^3$ × 3) and dried ($CaCl_2$). Removal of the solvent afforded a solid, which was chromatographed on silica gel with benzene–diethyl ethyl (8:2) as eluent to afford the title product **9** as a crystalline compound (2.58 g, 53%), m.p. 164–165 °C; $R_f$ 0.31 [benzene–EtOAc (4:1)] (Found: C, 63.5; H, 3.9; N, 11.2. $C_{13}H_9ClN_2O$ requires C, 63.8; H, 3.7; N, 11.5%); $\nu_{max}/cm^{-1}$ no absorption due to $CO_2Me$, 2250 (CN) and 1680 (ArCO); $\delta$ 2.6 (3 H, s, COMe), 3.7 (2 H, s, $CH_2CN$) and 7.7 (4 H, m, ArH).

*Methyl* N-(1-*Methyl*-3-*oxobut*-1-*enyl*)*anthranilate* **12**.—A solution of 4-ethoxypent-3-en-2-one (9.6 g, 0.075 mol) and methyl anthranilate (11.3 g, 0.075 mol) in *o*-dichlorobenzene (100 $cm^3$) was refluxed for 4 h. The solvent was removed under reduced pressure, and vacuum distillation then provided the desired *enaminone* **12** (12.30 g, 70%), b.p. 178–180 °C/15 mmHg, which solidified on cooling and was crystallized from benzene, m.p. 65–67 °C; $R_f$ 0.43 (benzene) (Found: C, 66.8; H, 6.4; N, 6.1. $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%); $\nu_{max}/cm^{-1}$ 3220 (NH), 1725 ($ArCO_2R$) and 1678 (Ac); $\delta$ 2.0 (3 H, s, vinylic Me), 2.6 (3 H, s, COMe), 3.98 (3 H, s, $CO_2Me$), 5.26 (1 H, s, =CH), 7.2–7.6 (3 H, m, ArH), 8.05 (1 H, dd, *J* 2 and 8, ArH) and 9.1 (1 H, br, NH, $D_2O$ exchangeable).

3-*Acetyl*-4-*hydroxy*-2-*methylquinoline* **13**.—To a stirred solution prepared from Na (1.15 g, 0.05 mol) in methanol (80 $cm^3$) was added a solution of the enaminone **12** (11.6 g, 0.05 mol) in methanol (20 $cm^3$) and the mixture was stirred for 2 h. Solvent was removed, and the residue was dissolved in ice-cold water (30 $cm^3$) and acidified with AcOH. The solid was filtered off and crystallized from methanol to afford needles of the *title quinoline* **13** (8.7 g, 87%), m.p. 252–253 °C; $R_f$ 0.18 [benzene–MeOH (4:1)] (Found: C, 72.0; H, 5.8; N, 7.2. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 7.0%); $\nu_{max}/cm^{-1}$ no absorption due to ester, 3223–2977 (OH) and 1670 (ArCO); $\delta$ 2.06 (3 H, s,

Ar*Me*), 2.6 (3 H, s, COMe), 7.4–7.8 (3 H, m, ArH), 8.0 (1 H, d, *J* 8, ArH) and 14.02 (1 H, br, OH, $D_2O$ exchangeable).

3-*Acetyl*-4-*chloro*-2-*methylquinoline* **14**.—A solution of compound **13** (5.0 g, 0.025 mol) in $POCl_3$ (20 $cm^3$) was heated on steam-bath for 2 h and was then cooled, added to crushed ice, basified with $NH_4OH$, and then extracted with $CHCl_3$ (3 × 20 $cm^3$). The combined extracts were washed with brine (3 × 10 $cm^3$) and dried over $CaCl_2$. The solvent was evaporated off to leave behind the chloroquinoline **14** (4.9 g, 89%) as a TLC-pure, thick oil; $R_f$ 0.63 (benzene); $\nu_{max}/cm^{-1}$ no absorption due to OH, 1708 (ArCO); $\delta$ 2.4 (3 H, s, Ar*Me*), 2.64 (3 H, s, COMe) and 7.6–8.2 (4 H, m, ArH).

3-*Acetyl*-2-*bromomethyl*-4-*chloroquinoline* **15**.—A mixture of NBS (3.0 g, 0.017 mol), the 4-chloroquinoline **14** (3.3 g, 0.015 mol) and benzoyl peroxide (0.10 g) in $CCl_4$ (100 $cm^3$) was stirred and refluxed until TLC ($C_6H_6$) showed the absence of starting substrate **14** (36 h). The mixture was filtered, and the filtrate was concentrated to leave the bromo compound **15**, which was crystallized from n-hexane to furnish needles (3.3 g, 73%), m.p. 79–80 °C; $R_f$ 0.58 [benzene–n-hexane (4:1)]; $\nu_{max}/cm^{-1}$ 1698 (ArCO); $\delta$ 2.8 (3 H, s, COMe), 4.6 (2 H, s, $CH_2Br$), 7.7 (2 H, m, ArH) and 8.02 (2 H, m, ArH).

(3-*Acetyl*-4-*chloroquinolin*-2-*yl*)*acetonitrile* **9** (*Alternative Synthesis*).—To a stirred solution of compound **15** (2.4 g, 0.008 mol) in DMF (25 $cm^3$) at −5 °C was added NaCN (0.89 g, 0.018 mol) in small portions. After being stirred overnight at room temperature the mixture was decomposed with ice-cold water (150 $cm^3$) and extracted with $CHCl_3$ (50 $cm^3$ × 3). The combined extracts were washed with water (25 $cm^3$ × 3) and dried ($CaCl_2$). Removal of the solvent, followed by chromatography on silica gel, gave the crystalline product **9** (0.83 g, 42%), identical with the compound prepared by the earlier route (m.p., mixed m.p., TLC, IR, $^1H$ NMR).

2-(3-*Acetyl*-4-*chloroquinolin*-2-*yl*)-5-*methylhex*-4-*enonitrile* **10**.—To a suspension of $K_2CO_3$ (1.38, 0.01 mol) in DMF (30 $cm^3$) was added a solution of compound **9** (1.5 g, 0.006 mol) in DMF (30 $cm^3$), followed by a solution of 1-bromo-3-methylbut-2-ene (0.89 g, 0.006 mol) in DMF (10 $cm^3$). The reaction mixture was stirred for 30 h and then poured into ice-cold water (150 $cm^3$) and acidified with AcOH. After extraction with $CH_2Cl_2$ (25 $cm^3$ × 3), the combined extracts were washed with brine (25 $cm^3$ × 3) and dried ($CaCl_2$). Evaporation of the solvent, followed by chromatography over silica gel with benzene–EtOAc (4:2) as eluent gave the desired *product* **10** (0.92 g, 48%), m.p. 178–182 °C; $R_f$ 0.19 [benzene–EtOAc (9:1)] (Found: C, 69.3; H, 5.4; N, 8.8. $C_{18}H_{17}ClN_2O$ requires C, 69.1; H, 5.5; N, 9.0%); $\nu_{max}/cm^{-1}$ 2200 (CN) and 1685 (ArCO); $\delta$ [$(CD_3)_2CO$] 1.7 and 1.74 (each 3 H, 2 s, =$CMe_2$), 2.1 (2 H, poorly resolved t, *J* 7, $CH_2$CH=), 2.8 (3 H, s, MeCO), 4.3 (1 H, t, *J* 7, ArC*H*CN), 5.1 (1 H, m, CH=C<) and 7.7 (4 H, m, ArH).

*Methyl* 2-(3-*Acetyl*-4-*chloroquinolin*-2-*yl*)-5-*methylhex*-4-*enoate* **11**.—To anhydrous methanol (50 $cm^3$) saturated with HCl was added the nitrile **10** (3.1 g, 0.01 mol) and the mixture was stirred overnight and then refluxed for 1 h before being diluted with water. The methanol was then distilled off under reduced pressure to give a solid compound, which was crystallized from benzene–EtOAc (1:1) to give the *ester* **11** (2.38 g, 70%), $R_f$ 0.16 [benzene–EtOAc (9.5:0.5)] (Found: C, 66.0; H, 5.4; N, 4.2. $C_{19}H_{20}ClNO_3$ requires C, 66.0; H, 5.8; N, 4.0%); $\nu_{max}/cm^{-1}$ no band due to CN, 1730 ($CO_2Me$) and 1680 (ArCO); $\delta$ [$(CD_3)_2CO$] 1.7 and 1.78 (each 3 H, 2 s, =$CMe_2$), 2.05 (2 H, poorly resolved t, *J* 7, $CH_2$CH=), 2.7 (3 H, s, MeCO), 4.02 (3 H, s, $CO_2Me$), 4.2 (1 H, t, *J* 7, ArC*H*), 5.45 (1 H, m, CH=) and 7.65 (4 H, m, ArH).

1,3-*Dihydroxy*-4-(3-*methylbut*-2-*enyl*)-9-*acridone* **2**.—The keto ester **11** (3.8 g, 0.011 mol) was added to a stirred suspension of NaH (50%; 0.58 g, 0.012 mol) (made free of mineral oil by being washed with n-hexane) in THF (100 $cm^3$) and the mixture was then stirred for 0.5 h, refluxed for 3 h, cooled, diluted with ice-cold water (200 $cm^3$), acidified with AcOH, and extracted with EtOAc (3 × 100 $cm^3$). The combined extracts were washed with brine, then dried ($Na_2SO_4$), and the solvent was removed to leave behind a thick, reddish oil. This oil was heated with phenol (10 g) at 100 °C for 3 h and the mixture was then cooled and diluted with cold water (150 $cm^3$). The crude product which separated out was triturated with n-hexane and then refluxed with HCl (2 mol $dm^3$; 20 $cm^3$) in methanol (30 $cm^3$) for 10 h. The solvent was removed under reduced pressure and the residue was extracted with $CH_2Cl_2$ (50 $cm^3$ × 3). The combined extracts were washed with brine (50 $cm^3$ × 3) and dried. The residue obtained on removal of the solvent was chromatographed on silica gel. The desired product was obtained with n-hexane–benzene (1:5) as eluent. It was then crystallized from EtOAc–n-hexane (1:3) to provide the *acridone* **2** (0.98 g, 47%), m.p. 242–246 °C; $R_f$ 0.47 [benzene–EtOAc (7:1)] (Found: C, 73.6; H, 5.7; N, 4.6. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%); $\nu_{max}/cm^{-1}$ 3424 (OH), 1620 (CO) and 827 (C=$CMe_2$); $\delta$ [$(CD_3)_2CO$] 1.69 and 1.84 (each 3 H, 2 s, =$CMe_2$), 3.59 (2 H, d, *J* 7, $CH_2$CH=), 5.16 (1 H, br, CH=), 6.48 (1 H, s, 2-H), 7.4–7.9 (3 H, m, ArH), 8.4 (1 H, dd, *J* 8 and 2, 8-H), 8.8 (1 H, br, 3-OH, $D_2O$ exchangeable), 10.2 (1 H, s, NH, $D_2O$ exchangeable) and 13.8 (1 H, br, 1-OH, $D_2O$ exchangeable).

1,3-*Diacetoxy*-4-(3-*methylbut*-2-*enyl*)-9-*acridone* **3**.—To a stirred solution of the acridone **2** (0.96 g, 0.0033 mol) in $Ac_2O$ (10 $cm^3$) was added fused NaOAc (0.633 g, 0.008 mol) and the mixture was refluxed for 2 h before being poured onto crushed ice and left overnight. The solid product was filtered off, washed with water and dried, and was then crystallized from EtOAc to give *diacetate* **3** (1.03 g, 84%), m.p. 143–146 °C; $R_f$ 0.54 [benzene–EtOAc (5:1)] (Found: C, 69.3; H, 5.8; N, 3.5. $C_{22}H_{21}NO_5$ requires C, 69.7; H, 5.6; N, 3.7%); $\nu_{max}/cm^{-1}$ no absorption due to OH, 3108–3077 (NH), 1772 and 1760 (OAc), 1630 (ArCO) and 813 (CH=C); $\delta$ [$(CD_3)_2CO$] 1.73 and 1.82 (3 H each, 2 s, $CMe_2$), 2.14 (3 H, s, OAc), 2.34 (3 H, s, OAc), 3.54 (2 H, d, *J* 7, $CH_2$CH=), 5.3 (1 H, br, CH=), 6.4 (1 H, s, 2-H), 7.2–7.7 (3 H, m, ArH), 8.3 (1 H, dd, *J* 8 and 2, 8-H) and 11.3 (1 H, br, NH, $D_2O$ exchangeable).

1,3-*Dihydroxy*-N-*methyl*-4-(3-*methylbut*-2-*enyl*)-9-*acridone* (*Glycocitrine-II*) **1**.—A solution of the diacetate **3** (0.98 g, 0.0026 mol) in DMF (20 $cm^3$) was added to a cooled suspension of NaH (50% emulsion; 0.13 g, 0.0026 mol) (made free of mineral oil by being washed with n-hexane) in DMF (20 $cm^3$), and this was followed by the addition of a solution of MeI (0.37 g, 0.0026 mol) in DMF (5 $cm^3$). The reaction mixture was stirred for 18 h and was then added to ice–water (150 $cm^3$), upon which a blackish red solid separated out. The mixture was refluxed with methanol (25 $cm^3$) containing $K_2CO_3$ (1.3 g) for 2 h. After concentration, water (100 $cm^3$) was added and the mixture was acidified with AcOH and extracted with $CH_2Cl_2$ (100 $cm^3$ × 3). The combined extracts were washed with brine, then dried, and the solvent was evaporated off. The residue was chromatographed on silica gel. The required compound **1** was obtained with n-hexane–benzene (1:9) as eluent and was further purified by preparative TLC in benzene–EtOAc (9:1), followed by crystallization from methanol to give orange needles (0.40 g, 52%), m.p. 166–168 °C (lit.,[1] 168–169 °C); $R_f$ 0.48 [benzene–methanol (6:1)] (Found: C, 73.4; H, 6.3; N, 4.3. Calc. for $C_{19}H_{19}NO_3$: C, 73.8; H, 6.2; N, 4.5%);

$\nu_{max}$/cm$^{-1}$ 3410, 1615, 1590 and 1565; $\lambda_{max}$(MeOH)/nm (log $\varepsilon$) 227 (4.25), 250 (4.48), 266sh (4.52), 272 (4.7), 305 (4.1), 335 (4.02) and 405 (3.71); $\delta$ [$(CD_3)_2CO$] 1.66 and 1.72 (each 3 H, 2 s), 3.48 (2 H, d, *J* 7), 4.04 (3 H, s), 5.38 (1 H, m), 6.24 (1 H, s), 7.3 (1 H, t, *J* 8), 7.69 (2 H, m), 8.15 (1 H, dd, *J* 8 and 2), 10.46 (1 H, s, $D_2O$ exchangeable) and 13.98 (1 H, s, $D_2O$ exchangeable).

6-*Hydroxy*-3,3-*dimethyl*-3,12-*dihydro*-7H-*pyrano*[2,3-c]-*acridin*-7-*one* **5**.—A mixture of norglycocitrine-II **2** (0.92 g, 0.003 mol) and DDQ (0.68 g, 0.003 mol) was refluxed in toluene (50 cm$^3$) for 14 h. The solvent was removed under reduced pressure and the residue, as a solution in $CHCl_3$, was washed successively with aq. $Na_2CO_3$ (10%; 3 × 20 cm$^3$) and brine (3 × 15 cm$^3$). After drying ($Na_2SO_4$), the solvent was removed and the residue was chromatographed on silica gel (80 g). The product obtained with benzene–$Et_2O$ (5:1) was crystallized from benzene to give *compound* **5** as yellow crystals (0.46 g, 52%), m.p. 238–239 °C; $R_f$ 0.46 [benzene–EtOAc (5:1)] (Found: C, 73.7; H, 5.3; N, 4.8. $C_{18}H_{15}NO_3$ requires C, 73.7; H, 5.2; N, 4.8%); $\nu_{max}$/cm$^{-1}$ 3320 (NH) and 1637 (CO); $\delta$ 1.5 (6 H, s, 2 × Me), 5.5 (1 H, d, *J* 10, 2-H), 6.25 (1 H, s, 5-H), 6.5 (1 H, d, *J* 10, 1-H), 7.8–8.05 (3 H, m, ArH), 8.35 (1 H, dd, *J* 8 and 2, 8-H), 10.34 (1 H, br s, NH, $D_2O$ exchangeable) and 12.8 (1 H, br, OH, $D_2O$ exchangeable).

6-*Methoxy*-3,3,12-*trimethyl*-3,12-*dihydro*-7H-*pyrano*[2,3-c]-*acridin*-7-*one* (*Acronycine*) **4**.—To a stirred suspension of NaH (50%; 1.20 g, 0.025 mol) in DMF (50 cm$^3$) was added a solution of compound **5** (2.93 g, 0.01 mol) in DMF (10 cm$^3$). After 0.5 h, MeI (4 cm$^3$) was added and the mixture was heated at 60 °C for 18 h. The cooled reaction mixture was then diluted with water (100 cm$^3$), acidified (AcOH), and extracted with $CHCl_3$ (50 cm$^3$ × 3). The combined extracts were washed with brine (25 cm$^3$ × 3) and dried before being concentrated and then chromatographed on silica gel. The product obtained with benzene–EtOAc (1:5) was crystallized from methanol to give acronycine **4** (2.7 g, 85%), m.p. 175–176 °C (lit.,[7] 176–178 °C); $R_f$ 0.34 [benzene–MeOH (4:1)] (Found: C, 74.9; H, 6.1; N, 4.2. Calc. for $C_{20}H_{19}NO_3$: C, 74.8; H, 6.0; N, 4.4%); $\nu_{max}$/cm$^{-1}$ 1630 (CO); $\lambda_{max}$(MeOH)/nm (log $\varepsilon$) 224 (4.21), 278 (4.5), 292 (4.4), 305 (4.25) and 392 (3.88); $\delta$ 1.52 (6 H, s, $CMe_2$), 3.8 (3 H, s, NMe), 3.96 (3 H, s, OMe), 5.48 (1 H, d, *J* 9, 2-H), 6.28 (1 H, s, 5-H), 6.52 (1 H, d, *J* 9, ArC*H*=), 7.05–7.7 (3 H, m, 9-, 10- and 11-H) and 8.4 (1 H, dd, *J* 8 and 2, 8-H).

## References


1 T. S. Wu, H. Furukawa, C. S. Kuoh and K. S. Hsu, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1681.
2 J. Hlubucek, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, 1970, **23**, 1881.
3 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; G. H. Svoboda, *Lloydia*, 1966, **29**, 206.
4 G. H. Svoboda, G. A. Poore, P. J. Simpson and G. B. Boder, *J. Pharm. Sci.*, 1966, **55**, 758.
5 (*a*) J. R. Beck, R. Kwock, R. N. Booher, A. C. Brown, L. F. Patterson, P. Pranc, B. Rockey and A. Pohland, *J. Am. Chem. Soc.*, 1968, **90**, 4706; (*b*) W. M. Bandaranayake, M. J. Begley, B. O. Brown, D. G. Clarke, L. Crombie and A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1974, 998; (*c*) J. Reisch, I. Mester and S. M. E. M. Aly, *Liebigs Ann. Chem.*, 1984, 31; (*d*) S. Blechert, K. E. Fichter and E. Winterfeldt, *Chem. Ber.*, 1978, **111**, 439; (*e*) J. H. Adams, P. Brown, P. Gupta, M. S. Khan and J. R. Lewis, *Tetrahedron*, 1981, **37**, 209; (*f*) M. Watanabe, A. Kurosaki and S. Furukawa, *Chem. Pharm. Bull.*, 1984, **32**, 1264.
6 For preliminary communication see R. C. Anand and A. K. Sinha, *Heterocycles*, 1990, **31**, 1733.
7 P. L. Macdonald and A. V. Robertson, *Aust. J. Chem.*, 1966, **19**, 275.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