

REGIOSELECTIVE SYNTHESIS OF DEMETHOXYISOACRONYCINE
INVOLVING NUCLEOPHILIC ADDITION TO BENZYNE¹

Mónika Rudas,^{a,b} Miklós Nyerges,^{a*} László Tóke,^a and Paul W.
Groundwater^c

^aResearch Group of the Hungarian Academy of Sciences, Department of Organic
Chemical Technology, Technical University of Budapest; H-1521 Budapest
P.O.B. 91, Hungary

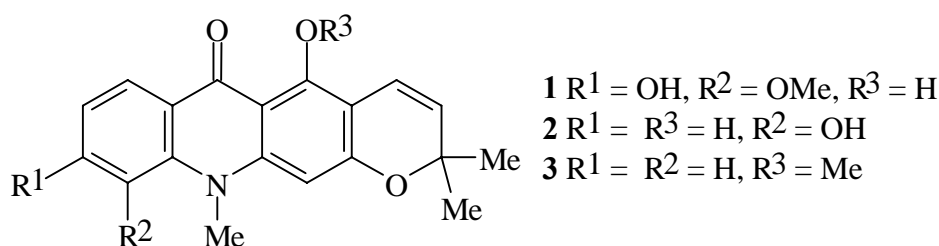
^bEGIS Pharmaceuticals Ltd., H-1475 Budapest P.O.B. 100, Hungary

^cInstitute of Pharmacy, Chemistry and Biomedical Sciences, School of Sciences,
University of Sunderland, Sunderland SR1 3SD, UK

Abstract – Demethoxyisoacronycine (**12**) has been prepared in seven steps using
the nucleophilic addition of aniline derivative (**4**) to benzyne (**5**) as a key step.

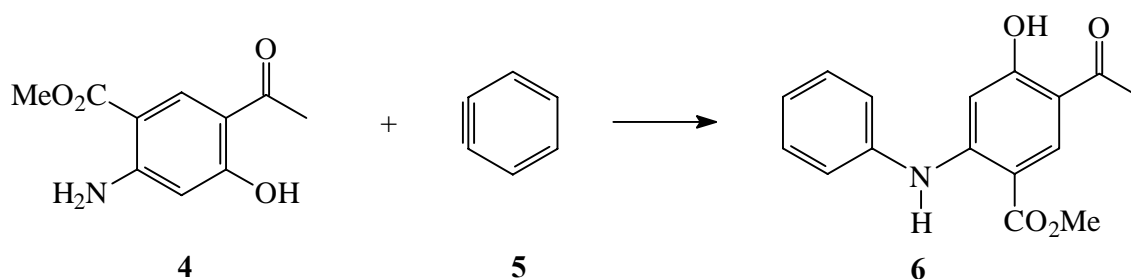
INTRODUCTION

Acronycine, a pyrano[2,3-*a*]acridone alkaloid from the bark of the Australian scrub ash *Acronychia baueri* Schott (Rutaceae) first reported in 1948,² has attracted much attention over the last few years, due to its broad spectrum of activity in experimental tumours, including X-5563 myeloma, S-91 melanoma, and the Ridgeway osteogenic sarcoma.³ Alkaloids based upon the isomeric pyrano[3,2-*b*]acridone ring system are rare but do occur in several *Citrus* species *e.g.* honyumine (**1**) from *Citrus grandis*⁴ and *Citrus funadako*⁵ or yukocitrine (**2**) from *Citrus yuko*.⁶ The only regioselective synthesis of pyrano[3,2-*b*]acridones was reported by Reisch *et al.*⁷ and most synthetic pyrano[3,2-*b*]acridones have been obtained as by-products during the preparation of, *e.g.* isoacronycine (**3**) or its derivatives have been obtained in low yields as by-products in most acronycine syntheses.⁸ In this report we describe a convenient and regioselective synthetic sequence for the preparation of a pyrano[2,3-*a*]acridones, demethoxyisoacronycine (**12**).



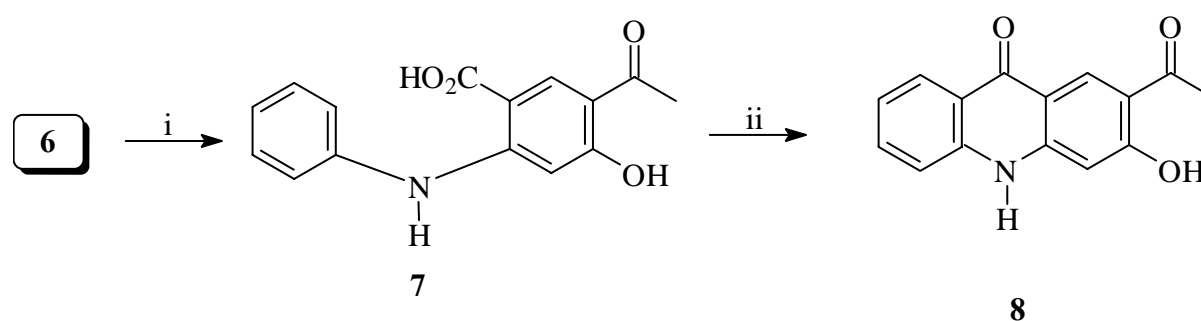
RESULTS AND DISCUSSION

The current synthetic approach is based upon the regioselective addition of the known tetrasubstituted aniline derivative (**4**)⁹ to benzyne generated *in situ*. Benzyne precursors have previously been utilized for the synthesis of some simple acridone derivatives and acronycine itself,⁹ but in these cases the less sensitive substituent pattern allowed the generation of arynes from the corresponding aryl halide using strong base. In our case, however, the presence of carbonyl groups in **4** did not allow a simple repeat of these methods. Instead, we have utilized benzenediazonium carboxylate as a benzyne precursor such that the careful thermal decomposition in the presence of **4** led selectively to the desired methyl 5-acetyl-4-hydroxy-2-phenylaminobenzoate (**6**) in good yield (Scheme 1).



Scheme 1

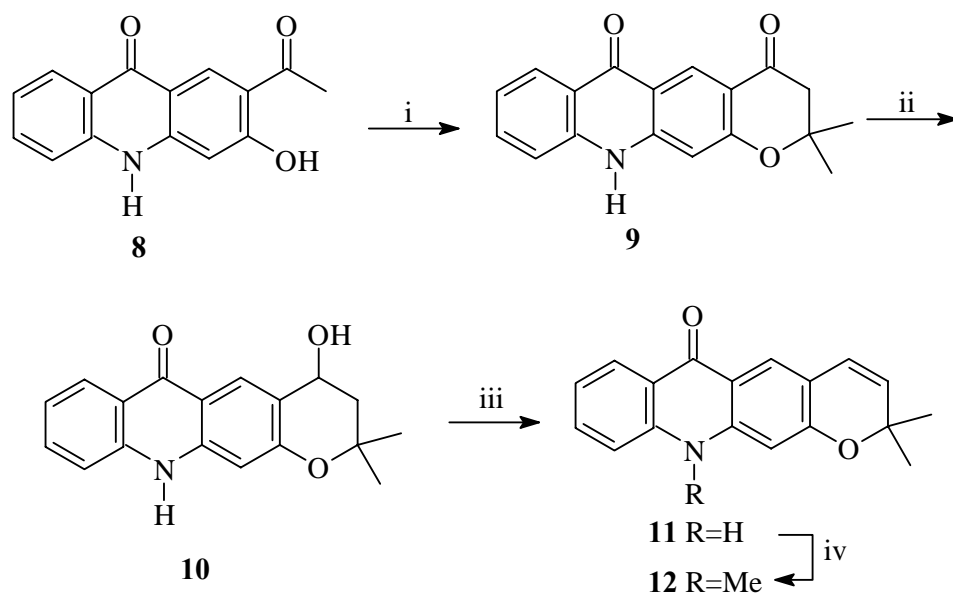
Alkaline hydrolysis of the ester (**6**), followed by the PPE mediated ring-closure of the acid (**7**) gave the unknown acridone derivative (**8**) in high yield (Scheme 2). Attempts to cyclise **7** to **8** in the presence of PPA or AlCl_3 were unsuccessful.



Scheme 2 Reagents and conditions: i. $\text{NaOH}, \text{H}_2\text{O}, \text{EtOH}, 80^\circ\text{C}, 100\%$; ii. PPE, $\text{CHCl}_3, 60^\circ\text{C}, 95\%$.

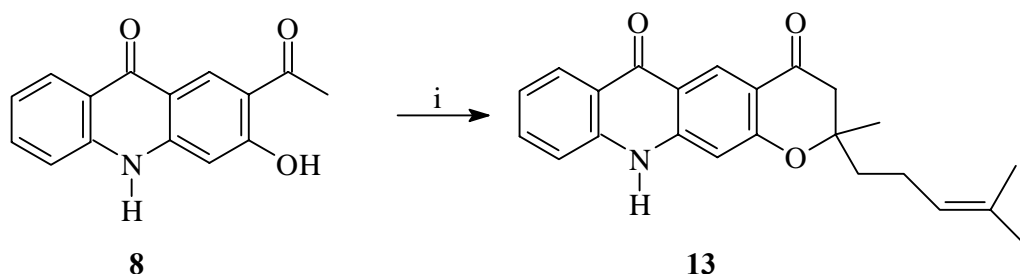
The reaction of the key intermediate acridone (**8**) with acetone, in the presence of piperidine as a base, gave pyranone (**9**), which was converted to demethoxynorisoacronycine (**11**) in two steps — the carbonyl group

of **9** was reduced with sodium borohydride quantitatively to give pyranol (**10**), which was subsequently dehydrated in the presence of catalytic PTSA in boiling toluene. Methylation of **11** with methyl iodide then gave the demethoxyisoacronycine (**12**) (Scheme 3). The overall yield of **12** from **4** was 46% over 7 steps.



Scheme 3 Reagents and conditions: i. excess MeCOMe , piperidine, DMF, 80°C , 83 %; ii. NaBH_4 , MeOH , CH_2Cl_2 , 100 %; iii. PTSA; toluene, THF, reflux, 100 %; iv. MeI , K_2CO_3 , Bu_4NBr , acetone, 95 %.

Using this method, we have attempted the synthesis of the core of glycofoline type acridone alkaloids^{6,11} starting from the acridone (**8**). The reaction with 6-methyl-5-hepten-2-one in the presence of piperidine gave tetracycle (**13**) in acceptable yield but the reduction of pyranone (**13**) with sodium borohydride, followed by acidic treatment of the product (PTSA , H_2SO_4 , HCl etc.) in all cases led to a complex mixture of products.



Scheme 4 Reagents and conditions: i. $\text{MeCOCH}_2\text{CH}_2\text{CH}=\text{CMe}_2$, piperidine, DMF, 80°C , 41.5 %.

EXPERIMENTAL

All starting materials were purchased from commercial suppliers and used without purification. Analytical TLC was carried out on aluminium sheets coated with Kieselgel 60 F_{254} and visualized with UV light. Column chromatography was performed with silica gel (Merck Kieselgel 60, 70-230 mesh). IR

spectra were obtained on a NICOLET FT-IR instrument. NMR spectra were obtained on a Bruker AM 500 (500 MHz for ^1H and 125 MHz for ^{13}C) and Bruker AC 250 (250 MHz for ^1H and 62.5 MHz for ^{13}C) instrument, at 30°C. Coupling constants (J) are given in Hz and all chemical shifts are relative to an internal standard of tetramethylsilane. Melting points are uncorrected.

Methyl 5-acetyl-4-hydroxy-2-phenylaminobenzoate (6): A suspension of benzenediazonium carboxylate (70 mmol, prepared from 9.6 g anthranilic acid) in dichloroethane (100 mL) was added dropwise to a refluxing solution of ester (4) (5.0 g, 23.9 mmol in 100 mL dichloroethane) and heating was continued until the starting material had disappeared (by TLC). The reaction mixture was then cooled and all precipitated solid was removed by filtration. The filtrate was evaporated *in vacuo* and the residue was triturated with hexane – ethyl acetate (1:1) to yield the product as a pale yellow solid (4.2 g, 62 %), mp 178 °C (cyclohexane - ethyl acetate); IR (KBr) 3259 (NH), 1692 (ester C=O), 1628 (ketone C=O), 1594 (C=C) cm^{-1} ; ^1H NMR (500 MHz, DMSO- d_6) δ = 12.84 (1H, s, OH), 10.03 (1H, br s, NH), 8.46 (1H, s, H-6), 7.40 (2H, t, J 7.9 Hz, H-3' and 5'), 7.26 (3H, m, 3H), 6.49 (1H, s, H-3), 3.92 (3H, s, CH_3O), 2.57 (3H, s, CH_3CO); ^{13}C NMR (125 MHz, DMSO- d_6) δ = 201.7 (quat.), 167.9 (quat.), 167.1 (quat.), 154.2 (quat.), 138.7 (quat.), 137.5 (CH), 129.6 (2 x CH), 125.6 (CH), 124.5 (2 x CH), 111.8 (quat.), 104.3 (quat.), 98.6 (CH), 51.9 (CH_3), 25.7 (CH_3); Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_4$: C, 67.4; H, 5.3; N, 4.9. Found: C, 67.5; H, 5.3; N, 4.9.

5-Acetyl-4-hydroxy-2-phenylaminobenzoic acid (7): Ester (6) (6.77 g, 23.7 mmol) was dissolved in ethanol (100 mL) and a solution of sodium hydroxide (10 g) in water (50 mL) was added. The reaction mixture was refluxed for 2 h. The ethanol was removed *in vacuo* and the residue was acidified with 5 % hydrochloric acid (200 mL). The precipitated product was filtered off, washed with water (200 mL) and dried to yield a white powder (6.40 g, 100 %), mp 212 °C (EtOAc); IR (KBr) 3305 (NH), 3026 (OH), 1670 acid C=O), 1639 (ketone C=O), 1592 (C=C) cm^{-1} ; ^1H NMR (500 MHz, DMSO- d_6) δ = 12.67 (1H, br s, OH), 11.02 (1H, br s, OH), 10.27 (1H, br s, NH), 8.47 (1H, s, H-6), 7.45 (2H, t, J 7.9 Hz, H-3' and 5'), 7.31 (2H, d, J 7.9 Hz, H-2' and 6'), 7.24 (1H, t, J 7.9 Hz, H-4'), 6.37 (1H, s, H-3), 2.56 (3H, s, CH_3CO); ^{13}C NMR (125 MHz, DMSO- d_6) δ = 201.7 (quat.), 169.4 (quat.), 165.9 (quat.), 153.4 (quat.), 138.8 (quat.), 137.9 (CH), 129.9 (2 x CH), 125.4 (CH), 123.9 (2 x CH), 111.9 (quat.), 105.1 (quat.), 97.7 (CH), 26.7 (CH_3); Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_4$: C, 66.4; H, 4.8; N, 5.2. Found: C, 66.6; H, 4.7; N, 5.1.

2-Acetyl-3-hydroxy-9(10H)-acridone (8): 5-Acetyl-4-hydroxy-2-phenylaminobenzoic acid 7 (2.00 g, 7.4 mmol) was dissolved in dry chloroform (100 mL) and freshly prepared polyphosphate ester (PPE) (10 g) was added. The solution was refluxed for 2 h, then the reaction mixture was cooled and neutralized with sat.

aq. sodium hydrogencarbonate solution. The precipitated product was filtered off, washed with water (300 mL) and dried to give the product as a white solid which could be used in the further steps without any purification (1.78 g, 95 %), mp 198 °C (ethyl acetate); IR (KBr) 3275 (NH), 3176 (OH), 1661 (ketone C=O), 1628 (amide C=O), 1595 (C=C) cm⁻¹; ¹H NMR (250 MHz, DMSO-d₆) δ= 12.35 (1H, s, OH), 11.75 (1H, s, NH), 8.73 (1H, s, H-1), 8.18 (1H, d, *J* 8.0 Hz, H-9), 7.73 (1H, t, *J* 8.0 Hz, H-7), 7.46 (1H, d, *J* 8.0 Hz, H-6), 7.27 (1H, t, *J* 8.0 Hz, H-8), 6.78 (1H, s, H-4), 2.71 (3H, s, COMe); ¹³C NMR (62.5 MHz, DMSO-d₆) δ= 203.2 (quat.), 176.2 (quat.), 163.6 (quat.), 145.9 (quat.), 140.9 (quat.), 133.8 (CH), 132.8 (CH), 126.1 (CH), 121.8 (quat.), 120.6 (CH), 117.3 (CH), 116.5 (quat.), 114.1 (CH), 27.3 (CH₃); Anal. Calcd for C₁₅H₁₁NO₃: C, 71.1; H, 4.4; N, 5.5. Found: C, 70.9; H, 4.3; N, 5.5.

2,2-Dimethyl-3,4,6,11-tetrahydro-2H-pyrano[3,2-*b*]acridine-4,6-dione (9): 2-Acetyl-3-hydroxy-9(10*H*)-acridone (8) (0.40 g, 1.57 mmol) was dissolved in dry dimethylformamide (40 mL) and dry acetone (1 mL). Piperidine (0.2 mL) was added and the reaction mixture was stirred for 72 h at 80 °C, then the solvent was removed *in vacuo* and the residue was stirred with 1M aq. HCl solution (5 mL). The yellow precipitate was filtered off, washed with water (20 mL) and ether to yield the product as a yellow powder (0.38 g, 83 %). mp 155-156 °C (CH₃CN); IR (KBr) 3262 (NH), 1680 (ketone C=O), 1632 (amide C=O), 1584 (C=C) cm⁻¹; ¹H-NMR (500 MHz, DMSO-d₆) δ= 11.76 (1H, s, NH), 8.65 (1H, s, H-5), 8.17 (1H, d, *J* 8 Hz, H-7), 7.73 (1H, t, *J* 8 Hz, H-9), 7.47 (1H, d, *J* 8 Hz, H-10), 7.27 (1H, t, *J* 8 Hz, H-8), 6.92 (1H, s, H-12), 2.85 (2H, s, 3-H₂), 1.44 (6H, s, 2 × CH₃); ¹³C NMR (125 MHz, DMSO-d₆) δ=190.7 (quat.), 176.6 (quat.), 161.8 (quat.), 146.1 (quat.), 140.9 (quat.), 134.0 (quat.), 127.1 (CH), 126.1 (CH), 121.8 (CH), 120.5 (CH), 117.3 (CH), 115.6 (quat.), 115.4 (quat.), 102.1 (CH), 80.1 (quat.), 48.1 (CH₂), 26.3 (2xCH₃); Anal. Calcd for C₁₈H₁₅NO₃: C, 73.7; H, 5.1; N, 4.8. Found: C, 73.9; H, 5.2; N, 4.7.

2,2-Dimethyl-4-hydroxy-3,4,6,11-tetrahydro-2H-pyrano[3,2-*b*]acridin-6-one (10): 2,2-Dimethyl-3,4,6,11-tetrahydro-2H-pyrano[3,2-*b*]acridine-4,6-dione (9) (0.15 g, 0.51 mmol) was dissolved in methanol (20 mL) and dichloromethane (2 mL). To this solution sodium borohydride (0.19 g, 50 mmol) was added in small portions. The solvents were removed *in vacuo* and the residue was dissolved in 1 M aq. HCl solution (10 mL). The aqueous phase was extracted with chloroform (2 x 15 mL) and the organic layer was washed with water (10 mL), dried over magnesium sulfate and evaporated *in vacuo* to yield the title product as a yellow powder (0.15 g, 100 %), mp 157-159 °C (EtOAc-hexane); IR (KBr) 3262 (NH), 2854 (OH), 1638 (amide C=O), 1589 (C=C) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ= 11.43 (1H, s, NH), 8.38 (1H, s, H-5), 8.19 (1H, d, *J* 8 Hz, H-7), 7.66 (1H, t, *J* 8 Hz, H-9), 7.46 (1H, d, *J* 8 Hz, H-10), 7.19 (1H, t, *J* 8 Hz, H-8), 6.85 (1H, s, H-12), 5.59 (1H, d, *J* 6 Hz, OH), 4.81 (1H, br td, *J* 6 Hz and 10 Hz, H-4), 2.16 (1H, dd, *J* 6 Hz and 13 Hz, 3-H₂), 1.77 (1H, dd, *J* 10 Hz and 13 Hz, 3-H₂), 1.44 (3H, s, Me), 1.31 (3H, s, Me); ¹³C

NMR (125 MHz, DMSO- d_6) δ = 176.0 (quat.), 157.8 (quat.), 141.7 (quat.), 141.1 (quat.), 132.9 (CH), 126.7 (CH), 126.0 (CH), 122.3 (quat.), 120.4 (CH), 120.2 (quat.), 116.8 (CH), 115.0 (quat.), 100.9 (CH), 76.9 (quat.), 61.1 (CH), 41.7 (CH₂), 29.2 (2 \times CH₃), 25.7 (CH₃); Anal. Calcd for C₁₈H₁₇NO₃: C, 73.2; H, 5.8; N, 4.7. Found: C, 73.2; H, 6.0; N, 4.7.

2,2-Dimethyl-6,11-dihydro-2H-pyrano[3,2-*b*]acridin-6-one (11): 2,2-Dimethyl-4-hydroxy-3,4,6,11-tetrahydro-2H-pyrano[3,2-*b*]acridin-6-one (**10**) (0.15 g, 0.5 mmol) was dissolved in mixture of toluene (20 mL) and tetrahydrofuran (10 mL). The reaction mixture was heated under reflux in the presence of *p*-toluenesulphonic acid (10 mg) under an argon atmosphere for 1 h, cooled, and the solvents were removed *in vacuo*. The residue was dissolved in chloroform (30 mL) and water (10 mL). The organic layer was washed with sat. aq. sodium hydrocarbonate solution (10 mL) and brine (10 mL), then dried (MgSO₄) and evaporated *in vacuo* to yield the product as a pale yellow powder (0.14 g, 100 %), mp 182-183 °C (EtOAc); IR (KBr) 3216 (NH), 1630 (C=O), 1588 (C=C) cm⁻¹; ¹H NMR (500 MHz, DMSO- d_6) δ = 11.58 (1H, s, NH), 8.17 (1H, d, *J* 8 Hz, H-7), 7.91 (1H, s, H-5), 7.68 (1H, t, *J* 8 Hz, H-9), 7.46 (1H, d, *J* 8 Hz, H-10), 7.22 (1H, t, *J* 8 Hz, H-8), 6.74 (1H, s, H-12), 6.61 (1H, d, *J* 9 Hz, H-4), 5.84 (1H, d, *J* 9 Hz, H-3), 1.44 (6H, s, 2 \times CH₃); ¹³C NMR (125 MHz, DMSO- d_6) δ = 175.6 (quat.), 157.2 (quat.), 142.4 (quat.), 140.6 (quat.), 132.8 (CH), 130.5 (CH), 125.8 (CH), 123.9 (CH), 121.3 (CH), 120.8 (CH), 120.4 (quat.), 116.9 (CH), 116.4 (quat.), 115.3 (quat.), 101.3 (CH), 77.4 (quat.), 28.1 (2 \times CH₃); Anal. Calcd for C₁₈H₁₅NO₂: C, 78.0; H, 5.5; N, 5.1. Found: C, 78.3; H, 5.6; N, 5.0.

2,2,11-Trimethyl-6,11-dihydro-2H-pyrano[3,2-*b*]acridin-6-one (12): 2,2-Dimethyl-6,11-dihydro-2H-pyrano[3,2-*b*]acridin-6-one (**11**) (0.10 g, 0.36 mmol) was dissolved in dry acetone (5 mL) and methyl iodide (0.25 g, 0.11 mL, 1.8 mmol), and potassium carbonate (0.10 g) and tetrabutylammonium chloride (10 mg) were added. The reaction mixture was stirred for 72 h at rt., then filtered. The filtrate was evaporated *in vacuo* and the residue was washed with water (15 mL) then recrystallised from ethyl acetate to yield demethoxyisoacronicyne (**12**) as a yellow solid (0.1 g, 95 %), mp 134-135 °C (EtOAc); IR (KBr) 1638 (C=O), 1611 (C=C), 1593 (C=C) cm⁻¹; ¹H NMR (500 MHz, DMSO- d_6) δ = 8.28 (1H, d, *J* 8 Hz, H-7), 8.00 (1H, s, H-5), 7.76 (2H, m, H-9, H-10), 7.29 (1H, t, *J* 8 Hz, H-8), 7.08 (1H, s, H-12), 6.62 (1H, d, *J* 10 Hz, H-4), 5.86 (1H, d, *J* 10 Hz, H-3), 3.84 (3H, s, NCH₃), 1.46 (6H, s, 2 \times CH₃); ¹³C NMR (125 MHz, DMSO- d_6) δ = 175.4 (quat.), 157.9 (quat.), 144.1 (quat.), 142.2 (quat.), 133.5 (CH), 130.9 (CH), 126.4 (CH), 124.4 (CH), 121.7 (CH), 121.2 (CH), 120.9 (quat.), 116.3 (CH), 116.1 (quat.), 116.0 (2 \times q), 102.0 (CH), 77.7 (quat.), 33.8 (CH₃), 28.2 (2 \times CH₃); Anal. Calcd for C₁₉H₁₇NO₂: C, 78.3; H, 5.9; N, 4.8. Found: C, 78.2; H, 6.0; N, 5.0.

2-Methyl-2-(4-methyl-3-pentenyl)-3,4,6,11-tetrahydro-2H-pyrano[3,2b]-acridine-4,6-dione (13):

2-Acetyl-3-hydroxy-9(10*H*)-acridone (**8**) (0.65 g, 2.56 mmol) was dissolved in dry dimethylformamide (70 mL) and 6-methyl-5-hepten-2-one (0.49 g, 0.57 mL, 3.9 mmol). Piperidine (0.13 mL) was added and the reaction mixture was refluxed for 72 h, then the dimethylformamide was removed *in vacuo* and the residue was stirred with 1M aq. HCl solution (20 mL). The yellow precipitate was filtered off, washed with water (20 mL) and diethylether (20 mL) to yield the product as a yellow powder which was purified by flash column chromatography eluting with ethyl acetate (0.37 g, 41.5 %), mp 112-113 °C (CH₃CN); IR (KBr) 1664 (ketone C=O), 1637 (amide C=O), 1583 (C=C) cm⁻¹; ¹H NMR (250 MHz, DMSO-d₆) δ= 11.83 (1H, br s, NH), 8.69 (1H, s, H-5), 8.23 (1H, d, *J* 8 Hz, H-7), 7.78 (1H, t, *J* 8 Hz, H-9), 7.52 (1H, d, *J* 8 Hz, H-10), 7.32 (1H, t, *J* 8 Hz, H-8), 6.90 (1H, s, H-12), 5.12 (1H, t, *J* 7 Hz, CH=), 2.91 (2H, s, H₂-3), 2.16-2.10 (2H, m, 3-CH₂), 1.79-1.72 (2H, m, 2-CH₂), 1.67 (3H, s, *trans*-CH₃), 1.59 (3H, s, *cis*-CH₃), 1.46 (3H, s, 2-CH₃); ¹³C NMR (250 MHz, DMSO-d₆) δ= 190.8 (quat.), 176.6 (quat.), 161.7 (quat.), 146.1 (quat.), 141.0 (quat.), 134.0 (quat.), 131.3 (quat.), 127.0 (CH), 126.1 (CH), 123.5 (CH), 121.8 (CH), 120.5 (quat.), 117.3 (CH), 115.8 (quat.), 102.2 (CH), 81.9 (quat.), 46.9 (CH₂), 38.9 (CH₂), 25.4 (CH₃), 23.8 (CH₂), 21.8 (CH₃), 17.4 (CH₃); Anal. Calcd for C₂₄H₂₇NO₃: C, 76.4; H, 7.2; N, 3.7. Found: C, 76.2; H, 7.1; N, 3.7.

ACKNOWLEDGEMENTS

This work was financially supported by the *National Fund for Science and Research* (OTKA Project No. F 23684). A grant from the *József Varga Foundation* provided to M.R. is gratefully appreciated. N.M. thanks the *Hungarian Academy of Sciences* for a Bolyai J. fellowship.

REFERENCES

1. Preliminary communication: M. Rudas, M. Nyerges, B. Pete, L. Töke, and P.W. Groundwater, *Tetrahedron Letters*, 1999, **40**, 7003.
2. G.K. Hughes, F.N. Lahey, J.R. Price, and L.J. Webb, *Nature*, 1948, **162**, 223.
3. F. Tillequin, S. Michel and A.-L. Skaltsansis, 'Alkaloids: Chemical and Biological Perspectives' Vol 12, ed. by S.W. Pelletier, Elsevier, Amsterdam, 1998, pp. 1-102.
4. M. Ju-ichi, K. Inoue, K. Sakiyama, M. Yoneda, and H. Furukawa, *Heterocycles*, 1987, **26**, 2057.
5. H. Furukawa, C. Ito, T. Mizuno, M. Ju-ichi, M. Inoue, I. Kajjura, and M. Omura, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1593.
6. J. Takemura, H. Uchida, M. Ju-ichi, C. Ito, K. Nakagawa, T. Ono, and H. Furukawa, *Heterocycles*, 1992, **34**, 2123.
7. J. Reisch, H.M.T.B. Hearsh and N.S. Kumar, *Liebigs Ann. Chem.*, 1991, 685.
8. P.W. Groundwater and M.A. Munawar, 'Advances in Heterocyclic Chemistry: Heterocycle-Fused

Acridines' Vol. 70, ed. by A.R. Katritzky, Academic Press, Inc., London, 1998, pp. 89-161.

9. S. Baker, L. Crombie, R.V. Dove, and D.A. Slack, *J. Chem. Soc., Perkin Trans. 1*, 1979, 677.
10. M. Watanabe, A. Kurosaki, and S. Furukawa, *Chem. Pharm. Bull.*, 1984, **32**, 1264.
11. T.-S. Wu and H. Furukawa, *Heterocycles*, 1983, **19**, 825; T.-S. Wu and H. Furukawa, C.-H. Kuoh, and K.-S. Hsu, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1681; T.-S. Wu, S.-C. Huang, T.-T. Jong, J.-S. Lai and H. Furukawa, *Heterocycles*, 1986, **24**, 41.