A NOVEL SYNTHESIS OF 6-DEMETHOXYACRONYCINE

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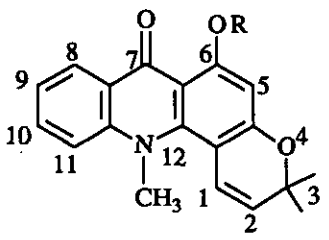
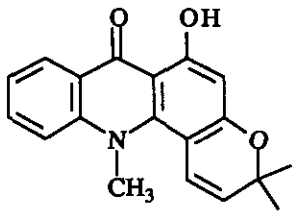
Abstract- The title compound was synthetized in six steps, starting from 3-nitrophenol. The key-step involves condensation of 2-bromobenzoic acid with 5-amino-2,2-dimethylchromene.

Acronycine (**1**) is a *Rutaceous* acridone alkaloid which exhibits a broad antitumour activity.[1-4] Several of its derivatives have been synthetized.[5-8] Among them, only 3,12-dihydro-6-dimethylaminoethyl-3,3,12-trimethyl-7*H*-pyrano[2,3-*c*]acridin-7-one (**2**) has shown a significant antitumor activity comparable with that of the parent coumpound.[5] In contrast, noracronycine (**3**)[9] has been reported to be inactive.[2] It should be noted that the electronic distribution of this latter compound is very different from that of acronycine itself, due to chelation of the 6-OH phenolic group by the carbonyl at the 7-position. It appeared therefore of interest to synthetize 6-demethoxyacronycine (**4**) in order to determine whether the presence of a substitutent at the 6-position on the basic skeleton was undispensible or not to the biological activity. Compound (**4**) had been previously prepared by condensation of *N*-methylisatoic anhydride with an enolate derived from a tetrahydrobenzopyranone, followed by DDQ oxidation.[10] Nevertheless, to the best of our knowledge, no biological data have been published for this compound.



R = CH_3 **1**

R = $(CH_2)_2N(CH_3)_2$ **2**



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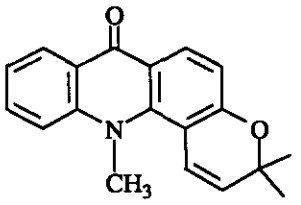

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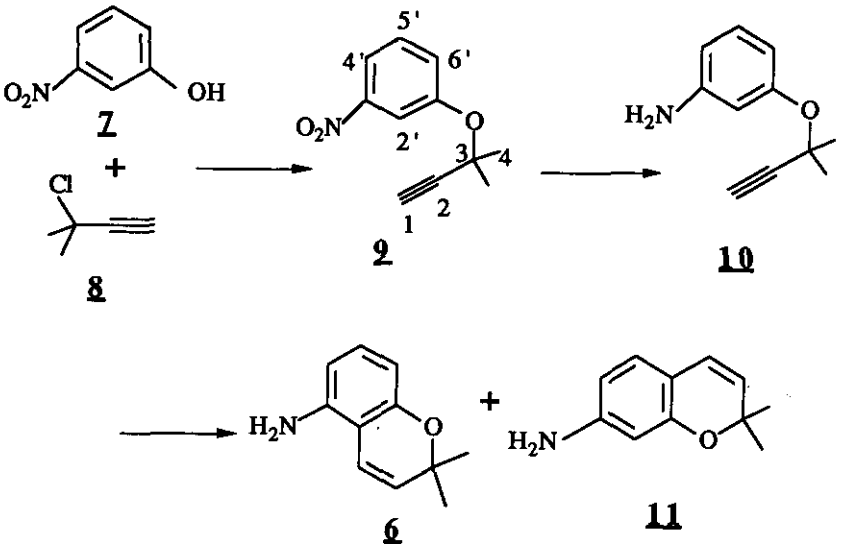
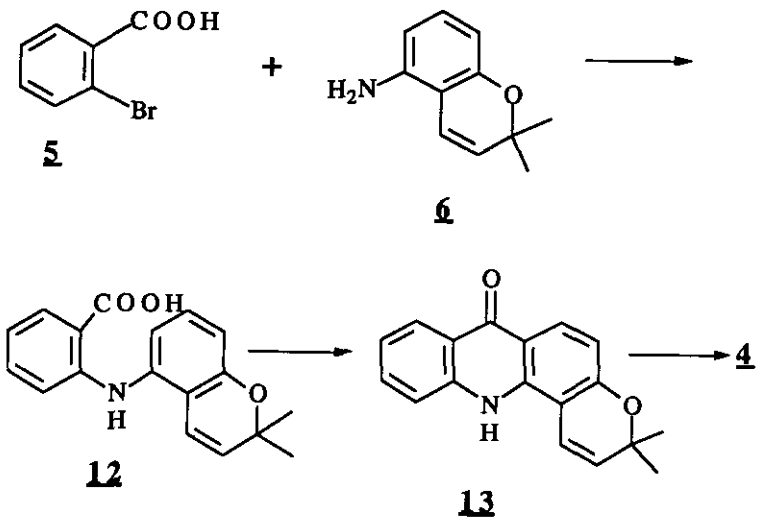
We wish to report here of new synthesis of 6-demethoxyacronycine (**4**) which key step is the condensation of 2-bromobenzoic acid (**5**) with 5-amino-2,2-dimethylchromene (**6**). This method has been chosen since compound (**6**), which had been previously used for the synthesis of pyrayaquinone-A,[11] appears as a potentially useful synthon for the preparation of various other Rutaceous alkaloids, including pyranocarbazoles,[12] and pyranofuroquinolines[13,14] by the classical Tuppy-Böhm method.[15-18]

Alkylation of commercially available 3-nitrophenol (**7**) by 3-chloro-3-methylbutyne (**8**)[19,20] led to 3-(3-nitrophenoxy)-3-methylbutyne (**9**) in almost quantitative yield. Reduction of **9** by iron powder[21] afforded smoothly 3-(3-aminophenoxy)-3-methylbutyne (**10**) in 48% yield. Claisen rearrangement[11, 22, 23] of **10** permitted to obtain, in 90% yield, a 80:20 mixture of 5-amino-2,2-dimethylchromene (**6**) and of 7-amino-2,2-dimethylchromene (**11**), from which the required compound (**6**) could be easily isolated either by column chromatography, or by fractionnal crystallization of its hydrochloride in methanol. The data of **6** are identical with those previously published for this coumpound prepared by a different method.[11]



Ullman condensation of **6** with 2-bromobenzoic acid (**5**) led to 2-[(2,2-dimethylchromen-5-yl)amino]benzoic acid (**12**) in 75% yield. Cyclization of **12** to des-*N*-methyl-6-demethoxyacronycine (**13**) was obtained in 85% yield by the use of trifluoroacetic anhydride in dichloromethane.[24] Finally, methylation of **13** by methyl iodide under phase-transfer catalyzed conditions[24] afforded 6-demethoxyacronycine (**4**) in 83% yield.



Preliminary evaluation of the cytotoxic activity of **4** was determined *in vitro*, against wild type (DC-3F) and actinomycin-D-resistant (DC-3F/ADX) Chinese hamster fibroblastic lung cell lines. When compared with acronycine itself (**1**) (ID_{50} =11.25 and 3.25 µg/mL respectively, after 72 h of incubation), 6-demethoxyacronycine (**4**) was found to have a higher potency (ID_{50}=8.75 and 2.75 µg/mL respectively). Further biological studies are currently in progress.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Spectra were recorded on the following apparatus : uv, Unicam SP 800 or Beckman MODEL 34 ; ir, Perkin-Elmer 1600 FT ; ms, Nermag R-10-10 C in electron impact (70 eV) ; ^{1}H-nmr, Bruker HX270 (270 MHz). *Chemical shifts are reported* in δ value (ppm) relative to TMS as internal standard. The following abbreviations are used : s = singlet, d =doublet, t = triplet, m = multiplet. Column chromatography was carried out on silica gel 60 H Merck or 60 Merck (230-400 mesh).

3-(3-Nitrophenoxy)-3-methylbutyne (9) : To a mixture of 3-nitrophenol (**7**) (5 g, 36 mmol), anhydrous K_2CO_3 (10 g) and KI (10 g) in dried acetone (100 ml), was added 3-chloro-3-methylbutyne (10.25 g, 100 mmol). The mixture was heated under reflux with stirring for 72 h. The solvent was removed under reduced pressure and the solid residue was taken up by CH_2Cl_2 (150 ml) and 1*N* aqueous NaOH (150 ml). The organic layer, dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure, gave **9** as a reddish-yellow oil (7.15 g, 97 %).; uv: λmax (EtOH) : 212, 276 nm; ir : ν max (film) : 3290, 2990, 2110, 1702, 1615, 1528, 1348, 1239, 1139, 809, 739 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ: 8.10 (t, J= 2.5 Hz, H-$C_{2'}$), 7.91 (ddd, J= 8, 2, 1 Hz, H-$C_{4'}$), 7.49 (ddd, J=8, 2, 1 Hz, H-$C_{6'}$), 7.42 (t, J= 8 Hz, H-$C_{5'}$), 2.70 (s, H-C_1), 1.70 (s, 2 x CH_3) ; ms (m/z) : 205 (M^+); Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found : C, 64.49; H, 5.32; N, 6.80.

3-(3-Aminophenoxy)-3-methylbutyne (10) : To a solution of 3-(3-nitrophenoxy)-3-methylbutyne (**9**) (4 g, 19.5 mmol) in MeOH (80 ml) and concentrated aqueous HCl (20 ml), was added iron powder (11 g, 195 mmol) in portions with stirring. After addition had been completed (*ca.* 35 min.), the mixture was stirred for another 30 min and sodium acetate (3 g) was added. The precipitate was removed by filtration. The filtrate was concentrated under reduced pressure, and extracted with Et_2O (200 ml). The organic layer was extracted with 1*N* aqueous HCl (3x100 ml). The acidic solution was alkalinized with NaOH pellets and then extracted with Et_2O (3x 100 ml). The organic layer, dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure, gave **10** as a yellow oil (1.66 g, 48 %), uv : λ max (EtOH) : 210, 237, 287 nm; ir : ν max (film): 3450, 3390, 3290, 2990, 2100, 1600, 1380, 1280, 885, 780 cm^{-1} ; ^{1}H-nmr ($CDCl_3$): δ: 7.05 (t, J= 8 Hz, H-$C_{5'}$), 6.65 (ddd, J= 8, 2, 1 Hz, H-$C_{6'}$), 6.55 (t, J= 2 Hz, H-$C_{2'}$), 6.40 (ddd, J= 8, 2, 1 Hz, H-$C_{4'}$), 2.55 (s, H-C_1), 1.65 (s, 2 x CH_3) ; ms (m/z) : 175 (M^+), 160, 109. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found : C, 75.29; H,7.53; N, 8.03.

5-Amino-2,2-dimethylchromene (6) : A solution of 3-(3-amino-phenoxy-3-methylbutyne (**10**) (1 g, 5.7 mmol) in 1,2-dichlorobenzene (5 ml) was heated under reflux for 10 h. The reaction mixture was diluted with Et_2O (100 ml), and extracted with 1*N* aqueous HCl (3x100 ml). The acidic solution was basified with 10 % KOH and then extracted with CH_2Cl_2 (3x100 ml). The organic layer, dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure, gave a 80:20 mixture (nmr) of 5-amino-2,2-dimethylchromene (**6**) and 7-amino-2,2-dimethylchromene (**11**) (900 mg, 90 % overall yield). Crystallization of the mixture in 1*N* methanolic HCl gave **6** as its hydrochloride (pale yellow prisms, mp : 190°C, decomp.). Alternatively, column chromatography of the mixture (solvent : CH_2Cl_2) permitted to obtain **6** as an oily free base (600 mg, 60 %), uv: λmax (EtOH) : 208, 233, 285, 325 nm; ir : ν max (KBr) : 3450, 3375, 3220, 2975, 1630, 1360, 1260, 1120, 790, 755 cm^{-1}; sm (m/z): 175 (M^+), 160 $(M-15)^+$; ^{1}H-nmr data were identical with those previously published.[11]

2-[(2,2-Dimethylchromen-5-yl)amino]benzoic acid (12) : A mixture of 5-amino-2,2-dimethylchromene (**6**) (263 mg, 1.5 mmol), 2-bromobenzoic acid (302 mg, 1.5 mmol), potassium acetate (327 mg), cupric acetate monohydrate (10 mg) and triethylamine (0.25 ml) in 2-propanol (7.5 ml) was heated under reflux for 24 h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 (20 ml) and 1*N* aqueous HCl (15 ml). The aqueous phase was extracted with CH_2Cl_2 (2 x 5 ml). The combined organic phase was dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. Column chromatography (solvent : cyclohexane-acetone-acetic acid, 80:20:0.5) of the residue afforded **12** (320 mg, 72 %), mp : 138°C (CH_2Cl_2); uv : λmax (EtOH) : 211, 280, 307, 347 nm; ir : ν max (KBr) : 3350, 3300, 2990, 1660, 1570, 1500, 1250, 760, 740 cm^{-1} ; ^{1}H-nmr ($CDCl_3$) : δ: 11.00 (s, COOH), 9.14 (s, NH), 8.05 (dd, J= 8, 2 Hz, H-C_6) , 7.31 (ddd, J= 8, 7, 2 Hz , H-C_4) , 7.13 (t, J= 8 Hz, H-$C_{7'}$) , 6.83 (d, J= 8Hz, H-$C_{6'}$ and dd, J= 8, 2 Hz, H-C_3), 6.72 (ddd, J= 8, 7, 2 Hz, H-C_5), 6.70 (dd, J= 8, 2 Hz, H-$C_{8'}$) , 6.48 (d, J= 10 Hz, H-$C_{4'}$), 5.65 (d, J= 10 Hz, H-$C_{3'}$),1.50 (s, 2x CH_3) ; ms (m/z) : 295 (M^+), 280 $(M-15)^+$, 262 . Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74 . Found : C, 73.08; H, 5.74; N, 4.79.

Des-N-methyl-6-demethoxyacronycine (13) : To a solution of 2-[(2,2-dimethyl-chromen-5-yl)amino]benzoic acid (**12**) (413 mg, 1.4 mmol) in CH_2Cl_2 (14 ml) was added trifluoroacetic anhydride (1 ml). The mixture was stirred at 20°C for 3 days, evaporated under reduced pressure and taken up by CH_2Cl_2 (20 ml) and saturated aqueous $NaHCO_3$ (20 ml). The aqueous phase was extracted with CH_2Cl_2 (2x10 ml). The combined organic phase was shaken for 5 min with 1*N* aqueous NaOH (15 ml) , dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure to provide **13** (329 mg, 85 %) as yellow prisms, mp : 262°C (cyclohexane-acetone, 80:20); uv : λmax (EtOH) : 207, 221, 261, 287, 342, 379, 405 nm ; ir : ν max (KBr) : 3280, 3200, 2990, 1630, 1595, 1560, 1290, 750, cm^{-1}; ^{1}H-nmr (*DMSO*-d_6) : δ: 8.30 (s, NH), 8.19 (dd, J= 8, 2 Hz, H-C_8), 8.06 (d, J= 9 Hz, H-C_6), 7.79 (dd, J= 8.0, 1.5 Hz, H-C_{11}) ,7.70 (td, J= 8, 1.5 Hz, H-C_{10}), 7.28 (td, J= 8, 1.5 Hz, H-C_9 and d, J= 10 Hz, H-C_1), 6.74 (d, J= 9 Hz, H-C_5),

5.91 (d, J= 10 Hz, H-C_2), 1.55 (s, 2 x CH_3); ms (m/z) : 277 (M^+), 262 (M-15)$^+$. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found : C, 78.04; H, 5.46; N, 5.02.

6-Demethoxyacronycine (4) : To a mixture of des-*N*-methyl-6-demethoxy-acronycine (**13**) (67 mg, 0.24 mmol), benzyltriethylammonium chloride (165 ml), 6*N* aqueous NaOH (1.20 ml) and 2-butanone (1.20 ml), was added methyl iodide (50 mg, 0.34 mmol). The mixture was heated under reflux for 3 h and diluted with CH_2Cl_2 (10 ml) and water (5 ml). The aqueous layer was extracted with CH_2Cl_2 (2x5 ml). The combined organic phase was dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. Column chromatography (solvent : cyclohexane-acetone 80:20) of the residue gave **4** (59 mg, 83 %) as yellow prisms, mp : 190-192°C; uv : λmax (EtOH) : 206, 228, 260, 276, 295(sh), 314, 366(sh), 386, 402(sh) nm ; ms (m/z) : 291 (M^+), 276, 261; ir and ^1H nmr data were identical with those previously published.[10]

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REFERENCES AND NOTES

1 G. H. Svoboda, G. A. Poore, P. J. Simpson, and G. B. Boder, *J. Pharm. Sci.*, 1966, **55**, 758.

2 G. H. Svoboda, *Lloydia*, 1966, **29**, 206.

3 M. Suffness and G. A. Cordell ' The Alkaloids ', Vol. 25, ed. by A. Brossi , Academic Press, Orlando, 1985, pp. 38-48.

4 T.-C. Chou, C.-C. Tzeng, T.-S. Wu, K.A. Watanabe, and T.-L. Su, *Phytother. Res.*, 1989, **3**, 237.

5 J. Schneider, E. L. Evans, E. Grunberg, and R. I. Fryer, *J. Med. Chem.*, 1972, **5**, 266.

6 K. J. Liska, *J. Med. Chem.*, 1972, **15**, 1177.

7 J. Reisch and S. M. El-Moghazy Aly, *Arch. Pharm. (Weinheim)*, 1986, **319**, 25.

8 C. Rivalle, C. Huel, and E. Bisagni, *J. Heterocycl. Chem.*, 1989, **26**, 577.

9 The semi-trivial nomenclature used in this paper is that generally used for acronycine derivatives, i.e., 6-hydroxy-3,12-dihydro-3,3,12-trimethyl-7*H*-pyrano[2,3-*c*]acridin-7-one is known as noracronycine, whereas 3,12-dihydro-3,3-dimethyl-6-methoxy-7*H*-pyrano[2,3-*c*]acridin-7-one is known as *N*-desmethylacronycine.

10 G. M. Coppola, *J. Heterocycl. Chem.*, 1984, **21**, 913.

11 H. Furukawa, M. Yogo, C. Ito, T.-S. Wu, and C.-S. Kuoh , *Chem. Pharm. Bull.*, 1985, **33**, 1320.

12 For a recent review on the synthesis of carbazole alkaloids, see : J. Bergman and B. Pelcman, *Pure Appl. Chem.*, 1990, **62**, 1967.

13 G. Baudouin, F. Tillequin, and M. Koch, *J. Nat. Prod.*, 1981, **44**, 546.

14 F. Tillequin, G. Baudouin, and M. Koch, *Heterocycles*, 1982, **19**, 507.

15 H. Tuppy and F. Böhm, *Angew. Chem.*, 1956, **68**, 388.

16 H. Tuppy and F. Böhm, *Monats. Chem.*, 1956, **87**, 720.

17 H. Tuppy and F. Böhm, *Monats. Chem.*, 1956, **87**, 774.

18 T. R. Govindachari, S. Prabhakar, V. N. Ramachandran, and B. R. Pai, *Ind. J. Chem.*, 1971, **9**, 1031.

19 T. Favorskaya, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 386.

20 G. F. Hennion and A. P. Boisselle, *J. Org. Chem.*, 1961, **26**, 725.

21 M. Harfenist and E. Thom, *J. Org. Chem.*, 1972, **37**, 841.

22 J. Hlubucek, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, 1970, **23**, 1881.

23 J. H. Adams, P. M. Brown, P. Gupta, M. S. Khan, and J. R. Lewis, *Tetrahedron*, 1981, **37**, 209.

24 D. G. Loughhead, *J. Org. Chem.*, 1990, **55**, 2245.

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