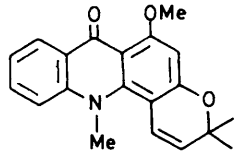
Synthesis of Acronycine Isosters

Johannes Reisch,* Iuliu Mester, and Samir M. El-Moghazy Aly †
Institute of Pharmaceutical Chemistry, University of Münster, D-4400 Münster, Federal Republic of Germany

The synthesis of the two key intermediates 6,8-dihydroxy-10-methylbenzo[*b*][1,8]naphthyridin-5(10*H*)-one (4b) and 6,8-dihydroxy-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (4d) for the synthesis of acronycine isosteres is described. The condensation of (4b) with 3-chloro-3-methylbut-1-yne afforded three isomers (5), (6), and (7), from which it was possible to distinguish between the angular isomer (5) and the linear isomer (6) with the aid of ^{13}C n.m.r. spectroscopy. The condensation of (4d) with 3-chloro-3-methylbut-1-yne yielded only one product (8). The action of dimethyl sulphate on 6-hydroxy-3,3-dimethyl-3*H*-pyrano[2′,3′:7,8]chromeno[2,3-*b*]pyridin-7-one (8) as well as on 6,8-dimethoxy-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (3b) is also reported.

Acronycine (1), an alkaloid first isolated from the Australian scrub ash *Acronychia baueri* Schott,[1] has been shown to exhibit antineoplastic activity against a very wide range of experimental neoplasm,[2] including the C-1498 myelogenous leukemia, a tumour which is singularly non-responsive to other antitumour agents. As an antitumour agent it inhibits the RNA synthesis.[3] Its clinical trials had a limited success because of its very low water solubility. Attempts have been made to overcome this difficulty (*e.g.* polyvinylpyrrolidone co-precipitate,[4] fluorosulphonate salt [5] or acetylacronycinium perchlorate prodrug [6]) but the products were of low stability.

Schneider [7] prepared some simple acronycine derivatives, none of which showed antineoplastic activity; this underlines the high selectivity of acronycine as an antitumour agent.



(1)

Results and Discussion

On the basis of bioisosteric considerations, our aim has been both to prepare acronycine analogues with improved water solubility and to study the structure activity relationship of acronycine.‡ Two acronycine analogues have therefore been prepared (Scheme 1) utilizing standard methods. The key intermediates 6,8-dihydroxy-10-methylbenzo[*b*][1,8]naphthyridin-5-one (4b) and 6,8-dihydroxy-5*H*-[1]benzopyrano-[2,3-*b*]pyridin-5-one (4d) were readily prepared by Ullmann condensation of 2-chloronicotinic acid with 3,5-dimethoxyaniline and 3,5-dimethoxyphenol respectively, followed by cyclisation with PPA to give (3a) and (3b). Compound (3a) was *N*-methylated then *O*-demethylated, while compound (3b) was directly *O*-demethylated to produce (4b) and (4d) respectively in admixture with the corresponding 3-methyl ethers (4a) and (4c). These intermediates, (4b) and (4d), were then condensed with 3-chloro-3-methylbut-1-yne in the presence of anhydrous potassium carbonate and potassium iodide in dry dimethylformamide (DMF) at 70 °C. In the case of (4b) three isomers, (5), (6), and (7), were isolated by preparative t.l.c. and identified on the basis of their spectroscopic properties. The dimethylprop-2-ynyl ether (7) was cyclised to (5) and (6) by heating under reflux in *N*,*N*-diethylaniline. Identification of the angular isomer (5) and the linear isomer (6) made use of the ^{13}C chemical shift to lower field recorded for the NCH_3 group of 4-substituted 10-methylacridones.[8,9] In contrast, the condensation of (4d) with 3-chloro-3-methylbut-1-yne under the same conditions yielded a single product.§ This had a molecular ion at *m/z* 295 ($C_{17}H_{13}NO_4$) and could be represented by any one of the three possible isomers (8), (9), or (10). The ^1H n.m.r. spectrum showed two doublets at δ 5.61 and 6.69 suggesting two olefinic protons of a chromen system; since, however, the i.r. spectrum showed no diagnostic band for C≡CH, structure (10) was excluded. A negative Gibb's test [10-13] provided evidence for the product having structure (8).

In an ^1H n.m.r. study to investigate the nature of the pyran ring fusion to the xanthone nucleus in pyranoxanthones we have noted the following. (i) A comparison of the 1-hydroxy-proton chemical shifts in $(CD_3)_2SO$ for 1,3-dihydroxyxanthones with those of their corresponding linear and angular pyranoxanthones shows that there is a large chemical shift to lower field (0.6—0.7 p.p.m.) for the linear isomers; the corresponding shift for the angular isomers is less (0.4 p.p.m.).[14]

(ii) Although the 2- and 4-protons in 1,3-dioxygenated xanthones have very similar chemical shifts,[15,16] the benzene-induced solvent shifts [Δ = δ ($CDCl_3$) − δ (C_6D_6)] are of diagnostic value,[17] since Δ(2-H) = 0.07 and Δ(4-H) = 0.2 p.p.m.; differentiation between linear and angular annelation is, therefore, possible.

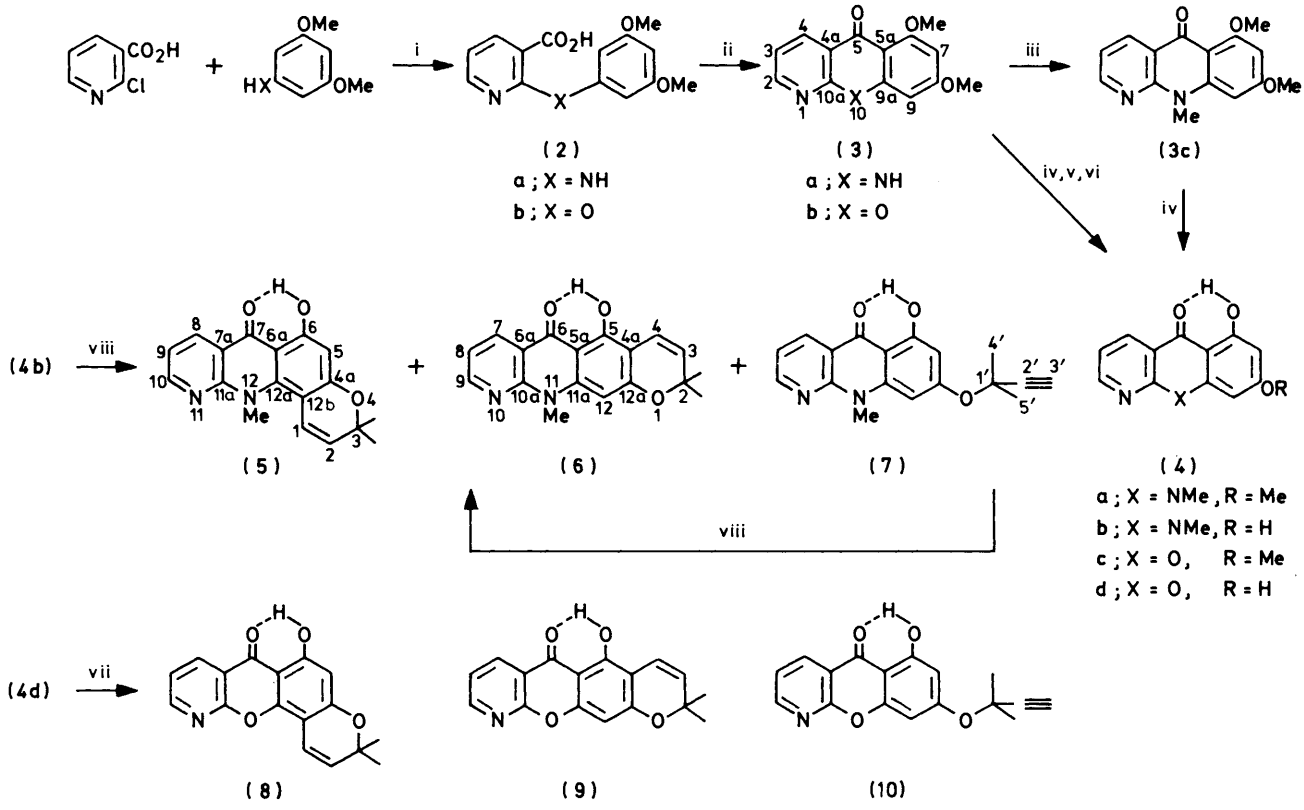
(iii) A hydroxy-group at the *peri*-position in chromens [18] causes downfield shifts of 0.3—0.5 p.p.m. for the γ-pyrano-proton in $(CD_3)_2SO$ compared with $CDCl_3$. This effect is not observed if other positions are hydroxylated.

The ^1H n.m.r. chemical shifts of (4d) and (8) recorded under different conditions (see Table), and interpreted in the light of the observations (i)—(iii) above, furnished further evidence for the angular annelation represented by (8).

In order to evaluate the nuclear Overhauser effect (n.o.e.)

† A part of Ph.D. Dissertation 1982.
‡ The pharmaceutical aspects will be published elsewhere.

§ This condensation was carried out many times with various reaction periods (20—48 h), the same product being isolated in all cases.



Scheme 1. *Reagents*: i, Cu, K_2CO_3, DMF; ii, PPA; iii, MeI, KOH, Me_2CO; iv, HBr, HOAc; v, BBr_3, CH_2Cl_2; vi, Py, HCl; vii, $ClCMe_2C{\equiv}CH$, K_2CO_3; KI, DMF; viii, $PhNEt_2$

Table. ^1H N.m.r. chemical shifts of (4d) and (8)

(4d)		(8)					
	δ[$(CD_3)_2SO$]		δ($CDCl_3$)	δ(C_6D_6)	δ($CDCl_3$)–δ(C_6D_6)	δ[$(CD_3)_2SO$]	δ($CDCl_3$)–δ[$(CD_3)_2SO$]
7-H	6.25	5-H	6.44	6.43	0.01	6.55	−0.11
9-H	6.46						
3-H	7.54	9-H	7.39	6.44	0.95	7.59	−0.20
4-H	8.50	8-H	8.58	8.12	0.46	8.58	0.00
2-H	8.72	10-H	8.67	8.16	0.51	8.78	−0.11
6-OH	12.42	OH	12.72	13.41	−0.69	12.84	−0.08
		1-H	6.69	6.84	−0.15	6.61	0.08
		2-H	5.61	5.15	0.45	5.81	−0.20
		CH_3	1.49	1.20	0.29	1.46	0.03

and so provide definitive evidence for the angular annelation in (8), we have tried to methylate the latter under mild conditions (DMF–NaH–MeI; heating for 3 h); this afforded (11) in a very poor yield with recovery of starting material.

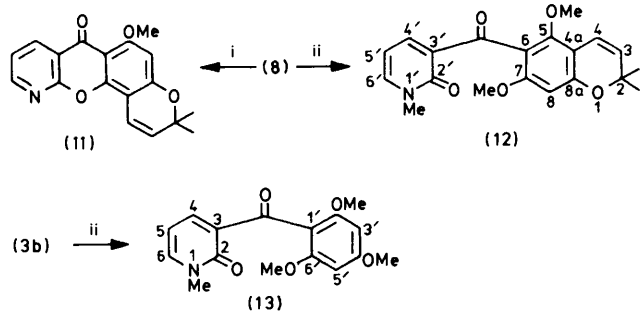
The double irradiation of the 6-methoxy-group in (11) caused 40% enhancement of the aromatic proton singlet corresponding to 5-H; the olefinic proton signals was not affected, thus confirming the angular annelation represented by (8).

Under forcing conditions (Me_2CO–Me_2SO_4–K_2CO_3 and heat) compound (8) failed to give (t.l.c.) any (11). When the reaction was continued for 20 h starting material disappeared completely and the resulting product was identified as (12) (Scheme 2) on the basis of its spectroscopic properties. The treatment of (3b) with dimethyl sulphate under the same conditions led also to ring opening and (13) was obtained.

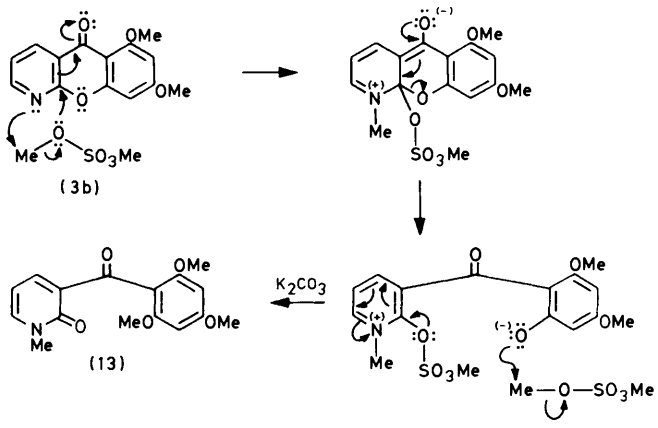
To postulate a mechanism for this ring opening, anhydrous potassium carbonate and compound (3b) were heated in dry acetone for 20 h, since starting material (3b) was recovered the reaction probably proceeds *via* dimethyl sulphate attack. The following mechanism (Scheme 3) may explain the ring-opening phenomenon.

Experimental

M.p.s are uncorrected. U.v. spectra were recorded on Perkin-Elmer 555 and i.r. spectra on Perkin-Elmer 457 and PYE Unicam SP 3-200 spectrophotometers. Mass spectra were obtained with Varian MAT 44 S spectrometer in connection with MAT 188 S at 70 eV. ^1H N.m.r. spectra were recorded on Varian T 60 and Bruker WH 90 instruments and ^{13}C n.m.r. spectra were obtained with Bruker WH 90. Silica gel 60 F 254 (Merck) was used for preparative t.l.c.



Scheme 2. *Reagents*: i, MeI, NaH, DMF; ii, Me_2SO_4, K_2CO_3, Me_2CO



Scheme 3

2-(3′,5′-*Dimethoxyanilino*)*nicotinic Acid* (2a).—2-Chloronicotinic acid (15.6 g) and 3,5-dimethoxyaniline (18.4 g) were refluxed for 3.5 h in dry DMF (50 ml) in the presence of anhydrous potassium carbonate (16 g) and copper powder (1 g). The solvent was then removed under reduced pressure and the residue was taken up in 1M-sodium hydroxide (200 ml), and the solution filtered and extracted with ether. The aqueous phase was acidified to pH 6 and the precipitate formed was collected. Crystallisation from toluene gave (2a) (12 g), m.p. 182—183 °C; $\nu_{max.}$ (KBr) 1 695 cm^{-1} (CO); $\lambda_{max.}$ (MeOH) 340 (log ε 3.75), 289 (4.42), 229sh (4.24), and 208 nm (4.54); δ_C[$(CD_3)_2SO$] 55.26 (2 × OCH_3), 94.35 (C-4′), 98.45 (C-2′, -6′), 108.03 (C-3), 114.21 (C-5), 140.69 (C-4), 141.57 (C-1′), 152.78 (C-6), 155.77 (C-2), 160.80 (C-3′, -5′), and 169.25 p.p.m. (CO) (Found: C, 61.35; H, 5.2; N, 10.05. $C_{14}H_{14}N_2O_4$ requires C, 61.31; H, 5.15; N, 10.21%).

6,8-*Dimethoxybenzo*[b][1,8]*naphthyridin*-5(10H)-*one* (3a).—A mixture of (2a) (11 g) and polyphosphoric acid (200 g) was heated at 100 °C for 3 h and then poured onto crushed ice (500 g); the mixture was basified with 30% sodium hydroxide and the crystalline precipitate formed was collected. Recrystallisation from ethanol gave (3a) (9.5 g), m.p. 265—266 °C; $\nu_{max.}$ (KBr) 1 640 cm^{-1} (CO); $\lambda_{max.}$ (MeOH) 367 (log ε 3.96), 314 (3.83), 290sh (3.90), 267 (4.77), 233 (4.38), 221 (4.39), and 201 nm (4.26); δ_H[$(CD_3)_2SO$] 3.88 (6 H, s, 2 × OCH_3), 6.28 (1 H, d, *J* 2.5 Hz, 7-H), 6.67 (1 H, d, *J* 2.5 Hz, 9-H), 7.22 (1 H, dd, *J* 8 and 4.8 Hz, 3-H), 8.42 (1 H, dd, *J* 8 and 2.1 Hz, 4-H), 8.63 (1 H, dd, *J* 4.8 and 2.1 Hz, 2-H), and 11.68 (1 H, s, NH); δ_C[$(CD_3)_2SO$] 55.35 and 55.68 (2 × OCH_3), 91.36 (C-9), 93.02 (C-7), 106.60 (C-5a), 116.84 (C-4a), 117.46 (C-3), 135.33 (C-4), 145.08 (C-9a), 150.41 (C-10a), 153.14 (C-2), 162.10 (C-6), 163.79 (C-8), and 175.30 (C-5) (Found: C, 65.5; H, 4.75; N, 10.8. $C_{14}H_{12}N_2O_3$ requires C, 65.62; H, 4.72; N, 10.93%).

6,8-*Dimethoxy*-10-*methylbenzo*[b][1,8]*naphthyridin*-5(10H)-*one* (3c).—A mixture of (3a) (9 g) and finely powdered potassium hydroxide (6.5 g) in dry acetone (180 ml) was refluxed for 15 min; methyl iodide (12 g) was then added. After a further 2.5 and 4 h, further methyl iodide, 6 and 12 g respectively, was added. The solvent was then evaporated under reduced pressure and the residue treated with water; the crystals which separated were collected and recrystallised from toluene to give (3c) (7 g), m.p. 207—208 °C, $\nu_{max.}$ (KBr) 1 655 cm^{-1} (CO); $\lambda_{max.}$ (MeOH) 370 (log ε 4.02), 318 (4.03), 292sh (3.92), 269 (4.81), 236 (4.45), 227 (4.42), and 201 nm (4.33); δ_H($CDCl_3$) 3.90 (3 H, s, NCH_3), 3.95 and 3.97 (2 × 3 H, 2 × s, 2 × OCH_3), 6.20 (1 H, d, *J* 2.3 Hz, 7-H), 6.42 (1 H, d, *J* 2.3 Hz, 9-H), 7.08 (1 H, dd, *J* 8 and 4.8 Hz, 3-H), 8.53 (1 H, dd, *J* 8 and 2 Hz, 4-H), and 8.65 (1 H, dd, J 4.8 2 Hz, 2-H); δ_C ($CDCl_3$) 31.31 (NCH_3), 55.29 and 56.07 (2 × OCH_3), 90.68 (C-9), 92.53 (C-7), 108.20 (C-5a), 117.36 (C-3), 118.79 (C-4a), 136.50 (C-4), 146.50 (C-9a), 151.61 (C-10a), 151.84 (C-2), 163.34 (C-6), 164.31 (C-8), and 176.50 p.p.m. (C-5) (Found: C. 66.4; H, 5.25; N, 10.3. $C_{15}H_{14}N_2O_3$ requires C, 66.65; H, 5.22; N, 10.37%).

Demethylation of (3c).—Compound (3c) (2.43 g) was refluxed with 47% hydrobromic acid (40 ml) and glacial acetic acid (15 ml) for 4 h, and then poured onto crushed ice (500 g); the crystals which separated were collected and shaked with 2% sodium hydroxide (20 ml). The insoluble material was filtered off, washed with water, and dried. Crystallisation from ethanol gave yellow crystals of 6-*hydroxy*-8-*methoxy*-10-*methylbenzo*[b][1,8]*naphthyridin*-5(10H)-*one* (4a) (0.25 g), m.p. 201—202 °C; $\nu_{max.}$ (KBr) 1 640 cm^{-1} (CO); $\lambda_{max.}$ (MeOH) 385 (log ε 3.71), 328 (3.79), 272 (4.60), 235 (4.26), 228sh (4.21), 203sh nm (3.98); δ_H($CDCl_3$) 3.88 (3 H, s, NCH_3), 3.95 (3 H, s, OCH_3), 6.24 (1 H, d, *J* 2.2 Hz, 7-H), 6.29 (1 H, d, *J* 2.2 Hz, 9-H), 7.17 (1 H, dd, *J* 7.8 and 4.5 Hz, 3-H), 8.60 (1 H, dd, *J* 7.8 and 1.9 Hz, 4-H), 8.68 (1 H, dd, *J* 4.5 and 1.9 Hz, 2-H), and 14.28 (1 H, s, OH); δ_C($CDCl_3$) 31.12 (NCH_3), 55.62 (OCH_3), 90.88 (C-9), 94.77 (C-7), 105.37 (C-5a), 116.03 (C-4a), 117.19 (C-3), 135.72 (C-4), 144.69 (C-9a), 151.19 (C-10a), 153.36 (C-2), 166.00 (C-6), 166.56 (C-8), and 180.92 (C-5) (Found: C, 65.5; H, 4.75; N, 11.15. $C_{14}H_{12}N_2O_3$ requires C, 65.62; H, 4.72; N, 10.93%). The alkaline filtrate was acidified and the precipitate formed was collected, washed with water, dried, and crystallised from ethanol to give 6,8-*dihydroxy*-10-*methylbenzo*[b][1,8]*naphthyridin*-5(10H)-*one* (4b) (1.54 g) as yellow crystals, m.p. 278—280 °C; $\nu_{max.}$ (KBr) 1 645 cm^{-1} (CO); $\lambda_{max.}$ (MeOH) 382 (log ε 3.86), 328 (3.97), 271 (4.72), 235 (4.46), 226sh (4.42), 216sh (4.38), and 202sh nm (4.33); δ_H[$(CD_3)_2SO$] 3.87 (3 H, s, NCH_3), 6.10 (1 H, d, *J* 2 Hz, 7-H), 6.36 (1 H, d, *J* 2 Hz, 9-H), 7.31 (1 H, dd, *J* 7.8 and 4.5 Hz, 3-H), 8.48 (1 H, dd, *J* 7.8 and 2 Hz, 4-H), 8.76 (1 H, dd, *J* 4.5 and 2 Hz, 2-H), and 14.29 (1 H, s, OH); δ_C [$(CD_3)_2SO$] 30.69 (NCH_3), 91.72 (C-9), 96.33 (C-7), 103.52 (C-5a), 114.76 (C-4a), 117.55 (C-3), 134.84 (C-4), 144.36 (C-9a), 150.11 (C-10a), 153.53 (C-2), 164.57 (C-6), 165.29 (C-8), and 179.36 (C-5) (Found: C, 63.95; H, 4.25; N, 11.55. $C_{13}H_{10}N_2O_3$ requires C, 64.46; H, 4.16; N, 11.57%).

Condensation of (4b) *with* 3-*Chloro*-3-*methylbut*-1-*yne*.—The dihydroxy-compound (4b) (1.21 g), 3-chloro-3-methylbut-1-yne (0.77 g), anhydrous potassium carbonate (1 g), and potassium iodide (1 g) in dry DMF (50 ml) were stirred under nitrogen at 70 °C for 22 h. The reaction mixture was then

poured onto crushed ice (300 g) and extracted with chloroform (2 × 50 ml). The chloroform extract was washed with 2% potassium hydroxide (50 ml) and then with water (2 × 50 ml), dried over anhydrous sodium sulphate, and evaporated to dryness under reduced pressure. The residue was streaked on preparative t.l.c. and run in toluene–ethyl acetate (4 : 1). The less polar band gave *5-hydroxy-2,2,11-trimethyl-2,11-dihydrochromeno*[7,6-b][1,8]*naphthyridin-6-one* (6) (185 mg) as yellow needles after crystallisation from ethanol, m.p. 217—218 °C; $\delta_H(CDCl_3)$ 1.49 (6 H, s, 2 × CH_3), 3.98 (3 H, s, NCH_3), 5.58 (1 H, d, *J* 10.1 Hz, 3-H), 6.34 (1 H, d, *J* 0.6 Hz, 12-H), 6.75 (1 H, dd, *J* 10.1 and 0.6 Hz, 4-H), 7.19 (1 H, dd, *J* 7.7 and 4.6 Hz, 8-H), 8.64 (1 H, dd, *J* 7.7 and 2.1 Hz, 7-H), 8.70 (1 H, dd, *J* 4.6 and 2.1 Hz, 9-H), and 14.62 (1 H, s, OH); $\delta_C(CDCl_3)$ 28.56 (2 × CH_3), 31.13 (NCH_3), 78.22 (C-2), 92.29 (C-12), 103.04 (C-4a), 105.25 (C-5a), 115.81 (C-3), 115.97 (C-6a), 117.53 (C-8), 127.02 (C-4), 135.67 (C-7), 144.36 (C-11a), 153.18 (C-10a), 153.28 (C-9), 159.81 (C-5), 160.59 (C-12a), and 180.77 (C-6) (Found: C, 69.95; H, 5.5; N, 9.05. $C_{18}H_{16}N_2O_3$ requires C, 70.12; H, 5.23; N, 9.08%).

Crystallisation of the second band from methanol gave *8-(1',1'-dimethylprop-2-ynyloxy)-6-hydroxy-10-methylbenzo*[b][1,8]*naphthyridin-5(10H)-one* (7) (161 mg), m.p. 120—122 °C; $\delta_H(CDCl_3)$ 1.78 (6 H, s, 2 × CH_3), 2.73 (1 H, s, ≡CH), 4.02 (3 H, s, NCH_3), 6.75 (2 H, s, 7- and 9-H), 7.20 (1 H, dd, *J* 7.8 and 4.5 Hz, 3-H), 8.63 (1 H, dd, *J* 7.8 and 2 Hz, 4-H), 8.70 (1 H, dd, *J* 4.5 and 2 Hz, 2-H), and 14.22 (1 H, s, OH); $\delta_C(CDCl_3)$ 29.73 (C-4' and C-5'), 31.10 (NCH_3), 72.59 (C-3'), 75.16 (C-1'), 85.07 (C-2'), 95.11 (C-9), 99.66 (C-7), 105.71 (C-5a), 115.81 (C-4a), 117.47 (C-3), 135.63 (C-4), 144.08 (C-9a), 153.25 (C-10a), 153.47 (C-2), 162.96 (C-6), 164.91 (C-8), and 180.93 (C-5).

Crystallisation of the lowest band from methanol gave *6-hydroxy-3,3,12-trimethyl-3,12-dihydrochromeno*[5,6-b][1,8]*naphthyridin-7-one* (5) (368 mg), m.p. 200—201 °C; $\delta_H(CDCl_3)$ 1.53 (6 H, s, 2 × CH_3), 3.99 (3 H, s, NCH_3), 5.51 (1 H, d, *J* 9.6 Hz, 2-H), 6.25 (1 H, d, *J* 0.8 Hz, 5-H), 6.62 (1 H, bd, *J* 9.6 Hz; 1-H), 7.23 (1 H, dd, *J* 7.8 and 4.5 Hz, 9-H), 8.58 (1 H, dd, 7.8 and 2 Hz, 8-H), 8.73 (1 H, dd, *J* 4.5 and 2 Hz, 10-H), and 14.36 (1 H, s, OH); $\delta_C(CDCl_3)$ 26.97 (2 × CH_3), 41.40 (NCH_3), 76.56 (C-3), 98.46 (C-5), 101.58 (C-12b), 107.04 (C-6a), 116.69 (C-7a), 118.12 (C-9), 121.56 (C-2), 123.32 (C-1), 135.28 (C-8), 143.98 (C-12a), 153.44 (C-11a), 153.57 (C-10), 162.12 (C-6), 165.33 (C-4a), and 181.26 (C-7) (Found: C, 69.55; H, 5.2; N, 9.15. $C_{18}H_{16}N_2O_3$ requires C, 70.12; H, 5.23; N, 9.08%).

Cyclisation of (7).—A solution of (7) (120 mg) in *N,N*-diethylaniline (5 ml) was refluxed under nitrogen for 3 h, then poured in 2M-hydrochloric acid (50 ml). After adjusting the pH to 6, the mixture was extracted with chloroform. The chloroform extract was worked up as mentioned above to give (5) (70 mg) and (6) (36 mg).

2-(3',5'-Dimethoxyphenoxy)nicotinic Acid (2b).—2-Chloronicotinic acid (7.8 g) and 3,5-dimethoxyphenol (7.65 g) were refluxed for 10 h in dry DMF (50 ml) in the presence of anhydrous potassium carbonate (12 g) and copper powder (0.1 g). The solvent was then evaporated under reduced pressure and the residue taken up in water (300 ml) and clarified with charcoal. On acidification with dilute hydrochloric acid (pH 2) a fine precipitate was formed (7.8 g) which crystallised from ethanol to give (2b) as fine white needles, m.p. 188—189 °C; $\nu_{max.}$ (KBr) 1 690 cm^{-1} (CO); $\delta_H[(CD_3)_2SO]$ 3.72 (6 H, s, 2 × OCH_3), 6.26 (2 H, d, *J* 2.1 Hz, 2'-, 6'-H), 6.34 (1 H, t, *J* 2.1 Hz, 4'-H), 7.22 (1 H, dd, *J* 7.4 and 4.9 Hz, 5-H), 8.23 (1 H, dd, *J* 7.4 and 2.1 Hz, 4-H), and 8.30 (1 H, dd, *J* 4.9 and 2.1 Hz, 6-H); $\delta_C[(CD_3)_2SO]$ 55.29 (2 × OCH_3), 96.63 (C-4'), 99.71 (C-2', -6'), 116.48 (C-3), 118.95 (C-5), 141.27 (C-4), 150.47 (C-6), 155.64 (C-2), 160.45 (C-1'), 160.93 (C-3', -5'), and 165.58 (CO) (Found: C, 60.4; H, 4.75; N, 5.05. $C_{14}H_{13}NO_5$ requires C, 61.09; H, 4.76; N, 5.09%).

6,8-Dimethoxy-5H-[1]benzopyrano[2,3-b]*pyridin-5-one* (3b).—2-(3',5'-Dimethoxyphenoxy)nicotinic acid (2b) (7.5 g) was heated at 110 °C with polyphosphoric acid (200 g) for 3 h. The reaction mixture was then poured onto crushed ice (400 g) and 40% potassium hydroxide (300 ml) was added (pH 3); a fine precipitate was formed and this was crystallised from aqueous acetic acid to give (3b) (6 g), m.p. 196—198 °C; $\nu_{max.}$ (KBr) 1 650 cm^{-1}; $\lambda_{max.}$ (MeOH) 324sh (log ε 4.11), 303 (4.25), 286sh (4.09), 226sh (4.49), 219 (4.52), and 209 nm (4.53); $\delta_H[(CD_3)_2SO]$ 3.92 (6 H, s, 2 × OCH_3), 6.43 (1 H, d, *J* 2.2 Hz, 7-H), 6.64 (1 H, d, *J* 2.2 Hz, 9-H), 7.44 (1 H, dd. *J* 7.7 and 4.6 Hz, 3-H), 8.46 (1 H, dd, *J* 7.7 and 2 Hz, 4-H), and 8.62 (1 H, dd, *J* 4.6 and 2 Hz, 2-H); $\delta_C(CDCl_3)$ 55.74 and 56.33 (2 × OCH_2), 93.51 (C-9), 95.64 (C-7), 106.99 (C-5a), 117.85 (C-4a), 120.87 (C-3), 137.15 (C-4), 152.78 (C-2), 159.41 (C-9a), 159.63 (C-10a), 162.10 (C-6), 165.52 (C-8), and 175.27 (C-5) (Found: C, 64.8; H, 4.3; N, 5.4. $C_{14}H_{11}NO_4$ requires C, 65.37; H, 4.31; N, 5.44%).

Demethylation of (3b).—(*a*) Compound (3b) (2 g) was stirred in CH_2Cl_2 (80 ml) with BBr_3 (2.5 ml) previously diluted with CH_2Cl_2 (30 ml) at −80 °C for 24 h. The reaction mixture was then diluted with water (200 ml) and CH_2Cl_2 was distilled off. The precipitate formed was shaken with 10% sodium carbonate solution (100 ml). The insoluble part was collected, washed with water, and dried to give *6-hydroxy-8-methoxy-5H-[1]benzopyrano*[2,3-b]*pyridin-5-one* (4c) (0.81 g) as yellow needles from aqueous acetic acid, m.p. 175—178 °C (decomp.); $\nu_{max.}$ (KBr) 1 645 cm^{-1} (CO); $\lambda_{max.}$ (EtOH) 390sh (log ε 3.13), 355sh (3.70), 303 (4.04), 283sh (3.83), 256 (4.15), 225 (4.31), and 209 nm (4.38); $\delta_H[(CD_3)_2SO]$ 3.89 (3 H, s, OCH_3), 6.37 (1 H, d, *J* 2.2 Hz, 7-H), 6.66 (1 H, d, *J* 2.2 Hz, 9-H), 7.57 (1 H, dd, *J* 7.7 and 4.6 Hz, 3-H), 8.53 (1 H, dd, *J* 7.7 and 2 Hz, 4-H), 8.75 (1 H, dd, *J* 4.6 and 2 Hz, 2-H), and 12.41 (1 H, s, OH); $\delta_C[(CD_3)_2SO]$ 56.20 (OCH_3), 93.44 (C-9), 97.37 (C-7), 102.96 (C-5a), 115.02 (C-4a), 121.65 (C-3), 136.04 (C-4), 154.53 (C-2), 156.77 (C-9a), 159.76 (C-10a), 162.42 (C-6), 166.88 (C-8), and 180.50 (C-5) (Found: C, 64.25; H, 3.9; N, 5.7. $C_{13}H_9NO_4$ requires C, 64.20; H, 3.73; N, 5.76%). The alkaline solution was acidified with dilute hydrochloric acid and the precipitate formed was collected, washed with water, and dried to give *6,8-dihydroxy-5H-[1]benzopyrano*[2,3-b]*pyridin-5-one* (4d) (0.4 g) as yellow needles from methanol, m.p. 308—310 °C; $\nu_{max.}$ (KBr) 1 660 cm^{-1} (CO); $\lambda_{max.}$ (EtOH) 390sh (log ε 3.17), 355sh (3.73), 305 (3.97), 283 (3.73), 256 (4.12), 225 (4.32), and 209 nm (4.36); $\delta_H[(CD_3)_2SO]$ 6.25 (1 H, d, *J* 2.2 Hz, 7-H), 6.46 (1 H, d, *J* 2.2 Hz, 9-H), 7.54 (1 H, dd, *J* 7.7 and 4.6 Hz, 3-H), 8.33 (1 H, s, 8-OH), 8.50 (1 H, dd, *J* 7.7 and 2 Hz, 4-H), 8.72 (1 H, dd, *J* 4.6 and 2 Hz, 2-H), and 12.42 (1 H, s, 6-OH); $\delta_C[(CD_3)_2SO]$ 94.71 (C-9), 98.54 (C-7), 102.02 (C-5a), 115.02 (C-4a), 121.49 (C-3), 135.91 (C-4), 154.24 (C-2), 156.84 (C-9a), 159.57 (C-10a), 162.72 (C-6), 166.46 (C-8), and 180.04 (C-5) (Found: C, 62.95; H, 3.2; N, 6.1. $C_{12}H_7NO_4$, C, 62.88; H, 3.08; N, 6.11%).

(*b*) A mixture of (3b) (2 g) and pyridine hydrochloride (10 g) was melted at 230 °C for 2 h; it was then poured onto crushed ice (300 g) and the precipitate formed was collected, washed with water, and dried to give (4d) (1.68 g). Compound (4c) was also demethylated in the same manner to give (4d) in 75% yield.

(*c*) Compound (3b) (1 g) was refluxed with 47% hydrobromic acid (15 ml) and glacial acetic acid (6 ml) for 4 h, and then poured onto crushed ice (300 g); the precipitate formed

was collected, washed with water, and dried. T.l.c. showed two products which were separated as in (*a*) to give (4c) (0.26 g) and (4d) (0.51 g).

6-*Hydroxy*-3,3-*dimethyl*-3H-*pyrano*[2',3':7,8]*chromeno*-[2,3-b]*pyridin*-7-*one* (8).—Compound (4d) (0.75 g) was stirred with 3-chloro-3-methylbut-1-yne (1 g) in dry DMF (50 ml), in the presence of anhydrous potassium carbonate (1 g) and anhydrous sodium iodide (1 g) under nitrogen at 70 °C for 20 h. The cooled reaction mixture was then diluted with water (300 ml), acidified with dilute hydrochloric acid, and extracted with chloroform (3 × 100 ml). The chloroform extract was washed with 2% potassium hydroxide (100 ml) and then with brine (50 ml). The aqueous phase was acidified with dilute hydrochloric acid and the precipitated starting material was recovered (585 mg). The chloroform extract was dried over anhydrous sodium sulphate and evaporated to dryness under reduced pressure. The residue (192 mg) was crystallised from acetone to give (8) as yellow needles, m.p. 218—220 °C; $\nu_{max.}$ (KBr) 1 650 cm^{-1} (CO); $\lambda_{max.}$ (EtOH) 331 (log ε 3.93), 282 (4.26), 279 (4.26), and 236 (4.16); δ_H ($CDCl_3$) 1.49 (6 H, s, 2 × CH_3), 5.61 (1 H, d, *J* 10.2 Hz, 2-H), 6.44 (1 H, d, *J* 0.8 Hz, 5-H), 6.69 (1 H, dd, *J* 10.2 and 0.8 Hz, 1-H), 7.39 (1 H, dd, *J* 7.6 and 4.7 Hz, 9H), 8.58 (1 H, dd, *J* 7.6 and 2.1 Hz, 8-H), 8.67 (1 H, dd, *J* 4.7 and 2.1 Hz, 10-H), and 12.72 (1 H, s, OH); δ_C($CDCl_3$) 28.45 (2 × CH_3), 78.62 (C-3), 95.94 (C-5), 103.45 (C-12b), 105.04 (C-6a), 115.05 (C-2), 115.67 (C-7a), 120.90 (C-9), 127.85 (C-1), 136.27 (C-8), 153.92 (C-10), 156.48 (C-12a), 157.56 (C-11a), 160.15 (C-6), 161.49 (C-4a), and 180.72 (C-7) (Found: C, 68.4; H, 4.5; N, 4.65. $C_{17}H_{13}NO_4$ requires C, 69.15; H, 4.44; N, 4.74%).

Methylation of (8).—(*a*) Compound (8) (70 mg) was warmed with sodium hydride (20 mg) in dry DMF (50 ml) until the effervescence ceased; excess of methyl iodide was then added and the reaction mixture was heated at 70 °C for 3 h. Water (100 ml) was then added and extracted with chloroform (2 × 50 ml). The chloroform extract was dried over anhydrous sodium sulphate and evaporated to dryness under reduced pressure. The residue was subjected to preparative t.l.c. (toluene–ethyl acetate–formic acid, 5 : 4 : 1) to give starting material (58 mg) and 6-*methoxy*-3,3-*dimethyl*-3H-*pyrano*[2',3':7,8]*chromeno*[2,3-b]*pyridin*-7-*one* (11) (10 mg), m.p. 188—192 °C; the product showed only one spot on t.l.c. (toluene–ethyl acetate–formic acid, 5 : 4 : 1), R_F 0.34; δ_H ($CDCl_3$) 1.50 (6 H, s, 2 × CH_3), 3.96 (1 H, s, OCH_3), 5.73 (1 H, d, *J* 10.1 Hz, 2-H), 6.68 (1 H, d, *J* 0.5 Hz, 5-H), 6.73 (1 H, dd, *J* 10.1 and 0.5 Hz, 1-H), 7.32—7.46 (2 H, m, 8-, 9-H), 8.66 (1 H, bd, *J* 6.5 Hz, 10-H) (*m/z* 309.1004, M^+, 10%. $C_{18}H_{15}NO_4$ requires *M*, 309.1001).

(*b*) Compound (8) (150 mg) was refluxed in dry acetone (50 ml) with an excess of dimethyl sulphate in the presence of anhydrous potassium carbonate (1 g) for 20 h; the mixture was then cooled and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue purified by preparative t.l.c. (toluene–ethyl acetate–formic acid, 5 : 4 : 1) to give 2,2-*dimethyl*-5,7-*dimethoxy*-6-(1'-*methyl*-2'-*oxo*-3'-*pyridylcarbonyl*)-2H-*benzopyran* (12) (113 mg), m.p. 66—68 °C; the product showed only one spot on t.l.c. in different solvent systems (toluene–ethyl acetate–formic acid, 5 : 4 : 1; R_F 0.22; toluene–acetone–methanol, 7 : 2 : 1; R_F 0.72), $\nu_{max.}$ (KBr) 3 450br (NCH_3), 2 885 (OCH_3), and 1 665 (CO); $\lambda_{max.}$ (EtOH) 340 (log ε 3.99), 321sh (3.91), 280sh (3.88), and 210 nm (4.58); δ_H ($CDCl_3$) 1.43 (6 H, s, 2 × CH_3), 3.54 (3 H, s, NCH_3), 3.66 and 3.71 (2 × 3 H, 2 × s, 2 × OCH_3), 5.48 (1 H, d, *J* 9.9 Hz, 3-H), 6.19 (1 H, d, *J* 0.5 Hz, 8-H), 6.22 (1 H, dd, *J* 7.2 and 6.5 Hz, 5'-H), 6.49 (1 H, dd, *J* 9.9 and *ca.* 0.1 Hz, 4-H), 7.51 (1 H, dd, *J* 6.5 and 2.2 Hz, 6'-H), and 7.97 (1 H, dd, *J* 7.2 and 2.2 Hz, 4'-H); δ_C($CDCl_3$) 28.10 (2 × CH_3), 38.00 (NCH_3), 55.87 and 63.12 (2 × OCH_3), 76.71 (C-2), 96.11 (C-8), 104.88 (C-5), 107.87 (C-4a), 116.74 (C-3), 117.30 (C-6), 127.21 (C-4), 129.25 (C-3'), 142.80 (C-6'), 143.43 (C-4'), 154.69 (C-5), 155.99 (C-7), 158.27 (C-8a), 160.41 (C-2'), and 191.68 (CO) (*m/z* 355.1409, M^+, 18%. $C_{20}H_{21}NO_5$ requires *M*, 355.1419).

Action of Dimethyl Sulphate on (3b).—Compound (3b) (200 mg) was refluxed in dry acetone (50 ml) with an excess of dimethyl sulphate in the presence of anhydrous potassium carbonate (1 g) for 20 h. The reaction mixture was worked up as above to give 3-(2',4',6'-*trimethoxybenzoyl*)-N-*methyl*-2-*pyridone* (13) (153 mg), m.p. 147—148 °C; the product showed only one spot in t.l.c. in different solvent systems (toluene–ethyl acetate–formic acid, 5 : 4 : 1; R_F 0.096; toluene–acetone–methanol, 7 : 2 : 1; R_F 0.69), $\nu_{max.}$ (KBr) 3 450br (NCH_3), 2 885 (OCH_3), 1 660 (CON), and 1 590 cm^{-1} (CO); $\lambda_{max.}$ (EtOH) 344 (log ε 3.97), 290sh (3.68), 282sh (3.63), 270sh (3.92), and 205 nm (4.57); δ_H($CDCl_3$) 3.51 (3 H, s, NCH_3), 3.70 (6 H, s, 2 × OCH_3), 3.81 (3 H, s, OCH_3), 6.12 (2 H, s, 3', 5'-H), 6.21 (1 H, dd, *J* 7.2 and 6.5 Nz, 5-H), 7.51 (1 H, dd, *J* 6.5 and 2.2 Hz, 6-H), and 8.03 (1 H, dd, *J* 7.2 and 2.2 Hz, 4-H); δ_C ($CDCl_3$) 37.94 (NCH_3), 55.20 (2 × OCH_3), 55.88 (OCH_3), 90.84 (C-3',-5'), 104.88 (C-5), 120.40 (C-1'), 129.28 (C-3), 142.64 (C-6), 143.26 (C-4), 158.86 (C-2',-6'), 160.70 (C-2), 162.27 (C-4'), and 191.35 (CO) (*m/z* 303.1103, M^+, 51%. $C_{16}H_{17}NO_4$ requires *M*, 303.1107).

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