A Facile Synthesis of Some Benzothiopyrano-[4,3-*b*]pyrroles†

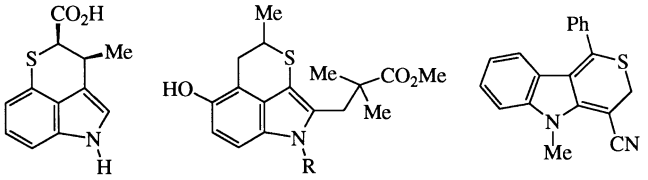
J. Chem. Research (S), 1997, 102–103†

Christopher D. Gabbutt, John D. Hepworth* and B. Mark Heron

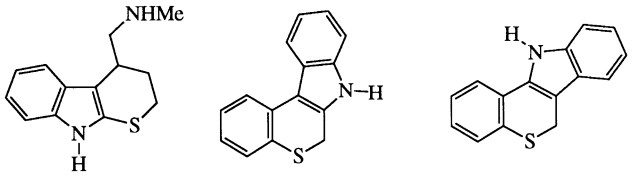
Department of Chemistry, University of Central Lancashire, Preston PR1 2HE, UK

A simple synthesis of some benzothiopyrano[4,3-*b*]pyrroles from benzothiopyran-4-ones is described which has been used to prepare the novel heterocyclic system 4*H*-naphtho[1′,2′:5,6]thiopyrano[4,3-*b*]pyrrole.

Since the isolation[1] and characterisation[2] of the thiopyrano-[2,3,4-*dc*]indole (chuangxinmycin) **1** from the soil micro-organism *Actinoplanes jinanensis* and its application by the Chinese as an antibiotic, particularly effective for the treatment of *Escherischia coli* infections,[1] there have been several reports on the synthesis of this ring system,[3] and of the isomeric thiopyrano[2,3,4-*cd*]indole **2**,[4] thiopyrano[3,4-*b*]indole **3**[5] and thiopyrano[2,3-*b*]indole **4**.[6] The syntheses of thiopyrano[3,4-*b*]pyrroles[5] and the benzothiopyrano-[3,4-*b*]- **5**[7] and -[4,3-*b*]-indoles **6**[8] have also been described.



1 **2** (R = C_6H_4-*p*-Cl) **3**

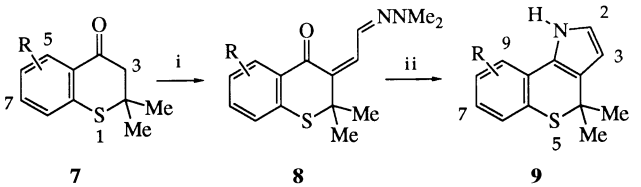


4 **5** **6**

As part of our study of condensed heterocycles containing the benzothiopyran unit,[9] we have devised a simple synthesis of some new benzothiopyrano[4,3-*b*]pyrroles, a ring system which has previously received scant attention.[10] The route has been adapted to provide access to fused analogues.

Discussion

The base-catalysed condensation of α-methylene ketones with glyoxal monohydrazones and subsequent reduction of the resulting hydrazono ethylidene derivatives affords γ-aminoketones which undergo a facile cyclisation to give pyrroles.[11] More recently, phenylacetylaldehyde has been shown to condense with glyoxal mono(*N*,*N*-dimethylhydrazone) in the presence of morpholine to afford 3-aminopyrroles directly.[12]



7 **8** **9**

Scheme 1 *Reagents and conditions:* i, glyoxal mono(dimethylhydrazone),KOBu^t, EtOH, heat; ii, excess sodium dithionite, EtOH, heat

The acidity of the C-3 methylene protons of 2,3-dihydro-1-benzothiopyran-4-one is well established.[13] When glyoxal mono(*N*,*N*-dimethylhydrazone)[12,14] was refluxed with 2,2-dimethyl-2,3-dihydro-1-benzothiopyran-4-one[15] **7** (R = H) in anhydrous ethanol containing one equivalent of potassium *tert*-butoxide, the 3-(*N*,*N*-dimethylhydrazonoethylidene) ketone **8** (R = H) was obtained after elution of the reaction mixture from silica (Scheme 1). The ^{1}H NMR spectrum of **8** (R = H) displayed singlets at δ 1.64 and 3.06 assigned to the methyl groups at C-2 and the dimethylamino function, respectively. The alkenyl and azomethine protons appeared as an AM pattern at δ 6.67 and 7.82 respectively, with a coupling constant of 9.3 Hz. The *Z*-stereochemistry of **8** was implied from nuclear Overhauser effect difference spectroscopic studies. Irradiation of the signal for the geminal methyl groups resulted in enhancement of the signal for the alkenyl proton, confirming their close proximity. Space-filling models further substantiate the proposed *s-trans* conformation of **8**, since significant steric interactions are indicated between the =N—NMe_2 group and the carbonyl function when an *s-cis* arrangement is adopted.

The condensation of the benzothiopyran-4-one **7** (R = 6-Me) and the naphtho[2,1-*b*]thiopyran-1-one **7** (R = 5,6-benzo) with glyoxal mono(*N*,*N*-dimethylhydrazone) gave the respective ketones **8** (R = 6-Me) and **8** (R = 5,6-benzo), which have comparable ^{1}H NMR data with **8** (R = H).

The reductive cyclisation of **8** (R = H) was achieved on refluxing in ethanol containing an excess of sodium dithionite. The pyrrole **9** (R = H) was obtained in moderate yield after recrystallisation. The ^{1}H NMR spectrum of this compound displayed triplets at δ 6.21 and 6.84 and a broad singlet at δ 8.4 which are assigned to H-3, H-2 and NH, respectively. Complete H–D exchange of the NH proton was observed after a sample was allowed to stand overnight with D_2O before recording the ^{1}H NMR spectrum. The exchange also resulted in the simplification of the signals for the pyrrole ring protons, which now appeared as doublets with J = 2.7 Hz. The low-field signal at *ca*. δ 8.4 exhibited by **9** (R = 8,9-benzo) is attributed to the *peri* proton (H-11).

It is likely that the formation of the pyrrole ring proceeds *via* an imine which on further reduction affords an amine. Subsequent 5-*exo-trig* ring closure with dehydration results in a 2*H*-pyrrole which undergoes a 1,5-H shift to give the pyrrole **9** (R = H). Cyclisation of **8** (R = Me and **8** (R = 5,6-benzo) was accomplished in an identical manner, although the benzologue **9** (R = 8,9-benzo), a new ring system, was somewhat unstable and gradually darkened on standing at room temperature.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM 250 MHz instrument for solutions in $CDCl_3$; J values are given in Hertz. Melting points are uncorrected. Flash chromatographic separations were performed on Sorbsil C60 silica gel.

Preparation of 3-(*Dimethylhydrazonoethylidene*)-2,2-*dimethylthiochroman*-4-*ones*.—Potassium *tert*-butoxide (10 mmol) was added in a single portion to a stirred solution of the thiochroman-4-one **7** (10 mmol) and glyoxal mono(*N*,*N*-dimethylhydrazone) (40 mmol) in anhydrous ethanol (35 cm^3). The resulting solution was boiled

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

under reflux for 2.5 h. On cooling, the ethanol was evaporated and the resulting sticky brown semi-solid was taken up in water (100 cm^3) and extracted with ethyl acetate (4×50 cm^3). Removal of the dried (Na_2SO_4) solvent afforded a dark brown oil which was eluted from silica gel with 20% (v/v) ethyl acetate–hexane to afford the title compounds as orange oils or solids. 3-(*Dimethylhydrazonoethylidene*)-2,2-*dimethylthiochroman*-4-*one* **8** (R = H) (54%) was a bright orange oil which decomposed upon distillation; δ_H 1.64 (6 H, s, 2-Me), 3.06 [6 H, s, $N(CH_3)_2$], 6.68 (1 H, d, *J* 9.3, =C*H*—CH=N—), 7.17–7.23 (2 H, m, Ar-H), 7.34–7.40 (1 H, m, Ar-H), 7.82 (1 H, d, *J* 9.3, CH=N—), 8.18 (1 H, dd, *J* 8.7, 1.7, 5-H) (Found: C, 65.6; H, 6.6; N, 10.1; S, 11.5. $C_{15}H_{18}N_2OS$ requires C, 65.7; H, 6.6; N, 10.2; S, 11.7%). 3-(*Dimethylhydrazonoethylidene*)-2,2,6-*trimethylthiochroman*-4-*one* **8** (R = 6-Me) (70%) was obtained as bright orange plates from light petroleum (bp 40–60 °C), mp 90–91 °C; δ_H 1.62 (6 H, s, 2-Me), 2.35 (3 H, s, 6-Me), 3.05 [6 H, s, $N(CH_3)_2$], 6.65 (1 H, d, *J* 9.3, =C*H*—CH=N), 7.11 (1 H, d, *J* 8.0, 8-H), 7.22 (1 H, dd, *J* 8.1, 1.8, 7-H), 7.82 (1 H, d, *J* 9.3, —CH=N—), 7.99 (1 H, d, *J* 1.7, 5-H) (Found: C, 66.4; H, 7.0; N, 9.7; S, 10.8. $C_{16}H_{20}N_2OS$ requires C, 66.6; H, 7.0; N, 9.7; S, 11.1%). 3-(*Dimethylhydrazonoethylidene*)-2,2-*dimethylbenzo*[f]*thiochroman*-4-*one* **8** (R = 5,6-benzo) (30%) was obtained as bright orange crystals from light petroleum (bp 40–60 °C), mp 118–119.5 °C; δ_H 1.70 (6 H, s, 2-Me), 3.07 [6 H, s, $N(CH_3)_2$], 6.70 (1 H, d, *J* 9.3, =C*H*—CH=N), 7.26 (1 H, d, *J* 8.7, 10-H), 7.42–7.49 (1 H, m, Ar-H), 7.59–7.66 (1 H, m, Ar-H), 7.75–7.80 (2 H, m, Ar-H), 7.97 (1 H, d, *J* 9.3, —CH=N—), 9.28 (1 H, dd, *J* 8.6, 1.8, 5-H) (Found: C, 70.2; H, 6.3; N, 8.6; S, 9.7. $C_{19}H_{20}N_2OS$ requires C, 70.3; H, 6.2; N, 8.6; S, 9.9%).

Preparation of 4H-*Benzo*[5,6]*thiopyrano*[4,3-b]*pyrroles*.—A solution of the 3-(dimethylhydrazonoethylidene)thiochroman-4-one **8** (5 mmol) and sodium dithionite (25 mmol) in ethanol (20 cm^3) and water (10 cm^3) was refluxed for 2 h. The resulting colourless solution was diluted with water (150 cm^3) and extracted with ethyl acetate (3×50 cm^3). The combined organic extracts were washed with water (2×50 cm^3), dried (Na_2SO_4) and evaporated to afford a pale yellow oil which crystallised upon cooling to give the crude pyrrole derivative which was purified by recrystallisation. 4,4-*Dimethyl*-4H-[1]*benzothiopyrano*[4,3-b]*pyrrole* **9** (R = H) (55%) was obtained as colourless crystals from n-hexane–ethyl acetate, mp 146–147 °C; δ_H 1.67 (6 H, s, 4-Me), 6.22 (1 H, t, *J* 2.6, 3-H), 6.84 (1 H, t, *J* 2.7, 2-H), 7.06–7.20 (2 H, m, 7-H and 8-H), 7.29 (1 H, dd, *J* 7.6, 1.3, 6-H), 7.38 (1 H, dd, *J* 7.5, 1.2, 9-H), 8.41 (1 H, m, N-H); δ_H ($CDCl_3 + D_2O$) 6.17 (1 H, d, *J* 2.7, 3-H), 6.80 (1 H, d, *J* 2.7, 2-H) and absence of N-H signal (Found: C, 72.7; H, 6.1; N, 6.4; S, 14.8. $C_{13}H_{13}NS$ requires C, 72.5; H, 6.1; N, 6.5; S, 14.9%). 4,4,8-*Trimethyl*-4H-[1]*benzothiopyrano*[4,3-b]*pyrrole* **9** (R = 8-Me) (46%) was obtained as colourless crystals from *n*-hexane–ethyl acetate, mp 151–152 °C; δ_H 1.61 (6 H, s, 4-Me), 2.34 (3 H, s, 8-Me), 6.16 (1 H, t, *J* 2.6, 3-H), 6.79 (1 H, t, *J* 2.8, 2-H), 6.88 (1 H, dd, *J* 7.9, 1.3, 7-H), 7.08 (1 H, d, *J* 1.2, 9-H), 7.23 (1 H, d, *J* 8.0, 6-H), 8.35 (1 H, bs, N-H). δ_H ($CDCl_3 + D_2O$) 6.15 (1 H, d, *J* 2.6, 3-H), 6.78 (1 H, d, *J* 2.6, 2-H) and absence of N-H signal (Found: C, 73.1; H, 6.6; N, 6.2; S, 14.2. $C_{14}H_{15}NS$ requires C, 73.3; H, 6.6; N, 6.1; S, 14.0%).

4,4-*Dimethyl*-4H-*naphtho*[1′,2′:5,6]*thiopyrano*[4,3-b]*pyrrole* **9** (R = 8,9-benzo) (62%) was a pale green solid which decomposed on attempted purification by recrystallisation or sublimation; δ_H 1.67 (6 H, s, 4-Me), 6.24 (1 H, m, 3-H), 6.96 (1 H, m, 2-H), 7.43–7.56 (3 H, m, Ar-H), 7.69–7.79 (1 H, m, Ar-H), 8.05–8.10 (1 H, m, Ar-H), 8.36–8.42 (1 H, m, Ar-H), 8.78 (1 H, bs, NH).

Received, 8th November 1996; Accepted, 4th December 1996
Paper E/6/07607F

References

1 Inst. Materia Medica, Chinese Acad. Med. Sci., *Scientia Sinica*, 1976, 295 (*Engl. Edn*., 1977, **20**, 106; *Chem. Abstr*., 1977, **87**, 98585g).
2 X.-T. Liang, X.-D. Xsu, Z.-P. Zhang, H.-E. Gu and W.-X. Wang, *Acta Chimica Sinica*, 1976, **34**, 129; X.-J. Xu, M.-C. Shao, Z.-E. Zhang, G.-B. Li, G.-D. Zhou and Y.-Q. Tang, *Kexue Tongbao*, 1980, **8**, 350.
3 A. P. Kozikowski, M. N. Greco and J. P. Springer, *J. Am. Chem. Soc*., 1982, **104**, 7622; M. J. Dickens, T. J. Mowlem, D. A. Widdowson, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc*., *Perkin Trans. 1*, 1992, 323; J. Y. L. Chung, R. A. Reamer and P. J. Reider, *Tetrahedron Lett*., 1992, 4717; H. Ishibashi, T. Tabata, K. Hanaoka, H. Iriyama, S. Akamatsu and M. Ikeda, *Tetrahedron Lett*., 1993, 489.
4 J. H. Hutchinson, E. J. McEachern, J. Scheigetz, D. Macdonald and M. Thérien, *Tetrahedron Lett*., 1992, 4713.
5 M. Murase, N. Nishino, N. Nara, Y. Nakanishi and S. Tobinaga, *Heterocycles*, 1994, **37**, 725; T. Saito, T. Shizuta, H. Kikuchi, J. Nakagawa, K. Hirotsu, H. Ohmura and S. Motoki, *Synthesis*, 1994, 727.
6 N. Ishizuka, *J. Chem. Soc*., *Perkin Trans. 1*, 1990, 813.
7 J. Mispelter, A. Croisy, P. Jacquignon, A. Ricci, C. Rossi and F. Schiaffela, *Tetrahedron*, 1977, **33**, 2383.
8 T. E. Young and P. H. Scott, *J. Org. Chem*., 1965, **30**, 3613; N. P. Buu-Hoi, A. Martani, A. Croisy, P. Jacquignon and F. Périn, *J. Chem. Soc. C*, 1966, 1787; T. E. Young, B. Pa and P. H. Scott, *US Pat*. 3,388,133, 1968; A. Croisy, P. Jacquignon and A. Fravolini, *J. Heterocycl. Chem*., 1974, **11**, 113; L. N. Borisova and T. A. Kartashova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1979, **15**, 162; G. Kolenz, R. Theuer, W. Ott, K. Peters, E.-M. Peters and H. G. von Schnering, *Heterocycles*, 1988, **27**, 479.
9 C. D. Gabbutt, J. D. Hepworth and B. M. Heron, *J. Chem. Soc*., *Perkin Trans. 1*, 1992, 2603; *Tetrahedron*, 1994, **50**, 7685; 1995, **51**, 13 277.
10 F. Eiden and E. Baumann, *Arch. Pharm. (Weinheim, Ger.*), 1983, **316**, 897.
11 Th. Severin and H. Poelhmann, *Chem. Ber*., 1977, **110**, 491.
12 A. Zinoune, J.-J. Bourguignon and C.-G. Wermuth, *Heterocycles*, 1989, **28**, 1077.
13 S. W. Schneller, *Adv. Heterocycl. Chem*., 1975, **18**, 59; A. H. Ingall, in *Comprehensive Heterocyclic Chemistry*, ed. C. W. Rees and A. R. Katritzky, Pergamon, Oxford, 1984, vol. 3, p. 885.
14 Th. Severin, R. Adam and H. Lerche, *Chem. Ber*., 1975, **108**, 1756.
15 S. E. Clayton, C. D. Gabbutt, J. D. Hepworth and B. M. Heron, *Tetrahedron*, 1993, **49**, 939.