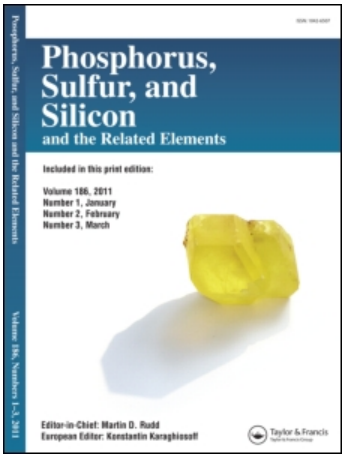

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SULPHUR ANALOGUES OF DEOXYVASICINONE (PART 7) THE SYNTHESIS OF PYRIDOPYRIMIDO[1,4]THIAZEPINONES

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SULPHUR ANALOGUES OF DEOXYVASICINONE (PART 7) THE SYNTHESIS OF PYRIDOPYRIMIDO[1,4]THIAZEPINONES

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The synthesis of the two novel pyridopyrimido[1,4]thiazepinones **1a–b** via the imidate **3** is described.

Keywords: Pyridopyrimido[1,4]thiazepinones; thiazepines; imidates; pyridines; aza quinazolones; O-ethylation

INTRODUCTION

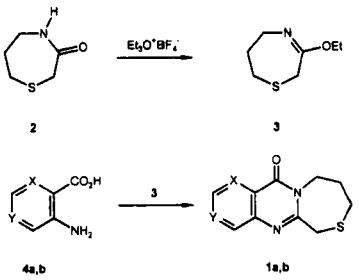
For some time we have been interested in quinazolines fused to sulphur containing rings[1] and have recently focused our attention on aza analogues of these systems. We now report the synthesis of two novel compounds of this type i.e. **1a–b**.

RESULTS AND DISCUSSION

The synthetic strategy adopted was that which we had previously successfully employed[2] for the preparation of aza analogues of deoxyvasicinone i.e. the interaction of the appropriate aminopyridine carboxylic acid with an imino ether. The desired precursor **2** was prepared essentially by the published procedure[3] from 1-amino-3-bromopropane and methyl thioglycolate in the presence of sodium methoxide (52% yield, mp 141–143°C). Conversion of **2** to the imidate **3**

was readily achieved by *O*-ethylation using triethyloxonium tetrafluoroborate. Compound **3** was obtained as a low melting crystalline solid after distillation of the crude reaction mixture but it did not prove possible to determine an accurate m.p. of this material. Treatment of the aminopyridine carboxylic acids **4a–b** with

Scheme



2 3 4a,b 1a,b

a X = CH, Y = N
b X = N, Y = CH

3 in DMF solution gave the pyridopyrimido[1,4]thiazepinones **1a–b** in 40% and 18% yield respectively.

EXPERIMENTAL

For general spectroscopic details etc. see[4]. 360 MHz ^{1}H-NMR was recorded with a Bruker AM-360.

3-Ethoxy-2,5,6,7-tetrahydro-1,4-thiazepine 3

A warm solution of the amide **2** (23.0g, 0.175 mole) in dry dichloromethane (250 ml) was added in one portion to freshly prepared triethyloxonium tetrafluoroborate (38g, 0.200 mole) and the mixture stirred vigorously at room temperature for 24 hours. The resulting clear solution was treated with a cold solution of anhydrous potassium carbonate (50g) in water (100 ml), the mixture stirred vigorously for 10 minutes and the organic layer was removed. The aqueous phase was extracted with three portions of dichloromethane (approx. 3 × 50 ml) and the combined organic extracts dried and concentrated at reduced pressure to afford a semi-solid mass. The latter was treated with a mixture of ether and petroleum ether (1 : 1, 50 ml) and filtered to yield some unreacted **2** (5.1g). The

filtrates were again concentrated *in vacuo* to afford an oil (ca. 15g, solvent wet). The oil was distilled under high vacuum to afford (a) a forerun b.p. 64–68° C/0.13 kPa (2.86g) and (b) a major fraction (9.60g) as a colourless oil b.p. 68–70°C/0.13 kPa which rapidly solidified in the receiver. The forerun also crystallised with time and was indistinguishable from (b) above (IR and ^{1}H-NMR). The total yield of **3** (based on recovered **2**) was 57%. ^{1}H-NMR (60 MHz): 1.23 (t, CH_3), 1.6–2.1 (complex, 2H-6), 2.84 (t, 2H-7), 3.24 (s, 2H-2), 3.3–3.7 (complex, 2H-6), 3.98 (q, OCH_2). IR (NaCl): 2890, 2850, 2770, 1570, 1320, 1200.

Anal. for $C_7H_{13}NOS$ (159.25)

Calcd.	C 52.80, H 8.23, N 8.80, S 20.13%.
Found	C 53.11, H 8.32, N 8.60, S 19.88%.

9,10-Dihydro-8H-pyrido[3',2':4,5]pyrimido[2,1-c][1,4]thiazepin-12(6H)-one **1a**

A mixture of **4a** (5.00g, 36.2 mmol) and **3** (4.50g, 28.3 mmol) in dry DMF (100 ml) was heated with stirring under gentle reflux for 2 hours. The crude product was isolated in two crops (2.35g and 0.31g, total yield 40%) as previously described[2]. The combined solids were recrystallised from ethanol to afford pure **1a** as colourless needles (2.05g) m.p. 221–222°C.

^{1}H-NMR (360 MHz): 2.20 (quintet, 2H-4), 2.98 (t, 2H-3), 3.99 (s, 2H-1), 4.44 (t, 2H-5), 8.01 (dd, $J_{8,11}$ = 0.87 Hz and $J_{8,9}$ = 5.2 Hz, H-8), 8.67 (d, $J_{8,9}$ = 5.2 Hz, H-9), 9.06 (d, $J_{8,11}$ = 0.87 Hz, H-11). IR (KBr): 3015, 2970, 1690, 1590, 1560. MS m/z (%): 233 (100), 204 (17), 200 (24), 187 (32), 186 (58), 161 (71).

Anal. for $C_{11}H_{11}N_3OS$ (233.29)

Calcd.	C 56.63, H 4.75, N 18.01, S 13.74%
Found	C 56.48, H 4.70, H 17.82 S 13.66%

4,5-Dihydro-3H-pyrido[3',4':4,5]pyrimido[2,1-c][1,4]thiazepin-7(1H)-one **1b**

A mixture of **4b** (5.00g, 36.2 mmol), **3** (4.50g, 28.3 mmol) and dry DMF (100 ml) was heated under reflux for 3 hours. The crude product (1.19 g, 18%) was isolated as described above and gave, after recrystallisation from ethanol, pure **1b** as colourless crystals (980 mg) m.p. 189–190°C. ^{1}H-NMR (360MHz): 2.23 (quintet, 2H-9), 2.98 (t, 2H-8), 3.97 (s 2H-6), 4.49 (t, 2H-10), 7.65 (dd, $J_{2,3}$ = 4.35 Hz, $J_{3,4}$ = 8.33 Hz, H-3), 7.96 (dd, $J_{2,4}$ = 1.55 Hz, $J_{3,4}$ = 8.33 Hz, H-4), 8.65 (dd, $J_{2,3}$ = 4.35 Hz, $J_{2,4}$ = 1.55 Hz, H-2). IR (KBr): 3080, 3070, 3010,

2960, 2930, 1680, 1580, 1560. MS m/z (%): 233 (100), 205 (31), 204 (21), 200 (43), 187 (31), 186 (75), 161 (85), 158 (23).

Anal. for $C_{11}H_{11}N_3OS$ (233.29)	
Calcd.	C 56.63, H 4.75, N 18.01, S 13.74%
Found	C 56.44, H 4.70, N 18.02, S 13.55%

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