The synthesis of a tricyclic pyrrolopyrimidine related to N^6-hydroxyadenine

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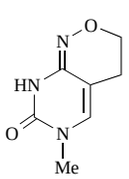
The synthesis of 9-methylpyrrolo[4,3,2-*de*]pyrimido[4,5-*c*]dihydrooxazepine 34, a tricyclic pyrrolo[2,3-*d*]pyrimidine analogue of the mutagenic purine N^6-hydroxyadenine, and several novel pyrrolo[2,3-*d*]pyrimidines is described. The presence of the third ring constrains the amino substituent of 34 to an *anti* orientation and is expected to improve dramatically the base-pairing characteristics of the analogue with both cytosine and thymine when present in DNA. An intramolecular cyclisation reaction of 5-(aminooxyethyl)-4-chloro-7-methyl-2-methylsulfonyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 30 gave 33, which was converted into the target molecule 34 *via* the displacement of the methylsulfonyl group with hydrazine followed by oxidation of the hydrazino group with mercuric oxide. An analogous cyclisation with 5-(aminooxyethyl)-4-chloro-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 31 was less effective, whilst the corresponding 2-amino derivative 32 failed to cyclise.

We have been interested in the synthesis of nucleoside analogues with ambivalent base-pairing properties.[1–3] The 2′-deoxyribosides of such analogues as **1**[1] (a bicyclic N^4-methoxycytosine analogue), N^6-methoxyadenine and N^6-methoxy-2,6-diaminopurine have been shown to be extremely useful in mixed sequence oligonucleotide primers used in PCR and DNA sequencing.[2] In addition, we have recently exploited the base-pairing characteristics[1,4] of the 5′-triphosphate of **1** in a PCR-based random mutagenesis procedure.[5] It was clear to us that conformationally restrained analogues such as **1** are more effective than N^4-methoxycytosine for such applications as exemplified by the thermal stabilities of oligonucleotide duplexes containing **1**.[1] In the same way we envisaged the tricyclic pyrrolo[2,3-*d*]pyrimidines of the type **2** (R=H, NH_2 *etc.*)



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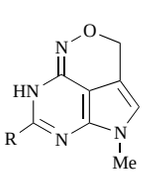

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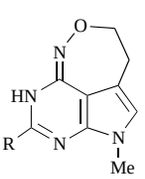


3

as correspondingly restrained analogues of *N*-hydroxypurines. In previous work[6] we attempted to prepare such compounds in order *inter alia* to investigate their tautomeric equilibria. The lack of success in a variety of reactions designed to achieve closure of the third ring was ascribed in part to angle strain and, where it applied, to the intrinsically low reactivity of halo-substituents at C-4 in pyrrolo[2,3-*d*]pyrimidines, in particular those deactivated by a 2-amino substituent.[7]

In the present paper we describe the synthesis of the homologous ring system, **3** which includes the tricyclic derivative 9-methylpyrrolo[4,3,2-*de*]pyrimido[4,5-*c*]dihydrooxazepine **34**.†

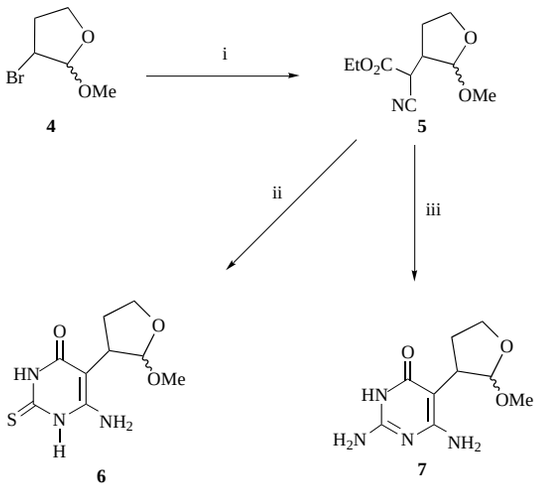
† Such compounds are more correctly named according to the IUPAC rules of nomenclature as: 2,6,8,9-tetrahydro-7-oxa-2,3,5,6-tetraaza-benzo[*cd*]azulenes.

Results and discussion

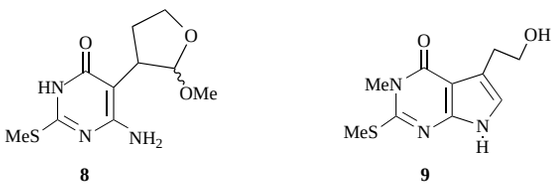
In the earlier experiments[6] we introduced the carbon substituent at C-5 of the pyrrolo[2,3-*d*]pyrimidine ring using a Mannich-type reaction. In order to introduce the two-carbon substituent at C-5 in **3** it was decided to generate an hydroxyethyl residue during the pyrrole ring-closure, thus involving an acid-catalysed, intramolecular cyclisation of a suitable 5-(acetal)-6-amino pyrimidine, based on earlier chemistry.[8] The resulting hydroxyethyl derivative would then be converted into an aminooxyethyl residue to allow nucleophilic displacement of a suitable substituent at C-4 of the pyrrolo[2,3-*d*]pyrimidine ring. To this end, dihydrofuran was converted into 2-methoxy-3-bromotetrahydrofuran **4** by bromination at −78 °C in methanol[9] or, more conveniently and in higher yield, *via* the 2,3-dibromo adduct,[10] followed without purification, by methanolysis. In the former procedure a *trans*:*cis* ratio of 85:15 was obtained,[11] whilst a 32:68 mixture was obtained *via* the *trans*-dibromide. When **3** was heated in DMF at 140 °C for 20 h with the sodium salt of ethyl cyanoacetate (generated using sodium hydride) the derivative **5** was obtained in 15% yield as a mixture of diastereoisomers (Scheme 1). Although a wide variety of conditions were investigated, higher yields were not obtained. This was so regardless of the diastereoisomeric ratio of the starting material **4**. No product was obtained using weaker bases such as sodium ethoxide in the reaction.

We envisaged that the ring system **3** (R = NH_2) would be obtained either by cyclisation of a suitable 2-amino-7*H*-pyrrolo[2,3-*d*]pyrimidine precursor or by displacement of a 2-methylsulfonyl group subsequent to cyclisation. It was expected that the latter compound would be available from the corresponding 2-sulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine, which would also furnish a route to **3** (R = H). Thus, reaction of the cyano ester **5** with thiourea or guanidine in ethanol afforded the pyrimidines **6** and **7**, respectively. The presence of two diastereoisomers in each case was evidenced by both TLC and by the presence of two sets of signals for the 6-amino and 2′-H substituents in the respective ^{1}H NMR spectra.

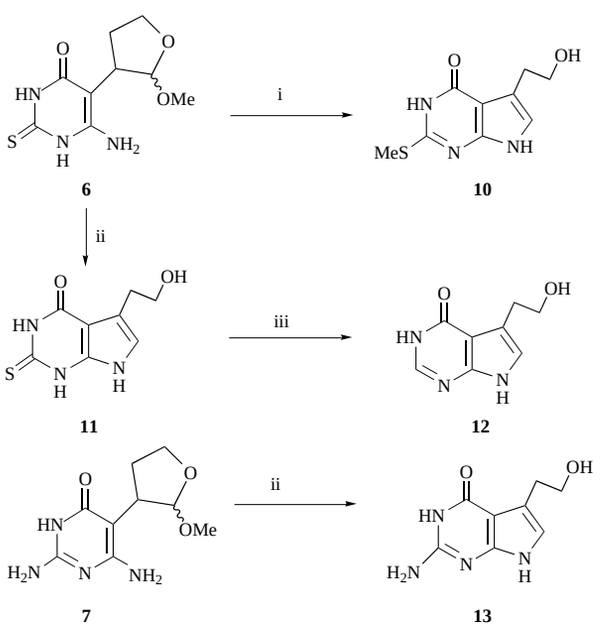
During initial attempts at methylation of **6** using dimethyl



Scheme 1 *Reagents and conditions:* i, $EtCO_2(CN)CH^-Na^+$, NaI, DMF, 140 °C, 20 h; ii, thiourea, EtONa, EtOH, reflux, 3 h; iii, guanidine hydrochloride, NaOEt, ethanol, reflux



sulfate and base, the methylsulfanylpyrimidine **8** was formed but in admixture with the dimethylated product **9** and the 2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine **10** as evidenced by ^{1}H NMR and mass spectral results. However, methylation of **6** with methyl iodide in DMF in the absence of base gave **10** directly and in high yield (Scheme 2). Clearly the acid formed in

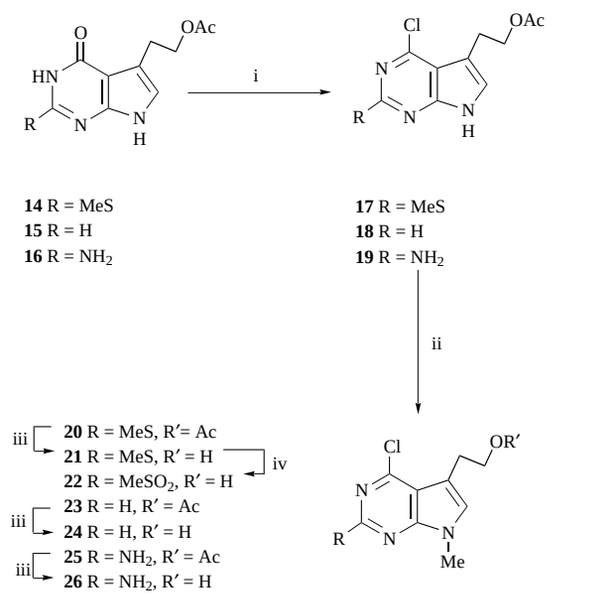


Scheme 2 *Reagents and conditions:* i, MeI, DMF, room temp. 6 h; ii, aq. HCl; iii, Raney Ni, water, reflux, 3 h

the alkylation was sufficient to activate the acetal function of the methoxytetrahydrofuranyl residue for cyclisation.

When **6** and **7** were treated with dilute hydrochloric acid, both cyclised in high yield to the corresponding 2-thioxo- and 2-amino-7*H*-pyrrolo[2,3-*d*]pyrimidines, **11** and **13**, respectively. The former was converted into the hypoxanthine analogue **12**, upon reduction with Raney nickel.

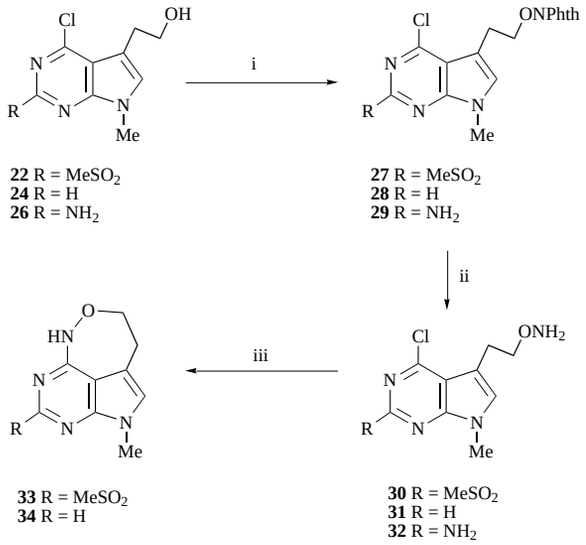
The 5-hydroxyethyl-7*H*-pyrrolo[2,3-*d*]pyrimidines **10**, **12** and **13** were then acetylated in pyridine to give the 5-(2-acetoxyethyl) compounds (**14**, **15**, **16**). Selective *O*-acylation of the 2-amino-7*H*-pyrrolo[2,3-*d*]pyrimidine **13** was achieved at 0 °C in the dark; solutions of compound **13** undergo rapid darkening in light and it appears as a bright blue spot on silica TLC plates when visualised under UV light. Attempted recrystallisation of crude **16** also led to darkening of the solution and the formation of side products. We have not investigated this further, but such instablity has also been reported in other 2-amino-7*H*-pyrrolo[2,3-*d*]pyrimidines.[12] Compounds **14**, **15** and **16** were then converted into the corresponding 4-chloroheterocycles (**17**–**19**) (Scheme 3) by heating under reflux with phosphoryl



Scheme 3 *Reagents and conditions:* i, $POCl_3$, $PhNMe_2$, $BzEt_3N^+Cl^-$, reflux; ii, NaH, MeCN, 30 min, then MeI; iii, aq. NH_4OH, MeOH, room temp., 6 h; iv, MMPP aq. EtOH, room temp.

chloride and dimethylaniline in the presence of benzyltriethylammonium chloride. Yields were poor, not least because of the dark decomposition products of dimethylaniline. The more recent halogenation using triphenylphosphine–carbon tetrachloride, used effectively by Napoli *et al.*[13] in the purine series, was ineffective in the present case, whilst thionyl chloride proved to be less efficient than phosphoryl chloride. Several other protecting groups for the alcohol were also examined. Thus, the *p*-*tert*-butylbenzoyl group was stable during the chlorination but could not be as easily removed, whilst several silyl protecting groups, notably even triphenylsilyl were removed to varying degrees during the halogenation. The 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidines (**17**–**19**) were treated with sodium hydride in acetonitrile followed by addition of methyl iodide to give the corresponding 7-methyl derivatives (**20**, **23** and **25**) in high yield. These were subsequently deacetylated to give the 5-(2-hydroxyethyl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidines (**21**, **24** and **26**).

Our earlier experience[6] of 4-halogeno-7*H*-pyrrolo[2,3-*d*]-pyrimidines had shown us that a 2-methylsulfonyl residue would be advantageous in increasing the reactivity at C-4; it was expected, too, to provide a residue at C-2 which could be more readily displaced by nucleophiles for the introduction of other functional groups. Oxidation of **21**, conveniently by magnesium monoperphthalate, gave the 2-methylsulfonyl derivative **22** in high yield. In order to introduce the aminooxyethyl residue for the cyclisation, the alcohols **22**, **24** and **26** were submitted to Mitsunobu coupling with *N*-hydroxyphthalimide to give the 5-(2-phthalimidooxyethyl) derivatives **27**–**29** (Scheme 4). Interestingly, the amino analogue **29** was obtained as an intense yellow solid, while in solution it was colourless. This suggested



22 R = $MeSO_2$
24 R = H
26 R = NH_2

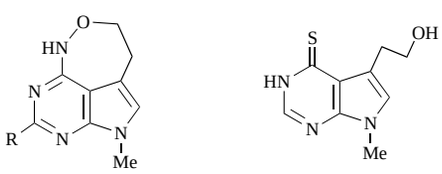
27 R = $MeSO_2$
28 R = H
29 R = NH_2

33 R = $MeSO_2$
34 R = H

30 R = $MeSO_2$
31 R = H
32 R = NH_2

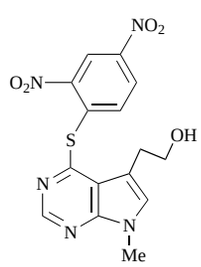
Scheme 4 *Reagents and conditions:* i, Ph_3P, DEAD, PhthNOH, THF, room temp.; ii, NH_3, dioxane, room temp. 6 h; iii, EtOH, reflux 1 d for **33**, THF 70 °C, 1 d for **34**

stacking of the phthalimide and pyrrolopyrimidine rings in the solid state; this feature had not been observed in a corresponding 5-phthalimidooxymethyl derivative prepared previously.[6] When the phthalimidooxy derivatives were treated with saturated ammonia in dioxane for 6 h at room temperature, the phthaloyl residue was removed. The aminooxyethyl derivatives **30**–**32** were observed on TLC, as slower-running products, but were not isolated. None showed any evidence of cyclisation under the deprotection conditions, or upon subsequent heating of the solution. However, when **30** was heated under reflux in ethanol, TLC indicated the appearance of a new, less polar product **33** which was isolated in 36% yield following silica chromatography and crystallisation from ethanol. ^{1}H NMR and mass spectral evidence showed that this was the desired tricyclic compound. When the aminooxy derivative **31** was heated in THF at 70 °C for 1 day in a sealed bottle, the tricyclic N^6-hydroxy-2′-deoxyadenosine analogue **34** was obtained although only in 5% yield. However, the same compound could be obtained more conveniently and in higher yield from **33**. The latter was efficiently converted into **35** by heating with hydrazine in ethanol, followed by oxidation of the hydrazino moiety with mercuric oxide in ethanol[14] to afford the desired compound in 29% yield. The side product, 2-ethoxy-7*H*-pyrrolo-[2,3-*d*]pyrimidine derivative **36**, was obtained in 13% yield in the reaction.



35 R = NH_2NH
36 R = EtO

37



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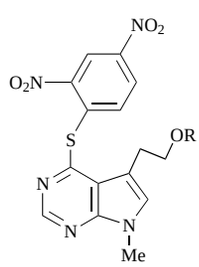

39 R = NPhth
40 R = NH_2

In order to obtain the corresponding 2-amino derivative of **34**, we initially tried heating **33** with ammonia in dioxane in a sealed bottle at 100 °C for 24 h but observed no reaction, whilst heating in aqueous ammonia for 48 h at 120 °C in a sealed tube gave unidentified decomposition products. Attempts to displace the methylsulfonyl group with sodioacetamide were equally unsuccessful, which may be due to ionisation of the 1-NH proton or the methylsulfonyl residue,[15] thereby discouraging attack of the nucleophile. In the former case, it is likely that the methylsulfonyl group decreases the pK_a of the proton sufficiently for this to occur and indeed we have found that in other compounds where this ionisation cannot occur, displacement with sodioacetamide proceeded readily (unpublished results). As an alternative route to **34** we considered an analogous cyclisation using the 5-aminooxyethyl derivative to displace a 4-(2,4-dinitrophenylsulfanyl)- rather than a 4-chloro-substituent. Thus, **23** was converted efficiently with thiourea into the 4-thioxo derivative **37**, which was then treated with 2,4-dinitrofluorobenzene to give **38** and converted into the *N*-hydroxyphthalimide derivative **39**. The corresponding aminooxyethyl derivative **40** was obtained following treatment of **39** with ammonia in dioxane and isolated by silica gel chromatography. When **40** was heated in ethanol no evidence for cyclisation was observed.

We[2,16] and others[17,18] have previously found that signals attributable to both the imino and amino tautomers are observed in the ^{1}H NMR spectra of both N^6-methoxy-2′-deoxyadenosine and 2-amino-N^6-methoxy-2′-deoxyadenosine. Furthermore, the ratio of the tautomers is strongly solvent dependent; in a polar solvent such as DMSO, the imino tautomer predominates, whilst in chloroform, the amino tautomer is preferred. However, the ^{1}H NMR spectrum of **34** in both DMSO and chloroform showed the presence of only one tautomer as was also found for the tricyclic derivatives **33**, **35** and **36**. It has been shown[18] that for N^6-methoxy-9-methyladenine, a significant upfield shift of the ^{1}H NMR signal corresponding to the 2-H ring proton occurs for the imino tautomer relative to both the corresponding amino tautomer and the parent compound, 9-methyladenine. In addition, coupling of the 2-H with the 1-NH proton (*J* 3.9 Hz) is observed for N^6-methoxy-9-methyladenine. On this basis, we have tentatively ascribed the amino tautomer of **34** as being the major species. It is noteworthy that ^{1}H NMR spectral evidence suggests that **1** also appears to exist as a single tautomer,[1] but is able to pair effectively with either adenine or guanine.[3–5] Furthermore, the tautomeric equilibrium of N^6-methoxyadenine is appreciably shifted to the amino or imino form upon the addition of uridine or cytidine, respectively.[17] For this reason, the ^{1}H NMR data for **34** presented here is compatible with our expectation that the analogue will base pair effectively with either cytosine or thymine/uracil.

We are currently investigating the tautomeric state and base-pairing properties of **34.**

Experimental

^{1}H NMR spectra were recorded at 250.13 MHz or at 300.13 MHz on a Bruker WM 250 or AM300 spectrometer with tetramethylsilane as the external standard (*J* values in Hz). D_2O was added to ^{1}H NMR samples for the identification of exchangeable protons. UV spectra were obtained using a Perkin-Elmer Lambda 2 spectrophotometer, all samples being dissolved in distilled water or analytical methanol (Aldrich). Mass spectra were recorded on a Kratos MS890 instrument. Melting points are uncorrected.

Anhydrous DMF was obtained from Aldrich. Pyridine and acetonitrile (Rathburn) were dried by refluxing over calcium hydride followed by distillation. THF (Merck) and dioxane (Merck) were dried by reflux over and distillation from sodium–benzophenone. All other reagents were obtained from Aldrich. Silica gel column chromatography used either Kieselgel 60 (<63

μm) or Kieselgel 60 H (where indicated) from Merck. Pre-coated silica gel F_{254} plates for preparative (1 mm) or thin-layer chromatography (TLC) (Merck) were developed using one of the following solvent systems: A, ethyl acetate–cyclohexane (1:2); B, methanol–chloroform (1:9); C, methanol–chloroform (2:8); D, methanol–chloroform (15:85); E, methanol–chloroform (2:98); F, methanol–chloroform (5:95). Tetrahydrofuranosyl derivatives were identified with anisaldehyde solution which contained anisaldehyde (9.2 cm^3), acetic acid (3.75 cm^3), conc. H_2SO_4 (1.25 cm^3) and 95% ethanol (388 cm^3).

3-Bromo-2-methoxytetrahydrofuran 4

The preparation was based on that described in ref. 10. Bromine (320 g, 104 cm^3, 2 mol) in carbon tetrachloride (200 cm^3) was added dropwise to a stirred solution of 2,3-dihydrofuran (154 g, 166 cm^3, 2.2 mol) in carbon tetrachloride (200 cm^3) whilst the reaction temperature was maintained between −30 and −40 °C. After a further 30 min, the resulting reaction mixture was added dropwise to a stirred solution of sodium methoxide (95%; 126 g, 2.2 mol) in methanol (800 cm^3) at 0 °C. The reaction mixture was then filtered through Celite and concentrated on a rotary evaporator to *ca.* 600 cm^3. This was then diluted with diethyl ether (2 l) and filtered again through Celite. The filtrate was washed with water (4 × 500 cm^3), dried (Na_2SO_4) and evaporated. Distillation of the residue under reduced pressure through a Vigreux column gave a colourless liquid (277 g, 1.53 mol, 77%) as a mixture of *cis* and *trans* isomers;[11] bp 61–63 °C/12 mmHg; R_F (in A), 0.85, 0.70 (stains black with anisaldehyde/H^+); δ_H([$^2H_6$]-DMSO) 5.09 (0.22 H, d, *J* 3.1, *trans*-2-H), 4.85 (0.78 H, d, *J* 4.0, *cis*-2-H), 4.20–3.90 (3 H, m, 3-H and 2 × 5-H), 3.41 (0.66 H, s, *trans*-MeO), 3.32 (2.34 H, s, *cis*-MeO) and 2.70–2.10 (2 H, m, 2 × 4-H).

Ethyl 2-cyano-2-(2-methoxytetrahydrofuran-3-yl)acetate 5

Sodium hydride (95%; 30.32 g, 1.2 mol) was suspended in anhydrous DMF (350 cm^3) in a 2 l, 3-necked flask and ethyl cyanoacetate (136 cm^3, 1.2 mmol) was added dropwise to it with stirring under argon over 1 h. After a further 15 min, **3** (75 g, 0.41 mol) was added to the mixture, followed by sodium iodide (2 g). The solution was then heated with vigorous stirring at 140 °C for 20 h under argon. After cooling, the reaction mixture was diluted with water (200 cm^3) and concentrated on a rotary evaporator to *ca.* 300 cm^3. It was then diluted with more water (200 cm^3) and extracted with diethyl ether (4 × 500 cm^3). The combined extracts were dried (Na_2SO_4), filtered and evaporated. Distillation of the residue under reduced pressure through a Vigreux column afforded a colourless liquid (13.28 g, 62.3 mmol, 15%). The cut bp 90–110 °C/0.4 mmHg was taken; R_F (in A), 0.45, 0.36 (stains yellow with anisaldehyde/H^+); δ_H([$^2H_6$]-DMSO) 5.00 (0.75 H, m, mixt. of *trans*-2-H), 4.89 (0.25 H, d, *J* 2.1, *cis*-2-H), 4.29–4.19 (2 H, 2 q, *cis/trans*-CH_2), 4.06–3.83 (2 H, 2 m, *cis/trans*-5-H), 3.39 (0.75 H, s, MeO), 3.36 (0.75 H, s, MeO), 3.35 (0.75 H, s, MeO), 3.31 (0.75 H, s, MeO), 2.78–2.70 (1 H, m, *cis/trans*-3-H), 2.30–1.71 (2 H, 2 m, 2 × *cis/trans*-4-H); *m/z* (EI) 213.1002 (M^+; Calc. for $C_{10}H_{15}NO_4$, 213.1023).

6-Amino-5-(2-methoxytetrahydrofuran-3-yl)-2-thioxo-pyrimidin-4-one 6

To a solution of thiourea (15 g, 197 mmol) in absolute ethanol (400 cm^3) was added 1 mol dm^{-3} sodium ethoxide solution (196 cm^3, 196 mmol), followed by a solution of **5** (37.28 g, 175 mmol) in absolute ethanol (100 cm^3). The mixture was refluxed for 3 h then evaporated to a foam. The residue was redissolved in water (150 cm^3) and extracted with diethyl ether (50 cm^3). The aqueous layer was neutralised with 50% aq. acetic acid, and after a short time at 4 °C, a pale brown solid (19.98 g) was precipitated. After concentration and chilling of the mixture, a further crop (2.76 g) was obtained; yield, 22.74 g (94 mmol, 54%). Crystallisation from ethanol gave white needles, mp >300 °C (darkens 205 °C) (Found: C, 44.3; H, 5.4; N, 17.4. $C_9H_{13}N_3SO_3$ requires C, 44.4; H, 5.4; N, 17.3%); R_F (in B), 0.45 and 0.39 (2 diastereoisomers) (stains red with anisaldehyde/H^+); δ_H([$^2H_6$]-DMSO) 11.76 (1 H, br s, NH), 11.46 (1 H, br s, NH), 6.22 (0.26 H, br s, 6a-NH_2), 6.06 (1.74 H, s, 6b-NH_2), 5.05 (0.13 H, d, *J* 3.4, 2′-Ha), 4.80 (0.87 H, d, *J* 4.7, 2′-Hb), 3.94–3.80 (3 H, m, 3′-H and 2 × 5′-H), 3.33 (0.39 H, s, a-MeO), 3.21 (2.61 H, s, b-MeO), 2.50 (1 H, m, 4′-H) and 1.70 (1 H, m, 4′-H); λ_{max}(MeOH)/nm 203 (25 200) and 282 (18 800).

2,6-Diamino-5-(2-methoxytetrahydrofuran-3-yl)pyrimidin-4-one 7

To a solution of guanidine hydrochloride (10.75 g, 112.6 mmol) in absolute ethanol (127 cm^3) was added 1 mol dm^{-3} sodium ethoxide solution (113 cm^3, 113 mmol) and the resultant precipitate was filtered off. To 85 cm^3 of the filtrate (40 mmol guanidine) was added 1 mol dm^{-3} sodium ethoxide solution (40 dm^{-3}, 40 mmol), followed by **5** (8.5 g, 40 mmol) in absolute ethanol (40 cm^3). The mixture was refluxed for 3 h and then evaporated to a foam. Work-up as for **6** gave a pale brown solid (5.10 g, 22.6 mmol, 56 %), crystallisation of which from ethanol gave white needles, mp 202–203 °C (Found: C, 47.5; H, 6.2; N, 24.9. $C_9H_{14}N_4O_3$ requires C, 47.8; H, 6.2; N, 24.8%); R_F (in B), 0.52 (stains red/purple with anisaldehyde/H^+); δ_H([$^2H_6$]-DMSO) 10.16 (1 H, br s, NH), 6.17 (0.5 H, s, 6a-NH_2), 6.13 (0.5 H, s, 6b-NH_2), 5.68 (2 H, br s, 2-NH_2), 5.05 (0.5 H, d, *J* 3.4, 2′-H), 4.73 (0.5 H, d, *J* 4.7, 2′-H), 3.97–3.53 (3 H, m, 3′-H and 2 × 5′-H), 3.21 (1.5 H, s, MeO), 3.19 (1.5 H, s, MeO) and 1.96–1.88 (2 H, m, 4′-H); λ_{max}(MeOH)/nm 212 (25 400), 240 (5100) and 276 (12 200).

Attempted preparation of 6-amino-5-(2-methoxytetrahydrofuran-3-yl)-2-methylsulfanylpyrimidin-4-one 8

Dimethyl sulfate (6.65 cm^3, 70 mmol) was added dropwise to a vigorously stirring solution of 1 mol dm^{-3} aq. sodium hydroxide (70 cm^3) containing **6** (15.07 g, 62 mmol). After 1 h, the solution was filtered to give a gummy, white solid (13.92 g) which comprised a mixture of **8**, **9** and **10**. A sample of **9** was obtained following silica gel chromatography with a gradient of 0–10% methanol in chloroform.

Compound **9** displayed; δ_H([$^2H_6$]-DMSO) 11.39 (1 H, br s, NH), 6.68 (1 H, s, 6-H), 4.48 (1 H, t, *J* 5.0, OH), 3.58 (2 H, t, *J* 7.1, OCH_2), 3.27 (3 H, s, CH_3N), 2.81 (2 H, t, *J* 7.1, OCH_2CH_2) and 2.49 (3 H, S, CH_3S); λ_{max}(MeOH)/nm 221, 292; *m/z* (EI) 239.0727 (M^+; Calc. for $C_{10}H_{13}N_3O_2S$, 239.0747).

5-(2-Hydroxyethyl)-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-one 10

To a solution of compound **6** (14.85 g, 61 mmol) in anhydrous DMF (100 cm^3) was added methyl iodide (4.06 cm^3, 65 mmol) and the reaction mixture was stirred for 6 h at room temp. Evaporation followed by trituration of the residue with diethyl ether (3 × 250 cm^3) gave a pale yellow solid (11.20 g, 49.8 mmol, 82%). Crystallisation of this from ethanol gave white needles, mp 237–238 °C (Found: C, 46.1; H, 5.2; N, 18.4. $C_9H_{11}N_3O_2S{\cdot}0.5H_2O$ requires C, 46.1; H, 5.2; N, 18.0%); R_F (in B), 0.33 (becomes pink/purple on plate under UV light); δ_H([$^2H_6$]-DMSO) 11.88 (1 H, br s, NH), 11.39 (1 H, br s, NH), 6.65 (1 H, d, *J* 1.5, 6-H), 4.51 (1 H, t, *J* 5.3, OH), 3.58 (1 H, m, OCH_2), 2.79 (1 H, t, *J* 7.2, OCH_2CH_2) and 2.48 (3 H, s, CH_3S).

5-(2-Hydroxyethyl)-2-thioxo-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one 11

Compound **6** (5.10 g, 21 mmol) was stirred in aq. hydrochloric acid (0.2 mol dm^{-3}; 125 cm^3) at room temp. for 4 h and then neutralised with dilute aq. ammonia solution to give a pale brown solid (3.38 g). Concentration of the filtrate gave an additional crop (673 mg); yield, 4.053 g (19.2 mmol, 91%). Crystallisation of the crude product from water gave pale brown needles, mp >300 °C (Found: C, 45.4; H, 4.3; N, 20.1.

$C_8H_9N_3O_2S$ requires C, 45.5; H, 4.3; N, 20.1%); R_F (in C), 0.21; δ_H([$^2H_6$]-DMSO) 13.06 (1 H, br s, NH), 11.73 (1 H, br s, NH), 10.92 (1 H, br s, NH), 6.48 (1 H, s, 6-H), 4.50 (1 H, t, *J* 4.7, OH), 3.54 (1 H, m, OCH_2) and 2.71 (1 H, t, *J* 7.13, OCH_2CH_2); λ_{max}(MeOH)/nm 243 (7700), 285 (9000) and 301sh.

5-(2-Hydroxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one 12

Compound **11** (528 mg, 2.5 mmol), was refluxed with Raney nickel (2 cm^3) in water (60 cm^3) containing aq. ammonia (35% w/v; 5 cm^3). After 3 h, the solution was filtered hot, and the catalyst washed with hot 2% aq. ammonia solution (3 × 100 cm^3). Evaporation of the combined filtrates afforded a white solid (414 mg, 2.31 mmol, 92%), R_F (in B), 0.14; δ_H([$^2H_6$]-DMSO) 11.61 (2 H, br s, 2 NH), 7.76 (1 H, s, 2-H), 6.80 (1 H, s, 6-H), 5.02 (1 H, br s, OH), 3.61 (2 H, t, *J* 7.1 , CH_2) and 2.83 (2 H, t, *J* 7.1, CH_2); *m/z* (EI) 179.0693 (M^+; Calc. for $C_8H_8N_4O_2$, 179.0695).

2-Amino-5-(2-hydroxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one 13

Compound **7** (5.65 g, 25 mmol) was stirred in aq. hydrochloric acid (0.2 mol dm^{-3}; 150 cm^3) at room temp. for 2 h. Work-up as for **11** gave pale brown flakes (4.225 g, 21.8 mmol, 87%), mp 251.5–253 °C (Found: C, 45.0; H, 5.7; N, 27.0. $C_8H_{10}N_4O_2{\cdot}H_2O$ requires C, 45.3; H, 5.7; N, 26.4%); R_F (in D) 0.12 (becomes purple in UV light on plate); δ_H([$^2H_6$]-DMSO) 10.67 (1 H, br s, NH), 10.15 (1 H, br s, NH), 6.38 (1 H, d, *J* 2.0, 6 H), 5.99 (2 H, br s, NH_2), 4.63 (1 H, t, *J* 5.3, OH), 3.58 (2 H, m, OCH_2) and 2.73 (2 H, t, *J* 7.1, OCH_2CH_2); δ_C([$^2H_6$]-DMSO) 159.62 (C-4), 152.17 (C-2), 151.34 (C-8), 115.31 (C-5), 114.24 (C-6), 99.02 (C-9), 62.27 (CH_2) and 30.16 (CH_2); λ_{max}(MeOH)/nm 220 (18 500), 260 (9700) and 280 infl. (7100).

5-(2-Acetoxyethyl)-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-one 14

To a suspension of compound **10** (11.25 g, 50 mmol) in dry pyridine (500 cm^3) was added acetic anhydride (8 cm^3, 85 mmol). The mixture was stirred overnight at room temp. in the dark after which it was evaporated. Co-evaporation of the residual pyridine with water, followed by recrystallisation of the residue from acetone–water (9:1) gave white needles (7.88 g, 29.5 mmol, 59%); R_F (in B), 0.56; δ_H([$^2H_6$]-DMSO) 11.99 (1 H, br s, NH), 11.53 (1 H, br s, NH), 6.73 (1 H, s, 6-H), 4.21 (2 H, t, *J* 7.0, OCH_2), 2.91 (2 H, t, *J* 7.0, OCH_2CH_2), 2.48 (3 H, s, CH_3S) and 1.96 (3 H, s, CH_3CO); λ_{max}(MeOH)/nm 221 and 287; *m/z* (EI) 267.0674 (M^+; Calc. for $C_{11}H_{13}N_3O_3S$, 267.0696).

5-(2-Acetoxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one 15

Compound **12** (313 mg, 1.75 mmol) was dissolved in dry pyridine (20 cm^3) and acetic anhydride (0.33 cm^3, 3 mmol) was added to the solution. After 2 h, silica TLC indicated the reaction to be complete, and the solution was evaporated. Crystallisation of the residue from aq. ethanol gave white needles (254 mg, 1.14 mmol, 65%); mp 236.5–237.5 °C (softens 229 °C) (Found: C, 54.1; H, 5.0; N, 19.0. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0); R_F (in B), 0.33; δ_H([$^2H_6$]-DMSO) 11.80–11.57 (2 H, 2 br s, 2 NH), 7.75 (1 H, s, 2-H), 6.84 (1 H, s, 6-H), 4.24 (2 H, t, *J* 7.1, OCH_2), 2.96 (2 H, t, *J* 7.1, OCH_2CH_2) and 1.97 (3 H, s, CH_3CO); λ_{max}(MeOH)/nm 217 and 264.

2-Amino-5-(2-acetoxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one 16

Compound **13** (2.53 g, 13 mmol) was suspended in dry pyridine (130 cm^3) at 0 °C in the dark and acetic anhydride (1.53 cm^3, 16.25 mmol) was added to it. The mixture was stirred in the dark at 0 °C overnight after which additional acetic anhydride (0.5 cm^3, 5.3 mmol) was added. After stirring of the mixture overnight, the reaction being complete, the solution was evaporated. Residual pyridine was removed by co-evaporation with toluene and then water. Water (50 cm^3) was then added to the residue and the product was filtered off, washed with an additional water (30 cm^3) and then dried *in vacuo* over P_2O_5 to give a pale brown solid (3.05 g, 12.92 mmol, 99%). Attempts to purify the crude product by chromatography or recrystallisation led to rapid darkening of solutions, R_F (in B), 0.26 (becomes green in UV light on plate); δ_H([$^2H_6$]-DMSO) 10.68 (1 H, br s, NH), 10.15 (1 H, br s, NH), 6.42 (1 H, s, 6-H), 5.97 (2 H, br s, NH_2), 4.21 (2 H, t, *J* 7.1, OCH_2), 3.54 (2 H, m, OCH_2CH_2) and 1.96 (3 H, s, CH_3CO); δ_C([$^2H_6$]-DMSO) 159.62 (C-4), 152.17 (C-2), 151.34 (C-8), 115.31 (C-5), 114.24 (C-6), 99.02 (C-9), 62.27 (CH_2) and 30.16 (CH_2); *m/z* (EI) 236.0908 (M^+; Calc. for $C_{10}H_{12}N_4O_3$, 236.0909).

5-(2-Acetoxyethyl)-4-chloro-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 17

Compound **14** (3.2 g, 12 mmol) and benzyl(triethyl)ammonium chloride (5.1 g, 24 mmol), dried in a vacuum oven at 70 °C over P_2O_5 overnight, were suspended in dry acetonitrile (65 cm^3). Dry dimethylaniline (2.13 cm^3, 12 mmol) was added to the suspension followed by freshly distilled phosphoryl chloride (6.75 cm^3, 72 mmol). The mixture was refluxed for 1.5 h after which the excess of phosphoryl chloride was removed by distillation. The resulting gum was added to crushed ice and after 0.5 h the mixture was extracted with chloroform (500 cm^3). The organic phase was washed with saturated aq. sodium hydrogen carbonate (50 cm^3), dried (Na_2SO_4) and evaporated. Silica gel column chromatography (52 × 400 mm) of the residue with chloroform as the eluent afforded a white solid (992 mg, 3.47 mmol, 29%); R_F (in F), 0.65; δ_H([$^2H_6$]-DMSO) 12.24 (1 H, br s, NH), 7.38 (1 H, s, 6-H), 4.26 (2 H, t, *J* 6.8, OCH_2), 3.08 (2 H, t, *J* 6.8, OCH_2CH_2), 2.52 (3 H, s, CH_3S) and 1.98 (3 H, s, CH_3CO); λ_{max}(MeOH)/nm 221, 252 and 311; *m/z* (EI) 285.0339 (M^+; Calc. for $C_{11}H_{12}ClN_3O_2S$, 285.0356).

5-(2-Acetoxyethyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine 18

Compound **15** (1.45 g, 7.5 mmol), benzyl(triethyl)ammonium chloride (3.42 g, 15 mmol), dry dimethylaniline (1.37 cm^3, 10.5 mmol) and freshly distilled phosphoryl chloride (3.5 cm^3, 37.5 mmol) were heated under reflux for 1 h in dry acetonitrile (40 cm^3) as for **17**. Excess of phosphoryl chloride was then removed by distillation, crushed ice added and after 1 h the pH of the solution was adjusted to 2 by addition of dilute aq. ammonia. The mixture was left in the refrigerator overnight after which the precipitate was filtered off and washed with water. Silica gel chromatography (32 × 150 mm) eluting with a gradient of 0–1% methanol in chloroform gave a white solid (573 mg, 2.72 mmol, 36%); R_F (in B), 0.35; δ_H([$^2H_6$]-DMSO) 12.34 (1 H, br s, NH), 8.52 (1 H, s, 2-H), 7.52 (1 H, s, 6-H), 4.28 (2 H, t, *J* 6.7, OCH_2), 3.54 (2 H, t, *J* 6.7, OCH_2CH_2) and 1.98 (3 H, s, CH_3CO); λ_{max}(MeOH)/nm 225, 269 and 295; *m/z* (EI) 239.0462 (M^+; Calc. for $C_{10}H_{10}ClN_3O_2$, 239.0476).

5-(2-Acetoxyethyl)-2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]-pyrimidine 19

Compound **16** (2.29 g, 11 mmol), benzyl(triethyl)ammonium chloride (4.70 g, 22 mmol), dry dimethylaniline (1.95 cm^3, 15 mmol) and freshly distilled phosphoryl chloride (6.2 cm^3, 66 mmol) were heated under reflux in dry acetonitrile (55 cm^3) for 30 min. A yellow solid (1.05 g, 4.64 mmol, 42%) was obtained following work-up as for **18**; R_F (in B), 0.28, (in E) and 0.12; δ_H([$^2H_6$]-DMSO) 11.26 (1 H, br s, NH), 6.92 (1 H, s, 6-H), 6.45 (2 H, br s, NH_2), 4.21 (2 H, t, *J* 6.9, OCH_2), 2.98 (2 H, t, *J* 6.7, OCH_2CH_2) and 1.98 (3 H, s, CH_3CO); λ_{max}(MeOH)/nm 234 and 320; *m/z* (EI) 254.0571 (M^+; Calc. for $C_{10}H_{11}ClN_4O_2$, 254.0787).

4-Chloro-5-(2-hydroxyethyl)-2-methylsulfanyl-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 21

A stirred suspension of **17** (1.50 g, 5.24 mmol) in dry acetonitrile (70 cm^3) under argon was treated with NaH (60% in oil; 220 mg, 5.5 mmol). After 30 min, methyl iodide (626 mm^3,

10 mmol) was added to the mixture and stirring continued for a further 30 min. The solution was evaporated *in vacuo* and the residue partioned between chloroform (500 cm^3) and water (100 cm^3). The organic phase was separated and evaporated and the crude product purified by silica gel chromatography (60 H, 32 × 200 mm) eluting with chloroform. The *N*-methyl-acetoxy derivative, **20** was obtained as a colourless solid, R_F (in F), 0.50; δ_H([$^2H_6$]-DMSO), 7.40 (1 H, s, 6-H), 4.24 (2 H, t, *J* 6.9, OCH_2), 3.72 (3 H, s, CH_3N), 3.08 (2 H, t, *J* 6.9, OCH_2CH_2), 2.56 (3 H, s, CH_3S) and 1.99 (3 H, s, CH_3CO).

Compound **20** was then suspended in MeOH–concentrated aq. ammonia (1:1; 300 cm^3) and stirred 6 h at room temp. Evaporation followed by recrystallisation of the residue from chloroform gave colourless needles **21** (1.10 g. 4.26 mmol, 81%); R_F (in F) 0.40; δ_H([$^2H_6$]-DMSO) 7.32 (1 H, s, 6-H), 4.70 (1 H, t, *J* 5.4, OH), 3.71 (3 H, s, CH_3N), 3.62 (2 H, m, OCH_2) and 2.91 (2 H, t, *J* 7.2, OCH_2CH_2); λ_{max}(MeOH)/nm 257 and 285; *m/z* (EI) 257.0384 (M^+; Calc. for $C_{10}H_{12}ClN_3OS$, 257.0407).

4-Chloro-7-methyl-2-methylsulfonyl-5-(2-hydroxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine 22

To compound **21** (750 mg, 3 mmol) in ethanol (60 cm^3) was added magnesium monoperphthalate (3.0 g, 6 mmol) in water (15 cm^3) and the solution stirred at room temp. overnight. The reaction mixture was then evaporated and the residue partitioned between chloroform (500 cm^3) and saturated aq. sodium hydrogen carbonate (100 cm^3). The organic phase was separated, dried (Na_2SO_4) and evaporated to give a white foam (510 mg, 1.77 mmol, 59%); mp 157–158 °C; R_F (in F), 0.17 (fluorescent); δ_H([$^2H_6$]-DMSO) 7.82 (1 H, s, 6-H), 4.76 (1 H, br s, OH), 3.87 (3 H, s, CH_3N), 3.67 (2 H, t, *J* 6.9, OCH_2), 3.41 (3 H, s, CH_3SO_2) and 3.02 (2 H, t, *J* 6.9, OCH_2CH_2); λ_{max}(MeOH)/nm 242 and 280; *m/z* (EI) 289.0305 (M^+; Calc. for $C_{10}H_{12}ClN_3O_3S$, 289.0287).

4-Chloro-5-(2-hydroxyethyl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 24

Compound **18** (925 mg, 3.86 mmol) was treated with NaH (60% in oil, 160 mg, 4.0 mmol) and methyl iodide (470 mm^3, 7.5 mmol) in dry acetonitrile (50 cm^3) as for the preparation of **20**, to give **23** as a white solid (850 mg, 3.35 mmol, 87%); R_F (in C), 0.87; δ_H([$^2H_6$]-DMSO) 8.57 (1 H, s, 2-H), 7.57 (1 H, s, 6-H), 4.28 (2 H, d, *J* 6.8, OCH_2), 3.80 (3 H, s, CH_3N), 3.16 (2 H, t, *J* 6.8, OCH_2CH_2) and 1.99 (3 H, s, CH_3CO). Compound **23** (850 mg, 3.35 mmol) was deacetylated as for **20** and the crude product purified by silica gel chromatography (32 × 250 mm) eluting with 3% methanol in chloroform. A white solid (560 mg, 2.65 mmol, 79%) was obtained; R_F (in C), 0.66; δ_H([$^2H_6$]-DMSO) 8.55 (1 H, s, 2-H), 7.49 (1 H, s, 6-H), 4.65 (1 H, br s, OH), 3.78 (3 H, s, CH_3N), 3.67 (2 H, d, *J* 6.8, OCH_2) and 2.98 (2 H, t, *J* 6.8, OCH_2CH_2); λ_{max}(MeOH)/nm 230, 271 and 305; *m/z* (EI) 211.0511 (M^+; Calc. for $C_9H_{10}ClN_3O$, 211.0527).

2-Amino-4-chloro-5-(2-hydroxyethyl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 26

Compound **19** (600 mg, 2.36 mmol) was treated with NaH (60% in oil, 100 mg, 2.5 mmol) and methyl iodide (313 mm^3, 5 mmol) in dry acetonitrile (30 cm^3) as for the preparation of **20**. The crude product was purified by silica gel chromatography (60 H, 20 × 200 mm) eluting with chloroform to give **25** as a white solid (470 mg, 1.75 mmol, 74%); R_F (in E), 0.34; δ_H([$^2H_6$]-DMSO) 6.84 (1 H, s, 6-H), 6.35 (2 H, br s, NH_2), 3.61 (2 H, t *J* 7.1, OCH_2), 2.83 (2 H, t *J* 7.1, OCH_2CH_2) and 1.98 (3 H, s, CH_3CO). Compound **25** (470 mg, 1.75 mmol) was deacetylated as for **20** and the crude product crystallised from chloroform to give colourless needles (350 mg, 1.55 mmol, 88%); R_F (in E), 0.14; δ_H([$^2H_6$]-DMSO) 6.89 (1 H, s, 6-H), 6.57 (2 H, br s, NH_2), 4.65 (1 H, t, *J* 5.4, OH), 3.60 (2 H, m, OCH_2), 3.52 (3 H, s, CH_3N) and 2.82 (2 H, t, *J* 7.2, OCH_2CH_2); λ_{max}(MeOH)/nm 239, 269 and 321; *m/z* (EI) 226.0616 (M^+; Calc. for $C_9H_{11}ClN_4O$, 226.0637).

4-Chloro-7-methyl-2-methylsulfonyl-5-(2-phthalimidooxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine 27

Compound **22** (3.47 g, 12 mmol) was suspended in dry THF (200 cm^3) containing triphenylphosphine (6.29 g, 24 mmol) and *N*-hydroxyphthalimide (3.89 g, 24 mmol). Diethyl azodicarboxylate (3.77 cm^3, 24 mmol) was then added to the solution after which it was stirred for 3 h at room temp. The mixture was then evaporated and the residue dissolved in chloroform (40 cm^3) and extracted with saturated aq. sodium hydrogen carbonate (3 × 20 cm^3). The organic layer was evaporated and the residue triturated with diethyl ether (30 cm^3). Crystallisation from ethanol gave white needles (3.69 g, 8.49 mmol, 71%); mp 240–241 °C (Found: C, 49.9; H, 3.4; N, 12.8. $C_{18}H_{15}ClN_4SO_5$ requires C, 49.2; H, 3.5; N, 12.9); R_F (in F), 0.65; δ_H([$^2H_6$]-DMSO) 8.00 (1 H, s, 6-H), 7.86 (4 H, s, phth-H), 4.46 (2 H, t, *J* 6.7, OCH_2),3.88 (3 H, s, CH_3N), 3.41 (3 H, s, CH_3SO_2) and 3.35 (2 H, t, *J* 6.9, OCH_2CH_2); λ_{max}(MeOH)/nm 219 and 240.

4-Chloro-7-methyl-5-(2-phthalimidooxyethyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidine 28

Compound **24** (560 mg, 2.66 mmol) was suspended in dry THF (40 cm^3) containing triphenylphosphine (790 mg, 3 mmol) and *N*-hydroxyphthalimide (400 mg, 3 mmol). Diethyl azodicarboxylate (470 mm^3) was then added to the solution after which it was stirred for 2 h at room temp. After this time the product was worked up as for **27**.The product crystallised from ethanol as white needles (740 mg, 2.09 mmol, 78%); mp 188–189 °C (Found: C, 54.6; H, 3.5; N, 15.0. $C_{17}H_{13}N_4O_3 \cdot H_2O$ requires C, 54.6; H, 3.5; N, 15.0%); R_F (in E), 0.61; δ_H([$^2H_6$]-DMSO) 8.58 (1 H, s, 2-H), 7.86 (4 H, s, phth-H), 7.70 (1 H, s, 6-H), 4.43 (2 H, t, *J* 6.9, OCH_2), 3.80 (3 H, s, CH_3N) and 3.30 (2 H, t, *J* 6.9, OCH_2CH_2); λ_{max}(MeOH)/nm 250 and 287.

2-Amino-4-chloro-7-methyl-5-(2-phthalimidooxyethyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine 29

Compound **26** (340 mg, 1.5 mmol) was suspended in dry THF (25 cm^3) containing triphenylphosphine (447 mg, 1.7 mmol) and *N*-hydroxyphthalimide (225 mg, 1.7 mmol). Diethyl azodicarboxylate (300 mm^3, 1.9 mmol) was then added to the solution after which it was stirred for 3 h at room temp. After this time the product was worked up as for **27**. Crystallisation of the crude product from ethanol gave yellow needles (90 mg, 1.05 mmol, 69%); mp 254.5–255.5 °C (Found: C, 54.6; H, 3.7; N, 19.0. $C_{17}H_{14}ClN_5O_3$ requires C, 54.9; H, 3.8; N, 18.8%); R_F (in C), 0.10; δ_H([$^2H_6$]-DMSO) 7.86 (4 H, m, 4 phth-H), 7.62 (1 H, s, 6-H), 6.71 (2 H, br s, NH_2), 4.35 (2 H, m, OCH_2), 3.53 (3 H, s, CH_3N) and 3.14 (2 H, m, OCH_2CH_2); λ_{max}(MeOH)/nm 291 and 318.

9-Methyl-2-methylsulfonylpyrrolo[4,3,2-*de*]pyrimido[4,5-*c*]-dihydrooxazepine 33‡

Compound **27** (300 mg, 0.70 mmol) was stirred in a solution of saturated ammonia in dry dioxane (30 cm^3) in a sealed bottle for 6 h. Silica TLC showed complete conversion to **30** [R_F (in F), 0.17] after this time. The solution was evaporated to dryness and the residue refluxed in absolute ethanol (50 cm^3) for 24 h. Evaporation, followed by silica gel chromatography (60 H, 32 × 70 mm) in chloroform and crystallisation from ethanol gave white needles (67 mg, 0.25 mmol, 36%); mp 221–222 °C (Found: C, 44.4; H, 4.4; N, 21.0. $C_{10}H_{12}N_4SO_3$ requires C, 44.8; H, 4.5; N, 20.9%); R_F (in B), 0.64; δ_H([$^2H_6$]-DMSO) 11.30 (1 H, br s, NH), 7.36 (1 H, s, 6-H), 4.34 (2 H, m, CH_2O), 3.77 (3 H, s, CH_3N), 3.30 (3 H, s, CH_3SO_2) and 2.98 (2 H, t, *J* 5.3, CH_2CH_2);

‡ Such compounds are more correctly named according to the IUPAC rules of nomenclature as: 2,6,8,9-tetrahydro-7-oxa-2,3,5,6-tetraaza-benzo[*cd*]azulenes..

$\delta_H(CDCl_3)$ 8.29 (1 H, br s, NH), 7.03 (1 H, s, 6-H), 4.48 (2 H, m, OCH_2), 3.88 (3 H, s, CH_3N), 3.33 (3 H, s, CH_3SO_2) and 3.07 (2 H, t, *J* 5.5, OCH_2CH_2); λ_{max}(MeOH)/nm 228 (1900), 280 (1800) and 310 (8900); *m/z* (EI) 268.0631 (M^+; Calc. for $C_{10}H_{12}N_4O_3S$, 268.0630).

9-Methylpyrrolo[4,3,2-*de*]pyrimido[4,5-*c*]dihydrooxazepine 34‡

Method A {from 9-methyl-2-hydrazinopyrrolo[4,3,2-*de*]-pyrimido[4,5-*c*]dihydrooxazepine 35}.‡ Compound **35** (125 mg, 570 μmol) was heated under reflux in absolute ethanol (10 cm^3) and mercury(II) oxide (494 mg, 2.28 mmol) added in four portions over 3 h. After a further 1 h, the reaction mixture was filtered through Celite; the material removed by the filtrate was then washed with hot ethanol (100 cm^3). The combined filtrates were evaporated and the residue purified by silica gel chromatography (60 H, 22 × 80 mm) eluting with chloroform and then a gradient of 0–1% methanol in chloroform. A white solid (31 mg, 164 μmol, 29%) was obtained; R_F (in B), 0.47; $\delta_H([^2H_6]$-DMSO) 10.56 (1 H, br s, NH), 8.20 (1 H, s, 2-H), 7.13 (1 H, s, 6-H), 4.29 (2 H, t, *J* 5.4, OCH_2), 3.70 (3 H, s, CH_3N) and 2.93 (2 H, t, *J* 5.4, OCH_2CH_2); $\delta_H(CDCl_3)$ 11.88 (1 H, br s, NH) 8.35 (1 H, s, 2-H), 6.78 (1 H, s, 6-H), 4.39 (2 H, t, *J* 5.6, OCH_2), 3.75 (3 H, s, CH_3N) and 2.97 (2 H, t, *J* 5.6, OCH_2CH_2); λ_{max}(MeOH)/nm 270 and 300; *m/z* (EI) 190.085 793 (M^+; Calc. for $C_9H_{10}N_4O$, 190.085 461).

The faster-running 2-ethoxy-compound **36** (18 mg, 76 μmol, 13%) was also obtained, as a white solid; R_F (in B), 0.87; $\delta_H([^2H_6]$-DMSO) 10.49 (1 H, br s, NH), 7.04 (1 H, s, 6-H), 4.27 (4 H, m, OCH_2 and CH_3CH_2O), 3.64 (3 H, s, CH_3N), 2.87 (2 H, t, *J* 5.4, OCH_2CH_2) and 1.27 (3 H, t, *J* 6.3, CH_3CH_2O); *m/z* (FAB) 235 $(M + 1)^+$ and 205 $(M - Et)^+$.

Method B {from 5-(2-aminooxyethyl)-4-chloro-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 31}. Compound **31** (100 mg, 0.58 mmol) was dissolved in THF (2 cm^3) and heated at 70 °C overnight in a sealed bottle. The mixture was evaporated and the residue purified by silica-gel chromatography (10 × 150 mm) eluting with chloroform. The initial UV-absorbing fraction was purified further on a silica gel TLC-plate developed with chloroform. A white solid was obtained (6 mg, 0.03 mmol, 5%) which was identical by silica TLC and NMR to **34** prepared by method A.

9-Methyl-2-hydrazinopyrrolo[4,3,2-*de*]pyrimido[4,5-*c*]dihydro-oxazepine 35‡

Compound **33** (250 mg, 0.93 mmol) was heated in a sealed bottle at 100 °C with anhydrous hydrazine (2 cm^3, 63.7 mmol) in absolute ethanol (25 cm^3) for 36 h. Storage of the mixture overnight at 4 °C gave white needles (174 mg, 0.79 mmol, 85%); R_F (in B), 0.18 streaks; $\delta_H([^2H_6]$-DMSO) 10.16 (1 H, br s, NH), 7.27 (1 H, s, NH_2NH), 6.69 (1 H, s, 6-H), 4.23 (2 H, t, *J* 5.3, OCH_2), 3.99 (2 H, br s, NH_2NH) 3.55 (3 H, s, CH_3N) and 2.84 (2 H, t, *J* 5.3, OCH_2CH_2); *m/z* (EI) 220.1072 (M^+; Calc. for $C_9H_{12}N_6O$, 220.1073).

5-(2-Hydroxyethyl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-4-thione 37

Compound **23** (423 mg, 2 mmol) and thiourea (170 mg, 2.25 mmol) were heated under reflux in absolute ethanol (20 cm^3) for 1 h. The mixture was then evaporated and the crude product recrystallised from chloroform to give yellow needles (350 mg, 1.67 mmol, 84%); R_F (in F) 0.3; $\delta_H([^2H_6]$-DMSO) 13.06 (1 H, s, NH), 7.97 (1 H, s, 2-H), 7.08 (1 H, s, 6-H), 4.44 (1 H, br s, OH), 3.67 (3 H, s, CH_3N), 3.65 (2 H, t *J* 6.9, OCH_2) and 3.12 (2 H, t, *J* 6.9, OCH_2CH_2); λ_{max}(MeOH)/nm 247 and 294; *m/z* (EI) 209.0625 (M^+; Calc. for $C_9H_{11}N_3OS$, 209.0623).

4-(2,4-Dinitrophenylsulfanyl)-5-(2-hydroxyethyl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 38

To solution of compound **37** (97 mg, 0.46 mmol) in dry acetonitrile (20 cm^3) was added triethylamine (300 mm^3) and 2,4-dinitrofluorobenzene (730 mg, 490 mm^3, 0.4 mmol). The reaction mixture was stirred for 40 min at room temp. and then evaporated. The residue was dissolved in chloroform (50 cm^3) and the solution washed with saturated aq. sodium hydrogen carbonate (25 cm^3), saturated brine (25 cm^3), water (25 cm^3), dried (Na_2SO_4) and evaporated. The pure product was obtained as a yellow solid (71 mg, 0.19 mmol, 42%) after silica gel chromatography (25 × 150 mm) eluting with chloroform; R_F (in F), 0.6; $\delta_H([^2H_6]$-DMSO) 8.89 [1 H, s, 3-H-$C_6H_3(NO_2)_2$], 8.57 (1 H, s, 2-H), 8.40 [1 H, d *J* 8.8, 5-H-$C_6H_3(NO_2)_2$], 7.79 [1 H, d *J* 8.8, 6-H-$C_6H_3(NO_2)_2$], 7.51 (1 H, s, 6-H), 4.65 (1 H, t, *J* 5.3, OH), 3.79 (3 H, s, CH_3N), 3.66 (2 H, t, *J* 6.2, OCH_2) and 2.96 (2 H, t, *J* 6.9, OCH_2CH_2); λ_{max}(MeOH)/nm 228, 303 and 354; *m/z* (EI) 375.0653 (M^+; Calc. for $C_{15}H_{13}N_5O_5S$, 375.0637).

4-(2,4-Dinitrophenylsulfanyl)-5-(2-phthalimidooxyethyl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 39

Compound **38** (142 mg, 0.38 mmol) was suspended in dry THF (6 cm^3) containing triphenylphosphine (113 mg, 0.43 mmol) and *N*-hydroxyphthalimide (57 mg, 0.43 mmol). Diethyl azodicarboxylate (67 mm^3) was then added to the reaction mixture after which it was stirred for 2 h at room temp. The solution was then evaporated and the residue triturated with diethyl ether (2 × 20 cm^3); after this it was dissolved in chloroform (300 cm^3) and extracted with water (2 × 50 cm^3). The combined extracts were dried (Na_2SO_4), evaporated and the crude product purified by silica gel chromatography (25 × 150 mm) eluting with chloroform. A yellow solid (160 mg, 0.31 mmol, 81%) was obtained, mp >300 °C (Found: C, 51.8; H, 3.0; N, 15.7. $C_{10}H_{12}N_4SO_3$ requires C, 51.3; H, 3.4; N, 15.6%); R_F (in F), 0.85; $\delta_H([^2H_6]$-DMSO) 8.87 [1 H, d, *J* 2.5, 3-H-$C_6H_3(NO_2)_2$], 8.65 (1 H, s, 2-H), 8.35 [1 H, dd, *J* 8.8 and 2.5, 5-H-$C_6H_3(NO_2)_2$], 7.81 (4 H, br s, phth), 7.76 [1 H, d, *J* 8.8, 6-H-$C_6H_3(NO_2)_2$], 7.81 (1 H, s, 6-H), 4.36 (2 H, t, *J* 7.3, OCH_2), 3.82 (3 H, s, CH_2N) and 3.35 (2 H, t, *J* 7.3, OCH_2CH_2); λ_{max}(MeOH)/nm 223 and 300.

4-(2,4-Dinitrophenylsulfanyl)-5-(2-aminooxyethyl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 40

Compound **38** (196 mg, 0.38 mmol) was dissolved in a saturated solution of ammonia in dioxane (100 cm^3) and the mixture stirred in sealed flask at room temp. overnight. The reaction mixture was then evaporated. A yellow solid (137 mg, 0.35 mmol, 93%) was obtained following silica gel chromatography (25 × 150 mm) eluting with chloroform; R_F (in F), 0.35; $\delta_H([^2H_6]$-DMSO) 8.89 [1 H, s, 3-H-$C_6H_3(NO_2)_2$], 8.59 (1 H, s, 2-H), 8.39 [1 H, d, *J* 8.8, 5-H-$C_6H_3(NO_2)_2$], 7.76 [1 H, d, *J* 8.8, 6-H-$C_6H_3(NO_2)_2$], 7.51 (1 H, s, 6-H), 6.20 (1 H, br s, ONH_2), 3.79 (3 H, s, CH_3), 3.74 (2 H, t, *J* 6.7, OCH_2) and 3.35 (2 H, t, *J* 6.7, OCH_2CH_2); *m/z* (EI) 375.0639 (M^+; Calc. for $C_{15}H_{13}N_5O_5S$, 375.0656). Attempts to cyclise this compound to **34** under a variety of conditions failed.

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