Some pyrrolopyrimidine chemistry directed to the synthesis of tricyclic purine analogues

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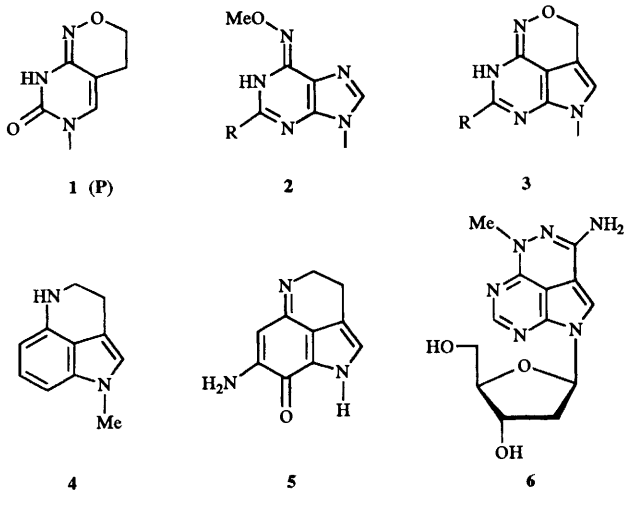
Chemistry directed to the synthesis of the tricyclic ring system **3**, a purine analogue with degenerate hydrogen-bonding potential, has been investigated and has resulted in the synthesis of several novel pyrrolo[2,3-*d*]pyrimidine derivatives as potential precursors. The known analogue 2-amino-7*H*-pyrrolo-[2,3-*d*]pyrimidin-4-one (7-deazaguanine) is converted by the Vilsmeier reagent into 4-chloro-2-dimethylaminomethyleneamino-6-formyl-7*H*-pyrrolo[2,3-*d*]pyrimidine **10**. Formylation at the α-position of the pyrrole ring was determined by the comparison of ^{13}C NMR data of the corresponding alcohol and the unsubstituted derivative and is in agreement with the regiospecificity reported for the Mannich reaction of this compound. In contrast, base-catalysed hydroxymethylation of 4-chloro-2-methylsulfanyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine with formaldehyde in aqueous THF occurs at the desired β-position to afford the 5-hydroxymethyl product **17**. 7-Methylation of the Bu^{t}Me$_2$Si-protected alcohol **17** led to several potential precursors of the desired tricyclic structure. The 5-phthalimidooxymethyl derivatives of either 2-methylsulfanyl- or 4-chloro-7-methyl-2-methylsulfonyl-7*H*-pyrrolo[2,3-*d*]pyrimidine with ammonia gave the aminooxymethyl derivatives but these subsequently failed to cyclise. Several approaches to cyclise 4-hydroxyamino-5-hydroxymethyl-7-methyl-2-methylsulfonyl-7*H*-pyrrolo[2,3-*d*]pyrimidine **27** afforded the corresponding 4-amino compound as the major component. Both the experimental and modelling results show that considerable strain is associated with the formation of **3**.

The use of oligonucleotide hybridisation probes and polymerase chain reaction (PCR) primers, based *inter alia* on protein amino acid sequences is now widespread. However, due to the redundancy in the genetic code it became important to design hybridisation probes and primers incorporating bases with hydrogen-bonding ambivalence at positions of codon degeneracy.[1] Initially, N^4-methoxycytosine was employed since it was known to have a tautomeric constant of about 0.3 (compare cytosine which exists almost exclusively as its amino tautomer, $K_T = \sim 10^5$) and was, therefore, in principle capable of forming Watson–Crick base pairs with either adenine or guanine. However the predominant *syn* conformation of the methoxy group reduced duplex stabilities.[2] This was corrected by incorporating the bicyclic analogue **P** (**1**).[3] The purines **2** (R = H, NH_2) both display degenerate hydrogen-bonding behaviour when present in duplexes. At least in the case of **2** (R = H), the *syn* conformation of the methoxy group is demonstrably present.[4] Consequently, in order to complement the analogue **P** we began the investigation of the synthesis of deoxynucleosides containing tricyclic systems such as **3** in which the N–O bond is *anti* with respect to the hydrogen-bonding face.

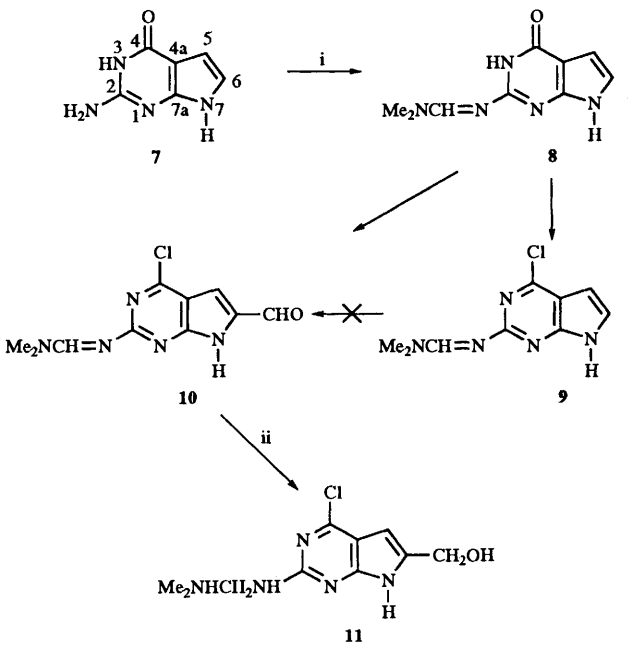
Known structures related to compound **3** are the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline **4**[5] and pyrrolo imino quinones such as **5**[6] based on the naturally occurring dehydrobufotenin and makaluvamines, respectively. In addition, the tricyclic nucleoside **6** has been prepared.[7] Here we present the synthesis of several pyrrolo[2,3-*d*]pyrimidine intermediates and attempts to effect ring closure to the tricyclic compound **3**.



Results and discussion

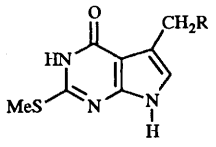
The synthetic approach to compound **3** that we envisaged required a suitably substituted pyrrolo[2,3-*d*]pyrimidine derivative. When the available 2-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (7-deazaguanine) **7**[8] was treated with the Vilsmeier reagent, initially the corresponding amidine **8**[9] was formed. Extended reaction times produced the 4-chloro derivative **9** together with a formylated product **10** isolated in 20% yield (Scheme 1). The amidine **9** was prepared independently from 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine[10] and dimethylformamide dimethyl acetal. Interestingly **9** could not be converted into **10** using the Vilsmeier reagent, demonstrating that formylation of the intermediate **8** was occurring and that this was followed by conversion to the 4-chloro derivative **10**.

In order to establish the site of formylation, **10** was reduced to the corresponding alcohol **11** by treatment with lithium boranuide ($LiBH_4$) in tetrahydrofuran (THF). Although the amidino group was concomitantly reduced to a dimethylaminomethyl moiety, comparison of ^1H NMR data of **9** and that of the $LiBH_4$-derived hydroxymethyl product **11** suggested that formylation had occurred at C-6 as indicated and not at the desired C-5 position. This was confirmed by ^{13}C NMR data on **9** and **11**, the latter showing a downfield shift of approximately 14 ppm for the C-6 signal, whilst that of C-5 remained comparatively unchanged (Table 1). This trend has been previously exploited for differentiating between the C-5 and the C-6



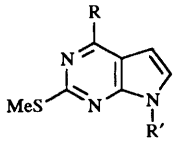
Scheme 1 *Reagents and conditions:* i, $POCl_3$, DMF, 70 °C; ii, $LiBH_4$ in THF

alkylated pyrrolo[2,3-*d*]pyrimidines.[8,11,12] Electrophilic substitution of the 7-deazaguanine ring at the 6-position with the Vilsmeier reagent is in agreement with the regioselectivity displayed in the Mannich reaction of this compound.[8] The reaction of the pyrrole analogue **7** at the α-position can be attributed to the relative stabilisation of the two possible intermediates formed by attack at C-5 or C-6. The latter intermediate may be stabilised by the amino group lone pair.[8]



12 R = NMe_2

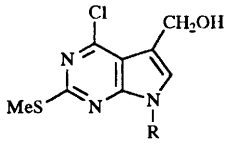
13 R = $N^+Me_3I^-$



14 R = Cl, R′ = H

15 R = OMe, R′ = H

16 R = Cl, R′ = $SiMe_2Bu^t$



17 R = H

18 R = CH_2OH

We also examined the reactivity of the N^2-pivaloyl derivative of 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine in the Vilsmeier reaction. Rather surprisingly the reaction led to apparently easy displacement of the pivaloyl group to produce compound **9** which was isolated in 38% yield after silica gel chromatography.

In order to circumvent the substitution problem we turned our attention to the corresponding 2-methylsulfanyl analogue of **7**, the Mannich reaction of which is known to give **12**.[12] Since the methylsulfanyl group may be easily oxidised to the corresponding sulfone, we envisaged its conversion into an amino function either by ammonia[13] or sodioacetamide[14] subsequent to introduction of the C-5 substituent. However, treatment of 2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one with the Vilsmeier reagent gave the 4-chloro analogue **14**, which, like **9**, was immune to further substitution. The corresponding 4-methoxy derivative **15**[12] was equally unreactive.

In an attempt to exploit the Mannich base **12**, it was converted into the trimethylammonium salt **13**. However, experiments directed to displacement of the trimethylammonium residue by the anion of *N*-hydroxyphthalimide, led to a mixture of several unidentified products.

Indole is known to react with paraformaldehyde in refluxing methanol in the presence of sodium methoxide to give 3-hydroxymethylindole.[15] The analogous reaction of **14** led to displacement of the chlorine by methoxide giving **15** as the major product. However, reaction with paraformaldehyde in refluxing methanol in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) or with aq. formaldehyde and KOH in THF afforded the alcohol **17** mixed with the corresponding 5,7-bis(hydroxymethyl) derivative **18**. The latter conditions proved to be the more convenient. Monitoring the reaction by TLC indicated the initial formation of the *N*-alkylated product; under the basic conditions the initial reversible reaction afforded the 5- and 5,7-bis(hydroxymethyl) derivatives, **17** and **18** respectively in approximately 1:1 ratio. Unlike pyrrole itself, the reaction is also reversible at room temperature giving the same product distribution but over more prolonged reaction times. Anderson and Groves[16] have removed an *N*-hydroxymethyl group from a pyrrole derivative by refluxing with benzyltrimethylammonium hydroxide in aqueous THF. However, when the same conditions were applied to the mixture of **17** and **18** the disappearance of the latter component was accompanied by an accumulation of polar products, which were attributed to displacement of the 4-chloro substituent. The pure **17** could only be partially separated from the bis-hydroxymethyl derivative **18** by silica gel chromatography and was obtained in 25% yield together with a further 22% (as determined by ^1H NMR) as a mixture. The site of alkylation of **17** was shown by comparison of ^{13}C NMR with **14**[12] to be C-5 (Table 1). As an alternative strategy we converted **14** into the corresponding 7-Bu^tMe_2Si derivative **16** by treatment of the sodio anion of **14** with *tert*-butyldimethylsilyl chloride in THF. The same *N*-protection has been used for indoles during organolithium-promoted electrophilic substitution.[17] Unfortunately, when this compound was heated with formaldehyde in aqueous THF solution, gradual loss of the protecting group resulted in compound **14** which led to the same mixture of **17** and **18** as that described previously.

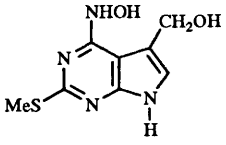
In order to investigate the use of **17** as a starting point for the synthesis of the required tricyclic derivatives of **3**, it was converted into the hydroxylamino derivative **19** on heating with ethanolic hydroxylamine at 80 °C for 20 h. Attempts to cyclise **19** under a variety of conditions, *e.g.* the Mitsunobu reaction, 1,3-dicyclohexylcarbodiimide (DCC), acid or base, failed. As an alternative, condensation of **17** with *N*-hydroxyphthalimide in the Mitsunobu reaction afforded the phthalimidooxy derivative **20**. Treatment of **20** with ammonia in dioxane removed the phthaloyl group to liberate the 5-aminooxymethyl derivative but failed to effect cyclisation. In each of these cases a mixture of products was formed. These results may be a consequence of elimination–addition reactions analogous to those well-documented for 3-hydroxymethylindoles[15,18] in the situations where the indole nitrogen is unsubstituted. Indeed, simple heating of **20** with methanol afforded the corresponding 5-methoxymethyl ether of **17** as identified by ^1H NMR.

In order to avoid such undesirable side reactions it was decided to prepare the corresponding 7-alkylated derivatives. These compounds were also envisaged to be valuable model compounds for the corresponding nucleoside derivatives. The alcohol **17** was converted into the corresponding Bu^tMe_2Si ether **22**. Silylation of the aforementioned mixture of alcohols **17** and **18** allowed resolution of **17** from the mixture by silica gel

Table 1 ^{13}C NMR data of selected pyrrolo[2,3-*d*]pyrimidines in $(CD_3)_2SO$

Compound	δ^a C-2	C-4	C-4a	C-5	C-6	C-7a	CH_2OH
9	161.29	154.08	111.66	98.72	125.55	150.56	—
11	157.60	154.13	110.28	95.82	139.54	150.14	56.49
14	162.80	152.77	113.32	99.02	126.73	150.50	—
17	162.73	153.39	115.65	111.24	124.58	150.48	55.44

[a] Chemical shifts are given relative to $SiMe_4$ as external standard.



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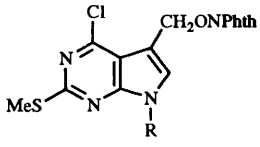

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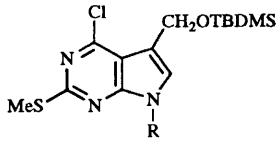
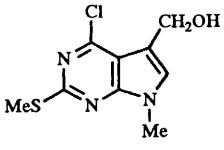
21 R = Me



22 R = H
23 R = Me



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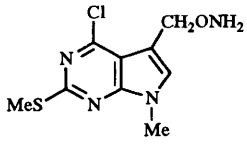

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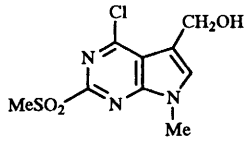

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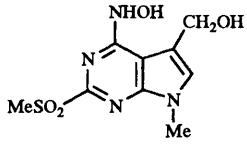

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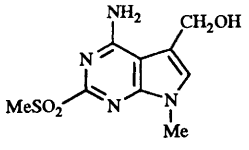

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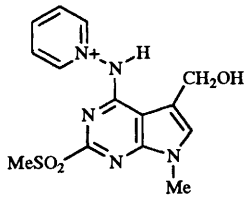

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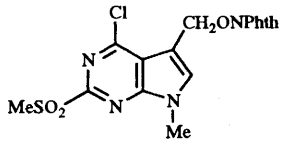

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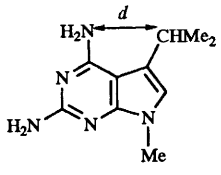
chromatography and thus afforded an additional amount of **22**. Treatment of **22** with sodium hydride in acetonitrile followed by alkylation with methyl iodide afforded the corresponding 7-methyl derivative **23**. This was subsequently desilylated by heating overnight with ammonium fluoride in methanol to give the *N*-methylated alcohol **24**, which was converted into the *N*-phthalimidooxy derivative **21**. Treatment of **21** with ammonia in dioxane at 60 °C gave rise essentially to a single, more polar (by TLC) component, which was identified by mass spectroscopy and ^1H NMR as the 5-aminooxymethyl derivative **25**. Attempts to effect cyclisation by heating solutions of **25** led only to complex mixtures of products.

Since it was planned ultimately to displace the methylsulfanyl group, **24** was oxidised to the corresponding sulfone **26** for which displacement of the 4-chloro substituent was expected to be considerably facilitated relative to the corresponding methylsulfanyl series of compounds. Although oxidation of the methylsulfanyl group was possible with *m*-chloroperbenzoic acid (MCPBA), the reaction was considerably cleaner using magnesium monoperphthalate (MMPP) in aqueous ethanol. Conversion of **26** with hydroxylamine in ethanol into **27** was complete at 50 °C in 4 h. We were unsuccessful in cyclising **27**; triphenylphosphine and diethyl azodicarboxylate (DEAD) led to deoxygenation and gave the 4-amino-5-hydroxymethyl derivative **28** as the major product. As an alternative cyclisation strategy, we considered the reaction of an oxyanion with an aminooxysulfonate which has been used to effect cyclisation in a related series.[19] However, treatment of **27** with triisopropylbenzenesulfonyl chloride in pyridine once again afforded the amino derivative **28**, together with two pyridinium derivatives, one of which was isolated as a mixture with **28** and displayed ^1H NMR and MS data consistent with the *N*-pyridinium derivative **29**. Presumably this was formed *via* the *N*-oxysulfonate derivative and is comparable to the preparation of *N*-aminopyridines using hydroxylamine-*O*-sulfonic acid. The methylsulfonyl substituted pyrrolopyrimidine moiety being electron-deficient presumably facilitates this reaction.

The *N*-hydroxyphthalimide derivative **30** was prepared by oxidation of **21** with MMPP in aqueous DMF. When **30** was treated overnight at room temp. with ammonia in dry dioxane, a single product was observed by silica TLC. This material was identified by ^1H NMR as the corresponding 5-aminooxymethyl derivative. Heating this compound in ammonia–dioxane or ethanol gave no evidence of cyclisation to **3** (R = $MeSO_2$).



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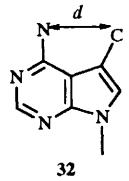

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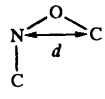

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Although we had expected strain in the target system **3**, we had not expected its prevention of cyclisation. In calculations kindly performed by Dr S. A. Salisbury, the model compound **31**, after energy minimisation by molecular mechanics (Macromodel; MM2 force field), displayed a distance *d* of 3.38 Å between the amino group and the methine carbon of the isopropyl substituent. Crystallographic data for four 5-substituted 4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidine derivatives obtained from the Cambridge Structural Data Base (general structure **32**) indicated the distance (*d*) to be between 3.26 and 3.37 Å. For several *N*,*O*-dialkylhydroxylamines (such as **33**) in the Data Base, the corresponding distance *d* varies from 1.4–2.4 Å.

We infer that there would be angle strain associated with the tricyclic target structure **3**, although the synthetic products **4**–**6** suggest that this should not be prohibitive. It is evident too that the reaction intermediate in the intramolecular displacement of

chlorine in **25** would also involve considerable strain. We are currently investigating the synthesis of homologues of **3**.

Experimental

^{1}H NMR spectra were recorded at 250.13 MHz on a Bruker WM 250 spectrometer and ^{13}C NMR spectra were recorded at 100.61 MHz or on a Bruker AM 400 spectrometer, both 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 analytical methanol (Aldrich). Mass spectra were recorded on a Kratos MS890 instrument. Mp are uncorrected.

Anhydrous dimethylformamide (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 heating under reflux and distillation from sodium and benzophenone. All reagents were obtained from Aldrich. Silica gel column chromatography used either Kieselgel 60 (< 63 mm) or Kieselgel 60 H (where indicated) from Merck. Precoated 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, methanol–chloroform (1:9); B, acetone–chloroform (1:3); C, methanol–chloroform (2:98); D, methanol–chloroform (5:95); E, methanol–dichloromethane (1:9); F, cNH_4OH–H_2O–Pr^{i}OH (5:25:70); G, dichloromethane. Hydroxyamino derivatives were detected as blue-black spots on a yellow background by staining TLC plates with 5% ferric chloride in ethanol.

4-Chloro-2-dimethylaminomethyleneamino-7*H*-pyrrolo[2,3-*d*]-pyrimidine 9

Method A {from 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine}. 2-Amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine[10] (843 mg, 5 mmol) was heated with dimethylformamide dimethyl acetal (5.96 g, 50 mmol) in anhydrous DMF (5 cm^3) at 60 °C for 1 h. The solution was then evaporated, and residual DMF removed by co-evaporation with toluene. The crude product was dissolved in methanol and evaporated onto a small amount of silica. The residue was chromatographed on a silica-gel column (32 × 80 mm) with chloroform followed by 1% methanol–chloroform as eluent to afford the title compound as a pale brown solid (445 mg, 2.0 mmol, 40%); R_f (in A), 0.42; δ_H([$^2H_6$]-DMSO) 11.83 (1 H, br s, NH), 8.57 (1 H, s, Me_2NCH), 7.33 (1 H, d, *J* 3.5, 6-H), 6.52 (1 H, d, *J* 3.5, 5-H), 3.18 (3 H, s, Me) and 3.16 (3 H, s, Me); δ_C([$^2H_6$]-DMSO) 161.29 (C-2), 157.74 (C, amidino), 154.08 (C-4), 150.56 (C-7a), 125.55 (C-6), 111.66 (C-4a), 98.72 (C-5), 40.40 (Me) and 34.53 (Me); λ_{max}(MeOH)/nm 262 and 296; *m*/*z* (EI) 223.0617 (M^+; Calc. for $C_9H_{10}ClN_5$, 223.0625).

Method B {from 4-chloro-3-pivalamidol-7*H*-pyrrolo[2,3-*d*]-pyrimidine}. Pivaloyl chloride was added to a stirred solution of 2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine[10] (1.4 g, 8.3 mmol) in dry pyridine (20 cm^3) cooled in ice. After being stirred at room temp. for 8 h, the mixture was evaporated and the residue redissolved in dichloromethane (250 cm^3). The resulting solution was extracted with saturated aq. sodium hydrogen carbonate (2 × 100 cm^3), dried (Na_2SO_4) and then evaporated. The residue was purified by silica-gel chromatography (40 × 62 mm) with chloroform as eluent followed by crystallisation from hexane–dichloromethane to afford colourless crystals (874 mg, 3.46 mmol, 42%); R_f (in A), 0.69; δ_H($CDCl_3$) 12.11 (1 H, br s, NH), 8.24 (1 H, br s, NH), 7.54 (1 H, d, *J* 3.5, 6-H), 6.53 (1 H, d, *J* 3.5, 5-H) and 1.39 (9 H, s, 3 Me). The pivaloyl derivative obtained (127 mg, 0.5 mmol) was then dissolved in anhydrous DMF (1 cm^3) and phosphorus oxychloride (163 mm^3, 1.75 mmol) was added to the resulting solution. The mixture was stirred at room temp. overnight and then evaporated. The residue obtained was partitioned between 5% aq. sodium carbonate (50 cm^3) and ethyl acetate (400 cm^3). The organic layer was separated, washed with water (2 × 50 cm^3), dried (Na_2SO_4) and evaporated. The crude product obtained was purified by silica gel chromatography (32 × 85 mm) eluting with chloroform followed by 0–10% ethanol–chloroform to afford a pale brown solid (42 mg, 0.19 mmol, 38%) which was shown to be identical (by silica TLC and ^{1}H NMR) to compound **9** prepared by Method A.

4-Chloro-2-dimethylaminomethyleneamino-6-formyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 10

Phosphorus oxychloride (0.4 cm^3, 4.3 mmol) and dry DMF (1.27 cm^3, 16.5 mmol) were stirred together whilst being cooled using an ice-bath. After 5 min the resulting mixture was added to 2-amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one[8] (200 mg, 1.33 mmol) suspended in dry DMF (2 cm^3) and heated in a sealed vial at 70 °C. After 12 h, additional phosphorus oxychloride (0.09 cm^3, 1 mmol) and dry DMF (0.1 cm^3, 1.3 mmol) were added, and the mixture was heated at 70 °C for a further 36 h. The resulting reaction mixture was then cooled to 0 °C, neutralised with 10% aq. sodium carbonate and extracted into ethyl acetate. The organic phase was dried (Na_2SO_4), filtered and evaporated. Silica gel chromatography (32 × 80 mm) of the residue with chloroform as eluent afforded the title compound as a yellow solid (60 mg, 0.27 mmol, 20%); R_f (in A), 0.60; has longwave UV absorption; δ_H([$^2H_6$]-DMSO) 12.67 (1 H, br s, NH), 9.77 (1 H, s, CHO), 8.65 (1 H, s, Me_2N–C*H*), 7.34 (1 H, s, 5-H), 3.17 (3 H, s, Me) and 3.06 (3 H, s, Me); δ_C([$^2H_6$]-DMSO) 182.48 (CHO), 164.02 (C-4), 158.61 (C, amidino), 155.19 (C-7a or C-4a), 154.48 (C-7a or C-4a), 135.33 (C-6), 112.06 (C-5), 111.55 (C-4), 40.61 (Me) and 34.75 (Me); λ_{max}(MeOH)/nm 249sh, 272, 290infl and 354; *m*/*z* (EI) 251.0571 (M^+; Calc. for $C_{10}H_{10}ClN_5O$, 251.0574).

4-Chloro-2-dimethylaminomethylamino-6-hydroxymethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 11

The formyl derivative **10** was stirred with a solution of lithium boranuide in THF (2 mol dm^{-3}; 1 cm^3, 2 mmol) at room temp. for 0.5 h. The reaction mixture was diluted with 5% aq. ammonium chloride (25 cm^3) and neutralised with dil. HCl. The solution was extracted with ethyl acetate (2 × 100 cm^3) and the combined extracts washed with water (20 cm^3) and evaporated. The crude product was dissolved in methanol and evaporated onto a small amount of silica gel. Purification by silica gel chromatography (12 × 150 mm) with a gradient of methanol in chloroform (1–2%) gave a white solid (24 mg, 0.94 mmol, 47%), R_f (in A), 0.42; δ_H([$^2H_6$]-DMSO) 11.81 (1 H, br s, NH), 7.97 (1 H, t, *J* 7.3, NH), 6.20 (1 H, s, 5-H), 5.27 (1 H, t, *J* 5.6, OH), 4.48 (2 H, d, *J* 5.6, CH_2OH), 3.36 (2 H, d, *J* 7.3, N–CH_2–N) and 2.40 (6 H, s, 2 Me); δ_C([$^2H_6$]-DMSO) 157.60 (C-2), 154.13 (C-4), 150.14 (C-7a), 139.54 (C-6), 110.28 (C-4a), 95.82 (C-5), 67.14 (N–CH_2–N), 56.49 (CH_2OH) and 47.64 (2 Me); *m*/*z* (FAB) 256 (M + 1)$^+$, 238 (M − OH)$^+$ and 211 (M − Me_2N)$^+$.

(2-Methylsulfanyl-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-ammonium iodide 13

To the Mannich base **12**[9] (2.38 g, 10 mmol) in dry DMF (75 cm^3) was added methyl iodide (685 mm^3). After 1 h at room temperature, the solution was evaporated. The title compound **13** crystallised from methanol as yellow needles (2.95 g, 7.2 mmol, 72%), mp > 300 °C (decomp.) (Found: C, 35.0; H, 4.9; N, 13.4. $C_{11}H_{17}IN_4OS$·CH_3OH requires C, 34.98; H, 5.10; N, 13.60); R_f (in F), 0.25; δ_H([$^2H_6$]-DMSO) 12.32 (1 H, br s, NH), 12.27 (1 H, br s, NH), 7.28 (1 H, br s, NH), 4.55 (2 H, s, CH_2), 3.03 (9 H, s, 3 Me) and 2.53 (3 H, s, MeS); *m*/*z* (FAB) 253 (M)$^+$ and 194 (M − Me_3N).

7-*tert*-Butyldimethylsilyl-4-chloro-2-methylsulfanyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine 16

Compound **14**[12] (400 mg, 0.2 mmol) was suspended in dry acetonitrile (20 cm^3) and sodium hydride (60% in oil; 88 mg, 2.2 mmol) added to it. The mixture was stirred under argon for 30 min after which a solution of *tert*-butyldimethylsilyl chloride (565 mg, 3 mmol) in dry THF (2.5 cm^3) was added to it. The solution was then evaporated and the residue partitioned between chloroform (500 cm^3) and saturated aq. sodium hydrogen carbonate (50 cm^3). The organic phase was separated, dried (Na_2SO_4) and evaporated and the crude product obtained purified by silica gel chromatography (20 × 120 mm) eluting with dichloromethane to afford the title compound as a white, waxy solid (556 mg, 1.77 mmol, 89%); R_f (in G), 0.71; δ_H([$^2H_6$]-DMSO) 7.51 (1 H, d, *J* 3.6, 6-H), 6.66 (1 H, *J* 3.6, 6-H), 3.55 (3 H, s, MeS), 0.87 (9 H, s, 3 Me) and 0.64 (6 H, s, 2 Me).

4-Chloro-5-hydroxymethyl-2-methylsulfanyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine 17

Compound **14**[12] (7.00 g, 35 mmol) was heated under reflux for 3 h with 37% aq. formaldehyde (7.70 cm^3, 105.5 mmol) in THF–water (700 cm^3, 1 : 1 v/v). The solution was then allowed to cool to room temp., after which it was neutralised with glacial acetic acid and extracted with ethyl acetate (3 × 600 cm^3). The combined extracts were dried, filtered and evaporated and the crude product obtained was purified by silica gel chromatography (52 × 450 mm) eluting with chloroform, followed by a gradient of 2–10% acetone in chloroform. The title compound crystallised as colourless needles from ethanol (2.03 g, 8.85 mmol, 25%). Mp > 300 °C, darkens 175 °C (Found: C, 42.0; H, 3.6; N, 18.10. $C_8H_8ClN_3OS$ requires C, 42.02; H, 3.08; N, 18.38); R_f (in B), 0.35; δ_H([$^2H_6$]-DMSO) 12.20 (1 H, br s, NH), 7.37 (1 H, s, 6-H), 5.02 (1 H, t, *J* 5.2, OH), 4.69 (2 H, d, *J* 5.2, CH_2) and 2.55 (3 H, s, MeS); δ_C([$^2H_6$]-DMSO) 162.73 (C-2), 153.39 (C-4), 150.48 (C-7a), 124.58 (C-6), 115.65 (C-4a), 111.24 (C-5), 55.44 (CH_2) and 13.84 (MeS); λ_{max}(MeOH)/nm 207 (10 300), 223 (10 500), 252 (24 400), 273infl (5400) and 311 (5100); *m/z* (FAB) 230 $(M + 1)^+$ and 212 $(M - OH)^+$.

Later fractions from the column afforded the bisalcohol **18**: R_f (in B), 0.24; δ_H([$^2H_6$]-DMSO) 7.46 (1 H, d, *J* 0.5, 6-H), 6.69 (1 H, t, *J* 7.4, OH), 5.52 (2 H, d, *J* 7.4, N–CH_2), 5.15 (1 H, t, *J* 5.2, OH), 4.70 (2 H, d, *J* 5.2, CH_2) and 2.57 (3 H, s, MeS).

4-Hydroxylamino-5-hydroxymethyl-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 19

Hydroxylamine hydrochloride (1.04 g, 15 mmol) was dissolved in boiling absolute ethanol (25 cm^3) and KOH in hot ethanol (3 mol dm^{-3}, 5 cm^3) was added to the solution. After this had been filtered **17** (276 mg, 1 mmol) was added to it and the whole was heated in a sealed bottle at 80 °C for 20 h. It was then evaporated. The crude product obtained was dissolved in methanol, evaporated onto a small amount of silica gel and purified by silica gel chromatography (60 H, 32 × 180 mm) with chloroform followed by a gradient of 2–25% ethanol in chloroform as eluents to afford a pale brown solid (86 mg, 0.38 mmol, 38%); R_f (in A), 0.23; δ_H([$^2H_6$]-DMSO) 11.41 (1 H, br s, NH), 9.54 (1 H, br s, NH), 8.96 (1 H, br s, OH), 6.92 (1 H, d, *J* 2.0, 6-H), 5.82 (1 H, t, *J* 4.8, OH), 4.52 (2 H, d, *J* 4.8, CH_2) and 2.46 (3 H, s, Me); δ_C([$^2H_6$]-DMSO) 163.01 (C-2), 158.45 (C-4), 151.83 (C-7a), 117.84 (C-6), 114.69 (C-4a), 97.45 (C-5), 56.75 (CH_2) and 13.54 (MeS); λ_{max}(MeOH)/nm 239 and 285; *m/z* (FAB) 227 $(M + 1)^+$.

4-Chloro-2-methylsulfanyl-5-phthalimidooxymethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 20

Compound **17** (459 mg, 2 mmol) was suspended in dry THF (40 cm^3) containing triphenylphosphine (554 mg, 2.5 mmol) and *N*-hydroxyphthalimide (408 mg, 2.5 mmol). Diethyl azodicarboxylate (394 mm^3, 1.5 mmol) was added to the mixture which was then stirred for 45 min at room temp. Evaporation, followed by trituration with diethyl ether (3 × 200 cm^3) gave a white solid (705 mg, 1.88 mmol, 94%); R_f (in C), 0.77; δ_H([$^2H_6$]-DMSO) 12.48 (1 H, br s, NH), 7.81 (4 H, m, phth), 7.71 (1 H, s, 6-H), 5.32 (2 H, s, CH_2) and 2.56 (3 H, s, MeS); λ_{max}(MeOH)/nm 222, 250, 305.

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

The hydroxymethyl derivative **24** (368 mg, 1.5 mmol) was suspended in dry THF (25 cm^3) containing triphenylphosphine (447 mg, 1.7 mmol) and *N*-hydroxyphthalimide (227 mg, 1.7 mmol) and diethyl azodicarboxylate (267 mm^3, 1.7 mmol) was added to the suspension. The solution was stirred for 2 h at room temp. after which it was evaporated and the residue triturated with diethyl ether (2 × 200 cm^3) and then 95% aq. ethanol (200 cm^3) to give a white solid (368 mg, 0.96 mmol, 64%). The title compound crystallised as a white solid, mp 203–204 °C (Found: C, 52.25; H, 3.3; N, 14.3. $C_9H_{10}ClN_3O_3S$ requires C, 52.51; H, 3.37; N, 14.41); R_f (in D), 0.79; δ_H([$^2H_6$]-DMSO) 7.82 (4 H, m, 4 phth. H), 7.77 (1 H, s, 6-H), 5.32 (2 H, s, CH_2), 3.72 (3 H, s, N-Me) and 2.60 (3 H, s, MeS).

5-*tert*-Butyldimethylsiloxymethyl-4-chloro-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 22

Compound **17** (2.00 g, 8.70 mmol) was dissolved in dry pyridine (80 cm^3) and *tert*-butyldimethylsilyl chloride (1.70 g, 11.3 mmol) was added to the solution. After the solution had been stirred overnight it was evaporated and the resulting residue redissolved in chloroform (750 cm^3). The chloroform solution was washed with saturated aq. sodium hydrogen carbonate (150 cm^3), dried (Na_2SO_4) and evaporated. The crude product obtained was purified by silica gel chromatography, loading in chloroform (50 × 300 mm) and eluting with dichloromethane. The white solid (2.67 g, 7.77 mmol, 89%) obtained crystallised from diethyl ether to give the title compound as a cream-coloured solid, mp 181–182 °C (Found: C, 48.9; H, 6.4; N, 12.3. $C_8H_8ClN_3OS$ requires C, 48.89; H, 6.44; N, 12.22); R_f (in C), 0.51; δ_H([$^2H_6$]-DMSO) 12.25 (1 H, br s, NH), 7.41 (1 H, s, 6-H), 4.86 (2 H, s, CH_2), 2.55 (3 H, s, MeS), 0.86 (9 H, s, 3 Me) and 0.05 (6 H, s, 2 Me); λ_{max}(MeOH)/nm 209 (14 800), 223 (16 400), 252 (30 900), 275infl (6 200) and 216 (5 600).

4-Chloro-5-hydroxymethyl-7-methyl-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 24

The Bu^tMe_2Si derivative **22** (550 mg, 1.6 mmol) was suspended in dry acetonitrile (25 cm^3) and stirred under argon. Sodium hydride (60% in oil, 70 mg, 1.75 mmol) was added to the suspension, followed, after 30 min, by methyl iodide (200 mm^3, 3.2 mmol). After being stirred for a further 30 min, the solution was evaporated and the residue partitioned between chloroform (250 cm^3) and water (50 cm^3). The organic phase was separated, dried and evaporated and the residue obtained was chromatographed on silica gel (32 × 250 mm) with chloroform as eluent to give **23** as a white solid (534 mg, 1.49 mmol, 93%); R_f (in C), 0.89; δ_H([$^2H_6$]-DMSO) 7.45 (1 H, s, 6-H), 4.86 (2 H, s, CH_2), 3.75 (3 H, s, N–Me), 2.58 (3 H, s, MeS), 0.88 (9 H, s, 3 Me) and 0.08 (6 H, s, 2 Me). Compound **23** (400 mg, 1.12 mmol) was then heated overnight at 60 °C in methanol (60 cm^3) containing ammonium fluoride (414 mg, 11.2 mmol) and the resulting mixture concentrated to 20 cm^3, diluted with chloroform (500 cm^3) and washed with saturated aq. sodium hydrogen carbonate (50 cm^3). The organic phase was dried and evaporated and the residue obtained was chromatographed on silica gel (32 × 250 mm) with chloroform then 2% acetone–chloroform as eluent.

The title compound (246 mg, 1.01 mmol, 91%) crystallised as colourless needles (ethanol), mp 226–227 °C (Found: C, 44.2; H, 4.0; N, 17.1. $C_9H_{10}ClN_3O_3S$ requires C, 44.36; H, 4.13; N, 17.24); R_f (in C), 0.25; δ_H([$^2H_6$]-DMSO) 7.41 (1 H, s, 6-H), 5.08 (1 H, t, *J* 5.1, OH), 4.69 (d, *J* 5.1, CH_2), 3.74 (3 H, s, N–Me) and 2.57 (3 H, s, MeS); λ_{max}(MeOH)/nm 209 (21 500), 224sh (18 800), 255 (33 000), 277infl (8 100) and 310 (6 100).

Attempted cyclisation of 5-aminooxymethyl-4-chloro-7-methyl-2-methylsulfanyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 25

Compound **21** (10 mg) was heated in saturated ammonia–dioxane solution (3 cm^3) in a sealed tube at 70 °C overnight. The resulting solution was then evaporated and the residue obtained purified by silica gel chromatography (12 × 20 mm) with chloroform then 0.5% methanol–chloroform as eluents to afford the title compound as a white solid. R_f (in D), 0.37; δ_H([$^2H_6$]-DMSO) 7.54 (1 H, s, 6-H), 6.04 (2 H, br s, NH_2), 4.73 (2 H, s, CH_2), 3.75 (3 H, s, MeAr), 2.58 (3 H, s, MeS); *m/z* (FAB) 259 $(M + 1)^+$, 242 $(M^+ - NH_2)$ and 226 $(M^+ - ONH_2)$. Further heating of this solid in ethanol or ammonia–dioxane solution gave rise to a complex mixture of products on TLC.

4-Chloro-5-hydroxymethyl-7-methyl-2-methylsulfonyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 26

The alcohol **24** (731 mg, 3 mmol) was dissolved in ethanol (60 cm^3) and magnesium monoperphthalate (2.98 g, 6 mmol) in water (15 cm^3) was added to the solution which was then stirred overnight. After the mixture had been evaporated the residue was partitioned between chloroform (500 cm^3) and saturated aq. sodium hydrogen carbonate (100 cm^3). The organic phase was separated, dried and evaporated to afford a white foam (770 mg, 2.79 mmol, 93%), crystallisation of which from ethanol gave the title compound as colourless needles, mp 145–147 °C (Found: C, 39.3; H, 3.6; N, 15.2. $C_9H_{10}ClN_3O_3S$ requires C, 39.21; H, 3.65; N, 15.24); R_f (in A), 0.44 (fluorescent); δ_H([$^2H_6$]-DMSO) 7.90 (1 H, s, 6-H), 5.28 (1 H, t, *J* 4.9, OH), 4.80 (2 H, d, *J* 4.9, CH_2), 3.89 (3 H, s, N–Me) and 3.42 (3 H, s, $MeSO_2$); λ_{max}(MeOH)/nm 206 (9000), 241 (18 700), 274 (3000) and 316 (2200).

4-Hydroxyamino-5-hydroxymethyl-7-methyl-2-methylsulfonyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 27

Hydroxylamine hydrochloride (2.50 g, 36 mmol) was dissolved in boiling absolute ethanol (75 cm^3), and KOH (2.00 g, 35.7 mmol) in hot absolute ethanol (25 cm^3) was added to the solution. The resulting solution was then filtered. Compound **26** (276 mg, 1 mmol) was added to 50 cm^3 of the filtrate which was heated in a sealed bottle at 50 °C for 4 h and then left at 4 °C overnight. The title compound crystallised out and was filtered off. The filtrate was concentrated and left at 4 °C to afford additional product (158 mg, 0.58 mmol, 58%); when heated darkens with decomp. > 170 °C (Found: C, 39.1; H, 4.5; N, 20.1. $C_9H_{12}N_4O_4S$ requires C, 39.7; H, 4.44; N, 20.58); R_f (in A), 0.28; δ_H([$^2H_6$]-DMSO) 10.12 (1 H, br s, OH), 9.42 (1 H, br s, NH), 7.35 (1 H, s, 6-H), 5.95 (1 H, t, *J* 4.6, OH), 4.80 (2 H, d, *J* 4.6, CH_2), 4.61 (2 H, d, *J* 4.6, CH_2), 3.74 (3 H, s, N–Me) and 3.33 (3 H, s, $MeSO_2$); λ_{max}(MeOH)/nm 228 (21 300), 275 (7000) and 310 (7000).

Attempted cyclisations of 27

Method A. Compound **27** (40 mg, 0.15 mmol) and triphenylphosphine (45 mg, 0.17 mmol) were dissolved in anhydrous DMF (2.5 cm^3) and diethyl azodicarboxylate (27 mm^3, 0.17 mmol) was added to the mixture with stirring. The solution was evaporated after 2 h and the residue co-evaporated with toluene and redissolved in chloroform (100 cm^3). The resulting solution was extracted with saturated aq. sodium hydrogen carbonate (20 cm^3), dried (Na_2SO_4) and evaporated. The major component was isolated by preparative silica TLC developed with system E. A pale brown solid **28** (12 mg, 0.05 mmol, 33%) was obtained; R_f (in A), 0.29; δ_H([$^2H_6$]-DMSO) 7.55 (2 H, br s, NH_2), 7.29 (1 H, s, 6-H), 5.87 (1 H, t, *J* 4.7, OH), 4.63 (2 H, d, *J* 4.7, CH_2), 3.70 (3 H, s, N–Me) and 3.29 (3 H, s, $MeSO_2$); λ_{max}(MeOH)/nm 222, 271 and 322; *m/z* (FAB) 257 $(M + 1)^+$.

Method B. Triisopropylbenzenesulfonyl chloride (154 mg, 0.5 mmol) was added to a solution of **27** in pyridine (5 cm^3) at 0 °C. The resulting mixture was then stirred at room temp. for 4 h. The mixture obtained was evaporated, redissolved in chloroform (400 cm^3) and extracted with saturated aq. sodium hydrogen carbonate (50 cm^3) and brine (50 cm^3). The organic phase was dried and evaporated and the residue obtained was co-evaporated with toluene. Purification by silica gel chromatography (60 H, 32 × 13 mm) with chloroform followed by a gradient of 0.2–1% methanol in chloroform as eluents afforded three components: component 1: fluorescent yellow solid, 10 mg, R_f (in A), 0.48; component 2: fluorescent yellow solid **29**; 1:1 mixture with compound **28**, 29 mg; R_f (in A), 0.38; δ_H([$^2H_6$]-DMSO) 8.91 (2 H, d, *J* 5.7, 2 pyr-H), 8.25 (1 H, t *J* 7.7, pyr-H), 7.96 (2 H, t, *J* 6.9), 7.30 (1 H, s, 6-H), 4.62 (2 H, s, CH_2), 3.67 (3 H, s, N–Me) and 3.98 (3 H, s, $MeSO_2$); *m/z* (FAB) 334 $(M)^+$, 316 $(M - H_2O)^+$ and 256 $(M - C_5H_5N)^+$. Component 3: white solid (10 mg) identical by silica TLC and ^1H NMR with **28** described above.

4-Chloro-7-methyl-2-methylsulfonyl-5-phthalimidooxymethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine 30

Compound **21** (193 mg, 0.5 mmol) was dissolved in DMF (45 cm^3) and magnesium monoperphthalate (495 mg, 1 mmol) in water (5 cm^3) was added to the solution. After being stirred at room temp. for 6 h, the reaction mixture was diluted with chloroform (500 cm^3) and extracted with 5% aq. sodium carbonate. The chloroform layer was dried and evaporated and the residue was redissolved in methanol and evaporated onto a small amount of silica gel. Chromatography (60 H, 32 × 100) eluting with chloroform and then a gradient of 0.2–2% methanol in chloroform gave a white solid (158 mg, 0.38 mmol, 76%) which crystallised from 95% aq. ethanol as a white powder, mp 211.5–213 °C (Found: C, 48.6; H, 3.4; N, 13.1. $C_{17}H_{13}ClN_4O_5S$ requires C, 48.52; H, 3.11; N, 13.31); R_f (in D), 0.48; δ_H([$^2H_6$]-DMSO) 8.24 (1 H, s, 6-H), 7.87 (4 H, m, 4 phth. H), 5.67 (2 H, s, CH_2), 3.88 (3 H, s, N–Me) and 3.47 (3 H, s, $MeSO_2$); λ_{max}(MeOH)/nm 209 (18 300), 221 (22 000), 229 (24 100), 274 (3900) and 303 (2800).

Later fractions from the column afforded the sulfoxide (40 mg, 0.10 mmol, 20%); R_f (in D), 0.47; δ_H(250 MHz; [$^2H_6$]-DMSO) 8.11 (1 H, s, 6-H), 7.83 (4 H, m, 4 phth. H), 5.40 (2 H, s, CH_2), 3.85 (3 H, s, N–Me) and 2.94 (3 H, s, MeSO).

Attempted cyclisation of compound 30. Compound **30** (75 mg) was stirred in saturated ammonia–dioxane solution (25 cm^3) in a sealed tube at room temp. overnight after which the solution was evaporated to dryness. Silica TLC indicated a single component. R_f (in D), 0.17; δ_H([$^2H_6$]-DMSO) 7.83 (4 H, s, phthalamide), 7.41 (1 H, s, 6-H), 6.77 (2 H, br s, NH_2), 4.72 (2 H, s, CH_2), 3.75 (3 H, s, MeAr) and 3.29 (3 H, s, $MeSO_2$). Further heating of this solid in ethanol or ammonia–dioxane solution gave rise to a complex mixture of products on TLC.

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