Synthesis of 1-[*cis*-3-(hydroxymethyl)cyclobutyl]-uracil, -thymine and -cytosine

Miriam Frieden, Matthieu Giraud, Colin B. Reese * and Quanlai Song

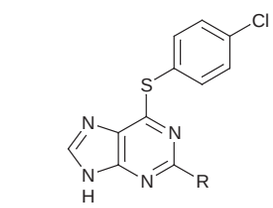
Department of Chemistry, King's College London, Strand, London, UK WC2R 2LS

4-(Benzylsulfanyl)pyrimidin-2(1*H*)-one 6a is prepared from 1-benzoyluracil 10a in three steps and in satisfactory overall yield. Reproducible conditions are found for the cycloaddition reaction between allyl benzyl ether and dichloroketene, leading to the cyclobutanone derivative 17 in good yield. *trans*-3-(Benzyloxymethyl)cyclobutan-1-ol 15 reacts under standard Mitsunobu conditions with the pyrimidine derivative 6a on *O*-2 to give compound 20, which is converted into 2-[*cis*-3-(hydroxymethyl)-cyclobutoxy]pyrimidin-4(3*H*)-one 24 in good overall yield. Under the same Mitsunobu conditions, 3-benzoyluracil 11a and 3-benzoylthymine 11b react with the *trans*-alcohol 15 on *N*-1 to give their 1-[*cis*-3-(benzyloxymethyl)cyclobutyl] derivatives 27a and 27b, respectively. The latter compounds 27a and 27b are converted into 1-[*cis*-3-(hydroxymethyl)cyclobutyl]uracil 13a and 1-[*cis*-3-(hydroxymethyl)-cyclobutyl]thymine 13b in satisfactory overall yields. The uracil derivative 13a is converted into 1-[*cis*-3-(hydroxymethyl)cyclobutyl]cytosine 14 in good yield.

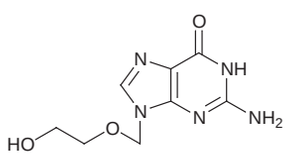
Introduction

We have previously reported[1,2] that 2-amino-6-[(4-chlorophenyl)sulfanyl]-9*H*-purine **1a**, its 2-*N*-phenylacetyl derivative **1b** and 6-[(4-chlorophenyl)sulfanyl]-9*H*-purine **1c** are useful and potentially versatile building blocks in the synthesis of 9-alkylpurine derivatives. The bulky (4-chlorophenyl)sulfanyl group promotes alkylation on *N*-9 (rather than on *N*-7) with a high degree of regioselectivity and, following oxidation with 3-chloroperoxybenzoic acid, the products readily undergo nucleophilic substitution at *C*-6. We first demonstrated[1] that the 2-aminopurine derivative **1a** could readily be converted into acyclovir **2** and its 6-deoxy derivative **3**. We have recently shown[2] that the other two purine building blocks **1b** and **1c** can be converted into 9-[*cis*-3-(hydroxymethyl)cyclobutyl]-guanine and -adenine (**4** and **5**, respectively), which are potential antiviral agents. In the present study, we first set out to examine whether a 4-(arylsulfanyl)- or 4-(alkylsulfanyl)-pyrimidin-2(1*H*)-one **6** would be a useful building block for the preparation of the corresponding 1-alkyl derivatives of uracil and cytosine.

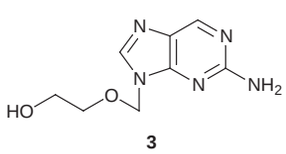
We selected 4-(benzylsulfanyl)pyrimidin-2(1*H*)-one **6a** as a suitable building block of this type. 4-(Benzylsulfanyl)-pyrimidin-2(1*H*)-one **6a** had previously been prepared[3] in 46% yield by allowing 4-thiouracil[4] **7** to react with benzyl chloride in aqueous sodium hydroxide. There are a number of literature reports[4–7] relating to the conversion of uracil **8a** into 4-thiouracil **7** by treatment with phosphorus pentasulfide[4–6] or with 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent)[7] **9**. However, in our hands, due most probably to the physical properties of 4-thiouracil **7**, work-up of the reaction products proved to be laborious. Furthermore, reaction between uracil **8a** and Lawesson's reagent **9** is reported[7] not to occur regiospecifically on *C*-4.



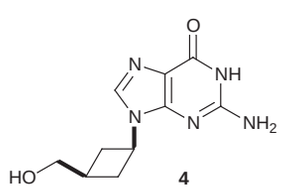
1 a; R = NH_2
b; R = $NHCOCH_2Ph$
c; R = H



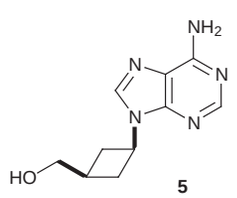
2



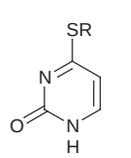
3



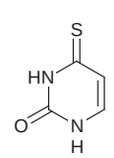
4



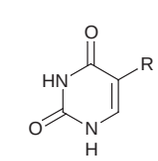
5



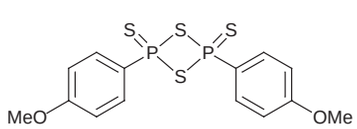
6 a; R = $PhCH_2$



7



8 a; R = H
b; R = Me

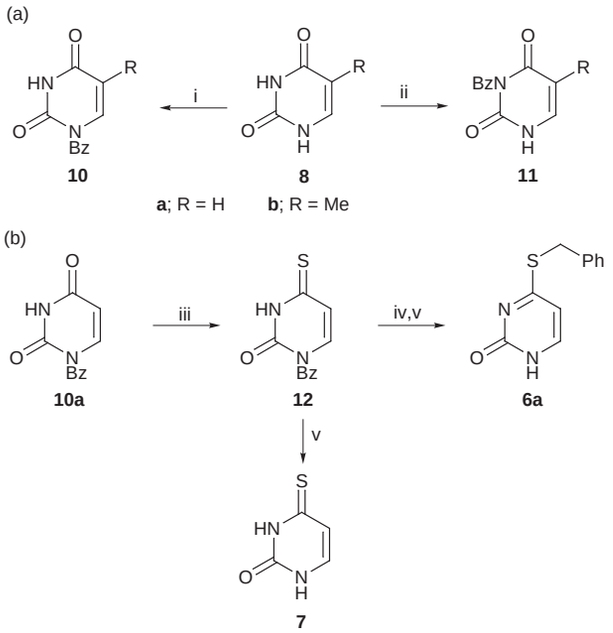


9

Results and discussion

It occurred to us that, if the 1,2-lactam function of uracil **8a** was protected, thiation would be completely regiospecific, and the physical properties of the intermediate would be such that the thiation and benzylation steps would both be facilitated. We had previously reported[8] [Scheme 1(a), step i] that uracil **8a** and thymine **8b** both react with a very slight excess of benzoyl chloride in pyridine–acetonitrile to give their 1-benzoyl derivatives (**10a** and **10b**, respectively) in good yields. We had further reported[8] that when uracil **8a** and thymine **8b** were treated with more than 2 mol equiv. of benzoyl chloride, and the products were then subjected to basic hydrolysis under mild conditions [Scheme 1(a), step ii], their 3-benzoyl derivatives (**11a** and **11b**, respectively) were obtained, also in good yields (see Experimental section).

We now report that when 1-benzoyluracil **10a** was heated, under reflux, with Lawesson's reagent **9**, it was converted

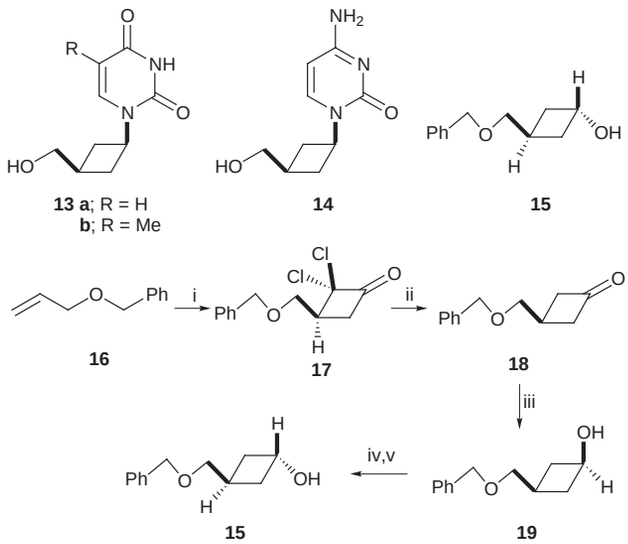


Scheme 1 *Reagents and conditions*: i, BzCl (*ca*. 1.1 mol equiv.), MeCN, C_5H_5N, room temp.; ii, (a) BzCl (*ca.* 2.2 mol equiv.), MeCN, C_5H_5N, room temp., 24 h, (b) K_2CO_3, H_2O–dioxane (1 : 2 v/v), room temp., 30 min; iii, Lawesson's reagent **9**, PhMe, reflux, 3–4 h; iv, $PhCH_2Cl$, Pr^i_2NEt, CH_2Cl_2, room temp., 7 h; v, $MeNH_2$, EtOH, room temp., 1.5 h

[Scheme 1(b), step iii] into its 4-thio derivative **12**, which was readily isolated as a crystalline solid in 79.5% yield. 1-Benzoyl-4-thiouracil **12** was then allowed to react with benzyl chloride in the presence of *N*,*N*-diisopropylethylamine in dichloromethane solution. As previously reported,[8] debenzoylation of 1-benzoyluracil **10a** occurs under very mild basic conditions. Therefore the intermediate 1-benzoyl-4-benzylsulfanyl derivative obtained was not isolated, but the crude products were treated directly with alcoholic methylamine to give the desired building block **6a** as a crystalline solid in 69% overall yield. 4-Thiouracil **7** was also very conveniently prepared and isolated as a crystalline solid in good yield by treating its 1-benzoyl derivative **12** with alcoholic methylamine. The above approach has the advantage of complete regiocontrol, and the intermediates involved both in the thiation and benzylation steps have very favourable solubility properties. We believe that these factors more than compensate for the two extra steps (*i.e.* benzoylation and debenzoylation) required.

In order to complement our previous work[2] on the synthesis of 9-[*cis*-3-(hydroxymethyl)cyclobutyl]-guanine and -adenine (**4** and **5**, respectively), we decided to investigate whether the pyrimidine building block **6a** could be used in the preparation of the 1-[*cis*-3-(hydroxymethyl)cyclobutyl]-pyrimidine derivatives **13a** and **14** which, to the best of our knowledge, had not previously been described in the literature. In the preparation of the purine derivatives, the cyclobutyl side-chain was introduced by means of a Mitsunobu reaction[9] involving *trans*-(3-benzyloxymethyl)cyclobutan-1-ol[2] **15**, the purine building block **1b** or **1c**, diethyl azodicarboxylate (DEAD) and triphenylphosphine.

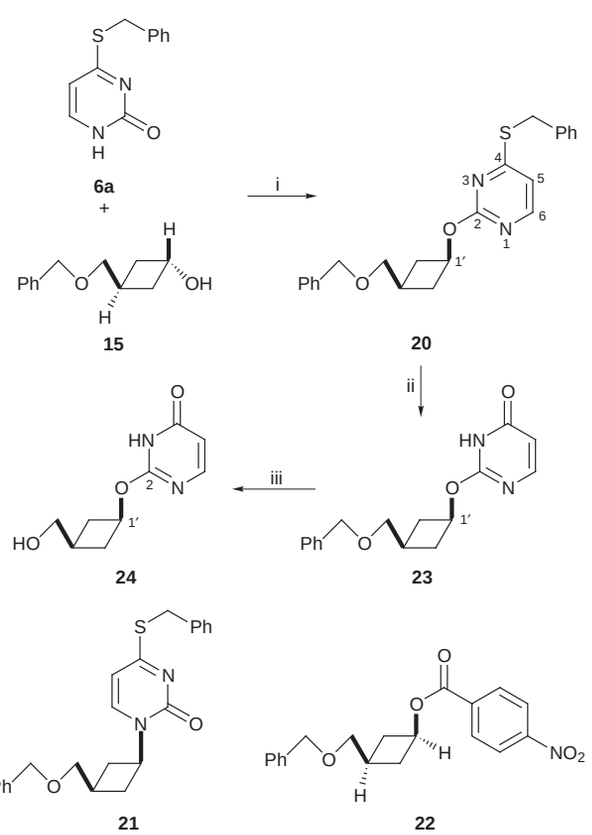
As can be seen from Scheme 2, the key intermediate **15**, required for the introduction of the 3-(hydroxymethyl)-cyclobutyl side-chain is prepared[2] in five steps from allyl benzyl ether **16**. Of these five steps, we regard the first (Scheme 2, step i), involving the *in situ* generation of dichloroketene and its cycloaddition to the olefin **16**, as being the most crucial. We were previously[2] unable to optimize the yield of the cycloaddition product **17**, and indeed attempts to increase the scale of the reaction led[2] to diminished yields. We now find that if the modification to the original reaction conditions suggested by Johnston *et al*.[10] is implemented, and 1,2-dimethoxyethane is



Scheme 2 *Reagents and conditions*: i, Cl_3CCOCl, Zn–Cu couple, $MeOCH_2CH_2OMe$, Et_2O, reflux, 100 h; ii, Zn dust, AcOH, reflux; iii, L-Selectride, THF, −78 °C; iv, 4-$(O_2N)C_6H_4CO_2H$, Ph_3P, $EtO_2CN{=}NCO_2Et$ (DEAD), THF, room temp.; v, NaOH, aq. dioxane, room temp.

added to the reactants (see Experimental section), a good yield (75%) of cycloadduct **17** can reproducibly be obtained. It should be noted that the cycloaddition reaction is surprisingly slow, and that a reaction time of *ca*. 4 days is required if a good yield is to be obtained.

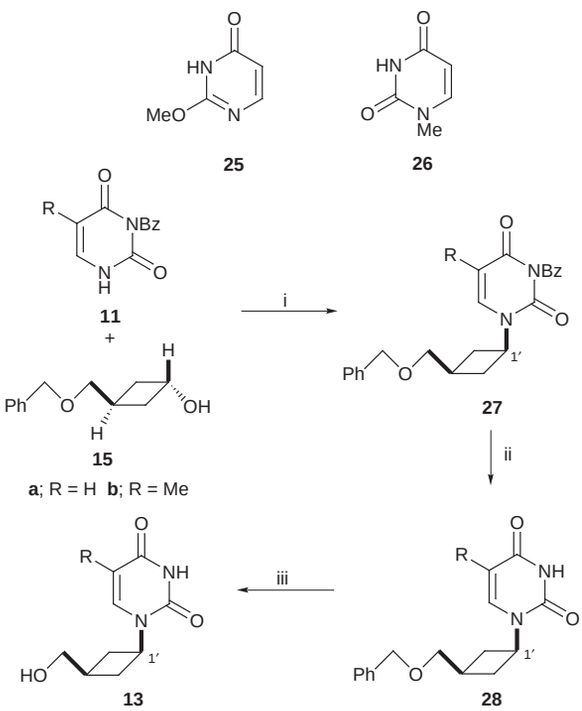
The cyclobutanol derivative **15** and the pyrimidine building block **6a** were coupled together in the presence of triphenylphosphine and DEAD in THF solution (Scheme 3), under standard Mitsunobu conditions,[9] to give a single product which



Scheme 3 *Reagents and conditions*: i, DEAD, Ph_3P, THF, 0 °C to room temp., 15 h; ii, (a) $[2\text{-}(HO_3C)C_6H_4CO_2]_2Mg$, EtOH, room temp., 1 h; (b) $MeC(=O)C(=NOH)Me$, $(Me_2N)_2C{=}NH$, MeCN, room temp., 20 h; iii, 10% Pd/C, HCO_2H, MeOH, room temp., 3 h

was isolated as a colourless oil in 90% yield. On the basis of its ^{13}C NMR spectrum [$\delta_C(CDCl_3)$ 68.3, assigned to C-1′], this product was believed to be 2-[*cis*-3-(benzyloxymethyl)-cyclobutoxy]-4-(benzylsulfanyl)pyrimidine **20** rather than the desired 1-[*cis*-3-(benzyloxymethyl)cyclobutyl]-4-(benzylsulfanyl)pyrimidin-2(1*H*)-one **21**. It is noteworthy that the chemical shift of the *C*-1 resonance signal in the ^{13}C NMR spectrum (in $CDCl_3$) of the 4-nitrobenzoate ester[2] **22** is 67.4 ppm, and the chemical shift of the *C*-1′ resonance signal in the ^{13}C NMR spectrum [in $(CD_3)_2SO$] of 9-[*cis*-3-(hydroxymethyl)cyclobutyl]adenine[2] **5** is 44.3 ppm. Oxidation of compound **20** with magnesium monoperoxyphthalate[11] followed by treatment with the N^1,N^1,N^3,N^3-tetramethylguanidinium salt of butane-2,3-dione monooxime[2,12] (Scheme 3) gave the benzyl ether **23**. The latter compound **23** was converted into 2-[*cis*-3-(hydroxymethyl)cyclobutoxy]pyrimidin-4(3*H*)-one **24** under transfer hydrogenation conditions.[13] The constitution of compound **24** {δ_C[$(CD_3)_2SO$] 68.2, assigned to C-1′} was confirmed by ultraviolet (UV) absorption spectroscopy. The UV spectrum of compound **24** [$\lambda_{max}(H_2O)$ 254 nm (ε 6200)] is closely similar to that of 2-methoxypyrimidin-4(3*H*)-one **25** [$\lambda_{max}(H_2O)$ 256 nm (ε 5800)],[14] but it is quite distinct from that of 1-methyluracil **26** [$\lambda_{max}(H_2O)$ 267 nm (ε 9700)].[14]

It was thus clearly evident that 4-(benzylsulfanyl)pyrimidin-2(1*H*)-one **6a** was not a suitable building block for the preparation of 1-[*cis*-3-(hydroxymethyl)cyclobutyl]-uracil and -cytosine (**13a** and **14**, respectively). The coupling reaction between 3-benzoyluracil[8] **11a** and the *trans*-alcohol[2] **15** was then carried out, also under standard Mitsunobu conditions (Scheme 4). A single pyrimidine derivative, which on the basis

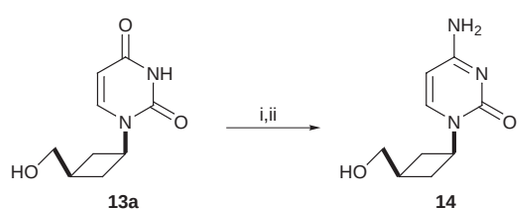


Scheme 4 *Reagents and conditions*: i, DEAD, Ph_3P, THF, 0 °C to room temp., 24 h; ii, $MeNH_2$, EtOH, room temp., 1 h; iii, 10% Pd/C, HCO_2H, MeOH, room temp., 3 h

of its ^{13}C NMR spectrum [$\delta_C(CDCl_3)$ 46.6, assigned to C-1′] was identified as 3-benzoyl-1-[*cis*-3-(benzyloxymethyl)cyclobutyl]uracil **27a**, was obtained in 73% isolated yield. The latter compound **27a** reacted with methylamine in ethanol solution to give 1-[*cis*-3-(benzyloxymethyl)cyclobutyl]uracil **28a**, which was isolated as a colourless crystalline solid in virtually quantitative yield. In the same way, 3-benzoylthymine[8] **11b** was converted in two steps into 1-[*cis*-3-(benzyloxymethyl)-cyclobutyl]thymine **28b** [$\delta_C(CDCl_3)$ 46.0, assigned to C-1′] in 70% isolated yield. Removal of the benzyl protecting group from the uracil derivative **28a** by transfer hydrogenolysis gave 1-[*cis*-3-(hydroxymethyl)cyclobutyl]uracil **13a** as a colourless crystalline solid in 94% isolated yield. The structure assigned to compound **13a** {δ_C[$(CD_3)_2SO$] 46.4, C-1′} was supported by its UV spectrum [$\lambda_{max}(H_2O)$ 268 nm (ε 10 000)], which is very similar to that of 1-methyluracil[14] **26** (see above). In the same way, the thymine derivative **28b** was converted into 1-[*cis*-3-(hydroxymethyl)cyclobutyl]thymine **13b** in 93% isolated yield.

It is not at all obvious why 4-(benzylsulfanyl)pyrimidin-2(1*H*)-one **6a** and 3-benzoyluracil **11a** should undergo alkylation, under Mitsunobu conditions, virtually regiospecifically on *O*-2 and *N*-1, respectively. It is perhaps worth noting that *O*-2 is more hindered in 3-benzoyluracil **11a** than it is in the 4-benzylsulfanyl derivative **6a**. However, this does not explain why the latter compound **6a** undergoes virtually regiospecific alkylation on *O*-2. It is particularly noteworthy that ^{13}C NMR has proved to be a much more useful analytical tool than ^1H NMR spectroscopy in distinguishing between *N*-1- and *O*-2-alkyl derivatives of uracil and thymine. Thus, while the C-1′ resonance signals [in $(CD_3)_2SO$] of 2-[*cis*-3-(hydroxymethyl)cyclobutoxy]pyrimidin-4(3*H*)-one **24**, 1-[*cis*-3-(hydroxymethyl)cyclobutyl]uracil **13a** and 1-[*cis*-3-(hydroxymethyl)-cyclobutyl]thymine **13b** are observed at δ 68.2, 46.4 and 46.1, respectively, their H-1′ multiplets resonate at δ 5.01, 4.59 and 4.60, respectively. The C-1′ and the H-1′ resonance signals [in $(CD_3)_2SO$] of 9-[*cis*-3-(hydroxymethyl)cyclobutyl]adenine[2] **5** are observed at δ 44.3 and 4.86, respectively.

Finally, 1-[*cis*-3-(hydroxymethyl)cyclobutyl]uracil **13a** was converted into the corresponding cytosine derivative **14** by the procedure indicated in Scheme 5. Following trimethylsilyl-



Scheme 5 *Reagents and conditions*: i, (a) Me_3SiCl, 1-methylpyrrolidine, MeCN, room temp., 1 h, (b) $(CF_3CO)_2O$, 0 °C, 35 min, (c) 4-nitrophenol, 0 °C, 3 h; ii, conc. aq. NH_3 (*d* 0.88)–dioxane (1 : 4 v/v), 50 °C, 24 h

ation of compound **13a** and activation with trifluoroacetic anhydride,[15] 4-nitrophenol was added.[16] The products of this one pot reaction were then treated with ammonia in aqueous dioxane at 50° to give 1-[*cis*-3-(hydroxymethyl)cyclobutyl]-cytosine **14**, which was isolated as a colourless crystalline solid in 84% overall yield. Unfortunately, although they were not found to be toxic, none of the unprotected nucleoside analogues **13a**, **13b**, **14** and **24** showed any significant anti-human immunodeficiency virus (anti-HIV) activity.

Experimental

Mps were measured with a Büchi melting point apparatus and are uncorrected. ^1H NMR spectra were measured at 360 MHz with a Bruker AM 360 spectrometer; ^{13}C NMR spectra were measured at 90.6 MHz with the same spectrometer. Tetramethylsilane was used as an internal standard, and *J* values are given in Hz. UV spectra were measured with a Perkin-Elmer Lambda-3 spectrophotometer; IR spectra were measured with a Perkin-Elmer model 983G spectrometer. Merck silica gel 60 F_{254} TLC plates were developed in solvent systems A [light petroleum (distillation range 40–60 °C)–ethyl acetate (3 : 7 v/v)], B [light petroleum (distillation range 40–

60 °C)–ethyl acetate (1:1 v/v)], C [chloroform–methanol (19:1 v/v)] and D [chloroform–methanol (9:1 v/v)]. Merck silica gel H was used for short column chromatography. Acetonitrile, THF, dioxane, 1,2-dimethoxyethane, pyridine, 1-methylpyrrolidine and *N*,*N*-diisopropylethylamine were dried by heating, under reflux, over calcium hydride, and were then distilled; N^1,N^1,N^3,N^3-tetramethylguanidine was dried by distillation over calcium hydride under reduced pressure. Toluene was dried by distillation at atmospheric pressure with the first 20% of distillate being discarded; diethyl ether and dichloromethane were dried over sodium wire and phosphorus pentaoxide, respectively, and were then distilled.

1-Benzoyluracil 10a †

Benzoyl chloride (1.28 cm^3, 11.0 mmol) was added in one portion to a stirred suspension of uracil **8a** (1.121 g, 10.0 mmol) in dry acetonitrile (10 cm^3) and pyridine (2 cm^3) at room temperature. After 2.5 h, the suspended product (0.671 g) was collected by filtration. A second crop of product precipitated from the filtrate; it was collected by refiltration, and a third crop was obtained by adding water to the resulting filtrate. Total yield of the *title compound* **10a**, 1.817 g (84%) (Found: M^+, 216.0533. $^{12}C_{11}{}^{1}H_{8}{}^{14}N_{2}{}^{16}O_{3}$ requires *M*, 216.0535), mp 167–168.5 °C; R_f 0.32 (system D); δ_H[$(CD_3)_2SO$] 5.85 (1 H, dd, *J* 2.0 and 8.1), 7.25 (2 H, m), 7.67 (1 H, m), 7.82 (2 H, m), 7.92 (1 H, d, *J* 8.1), 11.58 (1 H, br s); δ_C[$(CD_3)_2SO$] 103.7, 128.4, 129.6, 132.9, 133.7, 140.5, 149.4, 163.3, 169.7.

3-Benzoyluracil 11a †

Uracil **8a** (2.24 g, 20.0 mmol), benzoyl chloride (5.2 cm^3, 44.8 mmol), dry acetonitrile (20 cm^3) and dry pyridine (8 cm^3) were stirred together at room temperature. After 24 h, the products were concentrated under reduced pressure and the residue was partitioned between dichloromethane (100 cm^3) and water (100 cm^3). The organic layer was separated and then evaporated under reduced pressure. The residue was dissolved in a mixture of aqueous potassium carbonate (0.5 mol dm^{-3}, 20 cm^3) and dioxane (40 cm^3) at room temperature. After 30 min, the pH was lowered to *ca*. 5 by the careful addition of glacial acetic acid. The products were concentrated under reduced pressure, and the residue was stirred with saturated aqueous sodium hydrogen carbonate (100 cm^3) at room temperature. After 1 h, the products were filtered and the residue was washed with cold water (3 × 10 cm^3). Crystallization of this material from aqueous acetone gave the *title compound* **11a** as an off-white solid (3.65 g, 84%) (Found, in material recrystallized from absolute ethanol: C, 61.32; H, 3.66; N, 12.90. Calc. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96%) mp 173.5–175 °C; R_f 0.40 (system D); δ_H[$(CD_3)_2SO$] 5.75 (1 H, d, *J* 7.7), 7.60 (2 H, t, *J* 7.8), 7.67 (1 H, d, *J* 7.7), 7.77 (1 H, t, *J* 7.4), 7.96 (2 H, m), 11.62 (1 H, br); δ_C[$(CD_3)_2SO$] 100.4, 129.8, 130.6, 131.7, 135.8, 143.7, 150.4, 163.3, 170.4.

3-Benzoylthymine 11b†

Thymine **8b** (1.261 g, 10.0 mmol), benzoyl chloride (2.55 cm^3, 22.1 mmol), dry acetonitrile (10 cm^3) and dry pyridine (4 cm^3) were stirred together at room temperature. After 16 h, the products were worked up and treated with potassium carbonate as above in the preparation of 3-*N*-benzoyluracil **11a**. The product obtained was crystallized from aqueous acetonitrile to give the *title compound* **11b** as colourless needles (1.847 g, 80%) (Found: C, 62.57; H, 4.36; N, 12.32. Calc. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17%), mp 178–180 °C (followed by resolidification at *ca*. 190 °C and remelting at 210–215 °C); R_f 0.45 (system D); δ_H[$(CD_3)_2SO$] 1.82 (3 H, s), 7.58 (3 H, m), 7.77 (1 H, t, *J* 7.3), 7.94 (2 H, m), 11.40 (1 H, br); δ_C[$(CD_3)_2SO$] 11.7, 107.9, 129.5, 130.2, 131.4, 135.4, 138.8, 150.0, 163.6, 170.2.

† Experiment first carried out by Dr K. A. Cruickshank.[8,12]

1-Benzoyl-4-thiouracil 12

A mixture of 1-benzoyluracil **10a** (2.132 g, 9.9 mmol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) **9** (2.395 g, 5.9 mmol) in dry toluene (18 cm^3) was heated, under reflux, in an atmosphere of argon. After 3 h, the cooled products were concentrated under reduced pressure and recrystallized from acetonitrile to give the *title compound* **12** (1.821 g, 79.5%) (Found: C, 56.76; H, 3.36; N, 12.11. $C_{11}H_8N_2O_2S$ requires C, 56.89; H, 3.47; N, 12.06%) as yellow needles, mp 181 °C (decomp.); R_f 0.28 (system C); δ_H[$(CD_3)_2SO$] 6.43 (1 H, d, *J* 7.6), 7.52 (2 H, m), 7.68 (1 H, m), 7.78 (1 H, d, *J* 7.7), 7.86 (2 H, m), 12.92 (1 H, br s); δ_C[$(CD_3)_2SO$] 113.8, 128.4, 129.7, 132.3, 133.9, 135.0, 146.6, 169.3, 192.0.

4-Thiouracil 7

A solution of 1-benzoyl-4-thiouracil **12** (0.334 g, 1.44 mmol) in *ca*. 8 mol dm^{-3} ethanolic methylamine (14 cm^3, *ca*. 0.11 mol) was stirred at room temperature. After 1.5 h, the products were concentrated under reduced pressure and were then triturated with dichloromethane. The residue was recrystallized from aqueous methanol to give 4-*thiouracil* **7** (0.143 g, 77.5%) (Found: C, 37.60; H, 2.96; N, 21.77. Calc. for $C_4H_4N_2OS$: C, 37.49; H, 3.15; N, 21.86%) as yellow needles, mp 289 °C (decomp.) (lit.,[7] 292–296 °C decomp.); R_f 0.39 (system D); δ_H[$(CD_3)_2SO$] 6.18 (1 H, d, *J* 7.0), 7.31 (1 H, d, *J* 7.1), 11.53 (1 H, br), 12.43 (1 H, br); δ_C[$(CD_3)_2SO$] 111.6, 138.2, 148.6, 191.3.

4-(Benzylsulfanyl)pyrimidin-2(1*H*)-one 6a

N,*N*-Diisopropylethylamine (2.24 cm^3, 12.9 mmol) and benzyl chloride (1.49 cm^3, 12.9 mmol) were added to a stirred solution of 1-benzoyl-4-thiouracil **12** (1.50 g, 6.5 mmol) in dry dichloromethane (65 cm^3) at room temperature. After 7 h, the products were concentrated under reduced pressure and *ca*. 8 mol dm^{-3} ethanolic methylamine (16 cm^3, *ca*. 0.13 mol) was added. The resulting solution was stirred at room temperature for 1.5 h, and was then evaporated under reduced pressure. The residue was dissolved in chloroform (75 cm^3) and the solution was washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure and the residue was crystallized from aqueous methanol to give 4-(*benzylsulfanyl*)*pyrimidin*-2(1H)-*one* **6a** (0.973 g, 69%) (Found: C, 60.51; H, 4.56; N, 12.81. Calc. for $C_{11}H_{10}N_2OS$: C, 60.50; H, 4.62; N, 12.83%) as colourless crystals, mp 201–203 °C (lit.,[3] 202–204 °C); R_f 0.40 (system C); δ_H[$(CD_3)_2SO$] 4.38 (2 H, s), 6.27 (1 H, d, *J* 6.7), 7.28 (3 H, m), 7.40 (2 H, m), 7.64 (1 H, d, *J* 6.7), 11.54 (1 H, br); δ_C[$(CD_3)_2SO$] 32.3, 101.6, 127.1, 128.4, 128.9, 137.3, 143.5, 154.2, 176.3.

2,2-Dichloro-3-(benzyloxymethyl)cyclobutan-1-one 17

Redistilled trichloroacetyl chloride (20 cm^3, 0.18 mol) was added to a magnetically-stirred suspension of freshly prepared zinc–copper couple (13.3 g), allyl benzyl ether[2] (10.0 g, 67.5 mmol), dry 1,2-dimethoxyethane (33 cm^3) and dry diethyl ether (250 cm^3) in a flame-dried flask in an atmosphere of argon. The reactants were heated, under gentle reflux, for 100 h. The products were then filtered, and the residue was washed with ether. The residue was discarded. The combined filtrate and washings were concentrated under reduced pressure to *ca*. 80 cm^3. Light petroleum (bp 30–40 °C, 100 cm^3) was added, and the mixture was stirred vigorously. After 5 min, the supernatant was decanted and more light petroleum (*ca*. 40 cm^3) was added. After vigorous stirring the supernatant was again decanted and mixed with the original supernatant. The resulting solution was washed in turn with saturated aqueous sodium hydrogen carbonate (2 × 200 cm^3) and brine (100 cm^3). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure and the residue was distilled to give 2,2-dichloro-3-

(benzyloxymethyl)cyclobutan-1-one[2] **17** (13.1 g, 75%) as a pale yellow viscous liquid, bp 158 °C/3.0 mmHg; ν_{max}(film)/cm^{-1} 1811; δ_H($CDCl_3$) 3.08–3.22 (2 H, m), 3.41 (1 H, m), 3.68 (1 H, m), 3.83 (1 H, m), 4.56 (2 H, s), 7.35 (5 H, m); δ_C($CDCl_3$) 45.0, 45.3, 68.9, 73.3, 87.5, 127.7, 127.9, 128.4, 137.4, 192.3.

2-[*cis*-3-(Benzyloxymethyl)cyclobutoxy]-4-(benzylsulfanyl)pyrimidine 20

Diethyl azodicarboxylate (1.4 cm^3, 8.9 mmol) was added to a stirred solution of *trans*-3-(benzyloxymethyl)cyclobutan-1-ol[2] **15** (0.70 g, 3.6 mmol), 4-(benzylsulfanyl)pyrimidin-2(1*H*)-one **6a** (0.96 g, 4.4 mmol) and triphenylphosphine (2.31 g, 8.8 mmol) in dry THF (40 cm^3) at 0 °C (ice–water bath), and the reactants were allowed to warm up to room temperature. After 15 h, the products were concentrated under reduced pressure and the residue was fractionated by short column chromatography on silica gel. The appropriate fractions, which were eluted with light petroleum (bp 40–60 °C)–ethyl acetate (95:5 to 85:15 v/v), were combined and evaporated under reduced pressure to give 2-[*cis*-3-(benzyloxymethyl)cyclobutoxy]-4-(benzylsulfanyl)pyrimidine **20** as a colourless oil (1.30 g, *ca*. 90%); R_f 0.76 (system B); δ_H($CDCl_3$) 2.01 (2 H, m), 2.27 (1 H, m), 2.60 (2 H, m), 3.49 (2 H, d, *J* 6.4), 4.44 (2 H, s), 4.52 (2 H, s), 5.09 (1 H, m), 6.76 (1 H, d, *J* 5.5), 7.24–7.39 (10 H, m), 8.11 (1 H, d, *J* 5.3); δ_C($CDCl_3$) 26.9, 33.6, 33.9, 68.3, 73.0, 74.7, 112.4, 127.5, 127.6, 127.7, 128.4, 128.7, 128.9, 136.7, 138.5, 156.7, 163.9, 171.7.

2-[*cis*-3-(Benzyloxymethyl)cyclobutoxy]pyrimidin-4(3*H*)-one 23

Magnesium monoperoxyphthalate hexahydrate (*ca*. 80%, 0.928 g, *ca*. 1.5 mmol) was added to a stirred solution of 1-[*cis*-3-(benzyloxymethyl)cyclobutoxy]-4-(benzylsulfanyl)pyrimidine **20** (0.396 g, 1.0 mmol) in absolute ethanol (10 cm^3) at room temperature. After 1 h, the products were evaporated under reduced pressure. The residue was dissolved in dichloromethane (40 cm^3) and the solution was washed with water (2 × 20 cm^3). The dried ($MgSO_4$) organic layer was redissolved in acetonitrile (5 cm^3). Butane-2,3-dione monooxime (0.303 g, 3.0 mmol) and N^1,N^1,N^3,N^3-tetramethylguanidine (TMG, 0.38 cm^3, 3.0 mmol) were added to the stirred solution at room temperature. After 20 h, the products were concentrated under reduced pressure, and the residue was fractionated by short column chromatography on silica gel. The appropriate fractions, eluted with light petroleum (bp 40–60 °C)—ethyl acetate (60:40 v/v), were combined and evaporated under reduced pressure. Crystallization of the residue from ethyl acetate–light petroleum (bp 40–60 °C) gave the *title compound* **23** (0.264 g, *ca*. 91%) (Found: C, 67.09; H, 6.24; N, 9.78. $C_{16}H_{18}N_2O_3$ requires C, 67.12; H, 6.34; N, 9.78%), mp 134–135 °C; R_f 0.71 (system D); δ_H($CDCl_3$) 1.94 (2 H, m), 2.17 (1 H, m), 2.51 (2 H, m), 3.40 (2 H, d, *J* 6.0), 4.45 (2 H, s), 5.05 (1 H, m), 6.03 (1 H, d, *J* 6.6), 7.25 (5 H, m), 7.65 (1 H, d, *J* 6.6), 11.31 (1 H, br); δ_C($CDCl_3$) 25.7, 32.5, 68.5, 72.0, 72.9, 107.9, 126.6, 127.4, 137.2, 154.3, 155.5, 164.1.

2-[*cis*-3-(Hydroxymethyl)cyclobutoxy]pyrimidin-4(3*H*)-one 24

2-[*cis*-3-(Benzyloxymethyl)cyclobutoxy]pyrimidin-4(3*H*)-one **23** (0.23 g, 0.8 mmol), 10% palladium on activated carbon (0.23 g), formic acid (1.2 cm^3) and methanol (10.8 cm^3) were stirred together at room temperature. After 3 h, the products were filtered and the filtrate was evaporated under reduced pressure. The residual solid was recrystallized from dichloromethane–cyclohexane to give the *title compound* **24** (0.15 g, 95%) (Found: C, 54.82; H, 6.20; N, 14.00. $C_9H_{12}N_2O_3$ requires C, 55.09; H, 6.16; N, 14.28%), mp 179–181 °C; R_f 0.41 (system D); λ_{max}(H_2O)/nm 254 (ε 6200); λ_{min}/nm 232 (ε 4400); δ_H[$(CD_3)_2SO$] 1.85 (2 H, m), 2.01 (1 H, m), 2.35 (2 H, m), 3.37 (2 H, d, *J* 5.2), 4.60 (1 H, br), 5.01 (1 H, m), 5.91 (1 H, d, *J* 6.6), 7.67 (1 H, d, *J* 6.6), 12.22 (1 H, br); δ_C[$(CD_3)_2SO$] 28.5, 32.1, 63.8, 68.2, 108.4, 153.9, 157.2, 163.8.

3-Benzoyl-1-[*cis*-3-(benzyloxymethyl)cyclobutyl]uracil 27a

Diethyl azodicarboxylate (1.95 cm^3, 12.4 mmol) was added to a stirred solution of *trans*-3-(benzyloxymethyl)cyclobutan-1-ol[3] **15** (0.96 g, 5.0 mmol), 3-benzoyluracil **11a** (1.62 g, 7.5 mmol) and triphenylphosphine (3.28 g, 12.5 mmol) in dry THF (50 cm^3) at 0 °C (ice–water bath), and the reactants were allowed to warm to room temperature. After 24 h, the products were concentrated under reduced pressure and the residue was fractionated by short column chromatography on silica gel. The appropriate fractions, which were eluted with toluene–ethyl acetate (95:5 to 80:20 v/v), were combined and evaporated under reduced pressure to give a colourless solid. Crystallization of this material from aqueous methanol gave the *title compound* **27a** (1.43 g, 73%) (Found: C, 70.67; H, 5.56; N, 7.10. $C_{23}H_{22}N_2O_4$ requires C, 70.75; H, 5.68; N, 7.17%), mp 107–108 °C; R_f 0.57 (system A); δ_H($CDCl_3$) 2.23 (2 H, m), 2.38 (1 H, m), 2.51 (2 H, m), 3.49 (2 H, d, *J* 3.9), 4.55 (2 H, s), 4.86 (1 H, m), 5.67 (1 H, d, *J* 8.1), 7.35 (5 H, m), 7.47 (2 H, m), 7.63 (2 H, m), 7.92 (2 H, m); δ_C($CDCl_3$) 28.0, 31.2, 46.6, 72.1, 73.5, 102.1, 127.9, 128.0, 128.7, 129.3, 130.6, 131.6, 135.2, 138.3, 141.4, 149.8, 162.4, 169.2.

1-[*cis*-3-(Benzyloxymethyl)cyclobutyl]uracil 28a

A solution of 3-benzoyl-1-[*cis*-3-(benzyloxymethyl)cyclobutyl]uracil **27a** (1.17 g, 3.0 mmol) in ethanolic methylamine (8 mol dm^{-3}, 30 cm^3) was stirred at room temperature. After 1 h, the products were evaporated under reduced pressure, and the residue was fractionated by short column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane–methanol (100:0 to 99:1 v/v) were combined and evaporated under reduced pressure to give the *title compound* **28a** as a colourless solid (0.84 g, 97%) [Found, in material recrystallized from ethyl acetate–light petroleum (distillation range 40–60 °C): C, 67.11; H, 6.29; N, 9.79. $C_{16}H_{18}N_2O_3$ requires C, 67.12; H, 6.34; N, 9.78%], mp 92–93 °C; R_f 0.26 (system A), 0.68 (system D); δ_H($CDCl_3$) 2.19 (2 H, m), 2.38 (1 H, m), 2.50 (2 H, m), 3.49 (2 H, d, *J* 4.1), 4.55 (2 H, s), 4.90 (1 H, m), 5.60 (1 H, dd, *J* 2.2 and 8.0), 7.35 (5 H, m), 7.52 (1 H, d, *J* 8.1), 9.15 (1 H, br); δ_C($CDCl_3$) 27.9, 31.3, 46.2, 72.1, 73.4, 102.3, 127.9, 128.0, 128.6, 138.3, 141.4, 150.9, 163.5.

1-[*cis*-3-(Benzyloxymethyl)cyclobutyl]thymine 28b

Diethyl azodicarboxylate (1.95 cm^3, 12.4 mmol) was added to a stirred solution of *trans*-3-(benzyloxymethyl)cyclobutan-1-ol[3] **15** (0.96 g, 5.0 mmol), 3-benzoylthymine **11b** (1.73 g, 7.5 mmol) and triphenylphosphine (3.28 g, 12.5 mmol) in dry THF (50 cm^3) at 0 °C (ice–water bath). The reaction was allowed to proceed and the products were worked up and chromatographed as in the above preparation of 3-benzoyl-1-[*cis*-3-(benzyloxymethyl)cyclobutyl]uracil **27a** to give a colourless oil (*ca*. 1.5 g). A solution of the latter material in ethanolic methylamine (8 mol dm^{-3}, 30 cm^3) was stirred at room temperature. After 1 h, the products were evaporated under reduced pressure, and the residue was fractionated by short column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane–methanol (100:0 to 99:1 v/v) were combined and evaporated under reduced pressure to give the *title compound* **28b** as a colourless solid (1.05 g, 70%) (Found: C, 68.02; H, 6.70; N, 9.27. $C_{17}H_{20}N_2O_3$ requires C, 67.98; H, 6.71; N, 9.33%), mp 153–154 °C; R_f 0.36 (system A); δ_H($CDCl_3$) 1.79 (3 H, d, *J* 1.0), 2.19 (2 H, m), 2.38 (1 H, m), 2.47 (2 H, m), 3.50 (2 H, d, *J* 4.1), 4.55 (2 H, s), 4.91 (1 H, m), 7.34 (6 H, m), 9.37 (1 H, br); δ_C($CDCl_3$) 12.5, 28.0, 31.3, 46.0, 72.3, 73.4, 110.8, 127.8, 127.9, 128.6, 137.0, 138.5, 151.1, 164.1.

1-[*cis*-3-(Hydroxymethyl)cyclobutyl]uracil 13a

1-[*cis*-3-(Benzyloxymethyl)cyclobutyl]uracil **28a** (0.80 g, 2.8 mmol), 10% palladium on activated carbon (0.40 g), formic

acid (3 cm^3) and methanol (27 cm^3) were stirred together at room temperature. After 3 h, the products were filtered and the filtrate was evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane–methanol (97:3 to 95:5 v/v) were combined and evaporated under reduced pressure to give the *title compound* **13a** as a colourless solid (0.52 g, 94%) [Found, in material recrystallized from ethyl acetate–light petroleum (distillation range 40–60 °C): C, 54.75; H, 5.96; N, 14.12. $C_9H_{12}N_2O_3$·0.1H_2O requires C, 54.59; H, 6.21; N, 14.15%], mp 171–172 °C; R_f 0.37 (system D); $\lambda_{max}(H_2O)$/nm 268 (ε 10 000); λ_{min}/nm 233 (ε 1460); $\delta_H[(CD_3)_2SO]$ 1.97 (2 H, m), 2.15 (1 H, m), 2.26 (2 H, m), 3.40 (2 H, t, *J* 5.2), 4.62 (2 H, m), 5.59 (1 H, d, *J* 8.0), 7.74 (1 H, d, *J* 8.0), 11.20 (1 H, br); $\delta_C[(CD_3)_2SO]$ 29.7, 30.9, 46.4, 63.7, 100.9, 142.0, 150.7, 163.2.

1-[*cis*-3-(Hydroxymethyl)cyclobutyl]thymine 13b

1-[*cis*-3-(Benzyloxymethyl)cyclobutyl]thymine **28b** (0.60 g, 2.0 mmol), 10% palladium on activated carbon (0.30 g), formic acid (2 cm^3) and methanol (18 cm^3) were stirred together at room temperature. After 3 h, the products were worked up and fractionated as in the above preparation of 1-[*cis*-3-(hydroxymethyl)cyclobutyl]uracil **13a** to give the *title compound* **13b** as a colourless solid (0.39 g, 93%) [Found, in material recrystallized from ethyl acetate–light petroleum (distillation range 40–60 °C): C, 56.38; H, 6.61; N, 13.06. $C_{10}H_{14}N_2O_3$·0.15 H_2O requires C, 56.41; H, 6.77; N, 13.16%], mp 149–151 °C; R_f 0.48 (system D); $\lambda_{max}(H_2O)$/nm 274 (ε 9600); λ_{min}/nm 238 (ε 1780); $\delta_H[(CD_3)_2SO]$ 1.80 (3 H, d, *J* 1.0), 1.98 (2 H, m), 2.14 (1 H, m), 2.25 (2 H, m), 3.42 (2 H, d, *J* 5.1), 4.63 (2 H, m), 7.61 (1 H, m), 11.17 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 12.0, 29.7, 31.0, 46.1, 63.9, 108.6, 137.5, 150.6, 163.8.

1-[*cis*-3-(Hydroxymethyl)cyclobutyl]cytosine 14

1-[*cis*-3-(Hydroxymethyl)cyclobutyl]uracil **13a** (0.196 g, 1.0 mmol), 1-methylpyrrolidine (1.0 cm^3, 9.6 mmol), chlorotrimethylsilane (0.38 cm^3, 3.0 mmol) and dry acetonitrile (5 cm^3) were stirred at room temperature. After 1 h, the reactants were cooled to 0 °C (ice–water bath) and trifluoroacetic anhydride (0.7 cm^3, 5.0 mmol) was added dropwise over a period of 5 min. After a further period of 30 min at 0 °C, 4-nitrophenol (0.42 g, 3.0 mmol) was added, and the cooled reactants were stirred for 3 h more. The products were then poured into saturated aqueous sodium hydrogen carbonate (20 cm^3) and the resulting mixture was extracted with dichloromethane (3 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in dioxane (10 cm^3) and concentrated aqueous ammonia (*d* 0.88, 2.5 cm^3) was added. The reactants were heated in a sealed flask at 50 °C for 24 h. The resulting yellow solution was concentrated under reduced pressure and the residue was co-evaporated with absolute ethanol (3 × 10 cm^3). The residue was fractionated by short column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane–methanol–triethylamine (96.5:3:0.5 to 91.5:8:0.5 v/v) were combined and concentrated under reduced pressure to give the *title compound* **14** as a colourless solid (0.164 g, 84%) (Found, in material recrystallized from ethanol–ethyl acetate: C, 54.96; H, 6.73; N, 21.22. $C_9H_{13}N_3O_2$·0.1H_2O requires C, 54.87; H, 6.75; N, 21.33%), mp 202–205 °C; R_f 0.05 (system D); $\delta_H[(CD_3)_2SO]$ 1.87 (2 H, m), 2.13 (1 H, m), 2.25 (2 H, m), 3.39 (2 H, t, *J* 5.2), 4.57 (1 H, m), 4.63 (1 H, m), 5.70 (1 H, d, *J* 7.3), 6.99 (2 H, br), 7.66 (1 H, d, *J* 7.3); $\delta_C[(CD_3)_2SO]$ 29.7, 31.2, 46.9, 63.9, 93.2, 142.2, 155.6, 165.3.

Acknowledgements

We thank Professor Jan Balzarini of the Rega Institute, Leuven, Belgium and Dr Naheed Mahmood of the MRC Collaborative Centre, Mill Hill for carrying out the biological tests.

References

1 I. M. Buck, A. Eleuteri and C. B. Reese, *Tetrahedron*, 1994, **50**, 9195.
2 V. Kaiwar, C. B. Reese, E. J. Gray and S. Neidle, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2281.
3 E. Wyrzykiewicz, M. Stobiecki and K. Golankiewicz, *Pol. J. Chem.*, 1981, **55**, 1673.
4 Y. Mizuno, M. Ikehara and K. A. Watanabe, *Chem. Pharm. Bull. Jpn.*, 1962, **10**, 647.
5 D. J. Brown and K. Shinozuka, *Aust. J. Chem.*, 1980, **33**, 1147.
6 A. R. Lapucka, *Synthesis*, 1987, 256.
7 K. Kaneko, H. Katayama, T. Wakabayashi and T. Kumonaka, *Synthesis*, 1988, 152.
8 K. A. Cruickshank, J. Jiricny and C. B. Reese, *Tetrahedron Lett.*, 1984, **25**, 681.
9 O. Mitsunobu, *Synthesis*, 1981, 1.
10 B. D. Johnston, E. Czyzewska and A. C. Oehlschlager, *J. Org. Chem.*, 1987, **52**, 3693.
11 P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney and N. Thompson, *Synthesis*, 1987, 1015.
12 K. A. Cruickshank, Ph.D. Thesis, London University, 1982, p. 43.
13 B. ElAmin, G. M. Anantharamaiah, G. P. Royer and E. G. Means, *J. Org. Chem.*, 1979, **44**, 3442.
14 J. L. Wong and D. S. Fuchs, *J. Org. Chem.*, 1970, **35**, 3786.
15 R. Fathi, B. Goserami, P.-P. Kung, B. L. Gaffney and R. A. Jones, *Tetrahedron Lett.*, 1990, **31**, 319.
16 A. Miah, C. B. Reese and Q. Song, *Nucleosides & Nucleotides*, 1997, **16**, 53.

Paper 8/03878C
Received 22*nd May* 1998
Accepted 26*th June* 1998