C-Nucleoside Studies. Part 20.[1] Synthesis of Some Pyrazolo[4,3-*d*]pyrimidine Acyclonucleosides Related to (*S*)-(2,3,Dihydroxypropyl)adenine; A Direct Method for Double Functionalization of the Pyrazole Ring

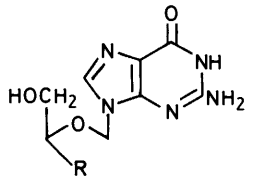
J. Grant Buchanan, Mark Harrison, and Richard H. Wightman
Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS
Michael R. Harnden
Beecham Pharmaceuticals Research Division, Biosciences Research Centre, Great Burgh, Epsom, Surrey KT18 5XQ

Treatment of 3(5)-alkylpyrazoles with ammonium nitrate and trifluoroacetic anhydride in trifluoroacetic acid gives 3-alkyl-1,4-dinitropyrazoles directly. This procedure, in conjunction with *cine*-substitution, offers a direct route for double functionalisation of the pyrazole ring.

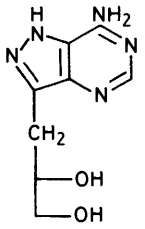
3(5)-Cyano-5(3)-[(*S*)-2,3-diacetoxypropyl]-4-nitropyrazole (**13**), prepared in this way, was elaborated into 5-amino-3-[(*S*)-2,3-dihydroxypropyl]-1*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one (**5**), 7-amino-3-[(*S*)-2,3-dihydroxypropyl]-1*H*-6-methylpyrazolo[4,3-*d*]pyrimidin-5(6*H*)-one (**6**), its *N*-demethyl analogue (**7**), and 4-amino-5-carbamoyl-3-[(*S*)-2,3-dihydroxypropyl]pyrazole (**8**), all of which are *C*-nucleoside analogues of the antiviral agent (*S*)-9-(2,3-dihydroxypropyl)adenine (**4**).

The discovery that acyclic analogues of the normal nucleosides, such as 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir) (**1**) and 9-[(1,3-dihydroxypropan-2-yloxy)methyl]guanine (ganciclovir) (**2**) possess potent, selective, antiherpes activity has led to extensive efforts to synthesize compounds of this type.[2] Amongst the analogues prepared have been acyclo-*C*-nucleosides, containing a carbon–carbon link between the heterocycle and the aliphatic unit.[2] A previous paper in this series has reported the synthesis of 7-amino-3-[(*S*)-2,3-dihydroxypropyl]-1*H*-pyrazolo[4,3-*d*]pyrimidine (**3**),[3] a carbon-linked analogue of the antiviral acyclonucleoside (*S*)-DHPA (**4**);[4] analogue (**3**) contains the chromophore of the *C*-nucleoside antibiotic formycin.[5] Since many of the most significant antiviral acyclonucleosides are guanine derivatives, we undertook to adapt our earlier work[3] towards the synthesis of the guanine-type analogue (**5**); in this paper we report the synthesis of compound (**5**), together with the 'isoguanine' analogues (**6**) and (**7**) and the pyrazole (**8**). Other workers have reported the synthesis of the pyrazolo[4,3-*d*]pyrimidine analogue (**9**) of acyclovir,[6,7] and the *N*-methyl derivative (**10**).[8] During the course of our work we have also uncovered a very direct route for the double functionalisation of the pyrazole ring.

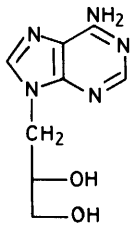
In our earlier synthesis of compound (**3**), the pyrazole derivative (**11**), readily accessible in chiral form,[3] was converted *via* a multistep procedure into the 1,4-dinitropyrazole (**12**). This sequence involved, *inter alia*, the conversion of (**11**) into its 1-(2,4-dinitrophenyl) (DNP) derivative, and stepwise introduction of the *C*- and *N*-nitro groups, the *C*-nitration being carried out by use of ammonium nitrate in trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA). The dinitropyrazole (**12**) could then be converted[3] into the nitro nitrile (**13**) by *cine*-substitution[9] with cyanide ion in aqueous ethanol (Scheme 1).



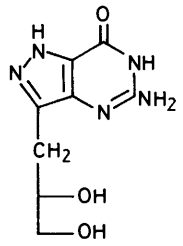
(**1**) R = H
(**2**) R = CH_2OH



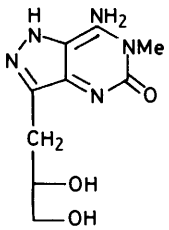
(**3**)



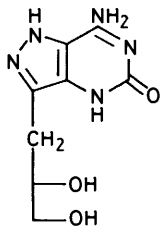
(**4**)



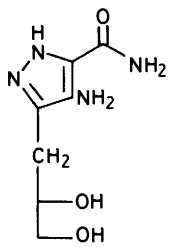
(**5**)



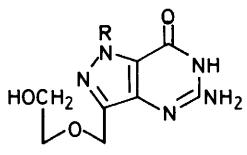
(**6**)



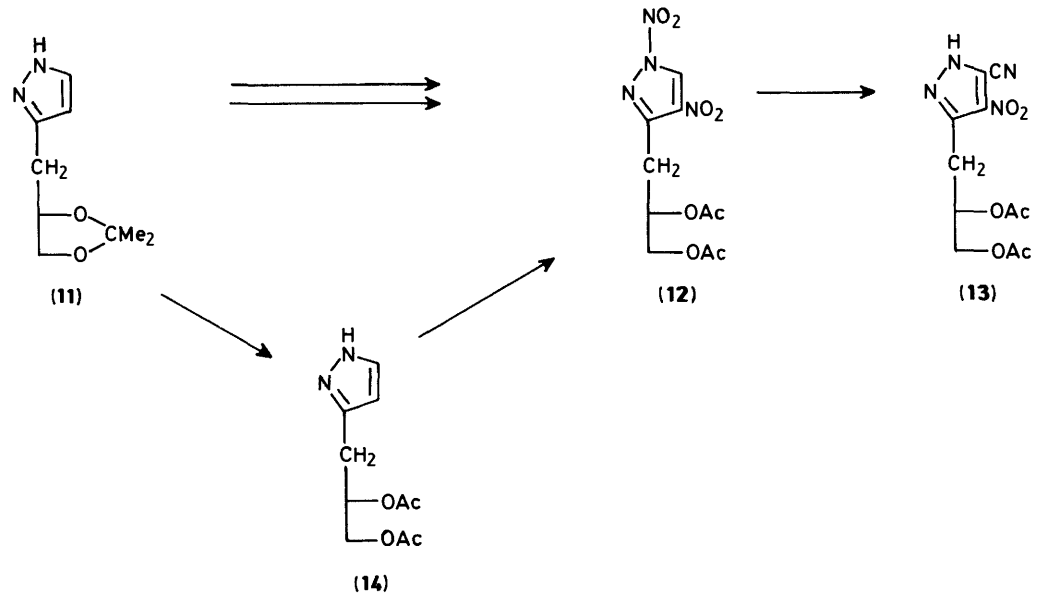
(**7**)



(**8**)

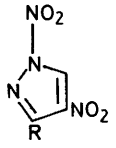


(**9**) R = H
(**10**) R = Me



Scheme 1.

Given the number of steps involved in the conversion of (**11**) into (**12**), we undertook to investigate if both *C*-and *N*-nitration could be carried out in a one-step process. We were therefore gratified to find that, when pyrazole was treated with ammonium nitrate and TFAA in TFA, 1,4-dinitropyrazole (**15**) was obtained in 75% yield. Similarly, 3-methylpyrazole under the same conditions gave an 80% yield of 3-methyl-1,4-dinitropyrazole (**16**).



(**15**) R = H
(**16**) R = Me

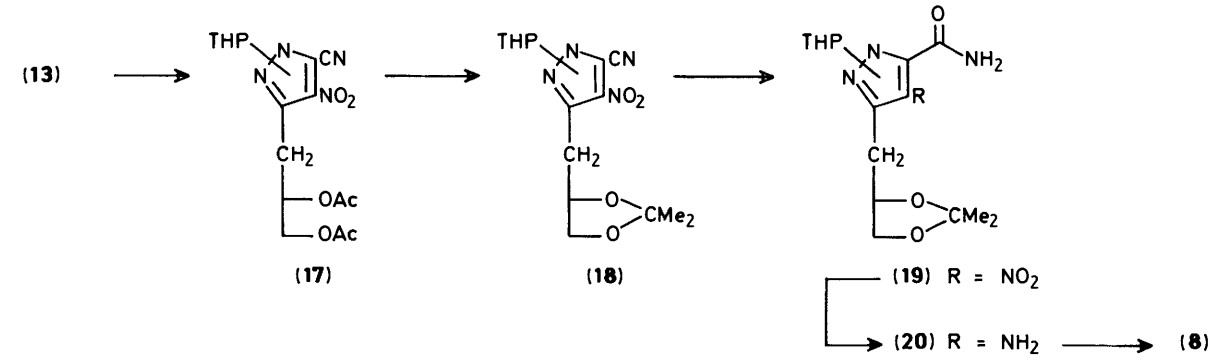
This direct route could also be applied to the synthesis of compound (**12**). Thus, compound (**11**) was converted by acid hydrolysis and acetylation into the diacetyl derivative (**14**) (Scheme 1); during the acetylation, some of the *N,O,O*-triacetyl derivative was formed, but selective deacetylation on nitrogen was easily accomplished by use of triethylamine in methanol. When diacetate (**14**) was treated with ammonium nitrate and TFAA in TFA, the dinitropyrazole (**12**) was obtained in 85% yield.

We have not studied in detail the mechanism of this double nitration, but we have observed that the use of a strong acid (TFA) as solvent is necessary, since, when 3-methylpyrazole was treated with ammonium nitrate and TFAA in dichloromethane,[10] only *N*-nitration occurred to give mostly 3-methyl-1-nitropyrazole, plus a little of the 5-methyl-1-nitro isomer. Formation of *N*-nitropyrazoles is also observed when pyrazoles unsubstituted on nitrogen are treated with nitric acid or nitrate salts in *acetic* anhydride,[11] whilst it has been known for many years that such pyrazoles give products of *C*-nitration under classical 'mixed acids' conditions.[12]

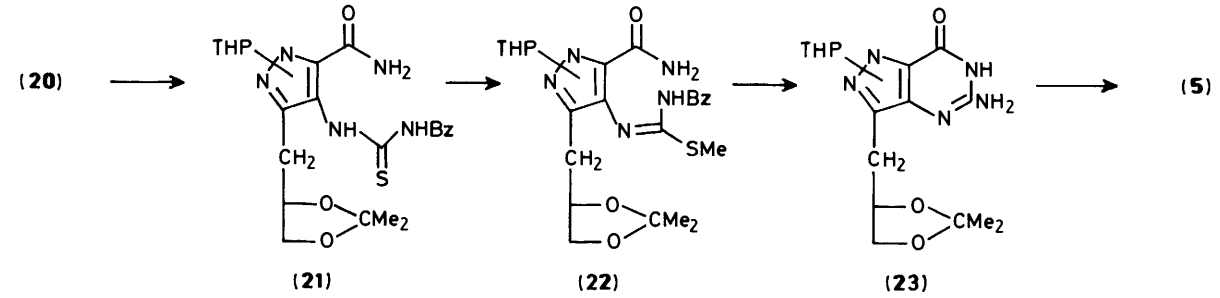
Since we have shown that the *cine*-substitution process exemplified by the conversion of (**12**) into (**13**) can be carried out with a wide range of different nucleophiles,[13] the two-step process of dinitration–*cine*-substitution would seem to offer a very direct route for the double functionalisation of the pyrazole ring.

In order to approach the synthesis of the guanosine-type analogue (**5**), we wished to convert nitro nitrile (**13**) into an analoguous amino amide [*i.e.* a protected form of (**8**)], since good methods are available for the formation of guanine derivatives from imidazoles with this type of substitution pattern,[14,15] and the earlier methodology [14] has been applied to the conversion of such pyrazoles into pyrazolo[4,3-*d*]pyrimidines with the guanosine type of substitution.[6,7,16]

In previous work in our laboratory, we had shown that it was necessary to mask the N–H bond of the pyrazole in order to carry out hydrolysis of nitrile to amide in compounds such as (**13**), and corresponding amino nitriles were equally resistant.[17] In our earlier work,[17] the tetrahydropyran-2-yl (THP) group had proved suitable, and it was again employed here. Thus, treatment of compound (**13**) with dihydropyran and toluene-*p*-sulphonic acid (PTSA) gave the *N*-THP derivative (**17**) (Scheme 2). Based on the complexity of the ^{1}H n.m.r. spectrum, with doubling of the signals for a number of positions, we formulate compound (**17**) as a mixture of two regioisomers, each of which is presumably a mixture of two diastereoisomers. Our previous experience,[17] where pure regioisomers were obtained, would not lead us to expect detectable differences in the ^{1}H n.m.r. spectrum due merely to diastereoisomers. The ^{13}C n.m.r. spectrum also showed a doubling of signals. The regioisomers could not be separated chromatographically on a preparative scale, but h.p.l.c. showed two peaks in the ratio ~3:2. Since, for a number of later steps, it was thought desirable to have base-stable protection for the sidechain, diacetate (**17**) was converted into the isopropylidene derivative (**18**) by treatment with methanolic ammonia, followed by acetone and PTSA. Hydrolysis of the nitrile to the amide (**19**) then proceeded cleanly using a solution of potassium carbonate and hydrogen peroxide in aqueous dioxane, and the amino amide (**20**) was produced quantitatively on catalytic reduction. Deprotection at this point gave target compound (**8**); it was necessary to carry out this deprotection using a cold solution of hydrogen chloride in dichloromethane,[18] use of aqueous hydrochloric acid or TFA giving a complex mixture.



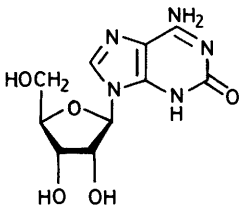
Scheme 2. THP = tetrahydropyran-2-yl



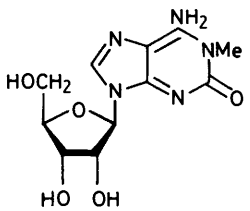
Scheme 3.

The synthesis of the guanosine analogue (**5**) then proceeded conventionally.[6,7,16] Treatment of compound (**20**) with benzoyl isothiocyanate gave the thiourea (**21**) (Scheme 3) in greater than 90% yield, and this with iodomethane and alkali gave the *S*-methyl derivative (**22**) (88%). Cyclisation was carried out by treatment with ammonia in dimethylformamide (DMF) in a sealed tube at 130 °C,[6] giving a 70% yield of compound (**23**) as an amorphous solid. Removal of the protecting groups with hydrogen chloride in dichloromethane then gave the required product (**5**).

We were prompted to prepare also the isoguanosine analogues (**6**) and (**7**) owing to the interesting biological properties of naturally occurring nucleosides of this type. Isoguanosine itself (**24**), also known as crotonoside, stimulates the accumulation of cyclic AMP in the brain, and its 5′-di- and -tri-phosphate are strong inhibitors of glutamate dehydrogenase,[19] whilst 1-methylisoguanosine (doridosine) (**25**) possesses muscle-relaxant and anti-inflammatory activity, and also lowers blood pressure.[20]



(**24**)



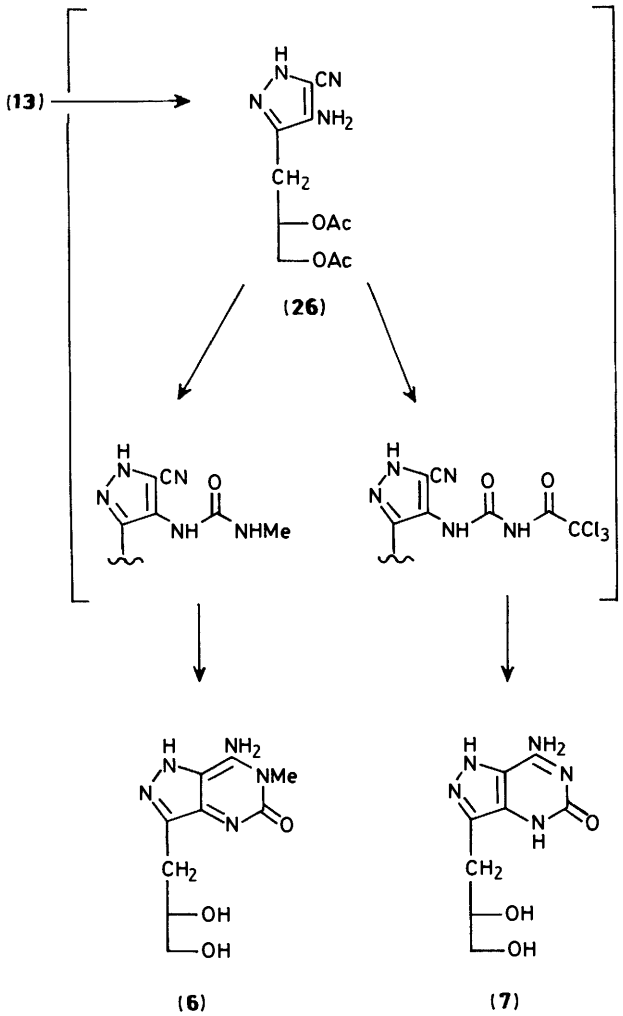
(**25**)

The nitro nitrile (**13**) served as a convenient precursor for both compounds (**6**) and (**7**). Catalytic hydrogenation gave the amino nitrile (**26**) (Scheme 4), which was without purification treated with methyl isocyanate. The resultant *N*-methylureido intermediate was cyclised by treatment with ammonia in methanol[21] to give the fluorescent pyrazolo[4,3-*d*]pyrimidinone (**6**). Similarly, amine (**26**), on treatment with trichloroacetyl isocyanate, and subsequent cyclisation–deprotection with methanolic ammonia,[21] gave the unsubstituted analogue (**7**). Both products (**6**) and (**7**) had u.v. spectra in good agreement with that of the isoguanosine analogue of formycin.[21]

Biological Data.—The novel acyclic *C*-nucleoside analogues prepared in this study (**5**)—(**8**) were tested for activity against representative RNA and DNA viruses in cell cultures. At concentrations up to 100 μg ml^{-1}, none of them inhibited the replication of influenza A (HK/1/68) virus or parainfluenza type 1 (Sendai) virus in Madin–Darby canine kidney cells, nor of herpes simplex type 1 (HFEM) virus or herpes simplex type 2 (MS) virus in Vero (African green monkey kidney) cells. At the concentrations examined, none of the compounds was toxic to the cell monolayer.

Experimental

I.r. spectra were recorded on Perkin-Elmer 157G or 580 instruments; u.v. spectra were obtained on a Shimadzu u.v.-240 spectrophotometer. Mass spectrometry was performed using an updated M.S.9, or VG 70-70 and ZAB instruments. N.m.r. spectra were recorded on Perkin-Elmer R12B, Bruker WP 80SY and WP 200SY and JEOL 270 MHz spectrometers with deuteriochloroform as solvent unless otherwise stated. Primed locants refer to the sidechain atoms. Specific rotations were measured at room temperature on a Bendix-NPL 143D automatic polarimeter (path length 1 cm). M.p.s were determined in capillaries and are uncorrected. Adsorption chromatography was carried out on Kieselgel H type 60 (Merck 7734); an external pressure was applied to the top of columns. For t.l.c., pre-coated aluminium-backed plates [Kieselgel HF_{254} type 60 (Merck)] were used. Light petroleum refers to material of b.p. 40—60 °C. Organic extracts were dried with anhydrous magnesium sulphate.



Scheme 4.

1,4-*Dinitropyrazole* (**15**).—To an ice-cold, stirred solution of pyrazole (68 mg, 1 mmol) and ammonium nitrate (360 mg) in TFA (4 ml) was added dropwise TFAA (0.63 ml). The mixture was allowed to warm to room temperature and, after 18 h, was poured onto ice–water. Extraction with dichloromethane, washing (aq. $NaHCO_3$), drying, and evaporation gave a yellow oil, which was chromatographed on silica, and eluted with light petroleum–acetone (2:1) followed by pure acetone to give 1,4-dinitropyrazole (**15**) (120 mg, 75%) as an oil; $\nu_{max.}$ 1 640, 1 270 (N–NO_2), 1 530 and 1 315 cm^{-1} (C–NO_2); δ_H (60 MHz) 8.21 (1 H, s, 3-H) and 9.12 (1 H, s, 5-H). Material prepared by the literature procedure[22] had identical properties.

3-*Methyl*-1,4-*dinitropyrazole* (**16**).—Treatment of 3-methylpyrazole (82 mg, 1 mmol) as described above gave the dinitro compound (**16**) (170 mg, 80%), m.p. 47—48 °C (from hexane) (lit.,[11a] 48 °C); $\nu_{max.}$ 1 630, 1 270 (N–NO_2) 1 560 and 1 315 cm^{-1} (C–NO_2); δ_H (60 MHz) 2.36 (3 H, s, Me) and 9.00 (1 H, s, 5-H).

3(5)-[(S)-*Diacetoxypropyl*]*pyrazole* (**14**).—A solution of isopropylidene derivative (**11**) (2 g) in TFA–water (9:1) was stirred overnight. The residue after evaporation was treated with acetic anhydride (50 ml) and pyridine (100 ml) overnight. The mixture was poured onto iced water and extracted with dichloromethane. The organic extracts were evaporated to give a syrup, which contained both title compound (**14**) and the *N,O,O*-triacetyl derivative. This mixture was treated with triethylamine (1 ml) in methanol (100 ml) overnight. Evaporation and chromatography on silica, with hexane–acetone (3:1) as eluant, gave the *di*-O-*acetyl derivative* (**14**) (2.05 g, 84%) as a syrup, $[\alpha]_D$ 5.0° (*c* 1 in $CHCl_3$); $\nu_{max.}$(film) 3 200 (NH) and 1 740 cm^{-1} (OAc); δ_H (200 MHz) 2.02, 2.04 (each 3 H, s, OAc), 3.0 (2 H, m, 1′-H_2), 4.25 (1 H, dd, *J* 11.9, 8.5 Hz, 3′-H_a), 4.45 (1 H, dd, *J* 11.9, 5.8 Hz, 3′-H_b), 5.30 (1 H, m, 2′-H), 6.13 (1 H, d, *J* 2.2 Hz, 4-H), and 7.52 (1 H, d, *J* 2 Hz, 5-H); δ_C (50 MHz) 20.68, 20.96 (Me), 28.94 (C-1′), 64.30 (C-3′), 70.84 (C-2′), 104.81 (C-4), 132.45 (C-5), 144.58 (C-3), 170.72 and 170.36 (CO) [Found: C, 53.2; H, 6.2; N, 12.1. $C_{10}H_{14}N_2O_4$ requires C, 53.1; H, 6.2; N, 12.4%. Found: $(M+H)^+$, 227.103 $C_{10}H_{15}N_2O_4$ requires *m/z*, 227.103].

3-[(S)-2,3-*Diacetoxypropyl*]-1,4-*dinitropyrazole* (**12**).—To a solution of diacetate (**14**) (5.3 g) and ammonium nitrate (8.4 g) in TFA (100 ml), cooled in an ice-bath, was added dropwise TFAA (15 ml). The mixture was allowed to warm to room temperature overnight, poured onto ice–water, and extracted with dichloromethane. The washed (aq. $NaHCO_3$), dried extract was evaporated to give a pale yellow oil, which was subjected to flash chromatography with light petroleum–ethyl acetate (7:3) as eluant to give the dinitro compound (**12**) (6.5 g, 87%) as a pale yellow oil, with properties identical with those of previously prepared material.[3]

5-*Cyano*-3-[(S)-2,3-*diacetoxypropyl*]-4-*nitro*-1- *and* -2-(*tetrahydropyran*-2-*yl*)-1H- *and* -2H-*pyrazole* (**17**).—A solution of nitro nitrile (**13**)[3] (2.54 g), PTSA (0.32 g), and dihydropyran (2.7 ml) in dichloromethane (50 ml) was stirred overnight, after which it was neutralised with anhydrous sodium carbonate, filtered, and evaporated. Chromatography on silica, with light petroleum–acetone (4:1) as eluant, gave the *THP derivative* (**17**) (2.65 g, 70%) as a syrup; $\nu_{max.}$(film) 2 250 (C≡N), 1 740 (CO), 1 525 and 1 370 cm^{-1} (C–NO_2); δ_H (270 MHz) 1.70 (4 H, m, THP), 1.99, 2.03, 2.06, and 2.10 (total 6 H, 4 s, OAc), 2.16 (1 H, m, THP), 2.44 (1 H, m, THP), 3.49 (2 H, m, 1′-H_2), 3.70 (1 H, m, THP 6-H), 3.88 (1 H, m, THP 6-H), 4.12 (1 H, dd, *J* 12, 5 Hz, 3′-H_a), 4.27 (1 H, dd, *J* 12, 5 Hz, 3′-H_b), 5.32 (1 H, m, 2′-H), and 5.66 (1 H, m, THP 2-H); δ_C (68 MHz) 20.59, 20.64, 20.69, and 21.27 (Me), 21.48, 21.72, 25.53, 26.25, and 26.39 (THP C-3, -4, -5), 28.04 and 28.89 (C-1′), 63.93 and 64.11 (C-3′), 67.12 and 67.87 (C-2′), 69.21 and 70.01 (THP C-6), 85.95 and 86.33 (THP C-2), 110.49 and 110.52 (C-3), 121.54 and 121.86 (CN), 139.97 and 140.97 (C-4 and -5), 169.68, 170.19, 170.31, and 170.35 (CO); *m/z* (FAB) 381 $(M+H)^+$ and 403 $(M+Na)^+$ (Found: C, 50.6; H, 5.4; N, 14.4. $C_{16}H_{20}N_4O_7$ requires C, 50.5; H, 5.2; N, 14.7%).

5-*Cyano*-3-[(S)-2,3-*isopropylidenedioxypropyl*]-4-*nitro*-1-*and* -2-(*tetrahydropyran*-2-*yl*)-1H- *and* -2H-*pyrazole* (**18**).—Ammonia was passed into an ice-cold solution of diacetyl compound (**17**) (1.3 g) in methanol (50 ml) until saturation. The mixture was left overnight in a refrigerator, evaporated to dryness, and the residue was treated overnight with PTSA (0.15 g) in acetone (50 ml). After neutralisation (anhydrous Na_2CO_3), filtration, and evaporation, the resultant syrup was chromatographed on silica, with light petroleum–acetone (4:1) as eluant, to give the *isopropylidene derivative* (**18**) (0.75 g, 68%) as a syrup; $\nu_{max.}$(film 2 240 (C≡N), 1 560 and 1 360 (C–NO_2), and 1 380 cm^{-1} (CMe_2); δ_H (270 MHz) 1.19, 1.29, and 1.33 (6 H, 3 s, CMe_2), 1.6—1.8 (3 H, m, THP), 2.0 (1 H, m, THP), 2.2 (1 H, m, THP), 2.4 (1 H, m, THP), 3.15 (1 H, dd, *J* 14, 10 Hz, 1′-H_a), 3.52 (1 H, m, 1′-H_b), 3.7 (2 H, m, 3′-H_a and THP 6-H), 4.0 (1 H, m, THP 6-H), 4.2 (1 H, m, 3′-H_b), 4.4 (1 H, m, 2′-H), and 5.8 (1 H, m, THP 2-H); δ_C (68 MHz) 24.51 and 24.86 (THP C-4), 25.39, 26.29, 26.67, and 27.04 (CMe_2), 28.08, 28.28, 29.76, 67.49, 67.55, 67.70, 69.23, 73.51, 73.88, 85.64, 86.31, 109.48 (CMe_2), 110.09 and 110.66 (C-3), 121.59 (CN), 142.06 and 142.76 (C-4 and

-5) [Found: $(MH)^+$, 337.1504. $C_{15}H_{21}N_4O_5$ requires *m/z*, 337.1512].

5-*Carbamoyl*-3-[(S)-2,3-*isopropylidenedioxypropyl*]-4-*nitro*-1- *and* -2-(*tetrahydropyran*-2-*yl*)-1H- *and* -2H-*pyrazole* (**19**).—Aqueous hydrogen peroxide (25 ml; 30% w/v) was added dropwise to an ice-cold, stirred solution of nitro nitrile (**18**) (1.0 g) and potassium carbonate (1.43 g) in aqueous dioxane (15 ml; 55% v/v). After 1 h, the mixture was neutralised with aqueous acetic acid and partitioned between water and ethyl acetate. The dried organic phase was evaporated to give a syrup, which was chromatographed on silica with light petroleum–acetone (4:1) as eluant to give the *nitro amide* (**19**) (0.6 g, 60%) as a foam; $\nu_{max.}$(KBr) 3 420, 1 700 ($CONH_2$), 1 550 and 1 320 ($C-NO_2$), and 1 340 cm^{-1} (CMe_2); δ_H (200 MHz) 1.25, 1.30, and 1.36 (6 H, 3 s, CMe_2), 1.6—1.8 (3 H, m, THP), 1.92 (1 H, m, THP), 2.15 (1 H, m, THP), 2.45 (1 H, m, THP), 3.00 (1 H, dd, *J* 12, 10 Hz, 1′-H_a), 3.40 (1 H, dd, *J* 10, 5 Hz, 1′-H_b), 3.65 (2 H, m, 3′-H_a and THP 6-H), 4.1—4.2 (2 H, m, 3′-H_b and THP 6-H), 4.42 (1 H, m, 2′-H), 5.69 (1 H, m, THP 2-H), 6.0 and 6.8 (each 1 H, br s, exchangeable with D_2O, NH_2); δ_C (50 MHz) 24.63, 24.75, 25.54, 26.38, 26.69, 27.20, 28.46, 28.71, 29.61, 67.85 and 69.20 (C-3′), 73.33 and 74.06 (C-2′), 76.70 and 77.32 (THP C-6), 85.15 and 85.88 (THP C-2), 109.31 and 109.87 (CMe_2), 132.00 (C-3), 140.58 and 142.00 (C-4 and -5), 161.06 and 161.23 ($CONH_2$) [Found: $(MH)^+$, 355.1621. $C_{15}H_{23}N_4O_6$ requires *m/z*, 355.1617].

4-*Amino*-5-*carbamoyl*-3-[(S)-2,3-*isopropylidenedioxypropyl*]-1- *and* -2-(*tetrahydropyran*-2-*yl*)-1H- *and* -2H-*pyrazole* (**20**).—The nitro amide (**19**) (0.5 g) was hydrogenated at 1 atm in ethanol (50 ml), using palladium–charcoal (10%) as catalyst. After filtration through Celite and evaporation, the residue was chromatographed on silica with light petroleum–acetone (4:1) as eluant to give *amino amide* (**20**) (0.45 g, 99%) as a solid, m.p. 64—66 °C; $\nu_{max.}$(KBr) 3 420, 3 330, 3 180, 1 670 (CO) and 1 370 cm^{-1} (CMe_2); δ_H (200 MHz) 1.36 and 1.37 (each 3 H, s, CMe_2), 1.55—1.7 (3 H, m, THP), 1.9 (1 H, m, THP), 2.1 (1 H, m, THP), 2.35 (1 H, m, THP), 2.82 (1 H, dd, *J* 15, 6 Hz, 1′-H_a), 3.02 (1 H, dd, *J* 15, 5 Hz, 1′-H_b), 3.65 (2 H, m, 3′-H_a and THP 6-H), 3.95 and 4.0 (each 1 H, m, 3′-H_b and THP 6-H), 4.32 (3 H, m, becomes 1 H, m on D_2O shake, 2′-H and 4-NH_2), 5.27 (1 H, m, THP 2-H), 5.30 and 6.67 (each 1 H, br s, exchangeable, $CONH_2$) (Found: M^+, 324.176. $C_{15}H_{24}N_4O_4$ requires *M*, 324.179).

4-*Amino*-3(5)-*carbamoyl*-5(3)-[(S)-2,3-*dihydroxypropyl*)*pyrazole* (**8**).—Hydrogen chloride gas was passed for 15 min into a solution of compound (**20**) (80 mg) in dichloromethane (10 ml) cooled in ice–salt. The reaction vessel was stoppered and, after 2 h, the mixture was evaporated to dryness. The residue was treated with triethylamine in DMF, and again evaporated. Chromatography on silica, with dichloromethane–methanol (4:1) as eluant, gave the *diol* (**8**) (45 mg, 55%) as an amorphous solid; $\nu_{max.}$(KBr) 3 200br (OH, NH) and 1 650 cm^1 (amide); δ_H (200 MHz; D_2O) 2.70 (1 H, dd, *J* 15, 5 Hz, 1′-H_a), 2.82 (1 H, dd, *J* 15, 8 Hz, 1′-H_b), 3.55 (1 H, dd, *J* 12, 6 Hz, 3′-H_a), 3.64 (1 H, dd, *J* 12, 3 Hz, 3′-H_b), and 3.90 (1 H, m, 2′-H) (Found: M^+, 200.0904. $C_7H_{12}N_4O_3$ requires *M*, 200.0909).

4-[N′-*Benzoyl*(*thioureido*)]-5-*carbamoyl*-3-[(S)-2,3-*isopropylidenedioxypropyl*]-1- *and* -2-(*tetrahydropyran*-2-*yl*)-1H-*and*-2H-*pyrazole* (**21**).—To a stirred, ice-cold solution of amino amide (**20**) (0.3 g) in DMF (5 ml) was added dropwise benzoyl isothiocyanate (0.15 ml). The mixture was allowed to warm to room temperature overnight, after which it was poured into water and extracted with ethyl acetate. The dried extracts were evaporated, and the oily residue was chromatographed on silica, with light petroleum–acetone (3:1) as eluant. Recrystallisation (ether) of the residue obtained after evaporation gave the *benzoyl*(*thioureido*) *derivative* (**21**) (0.36 g, 90%), m.p. 104—107 °C; $\nu_{max.}$(KBr) 3 450 and 3 320 ($CONH_2$), 1 670 (CO), 1 380 (CMe_2), and 1 160 cm^{-1} (C=S); δ_H (200 MHz) 1.30, 1.33, and 1.45 (6 H, 3 s, CMe_2), 1.5—1.7 (3 H, m, THP), 1.9 (1 H, m, THP) 2.1 (1 H, m, THP), 2.4 (1 H, m, THP), 3.10 (2 H, m, 1′-H_2), 3.65 (2 H, m, 3′-H_a and THP 6-H), 4.0 and 4.05 (each 1 H, m, 3′-H_b and THP 6-H), 4.35 (1 H, m, 2′-H), 5.35 and 6.75 (each 1 H, br s, exchangeable, $CONH_2$), 6.50 (1 H, m, THP 2-H), 7.55 (3 H, m, Ph), 7.90 (2 H, m, Ph), 9.2 and 12.1 (each 1 H, br s, exchangeable, NH); δ_C (50 MHz) 24.88, 25.43, 25.64, 27.72, 26.87, 28.73, 28.94, 29.10, 29.73, 67.42, 68.72, 69.27, 73.93, 74.38, 85.01, 85.36, 109.44 and 109.58 (CMe_2), 119.94, 120.48, 127.66, 129.07, 131.89, 133.49, 138.56, 138.68, 163.62 ($CONH_2$), 166.32 (Ph*C*ON), 180.68 (C=S); *m/z* (FAB) $(MH)^+$ 488, $(MNa)^+$ 510; *m/z* (EI) 324 (*M*-PhCONCS)$^+$ [Found: (*M* − PhCONCS)$^+$, 324.1799. $C_{15}H_{24}N_4O_4$ requires *m/z*, 324.1799].

4-(N-*Benzoyl*-S-*methyl*-3-*isothioureido*)-5-*carbamoyl*-3-[(S)-2,3-*isopropylidenedioxypropyl*]-1- *and* -2-(*tetrahydropyran*-2-*yl*)-1H- *and* -2H-*pyrazole* (**22**).—To a stirred solution of the thiourea (**21**) (0.3 g) in DMF (2.5 ml) was added aqueous sodium hydroxide (0.1M; 6.7 ml) followed by iodomethane (0.06 ml). After 4 h, partition between water and dichloromethane, evaporation of the dried organic phase, and chromatography on silica, with light petroleum–acetone (3:1) as eluant, gave a white solid, which was crystallised from ether to give the S-*methyl derivative* (**22**) (0.267 g, 88%), m.p. 144—147 °C; $\nu_{max.}$(KBr) 3 470 and 3 330 ($CONH_2$), 1 690 (CO), and 1 375 cm^{-1} (CMe_2); δ_H (200 MHz) 1.25, 1.29, 1.35, and 1.48 (6 H, 4 s, CMe_2), 1.5—1.7 (3 H, m, THP), 2.0 (1 H, m, THP), 2.15 (1 H, m, THP), 2.40 (3 H, s, SMe), 2.45 (1 H, m, THP), 2.96 (2 H, m, 1′-H_2), 3.60 and 3.65 (each 1 H, m, 3′-H_a and THP 6-H), 4.10 and 4.15 (each 1 H, m, 3′-H_b and THP 6-H), 4.30 (1 H, m, 2′-H), 5.30 and 6.70 (each 1 H, br s, exchangeable, $CONH_2$), 5.70 (1 H, m, THP 2-H), 6.90 (1 H, br s, exchangeable, NH), 7.40 (3 H, m, Ph), and 8.30 (2 H, m, Ph); $\lambda_{max.}$(MeOH) 245 (ε 4 360 l mol^{-1} cm^{-1}) and 380 nm (6 620) (Found: C, 57.6; H, 6.3; N, 13.9; S, 6.2. $C_{24}H_{31}N_5O_5S$ requires C, 57.5; H, 6.2; N, 14.0; S. 6.4%).

5-*Amino*-1H- *and* 2H-3-[(S)-2,3-*isopropylidenedioxypropyl*]-1- *and* -2-(*tetrahydropyran*-2-*yl*)*pyrazolo*[4,3-d]*pyrimidin*-7-(6H)-*one* (**23**).—The *S*-methyl compound (**22**) (0.25 g) was dissolved in ice-cold DMF, and ammonia was passed into the solution for 0.5 h. The reaction vessel was sealed and heated at 130 °C for 4 h. Evaporation, and recrystallisation of the residue from ether, gave the *pyrazolopyrimidinone* (**23**) (0.13 g, 75%), m.p. 130 °C (decomp.); $\nu_{max.}$ 3 350, 3 150, 1 690, 1 640, and 1 380 cm^{-1}; δ_H (200 MHz) 1.22, 1.25, 1.31, and 1.47 (6 H, 4 s, CMe_2), 1.6—1.8 (3 H, m, THP), 1.95, 2.1, and 2.5 (each 1 H, m, THP), 3.2 (2 H, m, 1′-H_2), 3.7 (2 H, m, 3′-H_a, and THP 6-H), 4.05 (2 H, m, 3-H_b and THP 6-H), 4.70 (1 H, m, 2′-H), and 5.75 (1 H, m, THP 2-H) (Found: M^+, 349.1749. $C_{16}H_{23}N_5O_4$ requires *M*, 349.1750).

5-*Amino*-3-[(S)-2,3-*dihydroxypropyl*]-1H-*pyrazolo*[4,3-d]-*pyrimidin*-7(6H)-*one* (**5**).—Hydrogen chloride gas was passed for 3 min into an ice-cold solution of compound (**23**) (30 mg) in dichloromethane (5 ml). After 2 h, the solvent was evaporated off and the residue was treated with triethylamine and DMF and re-evaporated. The residue was adsorbed onto silica and applied to the top of a chromatography column which was then eluted with dichloromethane–methanol (4:1) to give the *pyrazolopyrimidinone* (**5**) (13 mg, 68%) as a hygroscopic powder; δ_H (200 MHz; D_2O) 2.92 (2 H, m, 1′-H_2), 3.45 (1 H, dd, *J* 12, 7 Hz, 3′-H_a), 3.57 (1 H, dd, *J* 12, 4 Hz, 3′-H_b), and 4.00 (1 H, m, 2′-H); $\lambda_{max.}$(pH 1) 280 nm; $\lambda_{max.}$(pH 11) 298 nm (Found: M^+, 224.0861. $C_8H_{11}N_5O_3$ requires *M*, 225.0862).

7-*Amino*-3-[(S)-2,3-*dihydroxypropyl*]-6-*methyl*-1H-*pyrazolo*[4,3-*d*]*pyrimidin*-5(6H)-*one* (**6**).—Nitro nitrile (**13**) (0.35 g) in ethanol (20 ml) was hydrogenated using 10% palladium–charcoal as catalyst. The mixture was filtered through Celite and evaporated. The crude amine (**26**) was dissolved in DMF (10 ml) and treated at 0 °C with methyl isocyanate (1 ml). After 3 h, the mixture was evaporated to dryness, and the residue was treated with ammonia in methanol for 60 h. Evaporation, and chromatography of the residue on silica, with dichloromethane–methanol (4:1) as eluant, gave the *diol* (**6**) (0.16 g, 57%) as a yellow powder, m.p. 210 °C; $\nu_{max.}$(KBr) 3 450, 3 260, 3 190, and 1 690 cm^{-1}; δ_H [200 MHz; $(CD_3)_2SO$] 2.70 (1 H, dd, *J* 15, 10 Hz, 1′-H_a), 2.82 (1 H, dd, *J* 15, 5 Hz, 1′-H_b), 3.25 (3 H, s, NMe), 3.29 (2 H, m, 3′-H_2), 3.65 (1 H, m, 2′-H), 4.04 (1 H, br s, exchangeable, NH), and 4.80 and 7.80 (each 2 H, br s, exchangeable, NH_2, OH); $\lambda_{max.}$(H_2O) 248 (4 620) and 298 nm (2 900); $\lambda_{max.}$(pH 1) 248 (11 900) and 296 nm (2 900); $\lambda_{max.}$(pH 13) 253 (3 450) and 310 nm (2 230) (Found: M^+, 239.102. $C_9H_{13}N_5O_3$ requires *M*, 239.102).

7-*Amino*-3-[(S)-2,3-*dihydroxypropyl*]-1H-*pyrazolo*[4,3-d]-*pyrimidin*-5(4H)-*one* (**7**).—Treatment of nitro nitrile (**13**) (0.35 g) in the same way as for the preparation of compound (**6**), but using trichloroacetyl isocyanate (1 ml) instead of methyl isocyanate, gave the *pyrazolopyrimidinone* (**7**) (0.165 g, 62%) as an amorphous yellow solid; $\nu_{max.}$(KBr) 3 250br and 1 640 cm^{-1}; δ_H (200 MHz; D_2O) 2.81 (1 H, dd, *J* 14, 8 Hz, 1′-H), 2.99 (1 H, dd, *J* 14, 8 Hz, 1′-H_b), 346 (1 H, dd, *J* 12, 6 Hz, 3′-H_a), 3.57 (1 H, dd, *J* 12, 4 Hz, 3′-H_b), and 3.96 (1 H, m, 2′-H); $\lambda_{max.}$(H_2O) 250 (6 450) and 300 nm (3 860); $\lambda_{max.}$(pH 1) 250 (4 020) and 315 nm (2 600); $\lambda_{max.}$(pH 13) 267 (6 100) and 308 nm (2 750); *m*/*z* 225 (M^+) and 194 ($M - CH_2OH$)$^+$ (Found: M^+, 225.0861. $C_8H_{11}N_5O_3$ requires *M*, 225.0862).

Acknowledgements

We thank SERC and Beecham Pharmaceuticals for financial support (CASE award to M. H.), Dr. C. T. Shanks (Beecham Pharmaceuticals, Great Burgh) for assistance in obtaining some spectroscopic data, and Mr. M. R. Boyd and his colleagues at Beecham Pharmaceuticals for carrying out the antiviral tests.

References

1 Part 19, J. G. Buchanan, D. Smith, and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1267.
2 For a review see C. K. Chu and S. J. Cutler, *J. Heterocycl. Chem.*, 1986, **23**, 289.
3 J. G. Buchanan, A. Millar, R. H. Wightman, and M. R. Harnden, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1425.
4 E. de Clercq, J. Descamps, P. DeSomer, and A. Holy, *Science*, 1978, **200**, 563.
5 M. Hori, E. Ito, T. Takita, G. Koyama, T. Takeuchi, and H. Umezawa, *J. Antibiot., Ser. A*, 1964, **17**, 96.
6 G. J. Ellames, I. M. Newington, and A. Stobie, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2087.
7 S. W. Schneller and K. H. Hefner, '5th International Round Table; Nucleosides Nucleotides and their Biological Applications,' Raleigh, N. C., 1982, Abstr. no. 7.
8 H. Griengl and F. Günzl, *J. Heterocycl. Chem.*, 1984, **21**, 505.
9 C. L. Habraken and E. K. Poels, *J. Org. Chem.*, 1977, **42**, 2893.
10 J. V. Crivello, *J. Org. Chem.*, 1981, **46**, 3056.
11 e.g., (*a*) R. Hüttel and F. Büchele, *Chem. Ber.*, 1955, **88**, 1586; (*b*) J. W. A. M. Janssen and C. L. Habraken, *J. Org. Chem.*, 1971, **36**, 3081.
12 e.g., E. Buchner and M. Fritsch, *Justus Liebig's Ann. Chem.*, 1893, **273**, 256; L. Knorr, *ibid.*, 1894, **279**, 188.
13 J. G. Buchanan, A. Stobie, and R. H. Wightman, *Can. J. Chem.*, 1980, **58**, 2624; R. R. Talekar, unpublished results, Heriot-Watt University.
14 A. Yamazaki and M. Okatsu, *J. Heterocycl. Chem.*, 1978, **15**, 353.
15 M. P. Groziak, J.-W. Chern, and L. B. Townsend, *J. Org. Chem.*, 1986, **51**, 1065.
16 A. F. Lewis and L. B. Townsend, *J. Am. Chem. Soc.*, 1982, **104**, 1073.
17 J. G. Buchanan, N. K. Saxena, and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2367.
18 *cf.* L. B. Townsend, V. G. Beylin, and L. L. Wotring, *Nucleosides Nucleotides*, 1985, **4**, 29.
19 V. Nair and D. A. Young, *J. Org. Chem.*, 1985, **50**, 406, and references therein.
20 J.-W. Chern and L. B. Townsend, *Tetrahedron Lett.*, 1985, **26**, 6419, and references therein.
21 S. N. Bose, S. Kumar, R. J. H. Davies, S. K. Sethi, and J. A. McCloskey, *J. Chem Soc., Perkin Trans. 1*, 1984, 2421.
22 J. W. A. M. Janssen, H. J. Koerners, C. G. Kruse, and C. L. Habraken, *J. Org. Chem.*, 1973, **38**, 1777.

Received 28*th October* 1988; *Paper* 8/04290J