# The Syntheses of Acycloformycins and 5-Amino-3-(2-hydroxyethoxy)-methylpyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one, an Analogue of the Antiviral Acycloguanosine

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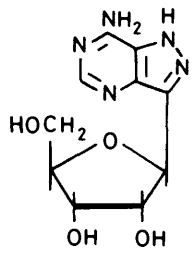
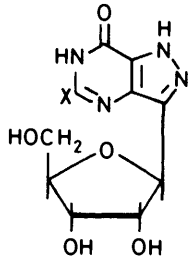
Syntheses of the novel acycloformycin A (**7**), acycloformycin B (**8**), and 5-amino-3-(2-hydroxyethoxy)-methylpyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one (**9**), an analogue of the antiviral acycloguanosine (**4**), are described. These syntheses involve as key intermediate isopropyl 3-hydroxymethyl-4-nitropyrazole-5-carboxylate (**20**) which was generated by treatment of isopropyl 5-methyl-1,4-dinitropyrazole-3-carboxylate (**23**) with triethylamine followed by aqueous acid.

The naturally occurring *C*-nucleosides formycin A[1] (**1**) and formycin B[2] (**2**) have been reported to have various anti-tumour, antiviral, antibacterial, and antiprotazoal activities.[3,4] Syntheses of these naturally occurring antibiotics have been reported by Acton *et al.*[5] Kalvoda,[6] and Buchanan *et al.*[7] In addition the synthesis of the corresponding unnatural guanosine analogue (**3**) has been reported by Lewis and Townsend.[8]

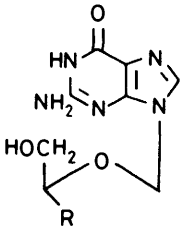


(**1**)

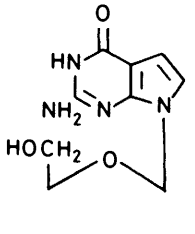


(**2**) X = H
(**3**) X = $NH_2$

Acycloguanosine, (Acyclovir), (**4**) is an efficacious antiviral agent with specific activity against Herpes simplex virus.[9] The activity of acycloguanosine has led to the synthesis of analogues with modified side-chains such as 9-[2-hydroxy-(1-hydroxymethyl)ethoxy]methylguanine[10,11] (**5**), and modified bases such as acyclo-7-deazguanosine (**6**)[12] and others.[13] Compounds have also been synthesized in which the side-chain has been attached at C-8 rather than N-9 of guanine.[14]

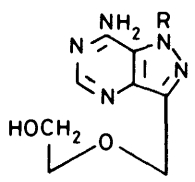


(**4**) R = H
(**5**) R = $CH_2OH$

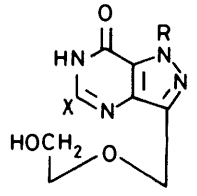


(**6**)

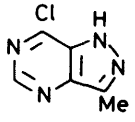
Acyclo derivatives of compounds such as the formycins and their analogues, *i.e.* (**7**), (**8**), and (**9**), might therefore also be considered as synthetic targets of interest in view of their possible biological activity. Indeed the 1-methyl derivatives of both acycloformycin A and acycloformycin B, *i.e.* (**10**) and (**11**), have recently been reported[15] to be synthesized from 7-chloro-3-methyl-1*H*-pyrazolo[4,3-*d*]pyrimidine[16] (**12**). In addition, a recent disclosure by Schneller and Heffner[17] of a feasible synthetic route to 5-amino-3-(2-hydroxyethoxy)methylpyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one (**9**) utilised the cycloaddition of ethyl diazoacetate with the alcohol (**13**) to give a mixture of the isomers (**14**) and (**15**), which were separated, and (**14**) elaborated to afford the acycloguanosine analogue (**9**). These publications have prompted us to disclose our own work in this area.



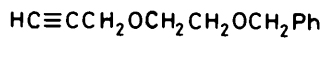
(**7**) R = H
(**10**) R = Me



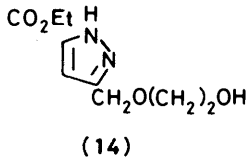
(**8**) X = H, R = H
(**9**) X = $NH_2$, R = H
(**11**) X = H, R = Me



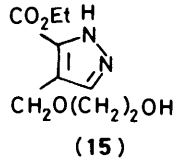
(**12**)



(**13**)



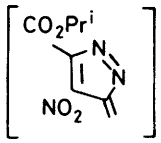
(**14**)



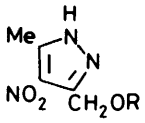
(**15**)

In their synthesis of formycin A, Buchanan *et al.* utilise a reaction, previously described by Habraken and Poels,[18] in which 1,4-dinitropyrazoles were reported to react with nucleophiles to afford substituted pyrazoles with loss of the 1-$NO_2$ group. Here we describe an extension of this reaction to the case of a fully substituted 1,4-dinitropyrazole, such as (**23**),

which, when treated with a non-nucleophilic base such as triethylamine, deprotonates and after quenching with aqueous acid, affords the hydroxymethylpyrazole (**20**) in good yield. A plausible mechanism for this reaction is given in Scheme 1, although the intermedicacy of radical species cannot be discounted. Support for this mechanism rather than one involving a diazafulvene intermediate such as (**16**) comes from the inability of added nucleophiles, *e.g.* 2-mercaptoethanol, to trap such an intermediate. Additionally, this mechanism might satisfactorily explain the formation of a mixture of products (**17**) and (**18**) resulting from the treatment of 1-nitro-3,5-dimethylpyrazole (**19**) with alkoxides reported[19] by Habraken and

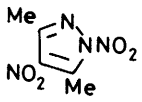


(**16**)



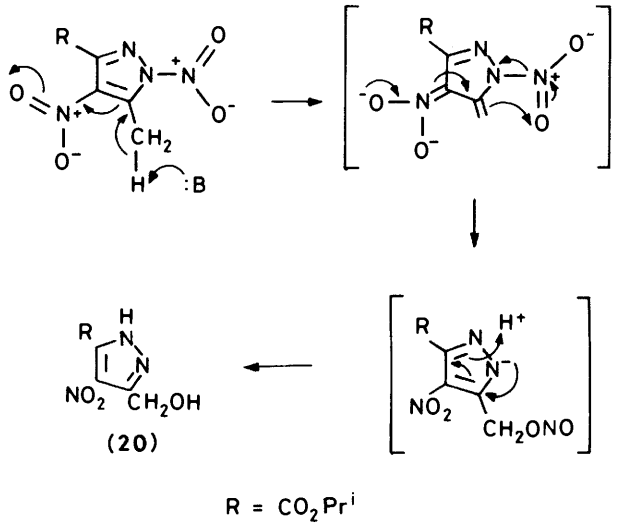
(**17**) R = H

(**18**) R = Alkyl



(**19**)

Bonser. In this case the lower electrophilicity of the deprotonated species could explain the formation of some diazafulvene and subsequent trapping either in an intra- or inter-molecular fashion, leading to the reported products.

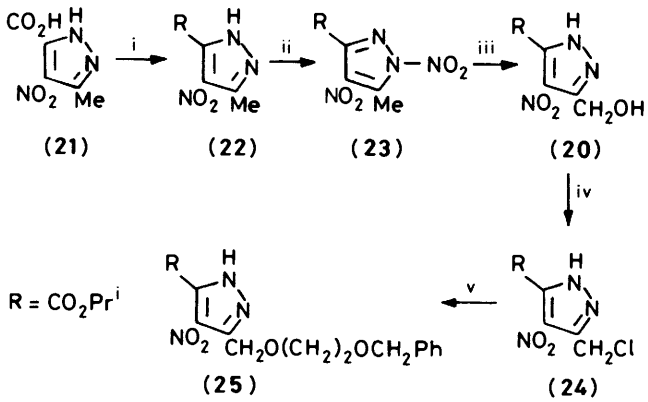


R = $CO_2Pr^i$

**Scheme 1.**

Synthesis of this key novel intermediate hydroxymethylpyrazole (**20**) and its elaboration to the ether (**25**) is outlined in Scheme 2.

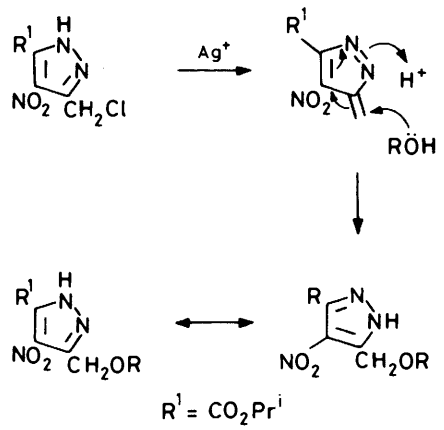
The pyrazolecarboxylic acid (**21**), prepared by the method of Musante,[20] was esterified to form the isopropyl ester (**22**) in good yield. *N*-Nitration of this pyrazole was then carried out by the method used by Habraken and Poels[18] to form the 1,4-dinitropyrazole (**23**) which was then treated with triethylamine



**Scheme 2.** *Reagents:* i, $Pr^iOH$, $H_2SO_4$, 3 h; ii, $HNO_3$, AcOH, $Ac_2O$, Rt, 1 h; iii, $NEt_3$, $CH_2Cl_2$, 0 °C, 15 min; iv, $SOCl_2$, trace DMF, 45 min; v, $AgBF_4$, 2,6-dimethylpyridine, $PhCH_2O(CH_2)_2OH$, MeCN, 50 °C, 18 h.

and then with dilute sulphuric acid to afford the desired hydroxymethylpyrazole (**20**). The effective oxidation of (**22**) to (**20**) was carried out in 45% overall yield.

Owing to the apparent instability of its dianion, compound (**20**) could not be directly alkylated to introduce the ether side-chain. However, treatment with thionyl chloride gave the chloride (**24**) which, without purification, was treated with ethylene glycol monobenzyl ether in the presence of 2,6-dimethylpyridine and silver tetrafluoroborate, to afford the desired ether (**25**). The use of these neutral alkylation conditions were essential owing to the base-sensitivity of the chloride (**24**). It is assumed that the silver tetrafluoroborate catalysed loss of HCl proceeds to give a diazafulvene (Scheme 3) which, in the presence of an alcohol as the only nucleophile, results in effective alkylation. To our knowledge this is the first example of a silver-mediated generation of a diazafulvene.

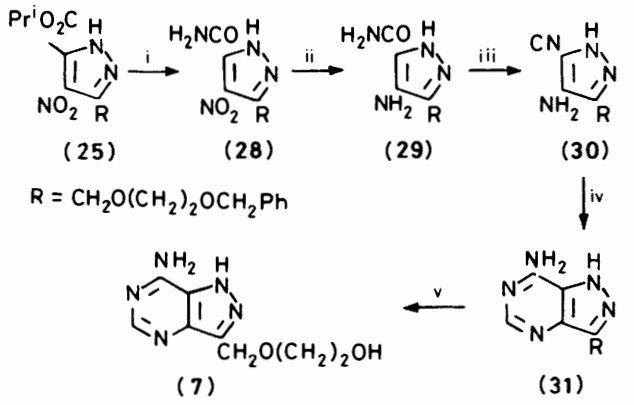


$R^1$ = $CO_2Pr^i$

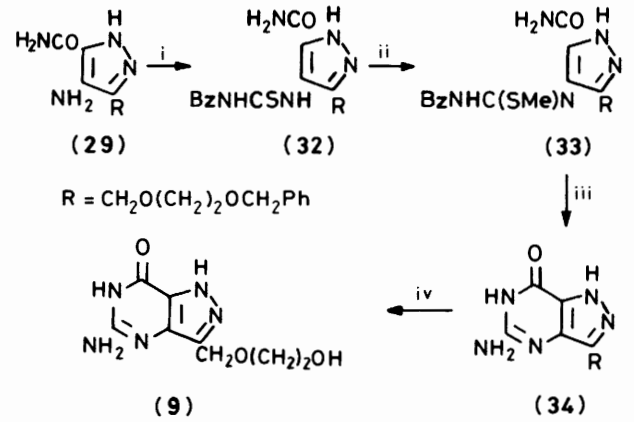
**Scheme 3.**

Complete separation of the ether (**25**) from residual ethylene glycol monobenzyl ether repeatedly proved to be unattainable when attempted on a small scale and thus this partially purified product was used in subsequent transformations such as the synthesis of acycloformycin A (**7**) as outlined in Scheme 4.

Conversion of (**25**) into the amide gave a product readily separable from the ethylene glycol monobenzyl ether by chromatography although the overall yield of amide (**28**) from alcohol (**20**) was only 21%. The nitro group of the amide (**28**)

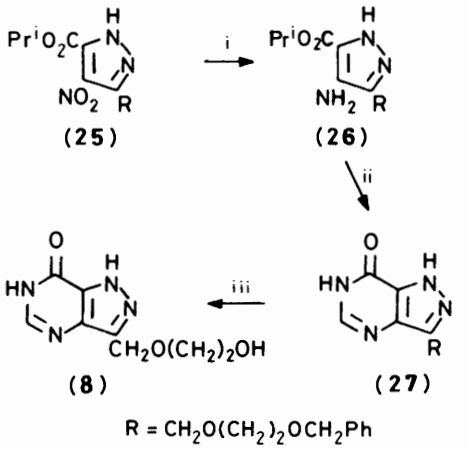



**Scheme 4.** *Reagents:* i, $NH_3$, dioxane, 110 °C, 8 h; ii, $NaS_2O_4$, $KHCO_3$, EtOH, 1 h; iii, $(CF_3CO)_2O$, py, dioxane, 1.5 h; iv, $NH_2CH{=}\overset{+}{N}H_2AcO^-$, $EtO(CH_2)_2OH$, 20 min; v, $BCl_3$, $CH_2Cl_2$, −78 to −22 °C, 1.5 h.




**Scheme 6.** *Reagents:* i, PhCONCS, DMF, room temp., 1.5 h; ii, MeI, NaOH, $H_2O$, DMF, room temp., 3 h; iii, $NH_3$, DMF, 135 °C, 3.5 h; iv, $BCl_3$, $CH_2Cl_2$, −78 to −22 °C, 1.5 h.

was reduced with sodium dithionite to give the amino amide (**29**) in 61% yield; this was dehydrated with trifluoroacetic anhydride to afford the amino nitrile (**30**) in 67% yield and this was cyclised with formamidine acetate to give benzylated acycloformycin A (**31**) in 71% yield. Debenzylation with boron trichloride and elution of the product through an ion-exchange resin afforded the desired acycloformycin A (**7**) in 64% yield. The synthesis of acycloformycin B (**8**) from the common intermediate ether (**25**) is outlined in Scheme 5.




**Scheme 5.** *Reagents:* i, $NaS_2O_4$, $KHCO_3$, EtOH, 1 h; ii, $NH_2CH{=}\overset{+}{N}H_2AcO^-$, $EtO(CH_2)_2OH$, 20 min; iii, $BCl_3$, $CH_2Cl_2$, −78 to −22 °C, 1.5 h.

The amino ester (**26**) was obtained, albeit in low yield, by reduction of the ether (**25**) with sodium dithionite. Treatment of the crude amino ester with formamidine acetate yielded the benzylated acycloformycin B (**27**) which was debenzylated as above to afford the desired acycloformycin B (**8**).

Synthesis of the acycloguanosine analogue (**9**) from the amino amide (**29**) is outlined in Scheme 6.

The amino amide (**29**) was treated with benzoyl isothiocyanate to give the thiourea (**32**) in 90% yield. Methylation with iodomethane and sodium hydroxide gave the methylisothiourea (**33**) in 86% yield and this was converted to the benzylated acycloguanosine analogue (**34**) in 53% yield. Debenzylation of (**34**) as above afforded the desired acycloguanosine analogue (**9**) in 90% yield.

The hydroxymethylpyrazole (**20**) is thus seen to be a convenient intermediate for the synthesis of various acycloformycin analogues. The use of suitably protected ethers or alternatively alkylated starting pyrazoles could lead to analogues with variously modified side-chains which might be expected to demonstrate interesting biological activities.

## Experimental

M.p.s were determined with a Reichert Thermovar melting point apparatus and are uncorrected. Novel compounds were routinely analysed by i.r. (Perkin-Elmer 197) and n.m.r. (Bruker WP250 or Varian FT80A) spectroscopy. Ether refers to diethyl ether.

*Isopropyl 3-Methyl-4-nitropyrazole-5-carboxylate* (**22**).—A solution of 3-methyl-4-nitropyrazole-5-carboxylic acid[20] (**21**) (987 g, 5.77 mol) in propan-2-ol (10 l) containing concentrated sulphuric acid (1 l) was heated under reflux for 3 h over molecular sieves. The reaction mixture was then decanted into water, neutralised with sodium hydrogen carbonate, and extracted with ethyl acetate. The organic phase was dried, evaporated, redissolved in chloroform, and the solution heated under reflux. The chloroform-insoluble material was filtered off, and the solution evaporated to dryness to yield the desired *ester* (**22**) (900 g, 73%), m.p. 111—112 °C (from $CCl_4$) (Found: C, 45.0; H, 5.2; N, 19.6. $C_8H_{11}N_3O_4$ requires C, 45.05; H, 5.2; N, 19.7%); $\nu_{max.}$(Nujol) 3 225 (NH), 1 700 (ester), and 1 580 and 1 360 $cm^{-1}$ ($NO_2$); $\delta_H(CDCl_3)$ 1.40 (6 H, d, *J* 6 Hz, 2 × Me), 2.72 (3 H, s, Me), 5.35 (1 H, septet, *J* 6 Hz, CH), and 7.25 (1 H, s, NH).

*Isopropyl 5-Methyl-1,4-dinitropyrazole-3-carboxylate* (**23**).—Fuming nitric acid (115 ml) was added to a solution of the pyrazole (**22**) (250 g, 1.17 mol) in acetic acid (500 ml) with the temperature maintained below 15 °C. Acetic anhydride (330 ml) was then added at a rate which enabled the temperature to remain as above. After the addition was complete the reaction mixture was allowed to warm to room temperature over 3—4 h before being decanted into vigorously stirred ice–water. The resulting solid was filtered off, dissolved in ether, dried, and triturated with hexane to afford the desired *dinitropyrazole* (**23**) (218 g, 72%), m.p. 63—65 °C (from $Et_2O$–hexane) (Found: C,

37.1; H, 3.9; N, 21.6. $C_8H_{10}N_4O_6$ requires C, 37.2; H, 3.9; N, 21.7%); $\nu_{max.}$ ($CH_2Cl_2$) 1 745 (ester), 1 660 ($NNO_2$), and 1 530 and 1 360 $cm^{-1}$ ($NO_2$); $\delta_H$($CDCl_3$) 1.40 (6 H, d, *J* 6 Hz, 2 × Me), 3.02 (3 H, s, Me), and 5.34 (1 H, septet, *J* 6 Hz, CH).

*Isopropyl 3-Hydroxymethyl-4-nitropyrazole-5-carboxylate* (**20**).—Triethylamine (90 ml) in dichloromethane (500 ml) was slowly added to a solution of the dinitropyrazole (**23**) (163 g, 0.63 mol) in dichloromethane (1.5 l), cooled in an ice–salt bath, at a rate of addition such as to maintain a temperature of 6 °C. After the addition was complete the reaction mixture was stirred for a further 10 min before being decanted into vigorously stirred ice-cold aqueous sulphuric acid. The solid that precipitated was filtered off, dissolved in ethyl acetate, and the solution washed with water, dried, and evaporated to yield the desired *alcohol* (**20**) (90 g, 63%), m.p. 102—104 °C (EtOAc–hexane) (Found: C, 41.6; H, 4.7; N, 18.2. $C_8H_{11}N_3O_5$ requires C, 41.9; H, 4.8; N, 18.3%); $\nu_{max.}$(Nujol) 3 440 (OH), 1 705 (ester), and 1 585 and 1 360 $cm^{-1}$ ($NO_2$); $\delta_H$ [$(CD_3)_2SO$] 1.31 (6 H, d, *J* 6 Hz, 2 × Me), 4.89 (2 H, s, $CH_2$), and 5.41 (1 H, septet, *J* 6 Hz, CH).

3-(2-*Benzyloxyethoxy*)*methyl*-4-*nitropyrazole*-5-*carboxamide* (**28**).—The alcohol (**20**) (90 g, 0.39 mol) was dissolved in thionyl chloride (750 ml) containing dimethylformamide (5 ml) and the solution heated under reflux for 3—4 h. Excess of thionyl chloride was evaporated off, and the residue partitioned between ether and water. The organic phase was washed with water, dried, and evaporated to leave the crude isopropyl 3-chloromethyl-4-nitropyrazole-5-carboxylate (**24**). This crude product was dissolved in acetonitrile (1 l), treated with 2,6-dimethylpyridine (90 ml), ethylene glycol monobenzyl ether (260 ml), and silver tetrafluoroborate (143 g) and the mixture stirred overnight at 50 °C. The acetonitrile was then evaporated off and the residue dissolved in ether and treated with aqueous hydrochloric acid. The solid silver chloride was filtered off and the organic phase washed with water, dried, evaporated, and the residue eluted through a short column of silica gel with ether. The ether was evaporated off to leave crude isopropyl-3-(2-benzyloxyethoxy)methyl-4-nitropyrazole-5-carboxylate (**25**). This was redissolved in dioxane (1 l) and concentrated ammonia solution (2.5 l) and heated at 110 °C for 8 h in a sealed vessel. The solvent was then reduced by evaporation to half its original volume and brought to pH 2 by addition of hydrochloric acid. The reaction mixture was then extracted with ethyl acetate and the organic phase dried and evaporated. Excess ethylene glycol monobenzyl ether was removed under reduced pressure (0.5 mmHg) at 110 °C. The residue was then chromatographed on silica gel in increasing proportions of acetone in dichloromethane to afford the desired *amide* (**28**) (27 g, 21%), m.p. 107—109 °C ($CH_2Cl_2$–hexane) (Found: C, 52.5; H, 4.9; N, 17.6. $C_{14}H_{16}N_4O_5$ requires C, 52.5; H, 5.0; N, 17.5%) $\nu_{max.}$($CH_2Cl_2$) 3 460 (NH), 1 660 (amide), and 1 560 and 1 360 $cm^{-1}$ ($NO_2$); $\delta_H$($CDCl_3$) 3.65 and 3.85 (2 × 2 H, 2 s, $CH_2CH_2$), 4.55 (2 H, s, $CH_2Ph$), 4.95 (2 H, s, $CH_2$), 6.7 (1 H, br s, NH), 7.25 (5 H, s, Ph), and 8.4 (1 H, br s, NH).

4-*Amino*-3-(2-*benzyloxyethoxy*)*methylpyrazole*-5-*carboxamide* (**29**).—A solution of the nitropyrazole (**28**) (27 g, 84.37 mmol) in ethanol (200 ml) and ethyl acetate (100 ml) was added dropwise to a solution of potassium hydrogen carbonate (125 g) and sodium dithionite (125 g) in water (1 l) and ethanol (500 ml). After the addition was complete the reaction was stirred for a further 1 h before the ethanol was evaporated off. The aqueous solution was then extracted with ethyl acetate and the organic phase dried and evaporated. The residue was dissolved in dilute hydrochloric acid and washed with ethyl acetate. The aqueous phase was neutralised with potassium carbonate and extracted with ethyl acetate. The organic phase was then dried and evaporated to yield the desired *amine* (**29**) (15 g, 61%), m.p. 63—67 °C ($CH_2Cl_2$–hexane) (Found: C, 57.6; H, 6.3; N, 19.4. $C_{14}H_{18}N_4O_3$ requires C, 57.9; H, 6.25; N, 19.3%); $\nu_{max.}$($CH_2Cl_2$) 3 700—3 100br (NH), and 1 670 $cm^{-1}$ (amide); $\delta_H$($CDCl_3$) 3.65 (4 H, s, $CH_2CH_2$), 4.5 (4 H, s, 2 × $CH_2$), and 7.3 (5 H, s, Ph).

4-*Amino*-3-(2-*benzyloxyethoxy*)*methyl*-5-*cyanopyrazole* (**30**).—A solution of the amide (**29**) (5.8 g, 20 mmol) in dioxane (100 ml) and pyridine (16 ml) was cooled to near its freezing point and then treated with trifluoroacetic anhydride (17.2 ml). The solution was then stirred for 1.5 h while being allowed to warm to room temperature. The solvents were then evaporated off and the residue partitioned between ether and aqueous sulphuric acid. The organic phase was washed with saturated aqueous sodium hydrogen carbonate and water before being dried and evaporated. The residue was dissolved in aqueous methanolic potassium carbonate (7% $K_2CO_3$ in water–methanol, 5:2; 500 ml) and stirred overnight. The methanol was evaporated off and the product extracted with ethyl acetate. The organic phase was dried and evaporated to afford the crude nitrile which was chromatographed on silica gel with increasing proportions of ethyl acetate in dichloromethane to yield the desired *nitrile* (**30**) (3.6 g, 67%), m.p. 89—92 °C ($Et_2O$) (Found: C, 61.55; H, 5.9; N, 20.65. $C_{14}H_{16}N_4O_2$ requires C, 61.75; H, 5.9; N, 20.55%); $\nu_{max.}$($CH_2Cl_2$) 3 405 and 3 200br (NH), and 2 220 $cm^{-1}$ (CN); $\delta_H$($CDCl_3$) 3.65 (4 H, s, $CH_2CH_2$), 4.53 (4 H, s, 2 × $CH_2$), 5.4 (3 H, br, 3 × NH), and 7.25 (5 H, s, Ph).

7-*Amino*-3-(2-*benzyloxyethoxy*)*methylpyrazolo*[4,3-d]*pyrimidine* (**31**).—A solution of the nitrile (**28**) (1 g, 3.7 mmol) in ethoxyethanol (20 ml) was treated with formamidine acetate (1 g, 9.6 mmol) and heated under reflux for 20 min. The solvent was then evaporated and the residue partitioned between brine and butanol. The organic phase, was dried and evaporated to afford the cyclised *product* (**31**) (785 mg, 71%), m.p. 178—180 °C (EtOAc); (Found: C, 59.65; H, 5.7; N, 23.35. $C_{15}H_{17}N_5O_2$ requires C, 60.2; H, 5.7; N, 23.4%); $\nu_{max.}$(Nujol) 3 320br $cm^{-1}$ (NH); $\delta_H$ [$(CD_3)_2SO$] 3.6 (4 H, m, $CH_2CH_2$), 4.45 (2 H, s, $CH_2Ph$), 4.78 (2 H, s, $CH_2$), 7.25 (5 H, s, Ph), and 8.20 (1 H, s, 5-H).

7-*Amino*-3-(2-*hydroxyethoxy*)*methylpyrazolo*[4,3-d]*pyrimidine* (**7**) (*Acycloformycin A*).—The benzyl ether (**31**) (700 mg, 2.34 mmol) was added to a solution of boron trichloride in dichloromethane (1M; 700 ml) at −78 °C and the reaction mixture stirred for 0.5 h; it was then warmed to −20 °C and stirred for a further 1.5 h. The reaction mixture was recooled to −78 °C and quenched with methanol (25 ml) in dichloromethane (25 ml), allowed to warm to room temperature, and the solvents evaporated off to leave the crude hydrochloride salt of the product (**7**). The salt was passed through a Dowex ($H^+$) resin in increasing proportions of ammonia in water to afford the desired *acycloformycin A* (**7**) (315 mg, 64%), m.p. 169—170 °C (MeOH–MeCN) (Found: C, 43.8; H, 5.1; N, 31.95. $C_8H_{11}N_5O_2 \cdot \frac{1}{2}H_2O$ requires: C, 44.15; H, 5.55; N, 32.2%); $\nu_{max.}$(Nujol) 3 410 (OH) and 3 300br $cm^{-1}$ (NH); $\delta_H$ [$(CD_3)_2SO$] 3.5 (4 H, s, $CH_2CH_2$), 4.72 (2 H, s, $CH_2$), 7.25 (2 H, br s, NH), and 8.15 (1 H, s, 5-H); *m/z* ($M^+$ + 1, 100%).

3-(2-*Benzyloxyethoxy*)*methylpyrazolo*[4,3-d]*pyrimidin*-7(6H)-*one* (**27**).—The amino ester (**26**) was prepared from the ether (**22**) by the method described for (**29**). Thus from the ether (**25**) (10 g, 31 mmol) was obtained the crude amino ester (**26**) which was chromatographed on silica gel in increasing proportions of ethyl acetate in dichloromethane to afford material (2.03 g, 22%) of sufficient purity for cyclisation. A

solution of this amino ester (**26**) (1.75 g, 5.3 mmol) in 2-ethoxyethanol (50 ml) was treated with formamidine acetate (1.75 g, 16.8 mmol) and heated under reflux for 3 h. The solvent was evaporated off and the residue partitioned between butanol and brine. The organic phase was dried and evaporated to leave the cyclised product (**27**) (500 mg, 31%), m.p. 147—149 °C (EtOAc–hexane) (Found: C, 59.6; H, 5.4; N, 18.9. $C_{15}H_{16}N_4O_3$ requires C, 60.00; H, 5.35; N, 18.65%); $\nu_{max.}$(Nujol) 3 160 (NH) and 1 715 $cm^{-1}$ (CO); $\delta_H$($CD_3OH$) 3.7 (4 H, dm, $CH_2CH_2$), 4.52 (2 H, s, $CH_2Ph$), 4.85 (2 H, s, $CH_2$), 7.30 (5 H, s, Ph), and 7.88 (1 H, s, 5-H).

3-(2-*Hydroxyethoxy*)*methylpyrazolo*[4,3-d]*pyrimidin*-7(6H)-*one* (**8**). (*Acycloformycin B*).—Acycloformycin B (**8**) was prepared from the ether (**27**) by the method described for the deprotection of the ether (**31**) to form acycloformycin A (**7**). Thus, from the benzyl ether (**27**) (450 mg, 1.5 mmol) was obtained a crude product which following chromatography on silica gel in increasing proportions of methanol in dichloromethane afforded *acycloformycin B* (**8**) (200 mg, 63%) m.p. 190—192 °C (MeOH) (Found: C, 45.5; H, 4.9; N, 26.65. $C_8H_{10}N_4O_3$ requires C, 45.7; H, 4.8; N, 26.65%); $\nu_{max.}$(Nujol) 3 460 (OH), 3 200br (NH), and 1 695 $cm^{-1}$ (CO); $\delta_H$ [$(CD_3)_2SO$] 3.5 (4 H, s, $CH_2CH_2$), 4.68 (2 H, s, $CH_2$), and 7.90 (1 H, s, 5-H).

4-(N′-*Benzoylthioureido*)*amino*-3-(2-*benzyloxyethoxymethyl*)*pyrazole*-5-*carboxamide* (**32**).—To a solution of the amine (**29**) (4.8 g, 16.5 mmol) in dimethylformamide (20 ml), cooled in a water-bath, was added benzoyl isothiocyanate (2.5 ml, 18.1 mmol); the mixture was allowed to warm to room temperature and was then stirred for a further 1.5 h. The reaction mixture was then decanted into water and the product extracted with ethyl acetate. The organic phase was dried and evaporated to leave the *thiourea* (**32**) (6.8 g, 90%), m.p. 173—175 °C ($CH_2Cl_2$–$CCl_4$) (Found: C, 57.85; H, 5.1; N, 15.45. $C_{22}H_{23}N_5O_4S$ requires C, 58.25; H, 5.1; N, 15.45%); $\nu_{max.}$($CH_2Cl_2$) 3 280br (NH), and 1 670 and 1 650 $cm^{-1}$ (amides and thiourea); $\delta_H$ [$(CD_3)_2SO$] 3.65 (4 H, s, $CH_2CH_2$), 4.45 (2 H, s, $CH_2Ph$), 4.6 (2 H, s, $CH_2$), 7.3 (5 H, s, $CH_2Ph$), and 7.6 and 8.0 (3 H and 2 H, m and d, Bz).

5-*Amino*-3-(2-*benzyloxyethoxy*)*methylpyrazolo*[4,3-d]*pyrimidin*-7(6H)-*one* (**34**).—To a solution of the thiourea (**32**) (6.8 g, 15 mmol) in dimethylformamide (50 ml) was added aqueous sodium hydroxide (0.1M; 165 ml, 16.5 mmol) and iodomethane (1.53 ml, 22.5 mmol). The reaction mixture was stirred for 3 h and then decanted into water and brought to pH 6 with addition of acetic acid. The solution was then extracted with ethyl acetate and the organic phase dried and evaporated before being chromatographed on silica gel in increasing proportions of ethyl acetate in dichloromethane. This afforded, as an oil, the methylisothiourea (**33**) (6 g, 86%) which was used directly in the following reaction.

A solution of the methylisothiourea (**33**) (5 g, 10.7 mmol) in dimethylformamide (100 ml) was cooled to 0 °C and saturated with ammonia. The system was then sealed and heated at 130 °C for 3.5 h. After cooling, the dimethylformamide was removed under reduced pressure to leave a crude product which on crystallisation from methanol afforded the desired cyclised *product* (**34**) (1.8 g, 53%), m.p. 225—227 °C (MeOH) (Found: C, 56.9; H, 5.4; N, 22.15. $C_{15}H_{17}N_5O_3$ requires C, 57.15; H, 5.45; N, 22.2%); $\nu_{max.}$(Nujol) 3 150br (NH), and 1 705 $cm^{-1}$ (CO); $\delta_H$ [$(CD_3)_2SO$] 3.6 (4 H, brs, $CH_2CH_2$), 4.45 and 4.55 (2 × 2 H, 2 s, 2 × $CH_2$), 6.1 (2 H, brs, $NH_2$), 7.35 (5 H, s, Ph), and 10.85 (1 H, br, NH).

5-*Amino*-3-(2-*hydroxyethoxy*)*methylpyrazolo*[4,3d]*pyrimidin*-7(6H)-*one* (**9**).—The acycloguanosine analogue (**9**) was prepared from the ether (**34**) by the method used in the generation of acycloformycin A (**7**) from the ether (**31**). Thus, the ether (**34**) (1.8 g, 5.7 mmol) afforded the hydrochloride salt of the desired *product* (**9**) (1.34 g, 90%), m.p. > 300 °C (MeOH—MeCN) (Found: C, 36.55; H, 4.65; Cl, 13.6; N, 26.4. $C_8H_{11}N_5O_3$·HCl requires C, 36.7; H, 4.6; Cl, 13.55; N, 26.75%); $\nu_{max.}$(Nujol) 3 450 br (OH and NH), and 1 730 $cm^{-1}$ (CO); $\delta_H$ [$(CD_3)_2SO$] 3.55 (4 H, s, $CH_2CH_2$), 4.70 (2 H, s, $CH_2$), and 8.15 (2 H, brs, $NH_2$). A solution of the salt (286 mg, 1.1 mmol) in water (10 ml) was treated with aqueous potassium carbonate (4M; 0.5 ml) and the solution left overnight at 4 °C. The resulting precipitate was filtered off, washed with cold water, and then recrystallised from hot water to afford the desired free base of (**9**) (186 mg, 75%) m.p. > 300 °C ($H_2O$) (Found: C, 41.2; H, 5.05; N, 30.0. $C_8H_{11}N_5O_3$·$\frac{1}{2}H_2O$ requires C, 41.05; H, 5.2; N, 29.9%).

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