Synthesis of Imidazo-fused Bridgehead-nitrogen *C*-Nucleosides *via* Dehydrative Coupling Reactions of 2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allonic Acid

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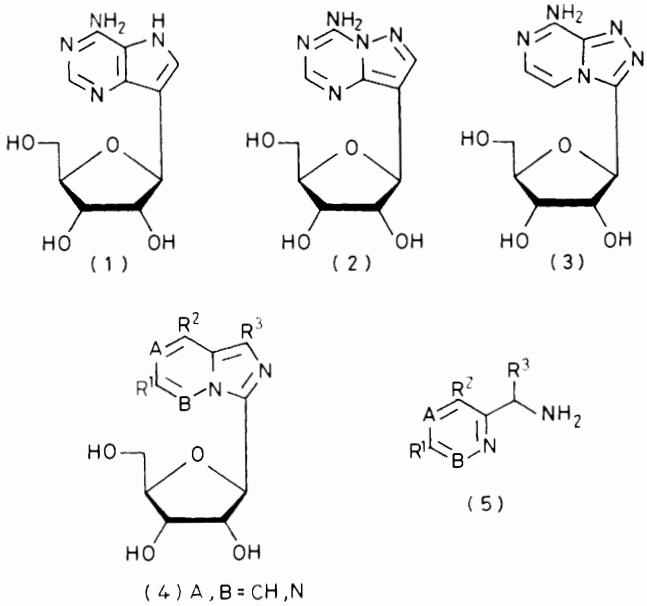
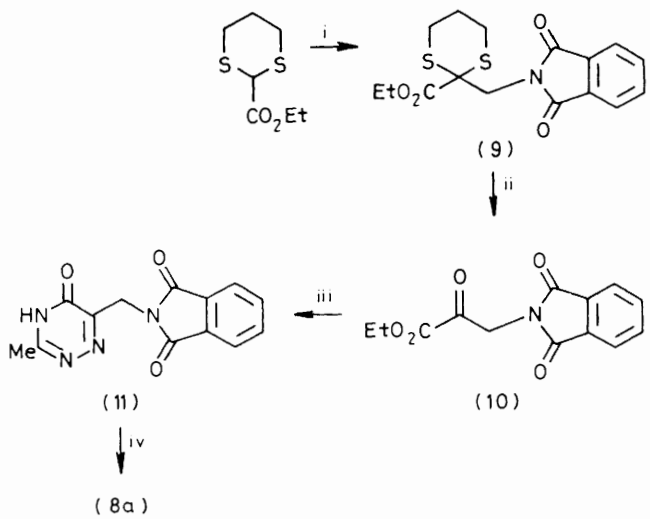
A short, efficient synthesis of novel imidazo-fused bridgehead-nitrogen *C*-nucleosides has been developed. Dehydrative coupling of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (14) with a series of aminoalkyl-substituted heterocycles (6)—(8) gives the amides (15)—(17). The latter are subsequently converted into novel imidazo[1,5-*a*]pyridine, imidazo[1,5-*a*]pyrazine, imidazo[1,5-*b*]pyridazine, and imidazo[5,1-*f*]-1,2,4-triazine *C*-nucleosides (20) and (21). The synthesis of a novel adenosine isostere, 8-amino-3-β-D-ribofuranosylimidazo[1,5-*a*]pyrazine (32), is described.

The synthesis of *C*-nucleosides related to the natural purine nucleosides and formycins has attracted considerable attention during recent years. Foremost in this research has been the synthesis of adenosine and formycin isosteres. For example, the Sloan-Kettering group has reported the synthesis of the adenosine isosteres 7-(β-D-ribofuranosyl)-4-amino-5*H*-pyrrolo[3,2-*d*]pyrimidine (9-deaza-adenosine) (1)[1] and 4-amino-8-(β-D-ribofuranosyl)pyrazolo[1,5-*a*]-1,3,5-triazine (2)[2] and also the related inosine[3,4] and guanosine[5] analogues. In addition, French workers have described the synthesis of a novel adenosine isostere (3), based on the 1,2,4-triazolo-[4,3-*a*]pyrazine ring system.[6] Both (1) and (2) are reported to exhibit pronounced antileukaemic activity.[1,3] Recently, a new guanosine isostere, 5-aminoformycin B, has been prepared from formycin.[7]

In this paper we describe the synthesis of novel imidazo-fused bridgehead-nitrogen *C*-nucleosides of general structure (4), including the guanosine and adenosine analogues (21c) and (32) respectively. This synthesis possesses a considerable degree of flexibility and allows retention or removal of ring nitrogen atoms (A,B) as well as variation in the peripheral substituents (R^1,R^2,R^3). At the outset we reasoned that these structures could be constructed from an aminoalkyl-substituted heterocycle (5) and a ribose derivative appropriately functionalized at C-1′ with a one-carbon unit. The aminoalkyl-substituted heterocycles selected for our studies comprised (6)—(8), with the ultimate aim of providing imidazo-[1,5-*a*]pyridine, imidazo[1,5-*a*]pyrazine, imidazo[1,5-*b*]-pyridazine, and imidazo[5,1-*f*]-1,2,4-triazine *C*-nucleosides. Compounds (7) and (8b,c) were prepared *via* acid hydrolysis of the corresponding benzamides.[8] 6-Aminomethyl-3-methyl-1,2,4-triazin-5(4*H*)-one (8a) was prepared *via* the sequence outlined in Scheme 1. Alkylation of ethyl 1,3-dithiane-2-carboxylate with bromomethylphthalimide afforded (9) which was deprotected to give the α-keto ester (10).† Condensation



† The corresponding α-keto acid has previously been synthesized[9] by a six-step sequence from *N*-phthaloylglycine.



Scheme 1. *Reagents:* i, *N*-Bromomethylphthalimide, NaH, DMF–C_6H_6; ii, NBS, aqueous acetone; iii, MeC(=NH)$NHNH_2$·HI, EtOH, heat; iv, 6M-HCl, heat

of (10) with acetamidrazone yielded (11) which on acid catalysed hydrolysis of the phthalimide group provided (8a), isolated as its dihydrochloride salt.

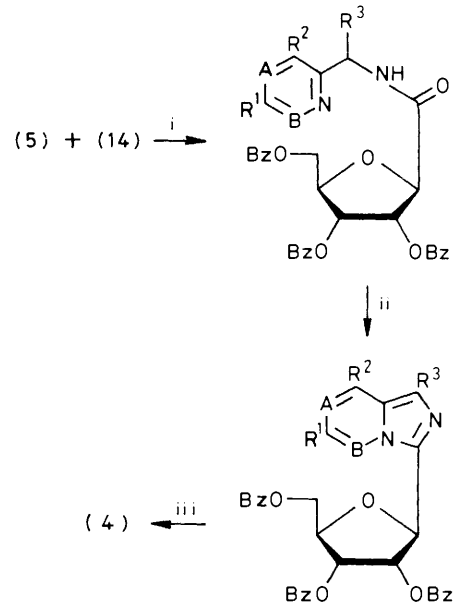
Initially, we chose to apply the methodology developed by Igolen and co-workers for the synthesis of 1,2,4-triazolo-fused bridgehead-nitrogen *C*-nucleosides.[6,10] However, when (7b) and (8b) were each heated with the (5-*O*-benzoyl-β-D-ribofuranosyl)thioformimidate (12) in pyridine at reflux, no bicyclic products were formed. The major reaction occurring was elimination of toluene-α-thiol from (12). This may have resulted from the use of the more basic aminoalkyl heterocycles compared with the hydrazines employed by the French workers.‡ Attempts to modify the reaction conditions were largely unsuccessful, although a low yield (*ca.* 10%) of the amide (13) was formed when (12) was treated with (7b) in n-butanol at reflux.

In view of these disappointing results we decided to explore the application of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (14) as the carbohydrate starting material for the synthesis of the target systems (4). Although first prepared 16 years ago,[13] the full potential of (14) in the synthesis of *C*-nucleosides has not been exploited [14,15] and it has been overshadowed by its immediate precursor: 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide.[13,16] In the event, use of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (14) has provided a short and efficient synthesis of the title compounds (Scheme 2). Thus, dehydrative coupling of (14) with heterocyclic amines (6)—(8) using dicyclohexylcarbodi-imide (DCC) afforded the amides (15)—(17) in good yield. Cyclization of (15a), (16a,b), and (17a—c), using the mild conditions of phosphorus oxychloride (3—7 molar equivalents) in 1,2-dichloroethane at reflux to preserve the sensitive carbohydrate moiety, gave the tri-*O*-benzoyl protected *C*-ribonucleosides (18a,c,d) and (19a—c). Conversion of (15b) into (18b) could not be effected using these conditions. However, this transformation was achieved in modest yield using phosphorus pentachloride in chloroform. Deprotection of (18) and (19) with methanolic ammonia or ethanolic methylamine provided the novel imidazo-fused bridgehead-nitrogen *C*-nucleosides (20) and (21), including the novel guanosine analogue (21c) based on the imidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-one system. The overall yields for this sequence, for a wide range of ring systems and substitution patterns, are generally good although the instability of the parent imidazo[1,5-*a*]pyrazine ring system resulted in a low yield of (20b).

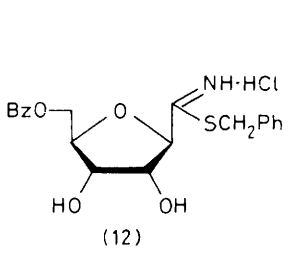
The ^{1}H n.m.r. spectral data for the *C*-nucleosides are summarized in the Table whilst those for the amides [(15)—(17), (29), and (30)] and the benzoates [(18), (19), (24), and (31)] are available as a Supplementary publication [SUP. No. 23778 (3 pp.)].§ The integrity of the bicyclic heterocyclic moieties of (20) and (21) was confirmed by comparison of their ^{1}H n.m.r. and u.v. spectral data with those of their non-riboside counterparts.[8,17,18] The electron impact mass spectra of the nucleosides (20a,b,d) were also recorded and each showed a base peak at B + 30, characteristic of *C*-ribonucleosides.[19] The β-configuration of the nucleosides (20) and (21) was confirmed by application of Imbach's rules [20] and by the 'geometry-only' method of Robins *et al.*[21] The 2′,3′-*O*-

‡ Reynaud *et al.*[11] have shown that while nitrile formation from thioimidates is not significant when aromatic amines are used as nucleophiles, it is the dominant pathway when aliphatic amines are employed. This observation has been confirmed by Schnur [12] who has recently reported a general synthesis of amidines from thioimidates using buffered protonic catalysis in non-aqueous medium.

§ For details of the Supplementary publications scheme, see Instructions for Authors (1984), *J. Chem. Soc., Perkin Trans. 1*, 1984, Issue 1.



Scheme 2. *Reagents:* i, DCC; ii, $POCl_3$, $ClCH_2CH_2Cl$, heat; iii, NH_3–MeOH or CH_3NH_2–EtOH



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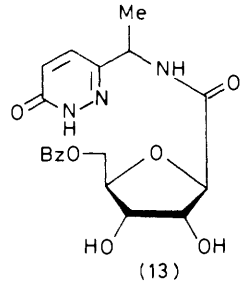
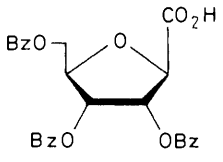
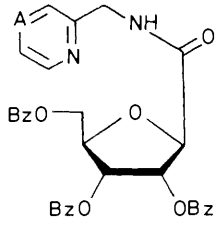


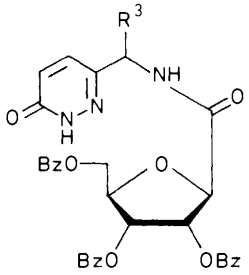
(13)



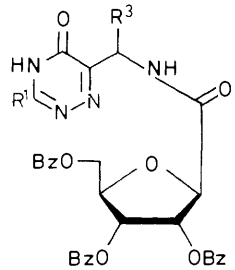
(14)



(15)
a; A = CH
b; A = N



(16)
a; R^3 = H
b; R^3 = Me



(17)
a; R^1 = Me, R^3 = H
b; R^1 = Me, R^3 = Me
c; R^1 = NH_2, R^3 = Me

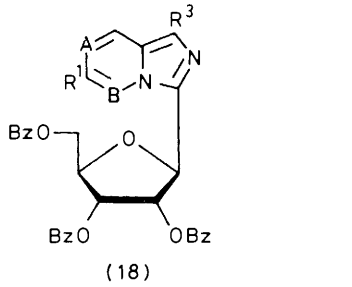
isopropylidene derivatives (22) and (23) were prepared from (20d) and (21b), respectively, and their ^{1}H n.m.r. spectra in [$^2H_6$]dimethyl sulphoxide examined. Both compounds, which meet the structural requirements defined by Imbach *et al.*,[20] exhibit $\Delta\delta$ of 0.17 p.p.m. for the difference in chemical shifts of the geminal dimethyl groups, indicative of a β-configuration. The 4′-H signals for (22) and (23) appear as multiplets (higher than triplets), also indicative of a β-configuration.[22] To verify these assignments further the 3′,5′-cyclic phosphate of (21b) was prepared.[23] The 1′-H signal of the nucleotide resonated as a singlet at δ 5.41, again consistent [21] with a β-configuration. In addition, for (20) and (21) the chemical shifts of 1′-H fell within the range δ 5.0—5.2, similar to β-anomers of other bridgehead-nitrogen *C*-ribonucleosides.[6,10] The ribosyl protons of (20a—c) and (21a,c) gave similar ^{1}H n.m.r. spectra to those of (20d) and (21b) thereby securing the β-configuration for all the new *C*-nucleosides (see Table).

The use of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (14) * has several advantages over the (5-*O*-benzoyl-β-D-ribofuranosyl)thioformimidate intermediate (12). First, it is readily accessible and does not require selective removal of 2- and 3-*O*-benzoyl protecting groups; the reaction conditions applied throughout the sequence are sufficiently mild to avoid elimination of benzoic acid and furan formation. Secondly, there is no liberated toluene-α-thiol to cause further undesirable displacement reactions [6] and thirdly there is no formation of α-anomers.

A series of typical nucleoside modification reactions have been carried out on (19b), (20c), and (20d). Thus, the 4-amino- and 4-methylamino-substituted imidazo[5,1-*f*]-1,2,4-triazine nucleosides, (25a) and (25b) respectively, were prepared from the tri-*O*-benzoate (19b) *via* the classical route (Scheme 3). The thione (26) was prepared by methanolic ammonia deprotection of (24). Treatment of the 2-chloro-substituted imidazo[1,5-*b*]pyridazine nucleosides (20c) and (20d) with liquid ammonia at 100 °C afforded the corresponding 2-amino derivatives (27a) and (27b), respectively, in good yield.

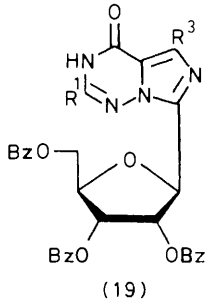
Finally, we turned our attention to the synthesis of an adenosine isostere, (32), based on the imidazo[1,5-*a*]pyrazine system. The known 2-amino-3-aminomethylpyrazine (28) [24] was coupled with (14) in the usual way, although addition of acetonitrile was necessary to solubilize the base, to afford the amide (29). We elected to protect the 2-amino group as its benzamide (30) to prevent a possible alternative mode of cyclization to the 3,4-dihydropteridine nucleoside (33). Cyclization of (30), using phosphorus oxychloride in 1,2-dichloroethane, followed by debenzoylation afforded 8-amino-3-β-D-ribofuranosylimidazo[1,5-*a*]pyrazine (32) in 14% overall yield from (14) (Scheme 4). The structure of (32) follows from a comparison of its ^{1}H n.m.r. and u.v. spectral data with those of 8-aminoimidazo[1,5-*a*]pyrazine [24] (for which there is excellent agreement) and its mass spectrum which, in addition to confirming the molecular formula, shows a base peak (B + 30) characteristic of *C*-ribonucleosides.

An efficient synthesis of a wide range of imidazo-fused bridgehead-nitrogen *C*-nucleosides of general structure (4) has been developed. In view of the continuing importance of *C*-nucleoside analogues as potential therapeutic agents, this synthesis and the application of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid in general [25] offer further useful approaches to this class of compound.



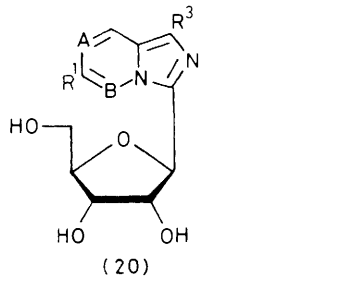
(18)

a; A = B = CH, R^1 = R^3 = H
b; A = N, B = CH, R^1 = R^3 = H
c; A = CH, B = N, R^1 = Cl, R^3 = H
d; A = CH, B = N, R^1 = Cl, R^3 = Me



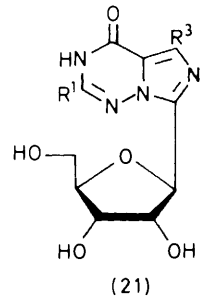
(19)

a; R^1 = Me, R^3 = H
b; R^1 = Me, R^3 = Me
c; R^1 = NH_2, R^3 = Me



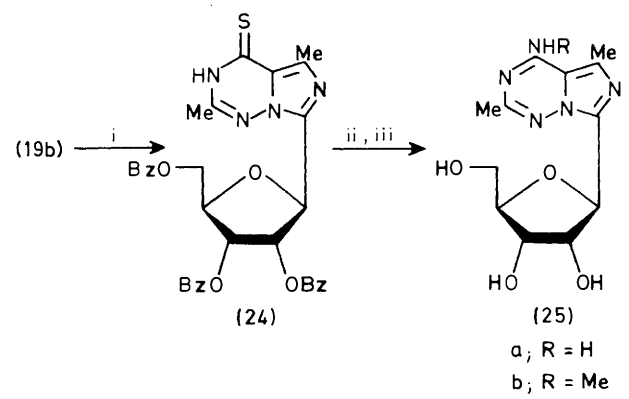
(20)

a; A = B = CH, R^1 = R^3 = H
b; A = N, B = CH, R^1 = R^2 = H
c; A = CH, B = N, R^1 = Cl, R^3 = H
d; A = CH, B = N, R^1 = Cl, R^3 = Me



(21)

a; R^1 = Me, R^3 = H
b; R^1 = Me, R^3 = Me
c; R^1 = NH_2, R^3 = Me

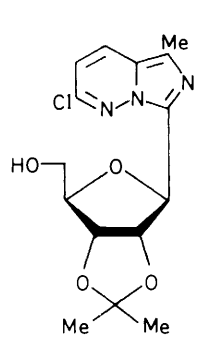


Scheme 3. *Reagents:* i, P_2S_5, dioxane, heat; ii, MeI, $NaHCO_3$, dioxane–MeOH; iii, NH_3–MeOH or $MeNH_2$–EtOH

Experimental

^{1}H N.m.r. spectra were measured [$SiMe_4$ or sodium 3-(trimethylsilyl)propane-1-sulphonate internal standards] on a Varian EM 390 (90 MHz) or a Bruker WM250 (250 MHz) spectrometer (by Dr. J. Hunt and his staff). I.r. spectra were recorded on Perkin-Elmer 357 or 377 spectrophotometers and

* During the course of our work Rosenthal and Lee [15] reported coupling of (14) with 2-hydrazinopyridine, using Woodward's Reagent K (*N*-ethyl-5-phenylisoxazolium-3′-sulphonate), to afford 2-(2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonoyl)hydrazidopyridine. This compound was subsequently converted into 3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*a*]pyridine *via* thermal cyclization and debenzoylation (NaOMe–MeOH).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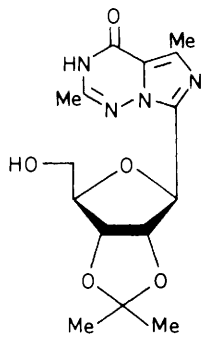
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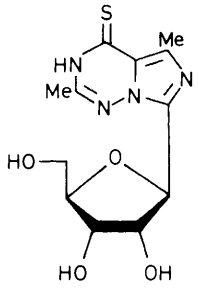
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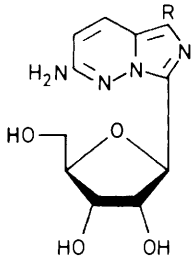

(27)

a; R = H
b; R = Me

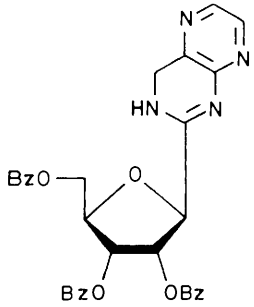
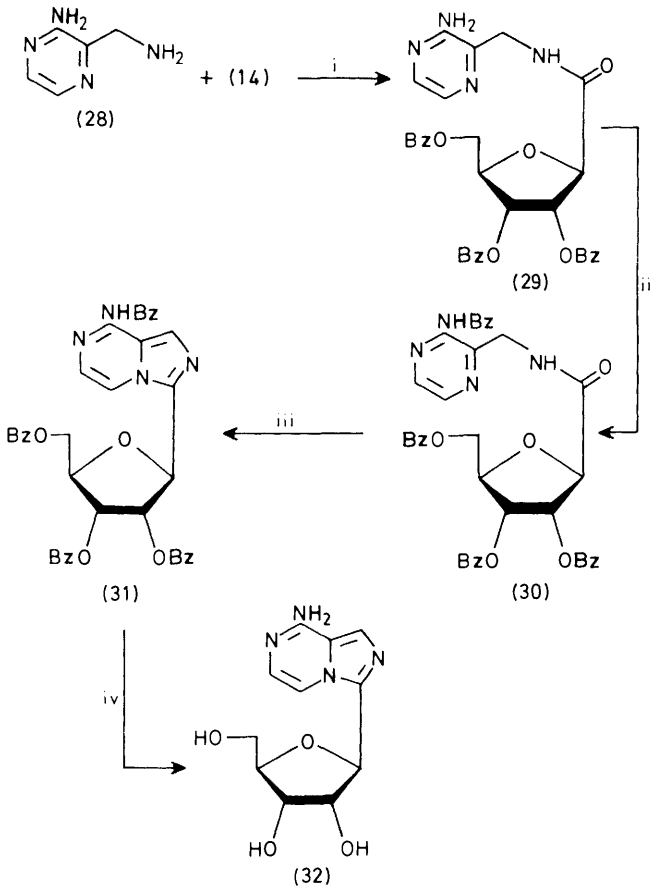

(33)

Table. ^{1}H N.m.r. chemical shifts (δ) [$(CD_3)_2SO$] and coupling constants (Hz) of *C*-nucleosides

Compd.	1′-H	2′-H	3′-H	4′-H	5′5″-H	Other	$J_{1'2'}$
(20a)	5.20 (d)	4.60 (m)	4.12 (m)	3.94 (m)	3.55 (m)	4.8—5.2 (m, 3 × OH), 6.60—7.00 (m, 5-H, 6-H), 7.42 (s, 1-H), 7.63 (dd, 7-H), 8.49 (d, 4-H)	6.5
(20b)	5.18 (d)	4.50 (m)	4.07 (m)	3.92 (m)	3.50 (m)	4.8—5.3 (m, 3 × OH), 7.55 (d, 5-H), 7.82 (s, 1-H), 8.48 (dd, 6-H), 9.10 (d, 8-H, *J* 1)	6.5
(20c)	5.18 (d)	4.60 (m)	4.17 (m)	3.92 (m)	3.50 (m)	4.80 (t, CH_2OH), 4.70—5.00 (2 × d, 2 × OH), 6.94 (d, *J* 10, 3-H), 7.70 (s, 5-H), 8.30 (d, 4-H, *J* 10)	6.0
(20d)	5.20 (d)	4.58 (m)	4.11 (m)	3.90 (m)	*ca.* 3.5 (m)	2.55 (s, CH_3), 4.70 (br, t, CH_2OH), 5.00, 5.15 (br, 2 × d, 2 × OH), 6.78 (d, *J* 10, 3-H), 8.28 (d, *J* 10, 4-H)	6.0
(21a)	5.12 (d)	4.47 (t)	4.09 (t)	3.86 (q)	*ca.* 3.5 (m)	2.27 (s, CH_3), 4.7—5.3 (br, 3 × OH), 7.77 (s, 5-H)	5.5
(21b)	5.10 (d)	4.45 (m)	4.09 (m)	3.86 (q)	3.50 (m)	2.26 (s, CH_3), 2.50 (s, CH_3), 4.7—5.1 (m, 3 × OH)	5.5
(21c)	5.02 (d)	4.39 (br, t)	4.07 (br, t)	3.81 (m)	3.50 (m)	2.41 (s, CH_3), 6.10 (br, s, NH_2), 10.8 (br, s, NH)	6.0
(25a)	5.18 (d)	4.52 (t)	4.12 (t)	3.90 (m)	3.3—3.7 (m)	2.20 (s, CH_3), 2.52 (s, CH_3), 4.5—5.2 (br, 3 × OH), 7.00—8.30 (br, s, NH_2)	6.0
(25b)	5.17 (d)	4.48 (t)	4.10 (t)	3.89 (m)	3.3—3.8 (m)	2.28 (s, CH_3), 2.54 (s, CH_3), 3.03 (d, $NHCH_3$), 3.90—5.00 (br, 3 × OH), 7.50 (q, $NHCH_3$)	6.0
(26)	5.04 (d)	4.40 (t)	4.03 (t)	3.80 (m)	3.50 (m)	2.23 (s, CH_3), 2.63 (s, CH_3)	6.0
(27a)	5.23 (d)	4.47 (m)	4.15 (m)	3.85 (m)	3.3—3.8 (m)	4.8—5.2 (m, 2 × OH), 6.33 (d, 3-H), 6.5 (br, s, NH_2), 7.28 (s, 5-H), 7.79 (d, 4-H)	5.5
(27b)	5.18 (d)	4.43 (m)	4.14 (m)	3.83 (m)	3.35—3.65 (m)	2.32 (s, CH_3), 4.90, 5.00 (2 × d, 2 × OH), 5.10 (m, CH_2OH), 6.23 (d, 3-H), 6.33 (br, s, NH_2), 7.80 (d, 4-H)	5.5
(32)	5.04 (d)	4.48 (t)	4.07 (t)	3.90 (dd)	3.40—3.65 (m)	4.80—5.30 (br, 3 × OH), 6.99 (d, 4-H), 7.06 (br, s, NH_2), 7.68 (d, 5-H), 7.72 (s, 1-H)	6.0



Scheme 4. *Reagents:* i, DCC, CH_2Cl_2–MeCN; ii, BzCl, pyridine, 5 °C; iii, $POCl_3$, $ClCH_2CH_2Cl$, heat; iv, $MeNH_2$–EtOH

u.v. spectra were measured on a Perkin-Elmer 402 spectrophotometer (by Dr. J. Hunt and his staff). Mass spectral data were obtained (by Dr. R. Tanner and Mr. S. Krolik) using either a Kratos MS 30 instrument interfaced to a DS 55 data system or a VG Analytical Ltd. VG 7070E instrument interfaced to a Multispec 11 data system. Microanalyses were performed (by Dr. T. Cholerton and his staff) using either a Carlo Erba Strumentazone Elemental Analyser, Mod. 1106, or a Hewlett Packard 185 CHN Analyser. All m.p.s are uncorrected.

Column chromatography was performed on Merck Kieselgel 60 (Art 7734; Art 9385 for flash chromatography [26]). Solvents were dried according to standard procedures.[27]

N-(2,3-*Dihydro*-3-*oxopyridazin*-6-*yl*)*methylamine Hydrochloride* (7a)·HCl.—*N*-(2,3-Dihydro-3-oxopyridazin-6-yl)-methylbenzamide [8] (9.24g) in 6M-hydrochloric acid (300 ml) was heated on a steam-bath for 16 h. The cooled reaction mixture was filtered and the filtrate extracted with ethyl acetate. The aqueous layer was evaporated to dryness and the residue boiled with ethanol. After cooling, the white solid *hydrochloride* (7a)·HCl (6.18 g, 94%) was collected by filtration, m.p. >290 °C (decomp.) (Found: C, 37.25; H, 5.0; N, 26.05. $C_5H_7N_3O$·HCl requires C, 37.15; H, 5.0; N, 26.0%); $\nu_{max.}$ (Nujol) 3 200—2 500 and 1 680 cm^{-1}; $\lambda_{max.}$ (EtOH) 224 (ε 6 200) and 293 nm (2 400); δ[$(CD_3)_2SO$] 3.95 (2 H, s, CH_2), 7.00 (1 H, d, 4-H), and 7.70 (1 H, d, 5-H).

N-1-(2,3-*Dihydro*-3-*oxopyridazin*-6-*yl*)*ethylamine Hydrochloride* (7b)·HCl.—This *compound* (70%) was prepared from *N*-1-(2,3-dihydro-3-oxopyridazin-6-yl)ethylbenzamide,[8] as described for the preparation of (7a), and was obtained as a white solid, m.p. 233—237 °C (from ethanol–ethyl acetate) (Found: C, 41.4; H, 5.85; N, 24.15. $C_6H_9N_3O$·HCl requires C, 41.05; H, 5.75; N, 23.95%); $\nu_{max.}$ (Nujol) 3 200—2 500 and 1 690 cm^{-1}; $\lambda_{max.}$ (EtOH) 225 (ε 6 300) and 297 nm (2 400); δ[$(CD_3)_2SO$] 1.53 (3 H, d, CH_3), 4.40 (1 H, q, C*H*Me), 7.00 (1 H, d, 4-H), and 7.75 (1 H, d, 5-H).

Ethyl 2-(1,3-*Dihydro*-1,3-*dioxo*-2H-*isoindol*-2-*ylmethyl*)-1,3-*dithiane*-2-*carboxylate* (9).—Sodium hydride (11.7 g of a 46% dispersion in oil, 0.223 mol) was washed by decantation under nitrogen with n-pentane (3 × 20 ml). Benzene (250 ml) was added and the mixture cooled to 5 °C. Bromomethylphthalimide (64.4 g, 0.268 mol) and ethyl 1,3-dithiane-2-carboxylate (42.9 g, 0.223 mol) in dry dimethylformamide (250 ml) were added during 1.5 h. After a further 1.5 h at 5 °C the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was poured into water (1 l) and extracted with diethyl ether (5 × 500 ml). The combined extracts were dried (Na_2SO_4), evaporated, and the residual oil purified by column chromatography on silica gel (1 kg). Elution with ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 2) afforded recovered ethyl 1,3-dithiane-2-carboxylate (14.3 g). Further elution with ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 1) gave the *title compound* (9) (34.0 g, 43%), m.p. 142—144 °C (Found: C, 54.55; H, 5.05; N, 3.95; S, 18.1. $C_{16}H_{17}NO_4S_2$ requires C, 54.7; H, 4.9; N, 4.0; S, 18.25%); $\nu_{max.}$ ($CHBr_3$) 1 773 and 1 720 cm^{-1}; $\lambda_{max.}$ (EtOH) 220 (ε 39 600), 239sh (10 000), and 294nm (1 900); δ($CDCl_3$) 1.34 (3 H, t, CH_2CH_3), 1.77—2.10 (2 H, m, $CH_2CH_2CH_2$), 2.85—3.15 (4 H, m, $CH_2CH_2CH_2$), 4.30 (2 H, q, CH_2CH_3), 4.42 (2 H, s, CH_2N), and 7.65—8.00 (4 H, m, ArH).

Ethyl 3-(1,3-*Dihydro*-1,3-*dioxo*-2H-*isoindol*-2-*yl*)-2-*oxopropionate* (10).—Ethyl 2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-ylmethyl)-1,3-dithiane-2-carboxylate (9) (19.3 g, 55 mmol) in acetone (190 ml) was added, during 1 min, to *N*-bromosuccinimide (68.4 g, 384 mmol) in acetone–water (97 : 3) (900 ml) maintained between −5 and +5 °C. After 45 min, the reaction mixture was poured into a mixture of n-hexane–dichloromethane (1 : 1) (600 ml) and aqueous saturated sodium sulphite (1.6 l). The aqueous phase was extracted with hexane–dichloromethane (1 : 1) (2 × 600 ml) and the combined organic extracts were dried (Na_2SO_4) and the solvent evaporated. The residual oil was treated with dichloromethane (70 ml), filtered (to remove succinimide), and the filtrate concentrated to an oil. Purification by column chromatography on silica gel (800 g), eluting with chloroform, gave the *title compound* (10) (9.54 g, 66%), m.p. 89—90 °C (Found: C, 59.7; H, 4.3; N, 5.3. $C_{13}H_{11}NO_5$ requires C, 59.75; H, 4.25; N, 5.35%); $\nu_{max.}$ ($CHBr_3$) 1 775, 1 755, and 1 720 cm^{-1}; $\lambda_{max.}$ (EtOH) 241sh (ε 8 300) and 293 nm (2 300); δ($CDCl_3$) 1.40 (3 H, t, CH_2CH_3), 4.39 (2 H, q, CH_2CH_3), 4.98 (2 H, s, CH_2N), and 7.65—8.05 (4 H, m, ArH).

3-*Methyl*-6-*phthalimidomethyl*-1,2,4-*triazin*-5(4*H*)-*one* (11).—The α-keto ester (10) (9.7 g, 37.2 mmol) and acetamidrazone hydroiodide [28] (7.64 g, 38.0 mmol) in ethanol (100 ml) were heated at reflux for 2 h. After cooling at 4 °C overnight, the deposited crystals of the 1,2,4-*triazin*-5(4H)-*one* (11) were collected by filtration (5.40 g, 54%). The filtrate, after flash chromatography, afforded a further quantity of (11) (0.94 g, 10%), m.p. 288—299 °C (decomp.) (Found: C, 57.5; H, 3.75; N, 20.4. $C_{13}H_{10}N_4O_3$ requires C, 57.8; H, 3.75; N, 20.75%); $\nu_{max.}$ (Nujol) 3 300—2 500, 1 775, 1 720, and 1 675 cm^{-1}; $\lambda_{max.}$ (EtOH) 263sh, 291sh, (ε 2 800) and 301sh nm; δ[$(CD_3)_2SO$] 2.30 (3 H, s, Me), 4.80 (2 H, s, CH_2N), 8.00 (4 H, s, ArH), and 13.7 (1 H, br, s, NH).

6-*Aminomethyl*-3-*methyl*-1,2,4-*triazin*-5(4H)-*one Dihydrochloride* (8a)·2HCl.—3-Methyl-6-phthalimidomethyl-1,2,4-triazin-5(4*H*)-one (11) (7.31 g, 27.1 mmol) in 6M-hydrochloric acid (450 ml) was heated on a steam-bath for 18 h. The reaction mixture was concentrated to *ca.* 200 ml, cooled, and phthalic acid removed by filtration. The aqueous filtrate was evaporated to dryness and the residue boiled with ethanol–ethyl acetate (3 : 2). After overnight cooling at 4 °C, the precipitated *title compound* (8a)·2HCl was collected by filtration (5.14 g, 89%), m.p. 184—190 °C (Found: C, 28.05; H, 4.75; N, 26.3. $C_5H_8N_4O$·2HCl requires C, 28.2; H, 4.75; N, 26.3%); $\nu_{max.}$ (Nujol) 3 200, 2 500, 1 730, and 1 635 cm^{-1}; $\lambda_{max.}$ (EtOH) 234nm (ε 9 200); δ[$(CD_3)_2SO$] 2.50 (3 H, s, Me), 4.04 (2 H, br q, CH_2), and 8.50—8.90 (3 H, br, NH, NH_2).

6-(1-*Aminoethyl*)-3-*methyl*-1,2,4-*triazin*-5(4H)-*one Dihydrochloride* (8b)·2HCl.—6-(1-Benzoylaminoethyl)-3-methyl-1,2,4-triazin-5(4*H*)-one [8] (19.9 g, 77 mmol) in 6M-hydrochloric acid (650 ml) was heated on a steam-bath for 18 h. The cooled reaction mixture was filtered and the filtrate extracted with ethyl acetate. The aqueous layer was evaporated to dryness and the residue boiled with ethanol. The insoluble product, which was the *title compound* (8b) (9.4 g, 54%) was collected by filtration. Concentration of the filtrate afforded further (8b) (3.1 g, 16%), m.p. >210 °C (decomp.) (Found: C, 31.55; H, 5.2; N, 24.3. $C_6H_{12}Cl_2N_4O$ requires C, 31.75; H, 5.3; N, 24.65%); $\nu_{max.}$ (Nujol) 2 800—2 500, and 1 730 cm^{-1}; $\lambda_{max.}$ (EtOH) 235 (ε 8 950) and 260sh nm (5 350); δ[$(CD_3)_2SO$] 1.50 (3 H, d, $CHCH_3$), 2.51 (3 H, s, Me), and 4.48 (1 H, m, $CHCH_3$).

3-*Amino*-6-(1-*aminoethyl*)-1,2,4-*triazin*-5(4H)-*one Dihydrochloride* (8c)·2HCl.—3-Amino-6-(1-benzoylaminoethyl)-1,2,4-triazin-5(4*H*)-one (25.3 g, 0.098 mol) in 6M-hydrochloric acid (650 ml) was heated on a steam-bath for 18 h. The cooled reaction mixture was filtered and the filtrate extracted with ethyl acetate. The aqueous layer was evaporated to dryness and the residue boiled with ethanol. The insoluble product, which was the *title compound* (8c) (14.7 g, 66%), was collected by filtration. Concentration of the filtrate afforded further (8c) (4.3 g, 19%), m.p. 286 °C (decomp.) (Found: C, 26.6; H, 4.85; Cl, 31.25; N, 30.7. $C_5H_{11}Cl_2N_5O$ requires C, 26.35; H, 4.85; Cl, 31.1; N, 30.7%); δ(D_2O) 1.60 (3 H, d, $CHCH_3$) and 4.55—5.00 (1 H, m, $CHCH_3$).

2,5-*Anhydro*-3,4,6-*tri*-O-*benzoyl*-D-*allonic Acid* (14).—This was prepared by the procedure of Bobek and Farkas [13] and was obtained as a light brown syrup which solidified with time at room temperature. Recrystallization from cyclohexane–ethyl acetate gave (14) as colourless crystals, m.p. 101—103.5 °C (Found: C, 66.45; H, 4.55. $C_{22}H_{27}O_9$ requires C, 66.1; H, 4.5%); $[\alpha]_D^{23}$ +28.8° (*c* 5.13 in chloroform) [lit.,[13] $[\alpha]_D^{25}$ +31.3° (*c* 0.50, in chloroform)]; δ($CDCl_3$) 4.6—4.8 (3 H, m, 5-H, 6-H), 4.88 (1 H, d, 2-H), 5.79 (1 H, t, 4-H), 6.00 (1 H, t, 3-H), 7.2—7.7 (9 H, m, ArH), 7.85—8.20 (6 H, m, ArH), and 10.35 (1 H, br, CO_2H).

N-2-*Pyridylmethyl*-2,5-*anhydro*-3,4,6-*tri*-O-*benzoyl*-D-*allonamide* (15a).—To a stirred solution of 2-aminomethylpyridine (6a) (1.25 g, 11.5 mmol) and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (14) (5.00 g, 10.2 mmol) in dichloromethane (350 ml) was added dicyclohexylcarbodi-imide (2.2 g, 10.6 mmol). The reaction mixture was stirred at room temperature for 12 h. The dicyclohexylurea was filtered off and the filtrate evaporated to dryness. The resultant residue was purified by column chromatography on silica gel, eluting with diethyl ether–ethyl acetate (2 : 1), to give the *title compound* (15a) (4.25 g, 72%) as a colourless foam (Found: C, 67.55; H, 5.25; N, 4.7. $C_{33}H_{28}N_2O_8$·½H_2O requires C, 67.2; H, 4.95; N, 4.75%); $\nu_{max.}$ ($CHBr_3$) 3 400, 1 720, 1 673, and 1 520 cm^{-1}.

N-*Pyrazin*-2-*ylmethyl*-2,5-*anhydro*-3,4,6-*tri*-O-*benzoyl*-D-*allonamide* (15b).—Coupling of 2-aminomethylpyrazine [17] (6b) with the allonic acid (14) was carried out as described for the preparation of (15a). The *amide* (15b) (45%) was obtained as a foam, after purification by column chromatography on silica gel [ethyl acetate–cyclohexane (3 : 1) eluant] (Found: $[M + H]^+$, 582.1848. $C_{32}H_{28}N_3O_8$ requires 582.1874); $\nu_{max.}$ ($CHBr_3$) 3 420, 1 725, 1 680, and 1 520 cm^{-1}; $\lambda_{max.}$ (EtOH) 230.5 (ε 36 300), 267 (8 500), 272sh (7 950), and 282sh nm (3 350).

N-(2,3-*Dihydro*-3-*oxopyridazin*-6-*ylmethyl*)-2,5-*anhydro*-3,4,6-*tri*-O-*benzoyl*-D-*allonamide* (16a).—To a stirred solution of *N*-(2,3-dihydro-3-oxopyridazin-6-yl)methylamine (7a) [from hydrochloride salt * (2.20 g, 13.6 mmol)] and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (14) (6.68 g, 13.6 mmol) in dichloromethane (150 ml) was added a solution of dicyclohexylcarbodi-imide (2.94 g, 14.3 mmol) in dichloromethane (25 ml). The reaction mixture was stirred at room temperature for 3.5 h. Insoluble material (dicyclohexylurea and sodium chloride) was filtered off and the filtrate evaporated to dryness. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford the *title compound* (16a) (5.55 g, 68%) as a white foam (Found: C, 64.25; H, 4.45; N, 6.9. $C_{32}H_{27}N_3O_9$ requires C, 64.3; H, 4.55; N, 7.05%); $\lambda_{max.}$ (EtOH) 229 (ε 41 300), 276 (4 300), and 283 nm (4 100).

N-[1-(2,3-*Dihydro*-3-*oxopyridazin*-6-*yl*)*ethyl*]-2,5-*anhydro*-3,4,6-*tri*-O-*benzoyl*-D-*allonamides* (16b).—Coupling of *N*-1-(2,3-dihydro-3-oxopyridazin-6-yl)ethylamine (7b) with the allonic acid (14) was carried out as described for the preparation of (16a). The *amides* (16b) (88%) were obtained as a foam, after purification by column chromatography on silica gel [ethyl acetate as eluant] (Found: M^+, 611.1898. $C_{33}H_{29}N_3O_9$ requires *M*, 611.1904); $\nu_{max.}$ ($CHBr_3$) 3 360, 1 772, 1 720, and 1 515 cm^{-1}; $\lambda_{max.}$ (EtOH) 229 (ε 39 100), 276 (4 100), 283 (4 000), and 300sh nm (2 000).

N-(4,5-*Dihydro*-3-*methyl*-5-*oxo*-1,2,4-*triazin*-6-*ylmethyl*)-2,5-*anhydro*-3,4,6-*tri*-O-*benzoyl*-D-*allonamide* (17a).—To a stirred solution of 6-aminomethyl-3-methyl-1,2,4-triazin-5(4*H*)-one (8a) [from dihydrochloride salt (3.30 g, 15.5 mmol)] and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (14) (8.50 g, 17.4 mmol) in dry acetonitrile (500 ml) was added dicyclohexylcarbodi-imide (3.26 g, 16.0 mmol). After stirring at room temperature for 16 h the reaction mixture was filtered and the filtrate evaporated to give a gum. The gum was purified by flash chromatography on silica gel, eluting initially with ethyl acetate–cyclohexane (1 : 1), then ethyl acetate and finally ethyl acetate–ethanol (9 : 1), to provide the *title compound* (17a) (7.58 g, 80%) as a white solid, m.p. 187—190 °C (Found: C, 62.75; H, 4.6; N, 9.0. $C_{32}H_{28}N_4O_9$ requires C, 62.75; H, 4.6; N, 9.15%); $\nu_{max.}$ (Nujol) 3 420, 1 720, 1 680, and 1 550 cm^{-1}.

N-[1-(4,5-*Dihydro*-3-*methyl*-5-*oxo*-1,2,4-*triazin*-6-*yl*)*ethyl*]-2,5-*anhydro*-3,4,6-*tri*-O-*benzoyl*-D-*allonamides* (17b).—To a stirred solution of 6-(1-aminoethyl)-3-methyl-1,2,4-triazin-

* The free bases (7) and (8) were liberated from their (di)hydrochloride salts by treatment with an equivalent amount of aqueous sodium hydroxide. Water was removed by repeated evaporation with ethanol and the dry residue was used directly in the coupling experiment.

5(4*H*)-one (8b) [from dihydrochloride salt (2.63 g, 9.1 mmol)] and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (14) (4.47 g, 9.1 mmol) in dichloromethane (275 ml) was added a solution of dicyclohexylcarbodi-imide (1.88 g, 9.1 mmol) and the reaction mixture stirred at room temperature for 18 h. Insoluble material was filtered off and the filtrate evaporated to dryness. The residue was purified by chromatography on silica gel, eluting with ethyl acetate–ethanol (19 : 1), to provide the *title compounds* (17b) (4.80 g, 85%) as a foam (Found: C, 63.0; H, 4.9; N, 8.85. $C_{33}H_{30}N_4O_9$ requires C, 63.25; H, 4.85; N, 8.95%); $\nu_{max.}$ ($CHBr_3$) 3 400—3 200, 1 720, 1 680, 1 660 and 1 520 cm^{-1}; $\lambda_{max.}$ (EtOH) 230 (ε 44 200), 266 (6 850) and 274sh nm (6 500).

N-[1-(3-*Amino*-4,5-*dihydro*-5-*oxo*-1,2,4-*triazin*-6-*yl*)*ethyl*]-2,5-*anhydro*-3,4,6-*tri*-O-*benzoyl*-D-*allonamide* (17c).—To a stirred solution of 3-amino-6-(1-aminoethyl)-1,2,4-triazin-5(4*H*)-one (8c) [from hydrochloride salt (10.0 g, 43.9 mmol)], 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (14) (21.5 g, 43.9 mmol) and 1-hydroxybenzotriazole (5.92 g, 43.9 mmol) in DMF (400 ml) was added dicyclohexylcarbodi-imide (9.82 g, 47.7 mmol). After being stirred at room temperature for 18 h the reaction mixture was filtered and the filtrate evaporated to dryness. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate–ethanol (4 : 1), to provide the *title compounds* (17c) (14.5 g, 53%) as a foam (Found: C, 61.0; H, 4.7; N, 10.9. $C_{32}H_{29}N_5O_9$ requires C, 61.25; H, 4.65; N, 11.15%).

N-(3-*Aminopyrazin*-2-*ylmethyl*)-2,5-*anhydro*-3,4,6-*tri*-O-*benzoyl*-D-*allonamide* (29).—To a solution of 3-amino-2-aminomethylpyrazine (28) [24] (1.31 g, 10.6 mmol) and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (14) (5.20 g, 10.6 mmol) in dry acetonitrile (500 ml) was added dicyclohexylcarbodi-imide (2.40 g, 11.6 mmol). The reaction mixture was stirred for 16 h at room temperature and then filtered through Hyflo. The filtrate was evaporated to give a gum which was purified by column chromatography on silica gel. Elution with ethyl acetate–cyclohexane (7 : 3) gave the *title compound* (29) (3.35 g, 53%) as a foam (Found: $M^{+\cdot}$, 596.1945. $C_{32}H_{28}N_4O_8$ requires 596.1907); $\nu_{max.}$ ($CHBr_3$) 3 340, 1 725, 1 670, and 1 530 cm^{-1}; $\lambda_{max.}$ (EtOH) 231 (ε 43 300), 276 (4 100), 283 (4 100), and 321nm (5 650).

N-(3-*Benzamidopyrazin*-2-*ylmethyl*)-2,5-*anhydro*-3,4,6-*tri*-O-*benzoyl*-D-*allonamide* (30).—To a cooled (0 °C) solution of the amide (29) (5.0 g, 8.4 mmol) in dry pyridine (25 ml) was dropwise added benzoyl chloride (1.32 ml, 1.60 g, 11.3 mmol). The solution was stored at 4 °C for 18 h and then treated with water (5 ml). The solvents were evaporated and the residue treated with saturated aqueous sodium hydrogen carbonate (150 ml) and extracted with ethyl acetate (3 × 100 ml). The combined ethyl acetate extracts were dried ($MgSO_4$) and evaporated to give a foam. Purification of this by column chromatography on silica gel, eluting with ethyl acetate–cyclohexane (7 : 3), afforded the *title compound* (30) (5.2 g, 88%) as a foam (Found: C, 66.85; H, 4.6; N, 8.0. $C_{39}H_{32}N_4O_9$ requires C, 66.35; H, 4.7; N, 8.0%) (Found: $M^{+\cdot}$, 700.2170. $C_{39}H_{32}N_4O_9$ requires *M*, 700.2169); $\nu_{max.}$ ($CHBr_3$) 3 400, 1 725, 1 680, and 1 530 cm^{-1}; $\lambda_{max.}$ (EtOH) 231 (ε 41 700), 276 (11 400), and 304nm (3 650).

3-(2,3,5-*Tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazo*[1,5-a]-*pyridine* (18a).—The amide (15a) (5.55 g, 9.47 mmol) and phosphorus oxychloride (5 ml, 54.4 mmol) in dry 1,2-dichloroethane (350 ml) were heated at reflux for 2 h. Dry pyridine (15 ml) was added and the reaction mixture heated at reflux for a further 2.5 h. The solvents and excess of phosphorus oxychloride were removed and the crimson residue partitioned between ethyl acetate (300 ml) and saturated aqueous sodium hydrogencarbonate (500 ml). The ethyl acetate phase was dried ($MgSO_4$) and the solvent evaporated. The residue was purified by column chromatography on silica gel, eluting with diethyl ether–cyclohexane (3 : 1), to give the *title compound* (18a) (4.45 g, 84%) as a colourless foam (Found: $[M + H]^+$, 563.1814. $C_{32}H_{27}N_2O_7$ requires 563.1818); $\nu_{max.}$ ($CHBr_3$) 1 725 cm^{-1}; $\lambda_{max.}$ (EtOH) 225 (ε 47 000), 281 (10 800), 292 (7 400), and 332 nm (2 100).

3-(2,3,5-*Tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazo*[1,5-a]-*pyrazine* (18b).—The amide (15b) (5.1 g, 8.76 mmol) was dissolved in dry chloroform (180 ml) and the solution cooled to −30 °C. Phosphorus pentachloride (3.65 g, 17.5 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 60 h the reaction was quenched by shaking with saturated aqueous sodium hydrogen carbonate. The chloroform layer was separated and the aqueous phase extracted with chloroform (3 × 100 ml). The combined chloroform phases were dried ($MgSO_4$) and the solvent evaporated. The residue was purified by column chromatography on silica gel, eluting with benzene–ethyl acetate (1 : 1), to give the *title compound* (18b) (1.1 g, 22%) as an off-white foam (Found: $[M + H]^+$, 564.1740. $C_{32}H_{26}N_3O_7$ requires 564.1769).

2-*Chloro*-7-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazo*-[1,5-b]*pyridazine* (18c).—The amide (16a) (5.26 g, 8.80 mmol) and phosphorus oxychloride (6 ml, 64.4 mmol) in dry 1,2-dichloroethane (150 ml) were heated at reflux for 3.5 h. The solvent and excess of phosphorus oxychloride were removed under reduced pressure and the residue thoroughly shaken with saturated aqueous sodium hydrogencarbonate (100 ml) and ethyl acetate (150 ml). The ethyl acetate phase was separated and the aqueous layer further extracted with ethyl acetate (2 × 150 ml). The combined ethyl acetate extracts were dried (Na_2SO_4) and the solvent evaporated to give a brown gum. This material was purified by flash chromatography on silica gel, eluting with diethyl ether–ethyl acetate (1 : 1), to provide the *title compound* (18c) (3.08 g, 59%) as a yellow solid, m.p. 161—162 °C (from EtOAc) (Found: C, 64.35; H, 4.05; N, 7.05. $C_{32}H_{24}ClN_3O_7$ requires C, 64.25; H, 4.05; N, 7.05%); $\nu_{max.}$ ($CHBr_3$) 1 730 cm^{-1}; $\lambda_{max.}$ (EtOH) 233 (ε 96 200), 264 (9 300), 272 (9 300), 281 (6 400), and 366 nm (2 600).

2-*Chloro*-5-*methyl*-7-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)-*imidazo*[1,5-b]*pyridazine* (18d).—This *compound* (74%) was prepared by cyclization of the amides (16b), as described for the preparation of (18c), and was obtained as a yellow foam (Found: C, 65.0; H, 4.4; N, 6.5. $C_{33}H_{26}ClN_3O_7$ requires C, 64.75; H, 4.3; N, 6.85%); $\nu_{max.}$ ($CHBr_3$) 1 725 cm^{-1}; $\lambda_{max.}$ (EtOH) 233 (ε 42 300), 276 (5 800), and 382nm (6 200).

2-*Methyl*-7-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)*imidazo*-[5,1-f]-1,2,4-*triazin*-4(3H)-*one* (19a).—The amide (17a) (10.65 g, 17.4 mmol) and phosphorus oxychloride (7.45 ml, 80 mmol) in dry 1,2-dichloroethane (500 ml) were heated at reflux for 3 h. The solvent and excess of phosphorus oxychloride were removed and the residue partitioned between saturated aqueous sodium hydrogencarbonate (500 ml) and ethyl acetate (500 ml). The ethyl acetate phase was separated and the aqueous layer further extracted with ethyl acetate (2 × 250 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to give a foam. This material was purified by flash chromatography on silica gel, eluting with ethyl acetate–dichloromethane (1 : 1), to give the *title compound* (19a) (7.86 g, 76%) as a colourless foam (Found:

C, 63.8; H, 4.4; N, 9.05. $C_{32}H_{26}N_4O_8 \cdot \frac{1}{2}H_2O$ requires C, 63.7; H, 4.5; N, 9.3%); $\nu_{max.}$ ($CHBr_3$) 3 380 and 1 725 cm^{-1}.

2,5-*Dimethyl*-7-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)-*imidazo*[5,1-f]-1,2,4-*triazin*-4(3H)-*one* (19b).—This *compound* (100%) was prepared by cyclization of the amides (17b), as described for the preparation of (19a), and was obtained as a colourless foam (Found: C, 64.8; H, 4.6; N, 8.8. $C_{33}H_{28}N_4O_8$ requires C, 65.15; H, 4.65; N, 9.2%); $\nu_{max.}$ ($CHBr_3$) 3 380 and 1 725 cm^{-1}.

2-*Amino*-5-*methyl*-7-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)-*imidazo*[5,1-f]-1,2,4-*triazin*-4(3H)-*one* (19c).—The amides (17c) (14.5 g, 23.13 mmol) and phosphorus oxychloride (7 ml, 75.1 mmol) in dry 1,2-dichloroethane (550 ml) were heated at reflux for 1.5 h. The solvent and excess phosphorus oxychloride were removed under reduced pressure and the residue partitioned between ethyl acetate (300 ml) and saturated aqueous sodium hydrogencarbonate (300 ml). The organic layer was separated and the aqueous phase further extracted with ethyl acetate (2 × 100 ml). The combined ethyl acetate extracts were dried (Na_2SO_4) and the solvent evaporated. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate, to give the *title compound* (19c) (10.2 g, 72%) as an off-white foam (Found: C, 62.6; H, 4.5; N, 11.2. $C_{32}H_{27}N_5O_8$ requires C, 63.05; H, 4.45; N, 11.5%); $\nu_{max.}$ ($CHBr_3$) 3 490, 3 390, 1 725, and 1 655 cm^{-1}.

2,5-*Dimethyl*-7-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)-*imidazo*[5,1-f]-1,2,4-*triazine*-4(3H)-*thione* (24).—2,5-Dimethyl-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo-[5,1-*f*]-1,2,4-triazin-4(3*H*)-one (19b) (11.2 g, 18.4 mmol) and phosphorus pentasulphide (5.9 g, 26.6 mmol) in dioxane (225 ml) were heated at reflux for 3.5 h. The reaction mixture was poured into water (1l), allowed to stand for 30 min, and then extracted with dichloromethane (4 × 200 ml). The combined dichloromethane extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with light petroleum (b.p. 40—60 °C)–ethyl acetate (3 : 2), to give the *title compound* (24) (8.3 g, 72%) as a yellow foam (after decolourisation with activated charcoal) (Found: $M^{+\cdot}$, 624.1737. $C_{33}H_{28}N_4O_7S$ requires *M*, 624.1678); $\nu_{max.}$ ($CHBr_3$) 3 360, 1 725, 1 633, and 1 560 cm^{-1}.

8-*Benzamido*-3-(2,3,5-*tri*-O-*benzoyl*-β-D-*ribofuranosyl*)-*imidazo*[1,5-a]*pyrazine* (31).—The amide (30) (5.7 g, 8.13 mmol) and phosphorus oxychloride (3.3 ml, 36 mmol) in dry 1,2-dichloroethane (300 ml) were heated at reflux for 28 h. The solvent and excess phosphorus oxychloride were removed and the reaction mixture worked up as described for (19a). The crude product was purified by column chromatography on silica gel, eluting with chloroform–ethyl acetate–cyclohexane (2 : 1 : 1), to afford the *title compound* (31) (3.06 g, 55%) as an off-white foam (Found: C, 68.2; H, 4.4; N, 8.05. $C_{39}H_{30}N_4O_8$ requires C, 68.6; H, 4.45; N, 8.2%).

C-*Nucleosides* (20), (21), *and* (26): *General Procedure*.—A solution of the tri-*O*-benzoate (5 mmol) in saturated methanolic ammonia (250 ml) was allowed to stand at room temperature for 3 days. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel.

3-β-D-*Ribofuranosylimidazo*[1,5-a]*pyridine* (20a).—This *compound* (78%) was obtained from the tri-*O*-benzoate (18a) as colourless needles, m.p. 188—190 °C (from ethanol) (Found: C, 57.7; H, 5.65; N, 11.25. $C_{12}H_{14}N_2O_4$ requires C, 57.6; H, 5.65; N, 11.2%); $\lambda_{max.}$ (EtOH) 270sh (ε 5 800), 279 (8 000), 289 (6 650) and 334nm (2 150); *m/z* 250 ($M^{+\cdot}$, 22%), 161 (*M* − 89, 38), 147 (B + 30, 100).

3-β-D-*Ribofuranosylimidazo*[1,5-a]*pyrazine* (20b).—This *compound* (54%) was obtained from the tri-*O*-benzoate (18b) as an amorphous hygroscopic solid [(Found: $M^{+\cdot}$, 251.0900. $C_{11}H_{13}N_3O_4$ requires 251.0906), *m/z* 162 (*M* − 89, 48%) and 148 (B + 30, 100)]; $\nu_{max.}$ ($CHBr_3$) 3 600—3 300, 1 670, and 1 620 cm^{-1}; $\lambda_{max.}$ (EtOH) 223 (ε 26 400), 266 (3 600), 275 (4 100), 286 (3 500), and 335nm (1 800).

2-*Chloro*-7-β-D-*ribofuranosylimidazo*[1,5-b]*pyridazine* (20c).—This *compound* (80%) was obtained from the tri-*O*-benzoate (18c) as a yellow solid, m.p. 207—210 °C (Found: $[M + H]^+$, 286.0587. $C_{11}H_{13}{}^{35}ClN_3O_4$ requires 286.0595).

2-*Chloro*-5-*methyl*-7-β-D-*ribofuranosylimidazo*[1,5-b]-*pyridazine* (20d).—This *compound* (87%) was obtained from the tri-*O*-benzoate (18d) as yellow rosettes, m.p. 196—198 °C (from ethanol–ethyl acetate) (Found: C, 48.4; H, 4.85; Cl, 11.4; N, 13.75. $C_{12}H_{14}ClN_3O_4$ requires C, 48.1; H, 4.7; Cl, 11.8; N, 14.0%); $\lambda_{max.}$ (EtOH) 237 (ε 27 100), 266 (3 750), 274sh (3 600), 284sh (2 300), and 388 nm (2 000); *m/z* 299 ($M^{+\cdot}$, 10%), 210 (*M* − 89, 87), and 196 (B + 30, 100).

2-*Methyl*-7-β-D-*ribofuranosylimidazo*[5,1-f]-1,2,4-*triazin*-4(3H)-*one* (21a).—This *compound* (90%) was obtained from the tri-*O*-benzoate (19a), m.p. 194—195 °C (from ethanol); $\nu_{max.}$ (Nujol) 3 550—3 000, 1 728, and 1 680 cm^{-1}; $\lambda_{max.}$ (EtOH) 221 (ε 25 200) and 249sh nm (8 400) (Found: C, 46.6; H, 5.05; N, 20.15. $C_{11}H_{14}N_4O_5$ requires C, 46.8; H, 5.0; N, 19.85%).

2,5-*Dimethyl*-7-β-D-*ribofuranosylimidazo*[5,1-f]-1,2,4-*triazin*-4(3H)-*one* (21b).—This *compound* (87%) was obtained from the tri-*O*-benzoate (19b), m.p. 245—248 °C (from ethanol) (Found: C, 48.6; H, 5.55; N, 18.6. $C_{12}H_{16}N_4O_5$ requires C, 48.65; H, 5.45; N, 18.9%); $\nu_{max.}$ (Nujol) 3 500—3 100 and 1 700 cm^{-1}; $\lambda_{max.}$ (EtOH) 223 (ε 24 200) and 255 nm (9 000).

2-*Amino*-5-*methyl*-7-β-D-*ribofuranosylimidazo*[5,1-f]-1,2,4-*triazin*-4(3H)-*one* (21c).—This *compound* (68%) was obtained from the tri-*O*-benzoate (19c), m.p. 221—224 °C (from ethanol) (Found: C, 44.3; H, 5.1; N, 23.3. $C_{11}H_{15}N_5O_5$ requires C, 44.45; H, 5.1; N, 23.55%); $\lambda_{max.}$ (EtOH) 229 (ε 29 800) and 267 nm (6 100).

2,5-*Dimethyl*-7-β-D-*ribofuranosylimidazo*[5,1-f]-1,2,4-*triazine*-4(3H)-*thione* (26).—This *compound* (51%) was obtained from the tri-*O*-benzoate (24), m.p. 247—250 °C (decomp.) (from ethanol) (Found: C, 46.4; H, 5.3; N, 17.6; S, 9.85. $C_{12}H_{16}N_4O_4S$ requires C, 46.15; H, 5.15; N, 17.95; S, 10.25%); $\nu_{max.}$ (Nujol) 3 360—3 200, 1 630, and 1 570 cm^{-1}; $\lambda_{max.}$ (EtOH) 261 (ε 11 100) and 325 nm (15 900).

4-*Amino*-2,5-*dimethyl*-7-β-D-*ribofuranosylimidazo*[5,1-f]-1,2,4-*triazine* (25a) 2,5-Dimethyl-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[5,1-*f*]-1,2,4-triazine-4(3*H*)-thione (24) (5.10 g, 8.2 mmol) and sodium hydrogencarbonate (0.69 g, 8.2 mmol) were dissolved in dioxane (15 ml)–methanol (30 ml), and methyl iodide (3.48 g, 24.5 mmol) was added. The reaction mixture was stirred at room temperature for 30 h. The solvents were removed and the residue partitioned between water (20 ml) and dichloromethane (50 ml). The dichloromethane layer was dried (Na_2SO_4), evaporated, and the residue purified by column chromatography on silica gel.

Elution with light petroleum (b.p. 60—80 °C)–ethyl acetate (3 : 2) gave 2,5-dimethyl-4-methylthio-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[5,1-*f*]-1,2,4-triazine (3.52 g, 68%) as a pale yellow foam. This compound (3.96 g, 6.2 mmol) was treated with saturated methanolic ammonia (300 ml) at room temperature for 65 h. The solvent was removed and the residue crystallized from ethyl acetate–ethanol to give the *title compound* (25a) (1.19 g, 61%), m.p. 200—204 °C (Found: C, 46.25; H, 6.05; N, 22.15. $C_{12}H_{17}N_5O_4 \cdot H_2O$ requires C, 46.0; H, 6.1; N, 22.35%); $\nu_{max.}$ (Nujol) 3 600—3 000 and 1 650 cm^{-1}; $\lambda_{max.}$ (EtOH) 240 (ε 27 400), 265sh (5 700), 275sh (4 000), and 310 nm (2 800).

2,5-*Dimethyl*-4-*methylamino*-7-β-D-*ribofuranosylimidazo*-[5,1-f]-1,2,4-*triazine* (25b).—2,5-Dimethyl-4-methylthio-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[5,1-*f*]-1,2,4-triazine (5.5 g, 8.6 mmol) (see above) was treated with 33% methylamine in ethanol (275 ml) at room temperature for 20 h. The solvent was evaporated and the residue purified by column chromatography on silica gel. Elution with chloroform–ethanol (1 : 1) gave the *title compound* (25b) (1.28 g, 48%), m.p. 186—191 °C (Found: C, 47.8; H, 6.25; N, 21.05. $C_{13}H_{19}N_5O_4 \cdot H_2O$ requires C, 47.7; H, 6.45; N, 21.4%); $\lambda_{max.}$ (EtOH) 246 (ε 30 300) and 305 nm (2 700).

2-*Amino*-7-β-D-*ribofuranosylimidazo*[1,5-b]*pyridazine* (27a).—To a cooled (−78 °C) autoclave containing 2-chloro-7-β-D-ribofuranosylimidazo[1,5-*b*]pyridazine (20c) (1.13 g) was added liquid ammonia (40 ml). The autoclave was heated on a steam-bath for 24 h and then cooled to −78 °C and vented. The residual material was dissolved in a minimum quantity of ethanol and applied to a column of silica gel (Merck 60, Art 9385). Flash chromatography, initially eluting with dichloromethane–ethanol (9 : 1), and then with dichloromethane–ethanol (3 : 1), provided 2-*amino*-7-β-D-*ribofuranosylimidazo*[1,5-b]*pyridazine* (27a) (0.31 g, 30%), m.p. 199—202 °C (decomp.) (from ethanol) (Found: C, 48.4; H, 5.25; N, 20.15. $C_{11}H_{14}N_4O_4 \cdot \frac{1}{2}H_2O$ requires C, 48.0; H, 5.5; N, 20.35%); $\nu_{max.}$ (Nujol) 3 400—3 200 and 1 640 cm^{-1}; $\lambda_{max.}$ (EtOH) 244 (ε 23 200), 302 (3 150), and 335sh nm.

2-*Amino*-5-*methyl*-7-β-D-*ribofuranosylimidazo*[1,5-b]-*pyridazine* (27b).—To a cooled (−78 °C) autoclave containing 2-chloro-5-methyl-7-β-D-ribofuranosylimidazo[1,5-*b*]-pyridazine (20d) (450 mg) was added liquid ammonia (40 ml). The autoclave was heated on a steam-bath for 24 h and then cooled to −78 °C and vented. The residual material was purified by flash chromatography on silica gel. Elution with chloroform–ethanol (4 : 1) gave 2-*amino*-5-*methyl*-7-β-D-*ribofuranosylimidazo*[1,5-b]*pyridazine* (27b) (280 mg, 67%), m.p. 214—217 °C (from ethanol–ethyl acetate) (Found: C, 51.1; H, 5.7; N, 19.6. $C_{12}H_{16}N_4O_4$ requires C, 51.4; H, 5.75; N, 20.0%); $\lambda_{max.}$ (EtOH) 250 (ε 23 000), 304 (2 750), 313sh, and 343nm (2 350).

8-*Amino*-3-β-D-*ribofuranosylimidazo*[1,5-a]*pyrazine* (32).—8-Benzamido-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazo[1,5-*a*]pyrazine (31) (4.49 g, 6.58 mmol) in ethanol (70 ml) was treated with a solution of 33% methylamine–ethanol (350 ml) and the reaction mixture allowed to stand at room temperature for 2.5 days. The solvent was evaporated and the resultant residue dissolved in water (200 ml) and washed with ethyl acetate (2 × 100 ml). Decolourisation (activated charcoal) of the aqueous solution and evaporation gave a gum which was crystallized from methanol to give 8-*amino*-3-β-D-*ribofuranosylimidazo*[1,5-a]*pyrazine* (32) (558 mg, 32%), m.p. 217—220 °C (decomp.) (Found: C, 48.8; H, 5.4; N, 20.0. $C_{11}H_{14}N_4O_4 \cdot \frac{1}{2}CH_3OH$ requires C, 48.95; H, 5.75, N, 19.85%) (Found: $M^{+\cdot}$, 266.1029. $C_{11}H_{14}N_4O_4$ requires *M*, 266.1015. Found: *M* − 89, 177.0805. $C_8H_9N_4O$ requires 177.0776. Found: *M* − 103, 163.0635. $C_7H_7N_4O$ requires 163.0620).

2,5-*Dimethyl*-7-(2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)-*imidazo*[5,1-f]-1,2,4-*triazin*-4(3H)-*one* (23).—2,5-Dimethyl-7-β-D-ribofuranosylimidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-one (21b) (4.91 g, 16.6 mmol), toluene-*p*-sulphonic acid (6.23 g, 32.8 mmol), and 2,2-dimethoxypropane (37.5 ml, 31.7 g) in dry acetone (600 ml) were stirred at room temperature for 20 h. The reaction mixture was basified by addition of ammonium hydroxide (*d* 0.88) and evaporated to dryness. The residue was purified by chromatography on silica gel, eluting with ethyl acetate, to furnish the *title compound* (23) (4.73 g, 85%) as a foam (Found: C, 53.6; H, 6.15; N, 16.4. $C_{15}H_{20}N_4O_5$ requires C, 53.55; H, 6.0; N, 16.65%); $\nu_{max.}$ ($CHBr_3$) 3 380, 3 200, 1 710, 1 690, and 1 645 cm^{-1}; $\lambda_{max.}$ (EtOH) 222 (ε 23 300) and 254 nm (8 700); δ[$(CD_3)_2SO$] 1.35, 1.52 [6 H, 2 × s, $(CH_3)_2C$], 2.25 (3 H, s, CH_3), 2.50 (3 H, s, CH_3), 3.2—3.6 (2 H, m, 5′-H, 5″-H), 4.10 (1 H, m, 4′-H), 4.85 (1 H, m, 3′-H), 5.1 (1 H, br, OH), and 5.2—5.3 (2 H, m, 1′-H, 2′-H).

2-*Chloro*-5-*methyl*-7-(2,3-O-*isopropylidene*-β-D-*ribofuranosyl*)*imidazo*[1,5-b]*pyridazine* (22).—This *compound* (77%) was prepared from the nucleoside (20d), as described for the preparation of (23), and was obtained as a yellow foam (Found: C, 53.2; H, 5.6; N, 12.0. $C_{15}H_{18}ClN_3O_4$ requires C, 53.0; H, 5.35; N, 12.35%); δ[$(CD_3)_2SO$] 1.38, 1.57 [6 H, 2 × s, $(CH_3)_2C$], 2.49 (3 H, s, CH_3), 3.38—3.55 (3 H, m, 5′-H, 5″-H, OH), 4.13 (1 H, m, 4′-H), 4.89 (1 H, dd, 3′-H), 5.35—5.42 (2 H, m, 1′-H, 2′-H), 6.85 (1 H, d, *J* 10, 7-H), and 8.30 (1 H, d, *J* 10, 8-H).

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Received 5th July 1983; *Paper* 3/1158