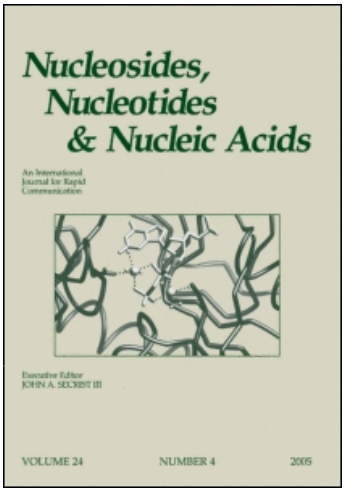

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Novel Acyclonucleosides. Part 2. 2, 3-Dihydroxy-1-Methoxypropyl-and 3-Hydroxy-1-Methoxypropyl-Substituted Purines

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NOVEL ACYCLONUCLEOSIDES. PART 2. 2,3-DIHYDROXY-1-METHOXYPROPYL- AND 3-HYDROXY-1-METHOXYPROPYL-SUBSTITUTED PURINES

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ABSTRACT
Novel purine nucleoside analogues in which the N-9 ribosyl moiety is replaced by a 2,3-dihydroxy-1-methoxypropyl or 3-hydroxy- 1-methoxypropyl substituent and their N-7 substituted isomers have been synthesized and tested for antiviral activity.

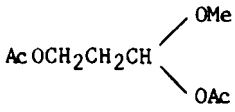
INTRODUCTION

A number of acyclic analogues of purine nucleosides with antiviral activity have been described in recent years[1]. In these compounds, the acyclic substituent in each case is related structurally to a portion of the carbohydrate moiety of a nucleoside. We have described previously[2] the preparation of a series of 1-(2,3-dihydroxy-1-methoxyprop-1-yl)- and 1-(3-hydroxy-1-methoxyprop-1-yl)-derivatives of pyrimidines. The acyclic substituents in these analogues can be regarded as the C(4')-O-C(1')-C(2')-C(3') portions of ribose and 2'-deoxyribose, respectively. In this publication we report our extension of this work to the synthesis of a series of novel purine derivatives substituted at either N-9 or N-7 with a 2,3-dihydroxy-1-methoxyprop-1-yl or 3-hydroxy-1-methoxyprop-1-yl moiety.

RESULTS AND DISCUSSION

Initial attempts to react 2,3-diacetoxy-1,1-dimethoxypropane (2) with pertrimethylsilylated 6-N-benzoyladenine and 2-N-acetylguanine in the presence of stannic chloride, using conditions similar to those under which N-1 substitution of pertrimethylsilylated pyrimidines was achieved[2], were unsuccessful. Since O-acyl groups are better leaving groups in nucleophilic displacements than are O-alkyl groups, the

reaction of pertrimethylsilylated purines with 1-acetyl-1-methoxy-substituted propanes was subsequently investigated. 1,3-Diacetoxy-1-methoxypropane (1) was prepared as described previously[2]. 1,2,3-Triacetoxy-1-methoxypropane (3) was obtained in 92% yield by treatment of 2 with acetic anhydride and concentrated sulphuric acid.



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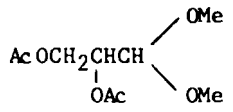

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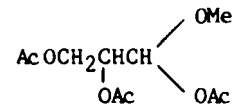


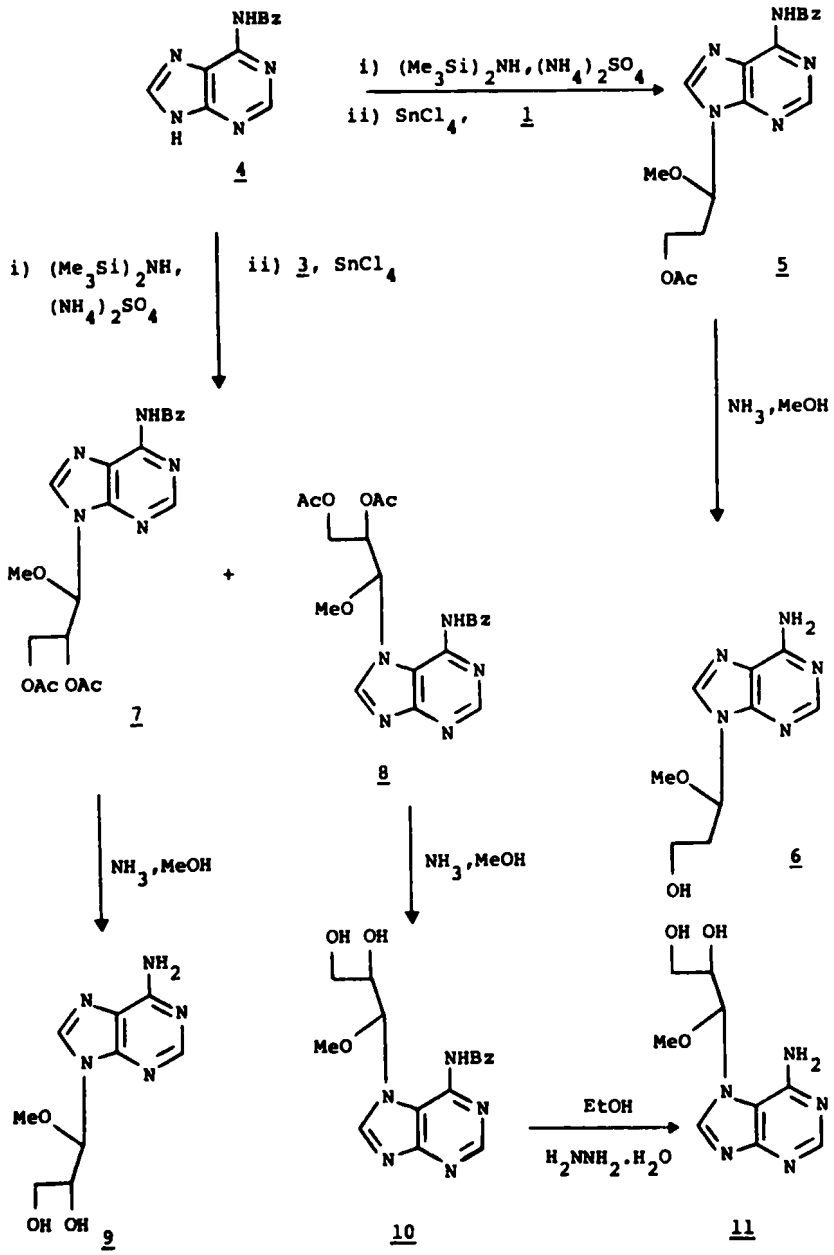
3

9(7)-(2,3-Diacetoxy-1-methoxyprop-1-yl)-(7,8,17,18,25/26,29,33), and 9(7)-(3-acetoxy-1-methoxyprop-1-yl)purines (5,13,14,22/23) were prepared in yields ranging from 9-81%, by reaction of 1,2,3-triacetoxy-1-methoxypropane (3) and 1,3-diacetoxy-1-methoxypropane (1), respectively, with pertrimethylsilyl derivatives of purines (4,12,21,28, 32) in anhydrous acetonitrile in the presence of stannic chloride, a modification of the Hilbert-Johnson reaction[3]. Acetyl and benzoyl groups were subsequently removed from N,O-protected acyclic nucleoside analogues by treatment with either ammonia in aqueous methanol at 25°C (Procedure A) or hydrazine hydrate in ethanol at reflux temperature (Procedure B), affording the required 9(7)-(2,3-dihydroxy-1-methoxyprop-1-yl)-(9,10,11,19,20,27,30,31,34) and 9(7)-(3-hydroxy-1-methoxyprop-1-yl)purines (6,15,16,24) in yields varying from 21-99%.

Reaction of the trimethylsilyl derivative of 6-N-benzoyladenine (4) with 1,2,3-triacetoxy-1-methoxypropane (3) afforded both N-9 (7) and N-7 (8) isomers in the ratio 2:3. The isomers were readily separated and 7 was treated with methanolic ammonia, providing the required 9-(2,3-dihydroxy-1-methoxyprop-1-yl)adenine (9) in 53% yield. In the case of the N-7 isomer (8), treatment with methanolic ammonia removed only the O-acetyl groups, giving the N-benzoyl derivative (10). Conversion of 10 to 11 was achieved with hydrazine hydrate.

Reaction of the trimethylsilyl derivative of 6-N-benzoyladenine (4) with 1,3-diacetoxy-1-methoxypropane (1), afforded only the N-9 isomer (5), which on deprotection in methanolic ammonia yielded 9-(3-hydroxy-1-methoxyprop-1-yl)adenine (6) (Scheme 1).

Adenine acyclonucleosides



SCHEME 1

Reaction of the trimethylsilyl derivative of 2-N-acetylguanine (12) with either 3 or 1, afforded both N-9 (17 and 13) and N-7 (18 and 14) isomers in the ratios 1:4 and 1:2, respectively. All four isomers were deprotected using hydrazine hydrate, providing 19,20,15 and 16 (Scheme 2).

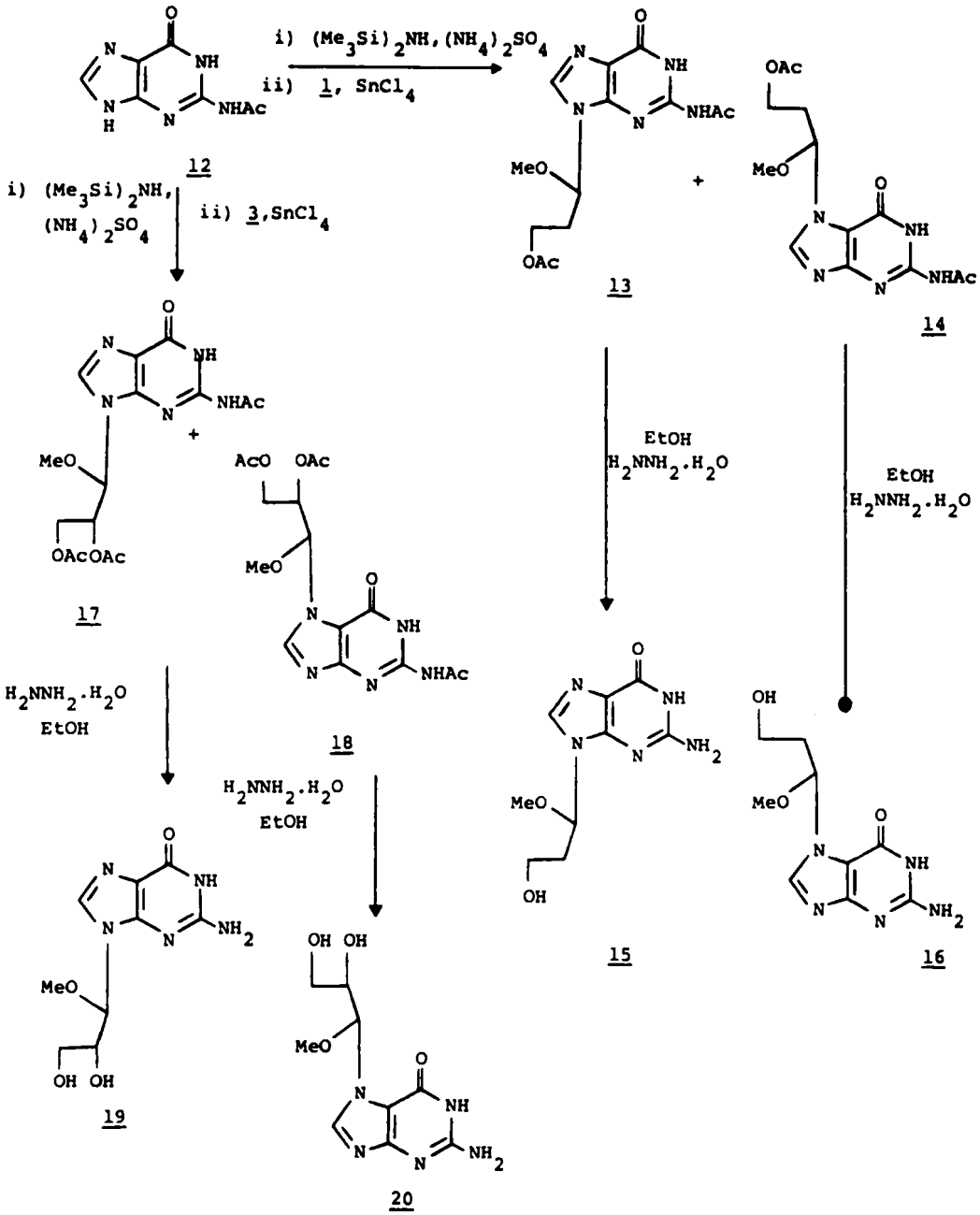
Reaction of the trimethylsilyl derivative of hypoxanthine (21) with 1,3-diacetoxy-1-methoxypropane (1) resulted in an inseparable mixture of N-9 and N-7 alkylated products (22 + 23), in the ratio 1.7:1 and also a small amount (9%) of a dialkylated product. Treatment of the mixture (22 + 23) with methanolic ammonia, gave a mixture of 9- and 7-(3-hydroxy-1-methoxyprop-1-yl)hypoxanthine from which only the 9-isomer (24) could be obtained pure by fractional crystallisation (Scheme 3). Reaction of the trimethylsilyl derivative of hypoxanthine (21) with 1,2,3-triacetoxy-1-methoxypropane (3) also gave an inseparable mixture of 9- and 7-alkylated products (25 + 26). Treatment of the mixture (25 + 26) with methanolic ammonia afforded a mixture of 9- and 7-(3,4,-dihydroxy-1-methoxyprop-1-yl)hypoxanthine, from which a small amount of one diastereoisomer of the N-9 substituted product (27a) was isolated pure by fractional crystallisation (Scheme 3). Confirmation of the structure of 27 was obtained by an independent synthesis from 9. Treatment of 9 with sodium nitrite and acetic acid gave 27, which was isolated as a 3:2 mixture of diastereoisomers (27b).

Reaction of the trimethylsilyl derivative of 2,6-diacetamido purine (28) with 3 afforded only one isomer, which was shown by ^{1}H and ^{13}C NMR to be the N-9 substituted derivative 29. Treatment of 29 with methanolic ammonia yielded the 2-N-acetyl derivative 30. Treatment of 30 with hydrazine hydrate achieved N-deacetylation giving 2,6-diamino-9-(2,3-dihydroxy-1-methoxyprop-1-yl)purine[4] (31) in 93% yield (Scheme 4).

Reaction of the trimethylsilyl derivative of theophylline (32) with 3, again afforded only one isomer, which was shown to be the N-7 substituted derivative 33. Deprotection of 33 with methanolic ammonia, gave the required 7-(2,3-dihydroxy-1-methoxyprop-1-yl)theophylline (34) in 81% yield (Scheme 5).

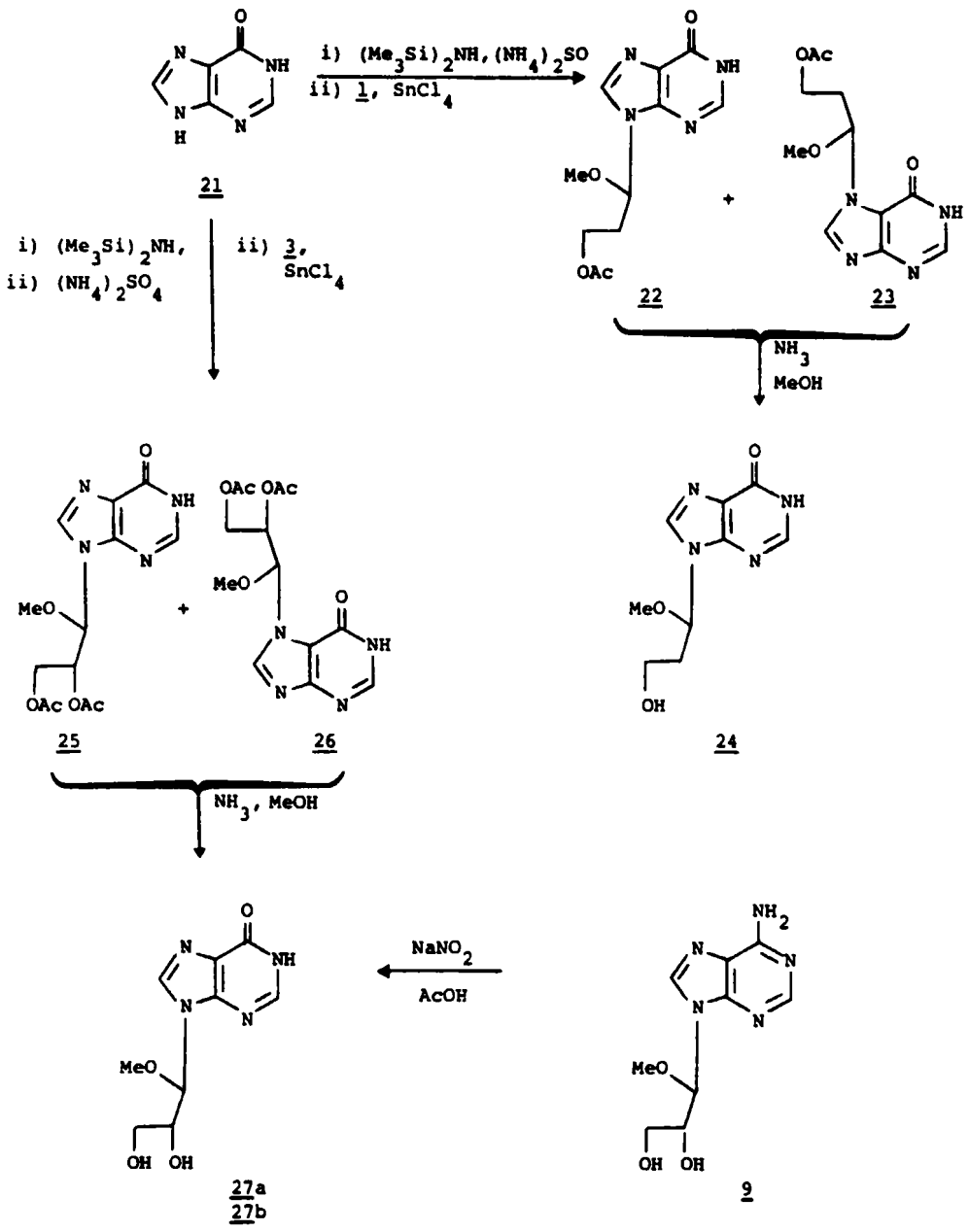
The ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) of the 9(7)-(2,3-diacetoxy-1-methoxyprop-1-yl)- (7,8,17,18,29,33) and 9(7)-(2,3-dihydroxy-1-methoxyprop-1-yl)purines (9,11,19,20,27,31,34) in the majority of cases indicated the presence of the two possible diastereo-

Guanine acyclonucleosides



SCHEME 2

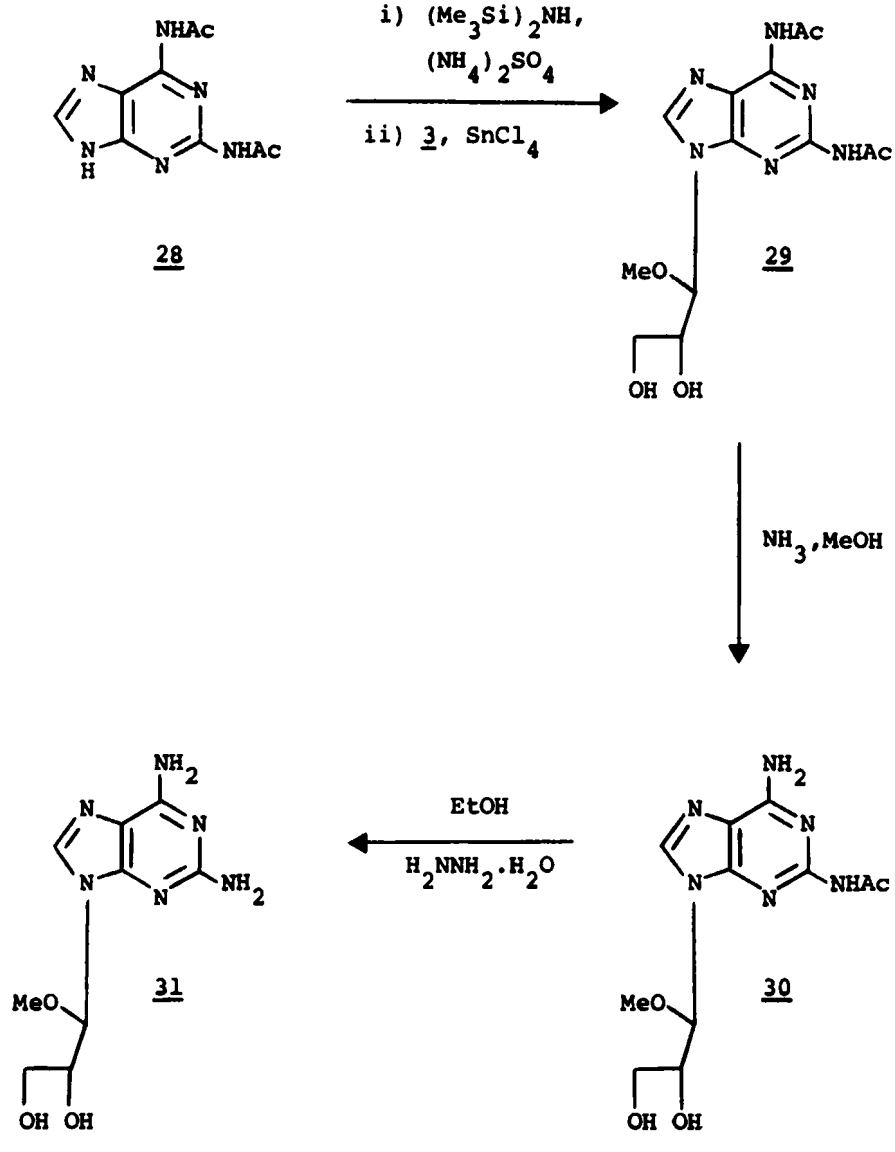
Hypoxanthine acyclonucleosides



a = one diastereoisomer
b = two diastereoisomers

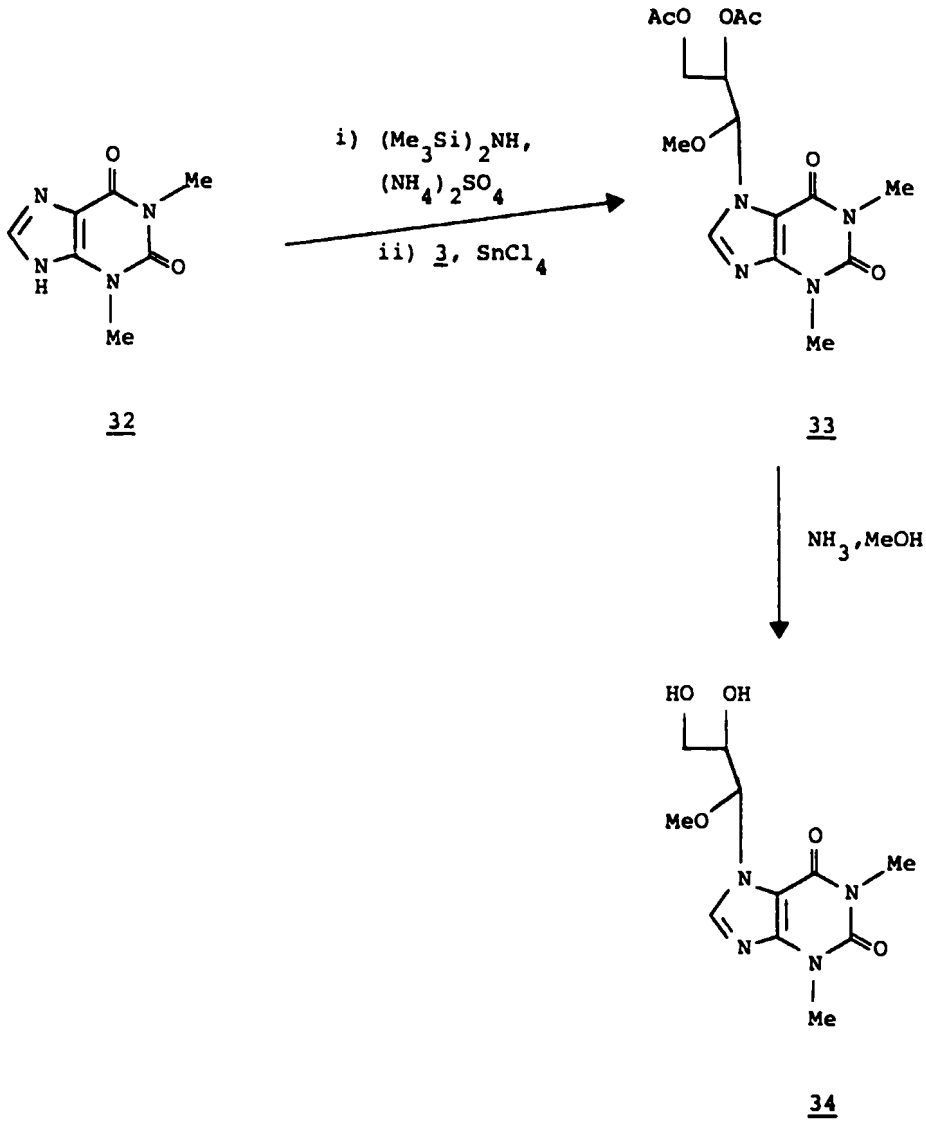
SCHEME 3

2,6-Diaminopurine acyclonucleosides



SCHEME 4

Theophylline acyclonucleosides



32 33 34

SCHEME 5

TABLE 1

^{13}C Chemical Shifts[a] for 9(7)-(2,3-Diacetoxy-1-methoxyprop-1-yl) and 9(7)-(2,3-dihydroxy-1-methoxyprop-1-yl)purines

Compound	C2	C4	C5	C6	C8	C-OMe	CH_3O	CHOR	CH_2OR
7	152·0	151.8 152.2	125·1	152·7	142.5 142.9	83.6 84.1	56.5 56.8	70.1 70.3	61.3 61.6
8	149·8	160·8	117·0	152·0	146·4	85.8 86.6	57.1 57.5	70.9 71.4	61.1 61.4
9	152·5	149.7 150.5	118·4	155·9	139.6 140.0	85.0 85.2	55.9 56.3	71.3 72.5	61.9 62.3
11	152·3	160.3 160.6	110·3	151·5	145.1 146.0	89·3	56·5	72.4 73.4	61.7 62.0
18	147·2	157·4	110.9 111.1	152.2 152.4	142.7 143.7	85.5 85.9	56.4 56.9	70·9	61.1 61.5
19	153.5 153.6	151.3 152.1	116.0 116.2	156·7	136.1 136.2	84.4 84.7	55.7 56.1	71.3 72.5	61.8 62.3
20	152·8	159·5	107.8 108.6	154·6	142.1 142.6	87·5	55.7 56.3	71.8 72.7	62.0 62.3
27a	148.4	145.7	123.6	156.6	138.9	85.4	56.4	72.4	61.7
27b	148.4 149.2	145.6 145.8	123·6	156·7	138.8 139.1	85.5 85.7	56.0 56.4	71.4 72.4	61.8 62.2
29	152.4 153.0	149·6	119.1 119.3	160·0	141.2 141.6	83.3 83.8	56.5 56.7	70.1 70.4	61.3 61.6
31	156.0	152.7	112.8	160.2	136.4	84.5	55.6	71.3	62.3
33	154.1 154.3	148·7	105.8 106.2	150·8	141.1 142.0	85.4 85.9	56.6 57.1	70·7	61.1 61.5
34	154.4	148.2	105.9	150.8	141.4	87.8	56.7	72.4	61.8

R = H or Ac

[a]Determined in $(CD_3)_2SO$ and quoted in ppm downfield from TMS

TABLE 2

^{13}C Chemical Shifts[a] for 9(7)-(3-Acetoxy-1-methoxyprop-1-yl) and 9(7)-(3-Hydroxy-1-methoxyprop-1-yl)purines

Compound	C2	C4	C5	C6	C8	C-OMe	CH_3O	CH_2	CH_2OR
5	151.6	150.3	125.4	152.4	142.8	83.6	55.9	33.1	59.7
6	152.6	149.8	118.7	156.0	139.2	82.8	56.5	37.5	55.7
13	147.8	148.7	120.3	154.8	138.1	83.4	59.7	33.2	55.7
14	147.0	157.5	111.2	152.4	142.9	85.8	59.7	34.3	55.9
24	148.6	145.8	124.1	156.8	138.7	83.5	56.5	37.2	55.9

R = H or Ac.

[a]Determined in $(CD_3)_2SO$ and quoted in ppm downfield from TMS.

isomers. No attempt was made to separate the isomers, although they were not always found in equal amounts. This is probably attributable more to differences in their behaviour during isolation (fractional crystallisation) than to any stereoselectivity during initial reaction of the acyclic alkylating agent with the purine base. This difference in behaviour of the diastereoisomers was clearly demonstrated when fractional crystallisation of a mixture of N-9 and N-7-(2,3-dihydroxy-1-methoxyprop-1-yl)hypoxanthines resulted in the isolation of a single diastereoisomer of the N-9 substituted hypoxanthine (27a). It is worth noting, that the presence of diastereoisomers cannot always be detected from ^{13}C NMR data. In the ^{13}C NMR spectra of compounds 31 and 34, only a single resonance was apparent for each carbon. The ^{1}H NMR spectra for these compounds however, demonstrate unequivocally that each is a mixture of diastereoisomers.

The UV data supported by the ^{13}C NMR data presented in Tables 1 and 2 was used to determine the position of alkylation in the N-7 and N-9

substituted isomers. It has been reported[7] that when the site of attachment of the acyclic substituent is changed from N-9 (eg. 19) to N-7 (eg. 20), the downfield shift of the C-4 resonance should approximately equal the upfield shift of the C-5 resonance. The data presented in Tables 1 and 2 are consistent with this observation.

All of the acyclonucleosides prepared in this study (5-11,13-20, 22-27,29,31,33,34) were tested for activity against representative RNA and DNA viruses in cell cultures. At concentrations up to 100μg/ml, 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 in Vero (African green monkey kidney) cells. At the concentrations examined, none of the compounds was toxic for the cell monolayer.

EXPERIMENTAL

Melting points were determined using a Reichert Kofler apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 197 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian EM-360 60 MHz or EM-390 90 MHz spectrometer. ^{13}C NMR spectra were determined with a Bruker 20.15 MHz instrument. Mass spectra were recorded using a V.G. 70-70 mass spectrometer and, unless otherwise stated, were performed at 70 e.v. and a source temperature of 200°C. Chromatography was performed on Merck 7736 60H silica gel. Elemental analysis was carried out on a Carlo Erba model 1106 analyzer.

1,2,3-Triacetoxy-1-methoxypropane (3)

2,3-Diacetoxy-1,1-dimethoxypropane[2] (2, 11g, 50mmol) and acetic anhydride (13.3g, 130mmol) were stirred in the presence of concentrated sulphuric acid (1 drop) at 25°C for 24h. The mixture was poured into iced water (100mL) and the aqueous solution extracted with chloroform (3 x 80mL). The chloroform layer was washed with dilute sodium bicarbonate solution (100mL) and water (100mL) and dried (anhydrous calcium chloride). The solvent was evaporated under reduced pressure to give a pale yellow liquid. This was chromatographed on silica eluting with chloroform, affording 3 (11.46g, 92%) as a clear oil, υ_{max} (film) (1740 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 9H, 3 x CH_3CO), 3.47 (s, 3H, CH_3O)m 4.30 (m, 2H, CH_2) 5.23 (m, 1H, CHOAc), 5.88 (m, 1H, CH(OMe)OAc); MS (Ammonia CI) m/z 266 (MNH_4^+, 28%), 189 (M^+ - OCH_3, 100%).

General Procedure for Synthesis of 9(7)-(2,3-Diacetoxy-1-methoxyprop-1-yl)purines (7,8,17,18,25,26,29,33) and 9(7)-(3-Acetoxy-1-methoxy-prop-1-yl)purines (5,13,14,22,23)

A mixture of the appropriate purine (10mmol) and 1,1,1,3,3,3-hexamethyldisilazane (50mL) was heated in the presence of a catalytic amount of ammonium sulphate at 160°C for 20h. Evaporation under reduced pressure afforded the pertrimethylsilylated purines, usually as mobile oils, which were used immediately without further purification.

To a solution of the pertrimethylsilylated purine (10mmol) in anhydrous acetonitrile (100mL) was added 1,2,3-triacetoxy-1-methoxypropane (3, 2.73g, 11mmol) or 1,3-diacetoxy-1-methoxypropane[2] (1, 2.09g, 11mmol). The resultant solution was cooled to -78°C and treated under nitrogen with anhydrous stannic chloride (0.3-2.5 molar equivalents). The reaction mixture was stirred at -78°C for 15 minutes then slowly allowed to attain room temperature before stirring at 25°C for 20h. The volume of the reaction mixture was reduced to ca 20mL under reduced pressure and saturated sodium bicarbonate solution (50mL) was cautiously added. The aqueous slurry was extracted with chloroform (3 x 80mL), the combined extracts dried (anhydrous magnesium sulphate) and the solvent evaporated under reduced pressure, affording the crude reaction products. Purification of the products was achieved by column chromatography, eluting with the solvent specified.

9-(3-Acetoxy-1-methoxyprop-1-yl)-N^6-benzoyladenine (5), isolated as a pale yellow hygroscopic foam in 81% yield after chromatography (ethyl acetate-methanol 50:1); υ_{max} (film) 3400 (NH), 1740 and 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H, CH_3CO), 2.47 (m, 2H, CH_2), 3.34 (s, 3H, CH_3O), 4.24 (t, 2H, J = 6Hz, CH_2OAc), 5.88 (t, 1H, J = 6 Hz, CH), 7.4 - 8.2 (m, 5H, aromatic), 8.17 (s, 1H, 2-H or 8-H), 8.77 (s, 1H, 2-H or 8-H), 9.23 (br.s, 1H, NH); MS m/z 223 (M^+, 14%).

Anal. Calcd. for $C_{18}H_{19}N_5O_4.0.5\ H_2O$: C, 57.21; H, 5.30; N, 18.50
Found : C, 57.41; H, 5.27; N, 18.29%.

N^6-Benzoyl-9-(2,3-diacetoxy-1-methoxyprop-1-yl)adenine (7), isolated as a white hygroscopic foam in 28% yield after chromatography (ethyl acetate-methanol 50:1); υ_{max} (nujol) 3200 (NH), 1740 and 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8 (s, 1.5H, CH_3CO), 1.98 (s, 1.5H, CH_3CO), 2.07 (s, 3H, CH_3CO), 3.30 (s, 1.5H, CH_3O), 3.35 (s, 1.5H, CH_3O), 4.24 (m, 2H, CH_2), 5.56 (m, 1H, CHOAc), 5.88 (d, 0.5H, J = 9 Hz, $CHOCH_3$),

5.95 (d, 0.5H, J = 7.5 Hz, $CHOCH_3$), 7.40 - 8.20 (m, 5H, aromatic), 8.16 (s, 1H, 2-H or 8-H), 8.73 (s, 0.5H, 2-H or 8-H), 8.78 (s, 0.5H, 2-H or 8-H), 9.26 (br.s, 1H, NH); MS m/z 427 (M^+, 6%).

Anal. Calcd. for $C_{20}H_{21}N_5O_6$: C, 56.20; H, 4.95; N, 16.39
Found : C, 56.10; H, 5.19; N, 16.57%.

Approximate diastereoisomeric ratio, 1:1.

N^6-Benzoyl-7-(2,3-Diacetoxy-1-methoxyprop-1-yl)adenine (8), isolated as a white hygroscopic foam in 40% yield during the isolation of 7; υ_{max} (nujol) 1740 and 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (m, 6H, 2 x CH_3CO), 3.44 (s, 0.4H, CH_3O), 3.50 (s, 0.6H, CH_3O), 4.30 (m, 2H, CH_2), 5.65 (m, 1H, CHOAc), 7.05 (m, 1H, $CHOCH_3$), 7.4 - 8.4 (m, 5H, aromatic), 8.36 (s, 1H, 2-H or 8-H), 8.44 (s, 1H, 2-H or 8-H); MS m/z 427 (M^+, 4%).

Anal. Calcd. for $C_{20}H_{21}N_5O_6.1.5\ H_2O$: C, 52.86; H, 5.32; N, 15.41
Found : C, 52.71; H, 5.14; N, 15.85%.

Approximate diastereoisomeric ratio, 3:2.

9-(3-Acetoxy-1-methoxyprop-1-yl)-N^2-acetylguanine (13), isolated in 12% yield after chromatography (chloroform-ethanol 50:1) and recrystallisation from methanol, m.p. 180 - 1°C; IR υ_{max} (KBr) 3600 - 2700 (NH), 1745, 1720, 1690 and 1620 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.92 (s, 3H, CH_3CO), 2.20 (s, 3H, CH_3CO), 2.50 (m, 2H, CH_2), 3.18 (s, 3H, CH_3O), 4.00 (t, 2H, J = 6 Hz, CH_2OAc), 5.50 (t, 1H, J = 6 Hz, CH), 8.15 (s, 1H, 8-H), 11.68 (br.s, 1H, NH), 12.06 (br.s, 1H, NH); MS m/z 323 (M^+, 2%).

Anal. Calcd. for $C_{13}H_{17}N_5O_5$: C, 48.29; H, 5.30; N, 21.66
Found : C, 48.28; H, 5.03; N, 21.40%.

7-(3-Acetoxy-1-methoxyprop-1-yl)-N^2-acetylguanine (14) isolated by recrystallisation from methanol in 21% yield during the isolation of 13; m.p. 160 - 2°C; IR υ_{max} (KBr) 3500 - 2700 (NH), 1750, 1670 and 1620 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 1.96 (s, 3H, CH_3CO), 2.23 (s, 3H, CH_3CO), 2.50 (m, 2H, CH_2), 3.26 (s, 3H, CH_3O), 4.04 (t, 2H, J = 6 Hz, CH_2OAc), 5.90 (t, 1H, J = 6 Hz, CH), 8.50 (s, 1H, 8-H), 11.68 (br.s. 1H, NH), 12.24 (br.s, 1H, NH); MS m/z 323 (M^+, 10%).

Anal. Calcd. for $C_{13}H_{17}N_5O_5$: C, 48.29; H, 5.30; N, 21.66
Found : C, 48.37; H, 5.08; N, 21.77%.

Mixture of 9- and 7-(3-Acetoxy-1-methoxyprop-1-yl)hypoxanthines (22+23)

The crude product from the reaction of pertrimethylsilylated hypoxanthine, 1 and stannic chloride (Scheme 3), was shown by t.l.c.

(chloroform–methanol 20:1) to be one major component (Rf 0.01) with a minor forerunning impurity. These were isolated by chromatography (chloroform–methanol 20:1). The component at Rf 0.01 was shown to be a mixture of 9- and 7-(3-acetoxy-1-methoxyprop-1-yl)hypoxanthines (22+23) (45% yield), containing 64% of the 9-isomer. The two isomers could not be separated by recrystallisation or by any chromatographic technique attempted (including h.p.l.c.); m.p. (mixture) 76 - 88°C; MS m/z 266 (M^+, 2%).

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04
Found : C, 49.56; H, 5.27; N, 21.10%.

The minor component (9%) was shown to be a di-alkylated product.

Mixture of 9- and 7-(2,3-diacetoxy-1-methoxyprop-1-yl)hypoxanthines (25, 26).

The crude product from the reaction of pertrimethylsilylated hypoxanthine, 3 and stannic chloride (Scheme 3) was shown by t.l.c. (chloroform–methanol 10:1) to be one major component (Rf 0.30). This was isolated by column chromatography (chloroform–methanol 20:1) as a white foam and shown by ^1H NMR and ^{13}C NMR to be a mixture of 9- and 7-(2,3-diacetoxy-1-methoxyprop-1-yl)hypoxanthines (25+26) (57% yield) in the ratio 1:2. The two isomers could not be separated by chromatography or crystallisation.

N^2-Acetyl-9-(2,3-diacetoxy-1-methoxyprop-1-yl)guanine (17), isolated in 9% yield after chromatography (ethyl acetate–methanol 20:1) and crystallisation (acetone–hexane); m.p. 197 - 208°C; υ_{max} (nujol) 3140 (NH), 1750, 1670, 1600 (C=O) cm^{-1}; ^1H NMR [$(CD_3)_2SO$] 1.7 - 2.3 (m, 9H, 3 x CH_3CO), 3.30 (s, 3H, CH_3O), 4.32 (m, 2H, CH_2), 5.60 (m, 2H, $CHOCH_3$ + CHOAc), 8.14 (br.s, 1H, 8-H), 11.19 (br.s, 2H, 2 x NH); MS m/z 381 (M^+, 3%).

Anal. Calcd. for $C_{15}H_{19}N_5O_7$: C, 47.24; H, 5.02; N, 18.37
Found : C, 46.91; H, 5.11; N, 18.24%.

Approximate diastereoisomeric ratio, 3:2.

N^2-Acetyl-7-(2,3-diacetoxy-1-methoxyprop-1-yl)guanine (18), isolated in 36% yield by crystallisation from acetone–hexane during the isolation of 17; m.p. 120 - 133°C; υ_{max} (nujol) 3270 - 3020 (NH), 1750, 1690, 1660, 1605 (C=O)cm^{-1}; ^1H NMR [$(CD_3)_2SO$] 1.8 - 2.3 (m, 9H, 3 x CH_3CO), 3.32 (s, 1H, CH_3O), 3.40 (s, 2H, CH_3O), 4.20 (m, 2H, CH_2), 5.61 (m, 1H, CHOAc), 6.00 (d, 0.6 H, J = 9.9 Hz, $CHOCH_3$), 6.07 (d, 0.4H, J = 8.3 Hz,

CHOCH$_3$), 8.39 (s, 0.6H, 8-H), 8.44 (s, 0.4H, 8-H), 11.7 (br.s, 1H, NH), 12.16 (br.s, 1H, NH); MS m/z 381 (M^+, 3%).

Anal. Calcd. for $C_{15}H_{19}N_5O_7$: C, 47.24; H, 5.02; N, 18.37
Found : C, 47.21; H, 5.26; N, 18.11%.

Approximate diastereoisomeric ratio, 2:1.

2,6-Diacetamido-9-(2,3-diacetoxy-1-methoxyprop-1-yl)purine (29), isolated in 31% yield after chromatography (chloroform-methanol 40:1) and recrystallisation (chloroform-cyclohexane and acetone-hexane); m.p. 147 - 157°C; ν_{max} (nujol) 3270 - 3080 (NH), 1750, 1720, 1660, 1620 (C=O)cm^{-1}; ^{1}H NMR [(CD$_3$)$_2$SO] δ 1.81 (s, 1.5H, CH$_3$CO$_2$), 1.90 (s, 1.5H, CH$_3$CO$_2$), 1.99 (s, 1.5H, CH$_3$CO$_2$), 2.06 (s, 1.5H, CH$_3$CO$_2$), 2.28 (s, 3H, CH$_3$CON), 2.36 (s, 3H, CH$_3$CON), 3.24 (s, 1.5H, CH$_3$O), 3.31 (s, 1.5H, CH$_3$O), 4.28 (m, 2H, CH$_2$), 5.70 (m, 1H, CHOAc), 5.85 (m, 1H, CHOCH$_3$), 8.45 (s, 1H, 8-H), 10.33 (s, 1H, NH), 10.51 (br.s, 1H), NH); MS m/z 422 (M^+, 5%).

Anal. Calcd. for $C_{17}H_{22}N_6O_7$: C, 48.34; H, 5.25; N, 19.90.
Found : C, 48.46; H, 5.80; N, 19.66%.

Approximate diastereoisomeric ratio, 1:1.

7-(2,3-Diacetoxy-1-methoxyprop-1-yl)-1,3-dimethyltheophylline (33), isolated in 27% yield after chromatography (chloroform-methanol 40:1); m.p. 105 - 123°C; ν_{max} (nujol) 1750, 1730, 1700, 1660, 1600 cm^{-1}; ^{1}H NMR [(CD$_3$)$_2$SO] δ 1.90 (s, 1.5H, CH$_3$CO), 1.99 (s, 1.5H, CH$_3$CO), 2.04 (s, 3H, CH$_3$CO), 3.27 (m, 6H, 2 x CH$_3$N), 3.47 (s, 3H, CH$_3$O), 4.20 (m, 2H, CH$_2$), 5.58 (m, 1H, CHOAc), 6.02 (m, 1H, CHOCH$_3$), 8.30 (s, 0.5H, 8-H), 8.36 (s, 0.5H, 8-H); MS m/z 368 (M^+, 1%).

Anal. Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21.
Found : C, 48.83; H, 5.12; N, 14.98%.

Approximate diastereoisomeric ratio, 1:1.

Synthesis of 9(7)-(2,3-Dihydroxy-1-methoxyprop-1-yl)purines (9,10,11,19,20,27,30,31,34) and 9(7)-(3-Hydroxy-1-methoxyprop-1-yl)-purines (6,15,16,24).

General procedures for deacylation

Procedure A-Methanolic Ammonia

The O- and N,O-acylated acyclonucleosides (6mmol) were dissolved or suspended in methanol (25mL) and treated with 0.88 ammonia solution (100mL) and the resultant solution stirred for 16h at 25°C. The solvents were removed under reduced pressure, affording the crude

reaction products which were purified by direct recrystallisation or column chromatography.

Procedure B-Hydrazine Hydrate

O- and N,O-acylated acyclonucleosides (5mmol) were dissolved or suspended in ethanol (100mL) and treated with hydrazine hydrate (20mL) and the resultant solution boiled under reflux for 16h. The solvents were removed under reduced pressure affording the crude reaction products, which were purified by direct recrystallisation or column chromatography.

9-(3-Hydroxy-1-methoxyprop-1-yl)adenine (6), Procedure A - isolated in 99% yield by ether crystallisation; m.p. 148-150°C; ν_{max} (nujol) 3400, 3400-3100 (NH_2, OH), 1660, 1600 (C=N) cm^{-1}; λ_{max} (H_2O) 207nm (ε20500), 259nm (ε14200); ^1H NMR [$(CD_3)_2SO$] δ 2.28 (m, 2H, CH_2), 3.16 (s, 3H, CH_3O), 3.37 (m, 2H, $\underline{CH_2}OH$), 4.63 (t, 1H, J = 5Hz, OH)), 5.75 (t, 1H, J = 6Hz, CH), 7.27 (br.s, 2H, NH_2), 8.15 (s, 1H, 8-H or 2-H), 8.30 (s, 1H, 8-H or 2-H); MS m/z 223 (M^+, 14%).

Anal. Calcd. for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37.
Found : C, 48.14; H, 6.04; N, 31.03%.

9-(2,3-Dihydroxy-1-methoxyprop-1-yl)adenine (9), Procedure A - isolated in 53% yield by recrystallisation from chloroform-methanol-cyclohexane and methanol-ether; m.p. 166-188°C; ν_{max} (nujol) 3480, 3370, 3180 (NH_2, OH), 1655, 1600 (C=N)cm^{-1}; λ_{max} (H_2O) 207nm (ε19500), 259nm (ε14000); ^1H NMR [$(CD_3)_2SO$] δ 3.15 (s, 1.5H, CH_3O), 3.20 (s, 1.5H, CH_3O), 3.44 (m, 2H, CH_2), 3.80 (m, 0.5H, $\underline{CH}OH$), 4.14 (m, 0.5H, $\underline{CH}OH$), 4.66 (m, 1H, OH), 5.15 (d, 0.5H, J = 6Hz, OH), 5.36 (d, 0.5H, J = 6Hz, OH), 5.52 (d, 0.5H, J = 7.5Hz, $\underline{CH}OCH_3$), 5.66 (d, 0.5H, J = 4.5Hz, $\underline{CH}OCH_3$), 7.21 (br.s, 2H, NH_2), 8.15 (s, 1H, 8-H or 2-H), 8.20 (s, 0.5H, 8-H or 2-H), 8.23 (s, 0.5H, 8-H or 2-H); MS m/z 239 (M^+, 14%).

Anal. Calcd. for $C_9H_{13}N_5O_3$: C, 45.18; H, 5.48; N, 29.27.
Found : C, 45.07; H, 5.72; N, 29.37%.

Approximate diastereoisomeric ratio, 2:1.

N^6-Benzoyl-7-(2,3-dihydroxy-1-methoxyprop-1-yl)adenine (10), Procedure A - isolated in 64% yield by chromatography (chloroform-methanol 2:1); m.p. 192-5°C; ν_{max} (nujol) 3400, 3300 (NH, OH), 1650, 1600 (C=O, C=N) cm^{-1}; ^1H NMR [$(CD_3)_2)SO$] δ 3.38 (s, 3H, CH_3O), 3.58 (m, 2H, CH_2), 4.10 (m, 1H, $\underline{CH}OH$), 4.95 (m, 1H, OH), 5.94 (m, 2H, OH + $\underline{CH}OCH_3$), 7.66 (m, 3H, 3 aromatic), 8.15 (m, 2H, 2 aromatic), 8.77 (m, 2H, 8-H + 2-H), 11.23 (br.s, 1H, NH); MS m/z 343 (M^+, <1%).

Anal. Calcd. for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; N, 20.40.
Found : C, 56.22; H, 5.28; N, 20.03%.

7-(2,3-Dihydroxy-1-methoxyprop-1-yl)adenine (11) (from 10, Procedure B) - isolated in 56% yield by chromatography (chloroform-methanol 2:1) and recrystallisation from acetone-ether; m.p. 193-9°C; ν_{max} (nujol) 3380, 3300 (NH_2, OH), 1640, 1600 (C=N) cm^{-1}; λ_{max} (H_2O) 273nm (ε_{9300}); ^1H NMR [$(CD_3)_2SO$] δ 3.26 (m, 2H, CH_2), 3.37 (s, 2H, CH_3O), 3.40 (s, 1H, CH_3O), 3.73 (m, 1H, CHOH), 4.76 (m, 1H, OH), 5.26 (d, 0.5H, J = 6Hz, OH), 5.53 (d, 0.5H, J = 6Hz, OH), 5.58 (d, 0.5H, J = 6.5Hz, $CHOCH_3$), 5.60 (d, 0.5H, J = 5.2Hz, $CHOCH_3$), 8.22 (s, 1H, 8-H or 2-H), 8.30 (s, 0.35H, 8-H or 2-H), 8.37 (s, 0.65H, 8-H or 2-H); MS m/z 239 (M^+, 11%).

Anal. Calcd. for $C_9H_{13}N_5O_3$: C, 45.18; H, 5.48; N, 29.27.
Found : C, 44.76; H, 5.00; N, 28.81%.

Approximate diastereoisomeric ratio, 2:1.

9-(3-Hydroxy-1-methoxyprop-1-yl)guanine (15), Procedure B - isolated in 64% yield by recrystallisation from methanol-water; m.p. >250°C; ν_{max} (KBr) 3600-2500 (NH, OH), 1690, 1630 (C=O)cm^{-1}; λ_{max} (H_2O) 252nm (ε13100); ^1H NMR [$(CD_3)SO$] δ 2.14 (m, 2H, CH_2), 3.14 (s, 3H, CH_3O), 3.40 (m, 2H, CH_2OH), 4.55 (t, 1H, J = 5Hz, OH), 5.52 (t, 1H, J = 6Hz, CH), 6.43 (s, 2H, NH_2), 7.80 (s, 1H, H-8), 10.53 (s, 1H, NH); MS m/z 239 (M^+, 10%).

Anal. Calcd. for $C_9H_{13}N_5O_3 \cdot 0.25\ H_2O$: C, 44.35; H, 5.58; N, 28.73.
Found : C, 44.15; H, 5.09; N, 28.96%.

7-(3-Hydroxy-1-methoxyprop-1-yl)guanine (16), Procedure B - isolated in 54% yield by recrystallisation from methanol; m.p. >250°C dec; ν_{max} (KBr) 3600-2600 (NH, OH), 1670 (C=O)cm^{-1}; λ_{max} (H_2O) 244nm (ε5900), 284nm (ε7100); ^1H NMR [$(CD_3)_2SO$] δ 2.26 (m, 2H, CH_2), 3.20 (s, 3H, CH_3O), 3.35 (m, 2H, CH_2OH), 4.52 (t, 1H, J = 5Hz, OH), 5.85 (t, 1H, J = 6Hz, CH), 6.11 (s, 2H, NH_2), 8.15 (s, 1H, H-8), 10.80 (s, 1H, NH); MS m/z 239 (M^+, 10%).

Anal. Calcd. for $C_9H_{13}N_5O_3$: C, 45.19; H, 5.48; N, 29.27.
Found : C, 45.00; H, 5.52; N, 28.70%.

9-(2,3-Dihydroxy-1-methoxyprop-1-yl)guanine (19), Procedure B - isolated in 49% yield by recrystallisation from methanol-chloroform-cyclohexane; m.p. >300°C; ν_{max} (nujol) 3400, 3250, 3100 (OH, NH), 1680, 1615, 1600 (C=O)cm^{-1}; λ_{max} (H_2O) 252nm (ε12800); ^1H NMR [$(CD_3)_2SO$] δ 3.13 (s, 1H, CH_3O), 3.17 (s, 2H, CH_3O), 3.45 (m, 2H, CH_2), 3.70 (m, 0.6H, CHOH),

4.03 (m, 0.4H, CHOH), 4.63 (m, 1H, OH), 5.08 (d, 0.4H, J = 6Hz, OH), 5.26 (d, 0.6H, J = 6Hz, OH), 5.35 (d, 0.4H, J = 6.8Hz, $CHOCH_3$), 5.45 (d, 0.6H, J = 4Hz, $CHOCH_3$), 6.44 (br.s, 2H, NH_2), 7.76 (s, 1H, 8-H), 10.56 (br.s, 1H, NH); MS m/z 255 (M^+, 10%).

Anal. Calcd. for $C_9H_{13}N_5O_4 \cdot 0.5\ H_2O$: C, 40.91; H, 5.34; N, 26.50.
Found : C, 40.74; H, 5.42; N, 26.74%.

Approximate diastereoisomeric ratio, 3:2.

7-(2,3-Dihydroxy-1-methoxyprop-1-yl)guanine (20), Procedure B - isolated in 97% yield by crystallisation with acetone; m.p. >300°C; ν_{max} (nujol) 3400, 3300, 3150 (OH, NH), 1660 (C=O)cm^{-1}; λ_{max} (H_2O) 214nm (ε20700), 285nm (ε7100); ^1H NMR [$(CD_3)_2SO$] δ 3.23 (s, 1H, CH_3O), 3.30 (s, 2H, CH_3O), 3.42 (m, 2H, CH_2), 3.80 (m, 0.65H, CHOH), 4.06 (m, 0.35H, CHOH), 4.64 (m, 1H, OH), 5.10 (d, 0.35H, J = 6Hz, OH), 5.25 (d, 0.65H, J = 6Hz, OH), 5.68 (d, 0.35H, J = 7.5Hz, $CHOCH_3$), 5.85 (d, 0.65Hz, J = 4.5Hz, $CHOCH_3$), 6.35 (br.s, 2H, NH_2), 8.10 (s, 0.65H, 8-H), 8.14 (s, 0.35H, 8-H), 11.20 (br.s, 1H, NH); MS m/z 255 (M^+, 8%).

Anal. Calcd. for $C_9H_{13}N_5O_4$: C, 42.35; H, 5.13; N, 27.44.
Found : C, 42.18; H, 5.26; N, 27.16%.

Approximate diastereoisomeric ratio, 2:1.

9-(3-Hydroxy-1-methoxyprop-1-yl)hypoxanthine (24), (from 22/23, Procedure A) - isolated in 21% yield by fractional crystallisation from chloroform-methanol-cyclohexane; m.p. 146-152°C; ν_{max} (nujol) 3400-3100 (OH, NH), 1710, 1660 (C=O)cm^{-1}; λ_{max} (H_2O) 249nm (ε11400); ^1H NMR [$(CD_3)_2SO$] δ 2.00-2.45 (m, 2H, CH_2), 3.21 (s, 3H, CH_3O), 3.20-3.66 (m, 3H, CH_2OH), 5.74 (t, 1H, J = 6Hz, $CHOCH_3$), 8.10 (s, 1H, 8-H or 2-H), 8.31 (s, 1H, 8-H or 2-H), 11.20 (br.s, 1H, NH); MS m/z 224 (M^+, 7%).

Anal. Calcd. for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99.
Found : C, 47.98; H, 5.70; N, 25.19%.

9-(2,3-Dihydroxy-1-methoxyprop-1-yl)hypoxanthine (27a) (from 25/26, Procedure A) - isolated in 2.5% yield by fractional crystallisation from methanol-acetone-cyclohexane; m.p. 226-9°C; ν_{max} (nujol) 3100-3400 (OH, NH), 1660 (C=O)cm^{-1}; λ_{max} (H_2O) 248nm (ε12000); ^1H NMR [$(CD_3)_2SO$] δ 3.22 (s, 3H, CH_3O), 3.40 (m, 2H, CH_2), 3.77 (m, 1H, CHOH), 4.72 (m, 1H, OH), 5.30 (m, 1H, OH), 5.64 (d, 1H, J = 3.2Hz, $CHOCH_3$), 8.05 (s, 1H, 8-H or 2-H), 8.13 (s, 1H, 8-H or 2-H), 12.31 (br.s, 1H, NH); MS m/z 240 (M^+, 7%).

Anal. Calcd. for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.32.
Found : C, 44.83; H, 5.24; N, 23.41%.

9-(2,3-Dihydroxy-1-methoxyprop-1-yl)hypoxanthine (27b) 9-(2,3-Dihydroxy-1-methoxyprop-1-yl)adenine (9, 0.4g, 1.7mmol) was dissolved in water (35mL), treated with sodium nitrite (1.5g, 21mmol) and glacial acetic acid (2.7mL) and stirred for 40h at 25°. The solvents were evaporated under reduced pressure and the residue chromatographed, eluting with chloroform-methanol (10:1 - 2:1). The resultant gum was crystallised from methanol-acetone-cyclohexane affording 9-(2,3-dihydroxy-1-methoxyprop-1-yl)hypoxanthine (0.15g, 38%); m.p. 223-6°C; ν_{max} (nujol) 3550-3120 (NH, OH), 1700, 1665 (C=O)cm^{-1}; λ_{max} (H_2O) 248nm (ε12200), ^1H NMR [$(CD_3)_2SO$] δ 3.11 (s, 1.2H, CH_3O), 3.19 (s, 1.8H, CH_3O), 3.38 (m, 2H, CH_2), 3.73 (m, 0.6H, CHOH), 4.05 (m, 0.4H, CHOH), 5.44 (d, 0.4H, J = 6.8Hz, $CHOCH_3$), 5.58 (d, 0.6H, J = 4.5Hz, $CHOCH_3$), 6.84 (br.s, 2H, 2 x OH), 8.00 (s, 1H, 8-H or 2-H), 8.06 (s, 0.6H, 8-H or 2-H), 8.12 (s, 0.4H, 8-H or 2-H); MS m/z 240 (M^+, 12%).

Anal. Calcd. for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.32.
Found : C, 44.97; H, 5.07; N, 22.68%.

Approximate diastereoisomeric ratio, 3:2.

2,6-Diamino-9-(2,3-dihydroxy-1-methoxyprop-1-yl)purine (31), Procedure A - isolated 2-acetamido-6-amino-7-(2,3-dihydroxy-1-methoxyprop-1-yl)-purine (30) in 36% yield by elution chromatography using chloroform-methanol (10:1 - 3:1); mp. 221-3°C. Treatment of 30 by procedure B afforded 31 in 93% yield by trituration with acetone; m.p. 204-6°C; ν_{max} (nujol) 3470-3100 (OH, NH_2), 1660, 1620 (C=O)cm^{-1}; λ_{max} (H_2O) 215nm (ε24900), 255nm (ε9000), 279nm (ε9800); ^1H NMR [$(CD_3)_2SO$] δ 3.14 (s, 3H, CH_3O), 3.35 (m, 2H, CH_2), 4.02 (m, 1H, CHOH), 4.64 (m, 1H, OH), 5.25 (m, 1H, OH), 5.30 (d, 1H, J = 6.8Hz, $CHOCH_3$), 5.80 (br.s, 2H, NH_2), 6.69 (br.s, 2H, NH_2), 7.77 (br.s, 1H, 8-H); MS m/z 254 (M^+, 20%).

Anal. Calcd. for $C_9H_{14}N_6O_3$: C, 42.52; H, 5.55; N, 33.05.
Found : C, 42.32; H, 5.49; N, 32.66%.

Approximate diastereoisomeric ratio, 1:1.

7-(2,3-Dihydroxy-1-methoxyprop-1-yl)theophylline (34) Procedure A - isolated in 81% yield by chromatography (chloroform-methanol 25:1) and recrystallisation from chloroform-cyclohexane; m.p. 173-173.5°C; ν_{max} (nujol) 3400-3120 (OH), 1700, 1650 (C=O)cm^{-1}; λ_{max} (H_2O) 205nm (ε26100), 274nm (ε9100); ^1H NMR [$(CD_3)_2SO$] δ 3.23 (s, 3H, CH_3N), 3.30 (s, 3H, CH_3N), 3.34 (m, 2H, CH_2), 3.45 (s, 3H, CH_3O), 3.72 (m, 0.5H, CHOH), 4.00 (m, 0.5H, CHOH), 4.60 (m, 1H, OH), 5.07 (d, 0.5H, J = 6Hz, OH), 5.17 (d, 0.5H, J = 6Hz, OH), 5.73 (d, 0.5H, J = 6.8Hz, $CHOCH_3$),

5.90 (d, 0.5H, J = 4.5Hz, $CHOCH_3$), 8.07 (s, 0.5H,8-H), 8.17 (s, 0.5H, 8-H); MS m/z 284 (M^+, 10%),

Anal. Calcd. for $C_{11}H_{16}N_4O_5$: C, 46.48; H, 5.67; N, 19.71.
Found : C, 46.31; H, 5.83; N, 19.43%.

Approximate diastereoisomeric ratio, 1:1.

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