[Chem. Pharm. Bull. 22(12)2851—2860(1974)]

UDC 547.857'456.057 : 547.963.32.057

# Studies on the Oxidation of "Reversed Nucleosides" in Oxygen. IV.[1] Synthesis of 4-(6-Aminopurin-9H-9-yl)-3(*R*)-hydroxy-2(*R*)-aminobutyric Acid[2]

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(Received April 22, 1974)

Reaction of 5-O-tosyl-3-benzyloxycarbonylamido-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (**21**) or 5-O-tosyl-3-acetamido-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (**30**) with the sodium salt of adenine afforded the corresponding isomeric "reversed nucleosides" in good yields. Hydrolysis of the masked compound (**22**) followed by hydrogenolysis afforded 5-(6-aminopurin-9H-9-yl)-3-amino-3,5-dideoxy-D-ribofuranose (**26**) hydrochloride in a good yield. After removal of the protective group, oxidation of 5-(6-aminopurin-9H-9-yl)-3-acetamido-3,5-dideoxy-D-ribofuranose (**33**) by oxygen in a dilute alkaline solution afforded sodium 4-(6-aminopurin-9H-9-yl)-3(*R*)-hydroxy-2(*R*)-acetamidobutyrate (**34**). To evaluate the biological activities, amino ester (**35**) and amino acid (**38**) were also synthesized.

Already we reported[4] that the oxidation of the reversed nucleosides, 5-(6-aminopurin-9H-9-yl)-pentoses, afforded easily eritadenine, a hypocholesterolemic substance isolated from *Lentinus edodes* SING.,[5] in good yield. More recently this method[1] was also extended successfully to other reversed nucleosides in which adenine moeity was replaced by some purine and pyrimidine bases. The success of the syntheses of eritadenine and eritadenine analogues by oxidation of reversed nucleosides in oxygen prompted us to proceed to further work on some reversed nucleosides of aminosugars. Since a naturally-occurring pyrimidyl α-amino acid, L-willardiine,[6] and some other purinyl and pyrimidyl amino acids with antitumor activity have been prepared[7] by direct alkylation of purine and pyrimidine derivatives, synthesis of 4-(6-aminopurin-9H-9-yl)-3(*R*)-hydroxy-2(*R*)-aminobutyric acid (**38**) using our method of the oxidation was of great interest from the chemical as well as the pharmacological point of view.

Two methods for synthesizing a reversed nucleoside of aminosugar have been attempted. One of them (method A) was the replacement of hydroxy group of a reversed nucleoside with amino group by a suitable method. The other (method B) was the condensation of the sodium salt of adenine with the 5-O-tosyl-aminosugar derivative.

Reaction of the 5-O-tosyl derivative (**2**)[8] with the sodium salt of adenine (**1**) in dimethyl formamide (DMF) afforded the corresponding reversed nucleoside (**3**)[9] (see Chart 1). Reaction of the 3-O-tosyl derivative (**4**), prepared from **3**, with sodium azide in DMF did not afford any product, and the starting material **4** was recovered.

1) Part III: T. Kanno and M. Kawazu, *Chem. Pharm. Bull.* (Tokyo), **22**, 2836 (1974).
2) Presented at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1973.
3) Location: *2-2-50, Kawagishi, Toda, Saitama.*
4) M. Kawazu, T. Kanno, S. Yamamura, T. Mizoguchi, and S. Saito, *J. Org. Chem.*, **38**, 2887 (1973).
5) *a*) I. Chibata, K. Okumura, S. Takeyama, and K. Kotera, *Experientia*, **25**, 1237 (1969); *b*) T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, *Tetrahedron*, **28**, 899 (1972).
6) A. Kjaer, A. Knudsen, and P. Olesen Larsen, *Acta. Chem. Scand.*, **15**, 1193 (1961).
7) *a*) M.T. Doel, A.S. Jones, and N. Taylar, *Tetrahedron Letters*, **1969**, 2285; *b*) A.J. Nollet, C.M. Huting, and U.D. Pandit, *Tetrahedron*, **25**, 5971 (1969); *c*) A.J. Nollet, and U.K. Pandit, *Ibid.*, **25**, 5983, 5989 (1969).
8) E.L. Hirst, T.K.N. Jones, and E. Williams, *J. Chem. Soc.*, **1947**, 1062.
9) D-Isomer had been prepared by us.[4]

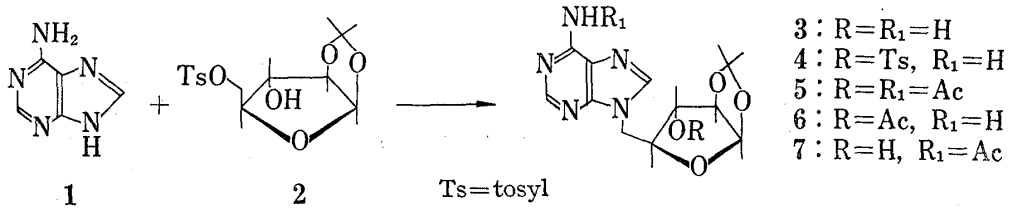



Chart 1

An alternative route to the 3-amino derivative *via* the ketoxime was next investigated. However, the oxidation of **3** with both chromium trioxide-pyridine[10] and dicyclohexylcarbodiimide-dimethylsulfoxide (DCC-DMSO)[11] in the usual manner did not give satisfactory results. In the former case, the starting material **3** was only recovered. Oxidation of **3** with DMSO-$Ac_2O$[12] was also attempted. However, only the O,N-diacetate (**5**) and the O-acetate (**6**) were isolated, and none of the oxidation product could not be detected in the reaction mixture. The O,N-diacetate (**5**) was easily hydrolyzed by passing through a column of aluminum oxide or with a dilute $Na_2CO_3$ solution to afford **6**, and hydrolysis of **6** with methanolic potassium hydroxide gave **3** (see Chart 1). Oxidation of the N-acetyl derivative (**7**), prepared by hydrolysis of **5**, with DMSO-$Ac_2O$ was attempted according to the method of Moffatt, *et al.*[12b] The O,N-diacetate (**5**) was the only isolable product in this reaction. Since it appeared that 6-amino group of an adenine moeity might play a role to inhibit this oxidation, preparation of the 6-methylthiopurine derivative (**10**) was carried out in order to investigate the role of 6-substituent. Condensation of the 5-O-tosyl derivative (**9**)[13] with the sodium salt of 6-methylthiopurine (**8**) in DMF gave the corresponding isomeric reversed nucleosides, (**10**), (**11**) and (**12**), whose structural assignments were based on ultraviolet (UV) spectral data.[14] Oxidation of **10** with DMSO-$Ac_2O$ afforded only the O-acetate (**13**) in 8% yield, and the most part of the starting material **10** was recovered (see Chart 2).

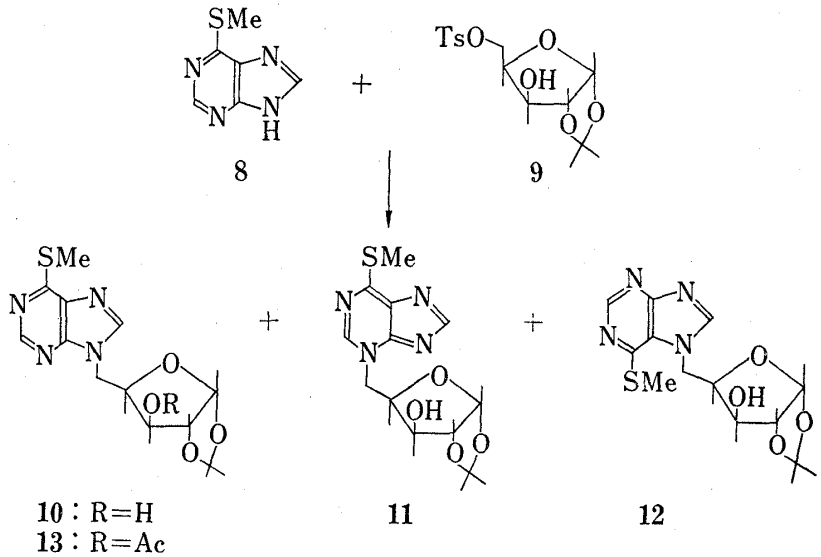
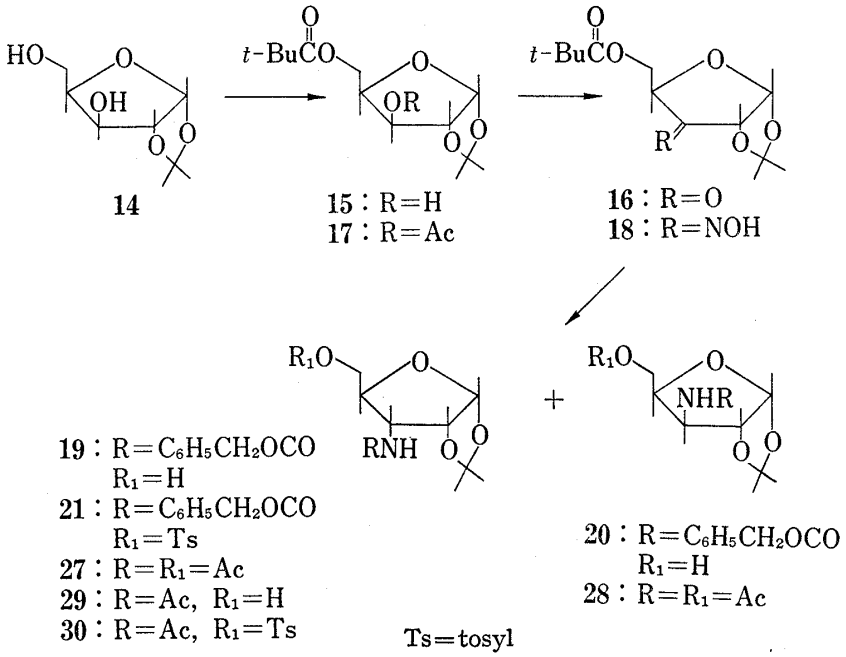



Chart 2

10) A.S. Jones, A.R. Williamson, and M. Winkley, *Carbohyd. Res.*, **1**, 187 (1965).
11) K.F. Pfitzner and J.G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661 (1965).
12) *a*) A.F. Cook and J.G. Moffatt, *J. Am. Chem. Soc.*, **89**, 2697 (1967); *b*) U. Brodbeck and J.G. Moffatt, *J. Org. Chem.*, **35**, 3552 (1970).
13) G. Helterich and M. Burgdorf, *Tetrahedron*, **3**, 274 (1958).
14) See ref. 8) of Part III[1] in this series.

Thus, all attempts at oxidation of the 3-hydroxy groups of the reversed nucleosides, **3**, **7** and **10**, were unsuccessful. Although Goldman, *et al.* reported[15] that the DMSO-$Ac_2O$ oxidation procedure was particularly useful for oxidation of sterically hindered hydroxy groups, in our cases this oxidation did not take place and O-acetylation was effectively favored over oxidation under these conditions. The reversed nucleoside of aminosugar could not be obtained by means of method A. Alternative method B was therefore undertaken.

Reaction of the 5-O-pivalyl compound (**15**), prepared from **14**[13] with DMSO-$Ac_2O$ afforded a mixture of the 3-keto derivative (**16**) (47%) and the 3-O-acetyl derivative (**17**) (11%). Compound **15** was found to be more effectively oxidized with DCC-DMSO in the presence of pyridinium trifluoroacetate[16] to give a 80% yield of **16**. The oxime **18**, prepared from **16**, resisted catalytic hydrogenation on $PtO_2$ or Pd-C under several conditions. Lithium aluminum hydride reduction[17] of **18**, however, followed by Schotten-Baumann reaction with benzyloxycarbonyl chloride gave the 3-benzyloxycarbonylamido-ribofuranose derivative (**19**) in a fairly good yield. A small amount of the xylo epimer (**20**) was also formed in this reaction (see Chart 3).




**14**

**15** : R=H
**17** : R=Ac

**16** : R=O
**18** : R=NOH

**19** : R=$C_6H_5CH_2OCO$, $R_1$=H
**21** : R=$C_6H_5CH_2OCO$, $R_1$=Ts
**27** : R=$R_1$=Ac
**29** : R=Ac, $R_1$=H
**30** : R=Ac, $R_1$=Ts

**20** : R=$C_6H_5CH_2OCO$, $R_1$=H
**28** : R=$R_1$=Ac

Ts=tosyl

Chart 3

Condensation of the 5-O-tosyl derivative (**21**), prepared from **19**, with sodium adenide in DMF afforded the corresponding three isomeric reversed nucleosides, which could be separated by column chromatography on silica gel into a major, the N(9)-isomer (**22**) in 61% yield and two minors, the N(3)-isomer (**23**) in 13% yield and the N(7)-isomer (**24**) in 6% yield. Structural assignments of these isomers were made from their UV and nuclear magnetic resonance (NMR) spectra. These data were in good accordance with the observation reported by Townsend, *et al.*[18] (see Table I).

Hydrogenolysis of **22** on $PtO_2$ or Pd-C in the presence of HCl in EtOH resulted in recovery of the starting material. However, the 3-benzyloxycarbonylamido-1,2-dihydroxy derivative

15) J.D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **89**, 2416 (1967).
16) *a*) K.F. Pfitzner and J.G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963); *b*) H. Yanagisawa, K. Kinoshita, S. Nakada, and S. Umezawa, *Bull. Chem. Soc. Japan.*, **43**, 246 (1970).
17) A.N. Fujiwara, E.M. Acton, and L. Goodman, *J. Heterocyclic Chem.*, **7**, 891 (1970).
18) *a*) L.B. Townsend, P.K. Robins, R.N. Loeppky, and N.J. Leonard, *J. Am. Chem. Soc.*, **86**, 5320 (1964); *b*) K.R. Dornall and L.B. Townsend, *J. Heterocyclic Chem.*, **3**, 371 (1966).

Table I. UV Spectral Data and Differences of Chemical Shift between the Signals Observed for the 2- and 8-Aromatic Protons

| | Compound | $\lambda_{max}$ mμ ($\varepsilon \times 10^{-3}$) | $\lambda_{min}$ mμ ($\varepsilon \times 10^{-3}$) | $\Delta\lambda_{min}$ mμ[a] | $\Delta\delta$(Hz)[b] |
|---|---|---|---|---|---|
| | [c] | 259 (14.0) | 231.5(3.2) | | |
| 22 | EtOH | 260.5(14.3) | 227 (2.3) | +4.5 | 11 |
| | [d] | 261 (14.1) | 227 (2.0) | | |
| | [c] | 278 (18.1) | 239 (3.4) | | |
| 23 | EtOH | 279 (12.7) | 246 (3.1) | −7 | 27 |
| | [d] | 278.5(12.2) | 246 (2.7) | | |
| | [c] | 276.5(14.6) | 240 (4.3) | | |
| 24 | EtOH | 270 (10.0) | 233 (4.5) | +7 | 6 |
| | [d] | 271 ( 9.6) | 237 (4.1) | | |
| | [c] | 259.5(13.7) | 231.5(3.0) | | |
| 31 | EtOH | 260.5(13.9) | 227 (2.2) | +4.5 | 7 |
| | [d] | 261 (13.6) | 227.5(2.1) | | |
| | [c] | 278 (17.6) | 239 (3.3) | | |
| 32 | EtOH | 279 (12.2) | 246 (2.8) | −7 | 26 |
| | [d] | 279 (12.0) | 247 (2.7) | | |

a) $\Delta\lambda_{min}=\lambda_{min}^{c)}-\lambda_{max}^{EtOH}$
b) $\Delta\delta=|\delta_{C_2\text{-}H}-\delta_{C_8\text{-}H}|$, and determined in DMSO-$d_6$
c) measured in EtOH-1N HCl (99:1)
d) measured in EtOH-1N NaOH (99:1)

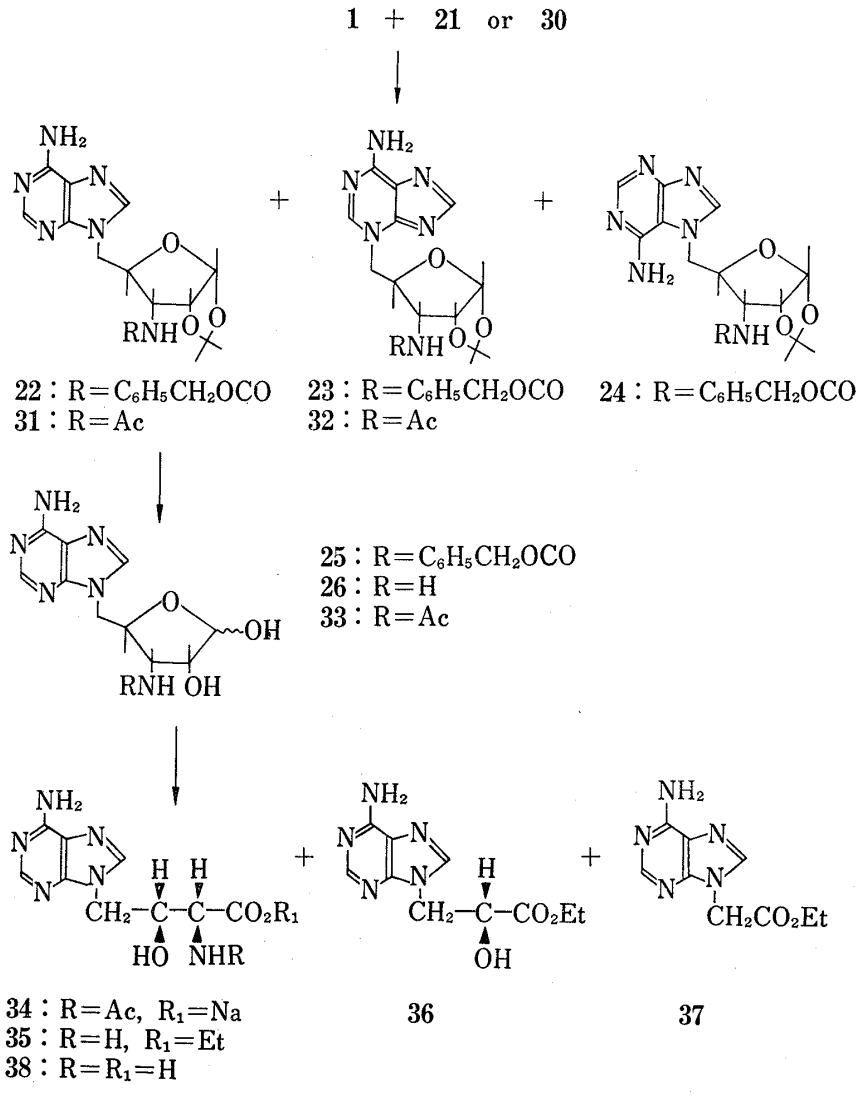



Chart 4

(**25**), prepared from **22**, was smoothyl hydrogenated on Pd-C in a dilute acidic solution to give the reversed nucleoside of aminosugar (**26**) hydrochloride in a good yield (see Chart 4). The different behavior of **22** and **25** on the hydrogenolysis is apparently due to the effect of the steric hindrance of isopropylidene group in **22** and the neighboring group participation of the hydroxy group in **25**. When a solution of **26**·hydrochloride was neutralized with an alkaline solution, apparently polymerization of the resultant free base took place. Accordingly, oxidation of **26** could not be undertaken in alkaline conditions.

Therefore, oxidation of the 3-acetamide derivative (**33**) was next investigated. The O,N-diacetate (**27**)[19] was prepared from **16** with the method similar to that described above by using $Ac_2O$ instead of benzyloxycarbonyl chloride. Hydrolysis of **27** followed by tosylation in the usual manner gave the 5-O-tosyl derivative (**30**) in a good yield (see Chart 3). Condensation of **30** with sodium adenide in DMF afforded a mixture of the N(9)-isomer (**31**) and the N(3)-isomer (**32**) in ratio of 7: 2, but the N(7)-isomer could not be detected in this case. These structures were also determined by means of UV and NMR spectral data (see Table I). Hydrolysis of **31** gave 5-(6-aminopurin-9H-9-yl)-3-acetamido-3,5-dideoxy-D-ribofuranose (**33**) in a good yield (see Chart 4).

The 3-acetamide derivative **33**, thus obtained, was oxidized by oxygen in a dilute alkaline solution.[1] The mixture of products, after removal of adenine (16%) by passing through a column of Sephadex LH-20, gave a small amount of the sodium salt (**34**). The residue was esterified with EtOH and HCl to afford ethyl 4-(6-aminopurin-9H-9-yl)-3(*R*)-hydroxy-2(*R*)-aminobutyrate (**35**)·hydrochloride as a major product along with small amounts of the ethyl α-hydroxypropionate (**36**)[4] and the ethyl acetate (**37**)[4] derivatives. Hydrolysis of **35** gave α-amino acid (**38**) of eritadenine analogue in a good yield (see Chart 4). NMR spectrum and elemental analysis were in good accord with the structure of **38**.

Hypocholesterolemic activity of **35** was almost equal to that of eritadenine. The details of this activity will be reported elsewhere.

## Experimental

Melting points were taken on a Yanagimoto capillary melting point apparatus Model MP-1 and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrophotometer. UV spectra were measured on a Hitachi 323 spectrophotometer. Optical rotations were measured with a JASCO DIP-180 polarimeter. NMR spectra were determined on a Model JEOL ME-60 instrument with tetramethylsilane as an internal standard unless otherwise indicated. Organic extracts were dried over anhyd. $Na_2SO_4$. All evaporations were performed on rotary evaporators *in vacuo*.

**5-(6-Aminopurin-9H-9-yl)-5-deoxy-1,2-O-isopropylidene-α-L-arabofuranose** (3)——*a*) Two solutions of **1** (3.65 g) and NaH (1.02 g, 64% in mineral oil) in DMF (80 ml) and **2** (9.0 g) in DMF (100 ml) were allowed to react and treated in the same manner as described in the synthesis of β-D-isomer.[4] **3** was yielded in 4.4 g (56%); mp 246—247° (D-isomer, mp 240—241°). $[\alpha]_D^{20}$ −134° (*c*=0.5, $H_2O$) (D-isomer $[\alpha]_D^{18}$ +135°). IR spectrum of **3** was completely agreed to that of β-D-isomer.

*b*) KOH (20 mg) was added to a solution of **6** (161 mg) in MeOH (4 ml). The solution was warmed for 5 min on a water-bath. After evaporation of MeOH, the residual solid was recrystallized from $H_2O$ to afford **3** as colorless needles; mp 244—245°. This product was identical in IR spectrum with an authentic sample **3**.

**5-(6-Aminopurin-9H-9-yl)-3-O-tosyl-5-deoxy-1,2-O-isopropylidene-α-L-arabofuranose** (4)——To a solution of **3** (307 mg) in pyridine (5 ml) was added dropwise a solution of *p*-toluenesulfonyl chloride (491 mg) in pyridine (5 ml) under ice cooling, and the mixture was stirred for 50 hr at room temperature. Usual work-up afforded 201 mg (43%) of **4**. Recrystallization from MeOH afforded an analytical sample of **4** as colorless prisms; mp 224—225°. $[\alpha]_D^{15}$ −27° (*c*=1.0, DMSO). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3210 and 3080 ($-NH_2$), 1654, 1600, 1370 and 1190 ($SO_2$). NMR (DMSO-$d_6$) δ: 8.16 (1H, s), 8.07 (1H, s), 7.62 (2H, d, *J*=7.0 Hz), 7.38 (2H, d, *J*=7.0 Hz), 6.06 (1H, d, *J*=4.0 Hz, $C_1$-H), 5.07 (1H, s, $C_3$-H), 4.15 (1H, d, *J*=4.0 Hz, $C_2$-H), 4.38 (broad s, 3H), 2.30 (3H, s, $-C_6H_4-CH_3$), 1.50 and 1.27 (3H, 3H, s, $>C(CH_3)_2$). UV $\lambda_{max}^{EtOH}$ mμ (ε): 261 (12700). *Anal.* Calcd. for $C_{20}H_{23}N_5O_6S$: C, 52.06; H, 5.02; N, 15.18. Found: C, 51.82; H, 5.25; N, 14.95.

19) A.K.M. Amisuzzaman and R.L. Whistler, *J. Oerg. Chm.*, **37**, 3187 (1972).

**DMSO-$Ac_2O$ Oxidation f 5-(6-Aminopurin-9H-9-yl)-5-deoxy-1,2-O-isopropylidene-α-L-arabofuranose (3)**——To a solution of **3** (1.76 g) in anhyd. DMSO (17 ml) was added $Ac_2O$ (11.5 ml). After the solution had been stirred overnight at room temperature, $CHCl_3$ (100 ml) and $H_2O$ (100 ml) were added. The mixture was neutralized with satd. $Na_2CO_3$, and then extracted with $CHCl_3$. The extracts were washed with $H_2O$, dried and evaporated. The residue was chromatographed on silica gel. Elution with 1% MeOH–$CHCl_3$ gave 1.35 g (61%) of 5-(6-acetamidopurin-9H-9-yl)-3-acetoxy-5-deoxy-1,2-O-isopropylidene-α-L-arabofuranose (**5**). Recrystallization from benzene–isopropyl ether afforded an analytical sample of **5** as colorless needles; mp 99—100°. $[\alpha]_D^{15}$ +16.5° ($c$=1.0, $C_6H_6$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3130 and 3080 (>NH), 1730 and 1685 (C=O), 1585. NMR ($CDCl_3$) $\delta$: 8.73 (1H, s), 8.30 (1H, s), 7.36 (3H, s, 1/2 $C_6H_6$), 5.00 (1H, d, $J$=4.0 Hz, $C_1$-H), 5.17 (1H, s, $C_3$-H), 4.84—4.34 (4H, m), 2.58 (3H, s, –HN–Ac), 2.05 (3H, s, –OAc), 1.60 and 1.33 (3H, 3H, s, >$C(CH_3)_2$). UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$): 272 (18600), $\lambda_{max}^{EtOH\text{-}1N\ HCl}$ mμ ($\varepsilon$): 279 (15400), $\lambda_{max}^{EtOH\text{-}1N\ NaOH}$ mμ ($\varepsilon$): 267 (8500), 299.5 (11700). *Anal.* Calcd. for $C_{17}H_{21}O_6N_5 \cdot 1/2\ C_6H_6$: C, 55.79; H, 5.62; N, 16.27. Found: C, 55.66; H, 5.82; N, 16.52. Elution with 1—2% MeOH–$CHCl_3$ gave 470 mg (24%) of 5-(6-aminopurin-9H-9-yl)-3-acetoxy-5-deoxy-1,2-O-isopropylidene-α-L-arabofuranose (**6**). Recrystallization from MeOH afforded an analytical sample of **6** as colorless needles; mp 232—233° $[\alpha]_D^{15}$ −58.5° ($c$=1.0, DMSO). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3200, 3080, 1723, 1660, 1605. NMR (DMSO-$d_6$) $\delta$: 8.20 (1H, s), 8.09 (1H, s), 7.23 (2H, broad s, -$NH_2$), 5.98 (1H, d, $J$=4 Hz, $C_1$-H), 5.12 (1H, s, $C_3$-H), 4.73 (1H, d, $J$=4 Hz, $C_2$-H), 4.49 (broad s, 3H), 2.08 (3H, s, –OAc), 1.56 and 1.30 (3H, 3H, s, >$C(CH_3)_2$). UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$): 261 (12700). *Anal.* Calcd. for $C_{15}H_{19}O_5N_5$: C, 51.57; H, 5.48; N, 20.05. Found: C, 51.37; H, 5.64; N, 19.84.

While, **3** (307 mg), anhyd. DMSO (3 ml) and $Ac_2O$ (2 ml) were allowed to react and worked up in the manner described above. The crude mixture was chromatographed on $Al_2O_3$. Elution with 40% AcOEt–benzene gave 272 mg (78%) of **6** as a colorless solid. None of the other compounds was eluted from the column.

**5-(6-Acetamidopurin-9H-9-yl)-5-deoxy-1,2-O-isopropylidene-α-L-arabofuranose (7)**——To a solution of **5** (300 mg) in anhyd. MeOH (10 ml) was added 20% $NH_3$–MeOH (0.5 ml). After the solution had been stirred for 45 min at room temperature, the solvent was evaporated off. The residue was chromatographed on silica gel. Elution with 1% MeOH–$CHCl_3$ gave 54 mg (18%) of **5** with was identified by comparing its IR spectrum with that of an authentic sample. The first part of elution with 2% MeOH–$CHCl_3$ gave 17 mg (6%) of **6** which was also identified with the same manner as described above. The second part of elution with 2% MeOH–$CHCl_3$ gave 170 mg (63%) of **7**. Recrystallization from AcOEt afforded an analytical sample of **7** as colorless prisms; mp 135—136°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3370—3300, 1722 and 1695 (C=O), 1655. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$): 272 (16200). NMR (DMSO-$d_6$) $\delta$: 10.76 (1H, broad s, exchangeable with $D_2O$, AcNH–), 8.76 (1H, s), 8.46 (1H, s), 5.97 (1H, d, $J$=4.0 Hz, $C_1$-H), 5.96 (1H, d, $J$=4.5 Hz, exchangeable with $D_2O$, –OH), 4.58 (1H, d, $J$=4.0 Hz, $C_2$-H), 4.55—4.15 (4H, m), 2.30 (3H, s, –NH–Ac), 1.55 and 1.30 (3H, 3H, s, –$C(CH_3)_2$). *Anal.* Calcd. for $C_{15}H_{19}O_5N_5$: C, 51.57; H, 5.48; N, 20.05. Found: C, 51.24; H, 5.56; N, 19.75. Elution with 4% MeOH–$CHCl_3$ gave 32 mg (13%) of **3** which was identical in IR spectrum with an authentic sample.

**DMSO-$Ac_2O$ Oxidation of 5-(6-Acetamidopurin-9H-9-yl)-5-deoxy-1,2-O-isopropylidene-α-L-arabofuranose (7)**——A solution of $Ac_2O$ (1 ml) in anhyd. DMSO (10 ml) was added to a solution of **7** (400 mg) in anhyd. DMSO (10 ml). The solution was stirred overnight at room temperature and then $CHCl_3$ was added. The $CHCl_3$ solution was washed with cold 5% $NaHCO_3$, with $H_2O$, dried and evaporated. The residue was purified by chromatography on silica gel. Elution with 1% MeOH–$CHCl_3$ gave 80 mg (18%) of **5** as a colorless solid: mp 93—95°. This product was identified by comparing its IR, UV, and NMR spectra with those of an authentic sample **5**.

**Reaction of the Sodium Salt of 6-Methylthiopurine (8) with 5-O-Tosyl-1,2-O-isopropylidene-α-D-xylofuranose (9)**——The sodium salt of **8** was prepared from **8** (4.0 g) and NaH (890 mg, 65% in mineral oil) in DMF (100 ml) in the same manner as described previously.[1] A solution of **9** (8.6 g) in DMF (80 ml) was dropwise added. The mixture was stirred and warmed for 88 hr at 135° on an oil-bath. After evaporation of DMF, $H_2O$ (50 ml) was added. The solution was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with $H_2O$, dried and evaporated. The residue was chromatographed on silica gel. The first part of elution with 2% MeOH–$CHCl_3$ gave 3.12 g (28%) of 5-(6-methylthiopurin-9H-9-yl)-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**10**). Recrystallization from AcOEt afforded an analytical sample of **10** as colorless prisms; mp 180—182°. $[\alpha]_D^{23}$ +13.8° ($c$=1.0, EtOH). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3480 (–OH), 1575. NMR ($CDCl_3$) $\delta$: 8.80 (1H, s), 8.14 (1H, s), 6.27 (1H, d, $J$=4.0 Hz, $C_1$-H), 5.80 (1H, broad m), 4.69 (1H, d, $J$=4.0 Hz, $C_2$-H), 4.65—4.25 (3H, m), 4.03 (1H, broad s), 2.76 (3H, s, SMe), 1.45 and 1.30 (3H, 3H, s, >$C(CH_3)_2$. UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$): 284 (18500), 291 (17800), $\lambda_{max}^{EtOH\text{-}1N\ HCl}$ mμ ($\varepsilon$): 284.5 (17500), 291 (17200), $\lambda_{max}^{EtOH\text{-}1N\ NaOH}$ mμ ($\varepsilon$): 284 (18200), 291 (17400). *Anal.* Calcd. for $C_{14}H_{18}O_4N_4S$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.66; H, 5.11; N, 16.42. The second part of elution with 2% MeOH–$CHCl_3$ gave 680 mg (8.4%) of 5-(6-methylthiopurin-3H-3-yl)-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**11**). Two recrystallizations from AcOEt afforded an analytical sample of **11** as colorless prisms; mp 220—222° (decomp.). $[\alpha]_D^{23}$ +26.3° ($c$=1.0, EtOH). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3070 (–OH). 1590, 1560. NMR ($CDCl_3$) $\delta$: 8.82 (1H, s), 8.29 (1H, s), 6.03 (1H, d, $J$=3.5 Hz, $C_1$-H), 5.0—4.5 (5H, m), 4.33 (1H, m), 2.82 (3H, s, SMe), 1.35 and 1.29 (3H, 3H, s, >$C(CH_3)_2$). UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$): 238.5 (21700), 315 (24400), $\lambda_{max}^{EtOH\text{-}1N\ HCl}$mμ ($\varepsilon$): 237 (19500), 279 (18400), 318.5 (27200), $\lambda_{max}^{EtOH\text{-}1N\ NaOH}$mμ ($\varepsilon$): 238 (21600), 314 (24100). *Anal.* Calcd. for $C_{14}H_{18}N_4O_4S$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.30;

H, 5.65; N, 16.31. Elution with 2—5% MeOH–$CHCl_3$ gave 400 mg (4.9%) of 5-(6-methylthiopurin-7H-7-yl)-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**12**). Recrystallization from AcOEt afforded an analytical sample of **12** as colorless prisms: mp 168—170°. $[\alpha]_D^{23}$ +24° ($c$=1.0, EtOH). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3180 (–OH), 1570, 1545. NMR ($CDCl_3$) $\delta$: 8.91 (1H, s), 8.51 (1H, s), 6.13 (1H, d, $J$=4 Hz, $C_1$-H), 2.78 (3H, s, SMe), 1.43 and 1.30 (3H, 3H, s, >$C(CH_3)_2$). UV $\lambda_{max}^{EtOH}$ mμ ($\varepsilon$): 291 (14200), 299 (sh. 12100), $\lambda_{max}^{EtOH\text{-}1N\ HCl}$mμ ($\varepsilon$): 291 (13200), 299 (sh. 12100), $\lambda_{max}^{EtOH\text{-}1N\ NaOH}$mμ ($\varepsilon$): 291 (14000), 299 (12100). *Anal.* Calcd. for $C_{14}H_{18}O_4N_4S$–$1/2H_2O$: C, 48.41; H, 5.51; N, 16.13. Found: C, 48.66; H, 5.54; N, 15.81.

**DMSO–$Ac_2O$ Oxidation of 5-(6-Methylthiopurin-9H-9-yl)-1,2-O-isopropylidene-5-deoxy-α-D-xylofuranose (10)**——To a solution of **10** (338 mg) in anhyd. DMSO (10 ml) was added a solution of $Ac_2O$ (1 ml) in anhyd. DMSO (10 ml). The solution was stirred overnight at room temperature, and then warmed at 60—70° on an oil-bath for 5 hr. The mixture was worked up in the manner described above. The crude material was chromatographed on silica gel. The first part of elution with 1% MeOH–$CHCl_3$ gave 30 mg of 5-(6-methylthiopurin-9H-9-yl)-3-acetoxy-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**13**) as colorless syrup. IR $\nu_{max}^{Liquid}$ $cm^{-1}$: 1750 (C=O), 1570. NMR ($CDCl_3$) $\delta$: 8.83 (1H, s), 8.21 (1H, s), 6.05 (1H, d, $J$=3.5 Hz, $C_1$-H), 5.35 (1H, broad), 5.0—4.2 (4H, m), 2.75 (3H, s, SMe), 2.24 (3H, s, –OAc), 1.40 and 1.29 (3H, 3H, s, >$C(CH_3)_2$). The second part of elution with 1% MeOH–$CHCl_3$ gave 233 mg (69%) of the starting material **10**, as a colorless solid, which was identified by comparing its IR and NMR spectra with those of an authentic sample.

**5-O-Pivalyl-1,2-O-isopropylidene-α-D-xylofuranose (15)**——A solution of pivalyl cholride (20.5 g) in pyridine (100 ml) was added dropwise to the solution of 1,2-O-isopropylidene-α-D-xylofuranose (**14**)[13] (30 g) in pyridine (100 ml) under ice cooling. After being stirred for 1 hr, the mixture was worked up as usual. The crude material was purified by distillation to afford 32.2 g (74.5%) of the syrupy **15**, bp 134—136° (1.4 mmHg). IR $\nu_{max}^{Liquid}$ $cm^{-1}$: 3470 (–OH), 1730 (C=O). NMR ($CDCl_3$) $\delta$: 5.97 (1H, d, $J$=3.6 Hz, $C_1$-H), 4.65—4.0 (5H, m), 3.30 (1H, broad, exchangeable with $D_2O$, OH), 1.50 (3H, s), 1.31 (3H, s), 1.20 (9H, s, $t$-Bu).

**5-O-Pivalyl-1,2-O-isopropylidene-α-D-*erythro*-3-pentosulofuranose (16)**——5-O-Pivalyl derivative **15** (40 g) was dissolved in anhyd. DMSO (225 ml) and benzene (225 ml) containing pyridine (11.5 g) and trifluoroacetic acid (8.32 g). After the addition of a solution of DCC (84 g) in anhyd. DMSO–benzene (1 : 1, 200 ml), the sealed reaction flask was kept overnight at room temperature. Ether (800 ml) was added followed by a solution of oxalic acid (36.8 g) in methanol (45 ml). After gas evolution had ceased (about 3 hr), $H_2O$ (600 ml) was added and insoluble dicyclohexylurea was removed by filtration. The organic phase was washed with cold 5% $NaHCO_3$, with $H_2O$, dried, and evaporated. Ether (100 ml) was added to this residue and the solution was kept overnight at room temperature. The precipitate, dicyclohexylurea, was removed by filtration. The mother liquor was evaporated to give the crude product, 39 g, which was purified by means of chromotography on silica gel. Elution with 10% AcOEt–benzene gave 31.77 g (80%) of pure **16** as syrup. IR $\nu_{max}^{Liquid}$ $cm^{-1}$: 1755 and 1735 (C=O). NMR ($CDCl_3$) $\delta$: 6.12 (1H, d, $J$=4.0 Hz, $C_1$-H), 4.7—4.2 (4H, m), 1.49 (3H, s, $CH_3$), 1.43 (3H, s, $CH_3$), 1.15 (9H, s, $t$-Bu).

**DMSO–$Ac_2O$ Oxidation of 5-O-Pivalyl-1,2-O-isopropylidene-α-D-xylofuranose (15)**——A solution of **15** (4.04 g) in anhyd. DMSO (15 ml) was dropwise added to a mixture of $Ac_2O$ (30 ml) and anhyd. DMSO (30 ml) at 60°. The solution was allowed to warm at 65—70° and stirred for 1 hr, and then worked up in the manner described above. The crude material was chromatographed on silica gel. The first part of elution with 10% AcOEt–benzene gave 510 mg (11%) of 5-O-pivalyl-3-acetoxy-1,2-O-isopropylidene-α-D-xylofuranose (**17**) as colorless syrup. IR $\nu_{max}^{Liquid}$ $cm^{-1}$: 1735 and 1725 (C–O). NMR ($CDCl_3$) $\delta$: 5.79 (1H, d, $J$=4 Hz, $C_1$-H), 4.71 (1H, s, $C_3$-H), 4.61 (1H, d, $J$=4 Hz, $C_2$-H), 4.4—4.2 (3H, m), 2.17 (3H, s, –OAc), 1.50 and 1.32 (3H, 3H, s, >$C(CH_3)_2$), 1.20 (9H, s, $t$-Bu). The second part of elution with 10% AcOEt–benzene gave 1.90 g (47%) of colorless syrup. The IR and NMR spectra of this compound were agreed with those of an authentic sample **16**.

**3-Benzyloxycarbonylamido-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (19)**——A solution of **16** (22.48 g) in pyridine–EtOH (1 : 1, 100 ml) was added to a solution of $NH_2OH \cdot HCl$ (8.7 g) in pyridine–EtOH (1 : 1, 200 ml) under ice cooling. The mixture was stirred for 1.5 hr at room temperature. The solvent was removed and the syrupy residue was dissolved in $CH_2Cl_2$ (250 ml). The solution was washed with $H_2O$, cold 5% HCl, and $H_2O$, respectively, dried and evaporated to afford the crude oxime derivative (**18**) 22 g (92.5%) as viscous syrup. A solution of **18** (22 g) in anhyd. tetrahydrofuran (THF) (200 ml) was dropwise added to a suspension of $LiAlH_4$ (14.6 g) in anhyd. THF (250 ml) below 10°. The mixture was refluxed for 3 hr, then cooled and treated with THF–$H_2O$ (1 : 1, 100 ml). The solid was collected on a filter, washed with 20% $H_2O$–THF and THF. The filtrate combined was concentrated to give crude amino-alcohol derivative (13.62g, 94%) as colorless crystals, mp 63—65° (Lit.[17] mp 66—67°). To a solution of this amino-alcohol derivative and $NaHCO_3$ (7.5 g) in $H_2O$ (200 ml) was dropwise added benzyloxycarbonyl chloride (12.8 g) under cooling. The mixture was vigrously stirred overnight at room temperature. The solution was extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were washed with $H_2O$, dried and evaporated. The residual solid was crystallized from benzene–ether to afford 13.8 g of **19** as colorless prisms; mp 101—102°. $[\alpha]_D^{26}$ +109.4° ($c$=1.0, MeOH). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3445 (>NH), 3270 (–OH), 1715 (C=O). NMR ($CDCl_3$) $\delta$: 7.40 (5H, s, $-C_6H_5$), 5.86 (1H, d, $J$=3.9 Hz, $C_1$-H), 5.42 (1H, broad d, $J$=8 Hz, exchangeable with $D_2O$, –NH–), 5.14 (2H, s, $-CH_2-C_6H_5$), 4.60 (1H, t, $J$=3.9 Hz, $C_2$–H), 4.2—3.65 (4H, m), 2.15 (1H, broad, exchangeable with $D_2O$, OH), 1.51 and 1.33 (3H, 3H, s, >$C(CH_3)_2$). *Anal.* Calcd. for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.38; H, 6.45;

N, 4.25. The mother liquor was chromatographed on silica gel. Elution with 10—20% AcOEt–benzene gave 743 mg (2.8%) of 3-benzyloxycarbonylamido-3-deoxy-1,2-O-isopropyridene-α-D-xylofuranose (**20**). Recrystallization from isopropyl ether afforded an analytical sample of **20** as colorless prisms: mp 112—113°. $[\alpha]_D^{26}$ +6.8° ($c$=1.0, MeOH). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3455 (>NH), 3300 (–OH), 1725 and 1710 (C=O). NMR ($CDCl_3$) $\delta$: 7.35 (5H, s, $-C_6H_5$), 6.19 (1H, d, $J$=6 Hz, exchangeable with $D_2O$, –NH–), 5.85 (1H, d, $J$=3.9 Hz, $C_1$-H), 5.10 (2H, s, $-CH_2-C_6H_5$), 4.57 (1H, d, $J$=3.9 Hz, $C_2$-H), 4.4—3.7 (4H, m), 2.90 (1H, broad, exchangeable with $D_2O$, OH), 1.47 and 1.27 (3H, 3H, s, $>C(CH_3)_2$). *Anal.* Calcd. for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.33; H, 6.65; N, 4.32. Elution with AcOEt–benzene (1: 1) afforded further 907 mg of **19** as colorless crystals. After all, **19** was obtained in 55% yield from **16**.

**5-O-Tosyl-3-benzyloxycarbonylamido-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose** (**21**)——To a solution of **19** (13 g) in pyridine (70 ml) was dropwise added a solution of *p*-toluenesulfonyl chloride (8.06 g) in pyridine (30 ml) on an ice-salt bath, and the mixture was stirred overnight at room temperature. Usual work-up afforded 18.88 g (98%) of **21** as syrup, which was crystallized with ether after two months. Recrystallization from ether afforded an analytical sample of **21** as colorless needles, mp 76—77°. IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3375 (>NH), 1735 (C=O), 1355 and 1190 ($SO_2$). NMR ($CDCl_3$) $\delta$: 7.84 (2H, d, $J$=8.5 Hz), 7.35 (2H, d, $J$=8.5 Hz), 7.40 (5H, s, $-C_6H_5$), 5.71 (1H, d, $J$=4 Hz, $C_1$-H), 5.35—5.0 (1H, broad), 5.09 (2H, s, $-CH_2-C_6H_5$), 4.65—3.8 (5H, m), 2.40 (3H, s, $-C_6H_4-CH_3$), 1.45 and 1.27 (3H, 3H, s, $-C(CH_3)_2$). *Anal.* Calcd. for $C_{23}H_{27}O_8NS$: C, 57.85; H, 5.70; N, 2.93. Found: C, 57.67; H, 5.65; N, 2.93.

**Reaction of the Sodium Salt of Adenine** (**1**) **with 5-O-Tosyl-3-benzyloxycarbonylamido-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose** (**21**)——A solution of **1** (4.86 g) and NaH (1.33 g, 65% in mineral oil) in DMF (100 ml) and a solution of **21** (18 g) in DMF (200 ml) were allowed to react and treated in the manner described in the previous report.[1]. The resulting residue was extracted with hot $CHCl_3$ and the $CHCl_3$ extracts filtered were combined, washed with $H_2O$ and dried. After evaporation of the $CHCl_3$, 13 g of crude mixture was obtained as foams. This mixture was purified by chromatography on silica gel. The first part of elution with 2% MeOH–$CHCl_3$ afforded 9.65 g (61%) of 5-(6-aminopurin-9H-9-yl)-3-benzyloxycarbonylamido-3,5-dideoxy-1,2-O-isopropylidene-α-D-ribofuranose (**22**) as colorless foams, $[\alpha]_D^{22}$ +25° ($c$=0.4, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3420 ($-NH_2$), 1720 (C=O), 1630, 1585. NMR (DMSO-$d_6$) $\delta$: 8.13 (1H, s), 7.95 (1H, s), 7.30 (5H, s, $-C_6H_5$), 7.06 (3H, broad. >N-H and $-NH_2$), 5.74 (1H, d, $J$=3.9 Hz, $C_1$-H), 5.05 (2H, s, $-CH_2-C_6H_5$), 4.58 (1H, t, $J$=3.9 Hz, $C_2$-H), 4.50—3.70 (4H, m), 1.41 and 1.24 (3H, 3H, s, $>C(CH_3)_2$). The second part of elution with 2% MeOH–$CHCl_3$ afforded 917 mg (13%) of 5-(6-aminopurin-3H-3-yl)-3-benzyloxycarbonylamido-3,5-dideoxy-1,2-O-isopropylidene-α-D-ribofuranose (**23**) as colorless foams. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3400 ($-NH_2$), 1720 (C=O), 1640, 1560. NMR (DMSO-$d_6$) $\delta$: 8.26 (1H, s), 7.95 (2H, broad m, exchangeable with $D_2O$, $-NH_2$), 7.71 (1H, s), 7.35 (6H, s, 5H on the addition of $D_2O$), 5.74 (1H, d, $J$=3.9 Hz, $C_1$-H), 5.04 (2H, s, $-CH_2-C_6H_5$), 4.75—3.7 (5H, m), 1.34 and 1.21 (3H, 3H, s, $-C(CH_3)_2$). Elution with 5% MeOH–$CHCl_3$ afforded 336 mg (6%) of 5-(6-aminopurin-7H-7-yl)-3-benzyloxycarbonylamido-3,4-dideoxy-1,2-O-isopropylidene-α-D-ribofuranose (**24**) as colorless foams. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3425 and 3350 ($-NH_2$, >NH), 1720 (C=O), 1630, 1600. NMR (DMSO-$d_6$) $\delta$: 8.18 (1H, s), 8.09 (1H, s), 7.36 (6H, s, 5H on the addition of $D_2O$), 6.77 (2H, broad s, exchangeable with $D_2O$, $-NH_2$), 5.71 (1H, d, $J$=3.9 Hz, $C_1$-H), 5.09 (2H, s, $-CH_2-C_6H_5$), 4.60 (1H, t, $J$=3.9 Hz, $C_2$-H), 4.7—3.7 (4H, m), 1.40 and 1.23 (3H, 3H, s, $>C(CH_3)_2$).

**5-(6-Aminopurin-9H-9-yl)-3-benzyloxycarbonylamido-3,5-dideoxy-D-ribofuranose** (**25**)——A solution of **22** (4.0 g) and 6 N HCl (2.8 ml) in $H_2O$ (120 ml) was stirred and warmed at 80° for 2 hr. After being cooled, the solution was neutralized to pH 7 with 10% NaOH. The precipitate was collected by filtration to give 2.92 g (81%) of **25**. Recrystallization from $H_2O$–MeOH afforded an analytical sample of **25** as colorless prisms: mp 221—223° (decomp.). $[\alpha]_D^{22}$ +30° ($c$=0.5, DMSO). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3450, 3300, 3170, 1680, 1605, 1580. NMR (DMSO-$d_6$) $\delta$: 8.17 (1H, s), 8.05 (1H, s), 7.37 (5H, s, $-C_6H_5$), 7.08 (3H, broad s, >N–H and $-NH_2$), 6.46 (1H, broad, –OH), 5.35 (1H, broad m), 5.05 (3H, s, 2H on the addition of $D_2O$, $-CH_2-C_6H_5$), 4.5—3.7 (5H, m). UV $\lambda_{max}^{1N\ HCl}$ mμ (ε): 260 (14200). *Anal.* Calcd. for $C_{18}H_{20}O_5N_6$: C, 53.99; H, 5.04; N, 20.99. Found: C, 53.51; H, 5.28; N, 20.88.

**5-(6-Aminopurin-9H-9-yl)-3-amino-3,5-dideoxy-D-ribofuranose** (**26**)**·Hydrochloride**——A suspension of **25** (1.7 g) in $H_2O$ (150 ml) and 6 N HCl (1.42 ml) was hydrogenated on 10% Pd-C (170 mg) for 15 hr at room temperature. After removal of the catalyst by filtration, the filtrate was lyophilized. The residual solid was recrystallized from $H_2O$–EtOH to afford 1.21 g (94%) of **26**·hydrochloride as colorless prisms: mp 220—223° (decomp.). $[\alpha]_D^{20}$ +30° ($c$=0.5, $H_2O$). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3280, 3150, 2630, 2560, 1685, 1595. NMR ($D_2O$) $\delta$:[20] 8.41 (1H, s), 8.34 (1H, s), 5.7—5.1 (2H, m), 4.20 (2H, broad m), 3.82 (2H, broad m), UV $\lambda_{max}^{H_2O}$ mμ (ε): 260 (22800). *Anal.* Calcd. for $C_{10}H_{14}O_3N_6 \cdot HCl$: C, 39.67; H, 5.00; N, 27.76; Cl, 11.71. Found: C, 39.69; H, 5.17; N, 27.77; Cl, 11.98.

**5-Acetoxy-3-acetamido-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose** (**27**)——A solution of **16** (42.5 g) and $NH_2OH \cdot HCl$ (16.4 g) in pyridine–EtOH (1: 1, 600 ml) was allowed to react and treated in the same manner as described above to give the oxime derivative 43.11 g (96%). This oxime derivative was reduced with $LiAlH_4$ (28.4 g) in anhyd. THF (900 ml) by the method described above to afford the amino–alcohol

20) Sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used as an internal standard.

derivative 27.89 g (98%). To a solution of this amino-alcohol derivative in pyridine (200 ml) was added $Ac_2O$ (100 ml) under ice cooling, and stirred for 3.5 hr at room temperature. The solution was worked up as usual. The crude material was recrystallized from AcOEt to afford an analytical sample of **27**, 25.2 g, as colorless needles: mp 172° (Lit.[19] mp 165°). $[\alpha]_D^{27}$ +76° ($c$=1.0, $CHCl_3$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3410 (>NH), 1725 and 1690 (C=O). NMR ($CDCl_3$) $\delta$: 5.85 (1H, d, $J$=9.0 Hz, AcNH–), 5.75 (1H, d, $J$=4.0 Hz, $C_1$-H), 4.50 (1H, t, $J$=4.0 Hz, $C_2$-H), 2.03 (3H, s, –OAc), 1.97 (3H, s, –NH–*Ac*). *Anal.* Calcd. for $C_{12}H_{19}O_6N$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.58; H, 6.98; N, 4.98. The mother liquor was chromatographed on silica gel. Elution with benzene–AcOEt (1: 1) gave 123 mg (0.3%) of 5-acetoxy-3-acetamido-3-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**28**) as syrup. IR $\nu_{max}^{Liquid}$ $cm^{-1}$: 3500 (>NH), 1730 and 1650 (C=O). NMR ($CDCl_3$) $\delta$: 6.08 (1H, d, $J$=4 Hz, $C_1$-H), 5.20 (1H, d, $J$=8 Hz, AcNH–), 4.20 (1H, d, $J$=4 Hz, $C_2$-H), 2.19 (3H, s, –OAc), 2.05 (3H, s, –NH–*Ac*). Elution with AcOEt gave further 509 mg of **27** as crystals. After all, **27** was obtained in 62% yield from **16**.

**3-Acetamido-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (29)**——To a solution of **27** (10 g) in MeOH (100 ml) was added 17% $NH_3$–MeOH (4 ml), and stirred overnight at room temperature. MeOH was evaporated off. The resulting solid was triturated with AcOEt to afford 8.23 g (97%) of crude **29** (mp 154—155°). Recrystallization from AcOEt gave an analytical sample of **29** as colorless granulars: mp 156—157°. $[\alpha]_D^{26}$ +16° ($c$=1.0, $CHCl_3$). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3420 (>NH), 3280 (–OH), 1680 (C=O). NMR ($CDCl_3$) $\delta$: 6.30 (1H, broad, exchangeable with $D_2O$, AcNH–), 5.95 (1H, d, $J$=4.0 Hz, $C_1$-H), 4.68 (1H, t, $J$=4.0 Hz, $C_2$-H), 3.50 (1H, broad, exchangeable with $D_2O$, OH), 2.06 (3H, s, –NH–Ac), 1.56 and 1.37 (s, 3H, 3H, >$C(CH_3)_2$). *Anal.* Calcd. for $C_{10}H_{17}O_5N$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.58; H, 7.30; N, 5.96.

**5-O-Tosyl-3-acetamido-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (30)**——A solution of *p*-toluenesulfonyl chloride (10.5 g) in pyridine (50 ml) was added dropwise to a solution of **29** (12.0 g) in pyridine (70 ml) under ice cooling, and the mixture was stirred overnight at room temperature. Usual work-up afforded 17.18 g (81%) of **30** as colorless syrup. IR $\nu_{max}^{Liquid}$ $cm^{-1}$: 3425 (>NH), 1675 (C=O), 1365 and 1170 ($SO_2$). NMR ($CDCl_3$) $\delta$: 7.90 (2H, d, $J$=8.5 Hz), 7.41 (2H, d, $J$=8.5 Hz), 6.14 (1H, broad d, $J$=8.0 Hz, exchangeable with $D_2O$, AcNH–), 5.83 (1H, d, $J$=4.0 Hz, $C_1$-H), 4.60 (1H, t, $J$=4.0 Hz, $C_2$-H), 2.26 (3H, s, –$C_6H_4$–$CH_3$), 2.01 (3H, s, –NH–Ac), 1.55 and 1.35 (3H, 3H, s, >$C(CH_3)_2$).

**Reaction of the Sodium Adenide with 5-O-Tosyl-3-acetamido-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (30)**——Adenine (5 g), NaH (1.37 g, 65% in mineral oil) in DMF (100 ml) and **30** (15 g) in DMF (200 ml) were allowed to react and treated in the manner described in the previous general procedure.[1] The residual solid was extracted with hot $CHCl_3$, and the $CHCl_3$ extracts filtered were combined, washed with $H_2O$, dried and evaporated to give 15 g of crude mixture. This mixture was chromatographed on silica gel (350 g). Elution with 5% MeOH–$CHCl_3$ gave 9.07 g (70%) of 5-(6-aminopurin-9H-9-yl)-3-acetamido-3,5-dideoxy-1,2-O-isopropylidene-α-D-ribofuranose (**31**). Recrystallization from AcOEt–benzene afforded an analytical sample of **31** as colorless granulars; mp 147—150°. $[\alpha]_D^{26}$ +57.4° ($c$=1.0, EtOH). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3570, 3260, 3150, 1660 (C=O), 1600, 1570. NMR (DMSO-$d_6$) $\delta$: 8.26 (1H, s), 8.14 (1H, s), 8.10 (1H, d, $J$=7 Hz, exchangeable with $D_2O$, Ac–NH–), 7.34 (2H, broad s, exchangeable with $D_2O$, $-NH_2$), 5.84 (1H, d, $J$=3.9 Hz, $C_1$-H), 4.64 (1H, t, $J$=3.9 Hz, $C_2$-H), 4.50—3.90 (4H, m), 1.93 (3H, s, –HN–Ac), 1.44 and 1.26 (3H, 3H, s, >$C(CH_3)_2$). *Anal.* Calcd. for $C_{15}H_{20}O_4N_6 \cdot 1/2H_2O$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.55; H, 5.88; N, 23.14. Elution with 10% MeOH–$CHCl_3$ gave 2.45 g (19%) of 5-(6-aminopurin-3H-3-yl)-3-acetamido-3,5-dideoxy-1,2-O-isopropylidene-α-D-ribofuranose (**32**). Recrystallization from AcOEt afforded an analytical sample of **32** as colorless crystalline powder: mp 180—183°, $[\alpha]_D^{26}$ +79° ($c$=1.0, EtOH). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3270, 1675 (C=O), 1655, 1620. NMR (DMSO-$d_6$) $\delta$: 8.34 (1H, s), 8.15 (3H, broad m, exchangeable with $D_2O$, Ac–NH–, $-NH_2$), 7.90 (1H, s), 5.08 (1H, d, $J$=3.9 Hz, $C_1$-H), 4.70 (1H, t, $J$=3.9 Hz, $C_2$-H), 4.8—4.0 (4H, broad m), 1.94 (3H, s, –NH–Ac), 1.39 and 1.26 (3H, 3H, s, >$C(CH_3)_2$). *Anal.* Calcd. for $C_{15}H_{20}O_5N_6 \cdot 3/4H_2O$: C, 49.78; H, 5.99; N, 23.22. Found: C, 49.99; H, 5.85; N, 23.04.

**5-(6-Aminopurin-9H-9-yl)-3-acetamido-3,5-dideoxy-D-ribofuranose (33)**——A solution of **31** (1.85 g) and 6 N HCl (1.5 ml) in $H_2O$ (40 ml) and Amberlite IR-45 (wet 25 ml) were treated in the manner of the previous general procedure.[1] The resulting solid was recrystallized from $H_2O$ to afford an analytical sample of **33** as colorless prisms: yield 1.58 g (96%); mp 241—243° (decomp.). $[\alpha]_D^{26}$ +48° ($c$=0.5, DMSO). IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3375, 3280, 3160, 1678 (C=O), 1640, 1570. NMR (DMSO-$d_6$) $\delta$: 8.21 (1H, s), 8.13 (1H, s), 7.82 (1H, d, $J$=7 Hz, exchangeable with $D_2O$, AcNH–), 7.20 (2H, broad s, exchangeable with $D_2O$, $-NH_2$), 6.55 (1H, d, $J$=3 Hz, exchangeable with $D_2O$, –OH), 5.46 (1H, d, $J$=4 Hz, exchangeable with $D_2O$, –OH), 5.08 (1H, d, $J$=4 Hz, s on the addition of $D_2O$, $C_1$-H), 1.88 (3H, s, –NH–Ac). UV $\lambda_{max}^{H_2O}$ mμ ($\varepsilon$): 261.5 (20300). *Anal.* Calcd. for $C_{12}H_{16}O_4N_6 \cdot 1/4H_2O$: C, 46.07; H, 5.31; N, 26.87. Found: C, 46.26; H, 5.21; N, 26.77.

**Oxidation of 5-(6-Aminopurin-9H-9-yl)-3-acetamido-3,5-dideoxy-D-ribofuranose (33)**——A solution of **33** (2.70 g, 7.78 mmoles) and NaOH (1.10 g, 23.4 mmoles) in $H_2O$ (550 ml) was stirred at room temperature for 70 hr in an oxygen atomosphere. This solution was passed through a column of Amberlite IR-120 ($H^+$ form, wet, 50 ml). The adsorbed substance was eluted with 1.4% $NH_4OH$. The eluate (1.5 liters) was evaporated at 50—60° to give 2.2 g of crude mixture. Each 500 mg of this crude mixture was passed through a column of Sephadex LH-20 (75 g) by developing with MeOH. After this procedure was repeated four times, adenine (142 mg, 16%) was removed from the mixture. The crude mixture (1.68 g) was crystallized from EtOH–$H_2O$ to give 297 mg (12%) of sodium 4-(6-aminopurin-9H-9-yl)-3(*R*)-hydroxy-2(*R*)-acetamidobutyrate

(34) as colorless powder: mp 180—182° (decomp.). $[\alpha]_D^{22}$ +10° ($c$=1.0, DMSO). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3400—3000, 1700 (CO=), 1655, 1570. NMR (DMSO-$d_6$) $\delta$: 8.11 (1H, s), 7.99 (1H, s), 8.25—7.85 (1H, broad m, AcNH–), 7.08 (2H, broad m, $-NH_2$), 1.93 (3H, s, –NH–Ac). UV $\lambda_{max}^{H_2O}$ m$\mu$ ($\varepsilon$): 261 (20800). *Anal.* Calcd. for $C_{11}H_{13}N_6O_3Na \cdot 1/3H_2O$: C, 41.00; H, 4.26; N, 26.10. Found: C, 40.46; H, 4.56; N, 26.34. The mother liquor was esterified with satd. EtOH–HCl and worked up in the same manner as described previously.[1] The crude material was crystallized from EtOH–MeOH to give 514 mg of ethyl 4-(6-aminopurin-9H-9-yl)-3(*R*)-hydroxy-2(*R*)-aminobutyrate (**35**)·hydroxchloride, mp 185—187° (decomp.). Recrystallization from MeOH afforded an analytical sample of **35**·hydrochloride as colorless prisms: mp 208—210° (decomp.). $[\alpha]_D^{27}$ +50° ($c$=0.5, $H_2O$). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3260, 3180, 1760 (C=O), 1670, 1240. NMR (DMSO-$d_6$) $\delta$: 8.15 (1H, s), 8.05 (1H, s), 7.15 (2H, broad, exchangeable with $D_2O$, $-NH_2$), 4.8—3.9 (m, 6H), 1.26 (3H, t, $J$=7 Hz, $-CH_2-CH_3$). UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 261 (13600). *Anal.* Calcd. for $C_{11}H_{16}O_3N_6 \cdot HCl \cdot 1/2H_2O$: C, 40.55; H, 5.56; N, 25.80. Found: C, 40.94; H, 5.38; N, 26.04. The mother liquor was purified by means of chromatography on silica gel. Elution with 2% MeOH–$CHCl_3$ gave 29 mg (1.7%) of ethyl (6-aminopurin-9H-9-yl)acetate (**37**) as colorless prisms, mp 225—227°. Elution with 2—5% MeOH–$CHCl_3$ afforded 48 mg (2.4%) of ethyl 3-(6-aminopurin-9H-9-yl)-2(*R*)-hydroxypropionate (**36**) as colorless prisms, mp 176—178°. The structures of **36** and **37** were identified by comparing their IR spectra with those of authentic samples,[4] respectively. Elution of 5—10% MeOH–$CHCl_3$ afforded 279 mg of **35**. which was treated with EtOH–HCl to give **35**·hydrochloride. After all, **35**·hydrochloride was obtained in 31.4% yield from **33**.

**4-(6-Aminopurin-9H-9-yl)-3(*R*)-hydroxy-2(*R*)-aminobutylic acid** (**38**)——A solution of **35**·hydrochloride (328 mg) and NaOH (83 mg) in MeOH (25 ml) was stirred for 3 hr on an ice-bath. After evaporation of MeOH at room temperature, the residue was dissolved in $H_2O$ (2 ml), and then neutralized to pH 5—6 with 99% HCOOH. The resulting solid was collected by filtration to give 205 mg (78%) of crude **38**, mp 224—228° (decomp.). The crude **38** was dissolved again in dilute NaOH solution, and the solution was neutralized with 99% HCOOH to afford pure **38** as colorless powder; mp 227—229° (decomp.). $[\alpha]_D^{27}$ +43.3° ($c$=0.6, 1 N NaOH). IR $\nu_{max}^{Nujol}$ cm$^{-1}$: 3400—3000, 1695 (C=O), 1640, 1010. NMR ($D_2O$–NaOD) $\delta$:[20] 7.95 (1H, s), 7.90 (1H, s), 4.19 (3H, broad s), 3.50 (1H, broad m). UV $\lambda_{max}^{1N\ NaOH}$ m$\mu$ ($\varepsilon$): 261 (20300). *Anal.* Calcd. for $C_9H_{12}O_3N_6 \cdot 1/3H_2CO_3 \cdot H_2O$: C, 37.87; H, 5.02; N, 27.90. Found: C, 37.97; H, 4.92; N, 27.92.

**Acknowledgement** The authors are indebted to Mr. M. Yamazaki, director of this laboratory, for his generous support and encouragement. Thanks are due to the members of the analytical section presided over by Dr. K. Kotera for elemental and spectral analyses.