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Reaction of 6-Methylsulfonylpurine Riboside with Carbon Nucleophiles and the Synthesis of 6-Alkylpurine Nucleosides (Nucleosides and Nucleotides. XXIX[1])

Akira Yamane, Akira Matsuda, and Tohru Ueda

Faculty of Pharmaceutical Sciences, Hokkaido University[2]

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Treatment of 6-methylsulfonyl-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)purine with ethyl acetoacetate and sodium hydride in tetrahydrofuran afforded, after deblocking, 6-ethoxycarbonylmethyl-9-β-D-ribofuranosylpurine. Similarly, replacement of the 6-methylsulfonyl moiety with other carbanions derived from diethyl malonate, ethyl cyanoacetate, malononitrile, nitromethane, and sodium cyanide gave the corresponding 6-*C*-substituted purine nucleosides. Most of these derivatives exist as the 6-(1*H*)-exomethylene tautomeric forms. 6-Ethoxycarbonylmethylpurine riboside was further converted to 6-methyl, ethyl, propyl, butyl, and pentyl-purine ribosides by decarboxylation or prior alkylation of the methylene group followed by de-carboxylation. This reaction sequence facilitated the preparation of hitherto almost inaccessible alkyl or *C*-substituted purine nucleosides.

Keywords——nucleophilic aromatic substitution; carbon nucleophiles; purine nucleosides; UV; NMR; tautomerism

In a previous paper we reported[3] a facile substitution of the methylsulfonyl group in 2- and 8-methylsulfonyladenosines with cyanide to give 2- and 8-cyanoadenosines. As an extension of this work we report here the results of substitution of 6-methylsulfonylpurine nucleosides with various carbon nucleophiles. Several procedures have been reported for the synthesis of alkyl- or carbon-substituted purine nucleosides. The ribosylation of 6-methyl (and ethyl)-purine gives the nucleosides.[4] The photoaddition of methanol to 9-β-D-ribofuranosylpurine was reported to give 6-hydroxymethylpurine and its 1,6-dihydro derivatives.[5] The sulfur-extrusion reaction of 6-phenacylthiopurine nucleoside afforded the 6-phenacylpurine derivatives.[6,7] The Wittig reaction of fully trimethylsilylated 6-chloro-2-methyl-9-β-D-ribofuranosylpurine to give 2,6-dialkylpurine nucleosides has been reported recently.[8]

Although the replacement of the methylsulfonyl group in 6-methylsulfonyl-9-β-D-ribofuranosylpurine with various oxygen, nitrogen, and sulfur nucleophiles was successfully achieved by Wetzel and Eckstein,[9] our attempts to achieve substitution with carbon nucleophiles, under necessarily basic conditions, failed. It appeared that the protection of the sugar hydroxyl groups was crucial.

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2) Location: *Kita-12, Nishi-6, Kita-ku, Sapporo, 060, Japan.*
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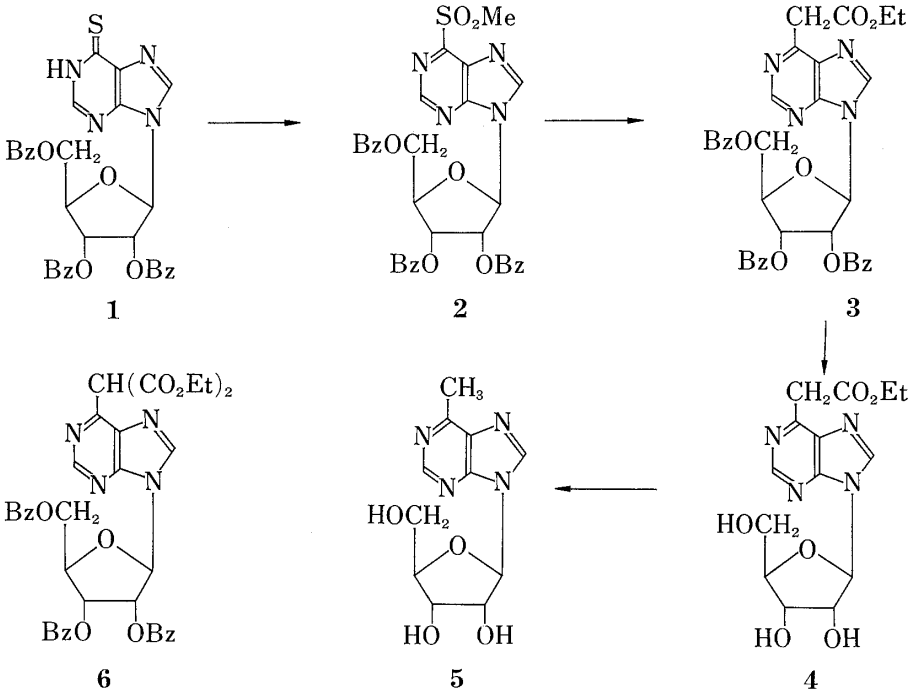


Chart 1

Thus, we selected 6-methylsulfonyl-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-purine as the key substrate. Treatment of 2′,3′,5′-tri-*O*-benzoyl-6-thioinosine (**1**) with methyl iodide in the presence of potassium carbonate in dimethylformamide (DMF), followed by oxidation of the 6-methylthio derivative with potassium permanganate in acetic acid, gave the crystalline 6-methylsulfonyl derivative (**2**) in almost quantitative yield. The action of ethyl acetoacetate and sodium hydride on **2** in tetrahydrofuran (THF) under reflux for 6 hours afforded 6-ethoxycarbonylmethylpurine nucleoside (**3**), after chromatographic purification. The nuclear magnetic resonance (NMR) spectrum of **3** showed no acetyl signal, indicating that retro-Claisen reaction of the initially formed purin-6-ylacetoacetate must have occurred. In fact, on reaction at room temperature, a new spot (at *Rf* 0.45) appeared on the thin-layer chromatogram (TLC); this disappeared on prolongation of the reaction time, or on heating the mixture, affording a spot of **3** (at *Rf* 0.29, silica gel, developed with benzene–AcOEt, 3: 1).

Treatment of **3** with sodium ethoxide in ethanol afforded 6-ethoxycarbonylmethyl-9-β-D-ribofuranosylpurine (**4**) in 85% yield, together with 6-methylpurine riboside (**5**) in 9%

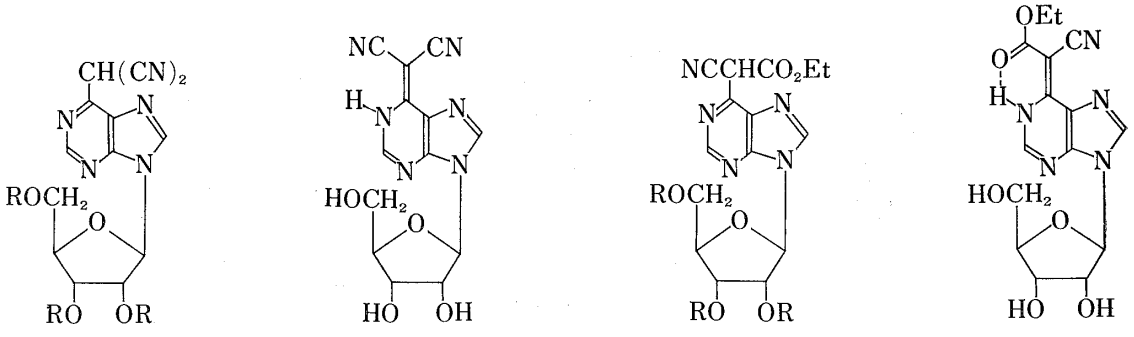
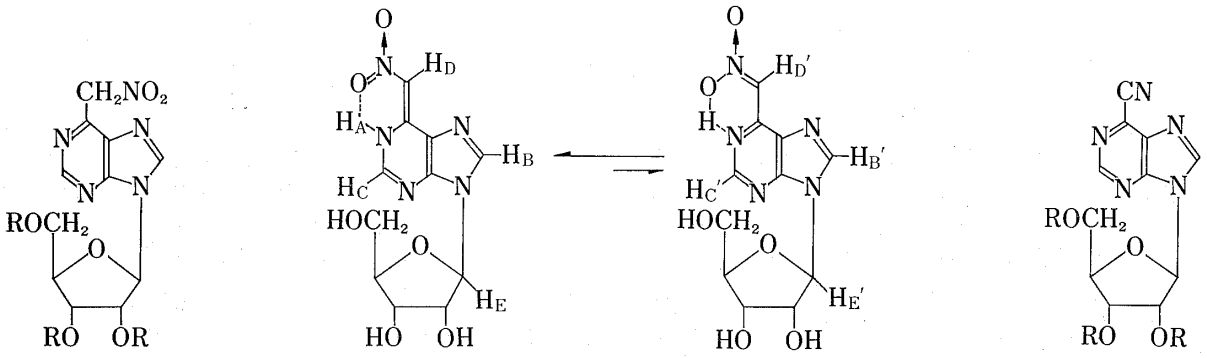


Chart 2

yield. Compound **5** was readily obtained by the treatment of **4** with aqueous alkali, followed by acidification.

Treatment of **2** with diethyl sodiomalonate at room temperature gave the 6-malonate derivative (**6**) in high yield. An attempt to remove the benzoyl group of **6** with sodium ethoxide in ethanol resulted in the formation of **4** and **5**. The action of sodiomalononitrile on **2** afforded the 6-dicyanomethylpurine derivative (**7**). The debenzoylation of **7** gave crystalline 6-dicyanomethyl-9-β-D-ribofuranosylpurine (**8**) in good yield. Similar treatment of **2** with ethyl cyanoacetate and sodium hydride afforded the condensation product (**9**), which was debenzoylated to give 6-ethoxycarbonylcyanomethylpurine riboside (**10**). The predominant tautomeric structures of the latter two ribosides (**8** and **10**) were found to be the exo-methylene forms having the N^1-protons, as detected by NMR measurements. Furthermore, the infrared (IR) spectra of **10** showed a single nitrile stretching band while those of **8** showed two. These findings are consistent with the tautomeric structures **8a** and **10a**. The presence of an absorption maximum in the ultraviolet (UV) spectra of **8** and **10** at longer wavelength than 300 nm is also indicative of conjugation of the chromophores through the exo-methylene group.

Treatment of **2** with sodium hydride and nitromethane in THF under reflux afforded the nitromethyl derivative (**11**). The debenzoylation of **11** gave the crystalline 6-nitrometh-



11 : R =Bz
12 : R =H

12a **12b**

13 : R=Bz
14 : R=H

Chart 3

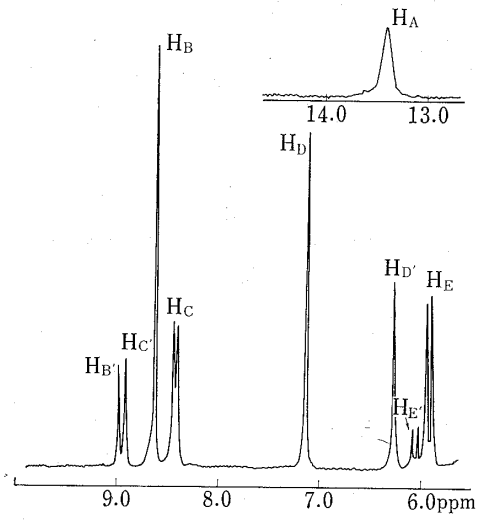
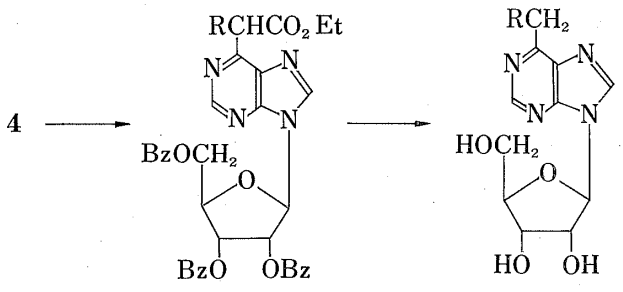


Fig. 1. NMR Spectrum of 6-Nitro methyl-9-β-D-ribofuranosylpurine in DMSO-d_6



15 : R=Me

16 : R=Me
17 : R=Et
18 : R=Pr
19 : R=Bu

Chart 4

ylpurine riboside (**12**). The NMR spectrum of **12** showed two sets of protons in the base moiety and anomeric carbon (Fig. 1). This can be rationalized in terms of a tautomeric equilibrium between **12a** and **12b**. The doublet at 8.5 ppm can be assigned to the proton of position 2 of **12a**, which was split by the proton at N^1 and coalesced to a siglet on addition of D_2O to the solvent (DMSO-d_6). The addition of D_2O to the solvent also shifted the equilibrium toward **12a**.

Treatment of 2 with sodium cyanide gave the 6-cyano derivative (**13**), which was very unstable and tended to give inosine on treatment with sodium ethoxide in ethanol. Treatment of 6-methylsulfonylpurine riboside[9] with sodium cyanide in DMF gave 6-cyano-9-β-D-ribofuranoasylpurine (**14**) in very low yield. The absence of nitrile absorptions in the IR spectra of both cyano compounds (**13** and **14**) is characteristic. Similar absence of the nitrile absorptions has been observed in a pyrazolopyrimidine derivative.[10]

For elongation of the methylene unit at the 6-position, **4** was utilized. Treatment of **4** with sodium ethoxide and methyl iodide in absolute ethanol at room temperature afforded a foamy compound (**15**) in quantitative yield after chromatographic purification. Treatment of **15** with 0.1 N NaOH followed by 0.1 N HCl and separation of the product on a silica gel column afforded 6-ethyl-9-β-D-ribofuranosylpurine (**16**) in 66% yield. The presence of the ethyl group at the 6-position was confirmed by NMR measurement. By similar procedures, 6-propyl, 6-butyl and 6-pentyl derivatives of purine riboside (**17**—**19**) were prepared in satisfactory yields.

In conclusion, the present method for the preparation of alkylpurine ribosides starting from the methylsulfonylpurine nucleoside may be widely applicable for the preparation of 2- or 8-alkylpurine nucleosides, including 2′-deoxyribosides. The C-substituted purine ribosides prepared in the present work may be suitable as substrates for further transformations in the base moieties. Experiments along these lines are under way in our laboratory.[11] Recently, a synthesis of 6-C-substituted purine ribosides from 6-chloropurine nucleosides has been reported.[12]

The results of evaluation of the present C-substituted purine nucleosides as chemotherapeutic agents will be reported separately.

Experimental

Melting points were determined with a Yanaco MP-3 melting point apparatus and are uncorrected. UV spectra were recorded on a Shimadzu UV-300 recording spectrophotometer. NMR spectra were taken with a JEOL JNM-FX 100 FT NMR spectrometer. Mass spectra were taken with a Hitachi RMU-7 mass spectrometer or a JEOL JMS-D 300 spectrometer. IR spectra were measured on a Hitachi 215 spectrophotometer. Thin-layer chromatography was carried out on Merck TLC plates (silica gel $60F_{254}$, pre-coated). Silica gel for column chromatography was Wakogel C-200. Ribonucleosides were purchased from Yamasa Shoyu Co. Ltd.

6-Methylsulfonyl-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-purine (2)——2′,3′,5′-tri-*O*-benzoyl-6-thioinosine[13] (30 g) in 100 ml of DMF was treated with 4 ml of methyl iodide and 7.6 g of K_2CO_3, and the solution was stirred for 1 hr. The reaction mixture was poured into 100 ml of ice-water and the precipitate was collected by filtration and washed with H_2O. The precipitate was dissolved in 700 ml of 90% AcOH, and 15 g of $KMnO_4$ was added with stirring. After 2 hr the reaction mixture was poured into 1500 ml of ice-water and the precipitate was collected and dried to give 31 g (96%) of **1**. The precipitate was used for further reaction without purification. A part of the crude **1** was crystallized from MeOH–AcOEt to give pure **1**, mp 124—126°. *Anal.* Calcd for $C_{32}H_{26}N_4O_9S$: C, 59.81; H, 4.08; N, 8.72; S, 4.98. Found: C, 59.76;

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H, 4.00; N, 8.70; S, 4.98. UV λ_{max}^{EtOH} nm (ε): 230 (38700), 275 (11500), 282 (sh, 9900). λ_{min}^{EtOH} 255 (6600). NMR ($CDCl_3$) δ: 8.92 (s, 1, 8-H), 8.66 (s, 1, 2-H), 6.58 (s, 1, 1′-H), 3.44 (s, 3, CH_3SO_2).

6-Ethoxycarbonylmethyl-9-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-purine (3)——A solution of 6.05 g of ethyl acetoacetate and 1.49 g of 50% NaH in 20 ml of THF was added dropwise to a solution of 10 g of **2** in 50 ml of THF and the solution was refluxed for 6 hr. After cooling, AcOH was added to neutrality, then the solvent was removed *in vacuo* and the residue was kept overnight at room temperature. The solidified residue was washed with H_2O and crystallized from iso-PrOH to give 8.0 g (78.9%) of **3**, mp 122—124°. *Anal.* Calcd for $C_{35}H_{30}N_4O_9$: C, 64.61; H, 4.65; N, 8.61. Found: C, 64.78; H, 4.65; N, 8.23. NMR ($CDCl_3$) δ: 8.85 (s, 1, 8-H), 8.24 (s, 1, 2-H), 4.24 (s, 2, 6-CH_2–), 4.22 (q, 2, $OC\underline{H}_2CH_3$), 1.24 (t, 3, $OCH_2C\underline{H}_3$, J=7.0 Hz). UV λ_{max}^{EtOH} nm (ε): 232 (30730), 266 (7060), 280 (sh, 2800), 323 (1010).

6-Ethoxycarbonylmethyl-9-*β*-D-ribofuranosylpurine (4)——A solution of 8.42 g of **3** in 200 ml of 0.05 N NaOEt in EtOH was stirred for 30 min at 60°. After neutralization with AcOH, the solvent was removed *in vacuo* and the residue was taken up in H_2O (100 ml). The aqueous solution was washed three times with $CHCl_3$ then the aqueous layer was concentrated and the residue was dissolved in EtOH to which a small amount of silica gel had been added. The solvent was removed and the residual powder was charged on a column of silica gel (120 g, packed with $CHCl_3$). The column was eluted with 12.5% EtOH in $CHCl_3$ and the eluent containing **4** was collected, and evaporated down to leave 3.70 g (85%) of **4** as a glassy solid. UV λ_{max}^{EtOH} 264 nm, λ_{min}^{EtOH} 255 nm. IR (film): 1740 cm^{-1} (–COO–). NMR (DMSO-d_6) δ: 8.88 (s, 1, 8-H), 8.81 (s, 1, 2-H), 6.04 (d, 1, 1′-H, J=6.0 Hz), 4.18 (s, 2, 6-CH_2–), 4.11 (q, 2, $-OC\underline{H}_2CH_3$), 1.18 (t, 3, $-OCH_2C\underline{H}_3$, J=7.0 Hz). MS m/e: 338 (M^+), 292, 249 (M−89), 207 (B+2), 206 (B+1).

6-Methyl-9-*β*-D-ribofuranosylpurine (5)[4]——Fractions eluted after those of **4** were collected and evaporated down to leave **5**, which was crystallized from EtOH–$CHCl_3$ giving a yield of 297 mg (9.0%), mp 208—210°. The physical constants were identical with those reported.[4] Compound **5** was also obtained by treatment of **4** with equimolar NaOH in H_2O, followed by acidification.

6-Bis(ethoxycarbonyl)methyl-9-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-purine (6)——A mixture of 745 mg of diethyl malonate and 149 mg of 50% NaH in 3 ml of THF was added to a solution of 1.0 g of **2** in 20 ml of THF and the solution was stirred for 1.5 hr at room temperature. After neutralization with AcOH, the solvent was removed *in vacuo* and the residue was partitioned with 50 ml of $CHCl_3$ and 20 ml of H_2O. The $CHCl_3$ layer was dried over Na_2SO_4 and the solvent was removed. The residue was taken up in C_6H_6 and applied to a column of silica gel (30 g), eluting with 12.5% AcOEt in C_6H_6. Fractions containing **6** were collected and the solvent was removed to leave 892 mg (80%) of foam. UV λ_{max}^{EtOH} nm: 230, 266, 328. λ_{min}^{EtOH} nm: 255, 299. NMR ($CDCl_3$) δ: 8.88 (s, 1, 8-H), 8.28 (s, 1, 2-H), 5.54 (s, 1, 6-CH), 4.28 (q, 4, $-OC\underline{H}_2CH_3$), 1.26 (t, 6, $-OCH_2C\underline{H}_3$, J=6.0 Hz).

Treatment of 6 with Sodium Ethoxide——A solution of 400 mg of **6** in 0.05 N NaOEt in EtOH (10 ml) was stirred for 1 hr at 60°. After neutralization of the solution with AcOH, the solvent was removed *in vacuo* and the residue was partitioned with $CHCl_3$ and H_2O. The aqueous layer was concentrated and the residue was separated on a silica gel column (15 g) as described for the preparation of **4**. Compound **4** was obtained in a yield of 117 mg (64%) together with **5** (11 mg, 7%). There was no fraction containing de-blocked **6** in the eluate.

6-Dicyanomethyl-9-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-purine (7)——A solution of 1.0 g of **2** in 15 ml of THF was treated with 150 mg of 50% NaH and 307 mg of malononitrile dissolved in 5 ml of THF. After stirring the solution for 1 hr, it was neutralized with AcOH and concentrated. The residue was taken up in $CHCl_3$, washed with H_2O, and the organic layer was applied to a column of silica gel (30 g). The eluent with 2% EtOH in $CHCl_3$ was concentrated to leave 0.74 g (76%) of **7** as an amorphous solid. *Anal.* Calcd for $C_{34}H_{24}N_6O_7$: C, 64.96; H, 3.85; N, 13.37. Found: C, 64.80; H, 3.94; N, 13.07. IR (KBr): 2230, 2210 cm^{-1} (CN). NMR (DMSO-d_6) δ: 13.86 (bs, 1, NH), 8.62 (s, 1, 8-H), 8.04 (bs, 1, 2-H), 7.91—7.51 (m, Phenyl), 6.59 (d, 1, 1′-H, J=4.6 Hz), 6.36 (m, 1, 2′-H), 6.16 (m, 1, 3′-H), 4.88 (m, 1, 4′-H), 4.66 (m, 2, 5′-H).

6-Dicyanomethyl-9-*β*-D-ribofuranosylpurine (8)——A mixture of 0.61 g of **7** and 0.25 g of NaOMe in 15 ml of MeOH was heated at 60° for 1 hr. The solvent was removed *in vacuo* and the residue was taken up in H_2O and neutralized with AcOH. The resulting precipitate was crystallized from H_2O–EtOH to give 0.21 g (68%) of **8**, mp 274—276° (dec.). *Anal.* Calcd for $C_{13}H_{12}N_6O_4$: C, 49.37; H, 3.82; N, 26.57. Found: C, 49.67; H, 3.80; N, 26.26. UV $\lambda_{max}^{H_2O}$ nm (ε): 333 (33600), 236 (sh, 7200). $\lambda_{min}^{H_2O}$: 258 (450). IR (KBr): 2230, 2210 cm^{-1} (CN). NMR (DMSO-d_6) δ: 13.16 (bs, 1, NH), 8.62 (s, 1, 8-H), 8.26 (s, 1, 2-H), 5.92 (d, 1, 1′-H, J=5.1 Hz), 4.47 (m, 1, 2′-H), 4.15 (m, 1, 3′-H), 3.98 (m, 1, 4′-H), 3.62 (m, 2, 5′-H). MS m/e: 298 (M−18), 249, 226, 184 (B+1).

6-Ethoxycarbonylcyanomethyl-9-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-purine (9)——A solution of 1.0 g of **2** in 15 ml of THF was treated with 526 mg of ethyl cyanoacetate and 149 mg of 50% NaH in 3 ml of THF, and the solution was stirred for 3 hr at room temperature. The product was purified through a silica gel column (30 g), as described in the synthesis of **6**, to give 880 mg (84%) of **9** as a foam. UV λ_{max}^{EtOH} nm: 338, 330. λ_{min}^{EtOH}: 256. IR (film): 2230 cm^{-1} (CN). NMR ($CDCl_3$) δ: 13.86 (bs, 1, NH), 8.28 (s, 1, 8-H), 8.20—7.2 (m, 16, Phenyl, and 2-H), 6.5—6.1 (m, 3, 1′,2′,3′-H), 4.8 (m, 3, 4′,5′-H), 4.30 (q, 2, $-OC\underline{H}_2CH_3$), 1.35 (t, 3, $-OCH_2C\underline{H}_3$, J=7.0 Hz).

6-Ethoxycarbonylcyanomethyl-9-β-D-ribofuranosylpurine (10)——Compound **9** (840 mg) was dissolved in 40 ml of 0.05 N NaOEt in EtOH and the solution was stirred for 1 hr at 60°. The solvent was evaporated off and the residue was partitioned with $CHCl_3$ (20 ml) and H_2O (50 ml) after neutralization with AcOH. The insoluble precipitate was collected and crystallized from H_2O–EtOH to give 268 mg (65%) of **10**, mp 230—233° as the hydrate. *Anal.* Calcd for $C_{15}H_{17}N_5O_6 \cdot H_2O$: C, 47.24; H, 5.02; N, 18.37. Found: C, 46.99; H, 4.97; N, 18.19. UV $\lambda_{max}^{H_2O}$ nm (ε): 338 (40000), 327 (sh, 34500). $\lambda_{min}^{H_2O}$: 257 (800). IR (KBr): 2220 cm^{-1} (CN). NMR (DMSO-d_6) δ: 13.62 (bs, 1, NH), 8.61 (s, 1, 8-H), 8.49 (s, 1, 2-H), 5.94 (d, 1, 1′-H, J=5.9 Hz), 4.23 (q, 2, $-OC\underline{H}_2CH_3$), 1.28 (t, 3, $-OCH_2CH_3$, J=7.0 Hz).

6-Nitromethyl-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-purine (11)——A solution of 10 g of **2** in 40 ml of THF was treated with a mixture of 2.80 g (3 eq) of nitromethane and 1.49 g of 50% NaH in 20 ml of THF. The solution was refluxed for 3 hr then neutralized with AcOH. The solvent was removed *in vacuo* and the residue was taken up in $CHCl_3$. This solution was washed with H_2O, and the solvent was evaporated off. The residue was dissolved in C_6H_6 and applied to a column of silica gel (200 g). The eluent with 30—40% AcOEt in C_6H_6 was collected and concentrated to leave 6.30 g (65%) of **11** as a foam. UV λ_{max}^{MeOH} nm: 398, 390, 248. λ_{min}^{MeOH}: 395, 320, 237.

6-Nitromethyl-9-β-D-ribofuranosylpurine (12)——Compound **11** (6.30 g) in 100 ml of 0.1 N NaOEt in EtOH was heated at 70° for 7 hr. The solution was then neutralized with AcOH and the solvent was removed *in vacuo* to leave a residue. This was taken up in H_2O, the solution was washed with $CHCl_3$, and the aqueous layer was concentrated. The residue was crystallized from H_2O–EtOH to give 1.49 g (47%) of **12**, mp 173° (dec.). *Anal.* Calcd for $C_{11}H_{13}N_5O_6$–1/4H_2O: C, 41.85; H, 4.27; N, 21.90. Found: C, 41.85; H, 4.27; N, 21.91. UV $\lambda_{max}^{H_2O}$ nm (ε): 398 (34900), 290 (35100), 245 (7000), 202 (16700). $\lambda_{min}^{H_2O}$: 395 (34700), 310 (1500), 225 (4900). NMR: See Fig. 1.

6-Cyano-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-purine (13)——A mixture of **2** (2.0 g) and NaCN (240 mg) in 10 ml of DMF was stirred for 1.5 hr at room temperature. The solution was neutralized with 0.1 N HCl and then concentrated *in vacuo*. The residue was taken up in MeOH, the insoluble material was removed, and the filtrate was diluted with AcOEt. The resulting crystals were collected to give 1.07 g (55%) of **13**, mp 133—136°. *Anal.* Calcd for $C_{32}H_{23}N_5O_7$: C, 65.19; H, 3.93; N, 11.88. Found: C, 65.15; H, 3.82; N, 11.79. UV λ_{max}^{EtOH} nm (ε): 282 (11000), 275 (sh, 10000), 230 (40000). λ_{max}^{EtOH}: 254 (5300). NMR ($CDCl_3$) δ: 8.94 (s, 1, 8-H), 8.54 (s, 1, 2-H), 6.54—6.20 (s, 3, 1′,2′,3′-H), 5.00—4.60 (m, 3, 4′,5′-H). Treatment of **13** with NaOMe in MeOH did not give the debenzoylated product, **14**, and the compound obtained gave the following NMR signals (DMSO-d_6, D_2O) δ: 9.08 (s, 1), 8.99 (s, 1), 6.10 (d, 1, J=5.3 Hz), 4.62 (t, 1), 4.27 (t, 1), 4.00 (s, 3), 3.66 (m, 3). The structure of the product was tentatively assigned as 6-methoxycarbonylpurine riboside.

6-Cyano-9-β-D-ribofuranosylpurine (14)——6-Methylsulfonyl-9-β-D-ribofuranosylpurine[9] (580 mg) was dissolved in 4 ml of DMF, and NaCN (86 mg) was added to the solution. After stirring for 2 hr, the solvent was removed *in vacuo* and the residue was dissolved in a small amount of MeOH. Silica gel was added to the solution and the solvent was evaporated off to leave a powder, which was applied to a silica gel column (30 g). Elution was performed with 20% MeOH in $CHCl_3$. The major component was identified as inosine. The minor product was crystallized from MeOH to give 30 mg (6%) of **14**. UV λ_{max}^{EtOH} 284 nm. λ_{max}^{EtOH} 230 nm. NMR (DMSO-d_6) δ: 9.16 (s, 1, 8-H), 9.14 (s, 1, 2-H), 6.09 (d, 1, 1′-H, J=6.0 Hz), 5.86 (d, 1, 2′-OH), 5.25 (d, 1, 3′-OH, J=5.0 Hz), 5.10 (t, 1, 5′-OH), 4.58 (dd, 1, 2′-H), 4.21 (dd, 1, 3′-H), 4.10 (q, 1, 4′-H), 3.67 (dd, 2, 5′-H). Addition of D_2O to the solvent led to the disappearance of the OH signals, and the signals of 2′ and 3′ protons changed to a doublet, respectively.

6-(α-Ethoxycarbonylethyl)-9-β-D-ribofuranosylpurine (15)——Compound **4** (100 mg) was added to 5 ml of 0.17 N NaOEt in EtOH. Methyl iodide (0.03 ml, 2 eq) was added to the solution, and the mixture was stirred overnight at room temperature. The solution was then neutralized with Amberlite IR 120 (H^+) resin and the filtrate was applied to a column of silica gel (10 g). The column was eluted with 10% EtOH in $CHCl_3$ and the eluate was concentrated to leave a foamy residue (**15**, 107 mg). MS *m/e*: 352 (M^+), 263 (M−89), 249 (B+30), 221 (B+2), 220 (B+1). NMR (DMSO-d_6) δ: 9.00 (s, 1, 8-H), 8.95 (s, 1, 2-H), 6.14 (d, 1, 1′-H, J=5.5 Hz), 1.60 (d, 3, $C\underline{H}_3CH$–).

6-Ethyl-9-β-D-ribofuranosylpurine (16)——Compound **15** (107 mg) was dissolved in 3 ml of 0.1 N NaOH and kept for 2 hr at room temperature. The solution was acidified to pH 3.5—4.0 by the addition of 0.1 N HCl and kept for 2 hr at room temperature. After neutralization of the solution with 1 N NaOH, the solvent was evaporated off and the residue was applied to a column of silica gel (10 g). The eluent with 10% EtOH in $CHCl_3$ was concentrated and the residue was crystallized from H_2O–EtOH to give 54 mg (66%) of **16**, mp 104—106° (mp 105°[4a]). *Anal.* Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.41; H, 5.80; N, 20.02. UV $\lambda_{max}^{H_2O}$ nm (ε): 262.5 (8300), 247 (sh, 6300). $\lambda_{min}^{H_2O}$: 224 (2300). NMR (DMSO-d_6) δ: 8.83 (s, 1, 8-H), 8.75 (s, 1, 2-H), 6.02 (d, 1, 1′-H, J=5.8 Hz), 3.12 (q, 2, 6-$C\underline{H}_2CH_3$, J=7.6 Hz), 1.35 (t, 3, 6-$CH_2C\underline{H}_3$). MS *m/e*: 280 (M^+), 191 (M−89), 177 (B+30), 149 (B+2), 148 (B+1), 145 (B).

6-*n*-Propyl-9-β-D-ribofuranosylpurine (17)——Compound **4** (200 mg) was ethylated with 190 mg of ethyl iodide by the procedure described above. The product (**17**) was obtained as a foam in almost quantitative yield (177 mg). UV $\lambda_{max}^{H_2O}$ 262.5 nm with a shoulder at 248 nm. NMR (DMSO-d_6) δ: 8.83 (s, 1, 8-H), 8.75 (s, 1, 2-H), 6.02 (d, 1, 1′-H, J=5.9 Hz), 3.08 (t, 2, 6-$C\underline{H}_2CH_2CH_3$), 1.85 (m, 2, 6-$CH_2C\underline{H}_2CH_3$), 0.93 (t,

3, 6-$CH_2CH_2C\underline{H}_3$). MS *m/e*: 294 (M^+), 266 (M−28), 205 (M−89), 191 (B+30), 163 (B+2), 162 (B+1), 147 (B−14), 134 (B−27).

6-*n*-Butyl-9-*β*-D-ribofuranosylpurine (18)——Using the above procedure, 200 mg of **4** and 196 mg of *n*-propyl iodide gave 115 mg (64%) of **18** as an amorphous material. UV $\lambda_{max}^{H_2O}$ 262.5 nm with a shoulder at 248 nm. NMR (DMSO-d_6) δ: 8.82 (s, 1, 8-H), 8.75 (s, 1, 2-H), 6.02 (d, 1, 1′-H, J=5.9 Hz), 3.10 (t, 2, 6-$C\underline{H}_2$Pr), 1.82 (m, 2, 6-$CH_2C\underline{H}_2$Et), 1.34 (m, 2, 6-$CH_2CH_2C\underline{H}_2CH_3$), 0.91 (t, 3, 6-$(CH_2)_3C\underline{H}_3$). MS *m/e*: 309 (M+1), 308 (M^+), 266 (M−42), 219 (M−89), 205 (B+30), 177 (B+2), 176 (B+1), 175 (B), 161 (B−14), 147 (B−28), 134 (B−41).

6-*n*-Pentyl-9-*β*-D-ribofuranosylpurine (19)——Using the above procedure, 200 mg of **4** and 213 mg of *n*-butyl iodide gave 91 mg (49%) of **19** as an amorphous material. UV $\lambda_{max}^{H_2O}$ 262.5 nm with a shoulder at 248 nm. NMR (DMSO-d_6) δ: 8.82 (s, 1, 8-H), 8.75 (s, 1, 2-H), 6.02 (d, 1, 1′-H, J=5.8 Hz), 3.09 (t, 2, 6-$C\underline{H}_2$Bu), 1.83 (m, 2), 1.34 (m, 4), 0.86 (t, 3, 6-$(CH_2)_4CH_3$). MS *m/e*: 323 (M+1), 322 (M^+), 266 (M−56), 233 (M−89), 219 (B+30), 191 (B+2), 190 (B+1), 189 (B), 175 (B−14), 161 (B−28), 147 (B−42), 134 (B−55).

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