The Use of the Wittig Reaction in the Modification of Purine Nucleosides (1)

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The Pfitzner-Moffatt oxidation of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine, 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-6-(methylthio)purine, and 2′,3′-*O*-isopropylideneadenosine gave the corresponding 5′-aldehydes (**3**, **13**, and **4**), which were allowed to react with a number of Wittig ylids. The resulting olefins, primarily *trans*, were reduced either catalytically or with diimide before removal of the 2′,3′-*O*-isopropylidene groups to give the desired 5′-substituted purine ribonucleosides.

Most cytotoxic purines and purine nucleosides must be converted to nucleotides to exert their lethal effects. For example, 6-mercaptopurine is converted to its ribonucleotide by hypoxanthine phosphoribosyltransferase in cells sensitive to this agent, and cells lacking this enzymatic activity are resistant to it (2). Similarly, 2-fluoroadenosine is phosphorylated by adenosine kinase in sensitive cells, and cells lacking the kinase are resistant to the agents (3). Nucleosides substituted at C_5' by the methylenephosphonate group or other moieties may penetrate cell membranes and inhibit critical enzymes by virtue of their similarity to nucleotides (4). Such agents might be effective against resistant cell lines and might be useful chemotherapeutic agents.

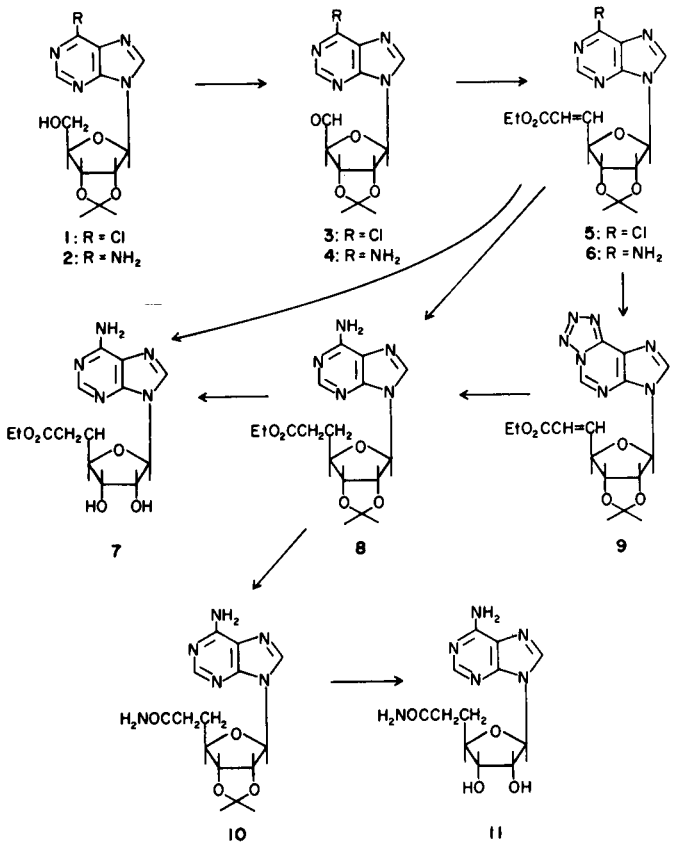
One approach to the synthesis of such compounds consists of the preparation and reaction of the appropriate sugar with purines or their mercury derivatives (5). Application of this approach to the synthesis of certain 5′-substituted purine ribonucleosides led, however, to complications, and mixtures of nucleosides that are difficultly separable were obtained (5,6).

Because of these complications, we turned to the preparation of 9-(2,3-*O*-isopropylidene-β-D-*ribo*-pento-1,5-dialdo-1,4-furanosyl)purines for reaction with the appropriate Wittig reagents.

Although a number of oxidative procedures were attempted to prepare the desired aldehydes, diethyl azidodicarboxylate, chromium oxide in pyridine, chromium (IV) oxide dipyridine, and pyridine-sulfur trioxide-triethylamine-DMSO, the only successful procedure was that of Pfitzner and Moffatt (7) using orthophosphoric acid and dicyclohexylcarbodiimide in DMSO. Jones and Moffatt used this procedure in the preparation of 6′-deoxyhomoadenosine-5′-phosphonic acid (8). Treatment of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-*ribo*-furanosyl) purine (**1**), prepared in good yield by reaction with acetone in the presence of perchloric acid (9), in this manner gave a 32% crude yield of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-*ribo*-pento-1,5-dialdo-1,4-furanosyl)purine (**3**), which was difficult to purify, but could be converted to its 2,4-dinitrophenylhydrazone for analysis. Subsequently, the dimethylsulfoxide solution of the aldehyde was neutralized with pyridine and used directly in the Wittig reaction. In this manner, the desired olefins (**5** and **17**) could be prepared in good yield.

2,6-Dichloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-purine, prepared as described above for **1**, was also converted to the aldehyde, but the Wittig reaction gave a complex mixture apparently due to reaction with the 6-chloro group (10). This procedure also worked well, however, with 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-6-(methylthio)purine (**12**). The pmr spectra of these aldehydes indicate that water and alcohols readily add to the carbonyl function.

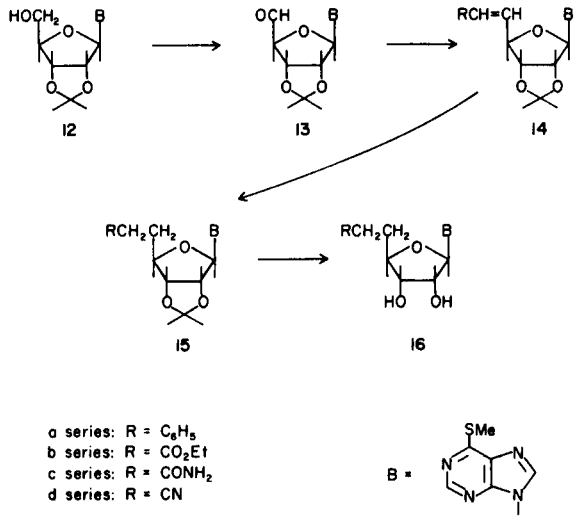
Reaction of **3** with ethoxycarbonylmethylenetriphenylphosphorane gave a 62% yield of ethyl 1-(6-chloropurin-9-yl)-1,5,6-trideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hept-5-enofuranuronate (**5**), which was allowed to react with sodium azide to give the tetrazolo[5,1-*i*]purine (**9**) (12). Catalytic hydrogenation of **9** reduced both the tetrazolo group and the olefinic double bond to give ethyl 1-(6-aminopurin-9-yl)-1,5,6-trideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-heptofuranuronate (**8**). Removal of the isopropylidene group of **8** by hydrolysis in dilute aqueous



alcoholic sulfuric acid gave the desired nucleoside, ethyl 1-(6-aminopurin-9-yl)-1,5,6-trideoxy-β-D-*ribo*-heptofuranuronate (**7**) (13), in low yield. Reaction of the ester **8** with ammonia was sluggish. Heating an ethanolic ammonia (saturated at 0°) solution of **8** at 110° for 72 hours gave a 58% yield of amide **10** and a 30% recovery of ester. Removal of the isopropylidene group of **10** was accomplished in aqueous trifluoroacetic acid (15) giving 1-(6-aminopurin-9-yl)-1,5,6-trideoxy-β-D-heptofuranuronamide (**11**). The ester **8** was also prepared by the reaction of 9-(2,3-*O*-isopropylidene-β-D-*ribo*-pento-1,5-dialdo-1,4-furanosyl)adenine (**4**) with ethoxycarbonylmethylenetriphenylphosphorane followed by catalytic reduction of the olefin **6**. Because the olefins (**5** and **6**) prepared by the Wittig reaction are predominantly *trans*, catalytic reduction (of **6** and **9**) is slow but proceed satisfactorily to give good yields of **8**.

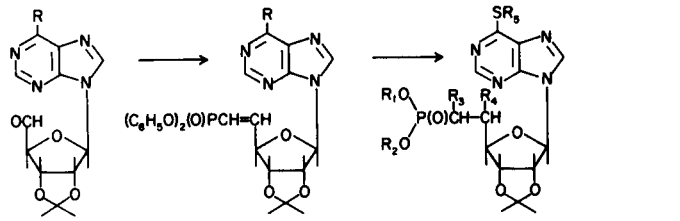
The presence of the 2,3-*O*-isopropylidene group in the nucleosides **5**, **8**, **9**, and **10**, as expected (16), reduces the coupling constant of $H_1'H_2'$ from *ca.* 5 Hz in **7** and **11** to *ca.* 2 Hz, confirming the integrity of the β-*ribo* configuration throughout this synthetic sequence.

6-(Methylthio)purine ribonucleoside is of interest because, since it is phosphorylated by adenosine kinase, it is active against cell lines resistant to 6-mercaptopurine and because it has shown useful anticancer activity in both experimental animal tumor systems and man. Consequently, the isopropylidene derivative of this nucleoside was also oxidized to the aldehyde by the Pfitzner-Moffatt procedure for reaction with ethoxycarbonylmethylenetriphenylphosphorane, benzylidenetriphenylphosphorane, and cyanomethylenetriphenylphosphorane. The double bond of the resulting nucleosides (**14a**, **b**, and **d**) could not be reduced catalytically but could be reduced by diimide generated from potassium azidodicarboxylate. The reduction, monitored by mass spectral analysis, had to be repeated in order to completely convert the olefins



to the saturated nucleosides (**15a**, **b**, and **d**). The *in situ* generation of diimide by the oxidation of hydrazine (17) was convenient for the reduction **14a** but could not be applied to **14b** because of its ester function. The resulting nucleosides (**15a**, **b**, and **d**) were converted to the desired derivatives of 6-(methylthio)purine ribonucleoside: 9-(5,6-dideoxy-6-phenyl-β-D-*ribo*-hexofuranosyl)-6-(methylthio)-purine (**16a**), ethyl 1,5,6-trideoxy-1-[6-(methylthio)purin-9-yl]-β-D-*ribo*-heptofuranuronate (**16b**), and 9-(6-cyano-5,6-dideoxy-β-D-ribohexofuranosyl)-6-(methylthio)purine (**16d**). Reaction of **16b** with ammonia proceeded more readily than with **6**, although surprisingly vigorous conditions, 16 hours at 80° in methanolic ammonia (saturated at 0°), still had to be employed.

Attempts to prepare the methylenephosphonate analog (**24**) of 6-(methylthio)purine ribonucleotide were not entirely successful. Reaction of the aldehyde **3** with diphenyl(triphenylphosphoranylidene)methylphosphonate (18) prepared by neutralization of the salt obtained from the potassium iodide catalyzed reaction of chloromethyldiphenylphosphonate with triphenylphosphine, proceeded readily, but reduction of the olefinic bond of **17** could not be effected without affecting the 6-chloro group also.



3: R = Cl
13: R = SMe

17: R = Cl
18: R = SMe

19: $R_1 = R_2 = R_5 = Me$, $R_3 = H$ or SMe, $R_4 = SMe$ or H
20: $R_1 = H$, $R_2 = C_6H_5$, $R_3 = H$ or SMe, $R_4 = SMe$ or H, $R_5 = Me$
21: $R_1 = R_5 = H$, $R_2 = C_6H_5$, $R_3 = H$ or SMe, $R_4 = SMe$ or H
22: $R_1 = R_2 = C_6H_5$, $R_3 = R_4 = H$, $R_5 = Me$
23: $R_1 = R_2 = C_6H_5CH_2$, $R_3 = R_4 = H$, $R_5 = SMe$
24: $R_1 = R_2 = R_3 = R_4 = H$, $R_5 = SMe$

Reaction of **17** with thiourea, under conditions that convert 6-chloropurine to 6-mercaptopurine, failed. Reaction of 6-chloro of **17** with sodium methyl mercaptide proceeded readily, but other reactions occurred simultaneously. First, addition of the elements of methyl mercaptan to the olefinic double bond occurred to give a mixture of nucleosides having the methylthio at C_5' in one case and C_6' in the other. Secondly, using about two equivalents of sodium methyl mercaptide in methanol at room temperature caused transesterification of the diphenylphosphono group to give the dimethylphosphono group (**19**). Using a methanol solution of two equivalents of sodium methoxide saturated with methyl mercaptan at elevated temperature was even more complex. Under these conditions, the diphenylphosphono group was hydrolyzed to the monophenylphosphono group, addition to the olefinic double bond occurred, and the 6-chloro group was replaced by the methylthio group and to a lesser extent by the mercapto group, giving a mixture of **20** and **21**. Alkylation of this mixture with methyl iodide in aqueous base converted the mixture to **20**. Because of the complexity of these reaction mixtures and the failure to prevent addition of methyl mercaptan to the double bond, the aldehyde **3** was replaced with the methylthio compound **13**. Reaction of **13** with the Wittig reagent gave the olefin **18** in good yield. Reduction of the olefin with diimide to give **22** also proceeded smoothly as did conversion of **22** to the dibenzyl ester **23** (8). Attempts to remove the benzyl groups by catalytic hydrogenolysis failed to give any reaction. Sodium in liquid ammonia appeared (pmr, electrophoresis, tlc) to remove the benzyl groups, but the reaction was complex and a number of other reactions occurred, including reductive removal of the methylthio group and glycosyl cleavage (purine was isolated and identified).

EXPERIMENTAL

Melting points were determined with a Mel-Temp apparatus and are not corrected. The pmr spectra were determined in the solvent indicated (TMS) with a Varian XL-100-15 spectrometer, and the correct integrals were obtained for the assignments indicated; chemical shifts quoted for multiplets were measured from the approximate centers. The mass spectra were determined with a Hitachi-Perkin Elmer RMU-6D-3 spectrometer. Chromatographic analyses were carried out on tlc plates of silica gel H (Brinkmann). The spots were detected by uv light after spraying with Ultraphor (WT, highly concentrated) and by charring after spraying with aqueous ammonium sulfate.

6-Chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (**1**) (19).

6-Chloro-9-β-D-ribofuranosylpurine (5 g., 17.4 mmoles) was added to a solution of 5.7 ml. of 2,2-dimethoxypropane and 7.8 ml. of perchloric acid (72%) in dry acetone (210 ml.). After one hour at room temperature, the mixture was neutralized with pyridine and filtered. Evaporation of the filtrate *in vacuo* gave an oil that was partitioned between chloroform and water. After it was dried over magnesium sulfate, the chloroform solution was evaporated to dryness and the residue recrystallized twice from alcohol, yield 3.18 g. (56%), m.p. 157-160° [lit. (19) 158-159°]; pmr (deuteriochloroform): δ 1.4 and 1.7 (2s, Me of isopropylidene), 3.9 (m, $C_5'H$), 4.5 ($C_4'H$), 4.8 (m, OH), 5.2 (m, $C_3'H$ and $C_2'H$), 6.1 (d, $C_1'H$, $J_{1'2'}$ 3 Hz), 8.4 (s, C_8H), 8.8 (s, C_2H).

2,6-Dichloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine.

2,6-Dichloro-9-β-D-ribofuranosylpurine (321 mg., 1 mmole) was added to a mixture of 2,2-dimethoxypropane (0.36 ml.) and perchloric acid (72%, 0.49 ml.) in acetone (13 ml.). After one hour at room temperature, the reaction mixture was neutralized with pyridine and evaporated to dryness. The glassy residue was partitioned between chloroform (20 ml.) and water (20 ml.). The residue from the chloroform extract was further purified by chromatography on a thick silica gel plate. The major band was eluted with ethyl acetate, yield 139 mg. (38%); mass spectrum: 360 $(M)^+$, 345 $(M\text{-}CH_3)^+$, 302 $(M\text{-}CH_3COCH_3)^+$, 271 $(M\text{-}CH_3COCH_3\text{-}CH_2OH)$, 217 (base + CHOH)$^+$, 189 (base + 2H), 188 (base + H)$^+$, 173 (sugar)$^+$, 142 (sugar-$CH_2OH)^+$, 115 (sugar-CH_3COCH_3); pmr (deuteriochloroform): δ 1.4 and 1.7 (2s, Me of isopropylidene), 3.9 (m, $C_5'H_2$ and OH), 4.5 (m, $C_4'H$), 5.1 (m, $C_3'H$ and $C_2'H$), 6.0 (d, $C_1'H$, $J_{1'2'}$ 3 Hz), 8.3 (s, C_8H).

6-Chloro-9-(2,3-*O*-isopropylidene-β-D-*ribo*-pento-1,5-dialdo-1,4-furanosyl)purine (**3**) 2,4-dinitrophenylhydrazone.

To a solution of **1** (327 mg., 1.0 mmole) and dicyclohexylcarbodiimide (1.03 g., 5 mmoles) in 5 ml. DMSO was added 0.5 ml. of 1 *M* orthophosphoric acid in DMSO, and the solution was stirred overnight before the precipitated urea was removed by filtration. The residue from evaporation of the DMSO *in vacuo* was triturated with petroleum ether and then dissolved in chloroform. After washing with bicarbonate solution and drying over magnesium sulfate, the chloroform was evaporated *in vacuo*. The residue was dissolved in ethanol and treated with 2,4-dinitrophenylhydrazine dissolved in 1 *N* sulfuric acid. The phenylhydrazone which precipitated (160 mg., 32%) was purified for analysis by chromatography on a thick silica gel plate using 2 benzene:1 ethyl acetate as eluant. The principal band was extracted with ethanol from which the product crystallized, m.p. 115-130° (slow dec.); pmr (deuteriochloroform): δ 1.5 and 1.7 (2s, Me of isopropylidene), 5.1 (m, $C_4'H$), 5.6 (m, $C_2'H$ and $C_3'H$),

6.3 (d, $C_1'H$, $J_{1'2'}$ 2 Hz), 7.4 (t, $C_5'H$), 7.6 (m, phenyl C_6H), 8.3 (s over m, C_8H over phenyl C_5H), 8.7 (s, C_2H), 9.0 (m, phenyl C_3H), 10.8 (broad s, NH).

Anal. Calcd. for $C_{19}H_{17}ClN_8O_7$: C, 45.24; H, 3.37; N, 22.22. Found: C, 45.11; H, 3.43; N, 22.11.

Ethyl 1-(6-Chloropurin-9-yl)-1,5,6-trideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hept-5-enofuranouronate (**5**).

A solution of **3**, prepared from **1** (4.58 g., 14 mmoles) as described above, was filtered and the filtrate neutralized with 1.7 ml. of anhydrous pyridine before the addition of 4.88 g. (14 mmoles) of ethoxycarbonylmethylenetriphenylphosphorane. After stirring overnight, the mixture was concentrated *in vacuo* to about 50 ml. before it was filtered into 500 ml. of water. The water was extracted with five 100-ml. portions of benzene. The dried extract was evaporated to dryness and the residue chromatographed on a silica gel column using 4 benzene:1 ethyl acetate as eluant. The chromatographically homogeneous oil (3.41 g., 62%) was used in the next step without further purification.

Ethyl 1-(6-Aminopurin-9-yl)-1,5,6-trideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hept-5-enofuranuronate (**6**).

The aldehyde **4** from the oxidation of **2** (3.07 g., 10 mmoles) (7,8) was allowed to react with ethoxycarbonylmethylenetriphenylphosphorane at room temperature overnight. The reaction mixture was poured into water (250 ml.) and the water solution evaporated to dryness. The residue was dissolved in chloroform (50 ml.) and the chloroform solution extracted with water with back extraction. The chloroform solution, after drying over magnesium sulfate, was evaporated to dryness and the residue purified by chromatography on a silica gel column using 4 benzene:1 ethyl acetate as eluant followed by 4 benzene:1 acetone and then by 2 benzene:1 acetone, which eluted the product. The product, a glass, 1.94 g. (52%), was used in the next step without further purification; mass spectrum: 375 $(M)^+$, 360 $(M\text{-}CH_3)^+$, 346 $(M\text{-}Et)^+$, 317 $(M\text{-}CH_3COCH_2)^+$, 164 (base + $CH_2O)^+$, 136 (base + 2H)$^+$, 135 (base + H)$^+$; pmr (deuteriochloroform): δ 1.2 (t, Me of Et), 1.4 and 1.6 (2s, Me of isopropylidene), 2.1 (q, $C_5'H_2$), 2.4 (q, $C_6'H$), 4.1 (q, CH_2 of Et), 4.2 (m, $C_4'H$), 4.9 (q, $C_3'H$), 5.5 (q, $C_2'H$), 5.9 (broad s, NH_2), 6.1 (d, $C_1'H$, $J_{1'2'}$ 2.5 Hz), 7.9 (s, C_8H), 8.4 (s, C_2H).

Ethyl 1-(6-Aminopurin-9-yl)-1,5,6-trideoxy-β-D-*ribo*-heptofuranuronate (**7**).

A solution of **6** (848 mg., 2.25 mmoles) in a mixture of 10 ml. of ethanol and 5 ml. of 1 *N* sulfuric acid was allowed to stand at room temperature for 142 hours before it was neutralized with barium hydroxide, filtered, and evaporated to dryness. The solid residue was recrystallized twice from ethanol and then dried at 78° to obtain the analytical sample, yield 156 mg. (21%), m.p. 99-101°; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 257 (14.6), *p*H 7, 259 (14.9), 0.1 *N* sodium hydroxide, 259 (15.2) [lit. (14) m.p. 86-91°; λ max in nm (ε x 10^{-3}): *p*H 1, 257 (14.9), *p*H 7, 259 (15.1), *p*H 13, 259 (15.2)]; $[\alpha]_D^{25}$ 0, pmr (DMSO-d_6): δ 1.1 (t, Me of Et), 2.0 (m, $C_5'H_2$), 2.4 (m, $C_6'H_2$), 4.0 (m, CH_2 of Et, $C_3'H$, $C_4'H$), 4.7 (t, $C_2'H$), 5.2 and 5.4 (2 broad d, OH), 5.9 (d, $C_1'H$, $J_{1'2'}$ 5 Hz), 7.2 (broad s, NH_2), 8.1 (s, C_8H), 8.3 (s, C_2H).

Anal. Calcd. for $C_{14}H_{19}N_5O_5 \cdot \frac{1}{4}H_2O$: C, 49.19; H, 5.75; N, 20.49. Found: C, 49.22; H, 5.79; N, 20.67.

Ethyl 1-(6-Aminopurin-9-yl)-1,5,6-trideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-heptofuranuronate (**8**).

A.

Compound **6** (955 mg., 2.5 mmoles) in 50 ml. of ethanol was reduced overnight in a Parr shaker at 51 psi using 100 mg. of platinum oxide catalyst. It was necessary to repeat the procedure to attain complete reduction of the double bond. The catalyst was removed by filtration through a Celite pad, and the filtrate was evaporated to dryness to give a glass that was dried *in vacuo*, yield 848 mg. (90%) of material that was used in the next step without further purification; mass spectrum: 377 $(M)^+$, 362 $(M\text{-}CH_3)^+$, 332 $(M\text{-}OEt)^+$, 319 $(M\text{-}CH_3COCH_3)^+$, 164 (base + $CH_2O)^+$, 136 (base + 2H)$^+$, 135 (base + H)$^+$.

B.

A solution of **5** (181 mg., 0.46 mmole) and sodium azide (30 mg., 0.46 mmole) in aqueous ethanol (80%) was refluxed for three hours and then an additional 15 mg. of sodium azide was added and the solution refluxed for an additional hour before it was evaporated to dryness. The dried residue (**9**) was extracted with three five-ml. portions of chloroform, which were combined and evaporated to dryness, yield 188 mg., mass spectrum: 401 $(M)^+$, 343 $(M\text{-}CH_3COCH_3)^+$, 162 (base + 2H)$^+$, 161 (base + H)$^+$. This material (**9**) (157 mg.) was reduced in ethanol with 5% Pd-C catalyst at 40 psi with several changes of the hydrogen atmosphere, yield 134 mg. The mass spectrum and chromatographic behavior of this material were identical with those of the sample described in A above.

1-(6-Aminopurin-9-yl)-1,5,6-trideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-heptofuranuronamide (**10**).

A solution of **8** (1.42 g., 3.8 mmoles) in 150 ml. of ethanolic ammonia (saturated at 0°) was heated at 110° for 72 hours. The residue from evaporation of the ethanolic ammonia was purified by chromatography on a silica gel column using a chloroform-methanol gradient (9:1 → 3:1) elution. Starting material (433 mg., 30% recovery) eluted first followed by 536 mg. (58% yield) of chromatographically homogeneous product, mass spectrum: 348 $(M)^+$, 333 $(M\text{-}Me)^+$. This material was used in the next step without further purification.

1-(6-Aminopurin-9-yl)-1,5,6-trideoxy-β-D-*ribo*-heptofuranuronamide (**11**).

A solution of **10** (500 mg., 1.3 mmoles) in 8 ml. of 9 trifluoroacetic acid:1 water was allowed to stand at room temperature for 10 minutes before it was evaporated to dryness. The product was purified by chromatography on a thick silica gel plate developed twice in 1 chloroform:1 methanol. The middle band was extracted with methanol which was evaporated to dryness. Recrystallization of the solid residue gave a white solid (105 mg., 26%) that analyzed as a fractional trifluoroacetate hydrate; λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 257 (14.4), *p*H 7, 0.1 *N* sodium hydroxide, 260 (14.7); pmr (DMSO-d_6): δ 1.9 (m, $C_5'H_2$), 2.1 (m, $C_6'H_2$), 3.3 (s, H_2O), 3.6 (m, $C_4'H$), 3.8 (m, $C_3'H$), 4.6 (m, $C_2'H$), 5.2 and 5.4 (2 broad d, OH), 5.9 (d, $C_1'H$, $J_{1'2'}$ 5 Hz), 6.7 (broad, NH of amide), 7.0 (broad C_6NH_2 and NH of amide), 8.1 (C_8H), 8.3 (C_2H).

This material was converted to its picrate by treatment with aqueous picric acid. Recrystallization from methanol gave a solvated picrate (69 mg.).

Anal. Calcd. for $C_{12}H_{16}N_6O_4 \cdot C_6H_3N_3O_7 \cdot \frac{1}{2}MeOH$: C, 40.15; H, 3.82; N, 22.78. Found: C, 40.07; H, 3.63; N, 22.78.

9-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-(methylthio)purine (**12**).

A solution of 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine-6(1*H*)thione (46.5 g., 0.14 mole) and methyl iodide (16 ml., 0.15

mole) in 440 ml. of 0.3 *N* sodium hydroxide was stirred vigorously at room temperature for four hours. The solid that formed was removed by filtration, washed with water, and recrystallized from water, yield 40 g. (83%), m.p. 115°; pmr (DMSO-d_6): δ 1.4 and 1.6 (2s, Me of isopropylidene), 2.7 (s, SMe), 3.6 (t, $C_5'H_2$), 4.3 (m, $C_4'H$), 5.1 (m, $C_3'H$ and OH, becomes a well-defined quartet on addition of deuterium oxide), 5.4 (q, $C_2'H$), 6.2 (d, $C_1'H$, $J_{1'2'}$ 2.5 Hz), 8.7 (s, C_8H), 8.8 (s, C_2H).

Anal. Calcd. for $C_{14}H_{18}N_4O_4S$: C, 49.69; H, 5.33; N, 16.56. Found: C, 49.55; H, 5.29; N, 16.63.

9-(2,3-*O*-Isopropylidene-β-D-*ribo*-pento-1,5-dialdo-1,4-furanosyl)-6-(methylthio)purine (**13**).

To a solution of **12** (3.38 g., 10 mmoles) and dicyclohexylcarbodiimide (10.3 g., 50 mmoles) in 50 ml. of DMSO was added 5 ml. of a 1 *M* solution of orthophosphoric acid in DMSO and the reaction mixture stirred overnight. After removal of the precipitated dicyclohexylurea, the DMSO solution of the aldehyde was used in the next step.

In a previous run the aldehyde was purified by chromatography on silica gel using 1 benzene:1 ethyl acetate as the eluant. It was identified by its mass spectrum: 336 $(M)^+$, 321 $(M\text{-}CH_3)^+$, 308 $(M\text{-}CO)^+$, 293 $(M\text{-}CH_3\text{-}CO)^+$, 270 $(M\text{-}2CH_3\text{-}CO)^+$, 195 (base + $CH_2O)^+$, 167 (base + 2H), by a positive aldehyde test of its spot on tlc and by its reduction by sodium borohydride back to 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-6-(methylthio)purine. The pmr spectrum indicated the carbonyl function is mostly solvated in solution.

9-(5,6-Dideoxy-2,3-*O*-isopropylidene-6-phenyl-β-D-*ribo*-hex-5-enofuranosyl)-6-(methylthio)purine (**14a**).

To a solution of 270 mg. (5 mmoles) of sodium methoxide in 16 ml. of dry methanol was added benzyltriphenylphosphonium chloride (5 mmoles). The solution was evaporated to dryness and the residue suspended in benzene. To this suspension was added a benzene solution (12 ml.) of **13** (1.68 g., 5 mmoles). After the mixture was stirred for four hours, it was filtered and evaporated to dryness. A solution of the orange residue in ether was filtered to remove salts before it was evaporated to dryness. The process was repeated twice, and the resulting pale yellow foam (2.19 g.) was further purified by chromatography on a silica gel column using 2 benzene:1 ethyl acetate as eluant. The glassy, chromatographically homogeneous product, 1.14 g. (56%) came off the column between 320 and 470 ml. It was used in the next step without further purification; pmr (deuteriochloroform): δ 1.4, 1.6, and 1.65 (3s, Me of isopropylidene), 2.7 (2s, SMe), 5.1 (m, $C_4'H$), 5.6 (m, $C_3'H$), 6.1 (d over m, $C_1'H$, $J_{1'2'}$ 2 Hz), 6.1 and 6.5 (m, $C_2'H$, $C_5'H$, and $C_6'H$), 7.3 (m, phenyl), 8.0 (s, C_8H), 8.7 (2s, C_2H). This spectrum shows the olefin to be a mixture of *cis* and *trans* isomers (*ca.* 1:2).

Ethyl 1,5,6-Trideoxy-2,3-*O*-isopropylidene-1-[5-(methylthio)purin-9-yl]-β-D-*ribo*-hept-5-enofuranuronate (**14b**).

A solution of **13**, prepared from **12** (5 g., 14.8 mmoles) as described above was neutralized with 1.8 ml. of dry pyridine before adding ethoxycarbonylmethylenetriphenylphosphorane (5.67 g., 16.3 mmoles). After standing overnight, the mixture was evaporated to dryness *in vacuo*, the residue suspended in 250 ml. water, and the water extracted with four 100-ml. portions of benzene. The filtered benzene solution was dried over magnesium sulfate before it was evaporated to dryness. The product was chromatographed on a dry alumina column, which was developed with 2 cyclohexane:1 ethyl acetate. The band containing the product was extracted with five 500-ml. portions of chloroform. The residue from evaporation of the chloroform was chromatographed on a silica gel column using 2 cyclohexane:1 ethanol as eluant. The yield of chromatographically homogeneous product was 4.07 g. (68%); pmr (deuteriochloroform): δ 1.3 (t, Me of Et), 1.4 and 1.6 (2s, Me of isopropylidene), 2.7 (s, SMe), 4.1 (q, CH_2 of Et), 4.8 (m, $C_4'H$), 5.1 (q, $C_3'H$), 5.6 (m, $C_2'H$), 5.8 (m, $C_6'H$), 6.2 (d, $C_1'H$, $J_{1'2'}$ 2 Hz), 6.9 (q, $C_5'H$, *trans* olefin), 8.0 (s, C_8H), 8.7 (s, C_2H).

9-(6-Cyano-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranosyl)-6-(methylthio)purine (**14d**).

To a solution of **13**, prepared from **12** (1.7 g., 10 mmoles) in dry DMSO, was added cyanomethylenetriphenylphosphorane (1.5 g., 5 mmoles). After standing overnight the reaction mixture was poured into 400 ml. of water and the water extracted with two 250-ml. portions of chloroform. The dried chloroform solution was evaporated to dryness, and the residue was purified by chromatography on a silica gel column using 9 benzene:1 chloroform as the eluant. The chromatographically homogeneous product (1.578 g.) was used in the next step without further purification; pmr (deuteriochloroform): δ 1.4, 1.65, 1.7 (3s, Me of isopropylidene), 2.7 (s, SMe), 4.8, 5.2, and 5.5 (3m, $C_4'H$, $C_3'H$, $C_2'H$, and $C_6'H$), 6.15 (m, $C_1'H$), 6.55 (q, $C_5'H$ of *cis* olefin), 6.8 (q, $C_5'H$ of *trans* olefin), 8.0 (s, C_8H of *trans*), 8.05 (s, C_8 of *cis*), 8.7 (C_2H). The multiplicity of signals clearly indicate a mixture of *cis* and *trans* olefins identified by the signals from the $C_5'H$ of the two.

9-(5,6-Dideoxy-2,3-*O*-isopropylidene-6-phenyl-β-D-*ribo*-hexofuranosyl)-6-(methylthio)purine (**15a**).

To a solution of **14a** (1.64 g., 4 mmoles), 7.8 ml. of hydrazine hydrate, 16 drops of saturated cupric sulfate solution, and 16 drops of glacial acetic acid in 35 ml. of DMSO was added dropwise 5.13 g. (24 mmoles) of sodium metaperiodate in 40 ml. of water over a period of 1.5 hours with some cooling. The mixture was poured into 350 ml. of water and extracted with chloroform (3 x 100 ml.). After drying over magnesium sulfate, the chloroform solution was evaporated to dryness. The treatment had to be repeated to attain complete reduction of the double bond. The product, a chromatographically homogeneous glass, yield 1.1 g. (73%), was used in the next step without further purification; pmr (deuteriochloroform): δ 1.4 and 1.6 (2s, Me of isopropylidene), 2.0 and 2.7 (m, $C_5'H_2$ and $C_6'H_2$), 2.7 (s over m, SMe), 4.2 (m, $C_4'H$), 4.85 (m, $C_3'H$), 5.5 (q, $C_2'H$), 6.1 (d, $C_1'H$, $J_{1'2'}$ 2 Hz), 7.15 (m, phenyl), 8.0 (C_8H), 8.7 (C_2H).

Ethyl 1,5,6-Trideoxy-2,3-*O*-isopropylidene-1-[6-(methylthio)purin-9-yl]-β-D-*ribo*-heptofuranuronate (**15b**).

To a mixture of **14b** (4.0 g., 9.8 mmoles) and potassium azidocarboxylate (9.6 g., 49 mmoles) in 90 ml. of pyridine was added dropwise with stirring 4.6 ml. (80 mmoles) of acetic acid in 22 ml. of pyridine. This procedure had to be repeated to attain complete reduction. The mixture was stirred overnight before it was filtered into 1500 ml. of water, which was extracted with chloroform. Evaporation of the dried chloroform extract gave 4.19 g., of material that was used in the next step without further purification; pmr (deuteriochloroform): δ 1.3 (t, CH_3 of Et), 1.4 and 1.6 (2s, Me of isopropylidene), 2.2 (m, $-CH_2CH_2-$), 2.7 (s, Me), 4.0 (m, CH_2 of Et), 4.1 (m, $C_4'H$), 4.9 (q, $C_3'H$), 5.5 (q, $C_2'H$), 6.0 (d, $C_1'H$, $J_{1'2'}$ 2 Hz), 8.0 (C_8H), 8.7 (C_2H).

9-(6-Cyano-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hexofuranosyl)-6-(methylthio)purine (**15d**).

Compound **14d** (1.57 g., 4.36 mmoles) was reduced as described above for **14b**. The residue from this procedure was

suspended in water, and the suspension was extracted with chloroform. The chloroform extract was evaporated to dryness and the residue triturated with acetone. The residual oil (1.47 g., 94%), which was chromatographically homogeneous, was used in the next step without further purification; pmr (deuteriochloroform): δ 1.4 and 1.6 (2s, Me of isopropylidene), 2.1 (m, $C_5'H_2$), 2.4 (m, $C_6'H_2$), 2.7 (s, SMe), 4.3 (m, $C_4'H$), 5.0 (m, $C_3'H$), 5.5 (q, $C_2'H$), 6.1 (d, $C_1'H$, $J_{1'2'}$ 2 Hz), 8.0 (s, C_8H), 8.7 (s, C_2H).

9-(5,6-Dideoxy-6-phenyl-β-D-*ribo*-hexofuranosyl)-6-(methylthio)-purine (**16a**).

A suspension of **15a** (629 mg., 1.2 mmoles) in 25 ml. of 0.1 *N* sulfuric acid (1 ethanol:1 water) gradually dissolved as it was heated at 50-60° for seven hours. After standing at room temperature for two days, the solution was neutralized with barium hydroxide, and the barium sulfate was removed by filtration before it was evaporated to dryness. The crude product (273 mg., 61%) was purified by chromatography on a thick plate of silica gel (eluant 9 benzene:1 methanol). The product from this treatment, which crystallized from a water-ethanol mixture, was recrystallized from a small volume of ethanol, yield 122 mg. (27%), m.p. 78°; $[\alpha]_D^{24}$ -8.7 ± 0.7° (c 0.90 ethanol); λ max in nm (ε x 10^{-3}): *p*H 7, 13-225 (sh), 286-293 broad (19.1); pmr (DMSO-d_6): δ 2.0 (m, $C_5'H_2$), 2.7 (s over m, SMe over $C_6'H_2$), 3.9 (m, $C_4'H$), 4.1 (m, $C_3'H$), 4.8 (q, $C_2'H$), 5.2 and 5.5 (2d, OH), 6.0 (d, $C_1'H$, $J_{1'2'}$ 3 Hz), 7.2 (m, phenyl), 8.7 (s, C_8H), 8.8 (s, C_2H).

Anal. Calcd. for $C_{18}H_{20}N_4O_3S$: C, 58.05; H, 5.42; N, 15.04. Found: C, 58.09; H, 5.48; N, 14.77.

Ethyl 1,5,6-Trideoxy-1-[6-(methylthio)purin-9-yl]-β-D-*ribo*-heptofuranuronate (**16b**).

A solution of **15b** (1.8 g., 4.4 mmoles) in 60 ml. of 0.125 *N* hydrochloric acid (aqueous ethanol, *ca.* 1:1) was heated at 100° for 30 minutes before it was neutralized with concentrated ammonium hydroxide and evaporated to dryness. The residue was dissolved in alcohol, and the inorganic salt removed by filtration before the solution was evaporated to dryness. The residue (1.11 g., 68% crude yield) was purified by chromatography on a column of silica gel (eluant ethyl acetate → 2 ethyl acetate:1 methanol), yield 554 mg. (34%).

The analytical sample was prepared by further chromatography on a thick plate of silica gel (ethyl acetate eluant), yield 249 mg. (15%); $[\alpha]_D^{25}$ -8.6 ± 0.4° (c 1.04 g. ethanol); λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 224 (11.3), 285 (sh), 293 (17.4), *p*H 7, 0.1 *N* sodium hydroxide, 224 (11.3), 286-296 broad (18.7); mass spectrum: 368 $(M)^+$, 350 $(M\text{-}H_2O)^+$, 333 $(M\text{-}H_2O\text{-}OH)^+$, 323 $(M\text{-}OEt)^+$, 281 $(M\text{-}CH_2CO_2Et)^+$, 263 $(M\text{-}CH_2CO_2Et\text{-}H_2O)^+$, 203 $(sugar)^+$, 195 $(base + CHOH)^+$, 167 $(base + 2H)^+$, 166 $(base + H)^+$.

Anal. Calcd. for $C_{15}H_{20}N_4O_5S$: C, 48.90; H, 5.48; N, 15.21. Found: C, 48.95; H, 5.55; N, 15.09.

1,5,6-Trideoxy-1-[6-(methylthio)purin-9-yl]-β-D-*ribo*-heptofuranuronamide (**16c**).

A solution of **16b** (1.73 g., 4.7 mmoles) in methanolic ammonia (100 ml. saturated at 0°) was heated at 80° for 16 hours. Evaporation of the solution gave a residue that was recrystallized from methanol and then ethanol, yield 620 mg. (40%), m.p. 210-212°, ir (potassium bromide): 1620 and 1665 (amide); pmr (DMSO-d_6): δ 1.1 (t, Me of ethanol), 2.1 (m of m, CH_2CH_2), 2.7 (s, SMe), 3.5 (m, CH_2 of ethanol), 4.0 (m of m, $C_4'H$ and $C_3'H$), 4.7 (q, $C_2'H$), 5.2 and 5.5 (2d, OH), 5.95 (d, $C_1'H$, $J_{1'2'}$ 5 Hz), 6.7 and 7.2 (2 broad s, NH_2), 8.7 (C_8H), 8.8 (C_2H). The presence of ethanol in the sample was established by the pmr spectrum; uv λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 224 (11.3), 285 (sh), 292 (17.4), 305 (sh); *p*H 7, 0.1 *N* sodium hydroxide, 224 (11.3), 288 (19.0).

Anal. Calcd. for $C_{13}H_{17}N_5O_4S$·¼EtOH: C, 46.21; H, 5.31; N, 19.96. Found: C, 46.27; H, 5.15; N, 19.88.

9-(6-Cyano-5,6-dideoxy-β-D-*ribo*-hexofuranosyl)-6-(methylthio)-purine (**16d**).

A solution of **15d** (1.588 g., 3 mmoles) in a mixture of 20 ml. of ethanol and 10 ml. of 1 *N* hydrochloric acid was allowed to stand at room temperature for 4 days before it was neutralized with Dowex 1-X8 ($CO_3^=$) and then evaporated to dryness. The resulting foam was purified by chromatography on a silica gel column using 19 chloroform:1 methanol as eluant. The product came off between 720 and 1850 ml. of eluant. The light colored glass could not be induced to crystallize, yield 808 mg. (83%); $[\alpha]_D^{25}$ 0; uv λ max in nm (ε x 10^{-3}): 0.1 *N* hydrochloric acid, 224 (11.6), 285 (sh), 298 (16.7), 308 (sh), *p*H 7, 0.1 *N* sodium hydroxide, 224 (11.6), 287-292 (18.3); ir (potassium bromide): 2240 (CN); pmr (deuteriochloroform): δ 2.1 (m, $C_5'H_2$), 2.5 (t, $C_6'H_2$), 2.7 (s, SMe), 4.2 (m, $C_4'H$), 4.4 and 4.9 (2t, C_2' and $C_3'H$), 5.95 (d, $C_1'H$, $J_{1'2'}$ 5 Hz), 3.5-6.2 (OH), 7.2 (s, chloroform), 8.1 (s, C_8H), 8.6 (C_2H); mass spectrum: 321 $(M)^+$, 195 $(base + CHOH)^+$, 167 $(base + 2H)^+$, 166 $(base + H)^+$, 83 $(CHCl_3\text{-}Cl)^+$. The sample analyzed as a chloroformate, and the presence of chloroform was confirmed by both its pmr and mass spectra.

Anal. Calcd. for $C_{13}H_{15}N_5O_3S$·1/6$CHCl_3$: C, 45.74; H, 4.47; N, 20.52. Found: C, 45.73; H, 4.60; N, 20.13.

Evaporation of a methanol solution of the sample replaced the chloroform with methanol.

Anal. Calcd. for $C_{13}H_{15}N_5O_3S$·1/3MeOH: C, 48.23; H, 4.96; N, 21.09. Found: C, 48.27; H, 4.82; N, 21.14.

Diphenyl(triphenylphosphoranylidene)methylphosphonate.

A mixture of diphenylchloromethylphosphonate (16 g., 56.6 mmoles), triphenylphosphine (14.8 g., 56.6 mmoles), and dry sodium iodide (52.5 g., 0.35 mmole) in 220 ml. of dry toluene was refluxed for three days. The oil which separated gradually crystallized on standing. This material was washed thoroughly with toluene, acetone, and ether and then dried *in vacuo*, yield 9.3 g. (30%), m.p. 188°; mass spectrum: 508 $(M\text{-}HI)^+$, 128 $(HI)^+$; pmr (deuteriochloroform): δ 5.0 (s, CH_2 of $C_6H_5CH_2$), 5.95 (d, CH_2 of CH_2P, J_{HP} 10 Hz), 7.3 (s, C_6H_5 of $C_6H_5CH_2$), 7.8 (m, C_6H_5 of $P(\text{-}C_6H_5)_3$).

Anal. Calcd. for $C_{31}H_{27}O_3P_2I$: C, 58.50; H, 4.28. Found: C, 58.51; H, 4.19.

This material, diphenyl(phosphonomethyl)triphenylphosphonium iodide, was converted to the ylid by neutralization of an aqueous solution, yield 7.1 g. (96%), m.p. 147° [lit. (17) 149-150°].

6-Chloro-9-(5,6-dideoxy-6-diphenylphosphono-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranosyl)purine (**17**).

To a solution of **3**, prepared from **1** (2.36 g., 7.2 mmoles) as described above, was added 0.87 ml. of dry pyridine followed by a DMSO solution (20 ml.) of diphenyl(triphenylphosphoranylidene)methylphosphonate (3.65 g., 7.2 mmoles). After 18 hours at room temperature, the solution was extracted with petroleum ether and then diluted with benzene (150 ml.) before it was extracted with 50 ml. of water. The dried (magnesium sulfate) benzene solution was evaporated to dryness and the residue purified by chromatography on a silica gel column using 19 benzene:1 methanol as eluant. From this

column was obtained 2.48 g. (68%) of product contaminated with triphenylphosphine oxide; pmr (deuteriochloroform): δ 1.4 and 1.7 (2s, Me of isopropylidene), 4.9 (m, $C_4'H$), 5.2 (m, $C_3'H$), 5.5 (m, $C_2'H$), 5.9 (m, $C_6'H$), 6.25 (d, $C_1'H$, $J_{1'2'}$ 2 Hz), 7.2 (m, $C_5'H$), 7.5 (m, phenyl), 8.2 (s, C_8H), 8.7 (s, C_2H). The multiplet signals from $C_5'H$ and $C_6'H$ indicate that the olefin is the *trans* isomer. The presence of triphenylphosphine oxide was confirmed by both the pmr spectrum and by elemental analyses.

Reaction of 6-Chloro-9-(5,6-dideoxy-6-diphenylphosphono-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranosyl)purine (**17**) with Sodium Methylmercaptide.

A.

To a solution of the title compound (643 mg. containing some triphenylphosphine oxide) in 8 ml. of methanol was added 1.2 ml. of 1 *N* sodium methylmercaptide in methanol and the solution allowed to stand 20 hours at room temperature before it was filtered, neutralized with 1 *N* hydrochloric acid, and evaporated to dryness *in vacuo*. The residue was triturated with benzene and the benzene solution extracted with water. The product was further purified by chromatography on a thick silica gel plate using 9 benzene:1 methanol as eluant. Repetition of the procedure gave, on elution with ethyl acetate, 74 mg. of essentially pure material identified by its mass spectrum (M^+ 490) and pmr (deuteriochloroform): δ 1.4 and 1.7 (2s, Me of isopropylidene), 2.2 (s over m, C_5' and C_6' SMe over C_5' and $C_6'H$), 2.7 (s, C_6 SMe), 3.2 (m, $C_5'H_2$), 3.7 (m, OMe), 4.5 (m, $C_4'H$), 5.2 (m, $C_2'H$ and $C_3'H$), 6.15 (2d, $C_1'H$), 8.1 (2s, C_8H), 8.7 (d of s, C_2H) as 9-(5,6-dideoxy-2,3-*O*-isopropylidene-6-dimethylphosphono-5(and 6)-(methylthio)-β-D-*ribo*-hexofuranosyl)-6-(methylthio)purine (**19**). Elution of the faster traveling band with ethyl acetate gave a white gum, the pmr spectrum of which indicated it to be a mixture of starting material, triphenylphosphine oxide, and two other nucleosides containing two methylthio groups and both phenylphosphonate and methylphosphonate groups. Further separation of this mixture was not attempted.

B.

To a solution of the title compound (1.23 g., 2.22 mmoles) in methanol (5 ml.) was added about 30 ml. of methanol saturated with methylmercaptan and containing 4.4 mmoles of sodium methoxide. The reaction mixture was heated in a bomb for 18 hours at 100° before it was evaporated to dryness. The residue was extracted with benzene, which in turn was extracted with water. The water solution was neutralized, extracted with chloroform, and then evaporated to dryness. Extraction of the dried residue with chloroform gave a glass (263 mg.) of essentially pure product which shown by its uv in ethanol [λ max 284 (sh), 290], its pmr spectrum (deuteriochloroform): 1.4 and 1.6 (2s, Me of isopropylidene), 2.0 (s over m, C_5' and C_6' SMe over C_5' and 2.7 (2s, C_6 SMe), 4.2, 4.5, and 5.2 (3m, $C_2'H$, $C_3'H$, and $C_4'H$), 6.15 (2d, $C_1'H$, $J_{1'2'}$ *ca.* 2 Hz), 7.0 (m, phenyl), 8.1 (s, C_8H), 8.6 (s, C_2H), and its chromatographic and electrophorectic behavior to be 9-(5,6-dideoxy-2,3-*O*-isopropylidene-6-monophenylphosphono-5(and 6)-(methylthio)-β-D-ribofuranosyl)-6-(methylthio)-purine (**20**). An analytical sample of the dihydrate was prepared by chromatography on a thick plate of silica gel using 6 butanol:1 water as eluant. The principal band was eluted with ethanol and dried *in vacuo*.

Anal. Calcd. for $C_{22}H_{27}N_4O_6PS_2 \cdot 2H_2O$: C, 45.99; H, 5.39; N, 9.75. Found: C, 46.03; H, 4.99; N, 9.24.

The residue from the benzene extraction described above was dissolved in water, the solution neutralized, extracted with chloroform, and evaporated to dryness. The residue was twice triturated with absolute ethanol leaving behind an inorganic residue. Evaporation of the ethanol gave a material that was shown by its uv spectrum (λ max ethanol, 284 (sh), 293, 324) to be an approximately 1:1 mixture of the methylthio compounds (**20**), and the corresponding thiones (**21**). Methylation of this mixture with methyl iodide in aqueous sodium hydroxide gave pure **20**, λ max ethanol, 283 (sh), 289.

9-(5,6-Dideoxy-6-diphenylphosphono-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranosyl)-6-(methylthio)purine (**18**).

To a solution of **13**, prepared from **12** (1.7 g., 5 mmoles) in the usual manner, in 50 ml. of DMSO was added with stirring 2.01 g. (4 mmoles) of triphenylphosphonomethylenediphenylphosphonate. After 18 hours, the reaction mixture was extracted with three 100-ml. portions of petroleum ether before it was diluted with benzene (100 ml.) and extracted with water (75 ml.). The dried (magnesium sulfate) benzene solution was evaporated to dryness and the residue chromatographed on a silica gel column using 1 benzene:1 ether as eluant, yield of chromatographically homogeneous material, 1.4 g. (50%); pmr (deuteriochloroform): δ 1.4 and 1.6 (2s, Me of isopropylidene), 2.6 (s, SMe), 4.8 (m, $C_4'H$), 5.2 (m, $C_3'H$), 5.6 (m, $C_2'H$), 5.8 (m, $C_6'H$), 6.2 (d, $C_1'H$, $J_{1'2'}$ 2 Hz), 7.2 (m, $C_5'H$ and phenyl), 8.0 (s, C_8H), 8.6 (s, C_2H). The pmr identified this material as the *trans* olefin. In addition, 389 mg. (13%), of material was obtained in the forerun from the column that was shown by pmr to be a mixture of the *trans* and *cis* nucleosides. Reduction of this mixture gave a single product identical to that obtained by reduction of the pure *trans* isomer.

9-(5,6-Dideoxy-6-diphenylphosphono-2,3-*O*-isopropylidene-β-D-*ribo*-hexofuranosyl)-6-(methylthio)purine (**22**).

Compound **18** (1.4 g., 2.5 mmoles) was reduced with diimide as described above. The mixture was filtered into 600 ml. of water, which was then extracted with 300 ml. of chloroform. The chloroform solution was dried over magnesium sulfate before evaporation to dryness, yield of chromatographically homogeneous product 1.26 g. (89%); pmr (deuteriochloroform): δ 1.4 and 1.6 (2s, Me of isopropylidene), 2.2 (m, $C_5'H_2$ and $C_6'H_2$), 2.7 (s, SMe), 4.3 (m, $C_4'H$), 4.9 (m, $C_3'H$), 5.5 (q, $C_2'H$), 6.1 (d, $C_1'H$, $J_{1'2'}$ 2 Hz), 7.2 (m, phenyl), 8.0 (s, C_8H), 8.7 (s, C_2H).

9-(6-Dibenzylphosphono-5,6-dideoxy-2,3-*O*-isopropylidene-β-D-ribo-hexofuranosyl)-6-(methylthio)purine (**23**).

To a solution of **22** (1.26 g., 2.2 mmoles) in 20 ml. of dry DMSO was added 8.9 mmoles of sodium benzyloxide in benzyl alcohol (22 ml.). After the mixture was stirred for 30 minutes, it was poured into cold water (400 ml.) and ether (500 ml.). Evaporation of the dried (magnesium sulfate) ether layer gave 1.27 g. of semisolid. Some of this material (80 mg.) was further purified by chromatography on a thick silica gel plate using 19 chloroform:1 methanol as eluant. The major band was eluted with ethyl acetate giving a chromatographically homogeneous product (48 mg.); pmr (deuteriochloroform): δ 1.4 and 1.6 (2s, Me of isopropylidene), 2.0 (m, $C_5'H_2$ and $C_6'H_2$), 2.7 (s, SMe), 4.2 (m, $C_4'H$), 4.8 (m, $C_3'H$), 4.9 and 5.0 (2s, $2OCH_2$-), 5.4 (q, $C_2'H$), 6.0 (d, $C_1'H$, $J_{1'2'}$ 2 Hz), 7.4 (s, phenyl), 8.0 (s, C_8H), 8.7 (s, C_2H).

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