**B. *p*-Toluenesulfonic Acid as Catalyst.**—To a magnetically stirred solution of methyl α-D-glucopyranoside (2.5 g, 0.12 mol) in anhydrous dimethyl sulfoxide (50 ml) was added *p*-toluenesulfonic acid (500 mg) followed by the addition of ethyl vinyl ether (2.3 g, 0.03 mol). Stirring was continued for 2 hr at 35–40°, sodium carbonate was added, and the mixture was agitated for 4 hr at room temperature. The reaction mixture was processed as described above. The major product was identical with methyl 4,6-*O*-ethylidene-α-D-glucopyranoside and the minor component was methyl α-D-glucopyranoside, as shown by thin layer chromatography (solvents D and E).

**Preparation of the Methyl 6-*O*-(1-Alkoxyethyl)-α-D-glucopyranoside from Methyl 2,3,4-Tri-*O*-acetyl-α-D-glucopyranoside.**—Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (0.7 g), prepared by a known method,[22] was dissolved in diethyl ether (20 ml) to which *p*-toluenesulfonic acid (10 mg) and methyl vinyl ether (0.5 ml) were added. The reaction appeared to be complete after the mixture had been shaken for 10 min, as indicated by thin layer chromatography (solvents D and E), and was stopped after 15 min by neutralizing the acid with sodium carbonate. The reaction mixture was filtered, and the salts were washed with ether. The combined filtrates were decolorized with carbon and concentrated to a syrup (0.790 g) with no hydroxyl group (ir spectroscopy) which was homogeneous by thin layer chromatography (solvents D and E) but resisted crystallization.

*Anal.* Calcd for $C_{16}H_{26}O_{10}$: C, 50.79; H, 6.87. Found: C, 50.62; H, 6.82.

A portion (0.350 g) of the above syrup was dissolved in absolute methanol (10 ml) to which was added 0.5 *N* sodium methoxide solution (1.5 ml). The mixture was shaken occasionally for 45 min at room temperature. After being treated with Amberlite IR-120 ($H^+$), the methanolic solution was concentrated to a syrup, which was found to contain trace amounts of methyl α-D-glucopyranoside by thin layer chromatography (solvents D and E). The syrup was shaken with chloroform and filtered and the filtrate was evaporated to dryness. The resultant solid compound was chromatographically identical with methyl 6-*O*-(1-methoxyethyl)-α-D-glucopyranoside obtained directly from methyl α-D-glucopyranoside, as described before, and on treatment with *p*-toluenesulfonic acid in chloroform this material was converted into methyl α-D-glucopyranoside (major) and methyl 4,6-*O*-ethylidene-α-D-glucopyranoside as shown by thin layer chromatography (solvent D).

Similarly, a compound was prepared from methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside, by reaction with ethyl vinyl ether followed by deacetylation, and was found to be chromatographically (thin layer chromatography, solvents D and E) identical with the mono-*O*-(1-ethoxyethyl) derivative obtained from methyl α-D-glucopyranoside by boron trifluoride catalysis.

**Registry No.**—**1**, 97-30-3; **3** (R = Me) ($C_{10}H_{20}O_7$), 15717-31-4; **3** (R = Et) ($C_{11}H_{22}O_2$), 15649-43-1; **4**, 13225-11-1.

(22) B. Helferich, H. Bredereck, and A. Schneidmüller, *Ann.*, **458**, 111 (1927).

# Purine Nucleosides. XIX. The Synthesis of Certain 8-Chloropurine Nucleosides and Related Derivatives[1]

JOHN F. GERSTER,[2] BARBARA C. HINSHAW, ROLAND K. ROBINS, AND LEROY B. TOWNSEND

*Department of Chemistry, University of Utah, Salt Lake City, Utah 84112*

*Received October 2, 1967*

A new and improved procedure for the preparation of 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine (II) has been accomplished using bromine water. The first displacement of bromine with chlorine on a purine nucleoside was successfully achieved with phosphorus oxychloride to furnish 2-amino-6,8-dichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (III) which, with subsequent deblocking, yielded 2-amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI). Nucleophilic displacement of the chloro groups on VI was demonstrated to occur preferentially at position 6 to afford several 8-chloro-2,6-disubstituted purine nucleosides. Nucleophilic displacement of both chloro groups was accomplished with thiourea to yield 2-amino-9-(β-D-ribofuranosyl)purine-6,8-dithione (VIII) and the completely deblocked 2,6,8-trichloro-9-(β-D-ribofuranosyl)purine (IX) was prepared for the first time *via* diazotization of VI.

The direct bromination of various purine nucleosides to afford the corresponding 8-bromopurine nucleosides has been recently reported[3–6] and was prompted primarily by the direct bromination studies of certain nucleic acids[7–9] (RNA and DNA). However, the first direct chlorination of a nucleic acid, soluble ribonucleic acid from yeast, with N-chlorosuccinimide has only recently been reported.[9] It was postulated[10] that 8-chloroguanosine was present as an intermediate prior to subsequent degradation. This is similar to other reports[11,12] which have previously described the degradation of guanine and guanosine when left in contact with an excess of brominating agent for an extended period of time. The present study describes the synthesis and chemical reactivity of several new and interesting 8-chloro-2,6-disubstituted purine nucleosides starting with readily available 2′,3′,5′-tri-*O*-acetylguanosine (I).

We have now developed a new and improved preparation of 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine in 90% yield from commercially available 2′,3′,5′-tri-*O*-acetylguanosine (I) using saturated bromine water. The crystalline nucleoside (II) prepared in this investigation was found to be identical in every respect with II prepared previously[5] (64%) by the direct bromination of I, using a mixture of glacial acetic acid, sodium acetate, and bromine. The anomeric configuration of all nucleosides reported herein is definitely established as β since the starting material in all cases was guanosine.

(1) This work supported by Research Contract No. PH-43-65-1041 with the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) 3M Co., St. Paul, Minn.

(3) R. L. Long, R. K. Robins, and L. B. Townsend, *J. Org. Chem.*, **32**, 2751 (1967).

(4) R. L. Long, R. K. Robins, and L. B. Townsend, "Synthetic Procedures in Nucleic Acid Chemistry," Interscience Publishers, Inc., New York, N. Y., in press.

(5) R. E. Holmes and R. K. Robins, *J. Amer. Chem. Soc.*, **86**, 1242 (1964).

(6) M. Ikehara, S. Uesugi, and M. Kaneko, *Chem. Commun.*, 17 (1967).

(7) K. W. Brammer, *Biochim. Biophys. Acta*, **72**, 217 (1963).

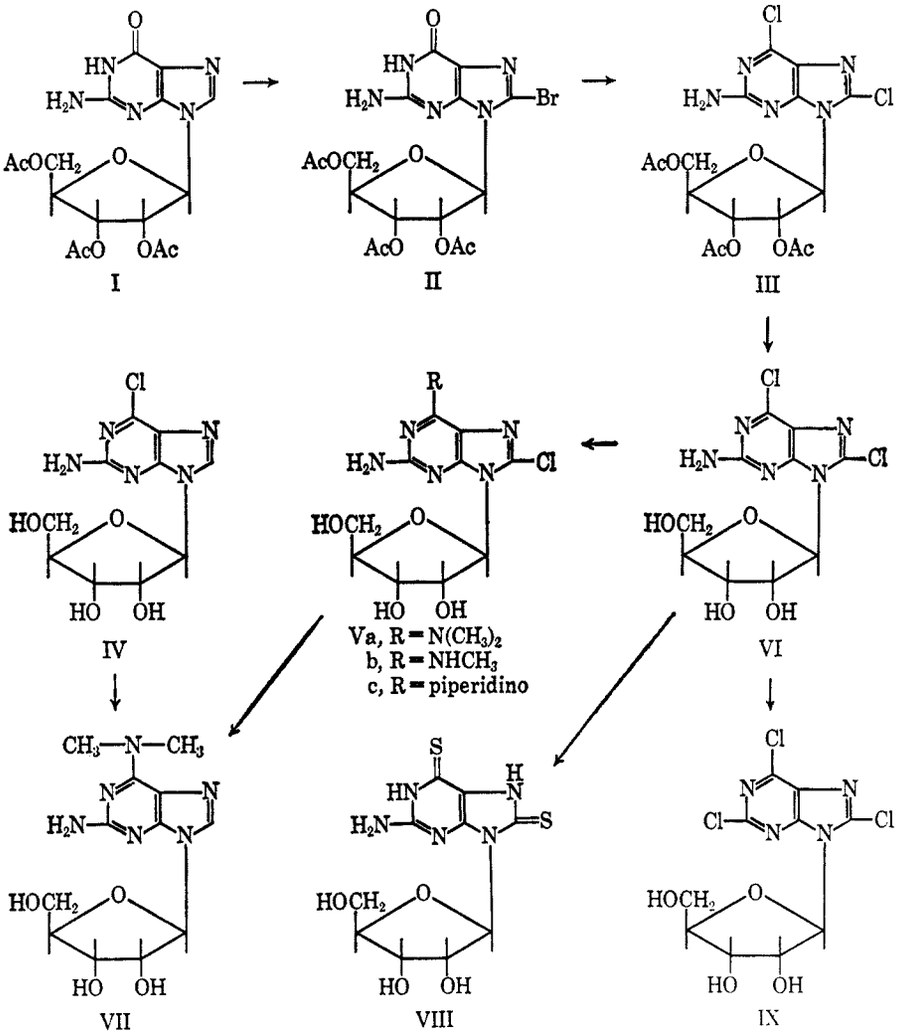
(8) J. Duval and J. P. Ebel, *Bull. Soc. Chim. Biol.*, **47**, 787 (1965).

(9) D. Londes, J. Duval, G. Aubel-Sadron, and J. P. Ebel, *ibid.*, **49**, 739 (1967).

(10) J. Duval and J. P. Ebel, *Compt. Rend.*, **263D**, 1773 (1966).

(11) E. Fischer and L. Reese, *Ann. Chem.*, **221**, 342 (1883).

(12) R. Shapiro and S. C. Agarval, *Biochem. Biophys. Res. Commun.*, **24**, 401 (1966).




Chlorination of II with phosphorus oxychloride in the presence of N,N-diethylaniline hydrochloride furnished what was at first assumed to be 2-amino-8-bromo-6-chloro-9-(2′,3′,5′,-tri-*O*-acetyl-β-D-ribofuranosyl)purine. However, it was soon discovered that the bromine had been replaced in position 8 to provide 2-amino-6,8-dichloro-9-(2′,-3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (III). This structural assignment was based on elemental analysis, including chlorine, and to our knowledge is the first report of a direct displacement of bromine by chlorine on a purine nucleoside.[13] Complete deacetylation without concomitant nucleophilic displacement of either chloro group was accomplished using methanolic ammonia at 5° to yield 2-amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI). The ready availability of VI suggested a study on the relative reactivity of the chloro groups in an effort to determine if they could be replaced with any degree of selectivity. Treatment of III with anhydrous dimethylamine and sodium bicarbonate in anhydrous ethanol at reflux temperature furnished a 58% yield of crystalline nucleoside which was assigned the structure 2-amino-8-chloro-6-dimethylamino-9-(β-D-ribofuranosyl)purine (Va) on the basis of the following data. That monosubstitution had occurred was apparent from a visual inspection of a pmr spectrum of the product in dimethyl sulfoxide-$d_6$ which displayed a sharp singlet (six protons) at δ 3.4. This singlet was attributed to the presence of only one dimethylamino group and this was further substantiated by elemental analysis. This left only the determination of the actual site at which nucleophilic displacement had occurred. Catalytic removal of the remaining chloro group from Va was accomplished smoothly with palladium on powdered charcoal to furnish a product with a melting point 203–205°. That dechlorination had occurred was evident by the appearance of a sharp singlet in the pmr spectrum (dimethyl sulfoxide-$d_6$) at δ 8.0 which could be attributed only to an aromatic proton at either C-6 or C-8. The mixture melting point with a sample of 2-amino-6-dimethylamino-9-(β-D-ribofuranosyl)-purine (VII) which was obtained[14] from 2-amino-6-chloro-9-(β-D-ribofuranosyl)purine (IV)[15] showed no depression. It was subsequently demonstrated that the nucleoside prepared from IV and from Va possessed identical ultraviolet absorption and pmr spectra. Therefore, nucleophilic displacement had occurred preferentially at position 6 to afford 2-amino-8-chloro-6-dimethylamino-9-(β-D-ribofuranosyl)purine (Va). Similar treatment of VI with anhydrous methylamine and piperidine yielded 2-amino-8-chloro-6-methyl-

(13) A similar displacement of bromine by chlorine has been reported to occur with 4,5-dibromo-3-pyridazone: R. N. Castle and K. Kaji, *Tetrahedron Lett.*, 393 (1962).

(14) J. F. Gerster, J. W. Jones, and R. K. Robins [*J. Org. Chem.*, **28**, 945 (1963)] also report the preparation of VII from 2-amino-6-iodo-9-(β-D-ribofuranosyl)purine.

(15) An improved preparation of IV has been developed and was utilized in this investigation: J. F. Gerster, A. F. Lewis, and R. K. Robins, "Synthetic Procedures in Nucleic Acid Chemistry," Interscience Publishers, Inc., New York, N. Y., in press.

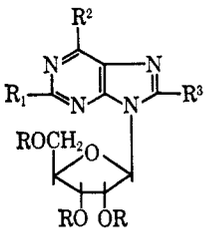
amino-9-(β-D-ribofuranosyl)purine (Vb) and 2-amino-8-chloro-6-(1-piperidyl)-9-(β-D-ribofuranosyl)purine (Vc), respectively.

That displacement of both chloro groups from VI could be achieved was demonstrated by the successful preparation of 2-amino-9-(β-D-ribofuranosyl)-6,8-dithione (VIII). Treatment of VI with aqueous thiourea in the presence of a catalytic amount of formic acid furnished a 64% yield of chromatographically pure VIII. The pmr spectrum of VIII in dimethyl sulfoxide-$d_6$ revealed the presence of broad singlets at $\delta$ 12.9 (one proton) and 12.1 (one proton) which were assigned to –NH protons at N-1 and N-7. This indicated that VIII exists in the thione form rather than the thiol form, at least in dimethyl sulfoxide-$d_6$. Additional corroboration for elimination of the thiol form was provided by the absence of an infrared absorption band at 2550–2600 $cm^{-1}$ usually attributed[16,17] to –SH stretching. There was observed an absorption band in the infrared spectrum (KBr) in the 1550–1600-$cm^{-1}$ area which was assigned[16,18] partially to —C=S stretching and partially to —C=N— stretching as part of a —N—C=S system.

The preparation of 2,6,8-trichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine[19] has been reported using the acid-catalyzed fusion procedure.[20] However, several attempts to obtain 2,6,8-trichloro-9-(β-D-ribofuranosyl)purine (IX) by deacetylation have been unsuccessful[21] because of the concomitant nucleophilic displacement of at least one of the chloro groups. We have now prepared IX for the first time by utilization of a procedure developed in our laboratory[22] for the preparation of 2,6-dichloro-9-(β-D-ribofuranosyl)purine.[23] Diazotization of VI with concentrated hydrochloric acid and sodium nitrite below −5° furnished 2,6,8-trichloro-9-(β-D-riboruranosyl)purine (IX). The ultraviolet absorption spectra of IX was very similar to the data reported[24] for other 9-substituted 2,6,8-trichloropurines. The ready availability of 2-amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (IX) from guanosine provides an excellent starting material for the preparation of unusual 2-aminopurine nucleosides containing substituents at positions 6 and 8.

The ultraviolet absorption spectral data for all purine nucleosides prepared in this study are listed in Table I.

TABLE I
ULTRAVIOLET ABSORPTION OF CERTAIN PURINE NUCLEOSIDES[a]



| Compd | R | $R_1$ | $R_2$ | $R_3$ | pH | $\lambda_{max}$ | $\epsilon_{max}$ |
|---|---|---|---|---|---|---|---|
| II | –C–$CH_3$ ‖ O | $NH_2$ | OH | Br | 1 | 262 | 16,600 |
| | | | | | 11 | 271 | 14,300 |
| III | –C–$CH_3$ ‖ O | $NH_2$ | Cl | Cl | 1 | 310 | 8,300 |
| | | | | | | 253 | 8,300 |
| | | | | | 11 | 310 | 8,800 |
| | | | | | | 253 | 8,800 |
| VI | H | $NH_2$ | Cl | Cl | 1 | 310 | 8,400 |
| | | | | | | 252 | 9,900 |
| | | | | | 11 | 310 | 8,700 |
| | | | | | | 251 | 10,000 |
| Vc | H | $NH_2$ | $NC_5H_{10}$ | Cl | 1 | 310[b] | 11,900 |
| | | | | | | 295 | 12,700 |
| | | | | | | 263 | 14,400 |
| | | | | | 11 | 296[b] | 16,900 |
| | | | | | | 289 | 18,100 |
| | | | | | | 235 | 18,500 |
| Vb | H | $NH_2$ | $NHCH_3$ | Cl | 1 | 308[b] | 6,720 |
| | | | | | | 292 | 11,200 |
| | | | | | | 260 | 13,400 |
| | | | | | 11 | 280 | 14,300 |
| | | | | | | 265[b] | 11,900 |
| | | | | | | 227[b] | 14,900 |
| Va | H | $NH_2$ | $N(CH_3)_2$ | Cl | 1 | 297 | 11,700 |
| | | | | | | 262 | 14,500 |
| | | | | | 11 | 285 | 16,200 |
| | | | | | | 269[b] | 13,100 |
| | | | | | | 232 | 18,300 |
| VIII | H | $NH_2$ | –SH | –SH | 1 | 372 | 31,500 |
| | | | | | | 361[b] | 21,000 |
| | | | | | | 295[b] | 9,260 |
| | | | | | | 273 | 19,500 |
| | | | | | 11 | 346 | 20,900 |
| | | | | | | 264 | 20,700 |
| IX | H | Cl | Cl | Cl | 1 | 285[b] | 10,700 |
| | | | | | | 279 | 11,700 |
| | | | | | | 253 | 5,700 |
| | | | | | 11 | 285[b] | 10,300 |
| | | | | | | 279 | 11,400 |
| | | | | | | 253 | 5,330 |
| VII | H | $NH_2$ | $–N(CH_3)_2$ | H | 1 | 298[b] | 11,800 |
| | | | | | | 291 | 12,000 |
| | | | | | | 256 | 13,200 |
| | | | | | 11 | 282 | 17,600 |
| | | | | | | 265 | 11,420 |
| | | | | | | 229 | 21,600 |

[a] Beckman DK-2 spectrophotometer. [b] Inflection or shoulder.

## Experimental Section[25]

**2-Amino-8-bromo-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-purin-6-one (II).**—2′,3′,5′-Tri-*O*-acetylguanosine (I) (40 g) was slowly added with stirring to 1 l. of water to form a thick slurry. This slurry was stirred vigorously at room temperature while saturated bromine water was slowly added. The addition of bromine water was made in approximately 50-ml aliquots and at such a rate that the yellow color of the reaction mixture disappeared between each addition. The total time for complete addition was approximately 20 min at which time the color of the reaction mixture remained a pale yellow. This reaction mixture was allowed to stir for an additional 20 min at room temperature and the solid collected by filtration and immediately recrystallized from a mixture of acetone–water to yield 44 g (90%) of chromatographically pure 8-bromo-2′,3′,5′-tri-*O*-acetylguanosine (II), mp 220–221°.

*Anal.* Calcd for $C_{16}H_{18}BrN_5O_8$: C, 39.40; H, 3.72; N, 14.33. Found: C, 39.32; H, 3.88; N, 14.11.

**2-Amino-6,8-dichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine (III).**—Compound II (25 g) was added to 150 ml of phosphorus oxychloride containing 26 g of N,N-diethylaniline hydrochloride (anhydrous). This mixture was heated at reflux temperature for 6 min and the excess phosphorus oxychloride was

(16) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed, 1967, p 100.

(17) D. Harrison and J. T. Ralph, *J. Chem. Soc., Sect. B*, 14 (1967).

(18) J. R. Dyer, "Application of Absorption Spectroscopy of Organic Compounds," Prentice Hall Inc., Englewood Cliffs, N. J. (1965), p 38.

(19) J. Davoll, B. A. Lowy, *J. Amer. Chem. Soc.*, **74**, 1563 (1952); T. Sato, T. Shimadachi, and R. Ishido, *Nippon Kagaku Zasshi*, **81**, 1440 (1960).

(20) R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **4**, 311 (1967), and references cited therein.

(21) Unpublished observations from this laboratory.

(22) J. F. Gerster and R. K. Robins, *J. Org. Chem.*, **31**, 3258 (1966).

(23) Preparation of this nucleoside by deacetylation of 2,6-dichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)purine has been unsuccessful since a concomitant nucleophilic displacement of chlorine from position six occurs: H. J. Schaeffer and H. J. Thomas, *J. Amer. Chem. Soc.*, **80**, 3738 (1958).

(24) E. Y. Sutcliffe and R. K. Robins, *J. Org. Chem.*, **28**, 1662 (1963).

(25) Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. All pmr spectra were obtained on a Varian A-60 nmr spectrometer and values are recorded in δ units with TMS as an internal standard. Infrared spectra were obtained on a Beckman IR-5A spectrometer with pressed KBr pellets.

then removed *in vacuo* on a steam bath. The residue was poured onto 500 ml of crushed ice with vigorous stirring and additional ice was added as needed to keep the temperature of the solution below 0°. The solution was extracted with three 150-ml portions of methylene chloride and the combined extracts were washed with water until the washings were neutral to pH paper, then dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the resulting dark syrup was dissolved in 50 ml of ethanol. This solution was allowed to stand at 5° until a solid separated from solution and was collected by filtration. For analysis the solid was recrystallized from ethanol to yield 12.5 g (52%) of III, mp 138–140° and $[\alpha]^{22}D$ −3.85° (*c* 1, ethanol).

*Anal.* Calcd for $C_{16}H_{17}Cl_2N_5O_7$: C, 41.60; H, 3.72; N, 15.30; Cl, 15.35. Found: C, 41.53; H, 3.70; N, 15.33; Cl, 15.16.

**2-Amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI).**—2-Amino-6,8-dichloro-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-purine (III) (5 g) was dissolved in methanolic ammonia (previously saturated at −10°) and allowed to stand at 5° for 5 hr. The solution was evaporated to dryness *in vacuo* and the temperature of the water bath was maintained below 20°. The resulting solid was triturated with 10 ml of water and the solid collected by filtration to yield 3.7 g of crude product. Recrystallization from ethanol yielded 3.4 g of pure VI, mp 196° dec.

*Anal.* Calcd for $C_{10}H_{11}Cl_2N_5O_4$: C, 35.80; H, 3.30; N, 20.80. Found: C, 35.50; H, 3.78; N, 20.20.

**2-Amino-8-chloro-6-dimethylamino-9-(β-D-ribofuranosyl)purine (Va).**—To 50 ml of ethanol was added 1 g of 2-amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI). Anhydrous dimethylamine (1 ml) and 1 g of sodium bicarbonate was added and the mixture heated at reflux temperature for 1 hr. The solid sodium bicarbonate was removed by filtration and the ethanol removed *in vacuo*. Additional ethanol (50 ml) was added to the residue and the solution was again evaporated to dryness *in vacuo;* this process was repeated several times to remove all traces of dimethylamine. The residual oil was triturated with diethyl ether and the resulting solid recrystallized from toluene to yield 600 mg (58%) of analytically pure product, mp 193–194°. The product was dried for 1 hr at 110° at approximately 0.1 mm over $P_2O_5$ for analysis.

*Anal.* Calcd for $C_{12}H_{17}ClN_6O_4$: C, 41.80; H, 4.97; N, 24.37. Found: C, 41.98; H, 5.10; N, 24.15.

**2-Amino-8-chloro-6-methylamino-9-(β-D-ribofuranosyl)purine (Vb).**—2-Amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI) (1 g) was dissolved in 50 ml of ethanol and to this solution was added a mixture of 1 g of sodium bicarbonate and 1 ml of anhydrous methylamine. The reaction mixture was heated at reflux temperature for 1 hr, the sodium bicarbonate removed by filtration, and the filtrate evaporated to dryness *in vacuo*. The resulting crude solid was recrystallized from a mixture of acetone–ligroin (110–115°) to yield pure crystals (540 mg, 56%), mp 198–199° dec.

*Anal.* Calcd for $C_{11}H_{15}ClN_6O_4$: C, 40.00; H, 4.57; N, 25.40. Found: C, 40.01; H, 4.80; N, 25.18.

**2-Amino-8-chloro-6-(1-piperidyl)-9-(β-D-ribofuranosyl)purine (Vc).**—2-Amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI) (1 g) was added to a solution of 0.6 ml of piperidine in 50 ml of ethanol. There was then added 1 g of sodium bicarbonate and the reaction mixture refluxed for 1 hr. The solid was collected by filtration and discarded and the filtrate evaporated to dryness *in vacuo*. The residue was then triturated with 10 ml of diethyl ether. The resulting solid was collected by filtration and recrystallized from toluene to yield 0.6 g (37%) of crystals melting at 193–194°. The product was dried at 110° for 1 hr at approximately 0.1 mm for analysis.

*Anal.* Calcd for $C_{15}H_{21}ClN_6O_4$: C, 47.10; H, 5.76; N, 21.80. Found: C, 47.04; H, 5.54; N, 21.69.

**2-Amino-9-(β-D-ribofuranosyl)purine-6,8-dithione (VIII).**—2-Amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI) (1 g) was dissolved in 15 ml of water containing 1 g of thiourea. One drop of 25% formic acid was added and the solution heated at 80–85° for 1 hr while the reaction mixture was maintained at approximately pH 5 with concentrated ammonium hydroxide. The solution was a clear, bright yellow when the reaction was complete. The solution was evaporated to a syrup *in vacuo* and triturated with diethyl ether (50 ml). The resulting solid was recrystallized from methanol with a minimum amount of water. The solution was allowed to stand for 10–14 days and as the oil dissolved the product slowly crystallized from solution. There was obtained a yield of 625 mg (64%) of yellow product, mp 215–216° dec. This product was dried at 100° for 1 hr at approximately 0.1 mm over $P_2O_5$ for analysis, $[\alpha]^{26}D$ −48.48° (*c* 1.0, 0.0844 *N* NaOH).

*Anal.* Calcd for $C_{10}H_{13}N_5O_4S_2$: C, 35.35; H, 4.16; N, 20.60. Found: C, 35.35; H, 4.18; N, 20.10.

**2,6,8-Trichloro-9-(β-D-ribofuranosyl)purine (IX).**—2-Amino-6,8-dichloro-9-(β-D-ribofuranosyl)purine (VI) (1 g) was added to 10 ml of concentrated hydrochloric acid which had been previously cooled to −10°. Sodium nitrite (415 mg) in 2 ml of water was added dropwise while maintaining the temperature between −5 and −10°. The resulting solution was allowed to stir at −5° for 20 min and then neutralized with concentrated ammonium hydroxide below −10°. The solution was then extracted with three 20-ml portions of cold methylene chloride. The combined methylene chloride extracts were washed once with water and dried over anhydrous magnesium sulfate. The methylene chloride was removed *in vacuo* and the remaining residue crystallized from acetone to yield 260 mg (24.6%) of pure product melting at 168°.

*Anal.* Calcd for $C_{10}H_9Cl_3N_4O_4$: C, 33.80; H, 2.53; N, 15.75. Found: C, 34.00; H, 2.65; H, 15.48.

**2-Amino-6-dimethylamino-9-(β-D-ribofuranosyl)purine (VII).**

**Method 1.**—2-Amino-8-chloro-6-dimethylamino-9-(β-D-ribofuranosyl)purine (Va) (1 g) was dissolved in 95% ethanol and 500 mg of 5% palladium on powdered charcoal was added. The mixture was hydrogenated at 45 psi in a hydrogen atmosphere at room temperature for 6 hr. The mixture was then filtered through a Celite pad and the filtrate evaporated to dryness *in vacuo*. Recrystallization of the residue from a mixture of acetone–methanol furnished 550 mg of the hydrochloride salt of VII, mp 199–200° dec. This salt was dissolved in 60 ml of water and 3.5 g of Dowex 3 was added to the aqueous solution. This mixture was allowed to stir at room temperature for 5 hr, the resin removed by filtration, and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from a mixture of acetone–methanol to afford a product which melted at 203–205°.

**Method 2.**—2-Amino-6-chloro-9-(β-D-ribofuranosyl)purine (IV) (1 g) was dissolved in 50 ml of anhydrous ethanol. Anhydrous dimethylamine (1 ml) was added and the solution heated at reflux temperature on the steam bath for 1 hr. The solution was taken to dryness *in vacuo* and additional ethanol added and again taken to dryness *in vacuo;* this process was repeated several times to remove the excess dimethylamine. The resulting oil was triturated with a 1:1 solution of acetone–diethyl ether. The residual oil solidified on standing and was recrystallized from a mixture of acetone–methanol two times to yield (0.55 g, 53%) a crystalline product melting at 203–204°. The product from method 1 and method 2 showed no depression in mixture melting point and possessed identical uv and pmr spectra.

$R_f$ values of VII (prepared by method 1) were 0.66 in 5% aqueous $NH_4Cl$ and 0.88 in EtOH–$H_2O$ (7:3, v/v). $R_f$ values of VII (prepared by method 2) were 0.67 in 5% aqueous $NH_4Cl$ and 0.85 in EtOH–$H_2O$ (7:3, v/v). Whatman No. 1 chromatography paper and descending technique were used.

**Registry No.**—II, 15717-45-0; III, 15717-46-1; Va, 15717-47-2; Vb, 15645-46-2; Vc, 15717-48-3; VI, 15645-47-3; VII, 15717-43-8; VIII, 15834-80-7; IX, 15717-44-9.