Registry No.—**3a**, 22850-58-4; **3b**, 22850-59-5; **3c**, 22850-60-8; **3d**, 22850-61-9; **3f**, 22850-62-0; **4b**, 22850-63-1; **5**, 22850-64-2; **6**, 22850-65-3; **7**, 22850-66-4; **12**, 22850-67-5; **13**, 22850-68-6; **14**, 22922-41-4; **16**, 22850-69-7; **16b**, 22850-70-0; **17a**, 24375-89-1; **17b**, 22850-71-1; **18b**, 22850-72-2.

Purine Nucleosides. XXVI. A General Synthesis of 6-Substituted 7-(β-D-Ribofuranosyl)purines. A Reinvestigation and Corroboration of the Position of Glycosylation of 6-Dimethylamino-"7"-(β-D-ribofuranosyl)purine[1]

ROBERT J. ROUSSEAU,[2a] RAYMOND P. PANZICA,[2b] STEPHEN M. REDDICK, ROLAND K. ROBINS, AND LEROY B. TOWNSEND[3]

Department of Chemistry and Department of Biopharmaceutical Sciences, University of Utah, Salt Lake City, Utah 84112

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A general method for the synthesis of 6-substituted 7-(β-D-ribofuranosyl)purines has been achieved *via* ring closure of an imidazole nucleoside. The preparation of 7-(β-D-ribofuranosyl)purine-6-thione (**7**) from 4-amino-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-5-carboxamide (**1**) has provided a route for the production of 6-alkylthio-, 6-alkylamino-, and 6-alkoxy-7-(β-D-ribofuranosyl)purines. An unambiguous synthesis of 6-dimethylamino-7-(β-D-ribofuranosyl)purine (**14**) has verified a previous investigation which shows that the site of glycosylation reported in the literature for 6-dimethylamino-"7"-(β-D-ribofuranosyl)purine was in error. The glycosyl linkage of 6-ethoxy-7-(β-D-ribofuranosyl)purine (**5**) has been shown to be unusually labile toward dilute sodium ethoxide solutions which generally do not affect purine nucleoside glycosidic bonds.

Considerable interest in the synthesis of 7-glycosylpurines was generated when the purine nucleoside isolated from pseudovitamin B_{12} was characterized as 7-α-D-ribofuranosyladenine. Other nucleosides which were isolated from pseudovitamin B_{12} analogs were also assumed to be 7-ribosylpurines.[4] Many of the nucleosides reported[5-9] in the literature which have been assigned as 7-glycosylpurines have been isolated only as minor products from a mixture by lengthy separation procedures. The preparation of 7-ribosylpurines *via* direct glycosylation of a preformed purine has also been shown to suffer from several inherent difficulties.[10,11] Recently, the synthesis of 6-substituted 7-glycosylpurines has been achieved from imidazole nucleosides,[12] but the routes[13-15] used were restrictive in that they provided only an amino or keto group at position 6 of the purine ring for monosubstituted nucleosides. It has been suggested that the structural assignments for several previously reported 6-substituted 7-glycosylpurines are questionable[16] and, therefore, a general method for the *unambiguous* synthesis of these nucleosides seemed desirable. This prompted the present investigation for a 6-substituted 7-(β-D-ribofuranosyl)-purine with a functional group at position 6 which would be amenable toward nucleophilic displacement. The ring closure of an imidazole nucleoside to a 7-glycosylpurine with a methylthio group at position 6 has been accomplished and was followed by the appropriate functional group transformations to achieve that goal.

An attempt was made to synthesize 7-(β-D-ribofuranosyl)purine-6-thione (**7**) from 4-amino-5-cyano-1-(β-D-ribofuranosyl)imidazole (**2**) by the usual procedure (treatment with a mixture of ethyl orthoformate–acetic anhydride, followed by ethanolic sodium hydrogen sulfide).[17] The crystalline solid isolated from this reaction mixture exhibited two spots by paper chromatography. Several recrystallizations from water gave a very small yield of a product with physical properties which were incompatible with the expected structure **7**. This observation was based partly on the pmr spectrum of the solid in dimethyl sulfoxide-d_6 which exhibited only one singlet (δ 8.90, one proton) in the region where the H_2 and H_8 signals were expected (δ 8 ± 1) as well as an unexpected signal at δ 2.5 (three protons). On the basis of elemental analysis and pmr spectra, the nucleoside was assigned the structure 2-methyl-7-(β-D-ribofuranosyl)purine-6-thione (**4**). Formation of **4** can be rationalized by the formation of the 4-N-acetyl intermediate **3** presumably *via* the facile reaction of excess acetic anhydride with the 4-amino group of 4-amino-5-cyano-1-(β-D-ribofuranosyl)imidazole (**2**, Scheme I), followed by annulation.

From the pmr spectrum in D_2O of the initial crystalline mixture it was calculated that **4** and another compound which was subsequently shown to be the desired

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(2) (a) This manuscript was part of a Ph.D. Thesis by R. J. Rousseau, University of Utah, 1969. (b) The recipient of a University of Utah Research Committee Fellowship, 1968–1969.

(3) Author to whom inquiries may be addressed at the University of Utah.

(4) For a recent and comprehensive review of vitamin B_{12} and naturally occurring analogs of vitamin B_{12}, the reader is referred to R. Bonnett, *Chem. Rev.*, **63**, 573 (1963); E. L. Smith, "Vitamin B_{12}," 2nd ed, Methuen Co., London, 1963; K. Bernhauer, O. Muller, and F. Wagner, *Angew. Chem. Intern. Ed. Engl.*, **3**, 200 (1964).

(5) H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Amer. Chem. Soc.*, **77**, 18 (1955).

(6) Y. Misuno, M. Ikehara, T. Itoh, and K. Sato, *J. Org. Chem.*, **30**, 4066 (1965).

(7) J. Baddiley, J. G. Buchanan, G. O. Osbourne, *J. Chem. Soc.*, 3606 (1958).

(8) K. Amai, A. Nohara, and M. Honjo, *Chem. Pharm. Bull.* (Tokyo), **14**, 1377 (1966).

(9) T. Hashizume and H. Iwamura, *J. Org. Chem.*, **33**, 1796 (1968).

(10) J. A. Montgomery and H. J. Thomas, *ibid.*, **28**, 2304 (1963).

(11) H. J. Thomas and J. A. Montgomery, *ibid.*, **31**, 1413 (1966).

(12) L. B. Townsend, *Chem. Rev.*, **67**, 533 (1967).

(13) R. J. Rousseau, L. B. Townsend, and R. K. Robins, *Chem. Commun.*, 265 (1966).

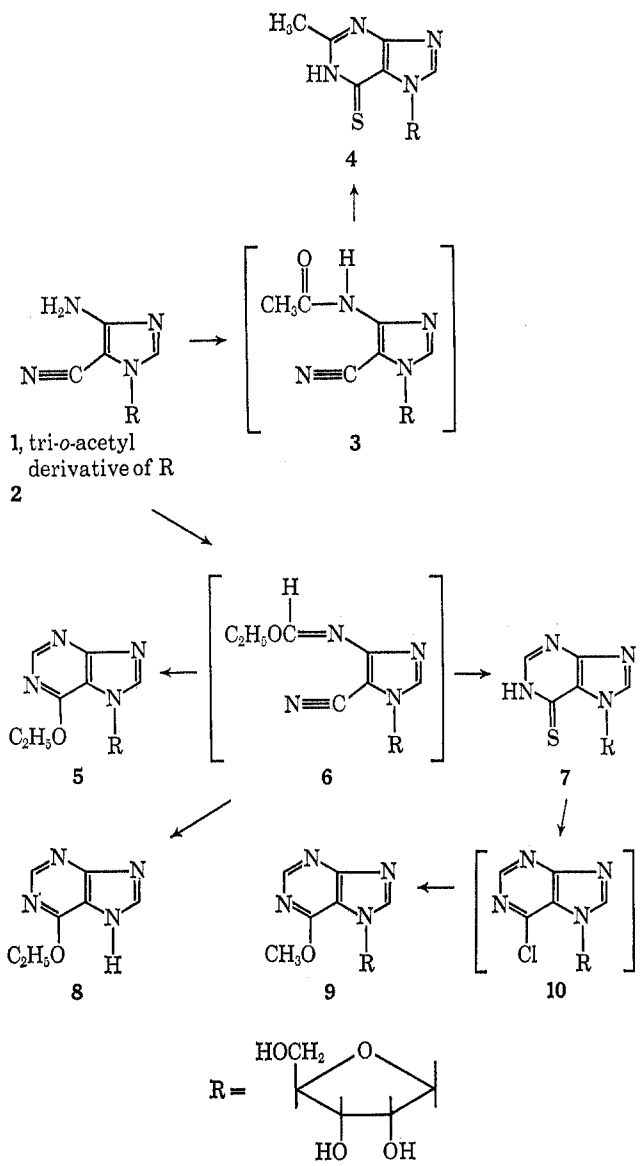
(14) R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, **90**, 2661 (1968).

(15) R. J. Rousseau and L. B. Townsend, *J. Org. Chem.*, **33**, 2828 (1968).

(16) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Amer. Chem. Soc.*, **86**, 5320 (1964).

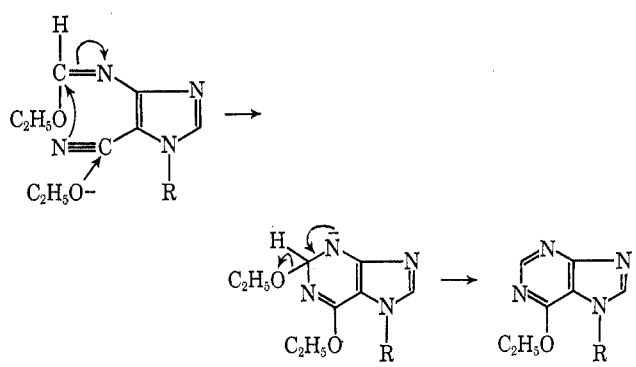
(17) E. C. Taylor, A. McKillop, and R. N. Warrener, *Tetrahedron*, **23**, 885 (1967).

SCHEME I



7-(β-D-ribofuranosyl)purine-6-thione (**7**) were present in a ratio of approximately 1:2. This determination was made by comparison of the signals observed for the combined anomeric protons from both compounds (two doublets centered at about δ 6.2) with the signal exhibited for the H_2 proton of **7** (δ 8.3). The overall yield of the crystalline mixture from **2** was about 14% 2-methyl-7-(β-D-ribofuranosyl)purine-6-thione (**4**) and 29% 7-(β-D-ribofuranosyl)purine-6-thione (**7**). To preclude the initial formation of **3**, diethoxymethylacetate[18,19] was utilized to form the ethoxymethylene intermediate **6** from 4-amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**1**). Ring closure of **6** with ethanolic sodium hydrogen sulfide gave 7-(β-D-ribofuranosyl)purine-6-thione (**7**) in varying yields. This reaction has been proposed[20] to occur *via* a *m*-thiazine intermediate; however, this mechanism has not been proved in the present investigation since we were unable to isolate the *m*-thiazine intermediate. Also it is quite possible that the initial nucleophilic attack may occur at the 5-cyano group rather than the ethoxymethylene moiety of the intermediate **6**.

A second product, subsequently isolated in a very small yield, melted several degrees higher than 7-(β-D-ribofuranosyl)purine-6-thione (**7**). This compound exhibited a sharp triplet centered at δ 1.5 (three protons), which had the same coupling constant (7 Hz) as a quartet centered at δ 4.7 (two protons) in the pmr spectrum in dimethyl sulfoxide-d_6. This suggested the presence of an ethyl group and, since the ultraviolet absorption spectra (Table I) was very similar to that of 6-methoxy-7-methylpurine,[21] the structure of 6-ethoxy-7-(β-D-ribofuranosyl)purine (**5**) was proposed. This structural assignment was further corroborated by elemental analysis. Under these reaction conditions it seems quite possible that the ethoxy anion was in direct competition with the thiol anion for attack on the 5-cyano group of **6**. To test this assumption the ethoxymethylene derivative **6** was heated at reflux temperature with an excess of ethanolic sodium ethoxide to furnish 6-ethoxypurine (**8**).[22] This was very unexpected and indicated that not only was the cyano group attacked by the ethoxy anion but also that the glycosidic linkage was labile to base under these reaction conditions. When **6** was refluxed with only a slight excess of sodium ethoxide in ethanol the intact nucleoside 6-ethoxy-7-(β-D-ribofuranosyl)purine (**5**) was produced in good yield. These are the first reported examples of the direct closure of an *o*-aminonitrile to an alkoxypyrimidine. Ring closure probably occurs by the following mechanism.



Therefore, the use of ethanolic sodium hydrogen sulfide on **6** to provide 7-(β-D-ribofuranosyl)purine-6-thione (**7**) possessed some obvious difficulties and the side reactions discussed above were probably responsible for the decreased yield of **7** by this route. This prompted us to investigate the reaction of hydrogen sulfide and refluxing pyridine on **6** which effected a facile ring closure. After deacetylation the latter method afforded a good yield of only one product, 7-(β-D-ribofuranosyl)purine-6-thione (**7**). That the sulfur group at position 6 existed in the thione rather than the thiol form was implied from the infrared spectrum when there was observed a strong signal at 1540 cm^{-1} which was assigned[23,24] as C=S stretching and part of

(18) The reactive intermediate from the reaction of ethyl orthoformate with acetic anhydride.

(19) J. A. Montgomery and C. Temple, *J. Org. Chem.*, **25**, 395 (1960).

(20) E. C. Taylor, A. McKillop, and S. Vromen, *Tetrahedron*, **23**, 891 (1967).

(21) R. N. Prasad and R. K. Robins, *J. Amer. Chem. Soc.*, **79**, 6401 (1957).

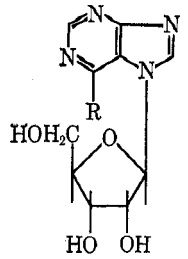
(22) G. Huber, *Chem. Ber.*, **90**, 698 (1957).

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

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

TABLE I

ULTRAVIOLET ABSORPTION DATA FOR CERTAIN 6-SUBSTITUTED 7-β-D-RIBOFURANOSYLPURINES[a]



		pH 1		MeOH		pH 11	
No.	R	λ_{max}, nm	$\epsilon \times 10^{-3}$	λ_{max}, nm	$\epsilon \times 10^{-3}$	λ_{max}, nm	$\epsilon \times 10^{-3}$
12	H	257	5.93	264	6.30	263	7.20
7	SH	330	18.70	332	16.00	317	20.40
						232	12.10
13	$NHCH_3$	279	22.40	273	17.00	273	17.00
14	$N(CH_3)_2$	293	12.50	290	12.80	292	13.20
		225	8.13	223	11.60	228	9.40
5	OC_2H_5	257	10.10	259	7.40	259	8.15
11	SCH_3	300	12.50	291	13.70	293	13.70
		225	9.25	252	4.17	252	4.17
				223	10.10	237	8.05

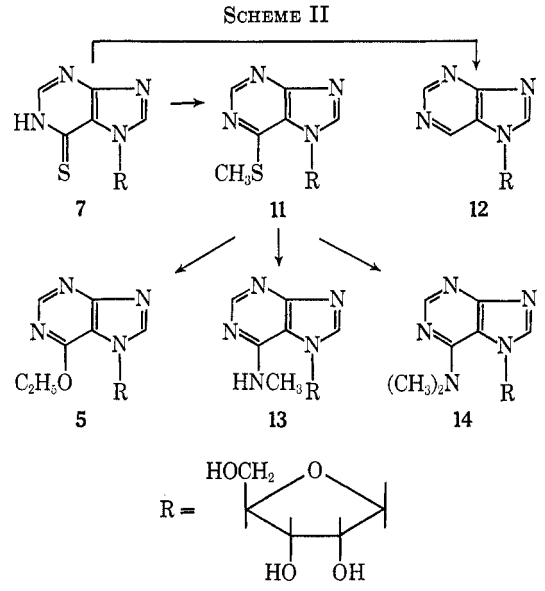
[a] Spectra were obtained on a Beckman DK-2 spectrophotometer.

an –NC=S system. The thiol form was also excluded by the absence of a band at 2550–2600 cm^{-1} attributable to S—H stretching.[24] Since 6-chloro-9-(β-D-ribofuranosyl)purine[25] has served as a valuable intermediate in the synthesis of numerous 6-substituted 9-(β-D-ribofuranosyl)purines, it was proposed that 6-chloro-7-(β-D-ribofuranosyl)purine (**10**) might be as useful for the synthesis of 6-substituted 7-(β-D-ribofuranosyl)-purines.

Chlorine gas was bubbled into a suspension of 7-(β-D-ribofuranosyl)purine-6-thione (**7**) in methanol[25] at low temperature. After a clear solution had been effected, the ultraviolet absorption spectra of the reaction mixture showed a maxima at 265 nm at pH 11 and 268 nm at pH 1. This is very similar to the spectra of 6-chloro-7-methylpurine[21] (268 nm, pH 11; 271 nm, pH 1) but quite different from the spectra of **7** and it was assumed that 6-chloro-7-(β-D-ribofuranosyl)purine (**10**) had been formed *in situ*. However, attempts to isolate **10** were unsuccessful since even careful neutralization with Dowex 1-X2 (OH^- form) afforded a 76% yield of a compound which was assigned the structure of 6-methoxy-7-(β-D-ribofuranosyl)purine (**9**) on the basis of ultraviolet spectral comparison with 6-methoxy-7-methylpurine,[21] pmr spectra, and elemental analysis.

It is possible that the electron-withdrawing effect of the riboside moiety at position **7** has activated the chloro group and made it more susceptible toward nucleophilic attack than the chloro group of the corresponding 9-riboside. In an effort to employ a less reactive leaving group, 7-(β-D-ribofuranosyl)purine-6-thione (**7**) was dissolved in ammonium hydroxide and stirred with an excess of methyl iodide. The resultant precipitate was assigned the structure of 6-methylthio-7-(β-D-ribofuranosyl)purine (**11**) since the ultraviolet spectra of **11** (Table I) was quite similar to that of 6-methylthio-7-methylpurine.[21] The possibility of methylation on a ring nitrogen rather than the sulfur group was excluded by the above uv comparison and the

SCHEME II



chemical shift observed in the pmr spectra for the exocyclic methyl group. (See Scheme II.)

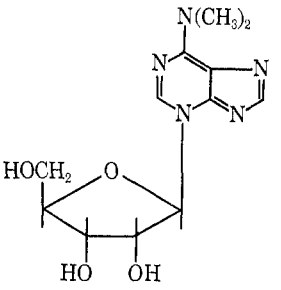
There was observed a facile conversion of 7-(β-D-ribofuranosyl)purine-6-thione (**7**) into 7-(β-D-ribofuranosyl)purine (**12**) with Raney nickel. This nucleoside has been previously reported as a minor reaction product from the direct glycosylation of purine.[6,9] The anomeric configuration of **12** (from direct glycosylation) has been proposed as β on the basis of the *trans* rule,[26] but the structure has not been rigorously established. Comparison of the data for **12** (prepared from **7** which has a known β-anomeric configuration) with the data reported for 7-(β-D-ribofuranosyl)purine[6,9] showed the products to have identical optical rotations and comparable melting points. This verified that the previous assignment[6,9] of β for the anomeric configuration of 7-(D-ribofuranosyl)purine was correct.

The 6-methylthio group of **11** was found to be susceptible toward nucleophilic attack and, therefore, **11**

(25) R. K. Robins, *Biochem. Prep.*, **10**, 145 (1963).

(26) B. R. Baker, *Ciba Found. Symp. Chem. Biol. Purines*, 120 (1957).

has proved to be an excellent intermediate for the formation of various 6-substituted 7-(β-D-ribofuranosyl)-purines. Treatment of **11** with anhydrous methylamine at 125° provided an excellent yield of 6-methylamino-7-(β-D-ribofuranosyl)purine (**13**). Similarly, the first unambiguous synthesis of of 6-dimethylamino-7-(β-D-ribofuranosyl)purine (**14**) was achieved by the action of anhydrous dimethylamine on **11**. When the data for **14** were compared with those reported[5] for "6-dimethylamino-7-(β-D-ribofuranosyl)purine," it was obvious that the nucleoside prepared in our laboratory was 6-dimethylamino-7-(β-D-ribofuranosyl)purine. Although the melting points were quite similar,[27a] the other data[27a] exhibited significant differences and lends further support of the proposal[16] that the reported



15

nucleoside is 6-dimethylamino-3-(β-D-ribofuranosyl)-purine (**15**).

When 6-methylthio-7-(β-D-ribofuranosyl)purine (**11**) was treated with 1 *N* ethanolic sodium ethoxide the unexpected product 6-ethoxypurine (**8**) was again obtained. To obtain this product, both nucleophilic displacement of the methylthio group as well as scission of the glycosyl bond under basic conditions must occur. Although the N-glycosyl linkage in purine nucleosides is generally stable to base, our results show that this linkage in **11** is unexpectedly unstable to excess base. The desired 6-ethoxy-7-(β-D-ribofuranosyl)purine (**5**) was obtained in excellent yield when only 1 equiv of base was utilized and found to be identical with the compound isolated *via* ring closure of the ethoxymethylene derivative **6** with sodium ethoxide.

This investigation has provided a general route for the preparation of various 6-substituted 7-(β-D-ribofuranosyl)purines from **11** which is dependent only on the nucleophile employed.

Experimental Section[28]

4-Amino-5-cyano-1-(β-D-ribofuranosyl)imidazole (2).—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole[14] (**1**, 6.0 g) was allowed to stand at room temperature for 16 hr in 500 ml of methanol saturated with ammonia at −10°. The solution was evaporated *in vacuo* to a syrup and then dissolved in 50 ml of ethanol. The crystals which had separated (2.0 g) were collected by filtration, the filtrate was evaporated *in vacuo* to a syrup, and the vacuum was continued for 1 hr with the flask immersed in a water bath at 85°. The residue was dissolved in a minimum amount of methanol and allowed to evaporate slowly to dryness in an open beaker. When 20 ml of ethanol was added, crystallization occurred to afford an additional 1.3 g of **2** (combined yield of 3.3 g, 82%). A small sample was recrystallized from ethanol to furnish an analytical sample, mp 137–138°.

Anal. Calcd for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.32. Found: C, 45.06; H, 5.05; N, 23.59.

2-Methyl-7-(β-D-ribofuranosyl)purine-6-thione (4).—4-Amino-5-cyano-1-(β-D-ribofuranosyl)imidazole (**2**, 1 g) and 10 ml of a 1:1 mixture of ethyl orthoformate and acetic anhydride (previously stored at room temperature for 2 weeks) were heated at reflux temperature for 3 hr. The orange solution was evaporated *in vacuo* to a syrup. This syrup was dissolved in toluene (50 ml) and again evaporated *in vacuo* to a syrup. This process was repeated once more. The orange syrup was dissolved in 100 ml of an ethanolic solution of sodium hydrogen sulfide[29] and heated at reflux temperature for 14 hr. The brown mixture was evaporated *in vacuo* to dryness, the residue was dissolved in 50 ml of water, and this solution was neutralized with Amberlite XE-89 (H^+ form). The resin was removed by filtration and the filtrate allowed to stand at 4° for 18 hr to yield 600 mg of product, mp 180–184°. Four recrystallizations from water yielded 100 mg of analytically pure product, mp 214–216°, $[\alpha]^{27}D$ +38.0 (*c* 0.5, 0.1 *N* NaOH).

Anal. Calcd for $C_{11}H_{14}N_4O_4S\cdot 2H_2O$: C, 39.52; H, 5.43; N, 16.76. Found: C, 39.14; H, 4.96; N, 17.13.

7-(β-D-Ribofuranosyl)purine-6-thione (7) and 6-Ethoxy-7-(β-D-ribofuranosyl)purine (5).—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**1**, 8 g) and 80 ml of diethoxymethylacetate[19] were heated at reflux temperature for 5 hr. The orange solution was evaporated *in vacuo* to a syrup and 250 ml of an ethanolic solution of sodium hydrogen sulfide[29] prepared from 4.2 g of sodium metal was added. This mixture was refluxed for 14 hr and then evaporated *in vacuo* to dryness. The residue was dissolved in 250 ml of water, the pH adjusted to 5 with concentrated hydrochloric acid, and the solution allowed to stand at room temperature for 16 hr. The precipitate was collected by filtration to afford yields of **7** varying from 20 to 84% with a typical yield of 4.1 g (66%), mp 203–205°. The crude product was recrystallized from water to yield pale yellow crystals, mp 205–206°, $[\alpha]^{27}D$ +96 (*c* 1.075, 0.1 *N* NaOH).

Anal. Calcd for $C_{10}H_{12}N_4O_4S\cdot H_2O$: C, 39.74; H, 4.67; N, 18.54. Found: C, 39.35; H, 4.68; N, 18.26.

When the filtrates were allowed to evaporate to near dryness at room temperature and pressure, 600 mg of a second product, mp 116–118° (**5**), crystallized in long needles. Recrystallization from water gave transparent, colorless needles, mp 220–222°, $[\alpha]^{28}D$ +12.1 (*c* 1, pyridine).

Anal. Calcd for $C_{12}H_{16}N_4O_5$: C, 48.65; H, 5.44; N, 18.91. Found: C, 48.70; H, 5.31; N, 18.91.

7-(β-D-Ribofuranosyl)purine-6-thione (7).—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**1**, 2.0 g) was heated at reflux temperature in 20 ml of diethoxymethylacetate[19] for 6 hr and the orange solution was then evaporated *in vacuo* to a syrup. This syrup was dissolved in pyridine (200 ml) and heated at reflux temperature while hydrogen sulfide gas was slowly bubbled through for 1 hr. The reaction solution was then refluxed without the addition of H_2S for an additional 16 hr. The dark solution was evaporated *in vacuo* to a semisolid, azeotroped several times with ethanol, and then treated with 150 ml of methanol which had been previously saturated at −10° with ammonia. This mixture was allowed to stand for 18 hr at room temperature and then evaporated *in vacuo* to a semisolid. The semisolid was dissolved in 50 ml of water, the pH adjusted to 6 with concentrated HCl, and the solution allowed to stand in a covered beaker at room temperature for 2 days. The precipitate (800 mg) which had separated from solution and an additional 400 mg obtained by concentration of the filtrate gave a combined yield of 1.20 g (73%, mp 204–206°). This product was found to be identical with **7** prepared by the preceding method.

(27) (a) Nucleoside **14**: mp 203–205°; $[\alpha]^{27}D$ −19.6 (*c* 1.025, 60% ethanol), positive $\Delta\lambda_{min}$ value,[16,27b] small $\Delta\delta$ value.[16,27b] Nucleoside **15**: mp 200–201°,[5] $[\alpha]^{24}D$ −85.5 (*c* 0.415, 60% ethanol), negative $\Delta\lambda_{min}$ value,[16] large $\Delta\delta$ value. (b) K. R. Darnall and L. B. Townsend, *J. Heterocycl. Chem.*, **3**, 371 (1967).

(28) Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. The proton magnetic resonance spectra were obtained on a Varian A-60 high resolution spectrometer utilizing tetramethylsilane as an internal standard and the chemical shifts are expressed as δ from tetramethylsilane. The infrared spectra were recorded with a Beckman IR-5A spectrometer. The optical rotations were obtained with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

(29) Sodium metal (480 mg) was dissolved in 100 ml of anhydrous ethanol and this solution saturated with hydrogen sulfide gas (dried by passing it through saturated aqueous barium hydroxide, Woelm neutral alumina, and finally phosphorus pentoxide). This solution was evaporated *in vacuo* to a solid, diluted to the appropriate volume with anhydrous ethanol, and used as an ethanolic solution of sodium hydrogen sulfide.

6-Methoxy-7-(β-D-ribofuranosyl)purine (9).—A mixture of anhydrous methanol (12 ml) and 7-(β-D-ribofuranosyl)purine-6-thione (7, 2.0 g, previously dried at 110° for 2 hr) was stirred in an ethanol–Dry Ice bath at −40°. Chlorine gas was passed into this suspension until all the solid had dissolved while the bath temperature was maintained between −30 and −40° for about 20-min total time. Dry air was then bubbled through the solution at a moderate rate for 45 min while the bath temperature was maintained at −10°. The yellow solution was poured into 50 ml of anhydrous methanol which had been previously cooled to −10°. The pH of the solution was adjusted to 6 with Dowex 1 X-2 (200–400 mesh, hydroxide form, which had been washed with methanol) while the temperature was maintained below −5°. The resin was collected by filtration and washed well with methanol, and the combined filtrate and washings were evaporated *in vacuo* to a semisolid. The residue was dissolved in a minimum amount of methanol and allowed to evaporate to near dryness in a petri dish. The precipitate which had formed (1.5 g, 76%) melted at 180–185°. Two recrystallizations from water gave a product with a melting point of 205–206°, $[\alpha]^{26}D$ −2.2 (*c* 1.0, pyridine).

Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.57; H, 5.44; N, 19.68.

6-Ethoxypurine (8).—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (1, 2.0 g) was refluxed for 6 hr in 20 ml of diethoxymethylacetate. This solution was evaporated *in vacuo* to a syrup and the syrup dissolved in 1 *N* ethanolic sodium ethoxide and heated at reflux temperature for 15 hr. The solution was evaporated *in vacuo* to dryness, dissolved in 45 ml of water, and neutralized with concentrated hydrochloric acid. The solution was allowed to stand at room temperature for 24 hr and the precipitate of fine needles (445 mg, mp 225–226°) was collected by filtration (lit.[22] mp 224°).

6-Ethoxy-7-(β-D-ribofuranosyl)purine (5). **Method A.**—4-Amino-5-cyano-1-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (1, 1 g, 2.74 mmol) was heated at reflux temperature in 20 ml of diethoxymethylacetate for 6 hr. This solution was evaporated *in vacuo* to a syrup and the syrup was treated with ethanol (20 ml) in which 250 mg (10.96 mg-atoms) of sodium metal had been dissolved. The reaction mixture was allowed to stand at room temperature for 1 hr and then heated at reflux temperature for 1 additional hr. The dark solution was evaporated *in vacuo* to a semisolid, dissolved in 20 ml of water, and neutralized with concentrated hydrochloric acid. The solution was allowed to stand at room temperature for 24 hr and the precipitate (300 mg, 67%) collected by filtration, mp 218–220°. Recrystallization from water gave colorless needles, mp 220–222°, which were identical in all respects (mixture melting point, paper chromatography, uv spectra) with the product isolated as the minor component in the preparation of 7 from 1.

Method B.—6-Methylthio-7-(β-D-ribofuranosyl)purine (11, 215 mg) and 20 ml of ethanol in which 116 mg of sodium metal had been dissolved were refluxed for 45 min. The solution was evaporated *in vacuo* and the residue dissolved in a small amount of water. This solution was neutralized with concentrated hydrochloric acid and allowed to crystallize at room temperature, yield 190 mg (89%), mp 222°. This nucleoside was identical (uv spectra, paper chromatography, and mixture melting point) with the material isolated as the minor product in the preparation of 7 from 1.

7-(β-D-Ribofuranosyl)purine (12).—7-(β-D-Ribofuranosyl)-purine-6-thione (7, 2.0 g), W-7 Raney nickel (14 g), and water (80 ml) were heated for 6 hr at reflux temperature. The catalyst was collected by filtration and washed with 200 ml of boiling water, and the combined filtrate and washings were evaporated *in vacuo* to dryness. The solid was recrystallized from a small amount of water to give 1.2 g (72%) of 12: mp 172–173° (lit.[9] mp 184–185°); $[\alpha]^{27}D$ −36.7 (*c* 1.015, H_2O), (lit.[9] $[\alpha]^{28}D$ −37.8 (*c* 1, H_2O)).

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.98; H, 4.98; N, 22.35.

6-Methylthio-7-(β-D-ribofuranosyl)purine (11).—7-(β-D-Ribofuranosyl)purine-6-thione (7, 1.0 g) was suspended in 10 ml of water at room temperature and concentrated ammonium hydroxide added slowly until a clear solution had been effected. To this solution was added 1.0 ml of methyl iodide; the mixture was stirred at room temperature until precipitation ceased (about 30 min). The solid was collected (750 mg, 76%) by filtration and recrystallized from water to afford long white needles, mp 216–217°, $[\alpha]^{27}D$ + 30.1 (*c* 0.50, pyridine).

Anal. Calcd for $C_{11}H_{14}N_4O_4S$: C, 44.34; H 4.74; N, 18.80. Found: C, 44.35; H, 4.81; N, 18.76.

6-Dimethylamino-7-(β-D-ribofuranosyl)purine (14).—6-Methylthio-7-(β-D-ribofuranosyl)purine (11, 1.0 g) and 50 ml of anhydrous dimethylamine were heated at 125° for 6 hr in a stainless steel reaction vessel. The excess dimethylamine was allowed to evaporate at room temperature and pressure and the last traces of dimethylamine were removed by boiling with benzene. The solid was collected by filtration (960 mg, mp 183–185°, 91%) and recrystallized from water to afford colorless needles, mp 203–205°, $[\alpha]^{27}D$ + 19.6 (*c* 1.025, 60% ethanol).

Anal. Calcd for $C_{12}H_{17}N_5O_4 \cdot H_2O$: C, 46.00; H, 6.11; N, 22.35. Found: C, 46.20; H, 5.61; N, 22.11.

6-Methylamino-7-(β-D-ribofuranosyl)purine (13).—Experimental conditions similar to those used for the preparation of 14 were used for the preparation of 13 except that anhydrous methylamine rather than dimethylamine was used. This afforded 800 mg of crude product (82%), mp 213–216°, which on recrystallization from water gave 13, mp 235–236°.

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot H_2O$: C, 44.15; H, 5.73; N, 23.40. Found: C, 44.30; H, 5.76; N, 23.20.

Registry No.—2, 17289-59-7; 4, 23042-03-7; 5, 23042-04-8; 7, 20187-89-7; 8, 17861-06-2; 9, 2605-77-8; 11, 20223-77-2; 12, 2149-71-5; 13, 23042-09-3; 14, 23042-10-6.

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