nolic sodium methoxide being added in portions to maintain an alkaline pH. The resulting dark red-brown solution was evaporated *in vacuo* to a tan glassy residue which was crystallized by trituration with a small amount of water. The water was removed *in vacuo* and the residue was triturated with absolute ethanol and filtered to yield 1.76 g. of crude **4** as tan crystals, m.p. 200–209° dec. From the mother liquor an additional 0.706 g. was obtained, giving a total of 2.47 g. (85%). Recrystallizations from N,N-dimethylformamide gave colorless crystals, m.p. 234–236° dec.; $[\alpha]^{25}D$ −28.9° (*c* 1.04, H_2O); $\lambda_{max}^{pH\ 6.8}$ 215 mμ (ε 23,800), 256 mμ (ε 9,200), 279 mμ (ε 9,750).

Anal. Calcd. for $C_{10}H_{15}N_7O_3$: C, 42.7; H, 5.38; N, 34.9. Found: C, 43.1, 43.0; H, 5.65, 5.63; N, 34.7.

Acknowledgment.—We wish to thank Mr. L. Brancone and staff for the microanalyses, Mr. W. Fulmor and staff for spectroscopic and polarimetric determinations, Dr. A. Vogel for antitumor assays, Dr. R. I. Hewitt for antitrypanosome assays, and Mr. J. C. VanMeter for enzyme inhibition studies.

Synthesis and Reactions of 3′-Amino-3′-deoxyribosides of 6-Chloropurine

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Received December 10, 1962

Blocked 6-chloro-3′-aminonucleosides (**3**, **14**) were synthesized and found to be excellent intermediates for the preparation of analogs of the puromycin aminonucleoside (**7**). Chloride was displaced from **3** and **14** by primary and secondary amines in methanol with simultaneous removal of the O-benzoyl groups. Primary amines removed the N-phthaloyl group of **3**, whereas secondary amines opened the N-phthaloyl group to produce N,N,N′-trisubstituted phthalamides. Primary amines cleaved the latter phthalamides to produce unblocked 3′-amino-3′-deoxynucleosides. Diisopropylamine failed to displace chloride from **3** and failed to open the phthalimide function. Several analogs of the puromycin aminonucleoside were found to possess enhanced trypanocidal activity. The application of p.m.r. spectral measurements to determination of anomeric configuration in ribofuranoses is discussed.

9-(3-Amino-3-deoxy-β-D-ribofuranosyl)-6-dimethylamino-9H-purine (**7**),[1] the aminonucleoside from puromycin,[2-4] has trypanocidal[5,6] and tumor-inhibiting[7] properties in experimental animals. It was desirable, therefore, to synthesize structural variants of **7** in order to determine the relation of structure to biological activity.[8] Analogs of **7** have been synthesized in which the methylthio group was substituted for hydrogen at C-2,[9] amino was substituted for dimethylamino,[10] the aminosugar was varied,[11] and pyrimidines were substituted for the purine moiety.[12]

This paper is concerned with the synthesis of analogs of **7** by nucleophilic displacements on 6-chloronucleosides **3** and **14** by amines[8] and methoxide. 3′-Amino-3′-deoxyinosine,[13,14] 2,3′-diamino-3′-deoxyadenosine,[14,15] 3′-amino-3′-deoxyguanosine,[15] and 3′-amino-3′-deoxycrotonoside[16] were synthesized by other paths.

Of the several routes available for the synthesis of the desired 6-substituted aminonucleoside analogs of **7**, the condensation of the chloromercuri (and/or bismercury) derivative of purine, bearing the desired 6-substituent, with a suitably blocked aminosugar may be mentioned. Some limitations of this route, the one by which the aminonucleoside from puromycin has been synthesized,[16] are the following: (1) for each analog the condensation of a specifically substituted purine with an aminosugar is required; (2) each purine may require a number of steps for its synthesis; (3) the specifically substituted purine must orient the aminosugar to the 9-position; (4) the attachment of purine to aminosugar must be β; and (5) the 6-substituent must survive the rigorous condensation conditions.

To obviate these difficulties it was decided to synthesize, as an intermediate, a nucleoside bearing a chlorine atom in the 6-position since it was expected that the chlorine atom could be displaced by a wide variety of nucleophilic reagents to produce the desired analogs.[17]

Following the procedure of Brown and Weliky[18] for the synthesis of 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-6-chloro-9H-purine, according to the general method of Davoll and Lowy,[19] a mixture of chloromercuri-6-chloro-

(1) B. R. Baker, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, **76**, 2838 (1954).

(2) Stylomycin®.

(3) J. N. Porter, R. I. Hewitt, C. W. Hesseltine, G. Krupka, J. A. Lowery, W. S. Wallace, N. Bohonos, and J. H. Williams, *Antibiot. Chemotherapy*, **2**, 409 (1952).

(4) P. W. Fryth, C. W. Waller, B. L. Hutchings, and J. H. Williams, *J. Am. Chem. Soc.*, **80**, 2736 (1958).

(5) R. I. Hewitt, A. R. Gumble, W. S. Wallace, and J. H. Williams, *Antibiot. Chemotherapy*, **4**, 1222 (1954).

(6) E. J. Tobie and B. Highman, *Am. J. Trop. Med.*, **5**, 504 (1956).

(7) P. L. Bennett, S. L. Halliday, J. J. Oleson, and J. H. Williams, "Antibiotics Annual 1954–1955," Medical Encyclopedia, Inc., New York, N. Y., 1955, pp. 766–769.

(8) For a preliminary account of some of the material described in this paper see L. Goldman J. W. Marsico, and R. B. Angier, *J. Am. Chem. Soc.*, **78**, 4173 (1956).

(9) B. R. Baker, J. P. Joseph, and R. E. Schaub, *ibid.*, **77**, 5905 (1955).

(10) B. R. Baker, R. E. Schaub, and H. M. Kissman, *ibid.*, **77**, 5911 (1955).

(11) (a) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954); (b) F. J. McEvoy, B. R. Baker, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 209 (1960), and references cited therein.

(12) H. M. Kissman and M. J. Weiss, *ibid.*, **80**, 2575 (1958).

(13) L. Goldman, J. W. Marsico and M. J. Weiss, Abstiacts of Papers, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958, p. 23M.

(14) L. Goldman, J. W. Marsico, and M. J. Weiss, *J. Med. Chem.*, **6**, 410 (1963).

(15) H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *ibid.*, **6**, 407 (1963).

(16) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, **76**, 4044 (1954).

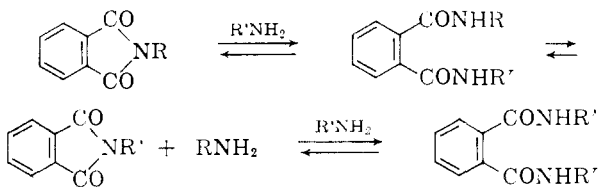
(17) When this investigation was initiated the displacement of halide from a halonucleoside by an amine had not been previously reported. The only displacements described were by ammonia; *cf.* E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914); J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951); see also ref. 18.

(18) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

(19) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **74**, 1563 (1952).

purine (**1a**) and bis(6-chloropurinyl)mercury (**1b**)[20,21] was condensed with 2,5-di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl chloride (**2**)[9] in boiling xylene to produce, in 92–100% yields, a glassy crude 6-chloro-3′-phthalimidonucleoside (**3**) varying in $[\alpha]_D$ from −9° to −45° in different experiments. The ultraviolet spectra showed that the sugar was attached only to the 9-position of the purine.[22,23] This crude product was crystallized from ethyl acetate–hexane to produce crystalline 9-(2,5-di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl)-6-chloro-9H-purine (**3**) solvated with ethyl acetate, $[\alpha]_D$ −62° to −68°, in yields of 46–69%. In the proton magnetic resonance spectrum[24] of **3** a signal was observed at 3.07 τ from the proton on the anomeric carbon which was split by the adjacent proton to produce a doublet with J = 4.5 c.p.s. From this evidence alone no anomeric assignment could be made[25] (*vide infra* for discussion of p.m.r. spectra).

The proof of structure of the chloronucleoside **3** was obtained by reaction with dimethylamine in methanol at 100° for 6 hr. in a sealed tube, conditions under which 6-chloropurine was smoothly converted by diethylamine to 6-diethylaminopurine.[26] Under these conditions chloride was displaced by dimethylamine, the O-benzoyl groups underwent transesterification with formation of methyl benzoate, and the phthalimide was aminolyzed to produce the phthalamide **6**.[27] The

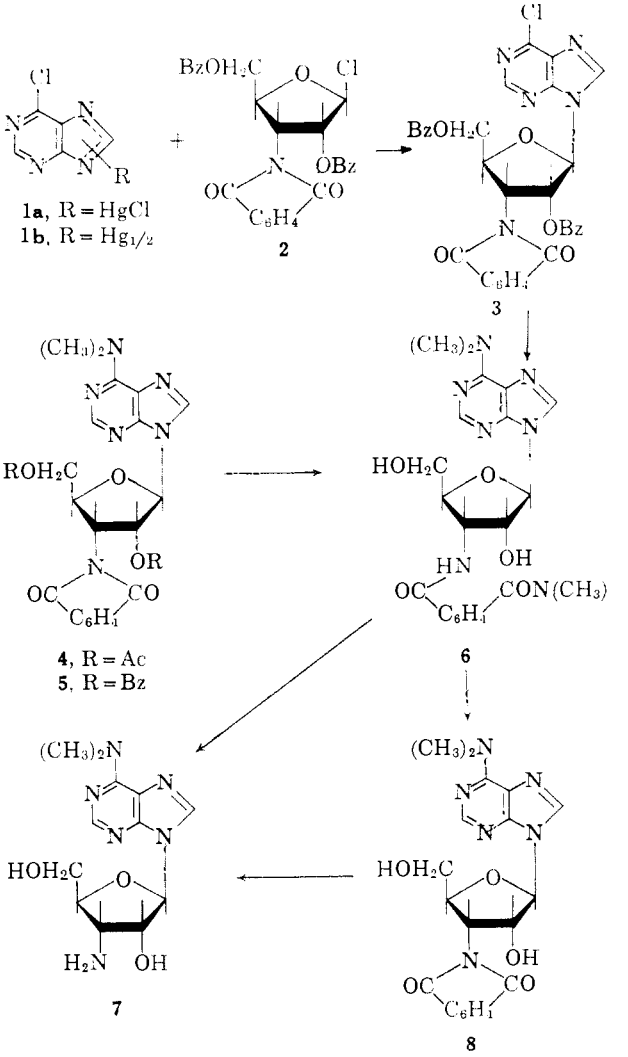


phthalamide **6** was obtained from 9-(2,5-di-O-acetyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl)-6-dimethylamino-9H-purine (**4**)[9] and the corresponding 2,5-di-O-benzoyl derivative **5**[9] under the same conditions. The phthalamide **6** was cyclized to the phthalimide **8**[9] in 58% yield by refluxing in N,N-dimethylformamide for 1 hr., dimethylamine being liberated.

Based on the finding that reaction of the blocked nucleoside **5** with refluxing methanolic butylamine for 16 hr. resulted in methanolysis and aminolysis with the formation of the aminonucleoside **7** in 89% yield (a 2 hr. reflux gave only 50% of **7**), methyl benzoate and N,N′-dibutylphthalamide,[27] and that reaction of the blocked nucleoside **8** with methanolic methylamine at 100° for 1.25 hr. in a sealed tube gave 83% of **7**, the phthalamide **6** was heated at 100° for 6 hr. with methanolic methylamine, affording 68% of **7**, identical with the aminonucleoside[1] from puromycin. Thus, the 6-chloro-3′-phthalimidonucleoside **3** is the β-anomer with the sugar attached to the 9-position of the purine.

The mother liquors from the crystalline chloronucleoside **3** were evaporated to non-crystalline residues varying in $[\alpha]_D$ from −7.9° to +52.3° in different experiments, and having infrared and ultraviolet spectra similar to **3**, indicating the possible presence of the α-anomer of **3**.

From numerous examples in the literature it is known that condensation of a 2-acyloxy-1-halo sugar with a heavy metal salt of a purine or pyrimidine gives, as the major product, a nucleoside where the purine or pyrimidine is *trans* to the 2-acyloxy group.[28,29] The forma-



(20) Utilizing the procedure of Davoll and Lowy (see ref. 19) for the preparation of chloromercuri derivatives of purines, a solution of 6-oxopurine in aqueous sodium hydroxide was treated with alcoholic mercuric chloride (*cf.* 18) to give a colorless crystalline product which, by elemental analysis, was a mixture of chloromercuri-6-chloropurine (**1a**) and bis(6-chloropurinyl)mercury (**1b**). The products of numerous runs varied in composition from 15% **1a** + 85% **1b** to 70% **1a** + 30% **1b**.

(21) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, *J. Org. Chem.*, **22**, 954 (1957), have described some vagaries observed in preparation of chloromercuri-6-chloropurine.

(22) *Cf.* J. M. Gulland and F. Story, *J. Chem. Soc.*, 692 (1938), and references cited for application of ultraviolet spectral data to assignment of carbohydrate moieties of purine nucleosides to the 7- or 9-positions of the purine ring.

(23) *Cf.* B. R. Baker, R. E. Schaub, and J. P. Joseph, *J. Org. Chem.*, **19**, 638 (1954).

(24) Proton magnetic resonance spectra were determined with a Varian Model A-60 spectrometer in deuteriochloroform. τ values were obtained in the usual manner with tetramethylsilane as internal standard.

(25) Calculations based on a Karplus type equation[23] [*cf.* plots by C. D. Jardetzky, *J. Am. Chem. Soc.*, **82**, 229 (1960), and H. Conroy, *Advan. Org. Chem.*, **2**, 311 (1960), for theoretical and observed values] coupled with the geometrical analysis of ribofuranose rings by Jardetzky,[25] leads to the unequivocal assignment of the β-configuration to that anomer with $J_{1-2} < 4.3$ c.p.s. Both α- and β-anomers can exhibit $J_{1-2} \geq 4.3$ c.p.s. (ϕ = 0° to 45° and 132° to 180°) and, therefore, where only one anomer of a pair is available, a configurational assignment cannot be made.

(26) 6-Substituted-aminopurines have been synthesized by reaction of 6-chloropurines with amines in refluxing butanol by J. W. Daly and B. E. Christensen, *J. Org. Chem.*, **21**, 177 (1956), and in refluxing 2-methoxyethanol by M. W. Bullock, J. J. Hand, and E. L. R. Stokstad, *J. Am. Chem. Soc.*, **78**, 3693 (1956).

(27) F. S. Spring and J. C. Woods, *Nature*, **158**, 754 (1946), and references cited therein, have shown that N-alkylphthalimides are readily opened by primary amines to N,N′-disubstituted phthalamides.

(28) The "C_1-C_2-*trans* rule" of Baker, *et al.*[11a]

(29) B. R. Baker, in G. E. W. Wolstenholm and C. M. O'Conner, "The Chemistry and Biology of Purines," J. and A. Churchill, Ltd., London, 1957, pp. 120–133.

tion of the anomeric nucleoside has been noted in several instances,[10,30] but always it was the minor product.

In one experiment the mother liquor gave a gum with $[\alpha]_D$ +29.0° which was chromatographed on alumina to give, in addition to more chloronucleoside **3**, a fraction containing the dextrorotatory 2,5-di-O-benzoyl-3-deoxy-3-phthalimido-D-ribofuranose (**9**).[9] Acetylation in pyridine gave an acetate **B**, m.p. 143–144° and $[\alpha]_D$ +127°, identical with the acetate obtained in the same manner by Baker, *et al.*,[9] and erroneously formulated by these investigators as the α-1-O-acetate **11**. This same acetate was obtained[9] by acetolysis of the blocked aminonucleoside **5** and by acetolysis of methyl 2,5-di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranoside.

Following the procedure of Baker, *et al.*,[9] the blocked aminonucleoside **5** was subjected to acetolysis to give 80% of acetate **B**, m.p. 144–147° and $[\alpha]_D$ +124°, and from the mother liquor 2% of an anomeric acetate **A**, m.p. 123.3–125° and $[\alpha]_D$ +157.5°. Using Hudson's isorotation rules[31] one can assign the α-1-O-acetate structure **11** to the most dextrorotatory anomer **A** and the β-1-O-acetate structure **10** to anomer **B**, obtained as the major product.

The above structural assignments were confirmed by examination of the p.m.r. spectra[24,32] of the anomeric acetates. In the spectrum of **A** a signal from the proton at C-1 was observed at 3.22 τ which was split by the proton at C-2 to produce a doublet with J_{1-2} = 4.8 c.p.s. Anomer **B** exhibited a signal from the C-1 proton at 3.47 τ as a singlet, and hence $J_{1-2} \leqslant 0.5$ c.p.s. Using a Karplus type equation[33] (eq. 1), but employing constants $J_0 = 9.26$ for $0° \leqslant \phi \leqslant 90°$ and $J_0 = 10.35$ for $90° \leqslant \phi \leqslant 180°$ as previously found suitable for furanose rings,[34] the appropriate dihedral angles (φ) between the H-(C-2)-(C-1) and (C-2)-(C-1)-H

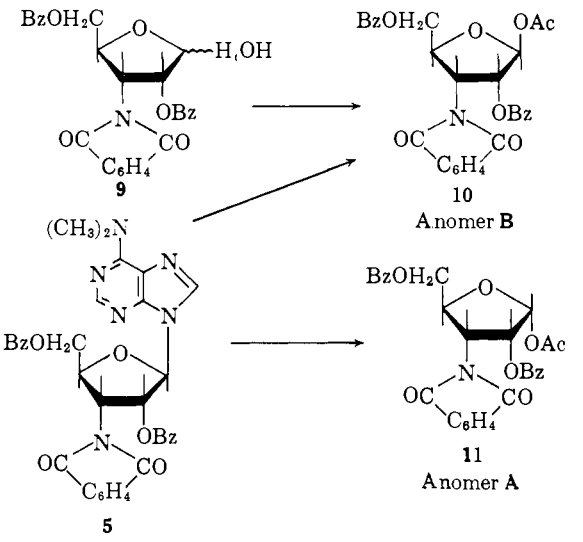
$$J = J_0 \cos^2 \phi - 0.28 \qquad (1)$$

planes were calculated. For anomer **A**, $\phi = 42°$ and for **B**, $\phi = 80$–$100°$.

From models, Jardetzky[35] has shown that in a ribofuranose ring the dihedral angle between the H-(C-2)-(C-1) and (C-2)-(C-1)-H planes in α-anomers [*cis* H-(C-1)-(C-2)-H configuration] can vary between 0° (planar) and 45° (maximally puckered) and in β-anomers [*trans* H-(C-1)-(C-2)-H configuration] from 120° (planar) to a minimum of 75° and a maximum of 165° (maximally puckered). Using eq. 1 and appropriate J_0 values[34] the calculated coupling constants are J_{1-2} = 9.0 to 4.3 c.p.s. for $\phi = 0°$ to 45° and J_{1-2} = 0.34, 2.3, and 9.4 c.p.s. for $\phi = 75°$, 120°, and 165°. For coupling constants where $J < 4.3$ c.p.s. eq. 1 gives values where $45° < \phi < 132°$ (for $J_{1-2} \sim 0$ c.p.s., ϕ = 80–100°), a range in which only β-anomers theoretically should fall. Where only one anomer of a pair is available and its $J_{1-2} \geqslant 4.3$ c.p.s., no configurational assignment can be made.[25]

In L-hydroxyproline and L-allohydroxyproline, nonrigid five-membered ring compounds, values reported for *cis* H-1, H-2 coupling are $J \geqslant 4.09$ c.p.s.[36] With adenosine-3′,5′ cyclic phosphate, having a half-chair conformation[37] of the ribose ring, a singlet is observed for the C-1 proton and hence for *trans* H-1, H-2 coupling $J \leqslant 1$ c.p.s.[35] Hexa-N-acetylneomycins *B* and *C* exhibit singlets for the C-1 proton ($J \leqslant 1$ c.p.s.) and were assigned the β-configuration at C-1 [*trans* H-(C-1)-(C-2)-H].[38] It is evident, therefore, that anomer **A** must have the α-1-O-acetate structure **11** and anomer **B** the β-1-O-acetate structure **10**, in agreement with conclusions drawn from Hudson's isorotation rules.

In an additional experiment the mother liquor from **3** was evaporated to a mixture of crystals and sirup which was fractionally crystallized from acetone and ether to give, in addition to more **3**, a colorless crystal-



line substance identical with "Compound A" of Kissman and Weiss.[12] The formula $C_{27}H_{19}NO_7$ was indicated by analysis. The p.m.r. spectrum was completely compatible with the ribal structure **12**; the olefinic C-1 proton exhibited a peak at 2.58 τ which was split by the allylic proton at C-3 into a doublet with J_{1-3} = 2.5 c.p.s.; the aromatic protons of the benzoyl and phthalimido groups were observed as a multiplet at 1.65–2.50 τ with intensity equivalent to 14 protons; the signal of the C-3 proton at 4.03 τ was split by the allylic proton at C-1 into a doublet with J_{1-3} = 2.5 c.p.s., which was split further by the C-4 proton into a quartet (J_{3-4} = 5 c.p.s.); the C-4 proton signal, seemingly a quartet centered at 4.75 τ, was split by the two C-5 protons into a triplet (J_{4-5} = 5.5 c.p.s.) which was split further by the C-3 proton into a doubled triplet (J_{3-4} = 5 c.p.s.); a two-proton signal from the C-5 protons, split by the C-4 proton, was observed as a doublet centered at 5.30 τ (J_{4-5} = 5.5 c.p.s.). The infrared spectrum confirmed the structural assignment. Absorption bands were exhibited by the phthalimido group at 5.61, 5.85, and 13.84 μ and by the benzoate groups at 5.78 and 7.86 μ. A shoulder at 5.73 μ was indicative of a vinyl benzoate and a band at 6.22 μ was assigned to the C=C stretching vibration.

The ribal **12** could arise by loss of chloride from 1-chlororibose **2** with formation of an anchimerically

(30) (a) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 2396 (1955); (b) H. M. Kissman and B. R. Baker, *ibid.*, **79**, 5534 (1957).

(31) C. S. Hudson, *ibid.*, **31**, 66 (1909); *cf.* W. Pigman, "The Carbohydrates," Academic Press, Inc., New York, N. Y., 1957, p. 70.

(32) R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961).

(33) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(34) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, cited by L. D. Hall, L. Hough, K. A. McLauchlan, and K. Pachler, *Chem. Ind.* (London), 1465 (1962).

(35) C. D. Jardetzky, *J. Am. Chem. Soc.*, **84**, 62 (1962).

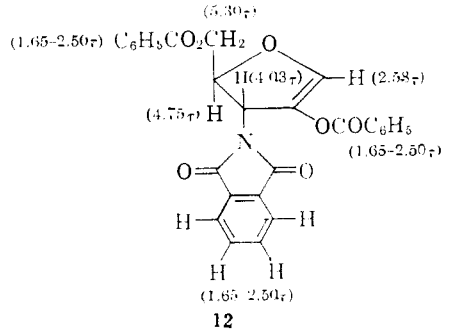
(36) R. J. Abraham and K. A. McLauchlan, *J. Mol. Phys.*, **5**, 195 (1962).

(37) F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, **81**, 4915 (1959).

(38) K. L. Rinehart, Jr., W. S. Chilton, M. Hickens, and W. v. Phillipsborn, *ibid.*, **84**, 3216 (1962).

assisted and resonance stabilized carbonium ion which then loses the C-2 proton.

The mixture of mercury derivatives **1a** and **1b** was condensed with 1-O-acetyl-3-acetamido-2,5-di-O-benzoyl-3-deoxy-D-ribofuranose (**13**)[16] in ethylene dichloride by treatment with titanium tetrachloride[39] to give 9-(3-acetamido-2,5-di-O-benzoyl-3-deoxy-D-ribofuranosyl)-6-chloro-9H-purine (**14**) as a glass in 75–87% yields and varying in $[\alpha]D$ from +38° to 48° in different experiments.



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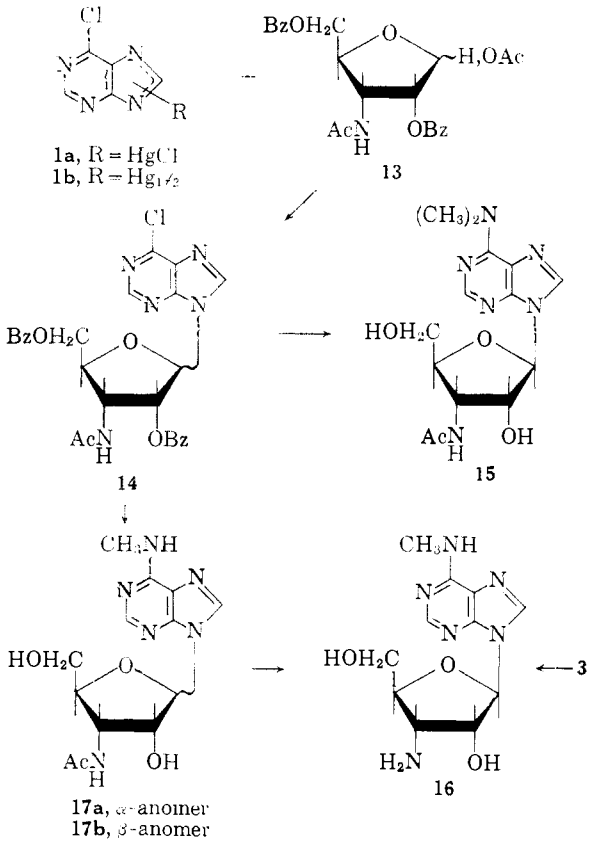
The ultraviolet spectra showed that the sugar was attached only to the 9-position of the purine.[22,23] That this material was an anomeric mixture was shown by reaction with methanolic methylamine to produce the crystalline α- and β-anomers **17a** and **17b** of 9-(3-acetamido-3-deoxy-D-ribofuranosyl)-6-methylamino-9H-purine in 15% and 26% yields, respectively. The less soluble α-anomer crystallized from the reaction mixture after removal of chloride ion by treatment with Amberlite IRA-400 (OH^-) resin. The material in the mother liquor was partitioned on Celite in chloroform–methanol–water (5:1:1 and 5:2:1) to yield the β-anomer from the percolate. Additional α-anomer, which remained on the column, was obtained by washing the column with methanol.

Barium hydroxide hydrolysis of the anomeric mixture of **17a** and **17b** gave the same crystalline 9-(3-amino-3-deoxy-β-D-ribofuranosyl)-6-methylamino-9H-purine (**16**) that was obtained in 84% yield by reaction of the 6-chloro-3′-phthalimidonucleoside **3** with methanolic methylamine.

Reaction of **14** with methanolic dimethylamine afforded 9-(3-acetamido-3-deoxy-β-D-ribofuranosyl)-6-dimethylamino-9H-purine (**15**), in 52% yield, identical with the N-acetyl derivative[16] of the aminonucleoside from puromycin.

A further interrelation of the two chloronucleosides **3** and **14** was obtained by refluxing the 6-chloro-3′-phthalimidonucleoside **3** with methanolic diethylamine to yield the phthalamide **18** which was aminolyzed with methanolic butylamine to yield 50% of 9-(3-amino-3-deoxy-β-D-ribofuranosyl)-6-diethylamino-9H-purine (**19**). The 6-chloro-3′-acetamidonucleoside **14** was refluxed with methanolic diethylamine to yield 47% of 9-(3-acetamido-3-deoxy-β-D-ribofuranosyl)-6-diethylamino-9H-purine (**20**). Barium hydroxide hydrolysis of **20** gave, in 62% yield based on **20** consumed, a deacetylated nucleoside identical with **19** from the 6-chloro-3′-phthalimidonucleoside **3**.

When the 6-chloro-3′-phthalimidonucleoside **3** was refluxed with methanolic sodium methoxide, chloride was displaced by methoxide, the benzoyl blocking groups were removed as methyl benzoate, and the phthalimide was opened to produce the sodium salt of the phthalamic acid **21**. This was cyclized to the 6-methoxy-3′-phthalimidonucleoside **23** in 39% yield by acidification with acetic acid followed by refluxing in N,N-dimethylformamide.

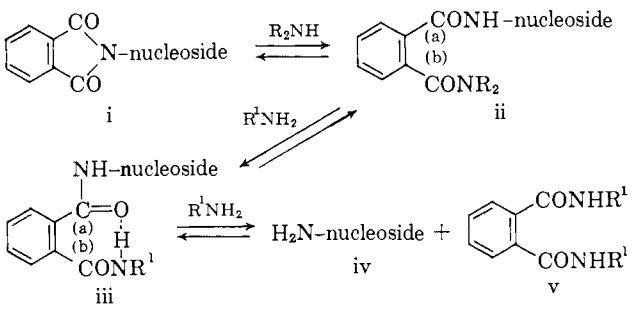


In an attempt to prepare the 6-diisopropylamino analog of **7**, the 6-chloro-3′-phthalimidonucleoside **3** was refluxed for 3 hr. with diisopropylamine in methanol, whereby the O-benzoates underwent transesterification and 6-chloro-9-(3-deoxy-3-phthalimido-β-D-ribofuranosyl)-9H-purine (**22**) was obtained. When more forcing conditions were tried (150° in a steel bomb for 5 hr.) the reaction product was found to consist of a mixture of the 6-methoxy-3′-phthalimidonucleoside **23** and diisopropylamine hydrochloride, resulting from displacement of chloride by solvent methanol.

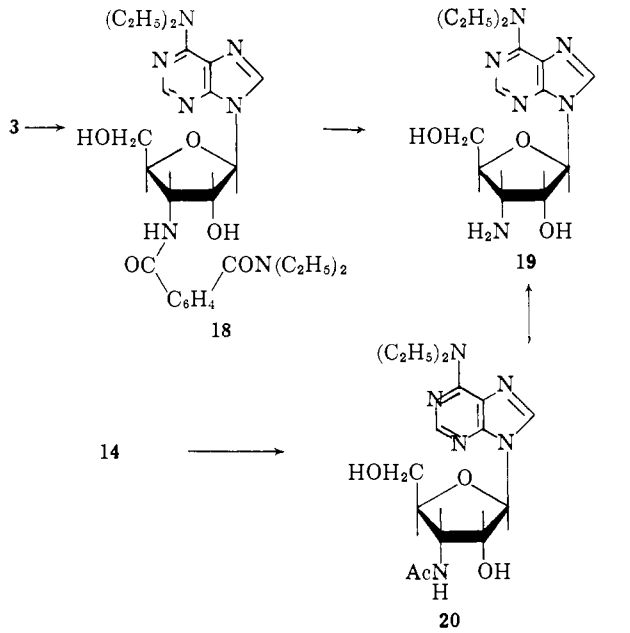
From the above experiments it may be seen that, in general, 6-chloronucleosides undergo displacement of chloride and O-acetates and O-benzoates are transesterified by the action of primary and secondary aliphatic amines in methanol. Phthalimidonucleosides are aminolyzed under these conditions, primary amines producing unblocked nucleosides and N,N′-dialkylphthalamides,[27] whereas secondary amines produce N,N,N′-trisubstituted phthalamides which are further aminolyzed by primary amines to give unblocked aminonucleosides.[40] Diisopropylamine, a sterically hindered

(39) Titanium tetrachloride was used for the condensation of **13** with chloromercuri-6-dimethylamino-2-methylthiopurine by Baker, *et al.*[16]; B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 12 (1955).

(40) A likely explanation for this finding is the following: the N,N,N′-trisubstituted-phthalamide (iii) is produced from the phthalimidonucleoside (i) and a secondary amine and, on treatment with a primary amine, ii suffers displacement on $C_{(a)}$ of the better leaving group (R_2N–) to produce the N,N′-disubstituted phthalamide (iii) which, being activated for nucleophilic attack on $C_{(a)}$ by hydrogen bonding, suffers displacement on $C_{(a)}$ by primary amine with formation of aminonucleoside (iv) and N,N′-disubstituted phthalamide (v).



amine, catalyzes the methanolysis of O-benzoates but fails to open phthalimides[41] and fails to displace chloride.



The product of the reaction of the 6-chloro-3′-phthalimidonucleoside **3** with methanolic cyclohexylamine was a glass exhibiting infrared bands at 5.80 and 6.08 μ, observed in the spectra of phthalamides such as **6**. It appears, therefore, that cyclohexylamine behaved in this reaction in the same manner as a secondary amine, possibly because of steric hindrance, producing the phthalamide **24**. When this product was heated with methanolic butylamine the unblocked 6-cyclohexylamino-3′-aminonucleoside **25** was obtained.

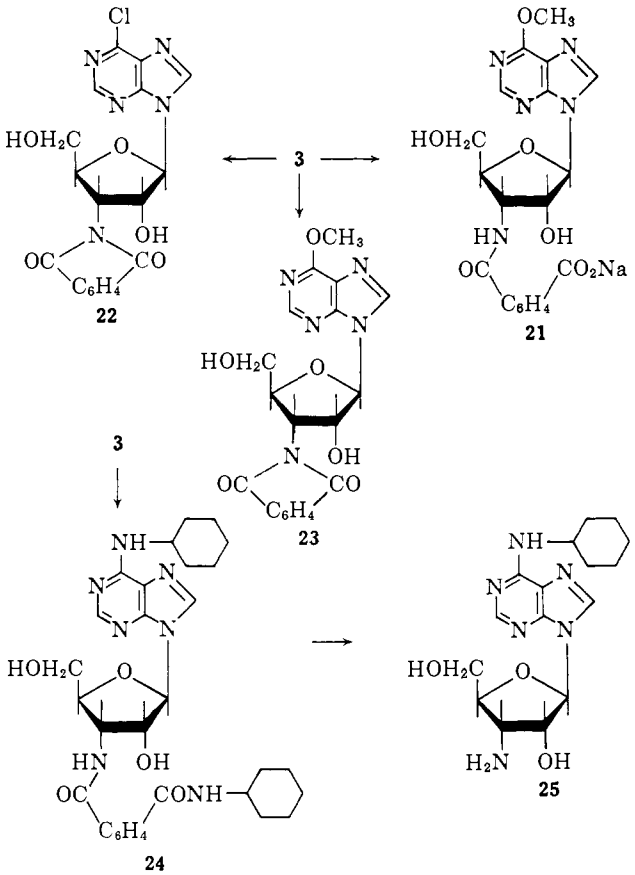
The aminonucleosides listed in Tables I and II were prepared by allowing the 6-chloro-3′-phthalimidonucleoside **3** to react with a number of primary and secondary amines in methanol.

The phthalamides v,[40] resulting from reaction of the 6-chloro-3′-phthalimidonucleoside **3** with isobutylamine, decylamine, and benzylamine, respectively, were isolated and characterized. N,N′-Diisobutylphthalamide was synthesized for comparison by reaction of phthalimide with aqueous isobutylamine.

The reaction of **3** with methanolic furfurylamine gave a product which was refractory to purification. The furfurylamino analog was obtained in 26% yield by reacting **3** with furfurylamine in refluxing 2-methoxyethanol followed by refluxing with methanolic butylamine.

(41) The selective reactivity of diisopropylamine in methanol was utilized in the synthesis of 3′-amino-3′-deoxyinosine,[13,14] 2,3′-diamino-3′-deoxyadenosine,[14,15] and 3′-amino-3′-deoxyguanosine.[15]

The ultraviolet absorption spectra of the 6-substituted-amino-3′-aminonucleosides were found to fall into two classes. The 6-monosubstituted amino derivatives had maxima at 262–264 mμ in 0.1 *N* hydrochloric acid, at 266–270 mμ in methanol or ethanol, and at 266–270 mμ in 0.1 *N* sodium hydroxide. The disubstituted amino derivatives, on the other hand, had maxima at 268–272.5 mμ in 0.1 *N* hydrochloric acid, 276–280 mμ in methanol or ethanol, and 276–281 mμ in 0.1 *N* sodium hydroxide.



Biological Activity.—Whereas the aminonucleoside **7** from puromycin was 4 times more active than puromycin against *Trypanosoma equiperdum* in the mouse, the 6-diethylamino, 6-(methyl)propylamino and 6-dipropylamino analogs were 16 times more active.[42] The most active 6-monoalkylamino analog was the 6-butylamino analog, 8 times as active as puromycin.[42] Against the transplanted mammary adenocarcinoma of the C_3H mouse there were no striking differences among the various aminonucleosides.[43] Against *Trypanosoma cruzi* in tissue culture, the dipropylamino analog was the most active analog.[44]

Experimental

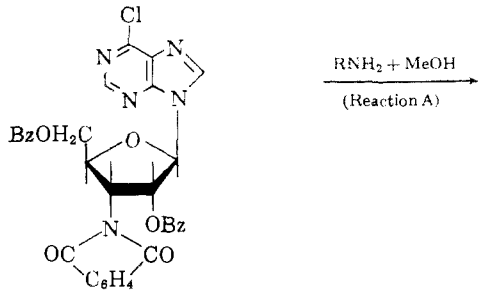
Melting points are corrected and were taken in soft glass capillaries. Ultraviolet spectra were determined on a Cary recording spectrophotometer (Model 11) and infrared spectra were determined on a Perkin—Elmer spectrophotometer (Model 21) in potassium bromide disks.

(42) R. I. Hewitt, A. R. Gumble, and H. Steinman, unpublished.

(43) J. J. Oleson and S. L. Halliday, unpublished.

(44) J. F. Fernandes, Laboratorio de Fisiologia Celular and Departmento de Parasitologia, Faculdade de Medicina, Universidade de São Paulo, Brasil, private communication; *cf.* L. H. P. Silva, S. Yoneda, and J. F. Fernandes, *Exptl. Parasitol.*, **8**, 486 (1959).

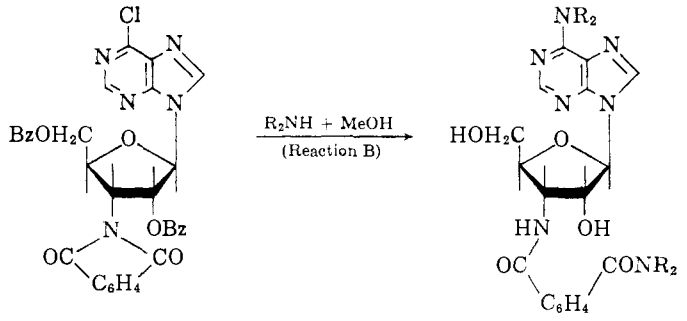
TABLE I



	Reaction A					Rotation			
	Temp.	Time, hr.	Yield, %	Recryst. solvent	M.p., °C.	α_D	Temp., °C.	Concn.	Solvent
NHC_4H_9	Reflux	12	31[a]	MeOH	177-178.5[b]	−43.7	25	0.87	EtOH
$NHCH_2CH(CH_3)_2$	Steam bath Sealed tube	6	56[c]	EtOH	175.5-176.5	−25.3	24	1.03	H_2O
NHC_6H_{13}	Reflux	16.5	40	$CHCl_3$	152.5-153.5	−39.1	25	1.07	MeOH
$NHC_{10}H_{21}$	Reflux	3.5	31[d]	EtOH	141-142	−40.0	25	1.00	EtOH
$NHCH_2C_6H_5$	Steam bath Sealed tube	2	50[e]	EtOH	177.5-178.5	−41.8	25	1.80	MeOH

[a] The deionized reaction mixture was chromatographed on 100 g. of Celite in 6:1:2 ethyl acetate–methanol–water, 35 10-ml. portions of eluate being collected. The nucleoside was obtained from fractions 5–18. [b] Sinters at 145°. [c] The evaporated reaction mixture was crystallized from aqueous ethanol to yield N,N′-diisobutylphthalamide. The evaporated residue from the deionized mother liquor was

TABLE II

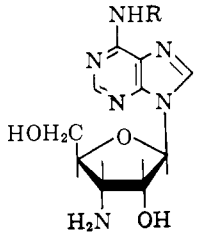


	Reaction B		Reaction C					
NR_2	Temp.	Time, hr.	RNH_2	Temp.	Time, hr.	Yield, %	Recryst. solvent	M.p., °C.
$N(CH_3)C_3H_7$	Reflux	2.5	$C_4H_9NH_2$	Reflux	15.75	68	EtOH + EtOAc	185-186
$N(C_2H_5)C_3H_7$	Reflux	5	$C_4H_9NH_2$	Reflux	15.75	63	MeOH + EtOAc	165-167
$N(C_3H_7)_2$	Steam bath sealed tube	6	CH_3NH_2	Steam bath sealed tube	6	49[a]	EtOAc	171.5-172.5
$N(CH_2CH{=}CH_2)_2$	Steam bath sealed tube	3.25	$C_4H_9NH_2$	Steam bath sealed tube	2	38	EtOH + EtOAc	164-167.5
$N(CH_3)C_6H_{11}$	Reflux	4	$C_4H_9NH_2$	Reflux	13	54	EtOH	181.5-182
$N(CH_3)CH_2CH_2CH(CH_3)_2$	Reflux	4.25	$C_4H_9NH_2$	Reflux	18.5	54	EtOH	176.5-177.5
$N(C_2H_5)C_4H_9$	Reflux	2.75	$C_4H_9NH_2$	Reflux	16.5	71	EtOH	178.5-179
$N(C_3H_7)C_4H_9$	Reflux	2.5	$C_4H_9NH_2$	Room	15.75	76	EtOH	185-186
$N(C_4H_9)_2$	Steam bath sealed tube	1.75	$C_4H_9NH_2$	Steam bath sealed tube	1.75	58[b]	EtOH	193-194
$N(C_6H_{11})_2$	Steam bath sealed tube	1.75	$C_4H_9NH_2$	Steam bath sealed tube	2	53	EtOH	175-176.5
$N(C_7H_{15})_2$	Steam bath sealed tube	2.25	CH_3NH_2	Steam bath sealed tube	2.75	62	EtOH	140-141
	Steam bath sealed tube	6	CH_3NH_2	Steam bath sealed tube	6	61[c]	MeOH	193-193.5

[a] The mother liquor from the first crop of crystals was freed of byproduct phthalamide v^{40} by absorption of the aminonucleoside on Amberlite IRC-50 (H^+) resin followed by elution with 3:1 ethanol–2 *N* ammonium hydroxide. Evaporation of this percolate gave

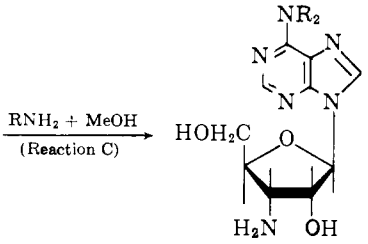
Acetolysis of 9-(2,5-Di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl)-6-dimethylamino-9*H*-purine (5) with Formation of 1-O-Acetyl-2,5-di-O-benzoyl-3-deoxy-3-phthalimido-α- and β-D-ribofuranoses (10 and 11).—The blocked aminonucleoside 5 (1839 g.) in 1.41 l. of acetic anhydride and 13 l. of glacial acetic acid was treated with 775 ml. of concd. sulfuric acid according to Baker, *et al.*,[9] to give 1186 g. (80%) of β-1-O-acetate (**10**) as colorless crystals, m.p. 144–147°, $[\alpha]_D^{25}$ +124° (*c* 1.23, $CHCl_3$). Concentration of the mother liquor gave 140 g. of colorless crystals, m.p. 117–122°, $[\alpha]_D^{25}$ +103° (*c* 1.09, $CHCl_3$). Three recrystallizations of a 10 g. sample from methanol afforded 2.03 g. (2%) of the α-1-O-acetate (**11**) as colorless crystals, m.p. 123.3–125°, $[\alpha]_D^{25}$ +157.5° (*c* 1.30, $CHCl_3$).

Anal. Calcd. for $C_{29}H_{23}NO_9$: C, 65.8, H, 4.38, N, 2.65.



Ultraviolet absorption maxima							Empirical formula	Elemental analyses					
0.1 *N* HCl		ROH			0.1 *N* NaOH			Carbon, %		Hydrogen, %		Nitrogen, %	
mμ	ε		mμ	ε	mμ	ε		Calcd.	Found	Calcd.	Found	Calcd.	Found
262.5	19,700	EtOH	268	18,600	269	19,300	$C_{14}H_{22}N_6O_3$	52.2	51.8	6.88	6.99	26.1	25.8
263.5	19,000	EtOH	268	17,700	268.5	18,000	$C_{14}H_{22}N_6O_3$	52.2	52.0	6.88	7.16	26.1	26.0
263	19,000	MeOH	267	17,500	267.5	17,500	$C_{16}H_{26}N_6O_3$	54.8	54.9	7.48	7.68	24.0	24.0
263	19,800	EtOH	268	18,000	268.5	17,700	$C_{20}H_{34}N_6O_3$	59.1	59.1	8.43	8.40	20.7	21.0
264	20,800	MeOH	270	20,600	270	21,200	$C_{17}H_{20}N_6O_3$	57.3	57.1	5.66	5.73	23.6	23.5

extracted with water and the nucleoside recovered from the aqueous solution. [d] The evaporated deionized reaction mixture was crystallized from methanol to yield N,N′-didecylphthalamide. The nucleoside was recovered from the mother liquor by crystallization. [e] The evaporated deionized reaction mixture was crystallized from ethanol to yield N,N′-dibenzylphthalamide. The nucleoside was recovered from the mother liquor by crystallization.



Product																	
Rotation				Ultraviolet absorption maxima						Empirical formula	Elemental analyses						
	Temp.,		Sol-	0.1 *N* HCl		MeOH		0.1 *N* NaOH			Carbon, %		Hydrogen, %		Nitrogen, %	
α_D	°C.	Concn.	vent	mμ	ε	mμ	ε	mμ	ε		Calcd.	Found	Calcd.	Found	Calcd.	Found
−48.5	25	0.95	EtOH	268	19,600	277	19,800	277	20,200	$C_{14}H_{22}N_6O_3$	52.2	52.3	6.88	6.64	26.1	25.9
−52.0	25	0.79	EtOH	270	19,900	278	20,200	279	20,200	$C_{15}H_{24}N_6O_3$	53.6	53.7	7.19	7.26	25.0	25.2
−45.0	24	1.00	MeOH	270	20,000	277.5	20,400	280	20,500	$C_{16}H_{26}N_6O_3$	54.8	54.7	7.48	7.46	24.0	24.2
−43.1	25	1.00	MeOH	269	19,400	276	21,800	277	21,300	$C_{16}H_{22}N_6O_3$	55.5	55.7	6.40	6.64	24.3	24.4
−48.6	25	0.39	EtOH	269	20,200	277	20,600	277	20,600	$C_{16}H_{26}N_6O_3$	54.8	55.1	7.48	7.21	24.0	23.9
−46.3	25	1.21	EtOH	269	18,700	277	19,700	278.5	19,900	$C_{16}H_{26}N_6O_3$	54.8	54.8	7.48	7.41	24.0	24.3
−50.1	25	1.02	EtOH	269.5	19,500	278	20,400	279	20,200	$C_{16}H_{26}N_6O_3$	54.8	55.1	7.48	7.80	24.0	24.3
−46.5	25	0.40	EtOH	270	19,800	278	20,400	280	20,500	$C_{17}H_{28}N_6O_3$	56.0	56.3	7.74	7.75	23.1	23.0
−38.8	26	0.51	MeOH	271	19,200	279	19,400	280	19,600	$C_{18}H_{30}N_6O_3$	57.1	57.2	7.99	8.05	22.2	22.5
−43.7	26	1.05	EtOH	271	20,000	279	20,600	280	20,400	$C_{20}H_{34}N_6O_3$	59.1	59.1	8.43	8.50	20.7	20.5
−36.9	25	2.22	EtOH	271	19,700	278	20,000	276	16,200	$C_{24}H_{42}N_6O_3$	62.3	62.4	9.15	9.44	18.2	18.3
−44.0	24	1.04	EtOH	272.5	17,900	280	22,500	281	22,400	$C_{15}H_{22}N_6O_3 \cdot 0.5 H_2O$	52.5	52.7	6.76	6.89	24.5	24.6

additional product. [b] Evaporation of the reaction mixture gave a crystalline residue which was recrystallized to give the nucleoside. Additional nucleoside was obtained after deionizing with Amberlite IRA-400(OH^-) resin. [c] The product crystallized directly from the cooled reaction mixture.

Found: C, 65.9; H, 4.68; N, 2.67.

By infrared spectral and optical rotation comparison, and by lack of melting point depression, the β-1-O-acetate 10 was identical with the 1-O-acetate of Baker, *et al.*,[9] of m.p. 138–140° and $[\alpha]_D^{25}$ +122° (*c* 0.5, $CHCl_3$), erroneously assigned the α-anomeric structure 11.

2,5-Di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl Chloride (2) from 1-O-Acetyl-2,5-di-O-benzoyl-3-deoxy-3-phthalimido-α-D-ribofuranose (11).—Dry hydrogen chloride gas was passed through an ice-cold suspension of 0.529 g. (0.001 mole) of **11** in 25 ml. of anhydrous ether containing 3 ml. of acetyl chloride. On standing overnight at 3° the solution deposited 0.255 g. of colorless crystals of **2**, m.p. 165–168° dec., $[\alpha]^{25}D$ +81.3° (*c* 1.11, dioxane).

Baker, *et al.*,[9] reported m.p. 160–162° dec. and $[\alpha]^{25}D$ +76.5° (*c* 1.1, dioxane) for **2** prepared from the β-1-O-acetate (**10**).

9-(2,5-Di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl)-6-chloro-9H-purine (3).—A stirred suspension of 21.6 g. (0.0621 mole) of a mixture[20,21] of 70% chloromercuri-6-chloropurine (**1a**) and 30% bis(6-chloropurinyl)mercury (**1b**) in 725 ml. of xylene was dried by distillation into a Dean and Stark trap. To the refluxing anhydrous suspension a hot solution of 28.7 g. (0.0565 mole) of 2,5-di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl chloride (**2**)[9] in 270 ml. of anhydrous xylene was added and the reaction mixture was stirred and refluxed for 5 hr. The hot suspension was filtered and the small amount of precipitate was washed with hot chloroform. The combined filtrate and washings were washed with two 100-ml. portions of 30% potassium iodide and three 100-ml. portions of water and dried over magnesium sulfate. Evaporation to dryness *in vacuo* gave 34.7 g. (97%) of a residual nearly colorless glass, $[\alpha]^{25}D$ −44.9° (*c* 1.56, $CHCl_3$).

Crystallization from ethyl acetate–hexane with the aid of Norit gave pale yellow crystals which were washed with hexane, air-dried overnight, and finally dried at 53° (0.01 mm.) for 6 hr. The yield of **3**, solvated with 0.5 mole of ethyl acetate, was 25.1 g. (66%); it sintered at 67–69° to an opaque glass and melted at 98–106° to a clear glass; $[\alpha]^{25}D$ −61.6° (*c* 2.01, $CHCl_3$). $\lambda_{max}^{0.1\ N\ HCl}$ 264 mμ (ε 12,100); λ_{max}^{MeOH} 265 mμ (ε 11,800); $\lambda_{max}^{0.1\ N\ NaOH}$ 264 mμ (ε 11,600).

Anal. Calcd. for $C_{32}H_{22}ClN_5O_7 \cdot 0.5EtOAc$: C, 61.1; H, 3.92; Cl, 5.31; N, 10.5; O–C_2H_5, 2.08. Found: C, 60.8; H, 3.91; Cl, 5.36; N, 11.4, 11.2; O–C_2H_5, 2.27.

The mother liquor was evaporated *in vacuo* to yield 8.70 g. of a yellow-tan glass, $[\alpha]^{26}D$ +4.1° (*c* 2.22, $CHCl_3$).

The presence of ethyl acetate of solvation was confirmed by p.m.r. spectral analysis on a sample of **3** with the following elemental and group analyses:

Anal. Calcd. for $C_{32}H_{22}ClN_5O_7 \cdot 0.3EtOAc$: C, 61.3; H, 3.78; Cl, 5.45; N, 10.8; O–C_2H_5, 1.34. Found: C, 60.9; H, 4.03; Cl, 5.61; N, 10.6; O–C_2H_5, 1.43.

The p.m.r. spectrum[24] of this sample showed a quartet centered at 5.82 τ, a singlet at 7.95 τ, and at riplet centered at 8.75 τ which, by integration, gave a proton count (using the aromatic region for calibration) equivalent to about 0.4 mole of ethyl acetate.

The condensation of 6.84 g. (0.025 mole) of a mixture of 17.5% **1a** and 82.5% **1b** with 11.86 g. (0.0232 mole) of **2** gave 13.36 g. (92%) of a pale yellow glass, $[\alpha]^{24}D$ −9.05° (*c* 2.10, $CHCl_3$): $\lambda_{max}^{0.1\ N\ HCl}$ 262 mμ (ε 9480); λ_{max}^{EtOH} 264 mμ (ε 8590); $\lambda_{max}^{0.1\ N\ NaOH}$ 264 mμ (ε 8590).

Anal. Calcd. for $C_{32}H_{22}ClN_5O_7$: C, 61.6; H, 3.56; Cl, 5.68; N, 11.2. Found: C, 64.4; H, 4.32; Cl, 4.02; N, 8.01; ash, 0.47.

Crystallization from ethyl acetate–hexane with the aid of Norit, followed by drying at 56° (0.01 mm.) for 4 hr., gave 7.18 g. (46%) of colorless long prisms of **3** (solvated with 0.5 mole of ethyl acetate); it sintered at 76–77° to an opaque glass and melted at 100–105° to a clear glass; $[\alpha]^{24}D$ −60.9° (*c* 2.04, $CHCl_3$): $\lambda_{max}^{0.1\ N\ HCl}$ 263 mμ (ε 12,100); λ_{max}^{MeOH} 263 mμ (ε 10,700); $\lambda_{max}^{0.1\ N\ NaOH}$ 263 mμ (ε 10,700).

Anal. Calcd. for $C_{32}H_{22}ClN_5O_7 \cdot 0.5EtOAc$: C, 61.1; H, 3.92; Cl, 5.31; N, 10.5. Found: C, 61.1; H, 3.69; Cl, 5.07; N, 10.4.

The mother liquor was evaporated *in vacuo* to yield a residual glass which was dissolved in ethyl acetate and filtered through Celite. Evaporation in a stream of nitrogen gave 5.10 g. of a tan-yellow glass, $[\alpha]^{26}D$ +52.3° (*c* 2.04, $CHCl_3$).

Condensation of 82.2 g. (0.237 mole) of a mixture of 68% **1a** and 32% **1b** with **2** derived from 114 g. (0.215 mole) of β-1-O-acetate (**10**) gave 129 g. (96%) of a glass, $[\alpha]^{25}D$ −32.9° (*c* 2.01, $CHCl_3$). Recrystallization from ethyl acetate gave 96 g. (69%) of **3** (solvated with 1/3 mole of ethyl acetate), $[\alpha]^{25}D$ −59.3° (*c* 2.04, $CHCl_3$). The mother liquor was evaporated *in vacuo* to yield 39.0 g. of a brown gum, $[\alpha]^{26}D$ +29.0° (*c* 2.14, $CHCl_3$).

A solution of 4.59 g. of the gum in 40 ml. of benzene was chromatographed on 110 g. of neutral alumina.[45] The column was successively eluted with benzene, solutions of ethyl acetate in benzene of increasing ethyl acetate content, ethyl acetate, and finally with ethanol. The eluates were collected in 100-ml. fractions and evaporated to dryness *in vacuo*. The 20% ethyl acetate:80% benzene eluate (cuts 4–12) gave 1.70 g. of a colorless glass, $[\alpha]D^{25}$ −18.4° (*c* 1.03, $CHCl_3$), which was crystallized from ethyl acetate to afford 0.632 g. (4%) of colorless crystals of **3** (solvated with 0.4 mole of ethyl acetate), which sintered at 59–63° to an opaque glass and melted at 110° to a clear glass; $[\alpha]^{26}D$ −62.5° (*c* 1.06, $CHCl_3$).

Anal. Calcd. for $C_{32}H_{22}ClN_5O_7 \cdot 0.4EtOAc$: C, 61.2; H, 3.85; Cl, 5.38; N, 10.6; O–C_2H_5, 1.76. Found: C, 61.0; H, 3.90; Cl, 5.17; N, 10.3; O–C_2H_5, 1.88.

Isolation of 2,5-Di-O-benzoyl-3-deoxy-3-phthalimido-D-ribofuranose (9).—Cut 16, an ethyl acetate eluate, was evaporated *in vacuo* to give 0.530 g. of crude **9**[9] as a colorless gum, $[\alpha]^{25}D$ +98.9° (*c* 1.03, $CHCl_3$), which gave a positive Benedict test. Acetylation of 0.360 g. of this material according to Baker, *et al.*,[9] gave 0.269 g. of 1-O-acetyl-2,5-di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranose (**10**) as pale green crystals, m.p. 142–143°. Recrystallization from methanol with the aid of Norit gave 0.202 g. of colorless crystals, m.p. 143–144°, $[\alpha]^{25}D$ +127° (*c* 0.542, $CHCl_3$).

Isolation of 2,5-Di-O-benzoyl-3-deoxy-3-phthalimido-D-ribal (12).—Condensation of 404 g. (1.04 mole) of chloromercuri-6-chloropurine[46] with 479 g. (0.95 mole) of **2** gave 614 g. (98%) of a gum. Recrystallization from ethyl acetate gave 350 g. (57%) of **3** (solvated with 0.25 mole of ethyl acetate), which sintered at 60–62° to an opaque glass and melted at 100–110° to a clear glass. The mother liquor was evaporated *in vacuo* to a gum. Crystallization of the gum from ethyl acetate–hexane gave 18.0 g. of gray crystals of a mixture of chloronucleoside **3** and ribal **12**. Evaporation of the mother liquor *in vacuo* to a mixture of crystals and syrup and dilution with acetone–ether (1:1) gave a second crop of 27.8 g. of crystals of a mixture of **3** and **12**. On standing the mother liquor deposited 8.80 g. of colorless needles of **12**, m.p. 146–148°. Recrystallization from ethyl acetate–ethanol gave 7.18 g. of **12** as colorless needles, m.p. 147.5–148°, $[\alpha]D^{25}$ +197° (*c* 2.03, $CHCl_3$).

Anal. Calcd. for $C_{25}H_{19}NO_7$: C, 69.1; H, 4.08; N, 2.98. Found: C, 69.4; H, 4.29; N, 3.13.

By comparison of infrared spectra and lack of melting point depression **12** was found to be identical with "Compound A," m.p. 140–141° and $[\alpha]D^{25}$ −202° (*c* 1.03, $CHCl_3$), of Kissman and Weiss.[12]

6-Dimethylamino-9-[3-deoxy-3-(o-N,N-dimethylcarbamoyl)-benzamido-β-D-ribofuranosyl]-9H-purine (6). A. From 9-(2,5-Di-O-acetyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl)-6-dimethylamino-9H-purine (4).—A mixture of 0.508 g. (0.001 mole) of **4**,[9] 1 ml. (0.68 g., 0.015 mole) of dimethylamine, and 20 ml. of anhydrous methanol was heated in a sealed tube on a steam bath for 2 hr. The resulting pale yellow solution was evaporated *in vacuo* to yield 0.485 g. (103%) of **6** as a nearly colorless glassy residue.

B. From 9-(2,5-di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl)-6-dimethylamino-9H-purine (5).—The reaction of 0.500 g. (0.78 mmole) of **5** hemihydrate[9] with 0.67 ml. (0.455 g., 1 mmole) of dimethylamine and 5 ml. of anhydrous methanol in a sealed tube on a steam bath for 6 hr. gave 0.364 g. (101%) of **6** as a colorless glass; $\lambda_{max}^{0.1\ N\ HCl}$ 267.5 mμ (ε 19,100); λ_{max}^{EtOH} 264 mμ (ε 19,400); $\lambda_{max}^{0.1\ N\ NaOH}$ 265 mμ (ε 19,500); λ_{max}^{KBr} 5.80, 6.05 μ.

9-(3-Deoxy-3-phthalimido-β-D-ribofuranosyl)-6-dimethylamino-9H-purine (8).—A solution of 0.173 g. (0.369 mmole) of phthalamide **6** in 5 ml. of N,N-dimethylformamide was refluxed for 1 hr. (strong odor of dimethylamine) and the resulting solution was cooled and poured into 50 ml. of water to produce a colorless precipitate. The suspension was chilled and filtered, and the colorless precipitate was washed with water and dried at 100° for 1 hr. The yield of **8**, m.p. 283–285° dec., was 0.091 g. (58%). Admixture with an authentic sample of **8**[9] did not depress the melting point.

9-(3-Amino-3-deoxy-β-D-ribofuranosyl)-6-dimethylamino-9H-purine (7). A. Reaction of 6-Chloro-3′-phthalimidonucleoside (3) with Methanolic Dimethylamine and then with Methanolic Methylamine.—A mixture of 0.969 g. (0.00145 mole) of **3** (solvated with 0.5 mole of ethyl acetate), 1.0 ml. (0.68 g., 0.015 mole) of dimethylamine, and 5 ml. of anhydrous methanol in a sealed tube was heated on a steam bath for 6 hr. The tube was cooled and opened and 2.1 ml. of an anhydrous methanol solution of 0.24

(45) Alumina was prepared by adding sulfuric acid to a stirred aqueous suspension of aluminum oxide (Merck) until the supernatant liquid had a pH of 4. The alumina was then washed well with water, air-dried, and activated at 170° overnight.

(46) Prepared by the "inverse" procedure of J. J. Fox; *cf.* ref. 21.

g. (0.0077 mole) of methylamine was added. The tube was resealed and heated on a steam bath for 6 hr. Chilling produced nearly colorless crystals which were collected by centrifugation, washed with methanol, and dried *in vacuo;* weight 0.368 g., m.p. 209–211° (with previous sintering). Recrystallization from absolute ethanol gave 0.258 g. of colorless crystals of **7,** m.p. 218–220°. A mixture m.p. with an authentic sample[1] of **7,** m.p. 219–221°, was 219–221°.

B. From 9-(2,5-Di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl)-6-dimethylamino-9H-purine (5) and Butylamine in Methanol.—A mixture of 1.000 g. (0.00156 mole) of **5** hemihydrate, 1.2 ml. (0.89 g., 0.012 mole) of butylamine, and 10 ml. of anhydrous methanol was refluxed on a steam bath for 16 hr. The resulting solution was evaporated to dryness on a steam bath and the crystalline residue was slurried with ethyl acetate and ether, removed by filtration, and washed with ethyl acetate and ether. The yield of **7,** m.p. 219.5–220°, was 0.410 g. (89%).

C. From 9-(3-Deoxy-3-phthalimido-β-D-ribofuranosyl)-6-dimethylamino-9H-purine (8) and Methylamine in Methanol.—A mixture of 1.00 g. (0.00236 mole) of **8**, 0.367 g. (0.0118 mole) of methylamine, and 7 ml. of anhydrous methanol in a sealed tube was heated on a steam bath for 1.25 hr. Complete solution was obtained after about 15 min., and then near the end of the heating period crystals deposited. The chilled reaction mixture was diluted with ethyl acetate and filtered to remove 0.806 g. of colorless crystals. Recrystallization from aqueous ethanol gave 0.495 g. of colorless crystals, m.p. 220–221°, which did not depress the melting point of an authentic sample of **7**. The mother liquor, when concentrated, gave an additional 0.079 g. of **7,** m.p. 213–218°; total, 0.574 g. (83%).

D. From Phthalamide 6 and Methylamine in Methanol.—A solution of 0.174 g. (0.000369 mole) of **6** and 0.114 g. (0.00369 mole) of methylamine in 5 ml. of anhydrous methanol in a sealed tube was heated on a steam bath for 5.5 hr. Evaporation to dryness *in vacuo*, followed by washing with ether, gave 0.136 g. of a nearly colorless crystalline residue, m.p. 181–194°. Recrystallization from ethanol gave, in two crops, 0.071 g. (65%) of colorless crystals of **7,** m.p. 215–220°, which did not depress the melting point of an authentic sample of m.p. 219–221°.

9-(3-Acetamido-2,5-di-O-benzoyl-3-deoxy-D-ribofuranosyl)-6-chloro-9H-purine (14).—To a stirred mixture of 7.60 g. (0.0169 mole) of 1-O-acetyl-3-acetamido-2,5-di-O-benzoyl-3-deoxy-D-ribofuranose (**13**)[16] and 5.85 g. (0.0211 mole) of a mixture[20,21] of 17.5% chloromercuri-6-chloropurine (**1a**) and 82.5% bis(6-chloropurinyl)mercury (**1b**) in 325 ml. of anhydrous ethylene dichloride at room temperature, 2.32 ml. (4.00 g., 0.0211 mole) of titanium tetrachloride was added dropwise. The resulting suspension was stirred and refluxed for 20 hr., chilled, and 300 ml. of cold 0.1 *N* hydrochloric acid added in 4 portions. Stirring was continued for 15 min. at room temperature and the mixture was then filtered. The precipitate was washed well with hot chloroform and the combined filtrate and washings were shaken well and the layers separated. The organic phase was washed with 60 ml. of water, 60 ml. of 30% potassium iodide, and 60 ml. of water, and dried over magnesium sulfate. Evaporation to dryness *in vacuo* gave 7.77 g. (85%) of **14** as a light tan glass; $[\alpha]^{24.5}D$ +39.2° (*c* 0.97, EtOH); $\lambda_{max}^{0.1\ N\ HCl}$ 233 mμ (ε 27,500), 265 mμ (ε 7890); λ_{max}^{EtOH} 230 mμ (ε 28,400), 264 mμ (ε 8300); $\lambda_{max}^{0.1\ N\ NaOH}$ 265 mμ (ε 7840).

Anal. Calcd. for $C_{26}H_{22}ClN_5O_6$: C, 58.3; H, 4.14; Cl, 6.62; N, 13.1. Found: C, 57.8; H, 4.52; Cl, 6.59; N, 11.4, 11.1.

Other runs gave **14** in 75–87% yield with $[\alpha]D$ +38.1° to +48.5° and % Cl, 5.24–8.23; % N, 8.14–14.8.

9-(3-Acetamido-3-deoxy-α- and β-D-ribofuranosyl)-6-methylamino-9H-purine (17a, 17b).—A mixture of 5.71 g. (0.0106 mole) of 6-chloro-3′-acetamidonucleoside (**14**), 3.35 g. of methylamine and 44 ml. of anhydrous methanol in a sealed tube was heated on a steam bath for 2 hr. The dark red-brown solution was evaporated to dryness *in vacuo* and the residue was twice evaporated to dryness with water *in vacuo*. A solution of the residue in 100 ml. of 1:1 methanol–water was stirred for 1 hr. with 15 g. of Amberlite IRA-400 (OH^-) resin and the filtered solution was evaporated to dryness *in vacuo*. The residue was evaporated to dryness *in vacuo*. The residue was evaporated to dryness *in vacuo* several times with absolute ethanol. The residue, 4.71 g., was crystallized from methanol to yield, in two crops, 0.869 g. of nearly colorless crystals, m.p. 214–223°. Recrystallization from methanol with the aid of Norit gave 0.145 g. of colorless crystals of the α-anomer **17a,** m.p. 252–257° dec.

The combined mother liquors from the α-anomer were evaporated to dryness *in vacuo* to yield a dark gummy residue which was partitioned on 120 g. of Celite in the system 5:1:1 chloroform–methanol–water; the column was eluted with the lower phase and 34 portions (10-ml.) of eluate were collected. The column then was eluted with the lower phase of the system 5:2:1 chloroform–methanol–water, 38 portions (10-ml.) of eluate being collected; and the column was finally eluted with methanol, a 176-ml. and 22 portions (10-ml.) of eluate being collected. Combined eluates 34–64 were evaporated to dryness *in vacuo* to give 0.886 g. (26%) of β-anomer **17b.** Combined eluates 73 and 74 were evaporated to dryness *in vacuo* to yield 0.367 g. of α-anomer **17a,** giving a total of 0.512 g. (15%).

The α-anomer **17a** was recrystallized several times from methanol to give colorless needles (containing 0.25 mole of water), m.p. 259–260° dec.; $[\alpha]^{28}D$ +114° (*c* 1.02, H_2O); $\lambda_{max}^{0.1\ N\ HCl}$ 262.5 mμ (ε 18,400); $\lambda_{max}^{H_2O}$ 264 mμ (ε 17,900); $\lambda_{max}^{0.1\ N\ NaOH}$ 265 mμ (ε 17,300).

Anal. Calcd. for $C_{13}H_{18}N_6O_3 \cdot 0.25H_2O$: C, 47.8; H, 5.70; N, 25.7. Found: C, 47.8; H, 6.03; N, 26.1.

The β-anomer **17b** was recrystallized several times from methanol to give colorless crystals (containing 0.25 mole of water), m.p. 232–233° dec.; $[\alpha]^{28}D$ −2.0° (*c* 1.05, H_2O); $\lambda_{max}^{0.1\ N\ HCl}$ 262.5 mμ (ε 18,000); $\lambda_{max}^{H_2O}$ 265 mμ (ε 16,700); $\lambda_{max}^{0.1\ N\ NaOH}$ 266 mμ (ε 17,000).

Anal. Calcd. for $C_{13}H_{18}N_6O_3 \cdot 0.25H_2O$: C, 47.8; H, 5.70; N, 25.7. Found: C, 48.0; H, 6.05; N, 26.0.

9-(3-Amino-3-deoxy-β-D-ribofuranosyl)-6-methylamino-9H-purine (16). A. From 6-Chloro-3′-phthalimidonucleoside 3.—A mixture of 6.68 g. (0.01 mole) of **3** (containing 0.5 mole of ethyl acetate), 4 g. (0.13 mole) of methylamine, and 85 ml. of anhydrous methanol in a sealed tube was heated on a steam bath for 4 hr. The resulting solution, when allowed to stand overnight at room temperature, deposited crystals which, after chilling, were removed by filtration and washed with ether, water, and ether and dried at 100°. The yield of colorless crystals of **16,** m.p. 231–234° (sinters 229°), was 1.02 g. The combined filtrate and washings were evaporated to dryness *in vacuo* and the residue was evaporated several times with aqueous ethanol to ensure removal of methyl benzoate. A solution of the residual amber gum in 1:1 methanol–water was stirred with Amberlite IRA-400 (OH^-) resin for 30 min. and evaporated to dryness *in vacuo*. Crystallization from absolute ethanol gave 1.11 g. of **16** as colorless crystals, m.p. 227–233°. From the mother liquor an additional 0.23 g. of **16,** m.p. 199–216°, was obtained; total yield, 2.36 g. (84%). When recrystallized from aqueous ethanol colorless crystals were obtained, m.p. 231.5–233.5°; $[\alpha]^{24}D$ −29.5° (*c* 1.02, H_2O); $\lambda_{max}^{1.0\ N\ HCl}$ 262.5 mμ (ε 17,600); λ_{max}^{EtOH} 267.5 mμ (ε 16,000); $\lambda_{max}^{0.1\ N\ NaOH}$ 267.5 mμ (ε 16,600).

Anal. Calcd. for $C_{11}H_{16}N_6O_3$: C, 47.1; H, 5.75; N, 30,0. Found: C, 46.9; H, 6.13; N, 29.4, 29.3.

B. Barium Hydroxide Hydrolysis of 9-(3-Acetamido-3-deoxy-D-ribofuranosyl)-6-methylamino-9H-purine (17a and 17b).—A solution of 8.11 g. (0.0207 mole) of a mixture of **17a** and **17b** in 150 ml. of saturated aqueous barium hydroxide was heated on a steam bath for 1 hr. Excess carbon dioxide was added and the precipitated barium carbonate was removed by filtration. The filtrate was evaporated to dryness *in vacuo* and the residue was dissolved in 200 ml. of absolute ethanol, filtered to remove a precipitate, and evaporated to dryness *in vacuo* to yield a residual brown glass. A solution of the glassy residue in 30 ml. of 1:1 methanol–water was percolated through a column of 20 g. of Amberlite IRC-50 (H^+) resin and the resin column was washed with 8 100-ml. portions of 1:1 methanol–water, the final eluate showing negligible absorption at 275 mμ. The combined eluates were evaporated to dryness *in vacuo* to yield 4.71 g. of a residual brown glass consisting mainly of recovered starting material. The resin column was then washed with six 100-ml. portions of 1:1 methanol–0.6 *N* ammonium hydroxide, the final eluate showing negligible absorption at 277 mμ. The combined eluates were evaporated to dryness *in vacuo* to yield 0.791 g. of residual crystals and glass.

This residue was partitioned on 22 g. of Celite in the system 5:2:1 chloroform–methanol–water and the column was eluted with lower phase; 18 portions (3.6 ml.) of eluate were collected and evaporated to dryness. Fractions 8–18 contained a total of 0.235 g. of nearly colorless crystals which were recrystallized from absolute ethanol to yield 0.120 g. of **16** as nearly colorless crystals, m.p. 230–232°. Concentration of the mother liquor gave an additional 0.058 g. of **16.** Recrystallization from ab-

solute ethanol with the aid of Norit gave **16** as colorless crystals, m.p. 233–234°; $[\alpha]^{25}D$ −26.9° (*c* 1.04, H_2O); $\lambda_{max}^{0.1\ N\ HCl}$ 262 mμ (ε 17,100); λ_{max}^{EtOH} 266 mμ (ε 16,200); $\lambda_{max}^{0.1\ N\ NaOH}$ 266 mμ (ε 16,300).

Anal. Calcd. for $C_{11}H_{16}N_6O_3$: C, 47.1; H, 5.75; N, 30.0. Found: C, 47.0; H, 6.00; N, 29.7.

9-(3-Acetamido-3-deoxy-β-D-ribofuranosyl)-6-dimethylamino-9H-purine (15).—A solution of 0.536 g. of 6-chloro-3'-acetamidonucleoside **14** and 1 ml. of dimethylamine in 10 ml. of anhydrous methanol in a sealed tube was heated on a steam bath for 2 hr. Evaporation *in vacuo* of the dark red-brown solution gave a gum which was evaporated twice *in vacuo* with aqueous ethanol to ensure removal of methyl benzoate and twice with absolute ethanol to yield 0.474 g. of a residual brown glass. A solution of 0.445 g. in 50 ml. of 50% methanol was stirred with Amberlite IRA-400 (OH^-) resin and the filtered solution evaporated to dryness *in vacuo* to yield 0.304 g. (96%) of a residual tan glass. Crystallization from 5 ml. of ethanol gave 0.165 g. (52%) of **15** as colorless crystals, m.p. 189.5–192.5°, $[\alpha]^{25}D$ −8.1° (*c* 1.96, pyridine), which did not depress the melting point of an authentic sample, m.p. 191–193.5°. Baker, *et al.*,[16] give m.p. 187–188° for **15**.

Anal. Calcd. for $C_{14}H_{20}N_6O_4$: C, 50.0; H, 5.99; N, 25.0. Found: C, 49.8; H, 6.19; N, 25.0.

9-(3-Acetamido-3-deoxy-β-D-ribofuranosyl)-6-diethylamino-9H-purine (20).—A solution of 3.68 g. (0.00688 mole) of 6-chloro-3'-acetamidonucleoside **14** and 7.2 ml. (5.1 g., 0.07 mole) of diethylamine in 35 ml. of anhydrous methanol in a sealed tube was heated on a steam bath for 2 hr. The dark red-brown solution was evaporated *in vacuo* and the residue was evaporated twice to dryness *in vacuo* with aqueous ethanol to ensure removal of methyl benzoate. A solution of the dark brown crystalline residue in 160 ml. of 50% methanol was stirred with Amberlite IRA-400 (OH^-) resin and the filtered solution was evaporated to dryness *in vacuo* to yield 1.94 g. (78%) of brown solid, m.p. 183–195° (sinters 158°). Recrystallization from 3:1 ethyl acetate–anhydrous ethanol with the aid of Norit gave, in two crops, 1.16 g. (47%) of **20** as colorless crystals, m.p. 211–214°. Recrystallization from ethanol gave colorless crystals, m.p. 218.5–219°; $[\alpha]^{24.5}D$ −26.0° (*c* 0.62, EtOH); $\lambda_{max}^{0.1\ N\ HCl}$ 269 mμ (ε 19,400); λ_{max}^{EtOH} 277.5 mμ (ε 19,400); $\lambda_{max}^{0.1\ N\ NaOH}$ 278 mμ (ε, 19,800).

Anal. Calcd. for $C_{16}H_{24}N_6O_4$: C, 52.7; H, 6.63; N, 23.1. Found: C, 52.9; H, 6.99; N, 22.8.

9-(3-Amino-3-deoxy-β-D-ribofuranosyl)-6-diethylamino-9H-purine (19). A. From 9-(3-Acetamido-3-deoxy-β-D-ribofuranosyl)-6-diethylamino-9H-purine (20).—A solution of 0.500 g. (0.00137 mole) of **20** in 50 ml. of 5% barium hydroxide was heated on a steam bath for 1 hr. Excess carbon dioxide was added and the precipitated barium carbonate was removed by filtration. The filtrate was evaporated to dryness *in vacuo* and a solution of the crystalline residue in 15 ml. of 50% methanol was passed through a column of 10 g. of Amberlite IRC-50 (H^+) resin. The resin column was washed with four 100-ml. portions of 50% methanol, the last eluate having negligible absorption at 277.5 mμ, and the combined eluates were evaporated to dryness *in vacuo* to afford 0.287 g. of unhydrolyzed **20**. The resin column washed with two 100-ml. and two 50-ml. portions of 1:1 methanol–0.6 *N* ammonium hydroxide, the last eluate having negligible absorption at 275 mμ, and the combined eluates were evaporated to dryness *in vacuo* to yield 0.133 g. (30%) of **19** as a tan crystalline residue, m.p. 168–178° (with previous sintering). The 0.287 g. of recovered **20** was hydrolyzed with 5% barium hydroxide as above to yield, from the 1:1 methanol–0.6 *N* ammonium hydroxide eluate of the resin column, 0.125 g. of tan crystalline residue which was washed with ethyl acetate to yield an additional 0.085 g. (19%) of **19** as buff colored crystals, m.p. 179–183° (with previous sintering). The 50% methanol eluate of the resin column gave, after passing through Amberlite IRC-50 (H^+) resin and evaporation to dryness *in vacuo*, 0.101 g. (20%) of recovered **20** as a buff-colored crystalline residue, m.p. 187–191°. The total yield of crude **19** was 0.218 g. (62% based on **20** hydrolyzed).

Recrystallization of crude **19** from 1:1 ethyl acetate–ethanol with the aid of Norit gave colorless crystals, m.p. 184–186°; $[\alpha]^{24.5}D$ −45.8° (*c* 0.52, EtOH); $\lambda_{max}^{0.1\ N\ HCl}$ 268 mμ (ε 19,700); λ_{max}^{EtOH} 277 mμ (ε 19,400); $\lambda_{max}^{0.1\ N\ NaOH}$ 277.5 mμ (ε 20,000).

Anal. Calcd. for $C_{14}H_{22}N_6O_3$: C, 52.2; H, 6.88; N, 26.1. Found: C, 52.0; H, 7.10; N, 25.9.

B. From 6-Chloro-3'-phthalimidonucleoside 3.—A mixture of 1.000 g. (0.00154 mole) of **3** (containing 0.3 mole of ethyl acetate), 25 ml. of anhydrous methanol, and 1.18 ml. (0.841 g., 0.0115 mole) of diethylamine was refluxed for 3 hr. Then 1 ml. (0.739 g., 0.01 mole) of butylamine was added and the solution refluxed for 16 hr. The solution was cooled, 5 ml. of water was added, and the solution stirred for 1 hr. with 5 g. of Amberlite IRA-400 (OH^-) resin. The filtered solution was evaporated to dryness *in vacuo* and the residue was evaporated to dryness *in vacuo* with absolute ethanol. The colorless crystalline residue was triturated with ethyl acetate and ether and filtered to yield 0.251 g. (50%) of **19** as colorless crystals, m.p. 180.5–183.5°. Recrystallization from absolute ethanol gave colorless crystals, m.p. 184–185.5°.

6-Chloro-9-(3-deoxy-3-phthalimido-β-D-ribofuranosyl)-9H-purine (22).—A mixture of 2.00 g. (0.00308 mole) of 6-chloro-3'-phthalimidonucleoside (**3**) containing 0.3 mole of ethyl acetate, 3.25 ml. (0.0232 mole) of diisopropylamine, and 50 ml. of anhydrous methanol was refluxed for 3 hr. and evaporated *in vacuo* to a glass. Crystallization from ethyl acetate gave colorless crystals which were washed with ethanol to yield 0.126 g. of product, m.p. 227–228° dec. Recrystallization from ethanol–ethyl acetate afforded 0.050 g. of colorless crystals of **22**, m.p. 233.5–234° dec.; $[\alpha]^{25}D$ −141° (*c* 0.52, pyridine); $\lambda_{max}^{0.1\ N\ HCl}$ 263 mμ (ε 10,700); λ_{max}^{MeOH} 263 mμ (ε 10 500); $\lambda^{0.1\ N\ NaOH}$ unstable.

Anal. Calcd. for $C_{18}H_{14}ClN_5O_5 \cdot 0.15EtOAc$: C, 52.4; H, 3.57; Cl, 8.26; N, 16.3; O–C_2H_5, 1.02. Found: C, 52.4; H, 3.72; Cl, 7.66, 8.06; N, 16.6; O–C_2H_5, 0.78.

9-(3-Deoxy-3-phthalimido-β-D-ribofuranosyl)-6-methoxy-9H-purine (23). A. Reaction of 9-(2,5-Di-O-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl)-6-chloro-9H-purine (3) with Sodium Methoxide.—A solution of 2.00 g. (0.00308 mole) of **3** containing 0.3 mole of ethyl acetate, 5 ml. of chloroform, 7 ml. of anhydrous methanol, and 9.24 ml. (0.00924 mole) of *N* methanolic sodium methoxide was refluxed for 2 hr. and then evaporated to dryness *in vacuo*. A suspension of the residual colorless glass in 45 ml. of N,N-dimethylformamide and 0.438 ml. (0.459 g., 0.00616 mole) of glacial acetic acid was refluxed for 1 hr. and filtered while hot. The filtrate was evaporated to dryness *in vacuo* and the tan crystalline residue was washed with absolute ethanol and water to yield 0.657 g. of **23** as tan crystals, m.p. 232–235° dec. The mother liquor was evaporated to dryness *in vacuo* and the crystalline residue was washed with ethyl acetate and water to yield an additional 0.207 g. of crude **23**, m.p. 212–218° dec., a total of 0.864 g. (68%). Digestion with warm 2-methoxyethanol gave 0.493 g. (39%) of colorless crystals, m.p. 247–248.5° dec. Recrystallization from absolute ethanol gave colorless crystals, m.p. 247.5–248° dec.; $[\alpha]^{25}D$ −101° (*c* 0.20, MeOH), $\lambda_{max}^{0.1\ N\ HCl}$ 234 mμ (ε 19,800), 241 mμ (ε 19,600), 298 mμ (ε 1,810); λ_{max}^{MeOH} 241.5 mμ (ε 19,500), 282 mμ, broad (ε 1,830); $\lambda_{max}^{0.1\ N\ NaOH}$ 247.5 mμ (ε 15,800).

Anal. Calcd. for $C_{19}H_{17}N_5O_6$: C, 55.5; H, 4.17; N, 17.0; O–CH_3, 3.65. Found: C, 55.3; H, 4.28; N, 16.9; O–CH_3, 3.65.

B. Reaction of 3 with Methanolic Diisopropylamine.—A mixture of 2.17 g. (0.003 mole) of **3** containing 0.3 mole of ethyl acetate, 3.14 ml. (2.27 g., 0.0224 mole) of diisopropylamine, and 40 ml. of anhydrous methanol in a steel bomb was heated by means of an oil bath at 150° for 5 hr. The resulting solution was evaporated to dryness *in vacuo* to yield a tan crystalline residue whose ultraviolet spectra indicated the presence of 6-methoxynucleoside **23** of about 80% purity (75% purity calculated for the mixture of nucleoside and diisopropylamine hydrochloride) and whose infrared spectra showed the presence of **23**. An attempt to separate the product from the amine hydrochloride by removal of chloride ion by treatment with Amberlite IRA-400 (OH^-) resin failed since the phthalimide ring opened and the resultant phthalamic acid was held by the resin.

9-(3-Amino-3-deoxy-β-D-ribofuranosyl)-6-cyclohexylamino-9H-purine (25).—A mixture of 6.504 g. (0.010 mole) of 6-chloro-3'-phthalimidonucleoside **3** containing 0.3 mole of ethyl acetate, 11.5 ml. (9.92 g., 0.100 mole) of cyclohexylamine, and 50 ml. of anhydrous methanol in a sealed tube was heated on a steam bath for 2⅓ hr. The resulting solution was evaporated to dryness *in vacuo* and the residue was evaporated to dryness *in vacuo* several times with aqueous ethanol and then absolute ethanol. A solution of the residual brown glass in 125 ml. of 4:1 methanol–water was stirred for 1 hr. with 20 g. of Amberlite IRA-400 (OH^-) resin. The filtered solution was evaporated to dryness *in vacuo* to yield 5.74 g. (99%) of phthalamide **24** as a residual tan glass, λ_{max}^{KBr} 5.80 and 6.08 μ. A mixture of 5.67 g. of the tan glass, 4.5 ml. of butylamine, and 50 ml. of anhydrous methanol in a sealed tube was heated on a steam bath for 2 hr. The resulting amber solution was evaporated to dryness *in vacuo* to a tan semisolid

residue. A solution of the residue in 75 ml. of 3:1 ethanol–water was percolated through a column of 25 g. of Amberlite IRC-50 (H^+) resin and the column was washed with 938 ml. of 3:1 ethanol–water, the final percolate having negligible absorption at 269 mμ. The column was then washed with 606 ml. of 3:1 ethanol–2 *N* ammonium hydroxide, the final percolate having negligible absorption at 269 mμ. The ethanol–2 *N* ammonium hydroxide percolate was evaporated *in vacuo* to yield 1.880 g. (45%) of **25** of 86% purity (by ultraviolet spectral analysis) as a colorless glass. The glass was partitioned[47] on 240 g. of Celite in the system 6:1:2 ethyl acetate–heptane–water and the column was eluted with upper phase. The eluate was measured spectrophotometrically at 269 mμ and two peaks were observed. The portions of eluate containing the second absorbing peak were combined and evaporated *in vacuo* to yield 1.390 g. (37%) of **25** (95% pure by ultraviolet spectral analysis) as a colorless glass, $[\alpha]^{25}D$ −42.5° (*c* 1.89, EtOH).

The glass was repartitioned[47] as above to yield 1.150 g. (32%) of **25** hemihydrate as a colorless hygroscopic glass; $[\alpha]^{25}D$ −41.5°(*c* 2.19, EtOH); $\lambda_{max}^{0.1\ N\ HCl}$ 264 mμ (ε 19,900); $\lambda_{max}^{ethanol}$ 269.5 mμ (ε 18,400); $\lambda_{max}^{0.1\ N\ NaOH}$ 270 mμ (ε 19,600).

Anal. Calcd. for $C_{16}H_{24}N_6O_3 \cdot 0.5H_2O$. C, 53.8; H, 7.05; N, 23.5. Found: C, 54.1; H, 7.07; N,23. 3.

General Reaction of 6-Chloro-3′-phthalimidonucleoside 3 with Amines (Tables I and II).—The aminonucleosides listed in Tables I and II were prepared by allowing the chloronucleoside **3** to react with primary and secondary amines in methanol, the reaction mixtures being heated by means of a steam bath either under reflux or in sealed tubes for times ranging from 1.75 to 16.5 hr. The intermediate phthalamides from the action of secondary amines were not isolated but were aminolyzed by adding methylamine or butylamine and heating the resulting solutions on a steam bath for 1.75 to 18.5 hr. either under reflux or in sealed tubes.

The reaction mixtures were worked up by evaporation *in vacuo* to remove methanol, excess amines, and methyl benzoate, and chloride ion was then removed by treatment of the residues in aqueous methanol or ethanol with Amberlite IRA-400 (OH^-) resin. The nucleosides were separated from the phthalamides v[40] by crystallization from solvents. Alternately, the reaction mixtures were diluted with water and chloride ion removed by treatment with Amberlite IRA-400 (OH^-) resin. The solvents were then removed *in vacuo* and the nucleosides obtained in 31–84% yields by crystallization. In the cases of the dibutylamino and diamylamino nucleosides, the products were obtained crystalline prior to deionization.

The mixtures resulting from reactions of the 6-chloro-3′-phthalimidonucleoside **3** with isobutylamine, decylamine, and benzylamine, after removal of chloride ion and evaporation, gave residues which were crystallized from methanol or ethanol to yield crystalline N,N′-dialkylphthalamides (v).[40] Further workup gave the desired aminonucleosides. In experiments where it was desired to separate the aminonucleoside from mother liquors containing the byproduct phthalamide v,[40] as with the cyclohexylamino and dipropylamino analogs, the mixture was percolated through a column of Amberlite IRC-50 (H^+) resin which retained the aminonucleoside and other strongly basic substances, allowing v to pass through. The resin was then washed with aqueous methanolic ammonia to remove the aminonucleoside which was then crystallized from the percolate.

N,N′-Diisobutylphthalamide. A. From 6-Chloro-3′-phthalimidonucleoside 3 and Isobutylamine.—The evaporated reaction mixture from 4.29 g. (0.00664 mole) of **3**·0.4EtOAc and 7.00 ml. (5.11 g., 0.070 mole) of isobutylamine in 60 ml. of methanol was crystallized from 20 ml. of 1:1 ethanol–water to yield 0.986 g. of N,N′-diisobutylphthalamide as colorless needles, m.p. 182–182.5°, which did not depress the melting point of authentic material (part B below).

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.5; H, 8.75; N, 10.1. Found: C, 69.4, H, 8.68; N, 9.87.

B. From Phthalimide and Isobutylamine.—A mixture of 4.43 g. (0.03 mole) of phthalimide, 5 ml. of isobutylamine, and 15 ml. of water was heated on a steam bath. Most of the phthalimide dissolved, then crystallization occurred to produce a stiff paste, and finally the solid melted to an oil. Ethanol was added until the oil dissolved and the solution was chilled and filtered to yield 5.13 g. of colorless small plates, m.p. 89–149° (with intermittent sintering and melting). A suspension of the plates in 5 ml. of isobutylamine and 25 ml. of water was allowed to stand at room temperature, samples being examined microscopically at intervals. After 4 hr. the plates were completely replaced by colorless needles. After 24 hr. the needles were removed by filtration, washed with water, and dried at 100°. The yield of product, m.p. 183°, was 4.91 g. (52%).

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.5; H, 8.75; N, 10.1. Found: C, 69.8; H, 9.11; N, 10.0.

N,N′-Didecylphthalamide.—The reaction mixture from 2.00 g. (0.00308 mole) of 6-chloro-3′-phthalimidonucleoside **3**·0.4EtOAc and 3.63 g. (0.0231 mole) of decylamine in 50 ml. of methanol, after treatment with 10 g. of Amberlite IRA-400 (OH^-) resin for 1 hr., was evaporated to a viscous residue which was crystallized from methanol to yield, in several crops, 0.579 g. (42%) of N,N′-didecylphthalamide as colorless crystals, m.p. 89–99°. Recrystallizations from methanol and ethyl acetate gave colorless crystals, m.p. 98.5–99.5°.

Anal. Calcd. for $C_{28}H_{48}N_2O_2$: C, 75.6; H, 10.9; N, 6.30. Found: C, 75.3; H, 11.0; N, 6.14.

N,N′-Dibenzylphthalamide.—The reaction mixture from 6.68 g. (0.01 mole) of 6-chloro-3′-phthalimidonucleoside **3**·0.5EtOAc and 10.9 ml. (10.7 g., 0.1 mole) of benzylamine in 65 ml. of methanol, after treatment with 20 g. of Amberlite IRA-400 (OH^-) resin for 1 hr., was evaporated to a crystalline residue which was recrystallized from absolute ethanol to yield, in several crops, 2.00 g. (58%) of N,N′-dibenzylphthalamide, m.p. 161–173°. Recrystallization from absolute ethanol gave colorless needles, m.p. 181°. Tingle and Lovelace[48] give m.p. 178–179° for N,N′-dibenzylphthalamide.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.7; H, 5.85; N, 8.13. Found: C, 76.8; H, 5.92; N, 7.93.

9-(3-Amino-3-deoxy-β-D-ribofuranosyl)-6-furfurylamino-9H-purine.—A solution of 5.73 g. (0.00906 mole) of 6-chloro-3′-phthalimidonucleoside **3**·0.5EtOAc, 8.3 ml. (8.7 g., 0.09 mole) of redistilled furfurylamine, and 25 ml. of 2-methoxyethanol was refluxed for 1 hr. The resulting amber solution was evaporated *in vacuo* to a brown gum, a solution of which in 9.90 ml. (7.31 g., 0.1 mole) of butylamine and 25 ml. of anhydrous methanol was refluxed for 4.25 hr. The resulting brown solution was evaporated *in vacuo* to a residue consisting of crystals and gum. A solution of the residue in 80 ml. of 80% ethanol was stirred for 1 hr. with 20 g. of Amberlite IRA-400 (OH^-) resin. The filtered solution was evaporated *in vacuo* to a residual gum which was evaporated *in vacuo* several times with absolute ethanol. The residue, brown crystals and gum, was recrystallized from absolute ethanol to yield 0.814 g. (26%) of product as nearly colorless crystals, sintering at 151°, m.p. 156°. Recrystallization from ethanol and then from ethyl acetate–ethanol gave colorless crystals, m.p. 160.5–161.5°; $[\alpha]^{26}D$ −43.5° (*c* 1.17, H_2O); $\lambda_{max}^{0.1\ N\ HCl}$ 264 mμ (ε 17,900); λ_{max}^{MeOH} 267.5 mμ (ε 18,400); $\lambda_{max}^{0.1\ N\ NaOH}$ 268 mμ (ε 19,200).

Anal. Calcd. for $C_{15}H_{18}N_6O_4$: C, 52.0; H, 5.24; N, 24.3. Found: C, 52.4; H, 5.33; N, 24.4.

Acknowledgment.—We wish to thank Mr. L. M. Brancone and staff for microanalyses, Mr. W. Fulmor and staff for ultraviolet, infrared, and optical rotation determinations, and Mr. J. Poletto for large-scale preparations.

(47) We thank Mr. C. Pidacks for the partition chromatography.

(48) J. B. Tingle and B. F. Lovelace, *Am. Chem. J.*, **38**, 642 (1907).