Anal. Calcd. for $C_{10}H_9N_5O_9S$: C, 32.0; H, 2.42; N, 18.7. Found: C, 31.9; H, 2.57; N, 18.5.

L-2-Amino-5,6-dihydro-4H-1,3-thiazine-4-carboxylic acid (XVIII) was prepared according to the procedure of Schöberl and Kawohl[5] and had m.p. 257–259° dec. (lit.[5] m.p. 238–240° dec.) after recrystallization from 50% aqueous ethanol. In the infrared it had λ_{max}^{KBr} (μ) 3.05–3.40 (NH_2 and/or NH_3^+), 6.05–6.35 (C=N, NH_2 and/or NH_3^+, and CO_2^-), 7.23 (CO_2^-); there was no carboxyl carbonyl absorption near 5.9 μ.

The picrate of XVIII was prepared by mixing hot solutions of 0.10 g. of XVIII in 10 ml. of water and of 0.20 g. of picric acid in 15 ml. of water. The yellow solid, 0.20 g., m.p. 218–220° (dec.), slowly precipitated and was recrystallized from 20 ml. of hot water, m.p. 217–218° (dec.). In the infrared it had λ_{max}^{KBr} (μ) 2.98 and 3.05 (NH), 3.17 (NH_3^+), 5.79 (carboxyl C=O), 6.10–6.15 (aryl CH and possibly $C{=}\overset{+}{N}H$), 6.42 and 7.50 (NO_2).

Anal. Calcd. for $C_{11}H_{11}N_5O_9S$: C, 33.9; H, 2.85; N, 18.0. found: C, 34.2; H, 3.09; N, 18.2.

2-Amino-2-thiazoline (XIX) was prepared according to the procedure of Gabriel[7] and had m.p. 79–80° (lit.[7] m.p. 86°) after two recrystallizations from benzene–petroleum ether (62–70°) (1:2). In the infrared it had λ_{max}^{KBr} (μ) 2.83 and 3.26 (NH), 6.08 (C=N), 7.42 and 10.06 (strong bands of unknown assignment).

Anal. Calcd. for $C_3H_6N_2S$: C, 35.3; H, 5.92. Found: C, 35.4; H, 5.98.

The picrate of XIX was prepared by mixing ether solutions of XIX and of picric acid, m.p. 236–239° dec. After one recrystallization from hot water it had m.p. 241–243° dec. (lit.[6,7] m.p. 235° dec.). In the infrared it had λ_{max}^{KBr} (μ) 2.90 and 3.10 (NH), 6.11 ($C{=}\overset{+}{N}H$), 6.40 and 7.52–7.57 (NO_2). There was no NH_3^+ absorption around 3.25 μ.

Acknowledgment. The authors are indebted to Dr. Peter Lim for infrared interpretation.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XV. Synthesis of 9-β-D-Glucofuranosyladenine

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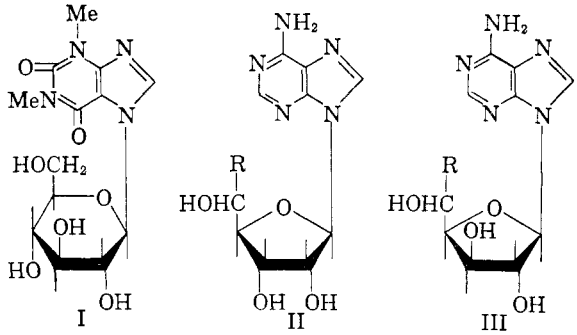
The title compound (VIII) has been prepared by coupling chloromercuri-6-benzamidopurine with 2,3,5,6-tetra-*O*-benzoyl-D-glucofuranosyl chloride (VI) in 24% yield and with 2-*O*-acetyl-3-*O*-benzoyl-5,6-*O*-carbonyl-D-glucofuranosyl chloride (XVI) in 7% yield. A useful preparative method for the intermediate, 1,2-*O*-isopropylidene-D-glucofuranose 5,6-carbonate (XII), has been developed.

D-Glucose, the most common sugar existing in natural products, was the first sugar to be converted to a synthetic nucleoside when Fischer and Helferich,[2] in 1914, described the synthesis of 7-β-D-glucopyranosyltheophylline (I). Since that time, many nucleosides that contain the D-glucopyranose moiety[3] have been synthesized, due to the ready availability and stability of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide.[4] In addition, the pyranose ring structure is usually observed in natural materials containing D-glucose.[5] However, no nucleoside derived from the furanose form of D-glucose has been described in the literature.



The program under investigation in this laboratory on *C*-alkylpentofuranosyl nucleosides as possible anticancer agents has led to the synthesis of the two isomeric 5-*C*-methyl-D-ribosides (II, R = CH_3), 9-(6′-deoxy-β-D-allofuranosyl)adenine[6] and

(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research. For the preceding paper in this series, *cf.* L. Goodman, A. Benitez, C. D. Anderson, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

(2) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914).

(3) (a) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1780 (1954); (b) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951); (c) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956); (d) D. W. Visser, I. Goodman, and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 1926 (1948); (e) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 4489 (1930); (f) J. J. Fox, N. Yung, I. Wempen, and I. L. Doerr, *J. Am. Chem. Soc.*, **79**, 5060 (1957); (g) A. Holland, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 965 (1948).

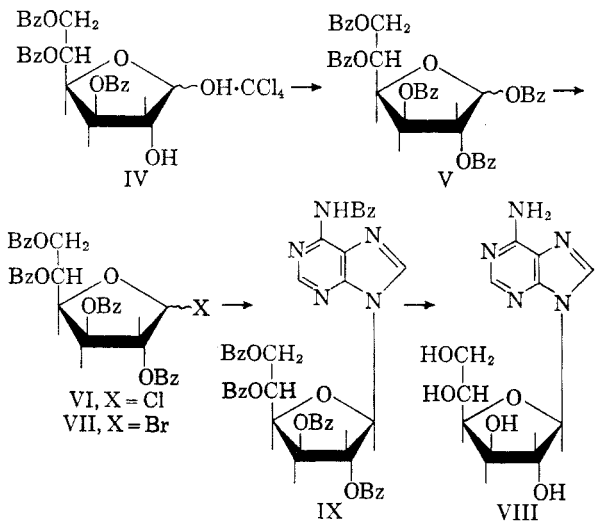
(4) C. E. Redemann and C. Niemann, *Org. Syntheses*, **22**, 1 (1942) and references therein.

(5) W. W. Pigman and R. M. Goepp, Jr., *Chemistry of the Carbohydrates*, second printing, Academic Press, Inc., New York, N. Y., 1952.

(6) E. J. Reist, L. Goodman, R. R. Spencer, and B. R. Baker, Paper IV of this series, *J. Am. Chem. Soc.*, **80**, 3962 (1958).

9-(6′-deoxy-α-L-talofuranosyl)adenine,[7] as well as the two isomeric 5-*C*-methyl-D-xylosides (III, R = CH_3), namely, 9-(6′-deoxy-β-D-glucofuranosyl)adenine[8] and 9-(6′-deoxy-α-L-idofuranosyl)adenine.[9] As a logical extension of this program, the synthesis of 9-β-D-glucofuranosyladenine (III, R = $HOCH_2$—) was investigated and is the subject of this paper.

D-Glucofuranose pentabenzoate (V), synthesized by benzoylation of 3,5,6-tri-*O*-benzoyl-D-glucofuranose (IV), has been separated into two crystalline anomers.[10-12] Since either of the anomeric pentabenzoates V can be expected to give the same halogen sugars (VI and VII), and since both anomers of the halogen sugars VI or VII can be expected to give a nucleoside (IX) with the β-configuration,[13] the separation of the anomeric pentabenzoates V for conversion to the nucleoside VIII was considered neither necessary nor advisable from an over-all yield standpoint. For synthesis of the nucleoside VIII, the crude pentabenzoate V, still contaminated with benzoic anhydride, but obtained in quantitative yield, was employed.



The crude pentabenzoate V was treated with saturated ethereal hydrogen chloride,[14] containing acetyl chloride,[15] to give the sirupy chloro sugar VI, then coupled with chloromercuri-6-benzamidopurine in the usual fashion.[6,16] The crude, blocked nucleoside IX was debenzoylated by refluxing a methanolic solution containing an excess of sodium methoxide for 3 hours.[17] After evaporation of the neutralized reaction mixture, the residue was partitioned between water and chloroform. The insoluble solid that separated proved to be the desired nucleoside VIII and was obtained in 21% yield. Further processing of the aqueous mother liquor with picric acid and regeneration of the picrate with Dowex 2 (CO_3)[6,16] afforded an additional 3% of 9-β-D-glucofuranosyladenine (VIII), a total yield of 24% based on IV. This compound was homogeneous when subjected to paper chromatography with R_{Ad} 1.42 in solvent A and R_{Ad} 0.41 in solvent B.[19] That this nucleoside VIII had the furanose structure was clearly shown by comparison[16] of its R_{Ad} values with those of 9-β-D-glucopyranosyladenine.[3b,20] The latter nucleoside had R_{Ad} 1.73 in solvent A and R_{Ad} 0.18 in solvent B. That the nucleoside VIII had the β-configuration is a relatively certain assumption.[13]

Condensation of 2,3,5,6-tetra-*O*-benzoyl-D-glucofuranosyl bromide (VII) with chloromercuri-6-benzamidopurine proceeded in a yield of less than 3%.

Unfortunately, condensation of the furanosyl chloride VI with chloromercuri-2,6-diacetamidopurine[16] gave only a 5% yield of 2,6-diamino-9-β-D-glucofuranosylpurine with R_{Ad} 0.90 in solvent A and R_{Ad} 0.13 in solvent B, in comparison to 2,6-diaminopurine that had R_{Ad} 0.57 in solvent A and R_{Ad} 0.40 in solvent B. Reaction of the furanosyl chloride VI with dithyminylmercury[3c] followed by debenzoylation gave no nucleoside (less than 1%) detectable by paper chromatography. The failure of these condensations suggested that a different blocking group for the 5- and 6-hydroxyls of D-glucose be investigated for the synthesis of these nucleosides. Since the failure of VI to form these two nucleosides might be attributed either to the

(7) E. J. Reist, L. Goodman, and B. R. Baker, Paper VIII of this series, *J. Am. Chem. Soc.*, in press.

(8) E. J. Reist, R. R. Spencer, and B. R. Baker, Paper X of this series, *J. Org. Chem.*, **23**, 1753 (1958).

(9) E. J. Reist, R. R. Spencer, and B. R. Baker, Paper XI of this series, *J. Org. Chem.*, **23**, 1757 (1958).

(10) H. H. Schlubach and W. Huntenberg, *Ber.*, **60**, 1487 (1927).

(11) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **76**, 513 (1928).

(12) An alternate synthesis of D-glucofuranose pentabenzoate (V) has been described by P. Brigl and H. Grüner, *Ber.*, **66B**, 1977 (1933); *Ann.*, **495**, 60 (1932).

(13) For a review on this subject, *cf.* B. R. Baker on Stereochemistry of Nucleoside Synthesis, Ciba Foundation Symposium on the Chemistry and Biology of Purines, J. and A. Churchill, Ltd., London, 1957, pp. 120–130.

(14) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

(15) The use of acetyl chloride to keep such a preparation anhydrous has been described by B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5900 (1955).

(16) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

(17) Since some blocked nucleosides[7,16] do not completely debenzoylate with catalytic amounts[18] of sodium methoxide, the use of excess reagent and a longer reflux period is considered a better general procedure.

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

(19) Paper chromatograms were run by the descending technique on Whatman No. 1 paper using 5% sodium phosphate (solvent A) or water saturated butanol (solvent B). The spots were located by visual examination with ultraviolet light. Adenine was used as a standard and R_{Ad} values were recorded with R_{Ad} 1.00 being assigned to adenine.

(20) We wish to thank Dr. J. J. Fox of the Sloan-Kettering Institute for Cancer Research for a sample of this compound prepared by Davoll and Lowy.[3b]

steric hindrance of the bulky 5,6-dibenzoate or to the participation of the 6-benzoate group with C_1 to form a C_6-C_1 ortho-ester-ion bridge that is incapable of forming a nucleoside, the use of the 5,6-cyclic carbonate blocking group (as in XIII) was considered worthy of investigation.[21] Due to the instability of the chloro sugar XVI, this blocking group was even less effective than the 5,6-dibenzoate V.

A suitable starting material for such an investigation is 1,2-*O*-isopropylidene-D-glucose 5,6-carbonate (XII), a compound previously synthesized from D-glucose with acetone and phosgene[22] in 15% yield or from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose and phosgene in unspecified yield.[23] Neither method was considered of preparative value, particularly since the first[22] gave no useful yield when run on a large scale.[24]

Since diethyl carbonate has proved to be a convenient reagent for conversion of glycols to cyclic carbonates by transesterification,[25] the action of this reagent on 1,2-*O*-isopropylidene-D-glucofuranose (X) was investigated. Treatment of X with an excess of diethyl carbonate[25] at 140° in the presence of a catalytic amount of sodium methoxide for 30 minutes gave an 11% yield of the desired 5,6-carbonate XII. Also isolated was 30% of starting material and, surprisingly, a 50% yield of 3,6-*anhydro*-1,2-*O*-isopropylidene-D-glucofuranose (XV). Since the 5,6-carbonate XII, when heated above its decomposition temperature (225°), is converted to the 3,6-anhydro-D-glucoside XV,[23] it was possible that the low yield in conversion of the 1,2-*O*-isopropylidene-D-glucofuranose (X) to the 5,6-carbonate XII was due to the simultaneous base-catalyzed conversion of XII to the 3,6-anhydro sugar XV. That this was indeed the case was shown by heating the 5,6-carbonate XII at about 140° in dimethylformamide in the presence of sodium methoxide, the anhydro sugar XV being formed in a 64% yield. When the lower temperature of 90° was used for the methoxide-catalyzed transesterification between ethyl carbonate and 1,2-*O*-isopropylidene-D-glucofuranose (X) in dimethylformamide, a 15% yield of the 5,6-carbonate XII was obtained in 30 minutes and 80% of the starting material X was recovered. Increase of the reaction time to 4 hours did not significantly increase the yield (18%) of 5,6-carbonate XII, since even at this temperature 40% of the 3,6-anhydro sugar XV was formed and 40% yield of starting material remained.

It seemed possible that the acylation of 1,2-*O*-isopropylidene-D-glucofuranose (X) with methyl chloroformate in pyridine to give the 6-*O*-carbomethoxy derivative XI followed by mild conditions for cyclization might give the desired 5,6-carbonate XII without the concomitant loss of carbon dioxide resulting in formation of the anhydro sugar XV. This sequence proved successful. The acylation of X with methyl chloroformate gave the desired carbomethoxy derivative XI that readily cyclized to the 5,6-carbonate XII in the presence of pyridine at 70°, giving a 58% over-all yield of 5,6-carbonate XII.

Treatment of the 5,6-carbonate XII with benzoyl chloride in pyridine gave an 84% yield of crystalline 3-benzoate XIV, m.p. 126–127°. In the first run a lower melting dimorphous form, m.p. 116–117°, was obtained that could be converted to the high melting form by seeding. However, the high melting form could not be converted to the low melting form by this technique. Acetolysis[8,9] of XIV with acetic acid containing sulfuric acid gave a 90% yield of 1,2-di-*O*-acetyl-3-*O*-benzoyl-D-glucofuranose 5,6-carbonate (XIII) as an amorphous mixture of anomers that was analytically pure.

When XIII was treated with ethereal hydrogen chloride[14] containing acetyl chloride[15] at 0° for 4 days, conversion to the oily furanosyl chloride XVI

(21) The use of a 2,3-cyclic carbonate derivative of D-ribose to avoid participation in reactions at C_1 has been described by G. M. Tener and H. G. Khorana, *J. Am. Chem. Soc.*, **79**, 437 (1957).

(22) W. N. Haworth and C. R. Porter, *J. Chem. Soc.*, 2796 (1929).

(23) K. Freudenberg, H. Eich, C. Knoevenagel, and W. Westphal, *Ber.*, **73B**, 441 (1940).

(24) A 15% yield of XII could be obtained starting with 10 g. of D-glucose, but the yield dropped to 2% when 100 g. of D-glucose was employed; unpublished results by B. R. Baker and J. P. Joseph, American Cyanamid Co.

(25) D. B. Pattison, *J. Am. Chem. Soc.*, **79**, 3455 (1957).

was complete, as shown by no further decrease in the acetate infrared absorption band at 8.2 μ. However, this chloro sugar, when reacted with chloromercuri-6-benzamidopurine in boiling xylene, underwent considerable carbonization and the yield of 9-β-D-glucofuranosyladenine (VIII) was only 3%. With toluene as a solvent, the yield of VIII was about 7%. No detectable yields (1%) of nucleosides could be obtained by the coupling of XVI with chloromercuri-2,6-diacetamidopurine.

Several other experiments were run to determine, if possible, why the yields of nucleosides from XVI were so low. Treatment of the 5,6-carbonate derivatives, XIII and XIV, with mercuric chloride in boiling xylene gave no change, showing that the 5,6-carbonate blocking group was stable to the coupling conditions. That the deacylation of the blocked nucleoside XVIII proceeded normally was indicated by the deacylation of 3-*O*-benzoyl-1,2-*O*-isopropylidene-D-glucofuranose 5,6-carbonate (XIV) with methanolic sodium methoxide to 1,2-*O*-isopropylidene-D-glucofuranose (X) in 60% yield; there was no formation of the 3,6-anhydro sugar XV under these conditions. The only known possible explanation was the instability of furanosyl chloride (XVI) to heat, since carbonization was observed during the coupling. Evidence for this instability was obtained when an attempt was made to make the furanosyl bromide XVII with hydrogen bromide in acetic acid as described for the preparation of 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl bromide.[26] Extensive disruption in the structure of XVII took place, since the infrared spectrum of the supposed bromo sugar XVII showed decreased absorption in the 5.8 μ carbonyl region. It follows that some type of spontaneous loss of blocking groups takes place with these halogen sugars and the remaining sugar moiety carbonizes on heating during the coupling reaction.

EXPERIMENTAL[19,27]

1,2-O-Isopropylidene-D-glucofuranose 5,6-carbonate (XII). (A) A mixture of 3.0 g. (13.5 mmoles) of 1,2-*O*-isopropylidene-D-glucofuranose (X),[29] 10 ml. of diethyl carbonate, and 50 mg. of sodium methoxide was refluxed for 30 min., then cooled, neutralized with acetic acid, and evaporated to dryness *in vacuo* (40°). The brown, gummy solid was partitioned between 20 ml. of chloroform and 20 ml. of water, filtered, and the solid was washed with 2 ml. of chloroform and 2 ml. of water to give 0.41 g. (11%) of 1,2-*O*-isopropylidene-D-glucofuranose 5,6-carbonate, m.p. 226–229°. Recrystallization from 95% ethanol gave 0.35 g. of white crystals, m.p. 230–231°; λ_{max}^{KBr} 2.98 μ (OH), 5.60 μ (carbonate C=O), 7.25 μ (CH_3), 8.48 μ (carbonate C—O—C), 9.10, 9.22, 9.45, 9.85 μ (C—O—C and C—OH).

The layers from the combined filtrate and washings were separated and the aqueous layer was washed with 5 ml. of chloroform. The combined chloroform layers were washed with 5 ml. of water, dried over magnesium sulfate, then evaporated to dryness *in vacuo* to give 1.36 g. (50%) of XV as a yellow sirup. A small amount was distilled, b.p. 55–60° (3 mm.), furnishing a colorless distillate which crystallized in the receiver, m.p. 52–54°, $[\alpha]_D^{26}$ +30.5° (1% in H_2O); λ_{max}^{KBr} 2.90 μ (OH), 7.25 μ (CH_3), 7.45 μ (3,6-anhydro ring), 9.10, 9.22, 9.45, 9.86 μ (C—O—C, C—OH).

Ohle[30] *et al.* reported m.p. 56–57°, $[\alpha]_D^{20}$ +29.3° (c, 3.1% in H_2O).

The combined aqueous solutions were taken to dryness and the residue was extracted with hot ethyl acetate (2 × 10 ml.). The filtered extracts were evaporated to dryness *in vacuo* to give 0.91 g., m.p. 149–155°, of X which gave no depression in melting point when mixed with starting material.

When dimethylformamide was used for a solvent in this reaction, essentially the same results were obtained.

When a mixture of 500 mg. of XII, 10 ml. of dimethylformamide, and 0.75 ml. of *N* methanolic sodium methoxide was refluxed for 30 min., then processed as described above, 0.23 g. (64%) of the anhydro sugar XV, m.p. 51–53°, was obtained that was identified by its infrared spectrum.

(B) To a stirred solution of 19.0 g. (0.087 mole) of X[29] in 100 ml. each of reagent pyridine and reagent chloroform cooled in an ice bath was added dropwise 11.8 ml. (0.157 mole) of methyl chloroformate over a period of 25 min., maintaining the temperature at 0–10° and protecting the mixture from moisture. After being stirred for 1 hr. at 0°, the mixture was allowed to stand at 5° for 48 hr. The mixture was poured into 200 ml. of ice water and the separated aqueous layer was extracted with chloroform (3 × 50 ml.). The chloroform solutions were washed with 25 ml. of saturated aqueous sodium bicarbonate and 25 ml. of water, then combined. Dried with magnesium sulfate, the chloroform solution was evaporated to a sirup *in vacuo* (bath 40°). When the bath temperature was increased to 70°, crystallization of XII began to take place. The mixture was kept at 70° for 1 hr. *in vacuo*. Recrystallization of the residue (18.3 g.) from 450 ml. of 90% ethanol gave 10.5 g. of product, m.p. 231–232° (dec.), in two crops.

Evaporation of the mother liquor to dryness *in vacuo* gave an oil that showed the presence of the carbomethoxy group absorption band at 5.64 μ. The residue was dissolved in 50 ml. of benzene containing 5% pyridine, then refluxed for 2 hr. Evaporation *in vacuo* and crystallization from 90% ethanol gave an additional 1.84 g. (total, 58%) of XII, m.p. 231–233° (dec.).

3-O-Benzoyl-1,2-O-isopropylidene-D-glucofuranose 5,6-carbonate (XIV). To a stirred solution of 12.2 g. (49.6 mmoles) of XII in 30 ml. of reagent pyridine, protected from moisture, was added dropwise 12.0 ml. (0.103 mole) of benzoyl chloride with ice cooling at such a rate that the temperature was maintained at 0–5°. After being stirred for an additional hour in the ice bath, the mixture was allowed to stand at room temperature for about 18 hr. The mixture was added to ice and excess sodium bicarbonate, then extracted with chloroform (3 × 50 ml.). The combined extracts, washed with 100 ml. of saturated aqueous sodium bicarbonate and with 100 ml. of water, were dried with magnesium sulfate, then evaporated to dryness *in vacuo*. After each addition of two 25-ml. portions of toluene, the solutions were evaporated *in vacuo* to remove pyridine. Crystallization from 150 ml. of methanol gave 14.6 g. (84%) of product, m.p. 127–128°. Recrystallization from methanol gave white crystals, m.p. 126–127°, $[\alpha]_D^{29}$ −43.4° (1% in $CHCl_3$); λ_{max}^{KBr} 2.91 μ

(26) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

(27) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined with a Standard Polarimeter Attachment, Model D, to the Beckman DU spectrophotometer using sucrose as a standard.[28]

(28) A. S. Keston, Abstracts of 127th Meeting, American Chemical Society, 18C (1955).

(29) S. C. Laland, *Acta Chem. Scand.*, **8**, 866 (1954).

(30) H. Ohle, L. Vargha, and H. Erlbach, *Ber.*, **61**, 1211 (1928).

(OH), 5.58 μ (carbonate C=O), 5.78 μ (benzoate C=O), 7.25 μ (CH_3), 7.90, 8.96 μ (benzoate C—O—C), 8.60 μ (carbonate C—O—C), 9.10, 9.32, 9.54, 9.75 μ (C—O—C).

Anal. Calcd. for $C_{17}H_{18}O_8$: C, 58.3; H, 5.18. Found: C, 58.6; H, 5.41.

In the first run, the purified product melted at 116–117° and had $[\alpha]_D^{31}$ −43.5° (2% in $CHCl_3$); its infrared spectrum was somewhat different than that of the high melting form in the fingerprint region.

Anal. Calcd. for $C_{17}H_{18}O_8$: C, 58.3; H, 5.18. Found: C, 58.3; H, 5.36.

Recrystallization of this low melting form from methanol by seeding with the high melting form gave white crystals, m.p. 127°.

When 500 mg. of XIV was refluxed in 5 ml. of reagent methanol containing 1 ml. of *N* methanolic sodium methoxide for 1 hr., a 60% yield of 1,2-*O*-isopropylidene-D-glucofuranose (X), m.p. 156–157°, was obtained when the reaction mixture was processed as described for XII (procedure B); no 3,6-*anhydro*-D-glucoside XV was present in the chloroform solution.

1,2-Di-O-acetyl-3-O-benzoyl-D-glucofuranose 5,6-carbonate (XIII). To a solution of 12.5 g. (35.6 mmoles) of XIV in 115 ml. of acetic acid and 13 ml. of acetic anhydride was added, with stirring, 7.0 ml. of 96% sulfuric acid, the temperature being maintained below 20° in an ice bath. The reaction solution was kept at room temperature for 24 hr., then poured into 400 ml. of ice water. This mixture was stirred for 30 min., then 50 ml. of chloroform was added, the organic layer was separated, and the aqueous layer was extracted with an additional 50 ml. of chloroform. The organic layer and chloroform extracts were washed with water (100 ml.), saturated aqueous sodium bicarbonate (2 × 100 ml.), and water (100 ml.), and then combined. Dried over magnesium sulfate, the solution was evaporated to dryness *in vacuo* (40°) to give 12.64 g. (90%) of a clear sirup which hardened to a clear glass upon cooling, $[\alpha]_D^{32}$ +17.7° (1.7% in $CHCl_3$); λ_{max}^{film} 5.50 μ (carbonate C=O), 5.70 μ (acetate C=O), 5.78 μ (benzoate C=O), 7.78, 8.92 μ (benzoate C—O—C), 8.10, 8.20 μ (acetate C—O—C), 8.50 μ (carbonate C=O), 9.15, 9.34, 9.60 μ (C—O—C).

Anal. Calcd. for $C_{18}H_{18}O_{10}$: C, 54.8; H, 4.6. Found: C, 54.5; H, 4.62.

D-*Glucofuranose pentabenzoate* (V). To a stirred solution of 13.95 g. (21.6 mmoles) of the carbon tetrachloride complex of 3,5,6-tri-*O*-benzoyl-D-glucofuranose (IV)[31] in 50 ml. of methylene chloride containing 4 ml. of pyridine was added 8.1 ml. (69.5 mmoles) of benzoyl chloride dropwise with stirring over a period of 20 min. The mixture, after being heated at 50° for 2.5 hr., was added dropwise to 200 ml. of a rapidly stirred mixture of ice and excess aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 50 ml.). The organic layer and chloroform extracts were washed with 20 ml. of saturated aqueous sodium bicarbonate and 20 ml. of water, then combined, dried over magnesium sulfate, and concentrated to dryness *in vacuo* (40°). The last traces of pyridine were removed by the addition and removal *in vacuo* of toluene (2 × 10 ml.) to give 17.27 g. of a tan sirup with λ_{max}^{film} 5.78 μ (benzoate C=O), 7.90, 9.02 μ (benzoate C—O—C), 9.12, 9.35, 9.58, 9.73 μ (C—O—C), that was suitable for nucleoside preparation. Although this compound could be crystallized, no attempt was made to separate the anomers.[10,11]

9-β-D-glucofuranosyladenine (VIII). (A) A solution of 6.21 g. (8.86 mmoles) of crude V in 150 ml. of ether which had been previously saturated with hydrogen chloride[14] at 0° and 10 ml. of acetyl chloride[15] was stored in a stoppered flask at 0° for 5 days. The solution was evaporated to dryness *in vacuo* with protection from moisture. Acetic acid was removed by the addition of dry benzene followed by its removal *in vacuo*. The sirup VI was dissolved in xylene and condensed with 5.55 g. (11.6 mmoles) of chloromercuri-6-benzamidopurine[32] in the usual manner.[6,16] Evaporation of the chloroform solution gave a yellow glass. Treatment of this material with 20 ml. of hot benzene, then cooling to room temperature for 2 hr., effected the precipitation of 1.06 g. of crystalline 6-benzamidopurine. Benzene was removed from the filtrate to give 6.22 g. of crude IX as a glass.

Debenzoylation was accomplished by heating a solution of IX in 50 ml. of methanol containing 5 ml. of *N* methanolic sodium methoxide at reflux for 3 hr. The solution was neutralized with acetic acid, then evaporated to dryness *in vacuo* (40°). The residue was treated with a mixture of 20 ml. of water and 20 ml. of chloroform to give a white, insoluble material which, after recrystallization from water, gave 0.55 g. (21%) of white crystals of VIII, m.p. 268–270°, $[\alpha]_D^{25}$ −58.0° (1% in *N* HCl); λ_{max}^{KBr} 2.99, 3.09, 3.20 μ (NH, OH), 5.97, 6.08, 6.21, 6.36 μ (NH and ring), 9.10, 9.27, 9.58, 9.75 μ (C—O—C, C—OH). Both the crude solid and recrystallized product were chromatographically pure, traveling as a single spot with R_{Ad} 1.42 and 0.41 in solvent systems A and B, respectively.[19] A sample of 9-β-glucopyranosyladenine[20] traveled at R_{Ad} 1.73 and 0.18 in these same solvent systems.

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.4; H, 5.09; N, 23.5. Found: C, 44.5; H, 5.23; N, 23.1.

The aqueous phase from the above extraction was extracted with an additional 10 ml. of chloroform and then evaporated to dryness *in vacuo*. Isolation and regeneration of the picrate in the usual manner[6,16] gave an additional 75 mg. of product, m.p. 264–266°, to give an over-all yield of 0.62 g. (24% based on IV).

When the bromo sugar VII, prepared by treatment of V with hydrogen bromide in acetic acid as described for 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl bromide,[26] was condensed with chloromercuri-6-benzamidopurine, a 3% yield of nucleoside was obtained.

(B) A solution of 1.83 g. of 1,2-*O*-acetyl-3-*O*-benzoyl-D-glucofuranose 5,6-carbonate (XIII) in 50 ml. of anhydrous diethyl ether which was previously saturated with hydrogen chloride at 0°[14] and 2 ml. of acetyl chloride[15] was stored at 0° for 3 days. At the end of this time, the solution was evaporated to dryness *in vacuo* and the last traces of acetic acid were removed by the addition and subsequent removal of two 10-ml. portions of benzene *in vacuo*. The resulting chloro sugar XVI was dissolved in toluene and heated at reflux with 2.56 g. (5.40 mmoles) of chloromercuri-6-benzamidopurine[32] with stirring for 6 hr. Work-up in the usual fashion[6,16] followed by methanolysis and purification *via* picrate formation and regeneration gave 0.11 g. (7%) of a white solid which still contained adenine as shown by its paper chromatograms, but which was otherwise identical with the nucleoside prepared by method A.

Attempts to prepare the bromo sugar XVII by use of hydrogen bromide in acetic acid[26] resulted in extensive decomposition.

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(31) E. Fischer and C. Rund, *Ber.*, 49, 88 (1918).

(32) This compound was prepared from mercuric chloride and 6-benzamidopurine as described for chloromercuri-2,6-diacetamidopurine.[16]