hr. during which air was passed through the mixture. After filtering the hot solution, almost colorless needles, m.p. 139–140°, deposited on cooling. The yield was 7.3 g. (73%). Recrystallization from methanol resulted in lowering of the melting point.

Anal. Calcd. for $C_{17}H_{17}Cl_2N_3$: C, 61.1; H, 5.1; N, 12.6. Found: C, 61.5; H, 5.1; N, 12.7.

2-Phenylquinoline-4-carbox-[4′-bis(2-chloroethyl)amino]-benzylidenehydrazide. A mixture of 5.0 g. (0.019 mole) of 2-phenylquinoline-4-carboxhydrazide.[23,24] 4.7 g. (0.019 mole) of III and 350 ml. of absolute ethanol was heated under reflux. After 1 hr. yellow needles began to separate. After heating for 5 hr. and cooling 9.2 g. (99%) of the hydrazide, m.p. 208.5–210.5° with darkening at 180°, separated. Recrystallization from 30 ml. of dimethylformamide and 200 ml. of ethanol gave clusters of fine yellow needles, m.p. 214.5–215.5° (dec.). The infrared spectrum showed bands at 3160 and 1650 cm.

Anal. Calcd. for $C_{27}H_{24}Cl_2N_4O_2$: C, 66.0; H, 4.9; Cl, 14.4; N, 11.4. Found: C, 66.1; H, 4.9; Cl, 14.6; N, 11.5.

4-Aminobenz[4′-bis(2-chloroethyl)amino]benzylidenehydrazide. This was prepared as in the above case from 4-aminobenzhydrazide.[25] The hydrazide separated after 10 min. and refluxing was continued for 20 min. The yield of crude material, m.p. 183.5–184.5°, was quantitative. Recrystallization from 1:5 dimethylformamide–absolute ethanol gave pale yellow needles, m.p. 185.5°. The infrared spectrum showed bands at 3350, 3200, and 1620 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{20}Cl_2N_4O$: C, 57.0; H, 5.3; Cl, 18.7; N, 14.8. Found: C, 57.1; H, 5.2; Cl, 18.6; N, 14.7.

4-Aminopyridinecarbox[4′-bis(2-chloroethyl)amino]benzylidenehydrazide. The procedure was the same as in the above cases starting from isonicotinic acid hydrazide.[26] After refluxing for 20 min., the deep yellow solution was filtered hot. On cooling the hydrazide, m.p. 202.5–204.5° (dec.) with darkening at 195°, crystallized. Recrystallization from 1:6 dimethylformamide–absolute ethanol raised the m.p. to 203–205.5° (dec.). The infrared spectrum showed bands at 3160 and 1650 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{18}Cl_2N_4O$: C, 55.9; H, 5.0; Cl, 19.4; N, 15.3. Found: C, 56.2; H, 4.9; Cl, 19.3; N, 15.6.

5-{4′-[N,N-bis(2-chloroethyl)amino]benzylidene}barbituric acid. A warm solution of 1.23 g. (0.005 mole) of III in 25 ml. of ethanol was added to a warm solution of 0.64 g. (0.005 mole) of barbituric acid in 6 ml. of water. After heating on the steam bath for 2 min., 1.1 g. of orange crystals, m.p. 268° (dec.) separated. From the mother liquor another 570 mg. was obtained, making the total yield 94%. No further purification was necessary. The compound is sparingly soluble in most solvents and quite soluble in dimethylformamide.

Anal. Calcd. for $C_{15}H_{15}Cl_2N_3O_3$: C, 50.6; H, 4.2; N, 11.7. Found: C, 50.7; H, 4.2; N, 11.9.

Acknowledgment. We acknowledge the assistance of James Hudson and Karl Lindfors in the preparation of certain intermediates.

ANN ARBOR, MICH.

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(26) Supplied by the Cancer Chemotherapy National Service Center.

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

Potential Anticancer Agents.[1] X. Synthesis of Nucleosides Derived from 6-Deoxy-D-glucofuranose

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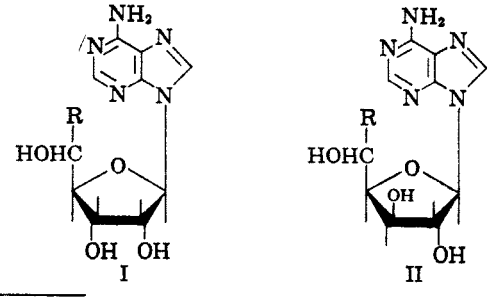
6-Amino- and 2,6-diamino-9-(6′-deoxy-β-D-glucofuranosyl)purine (XV and XVI) have been synthesized from D-glucose *via* the key intermediates 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII) and 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranose (IX).

Synthesis of 5′-*C*-alkylpentofuranosyl nucleosides as possible inhibitors of cellular synthesis or utilization of nucleosides (I, R = H) and nucleotides has been the subject of several previous papers of this series. 9-α-L-Rhamnofuranosyladenine[2] was synthesized from rhamnose. Similarly, the two possible 5-*C*-methyl-D-ribose nucleosides (I, R = CH_3), namely, 9-(6′-deoxy-β-D-allofuranosyl) adenine[3] and 9-(6′-deoxy-α-L-talofuranosyl)adenine,[4] have been described. Since 9-β-D-xylofuranosyladenine (II, R = H)[2] has shown weak anticancer activity against Carcinoma 755,[5] the synthesis 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 of Cancer Research. For the preceding paper of this series *cf.* R. Koehler, L. Goodman, J. DeGraw, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

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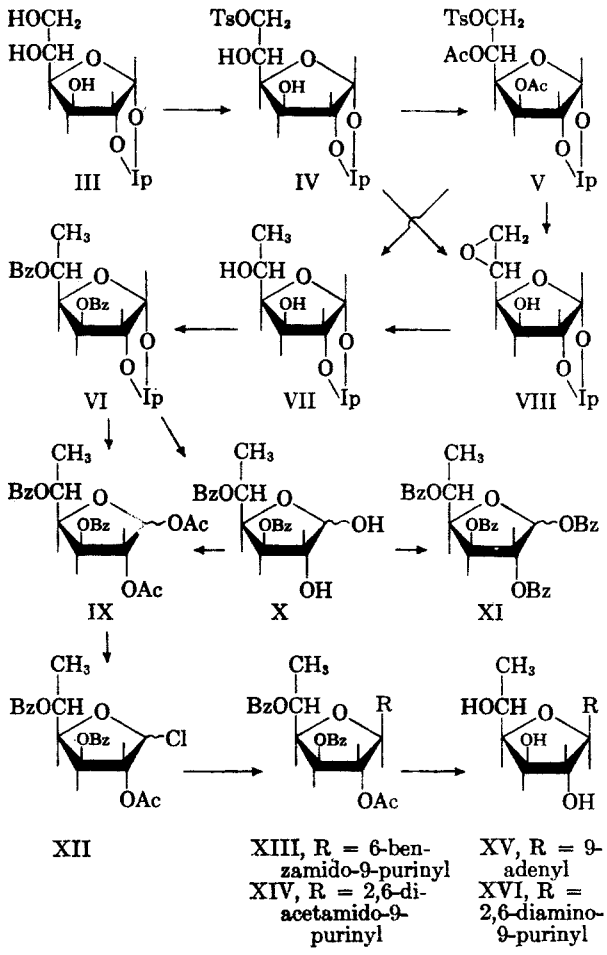
testing of its two 5′-*C*-methyl derivatives (II, R = CH_3) was considered to be of interest in this general program. Introduction of the 5′-C-methyl group in II gives an additional asymmetric center at the 5′-position, thus leading to two isomers of II. The synthesis of the nucleosides derived from one isomer, 6′-deoxy-D-glucofuranose, is the subject of this paper. The synthesis of nucleosides derived from the second isomer, 6′-deoxy-L-idofuranose, is the subject of a following paper.

The first key intermediate in the projected synthesis is 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII), which has been previously synthesized by hydrogenation of 5,6-anhydro-1,2-*O*-isopropylidene-D-glucofuranose (VIII) using a palladium[6] or Raney nickel catalyst.[7] It has now been found that lithium aluminum hydride is a convenient reagent for this reduction. Preparatively, the sequence was considerably shortened by tosylation, then acetylation of 1,2-*O*-isopropylidene-D-glucofuranose (III) in the same solution to give the crude diacetate V. Reduction of V with lithium aluminum hydride proceeded through the 5,6-anhydro sugar VIII, giving a considerably better over-all yield of 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII) than could be obtained by isolation of the various intermediates.

Benzoylation of VII afforded the dibenzoate VI as a crystalline solid with good crystallizing powers. It was found that the dibenzoate VI was more easily purified than VII; thus better over-all yields of the dibenzoate VI were obtained when VII was not purified. By not isolating each intermediate, the over all yield of VI from III was increased about threefold.

Although the diacetate of VII has been previously described,[6] the benzoyl blocking groups are considered superior to acetyl for further transformations[8] necessary to synthesize the required nucleosides.

Hydrolysis of the isopropylidene group of VI with a mixture of acetic acid and hydrochloric acid gave a 75% yield of 3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranose (X) as a glass that was homogeneous when chromatographed on acetylated paper[14] and was free of starting material (VI). Conversion of X to the tetrabenzoate XI or to the 1,2-diacetate IX proceeded smoothly, but neither anomeric mixture could be crystallized. The second key intermediate, 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranose (IX), was also prepared, in 93% yield, by acetolysis[9] of the isopropylidene derivative VI, a procedure considered to be more convenient and giving higher yields than the sequence *via* X.



Reaction of the amorphous diacetate (IX) with ethereal hydrogen chloride[10] containing acetyl chloride[11] gave the crude chloro derivative (XII). The conversion of the 1-*O*-acetyl group in IX to the halogen in XII could be readily followed by examination of the infrared absorption spectra of aliquots. The starting diacetate (IX) has acetate C—O—C bands at 8.10 and 8.20 μ. The reaction was run until the decrease in absorption in that region ceased, when conversion to XII was complete. Condensation of XII with chloromercuri-6-benzamidopurine afforded the crude blocked nucleoside (XIII). Deacylation with methanolic sodium methoxide gave the nucleoside (XV), isolated *via* its picrate. Regeneration of the base (XV) with Dowex 2 (CO_3) in the usual manner[3,12] gave the

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

(7) E. Vischer and T. Reichstein, *Helv. Chim. Acta*, **27**, 1332 (1944).

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

(11) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5900 (1955), have used acetyl chloride in this type of reaction to maintain anhydrous conditions.

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

pure nucleoside, 9-(6′-deoxy-β-D-glucofuranosyl) adenine (XV),[13] in 32% yield based on IX.

Similarly, condensation of 2-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranosyl chloride (XII) with chloromercuri-2,6-diacetamidopurine[12] to the blocked nucleoside (XIV) followed by deacylation gave 2,6-diamino-9-(6′-deoxy-β-D-glucofuranosyl)-purine (XVI)[13] in 16% yield based on IX.

EXPERIMENTAL[14–16]

3,5-Di-O-acetyl-1,2-O-isopropylidene-6-O-tosyl-D-glucofuranose (V). To a solution of 5.0 g. (23 mmoles) of 1,2-*O*-isopropylidene-D-glucofuranose (III)[18] in 55 ml. of reagent pyridine was added dropwise a solution of 4.28 g. (22.5 mmoles) of tosyl chloride in 70 ml. of methylene chloride over a period of 30 min. with vigorous stirring. After standing at room temperature for 24 hr. protected from moisture, the mixture was treated with 10 ml. (0.11 mole) of acetic anhydride with stirring, then allowed to stand an additional 24 hr. The mixture was poured into 300 g. of ice water and extracted with chloroform (3 × 30 ml.). The combined extracts were washed with excess aqueous sodium bicarbonate, then water. Dried with magnesium sulfate, the organic solution was evaporated to dryness *in vacuo*. The last traces of pyridine were removed by addition and evaporation of two 20-ml. portions of toluene, leaving 10.2 g. (97%) of an oil that only partially solidified on standing, but was suitable for reduction to VII. Recrystallization of a similar preparation from 83% aqueous methanol gave 4.82 g. (46%) of white crystals, m.p. 89–90°; λ_{max}^{KBr} 5.71 μ (C=O), 8.08 μ (acetate C—O—C), 8.50 μ (sulfonate).

Vischer and Reichstein[7] have recorded m.p. 90° for V and stated that the yield was quantitative starting with 1,2-*O*-isopropylidene-6-*O*-tosyl-D-glucofuranose (IV). The latter has been prepared in 56% yield,[19,20] and in 48% yield in this laboratory, from III. Compound IV was considerably more difficult to purify than was V.

5,6-Anhydro-1,2-O-isopropylidene-D-glucofuranose (VIII). A solution of 1.00 g. (2.1 mmoles) of pure V in 4.2 ml. of reagent chloroform was added to a solution of 0.38 g. of sodium methoxide in 6 ml. of reagent methanol cooled in an ice bath. After 30 min. at 0°, the gel-like mass was diluted with 5 ml. of water and the separated aqueous layer extracted with chloroform (4 × 5 ml.). The chloroform extracts were each washed with 10 ml. of water, then combined, dried with magnesium sulfate, and evaporated to dryness *in vacuo;* yield, 0.42 g. (96%) of white crystals, m.p. 116–122°. Recrystallization from 10 ml. of benzene gave 0.25 g. (57%) of pure product, m.p. 130–132°, $[\alpha]_D^{27}$ −26.6° (2.0% in $CHCl_3$); λ_{max}^{KBr} 2.97 μ (OH), 3.28 μ (epoxide CH), 7.21 μ (gem dimethyl), 9.00, 9.20, 9.36, 9.55, 9.85 μ (C—OH and ether C—O—C).

The same over-all yield (from III) of recrystallized product (VIII) was obtained starting with crude diacetate (V). Ohle and Vargha[21] have prepared this compound in 80% yield from IV and have given m.p. 133.5°, $[\alpha]_D^{20}$ −26.5° (4% in H_2O).

6-Deoxy-1,2-O-isopropylidene-D-glucofuranose (VII). To a mixture of 5.12 g. (0.183 mole) of lithium aluminum hydride and 130 ml. of reagent ether was added 2.22 g. (11.0 mmoles) of pure VIII over a period of about 4 min. The mixture, protected from moisture, was refluxed with stirring for 3 hr., then the excess hydride was decomposed by the dropwise addition of 21 ml. of ethyl acetate, then 21 ml. of water. After 47 ml. of 10% aqueous sodium hydroxide was added, the organic layer was decanted from the sludge. The latter was extracted with ethyl acetate (3 × 30 ml.). The combined organic extracts dried with magnesium sulfate, were evaporated to dryness *in vacuo*, leaving 1.32 g. (60%) of a yellow sirup. Distillation gave 1.23 g. (55%) of colorless oil, b.p. 76–79° (5 μ), that solidified in the receiver, m.p. 87–88°, $[\alpha]_D^{25}$ −21.3° (2.0% in $CHCl_3$); λ_{max}^{KBr} 2.90 μ (OH), 9.20, 9.84 μ (ether C—O—C), and no epoxide CH at 3.28 μ.

This compound (VII) has been prepared by catalytic hydrogenolysis of VIII in "good yield," m.p. 92°, $[\alpha]_D^{27}$ −26.3% (1% in $CHCl_3$).[6,7]

3,5-Di-O-benzoyl-6-deoxy-1,2-O-isopropylidene-D-glucofuranose (VI). To a mixture of 1.32 g. (0.035 mole) of lithium aluminum hydride in 40 ml. of anhydrous ether was added a solution of 8.0 g. (0.017 mole) of crude 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-tosyl-D-glucofuranose (V) in 20 ml. of dry benzene over a period of 40 min. The mixture, protected from moisture, was refluxed with stirring for 3 hr. The excess hydride was decomposed by the dropwise addition of 30 ml. of ethyl acetate, then 27 ml. of water followed by 65 ml. of 10% aqueous sodium hydroxide. The mixture was filtered through a Celite filter cake. The filter cake was washed with ethyl acetate (2 × 20 ml.), then continuously extracted with 100 ml. of chloroform for 3 hr. The combined chloroform and ethyl acetate extracts were dried with magnesium sulfate, then evaporated to dryness *in vacuo*, leaving 2.12 g. (60%) of crude VII as a yellow sirup.

To a solution of 1.82 g. (8.9 mmoles) of the preceding crude 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII) in 12 ml. of reagent pyridine was added dropwise 3.6 ml. (31 mmoles) of benzoyl chloride over a period of 30 min., the temperature being maintained below 5°. The reaction mixture was stirred at 0° for 1 hr., then for 1 hr. at room temperature. After standing overnight at room temperature protected from moisture, the reaction mixture was added dropwise to a mixture of ice and excess aqueous saturated sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted with three 10-ml. portions of chloroform. The combined extracts were washed with excess aqueous sodium bicarbonate, then water, dried with magnesium sulfate, and taken to dryness *in vacuo*. The last traces of pyridine were removed by the addition of toluene (2 × 10 ml.) and removal *in vacuo* to give 3.46 g.

(13) That this nucleoside has a C_1-C_2-*trans*-configuration, in this case β, is highly probable in view of the rule postulated for the stereochemistry of nucleoside formation. For a summary of reactions illustrating this point see 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) The paper chromatograms on the blocked sugars were run on Schleicher and Schull acetylated paper No. 2043B by the descending technique using methanol-water-benzene (6:1:2) as the solvent (solvent A), the spots being detected by visual examination with ultraviolet light; *cf.* T. Wieland and W. Kracht, *Angew. Chem.*, **69**, 172 (1957).

(15) The paper chromatograms on the nucleosides were run by the descending technique on Whatman No. 1 paper using 5% disodium phosphate (solvent B) or water-saturated butanol (solvent C) as solvents. Adenine was used as a standard and R_{AD} values are recorded with R_{AD} 1.00 being assigned to adenine.

(16) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.[17]

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

(18) Prepared in 74% yield, m.p. 159–160°, from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose according to the procedure of S. G. Laland, *Acta Chem. Scand.*, **8**, 866 (1954).

(19) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 139 (1946).

(20) H. Ohle and E. Dickhauser, *Ber.*, **58B**, 2593 (1925).

(21) H. Ohle and L. Vargha, *Ber.*, **62B**, 2435 (1929).

(94%) of a dark sirup. The crude product was recrystallized from methanol, giving 1.47 g. (40%) of VI in two crops, m.p. 108–110°. The over-all yield from III was 23%. On a large scale the over-all yield from III was 140 g. (26%).

In a pilot run, the benzoylation of pure 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII) gave 0.90 g. (59%) of VI, m.p. 111–113°. Two recrystallizations from methanol afforded white crystals, m.p. 113–113.5°, $[\alpha]_D^{25}$ −112.6° (2.0% in $CHCl_3$); λ_{max}^{KBr} 5.82 μ (benzoate C=O), 7.90, 8.92 μ (benzoate C—O—C), 9.11, 9.32, 9.72 μ (ether C—O—C).

Anal. Calcd. for $C_{23}H_{24}O_7$: C, 67.0; H, 5.87. Found: C, 66.9; H, 6.03.

Paper chromatography on acetylated paper in solvent A[14] showed only one spot with R_f 0.28.

3,5-Di-O-benzoyl-6-deoxy-D-glucofuranose (X). A solution of 0.45 g. (1.1 mmoles) of VI in 5.5 ml. of warm acetic acid was rapidly cooled to 15°, then treated with 3.0 ml. of 12*N* hydrochloric acid. After standing at room temperature for 30 min., the mixture was poured into 10 ml. of ice water and extracted with chloroform (3 × 10 ml.). The combined extracts were washed with water, excess aqueous sodium bicarbonate, and water. After being dried over magnesium sulfate, the solution was evaporated *in vacuo*, leaving 0.31 g. (75%) of product, probably an anomeric mixture, as a sirup that could not be crystallized; λ_{max}^{film} 2.93 μ (OH), 5.80 μ (C=O), 7.87, 8.98 μ (ester C—O—C). Chromatography on acetylated paper[14] with solvent A showed only one spot with R_f 0.66 and the absence of starting material with R_f 0.28.

Anal. Calcd. for $C_{20}H_{20}O_7$: C, 64.5; H, 5.41. Found: C, 64.8; H, 5.61.

Treatment of X with benzoyl chloride and pyridine, as described for the preparation of VI, gave the tetrabenzoate XI as an anomeric mixture that failed to crystallize but had R_f 0.09 when chromatographed on acetylated paper[14] with solvent A.

1,2-Di-O-acetyl-3,5-di-O-benzoyl-6-deoxy-D-glucofuranose (IX). To a stirred solution of 2.25 g. (5.46 mmoles) of crystalline VI in 27 ml. of acetic acid and 3 ml. of acetic anhydride was added dropwise with cooling 1.65 ml. of 96% sulfuric acid at such a rate that the temperature was 10–20°. After standing in a stoppered flask for 24 hr., the solution was poured into 200 ml. of ice water, then stirred for 30 min. The mixture was extracted with chloroform (3 × 25 ml.). The chloroform extracts were washed with 25 ml. of saturated aqueous sodium bicarbonate, then 25 ml. of water. The extracts were combined, dried with magnesium sulfate, and evaporated to dryness *in vacuo*; yield, 2.33 g. (93%) of a nearly colorless sirup; λ_{max}^{film} 5.68 μ (acetate C=O), 5.77 μ (benzoate C=O), 7.84 μ (benzoate C—O—C), 8.10 μ (acetate C—O—C). This compound, which failed to crystallize and was probably an anomeric mixture, traveled as a single spot on acetylated paper[14] in solvent A at R_f 0.28 and had $[\alpha]_D^{25}$ −67.0° (2.1% in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{24}O_9$: C, 63.2; H, 5.30. Found: C, 62.9; H, 5.40.

Acetylation of X in acetic anhydride–pyridine gave IX as a sirup that had an R_f in solvent A[14] and an infrared spectrum essentially identical with that of the above preparation.

9-(2′-O-Acetyl-3′,5′-di-O-benzoyl-6′-deoxy-β-D-glucofuranosyl)-6-benzamidopurine (XIII). A solution of 2.33 g. (5.1 mmoles) of IX in 5 ml. of acetyl chloride[11] was added to 55 ml. of reagent ether that had been previously saturated with hydrogen chloride.[10] After standing at −5° for 3 days in a stoppered container, the mixture was evaporated to dryness *in vacuo* with protection from moisture. Acetic acid was removed by addition of benzene (2 × 5 ml.) and evaporation *in vacuo*. The pale yellow, sirupy XII was dissolved in xylene and coupled with 2.64 g. of chloromercuri-6-benzamidopurine[22] in the usual manner.[3] Evaporation of the chloroform solution gave 2.72 g. of a gum that was dissolved in 50 ml. of hot benzene. The solution deposited 0.20 g. of 6-benzamidopurine,[23] m.p. 239–242°, that had an infrared spectrum identical with that of an authentic sample. Evaporation of the filtrate afforded 2.04 g. of crude, blocked nucleoside (XIII); λ_{max}^{film} 3.00 μ (NH), 5.68 μ (acetate C=O), 5.78 μ (benzoate C=O), 5.89 μ (amide C=O), 6.20, 6.28 μ (purine ring), 9.10, 9.31, 9.70 (C—O—C).

9-(6′-Deoxy-β-D-glucofuranosyl)adenine (XV). A solution of 2.04 g. of crude XIII in 50 ml. of reagent methanol and 6 ml. of 1*N* methanolic sodium methoxide was refluxed for 1.5 hr. The solution was neutralized with acetic acid, then evaporated to dryness *in vacuo*. The residue was partitioned between 20 ml. of water and 20 ml. of chloroform. The aqueous solution, washed once more with chloroform, was evaporated to dryness *in vacuo*. A solution of the residue in 20 ml. of water was treated with 30 ml. of 10% methanolic picric acid. After several hours at 0°, the mixture was filtered and the precipitate washed with methanol. Recrystallization from 20 ml. of water gave 0.65 g. of the picrate of XV as yellow crystals, m.p. 204–208° dec. The free nucleoside was regenerated from the picrate with 3.1 g. of Dowex 2 (CO_3) and 20 ml. of water in the usual fashion.[3,12] Evaporation of the aqueous solution to dryness *in vacuo* gave 0.29 g. (32%) of white solid, m.p. 118–120°. Recrystallization from ethanol afforded white crystals, m.p. 118–118.5°, $[\alpha]_D^{25}$ −59.9° (2% in H_2O); λ_{max}^{KBr} 2.95, 3.11 μ (OH, NH), 6.12, 6.25, 6.75 μ (NH and purine ring), 7.28 μ (CH_3), 9.21, 9.32, 9.62 μ (C—O—C and C—O—H). Both the crude and recrystallized products were chromatographically homogeneous and traveled at R_{AD} 1.53 in solvent B and at R_{AD} 0.91 in solvent C.[15] That the recrystallized nucleoside was an ethanol solvate was demonstrated by the ethoxyl determination.

Anal. Calcd. for $C_{11}H_{13}N_5O_4 \cdot C_2H_5OH$: C, 47.7; H, 6.47; N, 21.4; one ethoxyl, 1.0. Found: C, 47.5; H, 6.54; N, 21.9; ethoxyl, 0.90.

This nucleoside, as expected for structure XV, consumed 0.90 mole-equivalents of periodate in 96 hr.; the rate curve was then approaching 1.0 mole-equivalents asymptotically.

2,6-Diacetamido-9-(2′-O-acetyl-3′,5′-di-O-benzoyl-6′-deoxy-β-D-glucofuranosyl)purine (XIV). Condensation of XII, prepared from 2.60 g. (5.7 mmoles) of the diacetate (IX) with 2.88 g. (6.1 mmoles) of chloromercuri-2,6-diacetamidopurine[12] in the usual manner[3,12] gave 2.49 g. (70%) of crude, blocked nucleoside; λ_{max}^{film} 5.70 μ (acetate C=O), 5.80 μ (benzoate C=O), 6.18, 6.25 μ (NH and purine ring), 9.12, 9.28, 9.72 μ (C—O—C).

2,6-Diamino-9-(6′-deoxy-β-D-glucofuranosyl)purine (XVI). A solution of 2.49 g. of crude XIV in 20 ml. of reagent methanol and 3 ml. of *N* methanolic sodium methoxide was refluxed for 3 hr. The solution was neutralized with acetic acid, then processed through the picrate (0.53 g.) as described for XV. The free nucleoside was regenerated from the picrate with 2.09 g. of Dowex 2 (CO_3) and 20 ml. of water in the usual fashion.[3,12] Evaporation of the aqueous solution to dryness *in vacuo* gave 0.26 g. of a white solid, m.p. 129–132°. Recrystallization from ethanol-ether afforded white crystals, m.p. 172–175°, $[\alpha]_D^{25}$ −27.7° (0.37% in H_2O); λ_{max}^{KBr} 3.00, 3.12 μ (NH, OH), 6.10, 6.25, 6.75 μ (NH and purine ring), 7.25 μ (CH_3), 9.22, 9.48, 9.82 μ (C—O—C and C—O—H). Both the crude and the recrystallized products were chromatographically homogeneous[15] and traveled at R_{AD} 0.90 in solvents B and R_{AD} 0.51 in solvent C.

Anal. Calcd. for $C_{11}H_{16}N_6O_4.H_2O$: C, 42.0; H, 5.77; N, 26.7. Found: C, 42.5; H, 5.70; N, 26.6.

(22) Prepared from 6-benzamidopurine as described for the preparation of chloromercuri-2,6-diacetamidopurine.[12]

(23) This procedure effectively avoids the presence of adenine in a final deblocked nucleoside and is particularly useful if the blocked nucleoside cannot be crystallized.

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

Potential Anticancer Agents.[1] XI. Synthesis of Nucleosides Derived from 6-Deoxy-L-idofuranose

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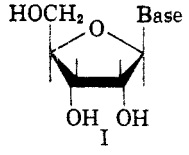
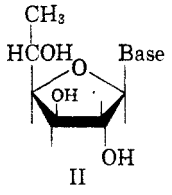
Lithium aluminum hydride reduction of 6-*O*-benzoyl-1,2-*O*-isopropylidene-5-*O*-tosyl-D-glucofuranose (IV) has led to a new and useful synthesis of 6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (IX). The latter was converted to 9-(6′-deoxy-α-L-idofuranosyl)adenine (XV) and to 2,6-diamino-9-(6′-deoxy-α-L-idofuranosyl)purine (XIV) *via* the key intermediate 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-L-idofuranose (VII).

In a preceding paper of this series,[2] the rationale for synthesizing 6-deoxy-L-idofuranosyl nucleosides (II) was presented. This paper describes the synthesis of 9-(6′-deoxy-α-L-idofuranosyl)adenine (XV) and 2,6-diamino-9-(6′-deoxy-α-L-idofuranosyl)purine (XIV), compounds that might be antagonists of natural D-ribofuranosyl nucleosides (I).



I



II

The key intermediate in the projected synthesis of the nucleosides XIV and XV is 6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (IX), which has been synthesized by the hydrogenation of 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-L-idofuranose (VI)[3] and by hydrogenation of the glucosene (XII).[4] A new synthesis of this key intermediate (IX) that is considered to be shorter and more convenient has now been developed.

Ohle and Dickhauser[5] have claimed that tosylation of 6-*O*-benzoyl-1,2-*O*-isopropylidene-D-glucofuranose (III) in pyridine-chloroform at 37° for 4 days gave the 5-*O*-tosyl derivative (IV) in 34% yield, but Meyer and Reichstein[3] obtained a yield of only 20% by this procedure. It was observed in this laboratory that the infrared absorption spectrum of 6-*O*-benzoyl-1,2-*O*-isopropylidene-D-glucofuranose (III) contained the benzoate carbonyl stretching band at 5.90 μ instead of at the normal position of 5.80 μ. Tosylation of III to give the 5-*O*-tosyl derivative (IV) caused this carbonyl stretching band to shift back to the normal 5.80 μ position, presumably because the 5-tosylate destroyed hydrogen bonding between an available hydroxyl and the 6-benzoate carbonyl of III. This shift in the position of the carbonyl band made it possible to determine the degree of completion of the reaction by the gradual disappearance of the band at 5.90 μ. Thus, the most optimum conditions found involved the use of pyridine–methylene chloride at 40–50° for 4 days, which gave IV in 43% yield; a shorter reaction time, a lower temperature, or chloroform as a solvent[5] gave less complete conversion.

Meyer and Reichstein[3] have converted the 5-tosyl derivative (IV) with methanolic sodium methoxide to 5,6-anhydro-1,2-*O*-isopropylidene-L-idofuranose (V) in 61% yield. In this laboratory, their procedure gave a 64% yield of partially crystalline product (V) that was difficult to purify since it readily decomposed. It has now been found that lithium aluminum hydride reduction of the tosylate (IV) gave a 78% yield of the desired 6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (IX), the reaction presumably proceeding *via* the anhydro L-idose derivative (V). The 6-deoxy-L-idose derivative (IX) agreed in melting point (90–92°) with that given by Meyer and Reichstein[3,4] and gave a large depression in melting point when mixed with the isomeric 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose,[2] a possible, though theoretically unlikely, product.

Treatment of 6-deoxy-1,2-*O*-isopropylidene-L-idofuranose (IX) with benzoyl chloride in pyridine gave the dibenzoate (VIII) in quantitative yield as an oil that could not be crystallized. Acetolysis of

(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.

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

(3) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 152 (1946).

(4) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, **29**, 139 (1946).

(5) H. Ohle and E. Dickhauser, *Ber.*, **58B**, 2593 (1925).