abstraction of a proton or a deuteron from the α-carbon and a prototropic shift in the imine intermediate. The reaction appears to be general acid and general base catalyzed through a mechanism of the push–pull type.

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Synthesis of 3′-Deoxynucleosides I

Synthesis of 9-(3-Deoxyaldofuranosyl) Adenines Derived from 3-Deoxy-D-galactose

By J. PROKOP and DANIEL H. MURRAY

Diacetone glucose was tosylated at the 3-position and the tosyl group eliminated with potassium hydroxide to yield the furanoseen which on reduction gave rise to 1, 2 : 5, 6-di-*O*-isopropylidene-3-deoxy-D-galactofuranose. This was hydrolyzed selectively to the 1,2-monoacetone derivative, which was converted *via* benzoylation and acetolysis to the 1,2-diacetate, 5,6-dibenzoate. Condensation of this compound with chloromercuri-6-benzamidopurine in the presence of titanium tetrachloride, followed by deblocking with methanolic sodium methoxide, yielded the nucleoside 9-(3-deoxy-β-D-galactofuranosyl) adenine. In a separate procedure, the 1,2-*O*-isopropylidene-3-deoxy-D-galactofuranose was oxidized with periodate and reduced with borohydride to give 1,2-*O*-isopropylidene-L-arabinofuranose, convertible to the corresponding adenine-L-arabinofuranoside by procedures similar to those employed for the galacto-derivative.

A NUMBER OF nucleosidic substances have been shown to have significant biological activity of type and degree which suggest a significant potential for the development of therapeutically useful substances. Among these are materials possessing antibiotic and/or antitumor properties, such as cordycepin (I); puromycin (II) and its aminonucleoside (III), its adenine analog (IV); xylofuranosyladenine (V); and psicofuranine (VI). In each of these cases, the base is adenine or its *N*-dimethyl derivative, and the major difference in structure from that of the naturally occurring analogs, adenosine (VII) and deoxyadenosine, resides in the sugar moiety.

In the attempt to design purines with antitumor activity, there have been extended series of changes made at the 2- and 6-positions of the purine nucleus. In only a relatively small number of instances—for example, in 6-mercaptopurine (VIII)—have such changes led to appreciable biological activity. Similarly, changes at the 9-position have resulted with one general exception in compounds with little if any activity. The exception occurs in cases where the 9-substituent is either a sugar moiety or other group which may be viewed as analogous to a sugar. Of the approximately 30 adenine nucleosides isolated or synthesized, some eight or more have had significant biological activity—for example, compounds I–VI. Moreover, in the case of the aminonucleoside of puromycin (III), a compound with both trypanocidal and carcinostatic activity, if the 6-dimethylamino group is replaced by amino (IV) or by other mono- or dialkylamino, considerable biological activity remains (1, 2). On the other hand, if the sugar moiety is replaced by ribose (IX), there is a loss of activity (3).

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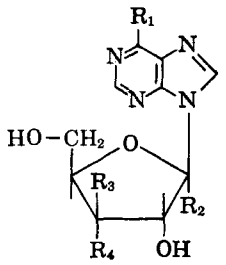
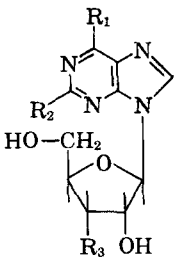
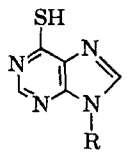
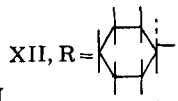


I, $R_1 = NH_2$, $R_2 = R_3 = R_4 = H$
II, $R_1 = N(CH_3)_2$, $R_2 = R_3 = H$,
$R_4 = C(=O)—CH(NH_2)—CH_2—C_6H_4—OCH_3$
III, $R_1 = N(CH_3)_2$, $R_2 = R_3 = H$, $R_4 = NH_2$
IV, $R_1 = R_4 = NH_2$, $R_2 = R_3 = H$
V, $R_1 = NH_2$, $R_2 = R_4 = H$, $R_3 = OH$
VI, $R_1 = NH_2$, $R_2 = CH_2OH$, $R_3 = H$, $R_4 = OH$
VII, $R_1 = NH_2$, $R_2 = R_3 = H$, $R_4 = OH$



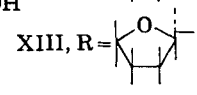


VIII, R = H



XII, R =

IX, $R_1 = N(CH_3)_2$, $R_2 = H$, $R_3 = OH$
X, $R_1 = OH$, $R_2 = R_3 = NH_2$
XI, $R_1 = R_3 = NH_2$, $R_2 = OH$



XIII, R =

Furthermore, if the aminonucleoside is modified by replacement of the base, as in 3-amino-3′-deoxyguanosine (X) and 3′-amino-3′-deoxycrotonoside (XI), inactive compounds result (4). All such findings point to the likelihood that biological activity resides at least to some degree in the presence of a modified sugar moiety.

Additional support for this hypothesis is adducible. For example, a number of 9-alkylpurines have been shown to be active against Adenocarcinoma 755 in experimental mice (5). Robins (6) has suggested that such 9-substituents take the place of a natural sugar moiety and that the purines are acting at the nucleoside level. Among the 9-alkyl purinethiols tested, the 9-cyclohexyl derivative (XII) was more inhibitory than any of the others (7). Similarly, Robins (6) has found that 9-tetrahydro-2-furyl purinethiol (XIII), active against Adenocarcinoma 755, has a therapeutic index of 33 compared with 13 for 6-purinethiol itself. Whether the activity of such nucleosidic materials is related to an improved transport process has not been established. However, the potential contribution to activity of a 9-substituent resembling a sugar moiety appears well established.

The adenine nucleosides synthesized or isolated to date have been tested for biological activity in a number of different systems, and the results are not necessarily related. Nevertheless, although there are a number of exceptions, certain admittedly imperfect generalizations may be identified at least as guidelines to a likelihood of biological activity. Among the fraudulent sugar nucleosides, the maximum likelihood for activity appears to reside in a requirement that the purine be *trans*-linked,[1] that the sugarlike moiety be furanosyl, and that there be no hydroxyl group down at the 3′-position. With the one exception of psicofuranine (VI), the antibiotic and/or antitumor compounds I–IV and 9-tetrahydro-2-furyl-6-mercaptopurine and xylofuranosyladenine (V) meet these requirements.

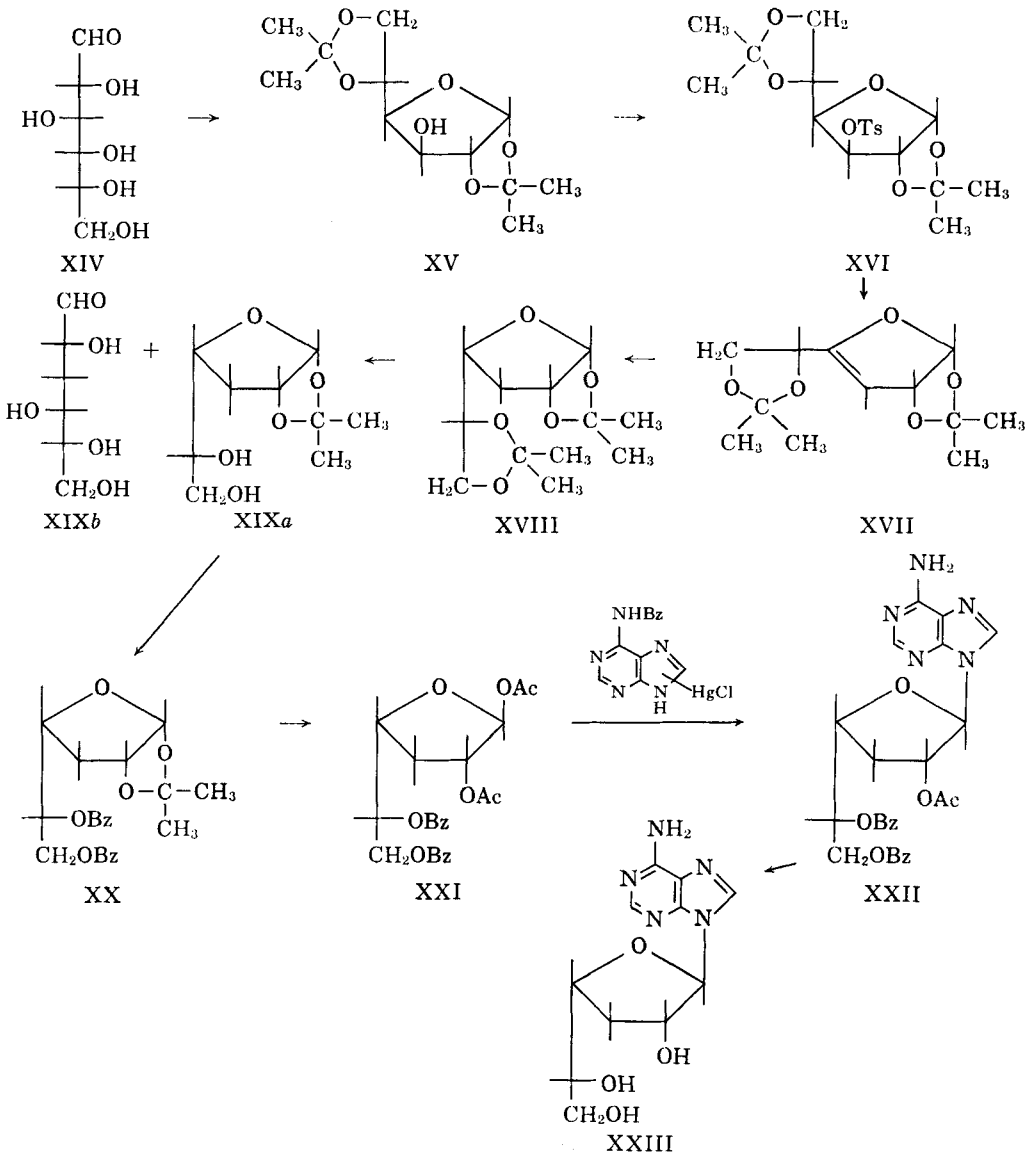
Since at least the majority of the presently known active nucleoside compounds fall within this requirement, including two antibiotics, it has been of interest in the present series to prepare a number of 3′-deoxyaldofuranosyl adenines. These may be viewed as analogs both of puromycin (II) and of cordycepin (I). The present paper outlines the preparation of two such adenine nucleosides derived from 3-deoxy-D-galactofuranose.

DISCUSSION

The key intermediate for these syntheses is 1,2:5,6-di-*O*-isopropylidene-3-deoxy-D-galactofuranose (XVIII), prepared according to the sequence illustrated in Scheme I (XIV–XVIII). Tosylate elimination from XVI was accomplished with solid potassium hydroxide, giving the glycoseen derivative (XVII) in a yield of 65%. The potassium hydroxide modification allowed the reaction to be conducted in considerably less time (6 hr. compared to 24 hr.) and with ordinary laboratory equipment so that a larger scale preparation of the glycoseen intermediate was achieved more readily. Reduction of XVII over 5% palladium-on-charcoal catalyst gave the desired 3-deoxygalactose derivative (XVIII) in quantitative yield.

Selective hydrolysis of diacetone-3-deoxygalactose (XVIII) was accomplished with 50% aqueous methanol containing hundredth normal hydrochloric acid, a modification of a procedure used earlier by Mehltretter (9) for the preparation of monoacetoneglucose. The reaction was conducted at 40° for 90 min. giving the monoacetone derivative (XIX*a*) as a crystalline solid in a yield of 52.5% (based on unrecovered starting material). This compound failed to reduce Benedict's solution, thereby locating the isopropylidene group at the 1,2-position. Subsequent oxidation with sodium metaperiodate confirmed its furanose structure. The diacetone-3-deoxygalactose recovered from the reaction could be recycled. When the same reaction was conducted for 4 hr., no starting material (XVIII)

[1] The arrangement of the base at C1 and hydroxyl at C2 of the sugar moiety.

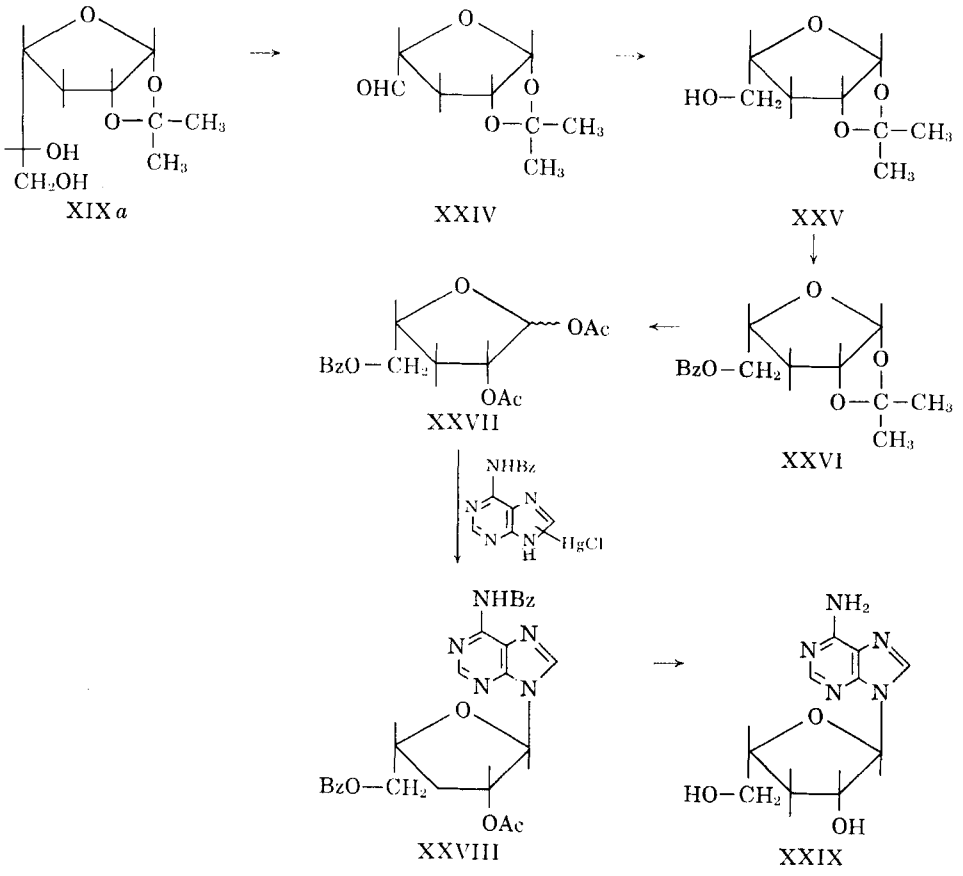


Scheme I

was recovered, and the product consisted mainly of 3-deoxy-D-galactose (XIX*b*). This increased lability of the 1,2-isopropylidene group in compounds XVIII and XIX*a* is consistent with the generalization that electronegative groups substituted at the 3-position of 1,2-isopropylidene aldoses stabilize isopropylidene groups against hydrolysis (*cf.* for example, the selective hydrolysis of diacetoneglucose under similar conditions employed by Mehltretter).

The mild acidic conditions used in the preparation of monoacetone-3-deoxygalactose also resulted in the isolation of 3-deoxy-D-galactose (XIX*b*) in crystalline form. This appears to be the first reported crystallization of this sugar, which was previously obtained by Weygand and Wolz (8) as a syrup when diacetone-3-deoxygalactose was subjected to considerably stronger acidic hydrolytic conditions. Such more drastic conditions of hydrolysis could possibly lead to formation of the 1,6-anhydro derivative of this sugar in significant amounts. A similar explanation in the case of 3-deoxy-D-glucose and 3-deoxy-D-mannose has been given by Pratt and Richtmyer (10), whose studies on these sugars included isolation and characterization of the 1,6-anhydro derivatives formed under acidic conditions.

Monoacetone-3-deoxygalactose (XIX*a*) was converted to the syrupy 5, 6-dibenzoate (XX) in a yield of 90%. Under acetolysis conditions, this compound gave the 1,2-diacetate (XXI) as a crystalline solid in a yield of 77%. The specific rotation of $-28°$ for this material suggested that it was probably the β anomer. When the 1, 2-diacetate was condensed with chloromercuri-6-benzamidopurine in the presence of titanium tetrachloride (11), the acylated nucleoside (XXII) was obtained as a crude glass,



Scheme II

Deacylation of this compound with methanolic sodium methoxide gave crystalline 9-(3-deoxy-β-D-galactofuranosyl) adenine (XXIII) in a yield of 39% from the 1, 2-diacetate (XXI). This nucleoside is presumed to be the *trans* isomer by application of the *trans* rule postulated by Baker (12). The moderately strong levorotation of this compound (−57°) also suggests it to be the β anomer. Although condensations of acylated sugars with chloromercuri-6-benzamidopurine in the presence of titanium tetrachloride have been shown in some instances to give rise to a mixture of α and β anomers (13), that isomer in which the configuration of Cl-C2 was *trans* predominated by a ratio of at least 3 to 1. Since condensation reactions of this type ordinarily proceed in yields of 30 to 50%, a yield of 39%, as above, would suggest that the compound isolated was the β anomer desired. The filtrates from this reaction currently are being investigated for the presence of the other anomer (presumed α).

Oxidation of monoacetone-3-deoxygalactose (XIXa) (Scheme II) with sodium metaperiodate gave the expected aldehydo-pentose (XXIV) as a distillable liquid giving a positive test with Benedict's solution. The infrared spectrum of this material showed typical aldehyde bands (C—H and C=O) and a weak hydroxyl peak, suggesting that the compound was partially hydrated. (Hydration was also suggested by the elementary analysis.) Reduction of XXIV with sodium borohydride gave the 1, 2-*O*-isopropylidene-3-deoxy-L-arabinofuranose as a syrup in a yield of 64% (based on XIXa). Benzoylation of this product gave the 5-benzoyl derivative (XXVI) as a crystalline solid in a crude yield of 88%, which was converted to the syrupy 1, 2-diacetate (XXVII) in 61% yield.

Condensation of the 1, 2-diacetate (XXVII) with chloromercuri-6-benzamidopurine in the presence of titanium tetrachloride, followed by deacylation in a manner analogous to that described for the hexose analog, gave 9-(3-deoxy-α-L-arabinofuranosyl) adenine (XXIX) as a crystalline solid in a two-step yield of 32%. The configuration of this compound at the Cl-C2 positions is presumed to be *trans* (α) for the same reasons given for the hexose analog. The specific rotation of −51° would tend to support this conclusion. The presence of the β anomer in the reaction is being investigated.

EXPERIMENTAL

1, 2:5, 6-Di-O-isopropylidene-3, 4-D-glucofuranoseen (XVII).—A finely ground mixture of 30.0 Gm. (72.5 mmoles) of 1, 2:5, 6-di-*O*-isopropylidene-3-*O*-(*p*-toluenesulfonyl)-D-glucofuranose (XVI) (14) and 60 Gm. of potassium hydroxide[2] was placed in a 1-L. suction flask equipped with a cold finger for sublimation and half-immersed in an oil bath. The

[2] Potassium hydroxide flakes were most suitable for this purpose.

pressure in the flask was adjusted to 3 mm., and the temperature of the bath was raised slowly to 90°,[3] at which time the product began to collect on the cold finger as a crystalline mass. The temperature was adjusted to 95–100° and held for 4 hr. (during which time the majority of the reaction was completed), then raised to 120°[4] for 2 hr. to complete the reaction. The yield of the white crystalline solid obtained from the cold finger was 11.4 Gm. (65.2%), m.p. 51–52°[5]; $\tilde{\nu}_{max.}^{KBr}$ (cm.$^{-1}$) 1670 (C=C), 1380 (gem-dimethyl). [Lit. (8) m.p. 51°.]

This material changes slowly to a syrup after a few days when allowed to stand at room temperature, and should, therefore, be used in the next step as soon as possible.

1, 2:5, 6-Di-O-isopropylidene-3-deoxy-D-galactofuranose (XVIII).—To a solution of 10.0 Gm. (41.3 mmoles) of XVII in 200 ml. of absolute ethanol was added 500 mg. of 5% palladium-on-charcoal catalyst, and the mixture was shaken with hydrogen at 35 p.s.i., for 2 hr., then filtered through Celite.[6] Evaporation of the filtrate to dryness *in vacuo* at 45° gave a white crystalline solid; yield, 9.77 Gm. (96.8%), m.p. 81–82°. Recrystallization from 50% aqueous methanol gave m.p. 83–84°. For analysis, a sample was sublimed at 90°/5 mm., m.p. 83–84°; $\tilde{\nu}_{max.}^{KBr}$ (cm.$^{-1}$) 1380 (gem-dimethyl) and no absorption at 1670 (C=C). [Lit. (8) m.p. 81.5°.]

Anal.—Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.97, H, 8.29.

1, 2-O-Isopropylidene-3-deoxy-D-galactofuranose (XIXa).—To 750 ml. of 50% aqueous methanol at 40°, 0.01 *N* with respect to hydrochloric acid, was added 15.0 Gm. (91.4 mmoles) of XVIII, m.p. 83–84°, and the stirred solution held at this temperature for 90 min. Neutralization of the reaction to the phenolphthalein end point with 1 *N* aqueous sodium hydroxide, and evaporation to dryness *in vacuo* at 40° gave a partially crystalline syrup partitioned between 300 ml. of water and 75 ml. of chloroform. The organic phase was separated, dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 50° to give a clear colorless liquid which crystallized rapidly on cooling; weight, 2.26 Gm. (15.1%), m.p. 80–82°. The infrared spectrum of this material was identical to that of the starting compound (XVIII).

The aqueous phase was evaporated to dryness *in vacuo* at 40° and the syrupy residue dried further by the addition of 150 ml. of absolute ethanol, followed by its removal *in vacuo*. A mixture of the partially crystalline residue with 15 Gm. of anhydrous magnesium sulfate was extracted with 150 ml. of boiling chloroform. After standing overnight at room temperature, the turbid extract was filtered through Celite and evaporated to dryness *in vacuo* at 50° to give a clear practically colorless syrup which crystallized slowly on standing; yield, 6.67 Gm. (52.5% based on unrecovered starting material, XVIII), m.p. 54–56°. This material was sufficiently pure for the next step. For analysis, a sample was sublimed twice at 90°/1 mm., m.p. 57–58°; $[\alpha]_D^{20}$ −31° [c, 1.36, $(CH_2Cl)_2$]; $\tilde{\nu}_{max.}^{KBr}$ (cm.$^{-1}$) 3520 (OH), 1380 (gem-dimethyl).

Anal.—Calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.92; H, 7.79.

3-Deoxy-D-galactose (Crystalline) (XIXb).—The dried residue obtained from the selective hydrolysis of 6.0 Gm. of diacetone-3-deoxygalactose by the above condition (after extraction with boiling chloroform) was extracted with 20 ml. of hot absolute ethanol. The extract was evaporated to dryness *in vacuo* (40°) and dried further over phosphorus pentoxide to give a clear colorless syrup (1.04 Gm.), which slowly crystallized on standing. The mixture was diluted with absolute ethanol and the product isolated in two crops; total yield, 0.52 Gm. (12%), m.p. 119° and 116–118°, respectively. An analytical sample was prepared by recrystallization of the first crop from 95% ethanol, m.p. 120°; $[\alpha]_D^{20}$ + 6.3° (equil.) (c, 1.2, H_2O). [Lit. (8), $[\alpha]_D^{22}$ + 6.59° (for the syrup).]

Anal.—Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 44.02; H, 7.40.

3-Deoxy-D-galactose-*p*-nitrophenylhydrazone.—To a suspension of 100 mg. (0.610 mmole) of crystalline 3-deoxy-D-galactose in 1.2 ml. of 95% ethanol was added 100 mg. (0.65 mmole) of *p*-nitrophenylhydrazine and the mixture heated to boiling (water bath) until a clear solution was obtained (2–3 min.). Evaporation of the solution *in vacuo* at 40° gave a crude crystalline solid, which was triturated with 2 ml. of ethyl acetate, collected on a filter, and dried; yield, 158 mg. (87%), m.p. 145.5–147° dec. For analysis, a sample was recrystallized twice from ethyl acetate—absolute ethanol (3:1), m.p. 147.5–149°.

Anal.—Calcd. for $C_{12}H_{17}N_3O_6$: C, 48.16; H, 5.72; N, 14.04. Found: C, 48.14; H, 5.81; N, 13.45.

5,6-Di-O-benzoyl-1,2-O-isopropylidene-3-deoxy-D-galactofuranose (XX).—To a well-stirred solution of 2.04 Gm. (10.0 mmoles) of crude XIX in 21 ml. of reagent pyridine at 0° was added dropwise, over a period of 5 min., 3.00 ml. (26.0 mmoles) of benzoyl chloride. After standing for 1 hr. at 0°, the mixture was stored at room temperature for 24 hr. The reaction was quenched by the addition of 5 drops of water, then poured with vigorous stirring into 250 ml. of ice water. The resulting mixture was extracted with chloroform (3 × 50 ml.), and the combined extracts were washed with aqueous saturated sodium bicarbonate (50 ml.) and water (50 ml.), then dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 50°. The last traces of pyridine were removed by the addition and removal *in vacuo* (50°) of toluene (2 × 20 ml.) to give a turbid yellow syrup. A solution of the syrup in 50 ml. of 95% ethanol was filtered through a thin layer of Nuchar[7] and the filtrate evaporated to dryness *in vacuo* at 50° (finally at 0.05 mm. pressure) to give a clear practically colorless syrup; yield, 3.70 Gm. (89.8%); $\tilde{\nu}_{max.}^{film}$ (cm.$^{-1}$) 1720 (benzoate C=O), 1600 (phenyl), 1380 (gem-dimethyl), 1275 (benzoate C—O—C), 710 (monosubstituted phenyl).

Anal.—Calcd. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 67.33; H, 6.04.

1,2-Di-O-acetyl-5,6-di-O-benzoyl-3-deoxy-D-galactofuranose (XXI).—To a well-stirred solution of 3.27 Gm. (7.94 mmoles) of XX in 32 ml. of glacial ace-

[3] If the temperature is raised too rapidly, the product may collect as a viscous syrup, and the reaction mass may decompose rapidly.

[4] Above 120° diacetoneglucose may begin to collect on the cold finger.

[5] Melting points were determined in an oil bath and are uncorrected.

[6] Celite is a product of Johns-Manville.

[7] Nuchar is a brand of activated charcoal.

tic acid and 3.2 ml. (34 mmoles) of acetic anhydride was added dropwise 1.79 ml. of concentrated sulfuric acid while maintaining the temperature at 15 to 20°. After storage at room temperature for 24 hr., the solution was poured into 200 ml. of vigorously stirred ice water, and the resulting mixture was extracted with chloroform (3 × 50 ml.). The combined extracts were washed with water (100 ml.), aqueous saturated sodium bicarbonate (100 ml.), and water (100 ml.), dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 50° to give a pale yellow syrup which solidified on standing and was sufficiently pure to be used in the next step; yield, 2.80 Gm. (77.4%). For analysis, a sample was recrystallized from methanol and again from 70% aqueous methanol, m.p. 114.5°; $[\alpha]_D^{20}$ −28° [c, 1.16, $(CH_2Cl)_2$]; $\bar{\nu}_{max.}^{KBr}$ ($cm.^{-1}$) 1745 sh (acetate C=O), 1725 (benzoate C=O), 1265 (benzoate C—O—C), 1230 (acetate C—O—C), 1090, 1070, 1030 (C—O—C), 705 (monosubstituted phenyl).

Anal.—Calcd. for $C_{24}H_{24}O_9$: C, 63.15; H, 5.30. Found: C, 63.00; H, 5.14.

6-Benzamidopurine.—A mixture of 5.40 Gm. (40.0 mmoles) of adenine and 27.2 Gm. (120 mmoles) of benzoic anhydride was melted, then heated at 180° for 15 min. On cooling, the clear melt solidified as a soft yellow cake, which was then dissolved in 330 ml. of boiling ethanol. The hot solution was treated with decolorizing carbon, filtered, then cooled, whereupon the product crystallized as white needles. The product was collected by filtration, washed with 10 ml. of cold ethanol, and dried; yield, 6.23 Gm. (65.2%), m.p. 238–239°; $\bar{\nu}_{max.}^{KBr}$ ($cm.^{-1}$) 3400 (NH), 1685 (amide C=O), 1600 (phenyl), 1515 (amide NH), 705 (monosubstituted phenyl). [Lit. (8); yield 71%, m.p. 239–242°.]

Chloromercuri-6-benzamidopurine.—To a stirred solution of 7.79 Gm. (28.7 mmoles) of mercuric chloride in 100 ml. of 50% aqueous ethanol was added 6.86 Gm. (28.7 mmoles) of 6-benzamidopurine. To the resulting suspension was added, dropwise and with stirring, 10.3 ml. of 10% aqueous sodium hydroxide (28.7 mmoles). The resulting mixture, which was yellow in color, was stirred at room temperature for 1.5 hr. After allowing it to stand at room temperature for 16 hr., the suspension became white. It was cooled and the solid collected by filtration, washed with 25 ml. of cold 50% aqueous ethanol, and dried *in vacuo* over phosphorous pentoxide; yield, 13.1 Gm. (96.3%). [Lit. (15) yield 99%.]

9-(3-Deoxy-β-D-galactofuranosyl) Adenine (XXIII).—A mixture of 2.06 Gm. (4.52 mmoles) of crude XXI, 2.68 Gm. (5.65 mmoles) of chloromercuri-6-benzamidopurine, 2.7 Gm. of Celite, and 190 ml. of ethylene dichloride was distilled until 25 ml. of distillate had been collected. To the partially cooled mixture was added a solution of 0.62 ml. (5.7 mmoles) of titanium tetrachloride in 8 ml. of ethylene dichloride, and the reaction was heated under reflux for 24 hr. The cooled mixture was stirred vigorously for 2 hr. with 85 ml. of aqueous saturated sodium bicarbonate and filtered through Celite. After washing the cake with chloroform (3 × 20 ml.), the organic phase was separated from the filtrate and evaporated to near dryness *in vacuo* at 40°. A solution of the residue in 35 ml. of chloroform was washed with 35 ml. of 30% aqueous potassium iodide and 35 ml. of water, dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 50° to give the crude blocked nucleoside (XXII) as a yellow foam which hardened to a glass; yield, 2.32 Gm. (80.8%); $\bar{\nu}_{max.}^{KBr}$ ($cm.^{-1}$) 3850 (NH), 1745 sh (acetate C=O), 1720 (benzoate C=O), 1700 sh (amide C + O), 1605, 1580 (purine ring and phenyl), 1280 (benzoate C—O—C), 1230 sh (acetate C—O—C), 1095, 1070, 1025 (sugar C—O—C), 710 (monosubstituted phenyl).

A mixture of 2.18 Gm. of the crude blocked nucleoside in 55 ml. of 0.1 *N* methanolic sodium methoxide was heated under reflux for 3 hr., with solution occurring at the boiling point. The cooled solution was neutralized with glacial acetic acid and stirred at 0° for 1 hr., which caused the separation of the crude crystalline nucleoside. The product was collected on a filter, washed with 2 ml. of cold methanol, and dried; yield 0.463 Gm. (39.0% from XXII), m.p. 226–229° dec. Two recrystallizations from 80% aqueous methanol, with light charcoaling, gave the analytical sample as a white crystalline solid, m.p. 231–232° dec.; $[\alpha]_D^{20}$ −57° (c, 1.24, H_2O); $\lambda_{max.}^{pH\ 1}$ (mμ) 257 (ε 14,800), $\lambda_{max.}^{pH\ 13}$ (mμ) 260 (ε 15,400), $\lambda_{max.}^{H_2O}$ (mμ) 260 (ε 15,200); $\bar{\nu}_{max.}^{KBr}$ ($cm.^{-1}$) 3500–3100 (broad OH and NH), 1610, 1565, (C=C and C=N).

Anal.—Calcd. for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.83; H, 5.35; N, 24.82.

1,2-O-Isopropylidene-3-deoxy-L-threo-pentodialdofuranose (XXIV).—To a well-stirred solution of 4.05 Gm. (19.8 mmoles) of crude XIX*a*, m.p. 54–56°, in 100 ml. of water, was added 4.24 Gm. (19.8 mmoles) of sodium metaperiodate. The pH of the reaction was adjusted to between 6 and 7 (pH paper) with 0.1 *N* sodium hydroxide solution and maintained within this range during the course of 1 hr. The solution was extracted then with chloroform (5 × 100 ml.), and the combined extracts were washed with 100 ml. of water, dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 40° to give the crude product as a colorless liquid contaminated with a gum but sufficiently pure for the next step; yield, 2.81 Gm. (82.2%). For analysis, a sample was sublimed at 60°/0.7 mm. to give a clear colorless liquid; $\bar{\nu}_{max.}^{film}$ ($cm.^{-1}$) 3550 weak (OH), 2720 (aldehyde C—H), 1370 [aldehyde (C=O)], 1380 (gem-dimethyl).

Anal.—Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Calcd. for $C_8H_{12}O_4 \cdot H_2O$: C, 50.52; H, 7.42. Found: C, 51.91; H, 7.11.

1,2-O-Isopropylidene-3-deoxy-L-arabinofuranose (XXV).—To a stirred solution of 1.14 Gm. (30 mmoles) of sodium borohydride in 40 ml. of water was added a solution of 2.58 Gm. (15.0 mmoles) of crude XXIV in 40 ml. of methanol. After 1 hr., the solution was neutralized with glacial acetic acid and evaporated to dryness *in vacuo* at 40°. The residue was dried further with 10 Gm. of anhydrous magnesium sulfate and extracted with hot chloroform (4 × 25 ml.). The combined extracts were evaporated to dryness *in vacuo* at 40°, finally at 0.05 mm., to give an almost clear and colorless syrup; yield, 2.04 Gm. (64% from XIX*a*). For analysis, a sample was sublimed at 65–70°/mm. to give a clear colorless syrup; $\bar{\nu}_{max.}^{film}$ ($cm.^{-1}$) 3550 (OH), 1380 (gem-dimethyl).

Anal.—Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.75; H, 8.50.

5-O-Benzoyl-1,2-O-isopropylidene-3-deoxy-L-arabinofuranose (XXVI).—To a well-stirred solution of 1.61 Gm. (9.26 mmoles) of crude XXV in 20 ml. of reagent pyridine at 0° was added dropwise, over a period of 10 min., 1.28 ml. (11.1 mmoles) of benzoyl chloride. After being stirred for 1 additional hr. at 0°, the mixture was stored at room temperature for 21 hr., quenched with 5 drops of water, and poured into a vigorously stirred mixture of 250 ml. of ice and aqueous saturated sodium bicarbonate. The crude product, which separated as a white solid, was collected on a filter, washed with cold water, and dried *in vacuo* over phosphorous pentoxide; yield, 2.25 Gm. (87.6%), m.p. 74–76°. Recrystallization from ethanol–cyclohexane (1:2) and again from methanol–water (1:3) gave the analytical sample, m.p. 86.5–87° $[\alpha]_D^{29}$ −44° (c, 1.25, $CHCl_3$); $\bar{\nu}_{max.}^{KBr}$ (cm.$^{-1}$) 1720 (benzoate C = O), 1600 (phenyl), 1380 (gem-dimethyl), 1270 (benzoate C—O—C), 708 (monosubstituted phenyl).

Anal.—Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.18; H, 6.73.

1, 2-Di-O-acetyl-5-O-benzoyl-3-deoxy-L-arabinofuranose (XXVII).—To a well-stirred solution of 1.67 Gm. (6.01 mmoles) of crude XXVI in 30 ml. of glacial acetic acid and 3.3 ml. of acetic anhydride was added dropwise 1.82 ml. of concentrated sulfuric acid while maintaining the temperature between 10 and 20°. The solution was allowed to stand overnight at room temperature, poured into 250 ml. of vigorously stirred ice water, and the mixture extracted with chloroform (3 × 30 ml.). The combined extracts were washed with aqueous saturated sodium bicarbonate (90 ml.) and water (90 ml.), dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 50°. The product was obtained as a clear colorless syrup; yield, 1.18 Gm. (61.2%); $\bar{\nu}_{max.}^{film}$ (cm.$^{-1}$) 1750 (acetate C = O), 1725 (benzoate C = O), 1600 (phenyl), 1275 (benzoate C—O—C), 1220 (acetate C—O—C), 710 (monosubstituted phenyl).

Anal.—Calcd. for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.71; H, 5.54.

9-(3-Deoxy-α-L-arabinofuranosyl) Adenine (XXIX).—A mixture of 0.932 Gm. (2.89 mmoles) of XXVII, 1.71 Gm. (3.61 mmoles) of chloromercuric-6-benzamidopurine, 1.75 Gm. of Celite, and 135 ml. of ethylene dichloride was distilled until 25 ml. of distillate had been collected. To the partially cooled mixture was added a solution of 0.40 ml. (3.6 mmoles) of titanium tetrachloride in 6 ml. of ethylene dichloride and the reaction heated under reflux for 24 hr. While the mixture was still warm, 55 ml. of aqueous saturated sodium bicarbonate was added, and the mixture was stirred vigorously for 2 hr., then filtered through Celite. After washing the cake with chloroform (3 × 20 ml.), the organic phase was separated from the filtrate and evaporated to near dryness *in vacuo* at 40°. A solution of the residue in 25 ml. of chloroform was washed with 25 ml. of 30% aqueous potassium iodide and 25 ml. of water, dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 50° to give the crude blocked nucleoside (XXVIII) as a yellow syrup which hardened to a glass on cooling; yield, 1.09 Gm. (75.2%); $\bar{\nu}_{max.}^{KBr}$ (cm.$^{-1}$) 1745 (acetate C = O), 1720 (benzoate C = O), 1700 (amide C + O), 1605, 1580 (purine ring and phenyl), 1270 (benzoate C—O—C), 1220 (acetate C—O—C), 1085, 1070, 1020 (sugar C—O—C), 708 (monosubstituted phenyl).

A suspension of 1.00 Gm. of crude blocked nucleoside in 25 ml. of 0.1 *N* methanolic sodium methoxide was heated under reflux for 2.5 hr. with solution occurring at the boiling point. The cooled solution was neutralized with glacial acetic acid and stirred at 0° for 2 hr., during which time the crude nucleoside separated as a nearly white crystalline solid. The product was collected on a filter, washed with cold methanol (2 × 5 ml.), and dried; yield, 0.215 Gm. (32% from XXVII), m.p. 239–241° dec. Two recrystallizations from 90% aqueous ethanol, with light charcoaling, gave the analytical sample as a white crystalline solid, m.p. 242.5–243°; $[\alpha]_D^{29}$ −51° (c, 0.815, *N* HCl): $\lambda_{max.}^{pH\ 1}$ (mμ) 257 (ε 14,400), $\lambda_{max.}^{pH\ 13}$ (mμ) 260 (ε 14,700), $\lambda_{max.}^{H_2O}$ (mμ) 259 (ε 14,700); $\bar{\nu}_{max.}^{KBr}$ (cm.$^{-1}$) 3500–3150 (based OH, NH), 1610, 1570 (C = C and C = N).

Anal.—Calcd. for $C_{10}H_{13}N_5$: C, 47.80; H, 5.22; N, 27.88. Found: C, 48.01; H, 5.37; N, 28.05.

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