C—O—C); $[\alpha]_D^{26}$ −70° (0.54% in H_2O). This material was slightly solvated.

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.8; H, 5.00; N, 19.9. Found: C, 46.2; H, 5.26; N, 19.3.

Examination by paper chromatography showed that this material traveled as a single spot with R_{Ad} 0.39.[34] There was no spot corresponding to starting material XI, thus demonstrating the efficiency of deamination and lead salt purification.

Attempts to prepare this compound by hydrolysis of 6-chloro-9-α-L-rhamnopyranosylpurine (VIII) with 0.1*N* sodium hydroxide at room temperature or with boiling water containing suspended silver carbonate resulted in rupture of the imidazole ring (cf. Discussion).

9-α-L-Rhamnopyranosylpurine. A solution of 400 mg. of crystalline 6-chloro-9-α-L-rhamnopyranosylpurine[11] in 10 ml. of water was stirred with 40 mg. of decolorizing carbon for 15 min., then filtered. To the combined filtrate and washings (20 ml.) were added 56 mg. of magnesium oxide and 136 mg. of 5% palladium-charcoal. The mixture was magnetically stirred with hydrogen at 1 atm. Hydrogen absorption ceased in 28 min. when 0.93 mole-equivalents of gas had been absorbed. The filtered solution was evaporated to dryness *in vacuo*.

A thoroughly mixed preparation of 3.5 ml. of butanol-saturated water and 7 g. of Celite 545[37] was packed in a 1.2 × 15 cm. column.[11] The hydrogenation residue was dissolved in 0.4 ml. of water, mixed with 0.8 g. of Celite 545, and packed on the top of column. Water-saturated butanol was passed through the column until ultraviolet inspection showed no more product was eluted. The product appeared between 10 and 35 ml. The 25 ml. of nucleoside containing eluate was evaporated to dryness *in vacuo*. A solution of the residue in water was washed twice with chloroform, then clarified by filtration through Celite.[37] The aqueous solution was evaporated to dryness *in vacuo* leaving 293 mg. (83%) of a colorless glass which traveled on paper as a single spot (R_{Ad} 0.93, blue-purple in u.v.)[34] and had $\lambda_{max}^{H_2O}$ 261 mμ (a_M 7500) and ν_{max}^{KBr} 3400 cm.$^{-1}$ (OH), 1600, 1585 cm.$^{-1}$ (C=C and C=N), 1110, 1085, 1060 (C—O—). For analysis and ultraviolet a sample was dried at 80° in high vacuum; the product still contained some water and had $[\alpha]_D^{26}$ −68° (0.39% in H_2O).

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.6; H, 5.30; N, 21.1. Found: C, 49.1; H, 5.15; N, 22.4.

Acknowledgments. We wish to thank Dr. W. C. Coburn, Jr., J. W. Murphy, and L. D. Norton for spectrophotometric data and rotations, Mr. J. P. Holmquist for the microanalyses, and Mr. W. E. Fitzgibbon, Jr., and staff for large scale preparation of some intermediates.

BIRMINGHAM 5, ALA.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. VIII.[2] Nucleosides Derived from L-Rhamnofuranose

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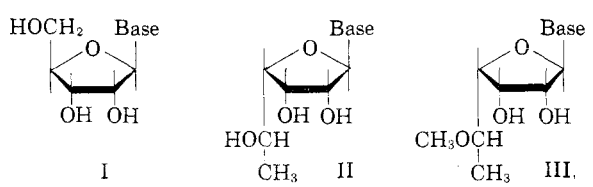
A four-step synthesis of 1,2,3,5-tetra-*O*-benzoyl-L-rhamnofuranose from L-rhamnose has been described. Two new nucleosides derived from L-rhamnofuranose containing adenine or 2,6-diaminopurine, have been synthesized from the tetrabenzoate *via* 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride.

It has been observed that by-product benzoic acid does not interfere with the coupling of a chloromercuri purine with a poly-*O*-benzoyl glycosyl halide. On this basis, a relatively simple synthesis of 9-β-D-xylofuranosyladenine in 47% yield has been found. The latter compound is a valuable nucleoside for further nucleoside transformations.

In the preceding paper of this series[2] the reasons for synthesizing L-rhamnofuranosyl nucleosides were discussed. This paper describes the synthesis of 9-α-L-rhamnofuranosyladenine and 2,6-diamino-9-α-L-rhamnofuranosylpurine (II), potential antagonists of the natural ribofuranosyl nucleosides (I). Since the adenine analog (II) failed to show any anticancer activity against Sarcoma 180 or Adenocarcinoma 755, it is clear that either the configuration at C_4 cannot be changed as in II or (less likely) that the extra C-methyl destroys activity.



Only one nucleoside derived from L-rhamnofuranose has been previously described, namely, 7-(5′-*O*-methyl-L-rhamnofuranosyl) theophylline (III).[3] The latter was obtained by condensation of 2,3-di-*O*-acetyl-5-*O*-methyl-L-rhamnofuranosyl bromide with silver theophylline followed by deactylation. Although the anomeric configuration was not assigned, the probability is high that an α-nucleoside with C_1-C_2-*trans*-configuration was obtained.[2,4,5]

(1) Affiliated with Sloan-Kettering Institute.

(2) This work was supported in part by the C. F. Kettering Foundation. For Paper VII of this series, *cf.* B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

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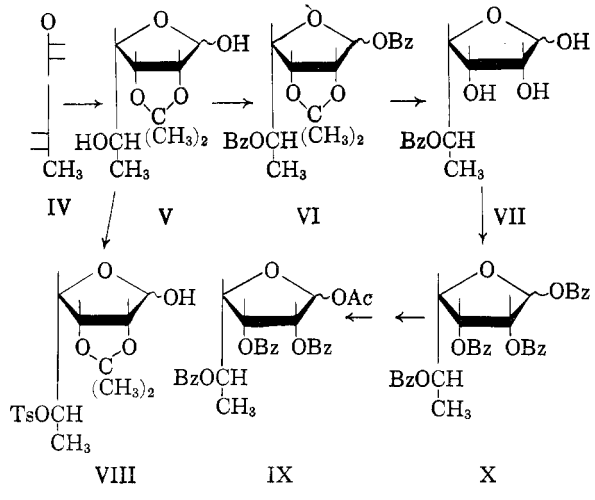
(3) P. A. Levene and J. Compton, *J. Biol. Chem.*, **117**, 37 (1937).

(4) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(5) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 2396 (1955).

The synthesis of these 9-α-L-rhamnofuranosyl purines required 1-*O*-acetyl(or benzoyl)-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose (IX and X) as a key intermediate. The synthesis started with 2,3-*O*-isopropylidene-L-rhamnofuranose (V) prepared in 73–80% yield by modification of a known procedure.[6] Even though V does not have its 5-hydroxyl group blocked and could be in equilibrium with its pyranose form, Levene and Compton[7] showed that the furanose form was maintained during acylation in pyridine. They observed that tosylation of V with *p*-toluenesulfonyl chloride in pyridine afforded 2,3-*O*-isopropylidene-5-*O*-tosyl-L-rhamnofuranose (VIII) and did not form any appreciable quantity of 2,3-*O*-isopropylidene-4-*O*-tosyl-L-rhamnopyranose. They prepared the latter compound by an alternate unambiguous method and found it to be isomeric with VIII. Thus, benzoylation of 2,3-*O*-isopropylidene-L-rhamnofuranose (V) should lead to 2,3-*O*-isopropylidene-1,5-di-*O*-benzoyl-L-rhamnofuranose (VI). That mainly the furanose (VI) was formed is shown below.



Benzoylation of V in pyridine at about 3° formed the di-*O*-benzoyl derivative (VI) in quantitative yield. Hydrolysis of VI with boiling 70% acetic acid not only removed the *O*-isopropylidene group as expected, but also cleaved most of the 1-benzoate and some of the 5-benzoate to regenerate L-rhamnose. After removal of the dilute acetic acid, the residue was partitioned between 1:1 ethyl acetate–benzene and water, the free L-rhamnose (about 25%) remaining in the aqueous phase. The organic layer was washed with aqueous sodium bicarbonate to remove benzoic acid. Evaporation of the organic phase afforded 5-*O*-benzoyl-L-rhamnofuranose (VII), contaminated with about 20% of innocuous 1,5-di-*O*-benzoyl-L-rhamnofuranose, in 73–78% yield.

At first glance it would appear that the preceding hydrolysis conditions were much too strenuous. However, if less strenuous conditions were used, then unchanged isopropylidene derivative (VI) remained.[8] For example, hydrolysis of VI with 50% acetic acid at the b.p. for 1.5 hr. left 40% of VI still unhydrolyzed. The unchanged isopropylidene derivative (VI) could be removed from the hydrolysis product (VII) by a partition system,[8] but the longer hydrolysis period gave a mixture that is somewhat simpler to separate.

Benzoylation of the 5-*O*-benzoyl-L-rhamnofuranose (VII) with benzoyl chloride in pyridine afforded a 92% yield of tetrabenzoate (X) as a glass suitable for nucleoside synthesis.

Treatment of the tetrabenzoate (X) with hydrogen bromide in acetic acid followed by silver carbonate in aqueous acetone afforded 2,3,5-tri-*O*-benzoyl-L-rhamnofuranose.[9] The latter was reacted with acetic anhydride in pyridine to give 73% 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose (IX) as a sirup suitable for nucleoside synthesis. This material was obtained analytically pure by chromatography on alumina, but the anomers could not be separated and the product was still a glass.

Reaction of the tetrabenzoate (X) with ethereal hydrogen chloride in the usual manner[10] afforded crude 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride (XI) contaminated with an equivalent of benzoic acid formed from the 1-benzoate. It has usually been assumed that benzoic acid or acetic acid would be detrimental to a condensation reaction between a poly-*O*-acyl glycosyl halide and a heavy metal salt of a purine since the carboxylic acid, being a stronger acid than a purine, could decompose the purine metal salt and form free purine unavailable for condensation.[10–12] Thus, the acetic acid formed was removed carefully by codistillation with benzene or toluene.[10,11] Since benzoic acid does not codistill appreciably with these solvents, a sugar 1-benzoate was not considered satisfactory for the synthesis of a nucleoside unless the surgar halide was stable enough to water to remove the benzoic acid with aqueous sodium bicarbonate,[12] a procedure which can surely decompose

(6) P. A. Levene and I. E. Muskat, *J. Biol. Chem.*, **106**, 761 (1934).

(7) P. A. Levene and J. Compton, *J. Biol. Chem.*, **116**, 169 (1936).

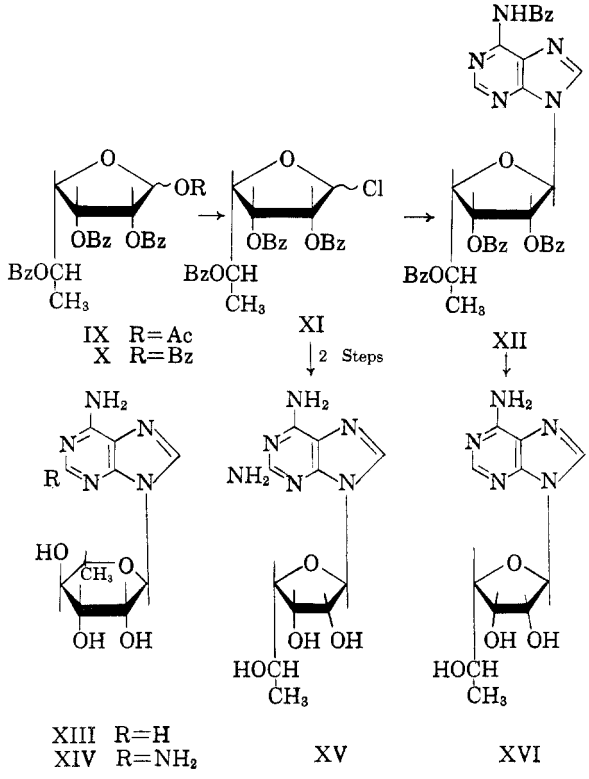
(8) The amount of unchanged VI could be determined readily by distribution of the hydrolysis mixture in the solvent system benzene/hexane/methanol/water:3/7/7/3. The unchanged acetonide (VI) had a distribution coefficient of about 30 in favor of the benzene-hexane layer. The hydrolysis products VII and 1,5-di-*O*-benzoyl-L-rhamnofuranose had distribution coefficients greater than 30 in favor of the methanol-water phase.

(9) H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **75**, 2624 (1953), has used this procedure for conversion of α-D-xylofuranose tetrabenzoate to 2,3,5-tri-*O*-benzoyl-D-xylofuranose.

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

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

(12) J. J. Fox, N. Jung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).



all—or at least part—of the glycosyl halide. This assumption that organic acid cannot be present during a nucleoside coupling reaction has now been proven to be false. Thus, it is no longer necessary to convert a sugar 1-benzoate to the 1-hydroxy or 1-acetate *via* the 1-bromide in order to use a 1-benzoate for nucleoside synthesis.[13]

Condensation of 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride (XI), contaminated with the by-product benzoic acid, with chloromercuri-6-benzamidopurine[14] afforded the crude blocked nucleoside (XII). Debenzoylation with methanolic sodium methoxide gave the nucleoside (XVI) isolated *via* its crystalline picrate. Regeneration of the base (XVI) with Dowex 1 (CO_3) in the usual manner[2] gave crude XVI free of inorganic material and sugar decomposition products, but contaminated with some pyranosyl nucleoside (XIII)[2] and some adenine.[15] Crystallization from ethanol—methyl ethyl ketone afforded 24% (based on X) of crystalline 9-α-L-rhamnofuranosyladenine (XVI)[17,18] free of adenine and pyranose (XIII)[3] as shown by paper chromatography.[16]

That benzoic acid did not interfere with the nucleoside condensation reaction was shown with another sugar. Thus, 9-β-D-xylofuranosyladenine was prepared in 47% overall yield from α-D-xylofuranose tetrabenzoate[9] *via* the 1-bromide[12] (without removal of the benzoic acid) and chloromercuri-6-benzamidopurine. This yield can be compared with 27% obtained from α-D-xylofuranose tetrabenzoate *via* 2,3,5-tri-*O*-benzoyl-D-xylofuranose[13] and the corresponding chloride where no benzoic acid or acetic acid was present. Since 9-β-D-xylofuranosyladenine is a valuable intermediate for further nucleoside transformations, the 3′,5′-*O*-isopropylidene and the 5′-*O*-trityl derivatives were prepared. Transformations of these blocked nucleosides to possible interesting anticancer agents are currently being investigated.

The fact that the crude 9-α-L-rhamnofuranosyladenine (XVI) was contaminated with some of the corresponding pyranose (XIII) showed that the L-rhamnofuranose tetrabenzoate (X) contained some of the corresponding pyranose tetrabenzoate since ring expansion has not been previously observed to take place during either formation of an *O*-benzoyl glycosyl halide or coupling with a purine. The pyranose tetrabenzoate (X) impurity arose during one or both of two reactions. Benzoylation of 2,3-*O*-isopropylidene-L-rhamnofuranose (V) could give rise to some 1,4-di-*O*-benzoyl-2,3-*O*-isopropylidene-L-rhamnopyranose since the furanose structure of V is not fixed. Secondly, during the acid treatment to remove the isopropylidene group from VI, it is possible for some of the 5-benzoate to have migrated to the 4-hydroxyl group, thus, giving rise to 4-*O*-benzoyl-L-rhamnofuranose.

Condensation of 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride (XI) (prepared from the tetrabenzoate, X) with chloromercuri-2,6-diacetamidopurine[2] proceeded poorly. After removal of the blocking groups with methanolic sodium methoxide, the crude nucleoside (XV) was isolated as the picrate. Regeneration of the nucleoside from the picrate with Dowex 1 (CO_3) and crystallization from water afforded a 4.2% overall yield of pure 2,6-diamino-9-α-L-rhamnofuranosylpurine (XV)[17] which had R_{Ad} 0.38 and was free of the corresponding pyranose (XIV)[2] and 2,6-diaminopurine as shown by paper chromatography.[16]

The synthesis of 2,6-diamino-9-α-L-rhamnofuranosylpurine (XV) from 1-*O*-acetyl-2,3,5-tri-*O*-ben-

(13) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5900 (1955).

(14) J. A. Johnson, Jr., and H. J. Thomas, Southern Research Institute, to be published.

(15) The relative quantities of furanose (XVI), pyranose (XIII), and adenine were readily demonstrated by paper chromatography.[16] The furanose had R_{Ad} 0.79, the pyranose R_{Ad} 0.56, and the adenine R_{Ad} 1.00.

(16) Paper chromatograms were run with water-saturated butanol by the descending procedure on 7 × 17 inch strips of Whatman No. 1 paper with spots 1 inch apart. The spots were located by visual examination with an ultraviolet lamp. Adenine was used as a standard in all cases and was arbitrarily assigned R_{Ad} 1.00. The distances moved by other spots were assigned R_{Ad} values with reference to adenine.

(17) That this nucleoside has a C_1-C_2-*trans*-configuration, in this case α, is highly probable in view of the rule postulated for the stereochemistry of nucleoside formation.[4,5]

(18) Pure 9-α-L-rhamnofuranosyladenine (XVI) was also prepared in 14% over-all yield from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose *via* 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride and chloromercuri-6-chloropurine.

zoyl-L-rhamnofuranose proceeded in even poorer yield. Finally, the condensation of 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride (XI) (prepared from either IX or X) with dithyminyl mercury[12] failed completely since after debenzoylation not even 1% yield of 1-α-L-rhamnofuranosylthymine could be detected by paper chromatography.[16] No explanation has been found for these low yields.

EXPERIMENTAL[16,19]

2,3-O-Isopropylidene-L-rhamnofuranose (V). A mixture of 33 g. of L-rhamnose hydrate, 60 g. of anhydrous copper sulfate, 600 ml. of reagent acetone, and 1.2 ml. of 96% sulfuric acid was stirred for 23 hr. in a closed flask. The filtered solution was neutralized with 4.5 ml. of 28% ammonia water, then filtered from ammonium sulfate through a Celite[21] pad. Evaporation of the filtrate to dryness *in vacuo* left a thick colorless sirup which was dissolved in 300 ml. of chloroform. After standing for 2 hr., the chloroform solution was filtered through Celite[21] to remove the last traces of insoluble ammonium sulfate. Evaporation of the chloroform *in vacuo* and distillation of the residue through a short path distillation apparatus afforded 29.5 g. (80%) of product, b.p. 118–120° (0.2 mm.), ν_{max}^{film} 3400 cm.$^{-1}$ (OH), 1380 cm.$^{-1}$ (C—Me). A similar preparation solidified on standing in a closed tube at 3° for several weeks.

Anal. Calcd. for $C_9H_{16}O_5$: C, 52.9; H, 7.84. Found: C, 52.7; H, 7.63.

Other runs afforded 73–80% yields. If the chloroform step was omitted, yields varied from 0–70% and considerable decomposition to a hard polymer sometimes took place during distillation.

Levene and Muskat[6] record b.p. 115° (0.2 mm.) and m.p. 90°, but do not specify the yield.

1,5-Di-O-benzoyl-2,3-O-isopropylidene-L-rhamnofuranose (VI). To a stirred solution of 8.6 g. of V in 43 ml. of reagent pyridine cooled in an ice-salt bath was added dropwise 11 ml. of benzoyl chloride at such a rate that the temperature was kept below 12°. After standing in a stoppered flask at 3° for 18 hr., the mixture was diluted with 25 ml. of chloroform and washed with 160 ml. of ice water. The combined chloroform solutions, washed with excess aqueous sodium bicarbonate and dried with magnesium sulfate, were evaporated to dryness *in vacuo*. The residue was dissolved in about 25 ml. of toluene and the evaporation repeated, leaving 20.0 g. (107%) of an amber sirup contaminated with benzoic anhydride. For analysis and infrared, a sample was dried in high vacuum at 80°; ν_{max}^{film} 1800 cm.$^{-1}$ (C=O of benzoic anhydride), 1735 cm.$^{-1}$ (C=O of benzoate), 1380 cm.$^{-1}$ (C—Me), 1275 cm.$^{-1}$ (C—O—C of benzoate), but only a trace of absorption at 3400 cm.$^{-1}$ (OH). The contaminating benzoic anhydride is removed in the next step.

Anal. Calcd. for $C_{23}H_{24}O_7$: C, 67.0; H, 5.83. Found: C, 67.5; H, 5.82.

5-O-Benzoyl-L-rhamnofuranose (VII). A solution of 14 g. of VI in 140 ml. of 70% acetic acid was refluxed for 3 hr., then evaporated to dryness *in vacuo*. The residue was partitioned between 75 ml. of 1:1 benzene–ethyl acetate and 50 ml. of water. The aqueous layer, containing about 25% yield of L-rhamnose, was rejected. The organic layer, washed with excess aqueous sodium bicarbonate and dried with magnesium sulfate, was evaporated to dryness *in vacuo;* yield, 6.65 g. (73%) of a glass; ν_{max}^{KBr} 3400 cm.$^{-1}$ (OH), 1710 cm.$^{-1}$ (C=O), 1265 cm.$^{-1}$ (C—O—C of benzoate). The analysis indicated 18% innocuous contamination with 1,5-di-*O*-benzoyl-L-rhamnofuranose.

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.3; H, 6.03. Found: C, 59.4; H, 6.19.

In other runs the yields were 73–78%.

1,2,3,5-Tetra-O-benzoyl-L-rhamnofuranose (X). To a stirred solution of 6.75 g. of VII in 33 ml. of reagent pyridine cooled in an ice-salt bath was added 11.3 ml. of benzoyl chloride dropwise at such a rate that the temperature was −5 to +5°. After standing overnight at 3° in a closed flask, the mixture was treated with 2 ml. of water, allowed to stand 15 min., then diluted with 33 ml. each of water and chloroform. The separated chloroform layer, washed with excess aqueous sodium bicarbonate and dried with magnesium sulfate, was evaporated to dryness *in vacuo*. The residue was dissolved in about 20 ml. of toluene and the evaporation repeated; weight, 14.2 g. of a glass suitable for further transformations. The yield, corrected for volatile material removable in high vacuum at 80°, was 13.4 g. (92%).

For analysis a 1.4-g. sample was dissolved in ether, filtered, then stirred with excess aqueous sodium bicarbonate for several hours. The ether solution, dried with magnesium sulfate and clarified with Norit, was evaporated to dryness *in vacuo* leaving a clear amber glass. This material was dried in high vacuum at 80° and had ν_{max}^{KBr} 1735, 1275 cm.$^{-1}$ (benzoate C=O and C—O—C) and no OH at 3400 cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{28}O$: C, 70.5; H, 4.88. Found: C, 69.7; H, 5.18

1-O-Acetyl-2,3,5-tri-O-benzoyl-L-rhamnofuranose (IX). To a solution of 2.30 g. of X in 5 ml. of methylene chloride was added 11.5 ml. of 30% hydrogen bromide in acetic acid. After 30 min. at room temperature, the solution was diluted with 5 ml. of methylene chloride and washed with an equal volume of water. The organic solution, washed thoroughly with excess aqueous sodium bicarbonate (final volume 27 ml.), was added to a mixture of 2.3 g. of silver carbonate, 60 ml. of acetone, and 0.6 ml. of water. After stirring for 30 min., the mixture was treated with Norit and filtered. The combined filtrate and acetone washings were evaporated to dryness *in vacuo* leaving 1.73 g. of 2,3,5-tri-*O*-benzoyl-L-rhamnofuranose as a glass.

A solution of 1.73 g. of the preceding compound in 8.65 ml. of reagent pyridine and 8.65 ml. of acetic anhydride was allowed to stand overnight in a stoppered flask. The solution was diluted with 85 ml. of ice water and extracted 3 times with 10-ml. portions of chloroform. The combined extracts, washed with ice water and excess aqueous sodium bicarbonate, and dried with magnesium sulfate, were evaporated to dryness *in vacuo*. The residue was dissolved in 2 volumes of toluene and the evaporation repeated. A solution of the residue in 10 ml. of ether was filtered through Celite,[21] clarified with Norit, and evaporated to dryness *in vacuo* leaving 1.55 g. (73%) of IX as a glass suitable for further transformations.

Anal. Calcd. for $C_{29}H_{26}O_9$: C, 67.2; H, 5.05. Found: C, 66.3; H, 5.53.

For analysis and rotation 1.106 g. was chromatographed with a column containing 60 g. of acid washed alumina.[22] No material was removed from the column with 5:1 or 1:1 hexane-benzene. The material was eluted with benzene, but no separation of the anomers occurred; yield, 0.565 g. of a glass; ν_{max}^{KBr} 1730 cm.$^{-1}$ (C=O), 1275 cm.$^{-1}$ (benzoate C—O—C), 1210 cm.$^{-1}$ (acetate C—O—C), 700 cm.$^{-1}$ (monosubstituted phenyl) and no absorption at 3400 cm.$^{-1}$

(19) The ultraviolet spectra were determined with a Beckman Model DK-2 spectrophotometer, the infrared spectra with a Perkin-Elmer Model 21 spectrophotometer, and optical rotations with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solution.[20] Melting points were determined in capillary tubes in a stirred oil bath and are uncorrected.

(20) A. S. Keston, Abstracts of 125th Meeting, AMERICAN CHEMICAL SOCIETY, 18C (1955).

(21) An analytical grade product of the Johns-Manville Corp.

(22) Merck and Co., Inc.

(OH); $[\alpha]_D^{27}$ +61° (0.5% in $CHCl_3$). The last traces of benzene could not be removed completely by drying at 80° in high vacuum since extended heating caused the compound to darken.

Anal. Calcd. for $C_{29}H_{26}O_9$: C, 67.2; H, 5.05. Found: C, 66.7; H, 5.54.

6-Benzamido-9-(2′,3′,5′-tri-O-benzoyl-α-L-rhamnofuranosyl)purine (XII). To a solution of 3.66 g. of crude tetrabenzoate (X) (containing 7% volatile material) in 3.7 ml. of acetyl chloride was added 100 ml. of reagent ether saturated with hydrogen chloride at 5°. The solution was kept in a glass sealed bottle at 3° for 6 days, then evaporated *in vacuo* (bath 40°). The residue was twice dissolved in about 10-ml. portions of reagent benzene and evaporated to dryness *in vacuo*. The residual 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride (XI) was dissolved in 40 ml. of xylene and added to an azeotropically dried mixture of 3.32 g. of chloromercuri-6-benzamidopurine,[14] 150 ml. of xylene, and 3.1 g. of Celite.[21] After being refluxed and stirred for 2 hr., the hot mixture was filtered through Celite[21] and the filter cake washed twice with chloroform (about 100 ml.). The xylene solution was evaporated to dryness *in vacuo* and the residue was dissolved in the chloroform washes. Washed successively with 100 ml. of 30% aqueous potassium iodide, water, and excess aqueous sodium bicarbonate, the chloroform solution was dried with magnesium sulfate, then evaporated to dryness *in vacuo;* yield, 4.07 g. of crude blocked nucleoside (XII), obtained as a glass.

9-α-L-Rhamnofuranosyladenine (XVI). (*A*). A mixture of 4.1 g. of crude 6-chloro-9-(2′,3′,5′-tri-*O*-benzoyl-α-L-rhamnofuranosyl)purine[23] and 75 ml. of methanol saturated with ammonia (at 0°) was stirred in an ice bath until solution was complete (1 hr.), then allowed to stand in a stoppered flask at 3° for about 18 hr. The solution was then heated in a steel bomb at 100° for 10 hr. The filtered solution was evaporated to dryness *in vacuo* and the residue partitioned between 25 ml. of water and 25 ml. of chloroform. The separated aqueous layer, washed twice more with chloroform, was evaporated to dryness *in vacuo*. To a solution of the residue in 20 ml. of methanol was added 10 ml. of 10% methanolic picric acid. After standing for 1 hr. at 3°, the mixture was filtered and the yellow solid washed with small amounts of ice-cold methanol; weight, 667 mg. of XVI picrate.

Regeneration of the nucleoside from the picrate with Dowex 1 (CO_3) in the usual manner[2] gave 325 mg. of glassy residue. This residue was shown by paper chromatography[16] to consist mainly of XVI (R_{Ad} 0.79), contaminated with smaller amounts of 9-α-L-rhamnopyranosyladenine (XIII)[2] (R_{Ad} 0.56) and adenine. The crude product was dissolved in 1 ml. of absolute alcohol. After the addition of 2 ml. of methyl ethyl ketone, during which time crystals began to separate, the mixture was kept at 3° overnight. The mixture was then diluted with 20 ml. more of methyl ethyl ketone, filtered, and the white crystals washed with methyl ethyl ketone; yield, 272 mg. (14% based on IX) of white crystals, m.p. 132–135°. This material was pure and free of pyranose (XIII) and adenine as shown by paper chromatography[16] and had $[\alpha]_D^{27}$ −18° (0.3% in H_2O). This compound was solvated with methyl ethyl ketone as shown by the presence of ketone C=O at 1705 cm.$^{-1}$ in the infrared (Nujol mull). The solvate band did not show in a KBr disc but other bands in KBr were 3320 cm.$^{-1}$ (OH), 1660 cm.$^{-1}$ (NH_2 of NH_2—C=N), 1640 cm.$^{-1}$ (NH), 1605 and 1577 cm.$^{-1}$ (C=C and C=N), 1140, 1065, 1045 cm.$^{-1}$ (C—O—).

Anal. Calcd. for $C_{11}H_{15}N_5O_4 \cdot {}^3/_4C_4H_8O_4 \cdot {}^1/_2H_2O$: C, 48.8; H, 6.45; N, 20.3. Found: C, 48.8; H, 6.22; N, 20.7.

This compound could also be crystallized from acetone as a white, crystalline acetone solvate, m.p. 50–135°. Again the presence of the solvate was shown by the presence of ketone C=O absorption at 1705 cm.$^{-1}$ in the infrared (Nujol mull). The ultraviolet absorption also showed a mol. wt. increase of 58 with $\lambda_{max}^{H_2O}$ 258 mμ.

Anal. Calcd. for $C_{11}H_{15}N_5O_4 \cdot C_3H_6O$: C, 49.7; H, 6.26; N, 20.6. Found: C, 49.5; H, 6.40; N, 20.4.

(*B*) A mixture of 4.07 g. of crude blocked nucleoside (XII), 30 ml. of methanol, and 4.1 ml. of 1*N* methanolic sodium methoxide was refluxed for 30 min.,[24] then neutralized with acetic acid. The solution was filtered through Celite[21] to remove traces of colloidal mercury, then evaporated to dryness *in vacuo*. The residue was partitioned between about 25 ml. each of water and chloroform. The separated aqueous layer, washed once more with chloroform, was evaporated to dryness *in vacuo*. The residue was dissolved in absolute alcohol, filtered from 200 mg. of inorganic material, and the solution evaporated *in vacuo*. To a solution of the residue in 15 ml. of methanol was added 13 ml. of 10% methanolic picric acid. After standing for 1 hr. at 3°, the mixture was filtered and the picrate washed with small amounts of ice-cold methanol, then with water; yield, 1.32 g.

The free nucleoside was regenerated from the picrate with Dowex 1 (CO_3) in the usual manner.[2] The aqueous solution was examined by paper chromatography[16] and was found to contain some adenine and some pyranose nucleoside (XIII), but was mainly the desired furanose nucleoside (XVI). The solution was evaporated to dryness *in vacuo*. Crystallization from 3 ml. of absolute alcohol by addition of 6 ml. of methyl ethyl ketone gave 398 mg. (24% based on X) of white crystals, m.p. 130° (gas). This material traveled as a single spot, identical with preparation A, on paper[16] and was free from adenine and pyranose (XIII). The material had an infrared spectrum identical with preparation A.

Evaporation of the mother liquor left 230 mg. of residue which contained adenine, furanose nucleoside (XVI), and pyranose nucleoside (XIII) as shown by paper chromatography.[16] Over half of the material was the desired furanose (XIII) and probably could be purified by Celite partition chromatography.[3]

6-Benzamido-9-(2′,3′,5′-tri-O-benzoyl-β-D-xylofuranosyl)-purine. A warm solution of 3.00 g. of α-D-xylofuranose tetrabenzoate[9] in 6 ml. of ethylene dichloride was quickly cooled to 30° and treated with 15 ml. of 30% hydrogen bromide in acetic acid. After standing at room temperature protected from moisture for 30 min., the solution was evaporated to a sirup *in vacuo* (bath 60–70°). The residue was twice dissolved in 9-ml. portions of xylene and the evaporation *in vacuo* repeated. The residual 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl bromide,[12] contaminated with benzoic acid, was dissolved in 30 ml. of xylene and condensed with 2.55 g. of chloromercuri-6-benzamidopurine[14] as described for XII; weight, 3.72 g. of crude product which was unblocked without further purification. This blocked nucleoside can be obtained as white crystals from benzene, m.p. 105–110° (turbid, clearing at 198°); ν_{max}^{KBr} 3400 cm.$^{-1}$ (NH), 1718 and 1255 cm.$^{-1}$ (benzoate C=O and C—O—C), 1690 cm.$^{-1}$ (shoulder) (amide C=O), 1510 cm.$^{-1}$ (amide NH); $[\alpha]_D^{27}$ +5.2° (0.8% in $CHCl_3$).

Anal. Calcd. for $C_{38}H_{29}N_5O_8$: C, 66.8; H, 4.28; N, 10.3. Found: C, 66.6; H, 4.69; N, 10.2.

9-β-D-Xylofuranosyladenine. Debenzoylation of 3.72 g. of crude 6-benzamido-9-(2′,3′,5′-tri-*O*-benzoyl-β-D-xylofuranosyl)purine as described for the preparation of XVI gave a highly insoluble picrate which was washed with methanol until no more brown color was removed from the solid, m.p. 208–214° (dec.). Regeneration with Dowex 1 (CO_3), by adding portions of resin and picrate to water at 70–80°, afforded 670 mg. (47% based on α-D-xylofuranose tetra-

(23) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Paper VI of this series, *J. Org. Chem.*, **22**, 954 (1957).

(24) If the *p*H is less than 9 when the solution is spotted on moist indicator paper, then additional sodium methoxide should be added and reflux continued until a total of 30 min. reflux time still gives *p*H greater than 9.

benzoate) of product as a colorless glass (R_{Ad} 0.50) contaminated with about 5% of adenine as shown by paper chromatography.[16]

Similarly, condensation of 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl chloride, prepared from 2,3,5-tri-*O*-benzoyl-D-xylofuranose,[13] with chloromercuri-6-benzamidopurine afforded a 27% yield (based on α-D-xylofuranose tetrabenzoate) of 9-β-D-xylofuranosyladenine contaminated with about 5% adenine.

An alternate, less efficient synthesis of this compound, isolated as a glass, has been previously described.[25] The intermediate picrate had m.p. 210° (dec.).

This nucleoside can be crystallized with considerable loss from ethanol and melts over the range 125–140°. This nucleoside was characterized by the following two derivatives.

9-(3′,5′-O-Isopropylidene-β-D-xylofuranosyl)adenine. To a stirred mixture of 338 mg. of amorphous 9-β-D-xylofuranosyladenine, 1.67 g. of anhydrous copper sulfate, and 20 ml. of acetone was added dropwise a solution of 1.0 ml. of mixed alkanesulfonic acid[26] in 8.7 ml. of acetone.[27] After being stirred for 1 hr., the mixture was filtered and the filter cake washed with two 9-ml. portions of acetone. The combined filtrate and washings were added to 67 ml. of 5% aqueous sodium carbonate. The mixture was extracted with chloroform (3 × 8 ml.). Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo* leaving 146 mg. of semicrystalline residue. Recrystallization from ethyl acetate afforded 95 mg. (24%) of product in two crops, m.p. 204–207°; ν_{max}^{KBr} 3360, 3300, 3160 cm.$^{-1}$ (OH and NH), 1645 cm.$^{-1}$ (NH_2 of $NH_2C{=}N$), 1600, 1570 cm.$^{-1}$ (C=N and C=C), 1475 cm.$^{-1}$ (C—Me), 1120, 1090, 1080 cm.$^{-1}$ (C—O—C); $[\alpha]_D^{27}$ −71.6° (0.3% in dimethylformamide).

Anal. Calcd. for $C_{13}H_{17}N_5O_4$: C, 50.8; H, 5.58; N, 22.8. Found: C, 51.1; H, 5.85; N, 22.9.

It is probable that the yield could be raised considerably by study of the variables since this reaction was run only once.

9-(5′-O-Trityl-β-D-xylofuranosyl)adenine. A solution of 500 mg. of amorphous 9-β-D-xylofuranosyladenine in 4 ml. of reagent pyridine was evaporated *in vacuo* to remove traces of water and alcohol. A solution of the residue and 575 mg. of triphenylmethyl chloride in 4 ml. of reagent pyridine was heated in a bath at 50° for 72 hr., the solution being protected from moisture. The cooled solution was diluted with 15 ml. of chloroform, then 30 ml. of water containing excess sodium bicarbonate. Dried with magnesium sulfate, the chloroform solution was evaporated to dryness leaving 1.033 g. of residue. Crystallization of 946 mg. from 10 ml. of benzene gave 697 mg. (80%) of product, m.p. 180–193°. Further trituration with hot benzene gave 310 mg. (36%) of nearly pure material, m.p. 193–196°. Two more recrystallizations from ethyl acetate–hexane afforded white crystals, m.p. 198–199°; ν_{max}^{KBr} 3350 cm.$^{-1}$ (OH), 3130 cm.$^{-1}$ (NH), 1635 cm.$^{-1}$ (NH_2 of $NH_2C{=}N$), 1080, 1070, 1050 cm.$^{-1}$ (C—O—), 700, 750 cm.$^{-1}$ (monosubstituted phenyl); $[\alpha]_D^{27}$ −24.9° (0.3% in $CHCl_3$).

Anal. Calcd. for $C_{29}H_{27}N_5O_4$: C, 68.3; H, 5.34; N, 13.8. Found: C, 67.7; H, 5.39; N, 13.6.

This compound is difficult to purify since the crude product is probably contaminated with N^6,5′-ditrityl-9-β-D-xylofuranosyladenine.[28]

2,6-Diamino-9-α-L-rhamnofuranosylpurine (XV). Condensation of XI (prepared from 12.0 g. of X) with 9.0 g. of chloromercuri-2,6-diacetamidopurine[2] as described for XII gave 10.4 g. of crude blocked nucleoside. Only 25% of the chloromercuri derivative reacted indicating the reaction proceeded poorly. The crude blocked nucleoside was refluxed with 104 ml. of methanol and 15 ml. of 1*N* methanolic sodium methoxide for 2 hr., then the solution was neutralized with acetic acid. The picrate was isolated as described for the corresponding pyranose (XIV).[2] Regeneration of the nucleoside from the picrate with Dowex 1 (CO_3)[2] gave an aqueous solution which contained both the pyranose (XIV) (R_{Ad} 0.24) and the furanose (R_{Ad} 0.41) as shown by paper chromatography.[16] The aqueous solution was evaporated to dryness *in vacuo* and the residue crystallized from 1 ml. of water; yield, 149 mg. (4.2%) of white crystals in two crops, m.p. 190–196° (dec.). Paper chromatography[16] showed this material to be pure with R_{Ad} 0.38. No pyranose (R_{Ad} 0.24) was present. Recrystallization from water gave one of two crystal forms, m.p. 190–196° (dec.) or 270–275° (dec.). Both had identical R_{Ad} values. The material with m.p. 270–275° had $\lambda_{max}^{pH\ 7,14}$ 255 mμ (a_M 9,640), 278 mμ (a_M 10,200); $\lambda_{max}^{pH\ 1}$ 252 mμ (a_M 10,900), 290 mμ (a_M 10,300); ν_{max}^{KBr} 3400, 3320, 3140 cm.$^{-1}$ (OH, NH), 1650 cm.$^{-1}$ (NH_2 or $NH_2C{=}N$), 1630 cm.$^{-1}$ (NH), 1585, 1495 cm.$^{-1}$ (C=C and C=N), 1140, 1095, 1040 (C—O—); $[\alpha]_D^{27}$ −80° (0.03% in 0.1*N* HCl).

Anal. Calcd. for $C_{11}H_{16}N_6O_4$: C, 44.6; H, 5.44; N, 28.4. Found: C, 44.5; H, 5.33; N, 27.7.

In other runs, starting with IX or X, the yields were 1.4–5.3%. Attempts to synthesize 1-α-L-rhamnofuranosyl nucleosides of thymine or cytosine were completely unsuccessful starting with either IX or X. The reasons for these low yields remain unknown.

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(25) P. Chang and B. Lythgoe, *J. Chem. Soc.*, 407 (1950).

(26) A mixture of methane- and ethanesulfonic acid obtained from the Indoil Co.

(27) A similar procedure has been used for synthesis of 2-methylmercapto-6-dimethylamino-9-(3′,5′-*O*-isopropylidene-β-D-xylofuranosyl)purine.[13]

(28) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **121**, 131 (1937), have observed that tritylation of adenosine gives a mixture of 5′-*O*-trityladenosine and N^6,5′-ditrityladenosine.