Acknowledgments. We wish to thank Dr. Jack J. Fox of the Sloan-Kettering Institute for making known to us the data on the new inverse method for preparation of chloromercuri purines. We are indebted to J. P. Holmquist for the microanalyses and to J. W. Murphy and L. D. Norton of this Institute for the spectral and rotation determinations.

BIRMINGHAM 5, ALA.

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

Synthesis of Potential Anticancer Agents. VII.[2] Nucleosides Derived from L-Rhamnopyranose

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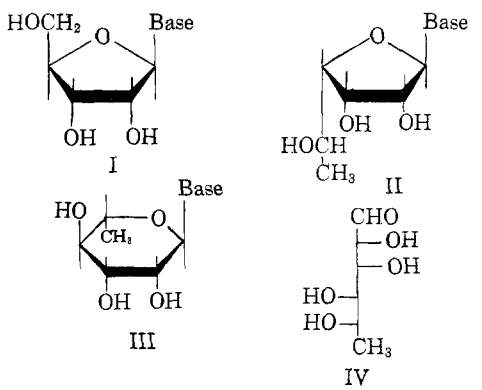
The syntheses of six nucleosides derived from L-rhamnopyranose have been accomplished by proper modification of standard procedures.

The most commonly available sugar, besides D-ribose, that has C_2-C_3-*cis*-hydroxyls of D-configuration is L-rhamnose (IV, 6-deoxy-L-mannose). From L-rhamnose, it should be possible to synthesize L-rhamnofuranosyl nucleosides (II) as well as L-rhamnopyranosyl nucleosides (III). Since L-*rhamno*-nucleosides with structures II and III have certain structural features in common with natural D-*ribo*-nucleosides (I) derived from nucleic acids, these L-rhamnonucleosides may inhibit some stage of nucleotide metabolism in the cell. The L-rhamnofuranosyl nucleosides (II) differ from the natural ribosides only in the size and configuration of the group at C_4 of the sugar moeity. The L-rhamnopyranosyl nucleosides (III) are similar to the natural nucleosides (I) in the configurations at C_1, C_2, C_3 and C_4 of the sugar moeity; however, the group at C_4 is hydroxyl in place of hydroxymethyl and, in addition, III has a pyranose ring rather than the natural furanose ring. This communication describes the synthesis of several nucleosides (III) derived from L-rhamnopyranose. An accompanying paper describes the synthesis of nucleosides (II) derived from L-rhamnofuranose.



A search of the literature revealed that only one nucleoside has been synthesized from L-rhamnopyranose, namely 7-L-rhamnopyranosyltheophylline.[4] Although the anomeric configuration was unknown, it is highly probable that an α-nucleoside was obtained. The formation of an α-nucleoside (III) would conform with the rule[5-7] that a nucleoside with C_1-C_2-*trans*-configuration will be obtained when a heavy metal salt of a purine (such as theophylline[4]) is condensed with an *O*-acylated glycosyl halide (such as 2,3,4-tri-*O*-acetyl-L-rhamnopyranosyl bromide[4]).

Since past experience has shown that *O*-benzoyl blocking groups for the glycosyl halide generally give higher yields of nucleosides than *O*-acetyl blocking groups,[8,9] 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI)[10] was employed for synthesis of these nucleosides.

9-α-L-Rhamnopyranosyladenine (XI). This nucleoside (XI) was synthesized by two routes. Condensation of chloromercuri-6-chloropurine (V) with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) afforded the blocked chloropurine nucleoside (VII), as previously described.[11] The crude blocked nucleoside was treated at 100° with

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(2) This work was supported in part by the C. F. Kettering Foundation.

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(4) E. Fischer and K. Fodor, *Ber.*, **47**, 1058 (1914).

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

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

(7) B. R. Baker, J. P. Joseph, and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5905 (1955).

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

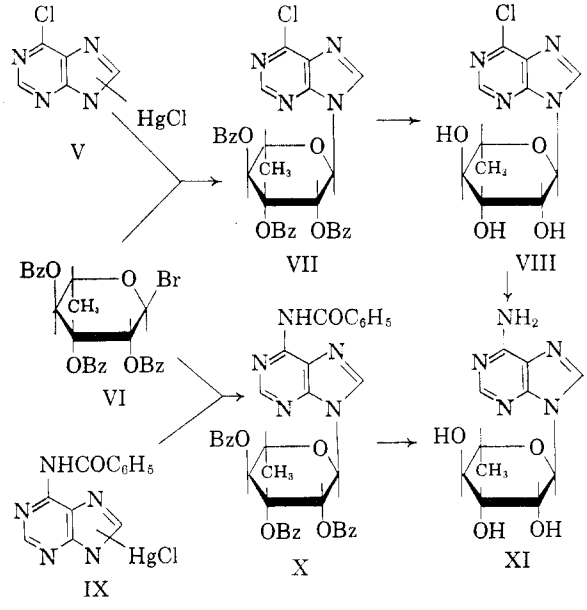
(9) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).

(10) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **73**, 296 (1951).

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

methanolic ammonia, which caused replacement of the chloro by amino as well as *O*-debenzoylation. The adenine nucleoside (XI) was isolated as its picrate. Higher yields of XI picrate were obtained if the blocked nucleoside (VII) was *O*-debenzoylated at 0° with methanolic ammonia to VIII,[11] then the solution heated at 100° to replace the 6-chloro group of the purine moiety with the amino group.[12]

Regeneration of the base (XI) from its picrate was accomplished by treatment of the picrate with Dowex I (Cl)[13] in aqueous suspension. Evaporation of the solution and crystallization from alcohol gave crystalline 9-α-L-rhamnopyranosyladenine (XI) in 46% overall yield from the sugar bromide (VI).[14]



The 9-α-L-rhamnopyranosyladenine (XI) could also be synthesized in good yield from 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide and chloromercuri-6-benzamidopurine (IX) by the standard method for syntheses of adenosine[13] as modified by Johnson and Thomas.[15] Isolation of the product *via* the picrate and regeneration with Dowex 1 (Cl) gave XI hydrochloride identical with that obtained by the 6-chloropurine method. The overall yield from VI was 51%. However, examination by paper chromatography showed that XI was contaminated with a small amount of adenine. Since the aqueous solution of the nucleoside (XI) from which the picrate was prepared contained no detectable adenine by paper chromatography, the presence of adenine must have arisen by hydrolysis either during preparation of the picrate or during regeneration of the nucleoside from the picrate or both.

The original procedure of Davoll and Lowy[13] for regeneration of adenosine from its picrate with Dowex 1 (Cl) called for neutralization of the generated hydrochloric acid with sodium hydroxide before evaporation. Adenosine is sufficiently insoluble in water to be readily separable from salt. However, 9-α-L-rhamnopyranosyladenine (XI) was extremely water soluble, a characteristic of all the rhamnopyranosyl nucleosides described in this paper. An attempt to regenerate XI from its picrate with freshly prepared Dowex 1 (OH) gave poor results since about half of the nucleoside was lost by adsorption on the resin. Two less basic forms of the resin were then considered, namely the carbonate and the acetate forms. The carbonate form of Dowex 1, which forms carbon dioxide during regeneration was found satisfactory. Although there was more adsorption than with Dowex 1 (Cl), the carbonate form was quite satisfactory provided the final solution of nucleoside was no more concentrated than about 0.001 molar. Thus, 9-α-L-rhamnopyranosyladenine (XI) was obtained as the crystalline free base in 43% overall yield based on the sugar bromide (VI). This nucleoside was free of adenine as shown by paper chromatography. An additional 7% of the nucleoside (XI) could be isolated from the alcoholic mother liquor as the hydrochloride, but was contaminated with a small amount of adenine. The use of Dowex 1 (Ac) was not investigated with this nucleoside since the Dowex 1 (CO_3) was considered satisfactory.[16]

The 9-α-L-rhamnopyranosyladenine (XI) failed to have any activity against Adenocarcinoma 755,[17] Sarcoma 180,[18] or *in vitro* against Endamoeba histolytica.[19]

At this point the question arose, "What are the minimum number of purines and pyrimidines that should be converted to a nucleoside with a given unnatural sugar in order to establish whether or not any biological activity will be obtained?" The lack of examples in the literature leaves this problem still unsolved. Nevertheless, consideration of what biological factors are known led to a more or less arbitrary selection of the following pyrimidine and purine nucleosides as a representative cross-sec-

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

(13) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).

(14) That the nucleoside has a C_1-C_2-*trans*-configuration is highly probable in view of the rule postulated for the stereochemistry of nucleoside formation.[5] The formation of this α-nucleoside would require a double Walden inversion during nucleoside condensation, a previously observed phenomenon (*cf.* ref. 6, footnote 16).

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

(16) Later work on nucleosides has shown that Dowex 1 in the acetate form is also satisfactory for regeneration of a nucleoside from its picrate.

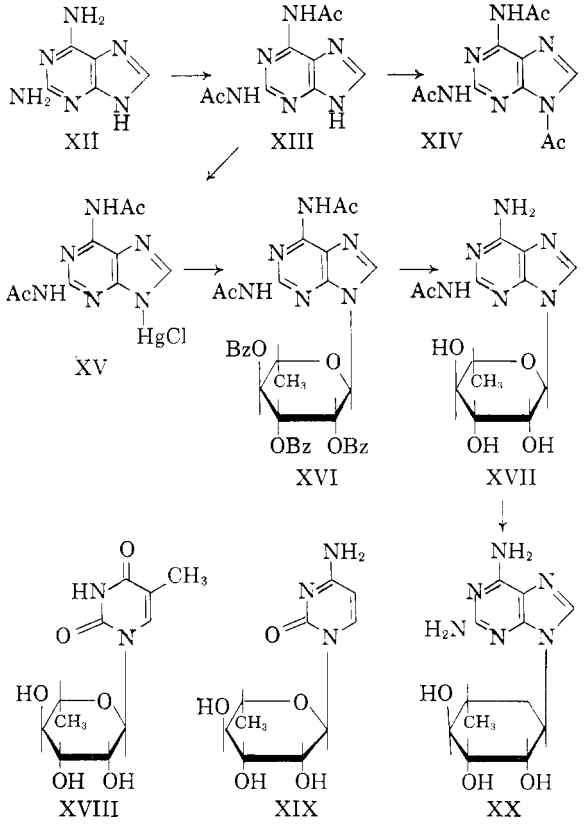
(17) Private communication from Dr. H. E. Skipper, Southern Research Institute.

(18) Private communication from Dr. C. C. Stock, Sloan-Kettering Institute.

(19) Private communication from Dr. E. F. Elslager, Parke, Davis & Co.

tion: (*1*) Adenine, (*2*) 2,6-Diaminopurine, (*3*) Thymine, (*4*) Cytosine or uracil.

2,6-Diamino-9-α-L-rhamnopyranosylpurine (XX). An apparently general method for the synthesis of 2,6-diaminopurine-9-glycosides has been described by Davoll and Lowy.[13] They acetylated 2,6-diaminopurine (XII) with acetic anhydride to form 2,6-diacetamidopurine (XIII), m.p. 295–300° (dec.), in 83% yield. Repetition of their procedure gave a mixture of XIII and its 9-acetyl derivative (XIV). That the 9-acetyl group was present was clearly shown by the C=O infrared absorption of an "active" *N*-acetyl at 1745 cm.$^{-1}$ and by the diminished acidic 9-N-H absorption at 2400–3000 cm.$^{-1}$. Recrystallization of the mixture from water served to hydrolyze the 9-acetyl group of XIV, thus forming pure 2,6-diacetamidopurine (XIII) in 59% yield. The lability of the 9-acetyl group on a purine nucleus was observed earlier in our laboratories.[20]



Reacetylation of the mixed products in the mother liquors raised the yield to 77%. Similar results were obtained by acetylation with acetic anhydride containing 20% acetic acid. The data of Davoll and Lowy[13] indicate that they obtained no 9-acetylation. The reason for this discrepancy is still unknown.

Conversion to chloromercuri-2,6-diacetamidopurine (XV) was effected in 100% yield by adding one equivalent of sodium hydroxide slowly to a solution of mercuric chloride containing the purine XII in suspension.[21] Condensation of the chloromercuri purine (XV) with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) gave crystalline 2,6-diacetamido-9-(2′,3′,4′-tri-*O*-benzoyl-α-L-rhamnopyranosyl) purine (XVI) in 32% yield. Treatment of XVI with excess methanolic sodium methoxide at the boiling point[13] removed both the *O*-benzoyl and *N*-acetyl blocking groups.[22] The 2,6-diaminopurine rhamnopyranoside (XX) was isolated as its beautifully crystalline picrate in 96% yield. Regeneration of the nucleoside from the picrate with Dowex 1 (CO_3) afforded crystalline XX with 74% recovery.

In order to try to avoid isolation of XX *via* the picrate, a method was sought which would not introduce inorganic material. Deacylation with boiling methanolic butylamine[24] was investigated. The major product, isolated in 55% yield, was 2-acetamido-6-amino-9-α-L-rhamnopyranosylpurine (XVII) and was readily differentiated from the 2,6-diaminopurine rhamnoside by paper chromatography or infrared analysis. The 2-acetamidopurine nucleoside could be prepared in 94% yield by use of methanolic ammonia, a reagent used by Davoll and Lowy[13] for synthesis of 2-acetamido-6-amino-9-β-D-ribofuranosylpurine.

1-α-L-Rhamnopyranosylthymine (XVIII). A new synthesis of thymine nucleosides has recently been discovered by Fox *et al.*[9] Coupling of dithyminyl mercury with *O*-acylglycosyl halides gave excellent results. This method has now been applied to the synthesis of 1-α-L-rhamnopyranosylthymine (XVIII).

Condensation of dithyminyl mercury with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) afforded the crude blocked nucleoside in quantitative yield which had a maximum purity of 53% based on nitrogen content. Debenzoylation with methanolic sodium methoxide gave a water soluble product. The by-product methyl benzoate was removed by extraction of an aqueous solution of crude XVIII with chloroform. The residue from evaporation of the aqueous solution was extracted with acetone. The acetone solution of XVIII was separated from insoluble inorganic materials. Evaporation gave a 58% yield of XVIII with a maximum purity of 85% based on ultraviolet analysis. The entire separation to this point was followed by ultraviolet examination of the various fractions. The nucleoside XVIII was further purified by Celite partition chromatography[8] using a

(20) J. A. Montgomery, Paper I of this series, *J. Am. Chem. Soc.*, **78**, 1928 (1956).

(21) We wish to thank Dr. J. J. Fox of Sloan-Kettering Institute for suggesting this inverse procedure for preparation of chloromercuri derivatives in quantitative yield.

(22) The use of the usual catalytic amounts of sodium methoxide[5,7,8,23] was not satisfactory since the 2-acetamido group did not undergo methanolysis at an appreciable rate.

(23) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1780 (1954).

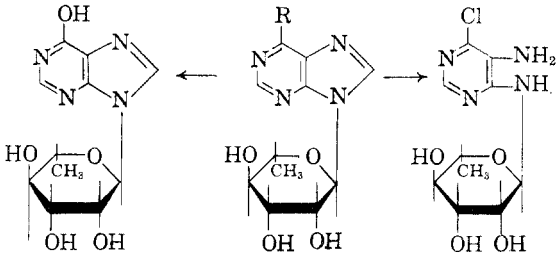
(24) L. Goldman, J. W. Marsico, and R. B. Angier, *J. Am. Chem. Soc.*, **78**, 4173 (1956).

stationary aqueous phase and mobile butanol phase. The peak fractions were characterized by ultraviolet absorption and paper chromatography. The major fraction was a colorless glass which showed $\lambda_{max}^{H_2O}$ 265 mμ (a_M 9930) and traveled on paper as a single ultraviolet absorbing spot in a butanol-water system. The ultraviolet spectrum compared favorably with that of a pure sample of thymidine. Although the nucleoside XVIII is apparently pure, it has not been obtained in crystalline form. The overall yield from 2,3,5-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) was 53%.

1-α-L-Rhamnopyranosylcytosine (XIX). The outstanding research of J. J. Fox and coworkers on new syntheses of pyrimidine nucleosides has also led to a new method for synthesis of cytosine nucleosides.[25] They found that *N*-acetylcytosine formed a 1:1 complex with mercuric ion which contained no halogen. This mercuri derivative, $C_6H_5HgN_3O_2$, could be condensed with *O*-acylglycosyl halides to form cytosine nucleosides; two moles of sugar halide were necessary for the reaction and one mole was not coupled.

Condensation of mercuri-*N*-acetylcytosine with two moles of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) gave a blocked nucleoside which was deacylated with methanolic sodium methoxide. The most difficult problem in this synthesis, as in the case of thymine rhamnoside (XVIII), was the isolation of the pure cytosine nucleoside (XIX) since the compound could not be crystallized. Again Celite partition chromatography[8] with a stationary water phase and mobile butanol phase was successful in giving the pure, although amorphous, nucleoside (XIX). The overall yield was 24% based on mercuri-*N*-acetylcytosine.

9-α-L-Rhamnopyranosylhypoxanthine (XXI). The synthesis of 6-chloro-9-α-L-rhamnopyranosylpurine (VIII) has previously been described.[11] Since Bendich, Russell, and Fox[26] have shown that treatment of 6-chloropurine with boiling 0.1 *N* sodium hydroxide gave a quantitative yield of hypoxanthine, the conversion of VII to XXI was investigated. Unfortunately, the action of 0.1*N* sodium hydroxide on 6-chloro-9-α-L-rhamnopyranosylpurine (VIII) followed a different course, and did not give 9-α-L-rhamnopyranosylhypoxanthine (XXI). That XXI was not formed was readily demonstrated by examination of the change in ultraviolet absorption spectrum of the chloropurine nucleoside (VIII) in 0.1*N* sodium hydroxide as a function of time at 100°. After each time interval, the solution was acidified to *p*H 1 and the absorption spectrum determined. The starting material has λ_{max} 263 mμ at *p*H 1,[11] whereas the hypoxanthine nucleoside



XXI VIII R = Cl XI R = NH_2 XXII

(XXI) should have λ_{max} about 247 mμ, about the same as inosine. The observed results were quite unexpectedly different. A new peak rapidly appeared at 307 mμ and there were slower changes in the 260 mμ region. This spectrum could best be explained by a cleavage of the imidazole ring of the 6-chloropurine nucleoside (VIII) with formation of 4,5-diamino-6-chloropyrimidine-N^5-rhamnoside (XXII) since 4,5-diamino-6-chloropyrimidine[27] was found to have λ_{max} 268 mμ (a_M 7380) and 305 mμ (a_M 10,100).[28]

A similar rupture of the imidazole ring of 9-β-D-ribofuranosylpurine with 0.1*N* base had been observed by Brown and Gordon.[29] These workers concurred with our interpretation of the base cleavage and informed us[29a] that they had observed earlier the same base cleavage with 6-chloro-9-β-D-ribofuranosylpurine.

The 6-amino group of adenosine and 2-chloroadenosine has been replaced by hydroxyl by use of nitrous acid.[30-33] When adenine-free 9-α-L-rhamnopyranosyladenine (XI) was treated with sodium nitrite and dilute acetic acid,[33] the resultant 9-α-L-rhamnopyranosylhypoxanthine (XXI), isolated *via* its lead salt, was obtained as an amorphous solid in 71% yield; this material was chromatographically pure, traveling as a single spot (R_{Ad} 0.39)[34] on paper.

(25) We wish to thank Dr. J. J. Fox of the Sloan-Kettering Institute for allowing us to use this procedure prior to publication.

(26) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

(27) R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Am. Chem. Soc.*, **75**, 263 (1953).

(28) Private communication from Dr. J. A. Montgomery, Southern Research Institute.

(29) (a) Private communication from Drs. G. B. Brown and M. P. Gordon, Sloan-Kettering Institute; (b) G. B. Brown, Ciba Foundation Symposium on "Chemistry and Biology of Purines," in London, England, May, 1956.

(30) P. A. Levene and W. A. Jacobs, *Ber.*, **43**, 3150 (1910).

(31) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **111**, 313 (1935).

(32) J. M. Gulland and E. R. Holiday, *J. Chem. Soc.*, 765 (1936).

(33) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 1685 (1948).

(34) Paper chromatograms were run with water-saturated butanol by the descending procedure on 7″ × 17″ strips of Whatman No. 1 paper with spots 1″ apart. The spots were located by visual examination with an ultraviolet lamp. Adenine was used as a control spot 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. Melting points were determined in capillary tubes in a stirred oil-bath and are uncorrected.

9-α-L-Rhamnopyranosylpurine. Brown and Weliky[12] have described the conversion of 6-chloro-9-β-D-ribofuranosylpurine to 9-β-D-ribofuranosyl-purine by hydrogenolysis with a palladium-charcoal catalyst in the presence of magnesium oxide as the acid acceptor. These conditions have now been applied to 6-chloro-9-α-L-rhamnopyranosylpurine (VIII). Hydrogenation proceeded smoothly. However, the product was soluble in alcohol and insoluble in acetone, the same as the by-product, magnesium chloride. Separation of the purine rhamnoside from magnesium chloride was effected smoothly by Celite partition chromatography[8] in a short column using water as the stationary phase and butanol as the mobile phase. The purine rhamnopyranoside was obtained as a glass in 83% yield from the chloropurine nucleoside (VII). Examination of this product with the aid of paper chromatography showed that there was no contamination with any other materials in the ultraviolet absorbing such as purines. A single spot with R_{Ad} 0.89 was obtained.[34] The starting material (VIII) had R_{Ad} 1.46 in the same solvent system.

Biological activity. None of these nucleosides had any effect on Adenocarcinoma 755 at 200 mg. per kg. (mouse) per day.[17]

EXPERIMENTAL[34,35]

9-α-L-Rhamnopyranosyladenine (XI). *A.* To 2.00 g. of the blocked nucleoside (VII), obtained by condensing chloromercuri-6-chloropurine (V) with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide[10] as previously described,[11] was added 70 ml. of methanol saturated with ammonia at 5°. The mixture was stirred in a closed flask until solution was complete (about 2–4 hr.). The solution was heated in a steel bomb at 100° for 10 hr. The bomb contents were evaporated to dryness *in vacuo* and the residue partitioned between 25 ml. of water and 25 ml. of chloroform. The separated aqueous phase, washed several more times with chloroform, was evaporated to dryness *in vacuo*. To a solution of the residue in 10 ml. of methanol was added 10 ml. of 10% methanolic picric acid. After 90 min. the picrate was collected on a filter and washed with small amounts of cold methanol; yield, 0.96 g. of yellow solid, which charred and partially melted at 210–225°. This crude picrate contained 5–10% of adenine picrate. The pure picrate was readily prepared from the pure base (described below) with methanolic picric acid and melted at 214–216° (dec.). This picrate showed broad OH–NH at 3400 cm.$^{-1}$ and C=NH$^+$ at 1710 cm.$^{-1}$ in the infrared (KBr); $[\alpha]_D^{26}$ −32° (0.66% in 50% H_2O-dimethyl formamide).

Anal. Calcd. for $C_{17}H_{18}N_8O_{11}$: C, 40.0; H, 3.57; N, 21.9. Found: C, 39.7; H, 3.67; N, 21.2.

The 0.96 g. of crude picrate was dissolved in 200 ml. of hot water with magnetic stirring. The solution was treated with portions of Dowex 1 (Cl) until the solution was colorless. Evaporation of the aqueous solution to dryness *in vacuo* left 0.61 g. of a gum. The gum was triturated with 5 ml. of absolute alcohol when the product crystallized. The mixture was allowed to stand overnight at room temperature. The product was collected and washed with absolute alcohol; yield, 414 mg. of XI hydrochloride (44% based on 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide), m.p. 170–171° dec.). The combined filtrate and washings were evaporated to dryness *in vacuo*. A solution of the residue in 1 ml. of absolute alcohol was treated with 0.1 ml. of 5% hydrogen chloride in methanol. An additional 15 mg. (total 47%) of product, m.p. 160–165° (dec.) was obtained. Two recrystallizations of 58 mg. of the first crop by solution in about 0.1 ml. of water, addition of about 5 ml. of acetone, then about 0.5 ml. of absolute alcohol afforded beautiful white crystals, m.p. 169–170° (dec.); ν_{max}^{KBr} 3000–3400 cm.$^{-1}$ (broad OH–NH), 1675 cm.$^{-1}$ (C=NH$^+$), 1605, 1500 cm.$^{-1}$ (C=N and C=C), 1120, 1015 cm.$^{-1}$ (OH and C—O—C).

Anal. Calcd. for $C_{11}H_{15}N_5O_4 \cdot HCl$: C, 41.6; H, 5.09; N, 22.1. Found: C, 42.0; H, 5.40; N, 21.8.

This compound traveled on paper as a single spot with water-saturated butanol (R_{Ad} 0.56) and with butanol-water-acetic acid (4:5:1) (R_{Ad} 0.72).[34]

B. To a stirred mixture of 3.94 g. of chloromercuri-6-benzamidopurine (IX), 3.82 g. of Celite,[37] and 170 ml. of xylene previously dried by distillation was added a warm solution of 4.12 g. of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) in 50 ml. of xylene. After being refluxed and stirred for 2 hr., the reaction mixture was processed as in Part A; yield, 5.82 g. (109%) of crude blocked nucleoside (X).

A mixture of 5.82 g. of crude blocked nucleoside (X), 50 ml. of methanol, and 5 ml. of 1*N* methanolic sodium methoxide was refluxed for 30 min., solution taking place at the boiling point. At the end of the reflux period, the solution still had the necessary *p*H 9 when spotted on moist indicator paper.[8] After being neutralized with 0.25 ml. of acetic acid, the solution was evaporated to dryness *in vacuo*. The residue was partitioned between about 20 ml. each of chloroform and water. The separated aqueous layer, washed once more with chloroform, was evaporated to dryness *in vacuo*. To a solution of the residue in 15 ml. of methanol was added 30 ml. of 10% methanolic picric acid. After 90 min. in an ice-bath, the mixture was filtered. The picrate was washed with 10 ml. of methanol, then two 15-ml. portions of water to remove sodium picrate.

The moist picrate was dissolved in about 200 ml. of warm water and treated with Dowex 1 (CO_3) until the solution was colorless (about 15 g. of wet resin required). The filtered solution was evaporated to dryness *in vacuo*. The residue was heated in a mixture of 1 ml. of water and 15 ml. of absolute alcohol. The gum dissolved and crystals began to separate from the hot solution. The mixture was allowed to stand at room temperature overnight. The crystals were collected and washed with absolute alcohol; yield, 918 mg. (43% based on VI), m.p. 209–210°. Since a second crop could not be isolated from the solution, the solution was treated with a little methanol containing excess hydrogen chloride. The solution was concentrated to about 1 ml. under an air stream, then diluted with about 5 ml. of acetone. The hydrochloride salt was collected and washed with acetone; yield, 150 mg. (7%).

A sample of the 918 mg. was dissolved in hot absolute alcohol by addition of sufficient water to cause solution. The cooled solution deposited white crystals, m.p. 210–211°; $\lambda_{max}^{pH\ 1}$ 257 mμ (a_M 13,800), $\lambda_{max}^{pH\ 7,14}$ 259 mμ (a_M 13,800); ν_{max}^{KBr} 3460, 3360, 3200 cm.$^{-1}$ (OH, NH), 1635 cm.$^{-1}$ (NH_2 of NH_2—C=N), 1597, 1575 cm.$^{-1}$ (C=N and C=C), 1115, 1083, 1075, 1055 cm.$^{-1}$ (OH and C—O—C); $[\alpha]_D^{26}$ −54° (0.44% in H_2O); R_{Ad} 0.56. The analysis and a_M values showed that the compound was slightly hydrated.

Anal. Calcd. for $C_{11}H_{15}N_5O_4$: C, 46.9; H, 5.41; N, 24.9. Found: C, 46.1; H, 5.44; N, 24.5.

Paper chromatography with water-saturated butanol

(35) 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 solutions.[36]

(36) A. S. Keston, Abstracts, 125th Meeting, American Chemical Society, 18C (1955).

(37) Johns-Manville Co.

showed that a sample of the 918 mg. was homogeneous (R_{Ad} 0.54).[34] The 150 mg. of hydrochloride contained a trace of adenine.

Chloromercuri-2,6-diacetamidopurine (XV). 2,6-Diaminopurine was acetylated with boiling acetic anhydride with stirring as described by Davoll and Lowy.[18] The acetic anhydride deposited white crystals which were mainly 2,6-diacetamido-9(or 7)-acetylpurine, m.p. 243–245° (dec.). Examination of the infrared spectrum of this material showed that the characteristic broad acidic NH absorption of a purine at 2400–3000 cm.$^{-1}$ was missing. In addition, an "active" 9(or 7)-acetyl C=O band[20] was present at 1745 cm.$^{-1}$.

Recrystallization of the solid from water caused loss of the 9(or 7)-acetyl group with formation of 2,6-diacetamidopurine in 59% yield, m.p. 285–289° (dec.); ν_{max}^{KBr} 3190 cm.$^{-1}$ (amide NH), 2400–3000 cm.$^{-1}$ (broad acidic NH), 1700, 1660 cm.$^{-1}$ (amid C=O), 1625, 1568 cm.$^{-1}$ (C=C and C=N), 1500 cm.$^{-1}$ (amide NH), 1370 cm.$^{-1}$ (C—Me).

The aqueous mother liquor from the recrystallization was evaporated to dryness *in vacuo*. Reacetylation and recrystallization from water, as above, gave additional 2,6-diacetamidopurine; total yield, 77%.

Davoll and Lowy[18] record a melting point of 305° (dec.) for the recrystallized product and a melting point of 295–300° (dec.) for the crude product obtained in 83% yield.

To a solution of 5.45 g. of mercuric chloride in 80 ml. of 50% alcohol was added 4.72 g. of recrystallized 2,6-diacetamidopurine. Then 8.04 ml. of 10% sodium hydroxide was added dropwise with stirring to the mixture over a period of 30 min. The mixture was diluted with an equal volume of water, then chilled at 0° for 30 min. After the addition of 10.00 g. of Celite (analytical grade)[37] the mixture was well slurried, then filtered. The product was washed with water, alcohol, and ether, then dried; yield, 19.4 g. or 9.4 g. (100%) of XV corrected for Celite.[37]

With larger batches, it is expedient to add the Celite before the base in order to obtain homogeneity.

2,6-Diacetamido-9-(2′,3′,4′-tri-O-benzoyl-α-L-rhamnopyranosyl)purine (XVI). A mixture of 2.00 g. of chloromercuri-2,6-diacetamidopurine (XV) and 2.14 g. of Celite suspended in 100 ml. of xylene was distilled with stirring until no more water was removed from the mixture (30 ml. of distillate). After the addition of a warm solution of 2.06 g. of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) in 40 ml. of xylene, the mixture was refluxed for 2 hr. protected from moisture. The mixture was filtered hot and the filtrate evaporated to dryness *in vacuo*. The filter cake was washed with two 50-ml. portions of hot chloroform. The xylene residue was dissolved in the combined chloroform washings. Washed with 30% potassium iodide solution and water, the chloroform solution was dried with magnesium sulfate. The drying agent was washed with several portions of boiling chloroform. The combined filtrate and chloroform washings were evaporated to about 20 ml. *in vacuo*. After standing overnight, the mixture was filtered and the white crystals washed with small amounts of cold chloroform; yield, 0.854 g. (32%), m.p. 239–242°. Recrystallization of a similar preparation (from a pilot run, m.p. 239–242°) from absolute alcohol gave white crystals, m.p. 204°, with shrinking at about 170°, resolidification and remelting at 224°; ν_{max}^{KBr} 3170 cm.$^{-1}$ (NH), 1730 cm.$^{-1}$ (benzoate C=O), 1640, 1630 cm.$^{-1}$ (amide C=O), 1605 (purine and phenyl) 1500 cm.$^{-1}$ (phenyl), 1515 cm.$^{-1}$ (NH of amide), 1265, 1110 cm.$^{-1}$ (C—O—C of benzoate), 1100, 1075, 1030 cm.$^{-1}$ (C—O—C of sugar), and 710 cm.$^{-1}$ (monosubstituted phenyl); $[\alpha]_D^{26}$ +33° (1% in $CHCl_3$). Apparently isomorphic crystals are obtained from chloroform or alcohol.

Anal. Calcd. for $C_{36}H_{32}N_6O_9$: C, 62.4; H, 4.66; N, 12.1. Found: C, 62.4; H, 4.61; N, 12.3.

2,6-Diamino-9-α-L-rhamnopyranosylpurine (X) *picrate*. A mixture of 770 mg. of crystalline 2,6-diacetamido-9-(2′,3′,4′-tri-*O*-benzoyl-α-L-rhamnopyranosyl)purine (XI), 15 ml. of reagent methanol, and 1.36 ml. of 1*N* methanolic sodium methoxide was refluxed for 2 hr., solution taking place at the boiling point. The solution was neutralized with acetic acid, then evaporated to dryness *in vacuo*. The residue was partitioned between 10 ml. of water and 10 ml. of chloroform. The separated aqueous layer, washed again with chloroform, was evaporated to dryness *in vacuo*. To a solution of the residue in 10 ml. of hot water was added 5 ml. of 10% methanolic picric acid. The picrate separated immediately. After several hours at 3°, the mixture was filtered and the picrate washed with several small portions of water; yield, 572 mg. (95%). The compound gradually decomposed from 215–230° without melting.

A similar preparation was recrystallized from water giving yellow leaflets which decomposed at 223–234° without melting.

Anal. Calcd. for $C_{17}H_{19}N_9O_{11}$: C, 38.2; H, 3.59; N, 23.6. Found: C, 38.4; H, 3.85; N, 23.2.

This compound showed bands in the infrared at 3200–3500 cm.$^{-1}$ (broad OH and NH); 1683 cm.$^{-1}$ (C=NH$^+$); 1640 cm.$^{-1}$ (NH); 1610 cm.$^{-1}$ (C=N); 1555, 1315 cm.$^{-1}$ (NO_2); 1085, 1060, 1030 cm.$^{-1}$ (OH and C—O—C).

2,6-Diamino-9-α-L-rhamnopyranosylpurine (XX). Regeneration of the nucleoside from 572 mg. of XX picrate with Dowex 1 (CO_3), as described for the adenine rhamnoside (XI), afforded 252 mg. of a glass on evaporation of the aqueous solution. This glass was dissolved in 0.5 ml. of water, diluted with 2 ml. of acetone, filtered from a trace of insolubles, then diluted with 2 ml. more of acetone and seeded. After standing overnight, the mixture was filtered and the crystals washed with 80% acetone; yield, 127 mg. of solvated crystals which partially melted at 120–160° and completely melted at 198°. Evaporation of the combined mother liquor and washings to dryness *in vacuo* and trituration of the residue with acetone gave an additional 105 mg. of solvated crystals with the same m.p.; total yield, 232 mg. (74%). Both fractions had identical infrared spectra and each traveled on paper as a single blue-fluorescing spot with R_{Ad} 0.23[34] in a water-saturated butanol system. A sample was recrystallized from water-acetone to give beautiful, colorless crystals melting 90–100°. After being dried in high vacuum at 80° for several hours, then at 110° for 3 hr., the crystals melted at 198° (dec.) with gas evolution starting at 140°. This material contained acetone of crystallization as shown by the acetone C=O at 1698 cm.$^{-1}$ in the infrared and by combustion analyses. The compound also had NH (of NH_2—C=N) absorption at 1630 cm.$^{-1}$, C=C and C=N at 1595 and 1475 cm.$^{-1}$, C—OH and C—O—C at 1115 and 1050 cm.$^{-1}$, and broad OH—NH absorption at 3250–3450 cm.$^{-1}$; $[\alpha]_D^{26}$ −75° (0.75% in H_2O).

Anal. Calcd. for $C_{11}H_{16}N_6O_4 \cdot {}^1/_2C_2H_6O$: C, 46.4; H, 5.83; N, 26.0. Found: C, 45.7; H, 5.78; N, 25.7.

2-Acetamido-6-amino-9-α-L-rhamnopyranosylpurine (XVII). *A*. A solution of 516 mg. of blocked nucleoside (XVI) in 5 ml. of hot methyl Cellosolve[38] was quickly cooled in an ice-bath, then treated with 10 ml. of methanol saturated with ammonia at 0°. After standing at 3° for 16 hr. in a stoppered flask, the solution was evaporated to dryness *in vacuo*. The residue was partitioned between 20 ml. each of water and chloroform. The aqueous solution, washed once more with chloroform, was evaporated to dryness *in vacuo* leaving 273 mg. (94%) of crystalline product. This compound traveled on paper as a single spot which was purple under ultraviolet light and which had R_{Ad} 0.57.[34]

Recrystallization from water afforded white crystals of a hydrate, m.p. 155–160°; ν_{max}^{KBr} 3150–3400 cm.$^{-1}$ (broad OH—NH), 1650 cm.$^{-1}$ (inflection, amide C=O), 1635 cm.$^{-1}$ (NH_2 of NH_2—C=N), 1595 cm.$^{-1}$ (C=C and C=N), 1055, 1112 cm.$^{-1}$ (C—O—); $[\alpha]_D^{26}$ −86° (0.94% in H_2O).

(38) Trademark for ethyleneglycol monomethyl ether.

Anal. Calcd. for $C_{13}H_{18}N_6O_5 \cdot H_2O$: C, 43.8; H, 5.68; N, 23.6. Found: C, 43.4; H, 5.83; N, 23.0.

B. A solution of 510 mg. of XVI in 14 ml. of methanol and 2 ml. of *n*-butylamine was refluxed for 6 hr., then evaporated to dryness *in vacuo* and worked up as in *A*. The water residue was recrystallized from 1 ml. of water by addition of 8 ml. of acetone; yield, 139 mg. (55%) of crystalline product, m.p. 158–160°. This compound has the same infrared spectrum and same R_{Ad} as the product in Part A. The mother liquor was evaporated to dryness *in vacuo*. The glassy residue had an infrared spectrum essentially the same as XX. Examination of this residue by paper chromatography showed that it was mainly XX, but was contaminated with XVII.

1-α-L-Rhamnopyranosylthymine (XVIII). Condensation of 1.50 g. of dithyminyl mercury[9] with 3.23 g. of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI), as described for the preparation of XVI, produced 3.63 g. (104%) of crude 1-(2′,3′,4′-tri-*O*-benzoyl-α-L-rhamnopyranosyl)thymine which could not be crystallized; ν_{max}^{KBr} 3240 cm.$^{-1}$ (NH), 1730 cm.$^{-1}$ (C=O of benzoate), 1688 cm.$^{-1}$ (non-conj. C=O of ring), 1600, 1490 cm.$^{-1}$ (phenyl). A nitrogen analysis indicated a maximum purity of 54%.

A mixture of 3.60 g. of crude 1-(2′,3′,4′-tri-*O*-benzoyl-α-L-rhamnopyranosyl)thymine, 32 ml. of reagent methanol, and 6 ml. of 1*N* methanolic sodium methoxide was refluxed for 1 hr. The amber solution, acidified with 0.2 ml. of acetic acid, was evaporated to dryness *in vacuo*. The residue was partitioned between water and ether. The aqueous layer was acidified with 3.0 ml. of 1*N* sulfuric acid, then evaporated to dryness *in vacuo*. The residue was triturated with absolute alcohol and filtered. The insoluble solids (344 mg.) were mainly inorganic, and ultraviolet inspection showed the absence of nucleosides. The alcohol filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in acetone and filtered from some insoluble solid (205 mg.). The latter contained little nucleoside as determined by ultraviolet inspection. Evaporation of the acetone solution to dryness *in vacuo* gave 980 mg. (59%) of a glass which had a maximum purity of 85% by ultraviolet analysis. This crude material contained the essential bands in the infrared expected for the nucleoside XVIII.

A mixture of 90 g. of Celite 545[37] and 45 ml. of water saturated with butanol was packed in a 3.1 × 37 cm. column in the usual fashion.[11] A solution of 360 mg. of the above crude 1-α-L-rhamnopyranosylthymine in 1.0 ml. of water saturated with butanol was mixed with 2.0 g. of Celite 545[37] and packed on the column. The column was eluted with butanol saturated with water and 4 ml. fractions were collected. Pigmented material was eluted from 0–80 ml. The major fraction was eluted from 84 ml. to 160 ml. (1 h.b.v.) with a peak at 115 ml. The elutions were followed by ultraviolet inspection of the fractions at 258 mμ.[39] The eluates from 84 ml. to 148 ml. were combined and evaporated to dryness *in vacuo*. A solution of the residue in water was washed several times with chloroform. Evaporation of the aqueous solution to dryness *in vacuo* gave 309 mg. (86% recovery) of a colorless glass. The overall yield from 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (I) was 53%. This compound was chromatographically pure and had R_{Ad} 1.03.[34] The compound had $\lambda_{max}^{H_2O}$ 265 mμ (a_M 9930) and ν_{max}^{KBr} 3400 cm.$^{-1}$ (broad OH—NH), 1680 cm.$^{-1}$ (non-conj. C=O of ring), 1655 cm.$^{-1}$ (conj. C=O of ring) (inflection), 1090, 1050 (C—O—); $[\alpha]_D^{26}$ −40° (0.82% in H_2O). For analysis and ultraviolet spectrum a sample was dried at 80° in high vacuum for several hours.

Anal. Calcd. for $C_{11}H_{16}N_2O_6 \cdot {}^1/_2H_2O$: C, 47.0; H, 6.10; N, 9.62. Found: C, 47.1; H, 5.97; N, 9.80.

1-α-L-Rhamnopyranosylcytosine (XIX). Condensation of 1.05 g. (3 mmoles) of mercuri-*N*-acetylcytosine[25] with 3.23 g. of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (VI) (6 mmoles) followed by deacylation of the blocked nucleoside with methanolic sodium methoxide (2.8 mmoles) as described for 1-α-L-rhamnopyranosylthymine (XVIII) gave a water-soluble nucleoside fraction. The water solution was evaporated to dryness *in vacuo*. The residue was triturated with absolute alcohol, filtered from sodium sulfate, then evaporated to dryness *in vacuo* leaving 535 mg. of crude nucleoside as a gum.

A 320-mg. sample of this material was purified in a column (3.1 × 35 cm.) made from 90 g. of Celite 545 as described for XVIII. Fractions of 3 ml. size were collected with an automatic volumetric fractionator.[39] The main fraction was eluted between fractions 104 and 150.

The fractions surrounding numbers 106 and 147 were examined by paper chromatography to determine which fractions free of slower and faster moving impurities should be combined for processing. Fractions 106–147 were combined and evaporated to dryness *in vacuo*. The residue was dissolved in water and washed several times with chloroform. Evaporation of the water solution to dryness *in vacuo* left a residue which was evaporated several times *in vacuo* with absolute alcohol to remove water. The nucleoside was chromatographically pure (R_{Ad} 0.39),[34] although analysis showed 13.5% alcohol was present that could not be removed from the glassy product by drying in high vacuum; yield, 105 mg. (21% based on mercuri-*N*-acetylcytosine and corrected for alcohol). The nucleoside had $\lambda_{max}^{pH\ 1}$ 275 mμ (a_M 11,500); $\lambda_{max}^{pH\ 14}$ 268 mμ (a_M 7,900); ν_{max}^{KBr} 3350 cm.$^{-1}$ (broad OH—NH), 1660 cm.$^{-1}$ (C=O), 1637 cm.$^{-1}$ (NH_2 of NH_2—C=N), 1600, 1520, 1490 cm.$^{-1}$ (C=C and C=N), 1042, 1085, 1110 (C—O—).

Anal. Calcd. for $C_{10}H_{15}N_3O_5$ (+ 13.5% EtOH): C, 47.3; H, 6.85; N, 14.1. Found: C, 46.8; H, 6.63; N, 13.9.

The compound could be further freed of solvent by solution in alcohol and precipitation with ether. After drying at 135° in high vacuum, the product still contained solvent.

Anal. Calcd. for $C_{10}H_{15}N_3O_5$: C, 46.7; H, 5.88; N, 16.3. Found: C, 45.7; H, 6.16; N, 15.2.

Treatment of a sample of XIX with sodium nitrite in dilute acetic acid as described for preparation of deoxyuridine[40] caused deamination to 1-α-L-rhamnopyranosyluracil. Examination by paper chromatography showed the presence of only one spot (R_{Ad} 0.77),[34] XIX no longer being present.

9-α-L-Rhamnopyranosylhypoxanthine (XXI). To a solution of 300 mg. of 9-α-L-rhamnopyranosyladenine (XI) hydrochloride (adenine free) in 15 ml. of water was added 457 mg. of sodium nitrite. When solution was complete 0.54 ml. of acetic acid was added. After standing for 7 hr., the solution was treated with 270 mg. of sodium nitrite and 0.33 ml. of acetic acid. The solution was allowed to stand an additional 17 hr., then it was evaporated to dryness *in vacuo* (bath 35°). To a solution of the residue in 10 ml. of water was added 0.9 g. of lead acetate. The solution was then treated dropwise with concentrated ammonium hydroxide until no more lead salt precipitated. After several hours the solid was collected on a filter and washed with water. A solution of the lead salt in 15 ml. of 4.5% acetic acid was treated with excess hydrogen sulfide, then allowed to stand for 30 min. The filtered solution was evaporated to dryness *in vacuo*. A solution of the residue in about 10 ml. of water was clarified by filtration through Celite,[37] then evaporated to dryness *in vacuo* leaving 252 mg. of residue. Trituration with acetone gave 220 mg. (83%) of amorphous solid, m.p. 148–153° (dec.). The compound had $\lambda_{max}^{pH\ 1}$ 249 mμ, $\lambda_{max}^{H_2O}$ 249 mμ, $\lambda_{max}^{pH\ 14}$ 254 mμ; ν_{max}^{KBr} 3380 cm.$^{-1}$ (OH), 1680 cm.$^{-1}$ (conj. C=O of keto form of purine), 1655, 1635, 1590, 1545, 1510 cm.$^{-1}$ (typical complex C=C, C=N of a 6-hydroxypurine), 1080, 1057, 1025 cm.$^{-1}$ (OH and

(39) An automatic volumetric fraction collector with attached ultraviolet absorption meter, purchased from Gilson Medical Electronics, Madison, Wis., was employed.

(40) R. E. Beltz and D. W. Visser, *J. Am. Chem. Soc.* **77**, 736 (1955).

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.

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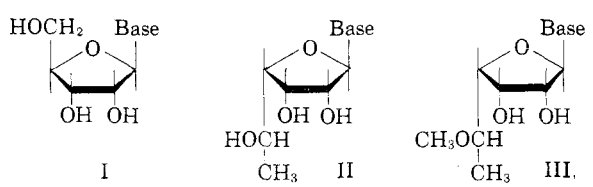
A four-step synthesis of 1,2,3,5-tetra-*O*-benzoyl-L-rhamnofuranose from L-rhamnose has been described. Two new nucleosides derived from L-rhamnofuranose containing adenine or 2,6-diaminopurine, have been synthesized from the tetrabenzoate *via* 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride.

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]

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