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

Synthesis of Potential Anticancer Agents. VI.[2] Use of *O*-Benzoyl Blocking Group for Synthesis of 6-Chloropurine Nucleosides

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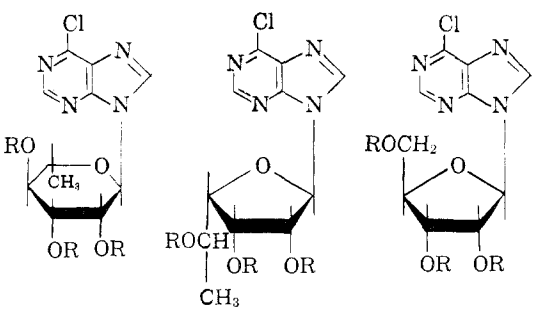
A general method for the synthesis of 6-chloropurine nucleosides, particularly valuable as intermediary nucleosides, is described. Condensation of chloromercuri-6-chloropurine with the proper *O*-benzoylated glycosyl chloride has afforded 9-α-L-rhamnopyranosyl-, 9-α-L-rhamnofuranosyl-, and 9-β-D-ribofuranosyl-6-chloropurines in 28–41% yields.

Since Fischer and Helferich[4] synthesized the first nucleoside, 7-glucopyranosyltheophylline, by condensation of silver theophylline with tetra-*O*-acetyl-α-D-glucopyranosyl bromide there have been only three improvements in the procedure. Davoll, Lythgoe, and Todd[5] observed that tri-*O*-acetylpentofuranosyl chlorides, due to their increased stability, gave higher yields of nucleosides than the corresponding furanosyl bromides. Another major improvement was the introduction of the use of chloromercuri derivatives of purines, rather than silver purines, by Davoll and Lowy.[6] The third major improvement was the introduction of *O*-benzoyl blocking groups, rather than *O*-acetyl for the sugar moiety by Kissman, Pidacks, and Baker[7]; that higher yields are obtained has been verified several times.[8–10] In certain cases, the use of the more hydrolytically stable *O*-benzoyl group is essential for transformation work necessary during synthesis of the blocked sugars.[7,11,12]

The use of *O*-benzoyl blocking groups for the synthesis of nucleosides may have the serious drawback that base-catalyzed removal of the group from base-labile nucleosides, such as those derived from 6-chloropurine, may not be feasible. The finding that 6-chloropurine nucleosides can be made from poly-*O*-benzoyl glycosyl halides in satisfactory yield is the subject of this paper.

The only example of a 6-chloropurine nucleoside described in the literature is the 9-β-D-ribofuranoside (VII). Brown and Weliky[13] synthesized this nucleoside (VII) from 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride and chloromercuri-6-chloropurine. They obtained a 26% yield of crude, colored nucleoside; recrystallization was attended by a considerable loss and the yield of pure material was not specified.



I, R = C_6H_5CO—
II, R = H

III, R = C_6H_5CO—
IV, R = H

V, R = CH_3CO—
VI, R = C_6H_5CO—
VII, R = H

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(3) Present address: Stanford Research Institute, Menlo Park, Calif.

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

(5) (a) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948). (b) An apparent exception that furanosyl chlorides can be expected to give higher yields of nucleosides than furanosyl bromides has been observed with the 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl halides.[9]

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

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

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

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

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

(11) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 7 (1955).

(12) B. R. Baker and K. Hewson, Paper VIII of this series, *J. Org. Chem.*, **22**, 966 (1957).

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

In order to employ the Brown-Weliky approach to nucleosides from a 6-chloropurine blocked nucleoside such as I, it was essential to establish whether or not the benzoyl groups of I could be removed preferentially without seriously affecting the base-labile 6-chloro group. This posed a serious problem since benzoates[8] react with basic reagents at about 10% of the rate of acetates.[14] If the benzoyl groups could not be removed from I without affecting the 6-chloro group, then it would be necessary to transform the 6-chloro group of the crude blocked nucleoside first to such groups as 6 —H, 6 —SH, etc., before hydrolyzing the benzoates. This latter approach has the serious drawback that each new nucleoside would still have the accumulated sugar decomposition products from the coupling reaction formed during synthesis of I. Since nucleosides can be notoriously difficult to purify when the sugar decomposition products are still present, this would lead to a difficult purification for each nucleoside. On the other hand if the benzoyl groups can be removed selectively from the blocked nucleoside, I, to give the 6-chloropurine nucleoside, II, in reasonable yield, then only one difficult purification, that of II, is necessary since the transformations on a pure 6-chloropurine nucleoside would appear to proceed smoothly.[13]

Brown and Weliky,[13] for preparation of 6-chloropurine riboside, used the standard conditions[4,5a,6,7,15,16] for removing *O*-acetyl groups from blocked nucleosides, namely methanol saturated with ammonia at 0° for 15–20 hr., even though there has been no time study made for this reaction. If one assumes that the benzoates will require ten times as long a reaction period,[14] then 6–8 days at 0° would be required to cleave the benzoates. This lengthy reaction time could seriously impair the yield of 6-chloro-9-α-L-rhamnopyranosylpurine (II) since the quantities of the corresponding adenine nucleoside could become appreciable, thus not only lowering the yield but aggravating the purification problem.

The blocked 6-chloropurine rhamnoside (I) was allowed to react with methanolic ammonia at 0° for 5 days. The products were partitioned between chloroform and water. The latter contained a nearly theoretical weight of debenzoylated nucleosides. Both fractions were subjected to paper chromatography with a water-saturated butanol system using an ultraviolet lamp to locate the spots and using 6-chloropurine (R_{Ad} 1.60, pink), adenine (R_{Ad} 1.00, purple), and 9-α-L-rhamnopyranosyladenine[17] (R_{Ad} 0.46, purple) as standards.[18] The water solution showed the presence of a spot corresponding to 9-α-L-rhamnopyranosyladenine (R_{Ad} 0.46) and a spot with R_{Ad} 1.46 which was purple at the back side shading into pink at the front side. There were also several strongly fluorescent spots, which when eluted, had no absorption in the ultraviolet and were not considered further. The pink to purple spot with R_{Ad}, 1.46 was considered the one most likely to be the desired 6-chloropurine nucleoside (II). Elution of this spot with water and determination of the ultraviolet maximum indicated 6-chloropurine nucleoside could be present, although the peak was broader toward the shorter wave lengths than it should have been. When the spot with R_{Ad} 1.46 was split in half to give mostly a pink front half and purple back half, then eluted, the ultraviolet peak of the pink spot was sharper at 262 mμ. Thus the pink spot was mostly the chloropurine nucleoside and the purple half of the spot was an impurity with a broad absorption peak about 240 mμ. The chloroform fraction of the debenzoylation reaction contained no purines of interest since there were no spots with R_{Ad} values less than that of 6-chloropurine.

A second methanolic ammonia debenzoylation was carried out at 0° for only 23 hr. The yield of debenzoylated nucleosides in the aqueous fraction was again quantitative showing that the reaction was more rapid than could be anticipated by the conditions described in the literature for removal of *O*-acetates. Paper chromatography of the same concentration of this material gave a strip very similar to the five-day run. The spots from both runs with R_{Ad} 0.46 corresponding to 9-α-L-rhamnopyranosyladenine were eluted with water. Determination of the ultraviolet spectrum of the eluates showed that there was about three times as much adenine nucleoside in the longer run. In addition, elution of the spot with R_{Ad} 1.46 corresponding to the 6-chloropurine nucleoside (II) showed that the peak at 262 mμ was sharper and higher in the one-day run than in the five-day run. Thus, it is quite clear that even at 0° the 6-chloro group is being replaced with ammonia and that the yield of 6-chloropurine nucleoside (II) is considerably higher after one day.

With a more optimum time established for the debenzoylation of the blocked 6-chloropurine nucleoside (I) and with some knowledge of the type of impurities established by paper chromatography, purification of the crude 6-chloropurine nucleoside (II) by column chromatography, since the crude material failed to crystallize, was then investigated. The first column was run with powdered cellulose using water-saturated butanol as the moving phase in order to approach the condi-

(14) K. Kindler, *Ann.*, **452**, 90 (1927); *Ber.*, **69B**, 2792 (1936).

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

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

(17) B. R. Baker and K. Hewson, *J. Org. Chem.*, Paper VII of this series, *J. Org. Chem.*, **22**, 959 (1957).

(18) Adenine was used as a standard and the R_{Ad} values were calculated by assigning the adenine spot R_{Ad} 1.00. The chromatograms were run with water-saturated butanol by the descending technic on Whatman No. 1 paper.

tions of the paper chromatography. Although some useful data were obtained in this column, purification was not completely satisfactory. The main difficulty was that almost all the material were moved through the column with less than one holdback volume (h.b.v.) of solvent. Fractions of about 0.03 h.b.v. were collected after the front moved off the column. These were examined by ultraviolet absorption. Some of the fractions showing purines absorbing the vicinity of 260 mμ were also examined by paper chromatography. The results indicated that the purple spot with R_{Ad} about 1.46 traveled most rapidly on the column. This compound is an impurity, probably a sugar decomposition product. The next fractions were richer in 6-chloropurine nucleoside (II). However, these were still somewhat contaminated with the brown pigment of the earliest fraction. However, the fraction richest in II, when evaporated, crystallized on standing. A somewhat more efficient separation occurred using a Celite partition column with water as the stationary phase and butanol as the mobile phase.[7] Again most of the material was eluted in the first h.b.v. following the front. However, purer fractions of II were obtained than from the cellulose column. The main fraction should have a distribution coefficient of 0.1–0.2 (mobile phase to stationary phase) to obtain good results.[7] It has now been found that the purest fraction of 6-chloropurine rhamnoside (II), which crystallized on standing, has a distribution coefficient in ethyl acetate–water of 0.22. Thus a Celite partition column with a stationary water phase and mobile ethyl acetate phase should give more efficient purification. This indeed proved to be the case, pure crystalline 6-chloro-9-α-L-rhamnopyranosylpurine (II)[19] being obtained in 41% over-all yield from 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide.[20]

The fact that butanol moved the 6-chloro-9-α-L-rhamnopyranosylpurine rapidly through a cellulose column suggested that simple butanol extraction might effect sufficient purification for crystallization without preliminary column purification, particularly in view of the fact that seed crystals were then available. Evaporation of the butanol extracts and crystallization of the residue from methyl ethyl ketone afforded the crystalline nucleoside (II) in 41% over-all yield. However, without preliminary butanol extraction, the crude nucleoside still could not be crystallized even with seeding.

Before the ammonia-methanol debenzoylation of I was studied, the Zemplen debenzoylation with methanolic sodium methoxide was investigated. Normally about 20–30 mole % of sodium methoxide is necessary to keep the solution alkaline enough to debenzoylate a crude nucleoside obtained in a chloromercuri coupling.[7] It was observed, however, that during debenzoylation of I, the solution continued to consume a total of 130 mole % of sodium methoxide before remaining alkaline. This experiment clearly demonstrated that the 6-chloro group was being replaced by 6-methoxy at room temperature. A run was then made allowing I to react in methanol with 130 mole % of sodium methoxide for 4 hr. The water-soluble fraction containing debenzoylated nucleosides was examined by ultraviolet absorption. The major peak was at 250 mμ in acidic, basic, or neutral solution with an inflection at about 260 mμ. The inflection shows the presence of some of the 6-chloropurine nucleoside (II). The major peak at 250 mμ could be compatible with that of a 6-methoxypurine nucleoside, but not compatible with a hypoxanthine nucleoside which gives shifts in ultraviolet maxima with changing *p*H. This approach to debenzoylation of a 6-chloropurine nucleoside was not considered worthy of further study.

In order to demonstrate that *O*-debenzoylation of blocked 6-chloropurine nucleosides with methanolic ammonia at 0° was a general reaction, two more 6-chloropurine nucleosides were investigated.

Condensation of crude 2,3,5-tri-*O*-benzoyl-L-rhamnofuranosyl chloride, obtained from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose,[12] with chloromercuri-6-chloropurine gave a crude blocked nucleoside (III) in 94% yield which had a maximum purity of 65% based on nitrogen analysis. Treatment of the blocked nucleoside (III) with methanolic ammonia at 0° for one day gave crude 6-chloro-9-α-L-rhamnofuranosylpurine (IV)[19] relatively free of 9-α-L-rhamnofuranosyladenine[12] as demonstrated by paper chromatography. The pure nucleoside (IV) was readily obtained by Celite partition chromatography using a stationary water phase and mobile ethyl acetate phase. Separation was quite sharp. The over-all yield of IV from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose was 33%. The nucleoside (IV) was obtained as a glass with the expected ultraviolet and infrared spectra. This glass traveled as a single spot on paper (R_{Ad} 1.49).[18]

Since Brown and Weliky[13] obtained unspecified, but probably poor yields of pure 6-chloro-9-β-D-ribofuranosylpurine (VII) by condensation of chloromercuri 6-chloropurine with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride, the synthesis of VII with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[7] was investigated. The crude blocked nucleoside (VI) was treated with methanolic ammonia at 3° for 18 hr. Crystalline 6-chloro-9-β-D-ribofuranosylpurine (VII) was readily isolated from methanol. Recrystallization from water afforded a 28% yield of pure nucleoside (VII).

Concomitant with this work, a thorough study of the variables in the synthesis of adenosine from 6-acylaminopurines and 2,3,5-tri-*O*-acyl-D-ribofu-

(19) For a discussion of the configuration of rhamnose nucleoside, *cf.* refs. 12, 17.

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

ranosyl chloride was being made in these laboratories.[10] One of the most important conclusions reached was that traces of mercuric oxide in the chloromercuri purines had a very deleterious effect on the nucleoside coupling reaction, this effect being greater on 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride than on the corresponding tribenzoate.[21] In fact, with good quality chloromercuri derivative there was little difference in over-all yield of adenosine using either the *O*-acetyl or *O*-benzoyl blocking groups. Since the chloromercuri-6-chloropurine used in all the experiments described in this paper was obtained in almost quantitative yield by the Fox modification[21] and was free of mercuric oxide, the condensation of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride with this mercuric oxide-free chloromercuri-6-chloropurine was reinvestigated. No difficulty was encountered in crystallizing and purifying the resultant 6-chloro-9-β-D-ribofuranosylpurine (VII), a 29% over-all yield of pure nucleoside being obtained.

Thus, there is little difference in yield of 6-chloro-9-β-D-ribofuranosylpurine (VII) prepared from either 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose[23] or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose.[7] However, since the benzoylated D-ribofuranose[7] is easier to obtain in quantity than the acetylated D-ribofuranose,[23] the *O*-benzoyl blocking group is still the blocking group of choice for synthesis of VII.[24]

EXPERIMENTAL[25]

Chloromercuri-6-chloropurine. To a solution of 7.38 g. of mercuric chloride in 100 ml. of 50% alcohol was added 4.20 g. of 6-chloropurine.[27] Then 10 ml. of 10% sodium hydroxide was added dropwise with good stirring at such a rate (10–15 min.) that the yellowish mercuric oxide color disappeared before the next drop was added. The addition was stopped if the solution acquired a yellow color. During this time, the reaction mixture thickened. After being stirred an additional 30 min., the mixture was filtered. The white product was washed successively with water, alcohol, and ether, then dried; yield, 10.12 g. (97%).

The amount of alkali necessary may vary slightly depending upon the extent of hydration in the 6-chloropurine used[28,29]; the production of a permanent slight yellow color is a good end point for the addition. If the crystal size of the 6-chloropurine is large, the 6-chloropurine should be dissolved in the 50% alcohol by warming, then the mercuric chloride added and finally the alkali. This last procedure was found particularly effective for 6-chloropurine-8-C^{14} where the crystal size was large and powdering of the crystals was not expedient. In large batches or in radioactive runs, filtration of the chloromercuri derivatives was aided considerably by addition of 1 g. of analytical grade Celite[30] per gram of 6-chloropurine to the reaction mixture just prior to addition of the base.

6-Chloro-9-α-L-rhamnopyranosylpurine (II). (A) *Preparation:* A stirred mixture of 7.4 g. of chloromercuri-6-chloropurine, 3.5 g. of Celite,[30] and 350 ml. of xylene was distilled until all moisture was removed. After the addition of a warm solution of 9.4 g. of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide[20] in 100 ml. of xylene, the mixture was refluxed and stirred for 2 hr., then filtered hot. The filter cake was washed with two 50-ml. portions of hot chloroform. The xylene filtrate was evaporated to dryness *in vacuo* and the residue dissolved in the chloroform washes. Washed with 100 ml. of 30% aqueous potassium iodide and with water, the chloroform solution was dried with magnesium sulfate, clarified with decolorizing carbon, and evaporated to dryness *in vacuo;* yield, 11.2 g. (105%) of crude, blocked nucleoside (I).

A mixture of 6.2 g. of crude blocked nucleoside (I) and 200 ml. of methanol saturated with ammonia at 0° was stirred in an ice bath until solution was complete (4 hr.). After standing at 3° in a stoppered flask for an additional 20 hr., the solution was filtered from a little brown solid and evaporated to a sirup *in vacuo* (bath 40°). The residue was partitioned between 25 ml. each of water and chloroform. The aqueous layer, washed twice more with chloroform, was evaporated to dryness *in vacuo* (bath 40°) leaving 3.08 g. (101%) of crude nucleoside (II) as a glass.

(B) *Purification by Celite partition chromatography.*[7] To 22.5 ml. of water saturated with ethyl acetate was added 45 g. of acid washed Celite 545[30] in portions. After each addition the paste was thoroughly mixed to give eventually a dry powder. A column with 2.1 cm. inside diameter was dry packed in 1–2 cm. layers to a height of 35 cm. A solution of 108 mg. of the above crude 6-chloro-9-α-L-rhamnopyranosylpurine (II) in 1.5 ml. of water saturated with ethyl acetate was mixed with 3 g. of Celite 545 and packed on top of the column. The column was developed with ethyl acetate saturated with water. A peak ultraviolet fraction of pigmented material was eluted with the first 15 ml. The ultraviolet absorption was then zero for the next 8.5 ml. The next main fraction appeared over the next 200 ml. of eluate; this solution was evaporated to dryness *in vacuo*. A solution of the residue in water was washed several times with chloro-

(21) Several years ago it was observed that condensation of 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-D-glucopyranosyl chloride with chloromercuri-2-methylmercapto-6-dimethylaminopurine was quite sensitive to impurities in the chloromercuri derivative, no nucleoside[16] being obtained if the chloromercuri derivative was off color.[22] J. J. Fox and coworkers of Sloan-Kettering Institute independently made the observation that yields of nucleosides were poor if the chloromercuri derivative of a purine or pyrimidine was not obtained in nearly quantitative yield. Fox *et al.* devised an inverse procedure for preparation of chloromercuripurines which gave pure products in nearly quantitative yield (*cf.* Experimental).

(22) B. R. Baker and F. J. McEvoy, American Cyanamid Company, unpublished results.

(23) G. B. Brown, J. Davoll, and B. A. Lowy, *Biochemical Preparations,* **4,** 70 (1955).

(24) H. M. Kissman and M. J. Weiss, *J. Org. Chem.,* **21,** 1053 (1956), have recently published an alternate method for use of 6-chloro-9-β-D-ribofuranosylpurine (VII) as an intermediate. They purified the blocked nucleoside (VI) by chromatography on acid-washed alumina. The 6-chloro group of VI was then replaced by other groups followed by *O*-debenzoylation.

(25) The ultraviolet spectra were determined with a Beckman Model DK-2 spectrophotometer, the infrared spectra with a Perkin-Elmer Model 21 spectrophotometer and the optical rotations with a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer calibrated with standard sucrose solutions.[26] Melting points were determined in capillary tubes in a stirred oil bath and are uncorrected.

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

(27) Purchased from Francis Earle Laboratories, Inc., Peekskill, N. Y.

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

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

(30) Johns-Manville Co.

form. The aqueous solution was evaporated to dryness *in vacuo* leaving 42 mg. of II as a glass. An acetone solution of this material was allowed to evaporate in air. The residue consisted of white crystals, m.p. 164–165° (dec.). Its infrared spectrum was identical with preparation (C). Thus the recovery of II was 39% and the over-all yield from 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide was 41%. On paper[18] this material traveled as a major spot which was pink in ultraviolet light and which had R_{Ad} 1.40. A trace of fluorescent material, previously shown to be negligible in the crude material, traveled at a slower rate.

(C) *Butanol purification:* A solution of 2.89 g. of crude nucleoside (II) in 15 ml. of water was extracted with four 15-ml. portions of redistilled butanol. The combined extracts were evaporated to dryness *in vacuo*. The residue was dissolved in about 20 ml. of warm methyl ethyl ketone by addition of a little alcohol and water. The solution was clarified with 0.5 g. of Norit. The solution was evaporated to a sirup in an air stream, then seeded. Crystals began to separate within 2 hr. After standing overnight, the mixture of crystals and oil was triturated with methyl ethyl ketone. The crystalline product was collected on a filter and washed with methyl ethyl ketone; yield, 0.761 g., m.p. 170–172° (dec.).

The filtrate was evaporated to a sirup under an air stream and seeded. After standing overnight, the mixture of crystals and oil was again triturated with methyl ethyl ketone; yield, 0.328 g. of white crystals, m.p. 172–174° (dec.). This material had $\lambda_{max}^{H_2O}$ 264 mμ (a_M 9300); ν_{max}^{KBr} 3410 cm.$^{-1}$ (OH), 1598, 1570 cm.$^{-1}$ (C=C and C=N), 1097, 1080, 1070 (C—O—). The infrared spectrum is in excellent agreement with the expected key peaks. The recovery of II in crystalline form was 38% and the overall yield from 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide was 40%. No solvent could be found for direct recrystallization of this material. It would only crystallize as the solution reached near dryness. A sample of the second crop was dried in high vacuum at room temperature and analyzed; $[\alpha]_D^{26}$ −62° (1.27% in H_2O).

Anal. Calcd. for $C_{11}H_{13}ClN_4O_4$: C, 44.0; H, 4.37; N, 18.7. Found: C, 44.3; H, 4.81; N, 17.9.

This compound traveled on paper in a butanol-water system as one major spot, pink in ultraviolet light, with R_{Ad} 1.40 and a negligible fluorescent spot with R_{Ad} 1.07.

6-Chloro-9-α-L-rhamnofuranosylpurine (IV). A solution of 9.79 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose[12] in 8 ml. of acetyl chloride[31] was treated with 300 ml. of reagent ether saturated with hydrogen chloride at 0°. After 3 days at 3° in a glass-stoppered container, the solution was evaporated to dryness *in vacuo* (bath 40°). The residue was dissolved in 50 ml. of reagent benzene and the evaporation repeated. The evaporation was repeated once more with 25 ml. of fresh reagent benzene. The crude 2,3,5-tri-*O*-benzoyl-α-L-rhamnofuranosyl chloride was immediately dissolved in 70 ml. of xylene and added to a mixture of 7.4 g. of chloromercuri-6 chloropurine, 3.7 g. of Celite[30] and 350 ml. of xylene previously dried by azeotropic distillation. After being refluxed and stirred for 2 hr., the mixture was processed as described for the corresponding pyranose (I). The chloroform residue was dissolved in 150 ml. of ether and the solution was washed with four 30-ml. portions of ice cold 3% sodium hydroxide. Dried with magnesium sulfate, clarified with Norit and filtered through Celite, the solution was evaporated to dryness *in vacuo;* yield, 10.8 g. (94%) of crude blocked nucleoside (III) which had a maximum purity of 65% based on nitrogen analysis and had ν_{max}^{Chf} 1730, 1285 cm.$^{-1}$ (C=O and C—O—C of benzoate); 1610, 1570 cm.$^{-1}$ (C=C and C=N).

The crude blocked nucleoside (III) (4.1 g.) was debenzoylated with 70 ml. of methanol saturated with ammonia of 0° as described for the pyranose (I), except that only 1 hr. stirring was required to effect solution; yield, 1.62 g. (82%) of crude IV.

For purification 111 mg. of crude nucleoside (IV) was chromatographed[7] on 46 g. of Celite 545[30] in a 2.1 cm. diameter column as described for the corresponding pyranose (II) using a stationary aqueous phase and mobile ethyl acetate phase. After elution of pigmented material at 0–40 ml., the product was eluted as a sharp peak at 56–104 ml. Evaporation of the latter solution to dryness *in vacuo* (bath 40°) afforded 48 mg. (33% based on 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-L-rhamnofuranose) of product as a glass. After being dried at 60° in high vacuum over P_2O_5 for several hours, the product still contained solvent. This compound traveled as a single spot (R_{Ad} 1.49)[18] on paper. $\lambda_{max}^{H_2O}$ 263 mμ (a_M 7,920 corrected for ethyl acetate); ν_{max}^{KBr} 3360 cm.$^{-1}$ (OH); 1557, 1587 cm.$^{-1}$ (C=C and C=N); 1020–1080 cm.$^{-1}$ (broad C—O—); $[\alpha]_D^{26}$ −42° (0.21% in H_2O).

Anal. Calcd. for $C_{11}H_{13}ClN_4O_4 \cdot {}^1/_4C_4H_8O_2$: C, 45.0; H, 4.72; N, 17.5. Found: C, 45.4; H, 5.22; N, 17.5.

The solvent could not be removed any more completely from this heat-sensitive compound, since at higher temperatures the compound darkened badly.

Although several smaller fractions were eluted from the column after the major peak, no attempt was made to identify them.

6-Chloro-9-β-D-ribofuranosylpurine (VII). (A) To 50 ml. of reagent ether saturated with hydrogen chloride at 0° were added 1.8 ml. of acetyl chloride[31] and 1.80 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose.[7] After 4 days at 3° in a stoppered flask, the solution was evaporated to dryness *in vacuo*. The evaporation was repeated with two 10-ml. portions of reagent benzene. The resultant chloro sugar was dissolved in 10 ml. of xylene and reacted with 1.51 g. of chloromercuri-6-chloropurine suspended in xylene as described for the corresponding rhamnopyranoside (II); yield, 2.47 g. of crude blocked nucleoside (VI).

This material was treated with methanolic ammonia as described for the debenzoylation of I and II. During concentration of the methanolic ammonia solution to a sirup *in vacuo*, the product crystallized. Trituration with methanol gave 334 mg. (33%) of product as cream-colored crystals, m.p. 180–182° (dec.); $\lambda_{max}^{H_2O}$ 263 mμ (a_M 9200); ν_{max}^{KBr} 3360 cm.$^{-1}$ (broad OH); 1560, 1595 cm.$^{-1}$ (C=C and C=N); 1047, 1090 cm.$^{-1}$ (C—O—). This compound traveled as a major spot (R_{Ad} 1.46) on paper[18]; also present was a fluorescent spot (R_{Ad} 0.63) of a trace impurity. The analysis also indicated that this compound was not quite pure; however, this material was suitable for further transformation work.

Anal. Calcd. for $C_{10}H_{11}ClN_4O_4$: C, 42.0; H, 3.88; N, 19.6. Found: C, 42.5; H, 4.18; N, 19.4.

A second crop (6%) of less pure material was obtained from the mother liquor.

(B) A larger run with 7.77 g. of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[7] gave the crude crystalline nucleoside (VII) in 43% yield, which was less pure than preparation A. Recrystallization from water with the aid of Norit afforded a 28% yield of pure material as light yellow crystals.

(C) By condensation of the 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride[5a] from 18 g. of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose[23] with 22 g. of chloromercuri-6-chloropurine in 500 ml. of xylene in the presence of 22 g. of Celite,[30] followed by deacylation of the blocked nucleoside (V), with methanolic ammonia (600 ml. saturated at 0°) as described in Part (A) was obtained 5.6 g. (35%) of crystalline nucleoside. One recrystallization from water with the aid of Norit gave 4.70 g. (29%) of pure nucleoside (VII) as nearly colorless needles, m.p. 179–180° (dec.), $\lambda_{max}^{Ph.7}$ 264 mμ (a_M 8900); $[\alpha]_D^{26}$ −45° (0.79% in H_2O).

Brown and Weliky[13] have recorded m.p. 170–171° (dec.), varying considerably with the rate of heating. They also recorded $\lambda_{max}^{pH\ 6}$ 264 mμ (a_M 8800).

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

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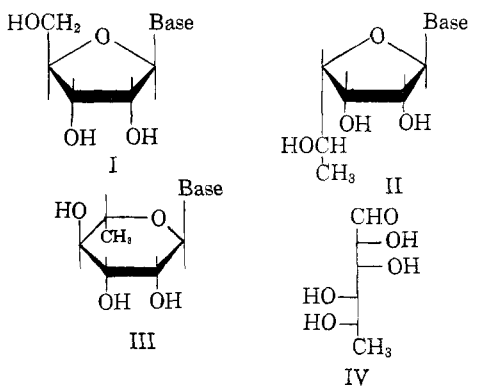
The syntheses of six nucleosides derived from L-rhamnopyranose have been accomplished by proper modification of standard procedures.

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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(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).