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Nucleosides. XIII. Synthesis of 3′-Amino-3′-deoxy-*arabinosyl*-uracil *via* 2′,3′-Epoxy-*lyxosyl* Nucleosides[1-3]

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A general and easily accessible method is described for the preparation of 2′,3′-epoxides of the 1-β-D-*lyxo*-furanosyluracils. These epoxynucleosides (IV) have been prepared from uridine in high yield *via* trimesyloxyuridine (I) by the action of aqueous base on 3′-mesyloxyarabinosyluracils (III). The syntheses of the 5′-iodo, 5′-deoxy, 5′-*O*-benzoyl, 5′-mesyloxy, and 5′-hydroxy epoxides are described. Cleavage of the 2′,3′-epoxy linkage with ammonia gave a 3′-aminonucleoside of the *arabino* configuration (V). The structure of V was established by its conversion to the known 3′-amino-3′-deoxyuridine (VI).

Recent reports[4,5] have described the replacement of the 2′-, 3′-, and 5′-mesyloxy groups of trimesyloxyuridine (I, Fig. 1) to yield a wide variety of

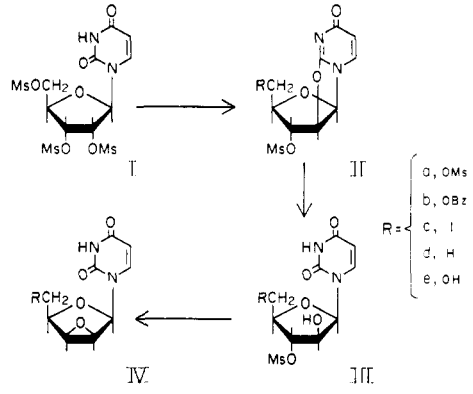

Figure 1

nucleoside derivatives. The present paper describes the synthesis of several 2′,3′-epoxynucleosides of the *lyxo* configuration (IV) from trimesyloxyuridine. It is anticipated that these epoxides will prove useful as intermediates in the preparation of compounds of potential biological interest. The synthesis of one such compound, a 3′-aminonucleoside, is described in this report.

Cleavage of the 2,2′-anhydro bond of 2,2′-anhydro-3′-*O*-mesyl-*arabino*-furanosyluracil derivatives[4] (II, Fig. 1) with dilute aqueous acid at room temperature gives nucleosides with the 2′-hydroxyl group in the "up" or *arabino* configuration III. When compounds III are boiled either in water or in dilute aqueous acid, attack by the 2-carbonyl of the pyrimidine occurs to give nearly quantitatively 2,3′-anhydro derivatives of the *lyxo* configuration.[5] It would appear that under alkaline conditions the 3′-mesyloxy group of III would be subject to intramolecular attack by both the 2-carbonyl of the pyrimidine and the anionic form of the 2′-hydroxyl group of the sugar. That the attack under alkaline conditions is made almost exclusively by the 2′-hydroxyl group is proven by the high yields of 2′,3′-epoxynucleosides (IV) obtained. Epoxides may be obtained also from the 2,2′-anhydro nucleosides II under alkaline conditions. An initial cleavage of the 2,2′-anhydro bond of compounds II gives 2′-hydroxy derivatives III, which then react further to yield the epoxides IV in high yield.

When trimesyloxyuridine (I) was allowed to stand at room temperature with three equivalents of sodium hydroxide in water and the resulting solution neutralized, a monomesylated nucleoside (IVa) crystallized from the solution (see Fig. 1). This substance exhibited an ultraviolet absorption spectrum which resembled that of uridine (i.e., a 1-β-D-aldopentofuranosyluracil) but was markedly different from that of a 2,2′-,[4,6] 2,3′-,[5-7a] or 2,5′-anhydronucleoside.[7] Elemental analyses were consistent with the presence of an epoxy linkage. IVa did not consume metaperiodate, which was indicative of the absence of free vicinal hydroxyl groups. It was subsequently found that both the 2,2′-anhydro derivative IIa[4] and the 2′-hydroxy nucleoside IIIa[5] gave the same product IVa upon treatment with aqueous sodium hydroxide. It is thus strongly indicated that the reaction I to IVa involved the formation of the two intermediates

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(2) A preliminary report of this work has appeared. See J. F. Codington, R. Fecher, and J. J. Fox, Abstract from the 19th Meeting of the American Chemical Society, 1961, p. 13D.

(3) For reasons of clarity the term "epoxy" is used to refer to an ether linkage in the sugar moiety. The term "anhydro" (as "anhydronucleoside") refers to an oxygen bridge between the C-2 of the pyrimidine and C-2′, C-3′, or C-5′ of the sugar moiety. [See J. J. Fox and I. Wempen, *Advances in Carbohydrate Chem.*, **14**, 283 (1959).]

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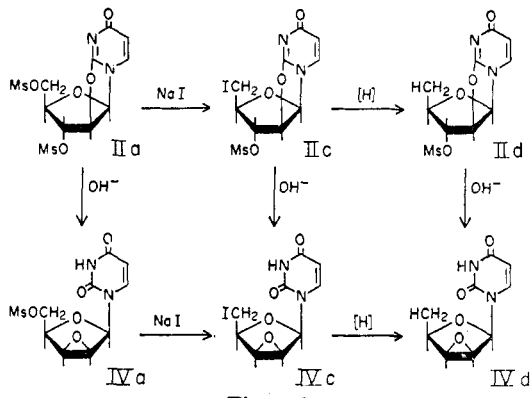

Figure 2

(IIa and IIIa) and proceeded *via* the scheme shown in Fig. 1.

It was established by means of the reaction scheme shown in Fig. 2 that IVa was indeed a 2′,3′-epoxide and could be neither a 2′,5′- or 3′,5′-epoxide. Two compounds of established structure,[8] 2,2′-anhydro-1-(5′-deoxy-5′-iodo-3′-*O*-mesyl-β-D-arabinosyl)uracil (IIc) and its 5′-deoxy analog IId, were found to yield epoxy derivatives IVc and IVd, respectively, in good yield upon treatment with aqueous sodium hydroxide. Since compounds IIc and IId (and therefore IVc and IVd) have been shown conclusively to be the 5′-deoxy-5′-iodo and 5′-deoxy derivatives, respectively, thus excluding the 5′-position, there can be no question regarding the 2′,3′-epoxy structure of these nucleosides (IV). The reaction of the epoxide obtained from trimesyloxyuridine (I) (namely, IVa) with sodium iodide in acetonylacetone gave a crystalline compound identical with the epoxide (IVc) obtained from IIc. Since compounds IVa, IVc, and IVd are formed from IIa, IIc, and IId, respectively, by a reaction well known for the synthesis of epoxides, namely, the attack by an anion of a hydroxyl group under alkaline conditions to remove a *trans* vicinal sulfonyloxy group, an "up" or *lyxo* epoxide would be expected. The identity of IVa as 1-(2′,3′-epoxy-5′-*O*-mesyl-β-D-lyxosyl)uracil is thus established. The reduction of IVc using palladium on charcoal in the presence of powdered silver carbonate gave the 5′-deoxy-epoxide (IVd) which was identical with a sample obtained from IId in aqueous base.

The 5′-hydroxy epoxide, 1-(2′,3′-epoxy-β-D-*lyxo*-furanosyl)uracil (IVe) (see Fig. 1) was synthesized from the previously described 5′-*O*-benzoyl anhydro derivative IIb.[4] When IIb was stirred with hydrochloric acid in a large volume of acetone-water (1:1) for twenty-four hours and the acetone removed *in vacuo*, a nearly quantitative yield of a 2′-hydroxy derivative IIIb[8] in crystalline form was obtained. Reaction of IIIb with 1*N* ammonium hydroxide yielded a crystalline epoxide IVb in high yield, with retention of the 5′-benzoyl group (Fig. 1). The blocking group was removed by the action of aqueous sodium hydroxide at room temperature to give IVe in almost quantitative yield. The overall yield of IVe from IIb was 77% and from uridine in a five-step process, 65%.

No 2′,3′-epoxy derivative of a pyrimidine nucleoside has been characterized heretofore, although the transitory existence of 1-(2′,3′-epoxy-β-D-*ribo*-furanosyl)uracils as intermediates has been postulated on several occasions.[4,9,10] The procedure described here for the preparation of epoxy derivatives of the *lyxo* configuration is general and easily accessible. Methods involving an attack by an anion of a hydroxyl group to remove a *trans* sulfonyloxy function have been employed in the preparation of 2′,3′-epoxy derivatives of purine nucleosides of both the *ribo*[11–13] and *lyxo*[14] configurations, as well as of methyl furanosides of both possible configurations.[15–18]

The role which amino sugars play in certain compounds having antibiotic activity[19] prompted the synthesis of an amino nucleoside from the epoxide IVe. Since cleavage of the 2,3-epoxy-β-D-*lyxo*-furanosides with ammonia has been found to yield mainly 3-amino-3-deoxy furanosides of the *arabino* configuration,[15,16,20] it was anticipated that the major product resulting from the cleavage of the epoxide linkage of IVe (Fig. 1) would be the 3′-amino-3′-deoxyarabinosyl nucleoside, compound V (see Fig. 3).

When IVe was heated in ethanol saturated with ammonia in a sealed container at 100° for six and one-half hours, a 38% yield of a crystalline compound V of high melting point, 214–216°, and positive optical rotation, $[\alpha]_D^{26}$ + 118°, was obtained. The identity of V was established by its conversion

(8) IIIb was converted in high yield to 1-(5′-*O*-benzoyl-β-D-*lyxo*-furanosyl)uracil by refluxing in water. In the synthesis of the same product from IIb under similar conditions IIIb was anticipated as an intermediate.[5] This is now substantiated.

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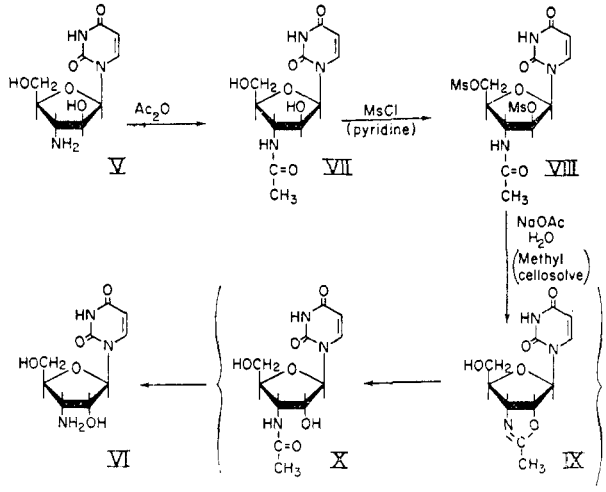

Figure 3

to the known 3′-amino-3′-deoxyuridine (VI) prepared through another route by Kissman and Weiss.[21] The conversion followed the reaction sequence utilized in the cyclohexyl series by McCasland, Clark, and Carter[22] and by Winstein and Boschan[23] and later applied to the carbohydrate field by Baker and Schaub[24] and by Baker, Schaub, and Williams.[16] The course of the reactions involved in the conversion of V to VI is shown in Fig. 3. Both the *N*-acetyl derivative VII and the dimesyloxy intermediate VIII were obtained in crystalline form. The conversion of VIII (*arabino* configuration) to an amino nucleoside of the *ribo* configuration was carried out in Methyl Cellosolve containing sodium acetate and water. The oxazolium ring structure IX is a probable intermediate in the reaction.[23] The product VI was obtained as colorless prisms, which exhibited a m.p. of 183–185°. This is similar to that reported by Kissman and Weiss[21] (m.p. 183–184°) for 3′-amino-3′-deoxyuridine (VI_{K-w}). A mixture of VI obtained from V and an authentic sample of the amino nucleoside[25] VI_{K-w} showed no depression of melting point. The optical rotations of the two samples agreed, $[\alpha]_D^{25} + 67°$, as did their ultraviolet absorption spectra.[21]

The infrared spectra (potassium bromide disks) of the sample VI obtained from V and the authentic sample VI_{K-w}[21] are shown in Fig. 4. The curve obtained for VI_{K-w} (crystallized from methanol-ethanol[21]) differed markedly from that of VI (absolute ethanol crystallized) (see Fig. 4a). That these differences are probably due to dimorphism and result from the retention in the KBr disks of differences in crystalline form is supported by the following data: Sample VI_{K-w} when crystallized from absolute ethanol gave crystals (m.p. 184–185°), the spectrum of which is identical with that of VI (Fig. 4b). Both of these KBr disks were heated at 100° for three hours.[26] The infrared spectra of both disks were again identical (Fig. 4c), and both were identical with that obtained for VI_{K-w}[21] (Fig. 4a). It has thus been possible to obtain and compare two different infrared spectra (Figs. 4b and 4c) for both VI and VI_{K-w}. The structure of the amino nucleoside VI obtained from the product of epoxide cleavage V is thus firmly established as 3′-amino-3′-deoxyuridine. Compound V, the amino nucleoside resulting from epoxide cleavage, is therefore 1-(3′-amino-3′-deoxy-β-D-*arabino*-furanosyl)uracil.

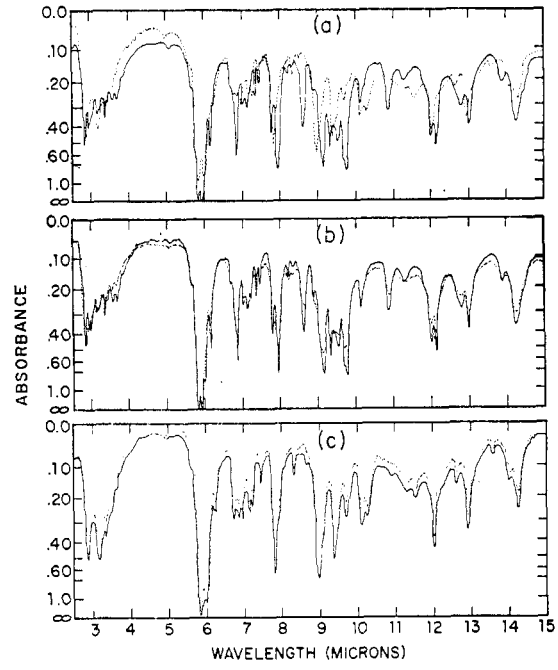

Fig. 4. Infrared spectra (potassium bromide disks) of samples of 3′-amino-3′-deoxyuridine.

Solid lines. Compound VI, prepared from V (see Fig. 3). *Dotted lines.* Authentic sample of 3′-amino-3′-deoxyuridine (VI_{K-w}).[21,25] (a) VI crystallized from absolute ethanol; VI_{K-w} crystallized from methanol ethanol.[21] (b) VI and VI_{K-w} crystallized from absolute ethanol. (c) Potassium bromide disks of VI and VI_{K-w} (Fig. 4b) heated at 100° for 3 hr.

The utilization of the 2′,3′-epoxy nucleosides for the synthesis of other 3′- (and possibly 2′-) substituted compounds of potential biological interest is underway in this laboratory.

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(25) The authors wish to thank Dr. H. M. Kissman of Lederle Laboratories, Pearl River, N. Y., for a sample of 3′-amino-3′-deoxyuridine.

(26) The authors would like to thank Mrs. Thomas F. Gallagher of this Institute for the suggestion of this experiment.

EXPERIMENTAL[27]

1-(2',3'-Epoxy-5'-O-mesyl-β-D-lyxosyl)uracil (IVa). *Method A.* A solution of 4.78 g. (0.010 mole) of crude 2',3',5'-tri-*O*-mesyluridine (I) in 30 ml. of sodium hydroxide (1.0*N*) was stirred for 1.5 hr. The mixture was neutralized with hydrochloric acid (2*N*) which caused a crystalline solid to precipitate. After the mixture had been cooled, the product was filtered off, washed with cold water and cold ethanol, and dried with ether. The pale yellow product weighed 2.1 g. (70%). Crystallization from ethanol gave colorless micaceous plates, which melted at 177–177.5°, $[\alpha]_D^{22}$ +16° (water, *c* 0.3).

Anal. Calcd. for $C_{10}H_{12}N_2O_7S$: C, 39.47; H, 3.98; N, 9.21; S, 10.54. Found: C, 39.30; H, 3.99; N, 8.86; S, 10.59.

Method B. A solution of 5.0 g. (0.013 mole) of crude 2,2'-anhydro-1-(3',5'-di-*O*-mesyl-β-D-arabinosyl)uracil (IIa) in 52 ml. of sodium hydroxide (0.5*N*) was stirred for 1 hr. at room temperature. The solution was neutralized with hydrochloric acid. After refrigeration, micaceous plates were filtered off, washed with cold water and ethanol, and dried with ether. The weight of product, m.p. 178–179.5°, was 3.3 g. (83%).

1-(2',3'-Epoxy-5'-deoxy-5'-iodo-β-D-lyxosyl)uracil (IVc). *Method A.* A solution of 1.5 g. (0.0036 mole) of 2,2'-anhydro-1-(5'-deoxy-5'-iodo-3'-*O*-mesyl-β-D-arabinosyl)uracil (IIc) in 15 ml. of sodium hydroxide (0.5*N*) was stirred for 1 hr. The solution was neutralized with hydrochloric acid. The product was filtered from the cooled solution and washed on the filter with cold water. The yield of crystalline material, m.p. 208–212° dec. (uncorr.), was nearly quantitative, 1.2 g. Crystallization from ethanol-water (1:1) (solubility 1.6%) gave colorless prisms melting at 218–220.5° dec., $[\alpha]_D^{26}$ −4° (dioxane, *c* 0.6).

Anal. Calcd. for $C_9H_9N_2O_4I$: C, 32.16; H, 2.70; N, 8.34; I, 37.76. Found: C, 32.14; H, 2.72; N, 8.39; I, 37.87.

Method B. Under anhydrous conditions 1.0 g. (0.0033 mole) of IVa and 2.5 g. (0.017 mole) of sodium iodide in 25 ml. of acetonylacetone were heated on a steam bath for 2 hr. Filtration of the hot mixture gave approximately one equivalent of sodium mesylate. The filtrate was concentrated nearly to dryness *in vacuo*, and about 50 ml. of cold water was added. After cooling the aqueous mixture, 0.16 g. (14%) of the product was collected. One crystallization from ethanol-water (1:1) gave colorless prisms which melted at 217–218° dec. Admixture with a sample prepared by Method *A* exhibited no depression of the melting point.

1-(5'-Deoxy-2',3'-epoxy-β-D-lyxosyl)uracil (IVd). *Method A.* A solution of 0.75 g. (0.0026 mole) of 2,2'-anhydro-1-(5'-deoxy-3'-*O*-mesyl-β-D-arabinosyl)uracil (IId) in 16 ml. of sodium hydroxide (0.5*N*) was stirred at room temperature for 15–17 hr. After treatment with Dowex 50 (H^+ form), the clear solution was evaporated to dryness *in vacuo* and the residue crystallized from ethanol. A yield of 0.35 g. (64%) of colorless micaceous plates, m.p. 146–146.5°, $[\alpha]_D^{26}$ +26° (water, *c* 0.6), was obtained.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.19; H, 4.83; N, 13.18.

Method B. A suspension of 0.21 g. (0.00063 mole) of IVc, 0.25 g. of palladium-charcoal (5%), and 0.30 g. of powdered silver carbonate in 20 ml. of ethanol was shaken under hydrogen at atmospheric pressure for 100 min. Approximately one equivalent of hydrogen had been consumed at 80 min., and no further uptake was observed at 100 min. The clear solution was filtered from the insoluble material present and taken to dryness *in vacuo*. The residue, which had a yellow color, was treated with activated charcoal in ethanol and the ethanol filtrate (6 ml.) cooled. Filtration gave 0.03 g. of starting material IVc. After reducing the volume of the filtrate to 2–3 ml. and cooling, 0.04 g. (31%) of glistening plates, m.p. 142–144°, was obtained. Admixture of this sample and the epoxide prepared by Method *A* gave no depression of melting point. Infrared spectra of the two samples were identical.

1-(5'-O-Benzoyl-3'-O-mesyl-β-D-arabinosyl)uracil (IIIb). To a suspension of 10.00 g. (0.0245 mole) of 2,2'-anhydro-1-(5'-*O*-benzoyl-3'-*O*-mesyl-β-D-arabinosyl)uracil (IIb) in 3 l. of acetone-water (1:1) was added 40 ml. of aqueous hydrochloric acid (12*N*). The mixture was stirred at room temperature for 24 hr., during which time all solid entered solution. The acetone was removed *in vacuo*, and colorless crystals separated from the aqueous residue. These were collected, washed well with water, and dried. The yield of colorless needles, m.p. 81–84°, was 94–97%. Crystallization was effected by solution in warm methanol, followed by the addition of an equal volume of water and cooling. Colorless needles, m.p. 103–106°, $[\alpha]_D^{22}$ +49° [acetone-water (1:1), *c* 0.9].

Anal. Calcd. for $C_{17}H_{18}N_2O_9S$: C, 47.88; H, 4.25; N, 6.57; S, 7.52. Found: C, 47.56; H, 4.47; N, 6.25; S, 7.04.

1-(5'-O-Benzoyl-2',3'-epoxy-β-D-lyxosyl)uracil (IVb). To 400 ml. of ammonium hydroxide (1*N*) was added with stirring 5.0 g. (0.012 mole) of IIIb. Within about 10 min. all solid had entered solution, and after an additional 15–20 min. crystals began separating. Stirring was continued for 20 min., at which time the mixture was neutralized with glacial acetic acid. After cooling, colorless crystals were collected, washed with water, and dried. Yields of 3.3 to 3.6 g. (86–90%) of epoxide, m.p. 187–190°, $[\alpha]_D^{25}$ +3° (chloroform, *c* 0.4), were obtained. Crystallization from ethanol gave colorless micaceous plates melting at 188.5–190°.

Anal. Calcd. for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.32; H, 4.39; N, 8.17.

1-(2',3'-Epoxy-β-D-lyxofuranosyl)uracil (IVe). A solution of 6.50 g. (0.020 mole) of IVb and 90 ml. of sodium hydroxide (0.5*N*) was stirred at room temperature for 50 min. The resulting solution was treated with Dowex 50 (H^+ form) in two batches, then filtered. After extracting well with ether, the aqueous layer was taken to dryness *in vacuo*. The addition of ethanol, followed by evaporation of solvent *in vacuo*, was repeated several times. The residue crystallized from a small amount of ethanol. It was filtered and washed on the filter with ether. The yield of colorless prisms, m.p. 137–140°, was 4.1 g. to 4.2 g. (92–94%). Crystallization from ethanol gave colorless prisms melting at 139.5–140.5°, $[\alpha]_D^{30}$ +34° (water, *c* 0.4).

Anal. Calcd. for $C_9H_{10}N_2O_5$: C, 47.78; H, 4.42; N, 12.39. Found: C, 47.77; H, 4.56; N, 12.17.

1-(3'-Amino-3'-deoxy-β-D-arabino-furanosyl) uracil (V). A solution of 3.0 g. (0.0133 mole) of IVe[28] in 100 ml. of ethanolic ammonia (17.6%) was heated in a sealed glass-lined steel container at 100° for 6.5 hr. The amber colored mixture containing some solid material was taken to dryness *in vacuo*, leaving an orange residue. This was dissolved in 25 ml. of water, and the solution partially decolorized by warming with activated charcoal.

The yellow solution was added to a column containing 40 ml. of Dowex 50 (H^+ form), and the resin washed with 100 ml. of water. A small amount of nonbasic material (< 0.05 g.) was collected. Basic products were then eluted with ammonium hydroxide (1*N*). The desired aminonucleoside was eluted with the first 30–60 ml. of the effluent of alkaline *p*H. This yellow colored fraction was taken to dryness *in vacuo*. All moisture was removed through repeated distillations *in vacuo* with ethanol, and the residue was then crystallized from ethanol. The yield of a yellow crystalline

(27) All melting points are corrected. Analyses were carried out by the Spang Microanalytical Laboratories, Ann Arbor, Mich. Infrared spectra were obtained on the Infracord, Model 137. Ultraviolet absorption curves were determined using the Cary recording spectrophotometer, Model 11.

(28) Compound V may be obtained under similar conditions from the 5'-*O*-benzoyl epoxide IVb. Isolation of the product involves extraction of the benzamide and ethyl benzoate present with ether.

solid, m.p. 192–204°, was 1.86 g. (57%). Two crystallizations from ethanol and treatment with activated charcoal gave 1.22 g. (38%) of colorless needles melting at 214–216° dec., $[\alpha]_D^{26}$ +118° (water, *c* 0.2). Spectral properties (water): At *p*H 6, ϵ_{max} (262 mμ) 10,100; ϵ_{min} (230 mμ) 2020. At *p*H 2, ϵ_{max} (260 mμ) 10,000; ϵ_{min} (229 mμ) 2120.

Anal. Calcd. for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.58; H, 5.26; N, 16.92.

1-(3′-Acetamido-3′-deoxy-β-D-arabino-furanosyl)uracil (VII). A mixture of 0.60 g. (0.0025 mole) of V in 125 ml. of methanol was warmed until the solution was complete. After cooling to 20°, 0.27 ml. (0.0029 mole) of acetic anhydride was added. The solution was stirred at room temperature for 5 hr., then taken to dryness *in vacuo* (bath below 25°). The residue was triturated with ether and filtered. The yield of colorless prisms, m.p. 235–238°, $[\alpha]_D^{27}$ +123° (water, *c* 0.4), was 0.67 g. (96%).

Anal. Calcd. for $C_{11}H_{15}N_3O_6$: C, 46.31; H, 5.30; N, 14.73. Found: C, 46.45; H, 5.36; N, 14.58.

1-(3′-Acetamido-3′-deoxy-2′,5′-di-O-mesyl-β-D-arabinosyl)-uracil (VIII). A solution of 0.64 g. (0.0023 mole) of VII in 7 ml. of dry pyridine was allowed to react with 0.81 g. (0.0071 mole) of methylsulfonyl chloride at 0–5° for 17 hr. and at room temperature for 40 min. A small amount of the reaction mixture gave no precipitate upon addition of water. The addition of a mixture of 25 ml. of ether and 10 ml. of petroleum ether (b.p. 30–60°) to the main batch caused the precipitation of an amber colored gum. This was triturated with cold water (10 ml.), and a pink crystalline solid was collected. Crystallization from ethanol (20 ml.) gave 0.38 g. (38%) of colorless prisms melting at 129–135°. Two crystallizations from ethanol gave prisms melting at 133–150°, $[\alpha]_D^{25}$ +126° (water, *c* 0.2).

Anal. Calcd. for $C_{13}H_{19}N_3O_{10}S_2$: C, 35.37; H, 4.34; N, 9.52; S, 14.53. Found: C, 35.43; H, 4.19; N, 9.55; S, 14.39.

1-(3′-Amino-3′-deoxy-β-D-ribo-furanosyl)uracil (*3′-amino-3′-deoxyuridine*, VI). A mixture of 0.30 g. (0.00068 mole) of VIII, 0.30 g. (0.0037 mole) of sodium acetate, and 0.30 ml. of water was refluxed in 5.0 ml. of Methyl Cellosolve for 18 hr. The resulting dark colored mixture was taken to dryness *in vacuo*. The addition, followed by distillation *in vacuo*, first of ethanol, then of benzene, removed all water and solvent. The residue was dissolved in 5 ml. of pyridine and allowed to react for 17 hr. with 1.3 g. of acetic anhydride at room temperature.[29] To the reaction mixture was added 30 ml. of ether–petroleum ether (1:1) to precipitate out all nucleoside material. The supernatant was decanted, and the residue washed with ether–petroleum ether and dried. The water-soluble residue was heated on a steam bath for 80 min. with 4 ml. of sodium hydroxide (0.5*N*) and passed onto a column containing 10 ml. of Dowex 50 (H^+ form). The column was washed well with water, eluting a small amount of nonbasic material. The aminonucleoside was then eluted using ammonium hydroxide (0.5*N*).

The fraction containing ultraviolet-absorbing material was taken to dryness *in vacuo*. The residue was triturated with ether and filtered. The yield of a colorless amorphous solid, m.p. 120–130°, was about 0.02 g. (12%). Crystallization from ethanol gave a nearly quantitative recovery of minute colorless prisms. The sample melted at 183–185° dec. and had an optical rotation, $[\alpha]_D^{25}$ +67° (water, *c* 0.7).[30] A mixture of this sample and a mixture of an authentic sample of 3′-amino-3′-deoxyuridine,[25] m.p. 184–186°, melted at 183–186°. The infrared spectra (potassium bromide disks) of the two samples (both crystallized from ethanol) were identical in every respect. The probability that 3′-amino-3′-deoxyuridine may exist in two different crystalline forms with decidedly different infrared spectral curves is discussed earlier.

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(29) This step was undertaken in the hope of isolating a water-insoluble intermediate. Unfortunately, the acetylated product entered solution upon the addition of water.

(30) Kissman and Weiss[21] report a melting point of 183–184° and an optical rotation, $[\alpha]_D^{25}$ (water, *c* 1.0), of +67°.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Synthesis of 1-β-D-Ribofuranosylimidazole-4(or 5)-acetonitrile, 1-β-D-Ribofuranosylimidazole-4(or 5)-acetic Acid, and 4(or 5)-(2-Aminoethyl)-1-β-D-ribofuranosylimidazole

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The synthesis of 1-β-D-ribofuranosylimidazole-4(or 5)-acetonitrile by condensation of the mercuric chloride complex of imidazoleacetonitrile with 2,3,5-tri-*O*-benzoyl-D-ribosyl bromide and subsequent debenzoylation is described. 1-β-D-Ribofuranosylimidazole-4(or 5)-acetic acid was obtained by the hydrolysis of the cyano group; 4(or 5)-(2-aminoethyl)-1-β-D-ribofuranosylimidazole (histamine ribose) by catalytic reduction of the cyano group.

From the urine of rats which had received injections of histamine or of imidazoleacetic acid, a compound was isolated by H. Tabor and O. Hayaishi, and by Karjala,[1] which was characterized as a riboside of imidazoleacetic acid (VI). This *in vivo* conversion prompted its chemical synthesis which was achieved simultaneously by the author[2] and by J. Baddiley *et al.*[3] This paper

(1) H. Tabor, *Pharmacol. Rev.*, **6**, 331 (1954); H. Tabor and O. Hayaishi, *J. Am. Chem. Soc.*, **77**, 505 (1955); S. A. Karjala, *J. Am. Chem. Soc.*, **77**, 504 (1955).

(2) H. Bauer, *Biochim. et Biophys. Acta*, **30**, 219 (1958). Note change in nomenclature: Imidazoleacetic acid riboside to 1-β-D-ribofuranosylimidazole-4(or 5)acetic acid and cyanomethylimidazole to imidazoleacetonitrile.

(3) J. Baddiley, J. C. Buchanan, D. H. Hayes, and P. A. Smith, *J. Chem. Soc.*, 3743 (1958).