# 2-Deoxy Sugars. III. Nucleosides Derived from 2,6-Dideoxy-D-*ribo*-hexopyranose (Digitoxose) and 2-Deoxy-D-*arabino*-hexopyranose (2-Deoxyglucose)[1]

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Previously, we reported the preparation of two crystalline *O*-*p*-nitrobenzoyl halides of 2,6-dideoxy-D-*ribo*-hexopyranose (digitoxose).[4] Subsequently, we were able to couple crystalline 3,4-di-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl chloride (I) with digitoxigenin to give, after removal of the protecting groups, a 2-deoxycardenolide.[5] This success prompted us to investigate the possibility of extending this direct method of synthesis of 2-deoxyglycosides to the preparation of some new 2′-deoxynucleosides as possible anticancer compounds.

The extreme reactivity of the chloride I precluded any conditions involving elevated temperatures lest elimination of hydrogen chloride take place before coupling could be accomplished. Fortunately, I coupled readily with chloromercuri-6-benzamidopurine in dry dichloromethane at room temperature to give the protected nucleoside IV as semiamorphous material. Without further purification, IV was deacylated giving crude 9-(2,6-dideoxy-D-*ribo*-hexopyranosyl)adenine (V), which was purified *via* its picrate salt and was isolated as a crystalline monohydrate. The yield of the nucleoside V was 28% based on chloromercuri-6-benzamidopurine. Colorimetric estimation of the digotoxose content of the nucleoside V employing xanthydrol reagent gave results in excellent agreement with the calculated value. A small quantity of V was hydrolyzed by means of dilute mineral acid and the resulting hydrolysis mixture was resolved by paper chromatography. This technique disclosed two components which were identified as adenine and digotoxose, respectively.

Repeated attempts to couple I at room temperature with mercury derivatives of thymine[6] resulted

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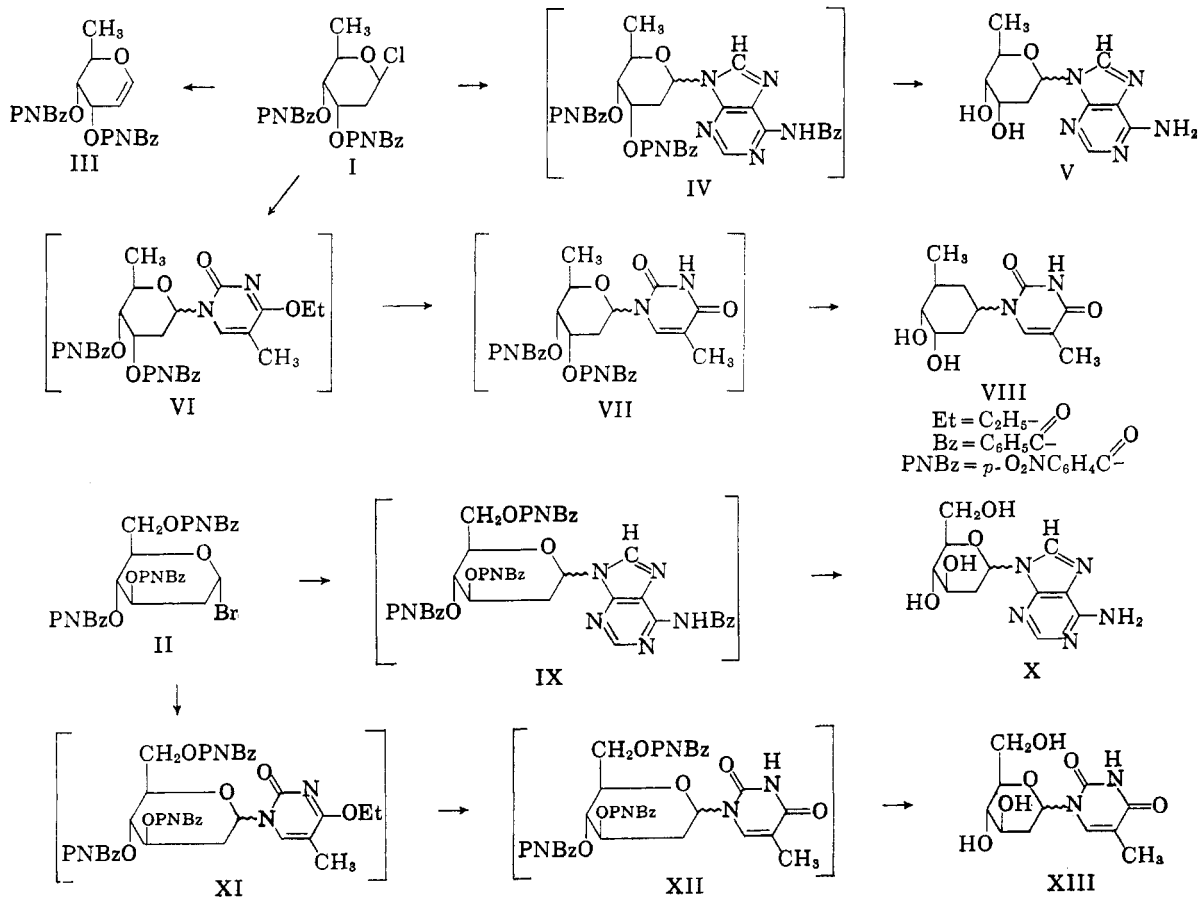
(3) This paper is taken from a dissertation submitted to the Graduate School of Georgetown University by G. Durr in partial fulfillment of the requirements of the Degree of Doctor of Philosophy in Chemistry.

(4) W. W. Zorbach and T. A. Payne, *J. Am. Chem. Soc.*, **80**, 5564 (1958).

(5) W. W. Zorbach and T. A. Payne, *J. Am. Chem. Soc.*, **81**, 1519 (1959); **82**, 4979 (1960).

(6) J. J. Fox, N. C. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956); M. Hoffer, R. Duschinsky, J. J. Fox, and N. C. Yung, *J. Am. Chem. Soc.*, **81**, 4112 (1959).



in failure. With monothyminyl mercury no reaction whatsoever took place, the mercury salt being returned in each case. When I was treated with dithyminyl mercury, mercury was eliminated from the base and appeared in the reaction mixture as mercuric chloride. Thymine could be recovered accordingly. In one instance, a carbohydrate product was isolated from the reaction mixture and had the composition of a 3,4-di-*O*-*p*-nitrobenzoyl-6-deoxy-D-*ribo*-hexopyranos-1-ene (III). In a separate experiment, the elimination of hydrogen chloride from the chloride I was provoked by heating I alone in absolute pyridine. The resulting material was identical to III obtained, in the foregoing experiment, and these findings lend support to our previous contention[4] that a consequence of the extreme reactivity of the chloride I was the facile elimination of hydrogen chloride under the mildest conditions of heating and basicity.

Finally an alternate procedure, developed by Hilbert and co-workers,[7] was investigated. Although chloride I in solution readily gives up hydrogen chloride on mild heating, it does not follow that the cyystalline material will behave similarly. In fact, determination of the melting point of I has shown that the material can be heated without decomposition to 96°, at which point the chloride I begins melting with effervescence. Consequently, it was possible to fuse I with an excess of 2,4-diethoxy-5-methylpyrimidine (m.p. 37°)[8] *in vacuo* at 50°. A gaseous product was evolved smoothly from the melt and, in accordance with the hypothesis that the nucleosidation proceeds *via* a quaternary ammonium halide with subsequent loss of the vicinal ethyl group and the halogen atom, the gas was most likely chloroethane.[9] The resulting protected nucleoside VI was deethylated to give VII, and VII was deacylated to furnish anhydrous 1-(2,6-dideoxy-D-*ribo*-hexopyranosyl)thymine (VIII), which was resistant to hydrolysis by mineral acid. It was not possible, therefore, to regenerate the carbohydrate and pyrimidine components for analytical purposes.

During the course of this investigation, two crystalline-*O*-*p*-nitrobenzoyl halides of 2-deoxy-D-*arabino*-hexopyranose (2-deoxyglucopyranose) were prepared in this laboratory as part of a separate study.[10] It was anticipated early in our work that nitrobenzoylated halides of 2-deoxyglucose might be, conceivably, considerably less reactive than similar halides prepared from digitoxose. A reasonable explanation to account for the high reactivity of 2,6-dideoxy-3,4- di-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl chloride(I) has been given[4] and takes into account the absence of "shielding" or protection by acyloxy function at C-2 and C-6, thus rendering C-1 easily susceptible to attack. In contrast, the 2-deoxyglucosyl bromide II carries a *p*-nitrobenzoyloxy group at C-6 and this large negative substituent may be considered to repel strongly incoming groups at C-1. Our experience with the bromide II (and the companion chloride) is compatible with this conjecture and it was found that II had a stability greatly superseding that of I.

Thus, coupling experiments employing II could be carried out at elevated temperatures, for example, in refluxing benzene. When II was treated with chloromercuri-6-benzamidopurine in this manner, the protected nucleoside IX was obtained, but the yield was considerably lower than that obtained with the halide I. This may be ascribed reasonably to the decreased reactivity of II and in an attempt to overcome the low yield, II was coupled with silver-6-benzamidopurine. Without further purification, the crude protected nucleoside IX was deacylated and the resulting 9-(2-deoxy-D-*arabino*-hexopyranosyl)adenine (X) was purified *via* its picrate salt and crystallized as a dihydrate. The yield of X by this latter procedure was 22% based on the bromide II. The nucleoside X, homogeneous on papergrams, was hydrolyzed using dilute mineral acid. Paper chromatography of the hydrolysis mixture yielded two spots, identified as adenine and 2-deoxyglucose, respectively.

As with I, the bromide II failed to couple with mercury derivatives of thymine and the alternate procedure previously described was invoked in which II was fused with 2,4-diethoxy-5-methylpyrimidine *in vacuo* at 50°. The resulting protected nucleoside XI was deethylated to give XII which was deacylated to give anhydrous 1-(2-deoxy-D-*arabino*-hexopyranosyl)thymine (XIII) in 14% yield. The nucleoside XIII travelled as a single spot on papergrams and could not be hydrolyzed by mineral acid.

The anomeric configurations of the four new nucleosides are not known.

## EXPERIMENTAL

All melting points were determined using a Kofler hot-stage. The Amberlite IRA-410 ($HCO_3$) anion exchange resin was prepared by mixing Amberlite IRA-410 ($OH^-$) anion exchange resin twice with a saturated aqueous solution of sodium bicarbonate and then washing well the resin with distilled water. Unless otherwise indicated all paper chromatograms were carried out as follows: 50 μg. of the material was spotted on Whatman No. 1 paper and the chromatogram was developed by an ascending technique in a system consisting of saturated aqueous ammonia sulfate–2-propanol–water (2:28:70). After developing, the paper was dried and the spots were located by visual examination under ultraviolet light. The 2-deoxy sugars were located by means of a boric acid spray reagent.[11] Either adenine or thymine was used as a standard and the spots were assigned

(7) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 4489 (1930); G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.*, **58**, 60 (1930); G. E. Hilbert, *J. Am. Chem. Soc.*, **59**, 330 (1937).

(8) W. Schmidt-Nickels and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 4511 (1930).

(9) G. E. Hilbert, *J. Am. Chem. Soc.*, **56**, 190 (1934).

(10) W. W. Zorbach and G. Pietsch, *Ann.*, *in press*.

(11) M. Pöhm and R. Weiser, *Naturwiss*, **24**, 582 (1956).

$R_{Ad}$ values where adenine was $R_{Ad}$ = 1.00 and $R_{Thy}$ values where thymine was $R_{Thy}$ = 1.00.

*9-(2,6-Dideoxy-D-ribo-hexopyranosyl)adenine* (V). A mixture of 464 mg. (1.0 mmole) of 2,6-dideoxy-3,4-di-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl chloride (I), 437 mg. (0.9 mmole) of dry chloromercuri-6-benzamidopurine, and 5 ml. of dry dichloromethane was stirred overnight at room temperature. The mixture, diluted with 10 ml. of dichloromethane, was filtered and washed with the same solvent. The residue (unchanged chloromercuri-6-benzamidopurine) was extracted in turn with ethanol and water and was then discarded. The aqueous ethanolic filtrate was refrigerated overnight, yielding a small quantity of solid, mercury-containing artefact which was likewise filtered and discarded. The resulting filtrate was evaporated to dryness and the residue was recrystallized once from absolute ethanol giving crude 6 - benzamido - 9 - (2,6 - dideoxy - 3,4 - di - *O* - *p* nitrobenzoyl-D-*ribo*-hexosyl)purine (IV), m.p. 136-139°. Without further characterization, the protected nucleoside IV was stirred for 16 hr. with 50 ml. of absolute methanol containing 1 ml. of 3 *N* sodium methoxide. The resulting solution was neutralized with glacial acetic acid and was evaporated to dryness *in vacuo* at 40°. The residue was dissolved alternately in water and chloroform and, after shaking and separating, the chloroform layer was discarded and the aqueous layer was evaporated to dryness at 40°, giving a residue amounting to 410 mg. This residue, dissolved in 8 ml. of methanol, was treated with 13 ml. of 10% methanolic picric acid. After cooling, the picrate was filtered and washed with methanol. After drying, the picrate (155 mg.) was added to 8 ml. of a stirring suspension of Amberlite IRA-410 ($HCO_3^-$) anion exchange resin. Stirring was continued for one hour after which time the yellow coloration disappeared. Enough water was added to clarify the solution, the resin was filtered and filtrate was evaporated to dryness at 40°. This treatment gave 73 mg. (28% based on chloromercuri-6-benzamidopurine) of crude nucleoside V. On recrystallization from water V was obtained as a monohydrate melting at 130–133°. Recrystallization from absolute ethanol gave anhydrous V, m.p. 248.5–250° (dec.), which decomposes slowly on standing, $[\alpha]^{25}D$ +41.2° (*c* 0.48 hydrate, pyridine), $[\alpha]^{25}D$ +42° (*c* 0.98 hydrate, water). The nucleoside V, homogeneous on paper chromatograms, fluoresced blue in ultraviolet light and gave a positive test with boric acid spray reagent.

*Anal.* Calcd. for $C_{11}H_{15}O_3N_5$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.94; H, 6.09; N, 24.61.

*Hydrolysis of* V. A solution of 1 mg. of the nucleoside V in 1 ml. of 0.01N hydrochloric acid was refluxed for 1 hr. After cooling, the solution was treated with a 10% excess of 0.05N ammonium hydroxide and was evaporated to dryness at 40°. The residue was redissolved in 1 ml. of methanol and was chromatographed on paper giving two spots, one corresponding to adenine and the other to digitoxose.

*Xanthydrol determination of the digitoxose content of* V. The procedure followed was identical to that described by Kaiser and co-workers[12] except that the optical densities were determined at a wave length of 546 mμ in a Beckman DU spectrophotometer.

*1-(2,6-Dideoxy-D-ribo-hexopyranosyl)thymine* (VIII). A mixture of 3.98 g. (8.57 mmoles) of 2,6-dideoxy-3,4-di-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl chloride (I) and 7.50 g. (41 mmoles) of 2,4-diethoxy-5-methylpyrimidine was heated at 55° under a reduced pressure of 20 mm. of mercury for 4 hr. The solid residue was extracted thoroughly with ether and, after filtration, was recrystallized once from absolute ethanol giving 1.88 g. (37.7%) of the crude, protected nucleoside VI, m.p. 223–227°. A solution of 1.88 g. of VI in 100 ml. of warm, absolute ethanol and 20 ml. of chloroform was treated with 30 ml. of 20% hydrogen chloride in methanol.

(12) F. Kaiser, E. Haack, and H. Spingler, *Ann.*, **603**, 75 (1957).

TABLE I

| Substance | Concn., μg. ml.$^{-1}$ | O. D. | $E^{1\%}_{1cm.}$ | Found | Calcd. |
|---|---|---|---|---|---|
| Digitoxose | 1.70 | 0.182 | 1.07 | (100) | 100 |
| 9-(2,6-Dideoxy-D-*ribo*-hexopyranosyl)-adenine monohydrate (V) | 3.46 | 0.193 | 0.558 | 52.2 | 52.3 |

After standing overnight the solution was evaporated *in vacuo* at 40° and the resulting residue was stirred for 1 hr. with warm ethanol, giving 1.72 g. (95%) of the deethylated product VII, m.p. 252–254°. A solution of 1.72 g. of the intermediate VII in 100 ml. of absolute methanol and 4 ml. of 3 *N* methanolic sodium methoxide was allowed to stand overnight. The solution was neutralized with glacial acetic acid, evaporated to dryness at 40°, and the residue was treated with 300 ml. of acetone. After filtering the insoluble materials, the filtrate was evaporated to dryness and the residue was dissolved in 75 ml. of hot absolute ethanol to which 2 drops of concentrated hydrochloric acid were added. The latter solution was concentrated to a volume of *ca.* 10 ml. whereupon the crude nucleoside VIII separated as crystalline material. Recrystallization from absolute ethanol gave 670 mg. (31% based on the chloride I) of anhydrous 1-(2,6-dideoxy-D-*ribo*-hexopyranosyl)thymine (VIII), subliming at 230° and melting at 242–244°; $[\alpha]^{22}D$ + 17 ± 2° (*c* 0.99, water); $\lambda_{max}^{H_2O}$ 265 mμ (3.97); $\nu_{max}^{Nujol}$ 3800 cm.$^{-1}$ (NH—OH band), 1690 cm.$^{-1}$ (nonconjugated C=O of ring), 1090 cm.$^{-1}$ (C—O—). The nucleoside VIII travelled as a single spot on paper ($R_{Thy}$ = 1.12), fluoresced with ultraviolet light and gave a negative test for 2-deoxy sugars.[12]

*Anal.* Calcd. for $C_{11}H_{16}O_5N_2$: C, 51.55; H, 6.29; N, 10.93. Found: C, 51.58; H, 6.40; N, 10.61.

*Conversion of the chloride* I *to 6-deoxy-3,4-di-O-p-nitrobenzoyl-D-ribo-hexopyranos-1-ene* (III) *during attempts to prepare the nucleoside* VIII *by the "mercuri" method.* To a stirring, anhydrous suspension of 225 mg. (0.5 mmole) of dithyminylmercury in 20 ml. of toluene was added a solution of 394 mg. (0.85 mmole) of the digitoxosyl chloride I in 10 ml. of dichloromethane. The mixture was refluxed under constant stirring for 2 hr. and was then filtered hot and washed with benzene. To the filtrate was added 10 ml. of *n*-pentane and the material which precipitated was separated by decantation. The solid material was dissolved in 15 ml. of chloroform and the resulting solution was extracted twice with 10-ml. portions of 30% aqueous potassium iodide. After separating, the chloroform layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to a sirup. The latter sirup was dissolved in 1 ml. of ethyl acetate and pentane was added dropwise to incipient turbidity. After standing overnight the separated crystalline material was filtered and recrystallized from ether, giving material which melted at 143–144° and had the composition of a 6-deoxy-3,4-di-*O*-*p*-nitrobenzoyl-D-*ribo*-hexopyranos-1-ene (III). Compound III, spotted on Whatman No. 1 paper, was chromatographed by an ascending technique using *n*-butyl alcohol saturated with water and travelled as a single spot ($R_{Thy}$ = 0.731).

*Anal.* Calcd. for $C_{20}H_{16}O_9N_2$: C, 56.10; H, 3.74; N, 6.54. Found: C, 55.96; H, 3.88; N, 6.25.

*Deliberate dehalogenation of the chloride* I. The conversion

(13) Pöhm and Weiser's boric acid spray reagent usually gives a positive test for 2-deoxy sugars bound in glycosides as well as the free sugars because of the hydrolytic power of the reagent. Thymine nucleosides are, however, resistant to hydrolysis by dilute mineral acid and, in accordance with our expectations, gave a negative test.

of 1190 mg. (2.0 mmoles) of 2,6-dideoxy-1,3,4-tri-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexose to the chloride I was carried out according to the original directions.[4] After the removal of the solvent by decantation, the crystalline material was dissolved immediately in 5 ml. of dry dichloromethane. After the addition of 5 ml. of anhydrous pyridine, the solution was boiled until its volume was reduced by two-thirds. The latter was transferred to a separatory funnel containing 400 ml. of ethanol-dichloromethane (1:4) and was extracted successive with *N* sulfuric acid, 5% aqueous sodium bicarbonate, and water. After drying over sodium sulfate, the separated ethanol-dichloromethane extract was evaporated *in vacuo* at 30°. The residue was dissolved in a minimum amount of acetone and the solution was transferred to a small petri dish. The solvent was evaporated carefully by warming and the residue thus obtained was transferred to a small Soxhlet thimble. After extracting continuously with 400 ml. of anhydrous ether for 24 hr., the extract was carefully boiled down to 15 ml., whereupon the desired material separated in crystalline form. By combining the latter with additional material obtained from the mother liquor and recrystallizing from acetone-ether (1:9), there was obtained a total of 385 mg. (45% based on 2,6-dideoxy-1,3,4-tri-*O*-*p*-nitrobenzyl-β-D-*ribo*-hexose) of pure 6-deoxy-3,4-di-*O*-*p*-nitrobenzoyl-D-*ribo*-hexopyranos-1-ene (III), m.p. 143–143.5° $[\alpha]^{20}D$ + 389°. When admixed with a specimen obtained in the preceding preparation, no depression in the melting point was observed.

*9-(2-Deoxy-D-arabino-hexopyranosyl)adenine* (X). To a solution of 674 mg. (1.0 mmole) of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*arabino*-hexosyl bromide (II)[10] in 17 ml. of dry benzene was added 392 mg. (1.13 mmoles) of silver 6-benzamidopurine and the mixture was refluxed with stirring for 12 min. After cooling, the reaction mixture was diluted with 10 ml. of chloroform and was filtered. After evaporation of the filtrate to dryness *in vacuo* at 40°, a crude mixture containing the protected nucleoside IX was obtained and, without further purifications, was dissolved in 50 ml. of warm methanol to which 1 ml. of 3 *N* sodium methoxide had been added. After stirring for 20 hr. the mixture was neutralized with glacial acetic acid and was evaporated *in vacuo* at 40°. The resulting oily residue was dissolved in 10 ml. of methanol and 15 ml. of 10% methanolic picric acid was added. The picrate salt, which formed immediately, was filtered and washed with cold methanol and amounted to 515 mg. The nucleoside X was regenerated from its picrate salt by a procedure similar to that described in the foregoing preparation of 9-(2,6-dideoxy-D-*ribo*-hexopyranosyl)adenine (V). The crude nucleoside X thus obtained was crystallized from 95% ethanol and melted at 136–137°, the temperature varying to a slight extent depending on the rate of heating. On recrystallization from absolute ethanol, some of X was obtained as the unstable, anhydrous nucleoside, softening at 220°, melting with recrystallization at 239–241° and remelting at 242–245°. The remainder of the material, amounting to 68 mg. (21.5% based on the bromide II), was obtained as the dihydrate of 9-(2-deoxy-D-*arabino*-hexopyranosyl)adenine (X), m.p. 141–160° (dec.), $[\alpha]^{27}D$ −4.7 ± 1.3° (*c* 0.50 dihydrate, water), $[\alpha]^{27}D$ + 53.2° (*c* 0.19 dihydrate, pyridine), $\lambda_{max}^{H_2O}$ 260 mμ (4.14).

The nucleoside X travelled as a single spot on papergrams ($R_{Ad}$ = 1.24), giving a blue fluorescence with ultraviolet light and a blue-violet color with boric acid spray reagent. The nucleoside was hydrolyzed in a manner identical to that described in the foregoing preparation of 9-(2,6-dideoxy-D-*ribo*-hexopyranosyl)adenine (V). Paper chromatography of the mixture disclosed two spots, one corresponding to adenine and the other to 2-deoxy-D-*arabino*-hexose.

*Anal.* Calcd. for $C_{11}H_{15}O_4N_5 \cdot 2H_2O$: C, 41.63; H, 6.04; N, 22.06. Found: C, 41.49; H, 6.15; N, 21.82.

*1-(2-Deoxy-D-arabino-hexopyranosyl)thymine* (XIII). A mixture of 6.74 g. (10 mmoles) of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*arabino*-hexopyranosyl bromide (II) and 7.00 g. (38.5 mmoles) of 2,4-diethoxy-5-methylpyrimidine was heated under a reduced pressure of 20 mm. of mercury for 4 hr. After cooling, the melt was extracted twice with 50-ml. portions of ether and was extracted further with 250 ml. of benzene. The crude protected nucleoside XI thus obtained amounted to 3.30 g. and melted at 230–245°. The latter material, without further purification, was dissolved in 50 ml. of chloroform and to this solution was added 50 ml. of 25% methanolic hydrogen chloride. After stirring overnight, the separated deethylated product XII was filtered and amounted to 1.70 g., softening at 155° with change in crystal form and melting at 241–245°. Without further purification, XII (1.70 g.) was transferred to 100 ml. of absolute methanol to which was added 3 ml. of *N* sodium methoxide and the mixture was stirred for 18 hr. at room temperature. After neutralizing the solution with glacial acetic acid and evaporating to dryness *in vacuo* at 40°, the residue was redissolved in 300 ml. of water and was extracted with 3–100 ml. portions of chloroform. After separating the aqueous phase and evaporating to dryness *in vacuo*, the residue was extracted twice with 100-ml. portions of hot 2-propanol. The 2-propanol extract was evaporated to dryness *in vacuo* and the residue was redissolved in 50 ml. of absolute ethanol. Four drops of concentrated aqueous hydrochloric acid were added, and the sodium chloride which separated was filtered. The filtrate was concentrated by boiling to 25 ml. from which, after cooling, there was obtained a total of 390 mg. (14% based on the bromide II) of 1-(2-deoxy-D-*arabino*-hexopyranosyl)thymine (XIII), subliming at 230° and melting at 231.5–232.5°; $[\alpha]^{27}D$ + 4.6 ± 0.9° (*c*, 0.975 water); $\lambda_{max}^{H_2O}$ 265 mμ (3.99); $\nu_{max}^{KBr}$ 3920 cm.$^{-1}$ (conjugated C=O of ring), 1810 cm.$^{-1}$ (broad C—O— band). The nucleoside XIII travelled on papergrams as a single spot ($R_{Thy}$ = 1.14), fluoresced under ultraviolet light, and gave a negative test with boric acid spray reagent.

*Anal.* Calcd. for $C_{11}H_{16}O_6N_2$: C, 48.55; H, 5.93; N, 10.28. Found: C, 48.82; H, 5.89; N, 10.01.

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## Nucleosides. XV. Synthesis of 1-β-D-Lyxofuranosylcytosine *via* Thiation of an Anhydronucleoside[1,2]

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Previous papers in another series[3,4] demonstrated that suitably protected pyrimidine nucleosides

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(2) A preliminary report has appeared. See J. J. Fox, N. Yung, I. Wempen, and R. Duschinsky, Abstracts, *Intern. Union Pure and Applied Chem.* (Symposium on Natural Products), Australia, 1960, p. 66.