was taken to dryness *in vacuo*. To the residue was added a solution of 15 g. of sodium acetate in 200 ml. of water. After stirring for a few minutes a colorless amorphous solid was collected and washed with water. The yield was nearly quantitative. The solid was purified by precipitating from an ether solution with petroleum ether, m.p. 90–140° (efferv.), $[\alpha]^{24}D$ +5° (*c* 0.2, acetone). Ultraviolet absorption properties in ethanol were λ_{max} 255, 229.5 mμ; λ_{min} 246.5 mμ; ratio 260/230 mμ 0.63.

Anal. Calcd. for $C_{17}H_{17}BrN_2O_8S$: C, 41.73; H, 3.50; Br, 16.33; N, 5.72; S, 6.55. Found: C, 41.43; H, 3.67; Br, 17.05; N, 6.25; S, 7.49.

5′-*O*-Benzoyl-2′-chloro-2′-deoxy-3′-*O*-mesyluridine [X(Cl)].—A suspension of 1.0 g. (2.45 mmoles) of VIII in 50 ml. of anhydrous dioxane was saturated with dry hydrogen chloride at 0°. The resulting clear solution was allowed to stand at 20–25° for 7 days. Solvent was removed *in vacuo*, and the resulting gum was dissolved in chloroform and extracted several times with water. The chloroform layer was dried over sodium sulfate, then taken to dryness *in vacuo*. Trituration in ether gave a colorless solid. This was filtered, washed with ether–petroleum ether, and dried. The yield of amorphous solid, m.p. 90–130° (efferv.), $[\alpha]^{24}D$ +3° (*c* 0.3, acetone), was 1.07 g. (98%). Ultraviolet absorption properties in ethanol were max. at 255 and 229 mμ, ϵ_{max} 9180 and 12,840, respectively; min. at 247 mμ, ϵ_{min} 5260.

Anal. Calcd. for $C_{17}H_{17}ClN_2O_8S$: C, 45.90; H, 3.86; Cl, 7.98; N, 6.31. Found: C, 45.88; H, 3.88; Cl, 8.01; N, 6.52.

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Nucleosides. XIX. Structure of the 2′-Halogeno-2′-Deoxypyrimidine Nucleosides[1]

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The halogeno deoxy nucleosides prepared by the reaction of hydrogen halides with 2,2′-anhydro pyrimidine nucleosides[2] (I) were proven to be 1-(2′-halogeno-2′-deoxy-β-D-ribofuranosyl)pyrimidines (II). 2′-Fluoro-2′-deoxyuridine [II(F)] was converted to the 3′,5′-di-*O*-trityl derivative (XIII). Reflux of XIII with base formed 1-(3′,5′-di-*O*-trityl-β-D-arabinofuranosyl)uracil (XV). XV also was formed from the tritylation of 1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil (XVIII). Detritylation of XV with acid gave only 1-β-D-arabinofuranosyluracil (XVI), proving both the 2′-position and *ribo* configuration of the fluoro function in II(F). Proof of analogous structures for 2′-chloro- [II(Cl)] and 2′-bromo- [II(Br)] 2′-deoxyuridines was obtained by their conversion to 3′,5′-di-*O*-mesyl-2′-halogeno derivatives [VIIIk(Cl) and VIIIk(Br)], identical with products obtained upon reaction of the corresponding hydrogen halides with the known 2,2′-anhydro-1-(3′,5′-di-*O*-mesyl-β-D-arabinosyl)uracil (IXk).

The previous paper[2] in this series describes the reaction of 2,2′-anhydro pyrimidine nucleosides with anhydrous hydrogen halides to yield fluoro-, chloro-, and bromodeoxy nucleosides. Although these reactions were expected to take the pathway illustrated by the reaction of 2,2′-anhydro-1-β-D-arabinofuranosyluracil (I) to give 2′-halogeno-2′-deoxy derivatives of the *ribo* configuration II (Scheme I), another plausible pathway existed. It appeared conceivable that, under the reaction conditions, a 2′,3′-*ribo* epoxide (III) could have formed from I. Such a reaction route was supported by data on the cleavage of 2,3′-anhydro-1-β-D-xylofuranosyluracil (IV) in refluxing aqueous acid, to yield (by paper electrophoretic examination) spots corresponding to 1-β-D-xylofuranosyluracil and 1-β-D-arabinofuranosyluracil.[3] Reaction of hydrogen halides with epoxide III would be expected to give mixtures of the 3′-halogeno derivative (*xylo* configuration, V) and the 2′-halogenonucleoside (*arabino* configuration, VI) with the 3′-halogeno derivatives (V) predominating.[4–6] In no case were mixtures of halogeno deoxy nucleosides isolated, but the possibility that an isomer was present, even in small yield, could not be excluded, since in no case were quantitative yields of halogeno deoxy nucleosides obtained.

Although III was not involved in *aqueous* acid cleavage of I (only 1-β-D-arabinofuranosyluracil was obtained as a product),[7] a reaction route similar to that considered above for *anhydrous* acid (hydrogen halide) cleavage of I (namely, I to III to V) was almost certainly involved when *anhydrous* alkaline reagents were employed.[8–12]

The present paper presents proof of structure for the halogeno deoxynucleosides described in the preceding paper.[2] Although this investigation has involved only deoxyuridine analogs, on the basis of chemical, physical[2] and biological[13] properties, it is highly probable that derivatives of thymidine and 5-fluorodeoxyuridine have analogous structures.

Despite the fact that the halogeno deoxy nucleosides could be converted back to the 2,2′-anhydro starting

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 03190-07).

(2) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964).

(3) N. Yung and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).

(4) See C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **81**, 898, (1959), and additional references therein.

(5) J. F. Codington, R. Fecher, and J. J. Fox, *J. Org. Chem.*, **27**, 163 (1962).

(6) G. Casini and L. Goodman, *J. Am. Chem. Soc.*, **85**, 235 (1963).

(7) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

(8) Brown, *et al.*,[9] treated compound I with sodium ethyl sulfide in dimethylformamide and obtained 1-(3′-ethylthio-3′-deoxy-β-D-xylofuranosyl)-uracil (V, (X) = -SEt).[10]

(9) D. M. Brown, D. B. Parihar, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958).

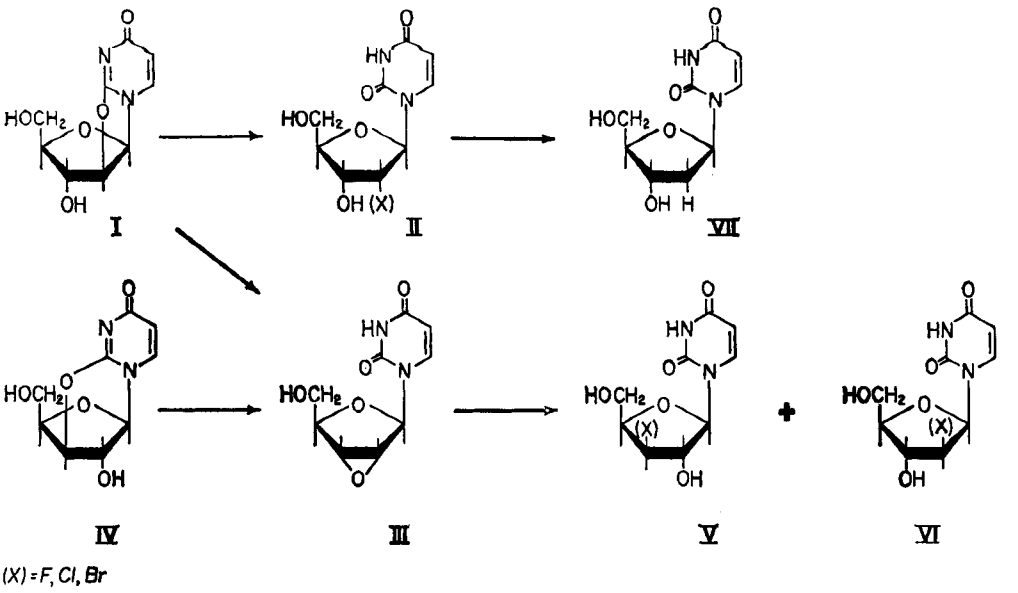
(10) The transient existence of III under alkaline conditions has been postulated on other occasions.[11,12]

(11) J. F. Codington, R. Fecher, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 2794 (1960).

(12) E. J. Reist, J. H. Osiecki, L. Goodman, and B. R. Baker, *ibid.*, **83**, 2208 (1961).

(13) J. F. Codington, I. L. Doerr, L. Kaplan, and J. J. Fox, *Federation Proc.*, **22**, 532 (1963).

SCHEME I

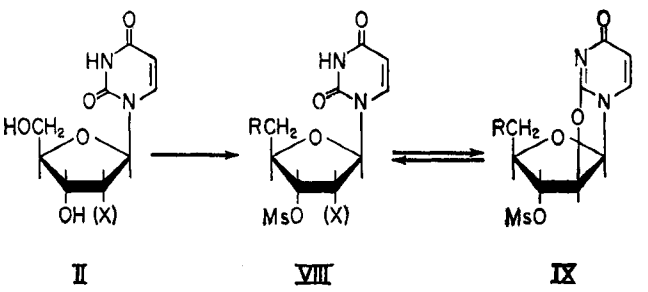


materials (I) in each case, such conversions do not constitute absolute proof of structure. Anhydro nucleoside formation could conceivably proceed by a reversal of the route postulated for the formation of structures V and VI, namely, V or VI to III, and III to I.[14] In order to establish the position of the substituent on, and the configuration of, the halogeno deoxy nucleosides, it would be necessary to effect 2,2′-anhydro formation with both free hydroxyls (3′ and 5′) blocked with appropriate groups in order to rule out the possibility of intermediary epoxide formation during the reaction.

In the case of 5′-*O*-benzoyl-3′-*O*-mesyl-2′-chloro-2′-deoxyuridine [VIIIj(Cl)] and its 2′-bromo analog VIIIj(Br) (see Scheme II) described in the previous paper,[2] structures were readily established, as both the 3′- and 5′-positions were blocked, and the blocking groups remained in position during anhydro formation. This was accomplished by heating VIIIj(Cl or Br) with sodium benzoate in acetamide[11,17] to give the known 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesylarabinosyl)uracil (IXj).[11]

The establishment of a 2′-*ribo* position for the halogeno substituents in VIIIj(Cl or Br) supported such a 2′-*ribo* position for the halogen atoms in the unblocked halogeno deoxy nucleosides. It was clear, however, that no alternate route (epoxide intermediate) could be postulated for the introduction of a chloro or bromo substituent into IXj as was true of I, which contained an unblocked 3′-hydroxyl.

SCHEME II



The structures of the chloro [II(Cl)] and bromo [II(Br)] deoxynucleosides (Scheme I) were established without undue complication (and by analogy for the corresponding thymidine analogs). It was found that the reaction of the structurally established 2,2′-anhydro-1-(3′,5′-di-*O*-mesyl-β-D-arabinosyl)uracil (IXk, Scheme II)[18] with hydrogen chloride in dioxane gave a crystalline monochlorodimesyloxy derivative [VIIIk(Cl)]. Compound VIIIk(Cl) was converted back to the dimesyloxy anhydro nucleoside (IXk) by means of sodium acetate in dimethylformamide,[19] thus establishing the position and configuration of the chloro substituent in VIIIk(Cl) as 2′-*ribo*. Mesylation of II(Cl) in pyridine yielded a crystalline product identical with VIIIk(Cl). Therefore, the position and configuration of the chlorine in II(Cl) is 2′-*ribo*.

The product of the reaction of the 2,2′-anhydro dimesyloxy nucleoside (IXk) with hydrogen bromide varied with the reaction conditions. With glacial acetic acid as solvent a crystalline monobromodimesyloxy nucleoside [VIIIk(Br)] was obtained. This proved to be analogous to the chlorodeoxy nucleoside

(14) A similar situation pertains to the structure of an iodo deoxy nucleoside prepared by Brown and co-workers[15] who assigned a 5′-*O*-acetyl-2′-iodo-2′-deoxyuridine structure. This compound was converted to the 2,2′-anhydro derivative,[15] which, upon reduction followed by deacetylation,[16] gave 2′-deoxyuridine (VII). Although these investigators assigned a 2′-*ribo* structure, the possibility that the iodo deoxy nucleoside had an *arabino* configuration (VI, 5′-*O*-acetyl, (X) = iodo) could not be discounted. The formation of the epoxide (III, 5′-*O*-acetyl) *en route* to I (5′-*O*-acetyl) was plausible. The elucidation of the structure of the halogeno deoxy nucleosides (II) in this paper strongly supports their structure for the iodo derivative.

(15) D. M. Brown, D. B. Parihar, and A. Todd, *J. Chem. Soc.*, 4242 (1958).

(16) D. M. Brown, D. B. Parihar, C. B. Reese, and A. Todd, *ibid.*, 3035 (1958).

(17) E. J. Reist, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 5775 (1958).

(18) R. Fecher, J. F. Codington, and J. J. Fox, *ibid.*, **83**, 1889 (1961).

(19) The reaction of IXk with sodium benzoate in dimethylformamide under less strenuous conditions replaces the 5′-mesyloxy group to give IXj.[11]

[VIIIk(Cl)]; it too was readily converted to IXk under conditions using sodium acetate in dimethylformamide. Mesylation of II(Br) in pyridine to give VIIIk(Br) established the structure of II(Br). At elevated temperature with benzene as a solvent, the reaction of IXk with hydrogen bromide yielded a dibromomonomesyloxy nucleoside. Proof that this material was 2′,5′-dibromo-2′,5′-dideoxy-3′-*O*-mesyluridine [VIIIh(Br)] was obtained by its conversion to IXj in hot acetamide–sodium benzoate.

Confirmation of the 2′-position (but not configuration) of the bromo substituent in compound II(Br) was obtained by its reduction to 2′-deoxyuridine (VII, Scheme I)[16] using palladium on charcoal in absolute ethanolic solution. Isolation of the product proved more difficult than anticipated because 5,6-dihydro derivatives also were formed in substantial amounts (20–30%).

Since the fluorodeoxy nucleosides were formed under considerably more vigorous conditions than either the chloro or bromo derivatives, an independent determination of the structure of II(F) was necessary. Attempts to reduce II(F) to the known 2′-deoxy-5,6-dihydrouridine[20] failed. The fluoro substituent was not removed after 48 hr. at atmospheric pressure with palladium on charcoal in ethanol–water. Attempted hydrogenation at high pressure (more than 100 atm.), with palladium on charcoal in dilute ethanol,[21] was likewise unsuccessful.

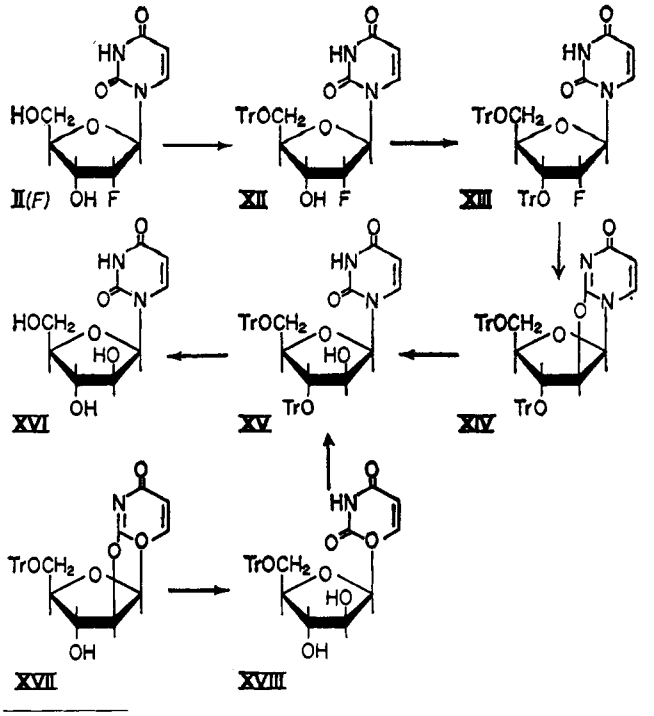
Reaction of the unblocked fluorodeoxyuridine II(F) with sodium *t*-butoxide in dimethylformamide[22] resulted in a 59% yield of crystalline 2,2′-anhydro-1-β-D-arabinofuranosyluracil (I, Scheme I). Since I might have arisen from the epoxide III, an attempt was made to establish the structure of II(F) by the method utilized successfully for II(Cl) and II(Br). This approach was unfortunately unsuccessful due to the fact that the reaction of anhydrous hydrogen fluoride with IXk in dioxane gave material not analogous to VIIIk-(Cl or Br) but containing more than one fluorine atom.[23]

Attention was turned to the use of trityl blocking groups. It had been demonstrated that the reaction of trityl chloride with pyrimidine nucleosides in pyridine produces under relatively mild conditions good yields of 5′-*O*-trityl nucleosides.[25] Investigating a report by Levene and Tipson[26] of the isolation of a di-*O*-trityl derivative of uridine, Yung and Fox[27] characterized this material as 2′,5′-di-*O*-trityluridine. Although these investigators[27] were unable to isolate 3′,5′-ditritylated uridine, they did obtain chemical evidence for its presence in small amounts in the reaction mixture. It thus appeared that tritylation of the 3′-hydroxyl of nucleosides was feasible.

Tritylation of II(F) in pyridine at room temperature gave the 5′-*O*-trityl derivative (XII, Scheme III) in crystalline form. As expected, tritylation of the remaining free hydroxyl group proved difficult. After reaction of XII with 2 equiv. of trityl chloride for 24 hr. at 75–100°, 75% of XII was recovered unchanged, but paper chromatography with an ethyl acetate–methanol–*n*-heptane system (solvent A)[2] detected a second compound. After more vigorous reaction conditions, 100–106° for 40 hr., such chromatography revealed the presence of two components, R_f 0.33 and 0.74, in approximately equal amounts. The slower moving component was identified as the mono-*O*-trityl starting material (XII) and the faster component as a di-*O*-tritylfluoronucleoside (XIII). Physical properties of the tritylated nucleosides are presented in Table I.

Separation of the components of the reaction mixture was achieved with Whatman 3MM paper, solvent

SCHEME III



(20) M. Green and S. S. Cohen, *J. Biol. Chem.*, **225**, 397 (1957).

(21) We are indebted to Dr. Robert Duschinsky of Hoffmann LaRoche, Inc., Nutley, N. J., for this experiment.

(22) R. Letters and A. M. Michelson, *J. Chem. Soc.*, 1410 (1961).

(23) Mesylation of II(F) gave an amorphous dimesyloxyfluoro derivative [VIIIk(F)] in only fair yield. An attempt to form this same product from the reaction of IXk with hydrogen fluoride in dioxane at 100–110° failed. An amorphous material (B) was obtained. On the basis of its infrared and ultraviolet absorption properties it appeared to be similar to, if not identical with, VIIIk(F), although subsequent experiments showed that little, if any, material of structure VIIIk(F) was present. Attempted crystallization of B from ethanol produced a small amount of colorless crystalline material C with a markedly different spectrum in the infrared from VIIIk(F). Although the general characteristics of the two spectra were related. C exhibited more, and more sharply defined, absorption bands in the 7–10-μ region than B which has an infrared spectrum almost identical with that of trimesyloxyuridine. The spectrum of C in the ultraviolet was similar to that of uridine (max. at 262 mμ, min. at 230 mμ); whereas, B exhibited a hyposchromic shift, as did VIIIk(F) (max. at 258 mμ, min. at 229 mμ). Passage of B through a cellulose column with 1-butanol–water (86:14) as solvent produced two distinct peaks. The first peak, representing an approximate yield of 30% based upon IXk, contained material (from a small cut at the center of the peak) with C, H, N, F, and S analyses corresponding to $C_{11}H_{16}F_2N_2O_7S_2$. Although the structure of this material remains unknown, it seems probable that at least one of the two fluorine atoms is attached to a sulfur atom of one of the two mesyloxy groups.[24] Material from the second peak proved to be identical with C isolated from B by crystallization from ethanol. Compound C was found to be present in the reaction mixture in approximately 6% yield based upon IXk. Elemental analyses (C, H, N, S, and F) were consistent with a formula of $C_{10}H_{14}F_2N_2O_6S$. In addition to the presence of two fluorine atoms, this crystalline product had clearly lost a mesyloxy group. Although the structure of C has not been established, the possibility of a 2′,3′- or 3′,5′-ortho ester type structure (oxygen–sulfur–oxygen bridge) with a fluorine attached to sulfur is suggested.

(24) Although no precedent could be found for a fluorine-substituted methanesulfonyl ester, a review article by H. L. Roberts [*Quart. Rev.* (London), **15**, 30 (1961)] on the chemistry of the sulfur–fluorine bond clearly indicates that such structures would not be improbable.

(25) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **104**, 385 (1934).

(26) P. A. Levene and R. S. Tipson, *ibid.*, **105**, 419 (1934).

(27) N. C. Yung and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).

TABLE I
PHYSICAL CONSTANTS OF TRITYL DERIVATIVES IN ETHANOL

		$[\alpha]^{24}D$	λ_{max} (ϵ_{max})	λ_{min} (ϵ_{min})	260/240
XVIII	5′-*O*-Tritylarabinosyluracil	+13°	261.5 (9800)	241 (5300)	1.81
XV	3′,5′-Di-*O*-tritylarabinosyluracil	+38°	261.5 (10,800)	244 (6550)	1.39
XII	5′-*O*-Trityl-2′-fluorodeoxyuridine	+23°	259 (8970)	242 (5380)	1.62
XIII	3′,5′-Di-*O*-trityl-2′-fluorodeoxyuridine	−12°	259 (9500)	244 (6560)	1.20
XVII	5′-*O*-Trityl-2,2′-anhydroarabinosyluracil	−25°	248 sh (6740)		0.66

A, and elution of XIII with ether. XIII was obtained as a colorless amorphous solid. Proof of the position and configuration of the fluoro function required the conversion of XIII to the 2,2′-anhydro derivative (XIV) without loss of the two trityl groups. Isolation and structural determination of either XIV or of the di-*O*-tritylarabinosyl nucleoside (XV), which could only have resulted from hydrolysis of XIV, was necessary. Initial attempts to convert XIII to the 2,2′-anhydro derivative (XIV) using sodium *t*-butoxide in dimethylformamide[22] failed. The high temperature (115–118°) necessary for the removal of the fluoro substituent produced fluorescent products. No chromatographic spot attributable to the desired product (XIV) was observed.

It was hoped that 3′,5′-di-*O*-tritylarabinofuranosyluracil (XV) could be isolated after alkaline hydrolysis of XIII, a reaction that would necessarily involve the formation of the 2,2′-anhydro nucleoside (XIV) as an intermediate. Proof of the structure of XV would establish the structure of II(F). Reflux of XIII with an ethanolic sodium hydroxide solution for 15 hr. gave a 40% conversion of XIII (R_f 0.79, solvent A) to a new di-*O*-trityl derivative (R_f 0.51). The mixture was chromatographed on Whatman 3MM paper (solvent A) and eluted with ether. Removal of the ether from the slower moving component gave a colorless amorphous solid. Elemental analysis and physical properties (see Table I) were consistent with the ditrityl structure (XV). This material was found to be identical (infrared and ultraviolet spectra and chromatographic properties) with the product obtained upon the tritylation of 1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil (XVIII). XVIII had been obtained from the alkaline hydrolysis of the 5′-*O*-trityl-2,2′-anhydro nucleoside (XVII).[2]

The trityl groups were removed from XV by refluxing in hydrochloric acid–water–ethanol. The ultraviolet absorption spectrum of the residue was that of a 1-β-D-aldopentofuranosyluracil. Paper electrophoresis in borate buffer of pH 9.3 revealed only one spot, which migrated with an authentic sample of 1-β-D-arabinofuranosyluracil (XVI) but at a different rate from the *xylo*, *lyxo*, or *ribo* isomers.

Since XVI could have been formed from XIII only through the 2,2′-anhydro intermediate (XIV) the isolation of XVI as the *only* 1-β-D-aldopentofuranosyluracil present proves conclusively *both* the position *and* the configuration of the fluoro substituent in II(F), and firmly establishes II(F) as 2′-fluoro-2′-deoxyuridine.

Based upon similar chemical, physical,[2] and biological[13] properties, and upon the similar reaction conditions under which they are formed,[2] the other halogeno (chloro, bromo, and fluoro) deoxy nucleosides described in the previous paper[2] are assigned 2′-*ribo* structures and are 2′-halogeno analogs of thymidine and 5-fluoro-2′-deoxyuridine.

Experimental[28]

2′-Chloro-2′-deoxy-3′,5′-di-*O*-mesyluridine [VIIIk(Cl)]. **Method A.**—A suspension of 2.55 g. (6.7 mmoles) of 2,2′-anhydro-1-(3′,5′-di-*O*-mesyl-β-D-arabinosyl)uracil (IXk) in 130 ml. of dioxane (distilled from potassium hydroxide) saturated with hydrogen chloride was heated in a closed stainless steel container at 70–80° for 19 hr. The amber-colored solution was taken to dryness *in vacuo*, and the gum residue was triturated with 300 ml. of water, whereupon crystallization occurred. Colorless crystals, 2.43 g. (87%), m.p. 147–150°, were collected. Crystallization from ethanol gave colorless micaceous plates, m.p. 151–152°, $[\alpha]^{24}D$ +23° (*c* 0.3, acetone).

Anal. Calcd. for $C_{11}H_{15}ClN_2O_9S_2$: C, 31.55; H, 3.61; Cl, 8.47; N, 6.68; S, 15.30. Found: C, 31.87; H, 3.56; Cl, 8.73; N, 6.81; S, 15.90.

VIIIk(Cl). Method B.—To a solution of 0.06 g. (0.23 mmole) of 2′-chloro-2′-deoxyuridine [II(Cl)] in 3 ml. of pyridine at 0° was added 0.13 g. (1.1 mmoles) of methanesulfonyl chloride. After remaining at 0° for 18 hr., the yellow solution was treated with a few drops of ethanol. Solvent removal *in vacuo* left a yellow gum, which was triturated in turn with 1:1 ether–petroleum ether (b.p. 30–60°) and water. The residue was dried and triturated with 2 ml. of ethanol. Pale yellow crystals, 0.09 g., m.p. 145–149°, were recrystallized from ethanol to give colorless crystals, melting at 150.5–152°, identical (melting point, ultraviolet, and infrared spectra) with a sample prepared by method A. A mixture of samples prepared by methods A and B showed no depression in melting point.

2′-Bromo-2′-deoxy-3′,5′-di-*O*-mesyluridine [VIIIk(Br)]. **Method A.**—A suspension of 0.95 g. (2.5 mmoles) of IXk in 100 ml. of glacial acetic acid was saturated with hydrogen bromide at 20–25°. After remaining in a sealed container at this temperature, with stirring, for 9 days, the resultant dark red liquid was taken to dryness *in vacuo*. The residue was triturated with ether, then with water. Treatment of a hot ethanolic solution with activated charcoal removed all color. Upon cooling, colorless platelets, 0.54 g. (47%), m.p. 142–146°, were obtained. Crystallization from 80% ethanol gave micaceous platelets, m.p. 151–155°, $[\alpha]^{23}D$ +30° (*c* 0.2, acetone).

Anal. Calcd. for $C_{11}H_{15}BrN_2O_9S_2$: C, 28.52; H, 3.26; Br, 17.26; N, 6.04; S, 13.83. Found: C, 28.59; H, 3.32; Br, 17.37; N, 6.08; S, 13.93.

VIIIk(Br). Method B.—A solution of 0.10 g. (0.33 mmole) of 2′-bromo-2′-deoxyuridine [II(Br)] in 3 ml. of pyridine was cooled to 0–5°. After the addition of 0.14 g. (1.3 mmoles) of methanesulfonyl chloride, the mixture was allowed to remain in the cold for 18 hr. The product was isolated in essentially the same manner as described above for VIIIk(Cl), method B. Colorless needles, 0.03 g., m.p. 141–150°, were obtained by crystallization from ethanol. An infrared spectrum (potassium bromide pellet) of this material was identical in every respect with a sample prepared by method A.

2′,5′-Dibromo-2′,5′-dideoxy-3′-*O*-mesyluridine [VIIIh(Br)].—A mixture of 1.0 g. (2.6 mmoles) of IXk in 100 ml. of dry benzene

(28) Melting points are corrected. Elemental analyses were made by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Ultraviolet absorption data were obtained on the Cary recording spectrophotometer, Model 15, and the Beckman spectrophotometer, Model DU. Infrared determinations were made with the Infracord spectrophotometer by use of the potassium bromide disk technique. Paper electrophoretic separations were made with an apparatus manufactured by the E. C. Apparatus Co.

was saturated with hydrogen bromide at 0–5°. The reaction mixture was heated in a sealed stainless steel container at 75–80° for 17 hr. After removal of solvent *in vacuo*, the dark-colored residue was triturated in turn with ether and water. A hot ethanol–water (4:1) solution was treated with activated charcoal and filtered. Colorless needles, 0.61 g. (51%), m.p. 197–205°, separated. Crystallization from 90% ethanol gave colorless needles, m.p. 198–204° dec., $[\alpha]^{23}D$ +16° (*c* 0.5, acetone).

Anal. Calcd. for $C_{10}H_{12}Br_2N_2O_6S$: C, 26.80; H, 2.69; Br, 35.67; N, 6.25; S, 7.15. Found: C, 26.75; H, 2.87; Br, 35.38; N, 6.10; S, 7.26.

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil (I) from II(F).—A mixture of 25 mg. (0.10 mmole) of II(F), 0.30 ml. of *t*-butyl alcohol containing 0.15 mmole of sodium *t*-butoxide and 2.5 ml. of dimethylformamide was heated at 100–110° for 2 hr. The cooled mixture was triturated with 50 ml. of ether–petroleum ether (2:3). The residue was taken up into hot ethanol (95%); the solution was decolorized with activated charcoal and cooled. Colorless crystals, 11 mg. (59%), m.p. 244–246°, were collected. This material was identical (melting point, ultraviolet, and infrared spectra) with an authentic sample. Admixture with an authentic specimen showed no depression of melting point.

2,2′-Anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinosyl)uracil (IXj). Method A.—A mixture of molten acetamide (1.8 g.), 0.10 g. (0.7 mmole) of sodium benzoate, and 0.10 g. (0.20 mmole) of VIIIj(Br) was heated at 100–105° for 20 min., then poured into 50 ml. of ice–water. After 30 min., crystals were collected, washed with water, then ether. The nearly colorless needles, 0.052 g. (64%), melted at 236–238°. Admixture with an authentic sample showed no depression and the two samples were identical with respect to ultraviolet and infrared spectra.

IXj. Method B.—A mixture of 19 mg. (0.043 mmole) of VIIIj(Cl) and 34 mg. (0.23 mmole) of sodium benzoate in 0.30 g. of acetamide was heated at 100° for 45 min. To the colorless solution was added 5 ml. of water. After 30 min. colorless crystals, 11.0 mg. (63%), m.p. 229–235°, were collected. Crystallization from 80% ethanol gave colorless needles melting at 237–238°. Mixture of this material and an authentic specimen of VIIIj showed no depression of melting point.

IXj. Method C.—To 0.20 g. (1.4 mmoles) of sodium benzoate in 2.0 g. of molten acetamide was added 0.10 g. (0.22 mmole) of 2′5′-dibromo-2′,5′-dideoxy-3′-*O*-mesyluridine [VIIIh(Br)]. The mixture was heated at 120–125° for 20 min., then poured into 30 ml. of ice–water. Tan crystals were collected and crystallized from ethanol–water (1:1). Colorless needles, 0.02 g. (22%), m.p. 233–235°, identical (infrared and ultraviolet absorption spectra) with an authentic sample of IXj, were obtained.

2,2′-Anhydro-1-(3′,5′-di-*O*-mesyl-β-D-arabinosyl)uracil (IXk). Method A.—A mixture of 0.10 g. (1.2 mmoles) of anhydrous sodium acetate and 0.10 g. (0.24 mmole) of VIIIk(Cl) in 6 ml. of dimethylformamide was heated at 110–115° for 30 min. The solvent was removed *in vacuo*, the gum residue was triturated with ether, and the ether was decanted. The material was dissolved in 0.5 ml. of hot ethanol–water (1:1) and cooled. The colorless needles, 0.006 g. (7%), m.p. 180–182°, collected were identical (infrared and ultraviolet absorption spectra) with an authentic sample of VIIIk.

IXk. Method B.—To a suspension of 0.20 g. (2.4 mmoles) of anhydrous sodium acetate in 15 ml. of dimethylformamide was added 0.20 g. (0.43 mmole) of VIIIk(Br). The mixture was heated at 100–110° for 40 min. Essentially the same procedure described for the isolation of IXk in method A (above), produced colorless needles, 0.006 g. (4%), m.p. 192–194°.[29] These were identical (infrared and ultraviolet spectra) with an authentic sample. A mixture of this material and an authentic sample gave no melting point depression.

2′-Fluoro-5′-*O*-trityl-2′-deoxyuridine (XII).—To a solution of 0.60 g. (2.4 mmoles) of II(F) in 12 ml. of pyridine, 1.36 g. (4.9 mmoles) of trityl chloride was added with stirring. The solution was stirred at 20–25° for 16 hr., then warmed at 60° for about 15 min. Ethanol (0.3 ml.) was added. After 30 min., removal of solvent *in vacuo* left a yellow gum that was triturated well with water. The water then was decanted. After drying, the material was triturated in ether–petroleum ether and filtered. The colorless crystals, 0.45 g. (38%), m.p. 186–194°, obtained were recrystallized from ethanol to give colorless platelets melting at 199–201°. Polarimetric and spectral data are found in Table I.

Anal. Calcd. for $C_{28}H_{25}FN_2O_5$: C, 68.84; H, 5.16; F, 3.88; N, 5.74. Found: C, 68.46; H, 5.39; F, 3.54; N, 5.10.

2′-Fluoro-3′,5′-di-*O*-trityl-2′-deoxyuridine (XIII).—A solution of 0.26 g. (0.53 mmole) of XII and 0.30 g. (1.1 mmoles) of trityl chloride in 3 ml. of pyridine was heated for 2 hr. at 78°, 31 hr. at 89–95°, and 7 hr. at 105–106°. To the dark amber-colored solution was added 0.2 ml. of ethanol. After 10 min. the still warm solution was poured with stirring into 200 ml. of ice–water. The tritylated nucleosides were extracted with chloroform, and the chloroform solution was extracted in turn with water and dried. The solvent, removed *in vacuo*, left a residue of 0.24 g. Paper chromatography with a system of *n*-heptane–ethyl acetate–methanol, solvent A,[2] revealed two spots of about equal intensity under ultraviolet light representing the mono-*O*-trityl (R_f 0.55) and the di-*O*-trityl (R_f 0.83) derivatives. The entire product was separated in this fashion (Whatman 3MM paper, solvent A). The di-*O*-trityl nucleoside (XIII) was eluted with ether, and the ether was removed *in vacuo*. The residue was triturated with water, filtered, and dried. The yield of colorless amorphous solid was 0.10 g. (26%). Polarimetric and spectral data are presented in Table I.

Anal. Calcd. for $C_{47}H_{39}FN_2O_5$: C, 77.24; H, 5.38; F, 2.60; N, 3.82. Found: C, 77.18; H, 5.50; F, 2.95; N, 4.29.

1-(5′-*O*-Trityl-β-D-arabinofuranosyl)uracil (XVIII).—The solution resulting from the addition of 3 ml. of 1 *N* sodium hydroxide to a suspension of 0.80 g. (1.7 mmoles) of 2,2′-anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil (XVII) in 40 ml. of ethanol–water (1:1) was stirred for 1 hr. at 20–25°, then neutralized by the dropwise addition of 2 *N* acetic acid. The product was collected, triturated with water, and crystallized from ethanol–water (1:1) to produce 0.72 g. (87%) of a colorless solid melting with effervescence at 119–120°. Spectral and polarimetric data are found in Table I.

Anal. Calcd. for $C_{28}H_{26}N_2O_6$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.00; H, 5.43; N, 5.79.

1-(3′,5′-Di-*O*-trityl-β-D-arabinofuranosyl)uracil (XV). Method A.—To a solution of 10 mg. of XIII in 7 ml. of 70% ethanol was added 1 ml. of *N* sodium hydroxide. The mixture was refluxed for 15 hr. After the removal of the solvent *in vacuo*, the residue was suspended in 8 ml. of water, and the solution was made slightly acidic by the addition of 1 drop of acetic acid. The solid was collected, washed well with water, and dried. Paper chromatography (ascending, S and S No. 597) with solvent A gave two spots, R_f 0.51 and 0.79, representing the di-*O*-trityl-arabinosyl derivative (XV) and starting material (XIII), respectively. The entire product was chromatographed on Whatman paper (3MM) to give a clear-cut separation. The XV-containing strip was eluted with ether. After removal of solvent *in vacuo*, the residue was triturated with water, filtered, and dried. This sample was identical with the material prepared by method B (see below) with respect to ultraviolet and infrared absorption properties and chromatographic behavior in solvent A.

XV. Method B.—A solution of 0.08 g. (0.16 mmole) of XVIII and 0.11 g. (0.39 mmole) of trityl chloride in 2 ml. of pyridine was heated at 90° for 15.5 hr. A few drops of ethanol were added to the mixture. Solvent was removed *in vacuo*, and the residue was triturated with water. After filtration, the solid was dried and triturated well with two 20-ml. portions of hot *n*-heptane. The solid was collected and dried. The colorless amorphous material weighed 0.08 g. (62%). Chromatography (Whatman 3MM paper, solvent A, ascending) of 0.06 g. gave a complete separation of the material into three components characterized as tritylethyl ether (migrating near the front), di-*O*-tritylspongouridine (XV, R_f 0.6–0.8), and mono-*O*-tritylspongouridine (XVIII, R_f 0.2–0.5). The middle strip containing XV was eluted with ether, and the ether was removed *in vacuo*. After trituration with water, the colorless amorphous residue was collected and dried. The product, 0.016 g., m.p. 145–160°, proved identical with a sample obtained by method A. Spectral and polarimetric data are found in Table I.

Anal. Calcd. for $C_{47}H_{40}N_2O_6$: C, 77.45; H, 5 53; N, 3.84. Found: C, 76.60; H, 5.81; N, 3.92.

Detritylation of XV.—A solution of approximately 2 mg. of XV, prepared by method A, and 0.50 ml. of 1 *N* hydrochloric acid in 2 ml. of ethanol was refluxed for 18 min. The resulting solution was taken to dryness and distilled five times with portions of benzene *in vacuo*. The residue was triturated with a little ether,

(29) Since the melting point of IXk varies with the rate of heating,[11] the difference in melting point (12°) found for IXk, prepared by the two different methods (A and B), is not surprising.

and the ether was decanted. This residue was dissolved in 2 drops of water. The ultraviolet absorption spectrum in water (max. at 262.5 mμ, min. at 230 mμ) corresponded to that of a 1-β-D-aldopentofuranosyluracil. Electrophoresis (Whatman 3MM paper, borate buffer, 0.07 *M*, pH 9.2, 800 v., 2.5 hr.) revealed only one spot of high intensity under ultraviolet light. Its anodic migration was 3.5 cm., which corresponded to that of a test sample of 1-β-D-arabinofuranosyluracil (XVI) of anodic migration, 3.5 cm. No absorption was found which corresponded to that of a test sample of 1-β-D-xylofuranosyluracil (anodic migration 13.5 cm.).

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Synthesis of Pyridines from Butadiene and Cyanogen-Like Molecules

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Experiments are described using a series of "cyanogen-like" molecules, *i.e.*, CF_3CF_2CN, $CF_3CF_2CF_2CN$, CF_2ClCN, and $CFCl_2CN$, as the dienophiles for the synthesis of new pyridines from 1,3-butadiene. The gas phase reaction proceeds smoothly at moderately high temperatures (350–450°) and atmospheric pressures. Pyridinic products are formed in very nearly 100% yields based on the nitrile having fluorine as the only substituent.

The formation of 2-perfluoromethylpyridine through the addition of perfluoroacetonitrile and butadiene and the reaction kinetics of this cyclization reaction in the homogeneous gas phase have been reported.[1b,c] As with cyanogen, the addition reaction proceeds[1d] at moderately high temperatures (350–400°) at atmospheric pressures in the homogeneous gas phase. The present work reports the results for experiments with related "cyanogen-like" molecules as dienophiles [*e.g.*, CF_3CF_2CN, $CF_3(CF_2)_2CN$, CF_2ClCN, and $CFCl_2CN$] in this new pyridinic synthesis.

Experimental

Chemicals.—Butadiene, 99.0% purity, b.p. −3.0° (Matheson Co., C.P. grade), was degassed three times (−195°) prior to use. The nitriles, CF_3CN, b.p. −60°; CF_3CF_2CN, b.p. −35°; $CF_3(CF_2)_2CN$, b.p. −5°; CF_2ClCN, b.p. −18.3°; and CCl_2FCN, b.p. 35°, each obtained in 98% purity (Peninsular ChemResearch Inc., Columbia Organic Chemicals Co.), were similarly treated.

Apparatus and Procedure.—The continuous flow assembly, previously described,[1d] was modified to take a large reaction vessel (5 l.). The latter was pretreated with an 8-hr. oxygen "sweep" (100 cc./min.) at 500°, prior to each experiment. The whole assembly was flushed with an inert gas (dry nitrogen, 2 hr., 100 cc./min.) after the oxygen pretreatment and prior to an experiment; on completion of each run a similar nitrogen "chase" was used to recover the materials remaining in the system. Gaseous reactants were monitored by precision Manostat flowmeters (Model No. FM 1043 B). A continuous feed injection assembly was used for liquid reactants (*e.g.*, CCl_2FCN). This consisted of a 50-cc. Perfektum syringe, gear driven at a constant rate (0.16 mole/hr.) through a Borg 3-phase motor (30 r.p.m.) and micrometer screw.

Table I summarizes the experimental conditions, material balances, conversions of reactants per pass, and yields of pyridinic products. Deviation of the over-all material balance (Table I) from 100% is attributed to experimental losses due to transfer steps in the crude product analysis (weighings, low temperature fractionations). The composition of the distillate was quantitatively established by vapor phase chromatography using 550-silicone and di-*n*-decyl phthalate columns. The refractive indices and boiling points for the three new pyridinic products together with the values for 2-perfluoroalkylpyridine are as follows: (1) 2-pentafluoroethylpyridine, $n^{25}D$ 1.3949, b.p. 151°; (2) 2-heptafluoro-*n*-propylpyridine, $n^{25}D$ 1.3814, b.p. 162°; (3) 2-difluoromonochloromethylpyridine, $n^{25}D$ 1.4646, b.p. 162°.

TABLE I

SYNTHESIS OF 2-PERHALOALKYLPYRIDINES

Run conditions	CF_3CN	CF_3CF_2CN	$CF_3CF_2CF_2CN$	CF_2ClCN
Contact time, hr.	0.44	0.46	0.49	0.38
Total time, min.	125	107	120	115
Temperature, °C. (±3°)	400	400	400	400
Butadiene, moles	0.19	0.17	0.19	0.31
RCN, moles	0.24	0.18	0.17	0.19
Material Recovery, wt. %	98	92	92	100
	Conversions per single pass, mole %			
Butadiene	71	54	89	59
RCN	45	33	22	31
	Yields of pyridinic product, mole %			
A[a]	79	62	22	4
B[b]	99	97	97	12

[a] Yield of pyridinic based on converted diene. [b] Yield of pyridinic based on converted nitrile.

The physical constants for 2-methylpyridine ($n^{25}D$ 1.4155, b.p. 143°) agreed with those previously reported.[1b]

Both 3-vinylcyclohexene-1 and styrene were confirmed as by-products but were not quantitatively assessed. An azeotrope (b.p. ~124°) containing 0.32 mole % of 2-trifluoromethylpyridine and 0.68 mole % of 3-vinylcyclohexene-1 was found to be present in the crude resulting from the reaction between CF_3CN and butadiene at 400°. No azeotropes were detected in the experiments with the other nitriles.

The experiments with $CFCl_2CN$ and 1,3-butadiene were less successful than for CF_2ClCN (Table I). The pyrolysis and side reactions were very extensive. While separation of the pyridinic product in trace amounts appeared possible, these experiments were not taken any further.

Results

Confirmation of the pyridinic products was through infrared and mass spectra, n.m.r. analysis, and microelemental combustion analysis for nitrogen. The results were as follows.

Infrared Spectra.—All spectra were gained with a Perkin-Elmer Model 21 double beam recording spectrophotometer having sodium chloride optics. A cell thickness of 0.025 mm. was used.

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