Recrystallization from 1700 ml. of diethyl ether gave 0.39 g. of white solid, m.p. 97–111°, $[\alpha]^{25}D$ +35° (0.25% in water), $\lambda_{max}^{pH\ 1}$ 268 mμ (ε 8840), $\lambda_{max}^{pH\ 7}$ 268 mμ (ε 4900), $\lambda_{max}^{pH\ 13}$ 268 mμ (ε 7260). The material traveled as one component in solvent A with R_{ad} 1.81. In solvent C, it travelled as an elongated spot with R_{ad} 1.29–1.37.

Anal. Calcd. for $C_9H_{11}FN_2O_4S$: C, 41.2; H, 4.23; F, 7.24; N, 10.7; S, 12.2. Found: C, 41.4; H, 4.30; F, 7.53; N, 10.6; S, 12.1.

5'-Thiouridine (III).—A solution of 0.47 g. of 5'-S-acetyl-2',3'-O-isopropylidene-5'-thiouridine (I)[28] in 5 ml. of 1 *N* methanolic hydrogen chloride was heated at 45° for 2.5 hr. then was filtered, and the filtrate was evaporated to dryness *in vacuo* to give a sirup which gave a strong positive nitroprusside test. The sirup was triturated several times with absolute ether to afford 0.366 g. (100%) of an amorphous solid, m.p. 109–111°, $\lambda_{max}^{pH\ 1,\ 7}$ 262 mμ (ε 7320), $\lambda_{max}^{pH\ 13}$ 262 mμ (ε 6500). The ultraviolet spectra at pH 1 and 7 indicated that approximately 25% of III had cyclized to the cyclonucleoside (IVb), whereas the spectrum at pH 13 appeared to be normal. The paper chromatograms showed major spots at R_{ad} 0.19 and 0.91 in solvents A and C, respectively. Both chromatograms showed traces of contaminants.

Anal. Calcd. for $C_9H_{12}N_2O_5S \cdot 0.5\ (C_2H_5)_2O$: C, 44.4; H, 5.76; N, 9.42; S, 10.8; SH, 11.1. Found: C, 44.2; H, 5.40; N, 9.39; S, 10.6; SH, 8.8.

Acknowledgment.—The authors are indebted to Dr. Peter Lim and staff for the paper chromatograms, optical rotations, ultraviolet spectra, iodine titrations, and interpretation of the infrared spectra.

Nucleosides. XVIII. Synthesis of 2'-Fluorothymidine, 2'-Fluorodeoxyuridine, and Other 2'-Halogeno-2'-Deoxy Nucleosides[1,2]

JOHN F. CODINGTON, IRIS L. DOERR, AND JACK J. FOX

The Division of Nucleoprotein Chemistry, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division of Cornell University Medical College, New York 21, New York

Received August 26, 1963

The reaction of 2,2'-anhydro nucleosides with anhydrous hydrogen halides gave 2'-halogeno-2'-deoxy nucleosides in good yields. By this reaction the 2'-fluoro, 2'-chloro, and 2'-bromo analogs of deoxyuridine [VIIa(F), VIIa(Cl), VIIa(Br)] and of thymidine [VIIb(F), VIIb(Cl), VIIb(Br)] were synthesized. The 2'-fluoro analog of 5-fluorodeoxyuridine [VIIc(F)] was prepared. Comparison was made of the stability of the 2'-halogeno-deoxyuridine derivatives in alkali, acid, and upon heating.

The unique role of the substituent (hydrogen or hydroxyl) on the 2'-carbon atom of nucleic acids as the distinguishing feature between deoxyribonucleic acids (DNA) and ribonucleic acids (RNA) prompted an investigation of the biological properties of nucleosides containing substituents other than hydrogen or hydroxyl at this position. Accordingly, the synthesis of 2'-halogeno-2'-deoxypyrimidine nucleosides, as compounds of potential biological interest, was undertaken. Of particular interest were the 2'-fluoro-2'-deoxy nucleosides, 2'-fluorothymidine [VIIb(F)] and 2'-fluorodeoxyuridine [VIIa(F)] (see Scheme I), analogs of thymidine and 2'-deoxyuridine, respectively. It is noteworthy that among the most active known antagonists of nucleic acid biosynthesis are 5-fluorodeoxyuridine[3] and 5-trifluoromethyldeoxyuridine,[4] both possessing fluorine in place of hydrogen in the pyrimidine moiety of naturally occurring deoxy nucleosides. VIIb(F) and VIIa(F), on the other hand, possess fluorine substituted for hydrogen in the sugar moiety of naturally occurring deoxy nucleotides.

The possibility of using 2,2'-anhydro nucleosides as starting materials for the synthesis of 2'-halogeno deoxy nucleosides was investigated.[5] Such an approach was supported by the work of Brown and co-workers.[12] These authors found that 2,2'-anhydro-1-(5'-*O*-acetyl-β-D-arabinofuranosyl)uracil was an intermediate in the synthesis of 5'-*O*-acetyl-2'-iododeoxyuridine in a reaction of the 2'-tosyloxy nucleoside with sodium iodide in acetonylacetone.[13] When the 2,2'-anhydro intermediate was used under the same conditions (sodium iodide in acetonylacetone at 100°) no reaction occurred. As pointed out by Fox and Miller,[14] the successful conversion of the 2'-tosyloxy derivative to its 2'-iodo analog by these workers was probably due to the presence of a small amount of toluenesulfonic acid liberated in the formation of the 2,2'-anhydro intermediate. The acid then served to catalyze the cleavage of the anhydro bridge by iodide ion. Brown, *et al.*,[13] did convert the anhydro nucleoside to the 2'-iodo derivative in small yield only after the addition of a small amount of acetic acid.

(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) Preliminary reports of this work have appeared. See J. F. Codington, I. Doerr, D. Van Praag, A. Bendich, and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 5030 (1961), and J. F. Codington, I. Doerr, L. Kaplan, and J. J. Fox, *Federation Proc.*, **22**, 532 (1963).

(3) R. Duschinsky, E. Pleven, J. Malbica, and C. Heidelberger, Abstracts, 132nd National Meeting of the American Chemical Society, New York, N. Y., 1957, p. 19C; M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *J. Am. Chem. Soc.*, **81**, 4112 (1959); K. U. Hartmann and C. Heidelberger, *J. Biol. Chem.*, **236**, 3006 (1961); S. S. Cohen, J. G. Flaks, H. D. Barner, M. R. Loeb, and J. Lichtenstein, *Proc. Natl. Acad. Sci. U. S.*, **44**, 1004 (1958).

(4) C. Heidelberger, D. Parsons, and D. C. Remy, *J. Am. Chem. Soc.*, **84**, 3597 (1962); C. Heidelberger, H. Gottschling, and G. D. Birnie, *Federation Proc.*, **22**, 532 (1963); W. Szybalski, N. K. Cohn, and C. Heidelberger, *ibid.*, **22**, 532 (1963).

(5) It had been found that the reaction of 2,2'-anhydro pyrimidine nucleosides with aqueous acid,[6-11] as well as aqueous base,[7-9] resulted in attack at C-2 of the pyrimidine with the formation of arabinosyl nucleosides. No study of the reaction of these compounds with anhydrous acid, however, had been made.

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

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

(8) J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959).

(9) N. C. Yung, J. H. Burchenal, R. Fecher, R. Duschinsky, and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 4060 (1961).

(10) J. J. Fox, J. F. Codington, N. C. Yung, L. Kaplan, and J. O. Lampen, *ibid.*, **80**, 5155 (1958).

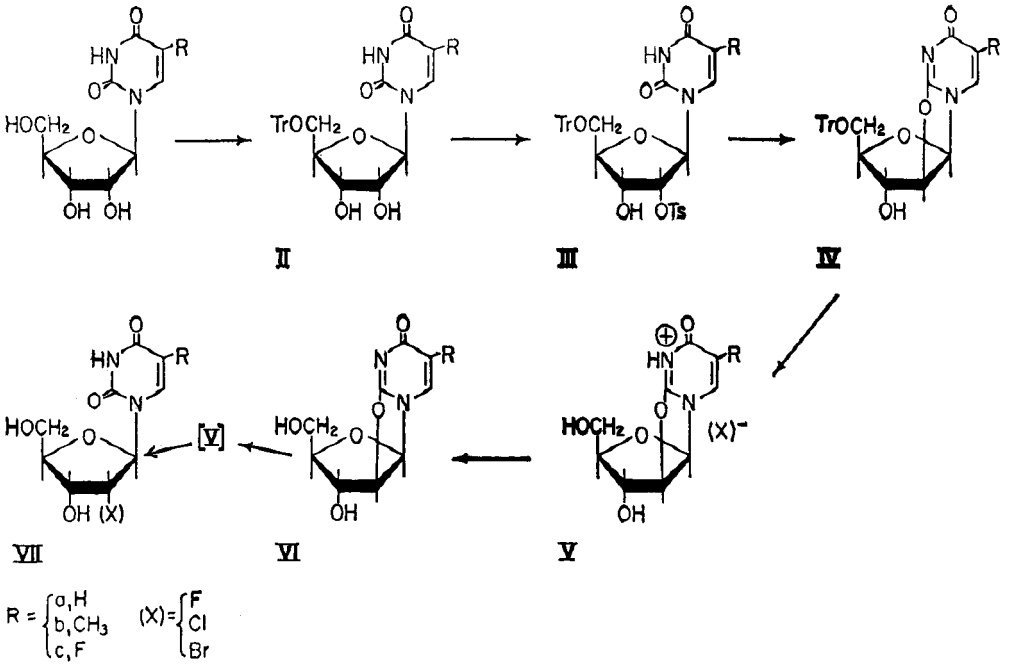
(11) R. Fecher, J. F. Codington, and J. J. Fox, *ibid.*, **83**, 1889 (1961).

(12) D. M. Brown, D. B. Parihar, C. B. Reese, and A. Todd, *J. Chem. Soc.*, 3035 (1958).

(13) D. M. Brown, D. B. Parihar, and A. Todd, *ibid.*, 4242 (1958).

(14) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).

SCHEME I

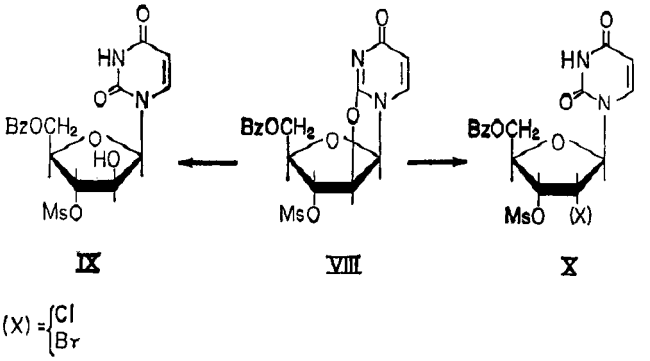


A further development occurred during the course of an investigation in this laboratory of the optimum conditions for cleavage of the anhydro bond of 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinosyl)-uracil (VIII)[7] (see Scheme II). It was found that 7 ml. of 3 *N* aqueous hydrochloric acid in 100 ml. of dioxane solution produced a mixture of the arabinosyl nucleoside (IX) and a second product containing chlorine. This led to the finding that the reaction of anhydrous hydrogen chloride *in ether for seven days* produced a single product, a 2′-chloro-2′-deoxy nucleoside [X(Cl)]. This reaction was extended to the preparation of the 2′-bromo analog [X(Br)] from VIII after prolonged treatment with anhydrous hydrogen bromide in ether. Yields of both X(Cl) and X(Br) were essentially quantitative.

In order to obtain 2′-halogeno analogs of the naturally occurring pyrimidine deoxy nucleosides, these studies were extended to the reaction of hydrogen halides with 2,2′-anhydro nucleosides VIa, VIb, and with their 5-fluoro analog VIc (Scheme I).[15] Synthesis of the 2,2′-anhydro intermediate (VIa) had been described,[6] but a less cumbersome route for its preparation appeared to lie in the reaction sequence I through VI. This procedure had been employed by Yung, *et al.*,[9] for the synthesis of 2,2′-anhydro-1-(β-D-arabinofuranosyl)-5-fluorouracil (VIc). It was adapted with modification to the synthesis of VIa and to VIb. Yields in each step in the three series were excellent, with the exception of the tosylation of the 5′-*O*-trityl nucleosides (II), which produced mixtures of tosylated products and unchanged starting material in each case, in which the 2′-tosyloxy derivatives (III) were present in 40–60% yields.

(15) K. C. Murdock and R. B. Angier [*J. Am. Chem. Soc.*, **84**, 3748 (1962)] prefer zwitterionic structures for pyrimidine anhydro nucleosides on the basis of solubility and dipole moment measurements. Although such dipolar structures aid in an understanding of certain properties of these compounds, they fail to explain the strong carbonyl band in the infrared at 6.02–6.05 μ, which strongly supports a covalent structure (VI). Since the extent to which zwitterionic (or covalent) forms exist has not been determined, 2,2′-anhydro nucleosides are presented in this paper as covalent structures.

SCHEME II



2′-Chloro-2′-deoxyuridine [VIIa(Cl)] was obtained in high yield in a reaction of VIa with hydrogen chloride at 75–80° in dioxane. The 2′-bromo nucleoside [VIIa(Br)] was likewise obtained in good yield. Trifluoroacetic acid was used as a solvent due to the reaction of hydrogen bromide with dioxane. The reaction of hydrogen fluoride in dioxane to yield the desired 2′-fluorodeoxyuridine [VIIa(F)][16] required a stainless steel container and higher temperatures.

In the reaction of hydrogen halides with 2,2′-anhydro-1-(β-D-arabinofuranosyl)thymine (VIb), under similar conditions, 2′-fluoro- [VIIb(F)], 2′-chloro- [VIIb(Cl)], and 2′-bromothymidine [VIIb(Br)] were obtained. The reaction of hydrogen fluoride with VIc in dioxane gave the 2′-fluoro analog of 5-fluoro-2′-deoxyuridine [VIIc(F)].

It is suggested that the reaction of the hydrogen halides with the 2,2′-anhydro nucleosides (VI) involves as a first step the protonation of VI to give V. Compounds V then react further with cleavage of the anhydro bond as a result of nucleophilic attack by halide ion on C-2′. Crystalline hydrochlorides (Va and Vb)

(16) The position of the halogen atom as 2′ and the *ribo* configuration of the halogeno deoxy nucleosides is conclusively established in the next part of this series: J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 564 (1964).

of the 2,2′-anhydro nucleosides (IVa and IVb) were isolated from the detritylation reaction of IV using anhydrous hydrogen chloride in ether. Melting (decomposition) points of the anhydro salts (V) were consistently lower than the neutral compounds (VI). The anhydro nucleoside salts (Va and Vb) can be converted to the corresponding 2′-halogeno deoxy nucleosides merely by heating. These results are consistent with a finding of Murdock and Angier.[17] In a reaction of 2,3′-anhydro-1-(*cis*-3′-hydroxycyclopentyl)thymine with anhydrous hydrogen chloride in chloroform these investigators isolated a crystalline hydrochloride of the anhydro starting material as an intermediate. Heating the original reaction mixture produced the 3′-chloro derivative.

In the reaction of 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinosyl)uracil (VIII, Scheme II) with hydrogen bromide in ether, a crystalline hydrobromide of VIII, melting at 127–130°, was isolated in quantitative yield. When permitted to react further, a 2′-bromo derivative was formed, which, like the corresponding 2′-chloro analog, was obtained analytically pure but only in an amorphous state.

Infrared spectra of the hydrogen halide salts of the anhydro nucleosides show marked differences from the anhydro nucleosides themselves, which is a reflection of expected changes in electron distribution in the pyrimidine moiety. Although the site of protonation remains unknown in compounds V (Scheme I), for convenience the proton is placed on N-3 in conformity with structures previously published.[17] It is clear that Va and Vb can exist in aqueous solution only at very high concentrations of strong acid. Indeed, ultraviolet absorption spectra of aqueous solutions of Va or Vb are identical with those of VIa or VIb, respectively.

As would be expected, the mechanism of 2,2′-anhydro bond cleavage under acid conditions varies greatly with the solvent used. When water-free dioxane is used as solvent and anhydrous hydrogen halides are reacted with the 2,2′-anhydronucleosides (VI), the 2′-halogeno-*ribo*-2′-deoxy nucleosides (VII) result. In this reaction protonation of the 2,2′-anhydro nucleoside presumably precedes nucleophilic attack by chloride ion, as evidenced by isolation of the hydrochloride salts (V). When dioxane was partially replaced by water in the reaction described above (VIII to give IX and X(Cl), Scheme II), 2′-chloro-*ribo*- and 2′-hydroxy-*arabino* derivatives were obtained. In the reaction of 2,2′-anhydroarabinosyluracil (VIa) with aqueous sulfuric acid (2 *N*), only arabinosyluracil resulted.[18] Therefore, in aqueous acid solution, even in the presence of a nucleophile, the hydrolytic reaction (which is a more rapid reaction than the nucleophilic attack on C-2′) takes place.

Fox and Miller[14,19] demonstrated that a weak acid (*e.g.*, benzoic acid) can catalyze the introduction of nucleophiles (*e.g.*, benzoate[14] or thiolbenzoate[19] ions) into the *ribo* configuration of the sugar moiety of 2,3′-anhydro nucleosides derived from thymidine. They postulated that protonation of the conjugated system in the aglycon of the anhydro nucleoside [*i.e.*, in 2,3′-anhydro-1-(5′-*O*-mesyl- or 5′-*O*-trityl-2′-deoxy-β-D-lyxosyl)thymine] by benzoic acid rendered C-3′ of the conjugate acid more susceptible to nucleophilic attack.[20]

As part of the present study, the 2,2′-anhydro nucleoside (VIa) was refluxed with acetic acid for 48 hr.[21] Cleavage of the anhydro bond (which, unlike the examples given above,[14,19] is adjacent to a free 3′-hydroxyl group) occurred with the formation of a chloroform-soluble product. Acid or alkaline hydrolysis of this product gave a mixture of uridine and spongouridine. From the composition of the hydrolysis product a mechanism other than protonation followed by anion attack is suggested in this case. Such a mechanism[22,23] can involve an initial esterification of the 3′-hydroxyl of the anhydro nucleoside (VIa) in the refluxing acid.[24] Attack by the neighboring carbonyl oxygen on C-2′ would cleave the anhydro bond with the formation of a 2′,3′-ortho ester ion intermediate, as postulated by Brown and co-workers.[18] This might be expected to react further to give an ortho ester acetate. Upon hydrolysis (either acidic or basic) this material would be expected to give only uridine. Uridine was in fact present in approximately 85% yield and spongouridine in 15% yield after treatment with either acid or base. The spongouridine was probably formed as a result of hydrolytic cleavage of the anhydro bond at the pyrimidine moiety, resulting from the presence of water (liberated in the esterification reaction). In the acidic hydrolysis of 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinosyl)uracil, Brown, *et al.*,[18] obtained a much higher proportion (57–67%) of spongouridine, possibly due to the greater amount of water present.

The electronegative character of the 2′-halogeno groups is reflected in certain characteristics of the ultraviolet absorption spectra of these deoxy nucleosides. The 2′ substituent is responsible for a slight hypsochromic shift of both the maximum and the minimum. This shift is about the same regardless of which halogen (F, Cl, or Br) is present, and amounts to deviations of 2 mμ in the maximum and 1–2 mμ in the minimum from the corresponding positions of the unsubstituted deoxy nucleosides. Spectral data for the halogeno nucleosides are presented in Table I. Similar hypsochromic shifts have been observed also for compounds containing mesyloxy groups in the sugar moiety.[11] The mechanism by which a 2′-halogeno group (or 2′- or 3′-mesyloxy group) exerts this influence upon the pyrimidine ring remains obscure.

The 2′-fluoro substituent in VIIa(F) appears to exert a weak effect upon the acidic dissociation in the pyrimidine moiety. The pK_a, as determined spectrophoto-

(17) K. C. Murdock and R. B. Angier, *J. Am. Chem. Soc.*, **84**, 3758 (1962).

(18) Murdock and Angier[15] reported a mixture of the 3′-*cis* and 3′-*trans* hydroxy derivatives in a cleavage reaction of a 2,3′-anhydro derivative of cyclopentylthymine using 0.1 *N* sulfuric acid.

(19) J. J. Fox and N. C. Miller, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 4C.

(20) The reaction of 2,3′-anhydro nucleosides took place with sodium benzoate plus benzoic acid in dimethylformamide at reflux temperature.

(21) VIa was refluxed in a similar manner with trifluoroacetic acid for 72 hr. Cleavage of the anhydro bond occurred. Although a mechanism similar to that postulated for cleavage by acetic acid may obtain in this case, the reaction is complicated by the presence in the reaction mixture of some uracil, as well as unacetylated uridine. Hydrolysis (acid or base) of the total product produced uridine (77–82%), spongouridine (11–13%), and uracil (10–15%).

(22) S. Winstein and R. Buckles, *J. Am. Chem. Soc.*, **65**, 613 (1943).

(23) S. Winstein and R. M. Roberts, *ibid.*, **75**, 2297 (1953).

(24) Reflux of uridine with acetic acid under similar conditions resulted in esterification of the free hydroxyl groups of the sugar moiety to give a chloroform-soluble product(s).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA[a] AND POLARIMETRIC VALUES FOR 2′-HALOGENO-2′-DEOXY NUCLEOSIDES

	ϵ_{max}	λ, mμ	ϵ_{min}	λ, mμ	$[\alpha]_D$ (water)
2′-Fluorodeoxyuridine [VIIa(F)]	9780	260	2120	229	+52°
	8570	206			
2′-Chlorodeoxyuridine [VIIa(Cl)]	10,300	260	2660	229	+18°
	9280	205			
2′-Bromodeoxyuridine [VIIa(Br)]	10,400	260	2470	229	+15°
	8870	205			
2′-Fluorothymidine [VIIb(F)]	9150	265	2480	234	+47°
	9100	206			
2′-Chlorothymidine [VIIb(Cl)]	9580	265	2580	233	−3°
	9130	205			
2′-Bromothymidine [VIIb(Br)]	9380	265	2570	233	−4°
	8950	205			
Deoxyuridine[b,c]	10,200	262	2200	231	+30°
Thymidine[b,c]	9650	267	2300	234	+18.5°
	9550	207			

[a] Water was used as a solvent. [b] W. S. MacNutt, *Biochem. J.*, **50**, 389 (1952). [c] J. J. Fox and D. Shugar, *Biochim. Biophys. Acta*, **9**, 369 (1952).

metrically,[25] was found to be 9.14 for 2′-fluorodeoxyuridine, as compared to 9.3 for deoxyuridine. Extinction coefficients of the halogeno deoxy nucleosides (see Table I) are about the same as for thymidine and deoxyuridine, respectively.

It may be noted that $[\alpha]_D$ and ϵ_{max} values for the fluoro derivatives listed in Table I differ markedly from those of their chloro and bromo analogs. Optical rotations for compounds VII(F) are much greater, and extinction coefficients are 3–6% lower. It is interesting to speculate that these "discrepancies" may be due to greater hydrogen-bonding properties of the fluoro substituent.

Stability of the 2′-Halogeno Nucleosides.—Comparison was made of the stability of the 2′-halogenodeoxyuridine analogs [VIIa(F), VIIa(Cl), and VIIa(Br)] in acid, alkali, and upon heating. Results are summarized in Table II. In each type of experiment the fluorodeoxy nucleoside was found to be far the most stable of the three analogs, with the bromo compound the least stable.[26]

The stability of compounds VII when refluxed with 2 *N* sulfuric acid was compared with that of uridine and deoxyuridine. As was expected, uridine remained unchanged after 5 hr. of reflux, but deoxyuridine had reacted completely to give uracil. 2′-Fluorodeoxyuridine was resistant to strong aqueous acid and appeared to be unaffected after 5 hr. The glycosylic bond of the chloro and bromo analogs appeared to be stable under these conditions,[27] but both compounds were converted to spongouridine. A 50% conversion of the chloro nucleoside to arabinosyluracil had occurred within 5 hr. of reflux. The corresponding bromo compound had reacted completely after 4 hr. The mechanism by which VIIa(Cl) and VIIa(Br) are converted to spongouridine in refluxing aqueous acid probably involves the 2,2′-anhydro intermediate (VIa). The anhydro bond was then rapidly cleaved under the strongly acid conditions. There is a precedent for such a reaction taking place in aqueous acid.[29]

When 2′-tosyloxyuridine was allowed to stand in 0.20 *N* sodium hydroxide at room temperature a smooth conversion to spongouridine took place. The reaction

TABLE II

RELATIVE STABILITY OF THE 2′-HALOGENO-2′-DEOXYURIDINES

A. Acid conditions. Samples refluxed in 2 *N* sulfuric acid

Compound	Major product	Time (hr.) for 50% conversion
2′-Fluoro	(No reaction in 5 hr.)	
2′-Chloro	Spongouridine	4–6
2′-Bromo	Spongouridine	1–2
Deoxyuridine	Uracil	1.9–2.1
Uridine	(No reaction in 5 hr.)	

B. Alkaline conditions. Samples in 0.20 *N* sodium hydroxide at 20–25°

Compound	Major product	Time (hr.) for 50% conversion
2′-Fluoro	(No reaction in 46 hr.)	
2′-Chloro	Spongouridine	36–38
2′-Bromo	Spongouridine	1.2–1.7
2′-Tosyloxy	Spongouridine	0.4–0.7

C. Thermal conditions. Samples heated at 210°[a]

Compound	Major product of thermal dec.	Time (sec.) for 20% conversion to uracil
2′-Fluoro	Uracil	220–240
2′-Chloro	Uracil	80–90
2′-Bromo	Uracil	<5
Deoxyuridine	Uracil	100–120
Uridine	(Unchanged after 240 sec.)	

[a] All samples have melted at this temperature. See Experimental section for melting points.

(25) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952); J. J. Fox and D. Shugar, *Bull. soc. chim. Belges*, **61**, 44 (1952).

(26) For a discussion of carbon-halogen bond strengths, see L. Pauling, "The Nature of the Chemical Bond," 3rd Ed., Cornell University Press, Ithaca, N. Y., 1960.

(27) The marked increase in the rates of hydrolysis of methyl glycosides of 2-deoxy sugars when compared to their 2-hydroxy analogs was attributed by Overend, Rees, and Sequeira[28] to the inductive effect of the 2′-hydroxyl group, presumably making more difficult the protonation of the glycosidic oxygen. Since a marked difference exists in the lability of the glycosylic bond of uridine and deoxyuridine in acid, it seems plausible to suggest that a similar phenomenon is operative in the case of the halogeno nucleosides. An electron-withdrawing effect of the halogeno substituent would make protonation at N-1 and subsequent glycosylic cleavage more difficult.

(28) W. G. Overend, C. W. Rees, and J. S. Sequeira, *J. Chem. Soc.*, 3429 (1962).

(29) It was demonstrated[11] that 1-β-D-lyxofuranosyluracils can be synthesized by refluxing 2,2′-anhydro-3′-*O*-mesylarabinosyluracils in water. The mechanism was shown to proceed first by cleavage of the 2,2′-anhydro linkage, followed by attack by the 2-carbonyl on C-3′ to form the 2,3′-anhydrolyxosyl nucleoside, with the liberation of methanesulfonic acid. Anhydro bond formation continued to take place in the acidic solution. The final step involved cleavage of the 2,3′-anhydro bond under the acidic conditions.

was complete in less than 1 hr. The reaction of base with 2′-bromodeoxyuridine was more complicated. Although spongouridine was formed as the major product, the solution became orange, and separation of the reaction mixture using borate buffer at pH 9.3 indicated at least one other compound present, in addition to spongouridine. No VIIa(Br) could be found in the reaction mixture after 3 hr. The reaction of the chloro analog was surprisingly slow under alkaline conditions. After 43 hr. both starting material and spongouridine were isolated from the mixture. Elution from a paper chromatogram [1-butanol–water (86:14)] indicated that the reaction had gone 58% to completion. The major reaction of compounds VII with aqueous base, as with the 2′-tosyloxyuridine,[6] probably involves an initial attack by the 2-carbonyl on C-2′ with the formation of the 2,2′-anhydro nucleoside (VI). The anhydro bond is then rapidly cleaved[7-9] to give the arabinosyl nucleoside.

In a study of thermal stability, uridine was found to be far more stable than deoxyuridine. Deoxyuridine at 210° was found to cleave at the glycosylic bond to give within several minutes a high yield of uracil and an as yet unidentified sugar fragment. Under the same conditions (210° for 4 min.) uridine remained essentially unchanged. There was no gas evolution and almost no color. Although the halogeno nucleosides produce uracil after varying periods of time, the mechanism by which they do so is probably different. Gas is evolved, and considerable color develops. As under acid and alkaline conditions the fluorodeoxy nucleoside is more stable than its chloro or bromo analogs. A quantitative expression of the relative stability of these compounds is found in Table II.

Experimental[30]

5′-*O*-Trityluridine (IIa).—Using a modification of the method of Levene and Tipson,[31] 20.0 g. (0.082 mole) of uridine in 240 ml. of pyridine was treated with 26.0 g. (0.093 mole) of trityl chloride. After stirring overnight, the bright yellow solution was heated for 3 hr. at 100–110°. The mixture was poured into 4 l. of ice–water; the gummy precipitate was separated and triturated well with water. Moisture was removed by repeated distillation with ethanol *in vacuo*. Crystallization of the amorphous solid was effected from about 200 ml. of ethanol yielding colorless crystals, 28 g. (70%), m.p. 198–201°, lit.[31] m.p. 200°. Ultraviolet absorption data showed λ_{max} 262 mμ, λ_{min} 243 mμ, ratio 230/260 mμ 1.04.

1-(5′-*O*-Trityl-β-D-ribofuranosyl)thymine (IIb).—The procedure of Fox, Yung, and Bendich[32] was used with modifications. After the addition of 4.7 g. (0.017 mole) of trityl chloride to a solution of 4.0 g. (0.0155 mole) of 1-β-D-ribofuranosylthymine (Ib) in 70 ml. of pyridine, the mixture was allowed to stand overnight, then heated for 3 hr. at 70–80°. After the addition of a few milliliters of water to the reaction mixture and subsequent addition to a large quantity of ice–water, the gummy precipitate was dissolved in chloroform and the solution was dried. The addition of petroleum ether (b.p. 30–60°, 60 ml.) to the chloroform solution (60 ml.) produced a colorless amorphous solid, m.p. 154–158°, 85% yield. The absence of di-*O*-trityl nucleoside was indicated by paper chromatography using solvent A (see below). This material was used without further purification for the preparation of IIIb.

Preparation of Chromatographic Solvent A.—The upper layer (340 ml.) from a mixture of 400 ml. of *n*-heptane and 200 ml. of methanol was added to 108 ml. of *n*-heptane and 208 ml. of ethyl acetate.

2′-*O*-Tosyl-5′-*O*-trityluridine (IIIa).—To a solution of 10.0 g. (0.0206 mole) of IIa in 55 ml. of pyridine at 0° was added with stirring 3.5 g. (0.018 mole) of tosyl chloride. After 1 hr. at 0° the mixture was maintained at 10–15° for 20 hr. Two milliliters of water was added. The solution was allowed to stand for 1 hr., then was poured into 2 l. of ice–water with stirring. A pale pink granular solid was collected, washed with water, and taken up in chloroform. The chloroform solution was extracted with water and dried. Solvent was removed *in vacuo*, leaving an amber colored sirup. Crystallization from 200 ml. of ethanol occurred slowly. Yields of 4.0 to 5.3 g. (30–40%) of colorless crystals, m.p. 174–175°, were obtained. Ultraviolet absorption data in ethanol showed λ_{max} 262 mμ, λ_{min} 246 mμ, shoulder at 220–235 mμ, ratio max./min. 2.46. As crystallization of IIIa was difficult, it was found advantageous to use the crude sirup (40–60% yield) in the preparation of IVa.

Anal. Calcd. for $C_{35}H_{32}N_2O_9S$: C, 65.61; H, 5.03; N, 4.37; S, 5.00. Found: C, 65.75; H, 5.29; N, 4.32; S, 4.88.

1-(2′-*O*-Tosyl-5′-*O*-trityl-β-D-ribofuranosyl)thymine (IIIb).—The reaction of IIb with tosyl chloride in pyridine proceeded in the same manner as that described above in the preparation of IIIa. Since crystallization of IIIb was difficult, as was the case with IIIa, the crude sirup was used directly in the preparation of IVb. Yields of IIIb, based upon the amount of IVb formed, ranged from 50 to 60%.

2,2′-Anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil (IVa).—A solution of 11.3 g. (0.078 mole) of sodium benzoate in 140 g. of molten anhydrous acetamide was poured into a flask containing IIIa as a crude sirup obtained from the tosylation of 10 g. of IIa. The solution was heated at 90–100° for 1 hr., then poured into 1.5 l. of ice–water, while stirring. The off-white amorphous solid was collected on the filter and washed with water. It was suspended while still slightly wet in 200 ml. of chloroform. Upon refrigeration for 1 hr., a colorless crystalline solid separated which was collected and dried. The yield of IVa, m.p. 204–214°, was 55% based upon IIa. Crystallization from ethanol gave micaceous plates, m.p. 210–214° (shrinks at 204°), $[\alpha]^{26}D$ −19° (*c* 0.9, methanol). Ultraviolet absorption data in ethanol showed shoulder at 245–252, small shoulder at 220 mμ, ratio 230/260 mμ 2.97.

Anal. Calcd. for $C_{28}H_{24}N_2O_5$: C, 71.77; H, 5.16; N, 5.98. Found: C, 71.32; H, 5.12; N, 6.42.

2,2′-Anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)thymine (IVb).—The same procedure as that described above for the preparation of IVa was utilized in the synthesis of IVb. Colorless crystals, m.p. 220–230°, were isolated in 61% yield. Crystallization from ethanol gave colorless micaceous plates, m.p. 230–232°. Ultraviolet absorption data in ethanol showed shoulder at 245–254 mμ, small shoulder at 225 mμ, ratio 230/260 mμ 2.13.

Anal. Calcd. for $C_{29}H_{26}N_2O_5$: C, 72.17; H, 5.43; N, 5.81. Found: C, 71.63; H, 5.27; N, 6.07.

2,2′-Anhydro-1-β-D-arabinofuranosyluracil (VIa).—Seven grams (0.015 mole) of IVa was suspended in 200 ml. of anhydrous ether at 0°. A stream of anhydrous hydrogen chloride was passed through the suspension for about 10 min. During this period the crystalline form changed. The flask was sealed and refrigerated at 0° for 1 hr. A yellow solid was collected on the filter, washed with ether, and dried *in vacuo*. A theoretical yield of the hydrochloride (Va), m.p. 167° dec., was obtained. Va was added to a suspension of Dowex 1 (acetate) in 20 ml. of water. After filtration the chloride-free filtrate was taken to dryness *in vacuo*. Crystallization from 95% ethanol gave 2.92 g. (86%) colorless prisms, m.p. 238–240°, $[\alpha]^{27}D$ −20° (*c* 0.4, water), identical with an authentic sample.[6]

2,2′-Anhydro-1-β-D-arabinofuranosylthymine (VIb).—The preparation of VIb followed the same procedure as followed for VIa. From 3.0 g. (2.0 mmoles) of IVb in 75 ml. of anhydrous ether treated with hydrogen chloride at 0°, a theoretical yield of the anhydro hydrochloride (Vb) was obtained, m.p. 168–172° dec. After treatment with Dowex 1 (acetate) and removal of solvent *in vacuo*, VIb was crystallized from ethanol. A yield of 1.04 g. (70%), m.p. 227–228°, $[\alpha]^{24}D$ −37° (*c* 1.4, water), of colorless prisms was obtained. Ultraviolet absorption in water showed max. at 254 and 224 mμ, ϵ_{max} 7080 and 5000, respectively; min. at 232.5 and 216 mμ, ϵ_{min} 4550 and 4470, respectively.

(30) Melting points are corrected. Elemental analyses were made by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Ultraviolet absorption data were obtained using the Cary recording spectrophotometer, Model 15, and the Beckman spectrophotometer, Model DU.

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

(32) J. J. Fox, N. Yung, and A. Bendich, *J. Am. Chem. Soc.*, **79**, 2775 (1957).

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.00; N, 11.68. Found: C, 50.22; H, 4.51; N, 11.80.

2′-Fluoro-2′-deoxyuridine [VIIa(F)].—To a suspension of 1.0 g. (4.4 mmoles) of VIa in 130 ml. of anhydrous dioxane in a stainless steel container was added cautiously 10–12 ml. of liquid hydrogen fluoride. The addition produces a vigorous reaction. The reaction mixture was closed and heated at 115–120° for 18 hr. After cooling, the clear yellow solution was poured into a Teflon container and diluted with 30 ml. of water. Neutralization with solid calcium carbonate, followed by filtration, removed nearly all inorganic fluorine. The solvent was removed *in vacuo*, the residue was taken up in water and treated with activated charcoal (Darco). After filtration and removal of water *in vacuo;* the oil residue was dried well *in vacuo*. The crude material was purified using a Celite (90 g.) column, as previously described.[10,33] As a solvent system, ethyl acetate–methanol–water–*n*-heptane (ratio of 10:6:5:3) was used. The desired halogeno nucleoside was contained in the 650–900-ml. fraction of effluent. After removal of solvent *in vacuo*, the residue was dissolved in 2 ml. of warm ethanol and allowed to stand at room temperature. Colorless elongated platelets, m.p. 148–150° (41–46%), were collected. Crystallization from ethanol gave crystals melting at 150–151°, $[\alpha]^{20}D$ +52° (*c* 0.3, water).

Anal. Calcd. for $C_9H_{11}FN_2O_5$: C, 43.90; H, 4.50; F, 7.72; N, 11.38. Found: C, 44.11; H, 4.73; F, 8.02; N, 11.95.

2′-Chloro-2′-deoxyuridine [VIIa(Cl)].—A suspension of 0.86 g. (3.8 mmoles) of VIa in 70 ml. of dry dioxane in a 125-ml. glass cylinder was saturated at 0° with anhydrous hydrogen chloride. The mixture was heated in a stainless steel container at 75–80° for 18 hr. After cooling, the container was opened and the yellow solution was taken to dryness *in vacuo*. To the residual sirup was added dry benzene, which was then evaporated *in vacuo*. The procedure of adding, then distilling benzene was repeated several times. Crystallization of the residue from ethanol gave 0.90 g. (89%) of colorless crystals. Recrystallization from ethanol gave platelets, 0.71 g., m.p. 207–212° dec., $[\alpha]^{26}D$ +18° (*c* 1.5, water). Va, the hydrochloride of VIa, can be used equally well. Ultraviolet absorption data are found in Table I.

Anal. Calcd. for $C_9H_{11}ClN_2O_5$: C, 41.15; H, 4.21; Cl, 13.50; N, 10.66. Found: C, 41.34; H, 4.46; Cl, 13.50; N, 10.42.

2′-Bromo-2′-deoxyuridine [VIIa(Br)].—A mixture of 0.50 g. (2.2 mmoles) of VIa and 15 ml. of trifluoroacetic acid, which had been saturated with dry hydrogen bromide at 0°, was sealed in a flask securely, then stirred for 4 days at 20–25°. The mixture was concentrated to dryness *in vacuo*, leaving a sirup. This was triturated thoroughly with petroleum ether. Crystallization of the sirup from ethanol–petroleum ether gave 0.56 g. (82%) of colorless crystals.

Recrystallization from water produced colorless plates, m.p. 186–190°, $[\alpha]^{26}D$ +15° (*c* 0.6, water). Ultraviolet absorption data are found in Table I.

Anal. Calcd. for $C_9H_{11}BrN_2O_5$: C, 35.19; H, 3.59; Br, 26.02; N, 9.12. Found: C, 35.28; H, 3.47; Br, 26.68; N, 9.45.

2′-Fluorothymidine [VIIb(F)].—A mixture of 1.02 g. (4.25 mmoles) of VIb and 125 ml. of dioxane (distilled over potassium hydroxide pellets) was placed in a stainless steel container. To this was added cautiously 10 ml. of anhydrous liquid hydrogen fluoride. The vessel was closed and heated, as described above for VIIa(F). The amber-colored solution was removed, neutralized with calcium carbonate after the addition of water, and filtered. The solution was taken to dryness *in vacuo;* the residue was dissolved in dilute ethanol and warmed with activated charcoal (Darco). After filtration, the solvent was removed *in vacuo*, the residue was dried, then dissolved in 4 ml. of ethanol. After crystallization occurred, 0.50 g. of colorless solid was obtained, m.p. 169–174°. Crystallization from ethanol gave some 1-β-D-arabinofuranosylthymine, m.p. 224–237°, as a contaminant. From the mother liquors 0.21 g. (19%) of colorless platelets, m.p. 183–185°, was obtained. Crystallization from ethanol produced crystals melting at 185–188°, $[\alpha]^{24}D$ +47° (*c* 0.2, water). Ultraviolet absorption data are found in Table I.

Anal. Calcd. for $C_{10}H_{13}FN_2O_5$: C, 46.16; H, 5.03; F, 7.30; N, 10.77. Found: C, 46.26; H, 5.02; F, 7.38; N, 10.48.

2′-Chlorothymidine [VIIb(Cl)].—A suspension of 0.70 g. (2.9 mmoles) of VIb in 50 ml. of dioxane (distilled over potassium hydroxide pellets) was saturated with anhydrous hydrogen chloride at 0°, sealed in a stainless steel container, and heated at 80–85° for 34 hr. The procedure followed that used in the preparation of VIIa(Cl). The resulting sirup was crystallized from ethanol giving 0.70 g. (87%) of colorless platelets, m.p. 198–200°, $[\alpha]^{24}D$ −3° (*c* 1.5, water). Ultraviolet absorption data are presented in Table I.

Anal. Calcd. for $C_{10}H_{13}ClN_2O_5$: C, 43.44; H, 4.74; Cl, 12.82; N, 10.13. Found: C, 43.37; H, 4.76; Cl, 12.75; N, 10.01.

2′-Bromothymidine [VIIb(Br)]. Method A.—A mixture of 0.43 g. (1.8 mmoles) of VIb in 10–15 ml. of trifluoroacetic acid which had been saturated with dry hydrogen bromide at 0° was heated in a stainless steel container at 33–37° for 48 hr. The orange solution was reduced in volume *in vacuo*, leaving a sirup. This was triturated well with petroleum ether, the petroleum ether was removed, and the residue was crystallized from ethanol to which a small amount of petroleum ether had been added. The yield of small colorless needles, m.p. 186–189° dec., $[\alpha]^{23}D$ −4° (*c* 0.6, water), was 0.23 g. (40%). Ultraviolet absorption data are found in Table I.

Anal. Calcd. for $C_{10}H_{13}BrN_2O_5$: C, 37.40; H, 4.08; Br, 24.88; N, 8.72. Found: C, 37.42; H, 4.47; Br, 25.08; N, 8.82.

2,2′-Anhydro-1-β-D-arabinofuranosylthymine Hydrobromide [Vb(Br)].—Anhydrous hydrogen bromide was passed into a suspension of 0.50 g. (1.05 mmoles) of IVb in 60 ml. of anhydrous ether at 0°. The color of the suspended solid changed from colorless to yellow. The mixture was cooled at 0° for 30 min.; the solid was collected on the filter and washed thoroughly with ether. After drying *in vacuo* the crystalline solid, m.p. 167–170°, weighed 0.37 g. (96%). The material was converted directly (25%) into VIIb(Br) by heating in dioxane at 75° for 20 hr.

2′-Fluoro-2′-deoxy-5-fluorouridine [VIIc(F)].—Anhydrous hydrogen fluoride (8 ml.) was added cautiously to a suspension of 1.0 g. (4.1 mmoles) of 2,2′-anhydro-1-β-D-arabinofuranosyl-5-fluorouracil (VIc) in 120 ml. of dioxane (distilled over potassium hydroxide pellets). The mixture was heated in a stainless steel container for 16 hr. at 95–100°. After the addition of 30 ml. of water to the solution and neutralization with calcium carbonate, as described above for VIIa(F), the product was examined spectrophotometrically. As it was found to contain considerable unchanged VIc, the material was dried and again heated with anhydrous hydrogen fluoride in dioxane for 22 hr. at 110–120°. After neutralization and treatment with charcoal, as described for VIIa(F), the resulting sirup was dried and separated on a Celite column[33,10] using the system, ethyl acetate–methanol–water–*n*-heptane (7.3:5:4:4).[34] Using a column of 70 g. of Celite, VIIc(F) was contained in the 900–1400-ml. fraction of effluent. The solvent from this fraction was removed *in vacuo* to leave a colorless gum. From ether–petroleum ether trituration, 0.21 g. of colorless solid was obtained. Crystallization was effected upon letting a concentrated 1-butanol solution stand at room temperature. Colorless needles, m.p. 134–136°, were obtained. Ultraviolet absorption data showed max. at 267, 204 mμ; min. at 232 mμ; ratio 267/232 mμ 4.74; ratio 267/204 mμ 0.98.

Anal. Calcd. for $C_9H_{10}F_2N_2O_5$: C, 40.91; H, 3.82; F, 14.38; N, 10.61. Found: C, 40.83; H, 4.07; F, 14.22; N, 10.35.

2,2′-Anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinosyl)-uracil hydrobromide [VIII(HBr)].—A suspension of 1.70 g. (4.2 mmoles) of VIII in 200 ml. of anhydrous ether was saturated with hydrogen bromide at 0°. An additional 100 ml. of ether was added, and the mixture was stirred at 20–25°. Within a short time a change in crystalline structure was noted. Stirring was continued for 17 hr. The crystalline solid was filtered and washed well on the filter with ether. The colorless needles, 2.01 g. (98%), melted at 127–130°. The product was insoluble in water, ethanol, and chloroform.

Anal. Calcd. for $C_{17}H_{17}BrH_2O_8S$: C, 41.73; H, 3.50; Br, 16.33; N, 5.72; S, 6.55. Found: C, 41.67; H, 3.71; Br, 16.20; N, 5.60; S, 6.78.

5′-*O*-Benzoyl-2′-bromo-2′-deoxy-3′-*O*-mesyluridine [X(Br)].—Anhydrous hydrogen bromide was passed into a suspension of 1.0 g. (2.45 mmoles) of VIII in 250 ml. of dry ether at 0–5° until near saturation. The flask was sealed, and the mixture was stirred at 20–25° for 70 hr. The reaction mixture, consisting of two layers

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

(34) In a preliminary experiment it was found that if the system employed successfully for VIIa(F) were used, VIIc(F) was contained, with contaminants, in the effluent from a 76-g. Celite column in the 200–315-ml. fraction.

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.

Acknowledgment.—The authors wish to thank Mrs. Dina Van Praag for valuable contributions to this work. They would like to express their appreciation to Dr. Aaron Bendich and to Dr. George B. Brown for helpful discussions and continued interest.

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

JOHN F. CODINGTON, IRIS L. DOERR, AND JACK J. FOX

The Division of Nucleoprotein Chemistry, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division of Cornell University Medical College, New York 21, New York

Received August 26, 1963

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).