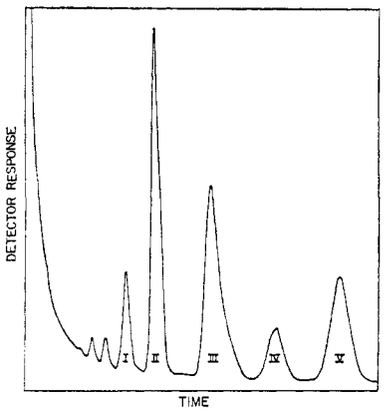

Figure 4.—Gas–liquid partition chromatography on column A of the trimethylsilyl derivative of the sodium borohydride reduced products from the alkaline treatment of 6.

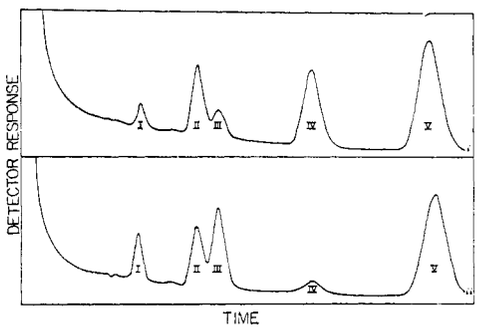

Figure 5.—Gas–liquid partition chromatography on column B of the trimethylsilyl derivative of alkali-treated 6 which had been (*i*) reduced with sodium borohydride and (*ii*) reduced with hydrogen in the presence of platinum oxide.

Cochromatography with authentic samples of *neo*-inositol, *cis*-inositol, and *epi*-inositol clearly showed that none of these three inositols was present in either mixture. The material giving rise to peaks I–III in Figure 5, chromatogram *ii*, was separated on a preparative scale using column B, equipped with a stream splitter. The homogeneity of each of the three fractions was confirmed by rechromatography on columns A and B. The material from peak III had the same retention time as the TMS derivative of DL-*chiro*-inositol; after hydrolysis and acetylation, it was chromatographed on column C at 180° and found to migrate as a single compound with the retention time of authentic DL-*chiro*-inositol hexaacetate. In column B the component from peak II had a retention time which was indistinguishable from that of the TMS derivatives of iditol, mannitol, and glucitol; in column A, however, the component from peak II shows a retention time which sharply differentiates it from these three hexitols. It is unlikely, therefore, that the minor peaks of short retention time in Figure 3 represent D-*xylo*-hexos-5-ulose. The identity of the material represented by peaks I and II remains unknown.

The identification of peaks III–V in Figure 5 is supported by further considerations. The catalytic reduction of inososes in neutral solution and in the presence of platinum oxide leads largely to the formation of axial hydroxyl groups while reduction with sodium borohydride gives a mixture of the epimeric axial and equatorial products.[30] This generalization is reflected in features of Figure 5, the ratio of *scyllo*-inositol to *myo*-inositol being much lower in the catalytic reduction (chromatogram *ii*) than when sodium borohydride was used (chromatogram *i*). Similarly, the ratio of DL-*chiro*-inositol to *myo*-inositol is larger when the mixture is reduced catalytically (chromatogram *ii*) than when sodium borohydride is used (chromatogram *i*); these are the results to be expected in the reduction of 9 and 10.

Registry No.—**2**, 19684-32-3; **3**, 19684-22-1; **7**, 488-59-5; **8**, 87-89-8.

Acknowledgments.—We are indebted to the staff of the Section on Microanalytical Services and Instrumentation of this institute for elemental analyses and spectra and to Dr. Alexander J. Fatiadi of the National Bureau of Standards for an authentic sample of 6.

(30) Th. Posternak, "The Cyclitols," Hermann, Paris, 1965, p 157.

Nucleosides. LVIII. Transformations of Pyrimidine Nucleosides in Alkaline Media. III.[1] The Conversion of 5-Halogenouridines into Imidazoline and Barbituric Acid Nucleosides[2,3]

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Reaction of 2′,3′-*O*-isopropylidene-5-bromouridine (**3b**) with alkoxide affords 5′,6-anhydro-2′,3′-*O*-isopropylidene-6-hydroxyuridine (**15**) which is converted by acid hydrolysis into 1-β-D-ribofuranosylbarbituric acid ("6-hydroxyuridine") (**18**) in high over-all yield. Treatment of **15** with NaOBz–DMF gives the 5′-*O*-benzoate of isopropylidene-6-hydroxyuridine (**19**). In aqueous alkali, 2′,3′-*O*-isopropylidene-5-fluorouridine (**3a**) is converted into 1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid (**20**) which, after acid hydrolysis, gives the unblocked imidazoline ribo nucleoside (**2**) in good over-all yield. A total synthesis of **2** *via* condensation of methyl 2-oxo-4-imidazoline-4-carboxylate with tri-*O*-benzoyl-D-ribofuranosyl chloride is given. Unlike the 5-fluoro derivative (**3a**), the 5-bromo (**3b**) and the 5-iodo (**3c**) analogs in aqueous alkali give poor yields of **20** along with other 2′,3′-*O*-isopropylidenated products, namely, 5′,6-anhydro nucleoside (**15**), uridine (**12**), 5-hydroxyuridine (**17**), and barbituric acid ribo nucleoside (**13**). It is shown that the conversion of nucleosides **3** into **12**, **17**, and **20** involves anchimeric assistance by the 5-hydroxyl group of the sugar moiety and, further, that the presence of a 2′,3′-*O*-isopropylidene group promotes this participation. Evidence obtained from a study of the 5′-deoxy analog (**9b**) of **3b** suggests that the formation of **13** from **3b** or **3c** occurs mainly by direct attack by hydroxide ion on C-6 and to a lesser extent by solvolysis of **15**.

Recent investigations in this laboratory have shown that 5-halogenated 1-β-D-arabinofuranosyluracils are converted in alkaline media into 2′,6-anhydro-6-hydroxyuracil- and 2-oxo-4-imidazoline-4-carboxylic acid

(1) For the previous paper in this series, see R. J. Cushley, S. R. Lipsky, and J. J. Fox, *Tetrahedron Lett.*, 5393 (1968).

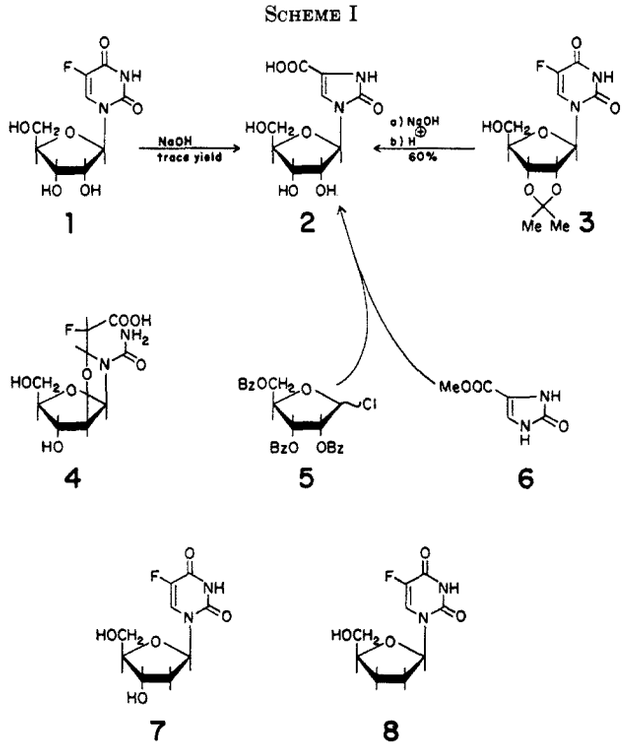
(2) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08478).

(3) A preliminary account of part of this work has been published: B. A. Otter, E. A. Falco, and J. J. Fox, *ibid.*, 2967 (1968).

nucleosides.[4] These reactions proceed *via* dihydropyrimidine intermediates formed as a result of nucleophilic attack of the 2'-hydroxyl group on C-6 of the pyrimidine ring. As an extension of this work we have examined the properties of some 5-halogenated 1-β-D-ribofuranosyluracils in alkaline media. The aim of this study was to determine whether the possible formation of 5',6-anhydrodihydropyrimidine intermediates would lead to rearrangements similar to those observed in the arabinofuranosyl series.

Previous studies[5] had shown that 5-fluorouridine (**1**) is stable is aqueous sodium hydroxide under conditions where the arabinosyl analog of **1** is completely converted into the 2',6-anhydro acyclic ureide **4**. We have since found that **1** is relatively stable under conditions where the ureide **4** is converted into an arabinosylimidazoline nucleoside. Thus, treatment of **1** with 1 *N* sodium hydroxide at 55° for 16 hr resulted in only ~15% decrease in the uv absorption peak at 268 mμ. Electrophoresis of the reaction mixture revealed the presence of starting material (**1**) and a trace of a uv-absorbing product which was identified as the imidazoline nucleoside **2** (Scheme I). These results indicate that the

SCHEME I



conversion of **1** into a 5',6-anhydro acyclic ureide (analogous to **4**) proceeds only to a minor extent. However, for reasons to be discussed later, it was expected that formation of 5',6-anhydro intermediates would proceed more easily from 2',3'-*O*-isopropylidene-5-fluorouridine (**3**). When **3** was treated with 1 *N* sodium hydroxide at 55° the initial absorption peak at 268 mμ decreased by 50% over a 40-min period. This rapid decrease was followed by the much slower appearance (~14 hr) of a new peak at 252 mμ. After acidic hydrolysis of the isopropylidene group, a 60% yield of 1-β-D-ribofuranosyl-2-oxo-4-imidazoline-4-carboxylic acid (**2**) was obtained. The structure of **2** was established by the similarity of the uv and nmr spectral characteristics to those previously reported[4b] for the corresponding arabinofuranosyl compound, and by total synthesis. Condensation of tri-*O*-benzoyl-α,β-D-ribofuranosyl chloride (**5**) with methyl 2-oxo-4-imidazoline-4-carboxylate (**6**), according to the mercuric cyanide–nitromethane procedure of Yamaoka, *et al.*,[6] afforded crude material from which a 20% yield of **2** was obtained after base-catalyzed removal of the protecting groups.

The proposed intermediates in the ring contraction of **3** are shown in Scheme II. Formation of the ureide **16a**, *via* the 5',6-anhydro intermediates **10a** and **11a**, occurs rapidly as shown by the initial loss of the uv absorption of **3**. Ring closure of **16a** to imidazoline **20** (λ_{max} 252 mμ) could then proceed by nucleophilic displacement of the 5-fluoro atom by the amide nitrogen (possibly with participation of the neighboring carboxyl group), followed by elimination of the sugar alcohol as previously suggested[4] for the *arabino* analog **2**.

The premise that 5',6-anhydro bond formation would be promoted by the presence of a 2',3'-*O*-isopropylidene group was based on our own work in another area[7] and on some previous reports on the properties of 5'-thiouridines. Thus 2',3'-*O*-isopropylidene-5'-thiouridine[10a,b] is completely converted at pH 3–7 into a 5',6 cyclic sulfide whereas, under similar conditions, a solution of 5'-thiouridine[10c] itself contained only 20% corresponding cyclic sulfide. To explain this difference it was suggested[10c] that the isopropylidene ring "forces the furanose ring into a conformation that favors the proximity of the thiol group to the uracil double bond." More recently, 5',6-anhydro nucleosides have been implicated in the base-catalyzed, deuterium exchange of H-5 in uracil nucleosides. Moreover, in both aqueous[1] and nonaqueous[11] base, the exchange reaction of isopropylideneuridine proceeds at a much faster rate than that of uridine itself, again indicating the ready formation of the 5',6-anhydro intermediate from the isopropylidenated compound. These observations were again rationalized on conformational grounds.

The striking difference observed in the reactivity of 5-fluorouridine (**1**) and its isopropylidene ketal (**3**) in aqueous base may also be due to conformational fac-

(4) (a) B. A. Otter and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 3663 (1967); (b) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **33**, 3593 (1968).

(5) J. J. Fox, N. C. Miller, and R. J. Cushley, *Tetrahedron Lett.*, 4927 (1966).

(6) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965).

(7) An indication that a 2',3'-*O*-isopropylidene group facilitated interaction between the 5' position and the aglycon of uridine derivatives came from some work on the reactions of 5'-iodouridines with silver salts. Treatment of 2',3'-di-*O*-acetyl-5'-deoxy-5'-iodouridine (i) with silver fluoride in pyridine affords the corresponding 4',5'-unsaturated nucleoside in high yield.[8] When 5'-deoxy-5'-iodo-2',3'-*O*-isopropylideneuridine (ii) was treated with AgF in pyridine, the major product was 5'-deoxy-5'-fluoro-2',3'-*O*-isopropylideneuridine (iii).[9] The same product (iii) was formed in high yield when 2,5'-anhydro-2',3'-*O*-isopropylideneuridine was treated with AgF in pyridine. It therefore appears that the isopropylidenated compound (ii), unlike the diacetate (i), reacts preferentially to give the anhydro nucleoside which is then converted into the 5'-fluoro nucleoside (iii).

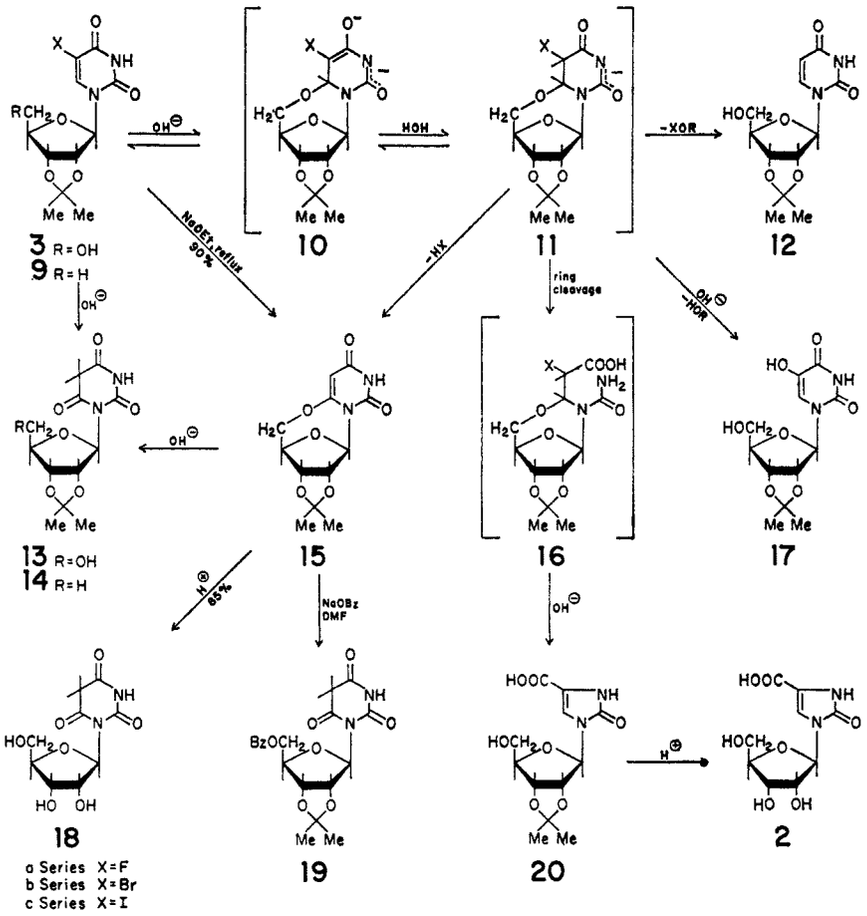
(8) J. P. H. Verheyden and J. G. Moffat, *J. Amer. Chem. Soc.*, **88**, 5684 (1966).

(9) B. A. Otter and J. J. Fox, unpublished results.

(10) (a) B. Bannister and F. Kagan, *J. Amer. Chem. Soc.*, **82**, 3363 (1960); (b) R. W. Chambers and V. Kurkov, *ibid.*, **85**, 2160 (1963); (c) E. J. Reist, A. Benitez, and L. Goodman, *J. Org. Chem.*, **29**, 554 (1964).

(11) D. V. Santi and C. F. Brewer, *J. Amer. Chem. Soc.*, **90**, 6236 (1968).

SCHEME II



tors.[12] Furanose rings can exist in a large number of conformations; for the maximally puckered envelope and twist conformations a total of 20 modes is possible. That compounds **1** and **3** occupy different parts of this conformational cycle is shown by the different H-1′,2′ coupling constants (4.0 and 2.5 Hz, respectively) observed in the nmr spectra determined in D_2O at 55°. It is therefore possible that the conformational population of **3** contains a much larger percentage of conformers in which the 5′-hydroxyl group can participate in the reversible saturation of the 5,6 double bond. It should be pointed out, however, that examples of 5′,6-anhydro bond formation in ribo nucleosides lacking an isopropylidene group are known. Lipkin[15a] has reported (in abstract) that treatment of 5-iodouridine under "alkaline conditions" affords 5′,6-anhydro-6-hydroxyuridine. Similarly, 5-azauridine was found to exist in neutral solution and the solid state as the 5′,6-anhydro derivative.[15b] In neither of these cases was the behavior of the corresponding isopropylidenated compound examined. On the basis of the present work it would be expected that the presence of an isopropylidene group in such compounds would facilitate the formation of the 5′,6-anhydro linkage.

It is probable that the 5-fluoropyrimidines (**1**, **3**, **7**, and **8**) undergo a reversible hydration of the 5,6 double bond initiated by attack of hydroxide ion on C-6. However, products arising from the 5-fluoro-6-hydroxy-5,6-dihydropyrimidine intermediates were not observed. Lozeron and coworkers[16] have shown that 5-fluoro-6-hydroxy-5,6-dihydrouracil is unstable in alkali, the initial products being urea and fluoromalonaldehydic acid. Similar decomposition may account for some of the decrease in uv absorption observed when **1**, **7**, and **8** were heated in alkali. As will be shown later, the reactions of isopropylidene-5-iodo- and -5-bromouridine (**3c** and **3b**) do involve attack of hydroxide ion on C-6. This intermolecular attack is competitive with the intra-

(12) Other factors to be considered are the relative acidities of the participating 5′-hydroxyl groups and the relative orientations of the 5,6 double bond with the 5′-hydroxyl group. Since ionization of the sugar moiety of **1** would occur first at the 2′ position,[13] there may be a small acid weakening effect on the 5′-hydroxyl group. Ionization of the 5′-hydroxyl group—and hence the attack on C-6[14]—would therefore take place less readily in **1** than in **3**. Further, repulsion between the ionized aglycon and the 5′-hydroxyl anion of **3** would restrict rotation about the glycosyl bond and favor a rotamer population in which the 5,6 double bond and the 5′-hydroxyl anion were in a favorable *endo* orientation. In **1**, however, the combined repulsion between the ionized aglycon and the 2′- and 5′-hydroxyl anions may lead to a rotamer population different from that of **3**. The attack of the 5′-hydroxyl anion on C-6 of **1** may therefore be less favorable or lead to the more unstable of the two possible C-6 diastereoisomers. To test the importance of the above factors, 2′-deoxy-5-fluorouridine (**7**) and 1-(2,3-dideoxy-β-D-glycero-pentofuranosyl)-5-fluorouracil (**8**) were treated with 1 *N* sodium hydroxide at 55°. In both cases the uv absorption at 268 mμ decreased by only ~10% over a 16-hr period. Since **7** and **8** lack a 2′-hydroxyl group, these results suggest that the ionization and orientation effects associated with the prior ionization of the 2′-hydroxyl group of **1** are not a major case of the lack of reactivity of this compound.

(13) The 2′-hydroxyl group is known to be more acidic than the 5′-hydroxyl group in ribo nucleosides. See J. J. Fox, L. F. Cavalieri, and N. Chang, *J. Amer. Chem. Soc.*, **75**, 4315 (1953); R. M. Izatt, J. H. Rytting, L. D. Hansen, and J. J. Christensen, *ibid.*, **88**, 2641 (1966).

(14) It is assumed that at pH 14 the attack on C-6 involves the 5′-hydroxyl anion. The undissociated 5′-hydroxyl group could participate under less strongly basic conditions but, since the conversion of the 5′,6-anhydro intermediates into the imidazoline nucleosides requires strong base, no overall reaction would result.

(15) (a) D. Lipkin, F. B. Howard, D. Nowotny, and M. Sano, Abstracts, *Intern. Cong. Biochem., 6th*, New York, Paper No. 1-117 (1964); (b) A. Piskala and F. Šorm, *Coll. Czech. Chem. Commun.*, **29**, 2060 (1964).

(16) H. A. Lozeron, M. P. Gordon, T. Gabriel, W. Tautz, and R. Duschinsky, *Biochemistry*, **3**, 1844 (1964).

molecular addition of the 5′-hydroxyl anion and products resulting from both these events are observed.

When 2′,3′-*O*-isopropylidene-5-iodouridine (**3c**) was treated with 1 *N* sodium hydroxide at 55°, the uv-spectral pattern of the monitored reaction differed from that observed for isopropylidene-5-fluorouridine (**3a**). The loss of the initial absorption band at 280 mμ occurred with the concomitant appearance of a new peak which reached a final λ_{max} of 260 mμ after 3 hr. Examination of the neutralized reaction mixture by tlc revealed two major and three minor uv-absorbing products. In addition, three nonchromophoric products were detected; these compounds were not investigated further. Both of the major products were isolated in crystalline form. One of these compounds was identified as 2′,3′-*O*-isopropylideneuridine (**12**) by comparison of the physical properties with those of an authentic sample. Quantitative uv analysis of **12** eluted from tlc plates indicated a yield of ~15%. The other major product, isolated in 30% yield, was 5′,6-anhydro-2′,3′-*O*-isopropylidene-6-hydroxyuridine (**15**). The structure of **15** was indicated by the elemental analysis ($C_{12}H_{14}N_2O_6$) and confirmed by the nmr spectrum in DMSO-d_6. The nmr spectrum showed clearly resolved signals including an NH proton (δ 11.4), a single vinylic proton (5.40, H-5), and a widely spaced quartet (centered at 4.4, $J_{5',5'}$ = 13 Hz). This quartet is characteristic of the H-5′ signals of anhydro nucleosides containing an oxygen bridge between C-5′ and the aglycon.[17]

The three minor products formed in the reaction of **3c** with sodium hydroxide were identified as 2′,3′-*O*-isopropylidene-5-hydroxyuridine[17] (**18**), the barbituric acid nucleoside **13**, and the imidazoline nucleoside **20**. These compounds were not isolated in crystalline form but their identities were established by comparison of chromatographic mobility with those of authentic samples, by uv spectra of eluted materials, and by characteristic color reactions.

The initial uv-spectral changes observed when 2′,3′-*O*-isopropylidene-5-bromouridine (**3b**) was treated with 1 *N* sodium hydroxide at 55° were similar to those described for the 5-iodo analog **3c**. After a reaction time of 3 hr, tlc revealed starting material and a mixture of the same products (**12**, **13**, **15**, **17**,[18] and **20**) as were formed from **3c**. After a longer reaction period (20 hr) the disappearance of starting material (**3b**) was noted along with a substantial decrease in the concentrations of the barbituric acid nucleoside **13** and the anhydro nucleoside **15**. Under these conditions the major product was the imidazoline nucleoside **20** (~20% yield).

Four of the products (**12**, **15**, **17**, and **20**) of the reactions of **3b** and **3c** with sodium hydroxide could be formed from the 5′,6-anhydro intermediates **11b** and **11c**. Like the fluoro analog **11a**, both **11b** and **11c** can undergo ring cleavage at the 3,4 position. The resulting ureides **16b** and **16c** could then be converted into the imidazoline nucleoside **20**, as suggested previously for the 5-fluoro analog **16a**. Because of the more reactive halogen substituent, however, compounds **11b** and **11c** could give rise to products not observed in the fluoro case. Thus, the major reaction of **11c**, and to a smaller extent of **11b**, is elimination of the elements of hydrogen halide to give the anhydro nucleoside **15**. Isopropylideneuridine (**12**) could be formed from **11b**–**11c** by elimination of XOR (OR = sugar moiety). Alternatively, displacement of the halogen atom of **11b**–**11c** by hydroxide ion, followed by the elimination of HOR would give isopropylidene-5-hydroxyuridine (**17**). The 5′-deoxy analogs of compounds **12**, **17**, and **20** were not formed when 5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (**9b**) was heated (55°) with 1 *N* sodium hydroxide. Since **9b** cannot be converted into the 5′,6-anhydro intermediate **11b**, this observation affords evidence that compounds **11b** and **11c** are intermediates in the formation of **12**, **17**, and **20** from **3b** and **3c**.

The only uv-absorbing product observed in the reaction of **9b** with sodium hydroxide was the 5′-deoxyribosylbarbituric acid **14**. Compound **14** is itself unstable in aqueous base and decomposes to nonchromophoric products. The formation of **14** from **9b** was not unexpected because it has been shown previously that 1-methyl-5-bromouracil,[4b] and other 5-halouracils,[19] are converted into barbituric acids on treatment with strong base. These barbituric acids are probably formed by dehydrohalogenation of 5-halogeno-6-hydroxy-5,6-dihydropyrimidine intermediates formed by attack of hydroxide ion on C-6 of the pyrimidine ring. The barbituric acid nucleoside **13** observed in the reaction of **3b** and **3c** with sodium hydroxide is formed *via* two pathways. The major pathway involves competitive attack of hydroxide ion on C-6, as described above, and the minor pathway involves solvolysis of the 5′,6-anhydro nucleoside **15**. When **15** was treated with 1 *N* sodium hydroxide at 55°, the uv maximum at 260 mμ decreased by 40% over a 24-hr period. Examination of the reaction mixture by tlc revealed a small amount of **13** and three nonchromophoric products which probably result from the decomposition of **13**. This finding explains the observed decrease in concentration (between 3 and 20 hr) of **15** formed in the reaction of **3b** with sodium hydroxide.

The formation of the barbituric acid nucleoside **13** by solvolysis of **15**, although of little practical value, indicated that the 5′,6-anhydro bond of **15** could be cleaved. It was therefore of interest to investigate this ring-opening reaction under conditions where the barbituric acid products would be expected to be stable. It was first necessary, however, to devise a higher yielding synthesis of **15** than that available (30% yield) from the 5-iodopyrimidine nucleoside **3c**. This was accomplished by treating isopropylidene-5-bromouridine (**3b**) with an excess of sodium ethoxide in refluxing ethanol. Under these conditions, the 5′,6-anhydro nucleoside **15** was obtained in 90% yield. Treatment of **15** with warm, dilute hydrochloric acid cleaved the anhydro bridge as well as the isopropylidene group to give an 85% yield of 1-β-D-ribofuranosylbarbituric acid (**18**).

(17) I. L. Doerr, R. J. Cushley, and J. J. Fox, *J. Org. Chem.*, **33**, 1592 (1968).

(18) It is of interest to note that isopropylidene-5-hydroxyuridine (**17**) is converted in high yield into the imidazoline nucleoside **20** when treated with dilute alkalis.[3] However, this rearrangement (which does not involve participation of a sugar hydroxyl group) does not take place under the present reaction conditions and in fact **17** is stable in 1 *N* NaOH at 55° as is shown by the constancy of the uv spectrum over a 24-hr period.[3] It is therefore concluded that **17** is not an intermediate in the formation of **20** from **3a**–**3c**. A detailed account of the ring contraction of **17** is presented in a forthcoming paper (*ibid.*, in press).

(19) E. R. Garrett, H. J. Nestler, and A. Somodi, *ibid.*, **33**, 3460 (1968); E. R. Garrett and G. J. Yakatan, *J. Pharm. Sci.*, **57**, 1478 (1968).

Compound **18** was therefore available from **3b** in an over-all yield of 77%. That compound **18** was a barbituric acid derivative was indicated by the similarity of the pK_a (3.75) and uv-absorption data to that reported[20] for 1-methylbarbituric acid (pK_a = 4.20). The ribofuranosyl structure of **18** was established by periodate oxidation; thus **18** consumed 2 equiv of sodium metaperiodate within 5 min, whereas 1-methylbarbituric acid consumed only 1 equiv of oxidant during this period. Both compounds then exhibited a much slower uptake of another equivalent of oxidant over a 48-hr period. The *rapid* uptake of the second equivalent by **18** is consistent with the *cis*-vicinal glycol system. The nmr spectrum of **18** in DMSO-d_6, although not well resolved, confirmed the nucleoside structure and indicated that **18** exists in this solvent in the trioxo form as shown. A total synthesis of the sodium salt of **18** from tri-*O*-benzoyl-β-D-ribofuranosylurea and malonic acid has been reported.[21] However, the over-all yield in this synthesis is low (37%) and the purity of the product is in doubt.[22] Since the completion of the present work, compound **18** has been prepared by an alternative method involving condensation of tribenzoylribofuranosyl bromide with the tristrimethylsilyl derivative of barbituric acid and deesterification of the blocked intermediate.[23]

An alternative approach to the ring opening of the 5′,6-anhydro nucleoside **15** is reaction with nucleophiles to give 5′-substituted ribosylbarbituric acids. Thus, treatment of **15** with sodium benzoate in hot DMF affords a 37% yield of 1-(5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)barbituric acid (**19**). The structure of **19** was established from the uv spectrum and from the nmr spectrum in DMSO-d_6 which showed an exchangeable, two-proton multiplet (δ 3.70) for the geminal H-5 protons in addition to the benzoyl, ring-proton, and isopropylidene resonances. Compound **19** is conveniently substituted with both acid- and base-labile protecting groups and is suitable for further studies on transformations of the sugar moiety. Such studies, together with investigations of the chemistry and biochemistry of barbituric acid nucleosides, are currently under investigation in this laboratory.

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are corrected. The uv spectra were determined on a Cary Model 15 spectrometer; the nmr spectra were determined on a Varian A-60 spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference. Chemical shifts are reported in parts per million (δ) and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), or m (complex multiplet). Values given for coupling constants (hertz) are first order. Thin layer chromatography was performed on glass plates (10 × 20 cm) coated with silica-gel GF (Merck), and developed with the following solvent systems: A, ethyl acetate; B, *n*-butyl alcohol–water, 86:14 v/v. Separated materials were detected with uv light and by spraying with 10% v/v sulfuric acid in ethanol followed by heating at *ca.* 110°. Evaporations were carried out *in vacuo* with bath temperatures kept below 45°. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

2′,3′-*O*-Isopropylidene-5-iodouridine (3c).—The general procedure of Hampton[24] was used with modifications. 5-Iodouridine (3.7 g, 10 mmol), (prepared according to the method of Prusoff[25]) was added to a solution of dimethoxypropane (10 ml) and di(*p*-nitrophenyl)phosphoric acid (340 mg, 1 mmol) in 100 ml of acetone. The suspension was stirred at room temperature for 1 hr, during which time the solid material dissolved. An excess of aqueous NH_4OH was added and the solution was concentrated to dryness. The syrupy residue was dissolved in 100 ml of 50% ethanol and the solution was treated with 5 ml of Dowex-1 (Cl^-). Crystallization of the product commenced during concentration and was completed by cooling. Recrystallization from aqueous ethanol afforded pure material (3.0 g, 73%): mp 225–227°; nmr δ 11.5 (1, broad s, NH), 8.27 (1, s, H-6), 5.80 (1, d, H-1′), 5.07 (1, t, 5′OH), 4.8 (2, m, H-2′, H-3′), 4.06 (1, m, H-4′), 3.5 (2, m, H-5′, H-5′), 1.43, 1.24 (two singlets, six protons, isopropylidene methyls) ($J_{1',2'}$ = 2.5, $J_{5',OH}$ = 5.0 Hz).

Anal. Calcd for $C_{12}H_{15}IN_2O_6$: C, 35.14; H, 3.69; N, 6.83. Found: C, 35.13; H, 3.75; N, 6.70.

5′-Deoxy-5-bromouridine.—An excess of bromine (~0.9 ml, ~17 mmol) was dissolved (dropwise addition) in a solution of 5′-deoxyuridine[26] (3.42 g, 15 mmol) in 100 ml of water. The acidic solution was then concentrated to dryness at 50°. The residue was dissolved in ethanol and the solution again was concentrated to dryness. A solution of the residue in ethyl acetate deposited crystals when diluted with petroleum ether (bp 30–60°). Recrystallization from the same solvent pair afforded pure material (3.7 g, 80%): mp 172–173° (eff) dec, darkened above 160°; nmr δ 11.9 (1, broad s, NH), 8.00 (1, s, H-6), 5.70 (1, d, H-1′), ~5.1 (2, broad s, 2′-OH, 3′-OH), ~4.4 (3, m, H-2′, H-3′, H-4′), 1.30 (3, d, 4′-methyl) ($J_{1',2'}$ = 5.0, $J_{4',5'}$ = 6.0 Hz).

Anal. Calcd for $C_9H_{11}BrN_2O_5$: C, 35.18; H, 3.61; N, 9.13. Found: C, 35.13; H, 3.55; N, 8.96.

5′-Deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (9b).—5′-Deoxy-5-bromouridine (1.54 g) was converted into **9b** as described above for the preparation of **3c**. The yield of pure **9b** (from aqueous ethanol), mp 108–110°, was 1.41 g (80%): nmr δ 11.9 (1, broad s, NH), 8.20 (1, s, H-6), 5.77 (1, d, H-1′), 5.07 (1, q, H-2′), 4.59 (1, q, H-3′), 4.10 (1, m, H-4′), 1.30 (3, d, 4′-methyl), 1.49, 1.29 (two singlets, six protons, isopropylidene methyls) ($J_{1',2'}$ = 2.4, $J_{2',3'}$ = 6.8, $J_{3',4'}$ = 4.5, $J_{4',5'}$ = 6.5 Hz).

Anal. Calcd for $C_{12}H_{15}BrN_2O_5$: C, 41.50; H, 4.35; N, 8.07. Found: C, 41.14; H, 4.28; N, 7.96.

Reactions of 2′,3′-*O*-isopropylidene-5-halouridines in Alkali. General Procedure.—The following proportions of reactants were used, although not all experiments were conducted on this scale. The halouridine (1 mmol) was dissolved in 1 *N* sodium hydroxide (10 ml, 10 mmol) and the solution was thermostated at 55°. Aliquots (0.1 ml), taken immediately, and at suitable intervals thereafter, were diluted to 100 ml with water (pH ~11, 1 × 10^{-4} *M* in starting material), and the uv spectra were recorded.

A. 2′,3′-*O*-Isopropylidene-5-fluorouridine (3a). Preparation of 1-β-D-Ribofuranosyl-2-oxo-4-imidazoline-4-carboxylic Acid (2).—When **3a** (151 mg, 0.5 mmol) was heated in NaOH the absorption maximum at 268 mμ decreased by 50% in 40 min. This decrease was followed by the appearance of a peak at 252 mμ which reached a maximum (OD 0.77) at 14 hr. Chromatography (solvent B) of the neutralized reaction mixture revealed a single uv-absorbing compound (**20**) with R_f 0.15. The cooled reaction mixture as passed through a column containing 7 ml of Dowex-50 (H^+). The acidic effluent and washings were concentrated to a syrup which crystallized when triturated with acetone. Recrystallization from aqueous acetone afforded colorless needles, 89 mg (60%) of 1-(β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid dihydrate (**2**): mp 107–110° (resolidified and remelted at 195–200°); $\lambda_{max}^{pH\ 1}$ 263 mμ, $\lambda_{max}^{pH\ 7}$ 252 mμ, $\lambda_{max}^{pH\ 14}$ 268 mμ.

Anal. Calcd for $C_9H_{12}N_2O_7 \cdot 2H_2O$: C, 36.49; H, 5.44; N, 9.46. Found: C, 36.67; H, 5.33; N, 9.22.

Anhydrous **2**, obtained by drying the hydrate at 130° over P_2O_5, melted at 174–176° (eff) dec: nmr δ 10.7 (1, broad s, NH), 7.50 (1, d, H-5), 5.47 (1, d, H-1′), ~5.5 (3, very broad band, hy-

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(22) Ukita, *et al.*,[21] reported that **18**, in 0.1 *N* HCl, was converted in part into an isomeric product with λ_{max} 252 mμ. Our product (**18**), however, is stable under these conditions. It is apparent that their product contains a substantial amount of another compound. This is reflected in the 30% *lower* extinction coefficient at pH 7 reported for their compound.

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droxyl protons), ~4.4–3.8 (3, m, H-2′, H-3′, H-4′), ~3.6 (2, m, H-5′, H-5′) ($J_{1',2'}$ = 5.5, $J_{5,NH}$ = 1.5 Hz).

When 5-fluorouridine[27] (1), 2′-deoxy-5-fluorouridine[28] (7), and "2′,3′-dideoxy-5-fluorouridine"[29] (8) were treated with 1 *N* NaOH, as described above, the uv-absorption maxima (268 mμ) decreased by only 10–15% over a 16-hr period. Paper electrophoresis (acetate buffer, pH 3.5) of the reaction mixture of 1 revealed starting material and trace amounts of a product which was identified as the imidazoline 2 by the uv spectrum of eluted material.

B. 2′,3′-*O*-Isopropylidene-5-iodouridine (3c).—The decrease in the absorption maximum (280 mμ) of **3c** (820 mg, 2 mmol) occurred concomitantly with the appearance of a new peak which reached a final λ_{max} of 260 mμ (OD 0.71) at 3 hr. In addition, a gradual increase in absorption at ~300–320 mμ (to OD 0.03) was noted. Chromatography (solvent A) of the neutralized reaction mixture revealed a trace of starting material (R_f 0.92), small amounts of uv-absorbing materials with R_f <0.1 and 0.2, and two major components with R_f 0.75 and 0.50. The material with R_f 0.75 was isolated by extraction of the neutralized (HOAc) reaction mixture with five 10-ml portions of chloroform. Concentration of the dried ($MgSO_4$) chloroform solution to dryness, and crystallization of the syrupy residue from ethanol afforded colorless needles of **15** (170 mg, 30%), mp 251–253°. The uv and nmr spectra of this compound were identical with those of **15** described below. Extraction of the aqueous layer (remaining after the removal of **15**) with ethyl acetate afforded a solution containing the material with R_f 0.50. A crystalline sample of this compound, obtained by preparative tlc (solvent A) gave an ir spectrum identical with that of isopropylidene uridine (**12**); the mixture melting point of the present sample with authentic **12** was undepressed (162–164°). The yields of **12** and **15** were 15 and 34%, respectively, as determined by uv analysis of materials eluted from tlc plates used to fractionate known amounts of the reaction mixture. The material with R_f 0.2 (solvent A) comigrated with authentic 2′,3′-*O*-isopropylidene-5-hydroxyuridine[3] (**17**); both samples gave a blue spot when sprayed with aqueous $FeCl_3$ solution. The absorption at ~300–320 mμ observed in the uv spectrum of the total reaction mixture is due to the presence of **17** ($\lambda_{max}^{pH\ 12}$ 304 mμ).

Chromatography of the reaction mixture using solvent B revealed **12** and **15** (both R_f 0.72), starting material (**3c**, R_f 0.89), **17** (R_f 0.55), and small amounts of two other uv-absorbing products with R_f 0.15 and 0.33. The component with R_f 0.15 was identified as the imidazoline nucleoside **20** (R_f 0.15, see section A above) from the characteristic uv spectrum of eluted material. The uv spectrum of the component with R_f 0.33 was characteristic of a barbituric acid derivative ($\lambda_{max}^{H_2O}$ 260 mμ, peak disappeared on acidification) and, in agreement with this formulation, the material gave an orange spot when sprayed with Erlich reagent. Furthermore, this material comigated with 2′,3′-*O*-isopropylidene ribofuranosyl barbituric acid (**13**, R_f 0.33) which was prepared *in situ* by treating compound **19** (see below) with dilute NaOH. (Barbituric acid itself had R_f ~0.1 in solvent B.) In addition to the above uv-absorbing products of the reaction of **3c** with NaOH, three nonchromophoric products (R_f 0.07, 0.50, and 0.80, solvent B) were detected with the H_2SO_4 spray. These compounds were not investigated further.

C. 2′,3′-*O*-Isopropylidene-5-bromouridine (3b).—The initial uv-spectral changes observed when **3b**[30] (363 mg, 1 mmol) was heated in 1 *N* NaOH were similar to those described above for **3c**. Thus, after a reaction time of 3 hr, peaks at 260 mμ (OD 0.53) and ~310 mμ (OD 0.08) were present. After a 20-hr reaction period, the 260-mμ peak had decreased in intensity (to OD 0.35) and shifted to 255 mμ. Chromatography (solvents A and B) of the 3-hr reaction mixture revealed starting material, small amounts of **12**, **13**, and **17**, and **20** and **15** as the major products. After 20 hr, the spot for **15** had decreased in intensity leaving **20** as the major product (20% yield based on the uv extinction of material eluted from quantitative tlc plates). The decrease in uv extinction observed between 3 and 20 hr is due to the decomposition of the 5′,6-anhydro nucleoside **15** and the barbituric acid nucleoside **13**. Thus, when **15** (1 mmol) was treated with 1 *N* NaOH at 55°, the absorption peak (260 mμ) decreased by 40% over a 24-hr period. Chromatography (solvent B) showed **15** (R_f 0.72), a trace of the barbiturate **13** (R_f 0.33), and three nonchromophoric products (R_f 0.07, 0.50, and 0.80).

D. 5′-Deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (9).—Spectra determined at pH 7 showed a gradual decrease in the absorption at 278 mμ and appearance of a peak which reached a final λ_{max} at 261 mμ (OD 0.84 at 4 hr). Spectra determined at pH 1 showed only the decrease at 278 mμ (50% loss in 4 hr), indicating that the product was a barbituric acid derivative. Chromatography (solvent B) showed starting material (R_f >0.95) and a *single* uv-absorbing product (**14**, R_f 0.37) which gave an orange spot when sprayed with Erlich reagent. The uv spectrum of **14** eluted from the tlc plate showed $\lambda_{max}^{H_2O}$ 261 mμ (peak disappeared on acidification) and $\lambda_{max}^{pH\ 14}$ 263 mμ. After a 20-hr reaction period, the peak at 261 mμ in the uv spectrum of the total reaction mixture had decreased to OD 0.15.

1-β-D-Ribofuranosyl-2-oxo-4-imidazoline-4-carboxylic Acid (2) by Total Synthesis.—A suspension of finely divided 6[4b] (1.42 g, 10 mmol) in 300 ml of nitromethane was dried by azeotropic distillation of 100 ml of solvent. A solution of 5[31] [prepared from 10.1 g (20 mmol) of 1-*O*-acetyl-tri-*O*-benzoylribofuranose], in nitromethane, and mercuric cyanide (2.52 g, 10 mmol) were added to the hot suspension. The mixture was refluxed for 30 min during which time most of the solid material dissolved. Unreacted 6 (200 mg) was filtered off and the dark filtrate was concentrated to dryness. The syrupy residue was partitioned between chloroform (200 ml) and 30% KI solution (two 40-ml portions). The chloroform extracts were washed with water, dried ($MgSO_4$), and concentrated to dryness. NaOH (1 *N*, 100 ml) was added to a solution of the residue in ethanol (100 ml) and the mixture was refluxed for 2 hr. The cooled solution was passed through a column containing an excess of Dowex-50 (H^+) and the effluent and washings were concentrated to a small volume. This solution was placed on a column (2 × 10 cm) of Dowex-1 (OAc^-). The column was eluted with 0.1 *N* acetic acid until the effluent was free of uv-absorbing materials and then with 0.5 *N* HCl. Fractions containing uv-absorbing material were combined and concentrated to a small volume. Some of the HCl was removed by repeated codistillation with water. Acetone was added to the concentrated solution (~2 ml); crystallization commenced on cooling. The product (120 mg, 20%) had mp and mmp 107–110° [resolidified and remelted at 195–200° (eff) dec] and gave ir and uv spectra identical with those of hydrated **2** prepared from **3a**.

5′,6-Anhydro-2′,3′-*O*-isopropylidene-6-hydroxyuridine (15).—A sample of **3b** (36.3 g, 0.1 mol) was dissolved in ethanol (1000 ml) containing sodium (5.75 g, 0.25 mol) and the solution was refluxed for 17 hr. The cooled solution was neutralized with acetic acid and evaporated to ~200 ml. Water (300 ml) was added and the solution was cooled, whereupon crystalline material (15.5 g) separated. Concentration of the filtrates afforded an additional 10 g (total yield 25.5 g, 90%) of material. Recrystallization of the product from ethanol, and then from ethyl acetate, afforded pure **15**: mp 251–253°; uv absorption at $\lambda_{max}^{pH\ 7}$ 261 mμ (ε 13,050) and λ_{min} 230 (2400), $\lambda_{max}^{pH\ 1}$ 261 mμ (ε 13,050) and λ_{min} 230 (1300), $\lambda_{max}^{pH\ 12}$ 262 mμ (ε 9300) and λ_{min} 241 (5000). The nmr spectrum of **15** showed an AB subspectrum for the 5′ protons [δ 4.08, 4.73 ($J_{5',5'}$ = 13 Hz, $J_{4',5'}$ ~ 1.0 Hz)] and another AB system for H-2′ and H-3′ [δ 5.00, 5.11 ($J_{2',3'}$ = 6.0, $J_{1',2'}$, $J_{3',4'}$ ~ 0 Hz)]. Other nmr signals were at 11.4 (1, broad s, NH), 6.43 (1, s, H-1′), 5.40 (1, s, H-5), 4.71 (1, narrow multiplet with poorly resolved splitting, H-4′), and 1.43 and 1.33 (two singlets, six protons, isopropylidene methyls).

Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 4.96; N, 9.93. Found: C, 51.03; H, 4.94; N, 9.97.

1-β-D-Ribofuranosylbarbituric Acid (18).—The 5′,6-anhydro nucleoside **15** (5.64 g, 20 mmol) was dissolved in a mixture of 200 ml of 1 *N* HCl and 200 ml of ethanol and the solution was heated at 50° for 8 hr. Triethylamine (19.4 g) was added to neutralize the HCl and the solution was evaporated to dryness. The residue was suspended in ethanol (75 ml) and the insoluble **18** (4.5 g, 86%) was removed by filtration. Recrystallization from ~300 ml of hot ethanol afforded colorless needles of the monoethanolate of **18**: mp 116–118° (eff); uv absorption at $\lambda_{max}^{pH\ 7}$ 260 mμ (ε 22,160), $\lambda_{max}^{pH\ 14}$ 265 (ε 15,225), $\lambda_{max}^{pH\ 0}$ 214 mμ (shoulder) and 260 (ε 7400 and <300); pK_{a1} = 3.75 ± 0.05 (determined

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spectrophotometrically). Integration of the nmr spectrum of **18** indicated 18 protons including peaks at δ 10.6 (1, broad s, NH), 5.97 (1, d, H-1'), and 1.06 (3, t, CH_3 of ethanol). A broad peak at δ 4.6 (hydroxyl protons) disappeared on addition of D_2O to reveal peaks at 4.4 (1, q, H-2') and 4.1 (1, t, H-3'). The remaining protons (H-4, H-5', H-5, H-5, and CH_2CH_3) gave rise to a seven-proton multiplet at δ 3.3–3.9 which decreased in area to a five-proton multiplet after deuterium exchange of the geminal H-5 protons ($J_{1',2'} = 3.2$, $J_{2',3'} = J_{3',4'} \simeq 6.0$ Hz).

Anal. Calcd for $C_9H_{12}N_2O_7 \cdot C_2H_5OH$: C, 43.14; H, 5.88; N, 9.15. Found: C, 43.00; H, 5.64; N, 9.34.

1-(5-*O*-Benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)barbituric acid (19).—Sodium benzoate (3.02 g, 21 mmol) was added to a solution of **15** (5.64 g, 20 mmol) in 600 ml of DMF and the mixture was heated at 120° for 3 hr. The cooled solution was concentrated to dryness and the residue was dissolved in water (150 ml). The solution was acidified (~pH 2) with 1 *N* HCl and the resulting precipitate was filtered off and washed with water. Recrystallization from 50% ethanol, and then from ethanol, afforded pure material (3.0 g, 37%): mp 163–166°; nmr δ 11.8 (1, broad s, NH), ~8.2–7.3 (5, m, aromatic protons), 6.30 (1, d, H-1'), ~5.0 (2, m, H-2', H-3'), ~4.50 (3, m, H-4', H-5', H-5'), 3.70 (2, broad s which exchanges in D_2O, H-5, H-5), 1.51, 1.31 (two singlets, six protons, isopropylidene methyls) ($J_{1',2'} = 1$ Hz); uv absorption at $\lambda_{max}^{H_2O}$ 232 and 260 mμ, $\lambda_{max}^{pH\ 1}$ 230 mμ.

Anal. Calcd for $C_{19}H_{20}N_2O_8$: C, 56.48; H, 4.95; N, 6.93. Found: C, 56.31; H, 4.91; N, 6.91.

Registry No.—**2**, 19556-57-1; **3c**, 19556-58-2; **9b**, 19556-59-3; **12**, 362-43-6; **14**, 19556-61-7; **15**, 19556-62-8; **18**, 19556-63-9; **19**, 19556-64-0; 5'-deoxy-5-bromouridine, 19556-65-1.

The Preparation of 6-Fluoropurines by the Modified Schiemann Reaction[1]

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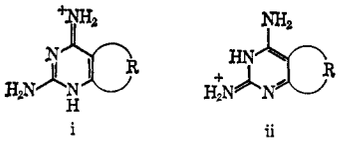
The use of forcing conditions in the modified Schiemann reaction has now permitted the preparation of a number of 6-fluoro- and 2,6-difluoropurines. In the latter cases, the 2-aminoadenines are converted first into the 2-fluoroadenines which nitrosate more favorably than the corresponding adenines and are then converted into the 2,6-difluoropurines.

In a systematic study of the action of nitrous acid on a number of condensed 2,4-diaminopyrimidine ring systems, Trattner, *et al.*,[2] found that in all cases including 2-aminoadenine, nitrosation of the 2- but not the 4-amino group took place giving the corresponding 2-hydroxy-4-amino heterocycles.[3] They explained their results by assuming that protonation takes place at N-1 rather than at N-3.[4,5] These results and those of other investigators[6-10] have led to the conclusion[11] that the modified Schiemann reaction[12] is limited to the synthesis of 2-fluoropurines and this conclusion has been generally accepted. Despite the foregoing precedents, we now wish to report cases in which we have found that derivatives of adenine and 2-aminoadenine do undergo a modified Schiemann reaction to give 6-fluoropurines.[13]

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2,6-dichloropurine[14] (**1a**), prepared by the fusion procedure,[15] was converted through diazide **2a** into 2-amino-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**3a**) (Scheme I). Treatment of **3a** with sodium nitrite in 48% fluoroboric acid gave a mixture from which 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)isoguanine (**4a**, 24%), 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2-fluoroadenine (**5a**, 13%), and 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2,6-difluoropurine (**6a**, 16%) were isolated by means of column chromatography on silica gel. **4a** was identified by its chromatographic behavior and by its infrared and ultraviolet spectra. **6a** was identified by its elemental analysis; by its ultraviolet, infrared, and pmr spectra; and by its conversion into 2-fluoro-9-β-D-xylofuranosyladenine (**5b**) by treatment with alcoholic ammonia. **5a** was also converted into **5b** by treatment with alcoholic ammonia. **5b** was initially prepared by the diazotization of **3b** in 48% fluoroboric acid.

It is logical to assume that **3a** is initially converted into **5a**, which reacts further to give **6a**, and evidence in support of this pathway is found in our inability to identify any 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-amino-6-fluoropurine[16] in the diazotization of 2',3',5'-tri-O-acetyl-2-aminoadenosine in fluoroboric acid,[17] and also in the conversion of 2',3',5'-tri-O-acetyl-2-fluoroadenosine (**9**) into 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine (**12**) in 25% yield (*vide*



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(3) In purine the numbering is not systematic so that 2-aminoadenine gives 2-hydroxy-6-aminopurine (isoguanine).

(4) Here again purine numbering causes confusion. Protonation in this case is at the ring nitrogen designated N-3 (i) not at N-1 (ii). In the other ring systems the designations are reversed.

(5) This line of reasoning might also explain why adenine is more resistant to nitrosation than 2-aminopurine, except for the fact that adenine is thought to protonate at N-1, at least in the crystal, even though it undergoes nucleophilic attack primarily at N-3.

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