Later fractions yielded 459 mg (21%) of the cyclic carbonate **20**: uv max (CH_3OH), 256 mμ (ε 8750); the ir spectrum ($CHCl_3$) was identical with that of an authentic sample.[5]

Reaction of 2′,5′-Di-O-trityluridine with 1.—A freshly prepared solution of **1** (0.88 ml) in DMF (5 ml) was added to a 0° solution of 2′,5′-di-O-trityluridine[21] (1.37 g) in pyridine (20 ml), and the mixture was stirred at 0° overnight. The usual isolation procedure was applied, and the product was purified by passage through a silica column (250 g), using chloroform–ethyl acetate (50:1). Recrystallization from ethyl acetate–hexane gave 1.15 g (60%) of **23**: mp 148–153°; uv max (dioxane), 256 mμ (ε 10,650); ir (KBr), 1750 cm^{-1} (C=O).

Anal. Calcd. for $C_{50}H_{41}Br_3N_2O_8$: C, 57.88; H, 3.96; N, 2.70. Found: C, 57.93; H, 3.98; N, 2.57.

Regeneration of 2′,5′-Di-O-trityluridine from 23.—A solution of **23** (250 mg) in 90% acetic acid (5 ml) was stirred with a zinc–copper couple (100 mg) for 35 min. The couple was removed by filtration, and washed with chloroform. The filtrate and washings were evaporated to dryness and extracted with dry benzene. The extracts were evaporated and crystallized from benzene–ether to give 156 mg (88%) of 2′,5′-di-O-trityluridine.

Treatment of 23 with 80% Acetic Acid.—A solution of **23** (518 mg) in 80% acetic acid (30 ml) was heated at 100° for 40 min, and evaporated to dryness. The residue was extracted with ether and dried *in vacuo* to give 120 mg (89%) of uridine 2′,3′-cyclic carbonate (**24**): uv max (CH_3OH), 255 mμ (ε 9780); the ir spectrum (KBr) was identical with that of an authentic sample.[5]

Reaction of 2′,3′-O-Isopropylideneadenosine with 1.—A freshly prepared solution of **1** in DMF (10 ml) was added to a 0° solution of **25** (1.2 g) in pyridine and the mixture was stirred at 0° for 1 hr. The usual isolation procedure was followed and the product was applied to a silica column (300 g) and eluted with chloroform–ethyl acetate (4:1, 2 l.) followed by ethyl acetate (2 l.).

The first compound to be eluted from the column was recrystallized from chloroform–hexane: 457 mg; mp 150°; uv max (CH_3OH), 287 mμ; ir (KBr), 1720, 1770 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{18}Br_6N_6O_8$: C, 24.66; H, 2.06; Br, 51.86. Found: C, 24.36; H, 1.95; Br, 51.93.

The second product from the column was isolated as a foam (440 mg): uv max (CH_3OH), 267 mμ; ir ($CHCl_3$), 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{19}Br_6N_6O_8$: C, 24.66; H, 2.06; Br, 51.86. Found: C, 24.94; H, 2.25; Br, 50.70.

The carbamate **26** was obtained, 736 mg (30%), and recrystallized from chloroform–hexane: mp 210–211°; uv max (CH_3OH), 279 mμ (ε 10,800); ir (KBr), 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{18}Br_3N_5O_6$: C, 31.18; H, 2.92; N, 11.36. Found: C, 30.88; H, 2.87; N, 11.19.

Compound **27**, 220 mg (9%), was isolated as a foam: uv max (CH_3OH), 258 mμ (ε 14,900); ir ($CHCl_3$), 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{18}Br_3N_5O_6$: C, 31.18; H, 2.92; Br, 38.93; N, 11.36. Found: C, 31.38; H, 3.16; Br, 38.90; N, 11.26.

Registry No.—**1**, 17182-43-3; **2**, 17182-30-8; **3**, 17182-31-9; **4**, 17182-32-0; **7**, 17182-33-1; **8**, 17188-71-5; **9**, 17182-34-2; **11**, 17182-35-3; **12**, 17182-36-4; **13**, 17188-72-6; **14**, 17182-37-5; **15**, 17182-38-6; **16**, 17182-39-7; **17**, 17182-40-0; **21**, 17222-08-1; **23**, 17182-41-1; **26**, 17188-73-7; **27**, 17182-42-2.

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Nucleosides. LII. Transformations of Pyrimidine Nucleosides in Alkaline Media. I. The Conversion of 5-Halogenoarabinosyluracils into Imidazoline Nucleosides[1]

BRIAN A. OTTER, ELVIRA A. FALCO, AND JACK J. FOX

Division of Biological Chemistry, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division of Cornell University Medical College, New York, New York 10021

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The reactions of 1-β-D-arabinofuranosyl-5-halogenouracils in alkali have been investigated under various conditions. The 5-fluorouracil nucleoside (**1**) is stable in hot sodium methoxide solution whereas the 5-bromo analog (**4**) is converted in high yield into 2′,6-anhydro-1-(β-D-arabinofuranosyl)-6-hydroxyuridine (**5**). Compound **5** is also formed in low yield when **4** is treated with warm aqueous sodium hydroxide. The major product of this aqueous reaction was shown to be 1-β-D-arabinofuranosyl-2-oxo-4-imidazoline-4-carboxylic acid (**3**). Nucleoside **3** was also prepared under similar conditions by ring closure of the 2′,6-anhydro acyclic ureide **2**. The structure of **3** was elucidated from chemical and nmr evidence and by comparison of the ultraviolet spectral and pK_a data of **3** and its derivatives with those of model N-alkylated imidazolinecarboxylic acids. Mechanisms involving attack of the 2′-hydroxyl group on C-6 of the pyrimidine ring are suggested for these novel transformations. 1-Methyl-5-bromouracil (**29**) does not undergo rearrangement to an imidazolinecarboxylic acid when treated with aqueous alkali but is converted into 1-methylbarbituric acid. Imidazoline nucleosides have also been prepared by total synthesis. Condensation of tetraacetyl-α-D-glucopyranosyl bromide (**19**) with 2-oxo-4-imidazoline-4-carboxylic acid methyl ester (**14**) affords a mixture of N-1 and N-3 glucosylated imidazoline derivatives. As with pyrimidine nucleosides, uv spectral shifts in the high alkaline region were observed with the 3-methyl derivative of the imidazoline nucleoside (**3**). These shifts are attributed to the effects of ionization of the sugar moiety on the aglycon.

Pyrimidine nucleosides containing the 1-β-D-arabinofuranosyl moiety have been studied extensively as antiviral and antitumor[2] agents. Recent investigations[3] into the synthesis of arabinosyl nucleosides for evaluation as chemotherapeutic agents have revealed some interesting chemical properties which result from the configuration of the sugar at C-2′. This structural feature allows a facile interaction between the 2′-hydroxy group and the aglycon which can result in the formation of a 2′,6-ether linkage.[3] For example, 1-β-D-arabinofuranosyl-5-fluorouracil (**1**) and its 5-fluorocytosine analog are rapidly transformed[3a] in warm,

(1) (a) 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 08748). (b) A preliminary account of part of this work has been published: B. A. Otter and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 3663 (1967).

(2) For a review on the biochemistry of D-arabinosyl nucleosides, see S. S. Cohen, *Prog. Nucleic Acid Res. Mol. Biol.*, **5**, 1 (1966).

(3) (a) J. J. Fox, N. C. Miller, and R. J. Cushley, *Tetrahedron Lett.*, 4927 (1966); (b) I. L. Doerr and J. J. Fox, *J. Org. Chem.*, **32**, 1462 (1967); (c) J. F. Codington, R. J. Cushley, and J. J. Fox, *ibid.*, **33**, 466 (1968).

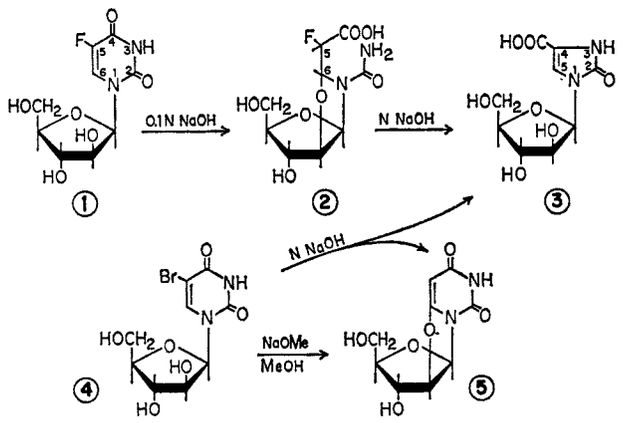


Figure 1.

0.1 *N* sodium hydroxide to the "2,6-anhydro" acyclic ureide **2**. The scope of these reactions has been investigated and we now wish to report some new transformations of 5-halogenated arabinosyl nucleosides (see Figure 1).

In contrast to the rapid reaction in aqueous base,[3a] the 5-fluoropyrimidine (**1**) is stable in hot, 0.1 *N* sodium methoxide in methanol as shown by the constancy of its ultraviolet spectrum over a 20-hr period. However, when 1β-D-arabinofuranosyl-5-bromouridine (**4**) was treated with sodium methoxide under these conditions, a rapid loss of absorption at 280 mμ was noted along with the simultaneous appearance of a new peak at 252 mμ. The crystalline product, isolated in 75% yield, was shown to be 2′,6-anhydro-1-(β-D-arabinofuranosyl)-6-hydroxyuridine (**5**).[4] The structure of **5** was established by the nmr spectrum in DMSO-d_6 which showed an NH proton (δ 10.97), a single vinyl proton (δ 5.01, H-5), and only two hydroxyl protons (doublet δ 5.86, 3′-OH; triplet δ 4.98, 5′-OH), indicating the presence of a 2′,6-anhydro linkage. The melting point of **5** (246–248°) differed from the reported value[4] (236°), but the uv spectral characteristics were in close agreement with the published data.

The 2′,6-anhydro compound (**5**) was formed in only 7% yield when the 5-bromo nucleoside (**4**) was heated at 55° for 6 hr in 1 *N* sodium hydroxide. The major product of the reaction (**3**), isolated in 65% yield as a crystalline monohydrate, had the empirical formula $C_9H_{12}N_2O_7 \cdot H_2O$. The same product (**3**) was also obtained in 55% yield when the acyclic ureide **2** was treated under similar conditions for 20 hr. This result strongly suggests that the 5-bromo analog of **2** is an intermediate in the conversion of **4** into **3**. Evidence presented below shows that **3** is 1-β-D-arabinofuranosyl-2-oxo-4-imidazoline-4-carboxylic acid and that the overall formation of **3** from **2** or **4** involves a ring contraction previously unreported in the nucleoside area.

Compound **3** (Figure 2) was acidic (pK_a = 3.31) and formed a methyl ester (**7**) when treated with 1 equiv of diazomethane. Compound **3** formed a crystalline tri-*O*-acetate (**6**). Unlike the precursor (**2**), compound **3** consumed 1 equiv of periodate. The rate of oxidation was slow (40 hr), consistent with the presence of a *trans* vicinal glycol system. These facts indicate that the sugar hydroxyl groups of **3** are unsubstituted and that the 2′,6-anhydro bond of **2** had therefore undergone cleavage in the conversion into **3**. This conclusion was supported by the nmr spectrum of anhydrous **3** in DMSO-d_6 which showed a group of three exchangeable protons (OH) at ~δ 5.5 The arabinofuranosyl (rather than xylofuranosyl) configuration of the sugar moiety was established by the failure of the methyl ester **7** to react with a solution of HCl (gas) in acetone. This reagent is known to cause 3′,5′-*O*-isopropylidene ring formation in 1-β-D-xylofuranosylpyrimidine nucleosides.[5] The nmr spectrum of **3** also showed an exchangeable proton (NH) at δ 10.65 which was coupled (J = 1.5 cps) to a single vinylic proton at δ 7.32. This long-range coupling disappeared on exchange of the NH proton by deuterium.[6] The chemical shift of the NH proton is typical of cyclic ureides and differs considerably from the chemical shift of the amide protons in **2**.[3a]

Further proof of the cyclic nature of **3** was obtained as follows. Methylation of **3** with an excess of diazomethane afforded an N-methylated methyl ester (**10**) which was purified *via* the tri-*O*-acetate **15**. Compound **15** was also prepared by an alternative route from the 3-methylpyrimidine nucleoside **11**. Compound **11**, which was prepared by methylation of **4** with diazomethane, was converted into the syrupy N-methyl nucleoside **16** on treatment with warm, 1 *N* sodium hydroxide. Esterification of **16** with diazomethane, followed by acetylation, afforded a tri-*O*-acetate (**15**) which was identical with that obtained by acetylation of **10**. The N-methyl signals in the nmr spectra of DMSO-d_6 solutions of **10** and **15**, and of the sodium salt of **16**, appeared as sharp *singlets* in the range δ 3.33–3.40. The fact that these peaks are singlets (and not doublets, as would be expected for an acyclic *N*-methylureide structure) establishes that the aglycon of **3** is cyclic.

The foregoing analytical, nmr, and chemical data are consistent with the formulation of **3** as an arabinofuranosyl derivative of 2-oxo-4-imidazoline-4-carboxylic acid (**26**) but do not rule out the isomeric 2-imino-4-oxazoline-4-carboxylic acid nucleoside.[7] The latter structure is eliminated, however, by the degradation and ultraviolet spectral studies now described.

Hydrolysis of **3** with hot perchloric or sulfuric acid afforded a dark mixture which gave ultraviolet spectral evidence for the presence of some 2-oxo-4-imidazoline-4-carboxylic acid. Cleavage of the aglycon of the methyl ester **7**, however, was accomplished under milder conditions by using the method of Khym and Cohn.[8] Oxidation of **7** with an excess of sodium metaperiodate, followed by treatment of the resulting dialdehyde **8** with phenylhydrazine, afforded the crystalline bisphenylhydrazone **9**. Treatment of **9** with phenylhy-

(4) While these studies were in progress, a communication appeared [M. Honjo, Y. Furukawa, N. Nishikawa, K. Kamiya, and Y. Yoshioka, *Chem. Pharm. Bull.* (Tokyo), **15**, 1076 (1967)] describing an alternative synthesis of **5** by reductive dehalogenation of the corresponding 5-iodo nucleoside. The latter compound was isolated (yield unstated) from a mixture of products obtained by iodination of 1-β-D-arabinofuranosylcytosine.

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

(6) The carboxyl proton of **3** was not evident in the nmr spectrum. The signals of the corresponding protons in 2-oxo-4-imidazoline-4-carboxylic acid (**26**), and the methylated derivatives **23**, **24**, and **27**, were so broad as to be barely discernible in the 60-Mc spectra in DMSO-d_6.

(7) However, it is unlikely that such a compound would survive either the alkaline reaction medium, or the acid conditions employed in the isolation procedure, without undergoing deamination or ring fission. Some ammonia is evolved during the reactions of **2** and **4** with alkali but this could result from the deamination of **2** or its 5-bromo analog.

(8) J. X. Khym and W. E. Cohn, *J. Amer. Chem. Soc.*, **82**, 6380 (1960).

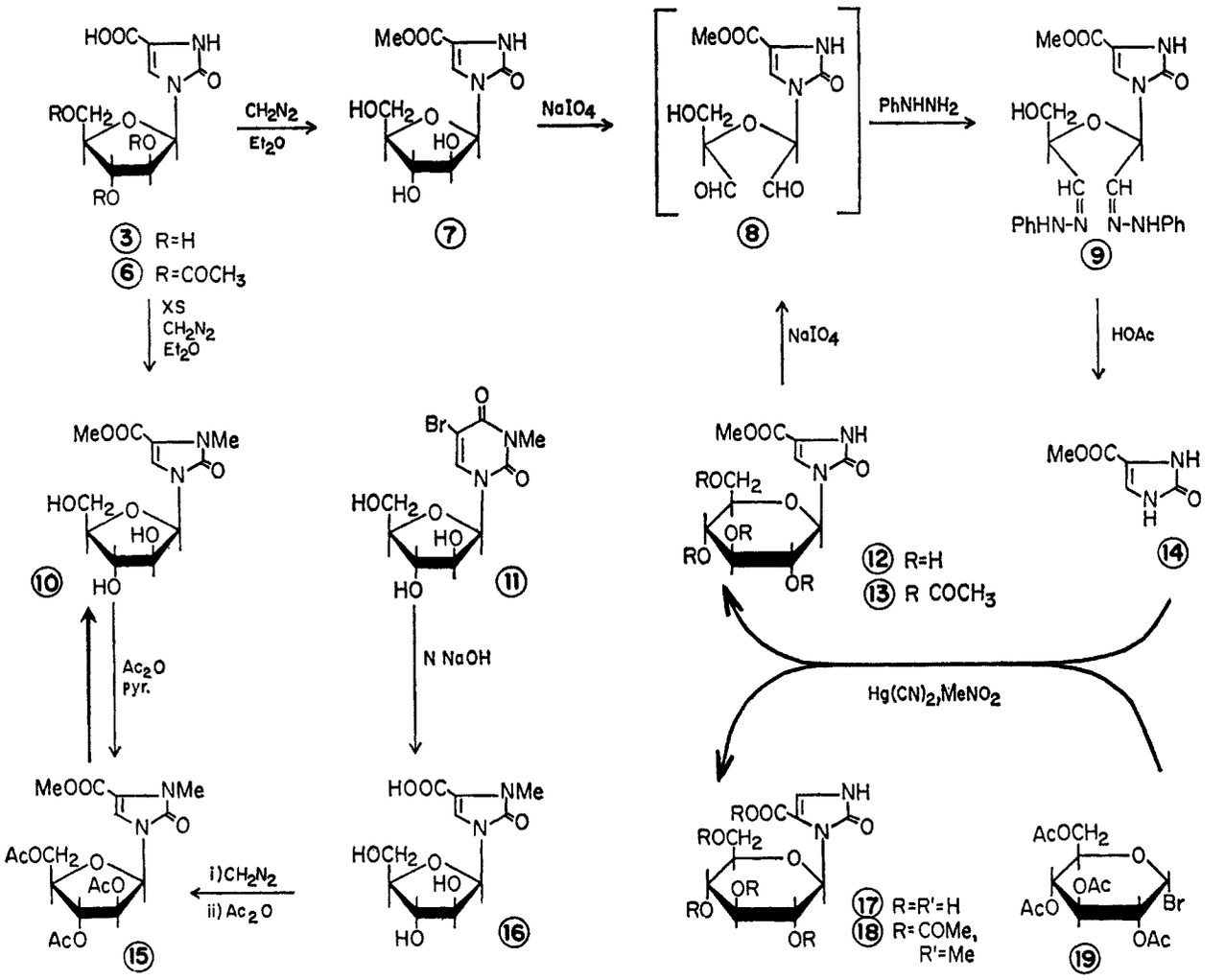


Figure 2.

drazine and acetic acid gave a mixture of products from which a small amount of a crystalline, ultraviolet absorbing product was isolated by preparative thin layer chromatography. This material showed chromatographic mobility, and absorption properties (infrared and ultraviolet) identical with those of the methyl ester (**14**) prepared by esterification of 2-oxo-4-imidazoline-4-carboxylic acid (**26**). These data establish that **3** and its derivatives are 2-oxo-4-imidazoline-4-carboxylic acid nucleosides.

It was possible, although unlikely, that the formation of **3** from **2** or **4** involved a migration of the sugar moiety. In order to determine the site of substitution of the imidazoline ring it was necessary to compare the ultraviolet spectral data of **3** with those of 1- and 3-methyl-2-oxo-4-imidazoline-4-carboxylic acid. The preparation of these alkylated imidazolines of unequivocal structure was accomplished as follows. Treatment of the ethyl ester of β,β-diethoxyalanine[9] (**20**, Figure 3) with methyl isocyanate afforded the *N*-methylureide **21** in quantitative yield. Ring closure of **21** in dilute sulfuric acid gave the ethyl ester (**22**) which was hydrolyzed with dilute sodium hydroxide to 1-methyl-2-oxo-4-imidazoline-4-carboxylic acid (**24**). Further confirmation of the structure of **24** was obtained by its conversion into 1,3-dimethyl-2-oxo-4-imidazoline-4-carboxylic acid (**27**), a known compound[10] previously prepared by methylation of **26**. Hilbert[10] demonstrated that the condensation of urea with tartaric acid in fuming sulfuric acid gave compound **26**. When *N*-methylurea was substituted for urea in this reaction, 3-methyl-2-oxo-4-imidazoline-4-carboxylic acid (**23**)

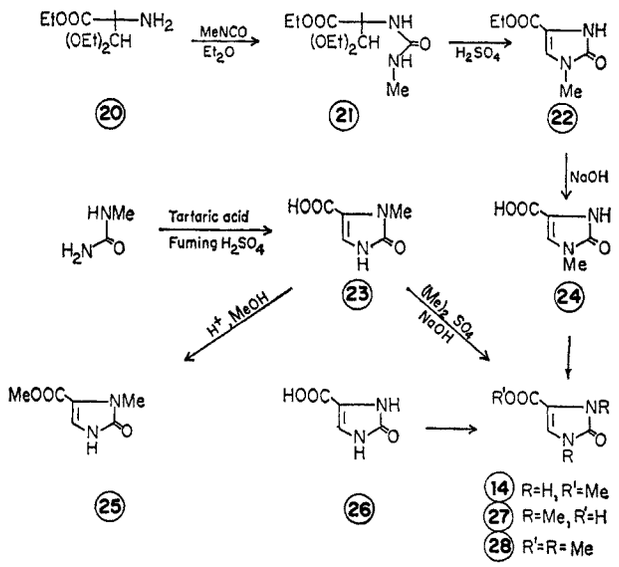


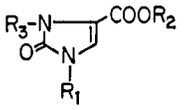
Figure 3.

(9) E. V. Brown, "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and Sir R. Robinson, Eds., Princeton University Press, Princeton, N. J., 1949, p 517.

(10) G. E. Hilbert, *J. Amer. Chem. Soc.*, **54**, 3413 (1932).

TABLE I

ULTRAVIOLET AND APPARENT pK_a DATA[a] FOR 2-OXO-4-IMIDAZOLINE-4-CARBOXYLIC ACID AND DERIVATIVES



				pH 1				pH 7				pH 14					
Compd	R_1	R_2	R_3	λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{min}, mμ	$\epsilon \times 10^{-3}$	λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{min}, mμ	$\epsilon \times 10^{-3}$	λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{min}, mμ	$\epsilon \times 10^{-3}$	pK_{a_1}	pK_{a_2}
26	H	H	H	262	11.45	223	1.38	250	9.93	221	3.15	275	12.61	228	1.16	3.37	*b*
3	Ara	H	H	263	11.38	226	1.82	252	9.64	224	3.66	268	7.55	233	1.58	3.31	12.4
24	Me	H	H	267	11.83	225	1.59	255	9.90	222	2.77	270	7.08	230	1.69	3.41	>13
23	H	H	Me	264	10.03	224	1.71	252	8.05	223	2.59	276	11.95	236	2.20	3.56	12.3
17	H	H	Glu	262	10.30	225	1.46	251	8.18	224	3.00	276	11.50	228	1.20	3.39	12.0
14	H	Me	H	263	10.66	223	1.02	263	10.66	223	1.02	288	~11.39[c]	235	~0.44[c]		
22	Me	Et	H	269	12.55	228	1.21	269	12.55	228	1.21	289	~9.36[c]	240	~1.02[c]		
7	Ara	Me	H	265	11.40	227	1.24	265	11.40	227	1.24	287	~9.17[c]	240	~1.12[c]		~10[c]
12	Glu	Me	H	265	11.69	227	1.46	265	11.69	227	1.46	284	~8.07[c]	238	~1.30[c]		
27	Me	H	Me	269	10.95	228	1.82	257	8.83	224	2.83	257	8.83	224	2.83	3.55	
16	Ara	H	Me	267	10.12	228	1.24	255	8.10	225	2.96	257	8.70	224	2.96	3.45	
28	Me	Me	Me	270	11.36	231	1.45	270	11.36	231	1.45		*d*		*d*		
10	Ara	Me	Me	269	11.60	226	1.24	269	11.60	226	1.24		*d*		*d*		
25	H	Me	Me	267	10.11	226	1.20	267	10.11	226	1.20	291	~13.85[c]	236	~0.87[c]		
18	H	Me	Glu Ac	264	10.80	226	0.92	264	10.80	226	0.92	292[e]	~15.86[c]	238	~0.24[c]		

[a] Determined spectrophotometrically by methods previously described [J. J. Fox and D. Shugar, *Bull. Soc. Chim. Belges*, **61**, 44 (1952)]. pK_{a_1} values refer to ionization of the carboxyl group and are accurate to ±0.05 pH unit. pK_{a_2} values refer to ionization of NH groups and are accurate to ±0.1 pH unit unless otherwise specified. [b] pK_{a_2} and pK_{a_3} values not determined. [c] The spectrum in alkali was determined as quickly as possible. Some deesterification takes place making determination of accurate pK_{a_2} values impossible. [d] Rapid deesterification occurs. [e] Determined at pH 12. pK_{a_3} (3-NH dissociation) is approximately 10 (see **7**).

was obtained; none of the isomeric 1-methyl derivative (**24**) was detected. The structure of **23** was confirmed by its conversion into the same dimethyl derivative (**27**) as was formed from **24** and **26**. Esterification of **23** with H_2SO_4–MeOH, and of **27** with diazomethane, afforded the methyl esters **25** and **28**, respectively.

The ultraviolet spectral data of the imidazolines **22**–**28**, and of the arabinosyl derivatives **3**, **7**, **10**, and **16** are recorded in Table I. The values obtained for the imidazoline nucleoside **3**, and its methyl ester **7**, are closely similar to those of the 1-methylimidazolines **24** and **22**, respectively, but differ from those of the 3-methylimidazolines **23** and **25**. Moreover, the values obtained for the N-methylated nucleosides **10** and **16** are in good agreement with those of the corresponding alkylated imidazolines **28** and **27**. These data confirm that **3** and its derivatives are N-1-substituted nucleosides.

The bathochromic shift (2 mμ) observed between pH 7 and pH 14 in the spectrum of nucleoside **16** is probably a consequence of ionization of the 2′-hydroxyl group. Such an ionization would cause electronic shifts in the imidazoline ring, possibly as a result of cleavage of a hydrogen bond between the 2′-hydroxyl group and the imidazoline moiety. This involvement of the 2′-hydroxy group is supported by the fact that the spectrum of the corresponding 1-methylimidazoline (**27**) showed no shift in the high alkaline region. An alkaline shift was also observed in the spectrum of the 3-methyl-5-bromouracil nucleoside (**11**). It should be noted that spectral shifts in the high alkaline region had been observed previously[11] for pyrimidine nucleosides and these were interpreted[12a] as a reflection of rupture of hydrogen bonding between the 2-carbonyl group and the sugar moiety, mainly with the 2′-hydroxyl function. Many examples of such spectral shifts in alkali, attributable to sugar ionization in pyrimidine nucleosides, have since been reported.[3c,12b,c] Spectral shifts caused by ionization of the 2′-hydroxyl group of nucleoside **3** are masked by the ionization of the NH group.

The high pK_{a_2} value found for **3** is to be expected because of prior ionization of the carboxyl group. When carboxyl ionization is prevented, as in the methyl ester **7**, the pK_{a_2} value decreases to ~10. As expected, the pK_{a_2} value (12.4) found for **3** is somewhat lower than the value observed (>13) for the corresponding 1-methylimidazoline **24**. Similarly, the NH dissociation constants of uracil nucleosides are lower than that of 1-methyluracil.[11]

The nmr spectra (DMSO-d_6) of the 1-alkylated imidazolines **22** and **24** revealed a long-range coupling of ~1.5 cps between N-3 H and H-5. These couplings, which were also observed in the spectra of the arabinosylimidazoline nucleosides **3**, **6**, and **7** and the 1-glucopyranosyl nucleoside **13**, disappeared on addition of D_2O and upon irradiation of the N-3 H signals. Couplings between N-1 H and H-5 in the 3-alkylated imidazolines **23** and **25** were not resolved but their presence was indicated by broad H-5 signals (half band width ~3 cps) which sharpened (half band width ~1 cps) on the addition of D_2O. A $J_{N\text{-}1\ H,H\text{-}5}$ value of 2.5 cps was found for the 3-glucopyranosyl nucleoside (**18**). Broad H-5 signals were also observed in the spectra of the imidazolines **14** and **26**. In these compounds coupling between H-5 and both N H protons is possible.

A possible mechanism (Figure 4) for the formation in alkali of the imidazoline **3** (65%) and the 2′,6-anhydro compound **5** (7%) from 1-β-D-arabinofuranosyl-5-bromouridine (**4**) would involve the initial formation of the

(11) J. J. Fox and D. Shugar, *Biochem. Biophys. Acta*, **9**, 369 (1952).

(12) (a) J. J. Fox, L. F. Cavalieri, and N. Chang, *J. Amer. Chem. Soc.*, **75**, 4315 (1953); (b) J. J. Fox, J. F. Codington, N. C. Yung, L. Kaplan, and J. O. Lampen, *ibid.*, **80**, 5155 (1958); (c) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *ibid.*, **81**, 178 (1959).

anion **A** (X = Br) by nucleophilic attack of the 2′-oxygen anion on C-6, as previously proposed[3a] for the formation of **A** (X = F) from **1**. Elimination of the elements of hydrogen bromide from **A** would give the monoanion of **5**. The major reaction of **4** in alkali, however, is ring opening to **B** (X = Br). Ring closure of **B** to **3** could proceed *via* intermediate **C** formed as a result of nucleophilic displacement of the halogen atom by the amide nitrogen. Elimination of the anhydro linkage (loss of sugar alcohol) from **C** would yield the imidazoline nucleoside **3**. The displacement of the halogen of **B** may involve neighboring-group participation by the carboxylate anion. Some evidence in support of this mechanism for imidazoline formation (**4** → **A** → **B** → **3**) is obtained in the 5-fluoro series. As already described,[3a] treatment of **1** with 0.1 *N* alkali gives crystalline **B** (X = F) which is converted into **3** on treatment with 1 *N* NaOH.

An alternative mechanism for the conversion of **B** into **3** in 1 *N* NaOH would involve displacement of the halogen (with or without participation of the carboxylate anion) by hydroxide ion. Elimination of the elements of sugar alcohol would give an α,β-unsaturated α-hydroxy acid which would rearrange to an α-keto acid. Ring closure of the α-keto acid to **3** would occur by attack of the amide nitrogen on the α-carbonyl group followed by elimination of water. Evidence against this mechanism is that treatment of **2** with 1 *N* sodium methoxide in hot, anhydrous methanol also yields the imidazoline **3**. In this case formation of an α-keto acid, by a mechanism involving methoxide rather than hydroxide ion, is impossible.

The fact that treatment of arabinosyl-5-bromouracil (**4**) with warm 0.1 *N* sodium methoxide gives a 75% yield of **5** without any detectable formation of imidazoline can be rationalized as follows. Ring cleavage of **A** by methoxide ion attack at C-4 would form the methyl ester of **B**. Such a reaction should be reversible since it has been demonstrated[3a] that esterification of the 6,2′-anhydro acyclic ureide derivative (**2**, Figure 1) causes rapid ring closure back to the 5-fluoropyrimidine nucleoside. Thus, the equilibrium [**A** ⇋ methyl ester of **B**] is highly displaced toward A which would favor the exclusive formation of **5** by the irreversible elimination of HBr.

It should be noted that, in all the reactions described leading to imidazoline nucleosides, participation of the sugar moiety is involved.[13] This conclusion is obviously warranted in the 5-fluoro series (**1** → **2** → **3**) where the intermediate **2** has been isolated. The postulated intermediate in the conversion of the bromo nucleoside **A** into **3**, namely the 5-bromo analog of **2**, has not been isolated, presumably because it undergoes rapid ring closure to **3**.

That the sugar moiety was involved in the conversion of **4** → **3** is indicated from model studies with 1-methyl-5-bromouracil (**29**, Figure 5). Treatment of **29** with 1 *N* NaOH at ~55° for 6 hr afforded a ~50% yield of 1-methylbarbituric acid (**31**). None of the 1-methyl-2-oxo-4-imidazoline-4-carboxylic acid (**24**) was formed in this reaction. 1-Methylbarbituric acid, however, undergoes a slow decomposition under these

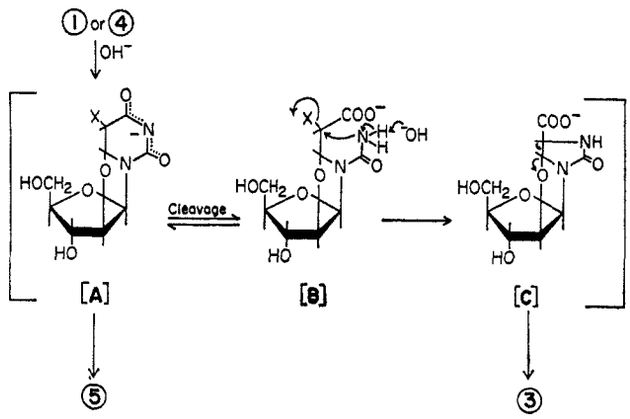


Figure 4.

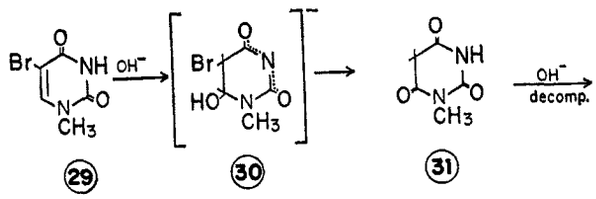


Figure 5.

alkaline conditions to product or products which at pH 7–8 are devoid of selective ultraviolet absorption. This decomposition accounts for the only fair yield obtained of 1-methylbarbituric acid. The formation of **31** is readily explained by the irreversible elimination of HBr from the postulated intermediate **30**, which is formed by hydroxide ion attack on C-6. The formation in 1 *N* sodium hydroxide of **31** from **29** is analogous to the formation of the 6-hydroxyuridine derivative (**5**) from arabinosyl-5-bromouracil (**4**).

2-Oxo-4-imidazoline nucleosides offer many possibilities for the synthesis of compounds of potential biochemical interest. The ribofuranosyl analog of the imidazoline nucleoside **3** has been prepared by base-catalyzed rearrangement of 2′,3′-*O*-isopropylidene-5-halogenouridines. This rearrangement proceeds with participation of the 5′-hydroxy group and will be reported in a subsequent paper in this series. An alternative procedure for the preparation of imidazoline nucleosides is by total synthesis, a method that we have used in the glucopyranosyl series. Condensation of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**19**, Figure 2) with the imidazoline methyl ester **14** by the $Hg(CN)_2$ nitromethane procedure[14] afforded two crystalline nucleosides, **13** and **18**. Deesterification of the minor product (**18**) with dilute alkali afforded the imidazolinecarboxylic acid nucleoside (**17**). The close similarity of the ultraviolet spectra of **17** and **18** with those of the corresponding 3-methylimidazolines **23** and **25**, respectively, establishes the N-3 glycosyl structure.[15] The H-1′,H-2′ coupling constant (~9.0 cps) observed for **17** and **18** indicates a *trans*-diaxial arrangement (*C1* conformation) and establishes the 1-β-D configuration. Deacetylation of the major component (**13**) with sodium methoxide in methanol afforded the methyl ester **12**. The N-1 glycosyl structure of **12** was established by the similarity of the ultraviolet spectral

(13) The base-catalyzed conversion of 5-hydroxyuracil nucleosides into 4-imidazoline-4-carboxylic acid nucleosides [B. A. Otter, E. A. Falco, and J. J. Fox, *Tetrahedron Lett.*, 2697 (1968)] proceeds by a mechanism which does not involve participation of a sugar hydroxyl group.

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

(15) An *O*-glucoside structure was originally suggested[1b] for this compound. However, the stability of the glycosyl bond to methanolic HCl and the uv data, establish the N-3 structure.

data to those of the 1-substituted imidazolinecarboxylic esters **7** and **22** and by conversion into the bisphenylhydrazone **9**. Thus, oxidation of **12** with sodium metaperiodate followed by treatment with phenylhydrazine afforded a bisphenylhydrazone with melting point behavior and spectral properties (infrared and ultraviolet) identical with those of the bisphenylhydrazone **9** obtained from the arabino nucleoside **7**. These results establish the 1-β-D configuration of **12** and **13** and also confirm the 1-β-D structure of the arabinosyl nucleoside **3** and its derivatives.

Experimental Section

General Procedures.—Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are corrected. The ultraviolet spectra were determined on a Cary Model 15 spectrometer; the nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer using DMSO-d_6 as solvent and tetramethylsilane as an 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 (given in cycles per second) are first order. Thin layer chromatography was performed on silica gel GF (Merck). Separated materials were detected with ultraviolet light and by spraying with 10% v/v sulfuric acid in ethanol followed by heating at 110°. Evaporations were carried out *in vacuo* with bath temperatures kept below 45°. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

1-β-D-Arabinofuranosyl-2-oxo-4-imidazoline-4-carboxylic Acid (3). Method A.—A solution of 140.1 mg (0.5 mmol) or **2**[3a] in 5 ml of 1 *N* NaOH was heated at 60°. Spectral examination of aliquots diluted to 1×10^{-4} *M* with water showed the gradual appearance of an absorption band at 252 mμ, which reached a maximum (OD = 0.57) at 20 hr. Electrophoresis of the reaction mixture in borate buffer at pH 9 showed only one uv-absorbing product. The pale yellow reaction mixture was passed through a column containing 7 ml of Dowex 50 (H^+). The column was eluted with water until the effluent was free of uv-absorbing material. Concentration of the eluate to ~1 ml, followed by cooling, afforded clusters of colorless needles (76 mg, 54%), mp 196–198° eff, dec (melts partially at 118–120° and resolidifies). Recrystallization from water afforded analytically pure material with unchanged melting behavior.

Anal. Calcd for $C_9H_{12}N_2O_7 \cdot H_2O$:[16] C, 38.87; H, 5.08; N, 10.07. Found: C, 39.24; H, 5.15; N, 10.05.

Anhydrous material, obtained by drying the hydrate over P_2O_5 at 100°, melted at 139–141°: nmr, 10.65 (1, broad s, NH), 7.32 (1, d, H-5), 5.75 (1, d, H-1′), ~5.5 (3, very broad band, 3 OH), ~4.0 (2, m, H-2′, H-3′), ~3.6 (3, m, H-4′, H-5′, H-5′), $J_{1',2'} = 4.0$ and $J_{5,NH} = 1.5$ cps.

Anal. Calcd for $C_9H_{12}N_2O_7$: C, 41.55; H, 4.66; N, 10.77. Found: C, 41.27; H, 4.66; N, 10.73.

When anhydrous **3** was recrystallized from MeOH–Et_2O (1:1), material with mp 230–233° eff, dec (darkening above 215°), was obtained. The infrared spectrum (KBr disk) of this material differed considerably from that of material with mp 139–141°. However, heating the KBr disk of the lower melting form at 110° for 30 min changed its infrared spectrum to that of the higher melting form.

Method B.—A sample of **4**[17] (3.23 g, 10 mmol) was dissolved in 100 ml of 1 *N* NaOH and the solution was heated at 55°. Spectral examination of aliquots diluted to 1×10^{-4} *M* with water showed a rapid loss of absorption at 277 mμ with concomitant appearance of peak at 252 mμ which reached a maximum (OD = 0.86) at 6 hr. The yellow solution was passed through a column containing an excess (~100 ml) of Dowex 50 (H^+), and the effluent and washings were concentrated to 30 ml. On cooling, 1.6 g (58%) of hydrated **3** was obtained with mp and mmp 196–198° eff, dec (melts partially at 118–120° and resolidifies). The ir and iv spectra of this product were identical with those of hydrated **3** above.

Electrophoresis of the mother liquor in borate buffer (pH 9) showed three uv-absorbing components. These were separated by chromatography on a column (2 × 10 cm) of Dowex AG-1X8 (OAc^-). Elution with water afforded two fractions which on evaporation yielded 175 mg (7%) of material identical with compound **5** described below, and 40 mg of starting material. Elution with 0.1 *N* HCl afforded a fraction from which 200 mg (7%, total yield 65%) of hydrated **3** was isolated.

1-Tri-*O*-acetyl-(β-D-arabinofuranosyl)-2-oxo-4-imidazoline-4-carboxylic Acid (6).—Acetic anhydride (0.3 ml, 3.2 mmol) was added to a solution of anhydrous **3** (260 mg, 1 mmol) in 10 ml of dry pyridine. The solution was kept at room temperature for 2 hr. Ethanol (1 ml) was added and the solution was concentrated to a syrup which crystallized on standing. Recrystallization from 50% aqueous ethanol afforded 347 mg (90%) of pure **6**: mp 250–252° eff (sinters at 247°); $\lambda_{max}^{pH\ 7}$ 252 mμ; $\lambda_{max}^{pH\ 1}$ 262 mμ; nmr, 10.85 (1, broad s, NH), 7.34 (1, d, H-5), 6.04 (1, d, H-1′), ~5.4 (2, m, H-2′, H-3′), ~4.3 (3, m, H-4′, H-5′, H-5′), 2.11, 2.08, 1.96 (three singlets, nine protons; acetyl methyls), $J_{1',2'} = 4.9$ and $J_{5,NH} = 1.5$ cps.

Anal. Calcd for $C_{15}H_{18}N_2O_{10}$: C, 46.64; H, 4.70; N, 7.25. Found: C, 46.42; H, 4.97; N, 7.34.

2′,6-Anhydro-1-(β-D-arabinofuranosyl)-6-hydroxyuridine (5).—A sample of **4** (1.62 g, 5 mmol) was dissolved in methanol containing sodium (575 mg, 25 mg-atoms) and the solution was refluxed for 22 hr. The cooled solution was treated with an excess (~25 ml) of ethanol-washed Dowex 50 (H^+) and the filtrate and washings were concentrated to dryness. Recrystallization of the residue from aqueous ethanol (charcoal) afforded 908 mg (75%) of product in two crops. A recrystallized sample had mp 246–248° (darkens above 240°) (lit.[4] mp 238°); $\lambda_{max}^{pH\ 1\text{-}7}$ 252 mμ (ε 15,950); $\lambda_{max}^{pH\ 14}$ 255 mμ (ε 11,650); nmr, 10.96 (1, broad s, NH), 6.27 (1, d, H-1′), 5.86 (1, d, 3′-OH), 5.28 (1, d, H-2′), 5.01 (1, s, H-5), 4.98 (1, t, 5′-H), 4.33 (1, q, H-3′), 4.03 (1, sextet, H-4′), 3.33 (2, t, H-5′, H-5′), $J_{1',2} = 5.2$, $J_{2',3'} \sim 0$, $J_{3',4'} = 2.0$, $J_{4',5'} = 5.1$, $J_{3',OH} = 4.5$, $J_{5',OH} = 5.1$ cps.

Anal. Calcd for $C_9H_{10}N_2O_6$: C, 44.63; H, 4.16; N, 11.57. Found: C, 44.72; H, 4.07; N, 11.47.

1-β-D-Arabinofuranosyl-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (7).—A solution of 602 mg (2.32 mmol) of anhydrous **3** in 20 ml of dry methanol was cooled to −5°. Diazomethane (2.4 mmol, estimated with benzoic acid) in ether was added dropwise over a period of 10 min. After the addition was complete, evolution of nitrogen ceased and the solution remained pale yellow. Tlc ($CHCl_3$–MeOH, 5:1) showed a major component, traces of starting material, and a fast moving component subsequently identified as **10**. The reaction mixture was concentrated to a syrup which failed to crystallize and was therefore fractionated by chromatography on silica gel (2 × 20 cm) with 5:1 $CHCl_3$–MeOH, as solvent. The syrupy major component was dissolved in 1:1 MeOH–Et_2O, and petroleum ether (30–60°) was added to turbidity. Crystals of **7** (500 mg, 79%) formed slowly on cooling. Recrystallized material melted at 100–102°: nmr, 10.82 (1, broad s, NH), 7.41 (1, s, H-5), 5.72 (1, d, H-1′), 5.55 (1, d, 2′-OH), 5.40 (1, d, 3′-OH), 5.01 (1, t, 5′-OH), ~4.0 (2, m, H-2′, H-3′), 3.76 (3, s, CO_2CH_3), ~3.66 (3, m, H-4′, H-5′, H-5′) $J_{1',2'} = 4.2$, $J_{2',OH} = 5.0$, $J_{3',OH} = 4.0$, $J_{5',OH} = 5.0$ cps ($J_{5,NH}$ not resolved but H-5 signal sharpens on D_2O addition).

Anal. Calcd for $C_{10}H_{14}N_2O_7$: C, 43.80; H, 5.15; N, 10.22. Found: C, 43.66; H, 5.20; N, 9.97.

1-(β-Tri-*O*-acetyl-D-arabinofuranosyl)-3-methyl-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (15).—A solution of 1.04 g (4 mmol) of anhydrous **3** in 80 ml of dry methanol was treated with an excess of diazomethane in ether. The solution was kept at room temperature for 5 hr and then concentrated to dryness. The syrupy residue, containing predominately compound **10**, was dissolved in pyridine (50 ml) and the solution was again evaporated to dryness. This procedure, which serves to remove methanol, was repeated. Acetic anhydride (1.4 ml, 15 mmol) was added to a solution of the syrup in pyridine (20 ml) and the mixture was kept at room temperature for 4 hr. The solution was concentrated to ~5 ml and then diluted with water (15 ml). Colorless needles of **15** separated on cooling. Recrystallization from aqueous ethanol afforded pure material (1.4 g, 87%): mp 116–118° (sinters at 105°); nmr, 7.51 (1, s, H-5), 6.06 (1, d, H-1′), ~5.56 (2, m, H-2′, H-3′), ~4.23 (3, m, H-4′, H-5′, H-5′), 3.80 (3, s, CO_2CH_3), 3.33 (3, s, NCH_3), 2.11, 2.08, 1.93 (three singlets, nine protons, acetyl methyls), $J_{1',2'} = 5.0$ cps.

Anal. Calcd for $C_{17}H_{22}N_2O_{10}$: C, 49.27; H, 5.35; N, 6.76. Found: C, 49.18; H, 5.35; N, 6.85.

(16) Water of crystallization confirmed by nmr spectroscopy.

(17) J. H. Hunter, U. S. Patent 3,155,646 (1964).

Silica gel chromatography of the reaction mixture obtained from methylation of **3** with excess diazomethane afforded material with mp 135–137°.[1b] Elemental analysis of this product indicated the formula, $C_{11}H_{16}N_2O_7$, to be consistent with **10**, and the product appeared to be homogenous (tlc) on several solvent systems. However, the presence of an impurity was indicated by the uv spectrum which showed a shift (264–266 mμ) on acidification (pH 1) of the neutral solution. This anomaly was not observed in the spectrum of **10** prepared by deacetylation of **15** as described below.

1-β-D-Arabinofuranosyl-3-methyl-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (10).—A solution of sodium (~20 mg) in 5 ml of dry methanol was added to a solution of **15** (414 mg, 1 mmol) in 10 ml of dry methanol and the solution was kept at room temperature for 5 hr. Sodium ions were removed by the addition of an excess (2 ml) of methanol-washed Dowex 50 (H^+). The filtrate was concentrated to a syrup which was then dissolved in MeOH–Et_2O (1:1). This solution deposited crystals (250 mg, 87%) when diluted with petroleum ether (30–60°). A further crystallization afforded pure **10**: mp 150–152°; nmr, 7.48 (1, s, H-5), 5.78 (1, d, H-1′), 5.53 (1, d, 2′-OH), 5.36 (1, d, 3′-H), 4.98 (1, t, 5′-OH), ~4.0 (2, m, H-2′, H-3′), ~3.70 (3, m, H-4′, H-5′, H-5′), 3.76 (3, s, CO_2CH_3), 3.36 (3, s, NCH_3), $J_{1',2'}$ = 4.0, $J_{2',OH}$ = 5.0, $J_{3',OH}$ = 4.0, $J_{5',OH}$ = 5.0 cps.

Anal. Calcd for $C_{11}H_{16}N_2O_7$: C, 45.83; H, 5.59; N, 9.72. Found: C, 45.61; H, 5.57; N, 9.59.

1-β-D-Arabinofuranosyl-5-bromo-3-methyluridine (11).—An excess of diazomethane in ether was added to a solution of **4** (2 g, 6.19 mmol) in 200 ml of ethanol. The yellow solution was kept at room temperature for 3 hr and then evaporated to dryness. The glasslike residue was crystallized from ethyl acetate–petroleum ether (30–60°). A single recrystallization from the same solvent pair afforded pure material (1.56 g, 75%) with mp 150–153°. In a subsequent preparation, dimorphic material with mp 184–186° was obtained. Both samples gave identical uv and nmr spectra: $\lambda_{max}^{pH\ 1-7}$ 280 mμ (ε 8590); $\lambda_{min}^{pH\ 1-7}$ 245 mμ (ε 1400); nmr, 8.18 (1, s, H-6), 6.06 (1, d, H-1′), 5.56 (1, d, 2′-OH), 5.48 (1, d, 3′-OH), 5.13 (1, t, 5′-OH), 4.2–3.5 (5, m, H-2′, H-3′, H-4′, H-5′, H-5′), 3.22 (3, s, NCH_3), $J_{1',2'}$ = 4.1, $J_{2',OH}$ = 5.0, $J_{3',OH}$ = 4.0, $J_{5',OH}$ = 5.0 cps.

1-β-D-Arabinofuranosyl-3-methyl-2-oxo-4-imidazoline-4-carboxylic Acid (16).—A sample of **11** (337 mg, 1 mmol) was dissolved in 10 ml of 1 *N* NaOH and the solution was heated at 55°. Spectral examination of aliquots diluted to 1×10^{-4} *M* with water showed an almost instantaneous loss of absorption at 280 mμ followed by appearance of peak at 255 mμ which reached a maximum (OD = 0.78) at 4 hr. The reaction mixture was processed as described in the preparation of **3** but, since the product failed to crystallize, it was characterized by conversion into **15**. Thus, esterification of 38 mg of syrupy **16** with diazomethane, followed by acetylation of the product (**10**) with acetic anhydride in pyridine, afforded colorless needles of **15** (46 mg, 80%) with mp and mmp 115–118° (sinters at 105°). The infrared spectrum of this sample was identical with that of **15** prepared as above.

A solution of syrupy **16** in 1 *N* NaOH was neutralized with an excess of Amberlite IRC-50. Evaporation of the filtrate to dryness afforded the sodium salt of **16** as an amorphous white solid: nmr (5:1 DMSO-d_6–D_2O), 6.96 (1, s, H-5), 5.77 (1, d, H-1′), 3.40 (3, s, NCH_3), $J_{1',2'}$ = 4.4 cps.

1-(Tetraacetyl-β-D-glucopyranosyl)-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (13) and 3-(Tetraacetyl-β-D-glucopyranosyl)-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (18).—A suspension of finely divided **14** (1.0 g, 7.04 mmol) in 200 ml of nitromethane was dried by azeotropic distillation of about 50 ml of solvent. Tetraacetyl-α-D-glucopyranosyl bromide (**19**) (5.7 g, 14.6 mmol) and mercuric cyanide (1.84 g, 7.3 mmol) were added to the hot suspension, whereupon **14** dissolved. The solution was refluxed for 1 hr, cooled, and evaporated to dryness. The amorphous residue was partitioned between chloroform (100 ml) and 30% w/w aqueous KI (20 ml). The chloroform solution was extracted with a further 30 ml of KI solution and with water and then dried ($MgSO_4$). Removal of solvent left a yellow syrup which crystallized from ethyl acetate to give crude **18** (650 mg in two crops) with mp 215–225°. Recrystallization from hot ethanol afforded pure material (560 mg, 17%) with mp 225–227°.

Anal. Calcd for $C_{19}H_{24}N_2O_{12}$: C, 48.31; H, 5.12; N, 5.93. Found: C, 48.51; H, 5.03; N, 5.82.

The mother liquors from above were fractionated by chromatography on a 3 × 30 cm column of silica gel. Elution with ethyl acetate afforded syrupy **13** which crystallized from ethyl acetate–petroleum ether (30–60°). The yield of pure **13** was 679 mg (20%): mp 108–110°; $\lambda_{max}^{pH\ 1-7}$ 262 mμ; $\lambda_{max}^{pH\ 13}$ 284 mμ. Further elution of the column with ethyl acetate gave 140 mg of a syrup which contained both **13** and **18**.

Anal. Calcd for $C_{19}H_{24}N_2O_{12}$: C, 48.31; H, 5.12; N, 5.93. Found: C, 48.24; H, 4.85; N, 5.81.

1-β-D-Glucopyranosyl-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (12).—A solution of sodium (~40 mg) in 5 ml of methanol was added to a solution of **13** (300 mg, 0.65 mmol) in 20 ml of dry methanol. The solution was kept at room temperature for 2 hr after which time tlc (1:7 MeOH–$CHCl_3$) showed that no starting material remained. Dowex 50 (H^+) (3 ml) was added to remove sodium ions; the resin was washed with water; and the filtrate and washings were concentrated to a syrup. Crystallization from ethyl acetate afforded 142 mg (74%) of pure **12**, mp 213–214°.

Anal. Calcd for $C_{11}H_{16}N_2O_8 \cdot {}^1/_2H_2O$:[16] C, 42.17; H, 5.45; N, 8.94. Found: C, 41.86; H, 5.56; N, 8.68.

3-β-D-Glucopyranosyl-2-oxo-4-imidazoline-4-carboxylic Acid (17).—A solution of 100 mg (0.21 mmol) of **18** in 5 ml of 1 *N* NaOH was kept at room temperature for 5 min. The solution was neutralized with an excess of Dowex 50 (H^+) and the filtrate and washings were concentrated to a syrup which crystallized spontaneously. Recrystallization from aqueous acetone afforded **17** as the monohydrate (55 mg, 90%) with mp ~225° (indistinct, extensive foaming).

Anal. Calcd for $C_{10}H_{14}N_2O_8 \cdot H_2O$:[16] C, 38.96; H, 5.26; N, 9.08. Found: C, 38.94; H, 5.72; N, 8.94.

Biphenylhydrazone 9. Method A.—A solution of the gluconucleoside **12** (35.6 mg, 0.117 mmol) in 4 ml of 0.1 *M* sodium metaperiodate was kept at room temprature for 3.5 hr. The solution was added to a column containing 3 ml of Dowex 1 (OAc^-) and washed through with 5 ml of 0.02 *N* acetic acid into a flask containing 500 mg of anhydrous sodium acetate. Phenylhydrazine hydrochloride (33.83 mg, 0.234 mmol) was added and the solution was left at room temperature for 1 hr. The pale yellow precipitate which formed was removed and dried over P_2O_5. The yield of **9** was 38 mg (70%): mp 110–120° (darkens from 95°);[18] λ_{max}^{EtOH} 279, 240 mμ, shoulder at 305 mμ; λ_{min}^{EtOH} 227, 248 mμ.

Method B.—The arabino nucleoside **7** (32.1 mg, 0.117 mmol) was oxidized with 4 ml of 0.05 *M* $NaIO_4$ and the resulting dialdehyde (**8**) was converted into the bisphenylhydrazone **9** (34 mg, 64%) as described above. The ir and uv spectra of this product were identical with those of the bisphenylhydrazone derived from **12**; a mixture melting point showed no depression.

A sample of **9** (100 mg, prepared from **7**) was dissolved in a mixture of 7 ml of ethanol, 14 ml of 4 *N* acetic acid, and 0.15 ml of phenylhydrazine. The solution was refluxed for 15 min, cooled, and extracted with two 15-ml portions of ether. Concentration of the aqueous phase afforded a yellow solution which contained (tlc, 1:7 MeOH–$CHCl_3$) several yellow components and a uv-absorbing compound with the same R_f as authentic **14**. Fractionation of part of the aqueous solution by preparative tlc afforded crystalline material with ir and uv spectral characteristics identical with those of authentic **14**.

2-(*N*′-Methylureido)malonaldehydic Acid Ethyl Ester Diethyl Acetal (21).—A solution of methyl isocyanate (0.41 ml, 5.18 mmol) in dry ether was added to a solution of freshly distilled β,β-diethoxyalanine methyl ester[9,19,20] (**20**) (1 g, 4.88 mmol) in 10 ml of dry ether. When the mildly exothermic reaction had subsided, the solution was concentrated to a thick syrup from which the last traces of solvent and methyl isocyanate were removed by storage under high vacuum. Crystallization of the syrup occurred spontaneously. The yield of crystalline material, mp 53–55°, was 1.2 g (100%): nmr, 6.13 (2, overlapping doublets, –NH–, $-NHCH_3$), 4.69 (1, d, CH–$CH(OEt)_2$, J = 4.9 cps), 4.40 (1, q, –CH–NH–, J = 8.8 cps), 4.13 (1, q, $-CO_2-CH_2CH_3$), 3.55 (4, m, acetal CH_2), 2.56 (3, d, $-NHCH_3$, J = 4.9 cps), ~1.15 (9, overlapping triplets, ester and acetal CH_3).

(18) As shown by Khym and Cohn,[8] the melting points of bisphenylhydrazone derivatives of nucleoside dialdehydes are rather broad. Compound **9** was somewhat unstable and was not analyzed.

(19) β,β-diethoxyalanine, the precursor of **20**, was prepared according to the method of Johnson.[20]

(20) O. H. Johnson, U. S. Patent 2,478,047 (1948).

Anal. Calcd for $C_{11}H_{22}N_2O_5$: C, 50.37; H, 8.46; N, 10.68. Found: C, 50.74; H, 8.23; N, 10.69.

1-Methyl-2-oxo-4-imidazoline-4-carboxylic Acid Ethyl Ester (22).—A solution of 1.75 g (6.87 mmol) of **21** in 50 ml of 0.1 *N* H_2SO_4 was heated at 45°. The ring closure was monitored by spectral examination of aliquots (diluted to 1×10^{-4} *M* with water) which showed the gradual appearance of an absorption band at 269 mμ. This peak reached a maximum (OD = 1.12) at *ca.* 24 hr. The cooled solution was neutralized with excess Amberlite IR-45 and the filtrate and washings were evaporated to dryness. The resulting yellow solid contained (tlc, 1:7 MeOH–$CHCl_3$) a major uv-absorbing component together with some nonmigrating, yellow impurity. The yellow contaminant was removed by passage of a solution of the product in MeOH–$CHCl_3$ (1:4) through a small column (1 × 10 cm) of silica gel. Concentration of the effluent afforded a colorless solid which after two recrystallizations from ethyl acetate melted at 132–134°. The yield of pure **22** was 800 mg (71%): nmr, 10.51 (1, broad s, N–H), 7.26 (1, d, H-5), 4.11 (2, q, $CO_2CH_2CH_3$), 3.10 (3, s, N–CH_3), 1.20 (3, t, $CO_2CH_2CH_3$), $J_{NH,5}$ = 1.5 cps.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.02; H, 5.73; N, 16.30.

1-Methyl-2-oxo-4-imidazoline-4-carboxylic Acid (24).—A solution of 262.3 mg (1 mmol) of **22** in 10 ml of 0.1 *N* H_2SO_4 was heated at 45° for 24 hr. The solution was cooled and made alkaline (1 *N* in NaOH) by the addition of 1.22 ml of 10 *N* NaOH. The solution was kept at room temperature for 24 hr and then acidified with HCl. The resultng precipitate (130 mg in two crops) was recrystallized from water to give pure **24** (120 mg, 84%): mp 274–276° eff, dec (but dependent on rate of heating); nmr, 10.33 (1, broad s, N–H), 7.16 (1, d, H-5), 3.08 (3, s, N–CH_3), $J_{5,NH}$ = 1.8 cps.

Anal. Calcd for $C_5H_6N_2O_3$: C, 42.26; H, 4.26; N, 19.17. Found: C, 42.11; H, 4.04; N, 19.50.

3-Methyl-2-oxo-4-imidazoline-4-carboxylic acid (23) was prepared from N-methylurea (12.3 g), tartaric acid (11.2 g), and 40 ml of 16% fuming sulfuric acid according to the method described by Hilbert[10] for the synthesis of 2-oxo-4-imidazoline-4-carboxylic acid (**26**). The yield of pure **23** (from aqueous ethanol), mp 253–255°, was 2.5 g (24%): nmr, 10.60 (1, broad s, –NH), 7.13 (1, s, H-5), 3.25 (3, s, NCH_3).

Anal. Calcd for $C_5H_6N_2O_3$: C, 42.26; H, 4.26; N, 19.71. Found: C, 42.38; H, 4.04; N, 19.53.

3-Methyl-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (25).—Esterification of 1 g (7.04 mmol) of **23** with methanol-concentrated H_2SO_4, as described by Hilbert[10] for the synthesis of the ethyl ester of 2-oxo-4-imidazoline-4-carboxylic acid, afforded **25** (from water), mp 216–218°, in 55% yield: nmr, 11.05 (1, broad s, NH), 7.49 (1, s, H-5), 3.80 (3, s, CO_2CH_3), 3.39 (3, s, NCH_3).

Anal. Calcd for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.07; H, 5.27; N, 17.78.

1,3-Dimethyl-2-oxo-4-imidazoline-4-carboxylic Acid (27). Method A.—Dimethyl sulfate (1.05 ml, 7.04 mmol) was added to a solution of **23** (500 mg, 3.5 mmol) in 3 ml of water containing 1 g of NaOH. The solution was stirred for 1 hr and then made strongly alkaline by the addition of 50% NaOH solution. The solution was heated for 1 hr on a steam bath and then acidified with HCl. The colorless solid which formed on cooling was recrystallized from water to give 44 mg (80%) of **27**: mp and mmp 230–232° (lit.[10] mp 229–230°); nmr, 7.30 (1, s, H-5), 3.30 (3, s, N-3 CH_3), 3.17 (3, s, N-1 CH_3).

Method B.—Methylation of 500 mg (3.5 mmol) of **24** with dimethyl sulfate, as described above, afforded a 85% yield of **27** with mp and mmp 230–232° eff. The ir and uv spectrum of **27** prepared from both **23** and **24** were identical with those of authentic material prepared according to Hilbert.[10]

2-Oxo-4-imidazoline-4-carboxylic acid methyl ester (14) was prepared from 7 g of **26** according to the method described by Hilbert[10] for the corresponding ethyl ester. The yield of **14**, mp 305–310° eff, was 4.25 g (55%): nmr, 10.06 (2, broad singlet, N-1 H, N-3 H), 7.26 (1, s, H-5), 3.74 (3, s, CO_2CH_3).

Anal. Calcd for $C_5H_6N_2O_3$: C, 42.26; H, 4.26; N, 19.71. Found: C, 42.44; H, 3.95; N, 19.71.

1,3-Dimethyl-2-oxo-4-imidazoline-4-carboxylic Acid Methyl Ester (28).—Methylation of 1 g (6.42 mmol) of **27** in methanol with an excess of diazomethane in ether, afforded a 90% yield of **28** (from methanol): mp 127–129°, (lit.[21] mp 127°); nmr, 7.52 (1, s, H-5), 3.92 (3, s, CO_2CH_3), 3.36 (3, s, N-3 CH_3), 3.24 (3, s, N-1 CH_3).

Conversion of 1-Methyl-5-bromouracil (29) into 1-Methylbarbituric Acid (31).—A solution of 1.5 g (7.3 mmol) of **29** in 73 ml of 1 *N* NaOH was heated at 60° for 6 hr. Spectral examination of aliquots diluted to 1×10^{-4} *M* with water showed a gradual loss of absorption at 283 mμ with the concomitant appearance of a peak at 258 mμ. The reaction was allowed to proceed until the extinction at 283 mμ showed a decrease of 70%. [It is advisable to stop the reaction at this time because the product (**31**) undergoes slow decomposition under these alkaline conditions to product(s), which are devoid of selective absorption in the ultraviolet.] The reaction mixture was cooled and passed through a column containing an excess of Dowex 50 (H^+). The acidic eluate was concentrated to ~20 ml and cooled. A crystalline precipitate (50 mg, mp 269–271°), identical with starting material, was removed by filtration and the filtrate was concentrated to dryness. The residue was dissolved in 50 ml of hot ethanol, filtered, and chilled. The resulting precipitate (400 mg, 54% based upon a 70% conversion) was washed once with ethanol and thrice with ether. Further recrystallization from ethanol gave a product which melted at 131–132° (lit.[22] mp 132.5–133°). The uv and nmr spectra of this product were identical with those of authentic 1-methylbarbituric acid.

Registry No.—**3**, 17245-46-4; **5**, 17245-47-5; **6**, 17245-48-6; **7**, 17245-49-7; **9**, 17245-50-0; **10**, 17245-51-1; **11**, 17245-65-7; **12**, 17245-52-2; **13**, 17245-53-3; **15**, 17245-54-4; **16**, 17245-55-5; **17**, 17245-56-6; **18**, 17245-57-7; **21**, 17245-58-8; **22**, 17245-59-9; **23**, 17245-60-2; **24**, 17245-61-3; **25**, 17245-62-4; **27**, 17245-63-5; **28**, 17245-64-6.

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