A preliminary search was made for possible by-products in the reaction of LTTFA with benzene. Gas chromatography demonstrated that both biphenyl and benzotrifluoride were absent. This suggests that even though the reactions are conspicuously "free radical" in nature they do not follow a route involving "free" trifluoroacetoxy radicals.[9]

In an attempt to determine the relative specificity of reaction with aromatic and aliphatic molecules, LTTFA was prepared in the presence of both benzene and *n*-heptane. Chromatographic and spectroscopic product identification demonstrated a higher yield of phenyl than of heptyl ester. This was anticipated since there are considerable data on the ease of free-radical aromatic substitution relative to aliphatic substitution in competition.[10]

Comparative acyloxylations of *activated* aromatic substrates are known. Indeed, polycyclic and heterocyclic aromatics are both acetoxylated and methylated by lead tetraacetate, with the free-radical methylation taking place at higher temperatures only. *Nonactivated* aromatics, *e.g.*, benzene, and saturated hydrocarbons remain unaffected by LTA.[11] There is general agreement that aromatic acyloxylation with lead(IV) carboxylates (other than LTTFA) follows an ionic reaction sequence. The fact that LTTFA reacts readily with heptane and benzene, to yield heptyl trifluoroacetates and phenyl trifluoroacetate, respectively, suggests that this oxidant has unique power.

Solvents found stable to LTTFA, even above 50°, are CF_3COOH and hexafluorobenzene.[12] The utility of the above reactions and the reaction of LTTFA with alcohols and amines (in C_6F_6 and CF_3COOH) are under investigation.

(9) Compare: D. Davies, *J. Chem. Soc.*, 2351 (1963); D. Harvey, *ibid.*, 4860 (1964); M. Szwarc, *J. Am. Chem. Soc.*, **76**, 5981 (1954).
(10) Table I in J. Shelton, *ibid.*, **88**, 5222 (1966).
(11) D. Harvey, *J. Chem. Soc.*, 4860 (1964); D. Hey, *ibid.*, 3963 (1955).
(12) There is no reaction of the fluorine atoms on polyfluoroaromatic compounds, under reflux conditions, with neutral $KMnO_4$, CrO_3 (HOAc, pyridine, or H_2SO_4), $Cu(OAc)_2$, MnO_2, and HNO_3 (private communication from Professor R. Filler, Illinois Institute of Technology). A recent report, however, does describe oxidation by peracid; *cf. Chem. Abstr.*, **66**, 4361 (1967).

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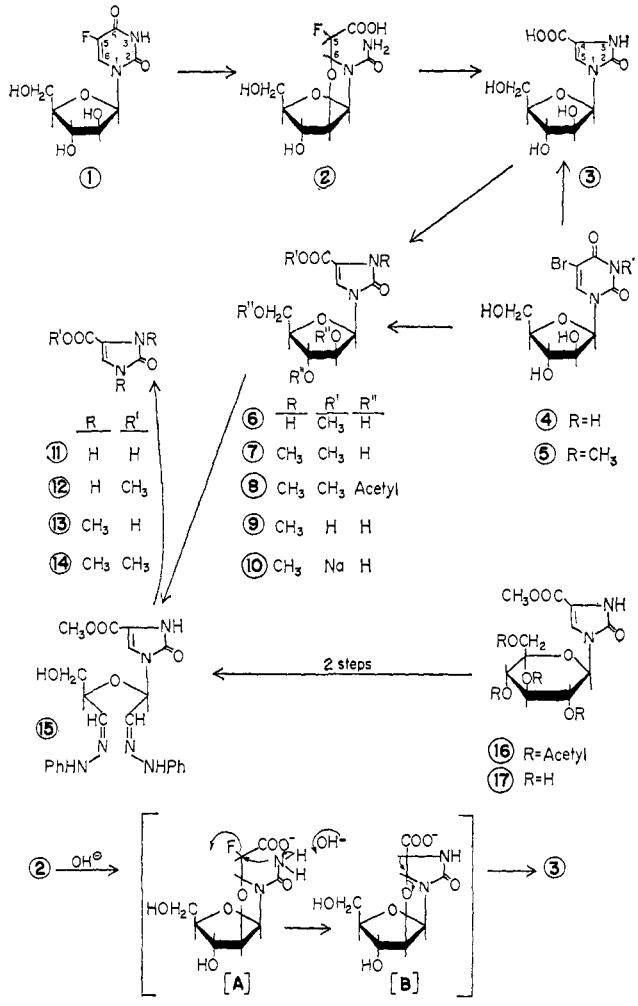
Nucleosides. XLII. A Nucleoside Rearrangement. Formation of 2-Oxo-4-imidazoline-4-carboxylic Acid Nucleosides[1]

Sir:

A recent report[2] from this laboratory demonstrated that the chemotherapeutically active[3] compounds, 1-β-D-arabinofuranosyl-5-fluorouracil (**1**, FUA) and its 5-fluorocytosine analog, are transformed in warm 0.1 *N* sodium hydroxide solution to the "6,2′-anhydro," open-chain ureide **2**. The properties of **2** have been investigated further and we now wish to report our preliminary findings on a new rearrangement of 5-halogenated arabinosyl nucleosides (see Chart I).

Chart I



The formation of **2** from FUA is accompanied by loss of ultraviolet absorption.[2] When **2** was heated in 1.0 *N* NaOH solution at 60° for 20 hr a new product was formed, as shown by the appearance of an absorption band at 267 mμ. The crystalline product **3**, mp (after drying) 230–233° dec (54% yield from water), was fluorine free and analyzed for $C_9H_{12}N_2O_7$.[4] The same product (**3**) was also obtained after 3 hr under similar reaction conditions in 61% yield *directly* from the known[5] 1-β-D-arabinofuranosyl-5-bromouracil (**4**). Evidence presented below shows that **3** is 1-(β-D-arabinofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid and that the over-all formation of **3** from **1** or **4** involved a ring contraction hitherto unreported in the nucleoside area.

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748).
(2) J. J. Fox, N. C. Miller, and R. J. Cushley, *Tetrahedron Letters*, 4927 (1966).
(3) J. J. Fox, N. Miller, and I. Wempen, *J. Med. Chem.*, **9**, 101 (1966), and leading references therein.
(4) Satisfactory elemental analyses were obtained for all crystalline compounds with melting points reported herein.
(5) J. H. Hunter, U. S. Patent 3,155,646 (1964). The authors are indebted to Dr. Masao Kunori, formerly of this laboratory, for a sample of **4**.

Compound **3** formed a crystalline tri-*O*-acetate (sinters 247°, melts 250–252°) and consumed 1 equiv of sodium metaperiodate slowly (40 hr), consistent with an *α-trans*-glycol system. The nmr spectrum of **3** in DMSO-d_6 showed a group of three exchangeable protons (OH) at δ 5.0–6.0 and a single exchangeable proton (NH) at δ 10.65 which was coupled (J = 1.5 cps) with a single vinylic proton at δ 7.32.[6] The NH signal and the long-range coupling disappeared upon addition of D_2O. The chemical shift of the NH proton is indicative of a cyclic amide and differs from the amide proton chemical shifts in 2.[2] These data show that the sugar hydroxyls are unsubstituted, that is, the "6,2′-anhydro" linkage of **2** was broken in the conversion to **3**, and, further, that cyclization of the aglycon of **2** had probably occurred. Compound **3** formed a methyl ester (**6**) (mp 100–102°) when treated with 1 equiv of diazomethane (CH_3 signal at δ 3.75, NH at 10.83). With an excess of diazomethane, compound **3** was converted to its N-methylated methyl ester **7** (mp 135–137°) which was acetylated to the tri-*O*-acetyl derivative **8** (mp 116–118°).

Proof of the cyclic structure of **3** was obtained as follows. Methylation of the 5-bromo nucleoside **4** with ethereal diazomethane gave a 70% yield of the N-methyl derivative **5**, mp 151–153°. Treatment of **5** with 1.0 *N* alkali at 55° caused a rapid loss of selective absorption in the ultraviolet followed by the gradual (over 4 hr) reappearance of selective absorption. A syrup (**9**) was obtained which was converted to an amorphous sodium salt (**10**). Methylation of **9** with excess diazomethane followed by acetylation yielded **8**, identical with that obtained by acetylation of **7**. The fact that the nmr signal for the N-methyl groups in **7**, **8**, and **10** was a *singlet* in the range δ 3.38–3.65 establishes the cyclic structure in **3**. (For an acyclic N-methylamide the methyl signal would have been a doublet.)

The foregoing analytical, nmr, and chemical data strongly suggest that compounds **3** and **6–10** are derivatives of 2-oxo-4-imidazoline-4-carboxylic acid (**11**), a known compound.[7] A comparison (see Table I) of the ultraviolet absorption spectra of **11** and its methylated derivatives **12–14** with nucleoside **3** and its methylated derivatives at pH 1 and 7 shows close similarity.[8] Attempts to degrade **3** to 2-oxo-4-imidazoline-4-carboxylic acid (**11**) under a variety of acidic conditions were unsuccessful. However, cleavage of the aglycon of the ester derivative **6** was accomplished by the method of Khym and Cohn.[9] Oxidation of **6** with excess periodate followed by treatment with phenylhydrazine afforded a crystalline bisphenylhydrazone (**15**), mp 110–120°.[10] Treatment of **15** with phenylhydrazine and acetic acid afforded a small amount of crystalline material which showed chromatographic mobility (tlc, chloroform–methanol, 5:1) and ultraviolet and infrared spectra identical with the methyl ester **12**.

Table I. Ultraviolet Absorption Properties of 2-Oxo-4-imidazoline Derivatives

Compd	pH 7 λ_{max}, mμ	pH 7 λ_{min}, mμ	pH 1 λ_{max}, mμ	pH 1 λ_{min}, mμ
11[7]	250	221	262	223
3	252	224	263	226
12[a]	263	223	263	223
6	265	227	265	227
13[7]	257	224	269	228
9	255	225	267	228
14[b]	270	231	270	231
7	264	227	266	225

[a] Mp 305–310° dec (effervescence). [b] Mp 127–129°.

The same bisphenylhydrazone **15** was obtained by total synthesis. Condensation of the methyl ester of 2-oxo-4-imidazoline-4-carboxylic acid (**12**) with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in nitromethane in the presence of mercuric cyanide, according to the procedure of Yamaoka, *et al.*,[11] afforded two crystalline compounds.[12] Deacetylation of the major product **16** (mp 108–110°, 20% yield) with sodium methoxide in methanol afforded the crystalline nucleoside **17**, mp 213–214°, which, when treated with excess metaperiodate and then with phenylhydrazine, afforded a bisphenylhydrazone with melting point behavior and infrared and ultraviolet spectral properties identical with those of **15**. These results offer independent proof of the structure of **3** and also establish the 1-β-D configuration in all the 2-oxo-4-imidazoline nucleosides listed in the flow chart. The arabinofuranosyl (rather than xylofuranosyl) configuration in **3**, **6–10** is further established by the failure of **6** to react with a solution of HCl (gas) in acetone. This reagent is known to cause 3′,5′-*O*-isopropylidene ring formation with 1-β-D-xylofuranosylpyrimidine nucleosides.[13]

A plausible mechanism for the conversion of **2** to **3** would involve first a nucleophilic attack of the amide nitrogen of A on C_5 with displacement of the halogen atom to give B, followed by elimination of the alcohol from B (loss of the "6,2′-anhydro" linkage) to form **3**.

2-Oxo-4-imidazoline nucleosides offer many possibilities as starting materials for the synthesis of compounds of potential biochemical interest. Studies in this area are currently under investigation. Preliminary results indicate that a similar type rearrangement occurs also with certain 5-halogeno-ribofuranosylpyrimidine nucleosides.

Acknowledgment. The authors are indebted to Mrs. Naishun C. Miller for assistance in the early stages of this investigation.

(6) The COOH proton of **3** was not evident in the nmr spectrum. We demonstrated later that the signal of the corresponding proton in 2-oxo-4-imidazoline-4-carboxylic acid (**11**) was so broad as to be barely discernible in the 60-Mc spectrum in DMSO-d_6.

(7) G. E. Hilbert, *J. Am. Chem. Soc.*, **54**, 3413 (1932).

(8) A more detailed analysis of the ultraviolet-absorption characteristics of the compounds in Table I, along with a consideration of their dissociation constants, will be described in a subsequent paper.

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

(10) As already shown by Khym and Cohn,[9] the melting points of bisphenylhydrazones in the nucleoside area are rather broad. Compound **15** was somewhat unstable and was not analyzed. The ultraviolet absorption spectrum of **15** was similar to that of the bisphenylhydrazone[9] derived from the dialdehyde of uridine.

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

(12) The minor component, mp 225–227°, separated from **16** by column chromatography on silica gel, was presumably the *O*-glucoside since it was easily degraded to the aglycon in alkaline media. This compound was not investigated further.

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

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