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SYNTHESIS OF 5-FLUORO-1-β-D-RIBOFURANOSYLIMIDAZOLE-4-CARBOXAMIDE, AN ANTIVIRAL AGENT AND INHIBITOR OF POLYNUCLEOTIDE BIOSYNTHESIS

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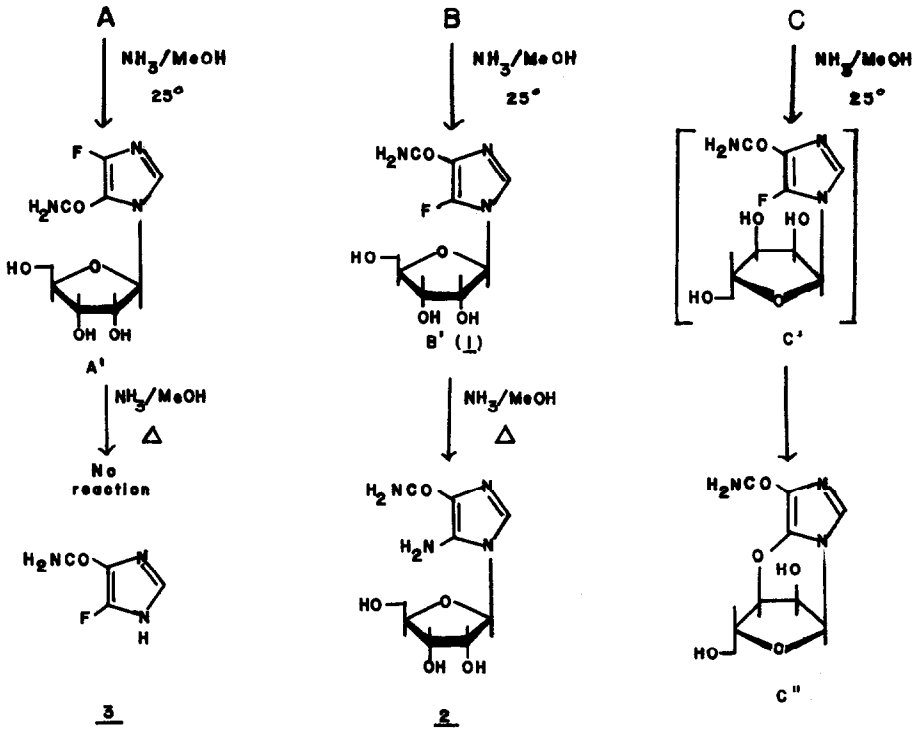
Recognition of the biomedical potential of ring-fluorinated analogs of natural imidazoles has provided the stimulus for concentrated synthetic efforts in this laboratory. Our discovery of a photochemical route to fluoroimidazoles[1] has led to the synthesis of 5-fluoro-1-β-D-ribofuranosylimidazole-4-carboxamide (1), a fluoro analog of 2, the biosynthetic precursor of adenosine and other purine nucleosides. The fluoro analog has been found an effective broad-spectrum antiviral agent and has been shown to block the biosynthesis of DNA and RNA in several cell culture systems.[2]

The most direct synthetic route to 1, *via* diazotization of 2 or its O-protected derivatives, was rejected because the diazonium group undergoes rapid cyclization with the adjacent carboxamide group,[3] and because the ribosylimidazole bond is cleaved in the fluoroboric acid medium. The synthesis of imidazole ribofuranosides by coupling of the base (or an appropriate derivative) with suitably protected and reactive ribofuranose derivatives has been accomplished in various ways;[4] nevertheless, several difficulties were anticipated in the present case: 1) The very low basicity of the imidazole ring in 3 could render the resultant N-alkylated imidazole excessively sensitive to hydrolytic cleavage.[5] 2) The electronic effects of the substituents could direct alkylation to the "wrong" nitrogen atom[5] or favor the undesired anomer.[6] 3) The conditions necessary for deblocking of the protected ribofuranose ring could result in nucleophilic displacement of the fluorine atom. 4) There seemed to be no simple method for structural elucidation of the products, short of x-ray crystallography; structural and stereochemical assignment based on earlier synthetic precedents were considered unreliable, in view of the anomalous behavior of fluoroimidazoles in other reactions.[1]

Reaction of 3 with trimethylsilyl chloride in hexamethyldisilazane (at 130-140°) gave a bis-derivative; this material was condensed with 2,3,5-tri-O-benzoylribofuranosyl chloride

(mixture of anomers)[7] in benzene, in the presence of mercuric acetate as proton acceptor (18 hr, 25°).[8] Silica-gel chromatography of the products provided isomeric protected nucleosides: isomer A (6% yield), mp 172-173°, Rf 0.42 (silica gel, ether); isomer B (42% yield), amorphous, Rf 0.04 (silica gel, ether).[9] With molecular sieve[10] [(40-45°, 10-14 days)] in place of mercuric acetate the major product (9% yield) was yet another isomer C, whose nmr spectrum differed from that of B although its ir spectrum and Rf value were the same.



Methanolic ammonia (25°, 22 hr) removed the benzoyl protecting groups from all three products to give the respective nucleosides, A', B', and C". Further exposure of B' to methanolic ammonia (50-60°, 12 days) resulted in nucleophilic displacement of the fluorine atom; spectroscopic, chromatographic, and optical rotatory properties of this material were identical with those of natural 2. Analogous replacement of the fluorine atom in A' could not be achieved, even after 32 days at 75°.[11] Analytical and mass spectral data for C" were consistent with loss of HF, suggesting that an intramolecular displacement of fluorine by a ribose hydroxyl group had occurred in the transient C'. A change in ring substituents in C" is also revealed by a bathochromic shift of 16 nm in its ultraviolet spectrum, relative to B'.

The nmr spectra of isomers A' and B' differ in that H-2 is a doublet in A' (δ 8.10, J_{HF} = 2 Hz, DMSO-d_6) and a singlet in B' (δ 7.77).[12] Examination of other N-alkylated fluoroimidazoles of known structure established the principle that when the N-alkylated nitrogen is flanked by fluorine and hydrogen, no spin coupling occurs; conversely, these substituents do couple when they are separated by the azine nitrogen atom.[13] In B', therefore, the nitrogen adjacent to fluorine must be alkylated (as had already been concluded from the conversion of B' to 2), and in A', the ribose moiety must be on the nitrogen atom next to carboxamide. The ultraviolet spectrum of B' shows λ_{max} 226 nm (MeOH), while that of A' occurs at 235 nm. These values are consistent[14] with the assignments based on nmr data. Since the conversion of B' to 2 establishes B and B' as β-anomers, C and C' must be the α-anomers at the same nitrogen atom.[15] A' is tentatively considered to have the β configuration at C-1'. Reliable assignment of stereochemistry to A' would require comparison with its anomer,[16] which has not yet been obtained. Even then, assignment may be equivocal and may require x-ray analysis.

It is fortunate that, of the three isomers obtained in condensations with 3, the desired B is formed in highest, and reasonable yield. It is also fortunate that deacylation of B is sufficiently faster than displacement of fluorine to permit isolation of B'. Such is not the case with C', because of the intramolecular rate advantage. We cannot yet account for the lack of reactivity of the fluorine atom in A'; however, we have found comparable differences in chemical reactivity in simpler N-alkylimidazole isomer pairs, and believe the phenomenon is unrelated to any special interaction with the ribofuranose moiety. Isomeric ribofuranosides have also been obtained from the carboxylic ester corresponding to 3, and from a variety of other fluoroimidazoles. In each case in which the geometry corresponds to A' or B', deacylation of the protected riboside can be achieved before loss of fluorine. We have also found nmr to be a most effective tool for structure elucidation in this series. Details of synthesis and results of biological testing of these compounds will be reported separately.

References and Footnotes

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