A Novel Stereospecific Synthesis of 5-Amino-1-β-D-fructofuranosylimidazole-4-carboxamide

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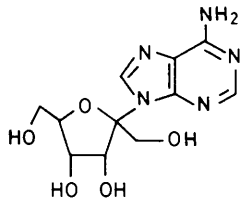
A β-D-fructofuranose fused oxazolidine-2-thione has been isolated as the t-butyldimethylsilyl derivative (**6**), which when desulphurised and treated with α-amino-α-cyanoacetamide gave the silylated 1-β-D-fructofuranosyl aminoimidazole (**2b**) which when deblocked with methanolic hydrogen chloride produced 5-amino-β-D-fructofuranosylimidazole-4-carboxamide (**2a**).

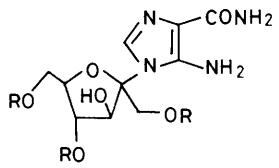
The anti-tumour activity of the naturally occurring antibiotic, psicofuranine (**1**), derived from *Streptomyces hygroscopicus*,[1] has focussed attention on similar ketohexosyl nucleosides. The antibiotic has been synthesised[2] in low yield by direct psicofuranosylation of adenine derivatives although mixtures of α- and β-anomers are obtained by this method. The cheapness of D-fructose makes the synthesis of related β-D-fructofuranosyl nucleosides of special importance since, apart from their intrinsic interest, such compounds could be valuable as easily available precursors to a variety of related nucleosides by appropriate inversion and other reactions. However fructofuranosylation of adenine derivatives produces only the α-anomer[3] and direct synthesis of β-D-fructofuranosylpurines or related aminoimidazoles has not been achieved hitherto.

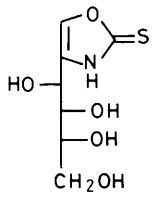
We now report a simple, direct, and unambiguous synthesis of 5-amino-1-β-D-fructofuranosylimidazole-4-carboxamide (**2a**) from inexpensive precursors; 5-aminoimidazole-4-carboxamides, including nucleosides, are readily converted into a variety of purine nucleosides by standard and well established procedures.[4]

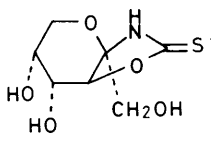
The reaction of D-fructose with KSCN and hydrochloric acid in aqueous solution has been examined by several workers and shown to produce, depending on the reaction conditions, three isomeric oxazolidine-2-thiones, namely the acyclic derivative (**3**), m.p. 216,[5] 218 °C,[6] the pyranose derivative (**4**), m.p. 189,[5] 188,[6] 185 °C,[7] and the α- or β-D-furanose derivative (**5**), m.p. 196 °C;[5] the anomeric assignment is not known with certainty in the latter compound. We have now found that when a solution of D-fructose (6 g) in water (8 ml) with KSCN (8.75 g) and 10 M-HCl was set aside at 4 °C for 8 weeks, then evaporated *in vacuo*, extraction of the residue with methanol gave, after evaporation of the extract, a residue which when dissolved in water and set aside for 1 week afforded a yellow crystalline precipitate, m.p. 190—196 °C in high (>80%) yield.

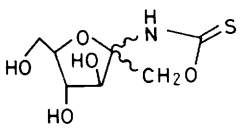
T.l.c. examination (EtOAc–MeOH, 4:1) of the material first thought to be the expected furanose isomer (**5**) showed it

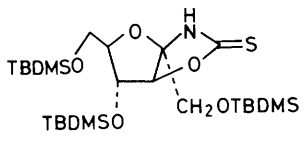

(1)

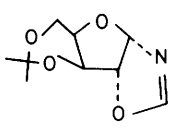

(2) a ; R = H
b ; R = TBDMS

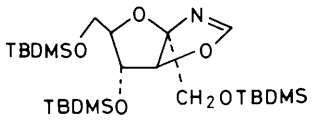

(3)


(4)


(5)


(6)


(7)


(8)

TBDMS = Bu^tMe_2Si

to be composed of two substances, a new compound with R_f 0.52, the major component, and the pyranose derivative (**4**), R_f 0.8, as the minor product. When the mixture was treated with t-butyldimethylsilyl chloride in dimethylformamide (DMF) a pure crystalline silyl derivative (**6**) was isolated in 40% yield. The structure assigned to the compound was supported by mass, and ^1H and ^{13}C n.m.r. spectroscopy.

Previously we have shown[8] that the oxazolino-sugar (**7**) is a valuable intermediate for the stereospecific synthesis of α-D-xylofuranosyl aminoimidazoles by reaction with α-amino-α-cyanoacetamide or ethyl α-amino-α-cyanoacetate. This particular oxazoline was prepared by the reaction of 3,5-*O*-isopropylidene-D-xylofuransylamine and either ethyl formimidate or dimethylformamide dimethyl acetal. However, related oxazolines have also been prepared by desulphurisation of oxazolidine-2-thiones. Accordingly, treatment of the oxazolidine-2-thione (**6**) with Raney nickel (freshly activated with acetic acid) and reaction of the oxazoline so formed, presumably (**8**), with α-amino-α-cyanoacetamide readily gave the β-D-fructofuranosylimidazole (**2b**), m.p. 146—148 °C, in 43% yield and the protecting group was removed with 0.05 M-HCl in methanol to give (**2a**), m.p. 164—166 °C, in 70% yield.

The β-configuration for (**2b**) was assigned initially by examination of the ^1H and ^{13}C n.m.r. spectra. In particular the ^1H spectrum revealed H-3′ as a slightly broadened triplet at 21 °C [Me_2SO, δ 4.28 J(3′,4′) 5 Hz] which was much broader at 60 °C owing to loss of coupling to the OH-3′ proton (δ 5.97, J 5.5 Hz at 21 °C, br. s at 60 °C). This observation confirms the involvement of the intermediate (**8**) resulting from stereospecific cyclisation to the 3′-position during formation of the oxazolidine-2-thione (**6**). The H-1′, H-1″ protons in (**2b**) showed no coupling to a hydroxy proton [δ 3.91, 4.05, J (1′,1″) 11.0 Hz], thus ruling out (**5**) as the precursor. It has been claimed[10] that α- or β-fructofuranose derivatives could be distinguished readily by the magnitude of J(3′,4′), since the α-anomers had values in the range 1.4—2.4 Hz, mean 2.0 Hz, whereas for the β-anomers the range was 5.5—9.7 Hz, mean 7.1 Hz. However these values are for peracetylated derivatives which are not nucleosides. In (**2a**) and (**2b**) J(3′,4′) has values 6.0 and <5.0 Hz, respectively, and the analogous 9-α-D-fructofuranosylhypoxanthine and 9-α-D-fructofuranosyladenine nucleosides have values 2.8 and 3.1 Hz, respectively. Thus the range of J(3′,4′) in both α- and β-anomers is extended in nucleosides and this criterion is less convincing. The ^{13}C n.m.r. spectra of these nucleosides were more useful since the C-2′ carbon in the β-anomer (**2b**) (δ 96.0) is upfield of C-2′ in both the anomers, δ 98.8 and 98.2 in hypoxanthine and adenosine nucleosides, respectively. These differences are similar to the value of Δ(β−α) observed for the fructofuranoses (−2.9 p.p.m.) and the corresponding methyl glycosides (−4.4 p.p.m.).[11] In addition, the specific rotation $[\alpha]_D^{25}$ of (**2a**) was −58° in contrast to specific rotations of α-D-fructofuranosylhypoxanthine of +23°, α-D-fructofuranosyladenine of +48° and α-D-fructofuranosyluracil of +24°; β-D-fructofuranosyluracil has $[\alpha]_D^{25}$ −10°. These relationships are maintained in fructofuranose glycosides. Thus methyl α-D-fructofuranoside tetra-*O*-acetate has $[\alpha]_D^{25}$ +88.1° and methyl β-D-fructofuranose $[\alpha]_D^{25}$ −26.2°.

Apart from indicating a valuable route to β-fructofuranosyl nucleosides the above results indicate that the reaction of D-fructose with KSCN and aqueous HCl is sensitive to subtle changes in reaction conditions.

We thank NATO for an International Collaboration Grant (to G. M. and A. G.).

Received, 19th November 1987; Com. 1687

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