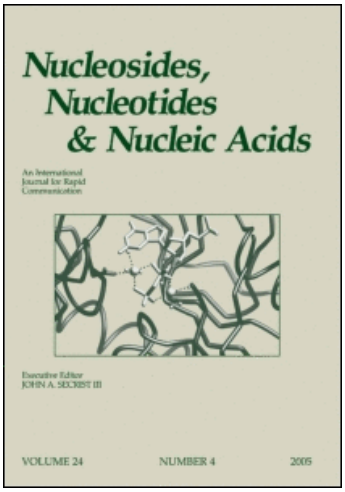

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Synthesis of Some 2-Alkylated-5-Aminoimidazoles Related to Intermediates in Purine Nucleotide *de novo* and Thiamine Biosynthesis

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SYNTHESIS OF SOME 2-ALKYLATED-5-AMINOIMIDAZOLES RELATED TO INTERMEDIATES IN PURINE NUCLEOTIDE *de novo* AND THIAMINE BIOSYNTHESIS

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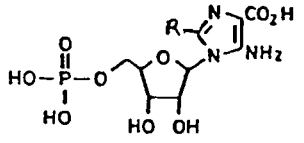
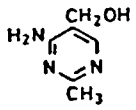
Abstract: Routes to 2-alkylated-5-aminoimidazole nucleosides have been investigated in which the 2-substituent has up to 3 carbon atoms and capable of being interconverted into suitable oxy and oxo alkyl derivatives for use in enzyme inhibition and biochemical incorporation studies involving both purine nucleotide *de novo* and thiamine biosynthesis.

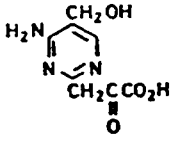
We have been interested to synthesize 2-substituted 5-aminoimidazole nucleosides and nucleotides involved in purine nucleotide *de novo* and thiamine biosynthesis. We have evidence[1] to suggest that AIR-carboxylase is the allosteric enzyme involved in both pathways and that CAIR (1a) is the branch point intermediate. Preliminary studies[2] and more recent investigations have shown (FIG) 2-methyl CAIR(1b) to inhibit this enzyme. It is not known whether the 2-methyl group in the pyrimidine moiety of thiamine is introduced at the imidazole or the pyrimidine stage, but there is evidence[3] that an oxidised three-carbon chain, probably derived from the ribosyl group in the nucleotide, is a precursor of the methyl group. In particular we wished to synthesize the oxo derivative (3) which has been proposed[4] as an intermeidate in thiamine biosynthesis.



(1) a; R = H
b; R = CH_3



(2)



(3)

Accordingly, we have explored routes to 2-substituted imidazoles including 1-D-ribofuranosides in which the 2-substituent has up to 3 carbon atoms and is capable of being converted into suitable oxy and oxo

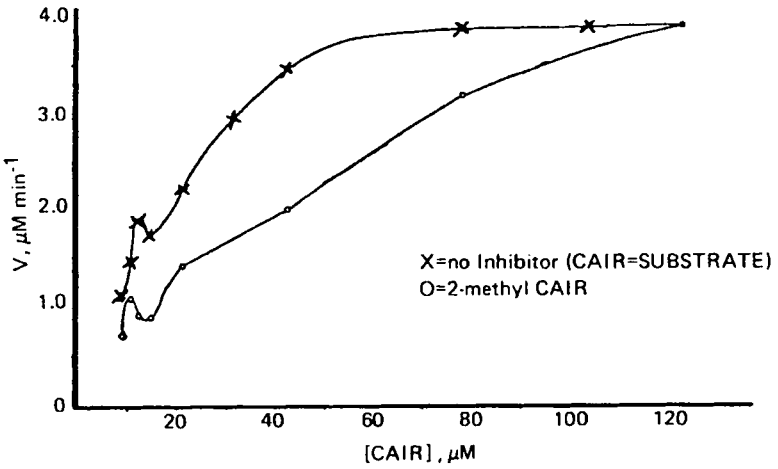
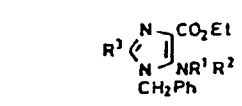


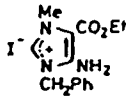
Fig.1 **Effect of substrate analogues on the rate of the enzyme catalyzed decarboxylation reaction of CAIR to AIR by EC 4.1.1.21**

alkyl derivatives which can be used in labelled form for appropriate biochemical incorporation studies. Apart from their intrinsic interest, the nucleoside derivatives are also a potential source, by acid hydrolysis, of the corresponding aglycones.

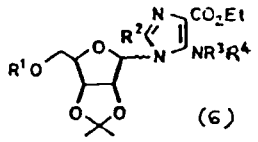
Direct alkylation at C-8 (analogous to the 2-position in imidazoles) of a variety of purines *via* their lithium derivatives in high yields has been reported[6] and the electrophiles used included a wide variety of alkyl halides and aldehydes. We have examined similar reactions with some analogous amino imidazoles. Ethyl 5-amino-1-benzylimidazole 4-carboxylate (4a) (m.p. 156°C), prepared from ethyl α-amino-α-cyanoacetate, triethyl orthofromate, and benzylamine was converted into a lithium derivative with butyl-lithium in THF and then treated with methyl iodide at -45°C. Three compounds were produced and two were identified as the *N*-methyl derivative (4b) and the quaternary salt (5), (m.p. 142°C) was also prepared by direct alkylation of (4a) with methyl iodide. In contrast, a similar reaction of the analogous isopropylidene nucleoside (6a)[7] with butyl-lithium followed by methyl iodide at -45°C gave, in addition to starting material (46%), two monomethyl derivatives namely the *N*-methyl- and 2-methyl-nucleosides (6b) (11%) and (6d) (26%) (m.p. 167°C) repsectively. The structure assigned to the latter compound was confirmed by comparison with a sample prepared by an alternative method involving reaction of the imidate (7) with 2,3-*O*-isopropylidene--D-ribosylamine (8)[7] and separation of the resulting α- and ß-anomeric nucleosides (6c) and (6d)[8] respectively. An attempt to react the lithium derivative of nucleoside (6a) with benzaldehyde however resulted in recovery of starting material in high yield. The structure of the former compound (6b) was confirmed by its negative reaction in the Bratton-Marshall[9] test for aromatic amines implying that the introduced methyl group was attached to the 5-amino group.



(4) a: $R^1=R^2=R^3=H$
b: $R^1=Me, R^2=H, R^3=H$
c: $R^1=R^2=Ac, R^3=H$
d: $R^1=Ac, R^2=R^3=H$
e: $R^1=R^2=H, R^3=Me$
f: $R^1=R^2=H, R^3=(CH_2)_2CN$
g: $R^1=R^2=H, R^3=CHO$

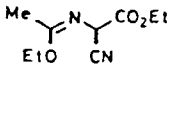


(5)

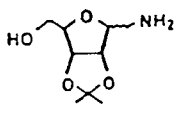


(6)

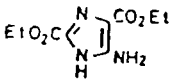
a: $R^1=R^2=R^3=R^4=H$, β-anomer
b: $R^1=R^2=R^3=H, R^4=Me$, β-anomer
c: $R^1=R^3=R^4=H, R^2=Me$, α-anomer
d: $R^1=R^3=R^4=H, R^2=Me$, β-anomer
e: $R^1=R^3=R^4=H, R^2=(CH_2)_2CN$, α-anomer
f: $R^1=R^3=R^4=H, R^2=(CH_2)_2CN$, β-anomer
g: $R^1=R^3=R^4=H, R^2=(CH_2)_2CO_2Et$, α-anomer
h: $R^1=R^3=R^4=H, R^2=(CH_2)_2CO_2Et$, β-anomer
i: $R^1=R^3=R^4=H, R^2=(CH_2)_2OEt$, β-anomer
j: $R^1=COBu^t, R^2=(CH_2)_2CO_2Et, R^3R^4=\!=CHNMe_2$, β-anomer
k: $R^1=COBu^t, R^2=CH_2COCO_2Et, R^3R^4=\!=CHNMe_2$, β-anomer
l: $R^1=COBu^t, R^2=(CH_2)_2CO_2Et, R^3=H, R^4=CONMe_2$, β-anomer.
m: $R^1=H, R^2=(CH_2)_2CO_2Et, R^3R^4=\!=CHNMe_2$, β-anomer



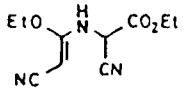
(7)



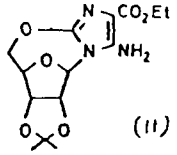
(8)



(9)



(10)



(11)

The problems encountered in the various attempts to introduce a 2-substituent directly into the aminoimidazole ring system prompted us to return to the synthesis of 2-substituted imidazoles from acyclic intermediates and recorded in earlier publication[8,10] in this series. This, the Shaw method,[10] involves the reaction of an α-amino-α-cyanoacetic acid derivative (ester, amide, nitrile, etc.) with either an imidate or an ortho ester followed by a primary amine.

Although the reaction has earlier been shown to work well both in model systems and with nucleosides using alkanoic acid imidates or ortho esters, an attempt to react ethyl α-amino-α-cyanoacetate with the imidate derived from ethyl cyanoacetate only produced the aminoimidazole diester (9), a compound which we have earlier shown[11] to from by heating ethyl α-amino-α-cyanoacetate, or by leaving it at room temperature for some weeks. Similar results were obtained using imidates derived from amino-malononitrile suggesting that the intermediate imidate produced in these reactions adopts the carbamate-like structure (10) in which the alkoxy group would be less likely to react readily with a primary amine. In support of this, and in direct contrast to the above results, reaction of ethyl α-amino-α-cyanoacetate with the monoimidate derived from the homologue of malononitrile namely succinonitrile, followed by benzylamine gave the crystalline ethyl 5-amino-1-benzyl -2-(cyanoethyl)imidazole-4-carboxylate (4f) (m.p. 196°C) yield (31%). 2,3-*O*-Isopropylidene-D-ribosylamine (8) with ethyl 3-cyanopropanimidate similarly gave a mixture of the α- and β-imidazole nucleosides (6g) and (6h) (m.p. 200°C) respectively.

However, only the β-anomer (6i) (m.p. 204°C) resulted from the treatment of 3-ethoxypropanimidate with the ribosylamine (8) followed by ethyl α-amino-β-cyanoacetate. Oxidation of ethyl 5-amino-2-methylimidazole-4-carboxylate (4e) with *N*-chlorosuccinimide and potassium hydroxide gave the corresponding 2-formyl derivative (4g) (m.p. 54°C) in contrast to

this reaction we have shown earlier[12] that oxidation of the 2-unsubsituted 5-amino-imidazole nucleoside (6a) with *N*-chlorosuccinimide leads to the cyclonucleoside (11). Accordingly, to avoid in (6h) by reaction with dimethylformamide dimethyl acetal to produce (6m) which, with pivalic anhydride, gave (6j). Attempts to produce an oxo derivative of type (6k) by treatment of (6j) with selenium dioxide in acetic anyhydride gave the urea (61) the structure of which is assigned on the basis of n.m.r. evidence. Notable points are (i) the absence of absorptions for the formamidino proton and carbon atoms (expected at δ_H8,2 and δ_C159 respectively); (ii) the NMe_2 group has δ_H2,11 and 2.50, and δ_C25.2 and 26.4 were more in keeping with an amide group than an amidino group.

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