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SYNTHESIS OF THE PYRROLO[3,2-d]PYRIMIDINE C-NUCLEOSIDE ISOSTERE OF INOSINE[1]

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ABSTRACT: The synthesis of "9-deazainosine," a new C-nucleoside analog of inosine and of formycin B is described. It involves conversion of a ribosylated 3-amino-2-carboalkoxypyrrole intermediate to the desired pyrrolo[3,2-d]pyrimidine system.

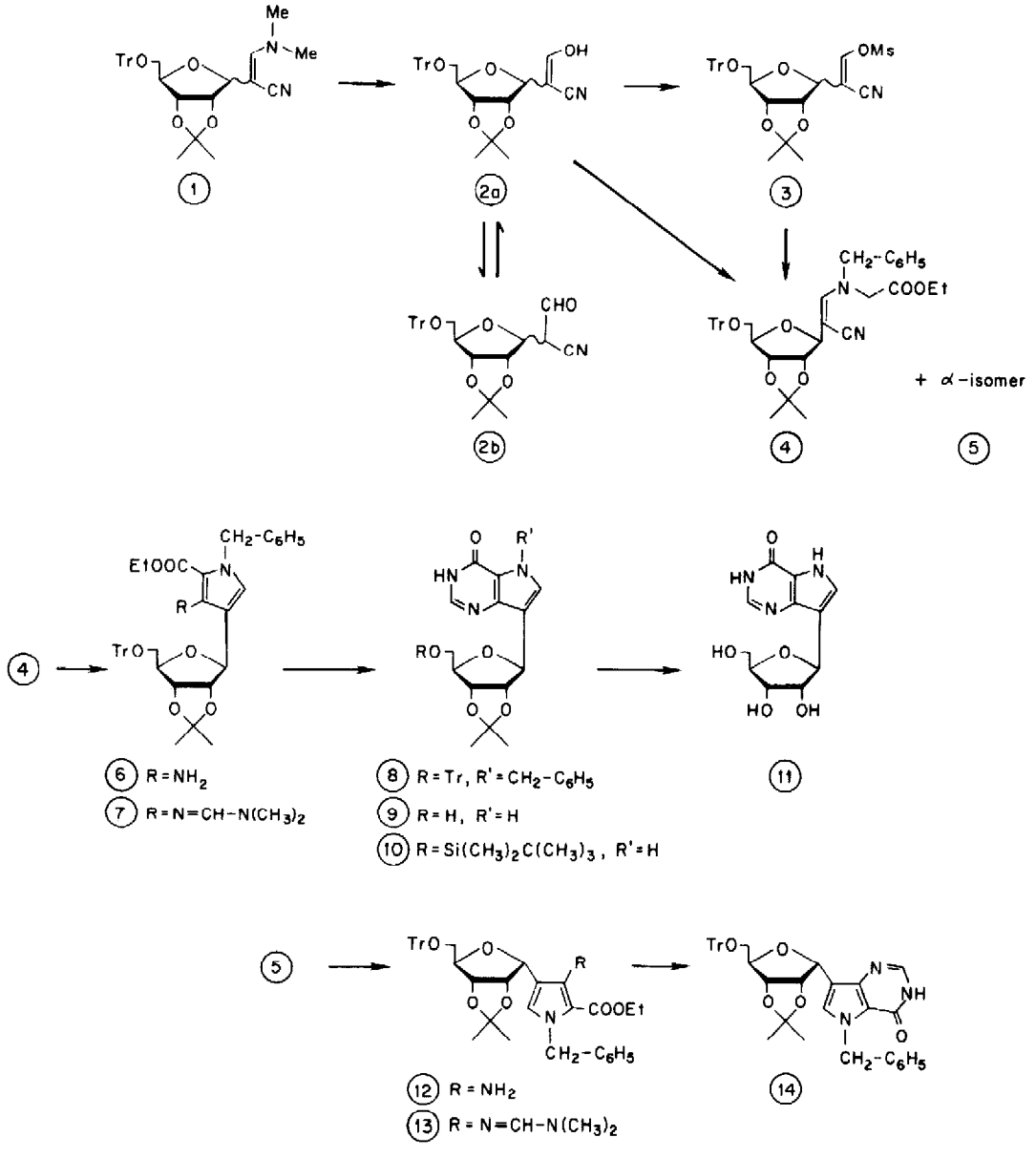
As part of an ongoing program for the design and biological evaluation of novel C-nucleosides of potential biomedical interest, we have recently reported the synthesis of several pyrazolo-[1,5-a]-1,3,5-triazine C-nucleosides[2] which are isosteric with common, naturally occurring purine nucleosides. The recently demonstrated antitumor activity of several of these compounds[3] in experimental animals prompted us to undertake the synthesis of the corresponding 5-H-pyrrolo-[3,2-d]pyrimidine C-nucleosides. Preliminary model studies[4,5] of several approaches to this heterocyclic system which could be applicable also to its C-ribosylated derivative suggested two promising routes: a) hydrogenolytic cleavage of pyrimido[5,4-c]pyridazines[4] and b) a two-step conversion of 3-amino-2-carboalkoxypyrroles.[5]

We describe here the synthesis of 7-(β-D-ribofuranosyl)-4-oxo-3H,5H-pyrrolo[3,2-d]pyrimidine 11 ("9-deazainosine"), an analog of inosine and of formycin B by an adaptation of approach b). A similar pyrrolo[3,2-d]pyrimidine C-nucleoside ("2-deazaoxoformycin") has been already reported.[6]

Our starting material for this synthesis (see Fig. 1) is the versatile 3-dimethylamino-acrylonitrile 1 which has been utilized in the preparation of oxazinomycin[7] and of several pyrazolo[1,5-a]-1,3,5-triazine C-nucleosides.[2b] Hydrolysis of 1 under mild acidic conditions in a two-phase system ($CF_3COOH/H_2O/CHCl_3$, 20°, 15 hr) provided the 2-(1-ribofuranosyl)-2-formyl-acetonitrile[8] 2 as a mixture of aldehyde/enol tautomers[9] of the α- and β- C-1' epimers in very good yields. Without further purification, 2 was treated with 1.5 equiv. of N-benzylglycine ethyl ester in benzene at reflux for 8 hr under a water separator to give the desired N-benzyl-enamines 4 and 5 as a mixture of the β- and α-isomers, respectively (4:5 ~ 1:5, 78% yield from 1). These could be readily separated by silica gel column chromatography with benzene-ethyl acetate (10:1) as the eluent.

An alternate procedure which affords the β-isomer 4 as a major product was finally adopted. Thus, 2-formylacetonitrile 2 was first converted to mesylates 3 (1.1 equiv. methanesulfonyl chloride, 1.2 equiv. Et_3N or DBN in $CHCl_3$ at 0° for 1 hr) obtained as a mixture of the α- and β- C-1' epimers (β:α ~ 10:1). This mixture was treated directly with 1.5 equiv. of N-benzyl-

Figure 1


Me
N
Me
CN
TrO
OH
OMs
CHO
$CH_2-C_6H_5$
COOEt
+ α-isomer
E1OOC
R
RO
HO
HN
N
H
R'
$R=NH_2$
$R=N=CH-N(CH_3)_2$
$R=Tr, R'=CH_2-C_6H_5$
$R=H, R'=H$
$R=Si(CH_3)_2C(CH_3)_3, R'=H$
NH
O
OH

glycine ethyl ester (Dimethylformamide [DMF], 80°, 18 hr) to give the same N-benzylenamines 4 and 5 (4:5 = 3:2) in a 54% overall yield from 1 (with Et_3N as base catalyst for 2 → 3).

Ring closure of purified β-N-benzylenamine 4 to the desired 3-aminopyrrole 6 (70% yield) was carried out under strongly basic conditions (EtONa in EtOH, 25°, 2 hr). Intermediate 6, in turn, was treated with 5 equiv. of DMF-dineopentyl acetal[10] (DMF, 80°, 24 hr) to afford the 3-dimethylaminomethyleneimine 7 in nearly quantitative yields. Treatment of 7 with saturated methanolic ammonia in a bomb at 80° for 24 hr gave the blocked pyrrolopyrimidine C-nucleoside 8 also in nearly quantitative yield. No epimerization at C-1' was observed during conversions 4 → 6 → 7 → 8. In order to establish the anomeric configuration at that position, the corresponding series of α-C-nucleosides was also prepared for comparison. By identical procedures, the 2-N-benzylenamine 5 was converted to 12, then 13, and finally to the blocked α-pyrrolo[3,2-d]pyrimidine C-nucleoside 14.

A comparison of the H^1-NMR spectra of the corresponding compounds in pairs 6-12, 7-13, and 8-14 (see Table) established conclusively the assignment of the epimeric configuration at C-1'. As with α- and β-nucleosides,[11] the chemical shifts of the H-1' are consistently further downfield for the α-isomers (12, 13, and 14) than for the corresponding β-isomers (6, 7, and 8). This relationship has been observed in the cases of the isomers of ψ-uridine,[12] pyrazomycin[13] and other purine-like C-nucleosides.[2,8a,14] Furthermore, the β compounds exhibit larger Δδ numerical values for the difference in chemical shifts of their isopropylidene gem-dimethyl groups than do their α-isomers.[15]

Debenzylation of 8 with 10 equiv. of sodium naphthylide[16] in THF at 20° for 18 hr was accompanied by detritylation to afford the 5H-pyrrolo[3,2-d]pyrimidine C-nucleoside 9 in 57% yield. This compound was further characterized as its 5-tert-butyldimethylsilyl derivative 10 (tert-butyldimethylsilyl chloride 1.1 equiv., Imidazole 2.5 equiv. in DMF). Removal of the isopropylidene group of 9 with 7% HCl/MeOH at 20° for 40 min. finally afforded 9-deazainosine 11 as its hydrochloride salt in 84% yield (dec. at 224°, MeOH-H_2O).

TABLE

H^1-NMR Data* ($CDCl_3$) for H-1' Epimeric Assignments

β- Series	6 (22.3, 4.79), 7 (24.4, 4.91), 8 (21.4, 5.22)
α- Series	12 (18.3, 5.10), 13 (14.0, 5.48), 14 (12.0, 5.53)

*The first number in the parentheses represents the Δδ value of the methyl isopropylidene signals (Hz). The second number represents the chemical shift δ of CH-1' (ppm).

References and Footnotes

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