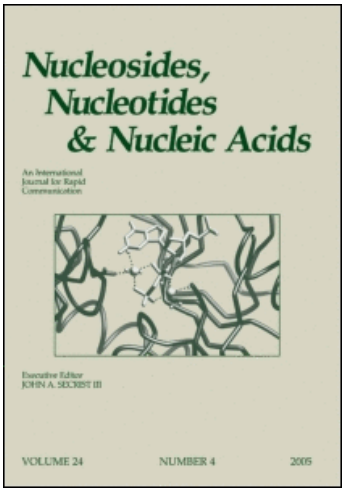

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Synteesis of Certain C-4 Substituted Pyrazolo[3,4-b]-Pyridine Nucleosides Structurally Related to Adenosine and Inosine by Tee Sodiw Salt Glycosylation Procedure

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SYNTHESIS OF CERTAIN C-4 SUBSTITUTED PYRAZOLO[3,4-b]-PYRIDINE NUCLEOSIDES STRUCTURALLY RELATED TO ADENOSINE AND INOSINE BY THE SODIUM SALT GLYCOSYLATION PROCEDURE

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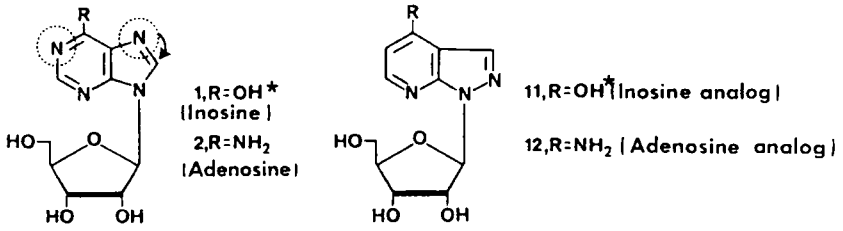
ABSTRACT: Several C-4 substituted pyrazolo[3,4-b]pyridine nucleosides have been synthesized using the sodium salt glycosylation procedure and evaluated for their biological activity.

As a continuing effort to design and synthesize potent inhibitors of nucleic acid metabolism, we[1] and others[2] have been interested in synthetic purine nucleoside analogs with an alteration within the heterocyclic moiety. The role of the various nitrogen atoms of purine nucleosides as binding sites for important enzymes in biological systems has become the subject of considerable interest.[3] Presently we have directed our efforts towards the synthesis of C-4 substituted pyrazolo-[3,4-b]pyridine nucleosides since these compounds are structurally related to both the chemotherapeutically potent 1-deazapurine and allopurinol nucleosides.



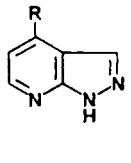
* Present as the oxo tautomer.

Preobrazhenskaya et al. reported[4] the synthesis of certain C-4 substituted pyrazolo[3,4-b]pyridine nucleosides, which subsequently were found[5] to be C-6 substituted pyrazolo[3,4-b]pyridine isomers. We have now prepared for the first time C-4 substituted pyrazolo[3,4-b]pyridine nucleosides (8-22) related to adenosine and inosine.

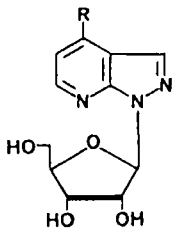
Several C-4 substituted pyrazolo[3,4-b]pyridines have been prepared[6] from the readily available 4-chloro derivative 4.[7] Treatment of 4 with aqueous NaOH/MeOH at 150°C for 16 h gave 4-methoxy-1H-pyrazolo-[3,4-b]pyridine (5) in 48% yield. Similarly, treatment of 4 with NaOBn/BnOH furnished 6 in 55% yield. Reaction of the TFA salt of 4 with NaN_3 in DMF gave 4-azido-1H-pyrazolo[3,4-b]pyridine (7) in 81% yield. Catalytic (Pd/C) hydrogenation of 4 gave 3 in almost quantitative yield.[8] The anion of 7 generated in situ[9] was treated with 1-chloro-2,3-O-isopropylidene-5-O-t-butyldimethylsilyl-α-D-ribofuranose[10] at room temperature to furnish 4-azido-1-(2,3-O-isopropylidene-5-O-t-butyldimethylsilyl-β-D-ribofuranosyl)pyrazolo[3,4-b]pyridine, which on treatment with aqueous TFA, followed by hydrogenation of the reaction product furnished the adenosine analog 4-amino-1-β-D-ribofuranosylpyrazolo[3,4-b]pyridine (12). The inosine analog 11 was obtained by the glycosylation of 6 in three steps as described for 12. Ribosylation[11] of compounds 3-5 were carried out under similar conditions to yield nucleosides 8, 9 and 10, respectively, in good yields.

The synthesis of the 2'-deoxyribonucleosides (13-17) was also accomplished by the sodium salt glycosylation procedure.[12] As a typical example, the sodium salt of 6 generated in situ was treated with 1-chloro-2-deoxy-3,5-di-O-p-toluoyl-α-D-*erythro*-pentofuranose[13] to furnish 4-benzyloxy-1-(3,5-di-O-p-toluoyl-β-D-*erythro*-pentofuranosyl)pyrazolo[3,4-b]pyridine, which on catalytic (Pd/C) hydrogenation, followed by deblocking of the carbohydrate moiety, furnished 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-4,7-dihydropyrazolo[3,4-b]pyridin-4-one (16) in 60% overall yield.

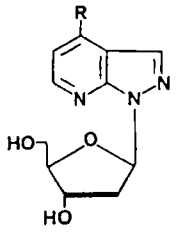
This general glycosylation procedure was also utilized for the preparation of the β-D-arabinofuranosyl nucleosides (18-22). As an example, glycosylation of the anion of 6 with 1-chloro-2,3,5-tri-O-benzyl-α-D-arabinofuranose[14] in anhydrous CH_3CN furnished 4-benzyloxy-1-(2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)pyrazolo[3,4-b]pyridine, which on catalytic [$Pd(OH)_2$] hydrogenation gave 1-β-D-arabinofuranosyl-4,7-dihydropyrazolo[3,4-b]pyridin-4-one (21) in 64% overall yield.



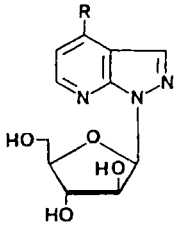
	R
3	H
4	Cl
5	OCH_3
6	OBn
7	N_3



	R
8	H
9	Cl
10	OCH_3
11	OH*
12	NH_2



	R
13	H
14	Cl
15	OCH_3
16	OH*
17	NH_2



	R
18	H
19	Cl
20	OCH_3
21	OH*
22	NH_2

* Present as the oxo tautomer.

The regiospecificity of these glycosylations was determined on the basis of UV spectral data and the anomeric configuration was established on the basis of ^1H NMR analysis. However, unequivocal structural assignment was made by single-crystal X-ray diffraction studies[15] of 8, 16 and 21 as an example of β-D-ribofuranosyl, 2-deoxy-β-D-erythro-pentofuranosyl, and β-D-arabinofuranosyl derivatives of pyrazolo[3,4-b]-pyridines, respectively.

All the deprotected pyrazolo[3,4-b]pyridine nucleosides (8-22) were tested against various viruses and certain tumor cell lines in culture. The inosine analog 11 exhibited a virus rating of 0.6 against Rhino 1-A; while other compounds were inactive against the viruses tested. Among various compounds tested for cytotoxicity, compound 9 had an ID_{50} of 18 μM for WI-L2 and 20 μM for L1210; compound 11 had an ID_{50} of 18 μM for WI-L2 and 100 μM and L1210. The effect of these compounds on the de novo purine and pyrimidine nucleotide biosynthesis was also evaluated. At a concentration of 100 μM, the following compounds were found to inhibit de novo purine nucleotide biosynthesis: 9, 94%; 11, 80%; and 12, 36%.

In conclusion we have prepared a series of pyrazolo[3,4-b]pyridine nucleosides including the adenosine and inosine analogs, by the sodium salt glycosylation procedure, and evaluated for their biological properties.

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