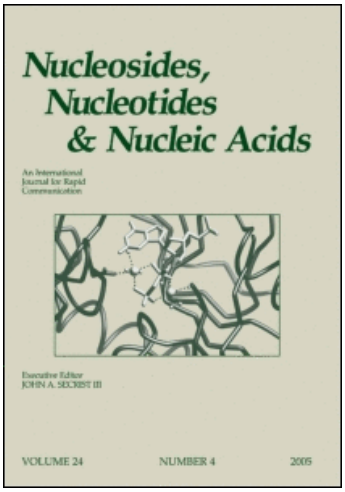

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THE ROLE OF MOLECULAR OXYGEN IN THE CATALYTIC HYDROGENATION OF HYDRAZINONUCLEOSIDES TO THE CORRESPONDING AMINONUCLEOSIDES.

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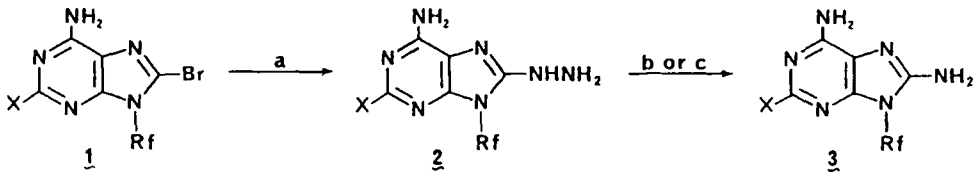
ABSTRACT: The hydrogenolysis of 2-amino-8-hydrazinoadenosine (2a) in water at reflux temperature in the presence of molecular oxygen provided 2,8-diaminoadenosine (3a) in 40-45% yield. 8-Aminoadenosine (3b) was synthesized in an analogous manner from 8-hydrazinoadenosine (2b) in comparable yield. The role of oxygen in these catalytic reductions will be discussed.

In our research in the area of nucleosides with altered metabolism, we have prepared several purine nucleosides with an 8-amino substituent, but thus far none of these has resulted in the production of a 6-oxo-8-amino nucleoside triphosphate. We were interested in what cellular effects such a compound would have if we could prepare a nucleoside that would be appropriately activated in cells. Toward that end we set as a goal, the synthesis of 2,6,8-triamino-β-D-ribofuranosylpurine thinking that at least a significant portion of this compound might end up as 8-amino-GTP in cells. One successful approach to this compound is summarized in Scheme I.

The easily obtainable 2-amino-8-bromoadenosine[1] 1a became an attractive precursor for the synthesis of 3a. Refluxing 1a with anhydrous hydrazine in ethanol for 16 hrs provided 2a in 50% yield. Hydrogenolysis of 2a with nickel in water at reflux temperature under nitrogen atmosphere proceeded rather sluggishly and the formation of 3a reached a plateau



Rf: β-D-ribofuranosyl-

a. $EtOH/NH_2{\cdot}NH_2$, Δ
b. H_2/Ni, Δ under N_2 (< 10% yield)
c. H_2/Ni, [$\cdot O_2\cdot$], Δ (40-45% yield)

a. Series X = NH_2
b. Series X = H

SCHEME I. SYNTHESIS OF 2,8-DIAMINOADENOSINE

in about 2 hrs (< 10% yield). Neither the addition of catalyst nor prolonged refluxing improved the yield of **3a**. However, when an oxygenated solution of **2a** was hydrogenated under otherwise similar conditions, there was a significant increase in the yield of **3a** demonstrating the effect of oxygen in the reduction of **2a**. When an oxygenated aqueous solution of **2b** was hydrogenated, there obtained two products: 8-aminoadenosine (35%) and adenosine (20-25%). Extensive dehydrazination occurred when an oxygenated solution of **2b** was treated with two drops of 30% hydrogen peroxide either in the presence of or in the absence of catalyst. Adenosine was also formed in excellent yield when a solution of **2b** was refluxed under oxygen atmosphere or hydrogenated at room temperature with nickel.

Chattaway[2] studied the oxidation of phenylhydrazine by molecular oxygen and the principal products of oxidation are benzene, nitrogen and a small amount of biphenyl. He proposed that these products arise from the unstable intermediate phenyldiazene.

Arylhydrazines are unstable to heat[3] and the products formed from thermally-induced decomposition of pentafluorohydrazine[4] at 180 °C are pentafluoroaniline (44%), nitrogen, ammonia and pentafluorobenzene (39%). The former arises from the abstraction of a hydrogen atom by anilino radical that is generated by the homolytic fission of N-N bond while pentafluorobenzene and nitrogen are due to the decomposition of pentafluorodiazene. This compares favorably with that of catalytic hydrogenation of **2b** with molecular oxygen. One may argue based on the similarity of products that hydrogenolysis of **2b** may involve fission of N-N bond. If indeed such a mechanism operates, it is expected that the formation of adenosine will be considerably more than **3b** as the oxidation, catalytic decomposition and reduction of **2b** all entail the same monosubstituted diazene intermediate Nu-N=N-H. Since the yield of adenosine is less than or is equal to **3b**, it is conceivable that catalytic hydrogenation **2a** or **b** at higher temperature may proceed by a different mechanism. We propose a speculative mechanism that will account for all the products and the necessity of oxygen for hydrogenation. Adenosine obtained in all cases arises from the monosubstituted diazene intermediate Nu-N=N-H. This intermediate reacts rapidly with molecular oxygen to give a hydroxydiazo compound, [Nu-N=N-OH]. The hydroxydiazo compound reacts further with **2a** or **2b** to give 1-tetrazene which isomerizes to a more stable 2-tetrazene. An unstable phenyltriazene intermediate has been invoked[5] for the formation of aniline from nitrosobenzene by hydrazine reduction. The loss of nitrogen from the 2-tetrazene intermediate gives an amino radical which abstracts a hydrogen atom to give 8-aminonucleoside.

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