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MODIFICATION OF THE 2'-POSITION OF PURINE NUCLEOSIDES: SYNTHESES OF 2'-α-SUBSTITUTED-2'-DEOXYADENOSINE ANALOGS

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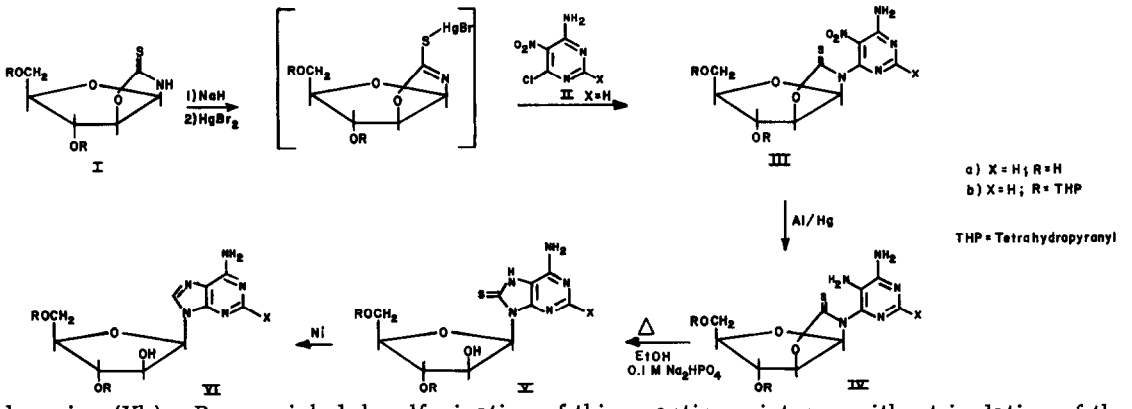
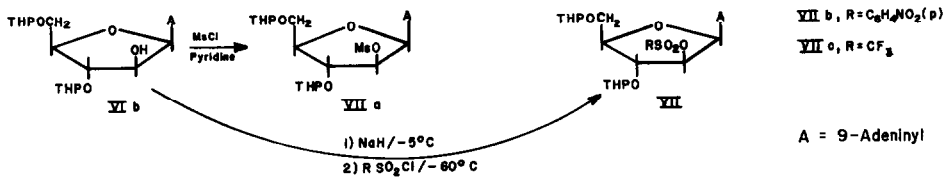
Nucleoside analogs with stereochemical and/or functional group modifications in the sugar residue have shown promise as anti-tumor, anti-viral, or immunosuppressive agents.[1] In addition to these properties, adenosine analogs have been of interest as hypotensive agents, as inhibitors of platelet aggregation, and as radio-protective agents.[1,2] Among the numerous purine nucleoside analogs that have been described, those with functional group modification at the 2'-position, with the 2'-substituent in the ribo-configuration, have been accessible, if at all, only with difficulty. The main routes to such derivatives have been either a nucleoside synthesis on suitably derivatized sugars, as in the synthesis of 2'-amino-2'-deoxyadenosine (XVI) by Wolfrom,[3] or by 2',3'-epoxide openings, as in the recent work of Mengel.[4] This paper describes a new and versatile synthesis of 2'-substituted-2'-deoxyadenosine analogs. Following this new approach several heretofore inaccessible compounds, which are of significant biological interest, have been synthesized.

A simple and direct synthesis of 2'-substituted-2'-deoxyadenosine analogs could be achieved, if nucleophilic displacement reactions could be carried out, readily and under mild conditions, at the 2'-position of suitably protected 2'-sulfonates of ara-adenosine (VIa). By employing a modification of the recently described[5] ara-adenosine (VIa) synthesis, 3',5'-diTHP-ara-adenosine (VIb) has been synthesized as described below. The arabinofurano-thionoxazolidine (Ia) was treated with dihydropyran in THF in the presence of PTS to obtain the corresponding 3',5'-diTHP derivative (Ib) in 66% yield, as a mixture of stereoisomers.[6] This mixture was used as such, without separation, in all the subsequent operations. Treatment of the protected thionoxazolidine (Ib) with sodium hydride in dry DMF, followed by the addition of equivalent amounts of mercuric bromide and 4-amino-6-chloro-5-nitropyrimidine (II), yielded the condensation product (IIIb), which was reduced with aluminum amalgam in dioxane-methanol (1:1) solution to obtain the protected diaminopyrimidinyl-thionoxazolidine (IVb) in 55% overall yield. The crude product (IVb) underwent smooth cyclization when heated in a mixture of 0.1 M sodium phosphate buffer (pH 9.0) and ethanol (3:1) to give diTHP-8-mercapto-ara-



adenosine (Vb). Raney nickel desulfurization of this reaction mixture, without isolation of the intermediate product (Vb), yielded 3',5'-diTHP-ara-adenosine (VIb) as a pale yellow foam in 50% yield from the compound (IVb).

To activate the 2'-OH group in diTHP-ara-adenosine (VIb) the following sulfonates were synthesized. Treatment of the compound (VIb) with excess methanesulfonyl chloride in dry pyridine yielded the corresponding mesylate (VIIa) in 90% yield. The more reactive sulfonates were prepared by generating the alkoxide ion of diTHP-ara-adenosine (VIb), using sodium hydride in dry THF, and then treating the reaction mixture with an equivalent amount of the respective sulfonyl chloride at -60.° By this means, the nitrobenzenesulfonate (VIIb) and the

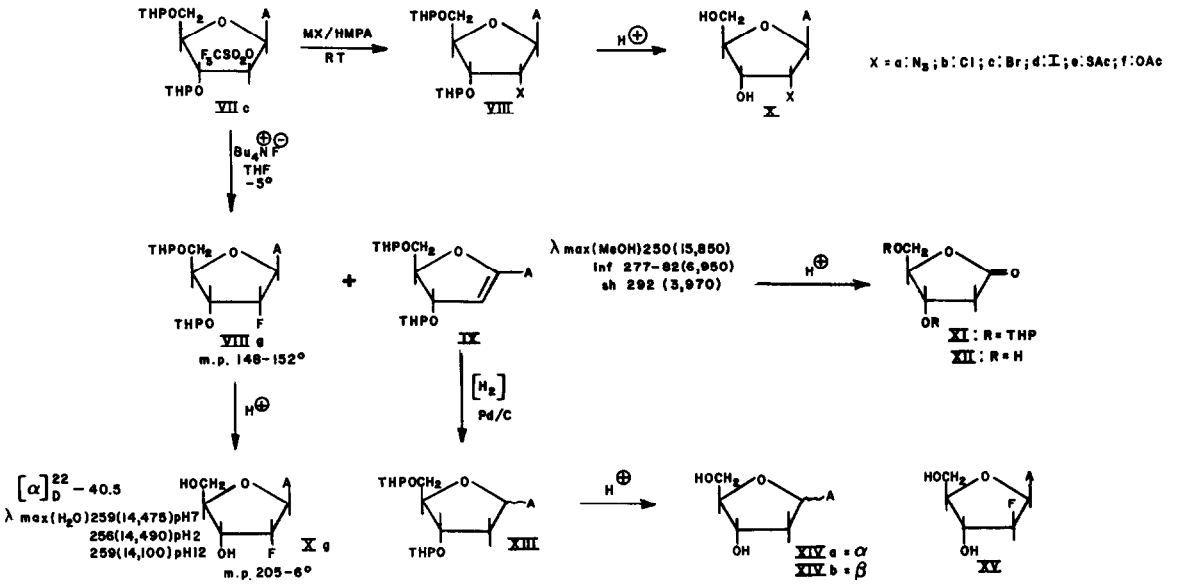


trifluoromethanesulfonate (VIIc) were isolated as stable crystalline solids, in 90% and 60% yields, respectively.

The reactivity of the mesylate (VIIa) and the nosylate (VIIb) in nucleophilic substitution reactions was initially estimated by treating each separately with LiN_3 in solvents like DMF, DMSO, or HMPA. These two sulfonates exhibited only a poor tendency to undergo nucleophilic displacement with the azide ion. DiTHP-2'-azido-2'-deoxyadenosine (VIIIa) was isolated in poor yield. This is mainly due to decomposition because of the high temperatures and prolonged reaction times employed. With other salts, these two sulfonates did not undergo nucleophilic displacements. When tetrabutylammonium fluoride (TBAF) was used, in lieu of LiF, desulfonation leading to diTHP-ara-adenosine (VIb) and elimination leading to the product (IX) resulted. The ratio of the two products was dependent on temperature, elimination being

favoured at higher temperatures.

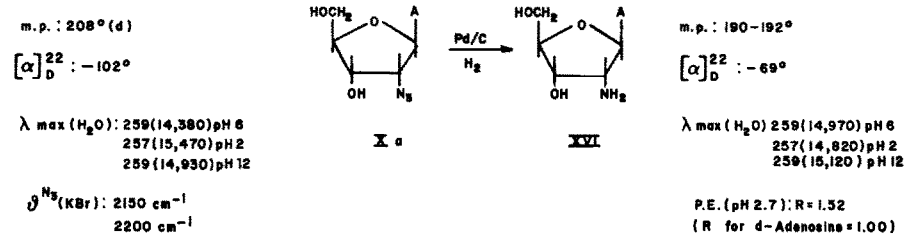
The triflate (VIIc) has proven to be a versatile intermediate for effecting nucleophilic displacement reactions at the 2'-position. In HMPA, the triflate (VIIc) reacted at room temperature readily with salts like LiN_3, LiCl, LiBr, NaI, NaOAc, or KSAc, to lead to the corresponding 2'-substituted-2'-deoxyadenosine derivatives (VIII) in high yields, without any side reactions like hydrolysis or elimination. The reactions with all the salts, except sodium acetate, were over in 10 min., the latter requiring a few hours. LiF did not react with the triflate (VIIc)



under many conditions that were studied. However, treatment of the triflate (VIIc) with TBAF in THF at -5° gave the expected diTHP-2'-fluoro-2'-deoxyadenosine (VIIIg), in 50% yield, along with 9-(3,5-diTHP-2-deoxy-erythro-pent-1-enofuranosyl)-adenine (IX), in 30% yield. The compound (IX) has been characterized on the basis of spectral data and also by acidic hydrolysis to diTHP-2-deoxyribonolactone (XI) under mild conditions, or to 2-deoxyribonolactone (XII) under more vigorous conditions. Compound (IX) has yielded a mixture of the anomers of diTHP-2'-deoxyadenosine (XIII), in 59% yield, by catalytic hydrogenation over Pd-C. Mild acid catalyzed deprotection of compound (XIII) has afforded a mixture of the anomers of 2'-deoxyadenosine (XIV), along with adenine. The mixture has been separated on a Dekker column[9] to obtain α-2'-deoxyadenosine (XIVa) (15% yield) and β-2'-deoxyadenosine (XIVb) (7% yield), which were indistinguishable from authentic specimens.[7]

Deprotection of diTHP-2'-O-acetyladenosine (VIIIf) by treatment with 80% acetic acid gave 2'-O-acetyladenosine (Xf), which, on further treatment with aqueous ammonium hydroxide, yielded adenosine, affording strong proof for the structure of the triflate (VIIc) and for the ribo- configuration at the 2'-position of the analogs that have been synthesized from it by

similar nucleophilic displacement reactions with the respective anions. Acid catalyzed deprotection of the compounds (VIIIa) and (VIIIg) has yielded 2'-azido-2'-deoxyadenosine (Xa) (64% yield) and 2'-fluoro-2'-deoxyadenosine (Xg) (66% yield) as crystalline solids. 2'-Fluoro-2'-deoxyadenosine (Xg) exhibited in its NMR spectrum the characteristic H-F coupling constants ($J_{1'H,F}$ 16.5 Hz; $J_{2'H,F}$ 52 Hz; $J_{3'H,F}$ 17 Hz) and it was chromatographically distinct from 2'-fluoro-2'-deoxy-ara-adenosine (XV), whose synthesis has earlier been reported by Fox and co-workers.[8] Catalytic hydrogenation of 2'-azido-2'-deoxyadenosine (Xa) over Pd-C



yielded 2'-amino-2'-deoxyadenosine (XVI), whose physical properties agreed closely with those reported in the literature.[3,4] Further work on the deprotection of the other new analogs whose syntheses have been described in this paper and on the phosphorylation and subsequent polymerization of these adenosine analogs is currently being pursued. Biological evaluation of these new anti-metabolites is also in progress.

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References

(1) A. Bloch, The Design of Biologically Active Nucleosides, In, Drug Design, Volume IV, (ed. E. J. Airens), Academic Press, New York, 1973, pp. 285-378.
(2) M. Shikita, Y. Takagi, F. Hatano, and S. Akaboshi, Chem. Pharm. Bull., 22, 1410 (1974).
(3) M. L. Wolfrom and M. W. Winkley, J. Org. Chem., 32, 1823 (1967).
(4) R. Mengel and H. Wiedner, Chem. Ber., 109, 433 (1976).
(5) R. Ranganathan, Tetrahedron Letters, No. 13, 1185 (1975).
(6) All new compounds described in this communication have shown satisfactory elemental analysis and UV, IR, NMR, and mass spectral data. The analytical samples were obtained by silica gel column chromatography or by crystallization.
(7) I am thankful to Dr. M. J. Robins, University of Alberta, Edmonton, Canada, for a sample of α-2'-deoxyadenosine.
(8) J. A. Wright, N. F. Taylor and J. J. Fox, J. Org. Chem., 34, 2634 (1969). I am indebted to Dr. J. J. Fox, Sloan-Kettering Institute, New York for a sample of 2'-fluoro-2'-deoxy-ara-adenosine.
(9) C. A. Dekker, J. Amer. Chem. Soc., 87, 4027 (1965).