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FACILE CONVERSION OF ADENOSINE INTO NEW 2'-SUBSTITUTED-2'-DEOXY-ARABINOFURANOSYLADENINE DERIVATIVES: STEREOSPECIFIC SYNTHESES OF 2'-AZIDO-2'-DEOXY-,2'-AMINO-2'-DEOXY-, AND 2'-MERCAPTO-2'-DEOXY-β-D-ARABINOFURANOSYLADENINES

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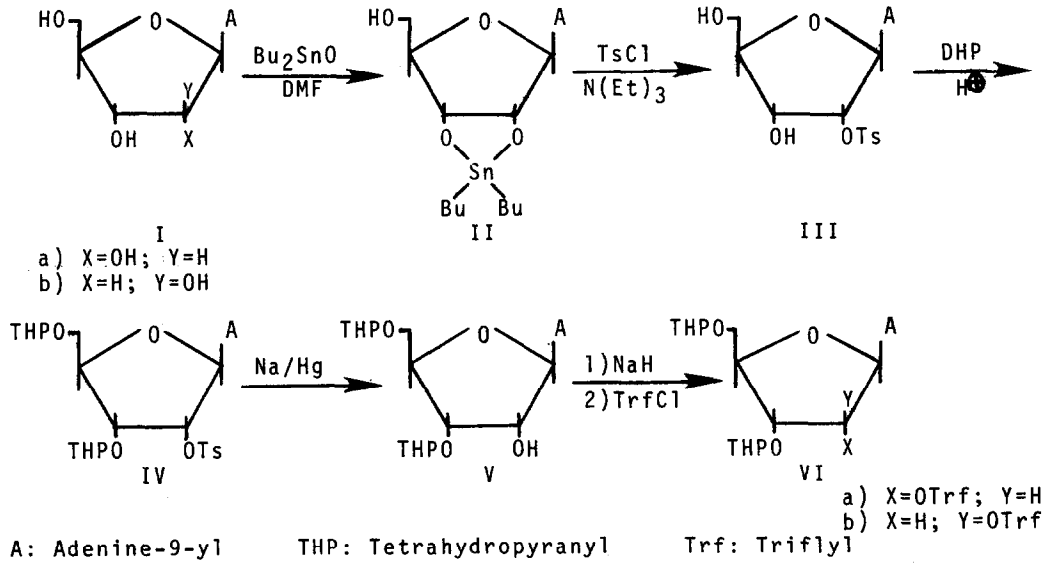
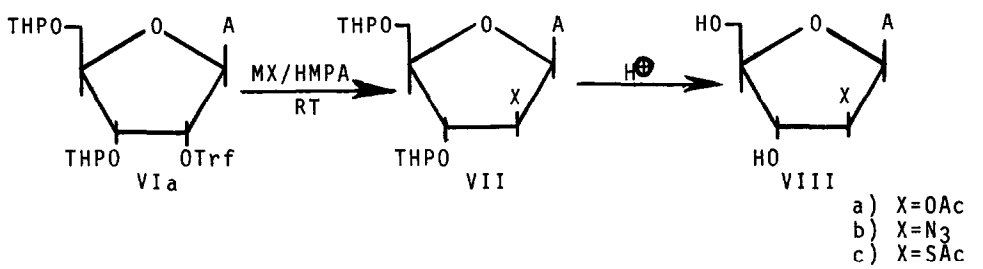
Recently there has been considerable interest in the synthesis of 2'-modified nucleosides[1], nucleotides and polynucleotides[2], stemming primarily from the interesting biological properties shown by ara-cytidine and ara-adenosine (Ib). The conformation of the sugar moiety in the 2'-modified analogs, for example, 2'-amino-2'deoxy-adenosine[3], which seems to be an important factor in the ability of double stranded 2'-modified-2'-deoxy-polynucleotides to act as interferon inducers[4] has also come under scrutiny. Our approach to the synthesis of these analogs consists in blocking the 3' and 5' positions with the non-participating tetrahydropyranyl (THP) groups and in the use of 2'-trifluoromethanesulfonate (triflate) as the leaving group[1a]. The protected triflate (VIb) was synthesized by a modification of our ara-adenosine synthesis[5] and it underwent facile displacement reactions with a number of nucleophiles to give 2'-modified-2'-deoxy-ribofuranosyladenine analogs. We wanted to further explore whether suitably protected 2'-ribo-triflates, for example compound (VIa), would undergo such displacement reactions. This question was particularly interesting in view of the observations of Wagner et al[6] that 2'-O-toluenesulfonyladenosine (III), when treated with nucleophiles at elevated temperatures in DMF gave only adenine. The present communication deals with our successful synthesis of 3',5'-di-THP-adenosine (V) and its conversion into 2'-azido-2'-deoxy-(VIIIb), 2'-amino-2'-deoxy-(IX), and 2'-mercapto-2'-deoxy-(X)-arabinofuranosyladenine derivatives. Other than ara-adenosine (Ib), related analogs, that have so far been reported, bear as the 2'-substituent fluorine[7], chlorine[8], bromine[8,9] or iodine[8].

2'-O-Toluenesulfonyladenosine(III) was prepared, in 82% yield, from adenosine (Ia) by a slight modification of the procedure described by Wagner et al[6]. The modification consisted in the use of DMF as the solvent and in treating the intermediate dibutylstannylidene derivative (II) in situ with an equivalent amount of triethylamine and p-toluenesulfonyl chloride at -40°. 2'-O-Toluenesulfonyladenosine (III) was converted into 3',5'-di-THP-2'-O-toluenesulfonyladenosine (IV), in 80% yield, by treatment with dihydropyran in dioxane in the presence of p-toluenesulfonic acid. Compound (IV) was detosylated by treatment with sodium amalgam in aqueous methanol at room temperature and the crude product was purified by silica gel column chromatography to obtain 3',5'-di-THP-adenosine (V)[10] as a colorless foam, in 75% yield. Treatment of compound (V) with sodium hydride in dry tetrahydrofuran at -20°, followed by further treatment



with an equivalent amount of trifluoromethanesulfonyl chloride at -70° yielded, after chromatographic purification, 3',5'-di-THP-2'-O-trifluoromethanesulfonyladenosine (VIa) as a colorless foam, in 70% yield. A preliminary attempt to directly triflylate compound (II) failed.

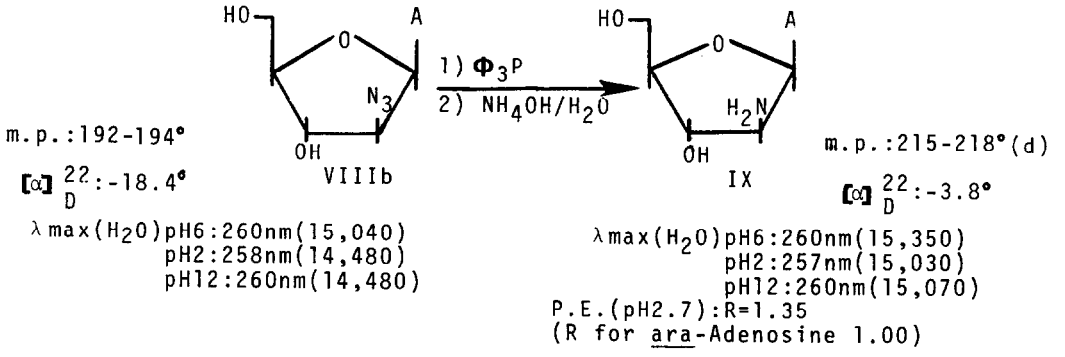
The reactivity of the ribo-triflate (VIa) in nucleophilic displacement reactions with several nucleophiles was comparable to that of the ara-triflate (VIb) reported earlier[1a]. In HMPA, the ribo-triflate (VIa) reacted readily at room temperature with salts like LiN_3, KSAc and NaOAc to give the corresponding 2'-substituted-2'-deoxy-arabinofuranosyladenine derivatives (VII) in high yields. There was no evidence of any side reactions such as desulfonylation or elimination.



The reaction time varied from a few minutes in the case of LiN_3 to a few hours in the case of NaOAc. The fully protected derivates (VIIa, VIIb, or VIIc) were purified by chromatography and isolated in yields of 61%, 88%, and 55%, respectively. If one of the stereoisomers of di-THP-adenosine (V), obtained by chromatographic separation, is used, the 2'-thioacetyl product (VIIc) could be purified by crystallization and isolated as colorless needles, m.p. 151-54°, in 58% yield.

Deprotection of 3',5'-di-THP-2'-O-acetyl-arabinofuranosyladenine (VIIa) by treatment with 80% acetic acid gave 2'-O-acetylarabinofuranosyladenine (VIIIa), which on further treatment with methanolic ammonium hydroxide, followed by crystallization, yielded 9-β-D-arabinofuranosyladenine (Ib) as the sole product in 42% overall yield. This observation afforded strong proof for the structure of the ribo-triflate (VIa) and for the ara-configuration at the 2'-position of the analogs synthesized from it by similar displacement reactions with the respective nucleophiles.

Acetic acid catalyzed deprotection of di-THP-2'-azido-2'-deoxy-arabinofuranosyladenine (VIIb) gave 2'-azido-2'-deoxy-arabinofuranosyladenine (VIIIb) as crystalline needles in 50% yield. Treatment of compound (VIIIb) with triphenylphosphine[11] and pyridine, followed by further treatment with concentrated ammonium hydroxide yielded a crude product, which was purified on a Dekker column[12], followed by crystallization from methanol to obtain 2'-amino-2'-deoxy-arabinofuranosyladenine (IX) as trigonal prisms in 50% yield.



m.p.:192-194°

$[\alpha]_D^{22}$:-18.4°

λmax(H_2O)pH6:260nm(15,040)
pH2:258nm(14,480)
pH12:260nm(14,480)

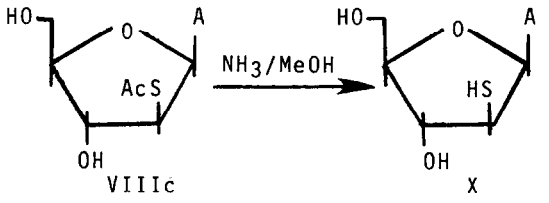
m.p.:215-218°(d)

$[\alpha]_D^{22}$:-3.8°

λmax(H_2O)pH6:260nm(15,350)
pH2:257nm(15,030)
pH12:260nm(15,070)

P.E.(pH2.7):R=1.35
(R for ara-Adenosine 1.00)

Deprotection of di-THP-2'-thioacetyl-2'-deoxy-arabinofuranosyladenine (VIIc), by treatment with 80% acetic acid, gave 2'-thioacetyl-2'-deoxy-arabinofuranosyladenine (VIIIc), as a white crystalline solid, which was deacetylated by brief treatment with anhydrous methanolic ammonia (14% by weight) at 0° to obtain, after crystallization from methanol, 2'-mercapto-2'-deoxy-arabinofuranosyladenine (X), as white crystalline needles (67% yield). Desulfurization of



m.p.:210-212° (d)

$[\alpha]_D^{22}$:-25.6°

λmax(H_2O):pH6:261nm(16,580)
pH2:259nm(16,390)
pH12:261nm(16,370)

2'-mercapto-2'-deoxy-arabinofuranosyladenine (X) with Raney Ni in DMF at 60°, in an atmosphere of hydrogen, gave β-D-2'-deoxyadenosine as the sole isolable product. Quantitative estimation for the thiol function using dipyridyldisulfide[13], gave a value of 94%. The contaminant is

obviously the corresponding disulfide of the thiol (X), as evidenced by thin layer chromatography over silica gel. Aqueous solutions of the thiol (X) slowly deposited the corresponding disulfide as white crystalline needles on letting stand at room temperature for a few days. To our knowledge, this is the first synthesis of a 2'-mercapto-2'-deoxy-purine nucleoside derivative. Attempts to make the ribo-analog of compound (X) have so far been unsuccessful[14].

Preliminary evaluation of the biological properties of these new analogs have shown that 2'-azido-2'-deoxy-arabinofuranosyladenine (VIIIb) possesses cytotoxic and antiviral properties comparable to those of ara-adenosine (Ib), while 2'-amino-2'-deoxy-(IX) and 2'-mercapto-2'-deoxy-(X) -arabinofuranosyladenine derivatives have much less activity. It is interesting to note that in the ribo- series 2'-amino-2'-deoxy-adenosine exhibits cytotoxic and antiviral properties, while 2'-azido-2'-deoxy-adenosine is devoid of any such activities. Further studies on these new adenosine analogs and the extension of this approach to the synthesis of nucleoside analogs containing bases other than adenine are currently in progress.

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