A NEW TYPE OF PURINE CYCLONUCLEOSIDE: 5'-O-TRITYL-3',6-ANHYDRO-7-α-D-ARABINOFURANOSYLHYPOXANTHINE[1]

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A new type of purine cyclonucleoside, 5'-O-trityl-3',6-anhydro-7-α-D-arabinofuranosylhypoxanthine (VI) was synthesized. This nucleoside was unusual in that VI was quite stable toward aqueous base and acid and absorbed ultraviolet light at a longer wavelength than the corresponding "parent" nucleoside.

The synthesis, chemical behavior and conformational aspect of pyrimidine and purine cyclonucleosides have been amply documented.[2, 3, 4] Especially, the versatility of a class of purine cyclonucleosides as intermediates for chemical transformation has been established by extensive work of Ikehara and his coworkers.[5] However, to our knowledge, no purine cyclonucleoside involving C-6 of purine, has been described in the literature. The chemistry of this type of cyclonucleoside remains unexplored. Conceivably, a cyclonucleoside of this type could be useful as a potential intermediate for the synthesis of pseudovitamin B_{12} nucleoside, 7-α-D-ribofuranosyladenine.

We wish to report the first synthesis of a purine cyclonucleoside having the

(O)-3',6-anhydro-linkage. A blocked nucleoside (I) was prepared in reproducible yield (45%) by a slight modification of the original procedure.[6,7] Free nucleoside (II) was obtained by deblocking I according to a reported procedure.[6] Tritylation of II afforded III, mp 222-224°[8] in 46.5% yield (based on I), which in turn was mesylated by a conventional method to give the corresponding 5'-O-trityl-2',3'-di-O-mesyl nucleoside (IV), mp 185-187°,[8] uv $\lambda_{max}^{pH\ 1}$ 256 nm, in 76.5% yield. Treatment of IV with 2 equivalents of 0.1 N ethanolic sodium ethoxide at refluxing temperature for 2 hr, followed by silica gel column chromatography gave VI in 40.5% yield, mp 218-220°.[8] The uv maximum (λ_{max} 262.5 nm) did not shift in acidic or basic media. Ir (KBr) spectral analysis showed the absence of amide (1690 cm^{-1}) and sulfonate (1275 cm^{-1}) bands which are present in IV. Combustion analyses were compatible with $C_{29}H_{24}N_4O_4$. The mass spectrum of VI confirmed the molecular weight and supported that VI was a cyclonucleoside: Compound (III) showed no molecular ion, while VI did. This is the expected difference between an open and a cyclonucleoside.[9] Other ions derived by simple cleavage of single bonds predominated in (III) and were suppressed in VI. Therefore, the base moiety plus one mass unit (m/e 136)[10] was intense in III, but not in VI. Likewise, the sugar moiety minus one mass unit (m/e 374) was intense in III, but not in VI. Another difference between acyclic and cyclonucleoside was also shown by the base moiety plus 30-ion.[11, 12] This fragment is more abundant in III (m/e 165) than in VI.

As pointed out earlier by Ikehara,[9] differentiation of O-2' from O-3' linkage with base could not be made from the mass spectrum.

Choice of the (O)-3',6-anhydro structure rather than the (O)-2',6-anhydro structure rests upon nmr spectra of VI and the acylated nucleoside (VII). The nmr spectrum of VI ($CDCl_3$) δ (ppm), aside from downfield signals due to aromatic protons, showed signals due to the remaining seven protons at 6.5 (s, 1H, H-1'), 5.5-6.3 (br, 1H, 2'-OH), 5.02 (d, J=2 Hz, 1H, H-3'), 4.68 (s, 1H, H-2'), 4.12 (br, 1H, H-4') and 3.55 (br, 2H, H-5').

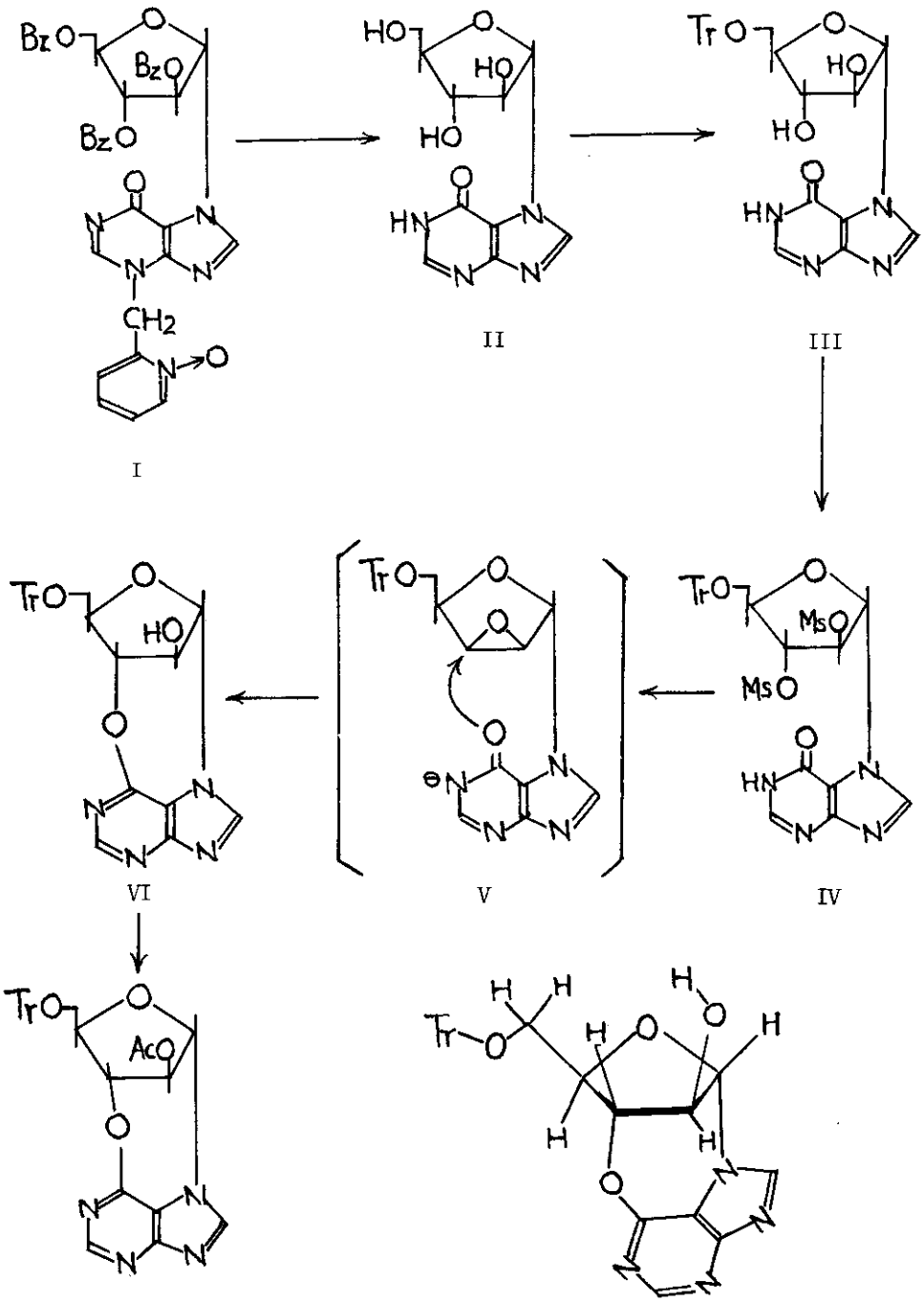

Fig. I

A double resonance experiment showed that H-4' was spin-coupled with H-3', hence adjacent to H-3' at 5.02. Irradiation at the frequency of H-3' (5.02) collapsed the broad signal at 4.12 to a triplet. Irradiation at the frequency of H-1' at 6.50 caused no change in signals at 5.02 (H-3') and 4.68 (H-2') because $J_{1',2'}$=0 Hz. The nmr spectrum of the acetylated product (VII, $CDCl_3$) showed signals at 6.32 (s, 1H, H-1'), 5.50 (s, 1H, H-2'), 5.23 (d, J=2.0 Hz, H-3'), and 2.04 (s, 3H, CH_3CO). Acetylation caused a remarkable downfield shift (ca. 0.8 ppm) of the signal due to H-2', signals due to H-5' and H-4' remaining completely unchanged. It is therefore reasonable to assume that the acetyl group was introduced at the 2'-hydroxyl and hence the anhydro bond in VI and VII was formed between 3'-O and C-6 of purine. Coupling constants calculated by the use of dihedral angles estimated from a molecular model of VI (Fig. 1) are also consistent with the observed values ($J_{1',2'}$=0 Hz, θ=90° and $J_{3',4'}$=2 Hz, θ=ca. 115°).

Alkaline hydrolysis of VI with 1 N KOH in EtOH failed to cleave both the anhydro and N-glycosyl bonds and VI was recovered nearly quantitatively. Neither did hydrazine in EtOH cleave both bonds. Treatment of VI with 1 N HCl at refluxing temperature gave only the detritylated product.

Presumably, VI was formed via an epoxide of the lyxo-type (V). There are a couple of precedents where the epoxide is formed from vicinal trans di-O-mesylated sugars.[13] Inspection of a molecular model of V showed that C-3' was more vulnerable to attack of the C=O group at position 6 of hypoxanthine than C-2'.

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10 A nucleoside is expressed in terms of base-sugars. Therefore, base moiety= C_5H_3NO, instead of C_5H_4NO; hypoxanthine=base moiety plus proton. The same holds in sugar moiety.

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