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SYNTHESIS AND PROPERTIES OF AN α-CYCLONUCLEOSIDE

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Although a number of cyclonucleosides derived from pyrimidine and purine nucleosides have been synthesized, cyclonucleoside having α-configuration in nucleosidic linkage has not yet been reported. We report herein synthesis of the first α-cyclonucleoside, 8,2'-anhydro-8-oxy-9-α-D-xylofuranosyladenine (I).

When N^6-benzoyladenine (1) was condensed with 1,2,3,5-tetra-O-acetyl-D-ribofuranose (2) by the fusion method (3) using p-toluenesulfonic acid as catalyst, a mixture of 6-benzamido-9-(2',3',5'-tri-O-acetyl-α- and β-D-xylofuranosyl)purine (II and III) was obtained in the yield of 47%. Deacylation with sodium methoxide and crystallization from methanol gave 9-β-D-xylofuranosyladenine (IV) (4) in the yield of 24%. The glass, which was obtained by the evaporation of the mother liquor of above crystallization containing α- and β-xylofuranosyladenine was dissolved in 0.5M acetate buffer (pH 4.0). Bromination with bromine-water (5) for 27 hr at room temperature and subsequent treatment with sodium hydroxide gave a crystalline compound (I) (m.p. 258-261°(decomp.), $[\alpha]_D^{26}$ = + 86.9° (c=0.77, DMSO), anal. calcd. for $C_{10}H_{11}O_4N_5.H_2O$: C, 42.40; H, 4.63; N, 24.73; found : C, 42.68; H, 4.57; N, 24.31; ultraviolet absorption properties : $\lambda_{max}^{0.1NHCl}$ 260 mμ (ε 16570), $\lambda_{max}^{H_2O}$ 257 mμ (ε 16800), $\lambda_{max}^{0.1NNaOH}$ 260 mμ (ε 16770); paper chromatography : Rf (A)* 0.54, Rf (B) 0.31, Rf (C) 0.66.). From these data the structure of compound I

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* Rf (A) stands for Rf value of chromatography performed in solvent A. Solvent used were : A, water adjusted to pH 10 with ammonia; B, n-butanol-water, 86 : 14,; C, n-propanol-conc. ammonia-water, 55 : 10 : 35.

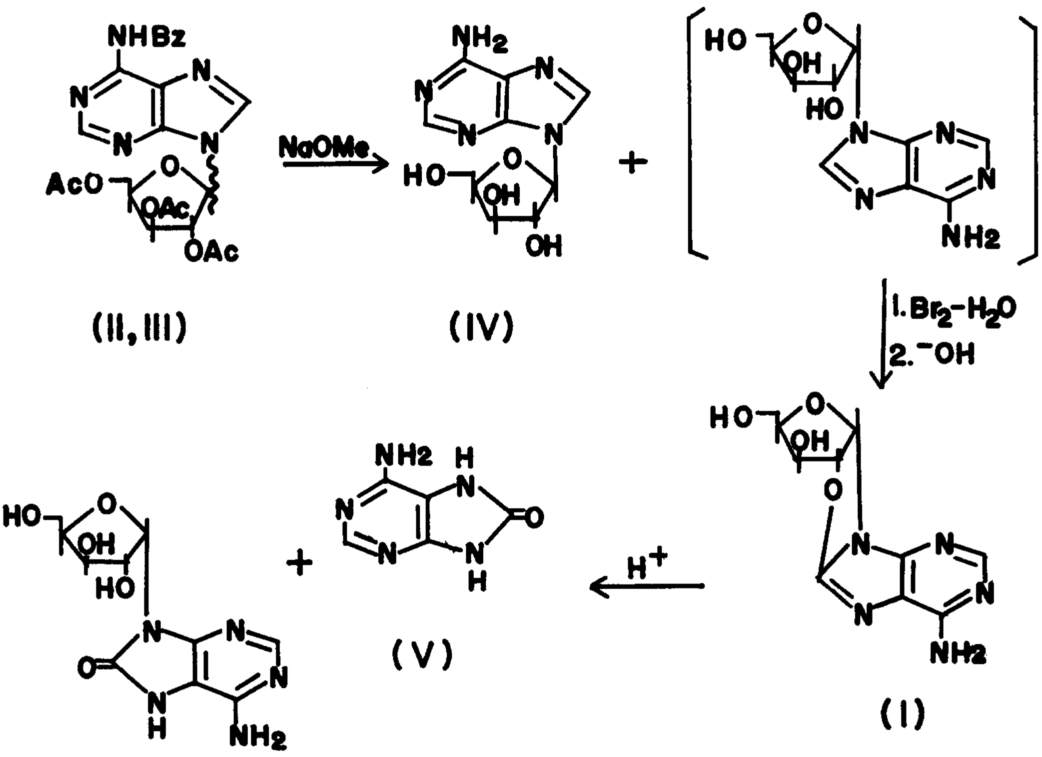
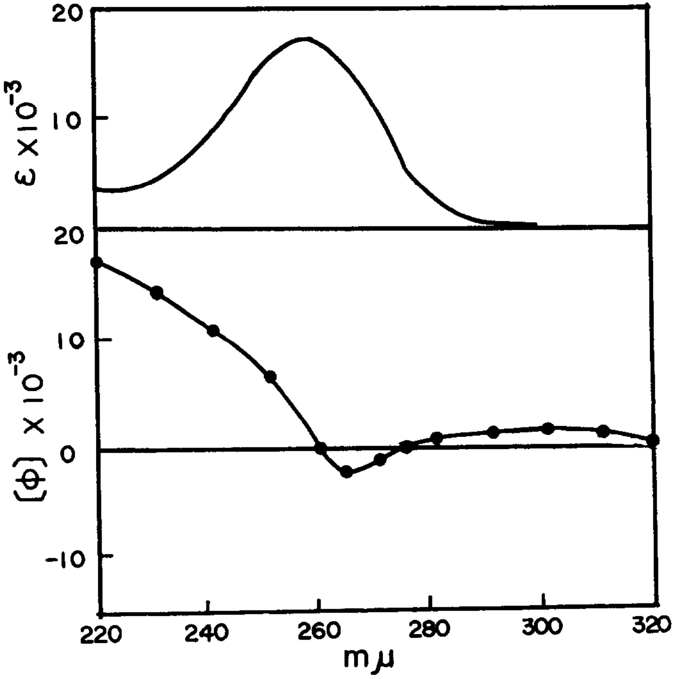

NHBz
N
N
N
N
O
AcO
OAc
OAc
NaOMe
NH2
HO
OH
OH
+
HO
O
OH
HO
NH2
1. Br2-H2O
2. ⁻OH
HO
O
OH
O
NH2
H+
NH2
H
N
O
N
H
+
HO
O
OH
HO
O
H
NH2
(II, III)
(IV)
(I)
(V)
(VI)

Fig I


ε × 10⁻³
20
10
[Φ] × 10⁻³
20
10
0
-10
220
240
260
280
300
320
mμ

was suggested to be a cyclonucleoside. N.m.r. taken in $(CD_3)_2SO$ at 60 mc showed peaks at (δ) 8.04 (1H, singlet, H_2), 6.80 (2H, singlet, 6-NH_2, exchangeable with D_2O), 6.52 (1H, doublet, J=5 cps, $H_{1'}$), 5.65-4.4 (5H, $H_{2'}$-$H_{5'}$), 5.65 (1H, doublet, 3'-OH , exchangeable with D_2O) and 4.71 (1H, triplet, J=5.3 cps, 5'-OH, exchangeable with D_2O). From the coupling constant of $H_{1'}$with $H_{2'}$, it was deduced that these protons were in *cis* configuration. Therefore, if the nucleosidic linkage of I is in α-configuration, the anhydro linkage must be in C_8 and $C_{2'}$ position. Also the fact that four protons were exchangeable with D_2O, supported this conclusion. Recent finding that in 8-bromo-9-β-D-arabinofuranosyladenine, 8,2'-O-cyclonucleoside was formed by the alkaline treatment (6), also suggested the possibility of this cyclization.

Hydrolysis of I in 2N sulfuric acid gave 8-oxyadenine (V) and a nucleoside, presumably 8-oxy-9-α-D-xylofuranosyladenine (VI) (λ_{max}^{1NHCl} 267, 288 mμ, $\lambda_{max}^{H_2O}$ 272 mμ, λ_{max}^{1NNaOH} 282 mμ; paper chromatography : Rf(A) 0.73, Rf(B) 0.28, Rf(C) o.65). Compound VI has ultraviolet absorption properties closely resembled to those of 8-oxy-9-β-D-xylofuranosyladenine (7) and slightly different Rf values in paper chromatography. From this hydrolysis experiment the structure of I was also suggested to be 8,2'-anhydro-8-oxy-9-α-D-xylofuranosyladenine.

O.r.d. of compound I showed a *negative* Cotton curve as in Fig. 1. Considering the fact that all (β)-purine cyclonucleosides having 8,2'-, 8,3'- and 8,5'-anhydro linkages have *positive* Cotton effect around major absorption band (8-10), inversion of the sign in α-cyclonucleoside is of highly interest in relation to the conformation of purine nucleosides, because in β-purine nucleosides small *negative* and in α-adenosine *positive* Cotton curves were observed.(11).

References

1. M. M. Baizer, J. R. Clark, M. Dub and A. Loter, *J. Org. Chem.*, **21**, 1276 (1956).
2. E. J. Reist and L. Goodman, *Biochem.*, **3**, 16 (1964).
3. T. Sato, T. Shimadate and Y. Ishido, *Nippon Kagaku Zasshi*, **81**, 1440 (1960).
4. P. Chang and B. Lythgoe, *J. Chem. Soc.*, 1992 (1950); B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).
5. M. Ikehara, S. Uesugi and M. Kaneko, *Chem. Commun.*, 17 (1967).
6. E. J. Reist, D. F. Calkins, L. V. Fisher and L. Goodman, *J. Org. Chem.*, **33**, 1600 (1968).
7. M. Ikehara, H. Tada and M. Kaneko, *Tetrahedron*, **24**, 3489 (1968).
8. M. Ikehara, M. Kaneko, K. Muneyama and H, Tanaka, *Tetrahed. Letters*, 3977 (1967).
9. M. Ikehara and M. Kaneko, *J. Am. Chem. Soc*, **90**, 497 (1968).
10. M. Ikehara, M. Kaneko and M. Sagai, *Chem. Pharm. Bull.*, **16**, 1151 (1968).
11. T. R. Emerson, R. J. Swan and T. L. V. Ulbricht, *Biochem.*, **6**, 843 (1967).