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SYNTHESIS AND PROPERTIES OF 8,2'-N-CYCLOADENOSINES

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In recent years the synthesis and properties of a variety of purine 8-cyclonucleosides have been reported.[1] These cyclonucleosides have oxygen or sulfur atom in their cyclo-bond and a purine-8-cyclonucleoside has not been reported which has nitrogen atom in its cyclo-bond. We reported herein the synthesis of the first purine 8-N-cyclonucleosides[2] starting from 8-bromo-2'-O-triisopropylbenzenesulfonyladenosine (8-Br-2'-TPS-adenosine).[3]

When 8-Br-2'-TPS-adenosine was treated with excess liquid ammonia in pyridine at 90-100° for 34 hr, 8-amino-2'-TPS-adenosine (II) was obtained in the yield of 66%. (m.p. 167-9°, IR. 1185 cm^{-1} (sulfonyl), nmr. (δ) 7.78 (1H, singlet, H-2), 6.62 (2H, singlet, 6-NH_2), 6.40 (2H, singlet, 8-NH_2). Cyclization of (II) with excess sodium acetate in dimethylformamide at refluxing temperature, gave compound (III) after purification of the reaction mixture through Dowex 1x4 (OH^-) resin. (mp. 260°(decom.), Anal. Calcd. for $C_{10}H_{12}O_3N_6$: C, 45.45; H, 4.58; N, 31.81; Found: C, 45.43; H, 4.62; N, 31.63, Ultraviolet absorption properties: $\lambda_{max}^{0.1N\text{-}HCl}$ 208 mμ (ε 18400), 273.5 mμ (ε 13900), $\lambda_{max}^{H_2O}$ 211.5 mμ (ε 20400), 272.5 mμ (ε 15100), $\lambda_{max}^{0.1N\text{-}NaOH}$ 276 mμ (ε 13200), 305 mμ (sh) (ε 3900) From these data, the structure of compound (III) was suggested to be a cyclonucleoside. NMR taken in $(CD_3)_2SO$ at 100 Hz showed peaks at (δ), 7.92 (1H, singlet, 2-H), 7.77 (1H, singlet, 8-NH, exchangeable with D_2O), 6.51 (2H, singlet, 6-NH_2, exchangeable with D_2O), 6.38 (1H, doublet, J=6.0 Hz, 1'-H), 4.63 (1H, doublet, J=6.0 Hz, 2'-H), 4.22 (1H,

singlet, 3'-H), 4.03 (1H, triplet, J=6.4 Hz, 4'-H), 3.19 (2H, doublet, J=6.4 Hz, 5'-CH_2). The fact that five protons were exchangeable with D_2O supports that the compound (III) has an anhydrobond. Furthermore, from the coupling constant $J_{1',2'}$ these protons have cis-configuration. In these respects compound (III) has an anhydrobond containing nitrogen atom between 8-position of adenine moiety and 2'-position of sugar moiety.

The structure of compound (III) was further supported from mass spectrum (see figure (I)) Characteristic strong molecular peak was found in the spectrum as in the case of 8,2'-O-cycloadenosine and 8,2'-S-cycloadenosine.[4] Another characteristic fragment peaks M-31, M-48, M-59, M-77, M-89 and M-101 were in good agreement with that of 8,2'-O and S-cycloadenosines. A strong peak at m/e 174 (M-90) is peculiar to this 8,2'-N-cycloadenosine.

8,2'-N-Methyl-cycloadenosine was synthesized in a similar manner as above. When 8-Br-2'-TPS-adenosine was refluxed with methylamine in methanol, 8-methylamino-2'-TPS-adenosine (IV) was obtained (mp. 176-8°). Cyclization of compound (IV) with sodium acetate in dimethylformamide at 150° for 30 min. afforded compound (V) in the yield of about 50%. (mp. 296-8°, Anal. Calcd. for $C_{11}H_{14}O_3N_6$: C, 47.47; H, 5.07; N, 30.20; Found: C, 47.52; H, 4.90; N, 30.20, Ultraviolet absorption properties: $\lambda_{max}^{0.1N\text{-}HCl}$ 278.5 mμ (ε 15800), 208 mμ (ε 20400), $\lambda_{max}^{H_2O}$ 276.5 mμ (ε 17000), 214.5 mμ (ε 23000), $\lambda_{max}^{0.1N\text{-}NaOH}$ 278 mμ (ε 17200). NMR taken in $(CD_3)_2SO$ at 60 Hz showed peaks at (δ), 7.95 (1H, singlet, 2-H), 6.49 (2H, singlet, 6-NH_2), 6.38 (1H, doublet, J 6.3 Hz. 1'-H). 4.46 (1H, doublet, J 6.3 Hz, 2'-H), 4.08 (1H, triplet, J 6.5 Hz, 4'-H), 3.25 (2H, doublet, J 6.5 Hz, 5'-CH_2) and 3.04 (3H, singlet, 8-NCH_3). These data suggest that the compound (V) must be cyclonucleoside and has its anhydrobond between 8 position of adenine moiety and 2' position of sugar moiety.

The structure of compound (V) was also further supported from mass spectrum (see figure (II)). The mass spectrum of compound (V) showed peaks at masses 278, 247, 230, 219, 201, 189 and 177. These peaks were in good agreement with the peaks, molecular peak, M-31, M-48, M-59, M-77, M-89 and M-101 of compound (III), respectively. In addition, a characteristic

strong peak at mass 188 (M-90) exists also in the spectrum of this cyclonucleoside. From these properties, it was concluded that the structure of compound (V) was 8,2'-N-methyl-cycloadenosine.

The chemical properties of these N-cycloadenosines are now under investigation in our laboratory.

References

1. M. Ikehara, Accounts of Chemical Research, 2, 47 (1969).
2. M. Kaneko, B. Shimizu and M. Ikehara, Reported at the Annual Meeting of the Pharmaceutical Society of Japan (1971).
3. M. Ikehara and M. Kaneko, Tetrahedron, 26, 4251 (1970).
4. M. Ikeda, Y. Tamura and M. Ikehara, J. Heterocyclic Chem., 7, 1378 (1970).

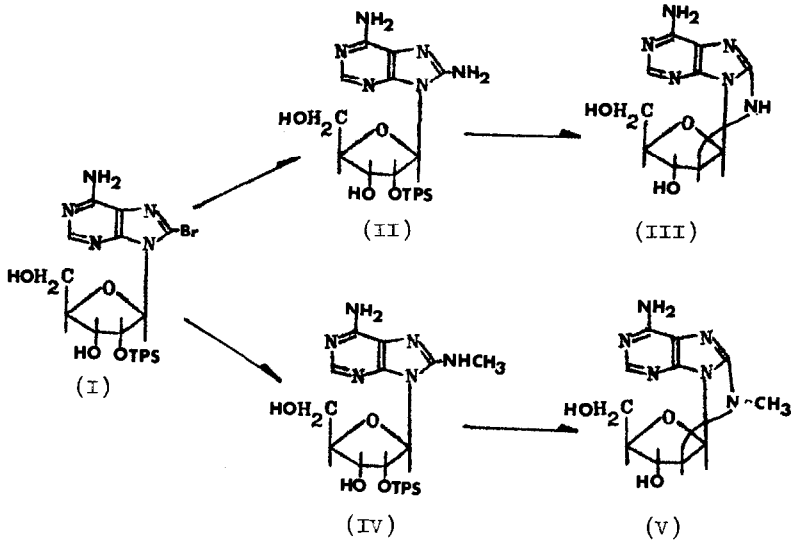

Figure I THE MASS SPECTRA OF 8,2'-N-CYCLOADENOSINE

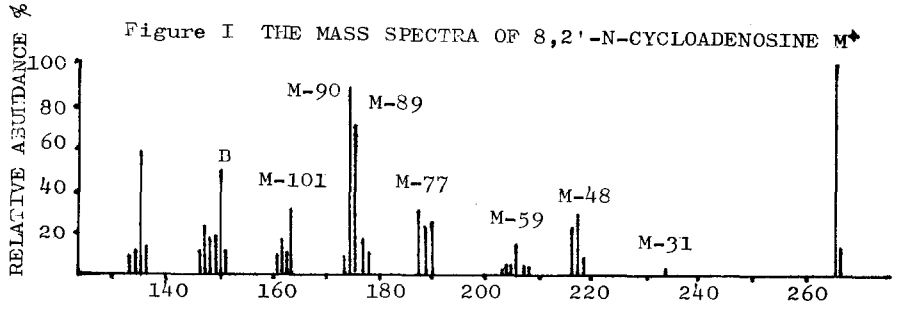

Figure II THE MASS SPECTRA OF 8,2'-N-METHYL-ADENOSINE