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A NOVEL REARRANGEMENT OF S- TO O-CYCLONUCLEOSIDES

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We have previously reported on the rearrangement of 8,2'-anhydro-9-oxy-β-D-arabinofuranosyladenine to 8,5'-cyclonucleoside by weak alkaline treatment (1). We now wish to report on the rearrangement of 8,3'-anhydro-8-mercapto-9-β-D-xylofuranosyladenine (I) (8,3'-S-cycloadenosine) (2) to 8,5'-O-cyclonucleoside via a sulfoxide intermediate (II).

When 8,3'-S-cycloadenosine (I) was oxidized with two equivalents of N-bromosuccinimide in 80% aqeous methanol at room temperature for 5-6 hr, a crystalline compound (II) was obtained in a yield of 58%. Compound II showed UV absorption spectra : $\lambda_{max}^{H^+}$ 274 nm (ε 10100) and $\lambda_{max}^{H_2O}$ 284 nm (ε 12500).* From the elemental analysis and molecular ion peak (M/e=297) in mass spectrum, the structure of compound II was shown to be a sulfoxide of 8,3'-S-cycloadenosine. As shown in Fig. 1, CD spectrum of II showed Cotton bands at 285 nm ([θ] = -13250), 250 nm (+17500) and 229 nm (+34500), which constituted completely inverted profile from that of I. This fact suggests that a new asymmetric center was introduced to 8-S atom of compound I. NMR spectra (taken in d_6-DMSO at 100 mHz, tetramethylsilane as internal standard) showed signals at 8.22 ppm (s, H-2), 6.04 (s, H-1'), 3.60 (d, H-2'), 4.68(q, H-3'), 4.12 (d, H-4') and 5.05(d, H-5'). Anomalous down field shift of the H-3' signal may be due to the introduction of S-O group to the 8,3'-anhydro bond. From these evidences the structure of sulfoxide should be assigned to compound II. The reason why the oxidation does not give two isomers of sulfoxides and does not proceed further to sulfone may be explained by shielding of one side of the S-atom by 5'-OH.

When the sulfoxide (II) was treated with weak alkali (0.01N sodium hydroxide or ammonia-methanol) at room temperature, it changed immediately to new compounds having UV absorption maxima at around 260 nm. This value is similar to that of O-cycloadenosines. Paper electrophoresis (PEP) of the mixture performed at pH 7.5 showed three spots having $R_{cyclicAMP}$ 1.0,

* Alkaline absorption could not be taken due to rapid conversion to the 8,5'-O-cyclonucleoside.

0.28 and 0.0. From the reaction mixture an insoluble material precipitated upon prolonged storage. This compound (III) showed no migration in PEP and had UV absorption maxima at 261 nm. Elemental analysis suggested that compound III would be thiolsulfinate of 8,5'-anhydro-8-oxy-9-β-D-(3-deoxy-3-thio-threopentofuranosyl)adenine. This was confirmed further by reductive cleavage of III with sodium bisulfite to give compounds having $R_{cyclicAMP}$ 1.0 and 0.28.

Second compound (IV) having $R_{cyclicAMP}$ 1.0 was isolated from the reaction mixture by thin layer chromatography (TLC) on Kieselgel in solvent ethanol-chloroform (15 : 5, vol/vol). Compound IV showed UV absorption maxima at 261 nm and negative test by fuchsin reagent. The compound IV was further obtained from III by reductive cleavage by sodium bisulfite treatment and successive air oxidation. These facts suggest that the compound IV must be 3'-deoxy-3'-sulfonic acid of 8,5'-anhydro-8-oxy-9-β-D-xylofuranosyladenine.

Finally a compound (V) having $R_{cyclicAMP}$ 0.28 was also obtained from the reaction mixture by preparative TLC. Compound V had UV absorption maxima at 261 nm and a thiol group was detected by nitroprusside reagent. When compound V was desulfurized with Raney nickel (W-2), 8,5'-anhydro-8-oxy-9-β-D(3-deoxy-erythropentofuranosyl)adenine (VI) was obtained. The structure of VI was confirmed by UV absorption spectra and direct comparison with a sample synthesized from 3'-deoxyadenosine (cordycepin) by bromination and sodium hydride treatment as described for adenosine (3).

CD spectra of compound III and V were shown in Fig 1. As found in 8,5'-O-cycloadenosine (4), a positive Cotton band at 260 nm is consistent with the cyclonucleoside structure for both compounds. However, relative magnitude of this band is far smaller than that of 8,5'-O-cycloadenosine. This is presumably due to unusual substituents of xylo configuration in 3'-position. The [θ] value of compound III was twice as large as that of V and it is consistent with the fact that III is the dimerized compound. Compound V readily converted to disulfide (VII), which was isolated from the mother liquor of recrystallization of compound III, by the air oxidation or by disproportionation of thiolsulfinate as described below. Compound VII also gave 8,5'-anhydro-3'-deoxy compound (VI) by Raney nickel desulfurization.

These results suggested that a rapid conversion of 8,3'-S-O bond of II to 8,5'-O-anhydro bond would occur first. This is as observed in case of the interconversion of 8,2'- and 8,5'-O-cyclonucleoside (1). This type of attack of 5'-OH group existing in a

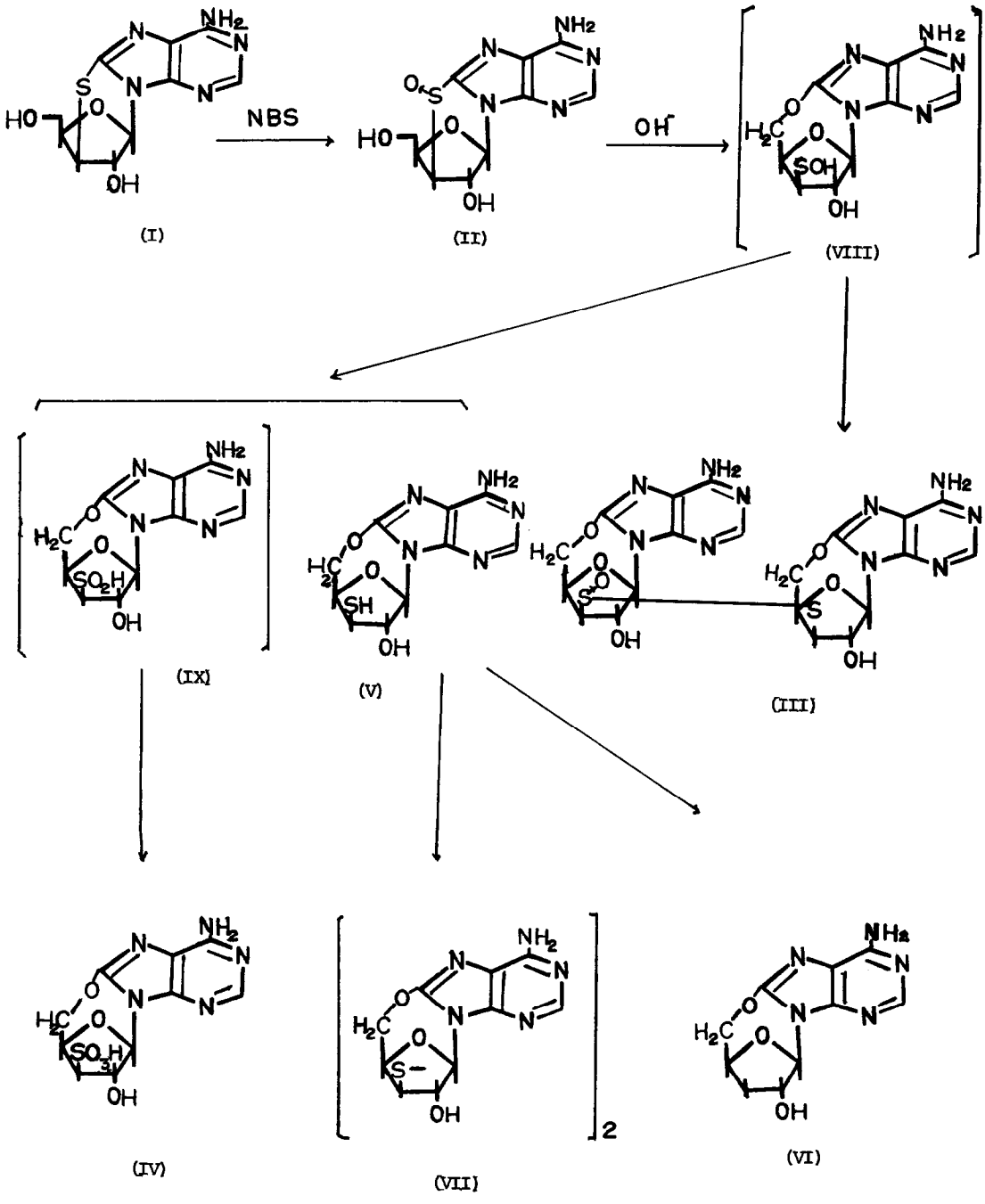
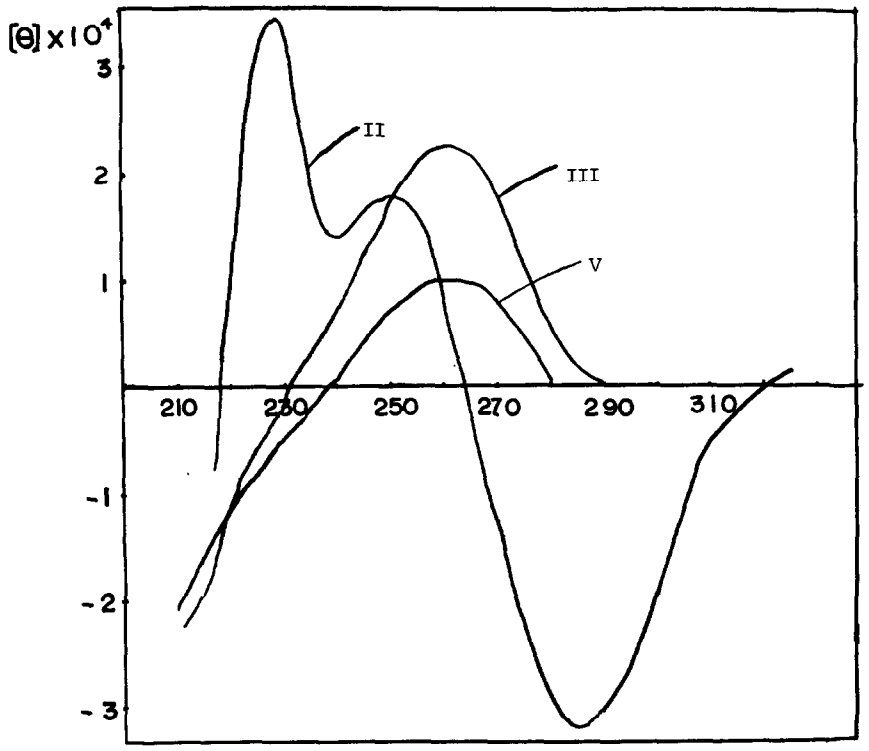

NBS
OH⁻
(I)
(II)
(VIII)
(IX)
(V)
(III)
(IV)
(VII)
(VI)

Fig. 1



sterically favored position could be expected, because in a CPK model of II proximity of 5'-OH to the C-8 was shown. The resulting 8,5'-O-cyclonucleoside having 3'-sulfenic acid o xylo configuration (VIII) was then dimerized to give thiolsulfinate (III). On the other hand, VIII would give sulfinic acid (IX) and thiol compound (V) by disproportionation. The former (IX) converted to sulfonic acid (IV) and the latter (V) to disulfide (VII) by air oxidation. Another route : RSOH + R-S(=O)-S-R ⟶ R-S-S-R + RSO_2H could not be excluded.

These reactions constitute the first conversion of S- to O-cyclonucleosides and further investigations on other cyclonucleosides are in progress in our laboratory.

References

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