Tetrahedron Letters No.10, pp. 713-716, 1970. Pergamon Press. Printed in Great Britain.

SELECTIVE TOSYLATION OF ADENOSINE 5'-MONOPHOSPHATE

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(Received in Japan 27 December 1969; received in UK for publication 28 January 1970)

During the course of our study on purine cyclonucleosides (1) we have found that adenosine 5'-monophosphate (AMP) and its 8-bromo derivative (BrAMP) were tosylated only at 2'-OH by the tosylation in alkaline solution. These tosylates gave rise to 8,2'-anhydro nucleoside phosphate by the treatment with NaSH. The latter compound easily gave 2'-deoxyadenosine phosphate.

AMP. Na_2 (1 mmole) was dissolved in 1.5 ml of N-aqeous sodium hydroxide. The solution of tosyl chloride (4 mmoles) in dioxane (4.5 ml) was added to this solution dropwise with vigorous stirring at room temperature. Analysis of the product after 1-2 hrs' reaction by paper chromatography* showed that the main product was mono-tosylated AMP (Rf 0.26, 54-61%) (1) and a small amount of unknown product (Rf0.36, 5-6%) and unreacted AMP (Rf 0.10, 11-23%) were found. In order to determine the position of tosyl group in compound 1, reaction mixture was subjected to the following treatments : i) bromination with bromine-water at position 8 to give 8-bromo-AMP (2) as described previously (2) and ii) cyclization with a qeous NaSH (3 mmoles) in DMF-water (2 : 1, vol/vol) for 15 hrs at room temperature. The reaction mixture was applied to a column of Dowex IX8 (formate) and the column was eluted with 0.05N formic acid, 0.1N formic acid, 0.01N formic acid+0.1M ammonium formate and 0.1N formic acid + 0.5M ammonium formate. 8,2'-Anhydro-8-mercapto-9-β-D-arabinofuranosyladenine 5'-mono-phosphate (3) was eluted as a completely resolved main peak, which was pooled and lyo-philized to a white powder (yield from AMP was 21-32%). Compound 3 was characterized by

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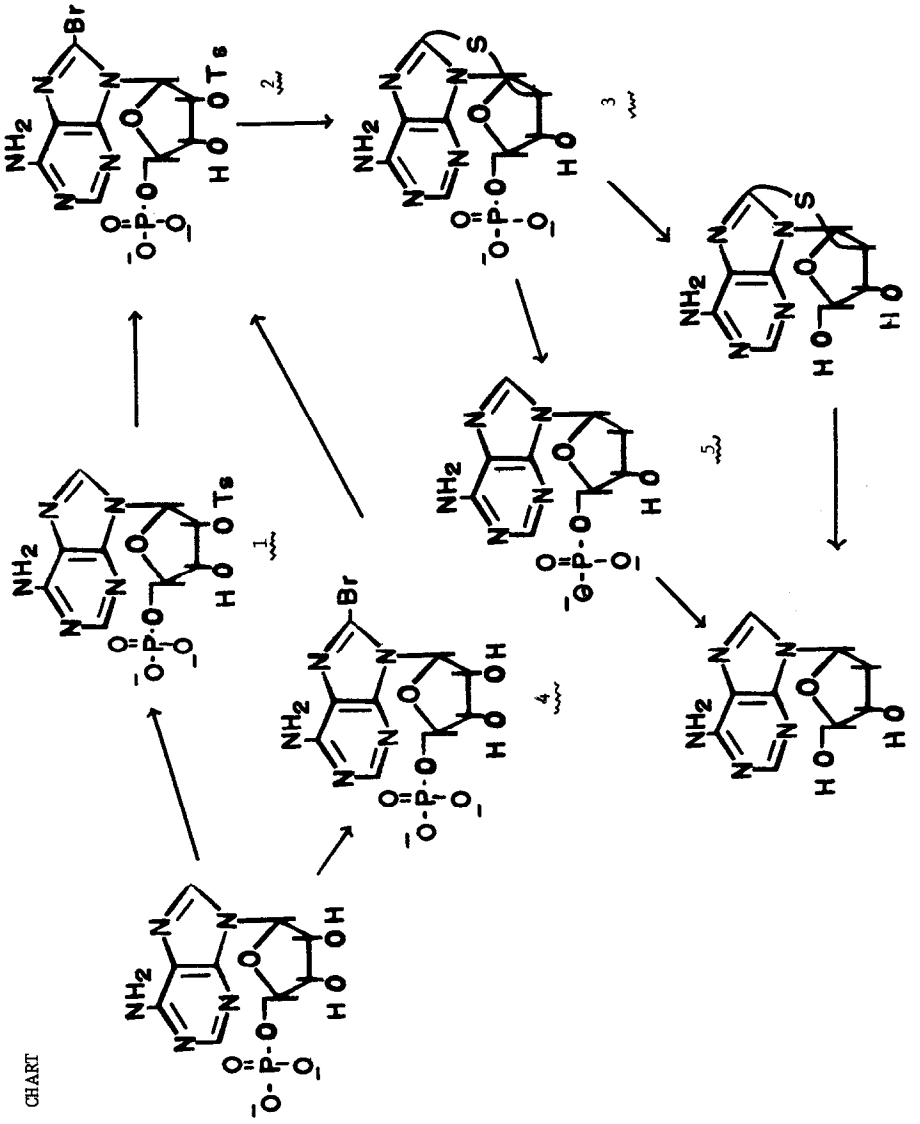
* Solvent, isopropanol-conc. ammonia-water, 7:1:2.

elemental analytical data (Anal. Calcd. for $C_{10}H_{12}O_6N_5PS.2H_2O$: C, 30.23; H, 4.06; N, 17.63. Found : C, 30.33; H, 4.67; N, 17.15.), ultraviolet absorption properties (λ_{max}^{pH1} 278 nm (ε 21500); λ_{max}^{pH7} 220.5 nm (ε 21900), 276 nm (ε 22500); λ_{max}^{pH13} 277 nm (ε 22000) identical with those of 8,2'-S-cycloadenosine (3), and analysis by Dekker's column (4) by which no 8,3'-compound was detected after dephosphorylation by an alkaline phosphatase. Thus monotosyl-AMP obtained as above was found to be 2'-tosyl-AMP. Accordingly the tosylation reaction of AMP in alkaline solution affords exclusively 2'-tosylate and shows the first exsample of selective sulfonylation of 2'- and 3'-OH group of nucleotides. This finding was further confirmed by the tosylation of 8-bromo-AMP (4). In the almost same reaction condition compound 4 gave only 2'-tosyl derivative (yirld 73%) which was cyclized to compound 3 as described above (yield 65%). In this case also no 8,3'-counterpart was detected. Although reason why this reaction gives only 2'-tosylate and not 3'-tosylate is not clarified as yet, the following may be considered : i) The fact that use of 4 mmoles of tosyl chloride gave the highest yield, suggests the formation of tosyl-phosphate anhydride, which covers 3'-OH from the attacking tosylate. ii) Higher "acidity" of 2'-OH than 3'-OH presumably induced by haterocyclic base and/or lactol O atom.

Compound 3 (51 mg) was treated with Raney nickel W-7 (100 mg) in refluxing water (50 ml) for one hour. After filtration of Ni the reaction mixture was applied to a column of Dowex IX8 (formate) and elution was carried out with formic acid as above. 2'-Deoxy-AMP (5) was obtained in a yield of 12%. Incubation of compound 5 with snake venom 5'-nucleotidase gave 2'-deoxyadenosine, which was identified by the comparison with an authentic sample and was confirmed as different from 3'-deoxyadenosine (Cordycepin) (5). By these reactions the first chemical conversion of ribo nucleotide to 2'-deoxyribo-nucleotide was accomplished.



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The Schotten-Baumann type reaction of other nucleotides are now in progress in our laboratory.

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