Tetrahedron Letters No.2, pp. 87-90, 1971. Pergamon Press. Printed in Great Britain.

DIRECT HALOGENATION OF SUGAR MOIETY OF NUCLEOSIDES

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(Received in Japan 30 November 1970; received in UK for publication 9 December 1970)

A number of 5'-halogenated derivatives of ribonucleoside have been reported including 5'-iodo(fluoro, chloro, bromo)-5'-deoxy-uridine (1-5) and 5'-iodo(chloro, bromo)-5'-deoxy-adenosine (6). The 5'-iodo(bromo)-5'-deoxy-nucleoside has been utilized for the synthesis of nucleotides (7), cyclonucleosides (1), sulfur analogs (8), phosphonic acid derivatives (8) and deoxynucleosides (9).

The synthesis of these 5'-halogenated ribonucleosides has been generally performed by introduction of p-toluene sulfonyl or methane sulfonyl group into the 5'-position of the suitably blocked ribonucleosides and subsequent replacement of the sulfonyl group with alkali halides to afford the blocked 5'-halogeno-5'-deoxy-ribonucleosides (1,4,6). Direct replacement of primary hydroxyl groups of suitably blocked nucleosides by iodine atom has been reported (2).

Recently Dods and Roth (3) reported a further simple preparative method of 5'-chloro (bromo)-5'-deoxy-uridine directly from uridine by means of Vilsmeier-Haack reagent. We applied the procedure to the synthesis of 5'-halogenated derivatives of ribonucleoside, but the reaction of cytidine and adenosine with the reagent did not gave the expected 5'-halogenated derivatives. It was found that the reaction of cytidine with Vilsmeier-Haack reagent, the mixture of thionyl chloride and N,N'-dimethylformamide, afforded 2,2'-cyclocytidine and its derivative(s) instead of 5'-chloro-5'-deoxy-cytidine (10).

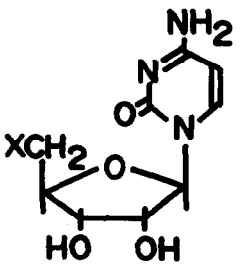
This paper deals with an improved and novel convenient method to prepare 5'-chlorinated and 5'-brominated ribonucleosides, which will be further converted into other 5'-substituted

derivatives.

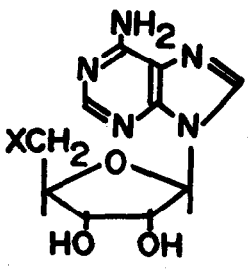
It was found that thionyl chloride or thionyl bromide when mixed with hexamethylphosphoroamide is a good reagent for the selective halogenation of the 5'-position of ribonucleoside. The mixture of thionyl chloride (or thionyl bromide) and hexamethylphosphoroamide provides relatively mild reaction conditions for the expected selective halogenation.

The general procedure is as follows. Thionyl chloride or thionyl bromide was dissolved in hexamethylphosphoroamide and to this mixture was added ribonucleoside and reacted at room temperature for 10-15 hours, and 5'-halogeno-5'-deoxy-nucleosides were isolated in a fairly good yield after an appropriate work-up procedure. In this way, we have synthesized 5'-chloro-5'-deoxy-cytidine (I), 5'-bromo-5'-deoxy-cytidine (II), 5'-chloro-5'-deoxy-adenosine (III) and 5'-bromo-5'-deoxy-adenosine (IV).

It has been reported that hexamethylphosphoroamide forms active 'onium' complexes with p-toluene sulfonic acid anhydride, p-toluene sulfonylchloride and thionyl chloride and the complexes are novel tools for the synthesis of the peptide bonds (11). In our halogenating reactions the 'onium' complex of hexamethylphosphoroamide and thionyl chloride (or thionyl bromide) would be an active species.



(I) X = Cl
(II) X = Br



(III) X = Cl
(IV) X = Br

Experimental section

General method

Thionyl chloride (or thionyl bromide)(1.5 ml) was dissolved in 10 ml of hexamethylphosphoroamide and to the solution was added 1.0 g of nucleoside. The mixture was stirred at room temperature for 15 hours, then poured into about 90 ml of water and the aqueous solution was directly applied to a column of Dowex 50 X4 (H^+ form)(300 ml). The column washed well with water was eluted with 1.0 l of 1 N ammoniacal water and the effluent was evaporated to small volume. 5'-Chloro-5'-deoxy-cytidine (I) and 5'-chloro-5'-deoxy-adenosine (III) were isolated in a crystalline state directly from the concentrated solution and 5'-bromo-5'-deoxy-cytidine (II) and 5'-bromo-5'-deoxy-adenosine (IV) were isolated by crystallization of the residue by adding ethanol and methanol respectively.

5'-chloro-5'-deoxy-cytidine (I): The compound (I) was obtained in a yield of 80 % and recrystallization from hot water gave white needles. M.p. 160-168° (decomp., uncorr.). $[\alpha]_D^{25°}$, +24.7° (C; 0.5 in H_2O). UV; λ max(pH 1) 280, λ min(pH 1) 241, λ max(pH 7) 271, λ min(pH 7) 251 mμ. Paper chromatography; Rf, 0.35 (solvent; BuOH-H_2O, 84:16). The compound consumed metaperiodate.

Anal. Calcd for $C_9H_{12}O_4N_3Cl$, C;41.30, H;4.62, N;16.06, Cl;13.55 %,
Found, C;40.96, H;4.57, N;16.28, Cl;13.83 %.

5'-bromo-5'-deoxy-cytidine (II): Pale yellow granules of (II) were obtained in a yield of 55 %, and melted at 205° (decomp., uncorr.). UV; λ max(pH 1) 280, λ max(pH 7) 271 mμ. Paper chromatography; Rf, 0.35 (solvent; BuOH-H_2O, 84:16).

Anal. Calcd for $C_9H_{12}O_4N_3Br$, C;35.31, H;3.95, N;13.73, Br;26.10 %,
Found, C;35.84, H;4.24, N;13.76, Br;26.06 %.

5'-chloro-5'-deoxy-adenosine (III): The compound (III) was obtained in a yield of 75 % and recrystallization from hot water gave colorless needles. M.p. 190° (decomp., uncorr.). $[\alpha]_D^{25°}$, -27.7° (C; 0.5 in H_2O). UV; λ max(pH 1) 257, λ min(pH 1) 229, λ max(pH 7) 260, λ min(pH 7) 227 mμ. Paper chromatography; Rf, 0.48 (solvent; BuOH-H_2O, 84:16). The compound consumed metaperiodate.

Anal. Calcd for $C_{10}H_{12}O_3N_5Cl$, C;42.04, H;4.23, N;24.51, Cl;12.41 %,
Found, C;42.40, H;4.38, N;24.41, Cl;12.80 %.

5'-bromo-5'-deoxy-adenosine (IV): Colorless granules of (IV) were obtained in a yield of 30 % and melted at 200° (decomp., uncorr.). UV; λ max(pH 1) 257, λ max(pH 7) 260 mμ. Paper chromatography; Rf, 0.44 (solvent; BuOH-H_2O, 84:16).

The properties of the compounds, (III) and (IV), shown above were quite identical to those of 5'-chloro-5'-deoxy-adenosine and 5'-bromo-5'-deoxy-adenosine reported in the literature (6).

Acknowlegement: The authors wish to express their sincere thanks to Mr. T.Nakamura, the Manager of this laboratory, for his continued interest and encouragement in this study.

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