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TRANSGLYCOSYLATION FROM PYRIMIDINES TO PURINES

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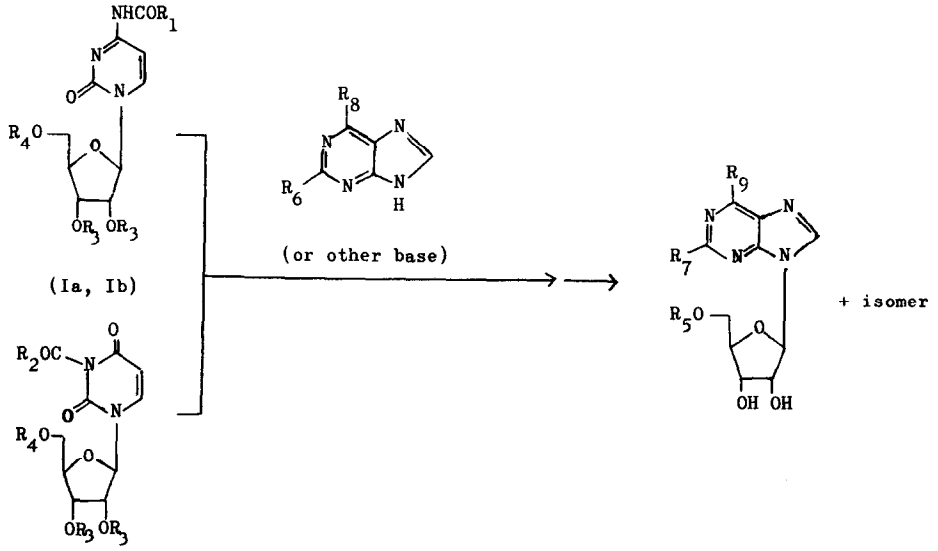
As previously reported[1], glycosyl groups migrate from the pyrimidine segment (N-3) to the imidazole ring (N-9) of purine derivatives by an intermolecular mechanism. Extension of this migration reaction led to the transglycosylation of pyrimidine nucleosides and nucleotides to purine bases. Such transfers of a sugar moiety from pyrimidines to purines have never been reported because of the stable glycosyl bonds of pyrimidine nucleosides. In order to undergo facile cleavage[1-2] of the glycosyl linkage, the pyrimidine nucleosides and nucleotides were acylated both at the heterocyclic and the glycosyl moiety and subsequently heated with purine bases in the presence of acid catalyst.

Treatment of cytidine with acetic anhydride and pyridine afforded 2',3',5'-tri-O-acetyl-N^4-acetylcytidine (Ia) [amorphous, $UV\lambda_{max}^{EtOH}$ mμ(ε): 250(15300) and 299(6300)]. When Ia was heated with N^6-benzoyladenine and mercuric bromide at 150° for 20 hours in a mixture of xylene and N,N-dimethylacetamide, the ribosyl group of Ia migrated to N^6-benzoyladenine to yield 2',3',5'-tri-O-acetyl-N^6-benzoyladenosines. Deacylation of the products followed by chromatography on Dowex-1(OH^-)[3] gave 9-β-D-ribofuranosyladenine (35% yield based on Ia) and 9-α-D-ribofuranosyladenine (6%). Similarly, N^6,N^6-dimethyladenosine[4], inosine, guanosine, 7-D-ribofuranosylguanine, 7-D-ribofuranosyltheophylline were obtained as shown in Table 1. These nucleosides were also prepared by heating free cytidine and purine bases with acetic or benzoic anhydride in the presence of a catalyst.



Ia: $R_1=CH_3$, $R_3=R_4=COCH_3$ $R_5=H$, $P(O)(OH)_2$

Ib: $R_1=CH_3$, $R_3=COCH_3$, $R_4=P(O)(OH)_2$ $R_6=H$, $NHCOCH_3$

Ic: $R_1=CH_3$, $R_3=COC_6H_5$, $R_4=P(O)(OC_6H_5)_2$ $R_7=H$, NH_2

IIa: $R_2=C_6H_5$, $R_3=R_4=COCH_3$ $R_8=NH_2$, $NHCOC_6H_5$, $N(CH_3)_2$, OH

IIb: $R_2=C_6H_5$, $R_3=COC_6H_5$, $R_4=P(O)(OC_6H_5)_2$ $R_9=NH_2$, $N(CH_3)_2$, OH

Cytidine-5'-phosphate was acylated with acetic anhydride in pyridine to afford pyridinium 2',3'-di-O-acetyl-N^4-acetylcytidine-5'-phosphate(Ib) [amorphous, $UV\lambda_{max}^{EtOH}$ mμ: 251 and 301]. The phosphoribosyl group was transferred to N^6-benzoyladenine to give the acylated adenine nucleotide which was converted to adenosine-5'-phosphate. The protected phosphoribosyl moiety of 2',3'-di-O-benzoyl-5'-diphenylphosphoryl-N^4-acetylcytidine(Ic) also migrated to N^6-benzoyl-adenine and theophylline as in case of Ib. Removal of the protecting groups of the purine derivatives gave 9-D-ribofuranosyladenine-5'-phosphate and 7-D-ribofuranosyltheophylline-5'-phosphate.

Acylation of uridine with acetic anhydride and benzoyl chloride afforded 2',3',5'-tri-O-acetyl-N^3-benzoyluridine(IIa) [amorphous, $UV\lambda_{max}^{EtOH}$: 252.5 mμ (ε 20200), IR: 1677, 1713 and 1745 cm^{-1} (C=O)]. An analogous transglycosylation was observed when IIa was heated with theophylline and stannic chloride at 130° for 30 minutes in a mixture of xylene and nitrobenzene to give 7-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-theophyllines. The substituted theophyllines were

converted to the free nucleosides which were separated by chromatography on Dowex-1(OH^-) furnishing 7-β-D-ribofuranosyltheophylline (8%) and its α-anomer (1%). When the migration reaction was carried out in the presence of benzoyl chloride, 7-D-ribofuranosyltheophyllines were obtained in better yields (β=24%, α=8%). 7-α-D-Ribofuranosyltheophylline was characterized by its physical properties [m.p. α:196-8°, β:192-4°, $UV\lambda_{max}^{pH\ 7}$ mμ(ε) α:274.5(8760), β:274.5(8770), NMR H_1, from dioxane in D_2O at 60Mc cps ($J_{1'-2'}$) α: -166(4.5), β: -140(3.5), $[M]_{288}^{H_2O}$ α: -4400, β: +1740].

The phosphoribosyl moiety of IIb migrated to yield the corresponding theophylline nucleotide which was converted to 7-D-ribofuranosyltheophylline-5'-phosphate.

Hydrogen halides, metal halides (stannic, mercuric, mercurous, antimony, lead, ferric etc.) and arylsulfonic acids were found to be effective catalysts for the transglycosylation reaction.

All nucleosides and nucleotides obtained were identified by comparison with authentic samples or with reported values of m.p., UV and NMR spectra, optical rotation and other physical properties.[5-10]

This direct transfer of the sugar moiety is simpler than the general synthetic procedure of purine nucleosides and nucleotides. The latter normally involves tedious steps in preparing the suitably protected sugar halides or acetates prior to condensation reactions. Moreover, conversion of pyrimidine nucleosides and nucleotides into purine derivatives will be valuable in the utilization of pyrimidine nucleotide by-products from the degradation of ribonucleic acid which accompany the purine nucleotides.

Improvements on this synthetic procedure and its applications to other glycosides are in progress.

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TABLE I

Yields of Purine Nucleosides and Nucleotides

Glycosyl Donor	Resulting Nucleoside, -tide	Yield(%) β	Yield(%) α
Tetra-acylcytidine(Ia)	Adenosine	35	6
	N^6,N^6-Dimethyladenosine	44	
	Inosine	10	
	Guanosine	21	
	7-D-Ribofuranosylguanine	20	
	7-D-Ribofuranosyltheophylline	36	2
	1-D-Ribofuranosyl-benzimidazole	20	
	1-D-Ribofuranosyl-5,6-dimethylbenzimidazole	30	
Pyridinium 2',3'-di-O-acetyl-N^4-acetylcytidine-5'-phosphate (Ib)	Adenosine-5'-phosphate	4	
2',3'-Di-O-benzoyl-5'-diphenylphosphoryl-N^4-acetylcytidine (Ic)	Adenosine-5'-phosphate	10	
	7-D-Ribofuranosyl-theophylline-5'-phosphate	10	
Tetra-acyluridine (IIa)	7-D-Ribofuranosyltheophylline	24	8
2',3'-Di-O-benzoyl-5'-diphenylphosphoryl-N^3-benzoyluridine (IIb)	7-D-Ribofuranosyl-theophylline-5'-phosphate	20	

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