A Convenient Synthesis of Nucleotides

The synthesis of nucleotides by the phosphorylation of properly protected nucleosides is a general route which has been widely applied during the recent years. In this respect, numerous phosphorylating agents have been investigated and reported in the literature. However, attempts to synthesize nucleotides by direct condensations of phosphorylated sugars with derivatives of pyrimidine or purine bases are very few^{1,2)} and have not been extensively explored.

In this communication, we wish to report a convenient synthetic procedure for natural and unnatural nucleotides by modifying the previously reported method^{3a-d)} for the synthesis of the pyrimidine and purine nucleosides starting from trimethylsilyl derivatives of the bases and acylhalogeno sugars.

When trimethylsilyl derivatives of various pyrimidines and purines were allowed to react at 90~100° with phosphorylated ribosyl or glucosyl bromide, then the protecting

Chart 1.

- 1) T. Ukita, H. Hayatsu : J. Am. Chem. Soc., **84**, 1879 (1962).
- 2) M. Matsui, A. Nobuhara : Agr. Biol. Chem., **27**, 650 (1963).
- 3) a) T. Nishimura, B. Shimizu, I. Iwai : This Bulletin, **11**, 1470 (1963); b) T. Nishimura, I. Iwai : *Ibid.*, **12**, 352, 357 (1964); c) T. Nishimura, B. Shimizu : Agr. Biol. Chem., **28**, 224 (1964); d) T. Nishimura, B. Shimizu, I. Iwai : This Bulletin, **12**, 1471 (1964).

(HALLOWELL) to yield the corresponding ribofuranosylpurine 5'-phosphates in good yields.

The structural confirmation of thus obtained nucleotides was achieved by chromatographic and spectral analyses, as well as comparison with the authentic samples prepared by the known methods.

The scope of reactions was investigated by applying several RNA and DNA bases, with phosphorylribosyl bromide and phosphorylglucosyl bromide. The results of such investigations are shown in Table I.

TABLE I. Physical Properties and Yields of the Synthetic Nucleotides and their Intermediate Compounds

	m.p. ^{a)} (°C)	$[\alpha]_D$	Yield ^{b)} (%)
1-(5-diphenylphosphoryl-2,3-di-O-benzoyl- D-ribofuranosyl)thymine	144	-51.3	48.1
Barium 1-β-D-ribofuranosylthymine 5'-phosphate* ²	—	-12.25	33.5
1-(5-Diphenylphosphoryl-2,3-di-O-benzoyl-D-ribofuranosyl) uracil	amorph.	-51.0	10.0
Barium 1-β-D-ribofuranosyluracil 5'-phosphate	—	-15	50
1-(5-Diphenylphosphoryl-2,3-di-O-benzoyl- D-ribofuranosyl)-4-ethoxy-2(1H)-pyrimidinone ^{c)}	147~148	-83.8	35.0
6-Benzamido-9-(5-diphenylphosphoryl-2,3-di- O-benzoyl-D-ribofuranosyl)purine	amorph.	—	37.6
Barium 9-β-D-ribofuranosyladenine 5'-phosphate	188	-45.5	47.3
9-(5-Diphenylphosphoryl-2,3-di-O-benzoyl- D-ribofuranosyl)hypoxanthine	amorph.	-65.7	59.2
Barium 9-β-D-ribofuranosylhypoxanthine 5'-phosphate	—	-18.5	36.0
7-(5-Diphenylphosphoryl-2,3-di-O-benzoyl- D-ribofuranosyl)theophylline	154~156	-30.2	73.3
Barium 7-β-D-ribofuranosyltheophylline 5'-phosphate	—	+20.0	34.2
1-[6-Bis(p-nitrophenyl)phosphoryl-2,3,4-tri- O-acetylglucopyranosyl]uracil	amorph.	—	18.5
Barium 1-β-D-glucopyranosyluracil 6'-phosphate	—	-2.5	27.0

a) Melting points are uncorrected.

b) Yields of the intermediates based on the reacted silyl compounds.

c) UMP was produced as a minor component in 2.7% yield.

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