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PREPARATION OF NUCLEOSIDE 3',5'-CYCLIC PHOSPHATES VIA 8-QUINOLYL NUCLEOSIDE 5'-PHOSPHATES AS A USEFUL INTERMEDIATE

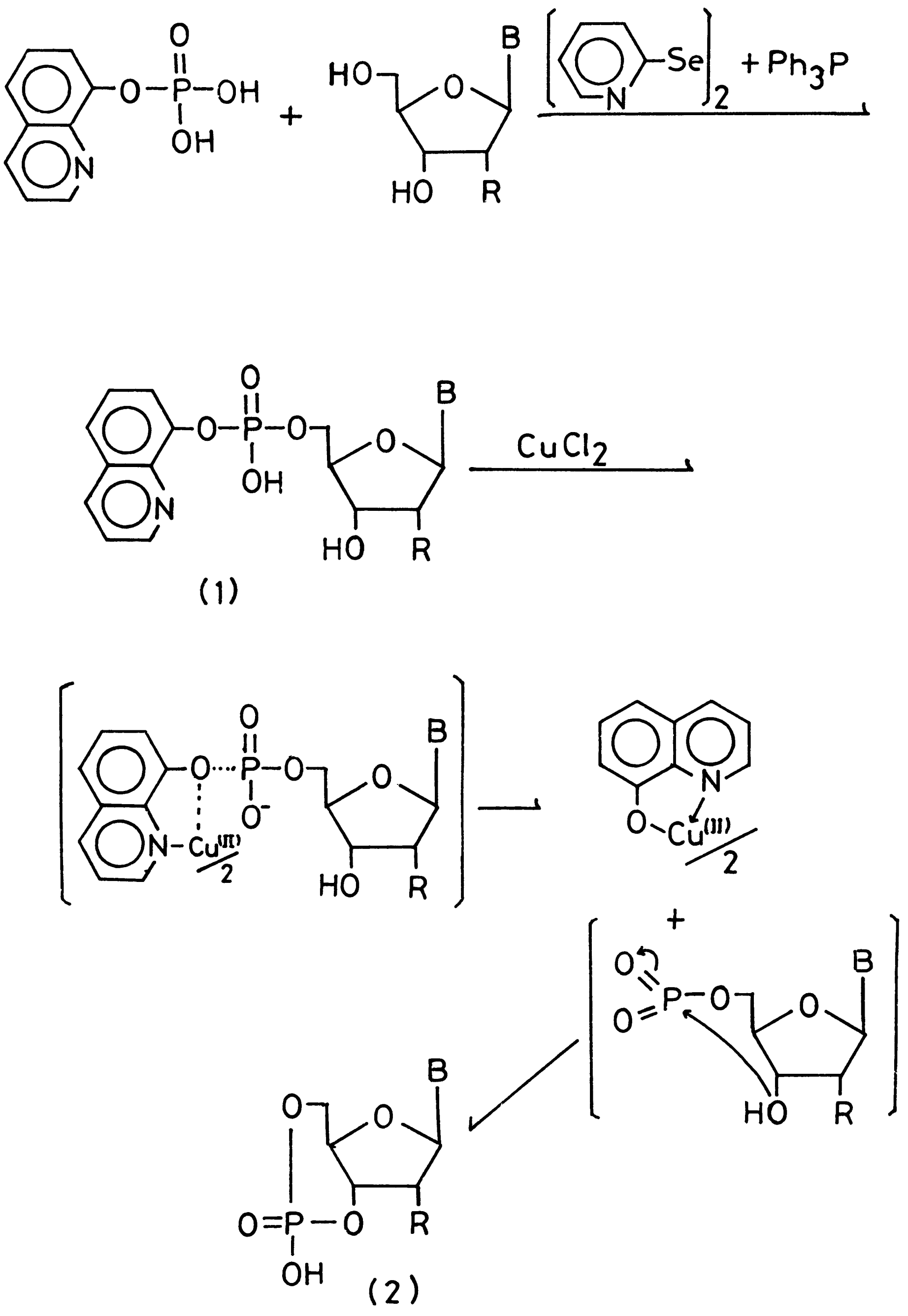
Hiroshi TAKAKU*, Masaathu KATO*, and Tsujiaki HATA**
*Laboratory of Organic Chemistry, Chiba Institute of Technology
Narashino-shi, Chiba 275, and **Department of Life Chemistry,
Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152

The intramolecular cyclization of 8-quinolyl nucleoside 5'-phosphates (1) with cupric chloride in pyridine led to the synthesis of nucleoside 3',5'-phosphates (2) in good yields by fission of the P-O bond of 8-quinolyl esters of nucleoside 5'-phosphate.

It was demonstrated in our recent study[1,2] that 8-quinolyl group is a useful reagent for the protecting group of phosphate moiety and the nucleoside polyphosphate synthesis. In order to test the utility of 8-quinolyl group, we examined the synthesis of 3',5'-cyclic phosphate derivatives by the intramolecular cyclization of 8-quinolyl nucleoside 5'-phosphates (1). Concerning the synthesis of nucleoside 3',5'-cyclic phosphate, most of literature methods involve the reaction of nucleoside 5'-phosphate with coupling reagents[3], and the reaction of an active ester of nucleoside 5'-phosphate with potassium t-butoxide[4].

In this communication, we wish to report the synthesis of nucleoside 3',5'-cyclic phosphates (2) by the reaction of 8-quinolyl nucleoside 5'-phosphates (1) with cupric chloride as an activating reagent of 8-quinolyl group.

The starting material, 8-quinolyl nucleoside 5'-phosphates (1) were prepared in good yields by the condensation of unprotected nucleosides with 8-quinolyl phosphate, using triphenylphosphine[Ph_3P] and 2,2'-dipyridyl



R= OH; B= uracil, cytosine, adenine, guanine

R= H; B= thymine

diselenide [$(PySe)_2$].[2,5]

In the present experiment, the intramolecular cyclization reaction is presumed to be caused by nucleophilic attack of the 3'-hydroxyl group of the intermediate, nucleoside 5'-metaphosphate, which was generated by cleavage of the P-O bond of 8-quinolyl esters of nucleoside 5'-phosphate by cupric chloride.

The usefulness of this approach to the preparation of nucleoside 3',5'-cyclic phosphate (2) was demonstrated by the synthesis of the biologically-important adenosine 3',5'-cyclic phosphate (2a). The triethylammonium salt of 8-quinolyl adenosine 5'-phosphate (1a) (0.2 mmol) was dissolved in dry pyridine.[6] To the solution cupric chloride (0.3 mmol) was added at once. After the mixture was stirred at 100°C for 3 hr, the solvent was concentrated to dryness. The oily residue was further treated with water and insoluble material (8-hydroxyquinoline-copper complex) was precipitated. After removal of the precipitate, the filtrate was concentrated to a small volume. The solution was applied to a column of activated charcoal. The column was washed with water (100 ml) and eluted with 50% ethanol containg 2% conc.ammonia (200 ml). The eluate was evaporated to dryness in vacuo. The residue was dissolved in water and applied to a column of DEAE cellulose (1.5 x 20 cm, HCO_3^-), which was eluted with a linear gradient of triethylammonium bicarbonate (TEAB) solution [water (2 l) + 0.1 M TEAB (2 l)]. Adenosine 3',5'-cyclic phosphate (2a) was eluted and obtained in 77% yield based on 8-quinolyl adenosine 5'-phosphate. It was homogeneous on paper chromatography.

Similarly, several nucleoside 3',5'-cyclic phosphates (2) were obtained as shown in Table 1.

The structures of the nucleoside 3',5'-cyclic phosphates (2) were characterized by Rf values on paper chromatography, mobility on paper electrophoresis, and uv spectra.

It is noteworthy that the 8-quinolyl phosphate method is successfully utilized in the preparation of nucleoside 3',5'-cyclic phosphate starting from unprotected nucleoside in two steps.

Table 1. Synthesis of Nucleoside 3',5'-Cyclic Phosphates*

Nucleoside	Yield** (%)	Rf value***	P.E.****	Spectral Data (at pH 7) $\lambda_{max}^{H_2O}$ ($\varepsilon \times 10^{-3}$)	$\lambda_{min}^{H_2O}$ (nm)
adenosine	77	0.35	0.56	258(14.65)	228
uridine	74	0.35	0.58	261 (9.94)	229
cytidine	65	0.38	0.60	272 (9.34)	249
guanosine	71	0.25	0.50	254(12.95)	223
thymidine	81	0.43	0.61	268 (9.60)	236

*These compounds were isolated as a triethylammonium salt. **Yields are based on 8-quinolyl nucleoside 5'-phosphates. ***Solvent system used was: isopropyl alcohol-concentrated ammonia-water(7:1:2 v/v). ****P.E.=Electrophoretic mobility relative to thymidine 5'-phosphate. The buffer solution used was phosphate (0.2M, pH 8.0).

References and Notes

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6) When the cyclization reaction was carried out in dimethyl sulfoxide(DMSO), nucleoside 5'-phosphate was obtained in almost quantitative yield.

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