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8-HYDROXYQUINOLINE AS A REAGENT FOR PROTECTION OF PHOSPHATES IN OLIGONUCLEOTIDE SYNTHESIS

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8-Hydroxyquinolyl group was used as a new protecting group on phosphates in the synthesis of oligonucleotides. This group was easily removed by treatment with cupric chloride in a mixture of dimethyl sulfoxide and water.

In the synthesis of oligonucleotides, several methods for protection of terminal phosphate group have been offered and examined.[1)]

We now wish to report a useful protecting group on phosphate in the synthesis of deoxyribooligonucleotides.

8-Hydroxyquinolyl group (Q)[2)] was chosen as the protecting group which is stable to acid and alkali, removal being achieved specifically by treatment with cupric chloride in a mixture of dimethyl sulfoxide and water (5:1 v/v).

When the reaction of 8-hydroxyquinoline (10 mmol) with 3'-O-acetylthymidine 5'-phosphate (d-pTOAc) (1 mmol) was carried out in the presence of triphenylphosphine (Ph_3P) (5 mmol) and 2,2'-dipyridyl disulfide [$(PyS)_2$] (5 mmol)[3)] in dry pyridine at room temperature for 6 hr, 8-hydroxyquinolyl thymidine 5'-phosphate (d-QpT) was obtained in 90% yield after removal of 3'-O-acetyl group by treatment with 0.1 N sodium hydroxide.

In a similar manner, 8-quinolyl esters of N^6-benzoyldeoxyadenosine 5'-phosphate (d-QpA^{Bz}), N^2-isobutyryldeoxyguanosine 5'-phosphate (d-QpG^{iBu}), and N^4-anisoyldeoxycytidine 5'-phosphate (d-QpC^{An}) were obtained in 85%, 93%, and 92% yields, respectively.

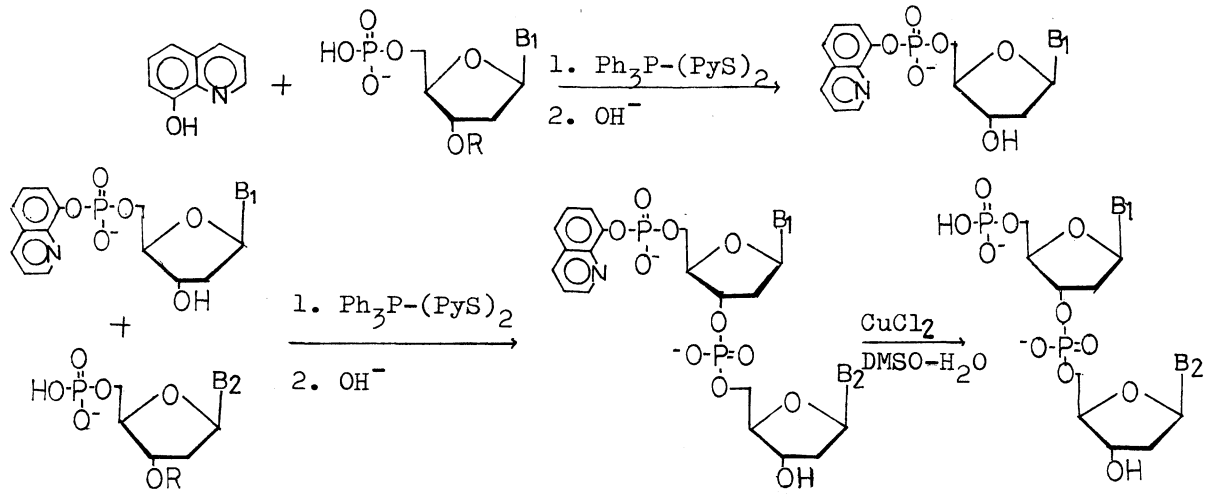
When d-QpT (0.2 mmol) prepared in the above experiment was treated with d-pTOAc (0.4 mmol) in the presence of Ph_3P (1.0 mmol) and $(PyS)_2$ (1.0 mmol) in dry pyridine (1 ml) at room temperature for 2 days, the dinucleotide, d-QpTpT was obtained in 74% yield after removal of acetyl group by treatment with 0.1 N sodium hydroxide.

Similarly, dinucleotide derivatives, such as d-QpTpA^{Bz}, d-QpTpC^{An}, d-QpTpG^{iBu},

and d-QpA^{Bz}pA^{Bz} were obtained in 59%, 58%, 55%, and 61% yields, respectively, by the reactions of d-QpT or d-QpA^{Bz} (0.2 mmol) with the corresponding 3'-O-acetylnucleoside 5'-phosphate (0.4 mmol) as described in the above experiment.

8-Hydroxyquinolyl group was easily removed from the dinucleotide derivatives by using cupric chloride in a mixture of dimethyl sulfoxide and water (5:1 v/v) at 40-45°C for 5 hr. For example, d-QpTpG^{iBu} (0.02 mmol) was treated with cupric chloride (0.02 mmol) in a mixture of dimethyl sulfoxide and water (5:1 v/v) (5 ml) at 40-45°C for 5 hr. The mixture was concentrated to dryness and it was further treated with methanolic ammonia for removal of isobutyryl group. The desired dinucleotide, d-pTpG, was obtained in 96% yield. The yield was estimated by spectrophotometrically after elution of the spot on paper chromatogram.

In a similar manner, d-pTpT, d-pTpC, and d-pApA were obtained in 95%, 98%, and 95% yields, respectively, based on the corresponding protected dinucleotides.



B_1,B_2= thymine, N^6-benzoyladenosine, N^4-anisoylcytosine, or N^2-isobutyrylguanine.
R = acetyl or isobutyryl

In conclusion, it is noted that 8-hydroxyquinolyl group can be used as a protecting group on terminal phosphate in oligonucleotide synthesis. This group was selectively and smoothly removed by treatment with cupric chloride in a mixture of dimethyl sulfoxide and water (5:1 v/v).

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