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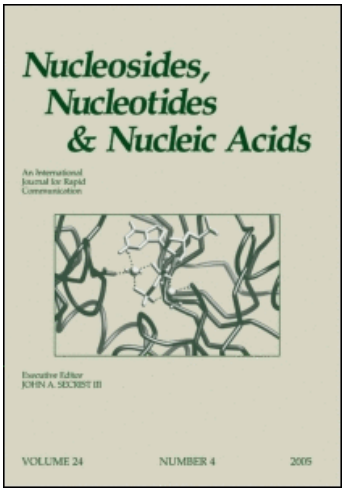

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SOME CHEMICAL AND STEREOCHEMICAL ASPECTS OF RIBONUCLEOSIDE H-PHOSPHONATE AND H-PHOSPHONOTHIOATE DIESTER SYNTHESIS

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ABSTRACT: *Some chemical and stereochemical aspects of condensation of ribonucleoside 3′-H-phosphonates, 3′-H-phosphonomonothioates and 3′-H-phosphonodithioates into the corresponding diesters **4** and **5** together with oxidation and sulfurization of the latter ones, are discussed.*

INTRODUCTION

Oligonucleotide analogues bearing chiral internucleotidic linkages are of potential significance for many enzymological and therapeutical uses.[1] Since these type of analogues are easily accessible *via* nucleoside H-phosphonate and H-phosphonothioate intermediates, we decided to check some chemical and stereochemical aspects of the following reactions: (i) condensation of a nucleoside with ribonucleoside 3′-H-phosphonates, (ii) condensation with ribonucleoside 3′-H-phosphono*mono*thioates, (iii) condensation with ribonucleoside 3′-H-phosphono*di*thioates, (iv) sulfurization of ribonucleoside H-phosphonate diesters, and (v) oxidation of ribonucleoside H-phosphonothioates.

As model compounds for these studies 5′-O-monomethoxytrityl-2′-O-t-butyldimethylsilyluridine 3′-H-phosphonate (**1**), 3′-H-phosphono*mono*-thioate (**2**) and 3′-H-phosphono*di*thioate (**3**) have been chosen. These compounds were condensed with 2′.3′-dibenzoyluridine [$U(OBz)_2$] and the obtained H-phosphonate diester **4** and H-phosphonothioate diester **5** have been oxidized or sulfurized (Scheme 1).

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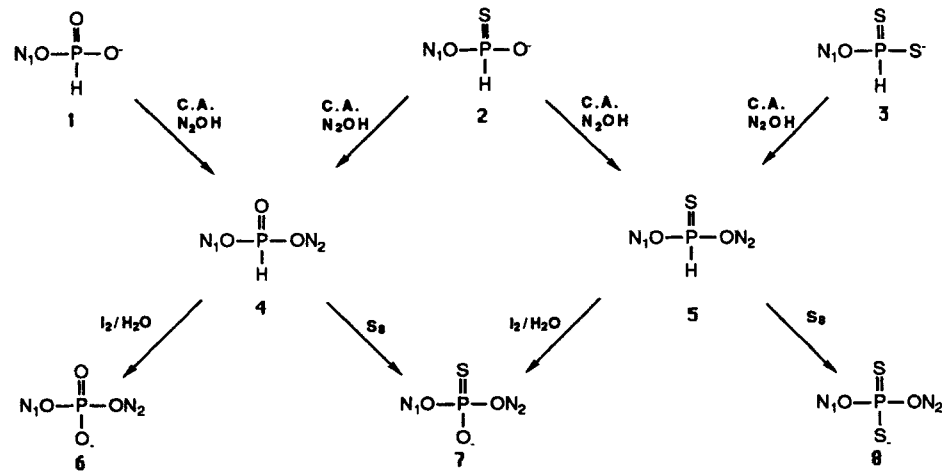

N_1=5′-O-monomethoxytrityl-2′-O-t-butyldimethylsilyluridin-3′-yl
N_2=2′,3′-dibenzoyluridine
C.A.=coupling agent: [pivaloyl chloride (PV-Cl), adamantanecarbonyl chloride (Ad-Cl), diphenylphosphorochloridate (DPCP), 5,5-dimethyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinane (NPCP), diisopropylcarbodiimide (DICl)]

Scheme 1

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RESULTS AND DISCUSSION

Synthesis of ribonucleoside H-phosphonate diester 4

Since the phosphorus centre in nucleoside H-phosphonate monoesters is prochiral two diastereoisomers are formed upon their conversion into diesters. In the deoxy series both stereoisomers are formed in practically equal amounts (ratio ~1.1 : 1)[2], however, in the ribo series (dimer **4**) we have found that one diastereoisomer (resonating at lower field in ^{31}P NMR), is formed in excess (ratio ~6:1, δ=9.64 and 8.67 ppm). This ratio has been independent of the nature of the coupling agent (PV-Cl, Ad-Cl, DPCP, NPCP) used for the condensation, as well as of the solvent composition (neat pyridine or its mixture with acetonitrile).

Synthesis of ribonucleoside H-phosphonothioate diester 5

Condensation of H-phosphono*mono*thioate **2** with $U(OBz)_2$ has been investigated using various condensing agents (Scheme 1). As is the case with H-phosphonate diester **4**, one diastereoisomer (that absorbing at lower field in ^{31}P NMR) was formed in excess (ratio ~6:1, δ=74.40 and 73.11 ppm). The reaction seems to be stereoselective since the same ratio of diastereoisomers was observed when pure diastereoisomers of **2** were

used as substrates. The condensation of the *mono*thio compound **2** with a nucleoside produced exclusively the desired diester **5** when NPCP or DPCP was used as a coupling agent. Pivaloyl chloride, as it was reported for the deoxy analogue of **2**[5], affords substantial amounts of side products, in contradistinction to another acyl chloride, Ad-Cl, which brought about much cleaner condensation to **5**. Formation of H-phosphonate **4** could not be detected by ^{31}P NMR analysis during the condensations. However, compound **4** was formed as the predominant species (~95%) when DICI was used for activation of **2**.

For the *dithio* H-phosphonate **3**[6], it was rather difficult to carry out a clean condensation to the diester **5**. The ratio of the diastereoisomers formed was the same as during conversion of **2** into the diester **5**, however, the condensation (PV-Cl) was slower and it was accompanied by formation of a substantial amount of side products. Replacement of PV-Cl by Ad-Cl did not offer any improvement. Another type of reagent, carbodiimides, should in principle be good coupling agents for the conversion of H-phosphono*di*thioate **3** to the diester **5**. However, probably due to the unavoidable presence of traces of moisture, the reaction with DICI afforded a mixture of **5** and **4** in a ratio of ca 1:1. Chlorophosphates (NPCP and DPCP), as expected, proved to be unreactive towards **3** and thus could not be used as condensing agents in this reaction.

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Synthesis of nucleoside phospho*rmono*thioate diester **7**

Since compound **7** can be produced from the H-phosphonate diester **4** *via* sulfurization or from the H-phosphonothioate **5** *via* its oxidation, we decided to check the stereochemical outcome of both reactions.

To this end the two diastereoisomers of **4** and a predominant isomer of compound **5**, have been isolated,[7] and subjected to sulfurization with elemental sulfur in pyridine, and to oxidation with iodine in aq. pyridine, respectively. It was found that sulfurization of **4** with elemental sulfur is stereospecific (apparently retention of configuration) and affords the same products as the reaction with 3*H*-1,2-benzodithiol-3-one 1,1-dioxide[8] (see also the other paper in this volume).

Oxidation of **5,** [containing one diastereoisomer (δ=74.40 ppm) in excess] with iodine in aq. pyridine produced **7**, with the diastereoisomer resonating at lower field in ^{31}P NMR being the major product. However, since the ratio of two diastereoisomers in the product **7** was slightly different from that of the starting material **5** used for the reaction,

apparently partial epimerization at the phosphorus centre occurred during the oxidation. The diastereoisomer produced in excess in this reaction was the same as the one obtained during sulfurization of the predominant diastereoisomer of **4**.

EXPERIMENTAL PART

Reactions were carried out in 10-mm n.m.r. tubes and spectra were recorded on a Jeol GSX-270 FT spectrometer. For ^{31}P n.m.r. experiments 2% H_3PO_4 in D_2O was used as external standard (coaxial inner tube). The values of the chemical shifts for the intermediates produced *in situ*, in some experiments varied (±1 ppm) depending on the reaction conditions.

General procedure for preparation of dimers 4 and 5

Mixtures of **1**,[2] **2**[3], or **3**[4] (0.5 mmol.) with dibenzoyluridine (1.1 equiv.) were made anhydrous by evaporation of added pyridine, dissolved in pyridine (2 ml) and a condensing agent (2 equiv.) (as indicated in the text) was added. After standard work-up and purification on silica gel, compounds **4** and **5** have been used for further reactions.

Oxidation and sulfurization

These reactions have been carried out on compounds **4** and **5** under standard conditions (2 equiv. of iodine in aq. pyridine or 2 equiv. of sulfur in pyridine or in acetonitrile in the presence of 2 equiv. of triethylamine) or as indicated in the text.

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