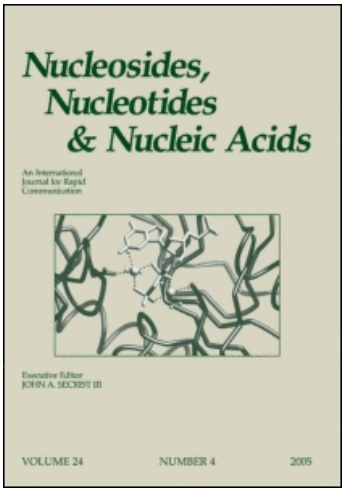

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Synthesis of 1-(2-Deoxy-β-D-ribofuranosyl)benzimidazole via Cyclonucleosides

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ABSTRACT

Starting from 2-chlorobenzimidazole and 1-O-acetyl-2,3,5-tri-O-benzoylribofuranose a β-D-ribonucleoside of 2-chlorobenzimidazole was obtained using Vorbrüggen's procedure. This compound was derivatized to a 2,2'-S-cyclonucleoside via 2'-O-tosylation and thiourea treatment. The cyclonucleoside was converted to 1-(2-deoxy-β-D-ribofuranosyl)benzimidazole by Raney nickel desulfurization.

INTRODUCTION

During the course of synthesizing oligodeoxynucleotides of defined sequence for probes of gene sequencing, we found a new method consisting of incorporation of a 2'-deoxyinosine residue at the wobble position of amino acid codons.[1] Instead of an inosine residue we wanted to incorporate a benzimidazole nucleoside, because this base has no hydrogen-bonding functions and has a strong stacking tendency. For that purpose a 2'-deoxyribofuranoside of benzimidazole should be synthesized as the starting material for the oligonucleotides.

We previously reported a method for converting ribo- to deoxyribonucleoside in good yield and in quantity via cyclonucleoside having an S-anhydro linkage between the 8- and 2'-positions.[2]

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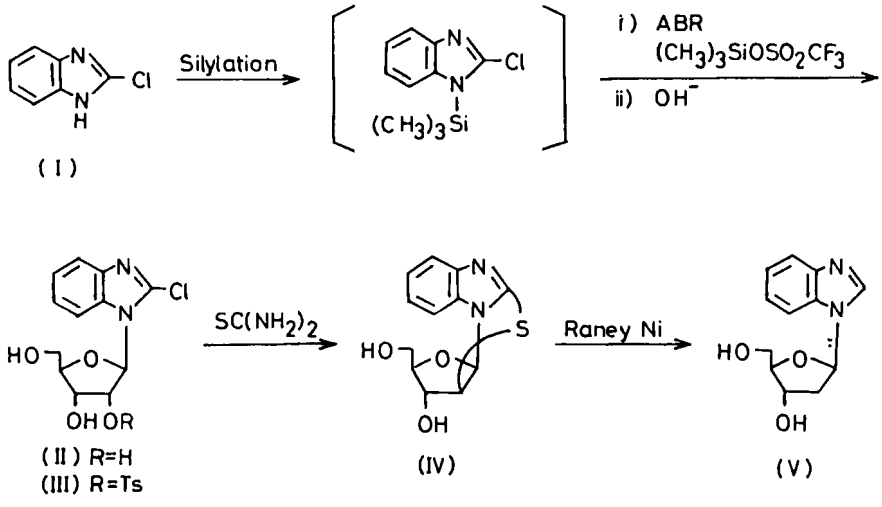
Condensation of 2-chlorobenzimidazole (I) with ribose was performed after conversion of the compound (I) to a trimethylsilyl derivative by heating with hexamethyldisilazane and trimethylchlorosilane as reported previously by Vorbrüggen et al.[3] 1-Trimethylsilyl-2-chlorobenzimidazole was obtained as a syrup, which was used for further steps without purification. The compound was then refluxed in ethylene dichloride with 1-O-acetyl-2,3,5-tri-O-benzoyl-ribofuranose (ABR) in the presence of trimethylsilyl triflate for 1 hr under a nitrogen atmosphere. After checking for the completion of the reaction by TLC, the solvent was removed by evaporation in vacuo. The residual oil was treated with 1N sodium hydroxide to remove all of the protecting groups. Crystalline 1-β-D-ribofuranosyl-benzimidazole (II) was obtained in a yield of 80.7 %. Compound II was determined to have the correct structure by UV absorption, ^{1}H NMR and elemental analysis. Comparison with reported data also supported the correct structure.[4]

In order to synthesize a cyclonucleoside, we treated compound II with tosyl chloride after conversion of II to a dibutyltin compound by Moffatt's procedure.[5] As previously experienced in the case of 8-bromoadenosine[6], incorporation of a tosyl group only at 2'-hydroxyl was confirmed by ^{1}H NMR showing a low field shift of the 2'-H signal from 4.54 to 5.07 ppm. Other structural confirmation was achieved by elemental analysis, UV spectroscopy, and migration in TLC. 2'-O-Tosyl derivative III, thus obtained, was then refluxed in n-butanol with thiourea. A cyclonucleoside, 2,2'-anhydro-1-(β-D-arabinofuranosyl)-2-mercaptobenzimidazole (IV) was obtained in a yield of 83%. Elemental analysis data and UV absorption properties, which resembled those of 2-mercaptobenzimidazole, confirmed the structure of IV. A coupling constant of 6 Hz for $J_{1'-2'}$ in ^{1}H NMR also supported the correct structure[8]. This is the first example of 2,2'-cyclobond formation on a benzimidazole nucleoside.

We next desulfurized compound IV by treatment with Raney nickel. When compound IV was refluxed in dioxane

with excess Raney nickel for 20 min, the UV absorption maximum around 281 nm changed to 273 nm, which showed that the reaction proceeded with the formation of the 2'-deoxyriboside. The structure of 1-(2-deoxy-β-D-ribofuranosyl)-benzimidazole (V) was further confirmed by elemental analysis, UV absorption spectra and ^{1}H NMR spectra.



(I)

(II) R=H
(III) R=Ts

(IV)

(V)

Comparison with reported data also supported the correct structure.[9]

The synthesis of various oligodeoxynucleotides containing benzimidazole deoxyriboside will be reported elesewhere.

EXPERIMENTAL

General Procedure

UV absorption spectra were recorded on a Hitachi 200-10 spectrophotometer. ^{1}H NMR (90 MHz) spectra were recorded with a Hitachi R-900 spectrometer operated in the FT mode. ^{1}H chemical shifts were measured downfield from DSS in DMSO-d_6.

2-Chloro-1-(β-D-ribofuranosyl)benzimidazole (II)

2-Chlorobenzimidazole (16.8 g, 110 mmole) was suspended in hexamethyldisilazane (250 ml) and trimethylchlorosilane

(7 ml) was added. The mixture was refluxed for 7 hrs under an atmosphere of N_2 gas. After cooling the solution was evaporated in vacuo to give a reddish syrup. The syrupy residue was dissolved in ethylene chloride (250 ml) and trimethylsilyl triflate (24.5 g, 110 mmole) and 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranos (45.4 g, 90 mmole) were added. The solution was refluxed under an atmosphere of N_2 gas. The reaction progress was checked by TLC ($CHCl_3$-MeOH, 10:1) showing that all starting material was ribosylated after 1 h. The reaction was diluted with ethylene chloride (200 ml) and the solution was washed with saturated $NaHCO_3$ solution. The organic layer was evaporated to remove ethylene chloride and the residue was taken up in a pyridine (270 ml)-tetrahydrofuran (180 ml) mixture. The solution was ice-cooled and 2N NaOH (360 ml) and EtOH (360 ml) were added. The two layered solution was homogenized by addition of water (ca, 200 ml) and kept at 0° for 10 min. After checking the reaction progress by TLC, the solution was poured onto Dowex 50 (pyridinium form) resin (720 ml) with cooling in an ice bath. After stirring the mixture for a while, the whole was packed in a column, which was eluted with 20% aqueous pyridine. The eluants were evaporated in vacuo to ca. 200 ml and ether was added and shaken. The resulting white precipitates were collected after keeping the mixture in a refrigerator overnight, to yield 20.7 g, 72.7 mmole (80.7 %), m.p. 163-165°. Anal. Calcd. for $C_{12}H_{13}N_2O_4Cl$: C, 50.63; H, 4.60; N, 9.84; Cl, 12.45. Found : C, 50.70; H, 4.60; N, 9.75; Cl, 12.21. UV (λmax in MeOH) 281 nm (ε 5120), 274 (5250, 266 (4210), 245 (8150). ^1H NMR (δ ppm, DMSO-d_6) 8.1-7.2 (m, 4H, H-arom), 5.90(d, 1H, H-1', $J_{1'-2'}$=7Hz), 4.54 (q, 1H, H-2', $J_{1'-2'}$=7 Hz, $J_{2'-3'}$=6 Hz), 4.18 (q, 1H, H-3', $J_{2'-3'}$=6Hz, $J_{3'-4'}$=3Hz), 4.1-3.9 (m, 1H, H-4'), 3.72 (d, 2H, H-5', 5", J=3 Hz).

2-Chloro-1-(2-O-p-toluenesulfonyl-β-D-ribofuranosyl)benzimidazole (III)

2-Chloro-1-(β-D-ribofuranosyl)benzimidazole (9.96 g, 35 mmole) and dibutyltin oxide (8.71 g, 35 mmole) were

refluxed in MeOH (525 ml) with stirring. After 50 min stirring the solution became transparent. After cooling, p-toluenesulfonyl chloride (53.4 g, 280 mmole) was added, then triethylamine (28.3 g, 280 mmole) was added dropwise at 0° under stirring. The reaction progress was checked by TLC($CHCl_3$-MeOH, 5:1) and MeOH was evaporated in vacuo after 1 h. To a syrupy residue water and ether were added and the product crystallized with trituration. Crystals were collected by filtration and washings with cold water and ether were separated. Evaporation of ether gave a residue, which was crystallized by trituration with ether as the second crop, 12.5 g, 28.5 mmole (83.9 %), m.p. 176-180°. Anal. Calcd. for $C_{19}H_{19}N_2O_6ClS$: C, 52.00; H, 4.36; N, 6.38. Found: C, 51.89; H, 4.28; N, 6.23. UV (λmax in MeOH) : 282 nm (ε 4040), 274 (4430); 267 (7770), 220 (14140). ^1H NMR (δ ppm, DMSO-d_6) : 7.8-6.8 (m, 8H, H-arom), 6.04 (d, 1H, H-1', $J_{1'-2'}$=8Hz), 5.07 (q, 1H, H-2', $J_{1'-2'}$=8 Hz, $J_{2'-3'}$=5 Hz), 4.36 (q, 1H, H-3', $J_{2'-3'}$=5 Hz, $J_{3'-4'}$=2 Hz), 4.2-4.0 (m, 1H, H-4'), 3.68 (d, 2H, H-5', 5", J=2 Hz), 2.16 (s, 3H, CH_3).

2,2'- Anhydro-2-mercapto-1-(2-deoxy-β-D-arabinofuranosyl)-benzi-midazole (IV)

2-Chloro-1-(2-O-p-toluenesulfonyl-β-D-ribofuranosyl)benzimida-zole (12.3 g, 28 mmole) and thiourea (2.34 g, 30.8 mmole) were suspended in N-BuOH (420 ml) and refluxed with stirring. The mixture became clear after several minutes reflux. The reaction progress was checked by TLC ($CHCl_3$-MeOH, 5:1) and the reaction was stopped after 30 min. The solvent was evaporated in vacuo and the residue was triturated with pyridine and water. Crystals were collected by filtration and washed with water, to yield 6.1 g, 23.2 mmole (83.0 %), m.p. 225-228°. Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.53: H, 4.58: N, 10.60; S, 12.13. Found: C, 54.49; H, 4.52; N, 10.59; S, 11.92. UV (λmax in MeOH) : 288 nm (10810), 281 (9980), 247 (9980). ^1H NMR (δ ppm, DMSO-d_6) : 7.5-7.0 (m, 4H, H-arom), 6.54 (d, 1H, H-1',

$J_{1'-2'}$=6 Hz), 5.81 (d, 1H, OH-3', J=4Hz), 4.9-4.7 (m, 2H, H-2' and OH-5'), 4.5-4.3 (m, 1H, H-3'), 4.1-3.9 (m, 1H, H-4'), 3.9-3.2 (m, 2H, H-5', 5").

1-(2-Deoxy-β-D-ribofuranosyl)benzimidazole (V)

2,2'-Anhydro-2-mercapto-1-(2-deoxy-β-D-arabinofuranosyl)benzimidazole (5.29 g, 20 mmole) was dissolved in water-dioxane (100 ml + 100 ml) mixture. Raney nickel (25 ml) was added and the whole was refluxed with stirring for 20 min. After confirmation of reaction extent by TLC ($CHCl_3$-MeOH 5:1), Raney nickel was filtered off. Washings and filtrate were combined and evaporated *in vacuo*. The crystalline residue was recrystallized from water to give colorless needles, 2.67 g, 11.4 mmole (57.0 %). Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found : C, 61.23; H, 6.05; N, 11.98. UV (λmax in MeOH) : 281 nm (ε 3810), 273 (4060), 265 (3480), 246 (7120). ^{1}H NMR (δ ppm, DMSO-d_6) : 8.40 (s, 1H, H-2), 7.7-7.1 (m, 4H, H-arom), 6.33 (t, 1H, H-1'. $J_{1'-2'}$=6 Hz), 5.30 (d, 1H, OH-3', J=4Hz), 4.92 (t, 1H, OH-5', J=5 Hz), 4.5-4.3 (m, 1H, H-3'), 4.0-3.8 (m, 1H, H-4'), 3.7-3.5 (m, 2H, H-5',5"), 2.6-2.4 (m, H-2', 2", overlapped with peak of DMSO).

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