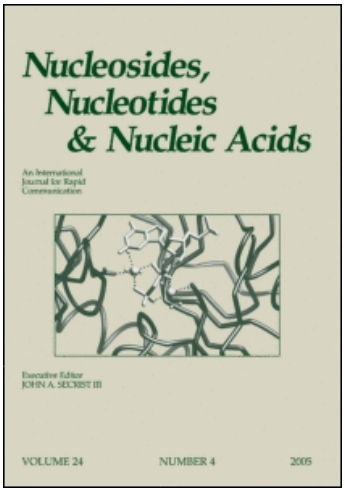

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Antiviral Evaluation of 2-Mercapto-5,6-dichlorobenzimidazole-β-D-ribofuranonucleoside Derivatives

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To cite this Article Mathé, C. , Périgaud, C. , Gosselin, G. and Imbach, J. -L.(1994) 'Synthesis and Antiviral Evaluation of 2-Mercapto-5,6-dichlorobenzimidazole-β-D-ribofuranonucleoside Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 13: 1, 437 — 446
To link to this Article: DOI: 10.1080/15257779408013253
URL: http://dx.doi.org/10.1080/15257779408013253

NUCLEOSIDES & NUCLEOTIDES, 13(1-3), 437-446 (1994)

SYNTHESIS AND ANTIVIRAL EVALUATION OF 2-MERCAPTO-5,6-DICHLOROBENZIMIDAZOLE-ß-D-RIBOFURANONUCLEOSIDE DERIVATIVES

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- Dedicated to the memory of Professor Roland K. Robins -

Abstract. 2-Mercapto-5,6-dichlorobenzimidazole ß-D-ribofuranonucleoside derivatives **8** - **10** have been synthesized and their antiviral properties examined. According to the glycosylation procedure used, the ß-D-*N*-1 isomer (and the *N,N*-bis-riboside) or the ß-D-S^2-isomer have been obtained. All the prepared compounds were tested for their activity against a variety of RNA and DNA viruses, but they did not show significant antiviral activity.

INTRODUCTION

Synthetic benzimidazole nucleosides,[1] especially those halogenated on their 5,6-positions,[2] have received much attention as potential chemotherapeutic agents. Among them, 5,6-dichloro-1-(ß-D-ribofuranosyl)benzimidazole (DRB, Figure 1) has been the most extensively studied compound.[3] Chemical modifications on the DRB structure have been made on both the benzene and sugar moieties. Modifications of the benzene moiety did not alter very much the properties of DRB.[3] Modifications on the sugar moiety have led to compounds having some antiviral and/or cytostatic activities.[4] As

* Dedicated to the memory of Dr. Roland K. Robins.

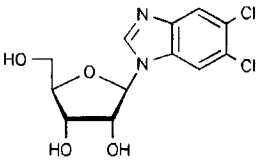


FIGURE 1: DRB

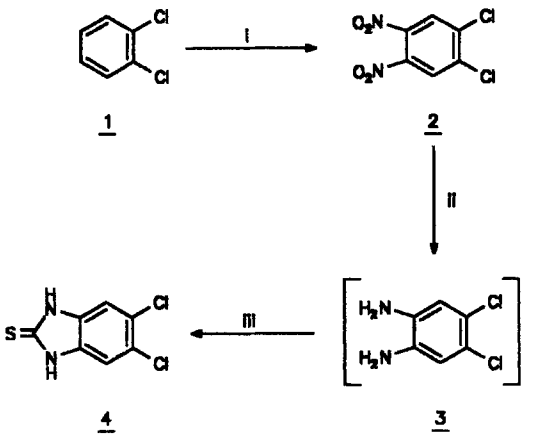
part of our ongoing research in the benzimidazole nucleoside field, we investigated the possibility of altering the biological profile of DRB by introducing chemical modifications at the 2-position of the imidazole ring. A literature survev revealed that little attention has been given to this topic.[1] This has prompted us to unambiguously synthesize the ß-D-ribofuranonucleosides of 2-mercapto-5,6-dichlorobenzimidazole and to evaluate their antiviral activities.[5]

RESULTS AND DISCUSSION

Chemistry

The synthesis of the aglycone 2-mercapto-5,6-dichlorobenzimidazole (**4**) was carried out following a Bückel's modified procedure.[6] Thus (Scheme 1), nitration of *o*-dichlorobenzene (**1**) gave crystalline 1,2-dichloro-4,5-dinitrobenzene (**2**) which was subsequently reduced in the presence of Raney Ni. The corresponding amine **3** was not purified but allowed to react with carbon disulfide in the presence of potassium hydroxide to afford the aglycone **4**

In accord with Baker's rule,[7] condensation of the commercial 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-ß-D-ribofuranose and the aglycone **4** was employed to prepare the protected *trans*-1',2'-ß-D-ribofuranosyl nucleosides **5**, **6** and **7** (Scheme 2). According to the glycosylation procedure used, the ß-D-1-*N* isomer **5** (and the *N,N*-bis-riboside **6**) or the ß-D-*S*[2] isomer **7** can be obtained. Thus, a mixture of the protected nucleosides **5** and **6** was formed when the peracylated sugar was reacted under reflux with silylated 2-mercapto-5,6-dichlorobenzimidazole in acetonitrile in the presence of trimethylsilyl triflate (TMSTf, 1.5 eq). On the other hand, only the *S*-nucleoside **7** was obtained when the sugar was condensed at room temperature with the unsilylated aglycone **4** in dichloroethane in the presence of TMSTf (1.1 eq). All protected ß-D-ribofuranonucleosides **5**-**7** were isolated after purification by silica gel column chromatography, then crystallized.



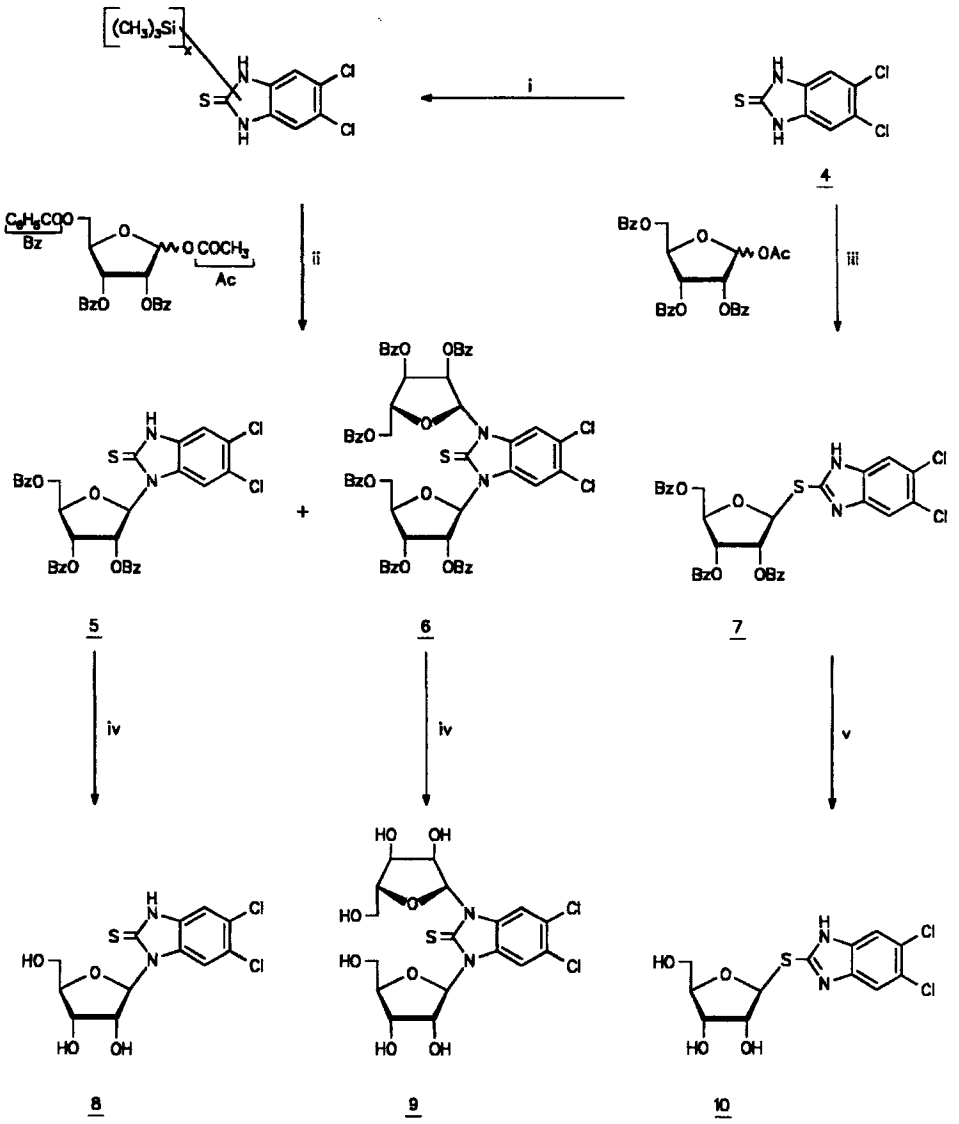
Scheme 1 - *Reagents and conditions*: i, HNO_3, H_2SO_4(30% SO_3); ii, Raney Ni, H_2, EtOH; iii, CS_2, KOH, EtOH-H_2O

Removal of the benzoyl groups with methanolic sodium methoxide or methanolic ammonia afforded the desired 2-mercapto-5,6-dichlorobenzimidazole ß-D-ribofuranonucleosides **8**-**10**.

Structural assignments for the reported compounds are based on elemental analysis and their physical properties. For the previously described compounds **2** and **4** our data were in accord with literature value, unless otherwise noted.

BIOLOGICAL EVALUATION

The prepared compounds **2**, **4**, **5**, **7**, **8**-**10** were tested for their *in vitro* inhibitory effects on the replication of a number of DNA viruses (*i.e.*, human cytomegalovirus, herpes simplex virus type 1 and type 2, vaccinia virus) and RNA viruses (parainfluenza virus type III, respiratory syncytial virus, Sindbis virus, Coxsackie virus B3 and polio virus-1) in three cell systems (MRC-5, Vero and KB cells). None of these compounds showed marked antiviral effects or detectable alteration of host cell morphology at the highest concentration tested (generally 10^{-4} M or 10^{-3} M), except the *S*-nucleoside **10** which had ED_{50} of 10^{-4} M against CMV in MRC-5 cells without toxicity at this concentration. When evaluated in two anti-human immunodeficiency virus (anti-HIV) assays, none of the tested compounds showed marked antiviral effect at a concentration less than 10- fold lower than the minimal concentration causing a detectable alteration of MT-4 and CEM host cell viability (10^{-3} M or 10^{-4} M).



Scheme 2 - *Reagents and conditions*: i, BSA, CH_3CN, reflux; ii, TMSTf, CH_3CN, reflux; iii, TMSTf, $(CH_2Cl)_2$, room temperature; iv, CH_3ONa, CH_3OH; v, NH_3, CH_3OH

CONCLUSION

From the present work, it is obvious that ß-D-ribofuranosyl substituted 2-mercapto-5,6-dichlorobenzimidazole does not induce inhibition of virus multiplication. Several hypotheses can explain this lack of activity, among them being the inability of these nucleoside analogues either to enter cells or to serve as substrates for the intracellular enzymes catalysing 5'-triphosphorylation. It is also possible that their triphosphate forms cannot inhibit viral or cellular polymerases. In this respect, it has been postulated that the phosphorylated forms are not involved in the mode of action of DRB[8] and that the anti-CMV activity of some benzimidazole ribonucleosides could be due to the interferance of assemblage of virus particles.[5] Further research is needed to test these hypotheses and complementary experiments in the 2-mercapto-5,6-dichlorobenzimidazole series are currently in progress in our laboratory.

EXPERIMENTAL SECTION

General Procedures

Evaporations of solvents were carried out with a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes on a Gallenkamp MFB-595-010 M apparatus and are uncorrected. The UV absorption spectra were recorded on an Uvikon 810 (KONTRON) spectrophotometer. ^{1}H-NMR spectra were run at ambient temperature in DMSO-d_6 with a Bruker AC 250 spectrometer. Chemical shifts are given in ppm, DMSO-d_5 being set at 2.49 ppm as reference. Deuterium exchange and decoupling experiments were performed in order to confirm proton assignments. All J-values are in Hz. FAB mass spectra were recorded in the positive- or negative-ion mode on a JEOL DX 300 mass spectometer operating with a JMA-DA 5000 mass data system. Xe atoms were used for the gun at 3 kV with a total discharge current of 20 mA. The matrix was 3-nitrobenzyl alcohol (NBA) or a mixture (50:50, v/v) of glycerol and thioglycerol (G-T). Specific rotations were measured on a Perkin-Elmer Model 241 spectropolarimeter (path length 1 cm), and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). Thin layer chromatography was performed on precoated aluminium sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualization of products being accomplished by UV absorbance followed by charring with 10% ethanolic sulfuric acid and heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385) at atmospheric pressure.

1,2-Dichloro-4,5-dinitrobenzene (2)

To a mixture of fuming nitric acid (d=1.50, 210 ml) and fuming sulfuric acid (30% SO_3, 86.0 ml), cooled in an ice bath, was added dropwise *o*-dichlorobenzene (1)

(31.0 ml, 275.2 mmol). The mixture was then brought to room temperature, left for two hours, and then heated for 2 h at 100°C. After cooling to room temperature, the mixture was poured slowly onto ice (1000 g). The resulting precipitate was collected by filtration, washed with cold water and crystallized from ethanol to provide pure **2** (29.95 g, 46%): mp 102-104°C (lit. mp 104°C,[9] 101-103°C,[10] 110°C,[11] 106°C,[12] 106-107°C [13]); UV (EtOH) λ_{max} 270 nm (ε, 8 100), 224 nm (ε, 18 300); λ_{min} 258 nm (ε, 7 100); ^{1}H-NMR δ 8,71 (2H, s, H-3 and H-6). Elem. anal. ($C_6H_2Cl_2N_2O_4$): calculated C: 30.40, H: 0.85, Cl: 29.92, N: 11.82; found C: 30.68, H: 0.91, Cl: 30.24, N: 11.80.

2-Mercapto-5,6-dichlorobenzimidazole (4)

Raney nickel (1.00 g), previously washed by ethanol, was added to a solution of **2** (1.00 g, 4.22 mmol) in the same solvent (70 ml). The reaction mixture was hydrogenated during 4 h at atmospheric pressure and room temperature. The catalyst was removed by filtration through a Celite pad and the filtrate was evaporated to dryness under reduced pressure to afford crude 1,2-dichloro-4,5-diaminobenzene (**3**). This compound was sufficiently pure (TLC) to be used directly. Thus, it was dissolved in ethanol (9.3 ml) and was added to a mixture of carbon disulfide (0.279 ml, 4.64 mmol) and 1.08 M aqueous potassium hydroxide (4.30 ml). The resulting solution was heated under reflux and the progress of the reaction was monitored by TLC. After 2h30, 1.1 equiv. of carbon disulfide and aqueous potassium hydroxide were added successively. After 5h of reflux, some starting material **3** could be still detected by TLC and 1.1 equiv. of carbon disulfide and aqueous potassium hydroxide were added again. After 21 h of reflux, the reaction mixture was cooled to room temperature and evaporated to dryness. The residue was dissolved in water (50 ml). Addition of acetic acid (2.6 ml) led to the precipitation of **4** (0.73 g, 79%) which was crystallized from acetonitrile : mp 331-333°C (lit. mp 355°C [6]); UV (EtOH) λ_{max} 323 nm (ε, 28 900), 253 nm (ε, 22 300), 228 (ε, 13 800); λ_{min} 278 nm (ε, 2 100), 238 nm (ε, 11 000); ^{1}H-NMR δ 12.78 (2H, s, 2 × NH) 7.30 (2H, s, H-4 and H-7); *m/z* (FAB>0, G-T) 219 $(M+H)^+$; *m/z* (FAB<0, G-T) 217 $(M-H)^-$. Elem. anal. ($C_7H_4Cl_2N_2S$. 1/5 C_2H_3N); calculated C: 39.10, H: 2.04, Cl: 31.19; N: 13.56, S: 14.11; found C: 39.15, H: 1.83, Cl: 31.38, N: 13.14, S: 13.98.

1-(2,3,5-Tri-*O*-benzoyl-ß-D-ribofuranosyl)-2-mercapto-5,6-dichlorobenzimidazole (5) and 1,3-bis(2,3,5-tri-*O*-benzoyl-ß-D-ribofuranosyl)-2-thio-5,6-dichlorobenzimidazole (6)

A suspension of 2-mercapto-5,6-dichlorobenzimidazole (**4**) (100 mg, 0.456 mmol) in anhydrous acetonitrile (2.3 ml) was treated with bis(trimethylsilyl)acetamide

(BSA, 0.33 ml, 1.35 mmol) during 12 h under reflux. To the resulting solution was added 1-*O*-acetyl-1,2,5-tri-*O*-benzoyl-ß-D-ribofuranose (commercial, 216 mg, 0.43 mmol) in acetonitrile (2.3 ml), followed by addition of trimethylsilyl triflate (TMSTf, 0.12 ml, 0.66 mmol). The solution was heated under reflux for 18 h. After cooling to room temperature, the reaction mixture was evaporated to dryness, and to the residue were added $CHCl_3$ (60 ml) and aqueous 2% sodium hydrogen carbonate (30 ml). The organic phase was separated, dried over sodium sulfate and evaporated to dryness under reduced pressure. Column chromatography of the residue on silica gel using as eluent a stepwise gradient of methanol (0-0.4%) in dichloromethane afforded successively **6** (13 mg, 3%, crystallized from ethanol) and **5** (210 mg, 74%, crystallized from acetonitrile).

5: mp 272-274°C; UV (EtOH) λ_{max} 326 nm (ε, 21 200), 313 nm (sh; ε, 14 600), 268 nm (sh; ε, 11 700), 256 nm (sh, ε, 14 300), 231 nm (ε, 41 900); λ_{min} 292 nm (ε, 4 200); ^{1}H-NMR δ 13.3 (1H, br s, NH), 8.1-7.4 (17H, m, 3×C_6H_5, H-4 and H-7), 7.60 (1H, d, $J_{1',2'}$ = 7.1, H-1'), 6.16 (1H, t, H-2'), 6.08 (1H, dd, $J_{2',3'}$ = 6.9 and $J_{3',4'}$ = 4.4, H-3'), 4.88 (1H, m, H-4'), 4.79 (2H, m, H-5' and H-5"); $[\alpha]_D^{20}$ - 181.0 (c 1.0 in DMSO). Elem. anal. ($C_{33}H_{24}Cl_2N_2O_7S$): calculated c: 59.73, H: 3.65, Cl: 10.69, N: 4.22, S: 4.83; found C: 59.57, H: 3.71, Cl: 10.97, N: 4.35, S: 4.55.

6: mp 160-162°C; UV (EtOH) λ_{max} 328 nm (ε, 35 600), 315 nm (sh; ε, 25 900), 284 (sh, ε, 15 200), 269 (sh, ε, 23 600), 230 (ε, 103 900); λ_{min} 291 nm (ε, 11 500); ^{1}H-NMR δ 8.1-7.3 (32H, 6×C_6H_5, H-4 and H-7), 7.08 (2H, d, $J_{1',2'}$ = 6.7, 2×H-1'), 6.10 (4H, m, 2×H-2' and 2×H-3'), 4.89 (2H, m, 2×H-4'), 4.80 (4H, m, 2×H-5' and 2×H-5"); $[\alpha]_D^{20}$ - 109.1 (c 1.0 in DMSO). Elem. anal. ($C_{59}H_{44}Cl_2N_2O_{14}S$): calculated C: 63.98, H: 4.00, Cl: 6.40, N: 2.53, S: 2.89; found C: 63.73, H: 4.08, Cl: 6.46, N: 2.53, S: 2.19.

S^2-(2,3,5-Tri-*O*-benzoyl-ß-D-ribofuranosyl)-2-mercapto-5,6-dichloro-benzimidazole (7)

To a suspension of **4** (1.00 g, 4.56 mmol) in 1,2-dichloroethane (20 ml) was added successively a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-ß-D-ribofuranose (2.42 g, 4.80 mmol) and TMSTf (0.96 mL, 5.29 mmol). The resulting solution was stirred for 12 h at room temperature, and then washed with aqueous 10% sodium hydrogen carbonate. The aqueous phase was extracted with ethyl acetate (3×60 mL), and the combined organic extracts were dried over sodium sulfate, then evaporated. The residue was subjected to silica gel column chromatography, with a stepwise gradient of

methanol (0-3%) in toluene to afford **7** (2.80 g, 92%) which was crystallized from diisopropyl ether: mp 135-137°C; UV (EtOH) λ_{max} 330 nm (sh; ε, 2 700), 307 nm (ε, 17 700), 298 nm (ε, 16 900), 266 (sh; ε, 10 200); 258 nm (sh; ε, 10 500), 223 nm (ε, 63 600); λ_{min} 303 nm (ε, 14 900), 278 nm (ε, 8 800); ^{1}H-NMR δ 13.1 (1H, br s, NH), 8.0-7.4 (17H, m, 3×C_6H_5, H-4 and H-7), 6.38 (1H, d, $J_{1',2'}$ = 4.8, H-1'), 5.99 (1H, t, H-2'), 5.90 (1H, t, H-3'), 4.84 (1H, m, H-4'), 4.57 (2H, m, H-5' and H-5"); *m/z* (FAB>0, G-T) 663 $(M+H)^+$, 445 $(S)^+$; *m/z* (FAB<O, NBA) 661 $(M-H)^-$; $[\alpha]_D^{20}$ - 42.4 (c 1.0 in DMSO). Elem. anal. ($C_{33}H_{24}Cl_2N_2O_7S$): calculated C: 59.73, H: 3.65, Cl: 10.69, N: 4.22, S: 4.83; found C: 59.60, H: 3.55, Cl: 10.29, N: 4.14, S: 4.51.

1-(ß-D-Ribofuranosyl)-2-mercapto-5,6-dichlorobenzimidazole (8)

A solution of **5** (4.00 g, 6.03 mmol) in a freshly prepared solution of 0.3N sodium methoxide (74.0 mL) was stirred during 1 h at room temperature, and neutralized by the addition of Dowex 50W×2 (pyridinium form) ion-exchange resin. The resin was filtered and washed with warm methanol, and the combined filtrates were evaporated to dryness. Column chromatography of the residue on silica gel using as eluent a stepwise gradient of methanol (0-6%) in dichloromethane afforded **8** (2.08 g, 98%) which was crystallized from methanol: mp 202-204°C; UV (EtOH) λ_{max} 324 nm (ε, 30 700), 254 nm (ε, 18 500), 233 nm (ε, 17 300); λ_{min} 282 nm (ε, 1 700), 242 nm (ε, 11 600); ^{1}H-NMR δ 13.1 (1H, br s, NH), 8.32 and 7.36 (2×1H, 2×s, H-4 and H-7), 6.43 (1H, d, $J_{1',2'}$ = 7.8, H-1'), 5.36 (1H, t, J = 4.6, 5'-OH), 5.22 (1H, d, J = 6.4, 2'-OH), 5.17 (1H, d, J = 4.2, 3'-OH), 4.42 (1H, m, H-2'), 4.11 (1H, m, H-3'), 3.92 (1H, d, H-4'), 3.66 (2H, m, H-5' and H-5"); *m/z* (FAB>0, NBA) 351 $(M+H)^+$; *m/z* (FAB<0, NBA) 349 $(M-H)^-$, 219 $(B)^-$; $[\alpha]_D^{20}$ - 22.4 (c 0.9 in DMSO). Elem. anal. ($C_{12}H_{12}Cl_2N_2O_4S$): calculated C: 41.03, H: 3.45, Cl: 20.19, N: 7.98, S: 9.13; found C: 40.73, H: 3.47, Cl: 20.29, N, 7.92, S: 8.99.

1,3-Bis(ß-D-ribofuranosyl)-2-thio-5,6-dichlorobenzimidazole (9)

The protected nucleoside **6** (606 mg, 0.546 mmol) was dissolved with stirring in a freshly prepared solution of 0.3N sodium methoxide (14.0 mL). After 1 h, the reaction mixture was neutralized by the addition of Dowex 50W×2 (pyridinium form) ion-exchange resin. The resin was filtered and washed with warm methanol, and the combined filtrates were evaporated to dryness. To the residue were added water (150 mL) and diethyl ether (100 mL). Evaporation of the aqueous phase gave pure **9** (240 mg, 90%) which was lyophilized from water: mp 140-145°C; UV (EtOH) λ_{max} 323 nm (ε, 20 500), 256 nm (ε, 12 100), 234 nm (ε, 14 500); λ_{min} 278 nm (ε, 1 600), 245 nm (8 900); ^{1}H-NMR δ 8.42 (2H, s, H-4 and H-7), 6.61 (2H, d, $J_{1',2'}$ = 7.7, 2×H-1'),

5.4-5.2 (6H, 3×br s, 2×2'-OH, 2×3'-OH and 2×5'-OH), 4.43 (2H, m, 2×H-2'), 4.13 (2H, m, 2×H-3'), 3.95 (2H, d, 2×H-4'), 3.68 (4H, m, 2×H-5' and 2×H-5"); *m/z* (FAB>0, G-T) 483 $(M+H)^+$, 219 $(BH_2)^+$, 133 $(S)^+$; $[\alpha]_D^{20}$ - 40.6 (c 1.0 in DMSO).

S^2-(β-D-Ribofuranosyl)-2-mercapto-5,6-dichlorobenzimidazole (10)

A solution of 7 (2.80 g, 4.22 mmol) in methanolic ammonia (previously saturated at -10°C and tightly stoppered; 110 ml) was stirred overnight at room temperature, evaporated under reduced pressure and the residue was co-evaporated under reduced pressure several times with methanol. Column chromatography of the crude product on silica gel using as eluent a stepwise gradient of methanol (0-10%) in dichloromethane afforded 10 (1.25 g, 84%) which was crystallized from ethyl acetate: mp 99-100°C; UV (EtOH) λ_{max} 307 nm (ε, 12 600), 264 nm (sh; ε, 5 600), 258 nm (ε, 5 900); λ_{min} 303 nm (ε, 10 400), 275 nm (ε, 3 200), 246 nm (ε, 4 200); ^{1}H-NMR δ 12.1 (1H, br s, NH), 7.71 (2H, s, H-4 and H-7), 5.83 (1H, d, $J_{1',2'}$ = 4.4, H-1'), 5.11 (1H, d, J = 5.5, 3'-OH), 4.8-4.6 (2×br s, 2H, 2'-OH and 5'-OH), 4.08 (t, 1H, H-2'), 3.99 (1H, q, H-3'), 3.86 (1H, q, H-4'), 3.45 (2H, m, H-5' and H-5", partially obscured by H_2O); *m/z* (FAB>0, G-T) 351 $(M+H)^+$; *m/z* (FAB<0, G-T) 349 $(M-H)^-$, 217 $(B)^-$; $[\alpha]_D^{20}$ - 128.0 (c 1.0 in DMSO). Elem. anal. ($C_{12}H_{12}Cl_2N_2O_4S$. $C_4H_8O_2$) calculated: C: 43.74, H: 4.59, Cl: 16.14, N: 6.38, S: 7.30; found C: 43.37, H: 4.61, Cl: 16.53, N: 6.34, S: 7.02.

Biological methods

The broad antiviral assays on cell cultures and the anti-HIV assays were performed by following previously established procedures as described in ref. 14.

Acknowledgements

The investigations were supported by Grants from the CNRS and INSERM, France "Agence Nationale de Recherche sur le SIDA". We gratefully acknowledge Dr. A.-M. Aubertin and Prof. G. Obert for the biological results.

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Received 7/27/93
Accepted 10/8/93