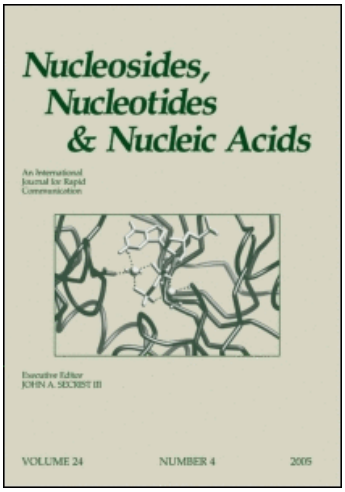

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SYNTHESIS OF 2S-DIOXO ISOSTERES OF PURINE AND PYRIMIDINE NUCLEOSIDES IV. SELECTIVE GLYCOSYLATION OF 4-AMINO-5H-IMIDAZO [4,5-c]-1,2,6-THIADIAZINE 2,2-DIOXIDE

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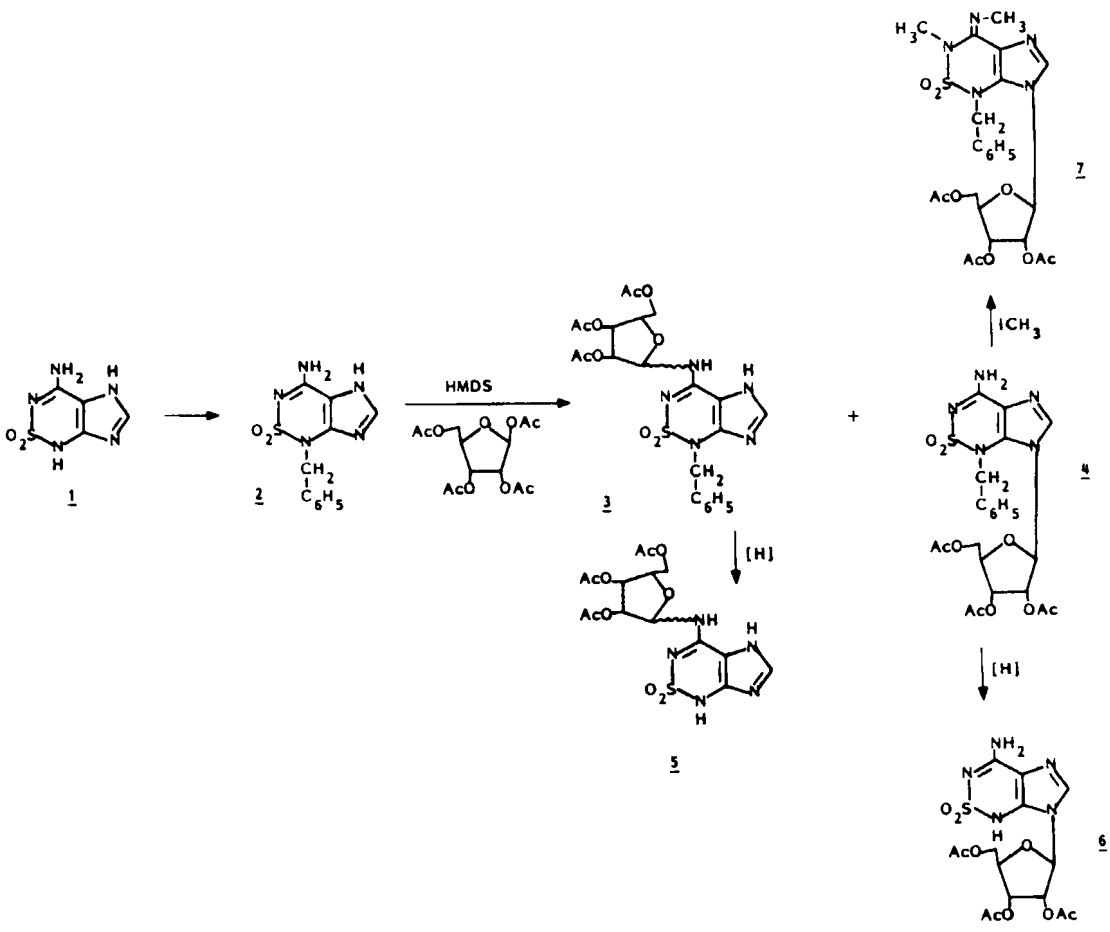
ABSTRACT. Selective glycosylation of 4-amino-5H-imidazo [4,5-c]-1,2,6-thiadiazine 2,2-dioxide (1) through its 1-benzyl derivative (2) is described. The structures of the compounds are discussed on the basis of ^{1}H nmr 2D homonuclear chemical shift correlations, NOE difference spectroscopy and iterative analyses.

In previous papers[1,2], we have described glycosylations of fused 1,2,6-thiadiazine 1,1-dioxide systems, which preferentially take place at the thiadiazine ring. We now wish to report our results on the preparation of the riboside of 4-amino-5H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxide (1)[3] which possesses the sugar moiety on the imidazole ring. This nucleoside can be regarded as an analog of the naturally-ocurring purine nucleosides.

Direct glycosylation of this heterocyclic system had been carried out by the mercuric cyanide/nitromethane, method affording mixtures of the N-1 mono and N-1, N-5 diribosides[4]. In order to selectively obtain the N-7 nucleoside, the following synthetic approach was undertaken: silylation[5] of 1-benzylthiadiazine, glycosylation and final removal of the benzyl group (Scheme I). A similar strategy had given good results in the preparation of the N-5 and N-7 monomethyl derivatives[6].



The starting 4-amino-1-benzyl-5H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxide (2),[6] prepared by benzylation of 1, was treated with hexamethyldisilazane under nitrogen to give the corresponding silyl derivative. Reaction of this compound with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in methylene chloride in the presence of boron trifluoride etherate afforded a complex mixture from which 4-(2,3,5-tri-O-acetyl-α,β-D-ribofuranosylamino)-1-benzyl-5H-imidazo [4,5-c]-1,2,6-thiadiazine 2,2-dioxide (3) and 7-(2,3,5-tri -O-acetyl-D-ribofuranosyl)-4-amino-1-benzylimidazo[4,5-c] -1,2,6-thiadiazine 2,2-dioxide (4) could be isolated. When this same reaction was carried out using stannic

TABLE 1. UV spectroscopic data

COMPOUND	λ max (nm)			Log ε			SOLVENT
2	222	232	298	3.88	3.91	3.85	H_2O/EtOH
A	220	230	298	4.03	4.07	3.85	EtOH
B	209		302	4.16		3.92	H_2O
3a	216	230	302	3.89	3.92	3.86	MeOH
3b		235	302		3.95	3.92	MeOH
4		228	283		3.97	3.92	MeOH
5a		234	308		3.75	3.70	MeOH
6	212		304	4.06		3.84	MeOH
7	208		272	4.11		3.83	MeOH

A=4-amino-1-benzyl-7-methylimidazo[4,5-c][1,2,6]thiadiazine 2,2-dioxide.
B=4-amino-7-methyl-1H-imidazo[4,5-c][1,2,6]thiadiazine 2,2-dioxide

chloride as the catalyst, the major product was 4 and only traces of 3 could be detected. Removal of the benzyl groups was achieved by hydrogenolysis (60 psi, 50 C, 10% palladium/charcoal) and thus, the corresponding N-4 and N-7 ribosides 5 and 6 could be isolated.

The structures of the ribosides were established according to their analytical and spectroscopic data (Tables 1 and 2). Based on comparisons with uv spectral data of known suitable alkyl derivarives[6] (Table 1) the uv spectra observed for all these compounds are in good agreement with their assigned structures. In the cases in which it was not possible to establish the anomeric configuration on the basis of ^{1}H nmr data, the ribosides have been tentatively assigned as according to well-documented mechanistic criteria[7].

The ^{1}H nmr (300 MHz) spectrum of 4 showed a singlet at 4.82 ppm for the two equivalent protons corresponding to the benzyl methylene group. The ribose protons appeared as multiplets too complex to be studied by first-order analysis. In order to assign the chemical shifts and to

TABLE 2. ^1H nmr parameters

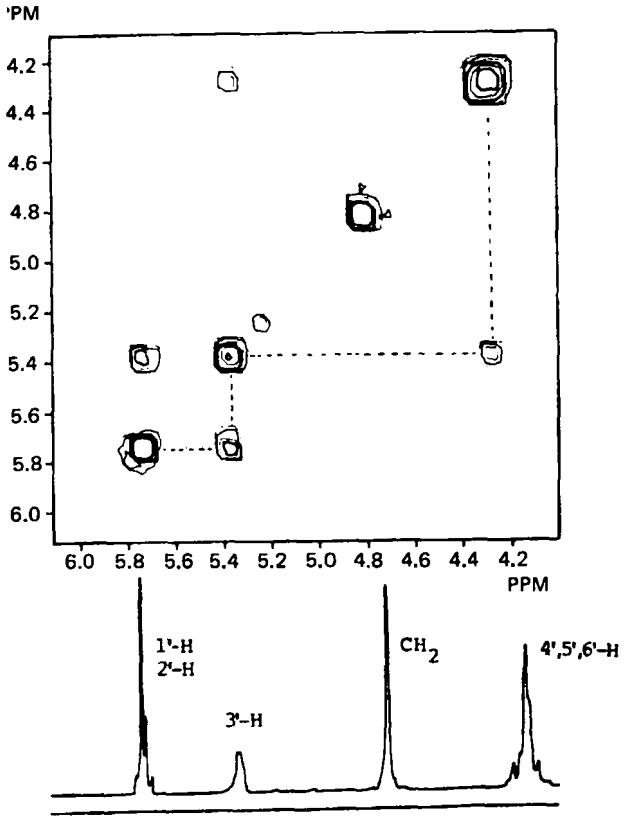
Chemical shift (ppm)

COMPOUND	H-1'	H-2'	H-3'	H-4',H-5'	H-6	CH_2	Ph	others
3a (α) (β)	6.21(q) 5.71(q)	5.44(t)	5.31(q)	4.3-4.1(m)	7.97(s) 8.13(s)	4.99(s) 4.98(s)	7.4-7.2(m)	8.18(NH)
3b	6.21(q)	5.44(t)	5.31(q)	4.3-4.1(m)	7.97(s)	4.98(s)	7.4-7.2(m)	8.20(NH)
4	5.72(m)	5.72(m)	5.36(m)	4.3-4.2(m)	8.18(s)	4.82(s)	7.3-7.2(m)	8.23(NH)
5a (α) (β)	6.12(q) 5.73(q)	5.42(t)	5.29(q)	4.3-4.1(m)	7.35(s) 7.89(s)	-	-	8.35(NH)
6	5.83(d)	5.69(t)	5.41(q)	4.3-4.1(m)	7.92(s)	-	-	
7	5.62(m)	5.62(m)	5.35(m)	4.3-4.1(m)	7.62(s)	4.95(d) 4.76(d)	7.3-7.2(m)	3.59(CH_3) 3.12(CH_3)

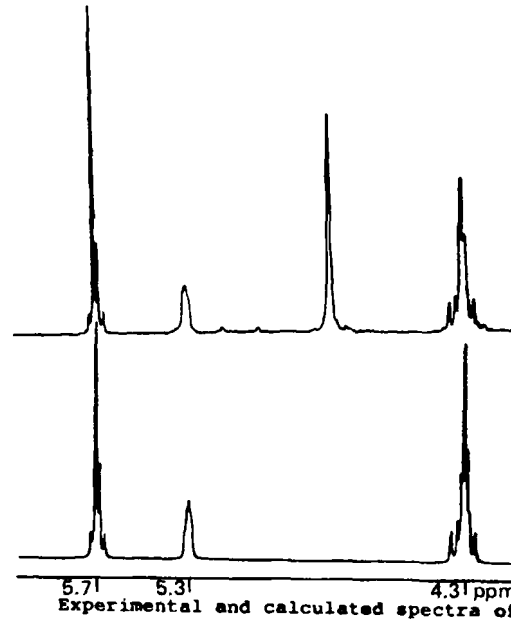
Coupling constants (Hz)

COMPOUND	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{NH,1'}$	$J_{A,B}$
3a (α) (β)	4.2 5.7	5.1	6.9	8.8 7.8	-
3b	4.2	4.2	5.3	8.8	-
4*	6.2	5.1	4.2	-	-
5a (α) (β)	3.7 1.9	4.7	8.4	9.4 5.5	-
6	6.0	6.1	4.2	-	-
7	-	-	-	-	-15.7

*Calculated parameters



2D homonuclear shift correlated contour plot of compound 4 in $CDCl_3$.



Experimental and calculated spectra of compound 4.

FIGURE 1

measure the vicinal coupling constants, a two-dimensional homonuclear shift correlation experiment[8] and iterative analysis were peformed. By means of the 2D spectrum it was possible to assign all the signals. Iterative analysis was carried out considering a six spin system (Figure 1). The experimental and calculated spectra from the resulting best values matched satisfactorily. From the calculated spectrum, all the chemical shifts and coupling constants were accurately obtained; however, from the value of the coupling constant of the anomeric proton $J_{1',2'}$ = 6.2 Hz, it

was not possible to assign an α or β configuration to the nucleosidic bond.

The structure determination of 4 was accomplished by using NOE difference experiments, in order to determine the location of the sugar. Irradiation of the CH_2 singlet at 4.82 ppm showed a NOE effect (8%) on the signal at 5.72 ppm corresponding to H-1' and so, the position of glycosilation was definitely established at N-7.

The ^1H nmr spectrum of the corresponding debenzylated riboside 6 was assigned by chemical correlation with 4. As in that case, the anomeric configuration could not be established on the basis of the coupling constant ($J_{1',2'}$ = 6.0 Hz).

The ^1H nmr spectrum of 3a, which was isolated as the α,β anomeric mixture, showed two singlets for the heterocyclic H-6 proton and two singlets for the N-CH_2. The fact that the two anomeric protons appeared as quartets which collapsed to doublets upon addition of D_2O indicated that the sugar moiety was located at the exocyclic 4-amino group. The assignment of the anomeric configurations was not possible from the values of the coupling constants ($J_{1',2'}$ = 4.2, $J_{1',2'}$ = 5.7), but the chemical shift of the anomeric protons could be used by analogy with previous data[9]. Thus, the signal appearing at higher field at 5.71 ppm was attributed to the β and that at 6.21 ppm to the α anomer. From this anomeric mixture, it was possible to obtain a small amount of the pure α riboside 3b.

The ^1H nmr spectrum of the debenzylated riboside 5a indicated that it was also the α,β mixture as the corresponding starting material 3a. In this case, however, the value of the coupling constant $J_{1',2'}$ = 1.9 Hz indicated a β configuration for the anomeric proton appearing at higher field, which was in agreement with the previous assignments in 3a and 3b.

In order to obtain the 2S-dioxo analog of doridosine (1-methylisoguanosine)[10] attempts were made to methylate 4 and 6. Treatment of 6 with methyl iodide afforded a

complex mixture from which one mono and one dimethyl derivative could be isolated in minor amount. The ^{1}H nmr spectra indicated that methylation had taken place at N-1 (3.29 ppm) and N-3, N-4 (3.17 and 3.71 ppm) respectively.

On the other hand, methylation of 4 afforded a dimethyl derivative 7, whose structure was definitely assigned on the basis of ^{13}C and ^{1}H nmr data. The position of the two methyl groups was established by ^{13}C nmr. The two signals appearing at 40.3 ppm and 39.4 ppm indicated two N-methyl groups at N-3 and N-4.

Its ^{1}H nmr spectrum showed two singlets corresponding to the two methyl groups and the signals of the ribose moiety with a similar pattern as in the starting material 4. The benzyl methylene protons were not equivalent, appearing as an AB system, and not as a singlet as in 4. The origin of nonequivalence of the methylene protons is uncertain. A variable temperature experiment showed that the two sets of doublets did not coalesce at temperatures as high as 373 K (DMSO). A possible explanation could be that the presence of substituents at positions 1 and 3 hinders the inversion of the thiadiazine ring (envelope ⇄ envelope equilibrium) thus giving rise to an intrinsic chirality.

EXPERIMENTAL

Ultraviolet spectra were measured on a Perkin-Elmer 350 spectrophotometer. Column chromatography was performed on Merck silicagel 60 (70-230 mesh), and preparative thin layer chromatography was performed on 20x20 cm glass plates coated with a 2 mm layer of silicagel PF_{254} (Merck). Compounds were detected with UV light (254 mm) or by spraying the plate with ethanol:sulphuric acid (3:1) and heating.

^{1}H nmr spectra were recorded at 293 K on a Varian XL-300 instrument operating at 300 MHz, using DMSO as

solvent and TMS as internal standard. Typical acquisition parameters were: spectral width, 3KHz; data memory, 32K, acquisition time, 5 s and pulse width, 8μs (53°). Variable temperature spectra were recorded at 313 K, 343 K and 373 K. NOE difference spectrum of 4 was measured on the same conditions, using a presaturation time of 3s and a effective decoupler power of $\gamma_H B_2/2\pi$ = 80Hz.

Two-dimensional scalar shift-correlated ^1H nmr spectra were recorded in the same spectrometer using the 90^0-t_1-90^0 pulse sequence referred to as COSY[7]. The following parameters were used: number of increments, 256; 90^0 pulse width, 13.5μs; relaxation delay, 2s; sweep width 1100 Hz in t_1 and 2200 Hz in t_2 and 512x512 transformed data points. Iterative analysis of ^1H spectra were carried out using the PANIC[11] program.

^{13}C nmr decoupled spectra were measured at 293 K on the same instrument operating at 75 MHz. Typical acquisition paramaters were: spectral width, 16 KHz; data memory, 64K; acquisition time, 2s; pulse width 7μs (54°).

4-(2,3,5-tri-O-acetyl-α and α,β-D-ribofuranosylamino)-1-benzyl-5H-imidazo[4,5,c]-1,2,6-thiadiazine 2,2-dioxide (3b) and (3a)

To a stirred solution of 0.53 g (0.0016 mole) of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in 50 ml of dry methylene chloride, a solution of the silyl derivative of 2 (prepared from 2 (0.46 g, 0.0016 mole) and hexamethyldisilazane (15 ml) in the presence of pyridine (10 ml) under N_2 atmosphere) in methylene chloride was added. The mixture was treated with 3 ml of boron trifluoride etherate and stirred overnight at room temperature with exclusion of humidity. The reaction mixture was then treated with saturated sodium hydrogen carbonated solution (100 ml). The organic phase was separated, dried over sodium sulphate and evaporated under reduced pressure. The residue (0,85 g), which was a very complex mixture, was chromatographed on silicagel column using chloroform:methanol 15:1 as eluent. The oily residue obtained was rechromatographed using

preparative TLC eluting with chloroform:methanol (25:1). The lower running band afforded 0.18 g (18 %) of the anomeric mixture 3a.

Anal. Calcd. for $C_{22}H_{25}N_5O_9S$: C, 49.34; H, 4.67; N, 13.08; S, 5.98.

Found: C, 49.67; H, 4.87; N, 12.98; S, 5.68.

Eluting with chloroform:methanol (3:1) it was possible to isolate the more polar anomer. The α-nucleoside 3b was obtained as a white glass in 5% yield.

Anal. Calcd. for $C_{22}H_{25}N_5O_9S$: C, 49.34; H, 4.67; N, 13.08; S, 5.98.

Found: C, 49.70; H, 4.99; N, 12,63; S, 6.12.

7-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-4-amino-1-benzyl-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxide (4)

According to the procedure described for the synthesis of 3a, 0.8 g (0.0025 mole) of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose was reacted with the silyl derivative obtained from 2 (0.7 g, 0.0025 mole). As catalyst, 2 ml of stannic chloride, were used. After work-up, the residue was chromatographed on silicagel column, using the same eluent as described in the previous reaction using boron trifluoride etherate. A second cromatography, on preparative TLC using cloroform:metanol (50:1) as eluent, was required to isolate pure 4 (0.2 g, 15%) as a white glass.

Anal. Calcd. for $C_{22}H_{25}N_5O_9S.H_2O$: C, 47.73; H, 4.88; N, 12.65; S, 5.78.

Found: C, 47.73; H, 4.88; N, 12.25; S, 5.31.

4-(2,3,5-tri-O-acetyl-α,β-D-ribofuranosylamino)-5H-imidazo [4,5-c]-1,2,6-thiadiazine 2,2-dioxide (5a)

A solution of 3a (0.13 g, 0.00025 mole) in 25 ml of absolute ethanol, was hydrogenated with 60 psi of hydrogen in the presence of 10% palladium/charcoal catalyst at 70 C. After 20 h, the reaction mixture was cooled filtered and the solvent evaporated under reduced pressure. The residue

was chromatographed on preparative TLC using chloroform: methanol (5:1) as the eluent, to give 5 (0.04 g, 40%) as a white glass.

Anal. Calcd. for $C_{15}H_{19}N_5O_9S$. H_2O: C, 38.87; H, 4.53; N, 15.11; S, 6.91.

Found: C, 39.19; H, 4.50; N, 15.12; S, 6.63.

7-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-5H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxide (6)

A solution of 4 (0.2 g, 0.0003 mole) in 25 ml of ethyl acetate, was hydrogenated with 60 psi of hydrogen in the presence of 10% palladium/charcoal catalyst at 70 C. After 20 h, the reaction mixture was cooled, filtered, and the solvent was removed "in vacuo". The residue was chromatographed on TLC plates using ethyl acetate as the eluent, to give 6 (0.07 g, 42%) as a white glass.

Anal. Calcd. for $C_{15}H_{19}N_5O_9S$: C, 40.44; H, 4.26; N, 15.73; S, 7.19.

Found: C, 40.76; H, 4.63; N, 15.34; S, 7.13.

7-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-1-benzyl-3-methyl-4-methylaminoimidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxide (7)

A stirred solution of 4 (0.2 g, 0.0003 mole) in 20 ml of anhydrous acetone reacted with methyl iodide (0.05 g, 0.0003 mole) in the presence of potassium carbonate (0.1 g). The reaction mixture was refluxed for 2 h and the solid was filtered off. The solvent was removed "in vacuo" and the residue was chromathographed on preparative TLC using ethyl acetate:hexane (1:1) as the eluent, to give 7 (0.15 g, 73%) as a white glass. ^{13}C nmr ($CDCl_3$) : 170.07, 169.87, 169.56 (C=O), 137.48 (C-4), 135.66 (C-7a), 131.49 (Cipso), 128.71, 128.47 (Co), 128.25, 128.19 (Cm), 128.11 (Cp), 121.59 (C-6), 111.16 (C-4a), 84.34 (C-1'), 80.99 (C-2'), 72.63 (C-3'), 70.98 (C-4'), 63.48 (C-5'), 57.02 (CH_2), 40.29 (N-CH_3), 39.37 (N-CH_3), 21.12, 20.81, 20.58 (CH_3).

Anal. Calcd. for $C_{15}H_{19}N_5O_9S.1.5H_2O$: C, 48.81; H, 5.42; N, 11.86.

Found: C. 48.90; H, 5.43; N, 11,47.

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