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The preparation of glucosyl and ribosyl derivatives of 3,4,5-triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**2**), 7-amino-4*H*-furazano[3,4-*c*]- and 7-amino-1*H*, 4*H*-imidazo[2,3-*c*][1,2,6]thiadiazine 5,5-dioxide (**3** and **4** respectively) is described. Different synthetic approaches have been used.

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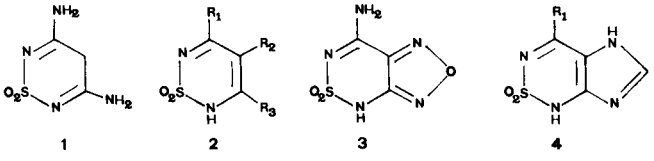
In previous papers (2) we have described the synthesis of some pyrimidine (**1** and **2**) and purine (**3** and **4**) analogs, derived from the 1,2,6-thiadiazine ring system.



1 **2** **3** **4**

$R_1 = OH, NH_2$

$R_2 = NO, NO_2, NH_2$

$R_3 = H, NH_2$

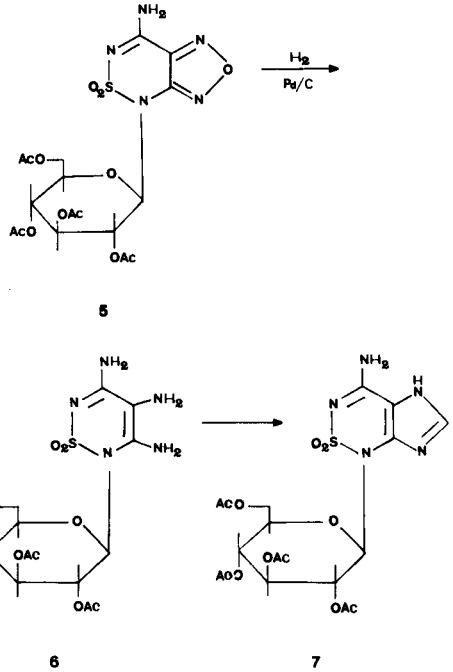
We have also studied their reactivity against electrophiles such as dimethyl sulfate, benzyl chloride and allyl bromide (1,3) and nucleophiles such as methylamine and benzylamine (3), and in the case of compound **1**, against glycosyl halides and acetates (1).

In this paper, we report the synthesis of new nucleosides derived from compounds **3** and **4** ($R_1 = NH_2$), by the mercuric cyanide-nitromethane (4) and silyl (5) procedures. Transformation of the *N*-4-nucleoside derived from **3** (**5**), led to a pyrimidine-like nucleoside (**6**) related to **2**, which in turn, could be converted to a purine-like one (**7**).

Results and Discussion.

Reaction of **3** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, following the mercuric cyanide-nitromethane procedure (4), led to 4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-7-aminofurazano[3,4-*c*][1,2,6]thiadiazine 5,5-dioxide (**5**) in 65% yield. The site of glycosidation of **5**, as well as that of the rest of the nucleosides described in this paper, was determined by comparing their uv spectra with those of the model substances previously synthesized (**3**). Due to the general stereospecificity of the mercuric cyanide-nitromethane procedure, the 1',2'-*trans* nucleosides were expected (6). In the case of **5**, the β-anomeric configuration was confirmed by the value of $J_{1',2'} = 9$ Hz in the ^{1}H-nmr spectrum (7).

Catalytic hydrogenation of **5** resulted in the opening of the furazane ring, to give 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3,4,5-triamino-1,2,6-thiadiazine

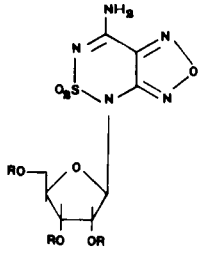


5 **6** **7**

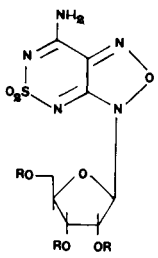
1,1-dioxide (**6**) in high yield. The structure of **6** was confirmed by its ^{1}H-nmr spectrum, which showed the signals of three amino groups, which disappeared by treatment with deuterium oxide, and by its uv spectrum, similar to that of the 2-methyl analog (3).

Following a similar reaction sequence to that used in our laboratory with the corresponding methyl derivative (3), treatment of **6** with an equimolar mixture of formic acid and acetic anhydride (8), led to 4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-7-amino-1*H*-imidazo[2,3-*c*]-[1,2,6]thiadiazine 5,5-dioxide (**7**), through the no isolated 4-formyl derivative of **6**. The anomeric configuration of **7** could not be stabilized on the basis of its ^{1}H-nmr spectrum, since the signal corresponding to the H-1' proton appeared together with those of H-2' and H-3' protons. We have assigned a β configuration, since in the conditions used, no anomerization seems likely to take place. The site of glycosidation of **7** was confirmed by its uv spectrum, similar to that of the 4-methyl analog (3).

Reaction of **3** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide following the same procedure, gave two isomeric products (**8a** and **9a**).



8a: R = Bz
8b: R = H



9a: R = Bz
9b: R = H

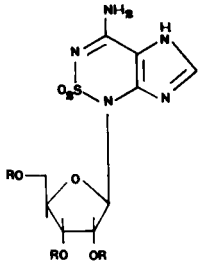
The major product was identified as 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7-aminofurazano[3,4-*c*][1,2,6]-thiadiazine 5,5-dioxide (**8a**). This structure is supported by the uv spectrum of the free nucleoside **8b** (λ max 215 and 276 nm), which agrees closely with the uv spectrum of **5**. Although the measured value of $J_{1',2'}$ = 4 Hz in the ^{1}H-nmr spectrum of **8a**, did not allow an unequivocal assignment of its anomeric configuration, we assigned it as β on the basis of the synthetic procedure (6).

The product obtained in minor amount, was tentatively assigned as 3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7-aminofurazano[3,4-*c*][1,2,6]thiadiazine 5,5-dioxide (**9a**) on the basis of its ^{1}H-nmr spectrum and the uv spectrum of **9b** (λ max 216 and 302 nm).

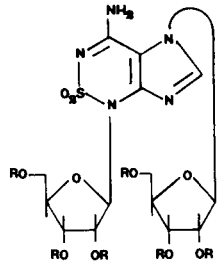
The glycosidation of **4** by the mercuric cyanide-nitromethane procedure (4) gave poor yields, due to its low solubility. In all the cases, different amounts of the starting material were recovered.

On reaction of **4** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, a crystalline nucleoside was obtained in 19% yield, identical in all respects with compound **7**.

From the reaction of **4** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide, 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7-amino-1*H*-imidazo[2,3-*c*][1,2,6]thiadiazine 5,5-dioxide (**10a**) in 17% yield and traces of a di-riboside were obtained.



10a: R = Bz
10b: R = H



11a: R = Bz
11b: R = H

The uv spectrum of the deprotected nucleoside **10b** (λ max 230, 240 (sh) and 292 nm), which agrees closely with the uv spectrum of **7** supported the structure of **10a**. As before, the β configuration was assigned on the basis of the method used for the synthesis (6).

Due to the low yields obtained in the glycosidation of **4**, the silylation method in the presence of Friedel-Crafts catalysts (5) was attempted. Reaction of the silylated imidazo-thiadiazine with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose in the presence of stannic chloride, afforded **7** in 32% yield. When the reaction was performed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, compound **10a** was obtained in 39% yield, along with the diriboside **11a**. The sites of glycosidation of **11a** were determined by its uv spectrum (λ max 227, 245 (sh) and 300 nm), which agrees with that of the 1,3-dimethyl analog (3). The ^{1}H-nmr spectrum of **11a** showed the signals of two anomeric protons with $J_{1',2'}$ = 4 Hz. Since it is generally assumed that Lewis acids, such as stannic chloride, promote the formation of acyloxonium ions of fully acylated ribofuranoses, which lead to the formation of 1',2'-*trans* nucleosides (6), a β configuration was assigned in both glycosidic unions.

EXPERIMENTAL

Melting points were taken on a Kofler melting point microscope and are uncorrected. The uv spectra were recorded on a Perkin-Elmer 350 and 402 spectrophotometers. The ^{1}H-nmr spectra were determined on a Varian XL-100 spectrometer with TMS as internal standard. The thin layer chromatography was performed on Merck silica gel plates PF_{254}.

The solvents were carefully purified. Nitromethane was distilled over phosphorus pentoxide. Acetonitrile was refluxed for 2 hours over phosphorus pentoxide and distilled; the procedure was repeated, and finally it was stored over 3 Å molecular sieves.

The silylation of the corresponding bases was performed according to standard methods. The addition of pyridine to the reaction mixture was necessary to favour solubilization of the starting material.

4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-7-aminofurazano[3,4-*c*]-[1,2,6]thiadiazine 5,5-Dioxide (**5**).

A suspension of 0.95 g (5 mmoles) of **3** and 2.52 g (10 mmoles) of mercuric cyanide in 500 ml of nitromethane, was dried by azeotropic distillation. To the stirred solution, 2.05 g (5 mmoles) of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide dissolved in 20 ml of nitromethane were added during 30 minutes with continuous gradual distillation of nitromethane. The mixture was refluxed for 4 hours and the solvent was slowly distilled off. The remainder of the solvent was removed *in vacuo* and the sirupy residue extracted with chloroform. The extract was washed twice with 50 ml of 30% aqueous potassium iodide and once with 50 ml of water, and the organic layer dried over sodium sulfate. After removal of the solvent *in vacuo*, a syrup was obtained, which when chromatographed on ten silica gel plates, gave on elution with chloroform-ethanol (10:1) the *N*-4 nucleoside **5**. Crystallization from ethanol gave 1.68 g (65% yield) of pure **5**, mp 238-239°; uv (ethanol): λ max 213 (ε, 6,100) and 274 nm (ε, 4,800); ^{1}H-nmr (DMSO-d_6): δ 5.94 (d, 1H, J = 9 Hz, H-1').

Anal. Calcd. for $C_{17}H_{21}N_5O_{12}S$: C, 39.31; H, 4.05; N, 13.48. Found: C, 39.08; H, 4.07; N, 13.17.

2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3,4,5-triamino-1,2,6-thiadiazine 1,1-Dioxide (**6**).

A suspension of 1 g (2 mmoles) of **5** in 30 ml of absolute ethanol, was hydrogenated with 40 psi of hydrogen in the presence of palladium/carbon 10% catalyst at 70°. After two hours, the reaction mixture was cool-

ed until white needles appeared mixed with the catalyst. The mixture was filtered and the solid extracted with boiling water. From solution, 0.76 g (77% yield) of **6** crystallized, mp 221-222°; uv (ethanol): λ max 220 (sh) (ε, 5,200), 235 (ε, 5,900) and 300 nm (ε, 10,100); ^{1}H-nmr (DMSO-d_6): δ 5.60 (d, 1H, J = 9.5 Hz, H-1').

Anal. Calcd. for $C_{17}H_{25}N_5O_{11}S$: C, 40.23, H, 4.93; N, 13.80. Found: C, 40.26; H, 4.96; N, 13.59.

3- and 4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-7-aminofurazano[3,4-*c*]-[1,2,6]thiadiazine 5,5-Dioxide (**8a** and **9a**).

Following the procedure described for the preparation of **5**, 0.95 g (5 mmoles) of **3**, 2.52 g (10 mmoles) of mercuric cyanide and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide [prepared (9) from 2.52 g (5 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose] were used. After work-up, the residue was chromatographed on silica gel plates, and eluted with the same solvent system mentioned above. The lower running band gave 0.4 g (12% yield) of **9a** as a pure yellow glass; uv (ethanol): λ max 210 (ε, 17,500), 233 (ε, 36,000), 277 (ε, 7,200) and 286 nm (ε, 6,000); ^{1}H-nmr (DMSO-d_6): δ 6.26 (s, 1H, H-1').

Anal. Calcd. for $C_{29}H_{23}N_5O_{10}S$: C, 54.97; H, 3.65; N, 11.05. Found: C, 54.68; H, 3.88; N, 10.88.

The faster running band afforded 2.3 g (64% yield) of **8a** as a white glass; uv (ethanol): λ max 206 (ε, 19,000), 230 (ε, 36,600), 275 (ε, 8,000) and 283 nm (ε, 7, 400); ^{1}H-nmr (DMSO-d_6): δ 6.25 (d, 1H, J = 4 Hz, H-1').

Anal. Calcd. for $C_{29}H_{23}N_5O_{10}S$: C, 54.97; H, 3.65; N, 11.05. Found: C, 54.77; H, 3.54; N, 11.04.

4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-7-amino-1*H*-imidazo[2,3-*c*]-[1,2,6]thiadiazine 5,5-Dioxide (**7**).

Method A: From **6**.

An equimolar mixture of 98% formic acid and acetic anhydride was allowed to stand at 0° for 1 hour. Compound **6** (1 g, 2 mmoles), was added to 20 ml of the above formylating solution. The reaction mixture was stirred at room temperature for 24 hours with exclusion of humidity, and the resulting solution evaporated *in vacuo*. The residue was dissolved in acetic acid and stirred at room temperature for 1 hour. After removal of the acid *in vacuo*, a syrup was obtained, which was chromatographed on silica gel plates. After elution with the system mentioned above, 0.43 g of **7** were obtained. Crystallization from ethanol gave 0.3 g (30% yield) of pure **7**, mp 188-189°; uv (ethanol): λ max 210 (sh) (ε, 5,800), 227 (ε, 6,900), 240 (ε, 6,500) and 287 nm (ε, 7,100); ^{1}H-nmr (DMSO-d_6): δ 5.28-5.89 (m, 3H, H-1', H-2' and H-3'), 7.82 (s, 1H, H-2).

Anal. Calcd. for $C_{18}H_{23}N_5O_{11}S.H_2O$: C, 40.37; H, 4.67; N, 13.08. Found: C, 40.21; H, 4.40; N, 12.81.

Method B.

According to the procedure described for the preparation of **5**, 0.93 g (5 mmoles) of **4**, 2.52 g (10 mmoles) of mercuric cyanide and 2.05 g (5 mmoles) of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide were used. During the whole time of reaction, the mixture did not become homogeneous because of the low solubility of **4** in nitromethane. Variable amounts of unaltered starting material were recovered. After the usual work-up, two chromatographic purifications gave 0.5 g (19% yield) of **7**.

Method C.

To a solution of 2.9 g (7.5 mmoles) of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose in 100 ml of dry acetonitrile, a solution of the silyl derivatives of **4** [prepared from 1.87 g (10 mmoles) of **4** by reaction with hexamethyldisilazane (10 ml) and trimethylchlorosilane (1 ml) in the presence of dry piridine (30 ml)], in acetonitrile was added. The mixture was cooled with ice and 1 ml of stannic chloride added with vigorous stirring and exclusion of humidity. The resulting mixture was stirred for 4 hours at room temperature. At this point it is advantageous to remove part of the acetonitrile *in vacuo* before dilution with 100 ml of 1,2-dichloroethane. The reaction mixture was then shaken with saturated sodium hydrogen carbonate and sodium chloride solution (100 ml) and the resulting emulsion filtered over sand-Celite. The filtering aid was carefully washed with 1,2-dichloroethane. The organic phase was separated, dried with sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on elution with chloroform-ethanol (10:1). After crystallization 1.24 g (32% yield) of **7** were obtained.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-7-amino-1*H*-imidazo[2,3-*c*]-[1,2,6]thiadiazine 5,5-Dioxide (**10a**) and 1,4-*bis*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7-aminoimidazo[2,3-*c*][1,2,6]thiadiazine 5,5-Dioxide (**11a**).

Method A.

Following the procedure described for the preparation of **5**, 0.93 g (5 mmoles) of **4**, 2.52 g (10 mmoles) of mercuric cyanide and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide [prepared (9) from 2.52 g (5 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose] were used. After work-up, chromatography on silica gel plates gave on elution with chloroform-ethanol (10:1) 0.64 g (17% yield) of **10a** as a white glass; uv (ethanol): λ max 240 (ε, 21,400), 277 (ε, 8,100) and 284 nm (ε, 8,600); ^{1}H-nmr (DMSO-d_6): δ 6.16 (d, 1H, J = 4 Hz, H-1').

Anal. Calcd. for $C_{30}H_{25}N_5O_9S$: C, 57.05; H, 3.99; N, 11.09. Found: C, 56.84; H, 4.34; N, 10.92.

Method B.

According to the procedure described for the synthesis of **7**, (Method C), 3.8 g (7.5 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose and the silyl derivatives obtained from 1.87 g (10 mmoles) of **4** were used. After work-up, the residue was chromatographed on silica gel plates and eluted with chloroform-ethanol (15:1). The lower running band gave 1.5 g (39% yield) of **10a**. The faster running band afforded 0.3 g (7% yield) of the di-riboside **11a**; uv (ethanol): λ max 239 (ε, 48,700), 276 (ε, 9,000), 284 (ε, 8,600) and 315 nm (ε, 8,200); ^{1}H-nmr (DMSO-d_6): δ 6.24 (d, 1H, J = 4 Hz, H-1'), 6.39 (d, 1H, J = 4 Hz, H-1').

Anal. Calcd. for $C_{56}H_{45}N_5O_{16}S.H_2O$: C, 61.48; H, 4.30; N, 6.40. Found: C, 61.77; H, 4.48; N, 6.35.

REFERENCES AND NOTES

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