Synthesis of 2-*S*-Dioxo Isosteres of Purine and Pyrimidine Nucleosides. I. Alkyl and Glycosyl Derivatives of 3,5-Diamino-4*H*-1,2,6-thiadiazine 1,1-Dioxide

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Preparation of alkyl and glycosyl derivatives of 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (**1**) is described. Reaction of **1** with dimethyl sulfate gave the 4-methyl and 2,4-dimethyl derivatives. With benzyl chloride and allyl bromide C-4 substituted compounds were obtained. Reaction of the disilyl derivative of **1** with either 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose in the presence of Friedel-Crafts catalysts afforded the α and β anomers of the N-2 nucleoside and the β-*O*-glucoside. When the reaction was performed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, a β-C-glycoside and the α and β anomers of the N-2 nucleoside were obtained. The structure of the corresponding nucleosides were elucidated by ^{1}H nmr and uv by comparing the latter with those of the alkyl derivatives.

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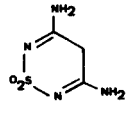
Our interest (1) in analogs of naturally occurring nucleosides led us to study the alkylation and glycosidation reactions of some 2-*S*-dioxo isosters of purines and pyrimidines (2). These compounds, incorporating a tetrahedral sulfur moiety, can be regarded as potential transition state analogs in the biosynthesis of purine and pyrimidine nucleosides (3).

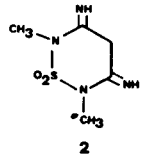
In the present paper, we report the results obtained in the preparation of alkyl and glycosyl derivatives obtained from 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (**1**) (4).



1

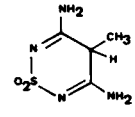
In order to obtain some models for the characterization of the desired nucleosides, we have studied the reactions of **1** with different alkylating agents.

Methylation of **1** with dimethyl sulfate had been described (4), and the resulting product was identified as 3,5-diimino-2,6-dimethyl-4*H*-1,2,6-thiadiazine 1,1-dioxide (**2**).



2

Our attempts to obtain the reported product, led to a solid with the same melting point as **2**, which according to its ^{1}H nmr spectrum appeared to be a mixture of the monomethyl and dimethyl derivatives (**3** and **4**) in a ratio of *ca.* 2:1.



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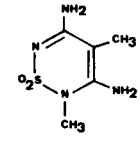

4

In order to obtain the pure dimethyl derivative, the reaction was performed with an excess of dimethyl sulfate. The only product thus obtained was identified as 3,5-diamino-2,4-dimethyl-1,2,6-thiadiazine 1,1-dioxide (**4**) on the basis of its ^{1}H nmr spectrum.

The ^{1}H nmr spectrum of **4** showed two singlets corresponding to two methyl groups, at δ 1.65 (CH_3-CH=) and δ 3.15 (CH_3-N), which excluded a symmetric structure. Compound **1** underwent selective *C*-alkylation with the first equivalent of dimethyl sulfate, and 3,5-diamino-4-methyl-4*H*-1,2,6-thiadiazine 1,1-dioxide (**3**) was obtained in the conditions of monomethylation, but it could not be entirely separated from the starting material. The ^{1}H nmr spectrum of **3** showed the signals of a methyl group as a doublet (J = 8 Hz) at δ 1.45 and a proton as a quartet (J = 8 Hz) at δ 3.05. Treatment with deuterium oxide caused the collapse of the doublet to a singlet and the disappearance of the quartet due to the easy interchange of the H-4 proton with deuterium. A similar behaviour was observed for the methylenic protons of the starting product.

When the alkylation reactions were carried out with other alkylating agents, such as benzyl chloride and allyl bromide, selective *C*-alkylation could also be observed. In all cases, the products were *C*-benzyl and *C*-allyl derivatives (**5a,b,c**). In no case was *N*-alkylation observed.

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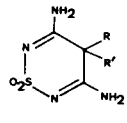


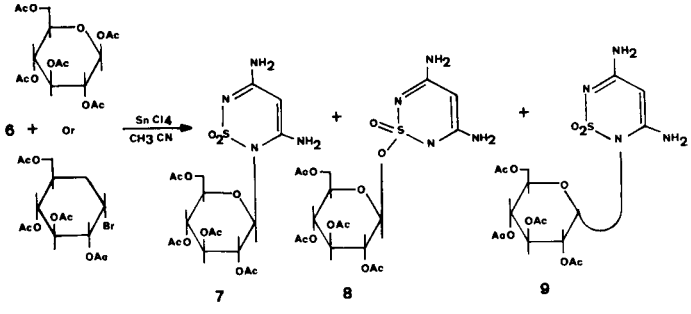
5a : R = Bn , R' = H
5b : R = R' = Bn
5c : R = R' = Allyl

The ^{1}H nmr spectrum of **5a** showed a complex signal at δ 3.22 due to the H-4 and the methylenic protons, which collapsed to a singlet on exchange with deuterium oxide. The ^{1}H nmr spectrum of **5b** showed one singlet at δ 3.06 corresponding to the four methylenic protons and one singlet at δ 7.25 for the two phenyl groups.

From the reaction of **1** with allyl bromide in the conditions of mono and dialkylation, the only product isolated showed a quantitative analysis according to the diallyl derivative **5c**. Its ^{1}H nmr spectrum showed one doublet at δ 2.74 assigned to the four α methylenic protons and a complex signal centered at δ 5.26 due to the six olefinic protons.

Attempts to apply the mercuric cyanide-nitromethane (5) or the fusion (6) methods to the preparation of nucleosides of **1** failed due to its extremely low solubility in organic solvents and its high melting point respectively. Glycosidation took place by the use of the silylation method in the presence of Friedel-Crafts catalysts (7).

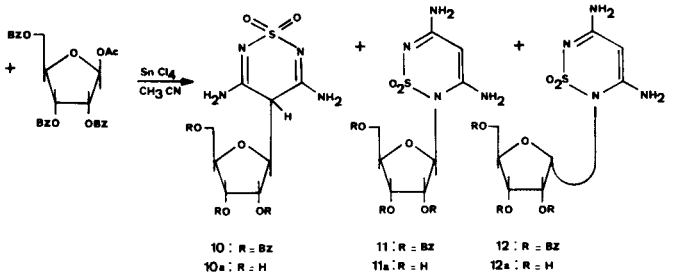
Silylation of **1** with hexamethyldisilazane (HMDS) in pyridine led to the isolation of a stable disilyl derivative of **1** as a crystalline solid (**6**). From the reaction of **6** with either 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose, 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3,5-diamino-1,2,6-thiadiazine 1,1-dioxide (**7**), 1-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]-3,5-diamino-1,2,6-thiadiazine 1-oxide (**8**) and traces of 2-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-3,5-diamino-1,2,6-thiadiazine 1,1-dioxide (**9**) were obtained.



The ^{1}H nmr spectra of **7** and **9** showed the absence of the signal corresponding to the two H-4 methylenic protons of **1** (δ 3.15) (8) and the presence of a singlet at δ 4.77 and 4.73 respectively due to the olefinic H-4 protons. The anomeric protons of **7** and **9** appeared at δ 5.70 ($J_{1',2'}$ = 9 Hz) and at δ 6.05 ($J_{1',2'}$ = 6 Hz). These data are in agreement with the assigned anomeric configuration. The uv spectra of **7** and **9** showed the same wavelengths of absorption, suggesting the same chromophore in both structures.

Compound **8** was identified as the corresponding *O*-glycoside of **1**. In the ^{1}H nmr spectrum of **8**, the singlet due to the H-4 proton is shifted downfield to δ 6.34, as expected for the proposed site of glycosidation. This is also confirmed by the bathochromic shift of the uv absorption in comparison to those of **7** and **9**, as a result of the regained cyclic resonance. The anomeric proton appeared as a doublet at δ 5.74 ($J_{1',2'}$ = 9.5 Hz), indicating a β configuration for the glycoside. Treatment of **8** with methanolic ammonia resulted in the ammonolysis of the glycosidic linkage.

Reaction of the silyl derivative **6** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose gave a nucleosidic mixture of 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4*H*-3,5-diamino-1,2,6-thiadiazine 1,1-dioxide (**10**), 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3,5-diamino-1,2,6-thiadiazine 1,1-dioxide (**11**) and traces of 2-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-3,5-diamino-1,2,6-thiadiazine 1,1-dioxide (**12**).



10 : R = Bz
10a : R = H
11 : R = Bz
11a : R = H
12 : R = Bz
12a : R = H

The uv spectrum of the free nucleoside **10a** was similar to that of compound **5a**, suggesting a C-C bond between the sugar moiety and the aglycon. The ^{1}H nmr spectrum of the benzoylated nucleoside **10** showed a doublet at δ 3.49 ($J_{4,1'}$ = 8 Hz), assigned to the H-4 proton. This signal disappeared on exchange with deuterium oxide, in a similar manner as the H-4 proton in **3**, **5a** and the starting material. The anomeric proton appeared as a doublet of doublets at δ 4.81 ($J_{1',4}$ = 8 Hz and $J_{1',2'}$ = 6 Hz) which collapsed to a doublet ($J_{1',2'}$ = 6 Hz) on treatment with deuterium oxide. This value of $J_{1',2'}$ does not allow to fix the anomeric configuration (9). We have assigned a *trans* configuration on the basis of the procedure used for the synthesis of **10**, which involves a vicinal participation of the acyloxy group in C-2′ (10). Similar mechanistic considerations have also been used to assigne the anomeric configuration of the other known *C*-glycosidic derivatives obtained by the trimethylsilyl method (11).

The uv spectra of **11a** and **12a** and the ^{1}H nmr data

for the thiadiazine moiety of **11** and **12** are similar to those of compounds **7** and **9**, thus indicating the same type of chromophore. The anomeric protons appeared at δ 6.10 ($J_{1',2'}$ = 2 Hz) and 6.55 ($J_{1',2'}$ = 4.5 Hz) respectively.

It is worth mentioning that the substitution on compound **1** depends considerably, as expected (12), on the solvent used in the reaction. Thus, protic solvents direct the substitution to the position 4 as a consequence of the solvation of the more electronegative atoms, whereas aprotic solvents favour the substitution of the nitrogen and oxygen atoms of **1**. The formation of compound **10** could be explained by the fact that the masked aldehyde carbon atom at C-1′ of a glucopyranose ring seems to be a harder electrophile than the corresponding of a ribofuranose ring.

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 Perkin-Elmer R-12 and a Varian XL-100 spectrometers with TMS as internal standard. The thin layer chromatography was performed on Merck silica gel plates PF_{254}.

The solvents were carefully purified: acetonitrile was refluxed for two hours over phosphorous pentoxide and distilled. The procedure was repeated, and finally it was stored over 3 Å molecular sieves. Stannic chloride was usually redistilled at normal pressure. The crystalline sugar derivatives were carefully powdered and dried at 40-50° (0.1 mm). The silylation of **1** was performed according to standard methods. The addition of pyridine was necessary to favour the solubilization of the starting material.

3,5-Diamino-2,4-dimethyl-1,2,6-thiadiazine 1,1-Dioxide (**4**).

A stirred solution of 1.62 g. (0.01 mole) of **1** and 3.5 g. of sodium hydrogen carbonate in 10 ml. of 1*N* sodium hydroxide was treated, dropwise, with 5.04 g. (3.7 ml., 0.04 mole) of dimethyl sulfate. The mixture was then stirred at room temperature for 24 hours and the resulting precipitate filtered off. Crystallization from water gave 0.8 g. (42%) of pure **4**, m.p. 273-275° dec.; uv (water): λ max 220 (ε, 8,300) and 297 nm (ε, 9,100); ^{1}H nmr (DMSO-d_6): δ 1.65 (s, 3H, CH_3-C), 3.15 (s, 3H, CH_3-N), 6.5 (b.s., 4H, NH_2).

Anal. Calcd. for $C_5H_{10}N_4O_2S$: C, 31.57; H, 5.30; N, 29.46. Found: C, 31.27; H, 5.24; N, 29.55.

3,5-Diamino-4-benzyl-4*H*-1,2,6-thiadiazine 1,1-Dioxide (**5a**).

To a stirred solution of 1.62 g. (0.01 mole) of **1** in 10 ml. of 1*N* sodium hydroxide, 1.26 g. (1.15 ml., 0.01 mole) of benzyl chloride were added dropwise. After stirring for 15 hours at room temperature, the white solid precipitate was filtered off. Crystallization from water gave 1 g. (39%) of pure **5a**, m.p. 282-284° dec.; uv (water): λ max 213 (ε, 14,700) and 293 nm (ε, 500); ^{1}H nmr (DMSO-d_6): δ 3.20 [m, 3H, CH_2-Ph and C*H* (4)], 7.20 (s, 5H, Ar-*H*), 7.36 and 7.52 (b.s., 4H, NH_2).

Anal. Calcd. for $C_{10}H_{12}N_4O_2S$: C, 47.61; H, 4.79; N, 22.21. Found: C, 47.92; H, 4.88; N, 21.94.

3,5-Diamino-4,4-dibenzyl-1,2,6-thiadiazine 1,1-Dioxide (**5b**).

A stirred solution of 1.62 g. (0.01 mole) of **1** in 20 ml. of 1*N* sodium hydroxide, was treated dropwise with 2.53 g. (2.3 ml., 0.02 mole) of benzyl chloride. The mixture was stirred for 24 hours and the resulting precipitate filtered off. After several crystallizations from ethanol, 1.6 g. of pure **5b** were obtained (46%); m.p. 325-326° dec.; uv (ethanol): λ max 222 (ε, 14,100), 234 (sh) (ε, 10,300) and 301 nm (ε, 5,700); ^{1}H nmr (DMSO-d_6): δ 3.55 (s, 4H, CH_2-Ph), 7.25 (s, 10H, Ar-*H*), 7.9 (b.s., 4H, NH_2).

Anal. Calcd. for $C_{17}H_{18}N_4O_2S{\cdot}H_2O$: C, 56.65; H, 5.55; N, 15.54. Found: C, 56.31; H, 5.24; N, 15.21.

3,5-Diamino-4,4-diallyl-1,2,6-thiadiazine 1,1-Dioxide (**5c**).

To a stirred solution of 1.62 g. (0.01 mole) of **1** in 20 ml. of 1*N* sodium hydroxide, was added dropwise, 2.42 g. (1.73 ml., 0.02 mole) of allyl bromide. After stirring overnight at room temperature, the white precipitate was filtered off. The solid was crystallized from water with difficulty, giving 1 g. (40%) of **5c** as colourless needles, m.p. > 315° dec.; uv (water): λ max 218 (ε, 8,200) and 229 nm (sh), (ε, 7,100); ^{1}H nmr (DMSO-d_6): δ 2.74 (d, 4H, -CH_2-CH=CH_2), 4.92-5.20 (m, 4H, -CH_2-CH=CH_2), 5.20-5.60 (m, 2H, -CH_2-C*H*=CH_2), 7.57 (b.s., 4H, NH_2).

Anal. Calcd. for $C_9H_{14}N_4O_2S$: C, 44.62; H, 5.82; N, 23.13. Found: C, 44.34; H, 5.75; N, 23.28.

Bistrimethylsilyl Derivative of 3,5-Diamino-4*H*-1,2,6-thiadiazine 1,1-Dioxide (**6**).

Compound **1**, 1.62 g. (0.01 mole) was suspended in a mixture of hexamethyldisilazane (10 ml.), pyridine (30 ml.) and trimethylchlorosilane (1 ml.). The suspension was refluxed for 6 hours, whereupon the solid was dissolved completely. Ammonia was evolved and ammonium chloride deposited in the reflux condenser. The solvents were removed at low pressure and finally at high vacuum. The stable solid resulting was washed with a small amount of absolute benzene. The product was dried *in vacuo* at 50° (2.7 g., 88%), m.p. 260°.

Anal. Calcd. for $C_9H_{22}N_4O_2SSi_2$: C, 35.29; H, 7.18; N, 18.30. Found: C, 35.16; H, 7.28; N, 18.38.

2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-3,5-diamino-1,2,6-thiadiazine 1,1-Dioxide (**7**) and 1-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]-3,5-diamino-1,2,6-thiadiazine 1-Oxide (**9**).

To a solution of either 3.1 g. (0.0075 mole) of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or 2.9 g. (0.0075 mole) of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose in 100 ml. of dry acetonitrile, a solution of 2.5 g. (0.008 mole) of **6** in acetonitrile was added. The mixture was cooled with ice and 1 ml. of stannic chloride in 10 ml. of acetonitrile was added with vigorous stirring and exclusion of humidity. The resulting solution was stirred at room temperature for 4 hours. 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 (3 g.) was chromatographed on silica gel plates and eluted with the system chloroform: ethanol (10:1) to give two major products. The lower running band afforded 0.75 g. (20%) of **7**, isolated as a pure white glass; uv (ethanol): λ max 220 (sh) (ε, 5,300), 236 (ε, 6,800) and 290 nm (ε, 16,200); ^{1}H nmr (DMSO-d_6): δ 4.77 (s, 1H, H-4), 5.70 (d, 1H, J = 9 Hz, H-1′).

Anal. Calcd. for $C_{17}H_{24}N_4O_{11}S$: C, 41.46; H, 4.91; S, 6.50. Found: C, 41.30; H, 5.09; S, 6.45.

The faster running band gave 1.2 g. (32%) of **8** as a pure white glass; uv (ethanol): λ max 220 (ε, 5,300), 245 (ε, 10,700) and 321 nm (ε, 13,500); ^{1}H nmr (DMSO-d_6): δ 5.74 (d, 1H, J = 9.5 Hz, H-1′), 6.34 (s, 1H, H-4).

Anal. Calcd. for $C_{17}H_{24}N_4O_{11}S$: C, 41.46; H, 4.91; S, 6.50. Found: C, 41.80; H, 4.93; S, 6.79.

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4*H*-3,5-diamino-1,2,6-thiadiazine 1,1-Dioxide (**10**) and 2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-3,5-diamino-1,2,6-thiadiazine 1,1-Dioxide (**11**).

To a solution of 3.8 g. (0.0075 mole) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 100 ml. of dry acetonitrile, a solution of 2.5 g. (0.008 mole) of **6** in 100 ml. of acetonitrile and 1 ml. of stannic chloride in 10 ml. of acetonitrile were added. The mixture was stirred for 4 hours at room temperature. After work up as described for the preparation of **7** and **8**, 3.6 g. of a syrup were obtained, which was chromatographed on silica gel plates and eluted with the same system mentioned above. Two major products were isolated and purified chromatographically with the same solvent system. The lower running band gave 1.25 g. (27%) of **10** as a pure glass; uv (ethanol): λ max 242 (ε, 22,400), 276 (ε, 5,600) and 283 nm (ε, 5,600); ^{1}H nmr (DMSO-d_6): δ 3.49 (d, 1H, J = 8 Hz, H-4), 4.81 (d.d., 1H, J = 8 Hz and J = 6 Hz, H-1′).

Anal. Calcd. for $C_{29}H_{26}N_4O_9S$: C, 57.42; H, 4.32; N, 9.23. Found: C, 57.18; H, 4.53; N, 9.23.

The faster running band afforded 0.8 g. (17%) of **11** as a white glass; uv (ethanol): λ max 238 (ε, 22,400) and 286 nm (ε, 14,400); ^{1}H nmr (DMSO-d_6): δ 4.87 (s, 1H, H-4), 6.10 (d, 1H, J = 2 Hz, H-1′).

Anal. Calcd. for $C_{29}H_{26}N_4O_9S \cdot H_2O$: C, 55.76; H, 4.48; N, 8.97. Found: C, 55.84; H, 4.49; N, 8.89.

REFERENCES AND NOTES

(1) P. Goya and M. Stud, *J. Heterocyclic Chem.*, **15**, 253 (1978).

(2) P. Fernández Resa, P. Goya and M. Stud, *Nucleic Acids Research*, Special Publication No. 4, 61 (1978).

(3) R. B. Meyer and E. B. Skibo, *J. Med. Chem.*, **22**, 944 (1979).

(4) V. M. Cherkasov and T. A. Dashevskaya, *Ukr. Khim. Zh.*, **36**, 77 (1970); *Chem. Abstr.*, **72**, 132684x (1970).

(5) K. A. Watanabe and J. J. Fox, *J. Heterocyclic Chem.*, **6**, 109 (1969).

(6) T. Sato, T. Shimidate and Y. Ishido, *Nippon Kagaku Zasshi*, **81**, 1440 (1961).

(7) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3654 (1974).

(8) G. García-Muñoz, R. Madroñero, C. Ochoa, M. Stud and W. Pfleiderer, *J. Heterocyclic Chem.*, **13**, 793 (1976).

(9) L. B. Townsend, "Synthetic Procedures in Nucleic Acid Chemistry", Vol. II, W. W. Zorbach and R. S. Tipson, Eds., Wiley Interscience, New York, N. Y., 1973, p. 267.

(10) K. A. Watanabe, A. H. Hollenberg and J. J. Fox, *J. Carbohydr., Nucleosides Nucleotides*, **1**, 1 (1974).

(11) S. Hanessian and A. G. Pernet, "Advances in Carbohydrate Chemistry and Biochemistry", Vol. 33, R. S. Tipson and D. Horton, Eds., Academic Press, New York, N. Y., 1976, p. 111.

(12) Tse-Lok Ho, *Chem. Rev.*, **75**, 1 (1975).