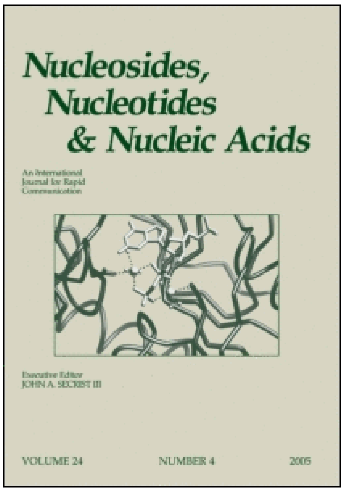

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A. de la Cruz[a]; P. Goya[a]; A. Martínez[a]; J. A. Páez[a]
[a] Instituto de Química Médica (C.S.I.C.) Juan de la Cierva, Madrid, Spain

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GLYCOSIDES OF PYRIDO[2,3-c]-1,2,6-THIADIAZINE 2,2-DIOXIDES

A. de la Cruz, P. Goya*, A. Martínez, and J.A. Páez

Instituto de Química Médica (C.S.I.C.)
Juan de la Cierva, 3. 28006 Madrid, Spain

Abstract: The synthesis and characterization of ribofuranosides and glucopyranosides of pyrido[2,3-c]-1,2,6-thiadiazine 2,2-dioxides are described. Conformational aspects related to the latter are discussed according to 2D-homonuclear ^1H nmr data and dynamic ^1H nmr spectral studies.

INTRODUCTION

Glycosides derived from fused systems of 1,2,6-thiadiazine 1,1-dioxide have been the subject of previous papers.[1] We now wish to report our results on the glycosylation of pyrido[2,3-c]-1,2,6-thiadiazine 2,2-dioxides which can be regarded as SO_2 analogs of pyrido[2,3-d]pyrimidines. Despite the extensive literature dealing with the latter, there are few reported examples of nucleosides of this system.[2,3] Most of them were prepared in connection with the antibiotic sangivamicin[4] and the simple homologue of this nucleoside did show antileukemic activity.[5] It was therefore of interest to study the glycosylation of pyrido[2,3-c]-1,2,6-thiadiazines and to evaluate the compounds as cytostatic agents.

RESULTS AND DISCUSSION

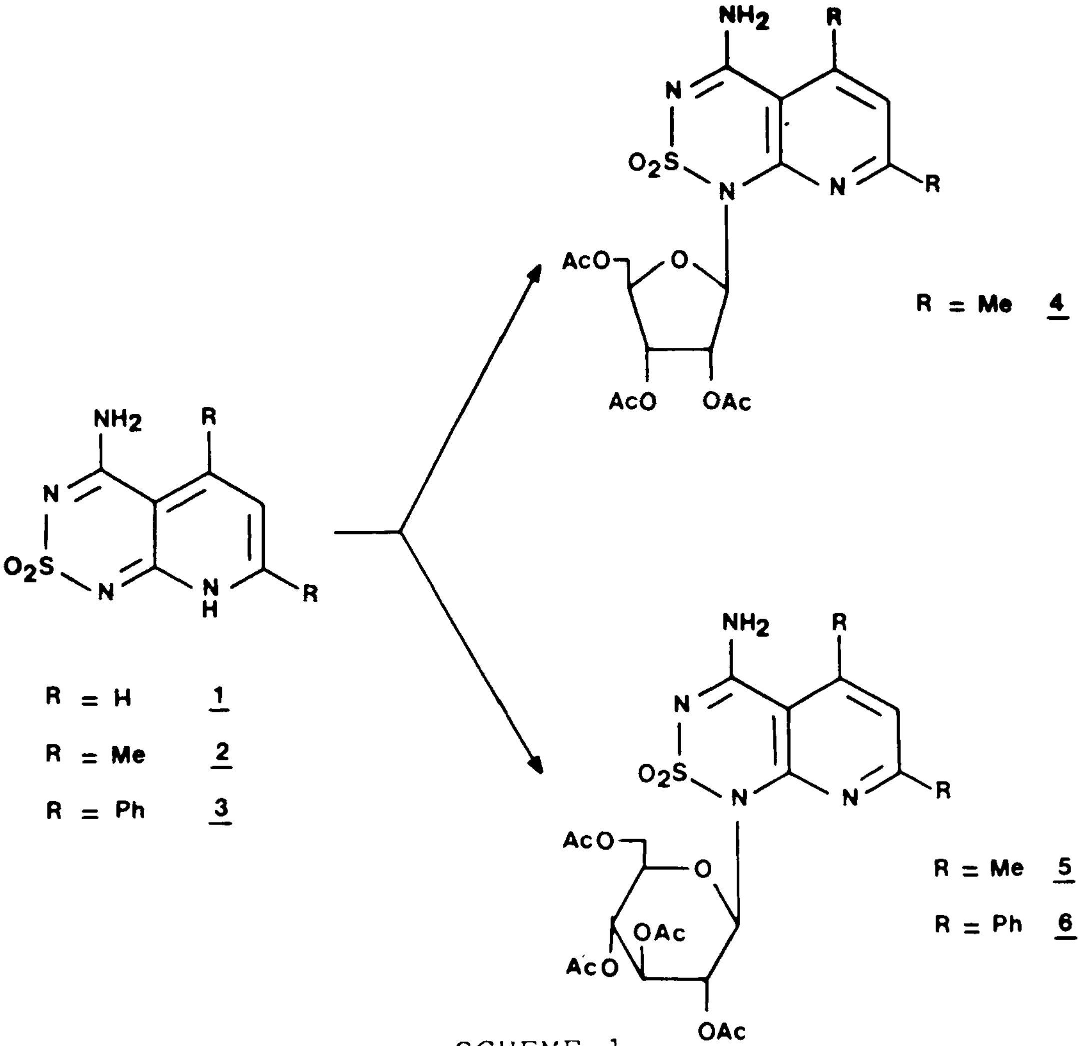
The pyrido[2,3-c]-1,2,6-thiadiazines used were prepared from the corresponding diaminothiadiazine and 1,3-dicarbonyl compounds.[6] The low solubility and high melting points of these heterocycles required the use of the "silyl procedure"[7] for their glycosylation. However, silylation was only possible when the system was 5,7-disubstituted and all attempts to silylate the parent compound **1** failed.

When the silyl derivative of **2** was treated with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in dichloromethane, in the presence of BF_3-Et_2O as catalyst the monoriboside **4** was obtained (Scheme I). A small amount of a diriboside could be isolated but not in sufficient amount to be definitely characterized. Under the same conditions, the silyl derivative of **3** afforded a complex mixture from which it was not possible to isolate a nucleosidic compound.

Treatment of the silyl derivatives of **2** and **3** with 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose under similar conditions afforded the corresponding N-1 glucosides **5** and **6** (Scheme I).

The structures of the glycosides were established according to their UV and NMR data. The fact that glycosylation had taken place at the thiadiazine ring and not at the pyridine moiety was confirmed by comparing the UV data with those of suitable N-alkyl models previously prepared[6] (N-1 substitution in this system is associated with a wavelength absorption at 320 nm whereas N-8 substitution effects a bathochromic shift to about 360 nm) (Table 1).

The ^1H nmr data of the glycosides are gathered in Table 2. The anomeric configuration of glucosides **5-7** was established as β on the basis of the coupling constant ($J_{1',2'}$=9 Hz) consistent with a trans-diaxial disposition. In the case of riboside **4**, it was not possible with the value of the coupling constant ($J_{1',2'}$=2.5 Hz) to fix the anomeric configuration which was tentatively assigned as β on the basis of the synthetic procedure used.



SCHEME 1

In the ^1H nmr spectra of glucosides **5** and **6** one of the protons of the glucopyranose rest appeared more deshielded than the corresponding anomeric one. The 2D-homonuclear shift correlated COSY experiment[8] (Figure 1) carried out on compound **6** indicated that this proton was 2'-H. This downfield shift can be explained assuming that these compounds exist in the syn conformation as related pyrazino[2,3-c]-1,2,6-thiadiazine glucosides[9]. In this

TABLE 1. UV spectroscopic data

Compound	λ_{max} (nm)				Log ε			
1^a		259	292	365		4.11	3.25	3.77
2^a	213	261	[292]	358	4.25	4.02	[3.13]	3.89
3^a		267	[296]	396		4.50	[4.17]	4.22
A^b	215	260		358	4.22	3.95		3.90
B^b	237	244		318	4.31	3.98		3.76
4^c	222	248		305	4.19	3.97		3.68
5^c	221	245		305	4.05	3.75		3.47
6^c		225	[284]	335		4.35	[4.14]	4.17
7^c		255	[285]	335		4.27	[4.05]	4.03

---

a) H_2O, neutral form b) H_2O c) MeOH.

A = 4-amino-5,7,8-trimethylpyrido[2,3-*c*]-1,2,6-thiadiazine 2,2-dioxide.

B = 4-amino-1,5,7-trimethylpyrido[2,3-*c*]-1,2,6-thiadiazine 2,2-dioxide.

rotamer the anisotropic effect of the SO_2 group is exerted on the 2'-H and not on the 1'-H as would be the case in the *anti* conformation.

Treatment of 6 with saturated methanolic ammonia afforded the deprotected nucleoside 7, which existed, at room temperature, as a mixture of *syn*:*anti* rotamers.

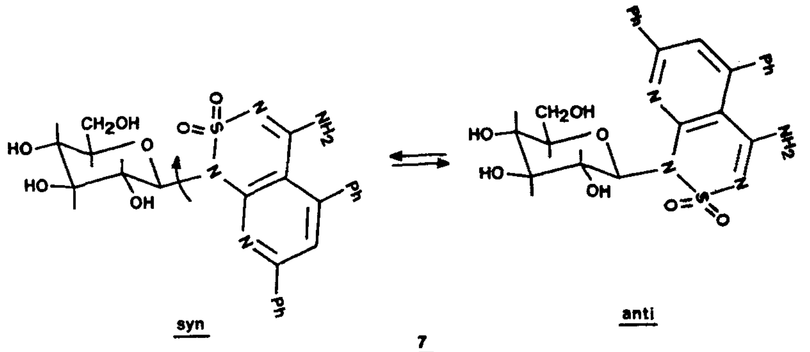


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TABLE 2. ^{1}H NMR parameters: chemical shifts (ppm)

Compound		1'-H	2'-H	3'-H	4'-H	5'-H	6a'-H	6b'-H	6-H	5-R	7-R	NH
4^a		6.33 (d)	5.96 (q)	5.90 (t)	---	4.47-4.08 (m)	---		6.86 (s)	2.64 (s)	2.57 (s)	
5^a		5.64 (d)	6.50 (d)	5.20 (t)	5.31 (t)	3.89 (m)	4.25 (dd)	4.13 (dd)	6.85 (s)	2.61 (s)	2.59 (s)	6.65 (bs) 6.10 (bs)
6^a		5.77 (d)	6.63 (t)	5.40 (t)	5.49 (t)	3.94 (m)	4.35 (dd)	4.14 (dd)	7.51 (s)	8.23-7.52 (m)		5.83 (bs) 4.95 (bs)
7^b	syn	5.20 (d)	4.52 (t)		-------	3.75-3.16 (m)	-------		7.52 (s)	8.23-7.52 (m)		
	anti	6.21 (d)	4.20 (t)									

TABLE 2 (Cont.). ^{1}H NMR parameters: coupling constants (Hz)

Compound		$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6a'}$	$J_{5',6b'}$	$J_{6a',6b'}$
4^a		2.5	6.4	7.8	-	-	-	-
5^a		9.0	9.3	9.3	9.5	4.5	1.5	-12.0
6^a		9.1	9.1	9.5	9.5	3.5	1.3	-12.5
7^b	syn	9.3	8.8	-	-	-	-	-
	anti	9.5	8.9	-	-	-	-	-

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[a] Solvent: $CDCl_3$. [b] Solvent: DMSO-d_6 + D_2O.

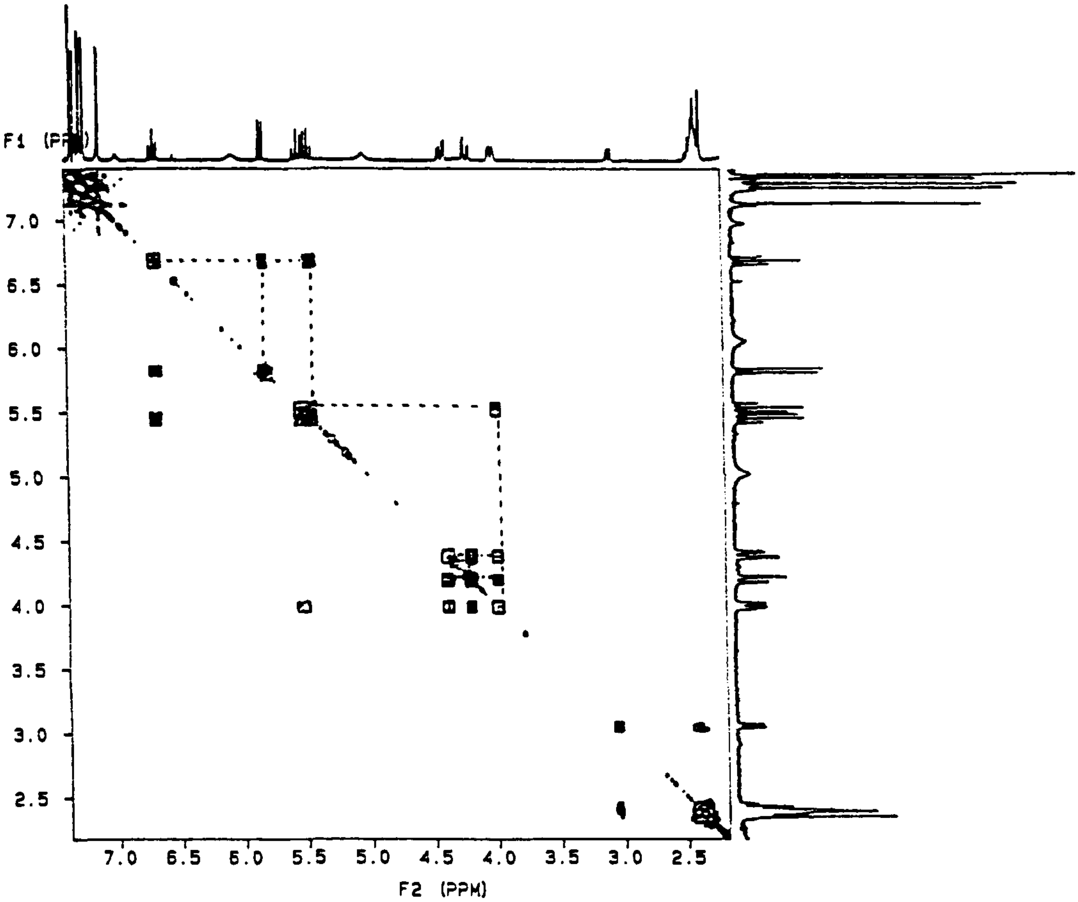

FIGURE 1. 2D homonuclear shift correlated contour plot of 6.

This was shown in the ^1H nmr spectrum in which both the 1'-H and 2'-H signals appeared double (Figure 2). By raising the temperature, both signals reached coalescence and thus, it was possible to estimate the barrier to rotation around the C-N bond. The value of $\Delta G^{\neq}=16.5$ kcal.mol^{-1}, obtained by use of the Eyring equation[10], is slightly higher than the one observed in related pyrazino[2,3-c]thiadiazine glucosides, in which this phenomenon also occurred.[9]

Finally, all the newly synthesized glycosides were tested for cytostatic activity against HeLa cell cultures[11], but none of the compounds showed significant activity.

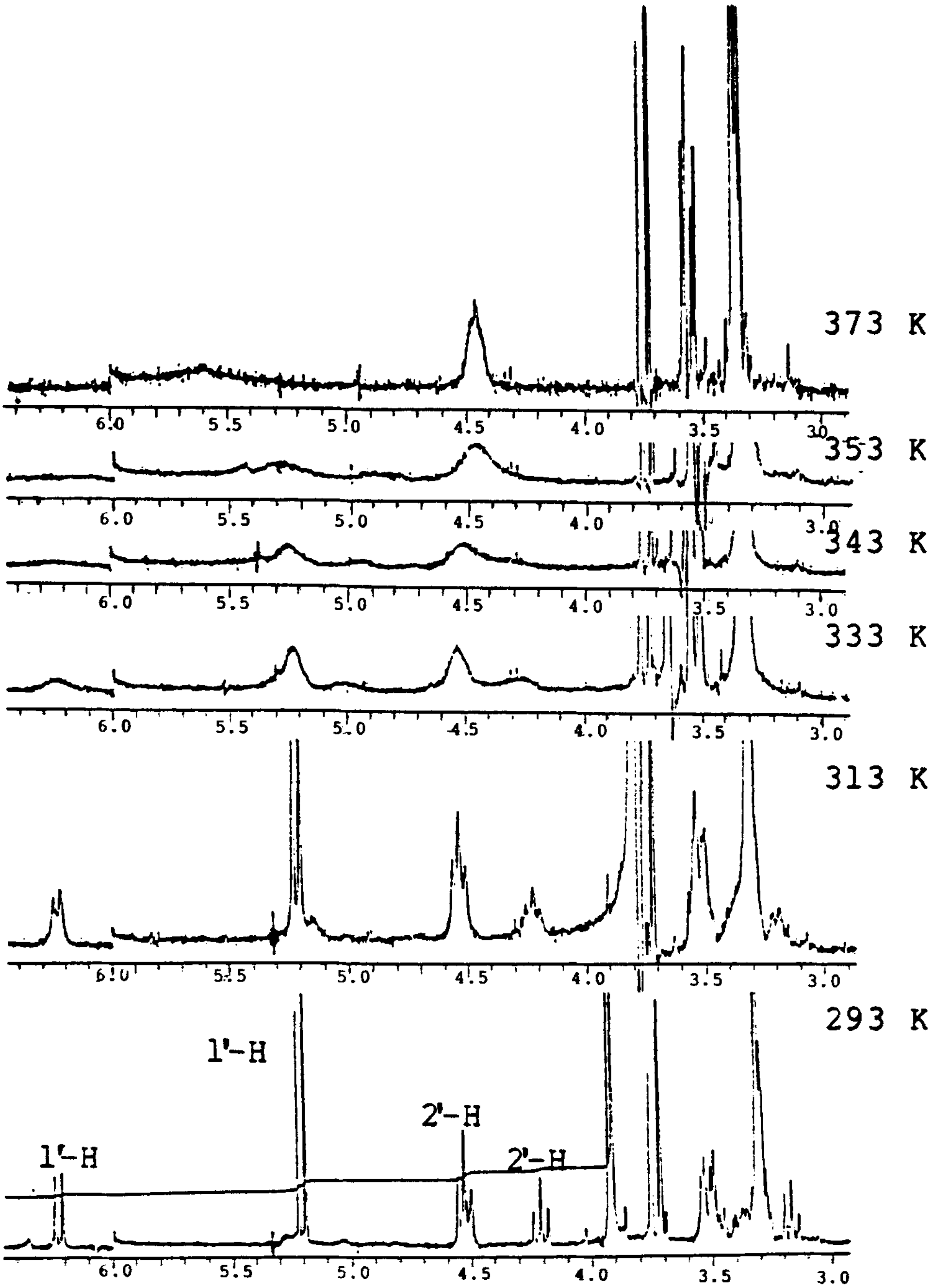

FIGURE 2. 300 MHz ^{1}H nmr spectra of 7 registered at increasing temperatures.

EXPERIMENTAL

Ultraviolet spectra were measured on a Perkin Elmer 550-SE spectrophotometer. Column chromatography was performed on Merck silica gel 60 (70-230 mesh), and preparative thin layer chromatography was performed on 20x20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck). Compounds were detected with UV light (254 nm) or by spraying the plate with ethanol:sulphuric acid (3:1) and heating.

^1H nmr spectra were recorded on a Varian XL-300 instrument operating at 300 MHz, using TMS as internal standard. Typical acquisition parameters were: spectral width 3 kHz; data memory, 32 k, acquisition time, 5 s and pulse width 8 μs (53°). Two-dimensional scalar shift-correlated ^1H nmr spectra were recorded using the $90°-t_1-90°$ pulse sequence referred to as COSY.[8] The following parameters were used: number of increments, 256; relaxation delay, 1 s; sweep width, 1564 Hz in t_1 and 1564 Hz in t_2, acquisition time, 0,3 s; and pulse width 58°.

General procedure for the glycosylations

To a dichloromethane solution of the 4-N-trimethylsilyl derivatives of the pyrido[2,3-c]-1,2,6-thiadiazine 2,2-dioxides **2** and **3**, [prepared by refluxing the base in hexamethyldisilazane (15 ml), pyridine (10 ml) and ammonium sulphate (catalytic ammounts) under nitrogen atmosphere], the corresponding fully acetylated sugar, dissolved in 25 ml of dichloromethane, was added. The mixture was cooled, and 3 ml of boron trifluoride etherate were added with vigorous stirring and exclusion of moisture. The resulting mixture was stirred for 4 h at room temperature and was then shaken with saturated sodium hydrogen carbonate solution (100 ml). The organic phase was separated, dried with sodium sulphate and evaporated under reduced pressure. The residue was first chromatographed on a silica gel column and then by TLC eluting with mixtures of chloroform/methanol in the proportions indicated for each particular case.

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

Following the general procedure, 0.50 g (2.20 mmol) of **2** and 0.64 g (2.20 mmol) of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose were used. After work-up, the sirupy residue was purified by silica gel column chromatography using chloroform/methanol (15:1) as eluent and then by TLC eluting with chloroform/methanol (30:1) to give 0.35 g (36%) of **4** as a colourless glass.

Anal. Calcd. for $C_{19}H_{24}N_4O_9S$: C, 47.10; H, 4.95; N 11.57; S, 6.61.

Found: C, 46.75; H, 5.22; N, 11.09; S, 6.51.

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-amino-5,7-dimethylpyrido[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (**5**)

Following the general procedure, 0.50 g (2.20 mmol) of **2** and 0.86 g (2.20 mmol) of 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose were used. After work-up, the residue was purified by column chromatography using chloroform/methanol (25:1) as eluent and by TLC using chloroform/methanol (50:1) to give 0.05 g (4%) of **5** as a colourless glass.

Anal. Calcd. for $C_{22}H_{28}O_{11}N_4S$: C, 47.48; H, 5.05; N, 10.07; S, 5.71.

Found: C, 47.67; H, 5.10; N, 9.94; S, 5.64.

1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-amino-5,7-diphenylpyrido[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (**6**)

According to the general procedure, 0.5 g (1.5 mmol) of **3** and 0.56 g (1.5 mmol) of 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose were used. After work-up, the oily residue was purified by column chromatography eluting with chloroform/methanol (50:1) and then by TLC using chloroform/methanol (100:1) to give 0.64 g (66%) of a yellowish glass.

Anal. Calcd. for $C_{32}H_{32}O_{11}N_4S$: C, 56.46; H, 4.74; N, 8.23; S, 4.71.

Found: C, 56.56; H, 4.34; N, 8.22; S, 4.86.

1-(β-D-glucopyranosyl)-4-amino-5,7-diphenylpyrido[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (7)

A solution of 0.1 g (0.2 mmol) of **6** in 15 ml of saturated methanolic ammonia was stirred at room temperature for 2 h. The solution was evaporated to dryness to yield 0.06 g (80%) of **7** as a pale yellow glass.

Anal. Calcd. for $C_{24}H_{24}O_7N_4S$: C, 56.25; H, 4.68; N, 10.93; S, 6.25.

Found: C, 56.32; H, 5.03; N, 10.74; S, 5.98.

REFERENCES

1. a) P. Goya, A. Martínez, M.L. Jimeno, W. Pfleiderer, Liebigs Ann. Chem. (1986), 1872.

   b) P. Goya, A. Martínez, C. Ochoa, M.L. Jimeno, Nucleosides and Nucleotides, **6** (1987), 631.
2. B. Rizkalla, A. Broom, M. Stout, R. Robins, J. Org. Chem., **37** (1972), 3975.
3. D. Bergstrom, H. Inoue, P. Anantha, J. Org. Chem., **47** (1982), 2174.
4. B. Rizkalla, A. Broom, J. Org. Chem., **37** (1972), 3980.
5. G. Anderson, A. Broom, J. Org. Chem., **42** (1977), 997.
6. P. Goya, C. Ochoa, J.A. Páez, Chem. Scrip., **26** (1986),607.
7. H. Vorbrüggen, U. Niedballa, J. Org. Chem., **39** (1974), 3654. Ibid, **39** (1974), 3660. Ibid, **39** (1974), 3668.
8. A. Bax, R. Freeman, G. Morris, J. Magn. Reson., **42** (1981), 169.
9. P. Goya, A. Martínez, M.L. Jimeno, W. Pfleiderer, Liebigs Ann. Chem., (1987), 961.
10. J.W. Emsley, J. Feeny, L.H. Sutcliffle, High Resolution Nuclear Magnetic Resonance Spectroscopy, Chap. 9, Pergamon Press, Oxford 1965.

11. T.I. Geran, N.H. Greenberg, M.M. McDonald, A.M. Schumacher, B.J. Abbot, *Cancer Chemother. Rep.*, Part 3, **3** (1959), 432.

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