Synthesis of Purine-Like Ring Systems Derived From 1,2,6-Thiadiazine 1,1-Dioxide

C. García-Muñoz†, *R. Madroñero, C. Ochoa, and M. Stud*

Instituto de Química Médica, Juan de la Cierva 3, Madrid-6 Spain

and

W. Pfleiderer

Universität Konstanz, Fachbereich Chemie, D-775 Konstanz, Germany

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7-Amino-1*H*,4*H*-imidazo[2,3-*c*][1,2,6]thiadiazine 5,5-dioxide was prepared by a multi-step reaction sequence form 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide. 7-Amino-4*H*-furazano-[3,4-*c*][1,2,6]thiadiazine 5,5-dioxide was obtained by lead tetraacetate oxidation of 3,5-diamino-4-hydroxyimino-4*H*-1,2,6-thiadiazine 1,1-dioxide.

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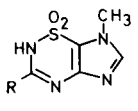
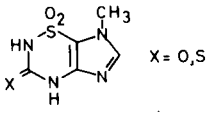
During the past years considerable attention has been directed toward the preparation of purine and pyrimidine analogs as antimetabolites in the biosynthesis of nucleic acids. Our continuous interest (1) in the synthesis of 1,2,6-thiadiazin-3-one 1,1-dioxide derivatives (*S*-dioxo analogs of uraciles) led us to investigate the preparation of purine-like heterocycles derived from 1,2,6-thiadiazine *S*-dioxide.

The only reported examples (2) of imidazothiadiazine derivatives were those represented by the structures I and II, prepared by condensing 1-methyl-4-amino-5-sulfamylimidazole with ortho esters, phosgene and thiophosgene respectively.



I



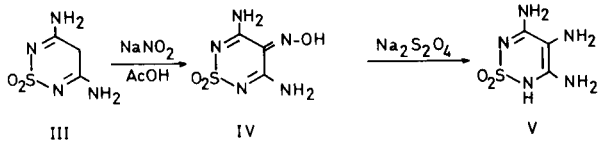
II

The present communication describes the synthesis of an *S*-dioxo analog of isoguanine, namely 7-amino-1*H*,4*H*-imidazo[2,3-*c*][1,2,6]thiadiazine 5,5-dioxide (VII). Also described is the preparation of the 7-amino-4*H*-furazano-[3,4-*c*][1,2,6]thiadiazine 5,5-dioxide (VIII) a compound which should be of potential interest in the synthesis of 2- and 3-substituted derivatives of VII, following the elegant procedure developed by Taylor (3) for the preparation of substituted adenines.

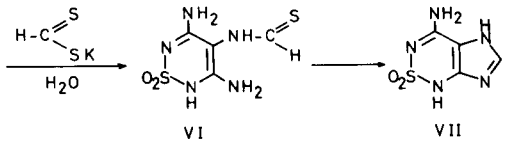
†Professor García-Muñoz died days before this manuscript was sent. His colaborators dedicate this paper to his memory.

Preparation of 7-Amino-1*H*,4*H*-imidazo[2,3-*c*][1,2,6]-thiadiazine 5,5-Dioxide.

The synthetic approach for the preparation of this compound is outlined in Scheme 1. The key intermediate needed, 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (III) had been previously synthesized by Cherkasov and Dashevskaya (4) from sulfamide and malonic acid diamidine. In a patent (5) Walter claimed that the reaction of sulfamide and malononitrile in ethanol solution at room temperature for about 1 hour led also in quantitative yield to III. Although several attempts were made to follow this easy procedure, our efforts were unsuccessful.



III IV V



VI VII

We have found that III was smoothly converted to the oxime IV, isomeric with a nitroso derivative, upon treatment with sodium nitrite in acetic acid solution. The

absence of signals for the protons at position 4 in IV which are found in the ^{1}H nmr spectrum of III, indicated that attack in this position had occurred. The ir spectrum of IV showed a broad hydroxyl absorption band at 3275 cm^{-1}. The ^{13}C nmr spectrum of this oxime derivative IV exhibited two peaks at δ 156.2 and 150.5 for the non-equivalent C-3 and C-5 atoms and one peak at δ 127.9 for the C-4 atom.

Reduction of IV with sodium dithionite resulted in smooth conversion to the triamino derivative V in high yield. Treatment of this latter compound with potassium dithioformate in water readily afforded a thioformamido derivative in 54% yield to which structure VI was assigned on the basis of similar reactions using 4,5,6-triaminopyrimidines (6). Further, an INDOR experiment on VI showed that the NH proton of the thioformamido group was only coupled to the thioformyl proton. Finally, ring closure to the desired VII was accomplished in 47% yield by heating VI in refluxing water.

A better yield (66%) of VII was obtained by treatment of V with potassium dithioformate followed by heating, without isolation of the intermediate VI.

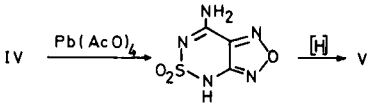
The structure of VII was evident from the method of synthesis (Traube synthesis) (6) and the analytical, nmr and mass spectrometry data. The ^{1}H nmr spectrum of VII was consistent with the proposed structure assignment and exhibited a singlet at δ 7.86 attributed to the imidazole ring proton, and a very broad multiplet at δ 7.7 attributed to the NH protons.

Preparation of 7-Amino-4*H*-furazano[3,4-*c*][1,2,6]thiadiazine 5,5-Dioxide.

The possibility of utilization of IV as the starting material for the synthesis of VIII was studied following the procedure developed by Taylor (3) for the preparation of 7-aminofurazano[3,4-*d*]pyrimidines which involves oxidation of 5-nitroso-4,6-diaminopyrimidines with lead tetraacetate. It has been suggested that in this reaction the nitrosoaminopyrimidines react in the imino-oxime tautomeric form (7).

In our case oxidation of IV with lead tetraacetate in acetic acid solution at room temperature resulted in the obtention of the desired furazane[3,4-*c*][1,2,6]thiadiazine derivative VIII. The structure of this compound was confirmed by X-ray crystallographic analysis (8).

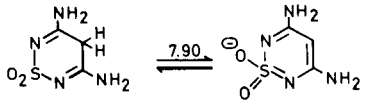
Catalytic hydrogenation of VIII resulted in opening of the furazane ring to give V identical with the compound obtained from the reduction of IV.



VIII

We also determined the p*K*a-values of compounds III, VII and VIII for further characterization in the normal *p*H-range by the spectrophotometrical method (10) (Table I).

Compound III turned out to be a relatively weak acid with an acidic p*K*a of 7.90 due to ionization at position 4. The uv spectrum of the neutral form is consistent with the tautomeric structure III showing end absorption, whereas the monoanion III absorbs at higher wave lengths as expected from the regained cyclic resonance.



III IIIa

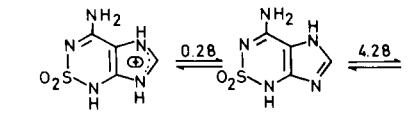
The 7-amino-1*H*,4*H*-imidazo[2,3-*c*][1,2,6]thiadiazine 5,5-dioxide (VII) showed 3 p*K*a at 0.28, 4.28 and 12.21. The lowest value must be regarded as the first basic p*K*a

Table I

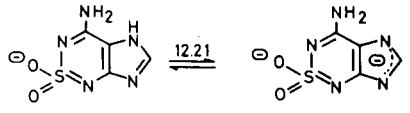
Physical Data of 1,2,6-Thiadiazine Dioxide Derivatives

Compound	p*K*a in water at 20°	Uv Absorption Spectra λ max (nm)	lg ε	*p*H	Molecular form
III	7.90 ± 0.07	204 [225]	4.34 [3.95]	5.0	o
		[225] 282	[3.83] 4.21	11.0	-
VII	0.28 ± 0.05	223 [245] 279 [305]	3.95 [3.71] 3.72 [3.58]	-2.0	+
	4.28 ± 0.1	231 300	3.96 3.80	2.0	o
	12.21 ± 0.1	207 [216] 300	4.13 [4.09] 3.89	7.0	-
		246 309	3.77 3.89	14.0	-
VIII	1.68 ± 0.1	265	3.72	-2.0	o
	12.96 ± 0.1	265 335	3.58 3.32	4.0	-
		285 335	3.48 3.42	14.0	-

due to protonation of the neutral form at position N-3 forming a monocation (VIIa) as seen from the hypsochromic shift of the longwave absorption band of the neutral form which itself is present only in a very small *p*H range at about *p*H 2. The first acidic p*K*a of 4.28 illustrates a profound acidic character of compound VII which forms a monoanion (VIIb) by ionization of the N-4 proton. The negative charge of VIIb influences further ionization to a large extent and dianion formation (VIIc) takes place only in strongly basic medium.

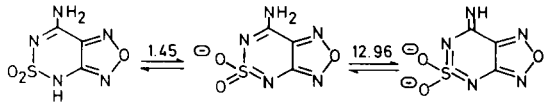


VIIa VII



VIIb VIIc

The 7-amino-4*H*-furazano[3,4-c][1,2,6]thiadiazine 5,5-dioxide (VIII) possesses the strongest acidic properties of the three investigated compounds since its acidic p*K*a is as low as 1.45. This unusual acidity may be explained by the quinoid-type annelation of the oxadiazole ring functioning as a strong electron-attractor. Anion formation (VIIIa) counteracts the π-electron deficiency and keeps the molecule over a large *p*H-range in this stable form. At high *p*H a dianion (VIIIb) could be detected from a further small change of the uv spectrum.



VIII VIIIa VIIIb

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 257 spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12 and a Varian XL-100 spectrometers with TMS as internal standard. Carbon nuclear magnetic resonance spectra were recorded on a Bruker HXE-90 spectrometer. Ultraviolet spectra were recorded on a Perkin-Elmer 350 and 402 spectrophotometer. Mass spectra were run on a Varian MAT spectrometer.

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

The published procedure was followed (4), m.p. 280° dec., lit. (4), m.p. 282-284°; uv λ max (water): 209 (ε, 11,850), 226 (ε, 7,100), 283 nm (ε, 630); ^{1}H nmr (DMSO-d$_6$, δ): 3.15 (s, 2H, CH_2), 7.74 (m, 4H, NH_2); ^{13}C nmr (DMSO-d$_6$, δ): 26.3 (1C, CH_2), 163.8 (2C, CNH_2).

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

A stirred solution of 26.56 g. (0.164 mole) of II and 11.5 g. (0.164 mole) of sodium nitrite in 164 ml. of 1*N* sodium hydroxyde at ice bath temperature was treated dropwise with 20 g. of glacial acetic acid. The mixture was then stirred at room temperature for 3 hours and the obtained reddish-yellow solution was acidified with concentrated hydrochloric acid. The now yellow solution was chilled in a refrigerator and the resulting precipitate was collected by filtration and dried in vacuum over calcium chloride and sodium hydroxide. Recrystallization from water gave 24.4 g. (78% yield) of IV as yellow needles, m.p. 265°; uv λ max (ethanol): 247 (ε, 6,950), 292 nm (ε, 7,300); ^{13}C nmr (DMSO-d$_6$, δ): 127.9 (1C, C=NOH), 150.5 (1C, CNH_2), 156.2 (1C, CNH_2); ir (KBr): 3275 cm^{-1} (broad band, OH).

Anal. Calcd. for $C_3H_5N_5O_3S$: C, 18.85; H, 2.63; N, 36.64. Found: C, 18.82; H, 2.65; N, 36.86.

3,4,5-Triamino-1,2,6-thiadiazine 1,1-Dioxide (V).

To 22.4 g. of IV dissolved in 670 ml. of 1*N* sodium hydroxide was added portionwise 85 g. of sodium dithionite ($Na_2S_2O_4.2H_2O$). The solution was acidified with glacial acetic acid (*p*H 5) and the mixture was maintained at room temperature overnight. The solid was collected by filtration (17.5 g.) and recrystallized from water to give pure V, m.p. 198-200° dec.; uv λ max (water): 204 (ε, 8,500), 281 nm (ε, 3,550); ^{1}H nmr (DMSO-d$_6$, δ): 4.8, 5.9, 7 (broad signals, 7H, NH and NH_2).

Anal. Calcd. for $C_3H_7N_5O_2S$: C, 20.34; H, 3.98; N, 39.54. Found: C, 20.40; H, 3.92; N, 39.73.

3,5-Diamino-4-thioformamido-1,2,6-thiadiazine 1,1-Dioxide (VI).

To a stirred suspension of 4 g. of V in 500 ml. of water at 40° was added 6 g. of potassium ditioformate (9). After being stirred for 20 hours, the mixture was acidified with glacial acetic acid, filtered, and evaporated to dryness *in vacuo*. The residue was dissolved in water and the solution passed through an Amberlite IR-120 (H^+) column (50 ml.). Elution with water provided crude VI which was recrystallized from water to give 2.7 g. (54% yield) of pure VI, m.p. 153-154° dec.; uv λ max (water): 226 (sh) (ε, 7,610), 280 nm (ε, 12,770); ^{1}H nmr (DMSO-d$_6$, δ): 6.23 (5H, NH and NH_2), 9.20 (d, 1H, CSH, J = 5.2 Hz), 10.29 (d, 1H, N*H*CSH, J = 5.2 Hz).

Anal. Calcd. for $C_4H_7N_5O_2S_2$: C, 21.72; H, 3.19; N, 31.67. Found: C, 21.81; H, 3.29; N, 31.55.

7-Amino-1*H*,4*H*-imidazo[2,3-c][1,2,6]thiadiazine 5,5-Dioxide (VII).

A. From VI.

A suspension of 168 mg. of VI in 10 ml. of water was heated at reflux for 24 hours. The resulting solution was filtered through active charcoal and allowed to stand for crystallization. The precipitate was filtered to give 67.7 mg. (47% yield) of VII. Recrystallization from water afforded pure VII, m.p. 290° dec.; uv λ max (water): 206.5 (ε, 11,040), 217 (ε, 10,330), 301 nm (ε, 7,210); ^{1}H nmr (DMSO-d$_6$, δ): 7.7 (bm, 4H, NH and NH_2), 7.86 (s, 1H, CH imidazole ring); mass spectrum, m/e (%): 187 (58) M$^+$, 159 (2.5), 132 (5), 123 (58), 108 (16), 96 (85), 81 (14), 69 (44), 64 (19), 43 (100).

Anal. Calcd. for $C_4H_5N_5O_2S$: C, 25.67; H, 2.69; N, 37.42. Found: C, 25.39; H, 2.59; N, 37.42.

B. From V.

with 6 g. of potassium dithioformate and allowed to stand for 7 hours. The mixture was acidified with glacial acetic acid and filtered. The filtrate was evaporated *in vacuo* to 60 ml., heated at reflux for 7 hours and treated with active charcoal. The solution was filtered, cooled at room temperature and acidified with hydrochloric acid (*p*H 1). Cooling of the yellow solution in a refrigerator and filtration gave 2.3 g. (54% yield) of VII identical in all respects with VII prepared by method A.

7-Amino-4*H*-furazano[3,4-c][1,2,6]thiadiazine 5,5-Dioxide (VIII).

A suspension of 1 g. (0.005 mole) of IV and 2.35 g. (0.005 mole) of lead tetraacetate in 15 ml. of glacial acetic acid was stirred overnight at room temperature under nitrogen. The mixture was chilled in a refrigerator for 2 hours and the solid (lead salt of VIII) was filtered and washed with acetic acid and ethanol. The solid was suspended in water and a stream of hydrogen sulfide was passed through the suspension. The mixture was filtered, the yellow filtrate was evaporated to dryness under reduced pressure and the residue (0.9 g.) was recrystallized from water to give VIII as yellow needles, m.p. 216° dec.; uv λ max (water): 204 (ε, 9,300), 262 (ε, 3,750), 337 nm (ε, 2,000); ^{1}H nmr (DMSO-d_6, δ): 9.25 (m, 2H, NH protons), 9.47 (m, 1H, NH proton).

Anal. Calcd. for $C_3H_3N_5O_3S$: C, 19.04; H, 1.58; N, 37.03. Found: C, 18.80; H, 1.68; N, 36.83.

3,4,5-Triamino-1,2,6-thiadiazine 1,1-Dioxide (V) by Hydrogenation of 7-Amino-4*H*-furazano[3,4-c][1,2,6]thiadiazine 5,5-Dioxide (VIII).

A solution of 0.95 g. of VIII in 100 ml. of water was hydrogenated with 50 psi of hydrogen in the presence of palladium/carbon 10% catalyst at room temperature. After 30 minutes, the reaction mixture was heated, filtered, concentrated, and chilled in a refirgerator to give 0.6 g. of V, m.p. 198-200° dec., identical in all respects with the material prepared above by reduction of IV.

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