

Synthesis of 7-Amino-2*H*,4*H*-*vic*-triazolo[4,5-*c*]-  
[1,2,6]thiadiazine 5,5-Dioxides

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7-Amino-2*H*,4*H*-*vic*-triazolo[4,5-*c*][1,2,6]thiadiazine 5,5-dioxide was prepared by two different ways from 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide and 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide respectively. 7-Amino-2-phenyl-4*H*-*vic*-triazolo[4,5-*c*][1,2,6]thiadiazine 5,5-dioxide was obtained by lead tetraacetate oxidation of 3,5-diamino-4-phenylazo-1,2,6-thiadiazine 1,1-dioxide.

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Our continuous interest in the synthesis of 1,2,6-thiadiazine-3-one 1,1-dioxide derivatives has led us to investigate the synthesis of some pyrimidine (1) and purine analogs I and II (2) as possible antimetabolites in the biosynthesis of nucleic acids.

Along these lines, we now wish to report the synthesis of new purine like heterocycles derived from 1,2,6-thiadiazine 5,5-dioxide, namely 7-amino-2*H*,4*H*-*vic*-triazolo[4,5-*c*][1,2,6]thiadiazine 5,5-dioxide (VI) and its 2-phenyl derivative (VIII).

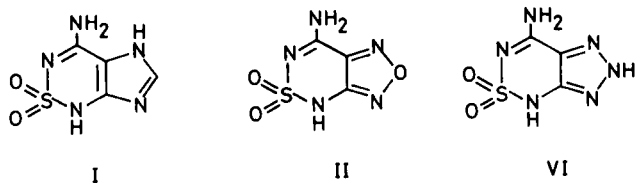
Preparation of 7-Amino-2*H*,4*H*-*vic*-triazolo[4,5-*c*][1,2,6]thiadiazine 5,5-Dioxide.

The preparation of compound VI was carried out in two different ways. The first method was started from 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide (III), whereas the second procedure was based on 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (V) as the starting material (3).

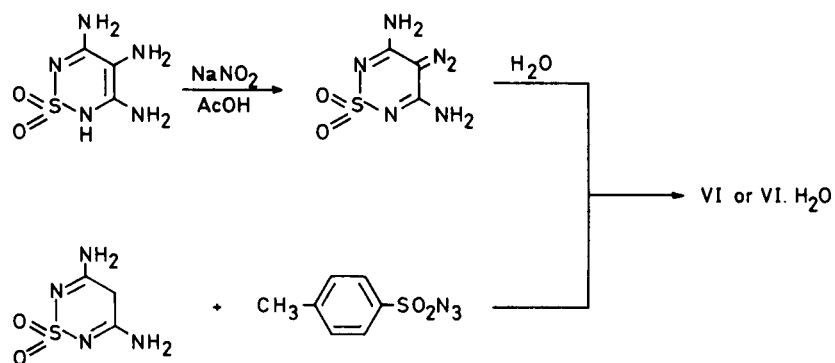
The two synthetic approaches are outlined in Scheme 1.

The diazotisation of III has to be carried out by slow addition of acetic acid to an alkaline solution of III and sodium nitrite in order to avoid the joint precipitation of III and IV.

The solid diazo compound (IV) could not be recrystallized from water, methanol, ethanol or sodium hydroxide solution since these treatments afforded cyclization to compound VI. Nevertheless a correct analysis was ob-



Scheme 1



tained for IV by washing the precipitate thoroughly with water and drying. The ir spectrum of IV showed a diazo absorption band at  $2,130\text{ cm}^{-1}$ .

On standing of a suspension of IV in water at room temperature for several days, a gradual formation of yellow needles was observed. This compound was assigned to have structure VI since its ir spectrum did not show the diazo band and its analysis fitted with the cyclized structure. The  $^1\text{H}$  nmr spectrum exhibited two broad multiplets overlapped at  $\delta$  8.45 and 8.60 for the groups NH and  $\text{NH}_2$ . This assignment was confirmed by X-ray crystallographic analysis (4). The hydrogen atom of the triazolo ring was found to be attached to N-2.

On cooling of a boiling aqueous solution of IV, separation of either the anhydrous compound VI, as yellow needles, or the monohydrated compound  $\text{VI}\cdot\text{H}_2\text{O}$ , as yellow plates, did occur.

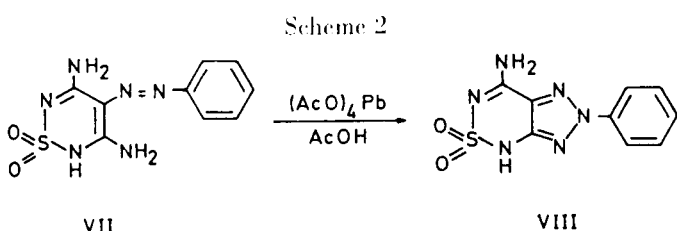
A correct analysis for the monohydrate could not be obtained due to the fact that its water of crystallization simply was lost on drying over calcium chloride. The  $^1\text{H}$  nmr spectrum of  $\text{VI}\cdot\text{H}_2\text{O}$  showed only one broad multiplet at  $\delta$  8.50 corresponding to all the molecule protons. The ir spectrum exhibited two absorption bands at  $3,600$  and  $3,520\text{ cm}^{-1}$  which disappeared when the compound was dehydrated.

The crystal structure of  $\text{VI}\cdot\text{H}_2\text{O}$  has been determined by single crystal X-ray diffraction techniques. This study confirmed that  $\text{VI}\cdot\text{H}_2\text{O}$  was the monohydrate of VI and that the packing in the crystal was determined by hydrogen bonds in which all available groups participated (5).

Treatment of IV with tosylazide afforded directly either of the cyclized compounds VI or  $\text{VI}\cdot\text{H}_2\text{O}$ : which were identical in all respects to those compounds obtained by the first synthetic method.

Preparation of 7-Amino-2-phenyl-4H-vic-triazolo[4,5-c]-[1,2,6]thiadiazine 5,5-Dioxide.

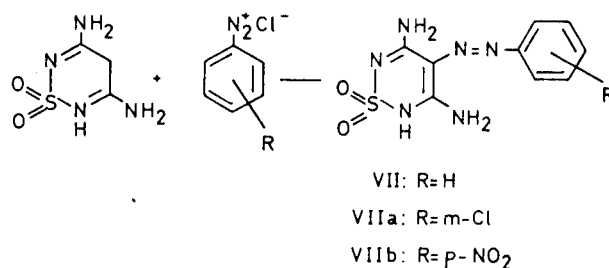
Compound VIII was obtained as shown in Scheme 2, following the procedure developed by Taylor (6) for the synthesis of 2-phenyl-vic-triazolo[4,5-d]pyrimidines.



The reaction of phenyldiazonium chloride with V in alkaline medium, led to a compound (m.p.  $310^\circ$ ) (3), which has to be considered as the sodium salt of VII. A correct analysis for this supposed salt could not be obtained. This compound at pH 1 yielded VII (m.p.  $211-212^\circ$ ).

Its  $^1\text{H}$  nmr spectrum exhibited three multiplets at  $\delta$  6.25, 6.85 and 10.15 attributed to the NH and  $\text{NH}_2$  protons and a multiplet at  $\delta$  7.40 for the aromatic protons.

We have also prepared, in very good yield, compounds VIIa and VIIb from 3,5-diamino-4H-1,2,6-thiadiazine 1,1-dioxide (V) and the diazonium salts of *m*-chloroaniline and *p*-nitroaniline, respectively.



All our attempts to oxidize VIIa and VIIb with lead tetraacetate have been unsuccessful so far.

The oxidation of the VII with lead tetraacetate in acetic acid solution afforded the desired cyclized compound VIII. A better yield of VIII was obtained by oxidation of the sodium salt of VII.

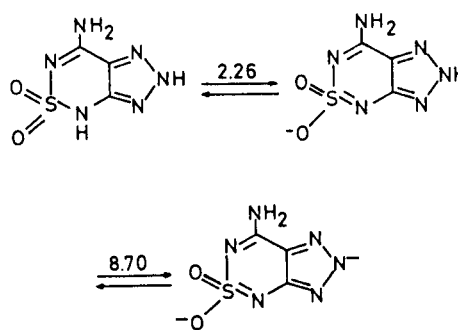
The  $^1\text{H}$  nmr spectrum of VIII showed a broad multiplet at  $\delta$  8.80 corresponding to the NH and  $\text{NH}_2$  protons, and one aromatic multiplet at  $\delta$  7.85.

We also determined the  $\text{pK}_a$ -values of compound VI its monohydrate and VIII for further characterization in the normal pH-range by the spectrophotometrical method (7).

The  $\text{pK}_a$ -values of VI and  $\text{VI}\cdot\text{H}_2\text{O}$  gave similar figures within the limits of error indicating identical structures. The uv spectra are also in agreement in the pH-range measured (-1 + 13).

Both  $\text{pK}_a$ -values at  $2.26 \pm 0.01$  and  $8.70 \pm 0.01$ , must be regarded as acidic since in both cases the dissociation of a proton was measured.

It could be admitted that the lowest value of  $\text{pK}_a$  is due to the ionization in the six-membered ring and that the second one is characterized by the loss of a proton in the triazole ring. This sequence is confirmed by the fact that the first acidic  $\text{pK}_a$  of the 2-phenyl derivative VIII is found at  $3.21 \pm 0.01$ .



## 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 spectrometer with TMS as internal standard. Ultraviolet spectra were recorded on a Perkin-Elmer 350 and 402 spectrophotometers.

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

A stirred solution of 2.5 g. (0.014 mole) of III and 1.53 g. (0.014 mole) of sodium nitrite in 15 ml. of 1*N* sodium hydroxide, was cooled in an ice bath and slowly treated dropwise with glacial acetic acid to pH 5. The yellow-orange precipitate was collected by filtration, washed repeatedly with water and dried over calcium chloride, yielding 2.25 g. (84%) of analytically pure product, m.p. 218°; ir (nujol):  $\nu$  (=N<sub>2</sub>), 2,130 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>3</sub>H<sub>4</sub>N<sub>6</sub>O<sub>2</sub>S: C, 19.15; H, 2.14; N, 44.62. Found: C, 19.03; H, 2.34; N, 44.72.

7-Amino-2*H*,4*H*-*vic*-triazolo[4,5-*c*][1,2,6]thiadiazine 5,5-Dioxide (VI).

## A. From IV.

Anhydrous form A suspension of 1 g. of IV in 50 ml. of water was stored at room temperature for several days. The yellow needles which slowly precipitated were collected by filtration, washed with cold water and dried *in vacuo* over calcium chloride, giving 0.8 g. (80%) of VI, m.p. 237-238° dec.; uv  $\lambda$  max (water): 226 ( $\epsilon$ , 7,990), and 294 nm ( $\epsilon$ , 3,300); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>,  $\delta$ ): 8.45 and 8.60 (b. multiplets, 4H, NH and NH<sub>2</sub>).

*Anal.* Calcd. for C<sub>3</sub>H<sub>4</sub>N<sub>6</sub>O<sub>2</sub>S: C, 19.15; H, 2.14; N, 44.62. Found: C, 19.09; H, 2.14; N, 44.69.

## Monohydrate Form.

Compound IV (1 g.) was dissolved in boiling water after cooling of this solution and storage at 0-5° overnight, either compound VI, as yellow needles (m.p. 237-238° dec.), or compound VI.H<sub>2</sub>O, as yellow plates (m.p. 227-228° dec.), precipitated; uv  $\lambda$  max (water): 226 and 295 nm; <sup>1</sup>H nmr (DMSO-d<sub>6</sub>,  $\delta$ ): 8.55 (b.m., 5H, OH, NH and NH<sub>2</sub>); ir (nujol):  $\nu$  3,600, 3,520 (OH water).

## B. From V.

To a stirred solution of 1.62 g. (0.01 mole) of V in 10 ml. of 1*N* sodium hydroxide, 2 g. (0.01 mole) of tosylazide (CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>-SO<sub>2</sub>N<sub>3</sub>) were added at once. The mixture was then stirred at room temperature for 24 hours and the resulting precipitate filtered off. The filtrate was passed through an amberlite IR-120 (H<sup>+</sup>) column (50 ml.). Elution with deionized water gave a solution which was evaporated to dryness *in vacuo*. Recrystallization from water of the residue afforded indistinctly VI or VI.H<sub>2</sub>O identical in all respects to those obtained by method A.

## 3,5-Diamino-4-phenylazo-1,2,6-thiadiazine 1,1-Dioxide (VII).

The diazonium salt solution obtained from 1 g. (0.014 mole) of aniline and 0.8 g. (0.014 mole) of sodium nitrite in 6 ml. of 6*N* hydrochloric acid, was added at 0° to a stirred solution of 1.62 g. (0.01 mole) of V in 23 ml. of 2*N* sodium hydroxide. Immediately a solid precipitated which was filtered, washed with water and dried over calcium chloride afforded 2.75 g. (94%) of sodium salt of VII, was recrystallized from water, m.p. 310° dec. The sodium salt of VII was suspended in water and was acidified with concentrated hydrochloric acid, with stirring. The resulting solid was collected by filtration, washed with water and dried in

vacuum over calcium chloride and sodium hydroxide, yielding 1.93 g. (72%) of VII. Recrystallization from water-ethanol gave VII as yellow needles, m.p. 210-212° dec.; uv  $\lambda$  max (water-ethanol): 221 ( $\epsilon$ , 6,000), 240 (sh) ( $\epsilon$ , 6,060), 277 ( $\epsilon$ , 4,400) and 370 nm ( $\epsilon$ , 11,800); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>,  $\delta$ ): 6.25 (b.s., 2H, NH<sub>2</sub>), 6.85 (b.m., 2H, NH<sub>2</sub>), 7.40 (m, 5H, A<sub>7</sub>H), 10.15 (b.m., 1H, NH).

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>N<sub>6</sub>O<sub>2</sub>S: C, 40.60; H, 3.78; N, 31.57. Found: C, 40.56; H, 3.81; N, 31.26.

3,5-Diamino-4-(*m*-chlorophenylazo)-1,2,6-thiadiazine 1,1-Dioxide (VIIa).

Following the procedure described for VII the reaction between 1.6 g. (0.01 mole) of V and the diazonium salt obtained from 1.4 g. (0.014 mole) of *m*-chloroaniline, yielded 2.5 g. (87%) of VIIa, m.p. 241° dec. (from water-ethanol); uv  $\lambda$  max (ethanol): 222 ( $\epsilon$ , 11,400), 252 ( $\epsilon$ , 9,200), 276 ( $\epsilon$ , 7,100) and 397 nm ( $\epsilon$ , 16,000); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>,  $\delta$ ): 7.65 (m, 4H, A<sub>7</sub>H), 7.90 (b.m., 5H, NH<sub>2</sub>).

*Anal.* Calcd. for C<sub>9</sub>H<sub>9</sub>ClN<sub>6</sub>O<sub>2</sub>S: C, 35.90; H, 2.90; N, 27.90. Found: C, 36.17; H, 3.00; N, 27.73.

3,5-Diamino-4-(*p*-nitrophenylazo)-1,2,6-thiadiazine 1,1-Dioxide (VIIb).

Following the procedure described for VII, the reaction between 1.6 g. (0.014 mole) of V and the diazonium salt obtained from 1.45 g. (0.014 mole) of *p*-nitroaniline, yielded 3 g. (96%) of VIIb, m.p. 280-281° dec. (from water-ethanol); uv  $\lambda$  max (ethanol): 211 ( $\epsilon$ , 17,490), 221 (sh) ( $\epsilon$ , 10,880) and 455 nm ( $\epsilon$ , 31,100); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>,  $\delta$ ): 8.15 (m., 4H, A<sub>7</sub>H), 7.9 (v.b. signal, NH, NH<sub>2</sub>, disappeared with D<sub>2</sub>O).

*Anal.* Calcd. for C<sub>9</sub>H<sub>9</sub>N<sub>7</sub>O<sub>4</sub>S: C, 34.73; H, 2.91; N, 31.50. Found: C, 34.87; H, 3.00; N, 31.31.

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

To a stirred suspension of 1.8 g. (0.006 mole) of the sodium salt of VII in 45 ml. of glacial acetic acid, 3.3 g. (0.007 mole) of lead tetraacetate were added, in portions, during 5 minutes. The reaction mixture was stirred for 24 hours under nitrogen atmosphere and its colour changed from orange to yellow. The precipitate was collected by filtration, washed with water, and dried over sodium hydroxide. The crude product was recrystallized from nitromethane to give 1.4 g. (82%) of VIII as yellow needles, m.p. 283° dec.; uv  $\lambda$  max (water): 202 ( $\epsilon$ , 1,500), 249 ( $\epsilon$ , 1,680), 353 nm ( $\epsilon$ , 1,060); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>,  $\delta$ ): 7.85 (m., 5H, A<sub>7</sub>H), 8.80 (b.m., 3H, NH and NH<sub>2</sub>).

*Anal.* Calcd. for C<sub>9</sub>H<sub>8</sub>N<sub>6</sub>O<sub>2</sub>S: C, 40.91; H, 3.05; N, 31.81. Found: C, 41.11; H, 3.19; N, 31.92.

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