Oxidation Reactions of 3,4,5-Triamino-1,2,6-thiadiazine 1,1-Dioxide. Preparation of 3,5-Diamino-4*H*-1,2,6-thiadiazin-4-one 1,1-Dioxide

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Oxidation reactions of 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide with hydrogen peroxide and chromium trioxide are reported. 3,5-Diamino-4*H*-1,2,6-thiadiazin-4-one 1,1-dioxide is synthesized by different methods.

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In a previous paper (1) the preparation of 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide (I) by reduction of 3,5-diamino-4-hydroxyimino-4*H*-1,2,6-thiadiazine 1,1-dioxide with sodium dithionite or by catalytic hydrogenation of 7-amino-4*H*-furazano[3,4-c][1,2,6]thiadiazine 5,5-dioxide has been reported.

Compound I is a very useful starting material for the preparation of different purine-like heterocyclic systems (1,2). In addition, compound I, similarly to its analog 4,5,6-triamino-2-oxodihydropyrimidine (X), (3,4), exhibits some biological activity.

When I is dissolved in water, the resulting yellow solution turns to red on contact with the atmospheric oxygen. Treatment of this solution with sodium dithionite makes its colour turn from red to yellow again. As in the case of X (5) when compound I is allowed to stand at room temperature for a long time it loses completely its biological activity.

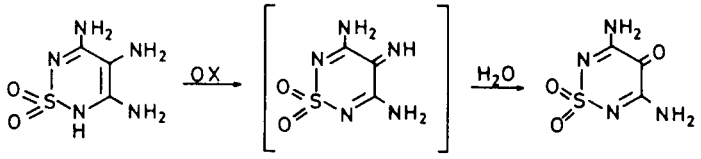
These facts suggest that compound I seems to be particularly sensitive to oxidation, giving the corresponding imine derivative II which, in turn, is readily converted into the starting compound (I) by the action of reducing agents (sodium dithionite).

The present communication describes the reaction of 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide (I) with different types of oxidation agents.

Reaction with Hydrogen Peroxide.

Treatment of an aqueous solution of I with hydrogen peroxide at room temperature, immediately altered the yellow colour of the solution turning it to red. No identificable product could be isolated from this red solution. The starting material (I) was recovered from the reaction mixture by treatment with sodium dithionite. However, when the red solution was heated or was acidified, its colour changed to yellow and then a compound was isolated, to which structure III was assigned.

It seems very likely that compound I was oxidized to the imine derivative II, which on hydrolysis afforded ketone III.



I II III

The ir spectrum of III showed a carbonilic absorption band at 1,690 cm^{-1}. The ^1H nmr spectrum exhibited one singlet at δ 8.15 ppm for the amino protons. The analytical and mass spectrometry data were also consistent with the proposed structure.

Ketone derivative III is very unreactive. It does not react with phenylhydrazine, 2,4-dinitrophenylhydrazine or hydroxylamine. Ketone III could not be obtained by hydrolysis of oxime IV.

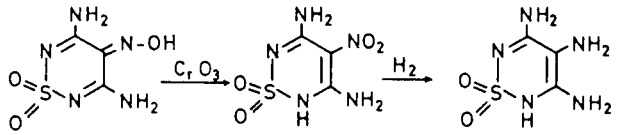
Reaction with Chromium Trioxide.

Reaction of compound I with chromium trioxide in acetic acid at room temperature yielded a yellow solid, identical in all respects with ketone III. In this case, the intermediate red colour could not be observed due to the dark colour of the reaction mixture.

On the other hand, reaction of 3,5-diamino-4-hydroxyimino-4*H*-1,2,6-thiadiazine 1,1-dioxide (IV) (1) with chromium trioxide in acetic acid gave the corresponding nitro derivative V.

The fact that in the oxidation of I neither traces of IV nor V could be observed confirmed that this reaction does not progress from the imine stage.

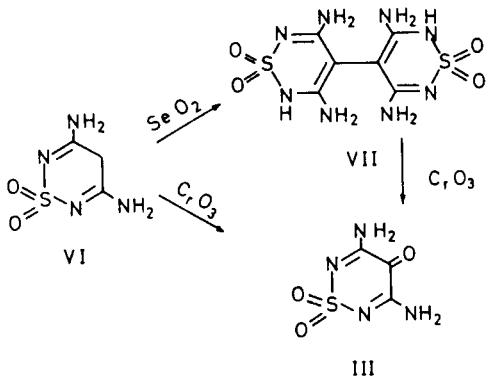
Catalytic hydrogenation of the nitro derivative V afforded compound I in very good yield (90%).



IV V I

Preparation of 3,5-Diamino-4*H*-1,2,6-thiadiazin-4-one 1,1-Dioxide.

Reaction of 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide (VI) with chromium trioxide in acetic acid (6) resulted in smooth conversion to ketone III in high yield. However, reaction of compound VI with selenium dioxide in aqueous medium, afforded compound VII, which by oxidation with chromium trioxide yielded ketone III.

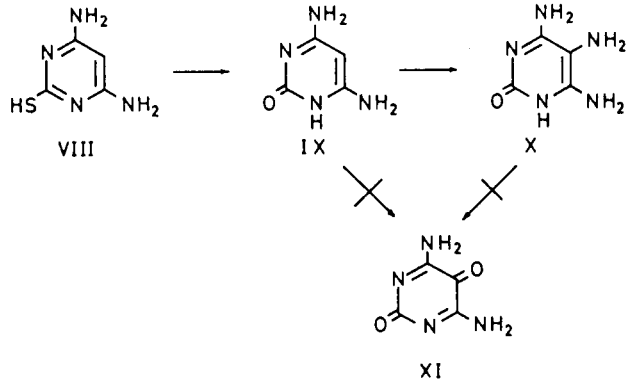


VI VII III

The ^{1}H nmr spectrum of VII showed only a broad multiplet at δ 5.95 ppm for the protons of the molecule. The absence of signals for the protons at position 4 in VII, which are found in the ^{1}H nmr spectrum of VI, indicated that the attack had occurred in this position. The analytical data were consistent with the hemihydrate of VII.

Attempts to extend this oxidation to amino 2-pirymidones, isosteric with the amino 1,2,6-thiadiazine 1,1-dioxides above mentioned have been unsuccessful.

In none of the cases did the oxidation of IX and X (7,8) lead to desired XI under the conditions described for I and VI. It should be noted that no reference for XI has been found in the literature.



VIII IX X XI

Transformation of VIII to IX, which is usually carried out with chloroacetic acid (9), was performed with chromium trioxide in acetic acid in very good yield.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12 spectrometer with TMS as internal standard; infrared spectra on a Perkin-Elmer 257 spectrometer; ultraviolet spectra on a Perkin-Elmer 350 and 402 spectrophotometers and mass spectra on a Varian MAT-711 spectrometer.

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

A. From I.

Method a).

A suspension of 1.77 g. (0.01 mole) of I in 20 ml. of ten volume hydrogen peroxide was heated under reflux for 15 minutes. The resulting yellow solution was cooled to room temperature and then drops of a solution of potassium permanganate were added to destroy the unreacted hydrogen peroxide. The solvent was evaporated under reduced pressure and the solid obtained was recrystallized from water-acetic acid to give 1 g. (59%) of III, m.p. 274-277° dec.; uv λ max (water): 216 (ϵ, 12,000), 240 nm (sh) (ϵ, 5,900); ^{1}H nmr (DMSO-d_6, δ): 8.15 (s, 4H, NH_2); ir (nujol) ν: 1,690 cm^{-1} (C=O); ms, m/e (1%): 176 (13.5) M^+, 90 (12.5), 64 (16), 48 (27), 44 (34), 42 (100), 32 (10), 28 (78.5).

Anal. Calcd. for $C_3H_4N_4O_3S$: C, 20.46; H, 2.28; N, 31.82. Found: C, 20.71; H, 2.29; N, 32.07.

Method b).

To a suspension of 1.77 g. (0.01 mole) of I in 8.5 ml. of acetic acid, 1.56 g. (0.01 mole) of chromic anhydride were added. The mixture was stirred at room temperature for 1 hour. The yellow solid which precipitated was filtered and washed, first, with glacial acetic acid and then with dry ether to give 1.7 g. (92%) of a compound which was identical in all respects to III.

B. From VI.

A three-necked flask equipped with a magnetic stirrer, a thermometer and a reflux condenser was charged with 8.5 g. of acetic acid, 1 ml. of water and 1.56 g. (0.01 mole) of chromic anhydride. The solution was cooled at room temperature whereupon 1.67 g. (0.01 mole) of VI were added. After stirring for 15 minutes the reaction mixture was heated at 60° for 1 hour. During this time a precipitate appeared, which, after cooling, was filtered and washed with glacial acetic acid and dry ether, yielding 1.62 g. (90%) of III.

C. From VII.

Following the method described above, 3.22 g. (0.01 mole) of VII were treated with 3.12 g. (0.02 mole) of chromic anhydride. The reaction mixture was heated at 60° for 24 hours. After cooling the solid precipitated was filtered, washed first with glacial acetic acid and then with dry ether, yielding 2 g. (55%) of III.

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

A three-necked flask equipped with a magnetic stirrer, a thermometer and a reflux condenser, was charged with 8.5 g. of acetic acid, 1 ml. of water and 1.56 g. (0.01 mole) of chromic anhydride. The solution was then cooled at room temperature and 1.91 g. (0.01 mole) of IV were added. The resulting mixture was heated at 60° for 24 hours and a yellow solid precipitated. On cooling, the solid was collected by filtration and washed with glacial acetic

acid and dry ether, yielding 1 g. (50%) of V, m.p. 243-245° dec. (water); uv λ max (water): 205 (ε, 10,730), 219 (sh) (ε, 9,050), 237 (sh) (ε, 6,330), 329 nm (ε, 9,310); ^{1}H nmr (DMSO-d_6, δ): 8.35 (broad signal, 5H, NH and NH_2).

Anal. Calcd. for $C_3H_5N_5O_4S$: C, 17.39; H, 2.43; N, 33.81. Found: C, 17.44; H, 2.47; N, 33.57.

4,4′-Bis(3,5-diamino-6*H*-1,2,6-thiadiazine 1,1-Dioxide) (VII).

To a suspension of 1.62 g. (0.01 mole) of VI in 50 ml. of water 1.10 g. (0.01 mole) of selenium dioxide were added and this mixture was refluxed for 6 hours. The metallic selenium which precipitated was filtered off and the filtrate was heated under reflux with charcoal for 10 minutes, after the charcoal has been removed and the solution cooled to 0°, 1.1 g. (65%) of white needles of VII precipitated. Recrystallization from water afforded pure VII, dec. 260°; uv λ max (water): 221 (sh) (ε, 17,500), 282 nm (ε, 28,500); ^{1}H nmr (DMSO-d_6, δ): 5.95 (b.m., 10H, NH, NH_2).

Anal. Calcd. for $C_6H_{10}N_8O_4S_2 \cdot 0.5H_2O$: C, 21.75; H, 3.32; N, 33.83. Found: C, 21.57; H, 3.46; N, 33.84.

4,6-Diamino-2-oxo-dihydropirymidine (IX).

A three-necked flask equipped with a magnetic stirrer, a thermometer and a reflux condenser, was charged with 8.5 g. of acetic acid, 1 ml. of water and 1.56 g. (0.01 mole) of chromic anhydride. The solution was cooled at room temperature whereupon 1.41 g. (0.01 mole) of VIII were added. After stirring for 15 minutes the reaction mixture was heated at 60° for 1 hour and a white solid precipitated. On cooling the solid was collected by filtration and washed first with glacial acetic acid and then with dry ether, yielding 1 g. (80%) of IX identical in all respects with the compound obtained by the usual method.

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