FIRST EXAMPLE OF A 4-AMINO-1,2,4,6-THIATRIAZINE 1,1-DIOXIDE DERIVATIVE

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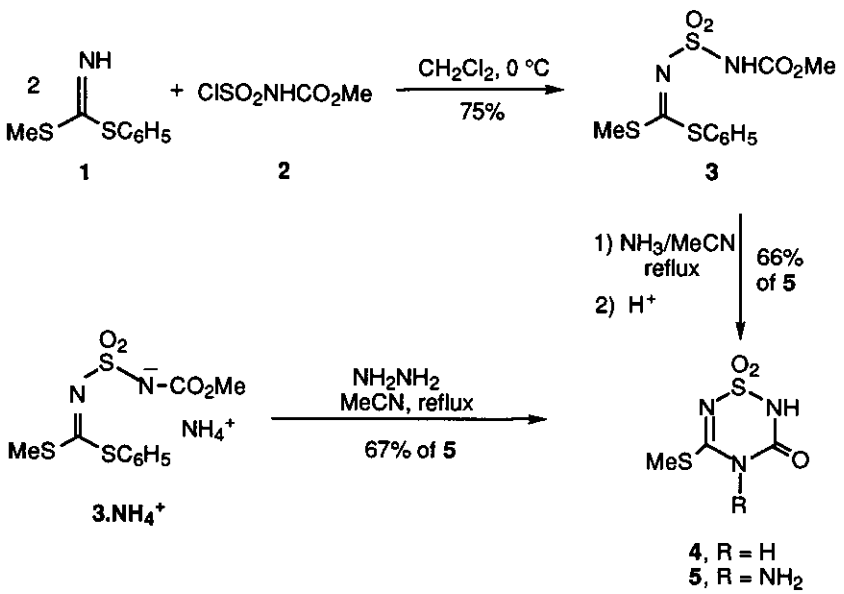
Abstract - For the first time, an N_4-amino derivative of 1,2,4,6-thiatriazine 1,1-dioxide (**5**) was prepared by cyclocondensation reaction of the appropriate sulfamoylcarbamate (**3**) with hydrazine. Reaction of **3** with ammonia yielded the cyclic 4*H*-derivative (**4**). Nucleophilic substitution reactions of **4** and **5** with hydrazine, as well as condensation of **5** with ethyl orthoformate were achieved. The antiprotozoal and anti-HIV properties of the new compounds were evaluated, but none of them showed significant biological activities.

Numerous papers dealing with the preparation of thiatriazine 1,1-dioxides were reported due to the herbicidal activity claimed in a number of patents.[1] However, no *N*-amino derivatives were described. Our interest in antichagasic drugs[2,3] prompted us to synthesize 4-amino-1,2,4,6-thiatriazine 1,1-dioxide derivatives in order to obtain some analogues of the antichagasic drug Nifurtimox.[4] In this context, and in continuing our work in this field,[1] we report here the synthesis of an *N*-amino-1,2,4,6-thiatriazine 1,1-dioxide derivative.

RESULTS AND DISCUSSION

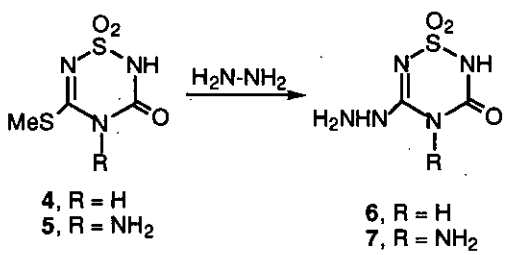
The synthesis of 4*H*- and N_4-amino-1,2,4,6-thiatriazine 1,1-dioxide derivatives (**4**) and (**5**) was achieved through the pathway shown in Scheme 1. Two moles of the dithioimidocarbonate (**1**)[5] were treated with one mole of the chlorosulfonylcarbamate (**2**)[6] to give the sulfamide derivative (**3**) in moderate yield. One of the two moles of compound (**2**) was necessary to capture the released hydrogen chloride. The hydrochloride of **1** was recovered from the reaction mixture. This procedure yielded better results in the synthesis of **3** than the one using triethylamine to trap the hydrogen chloride (yield 40%).



Scheme 1

When sulfamide (**3**) was treated with ammonia in THF or acetonitrile at 0 °C the ammonium salt (**3.NH$_4^+$**) precipitated from the solution and was isolated. However, if ammonia was bubbled through a solution of **3** or **3.NH$_4^+$** in refluxing acetonitrile the ammonium salt of **4** (**4.NH$_4^+$**) precipitated. Acid treatment of **4.NH$_4^+$** yielded free compound (**4**). To synthesize the desired N_4-amino derivative (**5**), it was necessary to treat the ammonium salt (**3.NH$_4^+$**) with hydrazine; the direct reaction of **3** allowed with hydrazine gave no compound (**5**) but only a little amount (8%) of compound (**6**), the nucleophilic substitution product of the *S*-methyl group by hydrazine. Compound (**5**) was directly isolated as free base from the reaction mixture showing that **5** is a less acidic compound than its 4*H*-derivative (**4**).

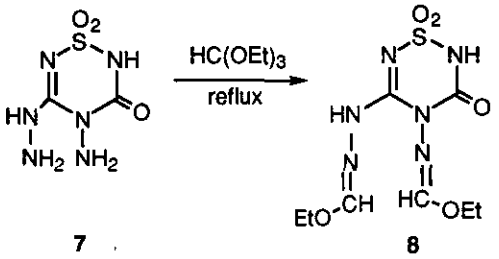
Up to now, no examples of *N*-amination reactions of 1,2,6-thiadiazine or 1,2,4,6-thiatriazine 1,1-dioxides were described, and only a report[7] dealing with *N*-amination of 1,2,4,6-thiatriazine 1-oxide was found. Attempts to obtain the N_4-amino derivative (**5**) from compound (**4**) by *N*-amination reactions by hydroxylamine-*O*-sulfonic acid (HOSA) and *O*-(2,4-dinitrophenylhydroxylamine) (DPH)[8] were unsuccessful, both the decomposition of the starting material being noticed.



Scheme 2

The methylthio group of compounds (**4**) and (**5**) underwent nucleophilic displacement by hydrazine to give 5-hydrazino derivatives (**6**) and (**7**) (Scheme 2). However, attempted substitution with propylamine yielded only the corresponding propylammonium salts of heterocycles.

Both primary amino groups of compound (**7**) reacted with an excess of ethyl orthoformate to give the disubstituted derivative (**8**) and no traces of any cyclic derivative were observed (Scheme 3).



7 **8**

Scheme 3

In order to obtain compounds related to Nifurtimox, condensations between the amino group of **5** and aryl aldehydes were attempted. All attempts, involving conventional as well as microwave assisted methods, afforded complex mixtures from which it was not possible to isolate the desired compounds.

New compounds were tested *in vitro* as antiprotozoal drugs against *Trichomonas vaginalis* and *Trypanosoma cruzi* but no significant activity was found. Compounds (**4**, **5** and **7**) were also evaluated on their anti-HIV-1 and anti-HIV-2 activities but were found inactive at subtoxic concentrations (>200 μg/ml for **7**, >24 μg/ml for **4** and >31 μg/ml for **5**).

EXPERIMENTAL

Mps were taken using a Reichert-Jung Thermovar and are uncorrected. Ir spectra were obtained using a Shimadzu Ir-435 spectrophotometer. ^{1}H-Nmr and ^{13}C-nmr spectra were recorded in a Varian Gemini-200 spectrometer at 200 and 50 MHz respectively. Merck silica gel 60GF_{254} was used for analytical and preparative tlc. Column chromatography was performed on Merck silica gel 60 (70-230 mesh). All solvents employed in reactions were dried just before use. Hydrazine hydrate was carefully distilled, under vacuum, on potassium hydroxide. After cooling, vacuum was removed, and the distilate on potassium hydroxide was kept in a refrigerator until use.

Methyl *N*-[(1-Methylthio-1-phenylthio)methylideneaminosulfonyl]carbamate (**3**). To a stirred solution of *S*-phenyl-*S'*-methyldithioimidocarbonate[5] (**1**) (3.9 g, 23 mmol) in dry CH_2Cl_2 (25 ml) at 0 °C, a solution of methyl chlorosulfonylcarbamate (**2**) (2.0 g, 11.5 mmol) in dry CH_2Cl_2 (20 ml) was slowly added. Then, the reaction mixture was stirred at room temperature for 3 h. The resulting solution was evaporated

to dryness under vacuum to give an oil which was kept in the refrigerator overnight. The reaction mixture was treated with THF to precipitate the hydrochloride of **1** which was filtered and led the free base. To obtain compound (**3**) the THF filtrate was evaporated and the residue purified by column chromatography using hexane/EtOAc (2/1) as eluent. Compound (**3**) was obtained (2.7 g, 75%) as a syrup which slowly crystallizes as colourless prisms; mp 105-07 °C. Ir (KBr): ν = 3150, 1720, 1340, 1150 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): δ = 8.20 (br s, 1H, NH), 7.50 (m, 5H, H_{arom}), 3.83 (s, 3H, CO_2Me), 2.34 (s, 3H, SMe). ^{13}C-Nmr (CD_3OD): δ = 189.0 (CO), 153.8 (C=N), 138.1 (C_o), 132.7 (C_p), 130.9 (C_m), 127.9 (C_i), 53.7 (OMe), 17.2 (SMe). *Anal.* Calcd for $C_{10}H_{12}N_2O_4S_3$: C, 37.50; H, 3.75; N, 8.75; S, 30.00. Found: C, 37.26; H, 3.81; N, 8.78; S, 29.84.

Ammonium Salt of Methyl *N*-[(1-methylthio-1-phenylthio)methyleneaminosulfonyl]carbamate (**3.NH$_4^+$**). Through a solution of compound (**3**) (950 mg, 3 mmol) in dry THF (57 ml), dry ammonia was bubbled during 8 min at 0 °C. Then, the reaction mixture was stirred at room temperature for 30 min. The white solid that appeared corresponded with the ammonium salt (**3.NH$_4^+$**) (1 g, 99%); mp 215-16 °C. ^{1}H-Nmr ($CDCl_3$): δ = 7.50 (m, 5H, H_{arom}), 3.62 (s, 3H, CO_2Me), 2.15 (s, 3H, SMe). ^{13}C-Nmr (CD_3OD): δ = 178.5 (CO), 162.0 (C=N), 138.3 (C_o), 131.9 (C_p), 130.4 (C_m), 129.7 (C_i), 52.6 (OMe), 16.7 (SMe). *Anal.* Calcd for $C_{10}H_{15}N_3O_4S_3$: C, 35.60; H, 4.45; N, 12.46; S, 28.48. Found: C, 35.46; H, 4.31; N, 12.25; S, 28.31.

Ammonium Salt of 2,3-Dihydro-5-methylthio-3-oxo-4*H*-1,2,4,6-thiatriazine 1,1-Dioxide (**4.NH$_4^+$**). Through a solution of sulfamoylcarbamate (**3**) (1 g, 3.1 mmol) in dry MeCN (40 ml), dry ammonia was bubbled at room temperature until saturation. Then, the reaction mixture was refluxed at 100 °C for 1.5 h, during this time a gentle stream of ammonia being passed through the reaction mixture. The white solid that appeared was collected and washed with $CHCl_3$. The solid was the ammonium salt of **4** (**4.NH$_4^+$**) (434 mg, 66%); mp 245-47 °C. Ir (KBr): ν = 3400 (NH), 3300-3050, 1430 (NH_4^+), 1660, 1580 (C=N), 1260-1220, 1120 cm^{-1} (SO_2). ^{1}H-Nmr1 (DMSO-d_6): δ = 7.99-7.61 (m 5H, NH, NH_4^+), 2.28 (s, 3H, SMe). ^{13}C-Nmr (CD_3OD): δ = 160.0 (C-5), 152.0 (C-3), 11.7 (SMe). *Anal.* Calcd for $C_3H_8N_4O_3S_2$: C, 16.98; H, 3.80; N, 26.40; S, 30.21. Found: C, 16.95; H, 3.73; N, 26.52; S, 30.35.

2,3-Dihydro-5-methylthio-3-oxo-4*H*-1,2,4,6-thiatriazine 1,1-Dioxide (**4**). An aqueous solution of **4.NH$_4^+$** (434 mg) was passed through Amberlite ir-120 (H^+) resine (30 ml total volume) to give compound (**4**) as white needles; yield 399 mg (100%); mp 196-98 °C (methanol). Ir (nujol): ν = 1740 (C=O), 1710 (C=N), 1280, 1180 cm^{-1} (SO_2). ^{1}H-Nmr (CD_3OD): δ = 2.57 (s, 3H, SMe). ^{13}C-Nmr (DMSO-d_6): δ = 167.3 (C-5), 149.4 (C-3), 13.8 (SMe). *Anal.* Calcd for $C_3H_5N_3O_3S_2$: C, 18.46; H, 2.56; N, 21.54; S, 32.82. Found: C, 18.31; H, 2.59; N, 21.33; S, 32.67.

4-Amino-2,3-dihydro-5-methylthio-3-oxo-1,2,4,6-thiatriazine 1,1-Dioxide (**5**). A solution of hydrazine (200 mg, 6 mmol) in MeCN (10 ml) was added dropwise to a stirred solution of the ammonium salt of sulfamoylcarbamate **3** (1 g, 3.1 mmol) in dry MeCN (30 ml). Then, the mixture was heated with stirring at

110 °C for 3 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was purified by column chromatography using $CHCl_3$/MeOH (3:1) as eluent. The phenyl disulfide formed was eluted first and then 440 mg (67%) of compound (**5**) was isolated; mp > 260 °C ($MeOH/NO_2Me$). Ir (KBr): ν = 3450 (NH_2), 3150 (NH_2), 3100 (NH), 1620 (C=O), 1300-1260, 1100 cm^{-1} (SO_2). ^{1}H-Nmr (DMSO-d_6): δ = 7.10 (br s 2H, NH_2), 5.00 (s, 1H, NH), 2.11 (s, 3H, SMe). ^{13}C-Nmr (DMSO-d_6): δ = 166.0 (C-5), 152.0 (C-3), 14.1 (SMe). *Anal.* Calcd for $C_3H_6N_4O_3S_2$: C, 17.14; H, 2.86; N, 26.67; S, 30.48. Found: C, 16.95; H, 2.80; N, 26.34; S.30.29.

2,3-Dihydro-5-hydrazino-3-oxo-4*H*-1,2,4,6-thiatriazine 1,1-Dioxide (**6**). In a 100 ml round bottom flask with exclusion of humidity, a mixture of thiatriazine 1,1-dioxide (**4**) (400 mg, 2.3 mmol) and hydrazine (0.1 ml, 4.5 mmol) in dry MeCN (50 ml) was stirred under reflux for 2 h. The resulting solution was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH/H_2O (50% v/v) to give 330 mg (90%) of **6** as white crystals; mp > 260 °C. ^{13}C-Nmr (DMSO-d_6): δ = 153.5 (C-5), 149.8 (C-3). *Anal.* Calcd for $C_2H_5N_5O_3S$: C, 13.41; H, 2.79; N, 39.10; S, 17.88. Found: C, 13.23; H, 2.83; N, 38.97; S, 17.54.

4-Amino-2,3-dihydro-5-hydrazino-3-oxo-1,2,4,6-thiatriazine 1,1-Dioxide (**7**). In a 100 ml round botton flask with exclusion of humidity, a mixture of thiatriazine 1,1-dioxide (**5**) (450 mg, 2.1 mmol) and hydrazine (0.1 ml, 4.5 mmol) in dry MeCN (50 ml) was stirred under reflux overnight. The resulting solution was evaporated to dryness under reduced pressure. The residue was dissolved in water (12 ml), acidified with acetic acid and kept in a refrigerator. Compound (**7**) (173 mg, 42%) precipitated as white needles; mp > 260 °C. ^{13}C-Nmr (DMSO-d_6): δ = 152.5 (C-5), 150.1 (C-3). *Anal.* Calcd for $C_2H_6N_6O_3S$: C, 12.37; H, 3.09; N, 40.30; S, 16.49. Found: C, 12.15; H, 3.00; N, 40.15; S, 16.25.

2,3-Dihydro-4-ethoxymethylenamino-5-ethoxymethylenehydrazino-3-oxo-1,2,4,6-thiatriazine 1,1-Dioxide (**8**). Thiatriazine 1,1-dioxide (**7**) (194 mg, 1 mol) was dissolved in an excess of ethyl orthoformate (20 ml). The mixture was refluxed for 16 h with exclusion of humidity. The solution was evaporated to dryness under vacuum and the resulting solid was purified by tlc using hexane/EtOAc (1/1) as eluent. Compound (**8**) was isolated as a white solid (226.4 mg, 74% yield); mp 251-53 °C. ^{1}H-Nmr (DMSO-d6): δ = 8.98 (s, 1H, =CH), 8.70 (s, 1H, =CH), 4.32 (q, 2H, ^{3}J = 6.2 Hz, CH_2), 3.83 (q, 2H, ^{3}J = 6.1 Hz, CH_2), 1.34 (t, 3H, ^{3}J = 6.2 Hz, CH_3), 1.26 (t, 3H, ^{3}J = 6.1 Hz, CH_3). *Anal.* Calcd for $C_8H_{14}N_6O_5S$: C, 31.37; H, 4.58; N, 27.45; S, 10.46. Found: C, 31.35; H, 4.67; N, 27.30; S, 10.19.

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